Contd. Annex 7

Approved
SNA
31/7/24.

REPUBLIC OF KENYA

PARLIAMENT OF KENYA
THIRTEENTH PARLIAMENT – THIRD SESSION – 2024

THE DIRECTORATE OF DEPARTMENTAL COMMITTEES OF THE NATIONAL ASSEMBLY
AND
THE DIRECTORATE OF SOCIAL ECONOMIC COMMITTEES OF THE SENATE

THE NATIONAL ASSEMBLY DEPARTMENTAL COMMITTEE ON HEALTH
AND
THE SENATE STANDING COMMITTEE ON HEALTH

REPORT ON THE APPROVAL OF DR. PATRICK OMWANDA AMOTH, EBS, NOMINEE FOR APPOINTMENT AS THE DIRECTOR-GENERAL FOR HEALTH

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JULY 2024

Cont. Annex 7

Annex 7

REPUBLIC OF KENYA

IN THE MATTER OF THE STATUTORY OATHS AND DECLARATIONS ACT CHAPTER 15 LAWS OF KENYA

-AND-

IN THE MATTER OF INVITATION TO SUBMIT MEMORANDA OF APPROVAL HEARING FOR DR. PATRICK OMWANDA AMOTH NOMINEE FOR APPOINTMENT TO THE POSITION OF DIRECTOR GENERAL FOR HEALTH

AFFIDAVIT (STATEMENT ON OATH)

I, **DR. WAHOME NGARE** resident in Nairobi of **Post Office Box Number 72071-00200** Nairobi in the Republic of Kenya do hereby make oath and Solemnly state as follows: -

1. **THAT,** I am an adult Kenyan of sound mind and duly competent and authorized to make this Affidavit *(statement under oath)* on my own behalf, being a Kenyan and a doctor in full time practice by profession.

2. **THAT,** I am the Chairman of the Kenya Catholic Doctors Association and founding Chairman of the African Sovereignty Coalition.

3. **THAT,** the **Health Act Chapter 241 Section 17** indicates the following as the function of the Director General:

   "(a) be the technical advisor to the Government on all matters relating to health within the health sector;

   (b) be the technical advisor to the Cabinet Secretary of health;

   (c) be responsible for preventing and guarding against the introduction of infectious diseases into Kenya;

   (d) promote the public health and the prevention, limitation or suppression of infectious, communicable or preventable diseases within Kenya;

   (e) advice the two levels of Government on matters of national security on public health;

   (f) promote and facilitate research and investigations in connection with the prevention or treatment of human diseases;

   (g) prepare and publish reports and statistical or other information relative to the public health;

   (h) obtain and publish periodically information on infectious diseases and other health matters and such procurable information regarding epidemic diseases in territories adjacent to Kenya or in other Countries as the interests of public health may require;

   (i) provide guidelines for registration, licensing, certification and gazettement of all health facilities;

Annex F

(j) be responsible for internship program for health workers;

(k) supervise the directorates within the national Ministry of health; and

(l) perform any other duties as may be assigned by the appointing authority and any other written law."

4. **THAT,** Dr. Patrick Amoth has been acting as Director General of Health since the year 2020 during which time it has become clear he is not fit and suitable to hand the said portfolio, whether in acting capacity or as confirmed due to the following reasons:

4.1 His management of the Covid19 crisis.

a) Deliberately subjecting innocent Kenyans and the unsuspecting members of public to wanton psychological torture by using the appeal to fear public health messaging fallaciously by indicating Covid19 had no treatment and that only a vaccine would allow us to go back to normal. Annex 1 Appeal to fear in health care.

b) He refused to acknowledge and recommend treatment of the viral replication phase of Covid19 with re-purposed drugs such as Ivermectin and Hydroxychloroquine as well supportive treatment with Vitamin D, yet all were safe and effective. In fact, the guidelines released under his watch clearly discouraged treatment of the early phase of the disease and recommended the use of Hydroxychloroquine in the second phase of the disease when it was ineffective! Annex 2 Interim guidelines on management of Covid19 in Kenya. Such treatment would have contributed significantly to reducing transmission as well as reduced mortality. Annex 3 Comparisons between the Neighboring States of Amazonas and Pará in Brazil and Annex 4 Preventive Vitamin D Supplementation and Risk for COVID-19 Infection.

c) I used the drugs to treat family, friends and patients during the crisis and am happy to report I did not loss any patient to Covid19.

d) Introducing lockdowns as a way of containing an aerosol or airborne spread respiratory disease. Countries like Sweden and Tanzania did not take this draconian route seeking rather to balance between the risk of disease and destroying the economy. Annex 5 Sweden's no-lockdown COVID strategy, Annex 6 Tanzania's position on the COVID-19 pandemic. Both Lockdown and contact tracing did not make any sense given that they overlook the well-established physics of respiratory emissions, where droplets of all sizes can be carried many meters within a moist and hot turbulent cloud of exhaled breath. and had good results, Annex 7 How did we get here?

e) Recommending the use of Covid19 "vaccines" without reviewing the phase I and II clinical trial results to ascertain they are safe and effective hence creating a national security risks taking into account that the health care workers and security forces were the first to be injected. Covid19 vaccinations were rolled out in Kenya in March 2021 with Dr Amoth as the index candidate yet the phase I and II clinical trial results only become available through a court order after Pfizer was sued under the Freedom of Information Act in the USA. Annex 8 Pfizer FOIA Order by judge.

f) These were experimental vaccines released for use under emergency use authorization that required participants to fully understand this fact and give informed consent. Even for those who willingly took the vaccine did not give a true informed consent as the risks were never disclosed beforehand, they only got assurance from WHO that the vaccines were safe and effective. Annex 9 WHO lists two additional COVID-19 vaccines for emergency use and COVAX roll-out. This is against the Nuremberg code. Annex 10 Nuremberg Code.

g) Similar concerns about Dr Amoth's suitability to hold office had been raised with the Public Service Commission by the Kenya Catholic Doctors Association on the 11th of August 2023. Annex 11 Gross misconduct of DG and Annex 12 Email to PSC sent on 12th August 2023.

5. **THAT** the Information from those who have analyzed the data from the Pfizer phase I and II clinical trials indicate that before releasing the Covid19 injections, Pfizer knew:

i) The mRNA vaccines did not work.

ii) The vaccine is distributed throughout the body in a couple of days, accumulating in the liver, adrenals, spleen and ovaries.

iii) The injections damaged the hearts of minors.

iv) 61 people in the trials died of strokes, and half of the stroke adverse events were within a couple of days after injection.

v) Five people in the trials died of liver damage—with, again, many of the liver damage adverse events sustained shortly after the injection.

vi) Neurological events, cardiac events, strokes, brain haemorrhages, blood clots, lung clots and leg clots were occurring at a massive scale.

vii) There was harm to sperm count, testis, and sperm motility; harm to ovaries, menstrual cycles, and placentas.

viii) Over 80 per cent of the pregnancies in one section of the Pfizer clinical findings documents ended in spontaneous abortion or miscarriage.

Annex 13 Pfizer and Moderna document analysis (https://www.ukcolumn.org/series/uk-situation-room-pfizermoderna-document-analysis).

6. **THAT,** the mRNA technology used in the Astra Zeneca vaccine given in Kenya is similar to that of Pfizer. Could the many sudden deaths we are noticing in Kenya be related to Covid19

vaccination? Can Dr Amoth furnish us with the clinical trial results of the phase I and II clinical trials of the Astra Zeneca vaccine that he used to approve its use in Kenya?

7. **THAT,** The Covid19 injections contain artificial viruses (Nano particle capsule or genetically modified Adenovirus containing the artificial mRNA (genetic material) that codes for the spike protein found on the SARS-Cov-2 virus). Unlike traditional viral vaccines where the dead or inactivated vaccine stimulates an immune response, the artificial virus is Covid19 injections actually infect normal human cells making them produce the spike protein – the exact same thing that caused the disease Covid19 disease! Annex 14 How Covid19 vaccines work and Annex 15 Astra zeneca insert 29th Jan 2021-pending-endorsement-european.

8. **THAT,** Viruses causing respiratory infections enter the body through mucus membranes and the body uses secretory IgA to prevent infection. For a vaccine to be effective against respiratory infections, it needs to stimulate production of secretory IgA. However, the Covid19 injections were given intramuscularly therefore producing systemic immunity as opposed to secretory IgA and this may explain why they were not effective in preventing infection. Annex 16 Inducing mucosal IgA.

9. **THAT,** one cannot develop a vaccine if the body's natural immunity cannot mount an effective immune response to the natural infection. It was wrong to make Covid19 vaccination mandatory by preventing those who had not been vaccinated from accessing services (hotels, restaurant, workplace) or traveling (out of and into the country). Such coercion is inconsistent with medical practice. In the Covid19 situation, the choices were between taking a chance with the infection and available treatment or taking a chance with the vaccination and its possible side effect. Each person's choice should have been respected and neither should have been discriminated against and or coerced into making any decision without full and frank disclosures. Annex 17 Comparing SARS-CoV-2 natural immunity to vaccine-induced immunity.

10. **THAT,** if a vaccine is safe and effective, then the person who has taken the injection has no reason to worry about the person who has not taken the vaccine! The unvaccinated person takes a risk with the infection but does not in any way threaten one who has been protected by the vaccine.

11. **THAT,** The mantra "no one is safe from COVID-19 until everyone is safe" is based on a misunderstanding of basic immunology. A story explaining why we must vaccinate health workers and highest-risk populations in all countries first and at the same time to protect ourselves locally suggested that vaccine doses must be shared globally and immediately. Unfortunately, this thought process is based on the assumption that the body does not have an effective natural immune system! Annex 18 No one is safe until we are all safe - mandatory vaccination. Both natural immunity and vaccine immunity contribute to herd immunity with natural immunity being more effective because the immune system responds to many different antigens on the virus while immunization generally uses one antigen from the virus. It follows that those who had healed from Covid19 did not need vaccination. Immunity from vaccination cannot be better than natural immunity. Annex 19 Comparing SARS-CoV-2 natural immunity to vaccine-induced immunity

12. **THAT**, he Approved the use of the RT PCR test as the gold standard, including testing people who did not have symptoms. The test detects the genetic material of the virus but cannot tell if the virus was active or dead at the point of sampling! Clinically, it would have made more sense to only test those with symptoms and still treat those with symptoms but who test negative. Testing people who were not sick knowing the RT PCR test had false positives would have exaggerated the number of "infections". Testing travelers who did not have symptoms also did not make medical sense. Annex 20 Recent advances and challenges of RT-PCR tests for the diagnosis of COVID-19. The RT PCR test emergency use authorization by the Food and Drug Administration was withdrawn in Dec 2021 because of its unreliability but the test continued being use in Kenya. Annex 21 Changes to CDC RT-PCR for SARS-CoV-2 Testing (cdc.gov).

13. **THAT,** Dr Amoth supports killing of unborn children contrary to medical ethic and the law:

    a) In May 2023, Dr Amoth, seemingly without the knowledge of the Cabinet Secretary Health, attempted to launch guidelines titled "A clinical handbook on the prevention and management of the big five direct causes of maternal morbidity and mortality in Kenya" which under medical uterine evacuation procedures (page 38 -39) illegally sanction the killing of unborn children up to 28 weeks' gestation (7 months of pregnancy) for "risky or unintended" pregnancy (Prevention No. iv on page 37). Annex 22 Guidelines, Standards & Policies Portal 11th Aug 2023. The country was only saved from this disaster when the Catholic Bishops and Kenya Catholic Doctors Association brought the matter to the attention of the CS of health, who then called off the launch.

14. **THAT, Article 26(4) of the Constitution of Kenya 2010** is very clear that ***"abortion is not permitted unless in the opinion of a trained health professional, there is need for emergency treatment or the life or health of the mother is in danger, or if permitted by any other law."*** Since the constitution is written in simple English and is not a medical document, the term abortion simply means bring to an end prematurely or terminate. This article of the Constitution prohibits the bringing to an end or termination of pregnancy unless by the opinion of a trained health professional. In other words, only the opinion of a trained health professional is valid when considering bringing to an end or terminating a pregnancy, even when permitted by any other law.

15. **THAT,** the **Health Act Section 6(2)** clearly defines a trained health professional as one with formal medical training. This means that it is medical ethics that must determine why and how a pregnancy is to be brought to an end or terminated. The terms "risky or unintended" pregnancies are social and not medical terms. In medicine, we use the phrase High Risk Pregnancy supported by a clear diagnosis. The terms "risky or unintended" pregnancy don't constitute a medical opinion of a trained health professional. Termination of pregnancy base on a pregnancy being "risky or unintended" would be inconsistent with the COK 2010 and the Health Act.

16. **THAT,** his management of malaria is wanting:

a) He has sanctioned the use of vaccination and GMO mosquitoes in the fight against Malaria in Kenya. Annex 23 Kenya to Release Genetically Modified Mosquitoes to Fight Malaria.

b) The UK eliminated Malaria in 1921 without using vaccination or GMO mosquitoes. Annex 24 The last British malaria outbreak.

c) The United States of America had been malaria free since 1951. In late 2020, 750 GMO mosquitoes were released in Florida Annex 25 Florida mosquitoes 750 million genetically modified insects to be released. Now by coincidence, 8 cases of locally acquired malaria were reported in the USA in 2023, 7 of them in Florida. Annex 26 Important Updates on Locally Acquired Malaria Cases Identified in Florida.

d) Malaria is a treatable disease and deaths from Malaria can be eliminated by ensuring the availability of life saving medication and use of safer environmental measures making Malaria vaccination totally unnecessary.

17. **THAT,** his management of HPV infection is wanting and is causing vaccine hesitancy:

a) The Ministry of Health campaigns presents HPV vaccination as prevention of cancer of the cervix yet it is for prevention of a sexually transmitted virus called Human Papilloma Virus. A person who has not engaged in sexual activity is not at risk of contracting HPV.

b) Where a person is infected with HPV, the body's natural immune systems destroys the virus up to 90% of the time. Only a small fraction of those who develop persistent HPV infection undetected for 15-20 years are at risk of developing cancer of the cervix.

c) The problem is therefore not HPV infection but persistent HPV infection. Persistent infection can be detected using pap smear and other simple tests 8 – 10 years before establishment of cancer of the cervix allowing for simple cheap treatment that would eliminate the risk of cancer.

d) Developed countries had reduced the risk of death from cancer of the cervix to negligible levels by simply encouraging all women who have ever engaged in sexual intercourse to have a pap smear test done once every 5 – 10 years. Annex 27 Human papillomavirus and cancer

e) HPV vaccination is not without risks, some lifelong e.g. premature ovarian failure or premature menopause. Annex 28 Benefits and harms of the HPV vaccines, Annex 29 Human papillomavirus associated premature insufficiency, Annex 30 Adolescent premature ovarian insufficiency HPV. Since there are other safer ways of preventing cancer of the cervix that target only the group at risk, HPV vaccination must remain

voluntary, with all the risks made clear to all parents so that they make an informed choice.

f) HPV vaccinations are sometimes being conducted in schools without parental consent, making parents very suspicious of the intension of the movement which is counterproductive.

g) The consent form being given to parents fall far short of standard consent forms as they fail to disclose how the disease is transmitted, the side effects of the vaccine and other available prevention modalities.

h) Setting out to achieve a vaccination targets of 90% of girls fully vaccinated with the HPV vaccine by the age of 15 as set by WHO, yet the vaccination is voluntary is counterproductive and defeatist and will lead to vaccine hesitancy. Annex 31 Cervical Cancer Elimination Initiative.

18. **THAT,** his submission without question to World Health Organization (WHO) initiatives and advisories risks compromising national sovereignty:

a) the management of Covid19, Malaria, HPV and abortion mentioned above are almost cut and paste from WHO.

b) He was elected to the executive committee of WHO as the Vice-chairman in May 2020 and later become the chairman in 2012. This is a clear conflict of interest that would not allow him to remain objective in case some WHO advisories were inconsistent with the interests of the county. Annex 32 Amoth appointed as WHO Executive Board chairperson.

19. **THAT,** he has not spoken against the IHR and new pandemic treaty despite the fact that some of the clauses threaten our national security and sovereignty. In fact, his office seems to be facilitating the process. If the action by WHO has been so disastrous with the little power they have under the IHR 2005, one shudders to imagine what they would do with more power. Annex 33 WHO IHR proposed amendments 2022. Fortunately for the Member States of WHO, the last World Health Assembly held from 27th May to 1st June that adopted amendments to the IHR 2005 did so in contravention of Article 55(2) of the same regulations that require that amendments "be communicated to all States Parties by the Director-General at least four months before the Health Assembly at which it is proposed for Consideration". This means the final text discussed in the last Health Assembly should have been communicated to all State Parties by January 27th 2024 which was not done, making the adopted amendments null and void. Annex 34 WHO international health regulations 2005.

20. **THAT,** The process of his appointment:

a) The Health Act Article 16(2) is clear that the Director-General for health shall be recruited by the Public Service Commission through a competitive process, vetted by

Parliament and appointed by the Cabinet Secretary. It is my understanding that Parliament would receive a report from the Public Service Commission indicating the candidates interviewed, marks awarded to each and the reason why the winning candidate was chosen. We are therefore surprised that it is the Cabinet Secretary of the Ministry of Health who forwarded the name to Parliament.

b) On 22nd June 2024, Justus Kiprono of the Business Today reported that the then Cabinet Secretary of the Ministry of Health Susan Nakhumicha, had nominated Dr Partick Amoth to be the Director General of Health. He further quotes the CS as saying "The advert does not exclude Amoth from applying. I have confidence, given the experience he has. He (Amoth) should emerge the best,". It would appear the interview was conducted before the CS of health had received the report from the Public Service Commission. If so, her utterances show bias, favoritism and amount to interfering with the independence of the Public Service as well as being unfair to other candidates. This is contrary to Article 6 and Chapter 10 of the Constitution of Kenya 2010. Annex 35 Dr Patrick Amoth Is CS Nakhumicha's Choice.

c) The invitation for Memoranda by Parliament published in various media early in July 2024 clearly indicates the nomination of Dr Amonth was communicated to Parliament by the CS as opposed to the Public Service Commission. This in our understanding is contrary to the law. Annex 36 Invitation to submit memoranda.

21. **THAT,** Given the gravity of the matter and considering many of the technical statements made may need further clarification, I request for an in person presentation and I do hereby attach the evidence relied upon and/or exhibits jointly marked as **"WN1"**

22. **THAT**, I make this statutory declaration conscientiously believing the same to be true and in accordance with the Oaths and Statutory Declaration Act.

S W O R N at Nairobi by the said)
DR. WAHOME NGARE)
)
this 19th day of July .....2024)
)
BEFORE ME)
)
)
COMMISSIONER FOR OATHS

DRAWN BY:

DR. WAHOME NGARE

P.O.BOX 72071-00200

NAIROBI

TO BE SERVED UPON

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AND SENATE

P. O. BOX 41842-001000

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"ANNEXURE WN 1"

IN THE MATTER OF INVITATION TO SUBMIT MEMORANDA OF APPROVAL HEARING FOR DR. PATRICK OMWANDA AMOTH NOMINEE FOR APPOINTMENT TO THE POSITION OF DIRECTOR GENERAL FOR HEALTH

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this is the exhibit marked "WN 1"
to in the annexed affidavit of DR WAHOME HGARE
sworn
declared
before me this 19TH day of July 20 24
at
Commissioner for Oaths
Notary Public

Simpson *Chiropractic & Manual Therapies* (2017) 25:27
DOI 10.1186/s12998-017-0157-8

Chiropractic & Manual Therapies

DEBATE Open Access

Appeal to fear in health care: appropriate or inappropriate?

J. Keith Simpson

Abstract

Aim: This paper examines appeal to fear in general: its perceived positive aspects, its negative characteristics, its appropriate as well as its fallacious use.

Background: Appeal to fear is a commonly used marketing method that attempts to change behaviour by creating anxiety in those receiving a fearful message. It is regularly used in public health initiatives such as anti smoking, anti-drunk driving campaigns as well as in hypertension awareness campaigns. Some chiropractors appear to use appeal to fear to promote subluxation awareness and thereby encourage the use of chiropractic treatment. Research supporting its use is equivocal; nevertheless, when used judiciously, appeal to fear probably has sufficient strengths to warrant its continued conditional use. When used to promote care for which there is no supporting evidence, its use is fallacious.

Discussion: Appeal to fear has been used in health promotion campaigns for sixty years or more with the intent of modifying behaviours. While there is evidence to suggest that appeal to fear may motivate some individuals to modify offending behaviour or adopt recommended behaviour there is growing resistance to the use of appeal to fear on ethical and psychological grounds. Using appeal to fear as a tool of persuasion can be valid or fallacious depending on the truth of the premises within the argument.
When used to raise awareness about genuine health concerns such as smoking, drunk driving and hypertension appeal to fear is considered to be a valid approach with certain caveats. However, when appeal to fear, not based on evidence or reason, is used as motivator to get others to accept unnecessary interventions for unproven disorders, the use of appeal to fear is fallacious.

Conclusion: In spite of the evidence against its use, it seems likely that appeal to fear will continue to be used in conjunction with other public awareness initiatives to modify recognized detrimental behaviours such as smoking and drunk driving as well as silent killers such as hypertension. However, when used to promote a treatment that has no evidentiary basis such as subluxation based practice in chiropractic the appeal to fear is a fallacy and must be stopped.

Keywords: Health care marketing, Appeal to fear, Appeal to fear fallacy, Chiropractic subluxation

Background: Believe me or else bad things will happen

Marketers use a variety of methods in an effort to persuade target audiences to modify behaviours in the interests of bettering their health. One of the ploys used by the developers of public health campaigns is to provoke an emotional response. Emotional appeals may include fear of ill health, death, disfigurement, as well as shame, scorn, humiliation or even disgust [1]. According to Witte [2] p.329 "Fear appeals are persuasive messages designed to scare people by describing the terrible things that will happen to them if they do not do what the message recommends." Appeal to fear is often presented as a warning:

X is something to fear; therefore Y should be implemented to prevent X.

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Examples of appeal to fear

1) Smoking kills in many ways ... quit smoking right now!

X (death) is something to fear; therefore Y (stopping smoking) should be implemented to prevent X.

2) Autism is a potentially devastating neurological disorder that can be caused by vaccinations. Protect your child from autism, do not vaccinate.

X (Autism) is something to fear; therefore Y (not vaccinating children) should be implemented to prevent X.

An appeal to fear in an argument can be valid or fallacious depending on whether the facts (premises) presented are true or false. The fallacy occurs when the level of fear created does not relate to the truth of the claim [3, 4].

In example 1 the facts are true (see below) rendering the argument valid: smoking does kill and stopping smoking does prevent smoking related deaths.

In example 2, the data do not support the premises rendering the argument invalid and making this appeal to fear fallacious.

The autism vaccine link began in 1998 with the publication of a descriptive study by Wakefield et al. [5] hypothesising a connection between the development of autism and the 8 children in the study having received a Measles-Mumps-Rubella vaccination (MMR) one month previously. In spite of Wakefield et al.'s paper providing no data supporting a causal association between MMR vaccine and autism and a lack of a plausible biological mechanism a world-wide fear emerged [6]. Even though the Wakefield et al. paper was retracted by The Lancet [7], the fear persisted prompting significant well-designed research projects to test the vaccine-autism hypothesis. The scientific evidence is clear – there is no link between vaccines in any form and autism [8–12] and any appeal to fear related to vaccination and autism is, by definition, fallacious.

As a motivational technique, appeal to fear has a certain intuitive appeal and is by no means new. According to Walton [13], Aristotle described appeal to fear as a fundamental rhetorical strategy and it has been a commonly used strategy in marketing and politics for six decades in the modern era [14]. Appeal to fear has many aliases, including argument from adverse consequences, scare tactics and threat appeals. It is generally perceived by health promoters and the general public as an effective device for changing attitudes and behaviours with little backfire effect. [15]. Backfire effect is the phrase coined by Nyhan and Reifler to describe the apparent psychological phenomenon whereby when an unsubstantiated belief is corrected by presenting data, instead of the opinion or belief changing, it becomes further strengthened [16].

While there is a perception of little backfire effect, the research into fear campaigns indicates that they may indeed backfire leading target audiences to increase engagement in the harmful behaviors [17–21] suggesting that other options for prompting behaviour change are more appealing [14, 22, 23]. Further, there is a growing number of authors suggesting that appeal to fear needs to be examined in light of its negative ethical and psychological implications [24–26].

Notwithstanding the negative findings, appeal to fear is considered to be a legitimate, if not caveat laden, method to employ in public health campaigns [27].

The appeal to fear fallacy occurs when baseless fear is employed in an excessive or exaggerated way to persuade others to accept a concept or adopt a behaviour [3, 4]. When used in this manner appeal to fear becomes fallacious scaremongering and is a particularly deceptive misrepresentation when the level of fear created does not relate to the truth of the claim.

This commentary provides an overview of appeal to fear and its effect on consumer behaviour. It then will consider the appropriateness or otherwise of using appeal to fear within the realm of mainstream health care by looking at four common usages:

- Anti-smoking campaigns[1]
- Anti-alcohol & drunk[2] driving campaigns
- Hypertension awareness campaigns
- Chiropractic anti-subluxation advertising

Appeal to fear: Overview

Use of the appeal to fear, in the form of threatening health messages, is commonly used as a strategy for changing behaviours within a population in relation to public health initiatives. The tactic involves using images or messages to elicit negative emotions such as anxiety in the expectation that the audience will be motivated to adopt the healthier behaviours [28].

Several examples exist within North America and Australia with anti-smoking and anti-alcohol campaigns being obvious ones with hypertension awareness campaigns being lesser known but widely used. Appeal to fear smoking campaigns have employed everything from graphic images of the lung damage caused by smoking to appealing to the smoker's children with varying degrees of success [29].

Early research into appeal to fear pointed to a use with caution approach and little has changed in the intervening decades. In 1953 Janis and Feshbach's seminal research identified three main types of emotional reactions to anxiety-arousing topics.

1. Inattentiveness – a defensive tendency to avoid thoughts related to the topic.

2. Aggressiveness – a defensive tendency to become aggressive towards the communicator, likely in the form of rejecting the arguments.
3. Defensive avoidances – attempts to ward off exposure to the anxiety causing communication typically in the form of failing to recall the message, losing interest in the topic, denying or minimizing the importance of the threat [30].

Janis and Feshbach suggested a negative association between fear producing messages and intended results. They found that a message that induced a minimal amount of fear was more effective than one evoking a high fear response in terms of both positive attitude change and resistance to subsequent attitudinal retrogression [30].

In an effort to better understand the relationship between fear inducing messages and persuasion, research continued throughout the 1960's and by end of the decade a clearer appreciation had been formulated. In short, fear appeared to be positively related to persuasion, but not necessarily on behaviour change. Rather, high fear produced greater intentions to act than did low fear, but did not result in changes in behaviour and messages delivered by highly credible sources resulted in a more immediate attitude change than messages delivered by sources with low credibility [23].

Seven theories have been put forward to explain fear appeals in behaviour change: The linear model of fear appeals the curvilinear model of fear appeals [31], the health belief model [32], the parallel process model [33], the extended parallel process model [34], the stage model [35], and the elaboration likelihood model [36]. It is beyond the scope of this paper to review them. For those interested, Ruiter et al. provide a comprehensive review of the state of the art in their 2014 paper [20].

The theories about fear appeals have focused on either the content of the message, the nature of the behavior recommended by the communication, or the characteristics of the audience receiving the message. However, all three of these aspects (message, behavior, and audience) are important and focusing on a singular aspect appears likely to yield ambiguous results. There does appear to be agreement that fear appeals are more effective when they involve health related behaviours, include an efficacy message which assures message recipients that they are capable of performing the fear appeal's recommended actions (self-efficacy) and/or that performing the recommended actions will result in desirable consequences [21]. However, fear-arousing messages may actually have deleterious consequences for recipients with low self-efficacy, as the message may strengthen the recipient's belief that they cannot avoid health threats [37].

Tannembaum et al.'s 2015 meta-analysis provides perhaps the best, if not controversial summary of appeal to fear research to date:

> Overall, we conclude that (a) fear appeals are effective at positively influencing attitude, intentions, and behaviors; (b) there are very few circumstances under which they are not effective; and (c) there are no identified circumstances under which they backfire and lead to undesirable outcomes [38] [p.1178].

This is a curious finding when most of the literature suggests when members of the target audience feel threatened but they are not convinced of their self-efficacy or of the effectiveness of the alternative behaviour the resulting behaviour may be defensive, more oriented toward avoidance of the anti-smoking fear message than action to quit smoking [19, 21, 35, 39, 40]. Furthermore, messages that arouse extreme fear may cause people to deny cancer risks and may inadvertently result in more smoking [41]. Perhaps Tannembaum et al.'s interpretation of the data relates to their combining various outcomes, – attitudes, intentions and behaviors - into one single effect size, and failure to report on studies with behavioral outcomes separately. Also, they compare a high fear condition with a condition designed to depict a lower level of fear or no fear instead of with alternative behavior change methods. In short, their work neither contains convincing arguments that fear appeals change actual behavior, nor that fear appeals would be more effective than an approach based on self-efficacy in combination with risk information.

So where does this leave us? As a marketing ploy appeal to fear has an intuitive appeal but paradoxically the outcomes are often ineffective or counterproductive [42] rendering it at best an equivocal tool for changing behaviours. In spite of this, appeal to fear continues to be widely and persistently used throughout the world [28]. There is general agreement that appeal to fear when used in this manner – to motivate individuals to adopt positive public health behaviours – is not a fallacy, but rather an appropriate positive rationally motivated form of argument [28, 43]. That said, use of fear in this manner must be approached cautiously and used judiciously [28, 44]. While some have argued that from a utilitarian perspective appeal to fear campaigns are ethical [45, 46] perhaps appeal to fear should be avoided altogether given the negative consequences highlighted above. Instead, health promoters should identify effective alternatives to fear arousal by carefully developing theory and evidence-based programs as outlined by Kok et al. [17].

If appeal to fear must be used, Witte and Allen provide sage advice:

> Fear appeals motivate attitude, intention, and behaviour changes—especially fear appeals accompanied by high-efficacy messages. Therefore, they can be quite useful to practitioners. However, fear appeals should be used cautiously, since they may backfire if target audiences do not believe they are able to effectively avert a threat [21] p. 605.

Some consideration needs to be given to special populations which are seen as more vulnerable to appeal to fear, specifically the elderly. Researchers have questioned the ethics of using appeal to fear marketing targeting the elderly, especially campaigns targeting health care initiatives given that there may be detrimental psychological reactions to fear provoking messages. The evidence available suggests however that the elderly are no more or less vulnerable to this type of advertising and may well be more discerning than their younger counterparts [46] and thus less likely to be affected positively or negatively.

Anti-smoking campaigns

Cigarettes or more correctly tobacco falls into a unique category amongst consumer products. On the one hand it is highly addictive and on the other hand it kills about 50 % of long-term users – a quarter while still in middle age [47]. Doll et al.'s fascinating prospective study of smoking and death among British doctors began in 1951 when the ill-effects of smoking first became known and continued for 50 years. The researchers confirmed the association between smoking habits and many severe diseases (vascular, neoplastic and respiratory diseases) and the suspected relationship between smoking and 12 types of cancer as well as increased mortality rate amongst all smokers. It clearly demonstrated that stopping smoking at any age brings with it an increase in life expectancy: stopping at age 60, 50, 40, or 30 gains, respectively, about 3, 6, 9, or 10 years of life expectancy. Doll et al. chose British doctors for pragmatic reasons. One could speculate also that Doll et al.'s study group, highly educated doctors who continued to smoke in the face of building evidence regarding its ill effects, is illustrative of the highly addictive nature of tobacco. This is borne out by La Torre et al.'s study examining knowledge, attitudes, and smoking behaviours among physicians specializing in public health [48].

Doll et al.'s research was also instrumental in motivating governments to develop and run anti-smoking campaigns aimed to decrease the numbers of people starting to smoke and to increase those stopping the habit. The campaigns are multimodal and include print, televised anti-smoking campaigns as well as graphic images and warning text messages on cigarette packaging.

Research into the impact of graphic and text messages points in the direction of motivating smokers towards cessation activity. Larger warnings are more effective than smaller ones and graphic images are more effective than printed warnings; strengthening pack warnings is associated with increased knowledge about the risks of smoking, increased Quitline calls, reduced smoking consumption, increased quit attempts, increased short-term smoking cessation, and reduced smoking prevalence [49–52].

While such approaches do appear to have a positive impact on smoking cessation or at least intent to stop, there are unwanted side effects. According to Hackley and Kitchen appeal to fear as found in anti-smoking campaigns violates ethical and social justice norms [53]. Further, Hastings et al. alert readers to the real possibility of collateral damage amongst non-smoking viewers caused by appeal to fear in anti-smoking advertising [37].

Whether the benefits outweigh the side effects of appeal to fear in anti-smoking campaigns is up for debate. Indeed, the courts in the USA are having such a debate with notable disagreement on the legality of using appeal to fear in the face of poor evidence that such advertising would directly cause a decrease in smoking [52]. The very fact that there is controversy reinforces the earlier statement: use of fear in this manner must be approached cautiously and used judiciously [29].

Anti-alcohol and drunk driving campaigns

Recent anti-alcohol and drunk driving campaigns in Australia have promoted the messages: 'If you drink then drive, you're a bloody idiot'; 'the faster you go, the bigger the mess' because alcohol is the main cause of Australian road deaths, accounting for a third of all road fatalities.

Over 70% of people with serious alcohol-related road injuries are male, while only 56% of people with non-alcohol-related road injuries were male. The average age of alcohol-related crash victims was 27.5 years with over 50% aged between 15 and 24 years. This is in contrast to the average age of 37.6 years for non-alcohol-related road injuries [54, 55]. In other words, teenage drivers, in particular teenage male drivers are an at risk group and thus the group whose behaviour society would most like to change [56].

In an effort to reduce alcohol related road fatality rates governments have funded and implemented targeted measures, including speed cameras, advanced laser speed detectors and compulsory breath testing. The major component from a budgetary perspective was, and continues to be, television advertisements focused on drunk driving and speed related themes, many of which include appeal to fear messages in the form of graphic

images. The State of Victoria in Australia has been running this type of campaign since 1989 with research examining the effectiveness of the Victorian initiative clearly demonstrating an association between levels of publicity supporting the speed and alcohol enforcement programs and reductions in casualty crashes when other major factors are held constant: between 1989 and 1992 there was a reduction of nearly 50% in road fatalities and 40% in serious injuries [57].

Overall however, research into the effectiveness of appeal to fear campaigns for modifying drunk driving has yielded mixed results [58]. For example, Macpherson and Lewis examined drunk driving offense rates and were unable to provide any evidence supporting the hypothesis that such advertising modified drunk driving behaviour [59], while Tay (1999) attributed a significant reduction in drunk driving behaviour [60] and alcohol related road fatalities [61] to the New Zealand advertising campaign.

Given such divergent findings, Tay and Ozanne undertook a study to examine the effect of the New Zealand advertising campaign among different subdivisions of New Zealand drivers [62]. They hypothesized that appeal to fear advertising would be effective, but only among some segments of the population. Their findings supported this hypothesis. Tay and Ozanne found that fatal accident rates had been reduced among three groups of drivers: female drivers aged between 15 and 24, female drivers aged between 25 and 34, and male drivers aged between 35 and 54. However, the fatal crash rate of the main target audience of the campaign, young male drivers, remained unaffected.

Thus we are drawn to the conclusion that used prudently appeal to fear campaigns to reduce drunk driving and alcohol related fatalities may or may not be effective for the overall population and are not effective in those most at risk: teenage male drivers.

Beware of silent killers

Appeal to fear in public awareness campaigns for hypertension (high blood pressure) – The silent killer

Up to this point I have considered public awareness campaigns aimed at modifying behaviours such as tobacco smoking and drunk driving. It is worth considering a campaign designed to raise awareness about a medical condition (hypertension) and motivate the target audience to take action (have their blood pressure checked).

Reports by the American Heart Association (AHA) and the Centers for Disease Control and Prevention [63, 64] paint a clear picture why hypertension is a primary public health concern.

- About 1 in 3 American adults or 75 million (29%) have high blood pressure.
- Only about half (54%) of people with high blood pressure have their condition under control.
- Nearly 1 of 3 American adults has prehypertension—blood pressure numbers that are higher than normal, but not yet in the high blood pressure range.
- More than **360,000** American deaths in 2013 (almost 1000 deaths per day) included high blood pressure as a primary or contributing cause [64].

High blood pressure increases risk for dangerous health conditions:

- First heart attack: About 7 of every 10 people having their first heart attack have high blood pressure.
- First stroke: About 8 of every 10 people having their first stroke have high blood pressure.
- Chronic (long lasting) heart failure: About 7 of every 10 people with chronic heart failure have high blood pressure.
- High blood pressure is a major risk factor for kidney disease [63].

Hypertension is a lifestyle modifiable, preventable, and controllable risk described by the World Health Organisation as The Silent Killer [65]. As detailed in the AHA report, hypertension is the primary and most common risk factor for heart disease, stroke and renal diseases. It is labeled the silent killer because hypertension has no symptoms therefore the only way to determine the presence of hypertension is by measuring one's blood pressure.

Hypertension is not confined to the developed world. Indeed, it is considered to be a worldwide epidemic and is the leading risk factor for death and disability globally. It is estimated that nearly one billion people are affected by hypertension worldwide, and this figure is predicted to increase to 1.5 billion by 2025. Nearly one-half of this population is unaware of their condition [65]. Thus, public awareness campaigns are designed to alert the target audience to the importance of

1. Having their blood pressure checked
2. Modifying lifestyle factors (diet, exercise, alcohol consumption)
3. Receiving medical attention and
4. Adhering to medical advice, including taking prescribed medication.

The World Hypertension League (WHL) is an international, nonprofit organization with membership from 85 countries; it works through its member countries to promote hypertension awareness, early detection, and the prevention and control of this modern epidemic. In 2005, in an attempt to improve the awareness of high

blood pressure, the WHL initiated World Hypertension Day (WHD). The aim of WHD is raising public awareness about hypertension, its life-threatening complications and measures to prevent it. Appeal to fear plays a role in raising awareness by alerting the target audience (all adults) to the complications of hypertension: heart attack, stroke, kidney disease, and death. WHD is considered to be highly successful and is being expanded on a yearly basis [65–67].

Subluxation: The other silent killer – Appeal to fear in chiropractic subluxation advertising

Thus far I have reviewed appeal to fear used in anti-smoking campaigns, driver safety and hypertension awareness campaigns. As discussed, to use appeal to fear in this manner is considered appropriate but its use may need to be reconsidered in terms of effectiveness and ethicality and collateral damage.

It is now appropriate to examine fallacious use of appeal to fear using chiropractic advertising as an example.

The putative lesion that chiropractors 'treat' is commonly referred to as chiropractic subluxation, vertebral subluxation complex (VSC) or simply 'subluxation' [differentiating the chiropractic lesion from orthopaedic subluxation]. Broadly speaking within chiropractic today the term 'subluxation' has two meanings: the Traditional Palmerian Subluxation (TPS), whereby the presence of subluxations leads to ill health and the second: The Modern Subluxation, whereby subluxations have a local biomechanical effect.

The TPS is the focus of this discussion. DD Palmer, who 'discovered' chiropractic in 1895 proposed that 95% of all disease (dis-ease) was due to subluxations of the spine and that the remaining 5% was caused by subluxations of the extremities, particularly the joints of the feet [68]. DD and his son BJ Palmer hypothesized that the chiropractic *vertebral subluxation* differed from the medical "subluxation" in that it interfered with the transmission of Innate Intelligence (a fraction of Universal Intelligence) [69], independent of what has come to be recognized as the action potential. However, Innate Intelligence remains a metaphysical construct [70].

The more contemporary position is that Palmerian subluxations cause interference within the nervous system, which leads to suboptimal health and symptomatic dis-ease, and that chiropractic health care is primarily involved in the detection and removal of subluxations [71]. Chiropractors who still adhere to the founder's paradigm – and there are many such practitioners – depict and market subluxation as an enemy that needs to be contained and eliminated.

Before examining examples of subluxation marketing, it is cogent to briefly discuss the history of chiropractic and its embracing of marketing to attract clientele. Chiropractic emerged in the late nineteenth century and, in spite of fierce opposition, grew rapidly in practitioner numbers and patient numbers during the first half of the twentieth century [72]. This is in part attributable to chiropractic adopting a unique professionalism. Unlike traditional professionalism wherein altruism is a central tenet [73], chiropractic professionalism favoured entrepreneurialism with recognition of financial success as a strong indicator for accomplishment [74]. While medical professionalism witnessed an ethical ban on advertising as early as 1847 [75], the emerging chiropractic profession embraced marketing. In fact, even chiropractic students were encouraged to advertise heavily [74, 76]. The Developer of Chiropractic, BJ Palmer advised his many readers:

> What you want to keep out of a news- paper is news.
>
> What you want to get into a newspaper is an advertisement [74] p. 44.

Whether or not current chiropractic advertising is a legacy from the early days of chiropractic is moot. It is evident however that advertising claims made by some chiropractors and indeed by some chiropractic colleges are suspect [77, 78]. A few examples of subluxation marketing are in order.

WH Koch, a chiropractic author makes the danger posed by subluxation abundantly clear:

> We must now look at this condition of 'disease', Vertebral Subluxation Complex, which is so disturbing to the flow of life force and innate expression in your body that it causes pain and the progressive breakdown of the body tissue known as pathology. The V.S.C. is the silent killer, one of the most serious health threats known to man [79] p. 34.

The World Chiropractic Alliance (WCA), is a worldwide organisation promoting subluxation based care. The WCA represents the interests of more than 70,000 doctors of chiropractic and chiropractic students, In 2006 the WCA issued a position paper stating that "chiropractic care to detect and correct vertebral subluxations offers benefits for all people, including those who do not demonstrate symptoms of a disease or health condition".

'Patient education' materials prepared by Chiropractis aims to educate patients to "believe choosing to be checked for the presence of vertebral subluxation throughout a lifetime is the only logical choice". Once patients understand 5 facts about their health, they are well on their way to being chiropractic patients for life. The five facts are:

1. Your **Spinal Cord** is located in the **spine** and is your **Nervous System's** information highway.
2. Your **Nervous System** controls and coordinates **every** part of your body.
3. Misalignments of your spine can **DISTORT nerve messages** and contribute to a wide range of health problems.
4. Misalignments of the spine are known as **vertebral subluxations** and negatively affect your **nervous system, health** and **well-being.**
5. Maintaining the health of your spine and nervous system should be a regular part of a health lifestyle and can dramatically improve your quality of life.

Koren Publication's What is a Subluxation? brochure tells readers that chiropractic has become so popular because "chiropractors are the only professionals trained to locate and remove subluxations. If subluxations are in your body, you cannot be truly healthy".

JC Smith, a prolific chiropractic author and subluxation advocate advises in his paper "Killer Subluxation".

"The idea of sudden cardiac arrest from a vertebral subluxation is just too far outside the consciousness of most people ... [however] "killer subluxations" actually may not be that far from the truth.

The subluxation brochure produced by Patient Media, Inc., is perhaps the most alarmist publication. Its Subluxation pamphlet provides a succinct description of how vertebral subluxations operate as well as the importance of their detection and removal.

> Maybe you've never heard of subluxations. That's OK. There probably was a time when you'd never heard of AIDS or Alzheimer's.
>
> There are three basic causes of subluxations. Physical causes include slips and falls, accidents, repetitive motions and improper lifting. Stress, anger and fear are examples of emotional causes of subluxations. Alcohol, drugs, pollution and poor diet can be chemical causes of subluxations. The result is the vertebral subluxation complex, or more simply, a subluxation.
>
> Subluxations are serious!
>
> However, the most important aspect of a subluxation is its effect on your nervous system. Compromising the way your nervous system controls and regulates your body can have grave consequences. Distorted communications between your brain and your body can cause all kinds of health problems beyond just headaches and backaches.
>
> You can have subluxations and not even know it. Like tooth decay or cancer, subluxations can be present before any warning signs appear. The results of a thorough examination can show the location and severity of any subluxations you may have.

In an essay entitled 'If You Don't Know Subluxation, You Don't Know Chiropractic' Dr. Carey N. Pabouet-Sigafoose alerts readers to the dangers of subluxations:

> There's loss of motion in the body causing death because of a subluxation. It's a major problem, a major killer, a major cause of disease in man and we've got to understand that. We've got to take ourselves in and give it the time and the space and the effort to get these things cleared up, not in just you, but your friends and your family. It's imperative.

These are but a select but indicative sampling of the 176,000 results obtained by conducting a Google search using 'subluxations kill'.

Chiropractors adhering to the TPS theory or its contemporary interpretation believe that subluxations have an effect on the overall health of the individual while those adopting the modern subluxation theory hold that the subluxation has a more local biomechanical affect. It is often reported that TPS practitioners represent only a small portion of the overall profession [80]. This is not the case. A survey of North American chiropractors found amongst respondents, in excess of 75% of those adhering to the modern subluxation construct believe that the adjustment of the vertebral subluxation complex usually elicits improvements in select visceral ailments [81]. Compounding the problem is the commonly relayed message that subluxations are only detectable by the skilled hands of a qualified chiropractor. Given this, one must ask: what is the evidence supporting the TPS ideology that minor vertebral displacements cause visceral disease?

Nansel and Szlazak [82] carefully examined this very question and concluded scientific consensus does not support the theory that nerve interference caused by vertebral misalignment or subluxation is a cause of visceral disease. Further, Nansel and Szlazak clearly state "there have been no appropriately controlled studies that establish that spinal manipulation or any other form of somatic therapy [manual therapy] represents a valid curative strategy for the treatment of any internal organ disease". It is noteworthy that Nansel and Szlazak's findings have never been challenged.

Worse yet, from an epidemiological perspective (strength of association, specificity, temporality, dose response, experimental evidence, biological plausibility, coherence and analogy), the subluxation is found to be wanting [83]

INTERIM GUIDELINES ON MANAGEMENT OF COVID-19 IN KENYA

COVID-19, Infection Prevention and Control (IPC) and Case Management

These consolidated guidelines provide recommendations for comprehensive prevention and case management strategies in Kenya

Scope of the Guidelines:

Infection prevention and control
Patient triage
Emergency Medical Services
Case management
Laboratory testing algorithm

Target Audience:

Health care workers taking care of patients suspected or confirmed to have COVID-19

FOREWORD

The interim guidelines and protocols for SARS-CoV 2 and COVID 19 were developed in response to the new Coronavirus Disease 2019 (COVID-19). COVID -19 is a serious respiratory viral infection caused by a novel coronavirus recently named SARS-COV2. The outbreak started in Wuhan City, Hubei Province in mainland China and has since spread globally, infecting more than 300,000 people resulting in over 13,000 deaths and occurring in 188 countries. This pandemic continues to pose grave danger to all populations, particularly those in Sub-Saharan Africa where overburdened health systems continue to struggle with scarcity of human and financial resources.

These guidelines combine both preventive and clinical management of the disease in Kenyan context. The protocol borrows various international recommendations including the World Health Organization, from experience of other countries such as China that has struggled with the outbreak for a longer time and from principles of virology and infectious disease management.

I expect every clinician and healthcare worker as well as the caregivers to adhere to these guidelines to effectively manage the Coronavirus epidemic. With these guidelines we expect highest quality care for the suspected and confirmed corona patients. As experience and knowledge on COVID-19 is rapidly evolving, these interim guidelines will be updated periodically.

Dr. Patrick Amoth
Ag. Director General for Health

ACKNOWLEDGEMENT

This Interim Case Management Protocol has been developed through the contributions of many individuals and institutions that are committed to ensuring effective management of COVID-19 patients. The Kenyan Ministry of Health (MOH) wishes to thank all the contributing authors led by the Panel of experts on Case Management for their expertise and time given to the writing of this protocol.



Dr. Simon K. Kibias, OGW
Ag. Director Directorate of Health Standards Quality Assurance and Regulations

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LIST OF ABBREVIATIONS

ARI	-	Acute Respiratory Infection
ARDS	-	Acute Respiratory Distress Syndrome
APRV	-	Airway Pressure Release Ventilation
BP	-	Blood Pressure
Bpm	-	Beats/minute
EMS	-	Emergency Medical Services
CPAP	-	Continuous Positive Airway Pressure
COVID-19	-	Coronavirus Disease 2019
FiO2	-	Fraction of inspired oxygen
IPC	-	Infection Prevention and Control
LRT	-	Lower Respiratory Tract
MAP	-	Mean Arterial Pressure
NIV	-	Non-invasive Ventilation
OI	-	Oxygenation Index
OSI	-	Oxygenation Index using SpO2
PaO2	-	Partial Pressure of Oxygen
PCR	-	Polymerase Chain Reaction
PEEP	-	Positive End-Expiratory Pressure

PPE	-	Personal Protective Equipment
RRT	-	Rapid Response Team
RT-PCR	-	Reverse Transcriptase – Polymerase Chain Reaction
SBP	-	Systolic Blood Pressure
SARI	-	Severe Acute Respiratory Illness
SARS-COV-2	-	Severe Acute Respiratory Syndrome – Coronavirus -2
SD	-	Standard Deviation
SIRS	-	Systemic Inflammatory Response Syndrome
SpO2	-	Oxygen Saturation
URT	-	Upper Respiratory Tract

INTRODUCTION:

Coronavirus disease 2019 (COVID-19) is an acute respiratory infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 belongs to the Sarbecovirus subgenus of the Coronaviridae family, and is the seventh coronavirus known to infect humans. Coronaviruses are a large family of enveloped RNA viruses, some of which cause illness in people (e.g., common cold, SARS, MERS), and others that circulate among mammals (e.g., bats, camels) and birds. Rarely, animal coronaviruses can spread to humans and subsequently spread between humans. Similar to SARS and MERS, it is thought that human transmission occurs via respiratory droplets produced when a person sneezes or coughs. Current estimates of the incubation period range from 1 to 14 days, according to the World Health Organization. The average incubation period is currently estimated to be 5 days. Transmission can occur during the incubation period.

The most common clinical presentation is that of a respiratory infection with a symptom severity ranging from a mild common cold-like illness (estimated 80% of cases), to a severe viral pneumonia leading to acute respiratory distress syndrome that is potentially fatal. WHO first declared COVID-19 to be a public health emergency of international concern on 30 January 2020 and subsequently declared it a pandemic on 11 March 2020. The first confirmed case in Kenya was reported on 13th March 2020

Infection prevention and Control (IPC) plan in Response to COVID-19

The main aim for IPC will be to enhance infection prevention and control measures at all levels of health care systems

(A) QUARANTINE AND SOCIAL DISTANCING

Quarantine is separation and restricted movement of well persons presumed exposed often at home or may be in designated residential facility or hospital. It can be applied at the individual, family or community level. Until the Ministry of Health establishes the existence of sustained community transmission, all confirmed COVID-19 cases identified should be monitored closely at a health facility isolation room. Contacts of cases are to be quarantined either at home or in designated facilities. Once sustained community transmission has been established, home management of mild cases should be encouraged. All personnel who have access to cases and the contacts should observe standard and transmission (contact and droplet) precautions. Maintain adherence to hand hygiene by washing with soap and water or using alcohol-based hand sanitizer. It is important to practice hand hygiene immediately after removing gloves and masks and after any contact with respiratory secretions or patient environments.

(B) IMPLEMENTING QUARANTINE

Methods of Quarantine

Quarantine can either be self-quarantine or carried out at a designated facility. Instructions for self-quarantine include:

- ☐ Limit visitors
- ☐ Continue to observe respiratory hygiene and cough etiquette
- ☐ Observe hand hygiene as advised
- ☐ Observe body temperature twice daily

(C) MODALITIES OF IMPLEMENTING SOCIAL DISTANCE

Measures to increase social distance

- ☐ School closures with the school children advised to avoid loitering in the estates and streets.
- ☐ Business and market closure
- ☐ Cancellation of events – Harambees, public barazas, etc.
- ☐ Movement restrictions – advice on use public transport
- ☐ Restriction on public gatherings – places of worship, bars, hotels, supermarkets, weddings, funerals etc.
- ☐ Supervision of burials
- ☐ Reducing crowding at hospitals, this may involve reducing the number of visitor's patients admitted to the facilities can receive

(D) RECOMMENDED ISOLATION PRACTICES

Isolation

Separation and restricted movement of ill persons with contagious disease, often in a hospital setting;

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In the community:

If an individual suspect to have a flu, practice self-triage based on:

Your symptoms and duration of symptoms;

Exposure history

- ☐ Whether you travelled to an area that has confirmed COVID-19 transmission or
- ☐ Whether you have been in close contact with someone from an area with COVID-19 transmission or
- ☐ Has been in contact with a probable or confirmed COVID-19 case or
- ☐ Has participated in cleaning a COVID-19 patient's room or articles

Seeking health care

If an individual has symptoms of fever, cough or difficulty breathing then they should call centre number (719), the individual will be directed to the nearest facility with capacity to screen, collect samples for the laboratory and manage the patient. If safe transport is not available, then an ambulance with appropriate personnel and PPE will be dispatched to pick the patient. Safe transportation includes a private car where all the occupants including the sick person use masks. Public transport (matatus, buses, Ubers, taxis) should not be used to transport sick individuals to the nearest isolation facilities as these are likely to propagate the spread of infection.

On arrival to a facility or arrival of the ambulance, health personnel will assess the patient to determine if they meet the case definition.

For patients who meet the case definition, on arrival to the facility, staff will ensure that they don appropriate PPE, move the patient to isolation, assess to get better history and conduct a physical exam

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On arrival to a health facility:

- Healthcare facilities should organize prompt triage services at the reception using a symptom criterion of fever, cough or difficulty in breathing.
- Older children should be assisted by their parents/caregivers to ensure that they wear the mask at all times
- All acute febrile patients with Influenza like illness (ILI) should be directed to a respiratory cohort area and promptly provided with a surgical face mask.
- The triage nurse should assess the patients to determine the nature of respiratory illness and;
    - Directs all acute febrile illness to a cohort area
    - Encourages patients to use a mask if not in respiratory distress
    - Teaches the cohorted patients on respiratory hygiene and cough etiquette.

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TRIAGE FORM FOR COVID-19 IN THE OUTPATIENT SETTING

1. COUGH, FEVER, SHORTNESS OF BREATH IN THE LAST 14 DAYS
CHECK TEMPERATURE, FEVER PRESENT (>38^{0}C)

NO → ROUTINE MANAGEMENT

YES → GIVE PATIENT MASK

2. EXPOSURE

TRAVEL TO HIGH RISK COUNTRIES IN **THE LAST 14 DAYS** (CHINA, ITALY, JAPAN, IRAN, KOREA, INDIA, SAUDI ARABIA **ETC**).

CONTACT WITH PEOPLE WHO HAVE TRAVELLED TO THESE COUNTRIES **IN THE LAST 30 DAYS**.

CONTACT WITH SOMEONE WITH **CONFIRMED COVID-19 IN THE LAST 14 DAYS**

WORKED AT OR VISITED HOSPITAL OR CLINIC WHERE THERE HAS BEEN PATIENTS WITH HOSPITAL-ASSOCIATED COVID-19 INFECTIONS

NO → QUARANTINE FOR 14 DAYS

INFORM PUBLIC HEALTH

YES → INFORM ISOLATION UNIT BY PHONE

REFER TO ISOLATION UNIT

SEPARATE PATIENTS BY 2 METRES

OBSERVE STANDARD, DROPLET AND CONTACT PRECAUTIONS

ISOLATE, CALL THE AMBULANCE SERVICE

OBTAIN NASOPHARYNGEAL/OROPHARYNGEAL SWAB IN FULL PPE

NEGATIVE → ROUTINE MANAGEMENT

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In-Patient care

- ☐ Isolate mild, moderate and severe cases
- ☐ Do not wait for lab confirmation before placing a patient in isolation
- ☐ Plan for large number of severe cases
- ☐ Provide medical and social care

Patient placement

Isolate patient/s in a well-ventilated single room or an isolation unit for a group of patients.
The room should have hand washing facilities – basin with flowing water or water pan with a receptacle or alcohol-based hand sanitizer.

ISOLATION FACILITIES FOR CHILDREN WITH SUSPECTED OR CONFIRMED SARS COVID-19 INFECTION

All referral hospitals should set up facilities for paediatric patients with COVID 19 infection away from the paediatric in-patient ward and separate from the adult isolation ward. Children most at risk are those with co-morbidities e.g. sickle cell anaemia, congenital or acquired heart diseases, cancer, HIV etc. The isolation ward should be able to accommodate a parents/caregiver to stay with the child during the duration of admission. Visitors to the child should be strictly limited.

Patient movement

If the patient requires to be moved to another department, the destination point should be notified in advance, while on transit the patient wears a surgical mask and the procedure is performed last when other patients have moved out.

Precautions by Healthcare Personnel

Healthcare personnel are defined as persons, including employees, students, contractors, attending clinicians, and volunteers, whose activities involve contact with patients in a healthcare or laboratory setting.

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PPE to Be Provided to Staff According to Risk Categories

Risk Category	Characteristic of Exposure of Staff	Examples of Staff	Surgical Masks	Gloves	Gown	Particulate Respirators (e.g. N95 masks)	Eye Protection (e.g. Goggles/ Face Shield)
1	Health care workers who manage patients clinically and have close contact (<1 meter) with known/suspected COVID-19 patients or their infectious material	E.g. Doctors, nurses who work in the fever clin	√	√	√	√	√
2	Non-health care worker staff who have close contact (<1 meter) with known/suspected COVID-19 patients or their infectious material	E.g. Security personnel, receptionist, cleaning staff who work in the fever clinic	√	√	√	X	X
3	Staff with close contact (<1 meter) with persons of "unknown" COVID-19 status	E.g., Essential duty travelers	√	X	X	X	X
4	Staff infected with COVID-19 influenza	E.g. Patients in the fever clinic	√	X	X	X	X
5	Staff with no known close contact (<1 meter) with known/ suspected COVID-19 patients or their infectious material	E.g. Critical staff "quarantined" in work space, and not working in the fever clinic	X	X	X	X	X

NB. Health workers should remember to observe hand hygiene and standard precautions. Maintain adherence to *hand hygiene by washing with soap and water or using alcohol-based hand sanitizer* immediately after removing gloves and other equipment and after any contact with respiratory secretions. While obtaining nasopharyngeal swabs for suspected cases and undertaking aerosol generating procedures (e.g. bronchoscopy, elective intubation, suctioning, administering nebulized medications, dental procedures), full personal equipment should be worn comprising of PPE suit, N95 mask, goggles, hair protection. The procedure should be undertaken in a well-ventilated separate room. In the setting of COVID-19 outbreak, these invasive procedures should be kept to a minimum to avoid generating large quantities of infectious aerosols. Intubation must be rapid sequence induction preceded by a long preoxygenation and where initial manual ventilation is carried out, this should be done using small tidal volumes

Isolation precautions

- Healthcare personnel entering the room of a patient in isolation should be limited to those performing direct patient care only.
- All healthcare personnel who enter the patient's room should take *standard and contact precautions.*
- Non-sterile gloves and N95 masks should be donned when entering a patient's room.
- All healthcare personnel who attend to patients in the isolation rooms should wear an N95 face mask and gloves while those who enter for short duration may use a standard surgical mask
- Minimize amount of time that health care personnel spend in the patient areas to only what is necessary to evaluate and manage the patient taking in to account the severity of illness.

Management of visitors

- Limit visitors for patients in isolation for COVID-19 infection to persons who are necessary for the patient's emotional well-being and care.
- Visitors who have been in contact with the patient before and during hospitalization are a possible source of COVID-19
- Visitors should be instructed to limit their movement within the facility.
- Visitors should be offered surgical masks and be required to practice hand hygiene on leaving the isolation room.

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Duration of precautions

- Isolation precautions should be continued for up to 14 days from symptom onset, whichever is longer.
- Persons with COVID-19 should be considered potentially contagious from two days before to 14 days following illness onset.
- Persons who continue to be ill longer than 7 days after illness onset should be considered potentially contagious until symptoms have resolved.
- Children, especially younger children, might be contagious for longer periods.

Surveillance of healthcare personnel

- In communities where transmission is occurring, healthcare personnel should be monitored daily for signs and symptoms of febrile respiratory illness.
- Healthcare personnel who develop these symptoms should be instructed not to report to work, or if at work, should cease patient care activities and notify their supervisor and infection control personnel.
- In communities without SARS-COV-2 transmission, healthcare personnel working in areas of a facility where there are patients being assessed or isolated for COVID-19 should be monitored daily for signs and symptoms of febrile respiratory infection.
- This would include healthcare personnel exposed to patients in an outpatient setting or the emergency department. Healthcare personnel who develop these symptoms should be instructed not to report to work, or if at work, should cease patient care activities and notify their supervisor and infection control personnel.
- Healthcare personnel who do not have a febrile respiratory illness may continue to work.
- Asymptomatic healthcare personnel who have had an unprotected exposure to COVID-19 should be quarantined (an appropriate quarantine facility should be provided. Hospitals could consider securing a guest house, hotel or staff houses for staff quarantine for 7 days at which time they should have a throat swab taken for COVID-19 testing, if this is negative then they should be allowed back to work, if positive, then isolation should continue for 14 days

Management of ill healthcare personnel

- Healthcare personnel should not report to work if they have a febrile respiratory illness.
- In communities where transmission is occurring, healthcare personnel who develop a febrile respiratory illness should be excluded from work and should be tested for COVID-19. If negative, then they should stay away from work until symptoms resolve. If positive then they should proceed to isolation for 14 days
- Healthcare personnel, who develop a febrile respiratory illness and have been working in areas of the hospital where SARS-COV-2 patients are present, should be excluded from work for 7 days or until symptoms have resolved, whichever is longer.

Stewardship of personal protective equipment and antivirals

Health Facilities should implement plans to ensure appropriate allocation of personal protective equipment, including gloves, masks, N95 respirators, and antiviral medications. Referral isolation centres should be adequately staffed, equipped with functional mechanical ventilators, oxygen, patient monitors and consumables.

Environmental infection control

Routine cleaning and disinfection strategies used during influenza seasons can be applied to the environmental management of SARS-COV-2Management of laundry, utensils and medical waste should also be performed in accordance with procedures for waste management (refer to the COVID-19 waste management guidelines).

Implementation of Respiratory Hygiene/Cough Etiquette

To prevent the transmission of all respiratory infections in healthcare settings, including SARS-COV 2, respiratory hygiene/cough etiquette measures should be implemented.

Elements of Respiratory Hygiene/Cough Etiquette include

1) Education of healthcare facility staff, patients, and visitors;
2) Posted signs in language appropriate to the population served with instructions to patients and accompanying family members or friends;
3) Source control measures (e.g., covering the mouth/nose with a tissue when coughing and disposing of used tissues, using surgical masks on the coughing person when tolerated and appropriate);
4) Hand hygiene after contact with respiratory secretions; and

5) Spatial separation, ideally > 1 metre (>3 feet), of persons with respiratory infections in common waiting areas when possible.

N.B. Covering sneezes and coughs and placing masks on coughing patients are proven means of source containment that prevent infected persons from dispersing respiratory droplets into the air. Physical proximity of <3 feet has been associated with an increased risk for transmission of infections via the droplet route and therefore supports the practice of distancing infected persons from others who are not infected.

Guidance for Emergency Medical Services (EMS) Systems for Management of Patients with Confirmed or Suspected COVID-19

Background

As a component of the Nation's critical infrastructure, emergency medical services (along with other emergency services) play a vital role in responding to requests for assistance, triaging patients, and providing emergency treatment to suspected COVID-19 patients. However, unlike patient care in the controlled environment of a fixed medical facility, pre-hospital EMS patient care is provided in an uncontrolled environment, often confined to a very small space, and frequently requires rapid medical decision-making, and interventions with limited information. EMS personnel are frequently unable to determine the patient history before having to administer emergency care.

Recommendations

Coordination among the EMS system, designated isolation healthcare facilities, and the public health system is important for a coordinated response to the COVID-19.

Infectious Period

Persons with COVID-19 should be considered potentially infectious from two days before to 14 days following illness onset. Persons who continue to be ill longer than 7 days after illness onset should be considered potentially contagious until symptoms have resolved. Children, especially younger children, might potentially be contagious for longer periods.

Non-hospitalized ill persons who are a confirmed or suspected case of COVID-19 are recommended to stay at home (voluntary isolation) for at least the first 14 days after checking with their health care provider about any special care they might need if they are pregnant or have a health condition such as diabetes, heart disease, asthma, or emphysema.

Recommendations for EMS

Patient assessment

Assess all patients for symptoms of acute febrile respiratory illness (fever plus one or more of the following: nasal congestion/ rhinorrhea, sore throat, or cough).

1. If acute febrile respiratory illness is present, use of appropriate PPE when coming into close contact with the patient is recommended.
2. This includes fit-tested disposable N95 respirator or a surgical mask and eye protection (e.g., goggles; eye shield), disposable non-sterile gloves, and gown,
3. If no acute febrile respiratory illness, proceed with normal EMS care
4. If no acute febrile respiratory illness, place a standard surgical mask on the patient (if tolerated) Use good respiratory hygiene – use non-sterile gloves for contact with patient, patient secretions, or surfaces that may have been contaminated. Follow hand hygiene including hand washing or cleansing with alcohol-based hand disinfectant after contact.

Infection Control

Emergency medical services personnel (EMS) should always practice basic infection control procedures including vehicle/equipment decontamination, hand hygiene, cough and respiratory hygiene, and proper use of the recommended medical personal protective equipment (PPE).

Recommendations:

- Because SARS-COV-2 is transmitted through droplets and contact with contaminated surfaces, EMS personnel who are in close contact with patients with suspected or confirmedCOVID-19 should wear a fit-tested disposable N95 respirator, disposable non-sterile gloves, eye protection (e.g., goggles; eye shields), and gown with hood, when coming into close contact with the patient.

All EMS personnel engaged in aerosol generating activities in the management suspected or confirmed COVID-19 patients (e.g. endotracheal intubation, nebulizer treatment, and resuscitation involving emergency intubation or cardiac pulmonary resuscitation) should wear a fit-tested disposable N95 respirator, disposable non-sterile gloves, eye protection (e.g., goggles; eye shields), and gown with hood, All patients with acute febrile respiratory illness should wear a surgical mask unless patient cannot tolerate the mask.

Inter-facility Transport

EMS personnel involved in the inter-facility transfer of patients with suspected or confirmedCOVID-19 should use standard, droplet and contact precautions for all patient care activities. This should include wearing a fit-tested disposable N95 mask/respirator, wearing disposable non-sterile gloves, eye protection (e.g., goggles, eye-shield) and gown with hood. The use of a surgical mask on the transported patient can help to minimize the spread of infectious droplets in the patient care compartment. Encourage good patient compartment vehicle airflow/ventilation to reduce the concentration of aerosol accumulation when possible.

Guidance for Cleaning EMS Transport Vehicles after Transporting a Suspected or Confirmed COVID-19 Patient

The following are general guidelines for cleaning or maintaining EMS transport vehicles and equipment after transporting a suspected or confirmed COVID-19 patient.

Routine cleaning with soap or detergent and water to remove soil and organic matter, followed by the proper use of disinfectants, are the basic components of effective environmental management of SARS-CCV-2. Reducing the number of SARS-COV-2virus particles on a surface through these steps can reduce the chances of hand transfer of virus. SARS-COV-2 virus is susceptible to inactivation by a number of chemical disinfectants readily available from consumer and commercial sources.

After the patient has been removed and prior to cleaning, the air within the vehicle may be exhausted by opening the doors and windows of the vehicle while the ventilation system is running. This should be done outdoors and away from pedestrian traffic. Routine cleaning methods should be employed throughout the vehicle and on non-disposable equipment.

EMS Transfer of Patient Care to a Healthcare Facility

When transporting a patient with symptoms of acute febrile respiratory illness, EMS personnel should notify the receiving healthcare facility so that appropriate infection control precautions may be taken prior to patient arrival. Patients with acute febrile respiratory illness should wear a surgical mask, if tolerated. Small facemasks are available that can be worn by children, but it may be problematic for children to wear them correctly and consistently.

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Biosafety Guidelines for Laboratory Workers

This guidance is for all individuals who may be processing or performing diagnostic testing on clinical specimens from patients with suspected COVID-19, or performing viral isolation. Reference should be made to the National Biosafety Guidelines for more information

Clinical Laboratory Testing (Laboratory Diagnostic Work)

Diagnostic laboratory work on clinical samples from patients who are suspected cases of COVID-19 should be conducted in a BSL2 laboratory. All sample manipulations with the potential for creating an aerosol should be done inside a biosafety cabinet (BSC) that is certified annually. Personal protective equipment should include.

- Gloves
- Laboratory coat
- Eye protection

Laboratory waste

All waste disposal procedures should be followed as outlined in your facility standard laboratory operating procedures. Steam autoclaving is the preferred method for all decontamination processes. Alternative methods may be considered based on applicable national regulations, as well as on a site-specific risk assessment.

Appropriate disinfectants

Several chemical disinfectants, including chlorine, alcohols, peroxygen, detergents, iodophors, quaternary ammonium and phenolic compounds, are effective against corona viruses if used at the correct concentration for the appropriate contact time as specified in the manufacturer's recommendations.

Work surfaces and equipment should be decontaminated as soon as possible after specimens are processed. Studies have shown that corona viruses can survive on environmental surfaces and can infect a person for up to 2–8 hours after being deposited on the surface.

Occupational Health

All personnel should self-monitor for fever and other symptoms such as cough, sore throat, runny or stuffy nose, body aches, headache, chills, and fatigue. Any influenza-like illness should be reported to your supervisor immediately.

Personnel who have had an occupational exposure to clinical materia or live virus from a confirmed case of SARS-COV-2 should immediately report to their supervisor. Antiviral chemoprophylaxis if available and should be monitored for 14 days

(G) GUIDANCE FOR EMERGENCY SHELTERS ON THE SARS-COV-2

Background

Emergency Shelters that serve refugees, IDPs and other displaced persons can help protect the health of their clients, staff, volunteers and local communities during this outbreak of COVID-19 by taking actions to prevent its spread. Recommendations to reduce transmission of SARS-COV-2 in this group setting are addressed below.

Influenza-like Illness (ILI) and COVID-19

Transmission

SARS-COV-2 is spread from person to person through the coughing or sneezing of infected people (droplet infection) or by touching something with SARS-COV-2 viruses on it and then touching their mouth nose, or eyes (contact transmission).

Symptoms

Symptoms of COVID-19 include fever and either cough or difficulty breathing. In addition, illness may be accompanied by other symptoms including headache, tiredness, runny or stuffy nose, chills, body aches, diarrhea, and vomiting. Like seasonal flu, COVID-19 in humans can vary in severity from mild to severe.

General Prevention Recommendations

- Encourage all persons within the shelter to cover their cough or sneeze with a tissue. Throw all tissues in the trash after use. Maintain good hand hygiene by washing with running water and soap, or using an alcohol-based hand sanitizer if available, especially after coughing or sneezing. Avoid touching eyes, nose and mouth.

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- Provide the means for appropriate hand cleansing readily available within the shelter, including common, food preparation and eating areas. Ideal means for hand cleansing include, running water, soap. Paper towels and waste baskets should be made available. Shelter staff, volunteers and clients should frequently wash their hands with soap and water, or use a hand sanitizer if hand washing with soap and water is not possible and hand sanitizers are available.
- Shelters settings should follow standard infection prevention precautions. These includes training staff in the control of infectious diseases, providing access to personal protective equipment and apparatus, and encouraging proper handwashing. Items that are often in contact with respiratory droplets and hands (e.g., doorknobs, faucets, etc.,) should be cleaned and disinfected regularly.
- Clean all common areas within the shelter routinely and immediately, when visibly soiled, with the cleaning agents normally used in these areas. Eating utensils should be washed with detergent and water. Cups and utensils should not be shared until after washing.
- Educational materials and information should be provided to clients in a way that can be understood by non-English and non-Kiswahili speakers.

Reducing Exposure and Spread of SARS-CoV Within Shelters

Shelter management should contact local and national health officials for more specific guidance. Shelters that have pregnant women should refer to MOH Guidance for Pregnant and breastfeeding mothers

Reduction of Risk of Introduction

- Shelter clients, staff and volunteers should be instructed to immediately inform shelter management if they have an influenza-like illness (ILI) or if they have had one in the previous 7 days.
- Direct persons with ILI symptoms to facilities or alternative care sites (ACS) where they can receive proper care, if such alternatives are available.
- Staff and volunteers with ILI should stay home (or be sent home if they develop symptoms while at the shelter), and remain at home for 7 days or until 24 hours after symptoms resolve, whichever is longer.

- Follow current vaccination recommendations and encourage staff and volunteers to take the upcoming season's influenza vaccine, when it is available.

Rapid Detection of Cases

- Shelter staff and volunteers should be diligent about early recognition of illness and placing those with ILI symptoms away from others (encourage self-quarantine).
- Instruct existing clients, staff and volunteers to report symptoms of ILI to the shelter management at the first sign of illness.
- Plan for how persons with ILI may be evaluated and treated, if necessary.
- Consider daily temperature checks with shelter clients who had contact with persons with ILI.

Management and Isolation of Suspect and Confirmed Cases

- Minimize the number of personnel directly exposed to ill people.
- For proper techniques in caring for an ill person, refer to the MOH Guidance for nCOV: Taking Care of a Sick Person in Your Home. Pregnant staff member(s) and others at high risk of severe illness from influenza should not be designated as caregivers for sick clients who are staying in the shelter.
- Refer to the guidance document on Personal Protective Equipment
- Actively monitor the number and severity of cases of ILI and inform the public health officials
- Ideally, sick persons should be confined to individual rooms and should avoid common areas. If individual rooms for sick clients are not available, consider using a large, well-ventilated room specifically for sick persons with beds at least 1 metre apart and the use of temporary barriers between beds, when possible.
- Designate staff to care for the sick persons and limit client movement between different parts of the institution to decrease the risk of spreading influenza to other parts of the shelter.
- Pre-exposure antiviral chemoprophylaxis should only be used in limited circumstances, and in consultation with local medical or public health authorities.

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- Provide sick clients with access to fluids, tissues, plastic bags for the proper disposal of used tissues, and a means to wash their hands with soap and water or alcohol-based hand sanitizers.
- Linens, eating utensils, and dishes belonging to those who are sick do not need to be cleaned separately, but they should not be shared without thorough washing. Linens (such as bed sheets and towels) should be washed using laundry soap and dried in the sun Individuals should wash their hands with soap and water or use alcohol-based hand sanitizer immediately after handling dirty laundry.

Caring for Persons at High Risk

The shelter should be aware of the special health needs of persons at increased risk of severe illness from influenza.

Persons at high risk for complications from nCOV infection may be similar to those who are at high risk for seasonal influenza complications and include the following: children 5 years and younger, persons age 65 years and older, pregnant women, persons of any age with chronic medical conditions (such as asthma, diabetes, or heart disease), and persons who are immunocompromised (for example, taking immunosuppressive medications or infected with HIV).

If severe symptoms of infection are identified, persons should be taken to receive medical attention from a physician or hospital. Severe symptoms include:

- Difficulty breathing or shortness of breath
- Pain or pressure in the chest or abdomen
- Sudden dizziness
- Confusion
- Severe or persistent vomiting
- Flu-like symptoms improve but then return with fever and worse cough

General Prevention Recommendations for the Facility

- Encourage all persons within the facility to cover their cough or sneeze with a tissue or onto their shoulders. Throw all tissue in the trash after use. Maintain good hand hygiene by washing with soap and water, especially after coughing or sneezing. Avoid touching eyes, nose and mouth without cleaning hands.
- Make the means for appropriate hand cleansing readily available within the facility, including intake areas where prisoners are booked and processed, visitor entries and exits, visitation rooms, common areas, and staff-restricted areas, in addition to toilets and food preparation and dining areas. The means for hand cleansing are ideally running water and soap, and hand drying machines or paper towels and waste baskets.
- Clean all common areas within the facility routinely and immediately, when visibly soiled, with the cleaning agents normally used in these areas. Eating utensils should be washed either in a dishwasher or by hand with water and soap. Cups and utensils should not be shared until after washing.
- Respiratory hygiene/cough etiquette should be implemented beginning at the first point of contact with a potentially infected person to prevent the transmission of all respiratory tract infections in the prison.

Reduction of Risk of Introduction into the Institution

- Potential visitors should be informed that anyone who had an influenza-like illness (ILI) in the 7 days prior or who still has symptoms of ILI 7 days after illness began may not enter the facility. When possible, facilities should use their usual communication channels to inform potential visitors of these rules before they travel to the facility.
- Exclude visitors who had ILI in the 7 days prior or who still have symptoms of ILI 7 days after illness began.
- Staff with ILI should stay home (or be sent home if they develop symptoms while at the facility), and remain at home for 7 days or until 24 hours after symptoms resolve, whichever is longer.
- If there is ILI in the facility, cancel internal group gatherings and stagger group meals and other activities to provide more personal space between individuals. Consider temporarily suspending visitation or modifying visitation programs, when appropriate.

CASE MANAGEMENT

Case management activities will involve;

- Create isolation areas for case management in COVID-19 designated hospitals
- Strengthen NIC – Reference laboratory to handle suspected COVID-19 samples
- Provision of viral taking sets and transportation kits
- Procure respirators (Intermittent Positive Pressure Respirators)
- Procure pharmaceutical and non-pharmaceutical supplies for supportive case management
- Distribution of all supplies to targeted areas
- Diagnostic Algorithm to be put in a poster format for use at screening point and OPDs and distributed accordingly
- Management should be at source most recommended to minimize spread,
- SOPs for home management - keep minimal contact with people.
- SOPs for health workers - have surgical masks when in working environment, retrain them on bio-safety when dealing with the patient, work in well ventilated environment, should contact DSRU or NIC, the local administration should be informed advise patient on self-quarantine (5 -7 day after onset of symptoms) but hospitalize severe cases – take sample, serve verity of disease not as highlighted – in public and media.
- PPE should be available to all health workers – ministry
- Strengthen critical care capacity by increasing access to oxygen, closed suction systems, availability of ventilation site and equipment and enable internet connectivity to assist medical personnel communicate on patient management issues in real time.

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Clinical management of severe acute respiratory infection when COVID-19 is suspected

Introduction

This document is intended for clinicians taking care of hospitalized adult and paediatric patients with severe acute respiratory infection (SARI) when COVID-19 is suspected. It is not meant to replace clinical judgment or specialist consultation but rather to strengthen clinical management of these patients and provide up-to-date guidance. Best practices for SARI including IPC and optimized supportive care for severely ill patients are essential.

Sections in this Document:

1. Triage: recognize and sort patients with SARI
2. Immediate implementation of appropriate infection prevention and contro (IPC) measures
3. Early supportive therapy and monitoring
4. Collection of specimens for laboratory diagnosis
5. Management of hypoxemic respiratory failure and acute respiratory distress syndrome (ARDS)
6. Management of septic shock
7. Prevent on of complications
8. Spec fic anti-nCoV treatments
9. Special considerations for pregnant patients
10. Direction on self-quarantine

Pre-Hospital Triage through the National and County Hotlines

The initial triage of patients will happen through the hotline (719). Patients with suspected COVID will be advised through the national and county hotlines on which designated facilities to present to. These facilities will have PPE and the HCWs will be trained to receive and handle these patients. Patients will be brought to hospital through the ambulance service or through safe transportation.

Self-initiated[1] or Clinician-initiated[2] Concern Over COVID-19

Contact National Call Centre[3]

Point of Entry Screening

Does the person fit COVID-19 case definition?

YES

NO

Reassure/
Refer the person to nearest health facility

National Call Centre contacts County Rapid Response Team[4]

County Rapid Response Team Visits Person

Does the person fit COVID-19 case definition?

YES

NO

Reassure

Symptoms MILD or SEVERE?

MILD

SEVERE

Transfer to nearest Capable Containment Unit[6] Manage while awaiting test result[6,7]

Self-Isolate unless symptoms worsen[5]

Contact Tracing[8]

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Do you have fever or cough or difficulty in breathing?

CALL THE NATIONAL HOTLINE

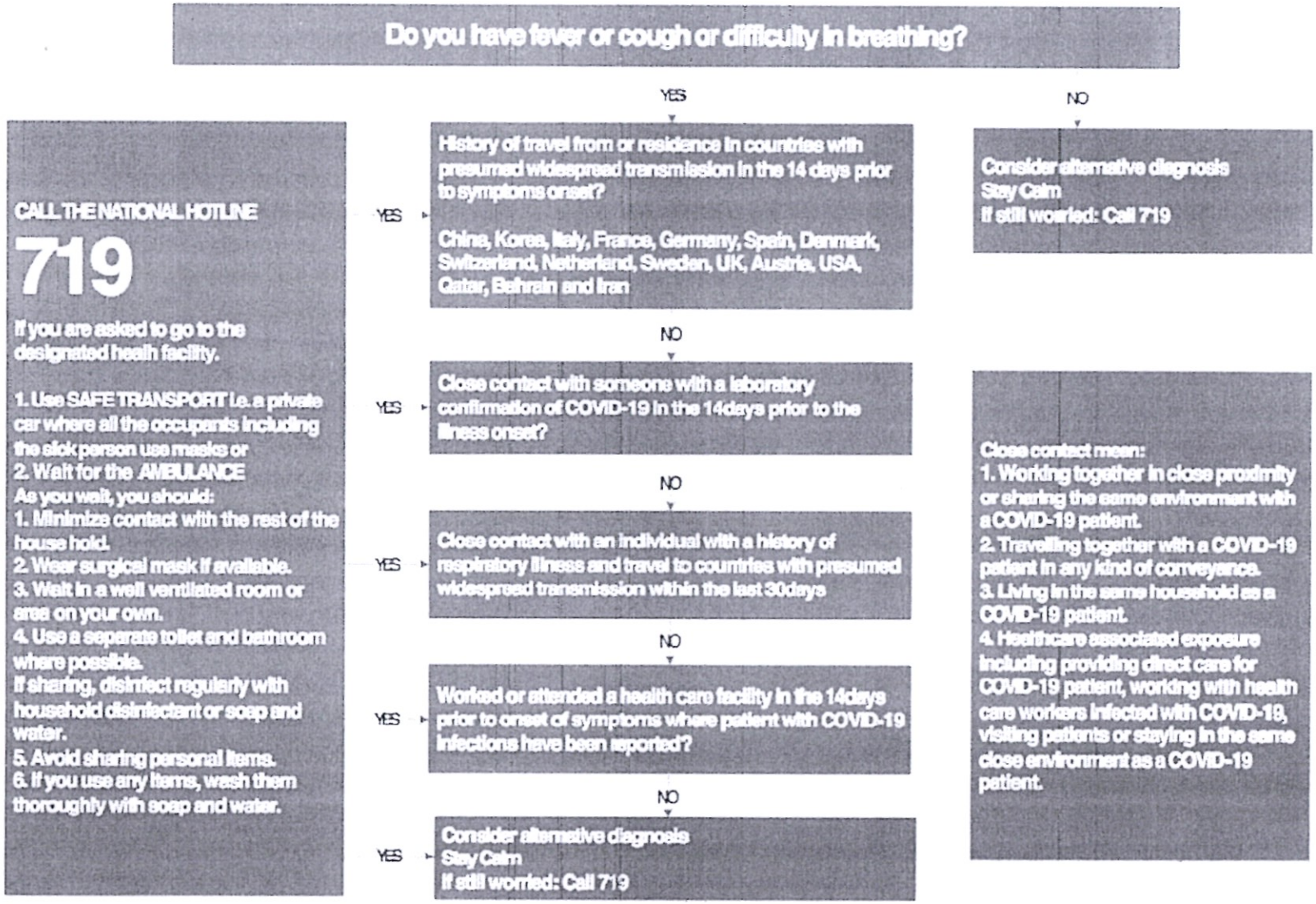
719

If you are asked to go to the designated health facility.

1. Use SAFE TRANSPORT i.e. a private car where all the occupants including the sick person use masks or
2. Wait for the AMBULANCE

As you wait, you should:

1. Minimize contact with the rest of the house hold.
2. Wear surgical mask if available.
3. Wait in a well ventilated room or area on your own.
4. Use a separate toilet and bathroom where possible.



If sharing, disinfect regularly with household disinfectant or soap and water.

5. Avoid sharing personal items.
6. If you use any items, wash them thoroughly with soap and water.

YES → History of travel from or residence in countries with presumed widespread transmission in the 14 days prior to symptoms onset?

China, Korea, Italy, France, Germany, Spain, Denmark, Switzerland, Netherland, Sweden, UK, Austria, USA, Qatar, Bahrain and Iran

NO → Consider alternative diagnosis
Stay Calm
If still worried: Call 719

YES → Close contact with someone with a laboratory confirmation of COVID-19 in the 14days prior to the illness onset?

NO → Close contact with an individual with a history of respiratory illness and travel to countries with presumed widespread transmission within the last 30days

YES → Worked or attended a health care facility in the 14days prior to onset of symptoms where patient with COVID-19 infections have been reported?

NO → Consider alternative diagnosis
Stay Calm
If still worried: Call 719

Close contact mean:

1. Working together in close proximity or sharing the same environment with a COVID-19 patient.
2. Travelling together with a COVID-19 patient in any kind of conveyance.
3. Living in the same household as a COVID-19 patient.
4. Healthcare associated exposure including providing direct care for COVID-19 patient, working with health care workers infected with COVID-19, visiting patients or staying in the same close environment as a COVID-19 patient.

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Case Definition for Novel Coronavirus Disease (COVID-19)*

The case definition is based on the current information available and may be revised as new information becomes available

Suspect case

A. A patient with any acute respiratory illness (fever or cough or shortness of breath) **AND**
   - A history of travel to a foreign country during the 14 days prior to symptom onset, **or**
   - Having been in contact* with a confirmed or probable case of COVID-19 (see definition of contact) in the 14 days prior to symptom onset.

B. A patient with severe acute respiratory illness (fever or cough or shortness of breath; **AND** requiring hospitalization) **AND** in the absence of an alternative diagnosis that fully explains the clinical presentation.

Probable case:

A. A suspect case for whom testing could not be performed for any reason **or**
B. A suspect case for whom testing for 2019-nCoV is inconclusive

Confirmed case:

A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms

***Definitions of a contact:**

A contact is a person who experienced any one of the following exposures during the 2 days before and the 14 days after the onset of symptoms of a probable or confirmed case. Close contact is defined as:

- Working together in close proximity or sharing the same environment with a COVID-19 patient
- Face-to-face contact within one meter and for more than 15 minutes
- Travelling together with a COVID-19 patient in any kind of conveyance
- Living in the same household as a COVID-19 patient
- Health care associated exposure, including providing direct care for COVID-19 patients, working with health care workers infected with COVID-19, visiting patients or staying in the same close environment as a COVID-19 patient

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Note: for confirmed asymptomatic cases, the period of contact is measures as the 2 days before through the 14 days after the date on which the sample was taken with led to confirmation

Triage patients and start emergency treatments based on disease severity.

NB:

COVID-19 may present with mild, moderate, or severe illness; the latter includes severe pneumonia, ARDS, sepsis and septic shock. Early recognition of suspected patients allows for timely initiation of IPC. Early identification of those with severe manifestations allows for immediate optimized supportive care treatments and safe, rapid admission (or referral) to intensive care unit according to institutional or national protocols. For those with mild illness, hospitalization may not be required unless there is concern for rapid deterioration. All patients discharged home should be instructed to return to hospital if they develop any worsening of illness.

IMMEDIATE IMPLEMENTATION OF APPROPRIATE IPC MEASURES

How to implement infection prevention and control measures for patients with suspected or confirmed COVID-19

At triage:

- ☐ Give suspect patient a medical mask and direct patient to separate area, an isolation room if available.
- ☐ Keep at least 1meter distance between suspected patients and other patients.
- ☐ Instruct all patients to cover nose and mouth with tissue or flexed elbow during coughing or sneezing
- ☐ Perform hand hygiene after contact with patient or patient environment
- ☐ Parents/caregivers need to support their children in maintaining cough hygiene by ensuring the child wears the mask or if the child becomes irritable and unable to tolerate the mask, the parent/caregiver should ensure they provide tissue for the child coughs into.
- ☐ Parents should ensure they guide hand washing for young children using soap and water.

Apply droplet precautions:

Droplet precautions prevent large droplet transmission of respiratory viruses.

- ☐ Use a medical mask if working within 1-2 metres from the patient.
- ☐ Place patients in single rooms, or group together those with the same etiological diagnosis.
- ☐ If an etiological diagnosis is not possible, group patients with similar clinical diagnosis and based on epidemiological risk factors, with a spatial separation.
- ☐ When providing care in close contact with a patient with respiratory symptoms (e.g. coughing or sneezing), use eye protection (face-mask or goggles), because sprays of secretions may occur.
- ☐ Limit patient movement within the institution and ensure that patients wear medical masks when outside their rooms and that patients' clean hands frequently either by washing with soap and water or use an alcohol hand rub.

Apply contact precautions:

Droplet and contact precautions prevent direct or indirect transmission from contact with contaminated surfaces or equipment (i.e. contact with contaminated oxygen tubing/interfaces).

- ☐ Use PPE (medical mask, eye protection, gloves and gown with hood) when entering room and remove PPE when leaving.
- ☐ If possible, use either disposable or dedicated equipment (e.g. stethoscopes, blood pressure cuffs and thermometers).
- ☐ If equipment needs to be shared among patients, clean and disinfect between each patient use.
- ☐ Ensure that health care workers refrain from touching their eyes, nose, and mouth with potentially contaminated gloved or ungloved hands.
- ☐ Avoid contaminating environmental surfaces that are not directly related to patient care (e.g. door handles and light switches).
- ☐ Ensure adequate room ventilation.
- ☐ Avoid movement of patients or transportation.
- ☐ Perform hand hygiene after touching each patient or patient environment.

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Apply airborne precautions when performing an aerosol generating procedure:

- ☐ Ensure that healthcare workers obtaining nasopharyngeal swabs, performing dental procedures and performing aerosol-generating procedures (i.e. open suctioning of respiratory tract, intubation, bronchoscopy, cardiopulmonary resuscitation) use PPE, including gloves, long-sleeved gowns, eye protection, and fit-tested particulate respirators (N95 or equivalent, or higher level of protection). (The scheduled fit test should not be confused with user seal check before each use.)
- ☐ When possible, use adequately ventilated single rooms when performing aerosol-generating procedures, meaning negative pressure rooms with minimum of 12 air changes per hour or at east 160 litres/second/patient in facilities with natural ventilation.
- ☐ Avoid the presence of unnecessary individuals in the room.
- ☐ Care for the patient in the same type of room after mechanical ventilation commences

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Clinical syndromes associated with COVID-19

Uncomplicatec illness	• **Patients with uncomplicated upper respiratory tract viral infection, may have non-specific symptoms such as fever, cough, sore throat, nasal congestion, malaise, headache, muscle pain or malaise.** • **The elderly and immunosuppressed may present with atypical symptoms.** • **These patients do not have any signs of dehydration, sepsis or shortness of breath**
Mild pneumonia	• Patient with pneumonia and no signs of severe pneumonia. • Child with non-severe pneumonia has cough or difficulty breathing + fast breathing: fast breathing (in breaths/min)
Severe pneumonia	Adolescent or adult: fever or suspectec respiratcry infection, plus one of respiratory rate >30 breaths/min, severe respiratory distress, or SpO2 <93% Child with cough or difficulty in breathirg, plus at least one of the following: central cyanosis or SpO2 < 90%; severe respiratory distress (e.g. gruntirg, very severe chest indrawing); signs of pneumonia with a general danger sign: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions (15). Other signs of pneumonia may be present: chest indrawing, fast breathing (in breaths/min): < 2 months: ≥ 60; 2–11 mor ths: ≥ 50; 1–5 years: ≥ 40 (16). While the diagnosis is made on clinical grounds; chest imaging may identify or exclude some pulmonary complications.
Critical cases	Cases meeting any of the following criteria: • Respiratory failure and requiring mechanical ventilations • Shock • Other organ failure that requires ICU care

Acute Respiratory Distress Syndrome	• Onset: within 1 week of a known clinical insult or new or worsening respiratory symptoms. • Chest imaging (radiograph, CT scan, or lung ultrasound): bilateral opacities, not fully explained by volume overload, lobar or lung collapse, or nodules. • Origin of pulmonary infiltrates: respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic cause of infiltrates/oedema if no risk factor present. Oxygenation impairment in adults: • Mild ARDS: 200 mmHg < PaO2/FiO2a ≤ 300 mmHg (with PEEP or CPAP ≥ 5 cmH2O, or non-ventilated) • Moderate ARDS: 100 mmHg < PaO2/FiO2 ≤ 200 mmHg (with PEEP ≥ 5 cmH2O, or non-ventilated) • Severe ARDS: PaO2/FiO2 ≤ 100 mmHg (with PEEP ≥ 5 cmH2O, or non-ventilated) • When PaO2 is not available, SpO2/FiO2 ≤ 315 suggests ARDS (including in non-ventilated patients). Oxygenation impairment in children: note OI = Oxygenation Index and OSI = Oxygenation Index using SpO2. Use PaO2-based • metric when available. If PaO2 not available, wean FiO2 to maintain SpO2 ≤ 97% to calculate OSI or SpO2/FiO2 ratio: • Bilevel (NIV or CPAP) ≥ 5 cmH2O via full face mask: PaO2/FiO2 ≤ 300 mmHg or SpO2/FiO2 ≤ 264 • Mild ARDS (invasively ventilated): 4 ≤ OI < 8 or 5 ≤ OSI < 7.5 • Moderate ARDS (invasively ventilated): 8 ≤ OI < 16 or 7.5 ≤ OSI < 12.3 • Severe ARDS (invasively ventilated): OI ≥ 16 or OSI ≥ 12.3.

Sepsis	**Adults**: life-threatening organ dysfunction caused by a dysregulated host response to suspected or proven infection, with organ dysfunction*. Signs of organ dysfunction include: altered mental status, difficult or fast breathing, low oxygen saturation, reduced urine output, fast heart rate, weak pulse, cold extremities or low blood pressure, skin mottling, or laboratory evidence of coagulopathy, thrombocytopenia, acidosis, high lactate or hyperbilirubinemia. **Children:** suspected or proven infection and ≥2 SIRS criteria, of which one must be abnormal temperature or white blood cell count
Septic shock	• Adults: persisting hypotension despite volume resuscitation, requiring vasopressors to maintain MAP ≥65 mmHg and serum lactate level >2 mmol/L. • Children (based on [12]): any hypotension (SBP 2 SD below normal for age) or 2-3 of the following: altered mental state; tachycardia or bradycardia (HR 160 bpm in infants and HR 150 bpm in children); prolonged capillary refill (>2 sec) or warm vasodilation with bounding pulses; tachypnea; mottled skin or petechial or purpuric rash; increased lactate; oliguria; hyperthermia or hypothermia Septic shock – Tachycardia definition for infants Heart rate > 160bpm child >1year HR >150bpm Bradycardia - Infant Heart rate <80bpm; child >1year HR <50bpm

Abbreviations: ARI, acute respiratory infection; BP, blood pressure; bpm, beats/minute; CPAP, continuous positive airway pressure; FiO2, fraction of inspired oxygen; MAP, mean arterial pressure; NIV, noninvasive ventilation; OI, Oxygenation Index; OSI, Oxygenation Index using SpO2; PaO2, partial pressure of oxygen; PEEP, positive end-expiratory pressure; SBP, systolic blood pressure; SD, standard deviation; SIRS, systemic inflammatory response syndrome; SpO2, oxygen saturation. APRV, airway pressure release ventilation; *If altitude is higher than 1000m, then correction factor should be calculated as follows: PaO2/FiO2 x Barometric pressure/760

Collection of specimens for laboratory diagnosis

- Collect specimens from the upper respiratory tract (URT nasopharyngeal and oropharyngeal) AND, where clinical suspicion remains and URT specimens are negative, collect specimens from the lower respiratory tract when readily available (LRT; expectorated sputum, endotracheal aspirate, or broncho-alveolar lavage in ventilated patient) for SARS-CoV-2 testing by RT-PCR and bacterial stains/cultures.
- Collect blood cultures for bacteria that cause pneumonia and sepsis, ideally before antimicrobial therapy. DO NOT delay antimicrobial therapy to collect blood cultures.

NB:

- Use appropriate PPE for specimen collection (droplet and contact precautions for URT specimens; airborne precautions for LRT specimens). When collecting URT samples, use viral swabs (sterile Dacron or rayon, not cotton) and viral transport media. Do not sample the nostrils or tonsils. In a patient with suspected SARS-CoV-2, especially with pneumonia or severe illness, a single URT sample does not exclude the diagnosis, and additional URT and LRT samples are recommended (vs. URT) samples are more likely to be positive and for a longer period. Clinicians may elect to collect only LRT samples when these are readily available (for example, in mechanically ventilated patients). Sputum induction should be avoiced due to increased risk of increasing aerosol transmission.
- Dual infections with other respiratory viral infections have been found in SARS and MERS cases. At this stage we need detailed microbiologic studies in all suspected cases. Both URT and LRT specimens can be tested for other respiratory viruses, such as influenza A and B (including zoonotic influenza A), respiratory syncytial virus, parainfluenza viruses, rhinoviruses, adenoviruses, enteroviruses (e.g. EVD68), human metapneumovirus, and endemic human coronaviruses (i.e. HKU1, OC43, NL63, and 229E).
- In hospitalized patients with confirmed COVID-19 infection, repeat URT and LRT samples should be collected to demonstrate viral clearance. The frequency of specimen collection will depend on local circumstances but should be at least after 7 days until there are two consecutive negative results (both URT and LRT samples if both are collected) in a clinically recovered patient at least 24 hours apart. If local infection control practice requires two negative results before removal of droplet precautions, specimens may be collected as often as daily

Management of mild COVID-19: symptomatic treatment and monitoring

Patients with mild disease do not require hospital interventions, but isolation is necessary to contain virus transmission. This will initially be done in hospital if there are only sporadic cases or small clusters. If the number of cases increases then facilities should be identified for isolation of mild cases outside of the hospitals.

Provide patients with mild COVID-19 with symptomatic treatment such as antipyretics for fever e.g. paracetamol 500mg -1gm TID for adults and for children 10-15mg/kg TID

Counsel patients with mild COVID-19 about signs and symptoms of complicated disease. If they develop any of these symptoms, they should seek urgent care through national referral systems.

Management of children

- Reassure parents and involve them in caring for their child, most children will have mild symptoms - much milder than those seen in adults.
- Be extra-vigilant in children with pre-existing conditions (e.g. long-term respiratory conditions, immunocompromise from disease or treatment and cyanotic heart disease) but reassure parents that the risks of co-morbidities are much greater in adults than children.
- Chest x-rays, bloods, and blood gases are not routinely indicated. Consider these only in children with persistent fever, altered fluid balance, signs of liver dysfunction, or respiratory failure.
- Although recommended in some adult studies, the following medical treatments are likely to have more side-effects than beneficial effects in children and are not routinely indicated: bronchodilators, systemic steroids, antibiotics, antivirals, and diuretics.
- Escalate respiratory support as per the respiratory failure pathway – do not use high flow nasal cannula oxygen if the child is saturating adequately with low flow oxygen.

Management of severe COVID-19: oxygen therapy and monitoring

Early supportive therapy and monitoring:

a. Give supplemental oxygen therapy immediately to patients with SARI and respiratory distress, hypoxaemia, or shock. Remarks: Initiate oxygen therapy at 5 L/min and titrate flow rates to reach target SpO2 ≥90% in non-pregnant adults and SpO2 ≥92-95 % in pregnant patients. Children with emergency signs (obstructed or absent breathing, severe respiratory distress, central cyanosis, shock, coma or convulsions) should receive oxygen therapy during resuscitation to target SpO2 ≥94%; otherwise, the target SpO2 is ≥90%. (All areas where patients with SARI are cared for should be equipped with pulse oximeters, functioning oxygen systems and disposable, single-use, oxygen-delivering interfaces (nasal cannula, simple face mask, and mask with reservoir bag). Use contact precautions when handling contaminated oxygen interfaces of patients with COVID-19.

b. Use conservative fluid management in patients with SARI when there is no evidence of shock because aggressive fluid resuscitation may worsen oxygenation, especially in settings where there is limited availability of mechanical ventilation.

c. Give empiric antimicrobials to treat all likely pathogens causing SARI. Give antimicrobials within one hour of initial patient assessment for patients with sepsis. The recommended antibiotics for a patient with SARI coming from the community would include Amoxicillin 1gm TID or Amoxicillin-clavulanic acid 625mg BD PLUS erythromycin 500mg BD or azithromycin 500mg OD or Clarithromycin 500mg BD (Paediatric dosing - Amoxicillin DT mild infection 25mg/kg/dose BD or severe infection 40-45mg/kg/dose BD or Amoxicillin-clavulanic acid 25-30mg/kg/day BD PLUS erythromycin 30-50mg/kg/day TID or azithromycin 100mg/kg)

d. Do not routinely give systemic corticosteroids for treatment of viral pneumonia or ARDS outside of clinical trials unless they are indicated for another reason.

e. Monitor patients with COVID-19 for signs of clinical deterioration, such as rapidly progressive respiratory failure and sepsis and respond immediately with supportive care interventions.

f. Haematology and biochemistry laboratory testing and ECG should be performed at admission and as clinically indicated to monitor for complications, such as acute liver injury, acute kidney injury, acute cardiac injury, or shock.

g. For pregnant patients, once the pregnant woman has been resuscitated and stabilized then fetal monitoring should be done

NB: Although the patient may be suspected to have COVID-19 administer appropriate empiric antimicrobials within ONE hour of identification of sepsis. Empiric antibiotic treatment should be based on the clinical diagnosis (community-acquired pneumonia, health care-associated pneumonia [if infection was acquired in healthcare setting], or sepsis), local epidemiology and susceptibility data, and treatment guidelines. Empiric therapy includes a neuraminidase inhibitor for treatment of influenza when there is local circulation or other risk factors, including travel history or exposure to animal influenza viruses. Empiric therapy should be de-escalated on the basis of microbiology results and clinical judgment.

During intensive care management of SARI determine which chronic therapies should be continued and which therapies should be stopped temporarily. Communicate proactively with patients and families and provide support and prognostic information. Understand the patient's values and preferences regarding life-sustaining interventions.

Management of critical COVID-19: acute respiratory distress syndrome (ARDS)

Recognize severe hypoxemic respiratory failure when a patient with respiratory distress is failing to respond to standard oxygen therapy and prepare to provide advanced oxygen/ventilatory support.

> Patients may continue to have increased work of breathing or hypoxemia even when oxygen is delivered via a face mask with reservoir bag (flow rates of 10–15 L/min, which is typically the minimum flow required to maintain bag inflation; FiO2 0.60–0.95). Hypoxemic respiratory failure in ARDS commonly results from intrapulmonary ventilation-perfusion mismatch or shunt and usually requires mechanical ventilation.

Endotracheal intubation should be performed by a trained and experienced provider using airborne precautions and rapid sequence.

> Patients with ARDS especially young children or those who are obese or pregnant, may desaturate quickly during intubation. Pre-oxygenate with 100% FiO2 for 5 minutes, via a face mask with reservoir bag. Rapid-sequence intubation is appropriate after an airway assessment that identifies no signs of difficult intubation.

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The following recommendations pertain to mechanically ventilated adults and paediatric patients with ARDS.

Implement mechanical ventilation using lower tidal volumes (4–8 mL/kg precicted body weight, PBW) and lower inspiratory pressures (plateau pressure < 30 cmH2O).

- Remarks for adults: This is a strong recommendation from a clinical guideline for patients with ARDS, and is suggested for patients with sepsis-induced respiratory failure who do not meet ARDS criteria. The initial tidal volume is 6 mL/kg PBW; tidal volume up to 8 mL/kg PBW is allowed if undesirable side effects occur (e.g. dyssynchrony, pH < 7.15). Permissive hypercapnia is permitted. Ventilator protocols are available. The use of deep sedation and initial neuromuscular blockade may be required to control respiratory drive and achieve tidal volume targets.

- Remarks for children: In children, a lower level of plateau pressure (< 28 cmH2O) is targeted, and lower target of pH is permitted (7.15–7.30). Tidal volumes should be adapted to disease severity: 3–6 mL/kg PBW in the case of poor respiratory system compliance, and 5–8 mL/kg PBW with better preserved compliance.

- In adult patients with severe ARDS, prone ventilation for 12–16 hours per day is recommended.

- Remarks for adults and children: Application of prone ventilation is strongly recommended for adult patients and may be considered for paediatric patients with severe ARDS but requires sufficient human resources and expertise to be performed safely; protocols (including videos) are available (https://www.nejm.org/doi/full/10.1056/NEJMoa1214103).

- There is little evidence on prone positioning in pregnant women. Pregnant women may benefit from being placed in the lateral decubitus position.

Use a conservative fluid management strategy for ARDS patients without tissue hypoperfusion.

In patients with moderate or severe ARDS, higher PEEP instead of lower PEEP is suggested and prone positioning with APRV recommended.

- PEEP titration requires consideration of benefits (reducing atelectrauma and improving alveolar recruitment) vs risks (end-inspiratory overdistension leading to lung injury and higher pulmonary vascular resistance). Tables are available to guide PEEP

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titration based on the FiO2 required to maintain SpO2. In younger children, maximal PEEP rates are 15 cmH2O. Although high driving pressure (plateau pressure − PEEP) may more accurately predict increased mortality in ARDS compared with high tidal volume or plateau pressure, data from RCTs of ventilation strategies that target driving pressure are not currently available.

- A related intervention of recruitment manoeuvres (RMs) is delivered as episodic periods of high continuous positive airway pressure (CPAP) (30–40 cmH2O), progressive incremental increases in PEEP with constant driving pressure, or high driving pressure; considerations of benefits vs risks are similar. Higher PEEP and RMs were both conditionally recommended in a clinical practice guideline. For PEEP, the guideline considered an individual patient data meta-analysis of three RCTs. However, a subsequent RCT of high PEEP and prolonged high-pressure RMs showed harm, suggesting that the protocol in this RCT should be avoided. Monitoring of patients to identify those who respond to the initial application of higher PEEP or a different RM protocol and stopping these interventions in non-responders are suggested.

In patients with moderate-severe ARDS (PaO2/FiO2 < 150), neuromuscular blockade by continuous infusion SHOULD not be routinely used as may result in myopathy.

- A trial found that this strategy improved survival in adult patients with severe ARDS (PaO2/FiO2 < 150) without causing significant weakness, but results of a recent larger trial found that use of neuromuscular blockade with high PEEP strategy was not associated with a survival benefit when compared with a light sedation strategy without neuromuscular blockade. Continuous neuromuscular blockade may still be considered in patients with ARDS, both adults and children, in certain situations: ventilator dyssynchrony despite sedation, such that tidal volume limitation cannot be reliably achieved; or refractory hypoxemia or hypercapnia.

Avoid disconnecting the patient from the ventilator, which results in loss of PEEP and atelectasis.

Use in-line catheters for airway suctioning and clamp endotracheal tube when disconnection is required (for example, transfer to a transport ventilator).

The following recommendations pertain to adult and paediatric patients with ARDS who are treated with non-invasive or high-flow oxygen systems.

- High-flow nasal oxygen (HFNO) should be used only in selected patients with hypoxemic respiratory failure.

- Non-invasive ventilation (NIV) should be used only in selected patients with hypoxemic respiratory failure.
- Patients treated with either HFNO or NIV should be closely monitored for clinical deterioration.

  - Adult HFNO systems can deliver 60 L/min of gas flow and FiO2 up to 1.0. Paeciatric circuits generally only handle up to 25 L/min, and many children will require an adult circuit to deliver adequate flow.

  - Because of uncertainty around the potential for aerosolization, HFO, NIV, including bubble CPAP with viral filters, should be used with airborne precautions until further evaluation of safety can be completed.

  - Compared with standard oxygen therapy, HFNO reduces the need for intubation. Patients with hypercapnia (exacerbation of obstructive lung disease, cardiogenic pulmonary oedema), hemodynamic instability, multiorgan failure, or abnormal mental status should generally not receive HFNO, although emerging data suggest that HFNO may be safe in patients with mild-moderate and non-worsening hypercapnia. Patients receiving HFNO should be in a monitored setting and cared for by experienced personnel capable of performing endotracheal intubation in case the patient acutely deteriorates or does not improve after a short trial (about 1 hour). Evidence-based guidelines on HFNO do not exist, and reports on HFNO in patients infected with other coronaviruses are limited.

Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: Interim guidance

- Patients receiving a trial of NIV should be in a monitored setting and cared for by experienced personnel capable of performing endotracheal intubation in case the patient acutely deteriorates or does not improve after a short trial (about 1 hour). Patients with haemodynamic instability, multiorgan failure, or abnormal mental status should NOT receive NIV in place of other options such as invasive ventilation.

- In situations where, mechanical ventilation might not be available, bubble nasal CPAP may be used for newborns and children with severe hypoxemia.

Prevention of Complications

Anticipated Outcome	Interventions
Reduce days of invasive mechanical ventilation	Use weaning protocols that include daily assessment for readiness to breathe spontaneously Minimize continuous or intermittent sedation, targeting specific titration endpoints (light sedation unless contraindicated) or with daily interruption of continuous sedative infusions
Reduce incidence of ventilator associated pneumonia	Oral intubation is preferable to nasal intubation in adolescents and adults • Keep patient in semi-recumbent position (head of bed elevation 30-45°) • Use a closed suctioning system; periodically drain and discard condensate in tubing • Use a new ventilator circuit for each patient; once patient is ventilated, change circuit if it is soiled or damaged but not routinely • Change heat moisture exchanger when it malfunctions, when soiled, or every 5–7 days
Reduce incidence of venous thromboembolism	Use pharmacological prophylaxis (low molecular-weight heparin [preferred if available] or heparin 5000 units subcutaneously twice daily) in adolescents and adults without contraindications. For those with contraindications, use mechanical prophylaxis (intermittent pneumatic compression devices).
Reduce incidence of catheter related bloodstream infection	Use a checklist with completion verified by a real-time observer as reminder of each step needed for sterile insertion and as a daily reminder to remove catheter if no longer needed
Reduce incidence of pressure ulcers	Turn patient every two hours
Reduce incidence of stress ulcers and gastrointestinal bleeding	Give early enteral nutrition (within 24–48 hours of admission) • Administer histamine-2 receptor blockers or proton-pump inhibitors in patients with risk factors for GI bleeding. Risk factors for gastrointestinal bleeding include mechanical ventilation for ≥48 hours, coagulopathy, renal replacement therapy, liver disease, multiple comorbidities, and higher organ failure score

Reduce incidence of ICU-related weakness	Actively mobilize the patient early in the course of illness when safe to do so

SPECIFIC ANTI-SARS-COV-2 TREATMENTS

Multiple clinical trials are ongoing or planned to assess the activity of various drugs in COVID-19. There is insufficient evidence to strongly recommend a particular drug.

There have been recent reports on the role of chloroquine and hydroxychloroquine in management of COVID 19. One small study reported that hydroxychloroquine alone or in combination with azithromycin reduced detection of SARS-CoV-2 RNA in upper respiratory tract specimens compared with a non-randomized control group but did not assess clinical benefit.

Recommendation:

- No antiviral treatment for patients with mild disease
- For patients with severe disease or who are rapidly deteriorating, in addition to the management described above, consideration may be given to adding hydroxychloroquine (Dose of 400mg BD on day 1 followed by 200mg BD on days 2-5).

Note that this is not a strong recommendation and may change as more data from clinical trials becomes available

Special considerations for pregnant patients

Pregnant women with suspected or confirmed COVID-19 should be treated with supportive therapies as described above, taking into account the physiologic adaptations of pregnancy. The use of investigational therapeutic agents outside of a research study should be guided by individual risk-benefit analysis based on potential benefit for mother and safety to fetus, with consultation from an obstetric specialist and ethics committee. Emergency delivery and pregnancy termination decisions are challenging and based on many factors: gestational age, maternal condition, and fetal stability. Consultations with obstetric, neonatal, and intensive care specialists (depending on the condition of the mother) are essential.

Guidance on discharge and de-isolation of patients with COVID-19

- SARS-CoV-2 virus can initially be detected 24-48 hours prior to symptom onset in upper respiratory tract samples; the virus can persist for 7–12 days in moderate cases and up to 2 weeks in severe cases (WHO mission to China Report) [1]. Prolonged viral shedding of up to 22 days has been noted in children even after mild infections.
- Mild cases can be managed from home as long as they are able to self-isolate If self-isolation is not possible, then they should be admitted for 14 days

How to move from the hospital:

Patient should be picked by only one person who should wear a mask.
Sit on the back-left seat of the vehicle (do not sit on the co-driver's seat)
Not have any physical contact with the driver

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If one is to self-isolate, then they must stay at home and not move out of their home for a period of 14 days and:

- ☐ While at home stay away from others. If possible, should stay in a specific room with adequate ventilation and use a separate bathroom. If sharing bathroom facilities then this should be disinfected regularly using household disinfectant or soap and water
- ☐ Wash hands often with soap and water for 20 seconds.
- ☐ Avoid sharing personal household items. After using personal items, such as silverware, dishes, towels, sheets and more, wash thoroughly with soap and water.
- ☐ Cover mouth and nose with a tissue when you cough and sneeze and then throw it into the trash.
- ☐ Wear a surgical mask.
- ☐ The rest of the family should be advised to minimize contact with the patient and to wear a mask if coming in to contact. They should frequently wash hands with soap and water

Patients admitted can be discharged from the facility if:

- ☐ Symptoms have resolved
- ☐ They are able to self-isolate as indicated above

Viral Clearance

Where capacity allows, viral clearance should be defined as:

- ☐ Resolution of symptoms
- ☐ Two documented negative Viral PCR tests in 2 respiratory samples collected at least 24 hours apart. Repeat testing to determine viral clearance should be repeated at least 10 days after diagnosis provided that all symptoms have resolved

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General considerations for health facilities:

Identify a room where individuals suspected to have COVID-19 can be isolated prior to being transferred to an isolation facility.

Set up a triage station near the entrance to the facility and follow the triage guidance given above

Isolation

facilities should identify and train personnel who will take care of patients with COVID-19, all the staff in the facility should be sensitized on COVID-19, facilities should also ensure they identify clinical or lab personnel that are trained on sample collection.

Hospitals should identify a comfortable location where health care personnel can stay for periods of quarantine and isolation.

Hospitals should reduce crowding at their facilities. Possible ways of doing this include:

- Reducing number of patients attending elective clinics by proper triage
- Reducing elective surgeries
- Only admitting patients who require in-patient care
- Reducing number of visitors, a patient can receive to only one per day
- Fill out longer prescriptions for patients on stable chronic care

Private outpatient clinics:

- Reduce number of patients seen in clinic to only those that require urgent or emergency care.
- Fill out longer prescriptions for patients on stable chronic care
- Triage patients on phone - those with respiratory symptoms or recent travel into the country should not come to clinic but should stay home on self-quarantine and call 719
- Ensure all the precautions highlighted below are adhered to

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Other measures that facilities and private clinics should implement include:

- Avoid crowding at the patient waiting area ensuring the 1-meter distance between patients is maintained.
- Ensure the waiting area is well ventilated.
- Any over flow of patients should be advised to wait outside in an open space until their appointment time arrives.
- A sanitizer must be present at the entrance of the waiting area with a minimum of 70% alcohol and should be used by each patient entering the waiting area.
- The clinicians, nurses and receptionist staff must avoid shaking hands with the patients and each other.
- Encourage use of electronic money transfer services for payment of clinical services
- The clinician must wash his hands thoroughly with soap and water following the d handwashing before and after coming into contact with each patient.
- Frequently decontaminate all surfaces and equipment using 0.5% chlorine

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REDUCING RISKS OF TRANSMISSION IN OPHTHALMOLOGY

- ☐ Ensure that there is adequate water and soap for Hand washing
- ☐ Ensure you sanitize your hands and the tools (including the slit lamps,) used to examine the patient, before and after examining the patients.
- ☐ Always when in the hospital/examination room, remain in a face mask, protecting the mouth, nose, with eye protection-googles/shields, besides usual dust/Lab coat
- ☐ Use available material to you/in your context to create a good barrier between the health worker and the Patient, especially while using a slit Lamp (see Fig. 1) Laminated materials, Transparencies or Old X-ray Films, remember to sanitize the barrier too
- ☐ Where possible use a slit lamp indirect ophthalmoscopy, or use head mounted Light source to do indirect ophthalmoscopy. Encourage minimal talking when using the slit lamp
- ☐ Only Patients with emergency conditions (painful conditions occurring in the last 5 days) should visit the hospitals during this period of Corona shutdown.
- ☐ Corona Conjunctivitis, may be mild, may be the first manifestation and will need basic antibiotic eye drop or Artificial Tears.
- ☐ Out Patient Clinics, Elective Surgical/Medical Procedures preferably should be deferred till when the situation is under control.
- ☐ At the end of the day, sanitize all the surfaces, including the furniture.

Creating a Slit Lamp Barrier





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Management of Dialysis

This section gives guidance on:

- Infection prevention practices within the dialysis unit during the COVID-19 pandemic
- Management of a patient on outpatient hemodialysis when suspected to have COVID-19 infection
- Management of a patient on outpatient hemodialysis when confirmed to have COVID-19 infection

Dialysis patients are at increased risk of COVID-19 infection as they represent an immunocompromised population. In Kenya, all patients with end stage renal disease (ESRD) undergo in-patient hemodialysis (HD) and so are constantly exposed to a hospital environment, thereby increasing their risk of infection. Further, a large percentage of the population are above the age of 65 years and hence at greater risk of complicated COVID-19 infection.

In Wuhan City, where the COVID-19 viral infection originated, in a single centre in Renmin Hospital, Wuhan University 37 of 230 HD patients, and 4 of 33 staff members developed COVID-19 infection between 14 January and 17 February 2020. These patients had less lymphopenia, lower serum levels of inflammatory cytokines and milder clinical disease than described in patients with comorbidities other than ESRD on HD. Nonetheless, mortality was 16.2% (6 patients) in the HD population within this one month.

MANAGEMENT OF PATIENTS ON DIALYSIS DURING COVID-19 PANDEMIC

In-center HD represents an increased risk of transmission of infection, not only to patients but to their family members, medical staff and other facility workers.

Information Updates and Group Activities:

A working team consisting of dialysis physicians, nursing staff and technologists should receive training in updated clinical knowledge of epidemic COVID-19, notification of infection at risk, epidemic prevention tools, and guidelines from the government and hospital authority.

Information on travel, occupation, contacts, and clusters history (TOCC) of each medical staff, dialysis patient, their family members, friends they have been in physical contact with, residents of the same institution, and colleagues at work, will be collected and updated regularly.

Group activities, including group rounds, group studies, and case discussions will be minimized.

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It is recommended that staff members have meals at different time to avoid dining together. Hands washed with flowing water before meals.

Precautions:

All patients entering the dialysis facility should be screened at triage and all appropriate IPC measures put in place including ensuring that:

- Staff shall self-monitor their symptoms and shall inform the team leader in case they or their family members develop symptom(s) suggestive of COVID-19 infection.
- Patients with suspected or confirmed COVID-19 infection should ideally be admitted to negative pressure isolation ward of specified hospitals.
- Where this is not possible, for those patients on 14-day self-quarantine for possible contact with COVID-19, the "Fixed Dialysis Care Model" as below is recommended.

Place of dialysis treatment: patients will continue hemodialysis at the original hemodialysis center and not change to another center.

Dialysis shift and personnel: Do not change dialysis shifts and caregiver staff to avoid cross contamination and infection. Minimize the relevant contacts.

If patients need vascular access intervention and are confirmed or suspected to have COVID-19 should be carried out in a designated room (for example negative pressure room in ICU if available) with necessary protection for medical staff.

Transportation: Public transport should not be used. Transport personnel and escorts should wear surgical grade or N95 masks throughout.

Hemodialysis management of suspected or confirmed COVID-19 infected case:

- Best efforts must be made to isolate patients with suspected or confirmed COVID-19.
- Separate rooms with the door closed may be used if available, except those rooms used for treatment of patients with hepatitis B.
- If no separate room is available, patients suspected to have COVID-19 should be cohorted on a designated isolation shift (preferably the last shift of the day), or dialyzed in a designated COVID-19 facility.
- If patients with COVID-19 must be treated at the same time as patients who are asymptomatic, patients who are symptomatic should be treated in a corner or end-of-row station. At least 6 feet of separation should be maintained between masked patients who are symptomatic and others.
- All personnel involved in the direct care of patients affected by COVID-19 must undertake full protection, including long-sleeved waterproof isolation clothing, hair caps, goggles, gloves and medical masks (FFP2 or FFP3 mask if available) filtering 95 to 99% of particulate matter and aerosols in inhaled air. Hand hygiene must be strictly implemented: carefully washing hands with soap and water and systematically using alcoholic solutions and disposable gloves.
- Consideration should be given to cohorting more than one patient with suspected or confirmed COVID-19 and the healthcare team caring for them together in the section of the unit and/or on the same shift (e.g., consider the last shift of the day). Avoid, however, mixing of suspected and confirmed cases.
- Healthcare team should be cohorted i.e. separate teams for management of high-risk and low risk patients. Only the minimum number of assigned healthcare team should enter the isolation room/cohort area, all non-scheduled team-mates should be excluded at all times.
- If a newly confirmed or highly suspected case of novel Coronavirus infection in dialysis centers is identified, disinfection must be carried out immediately. Areas in close contact with these patients must not be used for other patients until cleared.
- The medical waste from confirmed or suspected patients with novel Coronavirus infection must be considered as infectious medical waste and disposed accordingly.

- It is not a requirement that patients infected with COVID-19 be treated in an airborne infection isolation room.

Special Considerations:

a. Procedures

Patients who need vascular access surgery should be screened for COVID-19. Operations on patients with confirmed or suspected COVID-19 infection should be carried out in a designated room with necessary protection for medical staff.

b. Home haemodialysis and peritoneal dialysis

These patients should be assisted at home as far as is possible, using tele – reporting and home visits by healthcare staff, as deemed necessary.

c. Dialysis Frequency

- It can be considered to decrease the frequency of haemodialysis sessions from three to two times per week in patients that tolerate such a regimen. This could be considered:
- to decrease the need for travelling by taxi / ambulance in case of shortage of such transportation means
- to decrease the chance of dialysis patients getting infected by travelling back and forth to the dialysis unit
- to decrease the chance of dialysis patients spreading the infection to the dialysis unit or the hospital to decrease the need for supplies of which shortages are expected. (Especially with factories closing down (temporarily) and supply problems, your unit may run into logistical problems with shortage of material needed for dialysis. An early change from three to two haemodialysis sessions per week in a large part of your dialysis population may help to save material, allowing you to run your dialysis unit as long as possible).

Operational strategies for family member and caregivers

- All the family members living with dialysis patients must follow all the precautions and regulations given to patients to prevent person-to-person and within family transmission of the COVID-19, which include body temperature measurement, good personal hygiene, handwashing, and prompt reporting of potentially sick people.
- Dialysis patients, who have a family member or caregiver subject to "basic quarantine", can have dialysis as usual in accordance during the 14-day period.
- When transporting a suspected or confirmed COVID-19 infected case to hospital for hemodialysis, family members should wear a surgical or N-95 mask. The mode of transport and the route followed should remain the same

RECOMMENDATIONS FOR DENTAL PRACTICE IN RESPECT TO COVID19 PANDEMIC

Interim guidance on infection prevention and control during health care is recommended when COVID-19 infection is suspected. Dental professionals are uniquely exposed to COVID-19 due to regular contact with oral mucosa, and bodily fluids, saliva and blood. Most dental procedures result in production of droplet and aerosols, which can remain suspended in the air for some time before being inhaled or settling on environmental surfaces. Dental professionals should therefore have an understanding of COVID-19 transmission, detection of infection and extra precautions required when providing dental treatment to avoid contracting or transmitting the infection.

Provision of routine care

Care should be taken to avoid or minimize operations that can produce droplets or aerosols. **Routine dental visits should be deferred, pending advisories from the Ministry of Health.** Dental emergencies will continue to be managed non-invasively where applicable. Where procedures must be done, this should be done with presumption of COVID-19 exposure and appropriate precautions taken. It was reported that dental practice should be postponed at least 1 month for convalescing patients with SARS. It is unknown yet whether the same suggestion should be recommended for patients recovered from COVID-19.

Plan ahead

All clinics should have standard operating procedures in place for handling patients presenting to the clinic who have been potentially exposed to COVID-19. Standalone clinics should have a designated space to safely separate the patient potentially exposed to COVID-

19 from others who may be in the waiting area. This should be an area separated by a door. Clinics within hospitals should be aware of the designated point for handling suspected COVID-19 exposure. All professionals should be well versed with the country case definition for COVID-19 infection which may be amended from time to time as the situation evolves.

Evaluation of Patients

Where possible, patient triaging over the telephone should be done prior to arrival at the clinic. Patients with symptoms of respiratory tract infection should be advised to stay home until the condition resolves.

Where additional history reveals recent travel from a country with confirmed COVID-19 cases or contact with such individuals should be advised to call the national hotline 719 for further evaluation. Follow-up on compliance of the advisory to use the hotline should be done.

Where telephone triaging is not possible, dental clinics are recommended to establish precheck triages to measure and record the temperature of every staff and patient as a routine procedure. A contact free thermometer is strongly recommended. Precheck staff should ask patients questions about their health status and history of contact or travel. Patients who have a presentation and/or travel or contact history suggestive of COVID-19 exposure should be isolated pending transfer to designated hospitals screening COVID-19 cases, or if the clinic is within a hospital, the designated COVID-19 screening site. For patient transfer, calling the national hotline 719 will avail a rapid response team who will come to evaluate and evacuate the patient. Following the MOH advisory, patients who have been to epidemic regions within the past 14 days, will be quarantined for at least 14 days. Such patients should only be seen to address dental emergencies.

Oral Examination

The current literature suggests that a significant proportion of people infected with COVID-19 are asymptomatic. Preoperative antimicrobial mouth rinse could reduce the number of microbes in the oral cavity. Chlorhexidine mouthwash has been found to have poor virucidal activity against coronavirus. A pre-procedure mouth rinse with oxidative agents such as 1% hydrogen peroxide or 0.2% povidone is recommended. Intraoral x-ray examination is the most common radiographic technique in dental imaging; however, it can stimulate saliva secretion and coughing. Therefore, extraoral dental radiographies, such as panoramic radiography is advised.

Provision of dental care for confirmed COVID-19 infected patients.

- Provision of care for confirmed cases of covid-19 infection should be restricted to dental emergencies. Appropriate precautions should be taken to protect the patient and all staff in the operatory and minimize risk of contamination. Strict personal protection measures should be in place. All personnel should endure handwashing before and after examination, procedures, leaving the patient surroundings and after handling tissue, bodily fluids or contaminated material. Care should be taken by staff to avoid touching their own eyes, mouth and nose.

- PPE for all staff in the operatory should include: hair net, disposable gown, face masks and goggles/face shields, surgical gloves and waterproof footwear are recommended. Face shields and goggles are essential with use of high or low-speed drilling with water spray

- Care should be taken to avoid or minimize operations that can produce droplets of aerosols. Procedures that are likely to induce coughing should be avoided (if possible) or performed cautiously (WHO 2020a). Aerosol-generating procedures, such as the use of a 3-way syringe, should be minimized as much as possible. The 4-handed technique is beneficial for controlling infection. The use of saliva ejectors with low or high volume can reduce the production of droplets and aerosols. Rubber dams and high-volume saliva ejectors can help minimize aerosol or spatter in dental procedures.

- If a carious tooth is diagnosed with symptomatic irreversible pulpitis not controlled by medication, pulp exposure could be made with chemo mechanical caries removal under rubber dam isolation and a high-volume saliva ejector after local anesthesia; then, pulp devitalization can be performed to reduce the pain. The filling material can be replaced gently without a devitalizing agent later according to the manufacturer's recommendation. Where use of high-speed handpiece is unavoidable it recommended to schedule the procedure as the last patient in the day to decrease the risk of nosocomial infection. After treatment, environmental cleaning and disinfection procedures should be followed. Alternatively, patients could be treated in an isolated and well-ventilated designated treatment room. or negatively pressured rooms if available.

- The treatment planning of tooth fracture, luxation, or avulsion is dependent on the age, the traumatic severity of dental tissue, the development of the apex, and the duration of tooth avulsion. If the tooth needs to be extracted, if suturing is needed, absorbable suture

is preferred. For patients with facial soft tissue contusion, debridement and suturing should be performed. It is recommended to rinse the wound slowly and use the saliva ejector to avoid spraying.

- Dental emergencies can occur and exacerbate in a short period and therefore need immediate treatment. Life-threatening cases with oral and maxillofacial compound injuries or infections should be admitted to the hospital immediately, and chest imaging should be prescribed if available to exclude suspected infection because of the turnaround time for receiving COVID-19 test results. RT-PCR test, besides being time-consuming, needs a laboratory with pan-coronavirus or specific SARS-CoV-2 detection capacity.

Recommendations for Dental Education

It is worth advocating to encourage all dental professionals to engage in self-learning, make full use of online resources, and learn about the latest academic developments. With the increased knowledge of viral features, epidemiologic characteristics clinical spectrum, and treatment, strategies to prevent, control, and stop the spread of COVID-19 will continue to be developed.

Conclusion

- Only dental emergencies should be addressed at all levels until further communication.
- Patients are encouraged to call for consultation and only visit the dental clinic on the advice on the dental professional.
- If a stand-alone clinic does not have enough room/capacity to triage and isolate suspected cases, it should desist from operating.
- The dentists working in public dental facilities should liaise with the hospitals where they are working on how to handle the patients. In the absence of proper PPE as prescribed in the text above, they should not handle any patients.
- It is the responsibility of the dental practitioner to educate their patients on the risks of undertaking a non-urgent procedure and also to ensure their safety and the safety of other patients and staff.

Considerations for individuals with Diabetes Mellitus

The following Individuals with diabetes are considered most vulnerable:

- Those with inadequately controlled diabetes mellitus, specifically with a HBA1c reading > 7.6% or those with recently fluctuating sugars.
- Patients more than 55 years of age.
- Patients with diabetes and concomitant comorbidities such as heart failure, hypertension, chronic obstructive pulmonary disease, chronic kidney disease, cancer and HIV who are already known to have a significant impairment in their immune function.
- Specific points relating to diabetes mellitus and COVID-19 infection
- It is important to note that those patients living with diabetes who are well controlled with no significant comorbidities have a significantly lower risk of developing severe complications of COVID-19 and their risk is comparable to that of the general population. (12)
- The risk associated with COVID-19 infection is similar in individuals who have either type 1 or type 2 diabetes excluding other risk factors such as age, micro and macro vascular complications, comorbidities and glycemic control. (12)
- COVID-19 infection in individuals who have either type 1 or type 2 diabetes can put them at a higher risk of developing diabetic ketoacidosis. The same standard treatment protocol for managing diabetic ketoacidosis as outlined by the American diabetes association (ADA) is used to treat patients with diabetes who develop diabetic ketoacidosis secondary to COVID-19 infection (12)
- In individuals with Diabetes we recommend the following measures to prevent COVID-19 infection: (12 13)
- Frequent hand washing using the correct technique with water and soap is usually sufficient. If sanitizer is available, it should contain at least 70% alcohol to be considered effective.
- Social distancing - Keeping a one-meter distance from individuals in various spaces.
- Avoid being in crowded places or group meetings of more than 10 people at a time.

- Avoid touching your face.
- Only go to the hospital if it is absolutely necessary.
- or non-urgent clinical cases, we recommend you contact your health care provider and ensure you get a reasonable stock of medication supplies for the next eight weeks. This should be ensured until there is more clarity on the progress of the condition in the country.
- Ensure that you have current phone contacts of your treatment facility and ensure your family members have this contact as well in the event of any emergency.
- Try coughing either into your flexed elbow or a disposable tissue and away from people. Ensure proper and immediate disposal of the used tissues.
- Wear a face mask when coming into a crowded health care facility.
- Avoid non-essential local and international travel during this current phase.
- Avoid all crowded public areas and social gatherings such as in churches, temples, mosques, as well as entertainment areas such as clubs, gyms restaurants and bars.
- Minimize the number of visitors coming into your homes especially for those who are considered high risk individuals as per the criteria noted above.
- Caregivers taking care of patients living with diabetes must always thoroughly wash their hands with the correct technique before and after coming into contact with them.
- All utensils and surfaces must be thoroughly cleaned as frequently as possible.
- Avoid touching common surfaces such as handrails, elevator buttons, door handles, counter tops. If you do so, ensure you wash or sanitize your hands each time you come into contact with them.

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- Consult your doctor on phone if you note any form of glycemic variability that is off the recommended patient specific blood glucose targets. In general, the recommended glycemic targets are 5 to 7 mmol/l for fasting blood sugar and 5 to 10 mmol/l for 2-hour postprandial blood glucose.
- Encourage patients to review patient education material on how to avoid and manage hypoglycemia with their family members and caregivers. These materials are available online and can be availed on electronic platforms by clinic staff to patients to ensure preparedness on the part of the patient as well as his/her support system at home.
- Ensure that you have stocked a reasonable supply of strips and ensure your glucometer is well calibrated and in good working condition.
- For those with type I diabetes ensure that you have ketone strips on standby in the event you find you that you have persistent hyperglycemia and symptomatology to suggest impending diabetic ketoacidosis. Contact your clinician on phone in the event of marked hyperglycemia and a ketone reading of > 0.6 mmol/l. If you do not have access to ketone strips, inform your doctor if your sugars remain persistently high.

Recommendations for doctors' inpatient and outpatient clinical practice adapted from the CDC

1. Avoid admitting anyone living with diabetes who does not need to be in the inpatient setting to reduce further contact and exposure since the inpatient transmission rate is estimated to be as high 41% as noted by

2. Where possible, any elective procedures should be postponed till after the pandemic.

3. The strictest hygiene measures and laid down aseptic techniques of wound care must be observed when dealing with diabetes related wounds that may need frequent dressing such as diabetic foot or post-surgical wounds.

4. Coronavirus can survive up to 8 hours on fabric. It is therefore recommended that staff working in high turnover units such as high dependency units, accident and emergency, intensive care units, chemotherapy centres and dialysis units wear scrubs that can be laundered at the end of the shift to avoid possible transmission of infection to homes of medical personnel.

5. If outpatient clinics have to continue for those patients who need to be genuinely reviewed ensure the following precautions

- Avoid crowding at the patient waiting area ensuring the 1-meter distance between patients is maintained.

- Ensure the waiting area is well ventilated.
- Any over flow of patients should be advised to wait outside in an open space until their appointment time arrives.
- A sanitizer must be present at the entrance of the waiting area with a minimum of 70% alcohol and should be used by each patient entering the waiting area.
- The clinicians, nurses and receptionist staff must avoid shaking hands with the patients.
- Encourage use of electronic money transfer services for payment of clinical services to avoid coming into contact with currency notes and coins that are known vehicles of transmission.
- The clinician must wash his hands thoroughly with soap and water following the designated 7 steps of handwashing before and after coming into contact with each patient.
- We recommend 0.5 % chlorine-based solutions to decontaminate all floors, clinical surfaces including countertops, desk tops, tables, chairs.
- We recommend 0.05% chlorine-based solutions to decontaminate all clinic equipment e.g. stethoscopes, blood pressure machines and glucometers to prevent spread of the coronavirus.
- Ensure the clinicians desktop is sanitized as frequently as possible.
- Ensure that the examination couch is decontaminated regularly and draped in linen. Tissue liners should be rolled over the examination couch and discarded after each patient is examined.
- Avoid touching your nose, eyes and face.

All contacts of confirmed cases should be asked to self-quarantine. The information below should be given to individuals required to self-quarantine (Appendix 1)

CONSIDERATIONS FOR OBSTETRICS AND GYNAECOLOGY

The approach to prevention, evaluation, diagnosis, and treatment of pregnant women with suspected COVID-19 should be similar to that in nonpregnant individuals (as described above), with consideration that pregnant women with other potentially severe respiratory infections, such as influenza, severe acute respiratory syndrome (SARS)-CoV, or Middle East respiratory syndrome (MERS)-CoV, appear tc be more vulnerable to developing severe disease.

It is unknown whether the virus can be transmitted through breast milk; however, droplet transmission could occur through close contact during breastfeeding.

Recommendation:

- A mother with confirmed COVID-19 or who is symptomatic should take all possible precautions to avoid spreading the virus to her infant, including washing her hands before touching the infant and wearing a face mask, if possible, while breastfeeding. If expressing breast milk with a manual or electric breast pump, the mother should wash her hands before touching any pump or bottle parts and follow recommendations for proper pump cleaning after each use. If possible, consider having someone who is well to feed the expressed breast milk to the infant.

Elective surgeries

- In a situation where COVID-19 has caused stress on the health care system, it may be advantageous to identify and modify surgical scheduling, including for procedures that are medically indicated, when a patient's health and safety would not be harmed by such delay.
- Obstetric and gynecologic procedures for which a delay will negatively affect patient health and safety should not be delayed. This includes gynecologic procedures and procedures related to pregnancy for which delay would harm the patient health.

APPENDIX 1

Having come in to contact with an individual diagnosed to have COVID-19, you will be required to self-quarantine. This must be adhered to.

What is quarantine?

Quarantine separates and restricts the movement of people who were exposed to a contagious disease to see if they become sick. This means that you reduce contact with other people until the period of quarantine is over. The aim is to protect your loved ones and other members of the public from potentially acquiring an infection from you since you may have come into contact with the disease. This is an important public health measure that will be enforced.

How to move around:

- You should avoid using public transportation
- If you use a car:
  - You should be picked by only one person who should wear a mask.
  - Sit on the back-left seat of the vehicle (do not sit on the co-driver's seat)
  - Do not have any physical contact with the driver

If you are to self-quarantine, then you must stay at home and not move out of your home for a period of 14 days and:

- While at home stay away from others. If possible, you should stay in a specific room with adequate ventilation and use a separate bathroom. If you are sharing bathroom facilities then this should be disinfected regularly using household disinfectant or soap and water
- Wash your hands often with soap and water for 20 seconds.
- Avoid sharing personal household items. After using personal items, such as silverware, dishes, towels, sheets and more, wash thoroughly with soap and water.
- Cover your mouth and nose with a tissue when you cough and sneeze and then throw it into the trash.
- Postpone all non-essential appointments until you are out of quarantine.

If you are unable to self-quarantine, then you will be taken to a quarantine facility

If you develop any symptoms during the period of quarantine (such symptoms may include fever, cough, muscle pain, headache, sore throat, diarrhoea), then you should call **719** for direction to an isolation facility.

If you are safely able to present to an isolation facility (in a private vehicle accompanied only by the driver and you sit on the back seat without physical contact with the driver) then you can of on your own, otherwise you will be given further directions upon calling 719.

At the facility, you will be evaluated by a health care personnel and a swab of your throat and nose taken for laboratory testing and appropriate care offered.

We will collect your contact details (name, next of kin, physical address and telephone contact) to allow for follow-up on the progress of yourself quarantine. If at any time you feel you are unable to continue self-quarantine then call **719** and you will be directed to a self-quarantine facility.

Understand that if you break the self-quarantine then you risk exposing your loved ones and other members of the public to infection.

Your movements during this period of quarantine may be monitored by the Ministry of Health from time to time. If your break the self-quarantine, then Ministry of Health officials are authorized to admit you to a quarantine facility.

Ensure you give correct contact and address information. Please note that it is an offence under the Public Health Act to give false information

By signing this form, you agree to abide by these instructions (failure to agree means you accept to be Admitted to a government quarantine facility):

Name: _____ Next of Kin _____

ID/Passport number: _____

Telephone Number: _____ Next of kin contact _____

Physical contact: _____

Signature: _____

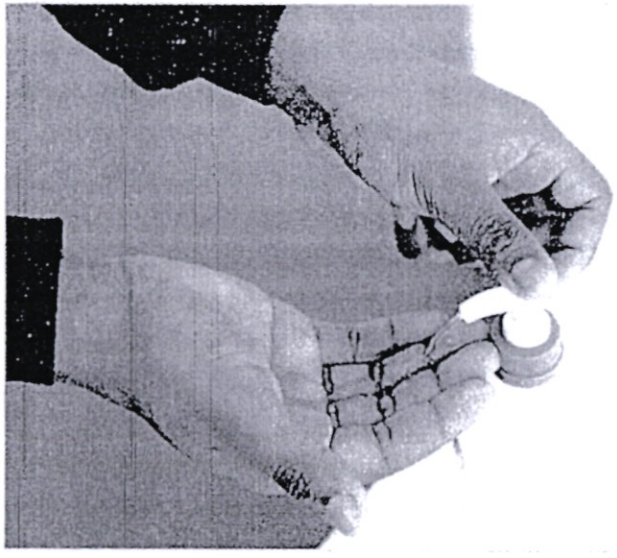
APPENDIX 2

Guidance for wearing and removing personal protective equipment in healthcare settings for the care of patients with suspected or confirmed COVID-19

****European Centre for Disease Prevention and Control Technical Report Feb 2020***

Before wearing the PPE for managing a suspected or confirmed COVID-19 case, proper hand hygiene should be performed (Figure 1).

Figure 1. Hand hygiene performed using alcohol-based solution



The first PPE to be donned (Figure 2) is the gown. There are different types of gowns (single use, reusable); this guidance presents a reusable long-sleeved water-resistant gown. When using a gown with back closure, as shown below, a second operator should assist in buttoning up the back (Figure 3).

Figure 2. Donning of a long-sleeved water-resistant gown



Figure 3. Buttoning up the backside of the gown; performed by an assistant

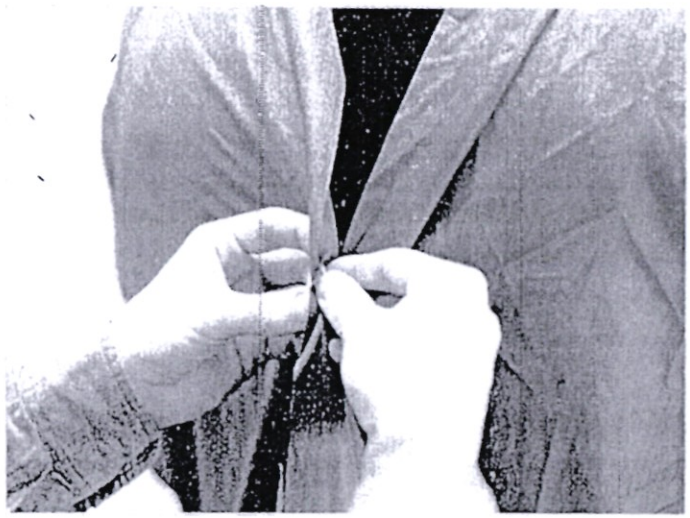
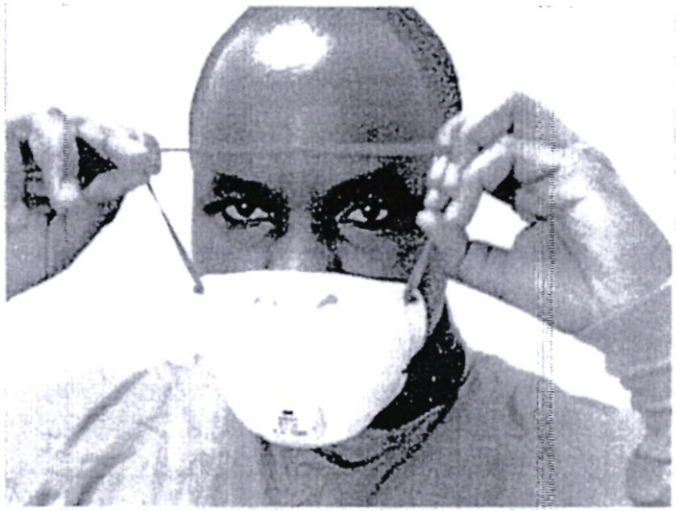


Figure 4. Wearing of an FFP (class 2 or 3) respirator



After wearing the gown, it is suggested to proceed with the respirator that protects from the inhalation of droplets and particles. It is important to perform a fitting test after the respirator has been put on, following the manufacturer's instructions.

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Figure 5. Fitting the respirator's metal nose clip

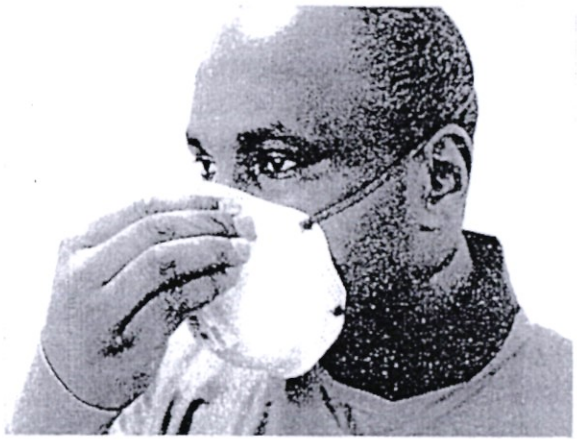

Figure 6. Wearing of a face mask (surgical mask)



The metal nose clip needs to be adjusted (Figure 5) and the straps have to be tightened to have a firm and comfortable fit. If you cannot achieve a proper fit, position the straps crosswise. However, this minor modification could imply a deviation from the recommendations in the manufacturer's product manual.

If a face mask (surgical mask) is worn as substitution for a respirator (Figure 6), it is important to correctly position it on the face and adjust it with the metal nose clip (Figure 7) in order to achieve a proper fit.

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Figure 7. Fitting the face mask's metal nose clip



Figure 8. Wearing of goggles with textile elastic strap



Once the respirator has been properly positioned, put on the goggles for eye protection. Place the goggles over the mask's straps and ensure that the textile elastic strap fits snugly – but not too tightly (Figures 8 and 9).

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Figure 9. Side view of goggles with an elastic textile strap



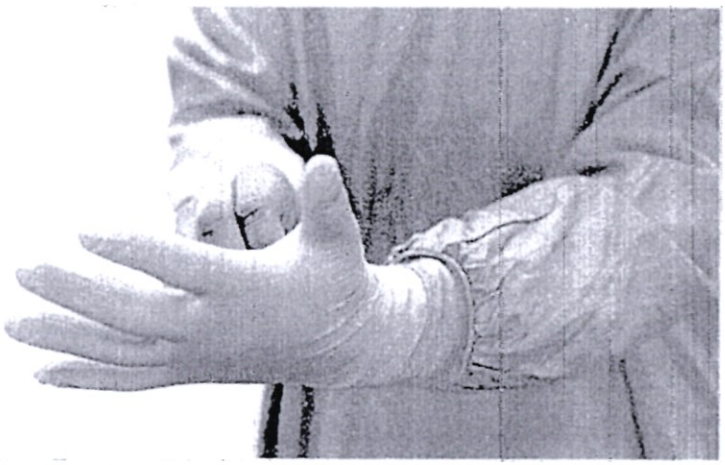
Figure 10. Wearing of goggles with temples



If goggles with temples are used, make sure that they are properly positioned and fit well (Figure 10).

After the goggles, the gloves are next. When wearing gloves, it is important to extend the glove to cover the wrist over the gown's cuffs (Figure 11). For individuals allergic to latex gloves, an alternative option, for example nitrile gloves, should be available.

Figure 11. Wearing of gloves



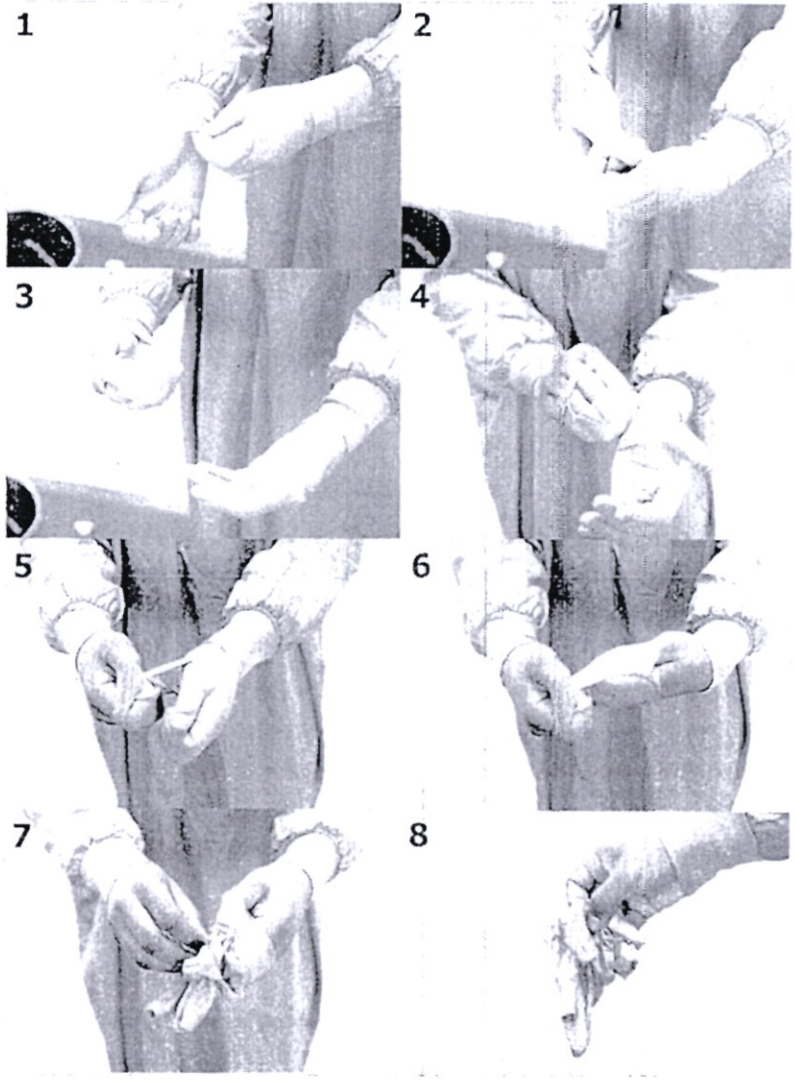
Removing (doffing) the PPE

Wearing the PPE correctly will protect the healthcare worker from contamination. After the patient has been examined, the removal (doffing) of the PPE is a critical and important step that needs to be carefully carried out in order to avoid self-contamination because the PPE could by now be contaminated.

The gloves are removed first because they are considered a heavily contaminated item. Use of alcohol-based hand disinfectant should be considered before removing the gloves. The gloves should be removed following eight steps (Figure 12).

Start by (1) pinching and holding the glove (with the other gloved hand) between the palm and wrist area, (2) peeling the glove away from the wrist (3) until it turns inside out covering the fingers. With the now half-gloved hand, (4) pinch and hold the fully gloved hand between the palm and wrist, (5) peel the glove away from the wrist (6) until it turns inside out and covers the fingers. Now that both hands are half-gloved, (7) remove the glove from one hand completely by grabbing the inside part of the glove and peeling it away from the hand and do the same for the remaining half-gloved hand using the non-gloved hand, while always grabbing the inside part of the glove. Dispose of the gloves (8) in a biohazard bin.

Figure 12. Removal of gloves (steps 1 to 8)



After the removal of gloves, hand hygiene should be performed and a new pair of gloves should be worn to further continue the doffing procedure. Using a new pair of gloves will prevent self-contamination.

With the new pair of gloves on, the gown should be removed. When using a gown with back closure (as used in this document), a second operator should assist in unbuttoning the backside of the gown (Figure 13). The assistant should wear gloves and a surgical mask, which need to be removed after opening the gown. After the gloves of the assistant are removed, hand hygiene should be performed using an alcoholic solution. After the gown has been unbuttoned, the gown can be removed by the healthcare worker by grabbing the back of the gown (Figure 14) and pulling it away from the body, keeping the contaminated front part inside the gown (Figure 15).

Figure 13. Unbuttoning of the backside of the gown, performed by an assistant



Figure 14. Removal of gown: grabbing the back of the gown



Figure 15. Removal of gown: pulling the gown away from the body



Single-use gowns can now be disposed of; reusable gowns have to be placed in a bag or container for disinfection (Figure 16).

Figure 16. Placing the gown in a biohazard container for disinfection



After the gown, the goggles should be removed and either disposed if they are single-use, or placed in a bag or container for disinfection. In order to remove the goggles, a finger should be placed under the textile elastic strap in the back of the head and the goggles taken off as shown in Figure 17. Touching the front part of the googles which can be contaminated, should be avoided. If goggles with temples are used, they should be removed as shown in Figure 18.

Figure 17. Removal of goggles with textile elastic strap (steps 1 to 4)

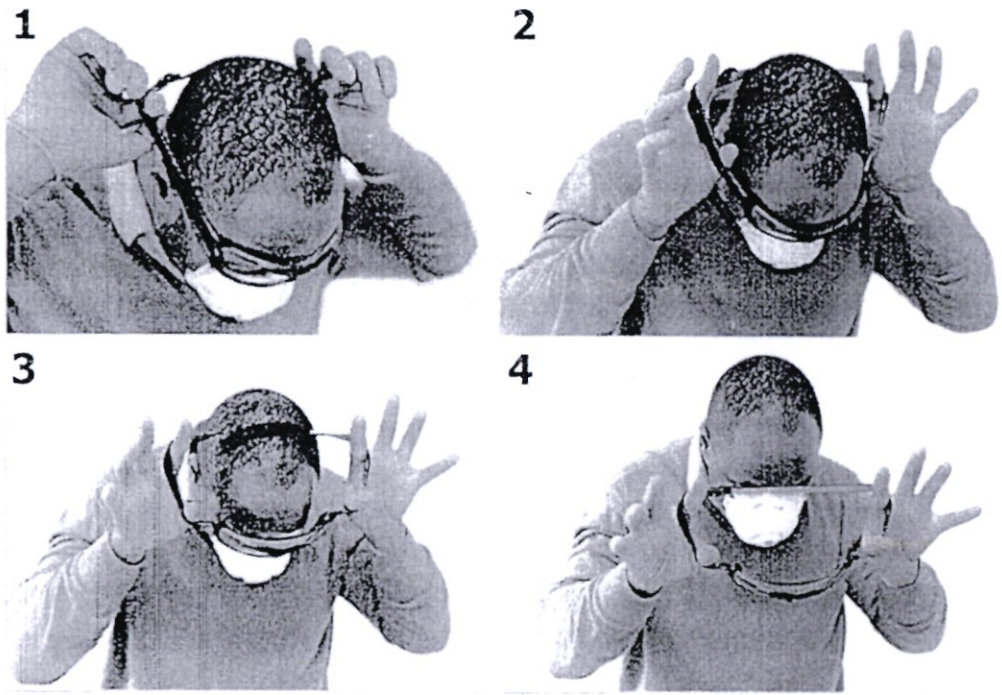
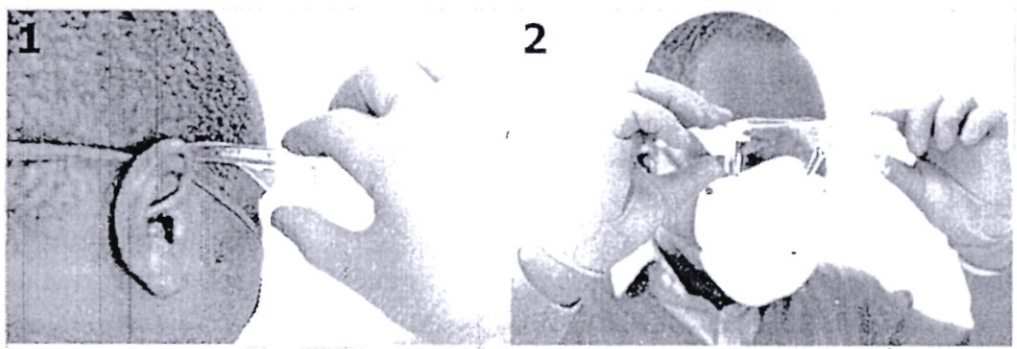


Figure 18. Removal of goggles with temples (steps 1 and 2)



The respirator should be removed next. In order to remove the respirator, a finger or thumb should be placed under the straps in the back and the respirator taken off as shown in Figure 19.

The respirator (or the surgical mask) should be disposed of after removal. It is important to avoid touching the respirator with the gloves (except for the elastic straps) during its removal.

Figure 19. Removal of respirator (steps 1 through 4)



The last PPE items that should be removed are the gloves. Use of alcohol-based solution should be considered before removing the gloves. The gloves should be removed in accordance with the procedure described above. After glove removal, hand hygiene should be performed.

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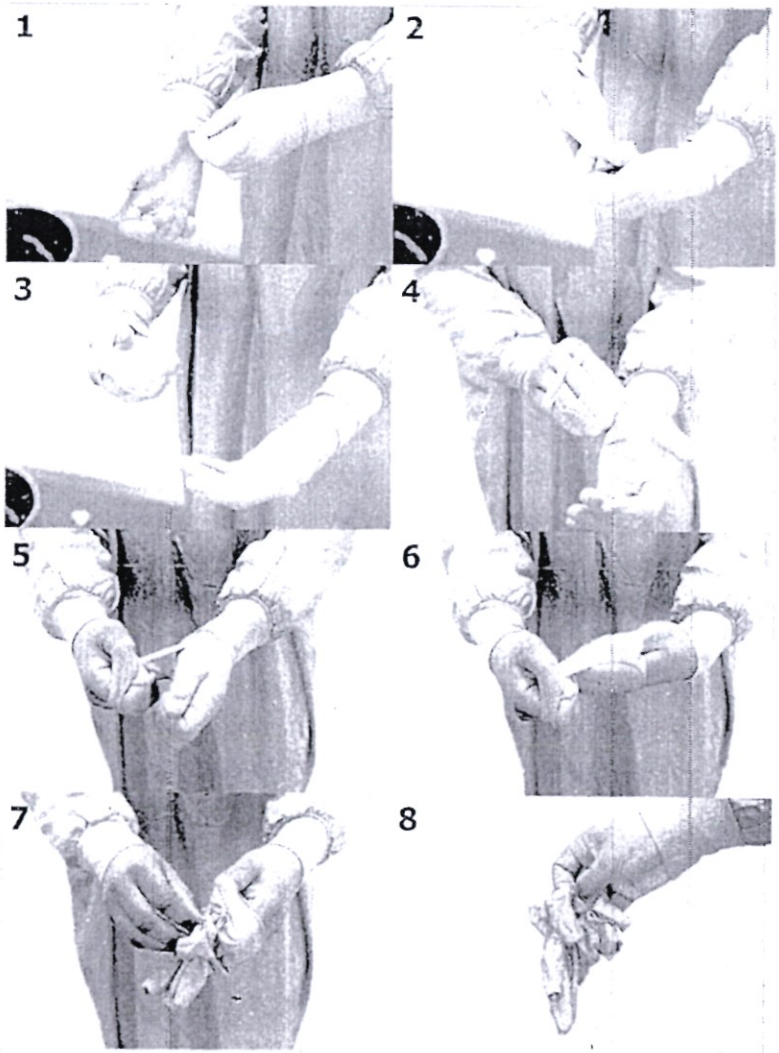
Figure 20. Removal of gloves (steps 1 through 8)



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APPENDIX 3

Notes on Testing:

All testing and reporting are coordinated by the Head of the Naticnal lab. All requests for testing should be directed to the EOC (0732353535/0729471414)

There are currently 4 labs that can test samples - National Influeza centre at the National Public Health laboratory (NIC), KEMRI labs in Nairobi, Kilifi and Kisumu.

Counties and facilities should identify and train clinical and lab personnel to collect samples.

Counties should identify and put in place at least 2 RRT teams who should be available to support case investigation, sample collection and transport to the lab.

For persons calling the Hotline number 719 from home or small health care facilities with no isolation capacity, the county/subcounty RRT team will respond and send a team to:

- assess whether the patient meets the case definition
- Collect a sample and transport to the lab
- Transfer patient to an appropriate isolation facility

For private hospitals in Nairobi, the facility should facilitate collection and delivery of a sample to the NIC, private hospitals in the counties should coordinate with the county RRT team.

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Figure 21: LAB FLOW



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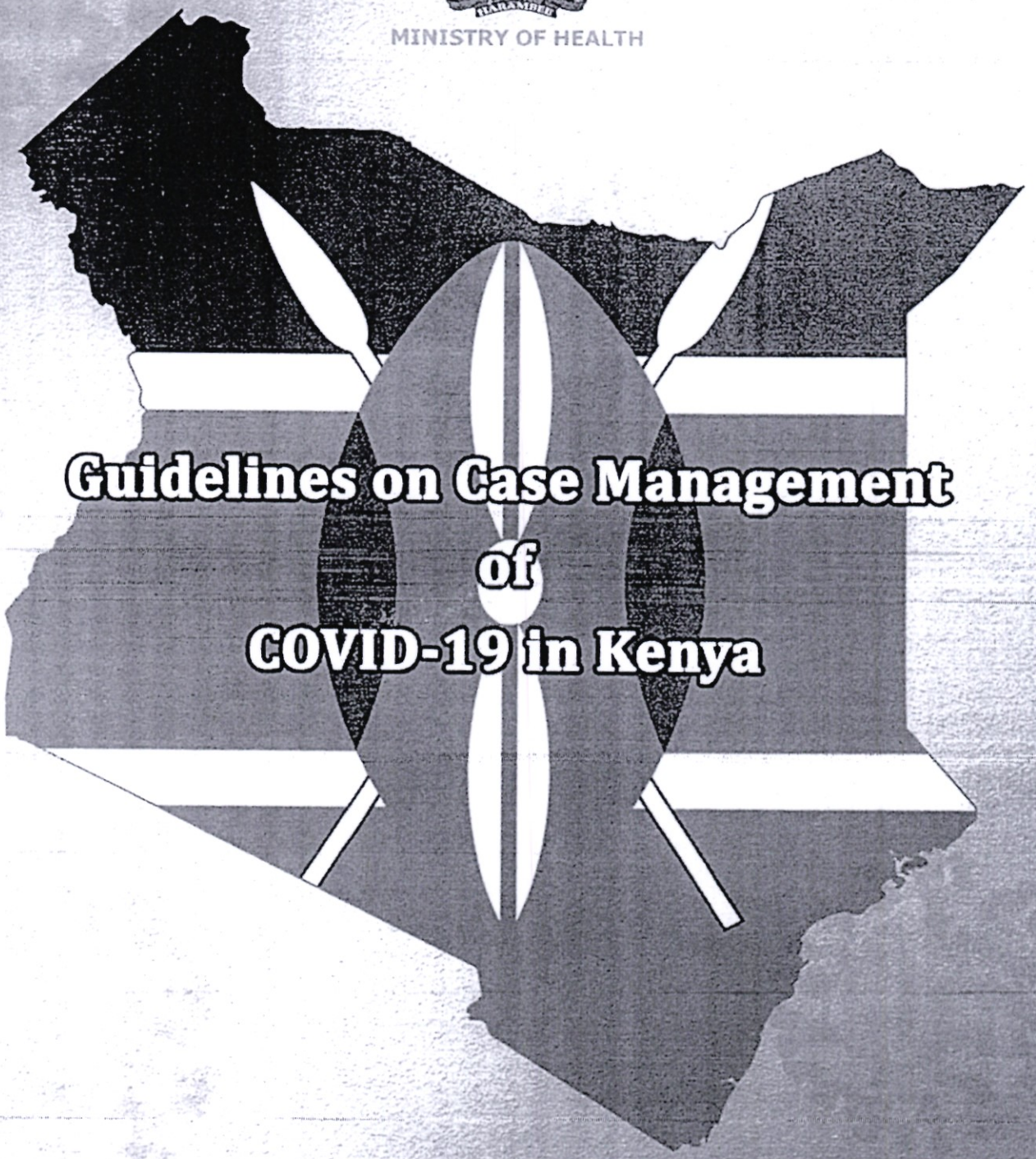
REPUBLIC OF KENYA

MINISTRY OF HEALTH



Guidelines on Case Management of COVID-19 in Kenya

2021 Edition

Foreword

It has been over a year since Kenya identified the first case of COVID-19 in the country. The Government formed the National COVID-19 task force, which supported the country's response through multi-sectoral technical working groups on testing, case management, risk communication and community engagement among others. An earlier version of the COVID case management guideline was released in April 2020 and capacity building of health care workers on diagnosis and treatment of COVID-19 was quickly carried out, even as counties prepared themselves by setting up isolation centres and supplies.

As at 18th of July, 2021, we have confirmed 192 758 people to have COVID-19, with 3775 deaths reported. Through all this, our health care workers are now armed with more knowledge on COVID-19, they have learnt who is at risk for severe COVID-19, they have learnt what treatment works and, in some cases, what does not work. We know which public health measures we need to focus on in order to combat the pandemic, and also have a few more shields in our armament, such as the COVID-19 vaccines.

These consolidated guidelines for the prevention, control and management COVID-19 in Kenya provide updated recommendations for comprehensive prevention and case management strategies in Kenya. They cover infection prevention and control measures including the use of vaccines. They also target the diagnosis and case management of COVID-19. These guidelines come at a critical time, especially since we continue to see several waves of the pandemic, to build the capacity of health care workers to handle patients with COVID-19 from their diagnosis, treatment and management.

This has been a collaborative effort bringing together health workers from all sectors-our universities, private and government facilities managing COVID-19 clients to determine and institute the best practices in their management.

We look forward to health workers using these guidelines to improve the quality of care given to all Kenyans, as we strive towards a healthy and productive nation.

Dr. Patrick Amoth, EBS
Ag. Director General for Health
Ministry of Health.

Acknowledgement

The Guidelines on Case Management of COVID-19 in Kenya 2021, have been developed through the contribution of many individuals and institutions that are committed to improving the outcome of persons infected with COVID-19, and reducing the risk associated with inappropriate therapies.

The Kenyan Ministry of Health wishes to thank all the contributing authors, led by the case management subcommittee of the National COVID-19 task force, for their expertise and time given to the wiring of these guidelines.

I take this opportunity to appreciate the efforts the following team of experts, led by Dr. Loice Achieng Ombajo, who wrote this guideline: Dr. Marybeth Maritim, Dr. Felix Riunga, Dr. Reuben Okioma, Dr. Anne Mugera, Dr. Fred Wangai, Dr. Christabel Khaemba, Dr. Duncan Nyukuri, Dr. Phoebe Juma, Dr. Agatha Olago, Dr. Andrew Owuor, Margaret Ogonga and Dr. Rosemary Wanjiru. I thank Collins Etemesi for working on the design and layout of the document. I also appreciate the efforts of the team that reviewed and contributed to the finalisation of this document as indicated in the list of contributors.

I acknowledge the tremendous support provided by the University of Nairobi and the World Health Organisation towards the finalisation of this guideline.

Brig. (Dr.) Francis Kuria,
Ag. Head, Directorate of Public Health
Ministry of Health.

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List of Abbreviations

AEFI	-	Adverse Events Following Vaccination
ARI	-	Acute Respiratory Infection
ARDS	-	Acute Respiratory Distress Syndrome
APRV	-	Airway Pressure Release Ventilation
BP	-	Blood Pressure
Bpm		Beats/minute
BVM	-	Bag Valve Mask
EMS	-	Emergency Medical Services
CPAP	-	Continuous Positive Airway Pressure
COVID-19	-	Coronavirus Disease 2019
FiO2	-	Fraction of inspired oxygen
IPC	-	Infection Prevention and Control
LRT	-	Lower Respiratory Tract
MAP	-	Mean Arterial Pressure
NIV	-	Non-invasive Ventilation
OI	-	Oxygenation Index
OSI	-	Oxygenation Index using SpO2
PaO2	-	Partial Pressure of Oxygen
PCR	-	Polymerase Chain Reaction
PEEP	-	Positive End-Expiratory Pressure
PPE	-	Personal Protective Equipment
RRT	-	Rapid Response Team
RT-PCR	-	Reverse Transcriptase – Polymerase Chain Reaction
SBP	-	Systolic Blood Pressure
SARI	-	Severe Acute Respiratory Illness
SARS-COV-2	-	Severe Acute Respiratory Syndrome – Coronavirus -2
SD	-	Standard Deviation
SIRS	-	Systemic Inflammatory Response Syndrome
SpO2	-	Oxygen Saturation
URT	-	Upper Respiratory Tract
ROX	-	Respiratory Oxygenation Index

Chapter 1: Introduction to COVID-19

Coronavirus disease 2019 (COVID-19) is an acute respiratory infection caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (1). SARS-CoV-2 belongs to the Sarbecovirus subgenus of the Coronaviridae family, and is the seventh coronavirus known to infect humans. Coronaviruses are a large family of enveloped RNA viruses, some of which cause illness in people (e.g., common cold, SARS, MERS), and others that circulate among mammals (e.g., bats, camels) and birds (2). Rarely, animal coronaviruses can spread to humans and subsequently spread between humans. Similar to SARS and MERS, it is thought that human transmission occurs via respiratory droplets produced when a person sneezes or coughs and, aerosol in certain circumstances including airway manipulation. The situations where aerosol generation occurs include coughing, nebulization, tracheal intubation and airway suctioning (1).

WHO first declared COVID-19 to be a public health emergency of international concern on 30 January 2020 and subsequently declared it a pandemic on 11th March, 2020. The pace at which COVID -19 spread throughout the world and in Kenya was hitherto unprecedented. Kenya discovered the first documented case of COVID-19 within its borders on 13th March, 2021 and as at 18th July 2021, the total number of confirmed cases was reported as 192,758, with 3775 deaths since the beginning of the outbreak (3). COVID-19 is highly transmissible and infectious, and runs the risk of overwhelming the capacity of the health system, with the need to support not just those with COVID-19, but also those with other illnesses. A lot of efforts have gone into reducing transmission of the virus, including restrictions on gatherings, contract-tracing, quarantine and isolation. With the spread of COVID-19 in the communities, the importance of preventive public health measures such as hand-washing and proper use of face-masks cannot be overemphasised. The introduction of the COVID-19 vaccines with a focus on groups at high risk such as health-workers and persons aged above 58 years and those who have comorbidities such as Diabetes Mellitus and Hypertension has added another prong to prevention measures against COVID-19.

The most common symptoms of COVID-19 include cough, loss of smell and/or taste, fever, difficulty in breathing, headache, sore throat, running nose, chest pain, myalgia, fatigue, general weakness and diarrhoea. The most common clinical presentation is that of a respiratory infection with a symptom severity ranging from a mild common cold-like illness (estimated to be 80% of cases), to a severe viral pneumonia in approximately 14%, leading to acute respiratory distress syndrome that is potentially fatal in about 5%. Current estimates of the incubation period range from 1 to 14 days, with a median incubation period of five to six days (4). Transmission can occur during the incubation period, even in the absence of symptoms.

Certain groups of people are at higher risk for transmission and severe disease including healthcare workers who work with COVID-19 patients. Vulnerable and marginalized groups such as people with disabilities may face challenges in accessing healthcare and have worse outcomes from COVID-19.

People of any age can catch COVID-19, but it most commonly affects middle-aged and older adults. The risk of developing severe COVID-19 disease increases with age from age 58. More than 80% of COVID-19 deaths occur in people over age 65, and more than 95% of COVID-19 deaths occur in people older than 45(5). Some conditions can result in higher severity of disease in adults of any age;

- Diabetes Mellitus (Type 1 or 2)
- Heart conditions (such as heart failure, coronary artery disease, cardiomyopathies or hypertension)

- Overweight and Obesity
- Smoking
- Cancer
- Chronic Kidney Disease
- Chronic lung diseases, including COPD (chronic obstructive pulmonary disease), asthma (moderate-to-severe), interstitial lung disease, cystic fibrosis, and pulmonary hypertension
- HIV Infection
- Immune Suppression
- Liver Disease
- Pregnancy
- Sickle cell disease
- Solid organ or blood stem cell transplant
- Cerebrovascular disease
- substance use disorders

Clinical manifestations of COVID-19 are generally milder in children compared with adults. Symptomatic children may present with non-respiratory symptoms such gastroenteritis more frequently than adults. An acute hyperinflammatory syndrome leading to shock or multi-organ failure has been described, known as the Multisystem Inflammatory Syndrome (MIS-C) which is temporally associated with COVID-19 in children and adolescents.

A notable challenge in the war against the pandemic appears to be the rate at which mutations occur, resulting in several variants of concern such as the Delta Variant B.1.617.2, that have been noted to be more transmissible and evade the immune system, resulting in more infections and increased severity of the disease. This brings out the importance of strengthening public health measures and vaccination strategies early in the response.

This document offers guidance on the following areas of COVID-19 management: case definition, infection prevention and control, diagnosis, stratification of patients according to severity of illness, management of asymptomatic, mild, severe and critical illness, management of co-morbidities such as diabetes in the context of COVID-19, discharge and de-isolation, management of post-acute covid illness and issues related to COVID-19 vaccination.

This is a living document and will be updated from time-to-time as more data and evidence becomes available.

Suspected case of SARS-CoV-2 infection:

1. **A person who meets the clinical AND epidemiological criteria:**

Clinical criteria:

- Acute onset cough AND fever; OR
- Acute onset of ANY TWO OR MORE of the following signs or symptoms:

Cough, fever, loss of taste or smell, difficulty breathing, sore throat, running nose, chest pain, fatigue/general weakness, headache, diarrhoea, altered mental status (Children may present with atypical symptoms)

AND

Epidemiologic criteria:

- Residing, working or travel (within the last 14 days) to an area with high risk of transmission of virus (In Kenya, this will be as reported by the Ministry of Health
- Where there is widespread community transmission in several regions of the country, then all patients will be considered to have met epidemiologic criteria
- Working in a healthcare facility
- International travel in the last 14 days

2. **A patient with severe acute respiratory illness (SARI)**

(SARI: Acute respiratory infection with or without fever; and cough; with onset within the last 10 days; and requires hospitalization)

Probable case of SARS-CoV-2 infection

- **A patient who meets clinical criteria above AND is a contact of a probable or confirmed case, or linked to a COVID-19 cluster**
- **A suspected case with chest imaging showing findings suggestive of COVID-19 disease**
- Recent onset loss of taste or loss of smell with no other identified cause
  (Common imaging findings include bilateral peripheral opacities with lower lung distribution. Opacities usually ground glass opacities that may progress to consolidations)
- Unexplained death in an adult with SARI prior to death AND had contact with a probable or confirmed case or linked to a COVID-19 cluster

Confirmed case of SARS-CoV-2 infection

- A person with a positive SARS-CoV-2 PCR test
- A person with a positive SARS-CoV-2 Antigen RDT AND meeting criteria for either suspected or probable case; OR has contact with a probable or confirmed case.

Multisystem Inflammatory Syndrome in Children (MIS-C

- Preliminary case definition: Children and adolescents 0–19 years of age with fever > 3 days
  AND
- Two of the following: rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet); hypotension or shock; features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities; evidence of Coagulopathy, acute gastrointestinal problems;
  AND
- No other obvious microbial cause of inflammation
  AND
- Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19.

Chapter 2: Infection Prevention and [illegible] COVID-19

Introduction

- The main aim for IPC is to prevent or limit the spread of SARS-COV 2 at all levels of healthcare

Facility preparedness

All facilities should have:

- An IPC program or a dedicated IPC focal person
- A functional screening and triage area for early case identification
- A holding area for cases awaiting results or transfer
- A mechanism to ensure standard and transmission-based precautions.
- Adequate healthcare workers to provide 24-hour patient care without exhaustion.
- A plan to conduct health worker exposure risk assessment
- Continuous training and refresher courses to the existing staff and any new staff.
- Adequate IPC supplies and equipment

1. Quarantine and Isolation

Quarantine

Quarantine is separation and restricted movement of well persons who have been exposed to persons with COVID-19. It can be applied at the individual, family or community level. All persons who have had contact with a confirmed case of COVID 19 should quarantine for 14 days and get a COVID 19 test if they develop any symptoms. Quarantine can either be self-quarantine or carried out at a designated facility.

Instructions for self-quarantine include:

- Limit the number of visitors
- Continue to observe respiratory hygiene and cough etiquette
- Observe hand hygiene by either use of soap and water or an alcohol-based hand rub
- Ensure proper ventilation of the facility or home
- Observe for fever or other symptoms daily.
- Watch for danger signs or signs of deterioration like dyspnoea and report to a health facility
- Use of either separate utensils or disposable utensils

Isolation

Isolation is the separation of sick people with a contagious disease from people who are not sick. All confirmed COVID-19 cases identified should be isolated. The location of isolation can be in a health facility for those with severe illness, at home for those who meet the self-isolation criteria or at a community isolation facility. Isolation precautions may be dropped 10 days after onset of symptoms, provided that one has had no fever without antipyretics for at least 24 hours.

Requirements for an isolation center

- The isolation facility should be set up relatively away from the main hospital facility or can be a designated isolation space set up with an exclusive passage at the entrance and exit to assist in proper flow of patients and staff.
- Should have provision for hand hygiene and waste management
- The designated area should have the three zones which can be colour coded green, red and the decontamination area. Zoning helps with cohorting of patients. The Green zone is the clean area where staff and persons who are presumed to not be infected can access. The red zone is the contaminated area such as the isolation ward for COVID-19 positive cases.
- Any COVID-19 service area, either outpatient, inpatient or clinic should have the 3 zones

GREEN ZONE areas (clean area)

1. Nurses and doctors' rooms and stations.
2. Medication preparation room
3. Tea room
4. Patients' pantry room
5. Non health workers offices

The area should accommodate minimal staff at any specific time to prevent infections

RED ZONE areas (Patient's area) -contaminated

1. Triage, Examination rooms and filter clinics where patients will be cohorted in groups according to signs and symptoms
2. Patients wards and isolation room, if possible, with negative pressure or well-ventilated rooms with beds spaced 1-2 meters apart
3. Laboratory or laboratory specimen holding area, if possible, with a refrigerator
4. Theatre, Critical care Unit, and delivery room

DECONTAMINATION ZONE areas (contaminated area)

1. Body holding area with a gate leading to the farewell home where bodies will be packed ready for collection to the farewell home
2. Equipment cleaning area where equipment will be cleaned and decontaminated before being taken for sterilization
3. Linen decontamination area
4. Boots and staff cleaning room
5. Waste management area

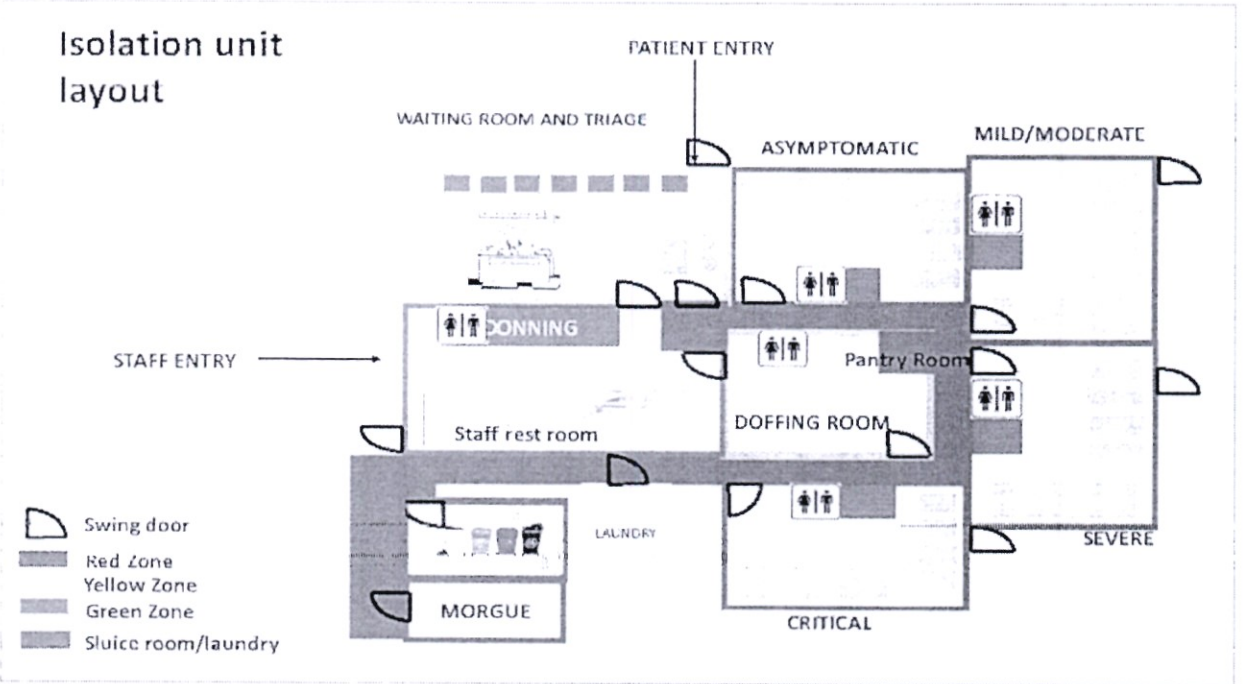


Figure 1: Facility Patient flow

Table 1: PPE to Be Provided to Staff According to Risk Categories

PROTECTION LEVEL	PROTECTIVE EQUIPMENT	SCOPE OF APPLICATION
	• Disposable surgical mask • Facility uniform • Gloves	• Triage • Outpatients' clinic • Private clinics
[illegible]	• Facility uniform • N95 mask • Caps • Waterproof Surgical gowns • Gloves • Eye protection e.g., face shield or goggles • Plastic apron	• Covid 19 clinics • Isolation wards and CCU • Radiology Unit for confirmed covid 19 patients • Decontamination and cleaning unit (public health) • Laboratory • Farewell home
LEVEL 3 PROTECTION	• Disposable scrubs • N95 mask • Waterproof surgical gown • Plastic apron • Face shield or goggle if available • Caps • Gloves	• During suctioning • Intubation • Bronchoscopy • Surgery • Endoscopy or colonoscopy

- Give the patient with suspected COVID-19 a medical mask and direct the patient to a separate area or an isolation room if available.
- Keep at least 1 meter distance between patients with suspected COVID-19 and other patients.
- Ensure areas are well ventilated with good airflow
- Instruct all patients to cover nose and mouth with tissue or flexed elbow during coughing or sneezing
- Perform hand hygiene after contact with patient or patient environment
- Use posters signage, audios and television clips advising all patients and relatives on signs and symptoms of COVID- 19 and IPC measures
- Parents/caregivers need to support their children in maintaining cough hygiene by ensuring the child wears the mask or if the child becomes irritable and unable to tolerate the mask, the parent/caregiver should ensure they provide tissue for the child to cough into.
- Parents should ensure they guide hand washing for young children using soap and water.
- Ensure rational use of PPE in order to avoid wastage.

These include

- Hand hygiene before and after contact with patients and patient environment
- Waste management
- Respiratory hygiene
- Rational use of PPE
- Physical distancing
- Environmental cleaning

Apply contact and droplet precautions:

Droplet precautions prevent large droplet transmission of respiratory viruses

- Perform hand hygiene after touching each patient or patient environment
- Use a medical mask if working within 1-2 metres from the patient
- Rational use of PPE for contact and droplet precaution (Gloves, medical masks, gown and Apron)
- Place patients in single rooms, or group together those with the same etiological diagnosis
- If an etiological diagnosis is not possible, cohort patients with similar clinical diagnosis and epidemiological risk factors, with a spatial separation
- When providing care in close contact with a patient with respiratory symptoms (e.g., coughing or sneezing), use eye protection (face-mask or goggles)
- Limit patient movement within the institution and ensure that patients wear medical masks when outside their rooms and that patients' clean hands frequently either by washing with soap and water or use an alcohol hand rub

- Ensure that health care workers refrain from touching their eyes, nose, and mouth with potentially contaminated gloves or ungloved hands
- Avoid contaminating environmental surfaces that are not directly related to patient care (e.g., door handles and light switches)
- Ensure vehicles and ambulances for transporting patients are cleaned and disinfected regularly

Apply airborne precautions when performing an aerosol generating procedure

- Ensure that healthcare workers obtaining nasopharyngeal swabs, performing dental procedures and performing aerosol-generating procedures (i.e., open suctioning of respiratory tract, intubation, bronchoscopy, cardiopulmonary resuscitation) use PPE, including gloves, long-sleeved gowns, eye protection, and fit-tested particulate respirators (N95 or equivalent, or higher level of protection)
- When possible, use adequately ventilated single rooms when performing aerosol-generating procedures. This could be either, meaning negative pressure rooms or well-ventilated single rooms
- Minimize the number of individuals present during the aerosol-generating procedure by avoiding the presence of unnecessary individuals in the room
- Care for the patient in the same type of room after mechanical ventilation commences

Cleaning and disinfection

- All surfaces in health facilities, especially frequently touched surfaces and those visibly soiled or contaminated by body fluids, should be **routinely** cleaned and disinfected.
- Use soap and water or enzymatic detergent for cleaning
- 0.5 % chlorine solution is recommended for routine disinfection.
- Patients' linen should be laundered in the decontamination zone and disinfected with 0.05 % chlorine solution
- Tubing and surgical equipment should be cleaned and disinfected following recommended guidelines
- On discharge, the patient's belongings should also be decontaminated and patient asked to take a shower prior leaving the isolation facility

Infectious Period

Persons with COVID-19 should be considered potentially infectious from two days before to 10 days following illness onset. Persons who continue to be ill longer than 7 days after illness onset should be considered potentially contagious up to 20 days. Children, especially younger children, might potentially be contagious for longer periods.

Non-hospitalised ill persons who are a confirmed or suspected case of COVID-19 are recommended to stay at home (home isolation) for at least the first 10 days after checking with their health care provider about any special care they might need if they are pregnant or have a health condition such as diabetes, heart disease, asthma, or other chronic lung disease.

Preparing and packing the body for transfer from a patient room in a health facility to an autopsy unit, mortuary, crematorium, or burial site

- Ensure that personnel who interact with the body (health-care or mortuary staff, or the team preparing the body for burial or cremation) apply infection prevention and control (IPC) standard and transmission-based precautions after performing a risk assessment.
- Prepare the body for transfer including removal of all catheters and other indwelling devices.
- If an autopsy is to be performed, follow local guidance on the procedures for preparation of the body.

Autopsy

- If necessary, use level 3 PPE for conducting autopsies

Burial or cremation

- Follow national and local regulations during burials and cremations
- Family and friends may view the body after it has been prepared for burials
- Those tasked with placing the body in the grave should observe contact precautions
- If a body will be buried or cremated without a casket or body bag, use surgical or waterproof rubber gloves to place the body in the grave and perform hand hygiene afterwards.
- The number of individuals conducting the burial or cremation should be kept at a minimum.

Donning and Doffing Steps (refer to figure 2 and 3)

Donning: putting on the personal protective equipment.

Doffing; Taking off the personal protective equipment.

- Each facility should prepare a room for donning which should be on the green zone and the doffing should be in the decontamination area, each of the rooms should have instructions on the steps and a full-length mirror to use during the steps.
- The donning area should be at the entry of the GREEN zone and the doffing at the DECONTAMINATION zone
- At the donning area there should be a log book indicating the entry time and body temperature and the doffing should have an exit book this is to approximate the time spent in the Covid treatment unit.
- A bathroom should be available at the doffing area

Rehydration is encouraged after exit to replace lost fluids after the ward procedures

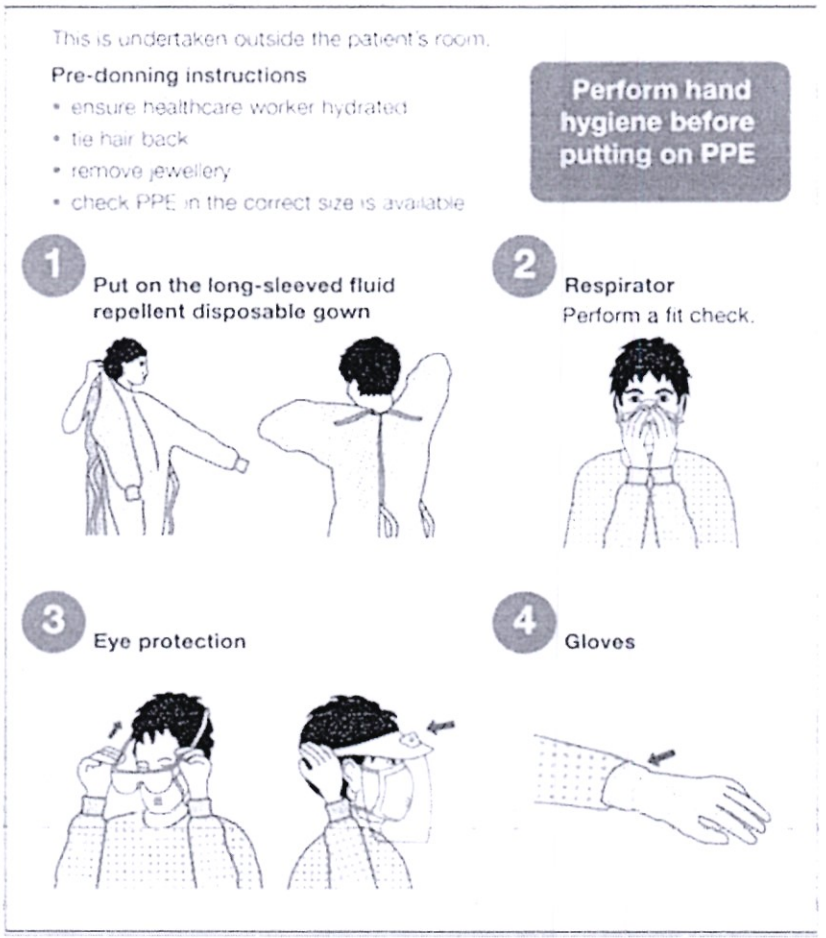


Figure 2: Pre donning instructions

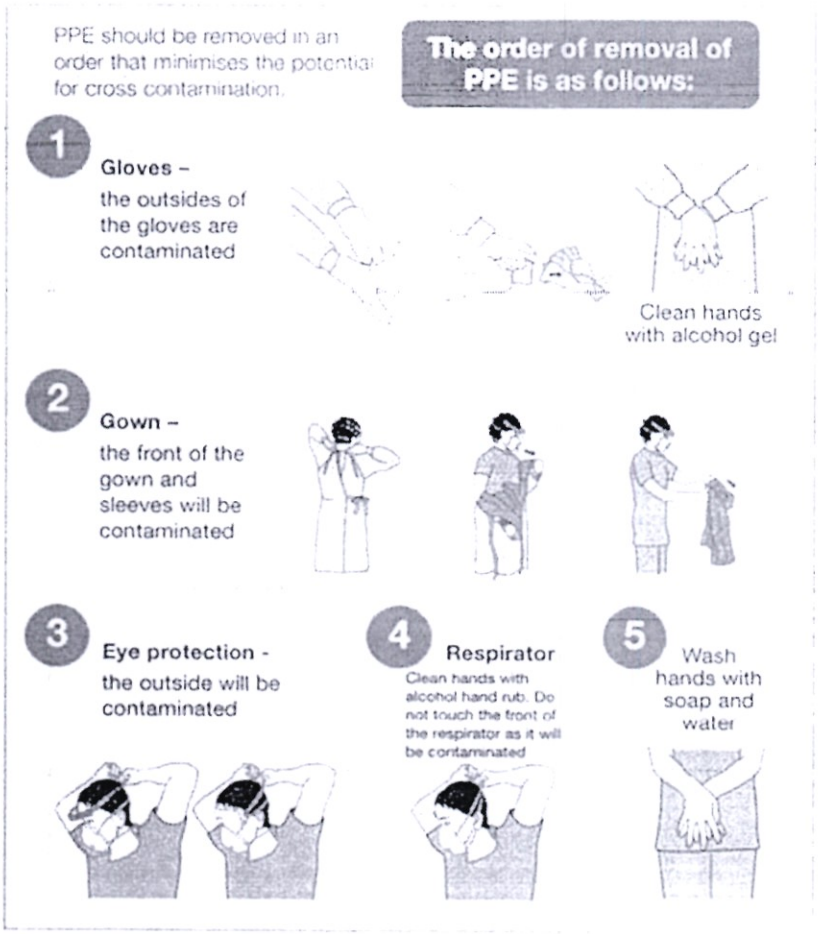


Figure 3: Order of removal of PPE

Chapter 3: Diagnosis of COVID-19

This chapter aims to provide guidance on who to test for COVID-19 and the preferred tests to use in the clinical setting. Testing is only recommended for diagnosis and not as an indicator of recovery from COVID-19. Testing should be offered to all persons meeting the case definition (refer to case definition on page 3)

3.1 Laboratory Tests

Nucleic Acid Amplification Tests (NAATs) such as the SARS-CoV-2 Polymerous Chain Reaction (PCR) are the preferred initial tests. Where access to a PCR test is limited or too costly then SARS-CoV-2 antigen testing can be utilized. Turn-around times for antigen tests are generally shorter than for PCR testing and thus an antigen test can help with quick identification of COVID-19 cases. Sensitivity of antigen tests is lower than that of NAATs. Therefore, a negative test may warrant confirmation by a PCR test in symptomatic patients. A positive antigen test does not warrant confirmation unless the patient is asymptomatic and the diagnosis is in doubt.

Serological tests i.e., SARS-COV-2 antibody detection tests should not be used for diagnosis of COVID-19. They can only be used to check for previous infection for example in the setting of serological surveys.

Indeterminate PCR test results usually indicate that only one of the 2 or more target genes being tested for was identified. These tests should be considered presumptively positive.

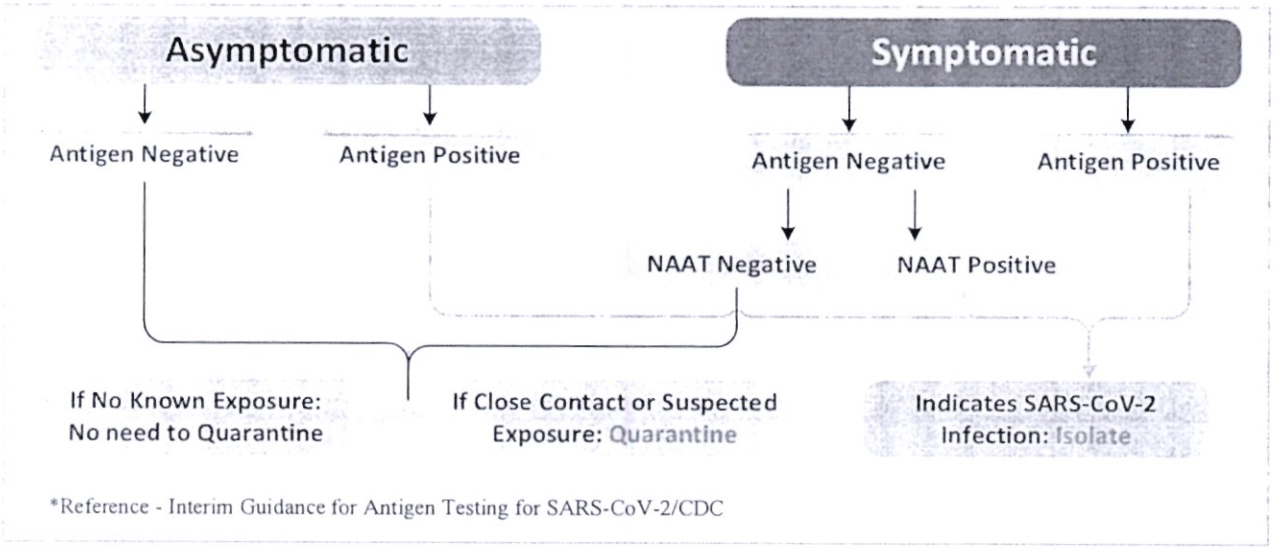


Figure 4: Antigen Testing Algorithm.

Specimens can be taken from the upper respiratory tract or the lower respiratory tract. Upper respiratory tract samples include nasopharyngeal swabs, oropharyngeal swabs and nasopharyngeal aspirates. Lower respiratory tract specimens include bronchoalveolar lavage specimens and expectorated sputum.

- Collect specimens from the upper respiratory tract (URT; nasopharyngeal and oropharyngeal) AND, where clinical suspicion remains and URT specimens are negative, collect specimens from the lower respiratory tract when readily available (LRT; expectorated sputum, endotracheal aspirate, or broncho-alveolar lavage in ventilated patient) for SARS-CoV-2 testing by RT-PCR and bacterial stains/cultures.

NB:

- Use appropriate PPE for specimen collection (droplet and contact precautions for URT specimens; airborne precautions for LRT specimens). When collecting URT samples, use viral swabs (sterile Dacron or rayon, not cotton) and viral transport media. Do not sample the nostrils or tonsils. In a patient with suspected SARS-CoV-2, especially with pneumonia or severe illness, a single negative URT sample does not exclude the diagnosis, and additional URT and LRT samples are recommended. LRT samples are more likely to be positive and for a longer period. Clinicians may elect to collect only LRT samples when these are readily available (for example, in mechanically ventilated patients). Sputum induction should be avoided due to increased risk of increasing aerosol transmission.
- Samples should be collected in a timely manner for clinical management and outbreak control. Ensure that staff responsible for collection of samples are well trained and available. Samples should be transported to the laboratory using Viral Transport Media and should be triple packaged. For further details on sample collection please refer to the Ministry of Health Targeted Testing Strategy for Coronavirus disease 2019 (COVID 19) in Kenya.

The role of radiological tests for diagnosis of COVID-19

Imaging including chest radiographs and high-resolution CT scans are useful in monitoring of the clinical course and evaluating disease severity. Chest CT scan images from patients with COVID 19 typically demonstrate bilateral peripheral ground glass opacities which are non-specific. These can be found other kinds of pneumonia. This makes the diagnostic value of chest CT scan in COVID 19 low and dependent on radiographic interpretation. Given the variability in chest imaging findings, chest radiograph or CT scan alone is not recommended for the diagnosis of COVID 19. [22]

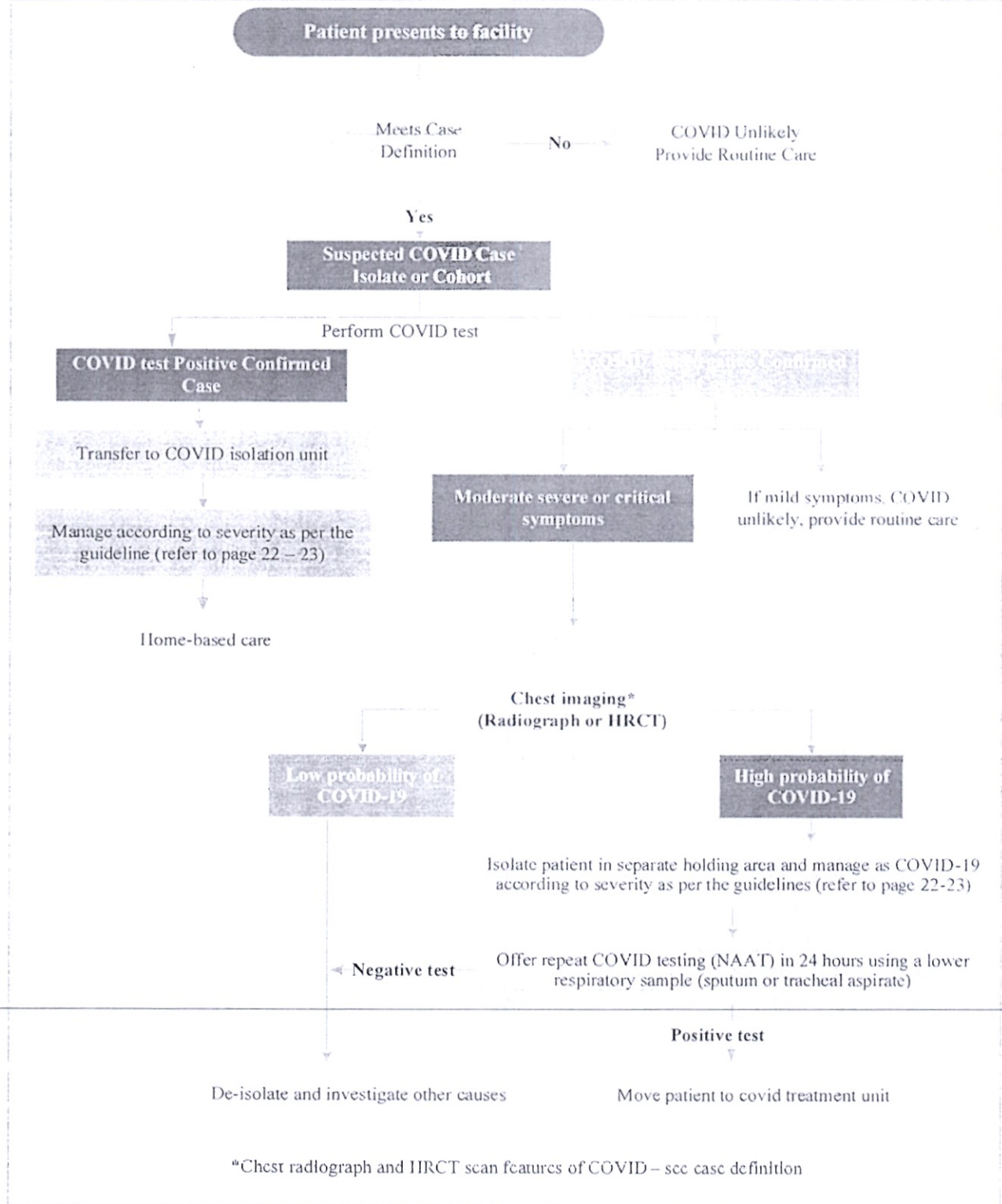


Figure 5: Triage and management of a patient presenting with symptoms of Covid 19

The management of patients with COVID-19 depends on severity of disease at presentation.

Once patient is CONFIRMED positive by a PCR or rapid antigen test categorize them into the following groups based on presentation

Table 2a: COVID-19 severity categorization in adults and adolescents

CATEGORY	FEATURES
1. Mild illness	Fever, cough, sore throat, malaise, headache, muscle pain BUT **No dyspnoea (shortness of breath)** and **No abnormalities on chest imaging**
2. Moderate illness	Clinical features of pneumonia (fever, cough, **dyspnoea**) AND/OR **radiological features of pneumonia** BUT **Oxygen saturations (SPO2) greater than or equal to 94% on room air**
3. Severe illness	Clinical and radiological features of pneumonia, tachypnea with RR>30 AND **oxygen saturation (SPO2) less than 94% on room air**
4. Critical illness	Features of severe illness AND Any of the following: • **respiratory failure** • **sepsis/septic shock** • **multiorgan dysfunction** • **acute thrombosis**

Table 2b: COVID-19 severity categorization in children

CATEGORY	FEATURES
1. Mild illness	Fever, cough, sore throat, malaise, headache, muscle pain **BUT** No dyspnoea (shortness of breath and No abnormalities on chest imaging
2. Moderate illness	Clinical signs of non-severe pneumonia (cough or difficulty breathing) **AND** Fast breathing* **AND/OR** chest indrawing *Fast breathing (in breaths/min): <2months: 360; 2-11months: 350; 1-5years: 340

	Child with clinical signs of pneumonia (cough or difficulty in breathing) + at least one of the following: • Central cyanosis or SPO2 <90%; • Severe respiratory distress (e.g., fast breathing*, grunting, very severe chest indrawing); • General danger sign: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions *Fast breathing (breaths/min): <2months: ³60; 2-11months: ³50; 1-5years: ³40
4. Critical illness	Features of severe illness AND Any of the following: • Acute respiratory distress syndrome • Respiratory failure requiring mechanical ventilation • Sepsis/Septic shock • Other organ failure requiring ICU care
5. MIS-C	Preliminary case definition: Children and adolescents 0–19 years of age with fever > 3 days **AND** Two/more of the following: • Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet); • Hypotension or shock; • Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities; • Evidence of coagulopathy, • Acute gastrointestinal problems; **AND** No other obvious microbial cause of inflammation **AND** Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19.

Supportive care

Supportive care should be offered to all patients diagnosed with COVID-19. This includes the following:

1. Counselling and psychosocial support
2. Symptomatic treatment
3. Adequate nutrition and hydration

Table 3: Management of asymptomatic, mild and moderate COVID-19

Asymptomatic or mild illness	**Assess for eligibility for home-based care** Patient qualifies if they have no risk factors for disease progression or poor outcomes (see below) and a suitable space is available at home (separate room with separate bathroom), has resources to access basic PPE for family members e.g., face masks and gloves, no house members who are increased risk of severe illness if exposed e.g., see below **Risk factors for poor outcome:** Age >60, coronary artery disease, stroke, diabetes, hypertension, cancer, chronic lung disease, frailty, pregnancy, immunosuppression, chronic kidney disease **Management** Symptomatic treatment for mild disease (paracetamol, antihistamines). **Steroids should NOT be used for patients with asymptomatic, mild or moderate disease.** (Isolation precautions as outlined in the IPC section)

Moderate illness	• Baseline tests - blood count, renal and liver function, HIV test, random blood sugar.
	• symptomatic treatment:
	  • Fever - Paracetamol
	  • Sore throat - gargles
	  • cough, nasal congestion - antihistamine
	• VTE prophylaxis with Enoxaparin 40mg once a day if admitted to a health facility
	  • Where enoxaparin is not available, use low dose unfractionated heparin at 5000units subcutaneous BD)
	  • Where patient unable to use standard anticoagulation therapy, consider use of direct-acting anticoagulants
	  • Consider prophylaxis for children older than 5 years with comorbidities and not ambulant. Refer to BNF for dosage guidelines for pediatrics
	Where there is pressure for space for isolation of patients, the following patients with moderate illness can be managed at home:
	• Young <60 years
	• Oxygen saturations >94% on room air
	• No comorbidities
	• Have easy access to a health facility in case of worsening of symptoms
	• Physically active

*Where the standard of care highlighted above cannot be offered to the patient due to contraindications or adverse reactions then consult a specialist

*Monitor patients for suspected adverse reactions and report at http://pv.pharmacyboardkenya.org/

Table 4: Management of severe and critical COVID-19

	• Baseline Tests (Total blood count, renal and liver function, HIV test, random blood sugar) • Symptomatic treatment • Oxygen supplementation to maintain SPO2s above 90% and above 92% in pregnant women (oxygen supplementation can be via nasal prongs, masks, non-rebreather masks or high flow nasal cannula - see below) • Dexamethasone 6mg per day for up to 10 days (where dexamethasone is not available, consider using prednisone 40 mg OD or methyl prednisone 32mg OD. This short duration of dosing does not require tapering) • For children - Dexamethasone 0.15mg/kg iv/PO OD to a maximum of 6mg or prednisolone 1mg/kg OD maximum 40mg OD, methylprednisolone 0.8 mg/kg IV OD maximum 32mg OD • VTE prophylaxis Enoxaparin 40mg OD once a day for the duration of hospitalization (Where enoxaparin is not available, use low dose unfractionated heparin at 5000units subcutaneous BD) • Self proning for 12 to 16 hours a day (see self-proning guide below) as tolerated
Critical Illness	• Baseline tests- total blood count, renal and liver function tests, HIV test, random bold sugar • Symptomatic treatment • Admit to a **Critical Care Unit.** • Mechanical Ventilation if no improvement in oxygenation with maximal oxygen flows with other modalities - see guide to noninvasive ventilation, tracheal intubation and ventilation below • Prone for 12 to 16 hours per day • Conservative fluid management i.e., give IV fluid only if hypovolemic • Closed suctioning of secretions where available • Give Dexamethasone 6 mg per day for up to 10 days (where dexamethasone is not available, consider using prednisone 40 mg OD or methylprednisolone 32mg OD. This short duration of dosing does not require tapering) • For children - Dexamethasone 0.15mg/kg iv/ PO OD to a maximum of 6mg or prednisolone 1mg/kg OD maximum 40mg OD, methylprednisolone 0.8 mg/kg IV OD maximum 32mg OD • VTE prophylaxis 40mg Enoxaparin OD SC (Where enoxaparin is not available, use low dose unfractionated heparin at 5000units subcutaneous BD) **Where possible, document advance directives for all patients e.g., do not resuscitate for patients who are unlikely to do well or have another terminal condition**

Should be done for all patients who are admitted and all patients with risk factors for poor outcomes: total blood count, random blood sugar, Urea Electrolytes Creatinine, Liver function tests. HIV testing should be offered to all patients.

Chest imaging is recommended in patients with severe illness who fail to improve on standard therapy and in all patients with critical illness. Include an ECG if indicated.

Where available a C-Reactive Protein (CRP) may be useful in managing patients who acutely deteriorate.

The following drugs may have a role in the management of COVID-19. Specialist input would be required in defining the appropriate patient population, weighing benefit against risk, and cost considerations. These agents are still investigational and under emergency use authorization. This means that a patient must be educated on the evidence around their use and must consent to their use prior to prescription. Their use should be reported to the Pharmacy and Poisons Board

Table 5: Other Therapeutic Agents

Drug	Mechanism of Action	Potential Indications
Tocilizumab	monoclonal antibody against IL-6	Hospitalized patients with severe and critical COVID-19 with disease progression and elevated markers of systemic inflammation (CRP >75) despite steroid use.
Baricitinib (with remdesivir)	Janus Kinase (JAK) 1 and 2 selective inhibitor	Hospitalized patients with severe COVID-19 with disease progression and elevated markers of systemic inflammation despite steroid use (Baricitinib alone) or in patients with severe COVID-19 in whom steroids are contraindicated (Baricitinib with remdesivir)
Remdesivir	an antiviral agent that inhibits SARS-Co-V-2 replication	Hospitalized patients with severe but not-critical COVID-19 who are within 10 days from the onset of symptoms. There is conflicting data on the use of remdesivir, with most clinical trials showing no mortality benefit. Some studies have shown that remdesivir may reduce duration of illness by few days and only if initiated very early after disease onset rather than at the time a patient is deteriorating.

Current evidence **does not support** the following interventions for treatment or prevention of COVID-19.

- Hydroxychloroquine or Chloroquine
  Azithromycin and empiric antibiotic therapy
- Ivermectin
- Convalescent plasma therapy
- Empiric therapeutic or intermediate dose anticoagulation
- Aspirin
- High dose steroids or steroid pulse or prolonged duration of steroid use beyond 10 days
- Vitamin C and D
- Zinc
- Ulinastatin
- Favipiravir

Mild illness	Moderate Illness	Severe Illness	Critical Illness
Fever, cough, sore throat, malaise, headache, muscle pain BUT **No dyspnoea (shortness of breath) and No abnormalities on chest imaging**	Clinical features of pneumonia (fever, cough, **dyspnoea**) AND/OR **radiological features of pneumonia** BUT **Oxygen saturations (SPO2) greater than or equal to 94% on room air**	Clinical and radiological features of pneumonia, tachypnea with RR>30 AND **oxygen saturation (SPO2) less than 94% on room air**	Features of severe illness AND Any of the following: • **respiratory failure** • **sepsis/septic shock** • **multiorgan dysfunction** • **acute thrombosis**

Assess for eligibility for home management
 	
Patient qualifies if has no risk factors for disease progression or poor outcomes (see below) and a suitable space is available at home(separate room with separate bathroom), has resources to access basic PPE for family members e.g. face masks and gloves, no house members who are increased risk of severe illness if exposed e.g. elderly, pregnancy
 	
Risk factors:
 	
Age >60, coronary artery disease, stroke, diabetes, hypertension, cancer, chronic lung disease, frailty, pregnancy, immunosuppression, chronic kidney disease
	• Baseline tests - blood count, renal and liver function, HIV test, random blood sugar.
	• symptomatic treatment.
	  ○ Fever - Paracetamol
	  ○ Sore throat - gargles
	  ○ cough, nasal congestion - antihistamine
	• VTE prophylaxis with Enoxaparin 40mg once a day if admitted to a health facility
	
	Where there is pressure for space for isolation of patients, the following patients with moderate illness can be managed at home:
	
	• Young <60 years
	• Oxygen saturations >94% on room air
	• No comorbidities
	• Have easy access to a health facility in case of worsening of symptoms
	• Physically active
		• Admit in ward with Oxygen
		• Baseline Tests (blood count, renal and liver function, HIV test, random blood sugar)
		• Symptomatic treatment
		• Oxygen supplementation to maintain SPO2s above 94% (oxygen supplementation can be via nasal prongs, masks, non-rebreather masks or high flow nasal cannula - see below)
		• Dexamethasone 6mg per day for up to 10 days (where dexamethasone is not available, consider using prednisone 40 mg OD or methylprednisone 32mg OD. This short duration of dosing does not require tapering)
		• VTE prophylaxis Enoxaparin 40mg OD once a day for the duration of hospitalisation (Where enoxaparin is not available, use low dose unfractionated heparin at 5000units subcutaneous BD)
		• Self proning for 12 to 16 hours a day (see self proning guide below) as tolerated
			• Admit to a **Critical Care Unit.**
			• Baseline Tests (blood count, renal and liver function, HIV test, random blood sugar)
			• Symptomatic treatment
			• Mechanical Ventilation if no improvement in oxygenation with maximal oxygen flows with other modalities - see guide to non invasive ventilation, tracheal intubation and ventilation below
			• Prone for 12 to 16 hours per day
			• Conservative fluid management i.e. give IV fluid only if hypovolemic
			• Closed suctioning of secretions where available
			• Give Dexamethasone 6 mg per day for up to 10 days (where dexamethasone is not available, consider using prednisone 40 mg OD or methylprednisolone 32mg OD. This short duration of dosing does not require tapering)
			• VTE prophylaxis 40mg Enoxaparin OD SC (Where enoxaparin is not available, use low dose unfractionated heparin at 5000units subcutaneous BD)
			
			Where possible, document advance directives for all patients e.g. do not resuscitate for patients who are unlikely to do well or have another terminal condition

Figure 6a: Management Algorithm for the adult patient with COVID-19

Mild Illness			Critical Illness	MIS-C
Fever, cough, sore throat, malaise, headache, muscle pain **BUT** no dyspnoea (shortness of breath) and No abnormalities on chest imaging	Clinical signs of non-severe pneumonia (cough or difficulty breathing) **AND** Fast breathing AND/OR chest indrawing Fast breathing (breaths/ min): <2months: ≥60; 2-11months: ≥50; 1-5years: ≥40	Child with clinical signs of pneumonia (cough or difficulty in breathing) + at least one of the following: Central cyanosis or SPO2 <90%; severe respiratory distress (e.g., fast breathing, grunting, very severe chest indrawing); general danger sign: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions Fast breathing (breaths/ min): <2months: ≥60; 2-11months: ≥50; 1-5years: ≥40	Any of the following: Acute respiratory distress syndrome, Respiratory failure requiring mechanical ventilation, Sepsis/Septic shock, other organ failure requiring ICU care	Case definition: Children and adolescents 0–19 years of age with fever > 3 days **AND** Two of the following: rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet), hypotension or shock; features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities; evidence of Coagulopathy, acute gastrointestinal problems; AND No other obvious microbial cause of inflammation AND Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19.

Assess for eligibility for home-based isolation and care
 	
Counsel caregiver on the following danger signs and when to return: difficulty breathing, fast breathing, grunting, inability to breastfeed/ drink, central cyanosis, confusion, reduced level of consciousness.
	• Baseline tests – Total blood count, renal and liver function, HIV test, random blood sugar.
	• Symptomatic treatment:
	  • Fever - Paracetamol
	  • Sore throat and cough-sooth the throat with safe remedies
	  • VTE prophylaxis with Enoxaparin: Consider prophylaxis for children older than 5 years with comorbidities and not ambulant. Refer to annex for paediatric dosage guidelines.
		• Admit in ward with Oxygen
		• Baseline Tests (Total blood count, renal and liver function, HIV test, random blood sugar)
		• Symptomatic treatment
		• Oxygen supplementation to maintain SPO2s above 90% (oxygen supplementation can be via nasal prongs, masks, non-rebreather masks or high flow nasal cannula - see below)
		• Dexamethasone or prednisolone or methylprednisolone (refer to annex for dosage)
		• VTE prophylaxis Enoxaparin
		• Consider prophylaxis for children older than 5 years with comorbidities and not ambulant. Refer to annex for paediatric dosage guidelines.
			• Admit to a Critical Care Unit.
			• Baseline Tests (Total blood count, renal and liver function, HIV test, random blood sugar)
			• Symptomatic treatment
			  • Conservative fluid management
			• Mechanical Ventilation if no improvement in oxygenation with maximal oxygen flows with other modalities - see guide to non-invasive ventilation, tracheal intubation and ventilation below
			• Closed suctioning of secretions where available
			• Dexamethasone or prednisolone or methylprednisolone
			• VTE prophylaxis Enoxaparin
			• Consider prophylaxis for children older than 5 years with comorbidities and not ambulant. Refer to annex for paediatric dosage guidelines.
				Supportive measures:
				• fluid resuscitation;
				• inotropic support;
				• respiratory support;
				• (In rare cases), extracorporeal membranous oxygenation (ECMO).
				• Intravenus Immunoglobulin (IVIG)
				• Steroids
				• Enoxaparin or
				• Refer to annex for paediatric dosage guidelines.

Figure 6a: Management of Pediatric COVID-19 Patients

Oxygen therapy: Oxygen via nasal cannulae is indicated in those with saturations of 94% or below. Up to 4 litres of oxygen can be administered via this route. Monitoring of response can be done both via pulse oximetry and arterial blood gases.

If the patient continues desaturating despite this, higher flow oxygen will be required. Current delivery systems available include the face mask (5-10L/min) and the non-rebreather mask (up to 15 L/min). High flow nasal cannula can support flows of up to 60L/min. If the patient requires high flow oxygen, please contact critical care/pulmonology team as escalation to the ICU may be necessary.

Remember that the risk of aerosolization increases once oxygen flows of above 4L/min per minute are required and an N95 mask should be used in addition to other precautions.



	Low Oxygen flow	Moderate Oxygen flow	High Oxygen flow	Very High Oxygen flow	Specialised form of pressure positive ventilation.	Invasive form of pressure positive ventilation.
	For regular hospital and home care.	For regular hospital and home care.	For regular hospital care.	Used in situations of respiratory failure.	Can be used for patients with apnea or to maintain an open airway.	Required when a patient's lungs are severely impaired.
OXYGEN FLOW	1-4 Litres/min	5 - 10 Litres/min	15 Litres/min	UP TO 60 Litres/min	AS PER LIFE SUPPORT NEEDS	AS PER LIFE SUPPORT NEEDS
FIO2 FRACTION OF INSPIRED OXYGEN	24 – 50%	40 – 60%	60 – 90%	UP TO 100%	UP TO 100%	UP TO 100%

* Adapted from BMJ 2020;369:m2446

Figure 7: Methods of oxygen delivery

Indicated for patients with oxygenation requirements exceeding 4 L/min to maintain goal saturations (>90% in non-chronic hypoxia cases) via nasal cannula or simple O_2 mask

Contraindications

- Chest wall and vertebral trauma or instability
- Trauma, fracture or major surgery to the anterior face, chest, abdomen or pelvis.
- In pregnancy states, one should seek obstetric clearance prior to proning
- Confusion, agitation, and physical inability to independently change position in bed
- Active nausea and/or vomiting

Procedure

- Assess for contraindications as above, alertness and ability to reposition in bed
- Attach monitoring leads, continuous pulse oximetry, BP cuff and SpO2
- Distractions (phones, tablets, TV etc.) can be availed to make the position more tolerable
- Documentation of vital signs should be made per ICU protocol by the bedside nurse
- Worsening oxygenation, increased work-of-breathing, worsening hypercapnia, worsening mental status, and worsening hemodynamics should prompt assessment for intubation
- Discontinuation of proning will be recommended by the ICU consultant when demonstrable improvement in respiratory status is noted or if the patient is unable to tolerate the procedure.
- Protocols on proning (including videos) are available (https://www.nejm.org/doi/full/10.1056/NEJMoa1214103)
- There is little evidence on prone positioning in pregnant women. Pregnant women may benefit from being placed in the lateral decubitus position

Table 6: Proning schedule

Start: 30 minutes to 2 hours lying fully prone (bed flat)
• 30 minutes to 2 hours lying on right side (bed flat)
• 30 minutes to 2 hours sitting up (30-60 degrees) by adjusting head of the bed
• 30 minutes to 2 hours lying on left side (bed flat)
• 30 minutes to 2 hours lying prone again
• Continue to repeat the cycle…….

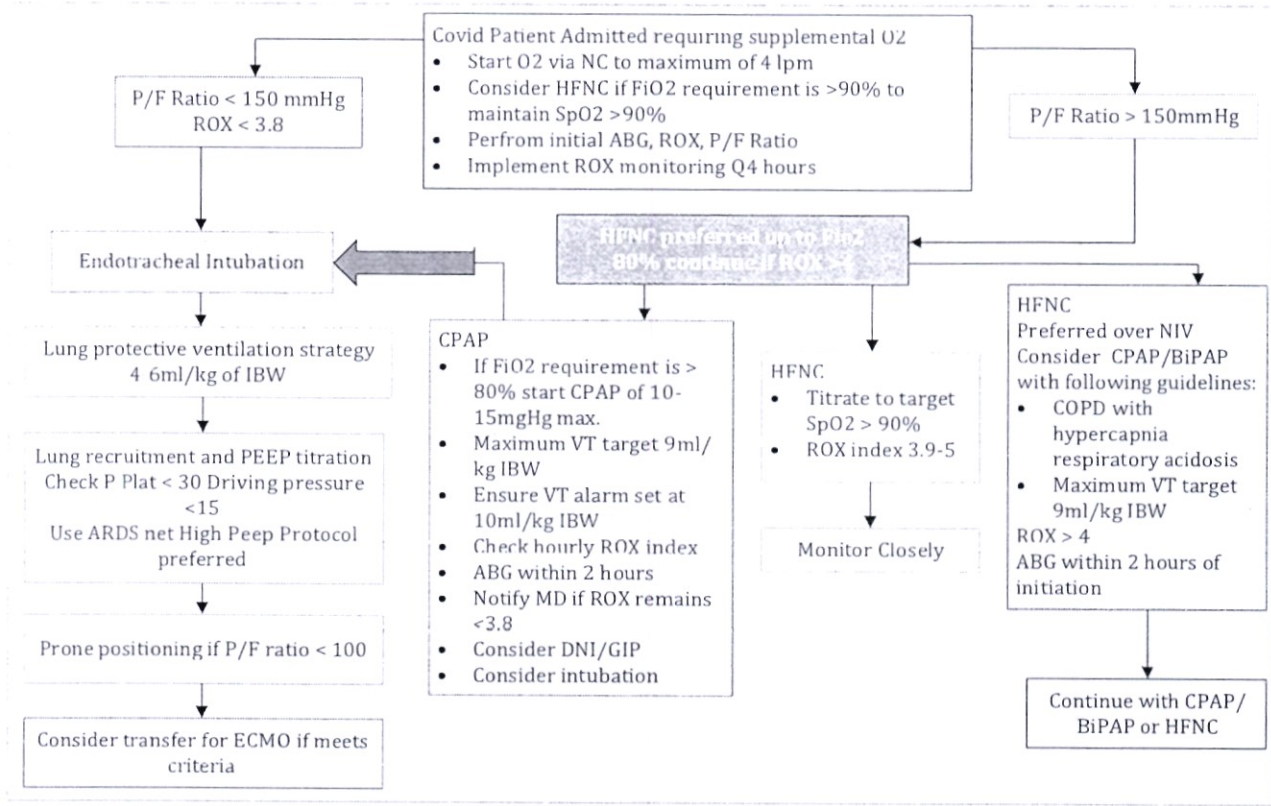


Figure 6: Decision making for ventilatory support

Table 7: COVID-19 Airway Management

Planning	○ Intervene early - aim to avoid emergency intubation. ○ Negative Pressure room or Normal pressure with strict door policy. ○ Clinicians proficient with intubation to be involved to increase first-pass success. ○ Early airway assessment to be done to anticipate difficult airway.
Prepare	○ Assemble 3-4-person Airway Team; – Airway Operator – Airway Assistant – In room runner – Door Runner ○ Share Airway Strategy. ○ Use a dedicated COVID intubation checklist ○ Use COVID-19 Intubation Tray (see below).

PPE	○ Hand Hygiene (HH). ○ Donning: HH > Gown > Mask > Eye-protection > Hat > HH > Gloves. ○ Spotter to perform "Buddy Check" to ensure correct PPE fit. ○ PPE includes; I. Impervious gown II. Theatre hat/hair net III. N95 mask IV. Consider face shield rather than goggles for eye protection V. Consider double gloves.
Pre-Oxygenation	○ 45 degrees head up position. ○ Pre-oxygenate with100% FiO_2 via a NRM mask using 2 hands for full 5 minutes. (Cover with surgical mask) ○ Ensure a square $ETCO_2$ waveform, to be confident of no leaks (if available) ○ Avoid Apneic Oxygenation techniques due to aerosolization risk.
Perform intubation	○ Use laryngoscope (with blade sized to patient) ○ Use rapid sequence intubation (RSI) technique. Initial neuromuscular blockade can be achieved with (1.5mg/kg IBW rocuronium OR 1.5mg/kg TBW suxamethonium). ○ Wait 60 seconds for paralysis to take effect - avoid triggering cough. ○ No ventilation prior to intubation unless for rescue oxygenation.
Post-intubation	○ Inflate cuff BEFORE initiating ventilation and monitor cuff pressures to minimize leak. ○ A nasogastric tube should be placed at the time of intubation to avoid further close contact with the airway ○ If COVID-19 status not already confirmed take a deep tracheal aspirate for virology using closed suction ○ Remove outer gloves (if on), dispose of airway equipment in sealed bag. ○ Doffing: Gloves > Gown > HH > Hat > Eye Protection > Mask > HH. Use a Spotter. ○ Chest X-ray should usually be performed to confirm tube position but should be delayed until after central line insertion to minimize staff entries into the room. ○ Debrief and share lessons.

Additional notes:

- To minimize the risk of virus aerosolization to the intubation team; Avoid nasal oxygen therapy, simple facemask and non-rebreather masks during pre-oxygenation.
- Awake intubation not indicated because of risk of aerosolization
- Connection / Disconnection (Apply the viral filter directly to the ETT. Only disconnect the circuit on the ventilator side of the viral filter). Clamp ETT prior to disconnection.
- Once the patient is intubated, closed suction systems should be used to minimize aerosolization of the virus.

Intubation [illegible]

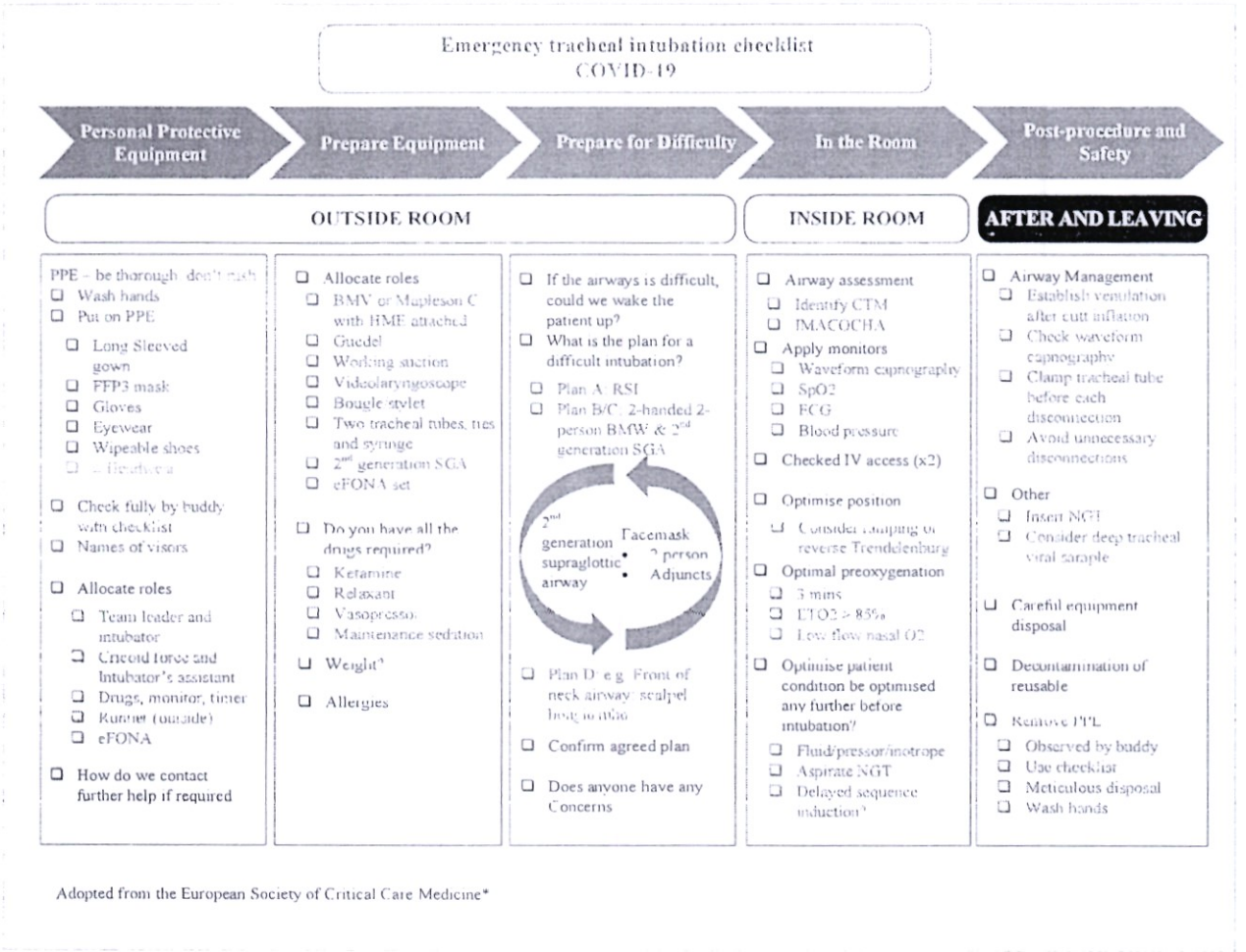


Figure 9: Emergency tracheal intubation checklist – COVID-19

1. Adult/paediatric BVM		2. PPE Sets for 4- 5 persons of the intubation team.	
3. Nasal Cannula/Non-rebreather mask		4. Cut down tray+ 2.0 Silk/Nylon stich- for CVC insertion	
5. Sachet lubricant (Opti-lube/KY jelly in sachet)		6. 100ml N/Saline or 10 vials water for injection	
7. In line suction catheter (closed tracheal suction system)		8. Sterile Wound dressing set- for urinary catheter insertion	
9. Oropharyngeal airway and nasopharyngeal airway (sized to patient)		10. Artery forceps/tube clamp – for clamping ET tube prior to connection/disconnection (to ventilator/BVM)	
11. Supraglottic airway/LMA/iGel (sized to patient		12. Local anaesthesia-1 bottle 1% Lidocaine for CVC	
13. CVC adult or paediatric		14. Heparin	
15. NG Tube		16. 70% alcohol or 2% chlorhexidine or Povidone-iodine	
17. Silicon/Foley's urinary Catheter		18. Clear CVS dressing	
19. Specimen bottles (Blood culture, red, purple, blue, green topped bottles, sputum, urine containers)		20. Clear Plastic(polythene) drape (plus frame) – to cover patient face during intubation	
21. Resuscitation Drugs (Adrenaline, Atropine, Amiodarone, Thrombolytic agent e.g., reteplase or alteplase)		22. Syringes 10 mlx10, 50ml x 2	
23. Defibrillator/Pacing Adhesive Pads		24. Point of care ultrasound machine (must be dedicated to COVID care)	

Induction Drugs **Neuromuscular blockers (Muscle relaxants)**	• Ketamine 1.5-2 mg/kg IBW OR • Fentanyl 2-10 mcg/kg TBW OR • Midazolam 0.1-0.3 mg/kg TBW OR Propofol 1-2.5 mg/kg IBW + (0.4 x TBW) (others simply use 1.5 mg/kg x TBW as the general guide) OR Thiopental 3-5 mg/kg TBW (Tailor to the patients and availability) • Succinylcholine 1-2 mg/kg TBW OR • Atracurium 0.2-0.4 mg/kg OR • Rocuronium 1.5 mg/kg IBW OR • Vecuronium 0.15-0.25 mg/kg IBW OR • Cisatracurium 0.15-0.2mg/kg bolus (Tailor to the patients and availability)	NO BAGGING BEFORE ETT To prevent cough, Consider pre-medication with lidocaine0.5-1.0mg/kg IV +Glycopyrrolate 200mcg IV USE BVM or NRM/NIV Mask(unvented) to pre-oxygenate.
Sedation	• 2% propofol 5-15ml/h OR • Morphine 0.005mg/kg/hour OR • Midazolam(50mg/50ml) 2-5ml/hr. • Dexmedetomidine 0.02-0.7 mcg/kg/hr. • Ketamine 1.5-2 mg/kg IBW	Refer to Table 8
Endotracheal tube	ETT tubes 7.0;7.5; 8.0 (Secure ET at level ET tube size X3 e.g., ET tube size 7, then secure tube at 21 cm mark.	
CVC	16cm Right sided insertion/20cm Left sided insertion sutured at hub	
Nasogastric tubes	14/16 or 18 Fr	
Initial Ventilator Settings	Individualize initial ventilator settings-based patient's mechanics. (NB: Pressure control modes may be preferable)	Start weaning if saturation 95-100 PO2>10Kpa (>75mmHg) at next ABG

	• FI02 100% (1.0) • PEEP ≥6 cm H2O to achieve oxygenation goal (oxygen saturation between 88 and 95 percent) • Ideal Tidal volume 4-6ml x Ideal Body Weight (estimate) but based on patient's lung mechanics. • RR 14-22 • I: E ratio 1:1(Insp time 1.25)	
Blood tests (Red, Blue, Green, Purple top, Blood Culture bottles, sputum containers)	• Initial ABGA at 2 hrs. post intubation • ABG every 4:6:12 hrs. • FBC, LFT, UE/Cr, every 24hrs • Procalcitonin when indicated • Tracheal aspirate (for COVID PCR, GeneXpert, MCS) on admission and subsequently as indicated. • Blood and urine culture on admission and subsequently when indicated • Troponin and fungal studies when indicated	
Acceptable parameters	• SPO2 88-95% • PaO2 between 55 and 80 mmHg (7.3 to 10.6 kPa) • Respiratory acidosis with PH >7.25 especially if prone • Plateau Pressure < 30mmHg	
Paralyze with Neuromuscular Blockers if any of the following	• Clinically significant Ventilator asynchrony despite optimum sedation. • Refractory hypoxemia: for lung recruitment maneuvers. • Intubated and prone position • For safe transportation	Refer to Table 8

Blood Pressure	• Accept MAP>65mmHg • Noradrenaline 0.01-3.3 mcg/kg/min • DILUTION (Formulation of 1mg/ml Norepinephrine/noradrenaline add 2 ml to 48ml in 5% dextrose by syringe pump OR Formulation of 1mg/ml Norepinephrine/noradrenaline add 20ml to 480ml 5% dextrose by drip counter (Soluset) initial rate 10ml/hr.(0.16mg/hr.) to 20ml/hr.(0.33mg/hr.) -FIRST LINE • If Noradrenaline>30ml/hr. add Adrenalin(epinephrine) (start at 20ml/hr.) • 2 fluid boluses/24 hrs. max • Consider dobutamine as 3rd line	Consider initial fluid bolus at 4ml/kg over 10-15 minutes to ascertain if the patient is fluid responsive. If fluid responsive then give maintenance infusion at 5ml-20/kg/24hr

If PH <7.25 (metabolic acidosis)
 	
Permissive hypercapnia
	• Match patient's minute ventilation demands.
	  • Increase RR (I:E ratio target of 1:1)
	  • Use flow-time scalar to avoid gas trapping
	  • In severe acidosis consider NaHCO3 Calculate deficit (1/2 the volume as bolus and ½ as infusion) and dialysis
	
	PH 7.25 and acceptable PCO2 55 mmHg	

If PO2 still <7kpa(60mmHg)	Adjust PEEP according to FiO2/PEEP combinations table below **Mild ARDS** **Moderate to Severe ARDS** FiO2 PEEP FiO_2 PEEP 0.3 5 0.3 12 0.4 5 0.3 14 0.4 8 0.4 14 0.5 8 0.4 16 0.5 10 0.5 16 0.6 10 0.5 18 0.7 10 0.5-0.8 20 0.7 12 0.8 22 0.8 14 0.9 22 0.8 14 1.0 22-24 0.9 16 0.9 18 1.0 18-24 Stepwise PEEP titration (increments of up to 2- 5 cmH20 Use lower inflexion point of deflection P-V loop Goal: PaO2 > 60 mmHg, Driving Pressure (Plateau pressure- PEEP) < 15cm H2O, best compliance (~50% of predicted compliance; > 40 cc/ cmH2oO) Prone positioning: P: F Ratio < 100 Consult an Anaesthetist / Intensivist with PEEP >14	ardsnet.org
Electrolytes targets	• K>4.0 mmol • Mg>1.0 mmol • PO4 >0.7 • Na >135 • Ca >2.2	If abnormal, correct as per standard guidelines

Table 8: Sedation and analgesia protocol

Aspects	Considerations
Global	• Patients with ARDS resulting in ventilator asynchrony despite ventilator adjustments may require lower RASS goals of -2 to -3. • If ventilator asynchrony persists despite RASS goal of -2 to -3, a RASS goal of -4 to -5 should be attempted. If ventilator asynchrony persists, consider neuromuscular blockage with a RASS goal of -4 to -5. • Daily evaluation of analgesia and sedation, as well as the need for neuromuscular blockade is imperative. Minimization of medications should be considered where possible to conserve supply. • In general, patients on vasopressors who are not considered resuscitated should not receive oral therapies. • When implementing the therapies below, consider patient specific factors such as history of substance abuse, age, or body weight. • Selection of agent may be impacted by availability at each institution.
Analgesia	Analgesic therapy should not be used with a goal of achieving a determined RASS goal. If a patient has a BPS<6, but higher than desired RASS, a sedative medication should be initiated. 1. Intermittent IV analgesia: Use of intermittent IV analgesia to achieve goal BPS or RASS is recommended as first line. 2. If goal RASS is not achieved or BPS remains >6 with the above measures, refer to the UPHS PAD guidelines for initiation of IV continuous infusion therapy. In mechanically ventilated patients that require continuous infusion analgesia that do NOT require frequent neurologic assessment, the following algorithm should be applied: 3. Continuous infusion analgesia: **a.** Fentanyl is the preferred analgesic for continuous infusion. Hydromorphone is an alternative analgesic for continuous infusion. **b.** Morphine is an alternative analgesic for continuous infusion, but not preferred in ICU patients. Patients with renal dysfunction may require lower doses due to accumulation. Monitor for hypotension upon initiation. 4. Oral analgesic therapy (Mechanical ventilation expected >24hrs): Following initiation of continuous infusion therapy, oral analgesic therapy could be considered to reduce intravenous requirements: ▪ Oxycodone 10-20 mg q6h standing (May titrate) ▪ Hydromorphone 4-6 mg Q4-6h standing (May titrate)

Sedation

- Sedation should be initiated in patients unable to achieve goal RASS despite achievement of BPS <6.
- In mechanically ventilated patients that require continuous sedation for agitation or ventilator synchrony, not requiring frequent neurologic assessment, the following algorithm should be applied.

A. If a patient has a RASS of -4/-5, but continues to demonstrate ventilator asynchrony, despite appropriate ventilator manipulation, therapy with a paralytic agent should be initiated.

B. Additional use of sedation with a low RASS WILL NOT aid in increased ventilator synchrony and will lead to inappropriate overdosing of patients and waste of medication.

1. Continuous infusion sedation

a. Propofol continuous infusion is the sedative of choice

i. Patients should be evaluated for baseline triglyceride (TG) monitoring and Q48h

ii. Discontinue agent if TG exceed 500 mg/dL.

b. Benzodiazepines

i. Midazolam or lorazepam are the preferred continuous infusion benzodiazepines (institutional preference or availability)

c. Dexmedetomidine

i. Achieves light sedation (RASS -1/-2). This agent should be used consistent with current UPHS guidelines and should not be used in patients requiring moderate to deep sedation (RASS -3 to -5) and/or neuromuscular blockade.

ii. Caution should be used in patients displaying signs of reduced ventricular function, bradycardia or heart block.

d. Ketamine 1.5-2 mg/kg IBW

2. Intermittent sedation

a. Consider the below therapies if propofol or continuous benzodiazepines are unavailable and dexmedetomidine is contraindicated or anticipated to be unsuccessful in achieving goal sedation.

i. Benzodiazepines

ii. Phenobarbital (IV to PO)

1. Loading dose: 130 mg IV x 1 dose
2. Maintenance therapy: 64.8 – 97.2 mg via gastric tube q8h (or 65 - 130 mg IV q8h if unable to tolerate orals)

a. Titrate to sedation goal while not exceeding a level of 50mg/L

3. Oral sedation therapy

a. Following initiation of continuous infusion therapy, oral therapies could be considered to reduce intravenous requirements:

i. Clonazepam 1-2 mg Q8h (May titrate)

ii. Lorazepam 1-2 mg Q6h (May titrate)

iii. Oxazepam 10 - 30 mg Q8h (May titrate)

	b. Other i. Quetiapine or alternative antipsychotic. Exercise caution in patients on adjunctive medications (consult with clinical pharmacy) other QTc prolonging medications. ii. Gabapentin iii. Valproic acid
Neuromuscular blockade	❖ Neuromuscular blockade is only required in the presence of ventilator dyssynchrony and deep sedation (RASS -4 to -5) ❖ Ensure adequate sedation and analgesia are achieved prior to neuromuscular blockade as evidenced by RASS -4 to -5 and BPS <6. If BIS is available, titrate to 40-60. ❖ Do not reduce analgesia or sedation once neuromuscular blockade has been established. ❖ Analgesics and sedatives SHOULD NOT be titrated to reduce hypotension Consider initiation of a vasopressor if hypotension persists. ❖ Paralytic requirement should be evaluated daily to limit use 1. **Intermittent dosing:** • Vecuronium is the preferred agent for intermittent dosing (Alternative: Rocuronium) o Dosing: 0.1 – 0.2 mg/kg every 4-6 hours o Dose and frequency will vary based on organ dysfunction; Patients with significant organ dysfunction may require smaller and less frequent dosing • If initial dosing of intermittent vecuronium or rocuronium does not achieve desired ventilator synchrony and/or TOF 1-2/4, increase dose or frequency as appropriate • If patient goals are not achieved or requires more than Q4h dosing, begin continuous infusion neuromuscular blocking agent 2. **Continuous infusion:** ➢ Atracurium is the preferred NMBA for patients without renal/liver dysfunction ➢ Cisatracurium is permitted for patients with significant organ dysfunction

Appendix 1: Opioid Conversion

Equianalgesic Dosing of Intravenous Opioids

Patients transitioning between agents should be given as a bolus with an equianalgesic dose of the new medication and started on an appropriate dose of continuous infusion. Prior intravenous therapy should then be discontinued.

Agent	Equianalgesic IV Dose
Fentanyl	200 mcg
Hydromorphone	3 mg
Morphine	20 mg

1. Patients should ideally be ready for extubation onto facemask. Patients should be assessed for readiness for extubation onto facemask.
2. NIV and HFNO should be avoided where possible.
3. Two staff members should perform extubation.
4. The same level of PPE should be worn for extubation as is worn by the team during intubation.
5. The patient should not be encouraged to cough.
6. A simple oxygen mask should be placed on the patient immediately post extubation to minimize aerosolization from coughing.
7. Oral suctioning may be performed, with care taken not to precipitate coughing

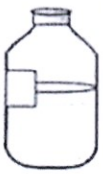
HEMODYNAMIC SUPPORT

up to 35% Preliminary data from China reported highly variable prevalence of shock in adults with COVID-19 (17-35%), depending on population, severity of illness, and definition of shock.

7 - 23% Cardiac injury reported in 7% to 23% with shock frequently cited as main reason for death, maybe at least partly due to fulminant mycarditis.

For adults with COVID-19 and shock, using dynamic parameters, skin temperature, capillary refilling time, and/or lactate over static parameters to assess fluid responsiveness is suggested due to availability and possible improvements in mortality, lenght of stay and duration of MV.

FLUIDS

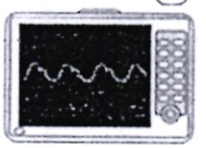


Using a conservative, over a liberal fluid stragegy is suggested for acute resuscitation. In the abscence of data demostrating a benefit from the use of liberal fluid strategies in critically ill patients with sepsis/ARDS (majority of COVID-19 ICU pts develop ARDS). Using crystalloids over colloids is recommended, with some colloids being harmful, all colloids being more costly, and limitedly availability of colloids in some settings. Using buffered/balanced crystalloids suggested over unbalanced crystalloids, in the abscence of apparent harm, and roughly equivalent costs availability restricted NaCl 0.9% reasonable alternative. It is Not recommended:

- Using hydroxyethyl starches due to clinically important harm/no suggestion of benefits.
- Using gelatins, in the abscence of any benefit, and with higher costs.
- Using dextrans due to possible increased risk of blood transfusion (bleeding)/higher costs.
- Routinely using albumin for initial resuscitation, dut to abscence of benefit, cost/limited availability.

VASOACTIVE AGENTS

Titrating to target MAP of 60-65 mmHg suggested due to indication of improved outcome if lower targets (& no firm indication of harm) **60 - 65 mmHg**



Norepinephrine (NE) suggested as fist-line agent, as most widely studied vasoactive agent with lower prior risk of undesirable effects. If NOT available, vasopressin or epinephrine suggested, both studied without clear evidence for harm; consider, when choosing, availability/contraindications (potential concerns for vasopressin include digital ischemia; tachycardia/excess lactate production for epinephrine).



Using dopamine is NOT recommended if NE is available, based on increased risk of harm including possible increased mortality. Adding vasopressin as a second-line agent is suggested, over titrating NE dose, if target MAP cannot be achieved. If shock with evidence of cardiac dysfunction & persistent hypoperfusion despite fluid resuscitation/NE, adding dobutamine, over increasing NE dose, is suggested based on a physiological rationale.

If refractory shock, low-dose corticosteroid therapy ("shock-reversal") is suggested, as may shorten time to resolution of shock, and ICU/hospital length of stay (major considerations with regards to costs)

SCC guidelines on management of critically ill with COVID-19

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Figure 10: Haemodynamic support

Table 9: Measures to prevent complications

Reduce days of invasive mechanical ventilation	• Use weaning protocols that include daily assessment for readiness to breathe spontaneously • Minimize continuous or intermittent sedation, targeting specific titration endpoints (light sedation unless contraindicated) or with daily interruption of continuous sedative infusions • Proning for 12-16 hours per day
Reduce incidence of ventilator associated pneumonia	• Oral intubation is preferable to nasal intubation in adolescents and adults • Keep patient in semi-recumbent position (head of bed elevation 30-45°) • Use a closed suctioning system; periodically drain and discard condensate in tubing • Use a new ventilator circuit for each patient; once patient is ventilated, change circuit if it is soiled or damaged but not routinely • Change heat moisture exchanger when it malfunctions, when soiled, or every 5–7 days
Reduce incidence of other hospital acquired infections	• Central line associated infections - use a checklist with completion verified by a real-time observer to remind of each step needed for sterile insertion and as a daily reminder to remove catheter if no longer needed • Catheter associated urinary tract infections - avoid urethral catheterization where possible. If a catheter is indicated, it should be removed as soon as possible • Avoid using antibiotics unless there is a clear infection. Practice antimicrobial stewardship
Reduce incidence of venous thromboembolism - Switch this row with the one below	• Use pharmacological prophylaxis (low molecular-weight heparin 40mg SC [preferred if available] or heparin 5000 units subcutaneously twice daily) in adolescents and adults without contraindications. • For patients who cannot use heparin consider direct acting anticoagulants e.g., fondaparinux and rivaroxaban • For those with contraindications, use mechanical prophylaxis (intermittent pneumatic compression devices)
Reduce incidence of pressure ulcers	• Turn patient every two hours • Use ripple mattresses for ICU patients

Reduce incidence of stress ulcers and gastrointestinal bleeding	• Give early enteral nutrition (within 24–48 hours of admission) • Administer histamine-2 receptor blockers or proton-pump inhibitors in patients with risk factors for GI bleeding *Risk factors for gastrointestinal bleeding include mechanical ventilation for ≥48 hours, coagulopathy, renal replacement therapy, liver disease, multiple comorbidities, and higher organ failure score
Reduce incidence of ICU-related weakness	• Actively mobilize the patient early in the course of illness when safe to do so

Reassure parents and involve them in caring for their child, most children will have mild symptoms - much milder than those seen in adults.

- Be extra-vigilant in children with pre-existing conditions (e.g., long-term respiratory conditions, immunocompromised from disease or treatment and cyanotic heart disease, sickle cell anemia).
- Chest radiographs, laboratory blood tests, and blood gases are not routinely indicated. Consider these only in children with persistent fever, altered fluid balance, signs of liver dysfunction, or respiratory failure.
- The following medical treatments are likely to have more side-effects than beneficial effects in children and are not routinely indicated: bronchodilators, antibiotics, antivirals, and diuretics.
- Escalate respiratory support as per the respiratory failure pathway – do not use high flow nasal cannula oxygen if the child is saturating adequately with low flow oxygen.

Pregnant women with suspected or confirmed COVID-19 should be treated with supportive therapies as described above, taking into account the physiologic adaptations of pregnancy. The use of investigational therapeutic agents outside of a research study should be guided by individual risk-benefit analysis based on potential benefit for mother and safety to foetus, with consultation from a specialist. Emergency delivery and pregnancy termination decisions are challenging and based on many factors: gestational age, maternal condition, and foetal stability. Consultations with obstetric, neonatal, infectious disease and intensive care specialists (depending on the condition of the mother) are essential.

A mother with confirmed COVID-19 or who is symptomatic should take all possible precautions to avoid spreading the virus to her infant, including washing her hands before touching the infant and wearing a face mask, if possible, while breastfeeding. If expressing breast milk with a manual or electric breast pump, the mother should wash her hands before touching any pump or bottle parts and follow recommendations for proper pump cleaning after each use. If possible, consider having someone who is well to feed the expressed breast milk to the infant.

Local experience has shown that up to 30% of patients presenting with severe disease have underlying poorly controlled comorbidities, the most common being cardiovascular disease, diabetes mellitus, HIV, hypertension, asthma and other chronic lung diseases.

It is important that comorbidities are identified early to allow appropriate management. Proper and complete history taking and physical examination is critical and should be carried out on each patient. A record of chronic medication should be indicated to avoid treatment disruptions. A multidisciplinary team should be involved in management of patients with comorbidities and early specialist consultation is encouraged.

It is important to note that those patients living with diabetes who are well controlled with no significant comorbidities have a significantly lower risk of developing severe complications of COVID-19 and their risk is comparable to that of the general population. (12)

- The risk associated with COVID-19 infection is similar in individuals who have either type 1 or type 2 diabetes excluding other risk factors such as age, micro and macro vascular complications, comorbidities and glycemic control. (12)

The following individuals with diabetes are considered most vulnerable:

- Those with inadequately controlled diabetes mellitus, specifically with a HBA1c reading > 7.6% or those with recently fluctuating sugars.
- Patients more than 55 years of age.
- Patients with diabetes and concomitant comorbidities such as heart failure, hypertension, chronic obstructive pulmonary disease, chronic kidney disease, cancer and HIV who are already known to have a significant impairment in their immune function.

Precautions with oral hypoglycemic agents

- Metformin should be withdrawn in patients with hypoxia or hypotension to avoid the risk of lactic acidosis.
- Sulfonylureas (chlorpropamide, glibenclamide, glimepiride, glyburide, glipizide) and meglitinides (repaglinide, nateglinide) should be used with caution in patients with reduced feeding to avoid risk of hypoglycemia.
- Sodium Glucose Transporter (SGLT-2) inhibitors (e.g., Dapagliflozin and Canagliflozin) should be stopped due to risk of dehydration and euglycemic ketoacidosis.

*Steroids can induce hyperglycemia even in a non-diabetic patient and steroid-induced hyperglycemia should be managed using insulin.

Feeding

- Enteral feeding should be encouraged.
- In critically ill patients commercial enteral or parenteral feeds can increase the insulin requirements.

- COVID-19 infection in individuals who have either type 1 or type 2 diabetes can put them at a higher risk of developing diabetic ketoacidosis. The same treatment protocols for managing diabetic ketoacidosis are used to treat patients with diabetes who develop diabetic ketoacidosis (DKA) or Hyperosmolar hyperglycemic state (HHS) secondary to COVID-19 infection.
- Hyperglycemia without DKA/HHS
  - The management of diabetes in hospitalized patients with COVID-19 is similar to the management of other hospitalized patients with diabetes, except for the presence of often extreme, labile insulin resistance that resolves with improvement in COVID-19, and the need to minimize injection frequency in order to maximize safety for health care staff.
  - In general, the goals of treatment are the same as in other hospitalized patients (e.g., avoid severe hyperglycemia, volume depletion, electrolyte abnormalities, hypoglycemia and ensure adequate nutrition).
    - Insulin is the preferred treatment for hyperglycemia in patients hospitalized with moderate to severe COVID-19
  - A blood glucose target of 6 to 10 mmol/L is reasonable for most hospitalized patients. Many patients have severe insulin resistance and require high doses of insulin to achieve these goals.
- Patients with type 1 diabetes have an absolute requirement for insulin at all times to prevent ketosis, whether or not they are eating. For patients with type 2 diabetes, the need for insulin therapy may be temporary.
  - If possible, a basal –bolus regimen is preferred, which refers to the combination of a long-acting basal insulin (Glargine, NPH) with a rapid-acting insulin at mealtimes.
  - The clinician should watch out for hypoglycemia especially for those with reduced caloric intake and as the inflammation reduces, and the insulin dose should be adjusted accordingly.

Table 10: Diagnostic criteria and severity of DKA/ HHS

	Mild DKA	Moderate DKA	Severe DKA	HHS
Plasma glucose (mmol/L)	>13.9	>13.9	>13.9	>33.3
Arterial pH	7.25-7.30	7.00-7.24	<7.00	>7.3
Serum bicarbonate (mEq/L	15-18	10-<15	<10	>15
Urinary ketones	Positive	Positive	Positive	Small
Mental status	Alert	Alert/ Drowsy	Stupor/ Coma	Stupor/Coma

- Mild to moderate DKA/ HHS: Subcutaneous insulin protocols (rather than intravenous insulin infusions) are being used with increasing frequency to treat mild to moderate DKA or HHS during the COVID-19 pandemic, when intra-venous insulin may not be practical owing to the need to limit frequency of contact of staff with patients. In this setting, dosing and monitoring should be performed every two to four hours.
- Subcutaneous insulin protocols are best used in patients with mild to moderate DKA without other serious comorbidities.
- Severe DKA: Insulin infusions should be used for patients with severe DKA, acute heart failure or coronary syndrome, chronic kidney disease (CKD) stage 4 or 5 or end-stage renal disease (ESRD), acute liver failure or cirrhosis, anasarca, weight >120 kg, treatment with high-dose corticosteroids, or in women who are pregnant.
- Diabetes UK Protocol (http://www.diabetesorg.UK/resourcesCOVIDDKA-SC-v3.3pdf)
    - Initiate basal insulin (NPH, Glargine) at 0.15units/Kg and administer every 24 hours.
    - 0.4 units/Kg of soluble/regular insulin is administered every 4 hours. When RBS is less than 13.9mmol/l, reduce to 0.2units/Kg every 4hours until DKA/HHS resolves.

1. HYDRATION

Fluid deficit approx. 100ml/kg (7l in 70kg person)
Assess:
- Fluid state
- Co-morbidities (i.e. Cardiac/ renal fnx)
- Response to fluids

2. POTASSIUM

URGENT-Blood gas (AB) result
Total K deficit ≈ 3.5mmol/L
If Hyperkalemia Risk:
(Recommended rates below do not apply)
Anuric renal failure
Chronic renal failure
HyperKalemia on presentation

3. Volume expansion commenced (>1 Litre) AND Potassium > 3.5

4. INSULIN

RAPID INSULIN – Rapid insulin 0.1U/Kg as infusion (PER TABLE BELOW)
NB: CAN GIVE 0.1U/KG IV STAT **If infusion rate per table below) is less<0.14U/kg/hour**

BASAL INSULIN Give subcutaneous basal insulin (i.e. lantus) even while on IV insulin infusion

HYPOVOLAEMIA SHOCK

Recommendation Fluid Rates

	Rate
Litre 1	Stat (not through infusion pump, No potassium added as waiting UE/Cr
Litre 2	Run over 1 hour Need UE/Cr to decide 0.9% Ringers or 0.45% saline
Litre 3	Run over 2 hour
Litre 4 and Above	Run over 4 (250ml/hr) to 12 (83ml/hr) hour (depending on fluid status/renal function)

Fluid – 0.9% saline or Ringer's lactate preferred
If sodium >148mmol 0.45% saline preferred or 5% dextrose

(To make 500ml 0.45% = 250ml 0.9% saline +250 ml sterile water to make 1000ml 0.45% saline 500ml 0.9% saline +500ml sterile water)

Discuss with ICU

Serum Potassim	Recommended Rate of KCL	Caution
<3.0	40mmol/hr	Using CVC + cardiac monitoring
3.0-4.0mmol/l	20mmol/hr	Using CVC + cardiac monitoring
4.0-5.5mmol/l	10mmol/hr	Using CVC or peripheral line
>5.5mmol/l	NIL	

CVC-central venous catheter; **Dilution** – 10mmol KCL in 100ml 0.9% saline of 5% dextrose

Monitor Potassium: Initially 1 hourly, then when K ≥ 4.0 every 2 hourly

RAPID INSULIN INFUSION RATES

RBS (mmol/L)	UNITS OF INSULIN/hr	UNIT ON PUMP
0-4	0	0
4.1-6.0	0.5	1
6.1-8.0	1	2
8.1-12.0	2	3
12.1-16.0	3	4
16.1-20.0	5	5
>20	7	10

When RBS ≤ 14mmol **ADD 5% Dextrose** 12hourly(125ml/hr) **but continue** with ringer's or 0.9% saline together but at slower rate

Figure 11: Diabetic ketoacidosis treatment chart (adults)

In order to stop transmission of COVID-19, and to aid public health prevention measures, it is paramount that at the time of discharge from isolation, patients are no longer transmitting infectious virus. In the context of widespread community transmission, there may be ongoing shortages of laboratory consumables and reagents that affect diagnostic capacity, as well as significant pressure on the health system. There is also an increasing need for timely discharge of stable patients from health facilities in order to maintain healthcare capacity for severe and critically ill patients.

This guidance for ending isolation for COVID-19 patients reflects information available at the time of publication and may change if more information on the incubation period, viral shedding, and infectivity of SARS-CoV-2 infection becomes available.

During the infectious course, COVID-19 viral RNA has been identified in respiratory tract specimens 1-2 days before symptom onset. Viral load persists up to eight days after symptom onset in mild cases and peaks 11 days after symptom onset in more severe cases, with detection of virus in nasopharyngeal swabs up to 37 days. In Kenya, we have had reports of patients testing positive for more than 40 days after diagnosis. RNA has been detected in stool (from day five after symptom onset and up to five weeks in moderate cases), as well as in whole blood, serum, saliva, and urine. Asymptomatic and pre-symptomatic transmission has been reported in many settings [9]. Additionally, patients with immune compromise may shed SARS-CoV-2 virus for prolonged periods. More data is still needed on viral dynamics in different patient populations and varying disease severity.

Detection of viral RNA does not necessarily mean that a person is infectious and able to transmit the virus to another person. Data suggests that viral shedding is highest prior to onset of symptoms and reduces thereafter, with most persons testing PCR negative on nasopharyngeal swabs by 21 days after onset of symptoms. Viable viruses have not been recovered in respiratory samples of patients with mild to moderate illness after 10days of symptom onset and 20 days in patients with severe illness or immunosuppressive conditions. This therefore guides the recommendation that patients can be discharged from isolation after 10 days post symptom onset for those with non-severe disease and after 20 days for those with severe disease or immune compromise.

Patients should be discharged from Covid-19 isolation when it is safe for the patient and when the likelihood of transmission of the virus to others is minimal. Patients who are stable and at low risk of disease progression can be discharged to home based care to complete the isolation period. Stable patients who do not meet the criteria for home- based care should be discharged after they meet the criteria of ending transmission-based precautions. Patients in need of further in-patient care should meet the criteria of ending transmission-based precautions before being transferred to the general wards.

Our recommendation is to use the time-based approach for discharge from isolation for all COVID-19 patients for the following reasons:

1. Reduce long periods of isolation reducing access of patients to care
2. Insufficient testing capacity to meet the requirements for test-based discharge criteria
3. Prolonged viral shedding leading to multiple repeat positive tests, despite little risk of viable virus

Table 11: Criteria for ending Isolation

Symptom-based	At least 3 days (72 hours) have passed since recovery defined as resolution of fever without the use of fever-reducing medications; **and** Improvement of respiratory symptoms (e.g., cough, shortness of breath); **and** At least 10 days have passed since the date of their first positive COVID-19 diagnostic test	Requires daily monitoring and recording of symptoms by patient.
Time-based	At least 10 days have passed since the date of their first positive COVID-19 diagnostic test, **and** They have not developed symptoms since their positive test	If they develop symptoms, then symptoms cannot be used to gauge where these individuals are in the course of their illness, it is possible that the duration of viral shedding could be longer or shorter than 10 days after their first positive test.

There is no need for repeat testing prior to ending isolation if the above criteria have been met

*Meeting criteria for discontinuation of Transmission-Based Precautions is not a prerequisite for hospital discharge

**Isolation should be extended to 20 days from symptom onset for those with severe disease or who are severely immunocompromised

***Isolation must be maintained at home (until the criteria above are met) if the patient returns home before discontinuation of Transmission-Based Precautions.

Patients with Covid-19 may remain symptomatic with new or persisting symptoms after recovery. The most common symptoms include dyspnoea, cough, fatigue, and muscle pains. Additionally, the patients may present with psychological and cognitive symptoms which include anxiety, depression, PTSD symptoms and problems with concentration, memory and continence. Patients who had severe or critical illness have a higher prevalence of symptoms when compared to patients with non-severe illness. The stages of post-covid 19 infections can be defined as follows:

- Acute COVID-19: signs and symptoms of COVID-19 for up to 4 weeks.
- Ongoing symptomatic COVID-19: signs and symptoms of COVID-19 from 4 to 12 weeks.

- Post-COVID-19 syndrome: signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis.

Time to complete recovery will depend on premorbid condition, severity of illness and the symptoms experienced by the patient during illness. Recovery time is different for everyone but for many people symptoms will resolve by 12 weeks

Patients who have had suspected or confirmed COVID-19 (of any disease severity) who have persistent, new, or changing symptoms should have access to follow-up care. Currently, there is limited information on the optimal strategies to manage persistent symptoms following recovery from acute covid-19 infection

The goal of post-COVID-19 management is to optimize function and quality of life through provision of holistic patient-centred care and partnering with patients to identify achievable health goals.

Initial evaluation should include a detailed history of the patient's COVID-19 disease course, severity of illness, and treatments received. Past medical history should include assessment for prior conditions that could impact the severity of COVID-19 disease. Social history should include assessment of the level of material and social support and resources available to the patient, and their potential impact on the capacity of patients to access health and recuperation services.

No laboratory test can definitively distinguish post-COVID-19 conditions from other aetiologies, in part due to the heterogeneity of post-COVID-19 conditions. Clinicians should maintain a high index of suspicion for other conditions presenting with similar symptoms and Laboratory testing should be guided by the patient history, physical examination, and clinical findings

A comprehensive management plan should be developed in consultation with other specialists based on the patient's presenting symptoms, underlying medical and psychiatric conditions, personal and social situations, and treatment goals. Expectations should be set with patients and their families that outcomes from post-COVID-19 conditions differ among patients, with some patients experiencing symptom improvement within the first three months, whereas others may continue to experience prolonged symptoms.

Continue follow-up over the course of illness, with considerations of broadening the testing and management approach over time if symptoms do not improve or resolve, while remaining transparent that there is much more to learn about post-COVID-19 conditions. Manage all underlying chronic medical conditions as appropriate.

COVID-19 vaccination is an important public health measure, helping to decrease transmission, disease severity and death. All eligible persons should be vaccinated as per the current National COVID-19 Vaccination Guidelines and Deployment Plan. Health workers and those with comorbidities are particularly encouraged to be vaccinated.

COVID-19 vaccination is recommended for all eligible persons including those who have previously been infected or tested positive for SARS-COV-2 infection. Eligible patients with active COVID-19 infection should be vaccinated after recovery from acute illness, that is, at least 2 weeks after. Having prolonged COVID-19 symptoms is not a contraindication to receiving the COVID-19 vaccine.

The ability of emerging virus variants to evade immune responses is however still under investigation.

COVID-19 vaccines have been found to be safe, though they may cause side-effects, most of which are minor. Adverse Events Following Immunization (AEFIs) include any untoward medical occurrence following vaccination, and may not necessarily have a causal relationship with the usage of the vaccine. Common side-effects include tenderness at the injection site with redness, swelling, itching or warmth, fever, fatigue, headache, myalgia, general body malaise, arthralgia and nausea (16). Most of these are self-limiting and may be managed supportively. Use of paracetamol does not affect the immune response to the vac-cine.

Look out for rare but severe adverse events following immunization such as anaphylaxis, high fever and thrombosis with thrombocytopenic syndrome (17). Appropriate consultations should be made in the management of these conditions.

AEFIs should be managed according to the current National guidelines for monitoring, reporting and managing adverse events following immunization (18) and Guidelines for safety and Vigilance of medical products and Health technologies (19). All AEFIS should be reported to the Pharmacy and Poisons Board via https://pv.pharmacyboardkenya.org/

It takes about 2 weeks to mount an adequate immune response after full vaccination, though there is some protection gained after the first dose. Full vaccination is recommended in order to get maximum protection against severe disease and death. While it remains possible for one to be infected with SARS-COV-2 after vaccination, most COVID-19 vaccines have been shown to be highly effective in protecting against severe disease and death.

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ANNEX

	Essential Health Service/ Area		
1	**COVID 19**	Case Management for COVID-19	https://www.health.go.ke/wp-content/uploads/2020/06/Updated-Case-Management-Guidelines-26_03_20-1.pdf
		Infection Prevention and Control	https://www.health.go.ke/wp-content/uploads/2020/04/Kenya-IPC_Considerations_For-Health-Care-Settings-1.pdf
		Home Based Care guidelines	https://www.health.go.ke/wp-content/uploads/2020/06/Home-Based-Isolation.pdf
		Addendum to the Home-based isolation and care-Paediatrics	Final-Adendum-of-Pediatrics-guide-on-HBIC-1.pdf (health.go.ke)
		Home and Residential Communities	https://www.health.go.ke/wp-content/uploads/2020/04/Homes-and-residential-communities.pdf
		Gated Communities	https://www.health.go.ke/wp-content/uploads/2020/03/Coronavirus_Gated_Community_Response.pdf.pdf
2	**Kenyan Guidance on Continuity of Essential Health Services**	Kenyan Guidance on Continuity of Essential Health Services	https://www.health.go.ke/wp-content/uploads/2020/05/KENYAN-GUIDANCE-ON-CONTINUITY-OF-ESSENTIAL-HEALTH-SERVICES-DURING-THE-COVID-OUTBREAK-20MAY-2020-complete.docx.pdf
3	**RMNH guidance**	Kenya COVID-19 RMNH guidance	https://www.health.go.ke/wp-content/uploads/2020/04/KENYA-COVID19-RMNH.pdf.pdf.pdf
4	**Nutrition**	Final guidance for nutrition management during COVID-19	https://www.health.go.ke/wp-content/uploads/2020/03/FINAL-GUIDANCE-FOR-COVID-19-NUTRITION-MANAGEMENT.pdf
		Nutrition management for the population	https://www.health.go.ke/wp-content/uploads/2020/03/FINAL-NUTRITION-MESSAGES-FOR-THE-POPULATION.pdf

5	**Child Health Services**	Kenya Pediatric COVID-19 Guidance	https://www.health.go.ke/wp-content/uploads/2020/06/PAEDIATRIC-Covid-Guidelines-Final.pdf
6	**Community Health Service**	Kenyan guidance on continuity of Community Health Services during the COVID-19 pandemic	https://www.health.go.ke/wp-content/uploads/2020/06/Kenya-Guidelines-on-Continuity-of-Community-Health-Services-in-the-Context-of-COVID-19-Signed.pdf
		Community Health Response Minimum Standards	https://www.health.go.ke/wp-content/uploads/2020/04/Covid-19-Community-Health-Response-Minimum-Standards.docx.pdf
		Utilizing the Community Health Strategy to respond to COVID-19	https://www.health.go.ke/wp-content/uploads/2020/04/Community-Response-to-COVID-2019_1.docx.pdf
9	**Pathology**	Targeted testing strategies for Coronavirus Disease 2019 in Kenya	Targeted-Testing-Strategy-for-COVID-19-in-Kenya.pdf
		Interim guidelines on handling of human remains infected with covid 19 in Kenya	https://www.health.go.ke/wp-content/uploads/2020/06/Interim-Guidance-on-Handling-of-Human-Remains-Infected-with-COVID-19.pdf
10	**HRH**	Human Resource for Health Protocol	https://www.health.go.ke/wp-content/uploads/2020/06/PROTOCOL-HRH-for-COVID_Draft-with-digital-signature.pdf
11	**Mental Health and Psychosocial services**	SOPs for Psychologists and Counsellors during the COVID-19 Pandemic	SOPs-for-Counsellors-and-Psychologists-in-the-MHPSS-for-COVID-19-Response-1.pdf-1.pdf (health.go.ke)
		Comprehensive guide for mental and psychosocial support during the COVID-19 pandemic	GUIDE ON MENTAL HEALTH AND PSYCHOSOCIAL SUPPORT DURING THE COVID-19 PANDEMIC.cdr

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Brief Report

Comparisons between the Neighboring States of Amazonas and Pará in Brazil in the Second Wave of COVID-19 Outbreak and a Possible Role of Early Ambulatory Treatment

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Abstract: Brazil and many countries are now experiencing a second wave of the COVID-19 outbreak. The objective of this study is to compare results with statistical samples involving millions of people in the two largest neighboring states in Brazil, Amazonas and Pará, which in the first wave were similar but now show significant different results in combating COVID-19. During the first wave, in May 2020, the maximums of the 7-day average daily deaths per population of Amazonas and Pará were similar: 15.7 and 17.1 deaths per day per million people, respectively, which means a ratio 15.7/17.1 = 0.92 ≈ 1. Now, in the second wave of COVID-19 outbreak, Amazonas has entered a serious situation; meanwhile, Pará has presented a much smaller growth in the mortality. The accumulated mortality per population from 11 November 2020 to 15 March 2021 of Amazonas and Pará are 1645 and 296 deaths per million people, respectively. As 1645/296 = 5.55, Amazonas is presenting an accumulated mortality per population more than five times that of Pará. Future in-depth research can provide a grounded answer to explain this significant difference, nonetheless the explicit support of the Pará state government, after 21 May 2020, to early ambulatory treatment may have played some role on this result.

Keywords: SARS-CoV-2; COVID-19; mortality; treatment; comparison; statistics; Brazil

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1. Introduction

The COVID-19 pandemic has been impacting the world since the beginning of 2020 [1,2] and two waves of COVID-19 outbreak [3] have hit many countries. As pointed out by Jindal et al. [4], according to the Centers for Disease Control and Prevention of the United States of America (USA), there are two ways to control the damage of a viral infection: (1) reduce the spread of the virus and, (2) decrease the associated disease severity. Concerning item (1), most countries issued complete or partial lockdown in many cities and measures of prevention such as social distancing, wearing a mask, washing hands, post-exposure prophylaxis, and staying at home quarantined under signals of infection [1,2,4,5]. Concerning item (2), some medicines such as hydroxychloroquine, azithromycin, ivermectin and others were proposed and tested against the SARS-CoV-2 virus in some stages of the disease [6–9], and several vaccines were developed in record time [10,11].

Some groups of researchers showed the advantages of early ambulatory treatments for COVID-19 [7,8,12–14], but, as commented on by Paul [15], the differences between patients given treatment for COVID-19 or not require exceptionally large sample sizes for appropriate adjustment. There are many recruitment difficulties [16] in conducting experimental studies involving large number of patients. Although studies with 10,000–20,000 patients or more are important, the scope and the objective of this research note is not to discuss them but to work on comparisons of statistical samples involving millions of people in two states of a country in the second wave of COVID-19 outbreak. This country is

Brazil, which occupies a vast area (about half of South America) with a relatively large population, which corresponds to about 45% of the population of South America, 30% of Europe and 65% of the USA. Therefore, cross-comparison for Brazil can be relevant and the information provided can be extrapolated to the world in many cases.

As pointed out by Pearce et al. [17], comparisons are important because, despite some difficulties, it is possible to learn a great deal from comparing countries, states, and regions, and they can play a major role in our learning what works best for controlling COVID-19. The number of options is not high, and some alternatives to comparisons, such as randomize a lockdown or other aspects of physical distancing, are impossible or unethical [17]. There could be trials of intensive population testing, or prophylactic treatment of household contacts, but few have been launched, and the clock is ticking accumulating more deaths [17].

Comparisons between countries of Africa, Asia, Europe, Central, North and South America, and Oceania were performed [18–28]. Most of these studies analyzed the diverse strategies in combating the disease and report parameters involving the number of cases and the mortality. Some of the studies involved themes such as testing coverage [23], economic valuation [24], response strategies [25], age distribution [26,27], and seasonal climate changes [28], among others.

Comparisons involving states and country regions were also presented [29–33]. For example, Rath et al. [29] studied selected states of India by analyzing parameters such as case fatality rate and population density. La Gatta et al. [30] used graph-based machine learning to compare the forecasts of the trained model with available data about the Covid-19 epidemic spread in different regions of Italy. Cavalcante et al. [32] described the evolution of the pandemic until 16 May 2020 in Brazil, analyzing the number of cases and mortality, making comparisons between states, regions, and also with other nine countries. Orellana et al. [33] studied the excess overall mortality until 19 May 2020 in the state of Amazonas (Brazil), focusing mainly on its capital, analyzing parameters such as age bracket, sex, place of death, epidemiological week, and specific causes of death. These authors [33] made comparisons with the pre-COVID-19 mortality in 2018–2019 and presented comments about other Brazilian states and the world.

Most of the mentioned comparisons studies [18–31] involve the first wave of COVID-19 outbreaks, and two of them were focused more specifically on Brazil and its states [32,33] analyzing results until 16–19 May 2020. The objective of the present work is to make comparisons between the neighboring states of Amazonas and Pará in Brazil in the second wave of the COVID-19 outbreak. This is particularly relevant because in the first wave of the COVID-19 outbreak, the maximums of the mortality rate in the states of Amazonas and Pará were quite similar considering their populations, but now, in the second wave, there are significant differences in the results. To the author's knowledge, the present work is one of the first comparison studies between two neighboring states that were quite similar during the maximum of the first wave, and now, in the second wave, are presenting significant different results in combating COVID-19.

Amazonas and Pará are the two largest states of Brazil by area, located in the northern region of the country and traversed by the Amazon River (cf. Figure 1). Their summed area corresponds to 33% of the country (Amazonas: 18.3% and Pará: 14.6%), and their populations are 4.208 and 8.691 million people, which correspond respectively to 2.0% and 4.1% of the total Brazilian population (211.8 million people). Although the population of Amazonas is 0.48 (about half) of Pará, the metropolitan regions of their state capitals (Manaus-AM and Belém-PA) have similar populations: Greater Manaus (13 municipalities): 2.72 million people and Greater Belém (7 municipalities): 2.51 million people. Excluding the two large metropolitan regions surrounding their capitals, the other municipalities, 49 in Amazonas and 137 in Pará, have average populations of 30 and 45 thousand people, respectively. Furthermore, among other factors, the two states are relatively similar in climate, in the public healthcare system, in the socioeconomic status (SES) distribution, in the level of education of the population, and in the age and gender composition

[34,35]; the Human Development Index (HDI) of 2010 for Amazonas, Pará and Brazil as a whole are, respectively, 0.674, 0.646 and 0.699. These inherent similarities of the two states, together with the specific circumstances during the first and in the second wave of COVID-19 outbreak, will evidence that the comparisons are appropriate and helpful. Looking for the main differences of behavior between the two states in the second wave may serve as an example for other states or other geographic entities in the combat of the COVID-19 pandemic.



Figure 1. Map of the states of Amazonas and Pará in Brazil and their neighboring states and international borders. Reproduced from http://www.geographicguide.net/america/brazil-map.htm (accessed on 15 February 2021)—Adapted with permission from copyright © Geographic Guide—World in Pictures.

An important starting point for the present work is to define what is the most appropriate parameter to use in the comparisons. The number of cases per million people is a rate that is frequently reported for comparison purposes, but the testing practice of different countries and states to identify cases may vary [24,36,37]. Other parameters, such as infection fatality ratio and case fatality ratio are other relevant measures, but they depend directly on the testing practices to identify cases, which usually are not uniform and vary. In the case of Brazil, the testing practice to identify COVID-19 cases varies from state to state and also between municipalities in the same state, so using a parameter such as the case fatality ratio to compare states may not be very appropriate.

Although deaths per million people is a crude rate, many consider it a useful comparator [24,36,37]. As pointed out by Fitzpatrick [37], although some COVID-19 reported deaths include just those tested positive, which is mainly the case in hospitalized patients; other reported deaths include those where COVID-19 is regarded highly likely, without confirmation. Despite the possibility of doubt in some circumstances, in the case of Brazil, the number of deaths by COVID-19 per million people is the parameter that may be more appropriate for comparisons between states and municipalities, because the statistics of the population is well performed by a federal institute (Instituto Brasileiro de Geografia e Estatística IBGE) since 1938, and, according to a federal regulation (Art. 77 of Law No. 6015 of 15 December 1973), the death is an event in which a physician is responsible for certifying the cause, and a death certificate must be issued in a civil registration office,

before burial. Only in cases where there is no physician, two qualified persons who have witnessed or verified the death can inform the cause. However, the great majority of the municipalities in Brazil have physicians, which are paid for with the support of the municipalities, the states, and the Brazilian Unified Health System (Sistema Único de Saúde—SUS). Despite the possibility of doubt in some cases of highly likely COVID-19 deaths, without confirmation, it is probably that these cases in Brazil may be distributed evenly among the municipalities and states of the regions, and not concentrated in certain municipalities and states (of the region). Therefore, taking into account all these reasons, it is appropriate to assume that the municipalities inside the regions of Brazil have reasonable uniformity in the criteria for the notification of the COVID-19 deaths of the patients. In addition, it is worth comment that the notifications from the municipalities are what generate the data for the states and for the country, which appear daily in the released statistics. All things considered, the number of deaths per million people is the parameter that will be used in the comparisons of the present work.

2. Materials and Methods

The daily deaths of COVID-19 in Brazil and other statistical data of the pandemic are provided by the municipalities and the states, and compiled by the Ministry of Health, which provides a spreadsheet in a CSV format available on its website (https://covid.saude.gov.br/ (accessed on 15 March 2021)). The File S1 used here was obtained on 15 March 2021, and is reproduced in the Supplementary Materials. It involves daily data since 25 February 2020 of the country, of the 27 federation units (26 states and one federal district), and of the 5570 municipalities.

As the present work involves the country and the federation units, it was sufficient to take the first part of the above spreadsheet and export the content of this primary data to the File S2 of three tabs created by the author, which is available openly in the Supplementary Materials for those who are interested. This spreadsheet contains the primary data, the determination of the useful parameters, and the data used to make the graphs. In the part of primary data, the columns of interest in the present study are region, state, date, population, accumulated deaths, and daily deaths. Other columns, such as: accumulated cases, new cases, new recovered cases, and follow-up new cases, were not used here, but may be of interest for other works. The averages of deaths per day were calculated on a 7-day basis, by taking the data of the considered day and the six previous days. The details of how the data were worked out in this spreadsheet are presented in Appendix A in the first three paragraphs.

The graphs were made in the Excel File S3 of 28 tabs, which is also available openly in the Supplementary Materials for those interested. This spreadsheet provides graphs of the country and all 27 federation units in a suitable resolution. Appendix A, in its fourth paragraph, provides details of how the data were worked out in the spreadsheet. The figures with the graphs shown in this work can be compared with graphs, normally of lower resolution, provided daily by the Brazilian press through the "Consórcio de Veículos de Imprensa". For example, the webpages of Uol and Globo, which present daily statistical graphs of COVID-19 for the country and the federation units, are indicated in the references [38,39].

3. Results and Discussion

As shown in Figure 2, Brazil suffered the first wave of COVID-19 outbreak between March and 10 November 2020. The period of highest mortality of the first wave occurred between the end of May 2020 and the beginning of September 2020, with the maximum of the 7-day average daily deaths occurring on 25 July 2020: 1097 deaths per day, which corresponds to 5.1 deaths per day per million people. The second wave of the pandemic began on 11 November 2020 and is affecting most states. It is worrying because the mortality rate now, in March 2021, is significantly higher than that of the maximum of the first wave, and it is mainly related to new, more contagious, variants of the virus [11,40], and also to

reductions in the measures of prevention. In February 2021, the 7-day average daily deaths was 1000–1200 deaths per day (4.7–5.7 deaths per day per million people). In March 2021, the mortality rate is increasing steadily; on 15 March 2021, the 7-day average daily deaths has reached 1841 deaths per day, the highest in the world at the moment (in absolute value), which corresponds to 8.7 deaths per day per million people.

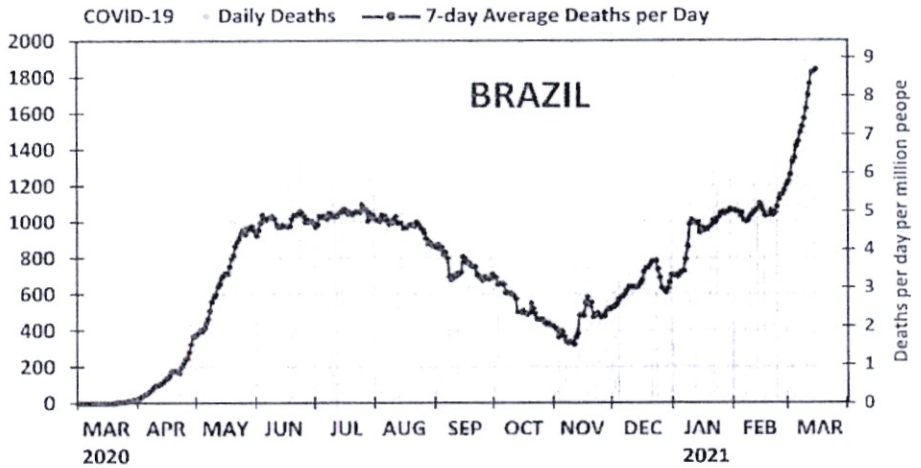


Figure 2. Daily deaths and 7-day average deaths per day of COVID-19 in Brazil from 01 March 2020 to 15 March 2021. The deaths per day per million people can be found using the secondary vertical axis on the right.

As shown in Figure 3, during the month of May 2020, Amazonas and Pará experienced strong first waves of COVID-19 outbreak. The maximums of the 7-day average daily deaths reached 66 deaths per day in Amazonas on 9 May 2020 and 149 deaths per day in Pará on 25 May 2020, which correspond to 15.7 and 17.1 deaths per day per million people, respectively. The difference in the daily deaths per population was only −9%, and therefore the two states were quite similar because the ratio $15.7/17.1 - 0.92 \approx 1$.

In that situation, in March-May 2020, each state and the municipalities separately adopted measures to contain the pandemic, because in Brazil the Supreme Federal Court has decided that the municipalities, the states and the federal government have autonomy of action, in their respective jurisdictions, to combat COVID-19 [41]. In general, the mayors and governors implemented partial lockdown in some cities and suggested measures of prevention such as those mentioned in Section 1. However, the government of the state of Pará had a different additional attitude because: (1) a private healthcare plan operator (Unimed Belém) was with successful results with early ambulatory treatment dispensing medicines such as those mentioned in Section 1 to their patients upon prescription from their physicians [42]; (2) some municipalities, such as Afuá, were already acquiring such medicines [43]; and (3) the municipality of Ourilândia do Norte (Center-South of Pará, 33.1 thousand people and HDI of 2010 = 0.624) was also with successful results with early ambulatory treatment dispensing medicines such as those mentioned in Section 1 to patients upon prescription from their physicians at its municipal public healthcare unit [44]. On 21 May 2020, the state government of Pará, as documented on the official state agency [45] and in the press [46], acquired hundreds of thousands of capsules of medicines for covid-19 to distribute to the municipalities in the state for use by people with symptoms or a confirmed diagnostic of COVID-19. On that occasion it was informed that the effectiveness of early ambulatory treatment for COVID-19 was not yet scientifically proven and that the medicines could only be prescribed by physicians if they so wish; it was informed that the main role of the state government of Pará was to guarantee the supply of

the medicines. A concise complementary discussion of this issue is left at the end of this section, supplemented with Appendix B.

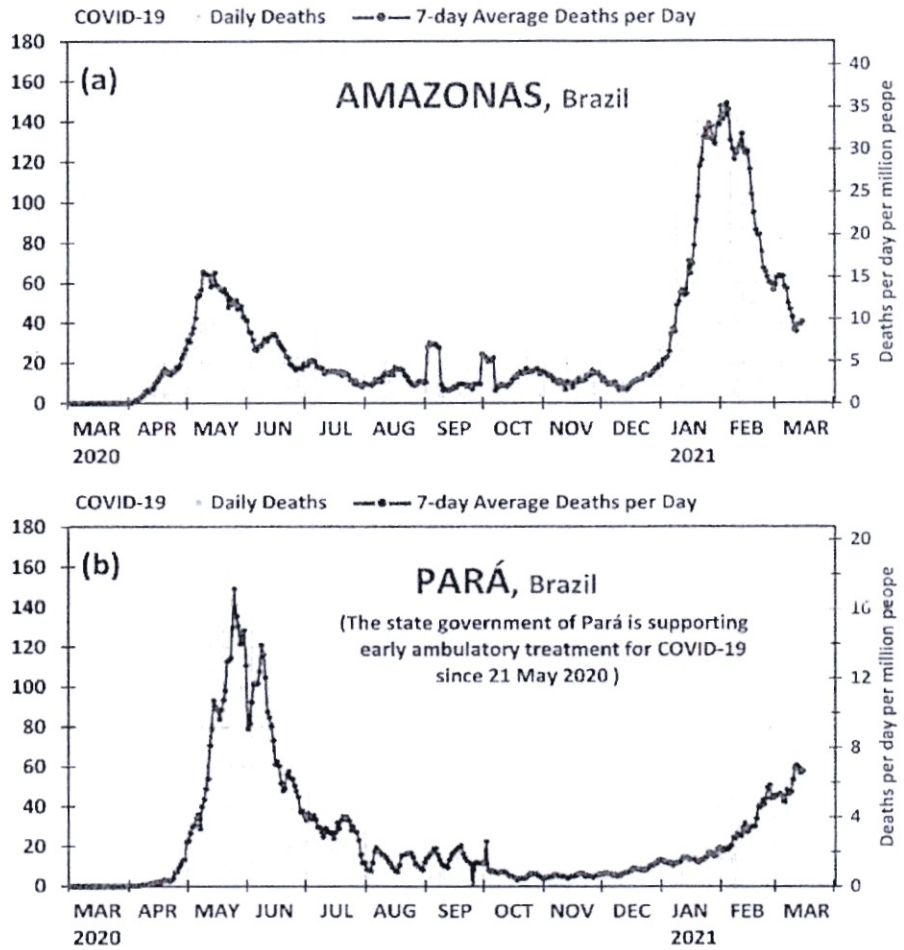


Figure 3. Daily deaths and 7-day average deaths per day of COVID-19 in the states of (**a**) Amazonas and (**b**) Pará in Brazil from 1 March 2020 to 15 March 2021. The deaths per day per million people can be found using the secondary vertical axis on the right.

As demonstrated in Figure 3, both states managed to control the first wave of COVID-19 outbreak; however, Pará presented a much faster reduction after the maximum of the first wave, not only in relation to the state of Amazonas, but in relation to all states in Brazil. After the first wave maximum, the state of Pará reduced the 7-day average daily deaths by 83% in 46 days (from 25 May 2020 to 10 July 2020) and by 95% in 70 days (from 25 May 2020 to 3 August 2020), which is a remarkable result.

Some points can be emphasized in this matter: (1) The physicians of the public healthcare system in the state of Pará started to know in May 2020 that the proposed early ambulatory treatment was working well for a private healthcare plan operator [42] and for a municipality [44]; (2) the state government of Pará, which have made early ambulatory treatment feasible by purchasing the medicines, has a great power of influence; and, importantly, (3) the patients and the municipalities did not have to purchase and pay for the medicines—the state government of Pará did so. Consequently, it is likely that the result obtained in Pará (the best in Brazil) in decreasing at the shortest time the maximum

of the death rates of the first wave of COVID-19 outbreak may be due to the explicit support of the state government and the adhering of the municipalities and their physicians in the public healthcare system to the early ambulatory treatment. The role of early ambulatory treatment in the second wave is discussed latter.

As can be observed in Figure 3, the second wave of the COVID-19 outbreak has hit the state of Amazonas severely. From the middle of December 2020, Amazonas presented an increase in the daily deaths, which grew significantly in January 2021. The 7-day average daily deaths in Amazonas remained above 120 deaths per day (15.3 deaths per day per million people) from 18 January 2021 to 15 February 2021, and then decreased to 60 deaths per day on 27 February 2021 and then to 40 deaths per day on 11 March 2021. Meanwhile, its neighboring state, Pará, which had a first wave as strong as that of Amazonas in May 2020, taking into account the populations, has been in a different situation. In the second wave Pará has presented a much smaller growth than Amazonas. The 7-day average daily deaths in Pará increased from 13 to 20 deaths per day from 1 to 31 January 2021, from 18 to 45 deaths per day from 1 to 28 February 2021, and from 46 to 58 deaths per day from 1 to 15 March 2021. The latter value corresponds to 6.7 deaths per day per million people. Despite the fact that Pará is in a situation where the maximum of the second wave is not yet defined as in Amazonas, it may be useful to make a comparison with the current situation. In the second wave (until 15 March 2021), the maximums of the 7-day averages of daily deaths were 149.0 deaths per day in Amazonas on 4 February 2021 and 61 deaths per day in Pará on 12 March 2021, which correspond to 35.4 and 7.0 deaths per day per million people, respectively. Since $35.4/7.0 = 5.1 \approx 5$, the ratio of the maximums of the 7-day average daily deaths per population between Amazonas and Pará has increased from about 1 to 5 from the first wave to the second wave.

It is worth commenting on the fact that the reduction of the daily deaths in Amazonas from the middle of February 2021 is related to several measures of prevention and partial lockdown in some cities that were issued from January–February 2021; mainly in Manaus and its metropolitan area. Moreover, the vaccination program in Brazil, which started on 17 January 2021, is also contributing to part of the decrease, because, due to the circumstances, the state of Amazonas has received priority: 8.07% of its population have received the first dose by 14 March 2021 (almost the double of the Brazil average, 4.59%) [47,48]. Older people, people with disabilities in care institutions, and health professionals have been included in the priority group, and over 60% of indigenous people above the age of 18 have received the first dose by 26 February 2021 [49]; and the indigenous of Amazonas are receiving a higher priority [50].

Since Amazonas has entered in a difficult situation during the second wave, and the graph of the state of Pará has already been shown, it is instructive to observe the panorama of the other neighboring states of Amazonas (Roraima, Acre, Rondônia, and Mato Grosso). Figure 4 provides the graphs of daily deaths and 7-day average deaths per day of Roraima, Acre, Rondônia, and Mato Grosso from 1 March 2020 to 15 March 2021.

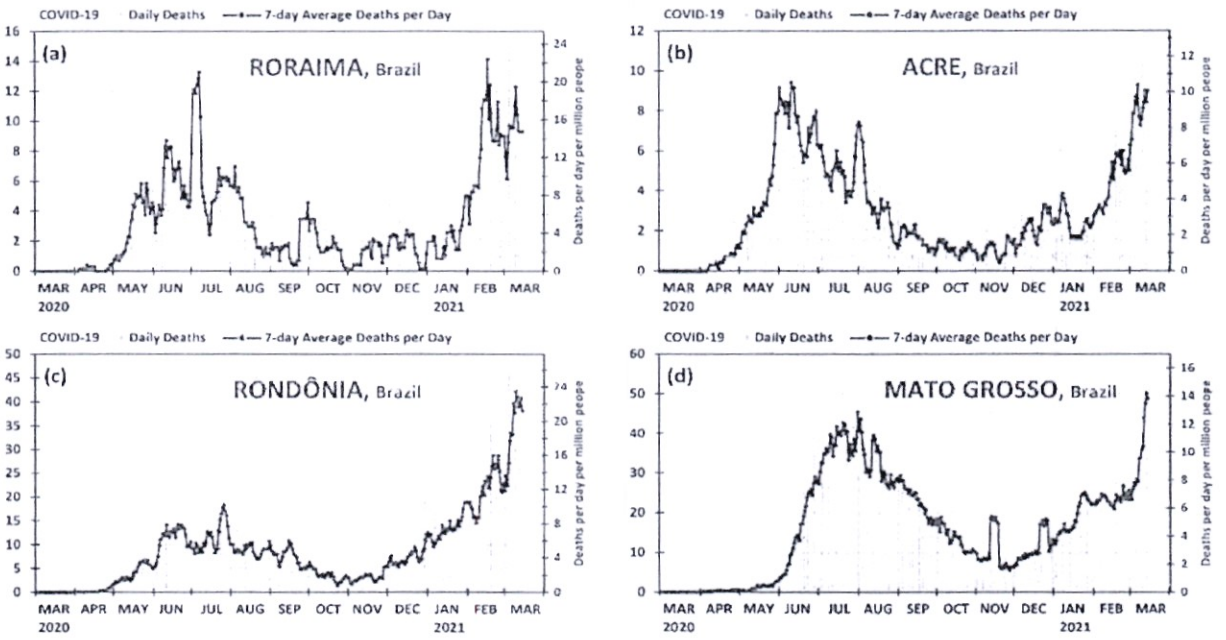


Figure 4. Daily deaths and 7-day average deaths per day of COVID-19 in the states of (**a**) Roraima, (**b**) Acre, (**c**) Rondônia and (**d**) Mato Grosso in Brazil from 1 March 2020 to 15 March 2021. The deaths per day per million people can be found using the secondary vertical axis on the right.

Positively, new, more contagious, variants of the virus COVID-19 have been contributing to the situation in Amazonas and many states of Brazil in the second wave. Although two variants have been verified in Brazil [40], P.1 (B.1.1.28) and VOC 202012/01 (B.1.1.7), the variant P.1 is the predominant [11,40]. In all likelihood, it is not a matter of timing that the new variants in the second wave may reach Pará with the intensity that Amazonas has been reached, since the second wave has already reached Brazil with severity (cf. Figure 2), and most states are presenting a high increase in daily deaths. In the case of Pará, the larger increases in the 7-day averages of daily deaths have occurred from 18 to 26 February 2021 and from 6 to 12 March 2021, but these increases are not as high as those of Amazonas from 4 to 25 January 2021. Moreover, as shown in Figure 4, all the other neighboring states of Amazonas (Roraima, Acre, Rondônia and Mato Grosso) are presenting accumulated mortality per population much larger than that of Pará, as will be detailed in Table 1. As shown in Figure 4, the situation is serious because these neighboring states of Amazonas are presenting high daily deaths; therefore, it is highly likely that the variant P.1 is one of the main causes of these significant increases in the daily deaths because it is the predominant variant in Brazil [11,40]. On 15 March 2021 the 7-day average daily deaths in the states of Roraima, Acre, Rondônia and Mato Grosso were 9.3, 9.0, 38.1 and 48.7 deaths per day, which corresponds, respectively, to 14.7, 10.1, 21.2 and 13.8 deaths per day per million people. These values are, respectively, 120%, 51%, 318% and 107% higher than that of Pará.

Table 1. Accumulated mortalities per population in the second wave of COVID-19 outbreak (from 11 November 2020 to 15 March 2021); and the ratios between the maximums of the 7-day average daily deaths in the second wave and in the first wave (from 1 March 2020 to 10 November 2021)—for all states of Brazil—in absolute values and in relation to the state of Pará.

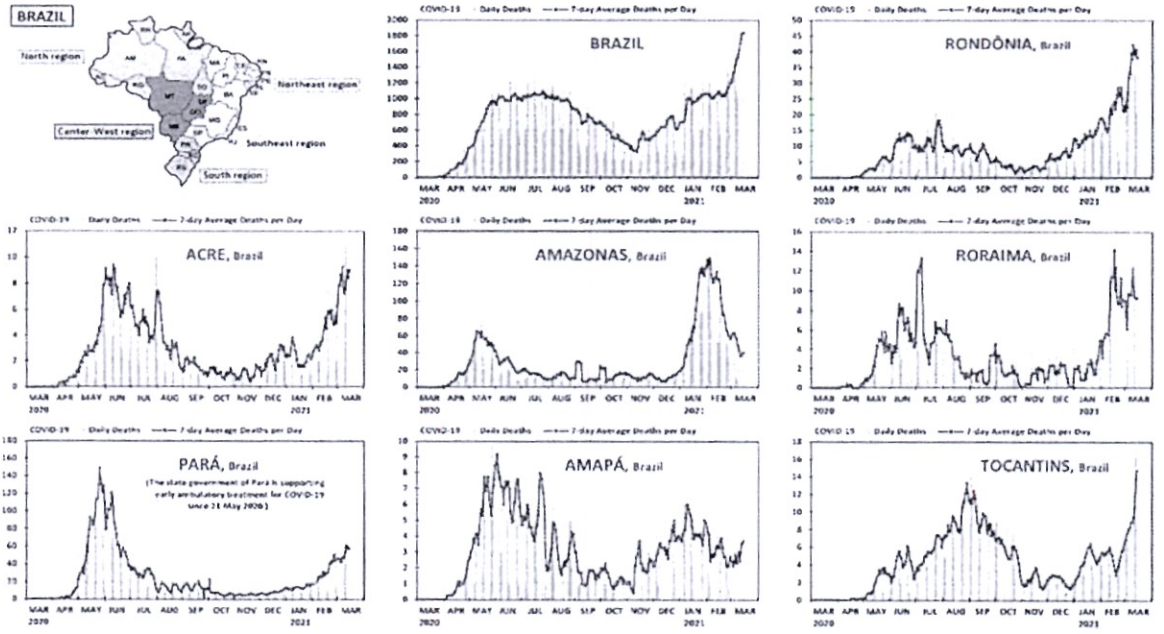
State	Abbr.	Region	Population	Accumulated Mortality Per Population in the Sec. Wave (Deaths Per Million People)	Accumulated Mortality Per Population in the Sec. Wave (in Relation to the State of Pará)	Max. 7-Day Av. Deaths Per Day Sec. Wave/ First Wave	Max. 7-Day Av. Deaths Per Day Sec. Wave/ First Wave (in Relation to the State of Pará)
Rondônia	RO	North	1,796,460	1076	3.63	2.31	5.68
Acre	AC	North	894,470	475	1.60	0.98	2.42
Amazonas	AM	North	4,207,714	1645	5.55	2.26	5.55
Roraima	RR	North	631,181	851	2.87	1.06	2.61
Pará	PA	North	8,690,745	296	1.00	0.41	1.00
Amapá	AP	North	861,773	489	1.65	0.66	1.61
Tocantins	TO	North	1,590,248	366	1.24	1.11	2.72
Maranhão	MA	Northeast	7,114,598	192	0.65	0.83	2.03
Piauí	PI	Northeast	3.281.480	355	1.20	0.87	2.14
Ceará	CE	Northeast	9,187,103	315	1.06	0.54	1.32
Rio Grande do Norte	RN	Northeast	3,534,165	376	1.27	0.65	1.59
Paraíba	PB	Northeast	4,039,277	452	1.53	1.24	3.04
Pernambuco	PE	Northeast	9,616,621	275	0.93	0.31	0.75
Alagoas	AL	Northeast	3,351,543	280	0.94	0.68	1.68
Sergipe	SE	Northeast	2,318,822	386	1.30	0.56	1.36
Bahia	BA	Northeast	14,930,634	369	1.24	1.50	3.68
Minas Gerais	MG	Southeast	21,292,666	539	1.82	1.59	3.91
Espírito Santo	ES	Southeast	4,064,052	687	2.32	0.77	1.88
Rio de Janeiro	RJ	Southeast	17,366,189	773	2.61	0.80	1.96
São Paulo	SP	Southeast	46,289,333	529	1.79	1.31	3.22
Paraná	PR	South	11,516,840	706	2.38	2.91	7.13
Santa Catarina	SC	South	7,252,502	765	2.58	1.90	4.67
Rio Grande do Sul	RS	South	11,422,973	797	2.69	3.68	9.04
Mato Grosso do Sul	MS	Center-West	2,809,394	708	2.39	1.40	3.44
Mato Grosso	MT	Center-West	3,526,220	689	2.33	1.10	2.70
Goiás	GO	Center-West	7,113,540	522	1.76	1.54	3.77
Distrito Federal	DF	Center-West	3,055,149	448	1.51	0.54	1.33
BRAZIL	BRA		211,755,692	550	1.86	1.68	4.12

To better compare Amazonas and Pará with the country and other federation units in the second wave of COVID-19 outbreak, some parameters of interest are provided in Table 1 for all states, the federal district, and the country as a whole. The last four columns of Table 1 provide the accumulated mortality per population in the second wave (from 11 November 2020 to 15 March 2021)—in absolute values and in relation to the state of Pará; and the ratio between the maximums of the 7-day average daily deaths in the second wave and in the first wave (from 1 Mar 2020 to 10 November 2021)—in absolute values and in relation to the state of Pará. It is worth commenting on that the data of these comparisons, and those of other comparisons such as the ratio between the accumulated mortality per population in the second wave and in the first wave, can be found in File S2 of Supplementary Materials. Because the second wave of the pandemic is still taking place, the ac-

cumulated mortality increases every day, especially for the various states where the average daily deaths is high or continues to increase. The last two columns, which depend on the maximum of the 7-day average daily deaths in the second wave, may also vary in cases where the maximum has not yet been reached.

The antepenultimate and the last columns of Table 1 demonstrate quantitatively that the state of Pará is the best of the North region (where the virus variant P.1 was first found in Brazil [11,40]) in the fight against COVID-19. Moreover, Pará, even located in the presently risky North region, has performed best against COVID-19 when compared with most states of the other regions, and with the country in general. Amazonas, Pará, and Brazil (as a whole) have presented (until 15 March 2021) an accumulated mortality per population in the second wave of 1645, 296, and 550 deaths per million people, respectively; this means that Amazonas and the country (as a whole) are presenting values that are 5.55 and 1.86 times that of Pará.

It is instructive to complement the prospects offered by Figures 3 and 4 with a unified panoramic view of the country, region by region. The graphs of daily deaths and 7-day average deaths per day—from 1 March 2020 to 15 March 2021—are presented in Figures 5 and 6 for all states of Brazil and its federal district, grouped by region, following the same order as in Table 1. The North and Northeast regions are shown in Figure 5, and the Southeast, South and Center-West regions in Figure 6. In both figures, there is a small map showing the positions of the states and regions. The country graph is shown at the beginning of Figure 6, so that all relevant graphs can be seen together in the same resolution.



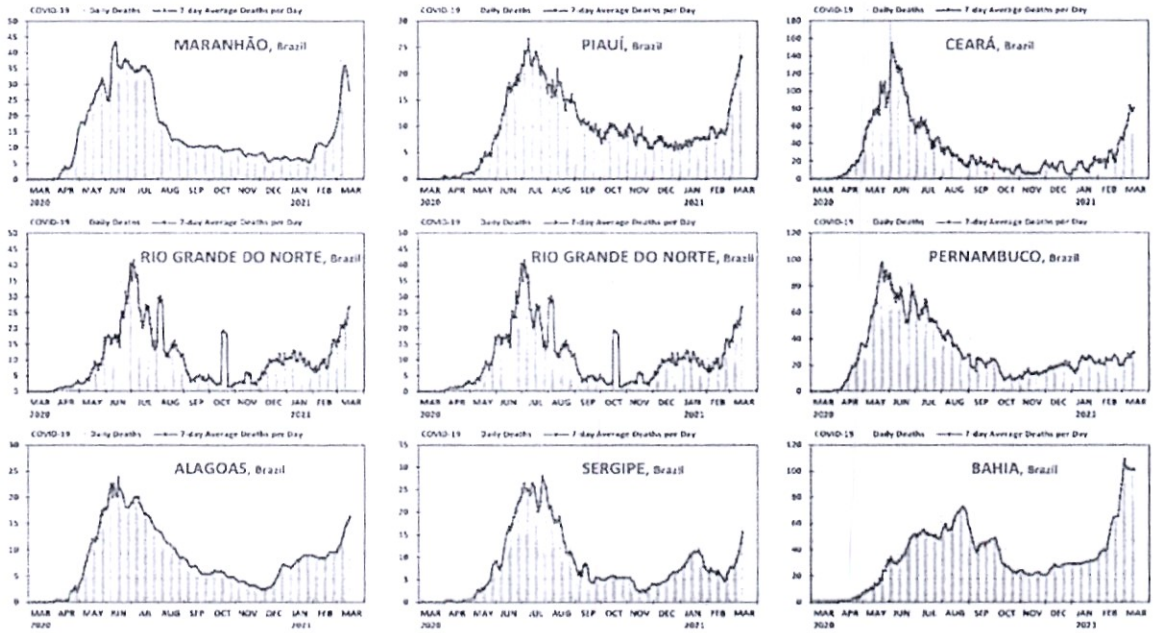


Figure 5. Daily deaths and 7-day average deaths per day of COVID-19 in Brazil and in the states of the North and Northeast regions of Brazil from 1 March 2020 to 15 March 2021.

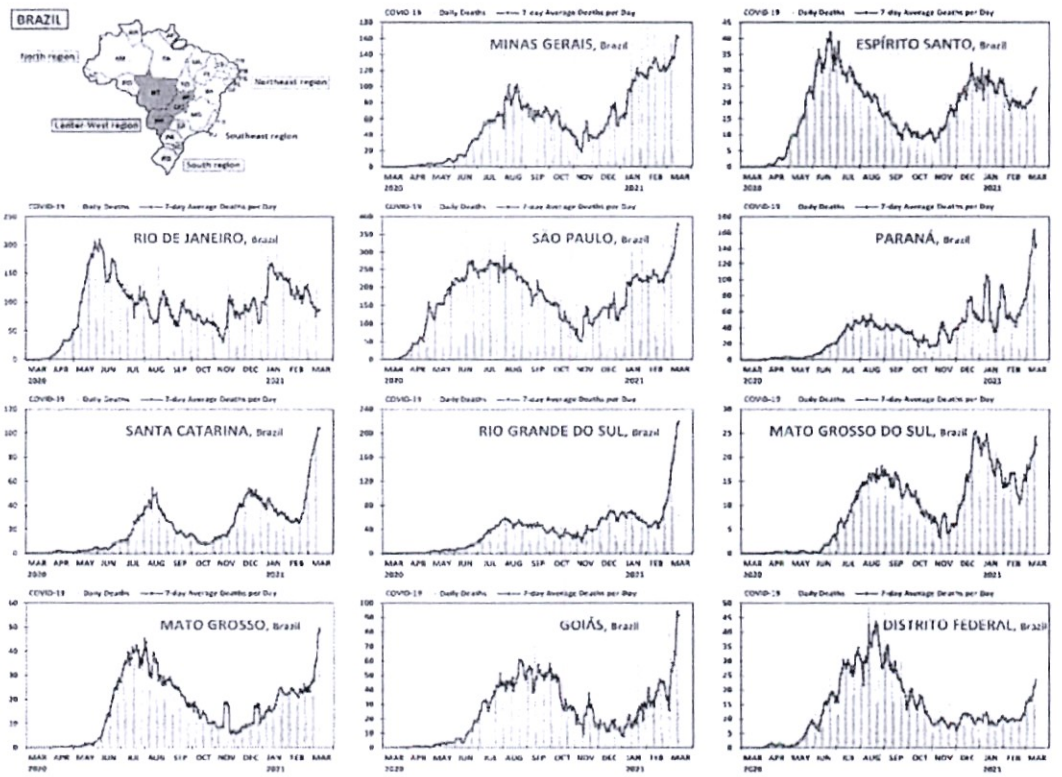


Figure 6. Daily deaths and 7-day average deaths per day of COVID-19 in the states of the Southeast, South and Center-West regions of Brazil from 1 March 2020 to 15 March 2021.

Although it is necessary to perform future in-depth research to provide a more grounded answer to explain with clarity the significant difference of the good result of Pará in combating COVID-19 in relation to that of Amazonas in the second wave (mainly in January–February 2021, when the virus variant P.1 was already present in the North region and in some states of Brazil), it is likely that the strong support of the Pará state government, after 21 May 2020, for early ambulatory treatment, may have played some role in the good result. This inference is being made because the two neighboring states were similar in the relative mortality rates at the maximums of first wave, and in the second wave they have presented significant differences, and the main difference of the behavior of the government of the two states, after 21 May 2020, was the strong support of the Pará state government to early ambulatory treatment.

It is worth commenting that since the municipalities in Brazil have autonomy in their jurisdictions to combat COVID-19, some of them have supported early ambulatory treatment policies, while others have not. Hence, it is difficult to generalize saying that a given state, as a whole, has implemented early ambulatory treatment or not. For example, in the state of Maranhão, the Regional Council of Medicine supported early ambulatory treatment from the beginning of May 2020 [51] with the medicines mentioned in Section 1, but the state government of Maranhão did not support early ambulatory treatment. In contrast to other states, in Pará there is a clear message and action of the state government that was passed to the population and to the municipalities. Most of the municipalities and the physicians of the public healthcare system in the state of Pará adhered to early ambulatory treatment after the difficult situation in May 2020, as it is detailed in Appendix B, which also discusses why this was not followed in the state of Amazonas.

As said previously in the discussion of the first wave, the measures of prevention and lock downs in April–May 2020 helped the state of Amazonas to reduce the mortality at that time. However, relaxations in measures of prevention and the more contagious P.1 variant have caused the increase in the mortality in Amazonas from December 2020, and especially from the middle of January 2021, with daily deaths higher than in May 2020. This situation (with the more contagious virus variant P.1) spread to the neighboring states of Amazonas, but Pará was the neighboring state that has suffered the least, as shown in Figure 4 and Table 1. This demonstrates that is very likely that the early ambulatory treatment implemented in the public healthcare system in the state of Pará may be one of the main causes for its relatively good results in the second wave.

Because the virus is still causing high mortality in most states of Brazil, which intensified in March 2021, as can be directly observed in Figures 5 and 6, measures of prevention [1,2,4,5] such as social distancing and wearing a mask, among others, must continue to be used; partial lockdown in some cities must also be issued, depending on the circumstances. The vaccines that were developed for COVID-19 in record time [10,11] are a major advance for humanity and for the science, technology, and innovation of the 21th century, and must be strongly supported by everyone. However, vaccination will not be so fast, especially in countries with large populations and less technological development, because most of them have not invested in advanced purchase of a significant number of doses. An additional difficulty is that in the second half of January 2021 the European Union and the United States of America—two major blocks of vaccine producers—announced some measures to restrict the export of vaccines [52,53]. The vaccination program in Brazil started in middle January 2021, and by 14 March 2021 4.59% of the population have received the first dose [47,48] (either Coronavac or Oxford/AstraZeneca). Two important research/development centers of Brazil (Instituto Butantan and Fiocruz) are producing the vaccines by using ingredients from China and India. The federal government and some state governments are negotiating with other producers; there is progress but there are also some difficulties to obtain large amounts of vaccine doses, mainly in the next months. Therefore, early ambulatory treatment for Covid-19 may still be important as shown by some groups of researchers [7,8,12–14]. The goal should always be to save as many lives as possible. The author considers that depending on the specific circumstances,

similar comparisons can be made in other geographically neighboring regions, involving countries, states, and municipalities.

4. Concluding Remarks

Amazonas and Pará, the two largest neighboring states in Brazil, were in a similar situation during the worse period of the first wave of COVID-19 outbreak in May 2020, and each state and the municipalities separately adopted procedures to contain the first wave of COVID-19 outbreak, such as partial lockdown in some cities and used several measures of prevention. However, the Pará state government, after 21 May 2020, started a strong support to early ambulatory treatment in the public healthcare system. The outcome was that Pará presented the faster reduction in Brazil of daily deaths after the maximum of the first wave: the 7-day average deaths per day decreased 95% in 70 days (from 25 May 2020 to 3 August 2020).

Now, in the second wave of COVID-19 outbreak, the state of Amazonas faced a serious situation, mainly from the middle of January to the middle of February 2021; meanwhile, the state of Pará has presented a much smaller growth in the death rates, presenting an accumulated mortality during the second wave much smaller than that of Amazonas, the other neighboring states of Amazonas, and also most of the other states of Brazil. The accumulated mortality per population so far in the second wave of COVID-19 outbreak, (from 11 November 2020 to 15 March 2021) of Amazonas and Pará are 1645 and 296 deaths per million people, respectively. This means that Amazonas is presenting an accumulated mortality per population in the second wave more than five times that of Pará, which is a significant difference. Fortunately, this large difference is decreasing because Amazonas has implemented several measures of prevention (mainly from January 2021); the vaccination program, which started in late January 2021, is also slightly contributing to decrease the daily deaths.

Although it is necessary to have future in-depth research to provide a grounded answer to explain with clarity this significant difference between Amazonas and Pará in the second wave of COVID-19 outbreak, mainly in January–February 2021 (when the virus variant P.1 was already present in the North region and in some states of Brazil), it is likely that the strong support of the Pará state government, after 21 May 2020, to early ambulatory treatment, and the adhering of the municipalities and their physicians in the public healthcare system to early ambulatory treatment, may have played a role in the good result of Pará for controlling COVID-19 (even with the presence of the virus variant P.1) in comparison with the states of the region and many states of Brazil. The comparisons offered in the present work indicates that early ambulatory treatment is an option that should not be a priori neglected in the public healthcare policies to combat COVID-19.

Depending on the specific circumstances, the type of comparison presented here can be applied, in a similar way, in other neighboring geographic entities, such as countries, states, regions, and municipalities.

Supplementary Materials: The following are available online at www.mdpi.com/1660-4601/18/7/3371/s1, File S1: provides the daily deaths and other statistical data of COVID-19 in Brazil from 25 February 2020 to 15 March 2021. File S2: contains the primary data, the determination of useful parameters, and the data used to make the graphs. File S3: provides the graphs of the country and of the federation units of Brazil.

Funding: This research received no external funding.

Data Availability Statement: The File S1 of Supplementary Materials was obtained online at https://covid.saude.gov.br/ (accessed on 15 March 2021). Each day the spreadsheet is updated, keeping the data of the past dates. The Files S2 and S3 of Supplementary Materials were made by the author as explained in Appendix A.

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Conflicts of Interest: The author declares no conflict of interest.

Disclaimer: The views expressed in this manuscript are those of the author, and they do not necessarily reflect the position or the policy of the Federal University of Espirito Santo.

Appendix A. Details on the Spreadsheets with the Data/Parameters and the Graphs

As the complete CSV File S1 is exceedingly long, mainly because it involves daily data of 5570 municipalities, it is convenient to use a TXT file editor to separate the suitable part of the data that is the focus of the analysis, before opening this part in a spreadsheet editor. As the present work involves only the country, the states and the federal district, and not the municipalities, it was sufficient to take the first 10,783 lines.

The primary data contained in the above lines were exported to the Excel File S2 of three tabs in the tab "CO-VIDBR_15mar2021-data-calc". The primary data is spread over an area of 17 columns and 10,781 rows kept intact (from column A to Q). Two rows (306 and 327) of the original spreadsheet were removed, because they were repeating the date of the previous row and the number of new deaths were zero in the original rows (306 and 327). Column R was left blank, and columns S, T, and U were used to place the necessary data of the graphs. Columns S and T provide the date and daily deaths and are copies of columns H and N. Column U provides the 7-day average daily deaths, which was calculated as 1/7 of the sum of daily deaths between the day considered and the previous six days. As there are no deaths before 17 March 2020, the 7-day average daily deaths from 1 March 2020 to 6 March 2020 was taken equal to zero in column U. From 7 March 2020 to the final date (15 March 2021) it was used the formula Un = (SUM(T(n − 6):Tn))/7, where n is the number of the row. For example, for row 13 (7 March 2020) it was used U13 = (SUM(T7:T13))/7. The number of rows in columns S, T and U for the graph of each federation unit is equal to the number of days between 1 March 2020 and 15 March 2021. For the country and each federation unit, the row corresponding to the initial date of the graphs (1 March 2020) was used, from column V to AK, to place the calculations of several parameters of interest, such as the accumulated mortality in each wave of the pandemic. All mathematical operations are simple (addition, subtraction, multiplication, and division) and can be seen in the formulas openly disclosed in the spreadsheet.

Two additional tabs ("Parameters-pop-2019" and "Parameters-pop-2020-final") were created to compile the results related with the parameters. The Parameters-pop-2019 tab was obtained by copying the data of the first tab from column V to AK and from row 7 to 10,781, and pasting the data as "values". As the spreadsheet with primary data from the Ministry of Health provides population data updated in 2019, an additional tab, Parameters-pop-2020-final, was copied from the previous one, replacing the data of the population of Brazil and its federation units updated for the year 2020 [54]. All parameters that depended on populations were recalculated. Other columns were included in this tab with several other parameters of interest. The data that appears in Table 1 were taken from that last tab.

All graphs were made in the Excel File S3 of 28 tabs. The order and the names of the tabs follow the order and abbreviations of the states and the federal district as shown in Table 1. In each tab, the columns from C to T, starting from row 7, were copied from the File S2, from column T to AK and from the rows between the start date of 1 March 2020 and the end date of 15 March 2021. It is worth observing that a technical difficulty was found in formatting the dates contained in the primary data spreadsheet, therefore, the dates that appear in column B of all tabs of File S3 were placed independently: the initial date of 1 March 2020 of cell B7 was placed manually; subsequent dates from cell B8 were obtained by adding 1 day to the previous day, for example, B8 = B7 + 1, until reaching the row of the final date (15 March 2021). Thus, the dates of the Files S2 and S3 exactly match. The formatting of the horizontal axis (containing the dates) and the secondary vertical axis (indicating the deaths per day per million people), which appear in the final graphs shown in Figures 2, 3, 4, 5 and 6, were made separately.

Appendix B. A Discussion about the Main Reasons for the Municipalities of Pará and Their Physician to Adhered to Early Ambulatory Treatment in the Public Healthcare System

To address this issue, five points are discussed: (1) Access of patients to the public healthcare system and/or to the private medical network; (2) Main approaches of the physicians to the first symptoms of COVID-19; (3) Need for a prescription for certain medicines, and availability of the medicines to private consumers; (4) Acquisition of medicines by the public sector; (5) Main causes for the municipalities and their physicians to adhere to early ambulatory treatment in the public healthcare system.

As already mentioned in Section 1, the states of Amazonas and Pará present similar SES distribution. The majority of patients have medium to low SES, and they can only have access to the public healthcare system, which is linked to the Brazilian SUS (Unified Health System). A smaller proportion of patients, primarily those with high SES, may have access to private physicians and/or to the private medical network, mainly through private healthcare plans (health insurance).

In general, two of the used approaches of the physicians to treat the first symptoms of COVID-19 are: (a) to make exams and treat the patients according to their symptoms because COVID-19 was a new disease and no medicine had been specifically approved by the control agencies (in the case of Brazil, ANVISA), and (b) to make exams and perform early ambulatory treatment according to medical protocols established early in the pandemic. It is outside the scope of the present work to discuss these protocols. Approach (a) usually involves the necessary medical exams, such as COVID-19 diagnostic test, if available. Usual medications are prescribed to treat the symptoms, such as an antipyretic in case of fever. The medicines in general can be purchased at pharmacies or, eventually, made available by the doctor or the healthcare unity that the patient is attended. Most patients do not progress to severe cases of the disease. However, if the patient's health condition became worse, appropriate medical interventions have to be performed. Sometimes it is necessary to admit the patient to an intensive care unit in hospital where intubation procedures may be required. Approach (b) usually involves the necessary medical exams, such as COVID-19 diagnostic test, if available, but an early ambulatory treatment begins if the patient presents the first symptoms of the disease, according to medical protocols established early in the pandemic. It is informed that such a procedure is important since part of the tests to detect COVID-19 take several days for the result to be released, and many tests give false-negative results [8,12,13]. As mentioned in Section 1, the medicines that have been recommended in scientific studies [7,8,12–14] are: hydroxychloroquine, azithromycin and ivermectin, among others. It is worthy to mention that it is outside the scope of the present work to discuss first symptoms of the disease, and the doses, the effects, and the actions of the medicines, combined or not. Some critics of approach (b) usually say that that there is no evidence that the medicines have any benefit at all stages of COVID-19 [10,55], and the patients can suffer from side effects from the medications [55]. However, the researchers that support early ambulatory treatment say that it is not possible to know, a priori, how the disease will develop in any particular person, and it is especially important starting the treatment as soon as possible at the first symptoms [7,8,12–14], because this improve the combating of the disease; they say that the benefits that can be achieved (in terms of saving lives) outweigh the harm caused by possible side effects from the medicines.

Concerning the need for a prescription for the medicines, in the beginning of the pandemic, only azithromycin, because it is an antibiotic, needed a medical prescription in Brazil. Hydroxychloroquine and ivermectin were over-the-counter drugs that could be obtained without a prescription. However, shortly after the beginning of the pandemic, a prescription was necessary to purchase hydroxychloroquine after 20 March 2020 [56] and ivermectin after 22 July 2020 [57]. The need for a prescription for ivermectin was revoked on 1 September 2020 [58], but that for hydroxychloroquine is still maintained. With regard to the availability of medicines, shortly after the start of the pandemic, the press, and the

social networks, mainly messaging apps such as WhatsApp, reported the possibility of using some medicines, such as those above mentioned, to combat COVID-19. It was also reported that some of the medicines might not work and that they could cause side effects. Even with the critical news, there was a great demand for these medicines in Brazil, and the price of two of them (hydroxychloroquine and ivermectin) increased substantially, and they were practically sold out in the pharmacies for some months. Therefore, the purchase of two of the medicine by patients individually was very restricted, even for those who had a prescription and had financial resources to purchase them. The purchase of these medicines by healthcare plan operators of the private medical network, such as Unimed Belém, was possible because the purchase was made directly from manufacturers or representatives.

Regardless of the pandemic, the purchase of medicines by the public healthcare system for distribution to patients is particularly important in Brazil, especially for low SES patients. In many cases, when public healthcare units do not provide the medications to the patients, even with a prescription and the medications available at pharmacies, many low SES patients have financial difficulties to purchase them. In Brazil, public organizations must make the purchase of medicines and other supplies through a bidding process, which requires time and work, in addition to financial resources. If there is urgency, as in the case of the beginning of the pandemic, the bidding process may be simplified, but the public organization lawyers must prepare and publish a document with grounded justifications for the procedure, as the municipality of Afuá-PA did on 13 May 2020 [43]. However, this is laborious and requires determination, in addition to depending on financial resources. The great difference of the state of Pará in relation to Amazonas and the other states of Brazil was that the state government made the purchase process in a centralized way for all municipalities in the state. The public healthcare system received the medications in their municipalities without having to follow the entire purchase process, which involve bureaucratic issues, publication of documents, search for suppliers, payment and, finally, the receipt of the medications.

In that situation of May 2021, with a high mortality rate, the physicians in the public healthcare system of the state of Pará were able to choose the approach of early ambulatory treatment after 21 May 2020, because: (1) the results of the other approach were not so successful (the number of deaths was increasing steadily); (2) the actions for COVID-19 of Unimed Belém and the municipality of Ourilândia do Norte-PA for their patient in the beginning of May 2020 [42,44] was an incentive; and (3) in Pará the medicines were available and provided free of charge by the state government. In the public medical healthcare units of Pará, the patients received the medicines directly at the end of the medical consultation; they did not need to go to the pharmacy. The particularly good practical result achieved from the fourth week of May 2020 in Pará gave credibility to the early ambulatory treatment in the public healthcare system.

In Amazonas, early ambulatory treatment was difficulted in the public healthcare system mainly because the state government did not support early ambulatory treatment, and, therefore, did not purchase the medicines.

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nutrients

MDPI

Systematic Review

Preventive Vitamin D Supplementation and Risk for COVID-19 Infection: A Systematic Review and Meta-Analysis

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Abstract: Over the past few decades, vitamin D has been found to play a crucial role in bone homeostasis, muscle function, oncogenesis, immune response and metabolism. In the context of the COVID-19 pandemic, numerous researchers have tried to determine the role vitamin D might play in the immune response to the virus. The aim of this systematic review and meta-analysis is to demonstrate that preventive vitamin D supplementation can play a protective role in the incidence of COVID-19, mortality and admission to intensive care units (ICUs). A comprehensive search on the PubMed/MEDLINE, Scopus, Cochrane and Google Scholar databases was performed on 15 May 2023, and two of the authors independently screened the literature. As effect measures, we calculated the Odds Ratios with their corresponding 95% confidence intervals (ICs). The assessment of potential bias and the evaluation of study quality will be conducted independently by two researchers. Sixteen publications were selected for inclusion in the meta-analysis. Our findings indicate that vitamin D supplementation has a protective effect against the incidence of COVID-19 in RCT studies (OR 0.403, 95% IC 0.218, 0.747), in the incidence of COVID-19 in analytical studies (OR = 0.592, 95% IC 0.476–0.736) and in ICU admission (OR 0.317, 95% IC 0.147–0.680). Subsequent analyses were conducted by type of subject treated (patient/healthcare workers) and type of supplementation (vitamin D vs. placebo/no treatment or high dose vs. low dose). Our meta-analysis suggests a definitive and significant association between the protective role of vitamin D and COVID 19 incidence and ICU admission.

Keywords: vitamin D; COVID-19; prevention

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1. Introduction

Vitamin D is a fat-soluble vitamin and is synthesized in the epidermis. In order to become active, it requires further metabolic processes. These processes occur in the liver via 25-hydroxylation and in the kidney. The primary end product of this process is 1,25-dihydroxyvitamin D, which binds to the vitamin D receptor (VDR). The majority of the effects of vitamin D are mediated by the VDR, which promotes the expression of genes containing specific DNA sequences and is expressed in almost all nucleated cells [1]. The resulting interplay between vitamin D, VDR and the promoter/repressor proteins plays a crucial role in influencing bone mineral density, with its deficiency causing rickets and osteomalacia in children and osteomalacia in adults. The interaction of vitamin D with its receptor increases the efficiency of intestinal calcium absorption from 10–15% to 30–40% and phosphorus absorption from 60 to 80%. Its deficiency causes a decrease in intestinal calcium absorption and an increased parathyroid hormone (PTH) level. PTH activates the transformation of preosteoclasts to mature osteoclasts, which dissolves the collagen

matrix in bone and causes phosphaturia, thus reducing the mineralization of the collagen matrix [2].

Vitamin D sufficiency is normally estimated by measuring 25 hydroxyvitamin D (25[OH]D); however, the optimal serum vitamin D level for skeletal health is controversial, mostly because the target may vary by stage of life and ethnicity [3–5]. The National Institutes of Health suggest that the skeletal health of people with vitamin D concentrations below 30 nmol/L (12 ng/mL) is at risk for vitamin D insufficiency, whereas this condition is also expected for the skeletal health of some people with vitamin D concentration levels of less than 50 nmol/L (20 ng/mL) [6].

For other authors, the minimum desirable concentration for the skeletal health of vitamin D ranges between 70 and 80 nmol/L [7]. As approximately 3 percent of the human genome is under the control of 1,25-dihydroxyvitamin D, the activity of vitamin D has been theorized to be involved in the regulation of other systems, such as muscle function, oncogenesis, immune response and metabolism. However, since there is no clear evidence in vivo regarding the potential advantages of vitamin D in the regulation of these systems, the establishment of a definitive cut-off value for vitamin D levels is still under scrutiny [8].

In the context of the association between vitamin D and infection, it is important to note that a definitive correlation between the impact of diminished or elevated levels of vitamin D and the occurrence or gravity of the infection remains elusive. On the other hand, vitamin D has been observed to attenuate the activation of the acquired immune system, to contribute to the synthesis of defensins, to be pivotal for enhancing the phagocytic activity of macrophages towards pathogens [9] and to modulate the immune system response by regulating the inflammatory cascade [10].

The overall effect of vitamin D has nonetheless been under evaluation in different diseases. Currently, the main areas of study regarding the role of vitamin D in the response to infections concern, to varying degrees, the respiratory system (COPD exacerbations, tuberculosis, upper respiratory disease and COVID-19) [11,12]. Regarding COVID-19, there is growing interest in understanding the role of vitamin D in the immune response to the virus, especially given its unique role as a pathogen compared to other viral forms that cause respiratory tract infections [13–15]. Based on current findings, the role of vitamin D in COVID-19 is still under investigation. There exist data supporting the proposition that adequate levels of serum vitamin D may confer protection against COVID-19 infections, both in terms of incidence and mortality. Authors who assert this correlation have relied on observational studies wherein vitamin D levels appeared protective even after adjustments for variables such as age, gender and comorbidities [16]. However, it is important to highlight that previous research has failed to validate this hypothesis, partially because they discovered that vitamin D deficiency was secondary to other factors correlated with a higher susceptibility to SARS-CoV-2 infection [17]. The objective of this current meta-analysis is to examine whether the administration of vitamin D for any purpose prior to the onset of COVID-19 disease could yield a beneficial outcome in terms of prevalence, complications and mortality. This will be accomplished by assessing studies that specifically considered the adjustment of other variables.

2. Materials and Methods

This systematic review and meta-analysis of the literature was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [18] to ensure the current standards for systematic review reporting were met. The investigated question was formulated using the PICO methodology. The population comprised patients or healthcare workers supplemented with vitamin D before COVID-19 infection, with the primary outcome being COVID-19 incidence and secondary outcomes including ICU admission and mortality. The study protocol was registered on the PROSPERO database (registration number CRD42023469817) [19].

2.1. Data Sources and Search Strategy

A comprehensive search on the PubMed/MEDLINE, Scopus, Cochrane and Google Scholar databases was performed for a combination of keywords ("COVID-19" OR "SARS-CoV-2" OR "coronavirus" OR "2019-nCoV") AND ("vitamin D" OR "cholecalciferol" OR "calcitriol") using Medical Subject Heading (MeSH) terms as vocabulary, according to the National Center for Biotechnology Information (NCBI) nomenclature and guidelines and, where appropriate, a wild-card option.

2.2. Selection of Studies

Inclusion criteria were (1) articles with relevant quantitative details and information on Vit D supplementation before a COVID-19 diagnosis and its protective role against COVID-19 infection, mortality and other clinically significant outcomes; (2) RCT, cohort, cross-sectional, case-control and quasi-experimental studies were considered.

Exclusion criteria were (1) items not directly pertinent to the query string; (2) articles not containing sufficient information on the relationship between vitamin D supplementation before COVID-19 infection and outcome; (3) articles not meeting the PICOS criteria (P: patients and healthcare workers; I: patients or healthcare workers supplemented with Vit D before COVID-19 infection; C: patients or healthcare workers who received the standard dose, a lower dose, no therapy or a placebo; O: COVID-19 incidence, ICU admissions and mortality; S: RCT, cohort, cross-sectional, case–control and quasi-experimental studies were considered); all such articles were consequently discarded. No time filter or language filter was applied. For further details of the search strategy, see Table 1.

Table 1. Search strategy adopted in the present systematic review and meta-analysis.

Search Strategy	Details	
Search string	("COVID-19" OR "SARS-CoV-2" OR "coronavirus" OR "2019-nCoV") AND ("vitamin D" OR "cholecalciferol" OR "calcitriol")	
Inclusion criteria	P (patients/population):	Patients and healthcare workers
	I (intervention/exposure):	Patients or healthcare workers supplemented with Vit D before COVID-19 infection
	C (comparisons/comparators):	Patients or healthcare workers who received the standard dose, a lower dose, no therapy or a placebo
	O (outcome):	COVID-19 incidence, ICU admissions and mortality
	S (study design):	RCT, cohort, cross-sectional, case–control and quasi-experimental studies were considered
Databases	PubMed/MEDLINE, Scopus, Cochrane and Google Scholar	
Exclusion criteria	Experimental studies investigating in vitro or animal models Study design: editorial, commentaries, expert opinions, letters to the editor, review articles, original non-prospective studies and articles with insufficient details	
Time filter	None (from inception)	
Language filter	None (any language)	

2.3. Data Extraction and Risk of Bias Assessment

Two authors independently screened the literature. Any case of disagreement was solved by discussion until consensus was reached. After the full test review, the papers included were retained for data extraction.

Data for the meta-analysis were extracted from the studies included by means of a standardized documentation form. The parameters extracted were the surname of the first author, the year and country of publication, the type of study, number of deaths, ICU admission, length of stay, endotracheal intubation, number of COVID-19 infections, age, sex, type of comparison performed in the study (i.e., vitamin D supplementation vs. no treatment; high-dose vs. low-dose vitamin D supplementation; vitamin D vs. placebo); duration of intervention; amount of vitamin D supplemented in the treated group and

where available also in the control group; number of patients enrolled and their subdivision in the subgroup.

As effect measures, we calculated the Odds Ratios with their 95% confidence intervals (CIs). The assessment of potential bias and the evaluation of study quality were conducted independently by four researchers employing distinct assessment tools tailored to the specific study design presented in the paper at hand. Specifically, for case series, we employed the "National Institutes of Health (NIH) quality assessment tool for case series studies". For papers presenting cohort or cross-sectional studies, we utilized the "National Institutes of Health (NIH) quality assessment tool for observational cohort and cross-sectional studies". In the case of case–control studies, we employed the "National Institutes of Health (NIH) quality assessment tool for case–control studies" and for the RCT, the "The National Institutes of Health (NIH) quality assessment tool of controlled intervention study" [20]. Any disagreement was solved by consensus.

Ten studies were classified as "good" [21–29], six as "fair" [30–35] and one as "poor" [36].

2.4. Statistical Analysis

Data synthesis, both qualitative and quantitative, was undertaken by a pair of researchers. Any inconsistencies or discrepancies encountered during this process were diligently resolved through direct confrontation and contributions from all the researchers. For the meta-analysis, we employed STATA SE 18, a robust statistical software package. During the meta-analysis, we also rigorously assessed statistical heterogeneity using both the I^2 statistics and the heterogeneity χ^2 test. Heterogeneity was deemed statistically significant when the p-value (χ^2) was <0.1. More specifically, we established that I^2 values of 25%, 50% and 75% corresponded to low, moderate and high levels of heterogeneity, respectively. In instances where heterogeneity reached a significant level, classified as either moderate or high, we employed a random-effects model for the meta-analysis. In the case of low heterogeneity, a fixed model was used. The results of our study analysis will be presented using summary outcome and effect measures.

The ORs of the meta-analyses were deemed significant when the confidence intervals did not contain the value "1". A narrower confidence interval than that of the individual studies indicates less imprecision.

To identify sources of variation, further stratification was performed with respect to study quality. In addition, in the sensitivity analyses, the stability of the pooled estimate with respect to each study was investigated by excluding individual studies from the analysis. Possible publication bias was visually inspected by means of a funnel plot. If asymmetry was detected by visual assessment, exploratory analyses using trim and/or fill analysis were performed in order to investigate and adjust this. In addition, the probability of publication bias was tested by means of Egger's linear regression, with a value of $p < 0.05$ being indicative of publication bias.

3. Results

A total of sixteen publications were included in the analysis (Figure 1). Among these publications, three [24,26,29] featured two studies each. In total, seven RCTs were evaluated, while the remaining studies were categorized as analytical studies. Among the seven RCTs [21,23,25,28,29,35,36], five were conducted on HCWs [28,29,35,36], while the other two focused on patients. Among the five RCTs conducted on HCWs, four compared a population undergoing vitamin D treatment with a population not undergoing treatment [28,29,36], while one compared a high-dose vitamin D regimen with a low-dose regimen [35]. As regards the two RCTs performed on patients, one compared a treated population with an untreated one [23], and the second compared a high-dose regimen with a low-dose regimen [25]. All studies conducted on HCWs were performed as RCTs. The remaining eight analytical studies evaluated the incidence of vitamin D supplementation in a patient population. Three analytical studies assessed the ICU admission rate [22,27,31] and eleven studies evaluated mortality, with ten being analytical and one being an RCT [21,22,24,26,27,30–32,34].

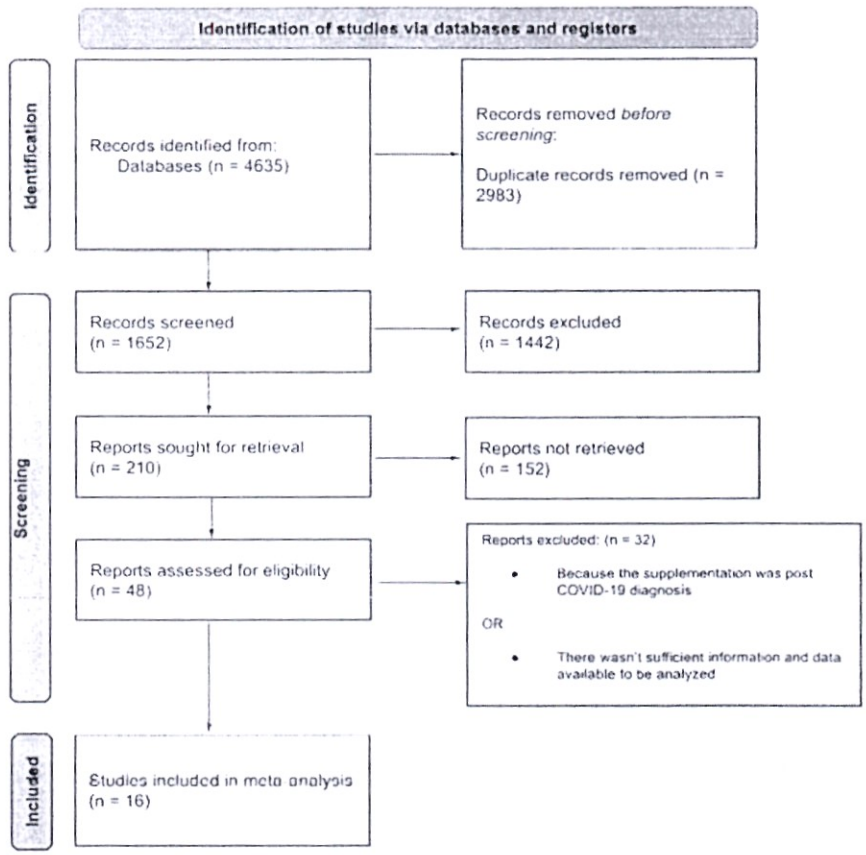

Figure 1. PRISMA 2020 flow diagram of study selection, inclusion and synthesis [18].

The main characteristics of studies included in the meta-analysis are presented in Table 2. In addition to the previously discussed features, such as study design, type of participants (patients or healthcare workers) and different treatment types, Table 2 provides information on the setting of each study, along with the number of participants, age (mean ± standard deviation or median and interquartile range (IQR)) and sex (in absolute number and percentage). These details are further subdivided into the group that received vitamin D supplementation and the control group.

Table 2. Characteristics of studies included in meta-analysis.

References	Study Design, Setting	Participants	Vitamin D Supplementation Group			Control Group			Outcomes (Relevant for This Meta-Analysis)
			No.	Age	Sex, Male	No.	Age	Sex, Male	
Annweiler, G. et al., 2020 [21]	Quasi-experimental with retrospective collection of data, France	Patients	29	88 (87–93)	9 (31.0)	32	88 (84–92)	19 (59.4)	Mortality
Hernandez, J.L. et. al., 2020 [22]	Case–Control, Spain	Patients	19	60.0 (59.0–75.0)	7 (36.8)	197	61.0 (56.0–66.0)	123 (62.4)	Mortality, ICU admission
Arroyo-Diaz, J.A. et al., 2021 [31]	Cross-Sectional, Spain	Patients	189	73.3 ± 13.7	62 (32.8)	1078	63.2 ± 16.3	634 (58.8)	Mortality, ICU admission
Cangiano, B. et al., 2021 [30]	Prospective Cohort, Italy	Patients	20	NA	NA	78	NA	NA	Mortality
Cereda, E. et al., 2021 [32]	Retrospective Cohort, Italy	Patients	18	68.8 ± 10.6	16 (42.1)	152	70.5 ± 13.1	141 (49.3)	Mortality
Ma, H. et al., 2021 [33]	Prospective Cohort, USA	Patients	363	59.1 ± 8.1	141 (38.8)	7934	57.4 ± 8.6	3964 (50.0)	SARS-CoV-2 Incidence
Orlstrell, J. et al., 2021 [34]	Case–Control, Spain	Patients	6252	70.2 ± 15.6	2656 (42.5)	12,504	70.7 ± 14.7	5319 (42.5)	Mortality, COVID 19 incidence
Brunvoll, S.H. et al., 2022 [23]	RCT, Norway	Patients	17,278	45.0 ± 13.5	6117 (35.4)	17,323	44.9 ± 13.4	6137 (35.4)	SARS-CoV-2 Incidence

Table 2. *Cont.*

References	Study Design, Setting	Participants	Vitamin D Supplementation Group			Control Group			Outcomes (Relevant for This Meta-Analysis)
			No.	Age	Sex, Male	No.	Age	Sex, Male	
Gibbons, J.B. et al., 2022 [24]	Retrospective Cohort, USA	Patients	33,216	58	29,130 (87.7)	33,216	58	29,097 (87.6)	Mortality, COVID-19 Incidence
	Retrospective Cohort, USA	Patients	199,498	63	179,349 (89.9)	199,498	64	179,748 (90.1)	Mortality, COVID-19 Incidence
Jolliffe, D.A. et al., 2022 [25]	RCT, UK	Patients	1346	60.7 (50.2–68.5)	506 (37.6)	1328	59.8 (50.3–67.4)	498 (37.5)	Mortality, COVID-19 Incidence
Karonova, T.L. et al., 2022 [35]	RCT, Russia	Healthcare Workers	38	34 ± 2	6 (15.8)	40	36 ± 2	6 (15.0)	COVID-19 Incidence
Oristrell, J. et al., 2022 [26]	Retrospective Cohort, Spain	Patients	108,343	70.0 ± 14.0	17,926 (16.5)	216,686	70.0 ± 14.6	35,272 (16.3)	Mortality, COVID-19 Incidence
	Retrospective Cohort, Spain	Patients	134,703	68.8 ± 14.9	29,474 (21.9)	269,406	68.8 ± 15.1	59,582 (22.1)	Mortality, COVID-19 Incidence
Parant, F. et al., 2022 [27]	Retrospective Cohort, France	Patients	66	NA	27 (40.9)	162	NA	102 (63.0)	Mortality, ICU admission
Van Helmond, N. et al., 2022 [36]	RCT, USA	Healthcare Workers	255	47 ± 12	55 (21.6)	578	50 ± 13	131 (22.7)	COVID-19 Incidence
Villasis-Keever, M.A. et al., 2022 [28]	Double-Blind RCT, Mexico	Healthcare Workers	94	36.0 (30–43)	NA	98	39.0 (31–48)	NA	COVID-19 Incidence
Romero-Ibarguengoita, M.E. et al., 2023 [29]	Prospective Quasi-Experimental, Mexico	Healthcare Workers	43	NA	17 (39.5)	42	NA	23 (54.8)	COVID-19 Incidence
	Prospective Quasi-Experimental, Mexico	Healthcare Workers	28	NA	8 (28.6)	85	NA	20 (23.5)	COVID-19 Incidence

NA = not applicable.

Finally, the outcomes (COVID-19 incidence, mortality and ICU admission) for each included study are reported. Globally, as indicated in Table 2, COVID-19 incidence was assessed in thirteen studies, mortality in eleven studies and intensive care unit admission in only three studies.

Table 3 provides details on the amounts of vitamin D administered and the type of comparison used in the two treatment arms (intervention and control) for each study, where available. The precise amount of vitamin D administered was available for 15 out of 19 studies and was reported in IUs (International Units), mg (e.g., 1 IU is equal to 0.000025 µg) or µg (e.g., 1 IU is equal to 0.025 µg). The frequency of vitamin D administration varied, with some studies using daily, weekly or monthly dosing. In 4 out of 19 studies, the amount of vitamin D administered was not reported, and in two studies, the vitamin D molecule was not mentioned.

The doses of vitamin D (cholecalciferol) administered as IU/daily were 5000, 4000, 3200, <1000 and 400; those administered as IU/weekly were 50,000 and 5600; and those administered as IU/monthly were 100,000, 90,000, 80,000, 52,000, 50,000, 25,000 and 10,000. The doses of vitamin D administered as calcifediol were 54,000 IU/monthly, 0.266 mg/monthly and 250 µg per dose. Ergocalciferol (vitamin D2) supplementation was only reported in one study. Calcitriol supplementation was also reported in only one study.

In 14 out of 19 studies, the control group did not receive vitamin D supplementation. In 2 out of 19 studies, the control group received a lower dose of vitamin D (2000 and 800 IU/d), and in 3 out of 19 studies, the control group received a placebo.

Additionally, Table 3 presents the number of events as absolute numbers (n/N) and percentages (%) for each analyzed outcome in both the intervention and control groups.

Table 3. Characteristics of the study outcomes included in the meta-analysis.

References	Treatment Arms	COVID-19 Incidence (*n*/N, %)		All-Cause Mortality (*n*/N, %)		ICU Admission (*n*/N, %)	
		Intervention	Control	Intervention	Control	Intervention	Control
Annweiler, G. et al., 2020 [21]	Intervention: 50,000 IU/month, 80,000 IU or 10,000 IU every 2–3 months (cholecalciferol); control: no vitamin D supplementation	NA	NA	2/29 10.53	10/32 31.25	NA	NA
Hernandez, J.L. et al., 2020 [22]	Intervention: (11 patients were taking cholecalciferol, 25,000 IU/monthly in 10 cases and 5600 IU/weekly in 1, and 8 patients were on calcifediol, 0.266 mg/monthly)	NA	NA	2/19 10.53	20/197 5.08	1/19 5.26	50/197 25.38
Arroyo-Diaz, J.A et al., 2021 [31]	Intervention: regularly supplemented with vitamin D (not specified); control: no vitamin D supplementation	NA	NA	50/189 26.46	167/1078 15.49	13/189 6.88	133/1078 12.34
Cangiano, B. et al., 2021 [30]	Intervention: 25,000 IU of cholecalciferol 2 times a month; control: no vitamin D supplementation	NA	NA	3/20 15	39/78 50	NA	NA
Cereda, E. et al., 2021 [32]	Intervention: 54,000 IU/month of calciferol; control: no vitamin D supplementation	NA	NA	7/18 38.89	40/152 26.32	NA	NA
Ma, H. et al., 2021 [33]	Intervention: regularly supplemented with vitamin D (not specified); control: no vitamin D supplementation	49/363 13.50	1329/7934 16.75	NA	NA	NA	NA
Oristrell, J. et al., 2021 [34]	Intervention: regularly supplemented with vitamin D (mean daily calcitriol dose: ≤0.1 µg/d; >0.1–0.2 µg/d; >0.2–<0.4 µg/d; ≥0.4 µg/d); control: no vitamin D supplementation	328/6252 5.25	703/12,504 5.62	76/6252 1.22	208/12,504 1.66	NA	NA
Brunvoll, S.H. et al., 2022 [23]	Intervention: 5 mL/day of cod liver oil (equal to 10 µg/d or 400 IU/d of vitamin D3); control: placebo	227/17,278 1.31	228/17,323 1.32	NA	NA	NA	NA
Gibbons, J.B. et al., 2022 [24]	Intervention: regularly supplemented with vitamin D (vitamin D2 or ergocalciferol); control: no vitamin D supplementation	716/33,216 2.16	987/33,216 2.98	65/33,216 0.19	86/33,216 0.26	NA	NA
	Intervention: regularly supplemented with vitamin D (vitamin D3 or cholecalciferol); control: no vitamin D supplementation	5315/199,498 2.56	6591/199,498 3.30	462/199,498 0.23	689/199,498 0.35	NA	NA

Table 3. *Cont.*

References	Treatment Arms	COVID-19 Incidence (*n*/N, %)		All-Cause Mortality (*n*/N, %)		ICU Admission (*n*/N, %)	
		Intervention	Control	Intervention	Control	Intervention	Control
Jolliffe, D.A. et al., 2022 [25]	Intervention: 3200 IU/day of vitamin D3; control: 800 IU/day	45/1346 3.34	55/1328 4.14	NA	NA	NA	NA
Karonova, T.L. et al., 2022 [35]	Intervention: 50,000 IU/week of cholecalciferol for 2 consecutive weeks, followed by 5000 IU/day for the rest of the study; control: 2000 IU/day	10/38 26.31	18/40 45.00	NA	NA	NA	NA
Orstrell, J. et al., 2022 [26]	Intervention: >250 µg of cholecalciferol per dose (equal to 10,000 IU); control: no vitamin D supplementation	4352/103,343 4.02	9142/216,686 4.22	716/108,343 0.66	1492/216,686 0.69	NA	NA
	Intervention: >250 µg of calcifediol per dose (equal to 10,000 IU); control: no vitamin D supplementation	5662/134,703 4.20	11,401/269,406 4.23	934/134,703 0.69	1859/269,406 0.69	NA	NA
Parant, F. et al., 2022 [27]	Intervention: <1000 IU/d or 80,000 IU or 100,000 IU every 2–3 months of cholecalciferol; control: no vitamin D supplementation	NA	NA	7/66 10.61	28/162 17.28	10/66 15.15	74/162 45.68
Van Helmond, N. et al., 2022 [36]	Intervention: 5000 IU/d of vitamin D3; control: placebo	0/255 0.00	36/578 6.23	NA	NA	NA	NA
Villasis-Keever, M.A. et al., 2022 [28]	Intervention: 4000 IU/d of cholecalciferol; control: placebo	6/94 6.38	24/98 24.49	NA	NA	NA	NA
Romero-Ibarguengoita, M.E. et al., 2023 [29]	Intervention: 52,000 IU/month of vitamin D3; control: no vitamin D supplementation	5/43 11.63	13/42 30.95	NA	NA	NA	NA
	Intervention: 90,000 IU/month of vitamin D3; control: no vitamin D supplementation	9/28 32.14	29/85 34.12	NA	NA	NA	NA

NA = not applicable.

3.1. Evidence from RCTs on COVID-19 Infection Risk

In the seven RCTs considered and assessed via a random-effects model, vitamin D supplementation was associated with a decreased infection risk (OR 0.403, 95% IC 0.218–0.747) despite substantial heterogeneity among the studies. Among the seven RCTs, five were conducted on healthcare workers (HCWs) and were more reliable in terms of heterogeneity (Figure 2).

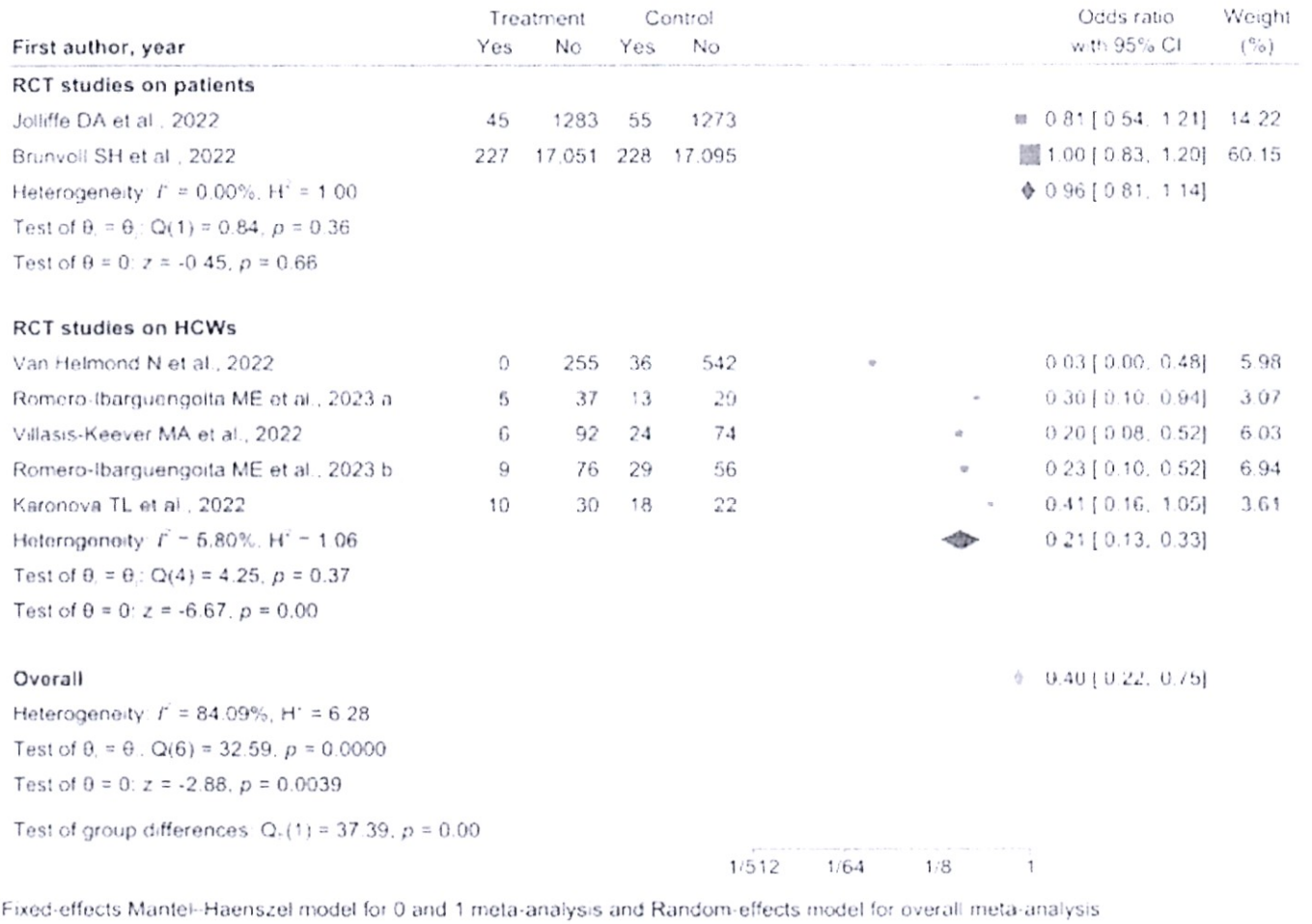

Figure 2. Forest plot of randomized controlled trials (RCTs) conducted separately on healthcare workers (HCWs) and patients, as well as collectively [23,25,28,29,35,36].

In the RCTs performed on HCWs, the overall reduction in risk in the population supplemented with vitamin D was approximately 80% (OR 0.210, 95% IC 0.132–0.332). The level of heterogeneity among the studies was negligible (I^2 = 5.80), and therefore a Mantel–Haenszel fixed-effects model was used. In four of the five RCTs, the follow-up time frame was adequate (at least 6 months); the only one with a shorter follow-up (45 days) was the only multicenter trial performed on HCWs. Vitamin D deficiency and insufficiency prevalence was consistent among the studies that included its measurement in their design (55–67% prevalence of vitamin D deficiency, 27–30% prevalence of vitamin D insufficiency and 6–15% of subjects presenting normal values).

Four out of the five RCTs performed on HCWs compared vitamin D supplementation with no treatment or dietary measures (treatment vs. no treatment). One evaluated the effect of a higher dosage versus a low vitamin D dosage. The treatment vs. no treatment analysis confirmed low heterogeneity among the studies and a higher protective effect of vitamin D supplementation (OR 0.177, 95% IC 0.104–0.301).

Regarding the effect of vitamin D supplementation on non-HCWs and registered by RCTs, there was no effect on the COVID-19 infection rate (OR 0.963, 95% IC 0.814–1.139). This may lead to some uncertainty concerning the effectiveness of vitamin D supplementation in the general population. However, it should be highlighted that in the study by Brunvoll, the treatment group was exposed to lower dosages of vitamin D supplementation (400 IU) in comparison to other studies. The combined low prevalence of vitamin D deficiency in the study population and low dosage of supplementation may have resulted in an absence of the effect of vitamin D supplementation.

Through the evaluation of the RCT results, we observed that vitamin D supplementation resulted in a benefit for the population when compared with a population not subjected to supplementation (OR 0.307, 95% IC 0.127–0.739) (Figure 3), while this benefit was not maintained when compared with a population subjected to vitamin D supplementation on a reduced dosage (OR 0.730, 95% IC 0.505–1.055).

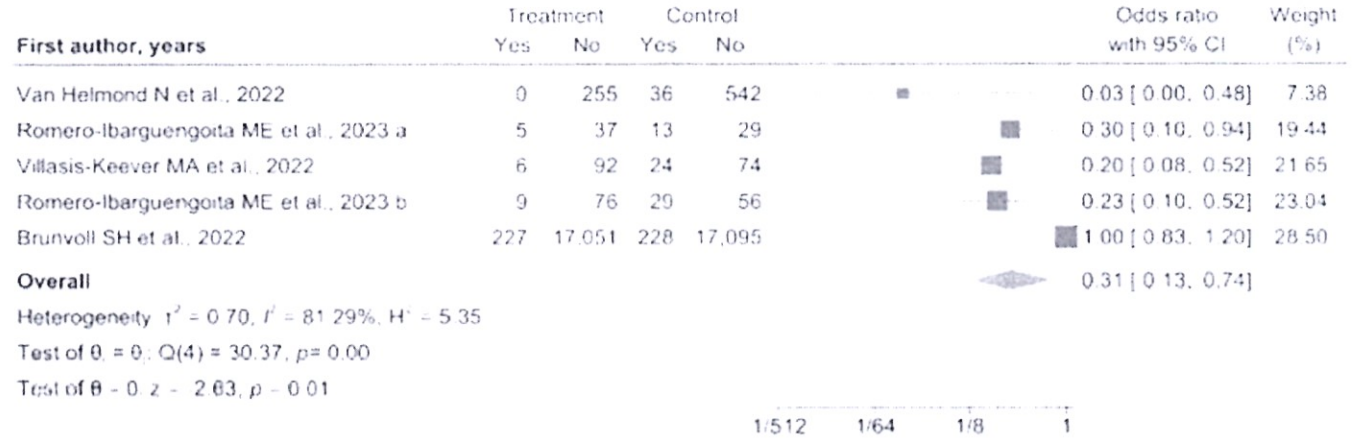

Figure 3. Forest plot of randomized controlled trials (RCTs) comparing vitamin D supplementation to no supplementation [23,28,29,36].

3.2. Evidence from Analytic Studies on COVID-19 Infection Risk

Since these studies analyzed people who were administered different dosages of vitamin D supplementation versus people who were not receiving treatment, there was no standardization of the intervention. Consequently, we found limited data regarding the prevalence of vitamin D deficiency and insufficiency. Conversely, the analytical studies were based on a greater number of patients and with longer study durations. The resulting meta-analysis confirmed the protective role of vitamin D supplementation (OR 0.592, 95% IC 0.476–0.736) despite high heterogeneity among the studies (I^2 = 98.99).

3.3. Evidence from RCTs and Analytical Studies on SARS-CoV-2-Related Mortality

The only RCT evaluating vitamin D supplementation prior to COVID-19 infection and subsequent mortality was performed on 66 participants. People receiving vitamin D (in this case, a single bolus of 80,000 IU) had significantly lower mortality after adjustment for all potential confounders. No other covariables were associated with mortality (OR 0.163, 95% IC 0.0.32–0.832).

Regarding the analytical studies, no association was found between vitamin D supplementations prior to COVID-19 infection and relative mortality (OR 0.882, 95% IC 0.667–1.165). Out of the ten studies included, only three demonstrated a protective action of vitamin D against mortality in multivariable analysis. It should be noted, however, that some selection biases might limit the generalizability of the conclusions drawn from such analytical studies. In several studies, we found significant differences in the populations at baseline, despite overall homogeneity in terms of confounding variables between

cases and controls. Most studies were carried out without adequate matching between cases and controls. In particular, some differences regarding BMI and age were found in two studies [27,30], while differences between the prevalence of chronic renal insufficiency, cardiovascular disease and the Charlson comorbidity index were found in another one [31]. Just three studies performed propensity score matching between cases and controls [24,26,34]. Furthermore, a high level of heterogeneity was found in the meta-analysis of the analytical studies (I^2 = 93.93)

3.4. Evidence from Analytical Studies on ICU Admissions

Three analytical studies evaluated the effect of previous vitamin D supplementation and ICU admission due to complications of COVID-19 infection. The meta-analysis performed with the random-effects model revealed that prior vitamin D supplementation may have a protective role against ICU admission (OR 0.317, 95% IC 0.147–0.680) (Figure 4).

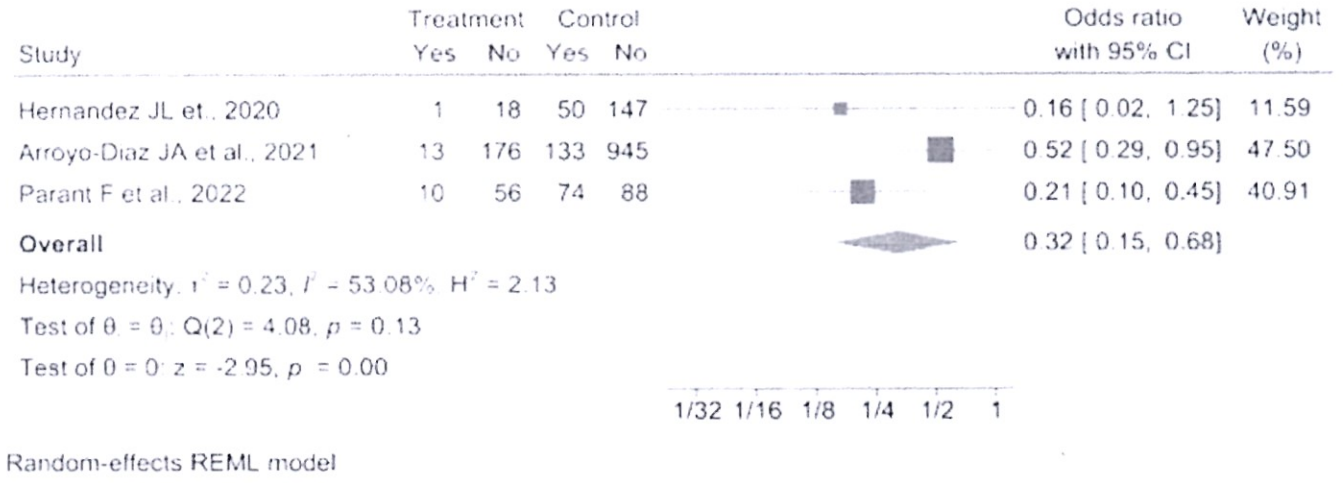

Figure 4. Forest plot demonstrating ability of vitamin D supplementation to reduce ICU admission [22,27,31].

It should be noted that among the three studies included, one study was based on two populations with differences at baseline, while the other two were conducted on populations with a high prevalence of vitamin D deficiency/insufficiency at baseline.

4. Discussion

In this meta-analysis of 19 studies, consisting of 7 RCTs and 12 analytical studies encompassing a total of 1,262,235 participants, we aimed to assess the potential protective role of vitamin D supplementation before COVID-19 infection in terms of the reduction in the incidence of COVID-19 infection, ICU admission and mortality. It was possible to evaluate the incidence of COVID-19 infection in 13 out of 19 studies, mortality in 11 out of 19 studies and ICU admission in only 3 out of 19 studies.

Both RCTs and analytical studies observed a decrease in the incidence of COVID-19 infection in the population subjected to vitamin D supplementation. However, certain aspects remain to be addressed. Concerning the RCTs, limitations such as sample size and their monocentric nature may impact the generalizability of their conclusion, while the analytical studies showed a lack of data regarding the prevalence of vitamin D deficiency/insufficiency at baseline. Nonetheless, the data appear to demonstrate a protective effect of vitamin D, especially in populations with a high incidence of vitamin D deficiency/insufficiency and if HCWs are involved in the study design, presumably demonstrating higher adherence to vitamin D supplementation during the pandemic. An interesting finding that emerges from this study concerns, in addition to the high incidence of vitamin D deficiency/insufficiency in HCWs, the protective role of vitamin D even in middle-aged people. Even though this result is in line with the general consensus of literature data [37–40], it should be underlined that the evidence found is not univocal and that there remain some studies that have not confirmed the protective role of vitamin

D [17,41,42]. In particular, in the study by Brunvoll, the overall effect of vitamin D was negligible. This may have been due to the low dosage of vitamin D supplemented in the treatment group and the low prevalence of vitamin D deficiency in the study group.

In terms of the severity of COVID-19, it has been observed that individuals receiving vitamin D supplementation exhibit a lower incidence of serious complications and a reduced requirement for intensive care, while no difference was noted in terms of overall mortality. It is therefore conceivable, though not yet demonstrable, that vitamin D supplementation may play a role in reducing the occurrence and complications of the pathology. However, it should be noted that the initial benefit may not be substantiated in individuals who still develop the pathology. Nonetheless, this conclusion is drawn from a small number of studies, and for this reason we believe it is useful to carry out further studies and measurements before being able to make concrete hypotheses. On the other hand, this conclusion is in line with the majority of literature data [16,43,44], despite many authors expressing concerns about the lack of robust data from large RCT series [41,42,45,46]. Additionally, it is important to highlight that much of the evidence available in the scientific literature stems from patients who received vitamin D after being diagnosed with COVID-19, which only partially overlaps with the population receiving supplementation prior to the diagnosis of the disease.

From this standpoint, Pal et al., in 2021 [47], found no association between the use of vitamin D before the COVID-19 diagnosis with intensive care unit admission and/or mortality (OR 0.71, 95% IC 0.16–3.03) in a subgroup analysis of only three studies.

Similarly, Beran et al. in 2021 [48] found, in a subgroup analysis, that there was no association between preventive vitamin D supplementation prior to COVID-19 infections and related mortality (OR 0.83, 95% IC 0.39–1.76). Although their analysis was conducted on only five studies, they found the same conclusions as our study regarding mortality. From this standpoint, the role of vitamin D supplementation and its impact on mortality in the context of different pathologies have been extensively studied. However, the conclusions of these studies are not unequivocal given the presence of issues related to the disease-attributable mortality and the role of comorbidities and confounding variables in population studies [49–51]. The potential protective function of vitamin D supplementation in mitigating complications associated with COVID-19 would be of heightened interest due to the potential decrease in hospitalization requirements within intensive care units. This reduction in intensive care demands could result in a consequential decrease in expenses, antibiotic therapies and the emergence of antibiotic-resistant strains, which was commonly observed during the pandemic and documented by numerous authors [52,53].

Limitation

The main limitations of this meta-analysis concern the number of studies analyzed, which, although being greater than the number of other meta-analyses on this topic, is still not ample. However, it should be noted that the previous meta-analyses were also partly focused on different aspects, such as the administration of vitamin D during COVID-19 infection and not before, like in our study. We should also point out that there is little evidence from studies regarding ICU admission. The remaining limitations correspond to those present in the studies analyzed (first of all, the absence of sample size calculation in several RCTs and, secondly, the retrospective nature of several analytical studies). Further limitations of the studies are the absence, in several studies, of data on the prevalence of vitamin D deficiency/insufficiency in the population at baseline and, finally, the use of various formulations of vitamin D (cholecalciferol and/or calcitriol) at different dosages, which further complicate the evaluation of the effect of vitamin D supplementation, as this is carried out at different dosages in populations with different rates of vitamin D deficiency/insufficiency.

5. Conclusions

To the best of our knowledge, a strength of our study lies in the fact that it is the first meta-analysis conducted exclusively on studies that considered preventive vitamin D

supplementation in people not affected by COVID-19 infection. Prior to our investigation, as reported in the Discussion, only two meta-analyses, which mainly focused on vitamin D supplementation post COVID-19 diagnosis, included subgroup analyses conducted on vitamin D supplementation pre COVID-19 diagnosis. We chose not to include studies in which vitamin D supplementation occurred following the diagnosis of COVID-19 infection in order to evaluate the actual impact on the incidence of the disease.

Finally, the results of our meta-analysis seem to support the use of vitamin D, especially in populations with vitamin D deficiencies, in the prevention of COVID-19 infection and in the prevention of related complications.

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Abbreviations

ICU	intensive care unit
IC	confidence interval
OR	Odds Ratio
PTH	parathyroid hormone
COPD	Chronic Obstructive Pulmonary Disease
HCW	healthcare worker
RCT	randomized control trial

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World

Sweden's no-lockdown COVID strategy was broadly correct, commission suggests

However, review commission also finds the country's response to the crisis was slow and sometimes confused

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A medical staffer at Södersjukhuset hospital in Stockholm stands at the entrance of a tent for testing and receiving potential COVID-19 patients on April 7, 2020, one of the worst-affected countries in the pandemic for Sweden. (Jonathan Nackstrand/AFP/Getty Images)

Sweden should have adopted tougher early measures and the government assumed clearer leadership as COVID-19 hit, though the mostly voluntary no-lockdown strategy was broadly correct, a commission reviewing the country's pandemic response said on Friday.

Sweden polarized opinion at home and abroad with its handling of the pandemic, opting against the lockdowns implemented by many countries and adopting a largely voluntary approach of promoting social distancing and good hygiene.

The commission — set up by the government under pressure from parliament — said Sweden's broad policy was "fundamentally correct."

"It meant that citizens retained more of their personal freedom than in many other countries," the report says.

But the panel of eight experts, including professors of economics and political science, said the government should have taken clearer leadership and acted sooner rather than rely on measures such as capacity limits and masks.

"The Government should have assumed leadership of all aspects of crisis management from the outset," the commission said in the report. It found the government had too one-sided a dependence on assessments made by the Public Health Agency.

"In February-March 2020, Sweden should have opted for more rigorous and intrusive disease prevention and control measures."

'Remarkable' delay in indoor caps cited

The findings could become a liability for the ruling Social Democrats with a general election due in September. More than 17,000 people have died from or with COVID-19 in Sweden, far more per capita than among Nordic neighbours but less than in most European countries that opted for lockdowns.

Figures from statistics agency Eurostat showed the country had 7.7 per cent more deaths in 2020 than its average for the preceding four years, among the lowest excess mortality rates in Europe.



Young Swedes take a selfie outside the 48 nightclub in Malmö early on Feb. 9, when Sweden lifted COVID-19 restrictions on its public. (Johan Nilsson/AFP/Getty Images)

"In the light of current knowledge ... the Commission is not convinced that extended or recurring mandatory lockdowns, as introduced in other countries, are a necessary element in the response to a new, serious epidemic outbreak."

Moreover, the report argues the "right balance" was struck in terms of the education sector. Preschool and elementary schools were kept open, with universities and the equivalent of high schools switched to remote learning.

But a number of criticisms were levelled at the central government and its main public health agency, including in areas concerning preparedness and unclear jurisdictional lines.

"In a crisis, there must be no uncertainty about who is in charge," the experts wrote.

Read the commission report summary:



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1 Premiers gather in Halifax with a message for Trudeau: stick to your lane

COVID-19: from hospitals to courts

Michele Usuelli[1] raised two questions to the international scientific community. First, whether there were errors in the management of the COVID-19 health emergency in Lombardy, Italy. Second, whether having 20 regional health services across Italy is useful in controlling a pandemic.

The answer to the first question will be useful to medical science and the civil conscience (by improving the decision making process) in Italy. Unfortunately, the process of a commission of inquiry is much slower than that of a pandemic, and therefore it is unlikely that the evidence gained will be useful during this pandemic.

The answer to the second question is self-evident. Unfortunately, a strong political movement is pressing to accentuate the transfer of fiscal resources from the national level to the regions where income is produced. If the tax income remained in the region that produced it, then there would be no national budget. This transfer would increase health inequity, with an unfair burden of this pandemic on people who are disadvantaged[2] and an inevitable negative effect on the health of the population.[3]

In the meantime, emergency conditions have changed the traditional way that doctors operate. Intensivists who treat patients with COVID-19 have high levels of compassion fatigue and occupational stress; they do not have daily contact with the patients' relatives anymore and can inform families only at the end of therapy if the treatment has not been successful.[4] The scarcity of interaction with relatives could increase misunderstandings and the risk of malpractice litigation, which is already high in Italy.[5] We reasonably expect that the pandemic, in addition to many grievances, will leave many claims for compensation.

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We declare no competing interests.

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Author's reply

I thank Nicola Magnavita and colleagues for raising important points regarding my Correspondence.[1]

I agree that the process of analysing the pandemic through a commission is slow, but citizens deserve to know the results of an audit. Some structural problems within health management existed before this pandemic; COVID-19 only emphasised them. Citizens now also fully understand that their regional vote affects their lives. Criticising decentralisation is valid, but the implementation of any law should be analysed before changing the law.

Within decentralisation, Italy foresaw central and regional quinquennial sociosanitary plans. The plans define and prospectively update the organisation of the health system. The most recent national plan was produced in 2006 and the regional plan for Lombardy, Italy, was produced in 2010. Plans for pandemic preparedness are out of date and have not been implemented.

Stress, grievance, and suffering can lead to conflict at every level. In Lombardy, hospital managers have penalised some doctors who stood up and spoke openly about mismanagements. Accountability, ownership, transparency, humility, and admission of mistakes by politicians and managers can powerfully de-escalate conflicts and are the first steps towards improvement.

I am regional councillor of Lombardy, president of +Europa/Radicali, and a member of the Regional Council of Lombardy's COVID-19 investigative commission.

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Tanzania's position on the COVID-19 pandemic

In a World Report about COVID-19 vaccine use in Tanzania,[1] local context was not sufficiently considered to fully understand the country's position on the COVID-19 pandemic and its use of COVID-19 vaccines. We maintain that the late President John Magufuli understood the severity of the COVID-19 pandemic, which merits joint and coordinated global efforts.

In the early months of the pandemic, between February and April, 2020, the Tanzanian Government quickly implemented various WHO-recommended measures, and, as of Feb 27, 2021, the Ministry of Health has issued 15 guidelines. The government decided not to implement a lockdown because that would have restricted public access to health services, especially for patients with chronic conditions like tuberculosis and HIV infection, which, in settings

like Tanzania with large burdens of infectious and non-infectious disease, would have had severe effects. Lockdown might have also prevented citizens from working, affecting households' ability to afford food or health care, pushing more people into poverty.

In February, 2021, the government reissued guidelines insisting on WHO-recommended measures and built local capacity to produce personal protective equipment. The government has also adopted complementary traditional remedies that are thought to boost immunity. Tanzania harbours a rich diversity of valuable medicinal plants and has plans to build capacity to intensify research on alternative remedies against COVID-19; such efforts are also supported by WHO.[2] However, such efforts have been misinterpreted as undermining control measures against COVID-19.

The suspended use of the Oxford–AstraZeneca COVID-19 vaccine in South Africa and emerging SARS-CoV-2 variants raised concerns in Tanzania.[3] President Magufuli urged the Ministry of Health to conduct a robust evaluation before accepting the use of vaccines in the country. In an interview with the BBC, the government's chief spokesperson Hassan Abbas reiterated that "we would like to see the accuracy [efficacy] of these vaccines first. Tanzania is not in denial of the vaccines, but we think that it is not the right time for now...at some point, yes, once they [the vaccines] have been clinically approved".[4]

Tanzania embraces vaccination programmes and consistently shows high immunisation coverage for infants younger than 5 years.[5] We uphold the spirit of working collaboratively with local and international agencies in the fight against the COVID-19 pandemic.

ANM is employed by the Tanzanian Ministry of Health. All other authors declare no competing interests. SGM and NPM contributed equally.

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Global health and its discontents

A year ago, a group of us gathered to reconsider how to build healthy and equitable societies.[1] During that meeting, we rehearsed critiques of the current practice of global health.[2] The COVID-19 pandemic has laid bare the truth in these charges, highlighting deficiencies in the pursuit of equity and in the capacity for multisectoral action—yet the pandemic has also provided inspiring examples of effective national and global public health action. After the 1918 influenza pandemic, many countries built new institutions, laws, and practices that laid the foundation for modern public health. As a global health community, we should not miss the opportunity from this crisis to reflect upon and remedy our shortcomings to better support global health equity.

First, despite genuine desire and goodwill, and the Paris and Accra declarations, global health remains insufficiently country-centred. COVID-19 has provoked impressive examples of global solidarity, but it has also shown that individual decisions at the national level matter more for health than regional and multilateral institutions and mechanisms, including global health treaties and strategies. Global health practice often fails to fully engage with the individual context, policy cycles, and political economy of national health and social systems. Too many global technical and policy documents provide insufficient direct guidance and detail for national decision makers or are pitched at the wrong level. The unpredictable, short-term, feast-or-famine nature of overseas development assistance for health has proved difficult to improve. Yet navigating the sometimes conflicting internal and external incentives that give rise to this incoherence remains essential to improving the utility, efficiency, and equity of global health efforts.[3]

Second, COVID-19 has already questioned and reworked the tools of global health. Resolutions, special sessions, high-level commissions, reports, frameworks, and global action plans can still be useful, but too often global health practice is delivered using the same means as were being used many decades ago. COVID-19, with its limitations on travel, has shown that a strong physical presence within countries is more important than ever.[4] Institutions dependent on fly-in, fly-out missions need to rethink their operations. At the same time, COVID-19 has also shown how much of global health travel, especially for generic stakeholder meetings, can be avoided, with benefits for staff, countries, and the planet.

Third, COVID-19 has brought to the boil the already simmering discontent

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How did we get here: what are droplets and aerosols and how far do they go? A historical perspective on the transmission of respiratory infectious diseases

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The COVID-19 pandemic has exposed major gaps in our understanding of the transmission of viruses through the air. These gaps slowed recognition of airborne transmission of the disease, contributed to muddled public health policies and impeded clear messaging on how best to slow transmission of COVID-19. In particular, current recommendations have been based on four tenets: (i) respiratory disease transmission routes can be viewed mostly in a binary manner of 'droplets' versus 'aerosols'; (ii) this dichotomy depends on droplet size alone; (iii) the cut-off size between these routes of transmission is 5 µm; and (iv) there is a dichotomy in the distance at which transmission by each route is relevant. Yet, a relationship between these assertions is not supported by current scientific knowledge. Here, we revisit the historical foundation of these notions, and how they became entangled from the 1800s to today, with a complex interplay among various fields of science and medicine. This journey into the past highlights potential solutions for better collaboration and integration of scientific results into practice for building a more resilient society with more sound, far-sighted and effective public health policies.

1. Introduction

The COVID-19 pandemic has exposed major gaps in our understanding of respiratory disease transmission through the air. These gaps led to heterogeneous and shifting transmission mitigation policies from governments and public health organizations. What physical distance should be recommended? What PPE should be used by workers in high-risk settings? Should masks be required among the general public? What types of businesses and activities should be curtailed, and which should remain open? Part of the uncertainty around these questions is rooted in the dissonance between the historical definitions of routes of transmission and current understanding of how pathogens are transported through the air. Traditionally, respiratory pathogens are thought to spread through: (i) direct physical contact between people; (ii) indirect contact through contaminated objects called 'fomites'; (iii) spray of *droplets* onto the mucous membranes, often considered a subcategory of direct contact transmission; and (iv) inhalation of *aerosols*.

During the first few months of the COVID-19 pandemic in early 2020, the World Health Organization (WHO) and other public health agencies downplayed the *airborne* or *aerosol transmission route*, recognizing it as a potential route for transmission *only* during certain medical procedures such as intubation. Thus, N95 respirators were recommended for healthcare workers only during such

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procedures but not when otherwise interacting with COVID-19 patients [1]. By the end of March 2020, the WHO posted on social media, 'FACT: COVID-19 is NOT airborne', and said that stating otherwise was 'misinformation' [2]. Meanwhile, the US Centers for Disease Control and Prevention (CDC) declared in March 2020 that SARS-CoV-2 spreads mainly 'through respiratory droplets produced when an infected person coughs, sneezes, or talks that can land in the mouths or noses of people who are nearby or possibly be inhaled into the lungs' [3]. The CDC did not begin using the words 'airborne' or 'aerosol' to describe transmission until October 2020. As we will see, the differentiation between *droplets* and *aerosols* by the WHO is based on an arbitrary cut-off in droplet diameter; particles larger than the cut-off are considered 'droplets' and those smaller are considered 'aerosols'.

Evidence that airborne transmission was important began emerging in Wuhan in late 2019 and early 2020. In particular, once full airborne precautions were implemented in hospitals, the number of healthcare workers who became infected dropped dramatically [4–6]. Reports emerged in early March of SARS-CoV-2 RNA found on air handling vents in hospital rooms [7,8]. Around this time, some began raising the alarm locally and informally across various countries and institutions. A March 2020 *JAMA* article [9] specifically called into question such recommendations, given that they overlook the well-established physics of respiratory emissions, where droplets of all sizes can be carried many metres within a moist and hot turbulent cloud of exhaled breath. The inability of contact tracing to distinguish between the dichotomous classification of 'droplet' and 'aerosol' routes is evident when one incorporates such physics of exhalations, from breathing, coughing, talking, sneezing or singing. The *JAMA* article called into question the classification of transmission routes that, at the time, categorically asserted for COVID-19 to be 'droplet' based. It also called for the need for masking of both healthcare workers and the general public as a result. More importantly, the author and others called into question the *presumed link* between the 1 and 2 m physical distancing rule and the droplet size-based definition of routes of respiratory disease transmission [10,11]. The links between these notions are the focus of this article. They are central to the debates and disagreements that followed [12–14] about the overall recognition of the role of airborne transmission for COVID-19, as raised in July 2020, by 239 scientists [13] in a letter directed to public health agencies.

Throughout these debates, public health agencies have gradually adopted guidance targeting airborne transmission, for example, regarding the need for universal masking as source control [15,16]. However, continued resistance to the role of the airborne route of transmission or misunderstanding of it in general, and for COVID-19 in particular, persists in public health organizations and among leading officials [17,18]. Such disagreements stem at least partly from misunderstandings induced by the very definitions of airborne/aerosol transmission routes. First, *droplet* and *aerosol* transmission are currently defined on the basis of size: 'droplets' are considered to be emissions larger than 5 or 10 µm in diameter, whereas those smaller than 5 µm are termed 'aerosols'. Second, droplets are assumed to follow a semi-ballistic trajectory and to settle within 1–2 m from the person who released them. Yet, these thresholds are not consistent with the physics of droplets and aerosols and the exhalation cloud shaping their transport [9,14,19–21]. To understand how ill-defined nomenclature can potentially hinder scientific and policy progress, it is critical to revisit the historical foundation of these concepts. Only then can we understand how various schools of thought from a range of scientific fields, driven by different trainings and dogmas (e.g. figure 1), have shaped our current knowledge. Historical events and disparate perspectives have also set up roadblocks to aligning fundamental notions of public health and epidemiology with current scientific understanding.

2. At the core of epidemics: transmission

The 1918 influenza epidemic provides a useful historical analogy for understanding how a critical public health situation provoked interest in the transmission of infectious diseases. On 14 September 1918, just a few days after the first civilian influenza cases were reported in the USA, a widely circulated warning from Surgeon General Rupert Blue asserted: 'Mode of transmission—by direct contact or indirect contact through the use of handkerchiefs, common towels, cups, mess wear, or other objects contaminated from fresh secretions. Droplet infection plays an important part' [22]. In the weeks that followed, a more detailed statement from the US Public Health Service elaborated on the warnings which referred to the mode of transmission in the headline: 'People Should Guard Against "Droplet Infection"', with an explanation that included measures to prevent infection: 'Influenza is always spread from person to person, the germs being carried with the air along with the very small droplets of mucus, expelled by coughing or sneezing, forceful talking, and the like by one who already has the germs of the disease' [23]. The recommended steps to prevent infection included mask-wearing for all nurses and hospital attendants while near patients, getting fresh air and avoiding crowded spaces, along with this final rhyming reminder: 'Cover up each cough and sneeze. If you don't, you'll spread disease' [23].

The similarities in messaging around the COVID-19 pandemic are striking. Dissemination of guidelines from the public health service and syndicated columns in 1918 provided the public with explanations of disease transmission useful in daily life. In 1918, as in 2020, however, these explanations had to strike the right balance between distilling complex and nuanced phenomena, ensuring scientific accuracy and effectively conveying warnings to the general public [24]. In the case of respiratory disease transmission via 'droplets' versus 'aerosols', this challenge continues to be exacerbated by the fact that scientific understanding of respiratory disease transmission is still evolving, and that fundamental insights are often lost in history, only to be cyclically re-discovered or re-interpreted.

3. The swinging pendulum of history: theories of respiratory disease transmission

The mid to late nineteenth century was a transition period in the understanding of infectious disease transmission, public health policy and infection control. The prevailing miasma theory of infectious disease transmission stipulated that diseases were caused by nebulous 'bad' air; it did not identify an underlying causative agent and offered little basis for infection control recommendations. While the competing germ theory predated

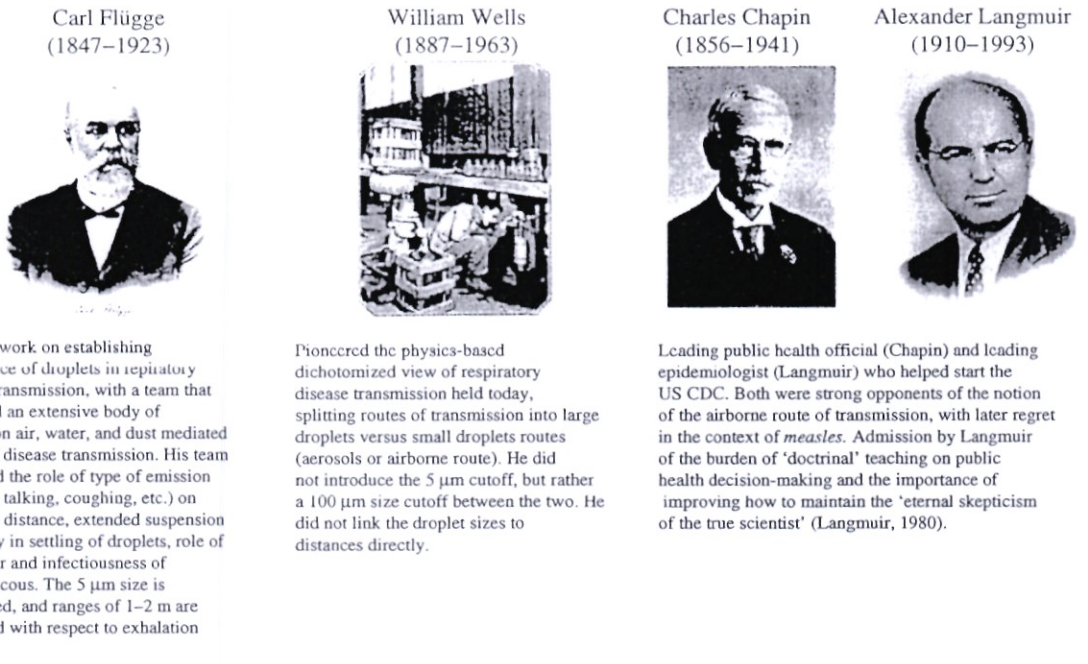

Figure 1. Contributions of key researchers and public health officials in shaping the understanding of respiratory infection transmission and infection control strategies. Mildred Wells and Cretyl Mills, not pictured, also made key contributions to the field.

Louis Pasteur and Robert Koch, their careful experiments in the latter part of the nineteenth century helped elevate it from a nascent theory to one with clear and actionable successes. Their scientific approach helped germ theory gain significant traction in the second half of the nineteenth century, as it pushed back against miasma theory [25,26]. With the advent of germ theory, public health officials in the late nineteenth and early twentieth centuries started focusing on hygiene and sanitation practices like handwashing, surface disinfection, waste removal and water purification, which had demonstrable successes for infection control [27]. Yet at the end of the nineteenth century, tuberculosis (TB)—a major public health challenge—remained poorly controlled.

3.1. Flügge in the late 1800s

Against this backdrop, Carl Flügge and his assistants in Breslau, Germany, began breaking with the prevailing paradigm that TB was transmitted through the inhalation of fine 'dust' of dried tuberculous sputum resuspended in the air from spit bowls, handkerchiefs or other objects. In a series of systematic and extensive experiments Flügge's team demonstrated the existence and efficiency of transmission via fresh exhalations [28,29]. They placed agar plates in rooms at various distances and heights from talking, coughing, singing and sneezing subjects to determine the distribution of contamination in space and time. They also established the infectiousness of the collected samples through transfection experiments on animals. Flügge and co-workers made several key contributions to the understanding of respiratory disease transmission. Initially, their primary focus was not on aerosols versus droplets but about showing that material freshly emitted (sprayed) from the respiratory tract was an important route of transmission *in contrast* with the 'dry dust' route. In particular, they emphasized that regular airflows indoors could not easily mechanically break up large volumes of dried sputum into fine dust [28,29]. Second, and contrary to what has later been propagated about their work, they applied the term 'droplets' to *all* respiratory emissions, irrespective of the initial droplet size or final constitution (dry or not) *as long* as the emissions *did not* yet settle on surfaces and as long as the emission payload of bacilli was still active. For example, Flügge's team understood that it would take time for respiratory spray emissions to settle, and they waited for up to 5 h following exhalations before removing the plates for analysis. Thus, their results and reference to 'droplets' encompass both what we now refer to as 'droplets' and 'aerosols/droplet nuclei' [28–31]. Third, air currents can have a significant influence on the range of the emitted droplets, and so control measures in the context of TB should include not just distancing, but also ventilation, in addition to avoiding crowding [28,29,31]. Fourth, they recognized the notion of pathogen-specific infectious dose to which they linked their recommendations of distancing and duration of exposure in the context of TB [32,33]. Others of the time, such as Koeniger, made clear that recommendations should be pathogen-specific [34]:

> …If the pathogenic germs are seldom present in the mouth and in small quantities, as we may assume for the time being from the tubercle bacilli, the danger is only slight in short periods of time with such patients. The probability of an infection then only exists for those people who are constantly in the vicinity of the sick (families, narrow work rooms). But if we were to learn […] that certain types of TB had particularly plentiful bacilli […] as with all other diseases, in which large amounts of pathogens tend to populate the oral fluid, a few coughs, even a few 'sharp' words, [would be] enough to completely infect the air of a medium-sized room and give every occupant the opportunity to become infected.

As Flügge's concept of droplet transmission of TB gained acceptance in the early twentieth century, the research, clinical and public health communities appear to have reduced Flügge's encompassing insights to a simplistic interpretation that *only* large visible *liquid droplets* matter in TB. This interpretation was then extrapolated to apply to other respiratory diseases, too. Finally, it was used to claim that airborne routes of transmission had been shown not to be important. This interpretation was also conflated with the idea that only

liquid droplets that rapidly fall to the ground are involved in close-range transmission. Transmission for respiratory illness would thus only occur over short distances of 1–2 m [35].

Yet, the works of the Flügge team were not so simplistic as portrayed above and by others [36,37]. Flügge emphasized that individual and environmental factors (frequency of coughing and number of droplets shed; number, age and behaviour of people in the vicinity of a patient; poor or cramped housing) need to be taken into account to reduce transmission risk and emphasized the need to keep a distance from *actively* coughing patients [32]. These more nuanced messages seem to have been lost on public health officials, most notably Chapin and Langmuir (figure 1), who forcefully focused only on 'large', presumably liquid, droplets, clearly a misrepresentation of the full body of Flügge's work.

3.2. Chapin's resistance to the notion of airborne transmission

At the start of the 1900s in the USA, Charles Chapin was a very influential figure in conversations about transmission (figure 1). At the time, Chapin was the Health Officer of Providence, Rhode Island (and later, the president of the American Public Health Association), who by the early twentieth century had gained national recognition in public health circles for his 'vigorous sanitary action' [38]. Credited as 'the foremost teacher of the paramount role of contact infection' [38], Chapin was convinced that communicable diseases were spread by close contact *only*, including contact with bodily fluids and liquid droplets, and certainly not by transmission of germs through the air. Because of his reputation and the successful implementation of contact-infection-prevention practices in a new hospital in Providence, Chapin's 1910 publication, *The sources and modes of infection*, quickly became a popular guide for public health officials and remained a seminal text for decades [39]. In it, Chapin took a disdainful approach towards the theory of airborne transmission, arguing that evidence did not support such a theory, and that focusing on an airborne transmission route would divert attention from the more relevant contact transmission prevention [27]. The influence of Chapin's doctrine, potentially magnified by a burgeoning public health field that was eager for forward-thinking practices in a post-miasma-theory bacteriological age, kept the focus on short-range contact transmission for the next 20 years.

3.3. 1930s Wells' physics-based work on respiratory disease transmission

It was not until the work of William and Mildred Wells in the early 1930s, again in the context of TB, that a systematic science-based approach to understanding respiratory transmission was revived [37]. The Wellses used novel technological advancements in air sampling in addition to physics-based conceptualization and systematic biological experiments. Revisiting the discussion of respiratory emissions, the Wellses introduced a time-scale competition laying the ground for a dichotomous framework of respiratory disease transmission: via *large respiratory droplets* that fall faster than they evaporate, leaving visible stains on agar plates and glass slides in the vicinity of a coughing or sneezing patient; or via *smaller respiratory droplets* that evaporate faster than the time it takes them to settle on a surface, leaving 'droplet nuclei' or 'residues/aerosols' suspended in the air for potentially long periods of time [40]. The research duo thought of the dried nuclei residues as potentially infectious, and they subsequently became referred to as aerosols in this context. The Wellses did not discuss the distance of fallout of contamination.

It is important to understand the context in which the Wellses' work was ongoing. From an epidemiological perspective, there were consistent and robust observations of ease of transmission in close proximity to infected individuals. Such robust epidemiological observation was, however, and continues to be erroneously interpreted by public health officials and epidemiologists, such as Chapin, to mean that transmission via droplets and fomites is the only relevant route of transmission, and that somehow ease of transmission with proximity discredits aerosol or airborne transmission. Because of this emphasis and association between unrelated concepts—of ease of transmission with proximity to large droplets—the Wellses' assertion that aerosols could be a non-negligible mode of transmission faced resistance. In an early paper, the Wellses note that some rejected a theory of airborne transmission because the term 'revive[d] the ancient and exploded theory of miasmas' [37]. They clearly recognized the perception that a theory of airborne transmission could be viewed as *regressive*, re-embracing obsolete ideas of 'bad air'. In addition to overcoming the erroneous association with miasma theory, another impediment to the acceptance of the Wellses' theory—that infectious aerosols can stay in the air—was the difficulty in establishing conclusive evidence of airborne infection. It was nearly impossible to control an environment well enough to rule out contact (including close-proximity droplet spray) infection.

Experiments from William Wells and his research team in the 1940s regarding air sterilization with UV light seemed promising [41], though subsequent studies failed to reach a satisfying epidemiological conclusion. As a result, many concluded that these failed efforts were because airborne infection was, in fact, not a primary route of transmission. It is surprising that throughout these discussions, the extensive work of Flügge's team seems not to have been revisited. Doing so would have saved time and effort as key concepts, experimental protocols and findings had already been established and tested at that time, which would have supported aspects and nuances of the airborne theory of transmission. Indeed, the Wellses also appear not to have grasped the full extent of Flügge's work, reducing it to ballistic droplets settling quickly as indicated in their quote above [37].

3.4. Langmuir and his legacy on the US CDC, and Wells, Riley and Mills

Among the sceptics of the Wellses and those on whom the nuances of Flügge's work appear to have been lost was also Alexander Langmuir (figure 1), the first Chief of Epidemiologic Services at the US Communicable Disease Center (the predecessor organization of the current CDC) until the 1970s. In 1951, Langmuir noted that although '[a] large amount of highly suggestive experimental data has been accumulated…, [t]he application of these engineering methods to the control of naturally occurring disease in general population groups […] has been most disappointing. It remains to be proved that airborne infection is an important mode of spread of naturally occurring disease' [42]. Yet in the late 1950s/early 1960s, the extensive work intellectually led by William Wells, organized by Richard Riley, and conducted by Cretyl Mills was finally published after the death of Wells providing definitive

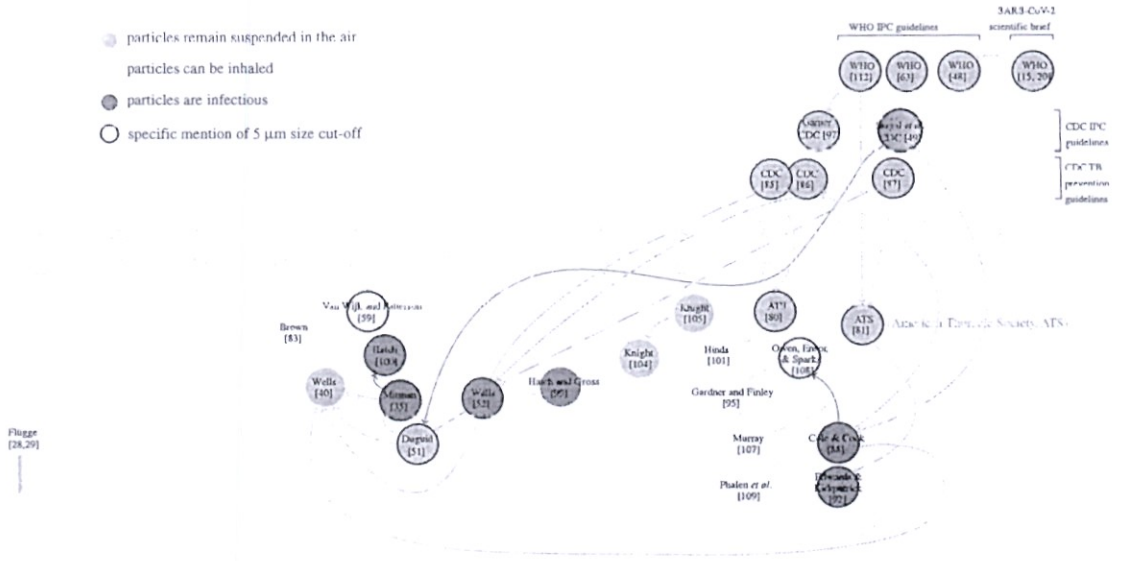

Figure 2. Tracing of how the term 'airborne' has been used and understood in the literature, beginning with WHO and CDC definitions as used in infection prevention and control (IPC) guidelines as well as in SARS-CoV-2 scientific briefs. A purple node indicates that a source primarily uses a definition of 'airborne' that means 'particles that remain suspended in the air'. A light green node indicates a source that primarily uses a definition of 'particles that can be inhaled', and a dark green node indicates a source that primarily uses a definition of 'particles that are infectious'. The colour of the arrow connecting the nodes indicates which definition the older source is being used to support in the more contemporary source, even if incorrectly. For example, Siegal *et al.* CDC [49] cite Duguid [51] to support an airborne definition regarding infectiousness, while Duguid [51] understands 'airborne' as only what remains suspended in the air. A dotted line indicates the older source is being cited in order to disagree or dismiss the findings of such source, such as Wells [52] and Flügge [28–31].

evidence of airborne transmission of TB using guinea pigs in the TB wing of a hospital [43]. It is of interest to note that the brunt of this tedious multi-year work was carried forward by Cretyl Mills, who subsequently contracted TB. Wells was the intellectual leader of this research until the very end of his life even while he was suffering from cancer. It is thus surprising that Riley had somehow omitted Wells' name from the final publication to his 'eternal shame' as Riley later admitted [44]. We shall thus refer to this publication as Wells, Riley, Mills *et al.* [43] here. From that point on, the airborne theory and Wells' dichotomy of routes of transmission started to become more widely accepted.

Decades after the Wellses' work, Langmuir started to timidly acknowledge that certain diseases were airborne. In the 1980s, Langmuir published a retrospective of his time at the CDC. Given the contemporary understanding of measles as an airborne disease, which he had previously insisted to be transmitted via large droplets/close contact only, he admitted that Wells was right all along [45]. In this pendulum swing of history, it is again interesting to note that in fact, the 'definitive' experiment of animal model infection had already been suggested in 1897 [30,46] and subsequently performed by 1899 by the Flügge school, also showing successful infection of animals upon exposure to TB coughing patients [29,47]. The differences were the smaller distance to the patient and less controlled airflow compared to the experiments of Wells, Riley, Mills and co-workers.

4. Droplets versus aerosols and origin of the 5 µm threshold

In contemporary recommendations about droplet transmission, including those regarding COVID-19, both the WHO and the CDC define a distinction between 'droplets' and 'aerosols' based on a size threshold of 5 µm [15,48,49]. Despite the prominence of this size threshold in the literature [14,50], a 5 µm threshold to distinguish between 'droplets' and 'aerosols' is not scientifically grounded. Thus, unsurprisingly, the 5 µm cut-off often lacks supporting sources when quoted in the literature, such as in the WHO recommendations [15]. Where citations are provided, they often trace back to William Wells, as shown in figure 2. Yet, Wells' 1934 papers do not mention a 5 µm size threshold. In quiescent ambient air, respiratory particles of this size take approximately 30 min to fall to the ground from a height of 1.5 m (see table 1 in Wells [40], which shows a 10 µm respiratory particle takes 10 min to fall from a height of 2 m and a 1 µm particle takes 16 h to fall the same height). This timescale leaves ample time for transport and inhalation exposure at long distance. In fact, Wells identified the size threshold between droplets that fall to the ground faster than they evaporate versus those that evaporate faster than they settle as 100 µm. To arrive at this number, Wells used a diffusion-based evaporation model in idealized quiescent conditions applied to isolated droplets. The settling timescale is then evaluated using Stokes' settling speed [52]. However, indoor environments are never quiescent, as temperature and pressure gradients lead to airflow velocities of at least a few centimetres per second. More fundamentally, it has been established over the past 10 years that exhalations in fact contain a continuum of droplet sizes embedded in a turbulent exhalation cloud trapping and transporting them [9,20,21]. Thus, a static fixed size cut-off, particularly in the range of 5 µm, is misleading [19,53].

4.1. So where does the 5 µm threshold come from, if not from Wells?

Why do references, particularly in the medical literature or guidelines, often mention 5 µm as the threshold between routes of transmission? In the 1930s, researchers from diverse

backgrounds, notably biology and agriculture, began studying microorganisms in the air using new tools and technologies [54], launching the field of aerobiology [55]. An interest in airborne microorganism dispersal sprouted in other disciplines, too, including mycology, dermatology and respiratory occupational health, pertaining, for example, to farmer's lung disease [56]. At the same time, interest in outdoor air quality was also growing. These efforts were focused mostly on the receiving end of the system: the inhalation of contaminants and their potential to deposit in the lungs. Therefore, discussion about particle size revolved mainly around its relationship to the potential for inhalation, penetration and deposition in different regions of the respiratory tract [57], and not on how the particles move through the air. In this general context, industrial hygiene studies from the 1930s and 1940s suggested that only the smallest particles—1–5 µm—could reach the deepest part of the lungs [58,59]. Thus, this size threshold became associated in the subsequent literature by public health and infectious disease researchers with what was thought to be most infectious [49]; see figure 2 for mentions of *inhalation* and *infectiousness* in the displayed references. Interestingly, the older works of the Flügge school appear to have been lost in translation again: they had already discussed 'bronchial droplets' for the droplets presumed to be most effective in TB infection. They claimed that exhaled droplets in a specific size range contained the largest amounts of TB bacilli [33,47]. In contrast with modern discussions of this concept, they considered bronchial droplets to be 20–60 µm in size. Conversely, Flügge noted difficulty in infection of animals for artificially sprayed droplets that were significantly larger than 40 µm [32].

5. Renewed interest in airborne infection: biological warfare

While Wells' work regarding airborne transmission was labelled as having 'failed' the 'challenge to the theory of contact and droplet infection' by Langmuir [42], his work was nonetheless considered foundational to understanding the *physics* of airborne infection. In the same 1951 presentation in which he disparaged Wells' belief that airborne infection could occur naturally, Langmuir [42] acknowledged that 'the knowledge accumulated during the past 15 years has clearly laid the scientific basis for the mechanisms of airborne infection' noting that airborne spread was now commonly recognized as a cause for *artificially* induced human infections. Delivered only months after the start of the Korean War, Langmuir's address was intended to prepare public health students for the possibility of airborne infection via biological warfare. This was the motivation for his sudden marriage of epidemiological concern and what he had dismissed in the prior decade regarding airborne transmission. The emerging aerobiology and aerosol science insights built over the previous decades included the recognition that upon inhalation, '[p]articles larger than 5 µm in diameter are almost completely removed in the nose and upper respiratory passages' while 'progressively increasing proportions of inhaled particles reach the terminal bronchioles and alveoli' when below 5 µm in size [42]. If airborne transmission was not considered to occur naturally but *was* understood to occur under artificial circumstances, the threat of aerosolized pathogens delivered *en masse* to the American population was a dramatic reason for the epidemiological community to focus again on airborne infection and public health, even if such a concern had been previously dismissed.

Embracing this marriage between epidemiology and aerosol science, William Wells published a book in 1955 [52] that expanded significantly on his theory of airborne transmission. Like Langmuir, Wells now referred to the research that showed particles 1–5 µm in size were small enough to reach deep into the lungs. The more sophisticated technologies developed in the subsequent 20 years seemed to encourage a new focus for Wells: not just what stayed suspended, but what could be truly *infectious* based on the ability to reach the deepest parts of the lungs. Though no association is made explicit in any of the literature we reviewed, this focus on particle deposition in the lungs likely popularized the 5 µm diameter cut-off. A turn *back* towards a theory of airborne infection with TB in the 1960s may have resulted in the entanglement of deposition in the lungs (5 µm cut-off) with Wells' dichotomized definition of droplet versus airborne transmission (cut-off of 100–200 µm) in infectious disease protocols and public health guidelines. Additionally, in public remarks made in 1964 [60], Langmuir used the 5 µm distinction between *large droplets* and *aerosols*, explicitly stating that droplet size *is* relevant because of where the aerosols are deposited in the lungs.

In sum, tracing the origins of the 5 µm threshold, as cited in public health literature (figure 2) ultimately revealed a conflation between various understandings and definitions of 'aerosols'. Most contemporary sources use this threshold only to explain which particles stay suspended in the air for longer times, yet the 5 µm distinction is clearly *not* based on what *stays airborne* but on what *reaches deepest in the lungs, irrespective of a pathogen's tropism*. It is this conflation of particle transport through the air and particle deposition in the lungs that appears to be the source of the error in distinguishing between droplet and aerosol transmission routes as defined by a 5 µm threshold. The problems created by this conflation are many. First, it fosters a misunderstanding among health professionals about most infectious particles (such as those carrying SARS-CoV-2) not remaining airborne. Second, it codifies a particle size based on the pathogenesis for TB that research shows does *not* apply to other infectious diseases. Viral receptors for SARS-CoV-2 are located throughout the respiratory tract for example [61], and initiation of infection in the nose and upper respiratory tract is thought to be important [62]. Therefore, unlike for TB, aerosols of sizes all the way up to the inhalable limit of 100 µm are capable of initiating infection. Third, the size of a droplet upon emission is not necessarily the size upon inhalation and is not a size that necessarily remains constant after exhalation and inhalation, due to evaporation and rehydration [20]. If a reference to a specific droplet size needs to be made, a standardized procedure for such measurement is key [20]. A size cut-off and dichotomy are useful for general conceptualization and broad understanding of the route of exposure and control measures. However, a detailed understanding of the droplet size physics, the flow dynamics (in space and time), and their measurement are critical to providing sound scientific underpinning of interventions and to eliminating inconsistencies in public health guidelines and associated false debates.

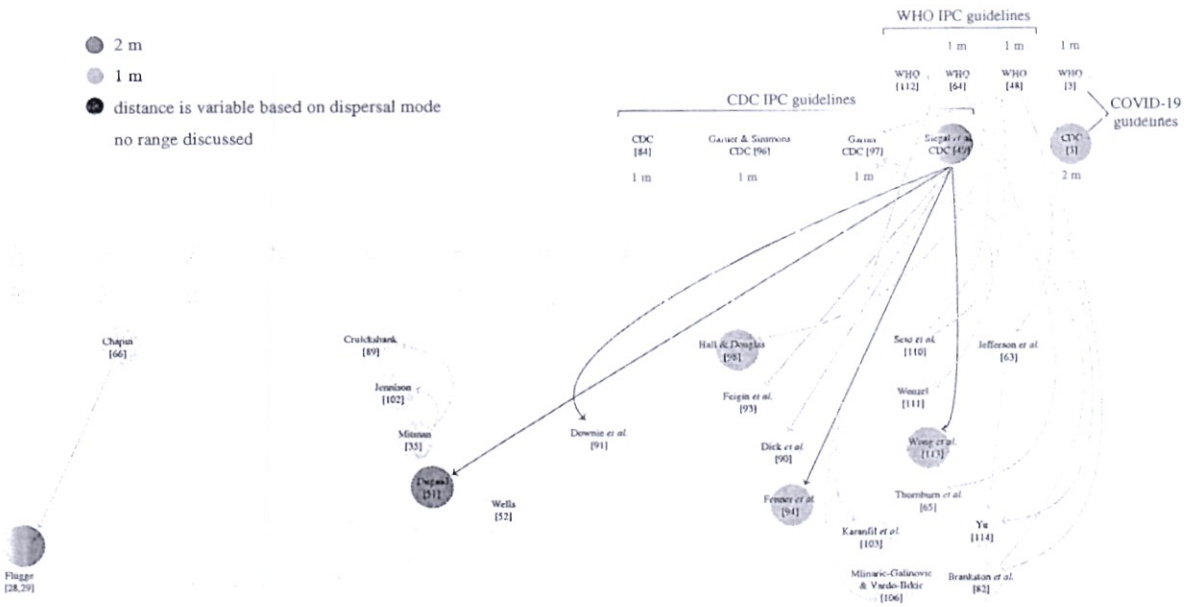

Figure 3. Tracing of citations of standard droplet infection ranges as used by both the WHO and the CDC. Nodes in blue indicate the use of a 6 foot/2 m designation, while nodes in peach indicate the use of a 3 foot/1 m designation. Sources in red argue for a variable range. Arrows between nodes indicate how an older source is cited in the newer. In some cases, the edge colour matches the node colour (e.g. WHO [48] cites Jefferson *et al.* [63] to support a 3 foot range) and in others, it does not (e.g. WHO [64] cites Thornburn *et al.* [65] to support a 3-foot range, but Thornburn *et al.* [65] do not use that distance, as indicated by its grey node colour). A few key sources in the historical droplet/aerosol conversation are included here despite being outside of the citation trace working backward from WHO/CDC guidelines, both to keep some continuity with figure 2 and to show historical shifts in understanding. For instance, Wells [52] is included, with a dotted edge to both Chapin [66] and Flügge [28–31] to indicate disagreement with how both sources understand droplet range.

6. Droplet sizes and range: origins of the 1–2 m rule

Alongside the common definition of aerosols as being smaller than 5 µm (figure 2), contemporary guidelines for infection control in healthcare protocols as well as in public health messaging distinguish spray-borne droplet infection from the airborne route by the *distance* travelled by a droplet or aerosol (figure 3). Such distance has been widely used to drive a range of *social/physical distancing rules worldwide*—from 1 to 2 m—also with heightened debates regarding implications for society's basic functioning [11]. Interestingly, the recommended distance to avoid infection varies from 1 m per WHO and in parts of Europe, to 1.5 m in Australia, to 2 m in the USA, Canada and the UK. The most recent CDC Guidelines for Isolation Protocols in Healthcare Settings note that, historically, the accepted distance for ballistic droplet transmission has been within 3 ft [49] (figure 3). They also note the more recent studies from SARS-CoV-1 in the early 2000s that demonstrate an infection distance of up to 2 m or more. Although the 2003 SARS-CoV-1 pandemic never became widespread enough in the USA to warrant non-pharmaceutical interventions, public-facing information about SARS-CoV-1 from the CDC indicated that droplet spread generally happened within 3 ft [67]. Thus, the current pandemic is the first recent implementation of a 6-foot recommendation in the USA, although public health warnings during the 1918 influenza epidemic included social distancing, based on research at the time about droplet infection [68,69]. We found that these short distances have been brought to institutional attention since at least the mid-nineteenth century. During the Crimean War (1853–1856), the Royal Commission recommended keeping beds in soldiers' barracks at least 3 ft apart, noting that such measures lowered incidences of respiratory illness as might be expected regardless of the route of transmission [70]. Likewise, Biernacki advocated spacing beds a certain distance apart to create an 'invisible barrier' to limit a 'pathogen's excursion' [71]. While such recommendations are based on correct empirical and epidemiological observation, namely that in general larger distancing reduces the incidence of respiratory disease transmission, the mechanistic justification for such recommendations, linking them *only* to short-range liquid droplet fallout on another person or surfaces to the exclusion of inhalation of aerosols, is erroneous. Hence, the *scientific basis* that inherently links respiratory disease transmission mechanisms to a prescribed distance of 1–2 m requires urgent and careful revisiting.

The first mechanistic investigations seem to date back, again, to Flügge [28,29]. Experiments in the late nineteenth century not only presented evidence of infectious droplets, but also provided material evidence of how far those droplets might travel in unprotected exhalations. In experiments by von Weismayr and by Laschtschenko from the Flügge school, for example, subjects were given a saline suspension of *Serratia marcescens* to rinse their mouths and were then asked to speak, sing, cough and sneeze. The results showed that colonies grew in Petri dishes positioned as far as about 2 m from the speakers, 4 m from the coughers and as far as 9 m from the sneezers [31,72], in the absence of notable background airflows. It is important to recall again that 'droplets', in the context of the Flügge school, encompassed both liquid and dry particles of all sizes prior to settling on a surface. This is why, contrary to many other studies that reported no contamination beyond 1 2 m, the Flügge team waited up to 5 h prior to plate collection [28,29,31]. These results

were confirmed by Koeniger [34], who additionally allowed for common indoor airflows to persist to increase the realism of the experiments; he noted that 'when speaking, a transfer of the droplets had taken place up to the extreme corners of the very large room', up to 12.5 m [34]. Finally, a speaker at the dispatch box of the expansive UK House of Commons also gargled with a broth culture of *Bacillus prodigiosus* before reciting Shakespeare passages in a loud voice to the empty room; although growth colonies were more numerous in plates near the speaker, cultures were apparent on plates over 21 m away [73]. Others followed suit with similar experiments [74]. So, what mechanistic study links historically to the 1–2 m rule? As mentioned above, it is only in the narrow context of TB transmission that Ziesché and Flügge made explicit reference to a distance of about 1 m associated with a specific exposure time linked to an extrapolated threshold of infectious dose of 400 bacilli [32,33]. Any concrete distance recommendation clearly requires revisiting in the context of specific pathogens, environments and infectious doses, as already pointed out by Koeniger in 1900 [34].

The limitations of the plate collection method were emphasized by the Wellses' observation in the 1930s that small particles would remain airborne without settling at all. Thus, plate collection over a short time was an inappropriate methodology for detection of microorganisms in the air. With the evolution of new measurement tools, particularly photography in the 1940s, it became possible to directly visualize the emissions from sneezing, coughing or talking. Such visualizations, however, were still limited to windows of observations 1–2 m in width, and the smallest particles still could not be detected by optical methods. The lack of imaging beyond the 1–2 m distance [75], combined with prior misrepresentations of Flügge's work and others on plate collections of organisms, reinforced the collective focus on this 1–2 m distance as a primary danger zone.

In recent years, a number of other studies have found organisms and respiratory emissions collected beyond a 1–2 m distance in the context of a range of respiratory diseases [10,11]. Recent findings in fluid dynamics of respiratory emissions also support the view that the framework of 'droplet' versus 'aerosol' routes of transmission is not a perfect dichotomy with a sharp boundary in particle size and distance and make clear that a 1–2 m distance is not compatible with the physics of respiratory emissions [9–11,21,76].

Given all the above, and that distancing and droplet size cut-off concepts did not originate together, it is puzzling that they continue to be linked. An entrenched belief persists that ballistic droplets are the primary route of infection and that above a particular fixed size, they settle out within 1 or 2 m, when in fact, as explained by Flügge, the concept of distance is linked to an infectious dose that can be reached also by inhalation of droplets of any size that have not yet settled. Such entrenched confusion between these concepts is the root of the neglect of the airborne route of infection in guidelines, despite the mounting casualties of the COVID-19 pandemic. Thus, similar to the recommendations from the late 1800s, guidance continues to be based largely on empirically observed infection mainly among close contacts, rather than a mechanistic understanding of where, how long and in which environments pathogen-laden droplets can remain airborne and infectious.

7. Outlook/discussion/conclusion: role of public health organizations—recommendations for changes

As case studies of transmission of COVID-19 continue to accumulate [77], it is increasingly clear that transmission is not accurately represented by the 'droplet route' and its erroneous association with the 1–2 m rule [9,10,13]. In fact, the importance of aerosol transmission is becoming obvious from a range of emissions from breathing to talking, to singing, to coughing, to sneezing (see fig. 3b in [19]), with a number of remaining open questions on the nature of their creation and pathogen load upon emission. A more nuanced understanding is required so as to guide also a more nuanced People-Air-Surface-Space (PASS) strategy of management of COVID-19 [11,19,20,78] that advocates an integrated approach to risk mitigation, combining personal protection, air and surface hygiene and space management to reduce the risk of infection.

What we hope to demonstrate in this essay is that although ideas about droplet size (figure 2) and range of spread (figure 3) are seemingly well accepted, their foundation is muddled and misleading, and is not consistent with physics. With the confusion over SARS-CoV-2 transmission that has led to conflicting public health recommendations, this is a crucial moment to clarify and realign infection control guidelines to match both historical and contemporary understandings of airborne transmission, including moving away from using TB as the reference standard of airborne infection.

Though researchers from multiple (and often disconnected) fields are studying airborne transmission from different perspectives, a move towards consistent conversations and research about airborne transmission—instead of ad hoc conversations that arise only in times of crisis—will give researchers, public health officials and infection control specialists the time needed to collaborate, discuss limitations and ultimately better implement science into policy. We call for a model in which this research is continually advanced, particularly between epidemics and pandemics. We also call for the inclusion of a broader range of expertise in key scientific and decision-making committees. For example, the WHO Infection Prevention and Control (IPC) committee contained multiple handwashing experts, but no airborne disease transmission experts, including expertise from aerosols to fluid dynamics, even though the modes of transmission of the new disease were very unclear. Closer and continuous integration of scientific results with policy is also important, with support, expansion and strengthening of initiatives such as training and pairing programmes between researchers and policy translators at the heart of engineering and science focused programmes rather than separate from them (e.g. International Policy Laboratory at MIT [79]). Additionally, closer integration mechanisms between research on academic campuses and at national/federal/global institutions could bridge this gap. This could be achieved through, for example, integrated research and policy translation teams, funding support for such purposes or specialized offices for aiding translation of research results into policing relevant information.

We hope that this closer look into history and revisiting the origin of these concepts, and how such concepts evolved to be adopted *or not* into public policy since the late 1800s, shows that the swinging pendulum of history is at play. Thus, maintaining a historical perspective is key to enable

productive communication between various scientific and public health communities aiming to design more sound, resilient, far-sighted and effective public health policies for slowing the transmission of respiratory infections when they emerge.

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UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF TEXAS
FORT WORTH DIVISION

PUBLIC HEALTH AND MEDICAL PROFESSIONALS FOR TRANSPARENCY,

Plaintiff,

v. **No. 4:21-cv-1058-P**

FOOD AND DRUG ADMINISTRATION,

Defendant.

ORDER

This case involves the Freedom of Information Act ("FOIA"). Specifically, at issue is Plaintiff's FOIA request seeking "[a]ll data and information for the Pfizer Vaccine enumerated in 21 C.F.R. § 601.51(e) with the exception of publicly available reports on the Vaccine Adverse Events Reporting System" from the Food and Drug Administration ("FDA"). *See* ECF No. 1. As has become standard, the Parties failed to agree to a mutually acceptable production schedule; instead, they submitted dueling production schedules for this Court's consideration. Accordingly, the Court held a conference with the Parties to determine an appropriate production schedule.[1] *See* ECF Nos. 21, 34.

"Open government is fundamentally an American issue"—it is neither a Republican nor a Democrat issue.[2] As James Madison wrote, "[a] popular Government, without popular information, or the means of acquiring it, is but a Prologue to a Farce or a Tragedy; or, perhaps, both. Knowledge will forever govern ignorance: And a people who mean to be their own Governors, must arm themselves with the power which

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[1]Surprisingly, the FDA did not send an agency representative to the scheduling conference.

[2]151 CONG. REC. S1521 (daily ed. Feb. 16, 2005) (statement of Sen. John Cornyn).

knowledge gives."[3] John F. Kennedy likewise recognized that "a nation that is afraid to let its people judge the truth and falsehood in an open market is a nation that is afraid of its people."[4] And, particularly appropriate in this case, John McCain (correctly) noted that "[e]xcessive administrative secrecy . . . feeds conspiracy theories and reduces the public's confidence in the government."[5]

Echoing these sentiments, "[t]he basic purpose of FOIA is to ensure an informed citizenry, [which is] vital to the functioning of a democratic society." *NLRB v. Robbins Tire & Rubber Co.*, 437 U.S. 214, 242 (1977). "FOIA was [therefore] enacted to 'pierce the veil of administrative secrecy and to open agency action to the light of public scrutiny.'" *Batton v. Evers*, 598 F.3d 169, 175 (5th Cir. 2010) (quoting *Dep't of the Air Force v. Rose*, 425 U.S. 352, 361 (1976)). And "Congress has long recognized that 'information is often useful only if it is timely' and that, therefore 'excessive delay by the agency in its response is often tantamount to denial.'" *Open Soc'y Just. Initiative v. CIA*, 399 F. Supp. 3d 161, 165 (S.D.N.Y. 2019) (quoting H.R. REP. NO. 93-876, at 6271 (1974)). When needed, a court "may use its equitable powers to require an agency to process documents according to a court-imposed timeline." *Clemente v. FBI*, 71 F. Supp. 3d 262, 269 (D.D.C. 2014).

Here, the Court recognizes the "unduly burdensome" challenges that this FOIA request may present to the FDA. *See generally* ECF Nos. 23, 30, 34. But, as expressed at the scheduling conference, there may not be a "more important issue at the Food and Drug Administration . . . than the pandemic, the Pfizer vaccine, getting every American vaccinated, [and] making sure that the American public is assured that this was not [] rush[ed] on behalf of the United States . . . ." ECF No. 34 at 46.

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[3]Letter from James Madison to W.T. Barry (August 4, 1822), *in* 9 WRITINGS OF JAMES MADISON 103 (S. Hunt ed., 1910).

[4]John F. Kennedy, Remarks on the 20th Anniversary of the Voice of America (Feb. 26, 1962).

[5]*America After 9/11: Freedom Preserved or Freedom Lost?: Hearing Before the S. Comm. on the Judiciary*, 108th Cong. 302 (2003).

Accordingly, the Court concludes that this FOIA request is of paramount public importance.

"[S]tale information is of little value." *Payne Enters., Inc. v. United States*, 837 F.2d 486, 494 (D.C. Cir. 1988). The Court, agreeing with this truism, therefore concludes that the expeditious completion of Plaintiff's request is not only practicable, but necessary. *See Bloomberg, L.P. v. FDA*, 500 F. Supp. 2d 371, 378 (S.D.N.Y. Aug. 15, 2007) ("[I]t is the compelling need for such public understanding that drives the urgency of the request."). To that end, the Court further concludes that the production rate, as detailed below, appropriately balances the need for unprecedented urgency in processing this request with the FDA's concerns regarding the burdens of production. *See Halpern v. FBI*, 181 F.3d 279, 284–85 (2nd Cir. 1991) ("[FOIA] emphasizes a preference for the fullest possible agency disclosure of such information consistent with a responsible balancing of competing concerns . . . .").

Accordingly, having considered the Parties' arguments, filings in support, and the applicable law, the Court **ORDERS** that:

1. The FDA shall produce the "more than 12,000 pages" articulated in its own proposal, *see* ECF No. 29 at 24, **on or before January 31, 2022.**
2. The FDA shall produce the remaining documents at a rate of **55,000** pages every **30 days**, with the first production being due **on or before March 1, 2022**, until production is complete.
3. To the extent the FDA asserts any privilege, exemption, or exclusion as to any responsive record or portion thereof, FDA shall, concurrent with each production required by this Order, produce a redacted version of the record, redacting only those portions as to which privilege, exemption, or exclusion is asserted.

4. The Parties shall submit a Joint Status Report detailing the progress of the rolling production by **April 1, 2022**, and every **90 days** thereafter.[6]

SO ORDERED on this **6th day** of **January, 2022.**

Mark T. Pittman
UNITED STATES DISTRICT JUDGE

[6]Although the Court does not decide whether the FDA correctly denied Plaintiff's request for expedited processing, the issue is *not* moot. Should the Parties seek to file motions for summary judgment, the Court will take up the issue then.

World Health Organization

WHO lists two additional COVID-19 vaccines for emergency use and COVAX roll-out

AstraZeneca/Oxford-developed vaccines to reach countries in the coming weeks

15 February 2021 | News release | Geneva, Switzerland | Reading time: 2 min (601 words)

العربية | 中文 | Français | Русский | Español

Today WHO listed two versions of the AstraZeneca/Oxford COVID-19 vaccine for emergency use, giving the green light for these vaccines to be rolled out globally through COVAX. The vaccines are produced by AstraZeneca-SKBio (Republic of Korea) and the Serum Institute of India.

WHO's Emergency Use Listing (EUL) assesses the quality, safety and efficacy of COVID-19 vaccines and is a prerequisite for COVAX Facility vaccine supply. It also allows countries to expedite their own regulatory approval to import and administer COVID-19 vaccines.

"Countries with no access to vaccines to date will finally be able to start vaccinating their health workers and populations at risk, contributing to the COVAX Facility's goal of equitable vaccine distribution," said Dr Mariângela Simão, WHO Assistant-Director General for Access to Medicines and Health Products.

'But we must keep up the pressure to meet the needs of priority populations everywhere and facilitate global access. To do that, we need two things – a scale-up of manufacturing capacity, and developers' early submission of their vaccines for WHO review."

The WHO EUL process can be carried out quickly when vaccine developers submit the full data required by WHO in a timely manner. Once those data are submitted, WHO can rapidly assemble its evaluation team and regulators from around the world to assess the information and, when necessary, carry out inspections of manufacturing sites.

In the case of the two AstraZeneca/Oxford vaccines, WHO assessed the quality, safety and efficacy data, risk management plans and programmatic suitability, such as cold chain requirements. The process took under four weeks.

The vaccine was reviewed on 8 February by WHO's Strategic Advisory Group of Experts on Immunization (SAGE), which makes recommendations for vaccines' use in populations (i.e. recommended age groups, intervals between shots, advice for specific groups such as pregnant and lactating women). The SAGE recommended the vaccine for all age groups 18 and above.

The AstraZeneca/Oxford product is a viral vectored vaccine called ChAdOx1-S [recombinant]. It is being produced at several manufacturing sites, as well as in the Republic of Korea and India. ChAdOx1-S has been found to have 63.09% efficacy and is suitable for low- and middle-income countries due to easy storage requirements.

WHO emergency use listing

The emergency use listing (EUL) procedure assesses the suitability of novel health products during public health emergencies. The objective is to make medicines, vaccines and diagnostics available as rapidly as possible to address the emergency, while adhering to stringent criteria of safety, efficacy and quality. The assessment weighs the threat posed by the emergency as well as the benefit that would accrue from the use of the product against any potential risks.

The EUL pathway involves a rigorous assessment of late phase II and phase III clinical trial data as well as substantial additional data on safety, efficacy, quality and a risk management plan. These data are reviewed by independent experts and WHO teams who consider the current body of evidence on the vaccine under consideration, the plans for monitoring its use, and plans for further studies.

As part of the EUL process, the company producing the vaccine must commit to continue to generate data to enable full licensure and WHO prequalification of the vaccine. The WHO prequalification process will assess additional clinical data generated from vaccine trials

and deployment on a rolling basis to ensure the vaccine meets the necessary standards of quality, safety and efficacy for broader availability.

WHO also listed the Pfizer/BioNTech vaccine for emergency use on 31 December 2020.

Listings

WHO recomendation AstraZeneca/SKBio - COVID-19 Vaccine (ChAdOx1-S [recombinant])

WHO recommendation Serum Institute of India Pvt Ltd - COVID-19 Vaccine (ChAdOx1-S [recombinant]) - COVISHIELD™

BRITISH MEDICAL JOURNAL No 7070 Volume 313: Page 1448,
7 December 1996.

Introduction

The judgment by the war crimes tribunal at Nuremberg laid down 10 standards to which physicians must conform when carrying out experiments on human subjects in a new code that is now accepted worldwide.

This judgment established a new standard of ethical medical behaviour for the post World War II human rights era. Amongst other requirements, this document enunciates the requirement of *voluntary informed consent* of the human subject. The principle of voluntary informed consent protects the right of the individual to control his own body.

This code also recognizes that the risk must be weighed against the expected benefit, and that unnecessary pain and suffering must be avoided.

This code recognizes that doctors should avoid actions that injure human patients.

The principles established by this code for medical practice now have been extended into general codes of medical ethics.

The Nuremberg Code (1947)

Permissible Medical Experiments

The great weight of the evidence before us to effect that certain types of medical experiments on human beings, when kept within reasonably well-defined bounds, conform to the ethics of the medical profession generally. The protagonists of the practice of human experimentation justify their views on the basis that such experiments yield results for the good of society that are unprocurable by other methods or means of study. All agree, however, that certain basic principles must be observed in order to satisfy moral, ethical and legal concepts:

1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

   The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs, or engages in the experiment. It is

a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.

10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

For more information see Nuremberg Doctor's Trial, *BMJ* 1996;313(7070):1445-75.

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KENYA CATHOLIC DOCTORS' ASSOCIATION (KCDA)

P.O BOX 19938 – 00200 NAIROBI KENYA

TEL: (+254) 722 731 378

EMAIL: info.kenyacatholicdoctors@gmail.com

11th August 2023.

Public Service Commission of Kenya

P. O. Box 30095 - 00100

Nairobi.

Through

The Chairperson

Amb. Anthony M. Muchiri, CBS

P. O. Box 30095 - 00100

Nairobi.

Dear Sir,

RE: GROSS MISCONDUCT AND DERELICTION OF DUTY BY THE ACTING DIRECTOR GENERAL OF HEALTH OF KENYA.

The purpose of this communication is to bring to your attention on the gross dereliction of duty to protect the lives of Kenyans, facilitating the undermining of our national sovereignty by the World Health Organization (WHO), lack of fidelity to the laws of Kenya, insubordination of Ministerial duty bearer and the State Law Office by the Acting Director General of Health (DG), Dr. Patrick Amoth, EBS.

We do this cognizant of your function and powers, specifically your power as his appointing authority and functions of exercising disciplinary control over his office, promoting the values and principles referred to in Articles 10 and 232 of the Constitution of Kenya 2010 (COK), investigating personnel practices, ensure that the public service is efficient and effective, and developing human resource in the public service.

On 3rd of July 2023, in the company of the Bishop in charge of the department of Health of the Kenya Conference of Catholic Bishops, Bishop Joseph Mbatia, we met with the Cabinet Secretary for health (CS) to share our concerns, among other things, the planned launch of the Clinical

Chairman	Vice-Chairman	Secretary	Ass. Secretary	Treasurer	Ass. Treasurer
DR. Wahome Ngare	DR. Mose Lagat	DR. A. K. Ndonga	DR. Lucy N. Wainaina	Dr. Dave Kihara	DR. A. M. Kiura

handbook on the Prevention and Management of the Big Five Causes of Maternal Morbidity and Mortality in Kenya and National Guidelines on the Combination of Mifepristone and Misoprostol (Combi-pack) that was scheduled for the 6th June 2023 spearheaded by the Acting DG, only to realize the CS had not been briefed on the matter. The Combi-pack is also extensively mentioned in chapter six of the Prevention and Management of the Big Five Causes of Maternal Morbidity and Mortality in Kenya, where it's recommended for use up to 28 weeks' gestation or about seven months of pregnancy.

Mifepristone is used to deliberately and intentionally kill the unborn child by separating the placenta from the womb while Misoprostol induces contractions and expulsion of the dead child in the induced miscarriage, or so called "safe abortion". The proposed clinical guidelines have their chief end being the sale and distribution of the miscarriage inducing Combi-pack and provision of abortion on demand, both of which are illegal in Kenyan law. Unfortunately, this illegal practice of "safe abortion" is being sanctioned and promoted locally by WHO, some United Nations (UN) agencies and some local civil society organizations such as Reproductive Health Network – Kenya.

It is surprising that the Acting DG had previously written to all County Executive Committees Members of Health, though the Chief Executive Officer (CEO) of the Council of Governors on 18th of May 2023, a letter that was received on 24th of May 2023, requesting the counties to give the "MOH implementing partners who are leading this initiative" the necessary support. The said letter also indicates that "the Combi-pack was included in the Maternal and Neonatal Health – Kenya Essential Medicines List and will be tendered by KEMSA for procurement for 2023 – 2024." Note carefully that the date of the said letter clearly precedes the 6th of August2023 that was the proposed launch date of the clinical guidelines that were then not known to, or sanctioned by CS health!

It important to note that there has been no vacuum that necessitated urgent development of new guidelines because the Ministry of Health (MOH) has existing National Quality of Care Guidelines in Obstetrics and Perinatal Care and Post Abortion Care (PAC) Guidelines. The existing guidelines have been disseminated to the 47 counties through the MOH and the County Governments. Curiously, but not surprisingly, is that the existing RH policy and the PAC guidelines were not available on the MOH Government Portal at the time of writing this letter. The on line availability and accessibility of Government policies, guidelines and services has been emphasized by none other than His Excellency, the President of the Republic of Kenya.

The newly proposed clinical guidelines are against the Constitution of Kenya 2010 (COK) that recognizes and protects the family unit and life from conception, as well as against the Ministry of Health (MOH) National Reproductive Health Policy 2022-2032 (RH). The existing RH policy is the overriding Government policy on all matters of Reproductive Health in Kenya, binding as it does all stakeholders in health, at the two levels of Government and all state and public officers in health service delivery. The document helps implement the COK, the Kenya Vision 2030, the

Kenya Health Policy 2014-2030, and guides on how non-binding international commitments such as the Sustainable Development Goals can be implemented in a manner that is respectful of the diverse cultural and religious values of Kenyans. We draw your attention to the petition number 27 of 2022 in the Kenya High Court of Nairobi (formerly constitutional petition number 36 of 2022 at the Kenya High Court in Kiambu Rachael Mwikali and 3 others vs the AG), a petition seeking to set aside the RH policy to create anarchy in the reproductive health space for Kenya, to enable the petitioners to continue indoctrinating children and adolescents with sexualizing and commodification ideologies to the detriment of this young and significant population.

The Acting DG also failed to protect his junior officers and seems to have abated, facilitated or permitted moves aimed at deliberately weakening MOH technical oversight divisions on matters reproductive health through unconstitutional deployment of technical officers from key technical divisions of the MOH. This took place at the time of incumbency and transition from the previous to the current government contrary to the order by the assumption of office committee at the time. During these targeted deployments, personnel with the requisite qualifications and competencies in matters health policy, were removed from leading technical units in reproductive health and left in limbo, while their previous positions were filled with less technically qualified officers, a move that denied the incoming administration critical sober stewardship on a matter of great public concern that may impact the health of Kenyans negatively.

Finally, this is not the first time the Acting DG has blindly followed the advice of WHO without due consideration of the sovereignty of the country and the wellbeing of Kenyans. We noted the same in his advise to the Government of Kenya on the handling of the Covid-19 crisis, including advise allowing and facilitating coercion of people into taking the experimental mRNA gene therapy injections and denying those who rejected the injections access to offices and other amenities, suggesting that those who did not take the experimental mRNA gene therapy injections were putting those who took the injections at risk contrary to available scientific evidence, promoting the experimental mRNA gene therapy injections for use by children and pregnant women without substantial scientific evidence, refusal to stop the use of the experimental mRNA gene therapy injections even after the Pfizer data revealed there were 1200 deaths during the clinical trials among many other instances of mishandling the Covid-19 crisis that bordered on abuse of human rights and jeopardized the occupational health and safety of MOH staff and the populace they serve. These injections have still not been stopped despite rising evidence of serious adverse effect. Many countries did not adhere to the advised blanket administration of experimental mRNA gene therapy injections and have even lifted embargoes on travel on those who have not received the injections. The Acting DG being a member of the WHO executive committee and its chair during the crisis is an obvious conflict of interest.

We request that the commission urgently investigates these matters and take the necessary action to save this country from a major Reproductive Health calamity, medical tyranny in the near future, and undermining of our sovereignty by WHO, UN and local civil society organizations. Kenya Catholic Doctors Association will be happy to assist, if and when called upon to do so.

Yours faithfully,

KENYA CATHOLIC DOCTORS ASSOCIATION
P. O. Box 19938 - 00202,
NAIROBI - KENYA

Email: kencathdocs@yahoo.com

Dr Wahome Ngare

Chairman – KCDA.

cc: Kenya Conference of Catholic Bishops

Kenya Christina Professionals Forum

Cabinet Secretary of Health

Attorney General

Office of the President

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GROSS MISCONDUNCT AND DERELICTION OF DUTY BY THE ACTING DIRECTOR GENERAL OF HEALTH OF KENYA

wahome ngare <wngare@hotmail.com>

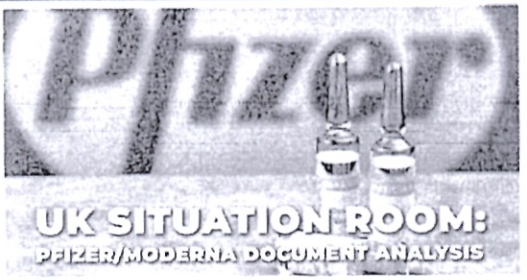
Sat 8/12/2023 11:16 PM

To:psck@publicservice.go.ke <psck@publicservice.go.ke>
Cc:cs@health.go.ke <cs@health.go.ke>;cd.nyahururu@gmail.com <cd.nyahururu@gmail.com>;fr.ngaruiya@catholicchurch.or.ke <fr.ngaruiya@catholicchurch.or.ke>;Jacinta Mutegi <jmutegi@catholicchurch.or.ke>;SACCO Ndonga <andrewndonga@hotmail.com>;feedback@president.go.ke <feedback@president.go.ke>;ag@ag.go.ke <ag@ag.go.ke>;Kenya Catholic Doctors Association <info.kenyacatholicdoctors@gmail.com>,Kenya Christian Professionals Forum <info.kcpf@gmail.com>
Bcc:Wahome Ngare <homes6619@gmail.com>

5 attachments (4 MB)

Gross misconduct of DG 11th Agu 2023.pdf; DG to county excom 18th May 2023.pdf; Combipack - MARIPRIST.docx; Guidelines, Standards & Policies Portal 11th Aug 2023.pdf; Amoth appointed as WHO Executive Board chairperson.pdf;

Dear Public Service Commission of Kenya,
Attached find a self explanatory letter with the above stated referene and necessary attachments.
The physical letter will be delivered on Monday 14th August 2023.
Regards
w.n.
Dr Wahome Ngare
Chairman - Kenya Catholic Doctors Association



Introduction

By Chris Grainger

> Never before has so much harm been done to so many by so few based on so little data.

Obtaining the Data

The Public Health Collaboration (PHC) is an organisation in the US made up of public health professionals, medical professionals, data analysts and journalists. PHC filed a FOIA request to the FDA to release documents relating to the medical trials data and information for the Pfizer/BioNTech and Moderna Covid-19 vaccines. A Summary of the FOIA request and the reasons why the PHC is requesting the documents, can be found on the PHC website. The full information for the FOIA request is also available on the PHC website.

On 19 November 2021, the FDA denied the PHC's request for expedited processing, claiming that the PHC did not demonstrate a compelling need that would warrant such treatment. The FDA's denial letter stated that the PHC's request was not an urgency, as it was the public's concerning a lapsed Federal Government shutdown.

The PHC request was eventually granted by the court order through the PHC's attorney, Aaron Siri. The judge in the matter ordered the FDA to release all 55,000 pages of documents over eight months, starting on the FDA planning to release the data for 75 years.

A copy of the FOIA request can be found on the PHC website, and the PHC explains that:

> Knowledge is a fundamental component of democracy.
>
> A key to that democratic principle is the trust and confidence in open information and access to data by the people.
>
> Lack of such information is, in fact, a threat to democracy. It paves the way for the public's trust and belief in their government to be undermined.

Analysing the Data

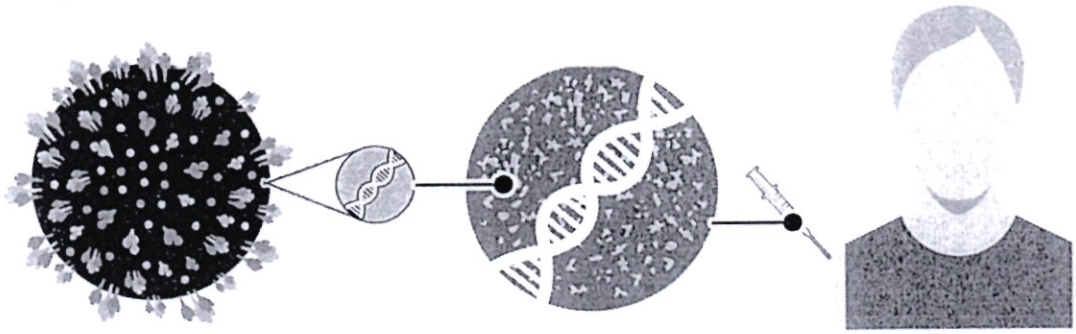
Dr Naomi Wolf, CEO of the PHC, is a well-known doctor with many years of experience in the United States and has said:

> We realised that the documents were impossible to analyse in the normal, linear, back-ways, due to their massive scope and the documents' use of terms from scientific and medical research.
>
> We created the tool [redacted] and released it in November 2022. We [redacted] and finally, in late January 2023, we released the entirety of the documents in a searchable, sortable, filterable format. Now, researchers, journalists, scientists, doctors, and citizens can search for specific drugs, diseases, adverse reactions, and other terms of interest to them, and see how frequently they appear in the documents. We also created a tool that allows users to see how frequently certain terms appear in the documents over time, and to see how frequently certain terms appear in the documents in relation to other terms. We have also created a tool that allows users to see how frequently certain terms appear in the documents in relation to other terms. These tools allow

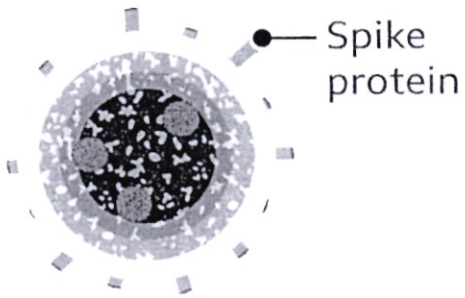
How the Oxford vaccine works

1 Scientists take genes for the spike protein on the surface of the coronavirus and put them into a harmless virus to make a vaccine

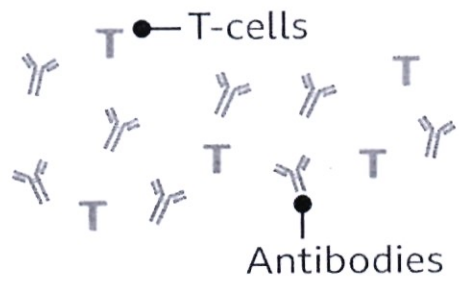
This is injected into the patient



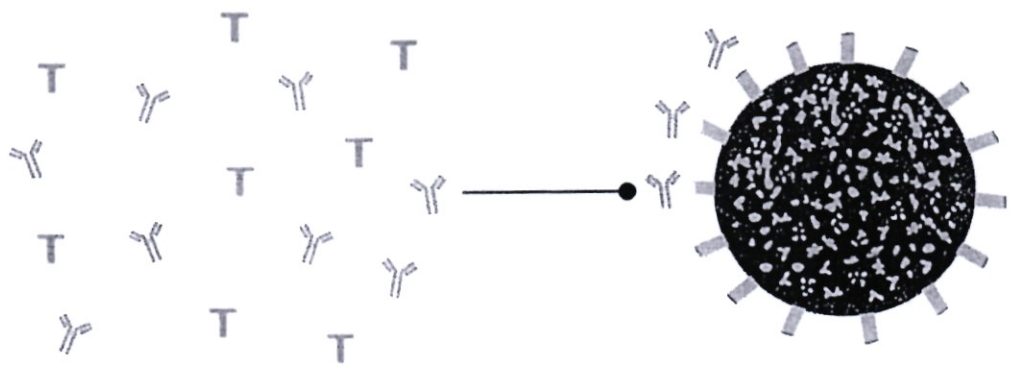
2 The vaccine enters cells which then start to produce the spike protein



The body's immune system reacts, produces antibodies and activates T-cells to destroy cells with the spike protein

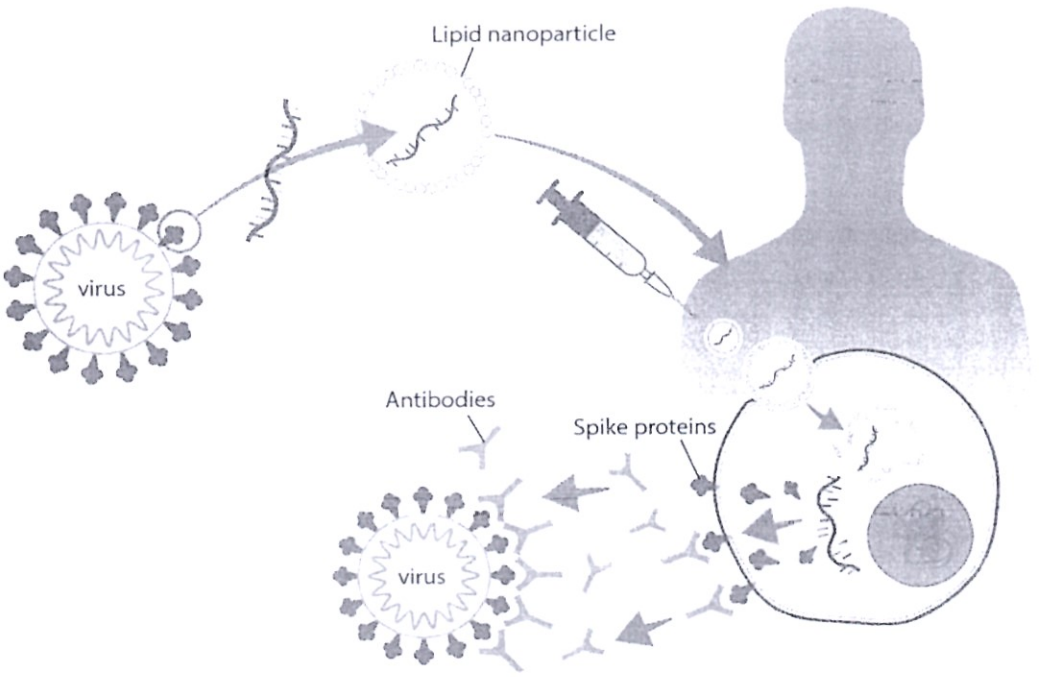


3 If the patient later catches coronavirus, antibodies and T-cells are triggered to fight the virus



Source: Nature

BBC


Lipid nanoparticle
virus
Antibodies
Spike proteins
virus

222

COVID-19 Vaccine AstraZeneca

Product Information as approved by the CHMP on 29 January 2021, pending endorsement by the European Commission

Includes:

Package leaflet (for patients)

Summary of product characteristics (for healthcare professionals)

Manufacturers and conditions of the marketing authorisation

Labelling

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

COVID-19 Vaccine AstraZeneca suspension for injection
COVID-19 Vaccine (ChAdOx1-S [recombinant])

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

These are multidose vials which contain 8 doses or 10 doses of 0.5 ml per vial (see section 6.5).

One dose (0.5 ml) contains:
Chimpanzee Adenovirus encoding the SARS-CoV-2 Spike glycoprotein (ChAdOx1-S)*, not less than 2.5×10^8 infectious units (Inf.U)
*Produced in genetically modified human embryonic kidney (HEK) 293 cells and by recombinant DNA technology.

This product contains genetically modified organisms (GMOs).

Excipient with known effect
Each dose (0.5 ml) contains approximately 2 mg of ethanol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection (injection).

The suspension is colourless to slightly brown, clear to slightly opaque with a pH of 6.6.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

COVID-19 Vaccine AstraZeneca is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 18 years of age and older.

The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Individuals 18 years of age and older
The COVID-19 Vaccine AstraZeneca vaccination course consists of two separate doses of 0.5 ml each. The second dose should be administered between 4 and 12 weeks (28 to 84 days) after the first dose (see section 5.1).

There are no data available on the interchangeability of COVID-19 Vaccine AstraZeneca with other COVID-19 vaccines to complete the vaccination course. Individuals who have received the first dose

of COVID-19 Vaccine AstraZeneca should receive the second dose of COVID-19 Vaccine AstraZeneca to complete the vaccination course.

Paediatric population
The safety and efficacy of COVID-19 Vaccine AstraZeneca in children and adolescents (less than 18 years of age) have not yet been established. No data are available.

Elderly population
No dose adjustment is required. See also sections 4.4 and 5.1.

Method of administration

COVID-19 Vaccine AstraZeneca is for intramuscular injection only, preferably in the deltoid muscle of the upper arm.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see section 4.4.

For instructions on handling and disposal, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity and anaphylaxis

Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine. Close observation for at least 15 minutes is recommended following vaccination. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of COVID-19 Vaccine AstraZeneca.

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions may occur in association with vaccination as a psychogenic response to the needle injection. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness

Vaccination should be postponed in individuals suffering from an acute severe febrile illness or acute infection. However, the presence of a minor infection and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders

As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as

haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

Immunocompromised Individuals

The efficacy, safety and immunogenicity of the vaccine have not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of COVID-19 Vaccine AstraZeneca may be lower in immunosuppressed individuals.

Duration of protection

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

Limitations of vaccine effectiveness

Protection starts from approximately 3 weeks after the first dose of COVID-19 Vaccine AstraZeneca. Individuals may not be fully protected until 15 days after the second dose is administered. As with all vaccines, vaccination with COVID-19 Vaccine AstraZeneca may not protect all vaccine recipients (see section 5.1).

Currently available clinical trial data do not allow an estimate of vaccine efficacy in subjects over 55 years of age.

Excipients

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per 0.5 ml dose, that is to say essentially "sodium-free".

Ethanol
This medicinal product contains 2 mg of alcohol (ethanol) per 0.5 ml dose. The small amount of alcohol in this medicinal product will not have any noticeable effects.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of COVID-19 Vaccine AstraZeneca with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is limited experience with use of COVID-19 Vaccine AstraZeneca in pregnant women.

Animal reproductive toxicity studies have not been completed. Based upon results from the preliminary study, no effects are expected on development of the fetus (see section 5.3).

Administration of COVID-19 Vaccine AstraZeneca during pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and fetus.

Breastfeeding

It is unknown whether COVID-19 Vaccine AstraZeneca is excreted in human milk.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

4.7 Effects on ability to drive and use machines

COVID-19 Vaccine AstraZeneca has no or negligible influence on the ability to drive and use machines. However, some of the adverse reactions mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

The overall safety of COVID-19 Vaccine AstraZeneca is based on an interim analysis of pooled data from four clinical trials conducted in the United Kingdom, Brazil, and South Africa. At the time of analysis, 23,745 participants ≥18 years old had been randomised and received either COVID-19 Vaccine AstraZeneca or control. Out of these, 12,021 received at least one dose of COVID-19 Vaccine AstraZeneca and 8,266 received two doses. The median duration of follow-up was 62 days post-dose 2.

The most frequently reported adverse reactions were injection site tenderness (63.7%), injection site pain (54.2%), headache (52.6%), fatigue (53.1%), myalgia (44.0%), malaise (44.2%), pyrexia (includes feverishness (33.6%) and fever >38°C (7.9%)), chills (31.9%), arthralgia (26.4%) and nausea (21.9%). The majority of adverse reactions were mild to moderate in severity and usually resolved within a few days of vaccination. When compared with the first dose, adverse reactions reported after the second dose were milder and reported less frequently.

Reactogenicity was generally milder and reported less frequently in older adults (≥65 years old).

The safety profile was consistent across participants with or without prior evidence of SARS-CoV-2 infection at baseline; the number of seropositive participants at baseline was 718 (3.0%).

Tabulated list of adverse reactions

Adverse drug reactions (ADRs) are organised by MedDRA System Organ Class (SOC). Frequencies of occurrence of adverse reactions are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000) and not known (cannot be estimated from available data); within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness.

Table 1 Adverse drug reactions

MedDRA SOC	Frequency	Adverse Reactions
Blood and lymphatic system disorders	Uncommon	Lymphadenopathy
Metabolism and nutrition disorders	Uncommon	Decreased appetite
Nervous system disorders	Very common	Headache
	Uncommon	Dizziness Somnolence
Gastrointestinal disorders	Very common	Nausea
	Common	Vomiting Diarrhoea
Skin and subcutaneous tissue disorders	Uncommon	Hyperhidrosis Pruritus Rash

MedDRA SOC	Frequency	Adverse Reactions
Musculoskeletal and connective tissue disorders	Very common	Myalgia Arthralgia
General disorders and administration site conditions	Very common	Injection site tenderness Injection site pain Injection site warmth Injection site pruritus Injection site bruising[a] Fatigue Malaise Feverishness Chills
	Common	Injection site swelling Injection site erythema Fever[b]

[a] Injection site bruising includes injection site haematoma (uncommon)
[b] Measured fever ≥38°C

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V and include batch/Lot number if available.

4.9 Overdose

There is no specific treatment for an overdose with COVID-19 Vaccine AstraZeneca. In the event of an overdose, the individual should be monitored and provided with symptomatic treatment as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vaccines, other viral vaccines, ATC code: J07BX03

Mechanism of action

COVID-19 Vaccine AstraZeneca is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of SARS-CoV-2. The SARS-CoV-2 S immunogen in the vaccine is expressed in the trimeric pre-fusion conformation; the coding sequence has not been modified in order to stabilise the expressed S-protein in the pre-fusion conformation. Following administration, the S glycoprotein of SARS-CoV-2 is expressed locally stimulating neutralising antibody and cellular immune responses, which may contribute to protection to COVID-19.

Clinical efficacy

Analysis of pooled data from COV002 and COV003

The clinical efficacy of COVID-19 Vaccine AstraZeneca has been evaluated based on an analysis of pooled data from two on-going randomised, blinded, controlled trials: a phase II/III study, COV002, in adults ≥18 years of age (including the elderly) in the UK; and a phase III study, COV003, in adults ≥18 years of age (including the elderly) in Brazil. The studies excluded participants with severe and/or uncontrolled cardiovascular, gastrointestinal, liver, renal, endocrine/metabolic disease, and

neurological illnesses; as well as those with severe immunosuppression, pregnant women and participants with a known history of SARS-CoV-2 infection. Influenza vaccines could be administered 7 days before or after any dose of COVID-19 Vaccine AstraZeneca. All participants are planned to be followed for up to 12 months, for assessments of safety and efficacy against COVID-19 disease.

In the pooled analysis for efficacy, participants ≥18 years of age received two doses (5×10^{10} viral particles per dose corresponding to not less than 2.5×10^{8} infectious units) of COVID-19 Vaccine AstraZeneca (N=6,106) or control (meningococcal vaccine or saline) (N=6,090), administered via IM injection.

Because of logistical constraints, the interval between dose 1 and dose 2 ranged from 3 to 23 weeks (21 to 159 days), with 86.1% of participants receiving their two doses within the interval of 4 to 12 weeks (28 to 84 days).

Baseline demographics were well balanced across COVID-19 Vaccine AstraZeneca and control treatment groups. In the pooled analysis, among the participants who received COVID-19 Vaccine AstraZeneca with a dose interval of between 4 and 12 weeks, 87.0% of participants were 18 to 64 years old (with 13.0% aged 65 or older and 2.8% aged 75 or older); 55.1% of subjects were female; 76.2% were White, 6.4% were Black and 3.4% were Asian. A total of 2,068 (39.3%) participants had at least one pre-existing comorbidity (defined as a BMI ≥30 kg/m^2, cardiovascular disorder, respiratory disease or diabetes). At the time of analysis the median follow up time post-dose 2 was 78 days.

Final determination of COVID-19 cases were made by an adjudication committee, who also assigned disease severity according to the WHO clinical progression scale. A total of 218 participants had SARS-CoV-2 virologically confirmed COVID-19 occurring ≥15 days post second dose with at least one COVID-19 symptom (objective fever (defined as ≥37.8°C), cough, shortness of breath, anosmia, or agcusia) and were without evidence of previous SARS-CoV-2 infection. COVID-19 Vaccine AstraZeneca significantly decreased the incidence of COVID-19 compared to control (see Table 2).

Table 2 COVID-19 Vaccine AstraZeneca efficacy against COVID-19[a]

Population	COVID-19 Vaccine AstraZeneca		Control		Vaccine efficacy % (95% CI)[b]
	N	Number of COVID-19 cases, n (%)	N	Number of COVID-19 cases, n (%)	
Licensing regimen					
4 – 12 weeks (28 to 84 days)	5,258	64 (1.2)	5,210	154 (3.0)	59.5 (45.8, 69.7)

N = Number of subjects included in each group; n = Number of subjects having a confirmed event; CI = Confidence Interval;

[a] Efficacy endpoint was based on confirmed COVID-19 cases in subjects aged 18 years and over who were seronegative at baseline, who had received two doses and were on-study ≥15 days post second dose.

[b] CI not adjusted for multiplicity.

Vaccine efficacy was 62.6% (95% CI: 50.9; 71.5) in participants receiving two recommended doses with any dose interval (ranging from 3 to 23 weeks), in a pre-specified analysis.

Regarding COVID-19 hospitalisation (WHO Severity grading ≥4) there were 0 (0.0%; N=5,258) cases of COVID-19 hospitalisation in participants who received two doses of COVID-19 Vaccine AstraZeneca (≥15 days post dose 2) as compared to 8 (0.2%; N=5,210) for control, including one severe case (WHO Severity grading ≥6), reported for control. In all participants who received at least one dose, as from 22 days post dose 1, there were 0 (0.0%, N=8,032) cases of COVID-19 hospitalisation in participants who received COVID-19 Vaccine AstraZeneca, as compared to 14 (0.2%, N=8,026), including one fatality, reported for control.

Participants who had one or more comorbidities had a vaccine efficacy of 58.3% [95% CI: 33.6; 73.9]; 25 (1.2%) vs 60 (2.9%) for COVID-19 Vaccine AstraZeneca (N=2,068) and control (N=2,040), respectively; which was similar to the vaccine efficacy observed in the overall population.

Evidence shows protection starts from approximately 3 weeks after first dose of vaccine and persists up to 12 weeks. A second dose should be given at a 4 to 12 week interval after the first dose (see section 4.4).

Elderly population

Among participants aged between 56 and 65 years old, 8 cases of COVID-19 were reported in those receiving COVID-19 Vaccine AstraZeneca (≥15 days post dose 2) compared with 9 cases for control; 2 and 6 cases of COVID-19 were reported in participants older than 65 years of age, for COVID-19 Vaccine AstraZeneca (≥15 days post dose 2) and control, respectively.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with COVID-19 Vaccine AstraZeneca in one or more subsets of the paediatric population in prevention of COVID-19 (see section 4.2 for information on paediatric use).

Conditional approval

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited.
The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on a conventional study of repeat dose toxicity.

Genotoxicity/Carcinogenicity

Neither genotoxicity nor carcinogenicity studies were performed. The components of the vaccine are not expected to have genotoxic potential.

Reproductive toxicity

Animal studies of potential toxicity to reproduction and development have not yet been completed.
A preliminary reproductive toxicity study in mice does not show toxicity in dams or foetuses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-Histidine
L-Histidine hydrochloride monohydrate
Magnesium chloride hexahydrate
Polysorbate 80 (E 433)
Ethanol

Sucrose
Sodium chloride
Disodium edetate (dihydrate)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products or diluted.

6.3 Shelf life

Unopened vial

6 months when stored in a refrigerator (2°C – 8°C)

Opened vial

Chemical and physical in-use stability have been demonstrated from the time of vial opening (first needle puncture) to administration for no more than 48 hours in a refrigerator (2°C – 8°C). Within this time period the product may be kept and used at temperatures up to 30°C for a single period of up to 6 hours. After this time period, the product must be discarded. Do not return it to the refrigerator.

From a microbiological point of view, after first opening the vaccine should be used immediately. If the vaccine is not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Keep vials in outer carton in order to protect from light.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Multidose vial

8-dose vial
4 ml of suspension in an 8-dose vial (clear type I glass) with stopper (elastomeric with aluminium overseal). Each vial contains 8 doses of 0.5 ml. Pack sizes of 10 multidose vials.

10-dose vial
5 ml of suspension in a 10-dose vial (clear type I glass) with stopper (elastomeric with aluminium overseal). Each vial contains 10 doses of 0.5 ml. Pack sizes of 10 multidose vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Handling instructions and administration

This vaccine should be handled by a healthcare professional using aseptic technique to ensure the sterility of each dose.

Do not use this vaccine after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.

Unopened multidose vial should be stored in a refrigerator (2°C – 8°C). Do not freeze.

Keep the vials in outer carton in order to protect from light.

The vaccine should be inspected visually for particulate matter and discolouration prior to administration. COVID-19 Vaccine AstraZeneca is a colourless to slightly brown, clear to slightly opaque suspension. Discard the vial if the suspension is discoloured or visible particles are observed. Do not shake. Do not dilute the suspension.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

The COVID-19 Vaccine AstraZeneca vaccination course consists of two separate doses of 0.5 ml each. The second dose should be administered between 4 and 12 weeks after the first dose. Individuals who have received the first dose of COVID-19 Vaccine AstraZeneca should receive the second dose of the same vaccine to complete the vaccination course.

Each vaccine dose of 0.5 ml is withdrawn into a syringe for injection to be administered intramuscularly, preferably in the deltoid muscle of the upper arm. Use a new needle for administration, when possible.

It is normal for liquid to remain in the vial after withdrawing the final dose. An additional overfill is included in each vial to ensure that 8 doses (vial of 4 ml) or 10 doses (vial of 5 ml) of 0.5 ml can be delivered. Do not pool excess vaccine from multiple vials. Discard any unused vaccine.

Chemical and physical in-use stability have been demonstrated from the time of vial opening (first needle puncture) to administration for no more than 48 hours in a refrigerator (2°C – 8°C). Within this time period the product may be kept and used at temperatures up to 30°C for a single period of up to 6 hours. After this time period, the product must be discarded. Do not return it to the refrigerator.

Disposal

COVID-19 Vaccine AstraZeneca contains genetically modified organisms (GMOs). Any unused vaccine or waste material should be disposed of in compliance with the local guidance for genetically modified organisms or biohazardous waste. Spills should be disinfected using agents with activity against adenovirus.

7. MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1529/001	10 multidose vials (8 doses per vial)
EU/1/21/1529/002	10 multidose vials (10 doses per vial)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance

Henogen S.A.
Rue de la Marlette 14
7180 Seneffe
Belgium

Catalent Maryland, Inc
7555 Harmans Road
Harmans, MD 21077
United States

Oxford Biomedica (UK) Limited
Unit A
Plot 7000
Alec Issigonis Way
Oxford OX4 2ZY
United Kingdom

Name and address of the manufacturer(s) responsible for batch release

MedImmune Pharma B.V., Nijmegen
Lagelandseweg 78
Nijmegen, 6545CG
Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the consistency of the active substance and finished product manufacturing process, the applicant should provide additional validation and comparability data and, introduce enhanced testing.	December 2021 with interim monthly updates beginning February 2021
In order to ensure consistent product quality, the applicant should provide additional information on stability of the active substance and finished product and review the finished product specifications following further manufacturing experience.	June 2022 with interim monthly updates beginning February 2021
In order to confirm the efficacy and safety of COVID-19 Vaccine AstraZeneca, the MAH should submit the final Clinical Study Reports for the randomised, controlled, COV001, COV002, COV003 and COV005.	31 May 2022
In order to confirm the efficacy and safety of COVID-19 Vaccine AstraZeneca, the MAH should provide the primary analysis (based on the 7th December data cut-off (post data-base lock) and final analysis from the pooled pivotal studies.	Primary analysis: 5 March 2021 Final pooled analysis: 31 May 2022
In order to confirm the efficacy and safety of COVID-19 Vaccine AstraZeneca in the elderly and subjects with underlying disease, the MAH should submit the overview and summaries of the primary analysis and final clinical study report for study D8110C00001.	Primary analysis: 30 April 2021 Final CSR: 31 March 2024

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON - EIGHT-DOSE VIAL, PACK OF 10 VIALS

1. NAME OF THE MEDICINAL PRODUCT

COVID-19 Vaccine AstraZeneca suspension for injection
COVID-19 Vaccine (ChAdOx1-S [recombinant])

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One dose (0.5 ml) contains not less than 2.5×10^8 infectious units

Chimpanzee Adenovirus encoding the SARS-CoV-2 Spike glycoprotein ChAdOx1-S

3. LIST OF EXCIPIENTS

Excipients: L-histidine, L-histidine hydrochloride monohydrate, magnesium chloride hexahydrate, polysorbate 80 (E 433), ethanol, sucrose, sodium chloride, disodium edetate (dihydrate), water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection
10 multidose vials
(8 doses per vial - 0.5ml per dose)
4 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use
Read the package leaflet before use.
For more information, scan here or visit www.azcovid-19.com
QR code to be included

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Keep vials in outer carton in order to protect from light.
Do not freeze. Do not shake.
For information on the shelf life after first opening and additonal storage information, see the package leaflet.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

This medicine contains genetically modified organisms (GMOs). Dispose of in compliance with the local guidance for GMOs or biohazardous waste.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1529/001 10 multidose vials (8 doses per vial)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN

NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL - EIGHT-DOSE VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COVID-19 Vaccine AstraZeneca injection
COVID-19 Vaccine (ChAdOx1-S [recombinant])

Intramuscular use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Multidose vial (8 × 0.5 ml doses)
4 ml

6. OTHER

AstraZeneca

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON - TEN-DOSE VIAL, PACK OF 10 VIALS

1. NAME OF THE MEDICINAL PRODUCT

COVID-19 Vaccine AstraZeneca suspension for injection
COVID-19 Vaccine (ChAdOx1-S [recombinant])

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One dose (0.5 ml) contains not less than 2.5×10^8 infectious units

Chimpanzee Adenovirus encoding the SARS-CoV-2 Spike glycoprotein ChAdOx1-S

3. LIST OF EXCIPIENTS

Excipients: L-histidine, L-histidine hydrochloride monohydrate, magnesium chloride hexahydrate, Polysorbate 80 (E 433), ethanol, sucrose, sodium chloride, disodium edetate (dihydrate), water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection
10 multidose vials
(10 doses per vial - 0.5 ml per dose)
5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use
Read the package leaflet before use.
For more information, scan here or visit www.azcovid-19.com
QR code to be included

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Keep vials in outer carton in order to protect from light.
Do not freeze. Do not shake.
For information on the shelf life after first opening and additonal storage information, see the package leaflet.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

This medicine contains genetically modified organisms (GMOs). Dispose of in compliance with the local guidance for GMOs or biohazardous waste.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1529/002 10 multidose vials (10 doses per vial)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL - TEN-DOSE VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COVID-19 Vaccine AstraZeneca injection
COVID-19 Vaccine (ChAdOx1-S [recombinant])

Intramuscular use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Multidose vial (10 × 0.5 ml doses)
5 ml

6. OTHER

AstraZeneca

B. PACKAGE LEAFLET

Package leaflet: Information for the user

COVID-19 Vaccine AstraZeneca suspension for injection
COVID-19 Vaccine (ChAdOx1-S [recombinant])

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before the vaccine is given because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What COVID-19 Vaccine AstraZeneca is and what it is used for
2. What you need to know before you are given COVID-19 Vaccine AstraZeneca
3. How COVID-19 Vaccine AstraZeneca is given
4. Possible side effects
5. How to store COVID-19 Vaccine AstraZeneca
6. Contents of the pack and other information

1. What COVID-19 Vaccine AstraZeneca is and what it is used for

COVID-19 Vaccine AstraZeneca is used for preventing COVID-19 caused by the SARS-CoV-2 virus.

COVID-19 Vaccine AstraZeneca is given to adults aged 18 years and older.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and specialised white blood cells that work against the virus, so giving protection against COVID-19. None of the ingredients in this vaccine can cause COVID-19.

2. What you need to know before you are given COVID-19 Vaccine AstraZeneca

The vaccine must not be given:
- If you are allergic to the active substance or any of the other ingredients of this vaccine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before you are given COVID-19 Vaccine AstraZeneca:
- If you have ever had a severe allergic reaction after any other vaccine injection or after you were given COVID 19 Vaccine AstraZeneca in the past;
- If you have ever fainted following any needle injection;
- If you have a severe infection with a high temperature (over 38°C). However, you can have your vaccination if you have a mild fever or upper airway infection like a cold;
- If you have a problem with bleeding or bruising, or if you are taking an anticoagulant medicine (to prevent blood clots);
- If your immune system does not work properly (immunodeficiency) or you are taking medicines that weaken the immune system (such as high-dose corticosteroids, immunosuppressants or cancer medicines).

If you are not sure if any of the above applies to you, talk to your doctor, pharmacist or nurse before you are given the vaccine.

As with any vaccine, the 2-dose vaccination course of COVID-19 Vaccine AstraZeneca may not fully protect all those who receive it. It is not known how long you will be protected for. Currently there are limited data on the efficacy of COVID-19 Vaccine AstraZeneca in individuals aged 55 and older.

Children and adolescents
COVID-19 Vaccine AstraZeneca is not recommended for children aged below 18 years. Currently there is not enough information available on the use of COVID-19 Vaccine AstraZeneca in children and adolescents younger than 18 years of age.

Other medicines and COVID-19 Vaccine AstraZeneca
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take, any other medicines or vaccines.

Pregnancy and breastfeeding
If you are pregnant or breastfeeding, think you may be pregnant, or are planning to have a baby, ask your doctor, pharmacist or nurse for advice before you receive this vaccine.

Driving and using machines
Some of the side effects of COVID-19 Vaccine AstraZeneca listed in section 4 (Possible side effects) may temporarily reduce your ability to drive and use machines. If you feel unwell after vaccination, do not drive or use machines. Wait until any effects of the vaccine have worn off before you drive or use machines.

COVID-19 Vaccine AstraZeneca contains sodium and alcohol (ethanol)
This medicine contains less than 1 mmol sodium (23 mg) per 0.5 ml dose, that is to say essentially 'sodium-free'.
This medicine contains 2 mg of alcohol (ethanol) per 0.5 ml dose. The small amount of alcohol in this medicine will not have any noticeable effects.

3. How COVID-19 Vaccine AstraZeneca is given

COVID-19 Vaccine AstraZeneca is given as an injection of 0.5 ml into a muscle (usually in the upper arm).

During and after each injection of the vaccine, your doctor, pharmacist or nurse will watch over you for around 15 minutes to monitor for signs of an allergic reaction.

You will receive 2 injections of COVID-19 Vaccine AstraZeneca. The second injection can be given between 4 and 12 weeks after the first injection. You will be told when you need to return for your second injection.

When COVID-19 Vaccine AstraZeneca is given for the first injection, the second injection to complete the vaccination course should also be with COVID-19 Vaccine AstraZeneca.

If you miss an appointment for your second injection of COVID-19 Vaccine AstraZeneca
If you forget to go back at the scheduled time, ask your doctor, pharmacist or nurse for advice. It is important that you return for your second injection of COVID-19 Vaccine AstraZeneca. If you miss a scheduled injection, you may not be fully protected against COVID-19.

4. Possible side effects

Like all medicines, this vaccine can cause side effects, although not everybody gets them. If you notice any side effects not mentioned in this package leaflet, please tell your doctor, pharmacist or nurse.

Get **urgent** medical attention if you get symptoms of a severe allergic reaction. Such reactions may include a combination of any of the following symptoms:
- feeling faint or light-headed
- changes in your heartbeat
- shortness of breath
- wheezing
- swelling of your lips, face, or throat
- hives or rash
- nausea or vomiting
- stomach pain.

The following side effects may occur with COVID-19 Vaccine AstraZeneca:

Very Common (may affect more than 1 in 10 people)
- tenderness, pain, warmth, itching, or bruising where the injection is given
- feeling tired (fatigue) or generally feeling unwell
- chills or feeling feverish
- headache
- feeling sick (nausea)
- joint pain or muscle ache

Common (may affect up to 1 in 10 people)
- swelling or redness where the injection is given
- fever (>38°C)
- being sick (vomiting) or diarrhoea

Uncommon (may affect up to 1 in 100 people)
- sleepiness or feeling dizzy
- decreased appetite
- enlarged lymph nodes
- excessive sweating, itchy skin or rash

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store COVID-19 Vaccine AstraZeneca

Keep this medicine out of the sight and reach of children.

Your doctor, pharmacist or nurse is responsible for storing this vaccine and disposing of any unused product correctly. The following information about storage, expiry, use and handling as well as disposal is intended for healthcare professionals.

Do not use this vaccine after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C).
Do not freeze.

Keep vials in outer carton in order to protect from light.

From the time of vial opening (first needle puncture) to administration store the vial for no more than 48 hours in a refrigerator (2°C–8°C). Within this time period the product may be kept and used at temperatures up to 30°C for a single period of up to 6 hours. After this time period, the product must be discarded. Do not return it to the refrigerator.

Discard the vial if the suspension is discoloured or particles are observed. Do not shake.

COVID-19 Vaccine AstraZeneca contains genetically modified organisms (GMOs). Any unused vaccine or waste material should be disposed of in compliance with the local guidance for genetically modified organisms or biohazardous waste. Spills should be disinfected using agents with activity against adenovirus.

6. Contents of the pack and other information

What COVID-19 Vaccine AstraZeneca contains
One dose (0.5 ml) contains:
Chimpanzee Adenovirus encoding the SARS-CoV-2 Spike glycoprotein ChAdOx1-S*, not less than 2.5×10^8 infectious units
*Produced in genetically modified human embryonic kidney (HEK) 293 cells and by recombinant DNA technology.

This product contains genetically modified organisms (GMOs).

The other excipients are L-histidine, L-histidine hydrochloride monohydrate, magnesium chloride hexahydrate, polysorbate 80 (E 433), sucrose, disodium edetate (dihydrate), water for injections (see section 2 "COVID-19 Vaccine AstraZeneca contains sodium and alcohol").

What COVID-19 Vaccine AstraZeneca looks like and contents of the pack
Suspension for injection (injection). The suspension is colourless to slightly brown, clear to slightly opaque.

Pack sizes:
- 8-dose multidose vial (4 ml) with stopper (elastomeric with aluminium overseal) in a pack of 10 vials. Each vial contains 8 doses of 0.5 ml.
- 10-dose multidose vial (5 ml) with stopper (elastomeric with aluminium overseal) in a pack of 10 vials. Each vial contains 10 doses of 0.5 ml.

Not all pack sizes may be marketed.

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SE-151 85 Södertälje
Sweden

Manufacturer
MedImmune Pharma B.V., Nijmegen
Lagelandseweg 78
Nijmegen, 6545CG
Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

This medicine has been given 'conditional approval'. This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Scan the QR code with a mobile device to get **this information in different languages**.

www.azcovid-19.com

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended **for healthcare professionals only**:

For storage and disposal, see section 5 "How to store COVID-19 Vaccine AstraZeneca".

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Handling instructions and administration

This vaccine should be handled by a healthcare professional using aseptic technique to ensure the sterility of each dose.

The vaccine should be inspected visually for particulate matter and discolouration prior to administration. COVID-19 Vaccine AstraZeneca is a colourless to slightly brown, clear to slightly opaque suspension. Discard the vial if the suspension is discoloured or visible particles are observed. Do not shake. Do not dilute the suspension.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

The COVID-19 Vaccine AstraZeneca vaccination course consists of two separate doses of 0.5 ml each. The second dose should be administered between 4 and 12 weeks after the first dose. Individuals who have received the first dose of COVID-19 Vaccine AstraZeneca should receive the second dose of the same vaccine to complete the vaccination course.

Each vaccine dose of 0.5 ml is withdrawn into a syringe for injection to be administered intramuscularly, preferably in the deltoid muscle of the upper arm. Use a new needle for administration, when possible.

It is normal for liquid to remain in the vial after withdrawing the final dose. An additional overfill is included in each vial to ensure that 8 doses (vial of 4 ml) or 10 doses (vial of 5 ml) of 0.5 ml can be delivered. Do not pool excess vaccine from multiple vials. Discard any unused vaccine.

ANNEX IV

CONCLUSIONS ON THE GRANTING OF THE CONDITIONAL MARKETING AUTHORISATION PRESENTED BY THE EUROPEAN MEDICINES AGENCY

Conclusions presented by the European Medicines Agency on:

- **Conditional marketing authorisation**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the conditional marketing authorisation as further explained in the European Public Assessment Report.

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Inducing mucosal IgA: A challenge for vaccine adjuvants and delivery systems

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Abstract

Mucosal IgA or secretory IgA (SIgA) are structurally equipped to resist chemical degradation in the harsh environment of mucosal surfaces and the enzymes of host or microbial origin. Production of SIgA is finely regulated and distinct T-independent and T-dependent mechanisms orchestrate immunoglobulin heavy chain α class switching and SIgA responses against commensal and pathogenic microbes. Most infectious pathogens enter the host via mucosal surfaces. To provide a first line of protection at these entry ports, vaccines are being developed to induce pathogen-specific SIgA in addition to systemic immunity achieved by injected vaccines. Mucosal or epicutaneous delivery of vaccines helps target the inductive sites for IgA responses. The efficacy of such vaccines relies on the identification/engineering of vaccine adjuvants capable of supporting the development of SIgA alongside systemic immunity and delivery systems that improve vaccine delivery to the targeted anatomic sites and immune cells.

Mucosal surfaces provide a physical barrier to the entry of foreign factors and microbes into the host while allowing important functions; such as uptake of air and food, reproduction, and vision to occur. The protection of these surfaces is ensured by the mucosal immune system, which consists of a complex network of cells and molecules designated as the Mucosal-Associated Lymphoid Tissues (MALT). The role of the MALT is clearly distinct from that of the systemic immune system, which primarily maintains the inner body sterile and free of microbes, foreign antigens, and altered or dead cells. The mucosal immune system is designed to tolerate commensal microbes and food, but also to initiate adaptive immune responses against invading pathogens and provide a first line of defense at their portal of entry. The SIgA represent the hallmark of immune response at mucosal sites and contribute to homeostasis via a variety of mechanisms (1). SIgA Abs are induced by postnatal exposure to commensal microorganisms indicating that these Abs play a role in sensing commensal microbes and limiting their overgrowth (2, 3). SIgA Abs also protect the host by binding to the surface of luminal microbes and toxins to prevent them from attaching to epithelial cells (Figure 1) (4). This exclusion mechanism limits the ability of microbial pathogen-associated molecular patterns (PAMPs) to trigger inflammatory responses and therefore contributes to the anti-inflammatory effect of SIgA. While induction of SIgA is desirable for optimum protection of mucosal surfaces and limiting systemic infections, production of these antibodies (Abs) is differently regulated than systemic IgG and IgA Abs

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and they are poorly induced by conventional injected vaccines. This review will discuss regulation of IgA responses and ongoing efforts toward the development of vaccines capable of promoting both systemic immunity and SIgA responses in mucosal tissues.

1. IgA and secretory IgA

Immunoglobulin A (IgA) is the most abundant immunoglobulin in mucosal tissues and represents the hallmark of mucosal immune response. This immunoglobulin isotype is also the second most abundant immunoglobulin isotype in the circulation. Structurally, IgA present in the circulation are either monomeric IgA or polymeric (pIgA) immunoglobulins, where monomers are grouped together by a joining chain (J-chain) (Figure 1). Secretory IgA (SIgA) are exclusively present at mucosal surfaces and consist of dimeric IgA linked via the J-chain to the secretory components (SC) (Figure 1). The latter is a portion of polymeric immunoglobulin receptor (pIgR) expressed at the basolateral surface of the epithelial cells, which is acquired during the release of IgA molecules in the lumen after transepithelial transport. The secretory component protects the SIgA from degradation by microbial and host proteolytic enzymes in the gastrointestinal tract and body secretions. Only one type of IgA molecule exists in mice. In contrast, human IgA molecules are divided into the IgA1 and IgA2 subclasses. The IgA1 are dominant in the serum. The IgA2, which are more resistant to proteolytic degradation are the main isoform found in mucosal secretions.

- Regulation of Ig class switch for production of IgA

B cells can undergo Ig class switch recombination (CSR) and acquire the ability to produce IgA after CD40-CD40L ligation in the presence of TGF-β with contribution from other cytokines including IL-4, IL-5, IL-6, IL-10, and IL-21 (5–8) (Figure 1). Other costimulatory signals such as B cell-activating factor of the TNF family (BAFF), a proliferation-inducing ligand (APRIL), retinoic acid (RA), and nitric oxide also facilitate CSR for the production of IgA (7, 9, 10). BAFF and APRIL further enhance IgA responses by providing survival signals, and/or inducing plasma cell differentiation and IgA secretion (10, 11). Retinoic acid, a metabolite of vitamin A, plays an important role in the production of mucosal IgA since in addition to acting synergistically with IL-5 and IL-6 to induce IgA secretion (12), it also induces expression of gut-homing receptors on B cells (12) (Figure 1). Additional cytosolic factors and transcription factors contribute to the regulation of IgA class switching. For example, the noncanonical IκB kinases TANK-binding kinase 1 (TBK1) in B cells was shown to negatively regulate IgA class switching by attenuating noncanonical signaling via the transcription factor NF-κB (13). The cytosolic protein clathrin, which controls receptor-mediated endocytosis and internalization of receptors, also influences antibody isotype switching and production of IgA (14). Thus, absence of clathrin light chain in B cells enhances immunoglobulin switch to IgA, an effect consistent with a defective endocytosis of TGFβR2 and subsequent increased TGFβR2 signaling (14).

- T-dependent and T-independent mechanisms of IgA induction

IgA can be produced by naïve B cells in gut-associated lymphoid tissues (GALT) or nasopharyngeal-associated lymphoid tissues (NALT) in response to stimulation by commensal microbes, microbial pathogens, or after vaccination. Comparison of naïve B

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cells in the intestinal Peyer's patches with IgA producing cells in the intestinal lamina propria have shown that a change of energy metabolism occurs during differentiation of B cells into IgA-producing cells (15). Hence, while both naïve and IgA-producing cells use the tricarboxylic acid cycle and fatty acid for energy production, glycolysis preferentially occur in IgA-producing cells (15). Immunoglobulin CSR and production of IgA can occur via T-independent or T-dependent mechanisms depending on the nature of antigen and the cellular origin of help received by B cells (Figure 1). High affinity IgA are generated in a T-dependent fashion, while IgA produced in a T-independent manner lack or only have limited antigen specificity due to limited somatic hypermutation. In the gut, IgA-producing cells are generated in germinal centers of the Peyer's patches, but also in other secondary lymphoid tissues (cryptopatch and cryptopatch-derived isolated lymphoid follicle) and microbe-induced tertiary lymphoid tissues. This process is finely regulated and it has now been shown to require prolonged interaction of B cells with dendritic cells in the subepithelial dome (SED) of the Peyer's patches and DC-mediated production of TGF-β via integrin αVβ8-mediated activation of TGF-β (16). Innate lymphoid cells play a role upstream of these interactions as they facilitate the maintenance of DCs in the SED (16).

Several T cell subsets are involved in the induction of IgA. Among these cells, follicular T helper (Tfh) cells (17) play a key role in both immunoglobulin CSR and somatic hypermutation in antigen recognizing regions and subsequent generation of high-affinity antibody producing plasma cells and memory B cells. The expression of CXCR5 by Tfh cells allow them to locate into B cell follicles, where they produce IL-21, an IgA promoting cytokine (5). Tfh were reported to differentiate from other Th cell subsets suggesting a plasticity of mucosal T cells and potential for rapid adaptation to the luminal environment and ultimately produce the mucosal IgA Abs needed to maintain homeostasis.

Fox3+ T cells were the first T cell subset shown to undergo differentiation into Tfh cells in the GALT to support IgA responses. Thus, following the adoptive transfer of Fox3+ T cells to T cell deficient mice, these cells could trigger formation of germinal centers in the Peyer's patches (18). Formation of germinal centers was limited to Peyer's patches and, to a lesser extend mesenteric lymph nodes, and the process was initiated by Fox3+ T cells that have lost expression of Foxp3. The re-differentiation of Fox3+ T cells appears to be gut-specific, since evidence of this process was not seen in the spleens or peripheral lymph nodes. Mechanisms leading to this re-differentiation of Foxp3 cells remains to be elucidated, but it is possible that gut-derived signals down regulate Foxp3 allowing the expression of the transcription factor Bcl6 and other characteristics of Tfh cells. The re-differentiation of GALT Fox3+ T cells into Tfh could not be confirmed in other studies (19). Nonetheless, a couple of reports suggest that a small subset of mucosal resident Treg can respond to T-dependent antigens and co-express Bcl6, upregulate CXCR5 and migrate into germinal centers to function as regulatory Tfh cells (20, 21).

Th17 cells are preferentially found in mucosal tissues and their presence in the intestine has been shown to depend on stimulation from commensal bacteria, such as *Segmented filamentous* bacteria (22, 23). Adaptive transfer studies have confirmed the tropism Th17 cells for mucosal tissues of the gut, but also demonstrated that in recipient host, these cells down-regulate their expression of Th17 characteristics (i.e., RORγt and IL-17A expression)

to acquire characteristic of Tfh cells, including the transcription factor Bcl6, the surface molecules CxCR5, PD-1, and the ability to produce the IgA-promoting cytokine IL-21 (19). In another study, adoptive transfer of T cells lacking MyD88 into germ-free Rag−/− mice helped demonstrate that gut microbiota-mediated signaling through MyD88 in $CD4^+$ T cells induce their differentiation into Tfh cells and promote the production of high-affinity SIgA (24).

A number of studies have now shown that immunoglobulin CSR and production of IgA can be induced in a T-independent manner in lymphoid structures of the GALT (i.e., Peyer's patches, isolated lymphoid follicles, cryptopatches and mesenteric lymph nodes) (7, 25, 26). It was also suggested that IgA production could take place in the intestinal lamina propria independently of cognate T cell help following interactions of APRIL with the transmembrane activator and CALM interactor (TACI) on B cells (27, 28). It is important to indicate that a major difference between T-dependent and T-independent production of IgA is the source of cytokines that provide help to B cells. Innate lymphoid cells, which are present in high number in mucosal tissues, can produce the same pattern of cytokines than T helper cells and thus may play a central role in the T-independent production mucosal IgA (29). The plasmacytoid dendritic cells (pDCs) are a source of APRIL, BAFF, IL-10 and IL-6 (30), and thus, could be key players in this process. In addition to soluble cytokines, membrane-bound lymphotoxin β (LTα1β2) produced by $ROR\gamma t^+$ ILCs was shown to be critical for T cell-independent IgA induction in the lamina propria (31). The list of cells potentially involved in the T-independent production of IgA continues to grow and now includes eosinophils, which are widely considered as proinflammatory and associated with allergy and eosinophilic gastrointestinal disorders (32). Eosinophils promote CSR and production of IgA by providing active TGFβ (32).

T-dependent IgA responses predominantly involved B2 cells, while T-independent IgA responses involve both follicular B2 cells and innate B1 cells that reside in the peritoneal cavity. A study that addressed the relative contribution of the B cell subsets to IgA responses toward commensal microbes has shown that most commensals elicit T-independent IgA responses by the orphan B1b and B2 cells, while only atypical commensal such as segmented filamentous bacteria elicits T-dependent IgA responses (33).

- Role of epithelial cells in production of SIgA

SIgA Abs contain a secretory component synthesized by epithelial cells. Host and microbial factors, which stimulate production of IgA-promoting cytokines (i.e., BAFF and TGF-β) by epithelial cells enhance production of SIgA (34). The pIgR which mediate the transepithelial transport of polymeric IgA and secretion of SIgA is expressed by different type of epithelial cells and the resolution of its crystal structure provides new information about multiple conformations used by the secretory component to protect mammals from pathogens (35). The transepithelial trafficking of the pIgR was shown to involve both the transcytotic pathway and one arm of the regulated secretory pathway (36). Factors which participate in the complex regulation of pIgR expression and transcytosis also contribute to optimizing SIgA production and mucosal immunity (37, 38). Both the classical and the alternative NF-κB pathway regulate pIgR expression (39, 40). Inflammatory (IL-1), Th1 (IFN-γ, TNF) and

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Th2 (IL-4) cytokines were shown to stimulate pIgR expression by epithelial cells (37), The fact that these cytokines, as well as those produced by Th17 cells, stimulate pIgR expression (41) highlights the central key role of SIgA in protection of mucosal tissues against intracellular pathogens, extracellular pathogens, and other toxins and foreign products.

2. Vaccine adjuvants and delivery systems for induction of mucosal IgA

Alum is the adjuvant the most widely used in injected subunit vaccines for induction of specific T cell responses in the bloodstream and serum IgG responses. Unfortunately, this adjuvant is not effective at triggering the molecular events that support IgA CSR or homing of effector B and T cells in mucosal tissues. Major efforts were dedicated to the development of new vaccine adjuvants for induction of SIgA (Table 1). As mentioned above, the cellular and molecular machinery that supports initiation of SIgA response is located in mucosal tissues and thus can be reached by needle-free vaccines via the oral, nasal, rectal, or ocular routes. The efficacy of such vaccines relies on delivery systems that improve vaccine delivery to the targeted anatomic sites and immune cells (Table 1). Imprinting of mucosal homing potential through induction of homing and chemokine receptors is another important step in the induction of SIgA responses in selected mucosal sites

- Mucosal homing of IgA producing cells and routes of vaccine delivery

Conventional injected vaccines generally induce specific T cell responses in the bloodstream and serum IgG responses. In contrast with injected vaccines, needle-free vaccines administered via the oral, nasal, rectal, or epicutaneous routes have the potential to induce mucosal IgA, in addition to systemic immunity. In this regard, mucosal homing of immune effector cells is finely orchestrated by expression of mucosal addressins and homing receptors, and chemokine receptors. Retinoic acid (RA) produced by antigen-presenting cells in mucosal tissues provides key signals for expression of the gut homing receptor $\alpha4\beta7$ (12, 42). Cytokines such as IL-5 and IL-6 enhance the effect of RA on $\alpha4\beta7$. The cytokine IL-21 was shown to induce the expression of the gut-homing receptor $\alpha4\beta7$, an effect enhanced by TGF$\beta1$ and RA (5). The chemokine receptor CCR9 together with $\alpha4\beta7$ represent the best-described factors regulating homing of immune cells into the gut (43). On the other hand, differentiation of IgA-producing cells in the absence of RA leads to induction of $\alpha4\beta1$, L-sectin and CCR10, which target B cells to other mucosal compartments including the airways, salivary gland, reproductive mucosa and colon (43). Oral immunization more effectively targets mucosal DCs, which are rich in RA, and this leads to generation of IgA-producing cells capable of migrating into the small intestine. Rectal immunization, which induces expression of both CCR10+ and CCR9+, generates effector cells capable of migrating on both the small and large intestine. Non-cytokines factors such as Sphingosine1-phosphate can fine tune homing of effector B cells to the intestine (44). Similarly, epicutaneous immunization was reported to promote SIgA responses in the gut. It has been suggested that migration of antigen from the skin to Peyer's patches and/or mesenteric lymph nodes could be a reason for induction of effector B cells expressing $\alpha4\beta7$ after epicutaneous immunization. However, supplementation of epicutaneous vaccine with RA may be the most effective way to consistently induce $\alpha4\beta7$+ cells IgA-producing cells capable of migrating to the gut (42)

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IgA class switch occurs in the organized structures of the Nasopharyngeal-Associated Lymphoid Tissues (NALT) (45). However, nasal immunization, which induces α4β1, L-sectin and CCR10, is generally not considered an effective approach for inducing SIgA in the gut. This notion has been challenged by a report indicating that NALT DCs possess the machinery for induction of RA and expression of α4β7+ on effector B cells, but stimulation by microbiota was required for these functions to develop (46). The sublingual route is used effectively for delivery of medication and allergen-specific immune therapy in humans and animals (47–50). This route has recently emerged as a mode of vaccine delivery capable of eliciting both systemic and mucosal immune responses while avoiding many of the side effects and formulation concerns associated with oral or intranasal vaccination (51–53). Perhaps because both routes use cervical lymph nodes as inductive sites, sublingual immunization generally induces IgA responses with similar mucosal tropisms than intranasal immunization. The ocular route has also investigated for delivery of experimental vaccines (54, 55). This route of immunization was found to induce SIgA in the tears, but also in the airways and in the genito-urinary tract (54). The nature of homing receptors imprinted in the Tear-Duct-Associated Lymphoid Tissues (TALT) has not been studies in detail. The fact that nasal immunization also induces SIgA in ocular tissues suggests the existence of TALT-NALT cross-talk via the tear duct bridges between the ocular and nasal cavities (55). Hence, ocular vaccines more likely promote the same homing receptors induced by nasal immunization.

- Vaccine adjuvants for induction of SIgA

Earlier studies with cholera toxin (CT) and heat-labile toxin I (LT-I) from *Escherichia coli* have helped established key principles, which guide current research on mucosal adjuvants. These closely related molecules are AB-type toxins consisting of two structurally and functionally separate enzymatic A subunits and binding B subunits. The B subunit of CT (CT-B) binds to GM1 gangliosides, while the B subunit of LT-I (LT-B) binds to GM1 as well as GM2 asialo-GM1 gangliosides. The A subunits of these toxins are ADP-ribosyl transferases. Binding of the B subunits to gangliosides receptors on target cells allows the A subunits to reach the cytosol where they elevate cAMP via activation of adenylate cyclase. Although the mechanisms underlying the mucosal adjuvant activity of these enterotoxins remain to be fully understood, it is now established that they stimulate APCs to enhance expression of MHC class II and costimulatory molecules, but also IgA-promoting cytokines such as IL-1, IL-6, and IL-10. Their adjuvant activity also induces antigen-specific Th2 and Th17 cells, which support the production of IgA via secretion of IL-4, IL-6, IL-10, and IL-17A (56–58). Despite their efficacy as mucosal adjuvant for needle-free vaccines in experimental animal models, the inherent toxicity of ganglioside-binding bacterial enterotoxins such as CT and LT-I prevent their use in humans.

Approaches used to dissociate the toxicity and the adjuvanticity of the bacterial toxins included partial or complete inactivation of the enzymatic activity of CT (59) and LT (60). Studies with a recombinant derivative of CT, which targets the enzymatic subunit of CT (i.e., CTA1) to B cells (CTA1-DD) have demonstrated that targeting ADP-ribosyl transferase to the right cells could alleviate the unacceptable side effects (CNS targeting and inflammatory responses) of the native CT and LT (61). Our own studies have shown that *Bacillus anthracis*

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edema toxin, an adenylate cyclase which targets anthrax toxin receptors and increases cAMP, is a mucosal adjuvant for nasally administered vaccines (62). Edema toxin was found to be potentially safer, as it did not target CNS or promote massive inflammatory responses in airways and lung tissues after intranasal administration (62). We also reported that only minimal (<20%) of edema factor activity was needed for *Bacillus anthracis* edema toxin to act as a mucosal adjuvant and induce mucosal IgA Ab responses (63). Cyclic di-nucleotides that bind Stimulator of Interferon Gamma Genes (STING) were recently shown to be potential alternatives to cAMP-inducing bacterial toxins and derivatives as vaccine adjuvants. For example, STING ligands of bacterial origin, including 3′3′-cGAMP, c-di-AMP, and c-di-GMP, have been shown to effectively elicit mucosal and systemic immune responses following intranasal administration (64–66). More recently, targeting STING with 3′3′-cGAMP was found to be an effective strategy for enhancing the magnitude of immune responses and promoting IgA by sublingual immunization (67). It is worth indicating that induction of Th17 responses is a common feature of all the adjuvants mentioned above, which enhance IgA responses by increasing intracellular levels of the cyclic nucleotide cAMP or directly releasing select cyclic nucleotides (i.e., STING ligands) in the cytosol of immune cells. This point is of importance since Th17 cells are believed to be crucial for production of high-affinity T-dependent IgA (19).

SIgA responses can be induced by adjuvants that target specific innate signaling pathways, or specific immune cells and their products. For example, CpG ODNs which target TLR9 can act as mucosal adjuvants for nasal vaccines and promote SIgA in a Th1 environment. Studies with plasmid DNA expressing FLt3L have shown that increasing the number of DCs in mucosal inductive sites is a strategy for inducing SIgA and Th2 responses (68). Mucosal tissues contain high numbers of natural killer T cells, which upon stimulation rapidly secrete large amounts of Th1 (IFN-γ and TNF-α), and Th2 (IL-4, IL-5, and IL-13) cytokines (69, 70). They also express CD40L and induce the expression of costimulatory molecules (i.e., CD40, CD80, and CD86) (71–76). The NKT cell ligand α-Galactosylceramide (α-GalCer), originally isolated from a marine sponge, has now been shown to be an effective adjuvant for induction of SIgA by nasal (77) and oral vaccines (78). Mast cell activators represent another class of mucosal adjuvants described during the last decade (79). These studies have shown that the mast cell activator compound 48/80 promotes SIgA responses by stimulating the migration of DCs into the T-cell areas of the NALT (79), and the development of mixed Th1/Th2/Th17 responses (80). Taken together, these studies suggest that targeting cells present in high numbers in mucosal tissues and capable of instantly release several pro-inflammatory mediators is beneficial for induction of SIgA. This notion is consistent with a recent study that showed that this is not the case for adjuvant targeting/recruiting neutrophils, an immune cell subset primarily found in the systemic compartment. Thus, using sublingual vaccination with Bacillus anthracis edema toxin as adjuvant, we identified an inverse relationship between the ability to recruit neutrophils in sublingual tissues and cervical lymph nodes, and the development of SIgA responses (81). It is worth noting that TGF-β and IL-10, two of the key IgA-promoting cytokines antagonize rather than stimulate neutrophil functions. Furthermore, other have shown that depletion of neutrophils in guinea pigs with primary *C. caviae* ocular infections, reduced rather than enhanced the ocular

pathology and that this correlated with increased titers of C. caviae-specific IgA in the tears (82).

- Delivery systems for SIgA-inducing vaccines

Delivery systems for needle-free vaccines currently used or under development include live recombinant bacterial and viral vectors. These vectors are either attenuated strains of pathogens or microbes that fail to induce infection in the host. Several of such live bacterial and viral vectors induce SIgA via various mechanisms depending on the PAMPs they stimulate and the type of the cargo (for example cytokines) they deliver together with the antigen. Non-living delivery systems such as virus-like particles, nano- and microparticles, liposomes or nanogels do not present the potential safety concerns sometimes associated with the use of live micro-organisms. Many of such non-living delivery systems induced SIgA after immunization by the oral, nasal, ocular, rectal, or vaginal route (55, 83). The overall immune responses to these particulate vaccines and more specifically the magnitude of SIgA responses they promote can be improved by adding surface targeting molecules or peptides to facilitate their uptake by antigen-presenting cells or other innate immune cells (iNK T cells, innate lymphoid cells, mast cells).

Plants were engineered to synthesize and assemble one or more Ags that retain both T- and B-cell epitopes, thereby inducing systemic and mucosal immune responses in both mice and humans (84, 85). Most recently, CT-B subunit has been expressed under the control of the rice seed storage protein glutelin promoter (MucoRice-CT-B). Oral feeding of powdered MucoRice-CT-B to mice and non-human primates resulted in the induction of both systemic and mucosal Ab responses for the protection against CT (86–88). In addition to binding antigen in the lumen, SIgA alone or SIgA in complex with antigen can bind to M cells and be transported from the intestinal lumen to sub-epithelial dendritic cells (DCs) and possibly other APCs. Human SIgA were shown to bind to the DC-specific ICAM-3 grabbing nonintegrin (DC-SIGN) and be internalized suggesting that binding to this receptor is a mechanism used by SIgA to prime adaptive immune responses in mucosal tissues (89). This concept was further confirmed by murine studies, which showed that when used as vaccine antigen delivery system, SIgA interacts specifically with M cells present in the GALT or NALT and delivers antigen to mucosal DC for optimal induction of antigen-specific mucosal and systemic immunity (90, 91).

Conclusions and perspectives

Despite major progress made in our understanding of IgA induction and regulation of their functions, much more remains to be elucidated about the contribution of different mucosal cells in these processes and cellular and molecular events that interfere with induction of SIgA in mucosal and non-mucosal sites. In this regards, cells that were previously not known to be involved in IgA responses prevent the development of IgA responses, as suggested by the report linking the presence of neutrophils in a mucosal inductive site with reduced IgA CSR and SIgA responses (81). The opposite may hold truth as suggested by the report that eosinophils also can regulate IgA production via production of IL-1β (92). The development of adjuvants and vaccine delivery systems capable of promoting high titers of

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IgA against microbial pathogens has been a major focus of mucosal immunologists. Since children and elderly are the most vulnerable to infectious diseases, the development of future mucosal vaccine should take into account the unique immunologic signatures that may occur in these populations (93). The increasing appreciation of the anti-inflammatory effects of pIgA and SIgA (94) and their potential role in dampening manifestations of allergic disease will certainly broaden the focus of future investigations and could influence future sublingual immunotherapies.

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Abbreviations

APRIL	a proliferation-inducing ligand
BAFF	B cell-activating factor of the TNF family
CSR	Class switch recombination
GALT	gut-associated lymphoid tissues
NALT	nasopharyngeal-associated lymphoid tissues
pIgA	polymeric IgA
pIgR	polymeric immunoglobulin receptor
SIgA	secretory IgA
RA	retinoic acid

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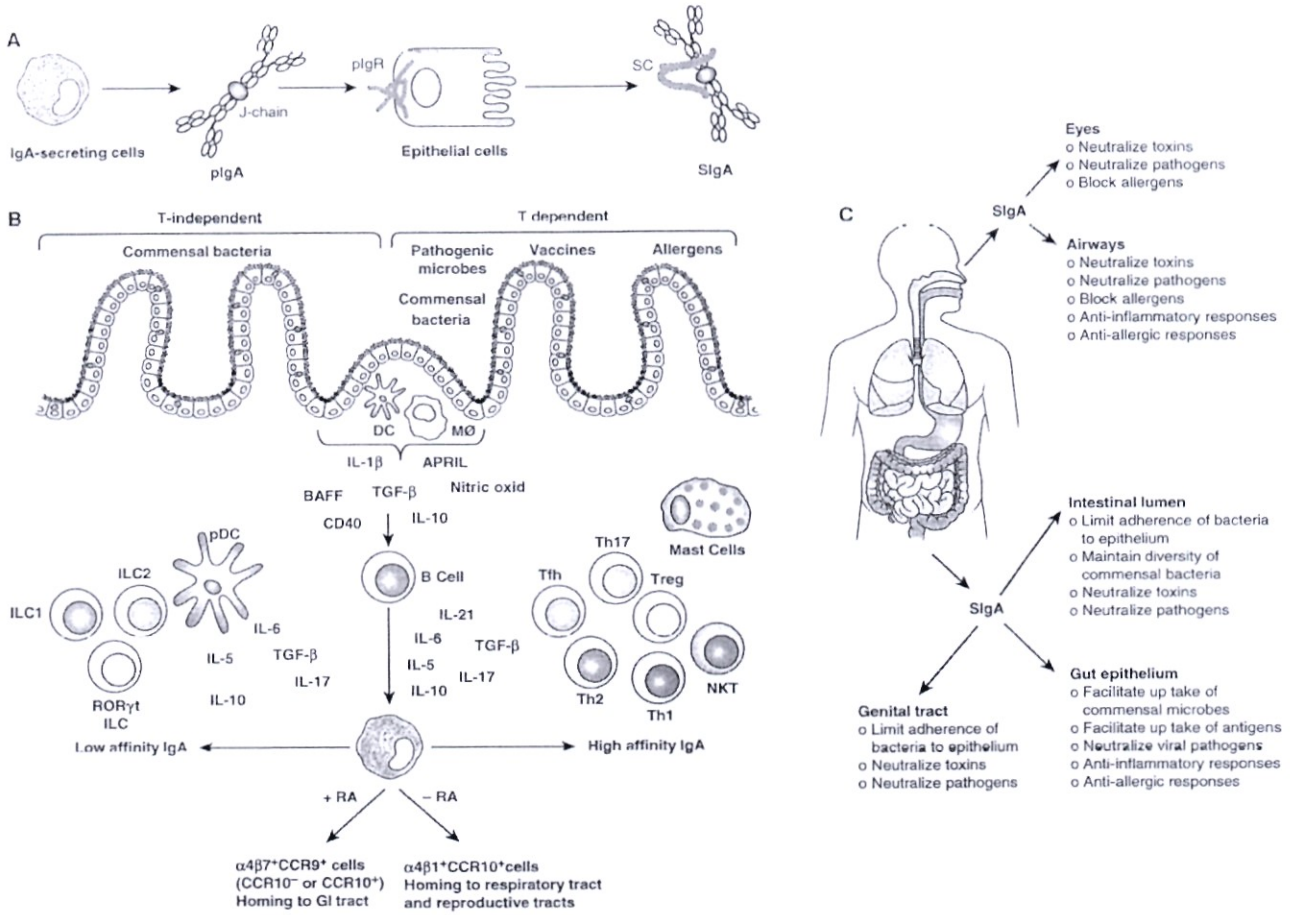

Figure 1. Mechanisms of induction of mucosal IgA and their protection role at mucosal surfaces

(A) Polymeric IgA (pIgA) and secretory IgA (SIgA). Polymeric IgA Abs are made of two monomers of IgA linked by a junction chain (J-chain) and bind to the polymeric immunoglobulin receptor (pIgR) at the basolateral membrane of epithelial cells. After transepithelial transport, they are released into the lumen as SIgA containing the secretory components (SC), a portion of the pIgR, which confers resistance to proteolysis. (B) Induction of IgA class switching and acquisition of mucosal homing capabilities. IgA class switching and production of mucosal IgA can occur in a T-independent or T-dependent fashion. In response to luminal stimulation by microbes, vaccines or allergen, epithelial cells and conventional antigen presenting cells in the Peyer's patches (PP), cryptopatches, isolated lymph follicles or lamina propria will produce cytokines (IL-1β, IL-10, TGF-β), nitric oxid (NO), and the B cell stimulating factors BAFF and APRIL. IgA class switching and production of IgA facilitated through the help of cytokines derived from Th cells and NKT cells (T-dependent) will yield high-affinity IgA. On the other hand, cytokine help from innate lymphoid cells (ILCs) and other innate cells such as plasmacytoid dendritic cells (pDC) (T-independent) will result in low-affinity IgA. The presence of retinoic acid (RA)

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imprints IgA-producing cells with homing receptors and chemokine receptors for homing to the gastrointestinal (GI) tract. (C) Mechanisms of protection by SIgA in mucosal surfaces.

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Table 1

Main groups of adjuvants and vaccine delivery systems for induction of mucosal IgA.

Adjuvants	Delivery systems
Toxin derivatives	**Live viral vectors**
ADP-ribosyl transferase enterotoxins	Attenuated or adapted viral vectors
Adenylate cyclase toxins	**Live bacterial vectors**
TLR agonists	Attenuated or adapted bacterial vectors
Lipid A-based (MPL)	Lactic acid bacteria
CpG	**Plants**
Flagellin	Rice
Other immune-modulators	**Nanoparticles and other targeting systems**
NKT cell ligands	Virus-like particles (VLP)
Mast cells activators	ISCOMs (Immunogenic immune stimulating complexes)
STING ligands	Nanoparticles
	Nano gels
	SIgA

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Title page

Comparing SARS-CoV-2 natural immunity to vaccine-induced immunity: reinfections versus breakthrough infections

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Abstract

Background:

Reports of waning vaccine-induced immunity against COVID-19 have begun to surface. With that, the comparable long-term protection conferred by previous infection with SARS-CoV-2 remains unclear.

Methods:

We conducted a retrospective observational study comparing three groups: (1)SARS CoV-2-naïve individuals who received a two-dose regimen of the BioNTech/Pfizer mRNA BNT162b2 vaccine, (2)previously infected individuals who have not been vaccinated, and (3)previously infected *and* single dose vaccinated individuals. Three multivariate logistic regression models were applied. In all models we evaluated four outcomes: SARS-CoV-2 infection, symptomatic disease, COVID-19-related hospitalization and death. The follow-up period of June 1 to August 14, 2021, when the Delta variant was dominant in Israel.

Results:

SARS-CoV-2-naïve vaccinees had a 13.06-fold (95% CI, 8.08 to 21.11) increased risk for breakthrough infection with the Delta variant compared to those previously infected, when the first event (infection or vaccination) occurred during January and February of 2021. The increased risk was significant ($P<0.001$) for symptomatic disease as well. When allowing the infection to occur at any time before vaccination (from March 2020 to February 2021), evidence of waning natural immunity was demonstrated, though SARS-CoV-2 naïve vaccinees had a 5.96-fold (95% CI, 4.85 to

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7.33) increased risk for breakthrough infection and a 7.13-fold (95% CI, 5.51 to 9.21) increased risk for symptomatic disease. SARS-CoV-2-naïve vaccinees were also at a greater risk for COVID-19-related-hospitalizations compared to those that were previously infected.

Conclusions:

This study demonstrated that natural immunity confers longer lasting and stronger protection against infection, symptomatic disease and hospitalization caused by the Delta variant of SARS-CoV-2, compared to the BNT162b2 two-dose vaccine-induced immunity. Individuals who were both previously infected with SARS-CoV-2 and given a single dose of the vaccine gained additional protection against the Delta variant.

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Introduction

The heavy toll that SARS-CoV-2 infection has been taking on global health and healthcare resources has created an urgent need to estimate which part of the population is protected against COVID-19 at a given time in order to set healthcare policies such as lockdowns and to assess the possibility of herd immunity.

To date, there is still no evidence-based, long-term correlate of protection[1]. This lack of correlate of protection has led to different approaches in terms of vaccine resource allocation, namely the need for vaccine administration in recovered patients, the need for booster shots in previously vaccinated individuals or the need to vaccinate low-risk populations, potentially previously exposed.

The short-term effectiveness of a two-dose regimen of the BioNTech/Pfizer BNT162b2 mRNA COVID-19 vaccine was demonstrated in clinical trials[2] and in observational settings[3,4]. However, long term effectiveness across different variants is still unknown, though reports of waning immunity are beginning to surface, not merely in terms of antibody dynamics over time[5–7], but in real-world settings as well[8].

Alongside the question of long-term protection provided by the vaccine, the degree and duration to which previous infection with SARS-CoV-2 affords protection against repeated infection also remains unclear. Apart from the paucity of studies examining long-term protection against reinfection[9], there is a challenge in defining reinfection as opposed to prolonged viral shedding[10]. While clear-cut cases exist, namely two separate clinical events with two distinct sequenced viruses, relying solely on these cases will likely result in an under-estimation of the incidence of reinfection.

Different criteria based on more widely-available information have been suggested[11], the Centers for Disease Control and Prevention's (CDC) guidelines refer to two positive SARS-CoV-2 polymerase chain reaction (PCR) test results at least 90 days

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apart.[12] Using similar criteria, population-based studies demonstrated natural immunity[13,14] with no signs of waning immunity for at least 7 months, though protection was lower for those aged 65 or older[9].

The Delta (B.1.617.2) Variant of Concern (VOC), initially identified in India and today globally prevalent, has been the dominant strain in Israel since June 2021. The recent surge of cases in Israel[15], one of the first countries to embark on a nationwide vaccination campaign (mostly with the BioNTech/Pfizer BNT162b2 vaccine), has raised concerns about vaccine effectiveness against the Delta variant, including official reports of decreased protection[16]. Concomitantly, studies have demonstrated only mild differences in short-term vaccine effectiveness[17] against the Delta variant, as well as substantial antibody response[18]. Apart from the variant, the new surge was also explained by the correlation found between time-from-vaccine and breakthrough infection rates, as early vaccinees were demonstrated to be significantly more at risk than late vaccinees[8]. Now, when sufficient time has passed since both the beginning of the pandemic and the deployment of the vaccine, we can examine the long-term protection of natural immunity compared to vaccine-induced immunity.

To this end, we compared the incidence rates of breakthrough infections to the incidence rates of reinfection, leveraging the centralized computerized database of Maccabi Healthcare Services (MHS), Israel's second largest Health Maintenance Organization.

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Methods

Study design and population

A retrospective cohort study was conducted, leveraging data from MHS' centralized computerized database. The study population included MHS members aged 16 or older who were vaccinated prior to February 28, 2021, who had a documented SARS-CoV-2 infection by February 28, 2021, or who had both a documented SARS-CoV-2 infection by February 28, 2021 *and* received one dose of the vaccine by May 25, 2021, at least 7 days before the study period. On March 2, 2021, The Israeli Ministry of Health revised its guidelines and allowed previously SARS-CoV-2 infected individuals to receive one dose of the vaccine, after a minimum 3-month-interval from the date of infection

Data Sources

Anonymized Electronic Medical Records (EMRs) were retrieved from MHS' centralized computerized database for the study period of March 1, 2020 to August 14, 2021.

MHS is a 2.5-million-member, state-mandated, non-for-profit, second largest health fund in Israel, which covers 26% of the population and provides a representative sample of the Israeli population. Membership in one of the four national health funds is mandatory, whereas all citizens must freely choose one of four funds, which are prohibited by law from denying membership to any resident. MHS has maintained a centralized database of EMRs for three decades, with less than 1% disengagement rate among its members, allowing for a comprehensive longitudinal medical follow-up. The centralized dataset includes extensive demographic data, clinical measurements, outpatient and hospital diagnoses and procedures, medications

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dispensed, imaging performed and comprehensive laboratory data from a single central laboratory.

Data extraction and definition of the study variables

COVID-19-related data

COVID-19-related information was captured as well, including dates of the first and second dose of the vaccine and results of any polymerase chain reaction (PCR) tests for SARS-CoV-2, given that all such tests are recorded centrally. Records of COVID-19-related hospitalizations were retrieved as well, and COVID-19-related mortality was screened for. Additionally, information about COVID-19-related symptoms was extracted from EMRs, where they were recorded by the primary care physician or a certified nurse who conducted in-person or phone visits with each infected individual.

Exposure variable: study groups

The eligible study population was divided into three groups: (1)fully vaccinated and SARS-CoV-2-naïve individuals, namely MHS members who received two doses of the BioNTech/Pfizer mRNA BNT162b2 vaccine by February 28, 2021, did not receive the third dose by the end of the study period and did not have a positive PCR test result by June 1, 2021; (2) unvaccinated previously infected individuals, namely MHS members who had a positive SARS-CoV-2 PCR test recorded by February 28, 2021 and who had not been vaccinated by the end of the study period; (3) previously infected *and* vaccinated individuals, including individuals who had a positive SARS-CoV-2 PCR test by February 28, 2021 and received one dose of the vaccine by May 25, 2021, at least 7 days before the study period. The fully vaccinated group was the comparison (reference) group in our study. Groups 2 and 3, were matched to the

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comparison group 1 in a 1:1 ratio based on age, sex and residential socioeconomic status.

Dependent variables

We evaluated four SARS-CoV-2-related outcomes, or second events: documented RT-PCR confirmed SARS-CoV-2 infection, COVID-19, COVID-19-related hospitalization and death. Outcomes were evaluated during the follow-up period of June 1 to August 14, 2021, the date of analysis, corresponding to the time in which the Delta variant became dominant in Israel.

Covariates

Individual-level data of the study population included patient demographics, namely age, sex, socioeconomic status (SES) and a coded geographical statistical area (GSA, assigned by Israel's National Bureau of Statistics, corresponds to neighborhoods and is the smallest geostatistical unit of the Israeli census). The SES is measured on a scale from 1 (lowest) to 10, and the index is based on several parameters, including household income, educational qualifications, household crowding and car ownership. Data were also collected on last documented body mass index (BMI) and information about chronic diseases from MHS' automated registries, including cardiovascular diseases[19], hypertension[20], diabetes[21], chronic kidney disease[22], chronic obstructive pulmonary disease, immunocompromised conditions, and cancer from the National Cancer Registry[23].

Statistical analysis

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Two multivariate logistic regression models were applied that evaluated the four aforementioned SARS-CoV-2-related outcomes as dependent variables, while the study groups were the main independent variables.

Model 1– previously infected vs. vaccinated individuals, with matching for time of first event

In model 1, we examined natural immunity and vaccine-induced immunity by comparing the likelihood of SARS-CoV-2-related outcomes between previously infected individuals who have never been vaccinated and fully vaccinated SARS-CoV-2-naïve individuals. These groups were matched in a 1:1 ratio by age, sex, GSA and time of first event. The first event (the preliminary exposure) was either the time of administration of the second dose of the vaccine *or* the time of documented infection with SARS-CoV-2 (a positive RT-PCR test result), both occurring between January 1, 2021 and February 28, 2021. Thereby, we matched the "immune activation" time of both groups, examining the long-term protection conferred when vaccination or infection occurred within the same time period. The three-month interval between the first event and the second event was implemented in order to capture reinfections (as opposed to prolonged viral shedding) by following the 90-day guideline of the CDC.

Model 2

In model 2, we compared the SARS-CoV-2 naïve vaccinees to unvaccinated previously infected individuals while intentionally *not* matching the time of the first event (i.e., either vaccination or infection), in order to compare vaccine-induced immunity to natural immunity, regardless of time of infection. Therefore, matching

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was done in a 1:1 ratio based on age, sex and GSA alone. Similar to the model 1, either event (vaccination or infection) had to occur by February 28, to allow for the 90-day interval. The four SARS-CoV-2 study outcomes were the same for this model, evaluated during the same follow-up period.

Model 3

Model 3 examined previously infected individuals vs. previously-infected-and-once-vaccinated individuals, using "natural immunity" as the baseline group. We matched the groups in a 1:1 ratio based on age, sex and GSA. SARS-CoV-2 outcomes were the same, evaluated during the same follow-up period.

In all three models, we estimated natural immunity vs. vaccine-induced immunity for each SARS-CoV-2-related outcome, by applying logistic regression to calculate the odds ratio (OR) between the two groups in each model, with associated 95% confidence intervals (CIs). Results were then adjusted for underlying comorbidities, including obesity, cardiovascular diseases, diabetes, hypertension, chronic kidney disease, cancer and immunosuppression conditions.

Analyses were performed using Python version 3.73 with the stats model package. $P < 0.05$ was considered statistically significant.

Ethics declaration

This study was approved by the MHS (Maccabi Healthcare Services) Institutional Review Board (IRB). Due to the retrospective design of the study, informed consent was waived by the IRB, and all identifying details of the participants were removed before computational analysis.

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Data availability statement

According to the Israel Ministry of Health regulations, individual-level data cannot be shared openly. Specific requests for remote access to de-identified community-level data should be directed to KSM, Maccabi Healthcare Services Research and Innovation Center.

Code availability

Specific requests for remote access to the code used for data analysis should be referred to KSM, Maccabi Healthcare Services Research and Innovation Center.

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Results

Overall, 673,676 MIIS members 16 years and older were eligible for the study group of fully vaccinated SARS-CoV-2-naïve individuals; 62,883 were eligible for the study group of unvaccinated previously infected individuals and 42,099 individuals were eligible for the study group of previously infected and single-dose vaccinees.

Model 1 – previously infected vs. vaccinated individuals, with matching for time of first event

In model 1, we matched 16,215 persons in each group. Overall, demographic characteristics were similar between the groups, with some differences in their comorbidity profile (Table 1a).

During the follow-up period, 257 cases of SARS-CoV-2 infection were recorded, of which 238 occurred in the vaccinated group (breakthrough infections) and 19 in the previously infected group (reinfections). After adjusting for comorbidities, we found a statistically significant 13.06-fold (95% CI, 8.08 to 21.11) increased risk for breakthrough infection as opposed to reinfection ($P<0.001$). Apart from age ≥60 years, there was no statistical evidence that any of the assessed comorbidities significantly affected the risk of an infection during the follow-up period (Table 2a).

As for symptomatic SARS-COV-2 infections during the follow-up period, 199 cases were recorded, 191 of which were in the vaccinated group and 8 in the previously infected group. Symptoms for all analyses were recorded in the central database within 5 days of the positive RT-PCR test for 90% of the patients, and included chiefly fever, cough, breathing difficulties, diarrhea, loss of taste or smell, myalgia, weakness, headache and sore throat. After adjusting for comorbidities, we found a 27.02-fold risk (95% CI, 12.7 to 57.5) for symptomatic breakthrough infection as

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opposed to symptomatic reinfection ($P<0.001$) (Table 2b). None of the covariates were significant, except for age ≥60 years.

Nine cases of COVID-19-related hospitalizations were recorded, 8 of which were in the vaccinated group and 1 in the previously infected group (Table S1). No COVID-19-related deaths were recorded in our cohorts.

Model 2 –previously infected vs. vaccinated individuals, without matching for time of first event

In model 2, we matched 46,035 persons in each of the groups (previously infected vs. vaccinated). Baseline characteristics of the groups are presented in Table 1a. Figure 1 demonstrates the timely distribution of the first infection in reinfected individuals. When comparing the vaccinated individuals to those previously infected at any time (including during 2020), we found that throughout the follow-up period, 748 cases of SARS-CoV-2 infection were recorded, 640 of which were in the vaccinated group (breakthrough infections) and 108 in the previously infected group (reinfections). After adjusting for comorbidities, a 5.96-fold increased risk (95% CI, 4.85 to 7.33) increased risk for breakthrough infection as opposed to reinfection could be observed ($P<0.001$) (Table 3a). Apart from SES level and age ≥60, that remained significant in this model as well, there was no statistical evidence that any of the comorbidities significantly affected the risk of an infection.

Overall, 552 symptomatic cases of SARS-CoV-2 were recorded, 484 in the vaccinated group and 68 in the previously infected group. There was a 7.13-fold (95% CI, 5.51 to 9.21) increased risk for symptomatic breakthrough infection than symptomatic reinfection (Table 3b). COVID-19 related hospitalizations occurred in 4 and 21 of the reinfection and breakthrough infection groups, respectively. Vaccinated

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individuals had a 6.7-fold (95% CI, 1.99 to 22.56) increased to be admitted compared to recovered individuals. Being 60 years of age or older significantly increased the risk of COVID-19-related hospitalizations (Table S2). No COVID-19-related deaths were recorded.

Model 3 - previously infected vs. vaccinated and previously infected individuals

In model 3, we matched 14,029 persons. Baseline characteristics of the groups are presented in Table 1b. Examining previously infected individuals to those who were both previously infected and received a single dose of the vaccine, we found that the latter group had a significant 0.53-fold (95% CI, 0.3 to 0.92) (Table 4a) decreased risk for reinfection, as 20 had a positive RT-PCR test, compared to 37 in the previously infected and unvaccinated group. Symptomatic disease was present in 16 single dose vaccinees and in 23 of their unvaccinated counterparts. One COVID-19-related hospitalization occurred in the unvaccinated previously infected group. No COVID-19-related mortality was recorded.

We conducted a further sub-analysis, compelling the single-dose vaccine to be administered *after* the positive RT-PCR test. This subset represented 81% of the previously-infected-and-vaccinated study group. When performing this analysis, we found a similar, though not significant, trend of decreased risk of reinfection, with an OR of 0.68 (95% CI, 0.38 to 1.21, *P*-value=0.188).

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Discussion

This is the largest real-world observational study comparing natural immunity, gained through previous SARS-CoV-2 infection, to vaccine-induced immunity, afforded by the BNT162b2 mRNA vaccine. Our large cohort, enabled by Israel's rapid rollout of the mass-vaccination campaign, allowed us to investigate the risk for additional infection – either a breakthrough infection in vaccinated individuals or reinfection in previously infected ones – over a longer period than thus far described.

Our analysis demonstrates that SARS-CoV-2-naïve vaccinees had a 13.06-fold increased risk for breakthrough infection with the Delta variant compared to those previously infected, when the first event (infection or vaccination) occurred during January and February of 2021. The increased risk was significant for a symptomatic disease as well.

Broadening the research question to examine the extent of the phenomenon, we allowed the infection to occur at any time between March 2020 to February 2021 (when different variants were dominant in Israel), compared to vaccination only in January and February 2021. Although the results could suggest waning natural immunity against the Delta variant, those vaccinated are still at a 5.96-fold increased risk for breakthrough infection and at a 7.13-fold increased risk for symptomatic disease compared to those previously infected. SARS-CoV-2-naïve vaccinees were also at a greater risk for COVID-19-related-hospitalization compared to those who were previously infected.

Individuals who were previously infected with SARS-CoV-2 seem to gain additional protection from a subsequent single-dose vaccine regimen. Though this finding corresponds to previous reports[24,25], we could not demonstrate significance in our cohort.

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The advantageous protection afforded by natural immunity that this analysis demonstrates could be explained by the more extensive immune response to the SARS-CoV-2 proteins than that generated by the anti-spike protein immune activation conferred by the vaccine[26,27]. However, as a correlate of protection is yet to be proven[1,28], including the role of B-Cell[29] and T-cell immunity[30,31], this remains a hypothesis.

Our study has several limitations. First, as the Delta variant was the dominant strain in Israel during the outcome period, the decreased long-term protection of the vaccine compared to that afforded by previous infection cannot be ascertained against other strains. Second, our analysis addressed protection afforded solely by the BioNTech/Pfizer mRNA BNT162b2 vaccine, and therefore does not address other vaccines or long-term protection following a third dose, of which the deployment is underway in Israel. Additionally, as this is an observational real-world study, where PCR screening was not performed by protocol, we might be underestimating asymptomatic infections, as these individuals often do not get tested.

Lastly, although we controlled for age, sex, and region of residence, our results might be affected by differences between the groups in terms of health behaviors (such as social distancing and mask wearing), a possible confounder that was not assessed. As individuals with chronic illness were primarily vaccinated between December and February, confounding by indication needs to be considered; however, adjusting for obesity, cardiovascular disease, diabetes, hypertension, chronic kidney disease, chronic obstructive pulmonary disease, cancer and immunosuppression had only a small impact on the estimate of effect as compared to the unadjusted OR. Therefore, residual confounding by unmeasured factors is unlikely.

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This analysis demonstrated that natural immunity affords longer lasting and stronger protection against infection, symptomatic disease and hospitalization due to the Delta variant of SARS-CoV-2, compared to the BNT162b2 two-dose vaccine-induced immunity. Notably, individuals who were previously infected with SARS-CoV-2 and given a single dose of the BNT162b2 vaccine gained additional protection against the Delta variant. The long-term protection provided by a third dose, recently administered in Israel, is still unknown.

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Tables and figures

Table 1a. Characteristics of study population, model 1 and 2.

	Model 1 – with matching of time of first event		**Model 2 – without matching of time of first event**	
Characteristics	Previously infected (n=16,215)	Vaccinated individuals (n=16,215)	Previously infected (n=46,035)	Previously infected *and* vaccinated (n =46,035)
Age years, mean (SD)	36.1 (13.9)	36.1 (13.9)	36.1 (14.7)	36.1 (14.7)
Age group – no. (%)				
16 to 39 yr	9,889 (61.0)	9,889 (61.0)	28,157 (61.2)	28,157 (61.2)
40 to 59 yr	5,536 (34.1)	5,536 (34.1)	14,973 (32.5)	14,973 (32.5)
≥60 yr	790 (4.9)	790 (4.9)	2,905 (6.3)	2,905 (6.3)
Sex – no. (%)				
Female	7,428 (45.8)	7,428 (45.8)	22,661 (49.2)	22,661 (49.2)
Male	8,787 (54.2)	8,787 (54.2)	23,374 (50.8)	23,374 (50.8)
SES, mean (SD)	5.5 (1.9)	5.5 (1.9)	5.3 (1.9)	5.3 (1.9)
Comorbidities – no. (%)				
Hypertension	1,276 (7.9)	1,569 (9.7)	4,009 (8.7)	4,301 (9.3)
CVD	551 (3.4)	647 (4.0)	1,875 (4.1)	1830 (4.0)
DM	635 (3.9)	877 (5.4)	2207 (4.8)	2300 (5.0)
Immunocompromised	164 (1.0)	420 (2.6)	527 (1.1)	849 (1.8)
Obesity (BMI ≥30)	3,076 (19.0)	3,073 (19.0)	9,117 (19.8)	8,610 (18.7)
CKD	196 (1.2)	271 (1.7)	659 (1.4)	814 (1.8)
COPD	65 (0.4)	97 (0.6)	218 (0.5)	292 (0.6)
Cancer	324 (2.0)	636 (3.9)	1,044 (2.3)	1,364 (3.0)

SD – Standard Deviation; SES – Socioeconomic status on a scale from 1 (lowest) to 10; CVD – Cardiovascular Diseases; DM – Diabetes Mellitus; CKD – Chronic Kidney Disease; COPD – Chronic Obstructive Pulmonary Disease.

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Table 1b. Characteristics of study population, model 3.

Characteristics	Previously infected (n=14,029)	Previously infected and single dose vaccinated (n=14,029)
Age years, mean (SD)	33.2 (14.0)	33.2 (14.0)
Age group – no. (%)		
16 to 39 yr	9543 (68.0)	9543 (68.0)
40 to 59 yr	3919 (27.9)	3919 (27.9)
≥60 yr	567 (4.0)	567 (4.0)
Sex – no. (%)		
Female	7467 (53.2)	7467 (53.2)
Male	6562 (46.8)	6562 (46.8)
SES, mean (SD)	4.7 (1.9)	4.7 (1.9)
Comorbidities		
Hypertension	892 (6.4)	1004 (7.2)
CVD	437 (3.1)	386 (2.8)
DM	529 (3.8)	600 (4.3)
Immunocompromised	127 (0.9)	145 (1.0)
Obesity (BMI ≥30)	2599 (18.5)	2772 (19.8)
CKD	137 (1.0)	162 (1.2)
COPD	30 (0.2)	53 (0.4)
Cancer	241 (1.7)	267 (1.9)

SD – Standard Deviation; SES – Socioeconomic status on a scale from 1 (lowest) to 10; CVD – Cardiovascular Diseases; DM – Diabetes Mellitus; CKD – Chronic Kidney Disease; COPD – Chronic Obstructive Pulmonary Disease.

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Table 2a. OR for SARS-CoV-2 infection, model 1, previously infected vs. vaccinated

Variable	Category	ß	OR	95%CI	P-value
Induced Immunity					
	Previously infected	Ref			
	Vaccinated	2.57	13.06	8.08 – 21.11	<0.001
SES		0.04	1.04	0.97 – 1.11	0.251
Age group, yr.					
	16-39	Ref			
	40-59	0.05	1.05	0.78 - 1.4	0.751
	≥60	0.99	2.7	1.68 – 4.34	<0.001
Sex					
	Female	Ref			
	Male	-0.03	0.97	0.76 – 1.25	0.841
Comorbidities					
	Obesity (BMI≥30)	0.01	1.01	0.73 – 1.39	0.967
	Diabetes mellitus	-0.36	0.7	0.39 – 1.25	0.229
	Hypertension	0.1	1.11	0.72 1.72	0.641
	Cancer	0.37	1.44	0.85 – 2.44	0.171
	CKD	0.53	1.7	0.83 – 3.46	0.146
	COPD	-0.46	0.63	0.15 – 2.66	0.529
	Immunosuppression	-0.1	0.91	0.42 – 1.97	0.803
	Cardiovascular diseases	0.26	1.3	0.75 – 2.25	0.343

OR – Odds Ratio; SES – Socioeconomic status on a scale from 1 (lowest) to 10; CVD – Cardiovascular Diseases; CKD – Chronic Kidney Disease; COPD – Chronic Obstructive Pulmonary Disease.

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Table 2b. OR for Symptomatic SARS-CoV-2 infection, model 1, previously infected vs. vaccinated

Variable	Category	ß	OR	95%CI	P-value
Induced Immunity					
	Previously infected	Ref			
	Vaccinated	3.3	27.02	12.7 – 57.5	<0.001
SES		0.04	1.04	0.96 – 1.12	0.312
Age group, yr.					
	16-39	Ref			
	40-59	0.19	1.21	0.88 – 1.67	0.25
	≥60	1.06	2.89	1.68 – 4.99	<0.001
Sex					
	Female	Ref			
	Male	-0.19	0.82	0.62 – 1.1	0.185
Comorbidities					
	Obesity (BMI≥30)	0.02	1.02	0.71 – 1.48	0.899
	Diabetes mellitus	-0.31	0.73	0.37 – 1.43	0.361
	Hypertension	0.12	1.13	0.69 – 1.85	0.623
	Cancer	0.37	1.45	0.8 – 2.62	0.217
	CKD	0.1	1.1	0.42 – 2.87	0.846
	COPD	-0.78	0.46	0.06 – 3.41	0.445
	Immunosuppression	-0.37	0.69	0.25 – 1.89	0.468
	Cardiovascular diseases	0.03	1.03	0.52 – 2.03	0.941

OR – Odds Ratio; SES – Socioeconomic status on a scale from 1 (lowest) to 10; CVD – Cardiovascular Diseases; CKD – Chronic Kidney Disease; COPD – Chronic Obstructive Pulmonary Disease.

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Table 3a. OR for SARS-CoV-2 infection, model 2, previously infected vs. vaccinated

Variable	Category	B	OR	95%CI	P-value
Induced Immunity					
	Previously infected	Ref			
	Vaccinated	1.78	5.96	4.85 – 7.33	<0.001
SES		0.07	1.07	1.03 – 1.11	<0.001
Age group, yr.					
	16-39	Ref			
	40-59	0.06	1.06	0.9 – 1.26	0.481
	≥60	0.79	2.2	1.66 – 2.92	<0.001
Sex					
	Female	Ref			
	Male	-0.01	0.99	0.85 - 1.14	0.842
Comorbidities					
	Obesity (BMI≥30)	0.12	1.13	0.94 – 1.36	0.202
	Diabetes mellitus	-0.15	0.86	0.61 – 1.22	0.4
	Hypertension	-0.12	0.89	0.67 – 1.17	0.402
	Cancer	0.2	1.22	0.85 – 1.76	0.283
	CKD	0.3	1.35	0.85 – 2.14	0.207
	COPD	0.48	1.62	0.88 – 2.97	0.121
	Immunosuppression	-0.03	0.98	0.57 – 1.66	0.925
	Cardiovascular diseases	0.08	1.09	0.77 – 1.53	0.638

OR – Odds Ratio; SES – Socioeconomic status on a scale from 1 (lowest) to 10; CVD – Cardiovascular Diseases; CKD – Chronic Kidney Disease; COPD – Chronic Obstructive Pulmonary Disease.

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Table 3b. OR for Symptomatic SARS-CoV-2 infection, model 2, previously infected vs. vaccinated

Variable	Category	ß	OR	95%CI	P-value
Induced Immunity					
	Previously infected	Ref			
	Vaccinated	1.96	7.13	5.51 – 9.21	<0.001
SES		0.07	1.07	1.02 – 1.12	0.003
Age group, yr.					
	16-39	Ref			
	40-59	0.09	1.1	0.9 – 1.33	0.35
	≥60	0.8	2.23	1.61 – 3.09	<0.001
Sex					
	Female	Ref			
	Male	-0.02	0.98	0.82 – 1.16	0.785
Comorbidities					
	Obesity (BMI≥30)	0.16	1.18	0.95 – 1.46	0.133
	Diabetes mellitus	-0.11	0.89	0.61 – 1.32	0.571
	Hypertension	-0.01	0.99	0.72 – 1.35	0.943
	Cancer	0.08	1.09	0.7 – 1.69	0.71
	CKD	0.13	1.14	0.65 – 1.98	0.654
	COPD	0.5	1.65	0.82 – 3.31	0.162
	Immunosuppression	0	1	0.54 – 1.85	0.999
	Cardiovascular diseases	0	1	0.67 – 1.5	0.99

OR – Odds Ratio; SES – Socioeconomic status on a scale from 1 (lowest) to 10; CVD – Cardiovascular Diseases; CKD – Chronic Kidney Disease; COPD – Chronic Obstructive Pulmonary Disease.

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Table 4a. OR for SARS-CoV-2 infection, model 3, previously infected vs. previously infected and single-dose-vaccinated

Variable	Category	ß	OR	95%CI	P-value
Induced Immunity					
	Previously infected	Ref			
	Previously infected and vaccinated	-0.64	0.53	0.3 – 0.92	0.024
SES		0.11	1.12	0.98 – 1.28	0.096
Age group, yr.					
	16-59	Ref			
	≥60	-0.81	0.44	0.06 – 3.22	0.422
Comorbidities					
	Immunosuppression	0.72	2.06	0.28 – 15.01	0.475

SES – Socioeconomic status on a scale from 1 (lowest) to 10

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Table 4b. OR for Symptomatic SARS-CoV-2 infection, model 2, previously infected vs. previously infected and vaccinated

Variable	Category	ß	OR	95%CI	P-value
Induced Immunity					
	Previously infected	Ref			
	Previously infected and vaccinated	-0.43	0.65	0.34 – 1.25	0.194
SES		0.06	1.06	0.9 – 1.24	0.508
Age group, yr.					
	16-59	Ref			
	≥60	-16.9	0	0.0 – inf	0.996
Comorbidities					
	Immunosuppression	1.15	3.14	0.43 – 23.01	0.26

OR – Odds Ratio; SES – Socioeconomic status on a scale from 1 (lowest) to 10.

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Table S1. OR for COVID-19-related hospitalizations, model 1, previously infected vs. vaccinated

Variable	Category	ß	OR hospitalized	95%CI	*P*-value
Induced Immunity					
	Previously infected	Ref			
	Vaccinated	2.09	8.06	1.01 – 64.55	0.049
SES		0.05	1.05	0.72 – 1.53	0.81
Age ≥60 yrs (16-39, ref)		5.08	160.9	19.91 – 1300.44	<0.001

OR – Odds Ratio; SES – Socioeconomic status on a scale from 1 (lowest) to 10

Table S2. OR for COVID-19-related hospitalizations, model 2, previously infected vs. vaccinated

Variable	Category	ß	OR hospitalized	95%CI	*P*-value
Induced Immunity					
	Previously infected	Ref			
	Vaccinated	1.95	7.03	2.1 – 23.59	0.002
SES		-0.07	0.93	0.74 – 1.17	0.547
Age ≥60 yrs (16-39, ref)		4.3	73.5	25.09 – 215.29	<0.001

OR – Odds Ratio; SES – Socioeconomic status on a scale from 1 (lowest) to 10

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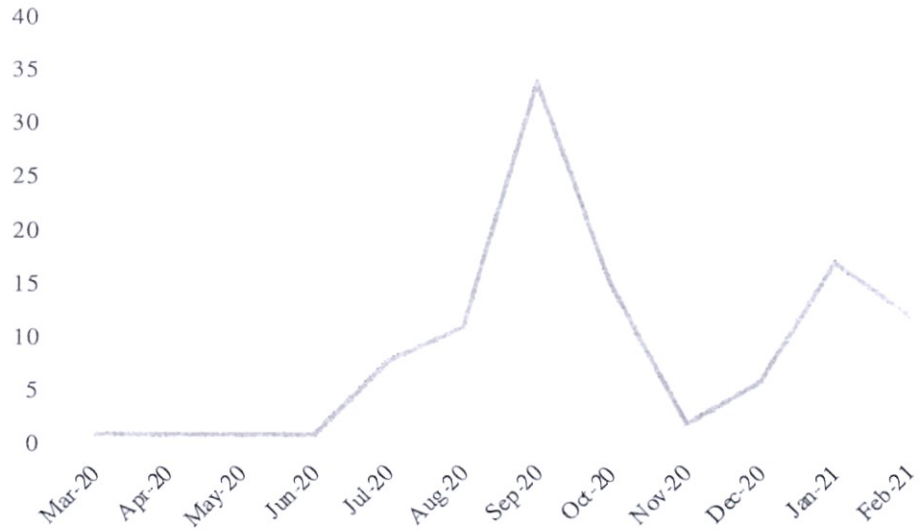
Figure 1. Time of first infection in those reinfected between June and August 2021, model 2.



World Health Organization

Monster Alert

A story of how we must act globally to protect ourselves locally from COVID-19





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Review

Recent advances and challenges of RT-PCR tests for the diagnosis of COVID-19

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ABSTRACT

Since the outbreak of the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the control of virus spread has remained challenging given the pitfalls of the current diagnostic tests. Nevertheless, RNA amplification techniques have been the gold standard among other diagnostic methods for monitoring clinical samples for the presence of the virus. In the current paper, we review the shortcomings and strengths of RT-PCR (real-time polymerase chain reaction) techniques for diagnosis of coronavirus disease (COVID)-19. We address the repercussions of false-negative and false-positive rates encountered in the test, summarize approaches to improve the overall sensitivity of this method. We discuss the barriers to the widespread use of the RT-PCR test, and some technical advances, such as RT-LAMP (reverse-transcriptase-loop mediated isothermal amplification). We also address how other molecular techniques, such as immunodiagnostic tests can be used to avoid incorrect interpretation of RT-PCR tests.

Abbreviations: cDNA, complementary DNA; CLIA, chemiluminescence immunoassay; COVID-19, Coronavirus Disease 2019; CRISPR, clustered regularly interspaced short palindromic repeats; CT, computed tomography scan; DNA, deoxyribonucleic acid; EDTA, ethylene-diamine-tetra-acetic acid; ELISA, enzyme-linked immunosorbent assay; IgG, immunoglobulin G; iLACO, isothermal LAMP-based method for COVID-19; NP, nasopharyngeal; NPV, negative predictive value; OP, oropharyngeal; RBD, receptor binding domain of the virus; RNA, ribonucleic acid; RT-LAMP, reverse transcription loop-mediated isothermal amplification; RT–PCR, reverse transcription of polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus; SRT, sampling-to-result time; TCEP, tris (2-carboxyethyl) phosphine.

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Introduction

In early December 2019, the first case of a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was reported in Wuhan, China, and ever since, there has been a growing spread of the coronavirus disease 19 (COVID-19) all over the world [1]. While the disease is widely known to be a deadly disease, some patients are asymptomatic but can still transmit the virus [2]. This has made tracing the disease difficult solely based on clinical symptoms, and undetected SARS-CoV-2 infection has posed serious challenges regarding control of the disease spread. Currently, the virus outbreak has reached pandemic proportions with over 3 million deaths across the world [2], underlining the rapid spread and the urgent need for control of disease transmission. Therefore, because widespread vaccination against SARS-CoV-2 will take some considerable time, keeping the disease transmission under control is a high priority, and there is a need to drastically improve the efficiency of the present diagnostic tests.

Currently, diagnostic techniques based on viral RNA amplification, specifically qRT-PCR (quantitative real-time polymerase chain reaction), are the gold standard diagnostic methods for COVID-19 [3,4]. Unlike other molecular tests that do not have perfect diagnostic specificity, qRT-PCR is highly specific with a specificity of almost 100 % [5]. This has led to RT-PCR becoming the gold standard molecular diagnostic test.

However, the RT-PCR test for SARS-CoV-2 virus does have some pitfalls that necessitate improvements in the way the method is used. As with immunodiagnostic tests, the RT-PCR test can have difficulties in distinguishing between true positive and true negative COVID-19 infected individuals [6]. The test fails in a considerable proportion of suspected and confirmed patients with clinical implications; as a result, it is a wise precaution not to rely on PCR test results alone, and to consider other clinical and molecular evidence [5]. This means that one always should take into account a combination of clinical and molecular evidence before sending a suspected patient home as disease-free. Furthermore, given the challenges with RT-PCR test results, repetition of the test over time and on multiple samples enhances the overall sensitivity of the test.

Moreover, it is necessary to improve the RT-PCR methodology to tackle the problem of less than perfect sensitivity. This could be achieved by designing more simple versions of the test. Simple tests provide opportunities for more wide-spread application among different components of the health care system. A simple test requires less training and could enable other health-care staff to use the test correctly. It also minimizes the risk of disease transmission to the staff, and test failure due to improper manipulation of the clinical samples. Furthermore, amplification of the test can shorten the gap between sampling and results, allowing the repetition of the test over time or on multiple samples if needed. Finally, the simpler the test is, the more likely it can be offered at a lower cost per test [7].

In the present paper, we will review publications discussing the diagnostic ability of the RT-PCR test as well as the implications of its failure, and some ways of maximizing the current molecular diagnosis for COVID-19 will be addressed. We cover the clinical evidence for RT-PCR results in COVID-19 patients, approaches adopted to enhance the test efficacy, and recent technological developments in the design of the test. The false-negative and false-positive results of the RT-PCR test are discussed, along with the advantages of the combined use of immunodiagnostic tests together with RT-PCR.

2. False-negative RT-PCR results in infected cases

False-negative results in a screening test can have serious implications during a pandemic, such as COVID-19 because a proportion of true infected cases are categorized as disease-free and can unintentionally transmit the disease. Unfortunately, there is no single molecular test that can guarantee the infection free status for a suspected case; therefore, the clinical history and social contacts of the individual should be always taken into account in the assessment of the infection probability. Repetition of the molecular tests over time also helps to increase the selectivity.

Reports have described RT-PCR on various specimens obtained from the respiratory tract; however, there are accumulating reports indicating the lack of adequate sensitivity for the test. RT-PCR examination of nasal and oropharyngeal swabs, nasopharyngeal washing or aspirate is recommended as the gold standard for the diagnosis of COVID-19 [8–10], However, the overall sensitivity of the RT-PCR test is reportedly between 45–60% in nasopharyngeal aspirate and swab samples [11]. For instance, Yang et al. reported a false negative rate of 11 % for sputum, 27 % for nasal, and 40 % for throat swabs within the first seven days from onset of illness in 213 patients hospitalized with COVID-19 [12]. Similarly, Zhao et al. reported a false negative rate of RT-PCR tests within the same range. These researchers reported that 33 % of respiratory samples gave false-negative results in 173 hospitalized patients with COVID-19 as diagnosed with typical chest CT scans and acute respiratory symptoms [12]. The false-negative rate ranged from 2% to 29 % in a systematic review of five other studies containing a total of 957 patients suspected or confirmed with COVID-19 [13].

One of the main reasons for such a high false-negative rate in RT-PCR results, is the time of sampling after the onset of symptoms. The time of sampling is important because it was shown that the false-negative rate of the test varies over time [14]. The false-negative rate of RT-PCR testing on nasopharyngeal (NP) and oropharyngeal samples was described as "shockingly high" in a study of 1330 confirmed cases. In their investigation, the authors pooled the data on the confirmed COVID-19 cases from seven previously published studies. They analyzed these data using a Bayesian hierarchical model to estimate the false-negative rate from 5 days before the onset of symptoms up to 21-days post-emergence of symptoms. They found that the median false-negative rate reduced gradually from 100 % to 20 % during days 3 and 4 post-onset of symptoms. The false-negative rate was 67 % one day before the onset of symptoms and 38 % on the day of symptom manifestation, and returned gradually to 66 % on day 21 post-onset of symptoms. Consequently, the false-negative rate of the test changes over time depending on when the samples were obtained from the onset of symptoms, and even at best, the RT-PCR fails to detect a considerable fraction (one out of five) of the infected cases [14].

Another explanation for the high negative rate of RT-PCR tests for COVID-19 could be related to the viral load present in the sampling site from each patient. This could vary among different specimens and patients. The highest viral loads are found in the lower respiratory tracts of COVID-19 patients compared to the upper respiratory tract [15]. However, sampling from the lower respiratory tract is difficult in patients with severe respiratory symptoms who are receiving oxygenation intervention [16]. In the upper tract, nasopharyngeal and oropharyngeal swaps or aspirates are recommended for early diagnosis of the infection. NP samples exhibited much higher viral loads compared to OP samples, giving a better chance detecting SARS-CoV-2 infection and lowering the risk of missing the infection [17]. Moreover, false-negative results occurred in some patients with gastrointestinal symptoms. In these patients, sampling from fecal samples revealed the presence of SARS-CoV-2 [16]. Therefore, some false-negative results are inevitable depending on the specimen chosen and the patient clinical symptoms.

Given the imperfect selectivity of the RT-PCR test, other diagnostic information should be taken into account to achieve the desirable sensitivity for true-positives or true-negatives for COVID-19. These factors include the clinical symptoms, immunodiagnostic test results, and prevalence of the disease within the community. These factors can help clinicians to better estimate how likely any particular case is to have disease. For instance, whether or not a case demonstrates the typical clinical symptoms of COVID-19 can give a primary estimate of the probability of the case being infected, and successive addition of the molecular test results (e.g. RT-PCR and serologic tests) will increase the

ıfidence to distinguish between disease-free or infected. Furthermore, RT-PCR in combination with an immunodiagnostic test will improve the overall selectivity [18]. For example, in a retrospective study of 375 patients, the combined selectivity of RT-PCR and antibody testing was significantly higher compared to each test alone. The diagnostic sensitivity of the RT-PCR and antibody test were 95.7 % and 92.2 % respectively, which rose significantly to 98.6 % when these tests were combined [17]. Lastly, the prevalence of the disease should be taken into account in deciding whether or not a particular result is enough to send a person home as disease-free. The low prevalence of disease implies a low probability of having the disease, and a post-test negative result with a given sensitivity (say 95 %) could suggest a person is highly likely to be disease-free. However, when the prevalence of disease increases throughout a community, that level of sensitivity is less valuable to ensure a suspected patient is disease-free. In technical terms, the negative predictive value (NPV) of the test decreases with an increase in the prevalence of the disease [19].

To sum up, the false-negative rate of RT-PCR is significant and varies across different specimens and time periods. However, the false-negative rate can be minimized when immunodiagnostic tests and clinical symptoms are considered along with the RT-PCR test result. reover, it is importannt to stick to social distancing and recom- ıded hygiene protocols to keep the prevalence of the disease as low as possible, in order to maintain the NPV of the tests at a high level. Otherwise, the negative results of PCR tests will no longer give us enough confidence that the suspected case is disease-free.

3. How to use the RT-PCR test more effectively given its false-negative results?

Due to the high rate of false-negative results in RT-PCR of COVID-19 patients, and the epidemiological prevalence, some improvements can be suggested.

The false-negative rate of the RT-PCR test can occur due to several reasons. Firstly, the viral load can be low or absent within the samples [19]. The viral load governs the amount of RNA in the samples. The higher the viral load in the sample, the more RNA with a better chance for a test to get a truly positive result. Secondly, the viral RNA might be subjected to denaturation or degradation in the samples due to improper manipulation or storage, which lowers the final amount of intact RNA for the test [20]. Thirdly, a sufficient viral load is limited to specific time periods when the virus rapidly replicates itself and is shed from the cells. Fourthly, the viral load has also shown to vary in terms of the anatomical ite from which the specimen is obtained Lastly, the virus is present at numbers or is absent in some specimens from some patients, while er specimens might have a higher viral load in the same patients [21]. Therefore, the variability of the false-negative rate depends on the viral load, which in turn, fluctuates over the course of the disease, and between specimens from patients with different clinical characteristics.

The above-mentioned problems can be solved with optimized RT-PCR diagnostic protocols. Given the mentioned viral load variability over time, specimen, and patients, an improved RT-PCR test should be more simple, rapid, and cost-effective to allow frequent repettition [22]. This will increase the chance of detecting the infection if the test is repeated over time and on different samples. If the test can be made rapid and less labor-intensive, the sampling-to-PCR gap time will be shortened, which will reduce the loss of viral RNA due to denaturation during this period. Moreover, a simplified test will require less sophisticated laboratory equipment. These simplified tests could enable rapid point-of-care sample manipulation and analysis, with a higher throughput.

The current RT-PCR test could be used more effectively by conducting the test in pooled samples. Pooling different samples from either the same patient or the patient's family members can reduce the number of tests and lower the costs positive rate of the test. Because in some patients the viral infection is limited to the lower respiratory tract, combining sputum, nasal and pharyngeal swabs coulsd be useful. In other patients with gastrointestinal involvement, the virus was only found in fecal material, while RT-PCR of the NP swabs and sputum were negative. Therefore conducting the test on pooled samples from different specimens can improve the probability of getting a sample with sufficient viral load to increase the accuracy of RT-PCR. The other benefit of pooling samples is to allow better at-home quarantine decisions amongst communities. For instance, pooled samples from the whole family of a suspected case can provide guidance on strict quarantine for the entire family, to reduce disease transmission in the community [23].

Therefore, the repetition of the RT-PCR test in pooled samples might offset the high false-negative rate of the test. Also, the conduction of the test in pooled samples appears to increase the utility of the test for screening purposes. To this end, recent cutting-edge technology has attempted to provide simple point-of-care or at home RT-PCR kits.

4. The preparation of point-of-care RT-PCR tests

The preparation of a simple, rapid, and inexpensive RT-PCR test requires understanding the technical difficulties that have restricted the use of the RT-PCR method. By overcoming these obstacles, the laboratory RT-PCR test can be turned into a convenient, rapid, and budget-friendly kit that can be used more widely in clinics.

5. The problems of the RT-PCR test for extensive use

Technically, the RT-PCR procedure for SARS-CoV-2-infected samples consists of several steps, and needs laboratory equipment that makes the process tedious and difficult to be conducted outside the laboratory setting. First of all, the RNA material must be extracted from the cells and the virions (viral particles) and preserved from destruction by RNase enzymes. This step needs laboratory equipment such as a centrifuge and a laminar flow cabinet, and might lose some of the RNA materials due to denaturation. Secondly, the process of PCR requires thermal-cycling equipment for creating a cyclic temperature change during the process of RNA amplification. The third difficulty is the readout method used, which in most cases required expensive sophisticated spectrofluorometric equipment [24].

Before the RT-PCR step, the viral RNA has to be extracted from the samples. During this process, certain laboratory chemicals and equipment are used for specific purposes. Firstly, the infected cells and the virions are disintegrated by the addition of lysis buffer typically containing detergents (Tween 20 or Triton X100). The lysis of the cells and virions causes all the biomolecules, including viral RNAs to be released into the medium and be readily available for the test. The lysis buffer also contains salts such as sodium iodide (NaI) or guanidinium thiocyanate (GuSCN) that facilitate the separation of the viral RNA from other biomolecules (e.g. cell and viral proteins). Centrifugation of samples containing these salts assists in the separation of these proteins from the viral RNA fraction. Besides, cellular RNase enzymes are inactivated by the addition of detergents and thermal treatment. Some detergents such as TCEP or EDTA are added to the samples, which are incubated at 95 °C for 5 min. The RNase inactivation inhibits the process of RNA denaturation and causes the RNA to be preserved for the RT-PCR test [25].

Subsequently, the RNA samples are amplified during the RT-PCR process using a thermal cycling program. In each cycle, the temperature of the samples is alternatively decreased to 70 °C and increased to 95 °C for a certain time, and at each cycle the number of RNA replicates is doubled. At 70 °C, the single stranded C-DNA replicates are used as the template for the synthesis of new stands of C-DNA. During this step, Taq DNA polymerase synthesizes a new strand of C-DNA from the template which gives rise to a double-strand DNA composed of the old and new strands of C-DNA. At 95 °C, these strands must be detached from each other to give twice the number of single strand templates for the next round of C-DNA replication. This cycle is repeated several times

. for 30 cycles) until the number of C-DNA replicates reaches an amount capable of being detected by spectrofluorimetric techniques. The thermocycler apparatus that provides this accurate cycle of temperature changes is expensive equipment that is often confined to a laboratory [25].

Finally, the increasing number of C-DNA replicates is monitored using a real-time spectrofluorimetric technique that is also expensive and not always available. This technique offers a readout of the C-DNA amplification on a computer screen based on the fluorescent signal that changes increases in line with C-DNA numbers. Different fluorescent probes are used for the quantification of C-DNA replicates in the PCR. For instance, in the SYBR green assay, the fluorescent probe intercalates into the C-DNA double strands that quenches the probe fluorescence. This fluorescent probe de-quenches upon the separation of the C-DNA strands from each other. In the TaqMan assay, the fluorescent probe is de-quenched by the binding of the TaqMan primer to the C-DNA templates. In both techniques, a spectrofluorimetric apparatus coupled to a computer is required for the final readout of the RNA amount in the samples. These pieces of equipment are expensive and may not be available everywhere in large numbers [25].

hanging RT-PCR towards a point-of-care test for COVID-19

Given the aforementioned difficulties of the RT-PCR test, enormous efforts have been made to produce an easier, faster, and more convenient test capable of being used outside the laboratory environment. A simple and rapid test can reduce the sampling-to-result time (SRT) and encourage its wider application. The test procedure should require fewer steps and laboratory tools. A shorter SRT and easier manipulation of the sample will have some other benefits, including an increase in the test sensitivity.

One important simplification in the nucleic acid amplification procedure was the invention of an isothermal PCR method that eliminated the need for a thermal cycling apparatus. This allowed the amplification of RNA or DNA using a widely available kitchen oven maintained at a specific constant temperature. In this method there is no need to increase the temperature up to 90 °C to unwind the double-stranded DNA. Instead, the DNA polymerase itself displaces one of the strands of the DNA as it acts on the other strand and synthesizes a new copy. During this process, primers fold back on themselves and create loops of DNA that provide 3′ starting points for the new round of DNA replication by DNA polymerases. Therefore, the technique is called the loop-mediated isothermal amplification (LAMP) technique, described in reference [26]. LAMP only needs an optimum temperature of 65 °C for DNA polymerase ivity. The provision of a constant temperature is technically much er than a temperature cycling program that is required for conventional PCR [19].

Another invention which has made the test more convenient and quicker is where the pre-PCR RNA extraction step is combined with the PCR step itself. This reduction in the number of steps of the test offers some advantages. Firstly, a single step preparation of RNA reduces the SRT and increases the potential of the test for wider application. A shorter SRT decreases the probability of disease transfer by individuals whose test results have yet to be determined. Secondly, a one-step preparation of the RNA samples is much easier for potential users to learn how to use the test correctly. Thirdly, during the extraction of RNA from the sample, there is a risk of viral transmission from the samples to the laboratory staff, and cross-sample contamination due to unintentionally errors in sample manipulation. A shorter and easier process of RNA preparation can minimize the mentioned risks. Fourthly, the use of an RNA purification protocol increased the sensitivity of the RT-LAMP test shown by a reduction in the detection limit of the test from 100 copies/μL to 1 copy/μL. Lastly, the combination of the steps has been shown to eliminate the need for apparatus that limits the test to a lab environment [19].

Furthermore, further simplification of RT-PCR can be achieved by providing RT-LAMP kits with simpler result readouts. In the case of COVID-19 infection, it is only necessary to know whether or not viral RNA is present in the samples; therefore, there is no need for expensive quantification methods like spectrofluorimetry. Instead of quantitation, qualitative readouts such as a color change are much easier to achieve, and are more appropriate for diagnosis of SARS-CoV-2 infection. By using these kinds of readout, one can simply observe the results with the naked eye [19]. For instance, Yu et al. [27], recently developed an iLACO assay (isothermal LAMP-based method for COVID-19) with a fluorescent readout. Using this kit, they could achieve the results within 15–40 min and observe the results without any need for expensive spectrofluorimetric equipment. In this test, the positive samples with Genefinder dye turned bright white, while the negative samples remained blue under blue light. Another example was the Penn-LAMP technique that produced a color change upon the amplification of the viral RNA. In this technique, the sample color changes from white to blue if the samples contained the amplified RNA material. Also, the entire RT-LAMP process can be done in a single vial without any need for specific equipment.

Previous studies have suggested using CRISPR/Cas systems in the diagnosis and treatment of COVID-19 [28,29]. Perhaps the best solution to produce a "fast and simple test" may be the "integrated RT-LAMP and CRISPR-Cas-12 method' (Fig. 1), that literally can be used anywhere by anyone. The method contains a kit with a lateral flow visual readout using a strip of paper. In this test, one just needs to dip the correct end of the designed strip in the vial of the final RT-LAMP product and wait to observe either a positive or negative result. These results appear in the form of a band at specific distances from the starting point. In the designed strip, the detection method relies on the CRISPR Cas-12 endonuclease enzyme and a trans-reporter molecule. The CRISPR Cas-12 detects a specific E gene and N gene sequence in the amplified viral DNA and acts as a "shredder" on other irrelevant RNA sequences. Therefore, all other RNA sequences are eliminated except for the target sequence that remains intact in the RT-LAMP product. The FAM-biotin trans-reporter is already placed and affixed to the strip. As the sample flows laterally across the strip, the remaining target sequence interacts with the FAM-biotin trans-reporter molecules on the strip producing the band. Using this DNA Endonuclease-Targeted CRISPR Trans Reporter (DETECTOR) technique, a fluorescently-labeled band can be observed in less than one minute [8].

Taken together, the RT-LAMP methodology has provided a new alternative for rapid, simple, and home-use molecular diagnostic tests. Being rapid and simple has enabled wider and more frequent use of these tests for COVID-19 detection bymembers of the public, therefore, overcoming the high negative rate of RNA-based tests. On the other hand, the false-positive rate of these tests poses some issues regarding the management of the COVID-19 pandemic that will be discussed in the following section.

7. False-positive RT-PCR rates in COVID-19 cases

Another question that needs to be addressed is to be certain that a positive PCR test result for COVID-19 truly reflects the infected status of the patient. To this end, a positive PCR test result can be confirmed when the sample is examined by the gold standard viral culture test. Although data on viral culture results are sparse, there is some evidence that can help us to evaluate the predictive value of the PCR test as a screening method under different conditions. To what extent a positive PCR result predicts the chance of someone being infectious may be governed by different factors. These factors include the time after symptom onset, symptom severity, and the specimen used when the PCR test is carried out [30].

First of all, we should consider the time of symptom onset when interpreting the probability of being infectious according to RT-PCR results. It has been reported that the viral load is maximum by the 3rd day from the onset of symptoms in samples from the upper respiratory

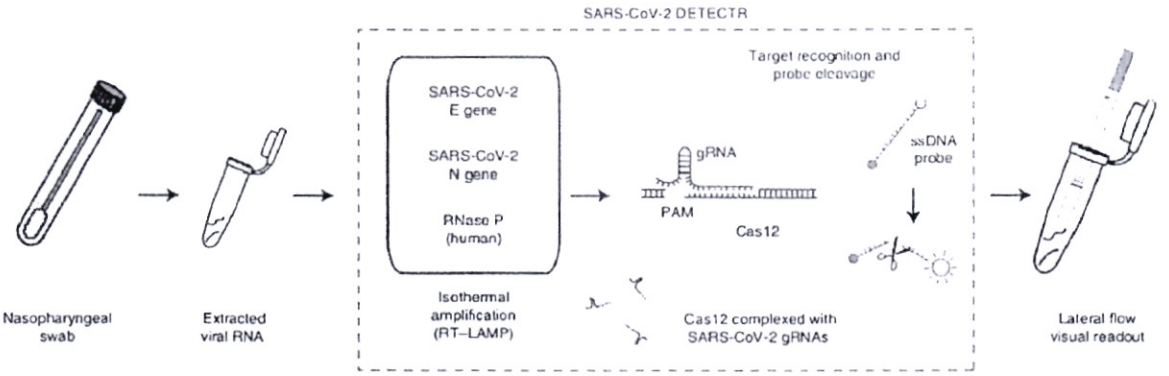

Fig. 1. Integrated RT-LAMP and CRISPR-Cas-12 for SARS-CoV-2 detection. Reprinted from ref. 10.1038/s41587-020-0513-4.

tract, and that live virus can still be detected at 8 days after the onset of the disease symptoms by the viral culture test. However, beyond this period the virus might no longer be infectious, although RT-PCR results continue to detect the presence of viral RNA material [31]. In one study conducted on 129 hospitalized patients with COVID-19, RT-PCR ing showed that the duration of virus shedding was longer, and ged from 0 to 20 days post-onset of symptoms. Moreover, it was reported that SARS-CoV-2 RT-PCR continued to detect the virus until the 63rd day from the onset of symptoms in one case report study. However, there is some evidence from serum samples suggesting that the RT-PCR could give positive results by detecting viral RNA remnants long after infectious virus had disappeared. Therefore, it is possible that the RT-PCR result was positive even after the infectious virus had been neutralized by the immune system.

The source of the specimen can also reflect the disease progression. Viral shedding can be detected only during a specific period that varies according to the sampling site. For example, within 5–6 days from the onset of symptoms, high viral loads were reportedly found in the upper and lower respiratory tracts in COVID-19 patients. As a result, nasopharyngeal (NP) and oropharyngeal (OP) swabs are recommended for early diagnosis of the infection. In this regard, NP samples were found to be better than OP samples in terms of the chance of detecting SARS-CoV-2 infection (63 % in NP swabs versus 32 % in OP swabs) showing there were higher viral loads in the nasal cavity. However, upper tract respiratory samples might fail to give sufficient viral load for detection purposes in a given time point of the infection [16]. For instance, one case report showed that the virus was only detected within the first 18 days the onset of respiratory specimens [33], while the presence of the s in fecal samples was detected for a longer period after respiratory amples became negative [34]. Some patients with COVID-19 pneumonia exhibited a longer-lasting shedding of the virus in the respiratory tract, whereas there had been high loads of SARS-CoV-2 in their fecal samples from the beginning of the symptoms [35–38]. The fecal shedding of the viral RNA continued between days 1–33, while at least 3-days post-onset of symptom was identified as the optimum timepoint for a high positive rate of RT-PCR test in upper respiratory tract samples [34]., The amount of virus in the serum correlates with infectious SARS-CoV-2, and once neutralizing antibodies are detected in the serum, the virus is no longer infectious [32]. Consequently, RT-PCR positive results in fecal and upper respiratory tract samples will continue for a specific period of time (probably longer for fecal samples), but the infectious status of the patient might be limited to the period when active virus can be detected in serum samples.

As with other RNA viruses, SARS-CoV-2 RNA can be detected long after the infectious virus has been neutralized by the immune system and disappeared. This is because that the RNA of the inactivated virus degrades slowly over time, and during this period, RT-PCR will still give a false positive result based on the RNA remnants. In this regard, the application of other molecular techniques, such as those that detect viral protein targets, or patient antibodies against these proteins is required to confirm the results of RT-PCR as "truly infectious" [39].

Lastly, the initial viral RNA load in the specimen can influence the likelihood of getting a positive PCR result and can result in the test being oversensitive. A lower initial viral RNA load can be detected by an increase in the sensitivity of the RT-PCR test, but at the same time, this can prolong the period of getting RT-PCR positive results [3]. The conventional RT-PCR fails to detect the infection in samples containing $<10^6$ copies/ml. (or copies per sample) [30]. This detection limit can be improved (lowered) by making modifications in the test, such as improving the viral RNA extraction method and the fluorescent probes. However, reducing the detection limit of the test might also increase the false positive rate of the test in the later stages of the infection, because lower amounts of remnant RNA from the inactivated virus would be sufficient to give a positive result. Therefore, other molecular and clinical evidence in combination with RT-PCR results should be used to confirm the status of the infection [39,40].

Taken together, the PCR results for COVID-19 should be carefully considered to confirm the infection, and special attention should be paid to the stage of disease development and the type of specimens collected for the test.

8. The public health implications of false-positive rates

The false-positive rate of the diagnostic tests might at first glimpse, seem not to be as important as the false-negative rate, given the current global prevalence of the disease. However, erroneous positive results are indeed important, and can have serious implications for public health services [3].

Currently, the global health policy is to maintain COVID-19 transmission as low as possible within communities. Therefore, COVID-19 hygienic protocols contain strict quarantine guidelines based on positive results of RT-PCR tests. This occurs despite knowing that the RT-PCR test suffers a low positive predictive value [3]. When the PCR test remains positive over time, the positive results will be taken seriously, and the suspect patient is recommended for stay-at-home quarantine as long as the repetition of the test gives positive results. For instance, as of September 19, 2020, the false positive rate of the swab tests was estimated to be between 0.8 % and 4.0 % in the UK population, which suggested a significant proportion of false-positive results were due to the low prevalence of the disease globally (the global prevalence of the disease was 0.50 % at that time) [3].

Despite the low positive predictive value for the test, patients are still recommended to follow a strict quarantine which will not cause a serious social problem.

However, the low positive predictive value of RT-PCR tests causes problems for health and social services. The prevalence of the disease is likely to be much higher in the health-care environment, and the high false-positive rate of PCR tests will lead to the quarantine of significant

numbers of social health-care workers and health-care personnel, that might have been avoided. This could cause a serious shortage of health-care workers especially at the peak of waves of disease transmission [3].

Therefore, the high false-positive rate of the RT-PCR test is indeed a problem among health-care personnel and the results of the test should be confirmed based on other clinical evidence.

9. Combination of RT-PCR and serologic testing during infection

Although the RT-PCR test is the frontline diagnostic test in the early stages, the test still suffers from a high rate of failure in the detection of true COVID-19 infections. However, when the RT-PCR test is accompanied by other diagnostic molecular tests, the sensitivity of COVID-19 testing is enhanced. Moreover, the RT-PCR and serologic tests display opposite trends in sensitivity during the infection, in which one test can cover the failure of the other as the disease progresses [18].

In the early phase of the infection, the rate of viral detection by the RT-PCR method is low; however, RT-PCR results are improved when ELISA molecular tests are used in combination. The combination of these techniques has already been shown to improve the sensitivity in the early stages. Within 5–6 days of the onset of the symptoms, RT-PCR a low chance of viral detection in nasopharyngeal samples; however, n RT-PCR tests and ELISA techniques were used in combination, the sensitivity improved dramatically [18]. Guo et al. [41] reported a set of 58 suspected cases with negative RT-PCR results, and showed that 93 % were positive when nasopharyngeal (NP) samples were tested by ELISA for the presence of IgM antibodies. Out of 82 RT-PCR confirmed cases, 76 % were also found to be positive by the IgM-ELISA test. The overall sensitivity of the RT-PCR alone was 52 %, failing to detect almost half the cases; however, the combined IgM-ELISA/RT-PCR sensitivity was much higher at 99 %. Besides, the rate of success in positive cases was found to be increased even further when the combined detection of IgG and IgM were combined with RT-PCR. In another study, over 70 % of suspected cases with negative RT-PCR results were identified as positive when IgG/IgM ELISA was used [42].

As the disease progresses, the sensitivity of the RT-PCR and serological tests both change. While the RT-PCR was highly sensitive during the first week after symptoms emerge, the serological tests had higher sensitivity in the second week, underlining the advantage of the combination [17]. During the course of the infection, Zhao et al. [12] followed the sensitivity using an ELISA test measuring total antibodies to the RBD viral antigen. In addition to serological testing, RT-PCR results were obtained as well. In the early (1–7) days after onset of symptoms, sensitivity of RT-PCR was 67 %, but decreased to 54 % between days 4, and to 46 % between days 15–39 post-onset of symptoms. In parison, the sensitivity of the total antibody ELISA significantly increased as the disease progressed, and reached a maximum of 100 % during the last 15–39 days. Interestingly, the combined sensitivity of both tests was much higher at 79 % during the first 1–8 days of the onset of symptoms, and grew to 97 % from the 8th day onward.

Therefore, the use of RT-PCR combined withg ELISA tests can enhance the overall sensitivity and reduce the false-negative rate. Besides, these tests follow opposite trends in the sensitivity during the infection period; therefore, the use of both tests can improve the

10. Relation of serological response with progression and severity of COVID-19

The results of serologic tests depends on the amount of antibodies produced, which may vary according to the severity of the disease. Some studies proposed the monitoring of antibody titers as a prognostic indicator for early aggressive treatment of the disease. Other studies observed higher antibody titers in elderly patients compared to other age groups regardless of the disease severity. Moreover, it is traditionally believed that seroconversion from IgM to IgG takes place during the development of the humoral immune response; however, some reports found that the expression of IgG and IgM could occur simultaneously, and the median time of appearance from onset of symptoms varied in different patients [18].

The median time of seroconversion of antibody isoforms may vary according to the type of immunodiagnostic test and the choice of the target antigen. In a large multicenter study conducted by Long et al. [43], the median time of seroconversion for both IgM and IgG was observed on day 13 by an NP and SP-targeted direct chemiluminescence immunoassay (CLIA). Zhao et al. [12] found a median seroconversion of IgM and IgG against RBD antigen, at 12th and 14th days after onset of symptoms, respectively. The median seroconversion time varied more widely in other studies. Guo et al. [41] used an ELISA kit for detection of antibodies to the NP antigen, and found that the IgM and IgG response appeared on day 5 and 14 after the onset of symptoms, respectively. In that study, IgA to the NP antigen was also found on day 5. Xiang et al. [44] also used an NP-targeted ELISA and found the median appearance of IgM and IgG at day 4 post-onset of symptoms. Overall, while IgM appearance preceded IgG in some studies appearing during the first week, in other studies both isoforms appeared simultaneously by two weeks from the onset of symptoms. In this regard, the detection time of antibody appearance may have been affected by the target antigens chosen and different immunodiagnostic assays used.

Few studies have examined the relationship between antibody titer and the disease aggressiveness. These studies investigated the relationship between specific antibody profiles and disease severity. There was generally a positive correlation between the level of antibodies and the severity of the disease. For example, Tan et al. [45] reported that they found an earlier presence of IgG, as well as higher IgG titers in severe patients compared to less severe patients. Wang et al. [46] reported significantly higher titers of IgM only in deceased patients ($n = 15$) compared to those with mild-to-moderate symptoms ($n = 115$, $p = 0.19$). No correlation was observed between IgG titer and disease severity in this study. This trend towards higher IgM and lower IgG levels was also observed in a large study of 338 confirmed COVID-19 patients. Also, the level of IgA was significantly increased in a cohort of 216 patients that was correlated with the severity of the disease [47].

Whether or not there is a relationship between IgG titer and disease severity may have depended on the choice of antigen used in the test. While some studies failed to show a relationship, other studies did find a relationship between IgG and disease severity. For instance, Sun et al. [46] reported that IgG titers against the SP antigen were significantly higher in non-ICU patients, while IgG titers to NP antigen were higher in ICU patients. This was in contrast with the results of To et al. [42] who failed to observe a relationship of any kind between IgG titers and disease severity when IgG titers to NP and RBD antigens were measured by an ELISA test.

Although there is a positive correlation between age and severity of the disease and poor outcomes, it was found that increasing age was associated with high antibody titers to both non-SARS-CoV-2 and SARS-CoV-2 infections. Given that an elevated antibody response to non-SARS-CoV-2 infection appears to have little effect on health, the high antibody titers seem not to be the cause of the disease severity in older age groups. Using neutralizing antibody assays, participants over sixty years of age exhibited a higher overall antibody titer compared to a healthy young adult with non–SARS-CoV-2 human coronavirus infection. This implies that the antibody response is stronger in the elderly than young adults in the case of non-SARS-CoV-2 infection, where no serious clinical outcomes are reported. Consequently, although the elderly and middle-aged patients who recovered from COVID-19 demonstrated higher titers of SP-reactive antibodies in their samples than young adults, this elevated antibody titer may not be related to the poor outcome of treatment in elderly COVID-19 patients [47,48].

11. Concluding remarks

Fig. 2 illustrates the benefits and shortcomings of the different

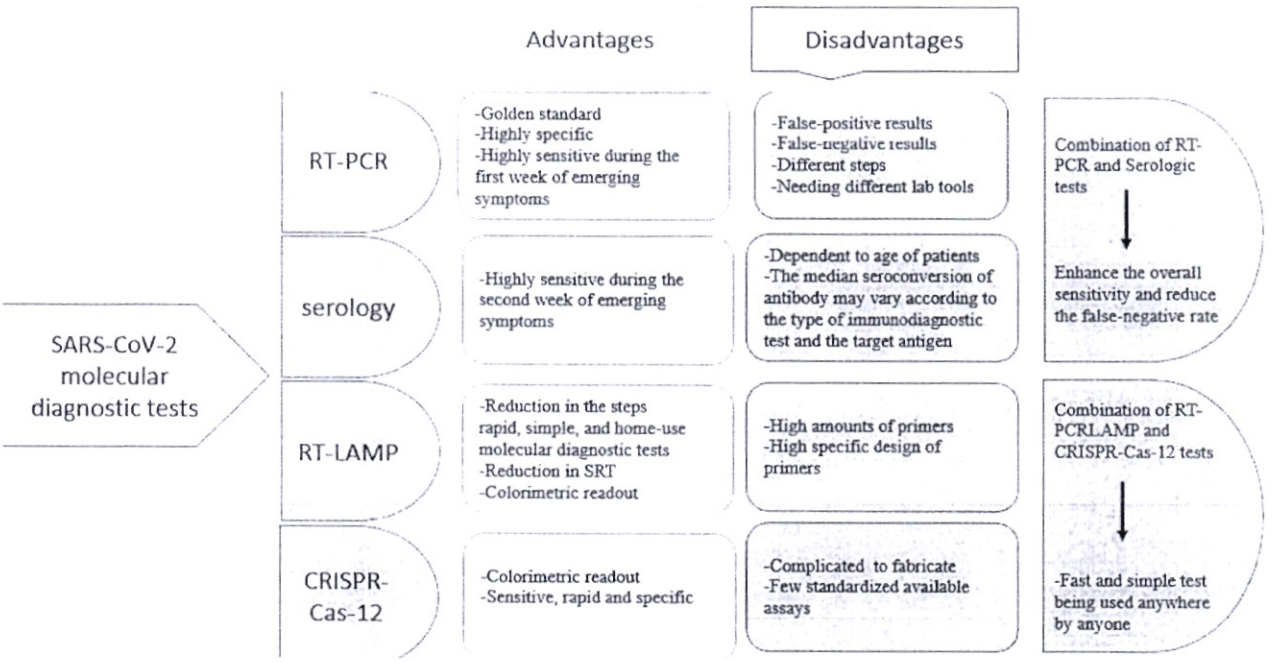

Fig. 2. An overview of the advantages and disadvantages of the SARS CoV-2 molecular diagnostic test.

screening tests discussed in this paper. We addressed the shortcomings and strengths of RT-PCR tests for the screening and diagnosis of COVID-19 patients. Up to now, the RNA PCR amplification tests are accepted as the gold standard method for the detection of SARS-CoV-2 infection in clinical samples. The test is highly specific for SARS-CoV-2 virus detection, and it can give a result within a short period. However, the test is too difficult to be widely used and it requires expensive laboratory equipment and highly-trained laboratory staff. The current RT-PCR test also suffers from a level of insensitivity. This implies that other clinical and immunodiagnostic tests should be also taken into account when interpreting the results of RT-PCR tests. PCR tests suffer from an alarming level of false-negative and false-positive results, so it is necessary to look for further improvements to the RT-PCR test.

As with other screening tests, the RT PCR method has some drawbacks when applied to clinical samples. There are a few factors that might interfere with the test reliability. Firstly, there is a narrow time dow to obtain high sensitivity depending on the viral load in the ples. The false-negative rate of the test varies over the time from the set of clinical symptoms. Within the first 3 days from the onset of symptoms, the RT-PCR test could offer the fewest false-negative results, however, the test failure was shockingly high for detection of the virus. Secondly, there is also variability in the test sensitivity in different clinical samples and patients with varying clinical symptoms. Lastly, the improper manipulation of clinical samples might result in test failure due to the viral RNA degradation and loss during the handling of the samples.

Therefore, the repetition of the RT-PCR test is recommended to enhance the likelihood of virus detection, which requires the test to be easier and more rapid for frequent repetition. It has been shown that repeating the test over time and on different clinical samples can enhance the overall positive rates of the test. The repetition of RT-PCR testing is currently recommended in standard protocols to allow clinicians to confirm the results in suspected cases, as it is more reliable than a single test result. Another point is that pooling the different clinical samples or samples from the patient's family could reduce the number of test repetitions required, but still reap the benefits of enhanced sensitivity. As a result, RT-PCR test repetition over time or on different samples can increase the overall sensitivity of the test. Therefore alternative RT-PCR tests which are simpler, less expensive, and easier to conduct are under investigation.

There are some obstacles regarding the widespread application of RT-PCR tests. Firstly, the test necessitates the use of sophisticated equipment that confines the test to the laboratory setting where everything is at hand. Secondly, the test takes many steps to be completed, and requires the staff to be well trained to follow every step correctly. Thirdly, the time between sampling and the result is lengthy, and should be shortened. Therefore, for the test to be applied more widely, it requires simplification and to be easily learned and completed.

Up to now, great strides have been made in the improvement of RT-PCR testing. Alternative methods of viral RNA amplification have already been implemented with a simpler technical procedure compared to the conventional RT-PCR method. With the invention of the RT-LAMP method, there is now no need for a thermal cycler apparatus for viral RNA amplification, and the viral RNA sequence can be amplified to a detectable level by incubation in an ordinary oven that provides a constant temperature. Steps have also been taken to enhance both the overall sensitivity of the test and allow the test to be carried out outside the laboratory setting. For instance, the sensitivity of the test has been improved by reducing the detection limit so that it will give positive results at a lower viral load in the sample. In the Penn-LAMP and DETECTOR techniques, the final result can be observed with the naked eye, and the need for the expensive spectrofluorimetric readout methods is eliminated.

Furthermore, a more reliable diagnosis can be achieved when the RT-PCR test and an immunodiagnostic test are applied together. It has been shown that the overall sensitivity is increased when these two test results are combined. Moreover, the sensitivity of the test can be improved over the course of the infection by combining both RT-PCR and serologic ELISA tests. The serologic monitoring of the patient's antibody response might give a picture of the disease progression and severity. However, the positive correlation of disease severity with antibody titer is uncertain, because confounding factors like the choice of the antigen and antibody can affect the results.

Taken together, the RT-PCR test is still the best choice for diagnosis of SARS-CoV-2 infection in patients; however, due to its above-mentioned drawbacks, the RT-PCR test should be used sensibly and

RT-PCR technical features should be improved.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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An official website of the United States government Here's how you know

CDC's Laboratory Outreach Communication System (LOCS)

07/21/2021: Lab Alert: Changes to CDC RT-PCR for SARS-CoV-2 Testing



Audience: Individuals Performing COVID-19 Testing

Level: Laboratory Alert

After December 31, 2021, CDC will withdraw the request to the U.S. Food and Drug Administration (FDA) for Emergency Use Authorization (EUA) of the CDC 2019-Novel Coronavirus (2019-nCoV) Real-Time RT-PCR Diagnostic Panel, the assay first introduced in February 2020 for detection of SARS-CoV-2 only. CDC is providing this advance notice for clinical laboratories to have adequate time to select and implement one of the many FDA-authorized alternatives.

Visit the FDA website for a list of authorized COVID-19 diagnostic methods. For a summary of the performance of FDA-authorized molecular methods with an FDA reference panel, visit this page.

eparation for this change, CDC recommends clinical laboratories and testing sites that have been using the CDC 2019-nCoV RT-PCR assay select and begin their transition to another FDA-authorized COVID-19 test. CDC encourages laboratories to consider adoption of a multiplexed method that can facilitate detection and differentiation of SARS-CoV-2 and influenza viruses. Such assays can facilitate continued testing for both influenza and SARS-CoV-2 and can save both time and resources as we head into influenza season. Laboratories and testing sites should validate and verify their selected assay within their facility before beginning clinical testing.

Opt in to receive updates from the CDC Laboratory Outreach Communication System (LOCS).

Online resources:

- FAQ: CDC Distribution of COVID-19 Assays
- Guidance for SARS-CoV-2 Point-of-Care Testing
- Interim Guidance for SARS-CoV-2 Antigen Testing
- Interim Guidelines for Collecting, Handling, and Testing Clinical Specimens for COVID-19
- equently Asked Questions about COVID-19 for Laboratories
- Information for Laboratories about COVID-19

- CDC COVID-19 Website
- Clinical Laboratory COVID-19 Response Weekly Calls
- CDC Laboratory Outreach Communication System (LOCS)

If you have any questions, please contact us at LOCS@cdc.gov.

Thank you,

The Laboratory Outreach Communication System

Laboratory Outreach Communication System (LOCS) | Division of Laboratory Systems (DLS)

Center for Surveillance, Epidemiology, and Laboratory Services (CSELS)

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MINISTRY OF HEALTH

Clinical Handbook

on the Prevention and Management of the BIG FIVE

Direct Causes of Maternal Morbidity & Mortality in Kenya



May 2023

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LIST OF ABBREVIATIONS

ABC	Airway, Breathing, Circulation
ACE	Angiotensin Converting Enzyme
ACLS	Advanced Cardiac Life Support
AFE	Amniotic Fluid Index
AMTSL	Active Management of Third Stage of Labour
APTT	Activated Partial Thromboplastin Time
ARB	Angiotensin Receptor Blocker
BEmONC	Basic Emergency Obstetric and Neonatal Care
BLS	Basic Life Support
CEmONC	Comprehensive Emergency Obstetric and Neonatal Care
CCT	Controlled Cord Traction
CHAI	Clinton Health Initiative
CS	Caesarean Section
CTG	Continuous Tocography
CPD	Cephalopelvic Disproportion
CPR	Cardiopulmonary Resuscitation
CRL	Crown Rump Length
DIC	Disseminated Intravascular Coagulopathy
DVT	Deep Venous Thrombosis
FIGO	International Federation of Gynaecology and Obstetrics
FHI	Family Health International
GA	Gestational Age
GBS	Group B Streptococcus
GTD	Gestational Trophoblastic Disease
HELLP	Haemolysis, Elevated Liver Enzymes, Low Platelet
HIV	Human Immunodeficiency Virus
IFAS	Iron and Folate Supplementation
INR	International Normalized Ratio

IPC	Infection Prevention and Control
IUGR	Intrauterine Foetal Restriction
KOGS	Kenya Obstetrical and Gynaecological Society
LMP	Last Menstrual Period
LSTM	Liverpool School of Tropical Medicine
MAK	Midwives Association of Kenya
MEOWS	Modified Early Warning Score
$MgSO_4$	Magnesium Sulphate
MOH	Ministry of Health
MPDSR	Maternal Perinatal Death Surveillance Response
MVA	Manual Vacuum Aspiration
NASG	Non-pneumatic Anti-shock Garment
NEWS	National Early Warning Score
NSAID	Non-Steroidal Anti-Inflammatory Drug
omSOFA	Obstetrically Modified Sequential Organ Failure Score
PAS	Placenta Accreta Syndrome
PCOS	Polycystic Ovarian Syndrome
PMCS	Perimortem Caesarean Section
POCs	Products of Conception
POCUS	Point of Care Ultrasound
PPH	Postpartum Haemorrhage
PRES	Posterior reversible Encephalopathy Syndrome
PROM	Premature Rupture of Membranes
RMHC-K	Reproductive and Maternal Health Consortium, Kenya
RHNK	Reproductive Health Network, Kenya
SOFA	Sequential Organ Failure Score
TVS	Transvaginal Scan
UON	University of Nairobi
USAID	United States Agency for International Development
WHO	World Health Organization

FOREWORD

As we endeavour to improve maternal health outcomes in Kenya, it is essential that healthcare providers have access to accurate and current information on the prevention and treatment of the leading causes of maternal mortality. According to the 2014 Kenya Demographic and Health Survey (KDHS), Maternal Mortality Rate (MMR) was 362 deaths for every 100,000 live births. The nation has not seen a major change in the patterns of maternal mortality despite developing policies, standards, recommendations, protocols, and algorithms addressing each main cause of maternal death and morbidity.

The Clinical Handbook on the Direct Causes of Maternal Mortality has been created as a resource for healthcare professionals in response to this problem. The five direct causes of maternal death—postpartum haemorrhage, severe preeclampsia and eclampsia, puerperal sepsis, obstructed labour, and unsafe abortion—are addressed in this handbook in a clear and useful manner. These cause the majority of maternal deaths in Kenya, and completely addressing them is vital for reaching the greatest standards of reproductive health, a basic human right guaranteed by the Kenyan Constitution of 2010.

Kenya's government is dedicated to preventing all maternal deaths. Maternal mortality reduction necessitates a thorough strategy integrating clinical teams at all levels of care. To keep up with the additional workload brought on by the provision of universal maternity care, efforts are being made to hire more health professionals, particularly nurses and midwives. The widespread application of this manual is a golden chance to raise the standard of maternal care and, eventually, to enhance the outcomes of pregnancies.

Best practices in the prevention and treatment of the major causes of maternal death are anticipated to be reinforced by this handbook. It is my hope that this handbook will be useful to medical professionals in their daily clinical work and that it will help bring about Kenya's long-overdue reversal of maternal mortality trends.

Every health professional, especially those working in maternal healthcare services, is urged to keep this handbook close at hand and refer to it frequently. The Ministry of Health remains committed to reducing maternal mortality and morbidity. Every life matters, and we can ensure that no woman dies while giving birth if we work together.

Dr. Patrick Amoth

Director General for Health.

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This Clinical Handbook on the Direct Causes of Maternal Mortality was created through a collaborative and participatory process with multi-disciplinary reproductive health partners. Experts from the Ministry of Health, counties, regulatory agencies, development partners, and other stakeholders were involved in the process.

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The Ministry thanks the Reproductive and Maternal Health Consortium, Kenya, the Reproductive Health Network, Kenya, and the Foreign, Commonwealth and Development Office of the United Kingdom for their logistical assistance.

Dr. Edward Serem

Head, Division of Reproductive and Maternal Health.

CHAPTER 1 EMERGENCY PREPAREDNESS AND RESPONSE IN OBSTETRICS

Definitions:

Preparedness/Readiness: the recognition of and response to public health emergencies involving many components of the health care delivery system, including guidelines, policy environment; system integration; implementation and service delivery; availability and coverage [1]. with lifesaving interventions extending at all levels of healthcare and addressing equity and social inclusivity.

Emergency risk communications (ERC) consist of "the real-time exchange of information, advice and opinions" between decision-makers, experts and the general public [2]. Emergency preparedness entails:

- enhancing the usefulness of training,
- improving timely emergency communications,
- creating and maintaining sustainable response systems, and
- generating effectiveness criteria and metrics

Preparedness/readiness forms a core component in public health related to natural calamities, humanitarian crises and emergent diseases such as Ebola, Zika, COVID-19, and Monkey Pox. Evolving trends to emergency preparedness/ readiness needs to include telemedicine, tele-consults, and self-care.

Important Elements for Emergency Preparedness/Readiness in Obstetrics

I. Coordination

Emergency preparedness may include a designated obstetric team (Rapid response team) that can be called upon in an emergency setting. Coordinated efficient interventions may require nurses or other direct clinical providers to step outside of their traditional comfort zone and embrace a shift in the patient care culture. The presence of a competent health workforce on matters of emergency frontline team members, such as the intake clerk or bedside nurse, should be empowered as a vital part of a purposeful team.

ii. Collaboration

Collaboration across departments and sectors is necessary for effective emergency preparedness. The implementation of audit programs and multidisciplinary collaboration with all staff members involved will optimize success.

iii. Evidence-based best practices

Protocols that include clinical triggers

Assessment of facilities reinforced by frequent emergency drills.

A schedule so that units regularly practice drills and become proficient at responding to emergencies.

iv. Health system strengthening

An analytical framework used by the World Health Organization (WHO) to describe health systems disaggregated them into 6 core components:

- Leadership and governance.
- Service delivery.

- Health system financing.
- Health workforce.
- Medical products, vaccines and technologies.
- Health information systems.

v. Emergency drills: by simulation and drills

Emergency drills allow team members to practice effective communication in crises. Periodic drills following designated protocols to manage emergencies improve a healthcare unit's ability to respond and mitigate an adverse health outcome.

These drills should mirror the existing clinical setting and resources.

By conducting a drill in the actual patient care settings, issues related to the physical environment may become obvious. Simulation training can identify and correct common clinical errors made during emergencies.

Leadership is important to actualizing the above.

vi. Crash (resuscitation) carts

These mobile units contain essential medications and equipment for the resuscitation of patients in emergency situations. They are recommended at any facility/unit dealing with patients with the potential for sudden deterioration during management, including obstetric care. Equipment and medications are placed in drawers in the crash cart based on how urgent they should be used in emergency setups. The defibrillator should be placed on the top shelf of the cart.



First drawer: Essential resuscitation medications. These medications are usually Displayed in a way that is easy to identify and administer to the patient quickly.

Second drawer: Intravenous fluids for hemodynamic support and equipment for intubation.

Third drawer: This compartment contains equipment for intravenous line insertion, phlebotomy and sample collection. These include intravenous cannulae of different gauge sizes, arterial lines, needles of different gauge sizes, and vacutainers of different colours (tops), depending on the investigations required.

Fourth drawer/ procedure drawer: Pre-packaged kits available for various urgent and emergency procedures are kept in this drawer.

Regular review of the emergency checklist at handover in the maternity unit.

Appropriate changes should be made to the crash cart as evidence-based changes are made to the Advanced Cardiac Life Support protocol, and all perishable supplies must be replenished.

vii. Essential Medical Equipment and Supplies

These Items - listed below - should be in place in both BEmONC and CEmONC facilities as appropriate:

IV Fluids	Drugs Used in Emergencies	Supplies and Equipment
Dextrose 10%	Oxygen and other medical gases	Oropharyngeal airway
	Magnesium sulphate	Bag and mask
Glucose (5%, 10%, 50%)	Oxytocin (5IU/ml)	Blood pressure machine
	Adrenaline	Stethoscopes (Maternal)
	Furosemide	Injection pad
Normal Saline	Aminophylline	Cannula G16, G18)
	Calcium Gluconate	Sterile water for injection
Ringer's lactate	Digoxin	Thermometer
	Calcium Gluconate	Oxygen Mask
	Diazepam	Fetoscope or Doppler
	Anti-hypertensive drugs (Methyldopa, Labetalol, Nifedipine/Hydralazine	Sterile gloves, examination gloves
	Heparin	Non-pneumatic anti-shock garment (NASG)
	Ergometrine, Carbetocin, Misoprostol	Foleys catheter and urine bag
		Oxygen tubing, nasal cannula
		Elbow gloves
		Blood giving sets
		Oxygen concentrator or cylinder maternal and neonatal)
		Baby warmer with firm, padded resuscitation surface
		Penguin sucker

Table 01: Essential equipment and supplies

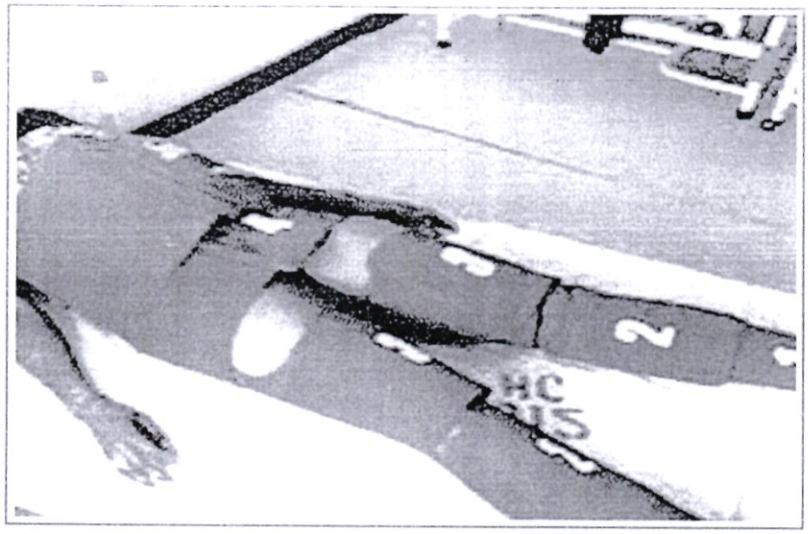


Figure 2: Non-pneumatic anti-shock garment

Others

- Blood and blood products
- Equipped and functional laboratory in support of the direct causes of maternal mortality
- Equipped and functional operating theatre
- An updated list of referral networks and standard referral guidelines [3]
- Reliable communication methods/tools, e.g. Cell phones
- Basic or advanced life support ambulance
- Basic data collection tools
- Infection prevention and control equipment and protocols

viii. Development of group norms (supportive work culture /Defined team member roles and responsibilities

- A multidisciplinary rapid response team should be in place.
- Responding to an emergency promptly and effectively requires that clinical team members know their roles and how the team should function.

For a prompt response to obstetric emergencies by the team, adequate preparedness and availability of the following is required:

- Conspicuously displayed emergency response plan
- Regularly conduct emergency medical drills.
- Effective referral system and facility follow-up of transfers.
- Accurate documentation and index case audit.

Team members must know:

- Clinical situations and their diagnoses and treatments.
- medicines, how they are used and administered and their side effects
- Emergency equipment and how it functions.
- Staff should be skilled in respectful maternity care
- The team should be proficient in effective communication.

The Rapid Response Team should have the knowledge and skills to apply the principles of Basic Life Support (BLS) and Advanced Cardiac Life Support (ACLS) Maternal Resuscitation - Refer to Maternal Collapse Chapter.

ix. Performance matrix, audits, accountability, and learning.

Data Tools that should be utilized to synthesize information are:

- Clinical audits,
- MPDSR, including near misses
- Near Miss,
- Perimortem CS
- Case fatality Rate

x. Breaking the Sad news of Maternal and Perinatal Deaths

The following is recommended in breaking abrupt Sad news upon maternal or perinatal death:

- Designate the team leader and assemble a disclosure team.
- Set a conducive private environment and provide adequate time.
- Check the completion of patient records at the case review.
- Identify the recipient of the news.
- Self-introduction by the team.
- Perform a quick emotional assessment of the recipient.
- Disclose the bad news narrating the events chronologically until death by:
  - Effective communication techniques.
  - Perform an emotional reassessment with validation of the recipient.
  - Offer empathy and reassurance.
  - Address concerns, questions, and feelings and provide continuous support.
  - Allow viewing or holding of the body if desired.
  - Address logistic administrative aspects.
- Engage workmates, friends or relatives with debriefing and closure with documentation.

xi. Managing patient complaints and grievances

- Design a process to capture and address all complaints and grievances.
- Implement policies, procedures and processes to investigate and resolve patient complaints and grievances.
- Respond promptly to patients' concerns to also help in preventing grievances.
- Listening to the patient's concerns about health care, allowing them reasonable, uninterrupted time to vent their concerns, and avoiding being defensive by responding calmly and personally can help.

xii. Patient-centred communication and feedback.

Communication skills needed for patient-centred care include eliciting the patient's agenda with open-ended questions early on, not interrupting and engaging in focused active listening. In addition, understanding the perspective of the situation of illness and expressing empathy are key features of patient-centred communication.

In emergency preparedness, the following considerations are important to avoid a siloed approach

1. A clinical system that embraces a multidisciplinary approach
2. Checklists for procedures outlines – e.g., theatre pre- operative → intraoperative → post-operative checklists
3. Protocols for managing the direct causes for of maternal mortality are clearly displayed at the health facility.

chapter 2 : POSTPARTUM HAEMORRHAGE (PPH)

Definition:

Postpartum haemorrhage (PPH) is excessive bleeding at any time from birth to 6 weeks after delivery. Bleeding is considered excessive when there is blood loss of 500 ml or more following a vaginal delivery or 1,000 ml following a Caesarean Section. Any blood loss that has the potential to cause hemodynamic instability is also considered to be PPH.

Classification:

PPH is classified according to when bleeding occurs following delivery:

1. Primary PPH - within 24 hours
2. Secondary PPH - occurs after 24 hours
3. Refractory PPH - when the bleeding is not controllable after the institution of first-line measures of PPH treatment.

Epidemiology:

Worldwide, PPH is the most common cause of maternal mortality at 25 %–□ In Kenya, 78% of maternal deaths are due to direct causes, 40% being contributed by postpartum haemorrhage □ Therefore, any woman is at risk of PPH.

Aetiology:

It may be helpful to think of the causes of PPH in terms of the four "T"s:

CAUSE	%	DEFINITION/EXAMPLES
TONE	70%	Failure of uterus to contract adequately
TRAUMA	20%	Ruptured uterus, cervical and vaginal tears
TISSUE	10%	Retained placenta, cotyledon, succenturiate lobe or Placenta Accreta Spectrum, membranes or blood clots
THROMBOPATHY	<1%	Pre-existing or acquired coagulopathy

Table 2□ Causes of PPH

More than one cause may be present, e.g., tone and tissue.

Risk Factors

Many women who have PPH have no identifiable risk factors. However, the following are recognized associated factors:

Antepartum	Intrapartum	Postpartum
• Maternal age above 35years, • Parity >3, • Prior uterine surgery, • Previous PPH, • Uterine fibroids, • Pre-eclampsia, • Anaemia, • Gestational diabetes, • Multiple pregnancy, • Polyhydramnios • Antepartum haemorrhage	• Induction of labour, • Prolonged 2nd stage, • Prolonged 3rd stage, • Retained placenta, • Instrumental vaginal birth, • Macrosomia, • General anaesthesia, • Genital tract injuries, • Infection after PROM or temperature above 38°C. • Caesarean section	• Subinvolution • Retained POCS • Sepsis

Some cultural/traditional factors may increase a patient's risk for PPH. For example:

- Use of traditional herbs/medications to manage labour
- Delay in seeking or refusal for treatment
- Refusal of blood transfusion
- Negative attitudes/perceptions/beliefs about health systems and health workers

Diagnosis

Diagnosis of postpartum haemorrhage is based on clinical symptoms and signs, and measurement of the amount of blood loss. Due to frequent underestimation of blood loss, PPH may first be detected through hemodynamic compromise, manifesting as maternal tachycardia and hypotension. Other than the quantity of blood loss, clinical signs and the shock index, in particular, are critical in obtaining a more accurate diagnosis of postpartum haemorrhage [4]. The shock index is obtained by dividing the heart rate by the systolic blood pressure '—[7].

Hemodynamic Status	Class I	Class II	Class III	Class IV
Shock	No shock (Compensation)	Mild shock	Moderate shock	Severe shock
Symptoms and Signs	Palpitations, Dizziness, Tachycardia	Weakness, Sweating, Tachycardia	Restlessness, Pallor, Oliguria	Collapse, Air hunger, Anuria
Blood Loss (ml)	500-1,000	1,000-1,500	1,500-2,000	2,000-3,000
Systolic BP	Normal	Slight decrease	Marked decrease	Profound decrease
SI at Admission	<0.6	≥0.6 to <1	≥1 to <1.4	≥1.4
Need of Blood Products	Observe	Consider use of blood products	Prepare transfusion	Prepare massive transfusion

Prevention of Postpartum Haemorrhage

PPH is the most common cause of maternal mortality. When it occurs, it can be fatal and thus health care providers must always anticipate it in all cases of delivery.

1. Service providers must always be current with knowledge and skills to prevent and manage PPH.
2. All units where PPH can occur must always be prepared to respond to PPH.
3. The protocol for the prevention of PPH must always be available, appropriately displayed and utilized.
4. Equipment, instruments, essential medicines, and non-pharmaceutical supplies necessary for the management of PPH must always be available.
5. Anaemia in the antenatal period must be prevented. Daily iron and folic acid supplementation with 30mg to 60mg of elemental iron and 400 ᴍg (0.4 mg) of folic acid started as soon as pregnancy is confirmed or at preconception if previous problems with folic acid deficiency have been encountered. Management of anaemia should be in reference to the National IFAS program/guidelines.
6. Active Management of the Third Stage of Labour (AMSTL): A guideline for AMSTL should always be available, appropriately displayed and utilized in the Delivery Room. The components of AMTSL are:
    - Administration of Oxytocin or another utcrotonic drug (Carbetocin, Misoprostol or Ergometrine) within 1 minute after birth, after ruling out multiple gestation.
    - Controlled cord traction (CCT): CCT on the umbilical cord and counter pressure on the uterus until delivery of the placenta.
    - Then uterine massage until contracted, then every 15 minutes for 2 hours by the provider or woman herself.
    - Empty bladder before 2nd stage and frequently after delivery.

7. 4th Stage Monitoring: Monitor the woman for 2 hours after delivery, then 4 hourly for 24 to 48 hours [8]. Important to monitor using the MEOWS Chart below.

MODIFIED EARLY OBSTETRIC WARNING SCORE							
Score	3	2	1	0	1	2	3
Respiratory rate (bpm)				9–18	19–25	26–30	>30
Pulse rate (bpm)		<40	40–50	51–100	101–110	111–129	>129
Temperature		<35	35-35.9	36-37.4	37.5-37.9	38.0-38.9	>39
Systolic blood pressure (mmHg)	<70	71–80	81–100	101–164	165–200	>200	
Diastolic blood pressure (mmHg)				<95	95–104	>105	
Conscious level	Unresponsive	Responds to pain	Responds to voice	Alert	Irritated		
Urine (ml/h) or in 24 h	0	<30 (<720 ml)	<45 (<1Lt)	>45 (>1000 ml)			

8. Blood transfusion services (blood and its products) must be available or accessible.
9. A functional referral system should be in place.
10. Public health PPH Prevention advocacy efforts through outreaches and community engagements should be ongoing.

Management of Postpartum Haemorrhage

Postpartum Haemorrhage Protocol should be in place that facilitates timely prevention, diagnosis and management of PPH.

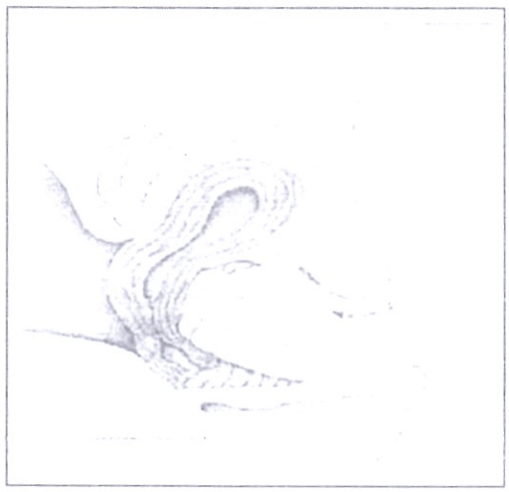
Management of PPH by Cause

1. Tone (Atonic Uterus):

This refers to the failure of the uterus to contract adequately for haemostasis. Any condition that interferes with uterine contractions will lead to an atonic uterus [9].

a) Catheterize to empty bladder to monitor kidney function by charting urine input/output.
b) Give Oxytocin/Misoprostol/Prostaglandin E2/Ergometrine/Tranexamic Acid Injections according to the Uterotonics Drugs Protocol for PPH management.

c) Bimanual uterine compression: after the delivery of the placenta, a fist with one hand is placed on the anterior vaginal fornix to apply pressure on the uterus anteriorly while the other hand is deep in the abdomen to apply pressure on the uterus posteriorly; pressure is maintained until the uterus contracts, bleeding controlled as other resuscitative measures are instituted.



d) Crossmatch and transfuse blood/blood products depending on the patient's hemodynamic status.

e) Aortic compression: temporary pressure occlusion of the aorta, to reduce blood flow to the uterus providing time to treat hypotension, identify the source of bleeding and undertake operative procedures. In young and otherwise healthy patients, pressure occlusion can be maintained for several minutes without permanent sequelae.



f) Uterine Balloon Tamponade: Condom Tamponade or the Free Flow System UBT, involves filling the uterine cavity with fluid to compress the blood vessels to stop bleeding. The catheter may be left for several hours to 2 days.



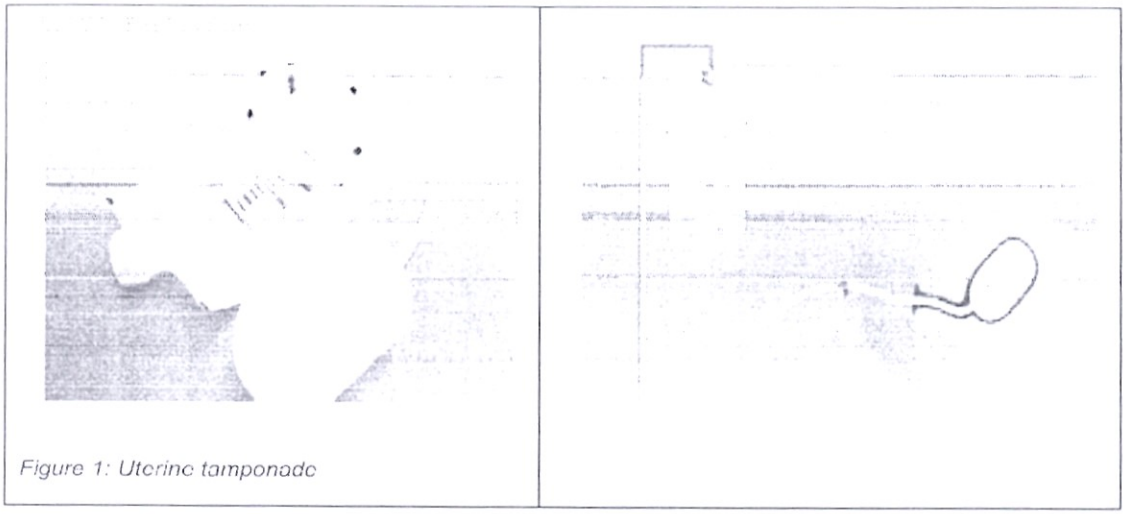


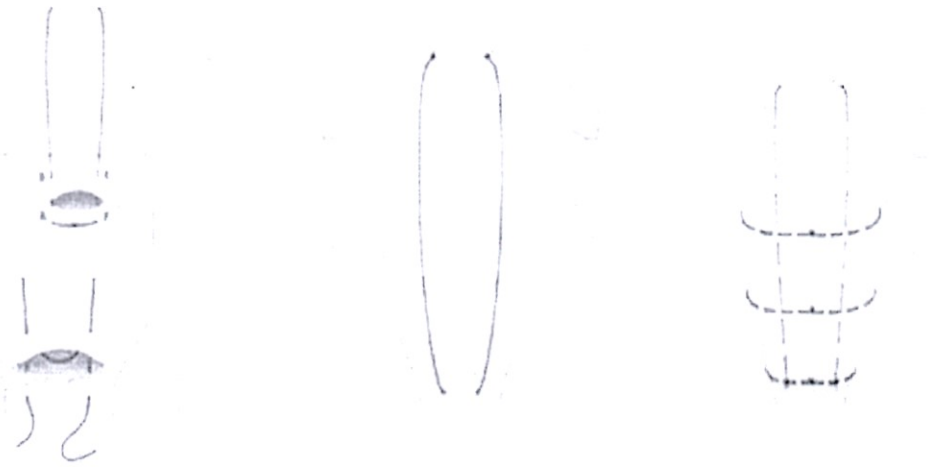
Figure 1: Uterine tamponade

g) Non-Pneumatic Anti-Shock Garment (NASG): a compression suit that limits persistent PPH by reducing blood volume in the lower extremities and increasing the blood volume to vital organs to treat hypovolemic shock. It is applied temporarily to sustain the stability of the patient's condition as she awaits theatre at the same facility or transportation to a higher level of care.



h) Laparotomy should be considered if non-invasive methods are not effective. At surgery, compression sutures can be applied to maintain uterine tone.

B-Lynch suture, Hayman suture, Pereira suture



2. Trauma

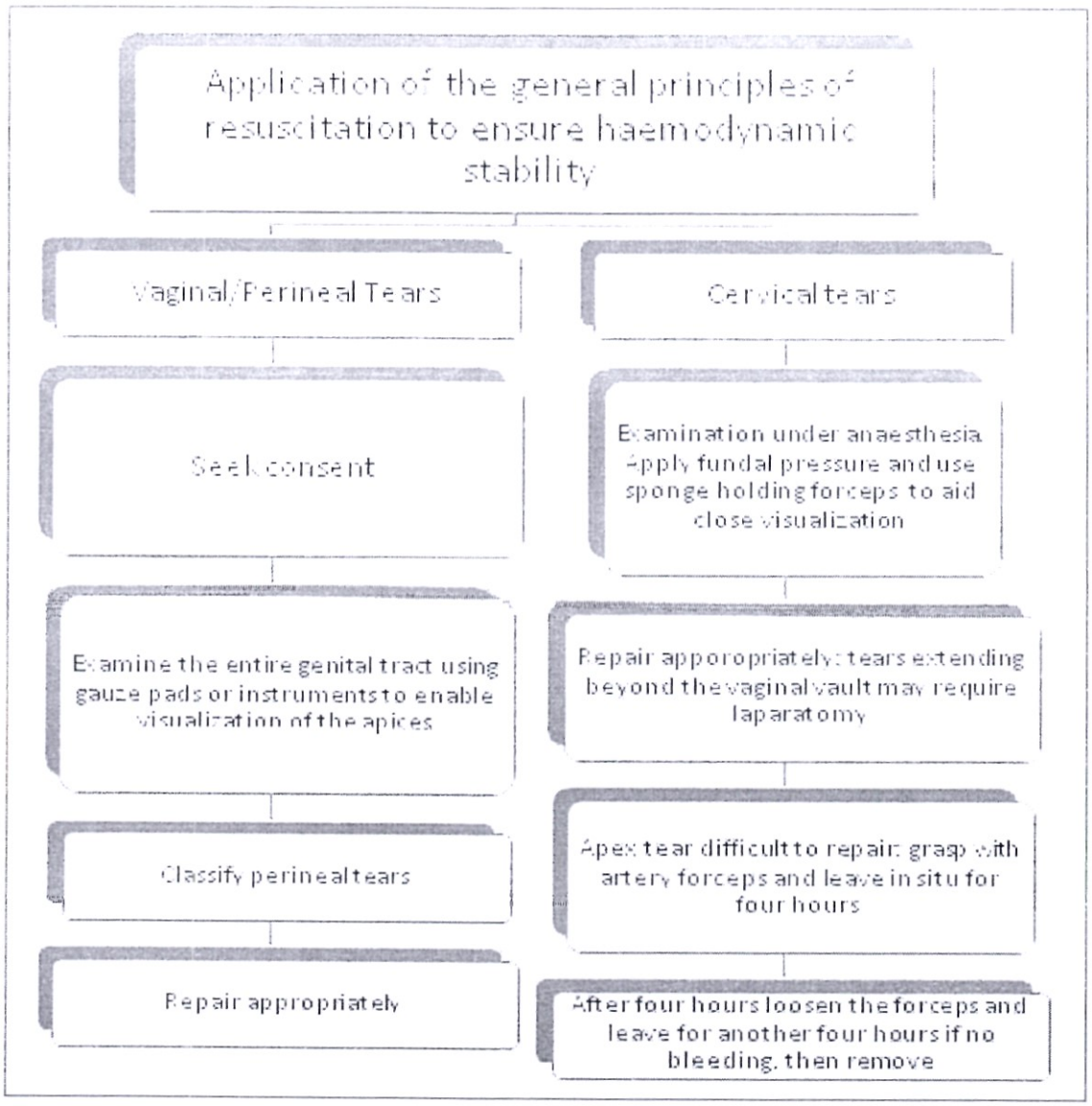
a: Cervical, vaginal, and perineal laceration, vulvar/pelvic secondary haematoma, uterine inversion and ruptured uterus:

a) Laparotomy is necessary for refractory PPH due to a ruptured uterus or excessive and uncontrolled bleeding. At laparotomy, consider:
   - Intermittent Compression of the aorta (as above)
   - Uterine haemostatic suture: B-lynch or COMOC-MG (Modified B-lynch) Stitch, Hayman Suture or Pereira Suture
   - Devascularization of the uterus.
   - Hysterectomy (subtotal/total hysterectomy)

b) For lacerations, repair depends on the depth of the tear(s), addressing haemostasis first.

c) Uterine inversion: stop uterotonics, placental detachment is done, and then the uterus is pushed cephalad, back (reduced) into position as crystalloids are infused.

The algorithm for the management of genital trauma following delivery is illustrated below.



3. **Tissue (Retained tissue/membranes, retained placenta, placenta accreta syndrome)**

   Retained Placenta or placental fragments result in PPH due to ineffective uterine contraction, therefore preventing closure of the exposed sinuses from other sites of placental attachment. The placenta may appear intact even with remaining products of conception, e.g. succenturiate lobe in the uterine cavity.

   Placenta Accreta Spectrum (PAS) or abnormal placentation (placenta accrete, increta and percreta) is a phenomenon where the placenta has grown too deeply into the uterine wall. It occurs in women at risk (with placenta previa, previous uterine surgeries or C/Section scars) and is diagnosed antenatally using Ultrasound Scan or MRI or clinically during delivery. It is treated by an early C/Section (at 34-37 weeks of gestation) and/or Caesarean Hysterectomy and is often accompanied with blood transfusion because of its high association with excessive bleeding.

4. **Thrombin: Coagulopathies (blood clotting disorders)**

APPROACH TO THE CARE FOR A PATIENT WITH RETAINED PRODUCTS AS A CAUSE OF PPH

Retained Products

- Application of general principles to ensure haemodynamic stability.
- Give a single dose of prophylactic antibiotics - ampicillin 2 g IV - OR cefazolin 1 g IV
- Administer tranexamic acid 1g (100mg/ml) 1 ml per minute over 10 minutes

Retained Placenta

- Empty bladder using self-retaining catheter
- Give additional 10 IU I of oxytocin.
- Apply controlled cord traction in a gentle fashion to avoid cord avulsion.
- If the placenta is still adherent , consider manual removal of the placenta.
- Examine the placenta for completeness
- Perform uterine exporation for any remaining fragments.
- Examine the Cervix, vagina and pemeal area for any tears.

Note: *If the placenta is still adherent despite the manual attempt at removal, consider laparatomy or a subtotal hysterectomy in extreme cases*

Retained Placenta Fragments

- Uterine exploration by hand
- Remove the fragments by hand, ovum forceps or wide curette.
- Examine the cervix, vagina and perineum for any tears and repair accordingly

Note: *For very adherent fragments, efforts at manual attempts may worsen bleeding or result in uterine perforation therefore laparatomy and hysterectomy may be indicated*

a) Coagulopathy

- Both cause and complicate massive obstetric haemorrhage, with Disseminated Intravascular Coagulation (DIC) being the most fatal.
- Thrombopathy can occur because of: abruptio placentae, foetal death in utero, amniotic fluid embolism, existing/inherited coagulation profile disorders and other causes.
- The clinical manifestations vary from massive haemorrhage with/without thrombolic complications to a clinical stable state.
- Thrombopathies may be detected through laboratory indices such as: Full haemogram with an interest in the platelet counts, International Normalized Ratio (INR), Activated Partial Thromboplastin Time (APTT), Evaluation of fibrinogen degradation products i.e., D-dimers.

b) **Management of thrombopathies**

- Use blood products to help control haemorrhage
- Give fresh whole blood to replace clotting factors and red cells. If fresh whole blood is not available, one of the following based on availability:
  - Packed (or sedimented) red cells for red cell replacement
  - Fresh frozen plasma for replacement of all clotting factors (15 mL/kg body weight)
  - Cryoprecipitate to replace fibrinogen and factor VIII in case of disseminated intravascular coagulation
  - Platelet concentrates (if bleeding continues and the platelet count is less than 20,000).

If the cause is known e.g. placenta abruption or eclampsia, aim to treat the cause.

Blood transfusion for patients meeting clinical criteria.

Complications of Postpartum Hemorrhage

a) **Early/ immediate PPH**

• Anaemia • Blood transfusion and reactions. • Dilutional coagulopathy • Fatigue	• Myocardial ischemia • Orthostatic hypotension • Adult respiratory distress syndrome.

b) **Late PPH**

- Anterior pituitary ischemia with delay or failure of lactation (i.e., Sheehan syndrome or postpartum pituitary necrosis) and/or secondary amenorrhoea
- Loss of fertility due to hysterectomy
- Death

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Chapter 3 HYPERTENSIVE DISEASE IN PREGNANCY

Definitions

Hypertension in pregnancy is a systolic blood pressure greater than or equal to 140 mmHg and/or diastolic blood pressure greater than or equal to 90 mmHg measured on 2 occasions and at least 4 hours apart.

Pre-eclampsia is a multi-system disorder of unknown aetiology characterized by elevated BP of 140/90 mm Hg or more either with proteinuria or with clinical or laboratory features of severity, with the onset after 20 weeks of gestation, in a previously normotensive and non-proteinuric woman.

Eclampsia is the occurrence of one or more generalized tonic-clonic seizures superimposed on pre-eclampsia. Seizures may occur antepartum, intrapartum, or postpartum, usually within 24 hours of delivery—[10].

Any convulsion in pregnancy must be treated as eclampsia until proven otherwise.

Risk Factors for Preeclampsia

• Extremes of age (maternal age <20 and >35 years) • Black race • Family history of preeclampsia • Nulliparity/primigravidae • Preeclampsia in a previous pregnancy • Change of male partner	• Diabetes • Obesity • Chronic hypertension • Renal disease • Collagen vascular disease • Antiphospholipid syndrome • Periodontal disease • Vitamin D deficiency • Inherited thrombophilias • Inter-pregnancy interval of >10 years
Pregnancy-related	
• Chromosomal abnormalities • Hydatidiform mole • Multiple pregnancy • In-vitro fertilisation, oocyte donation or donor insemination	

Prevention of Preeclampsia

Preventive interventions should be started before pregnancy, latest by 16 weeks gestation in women with risk factors.

Low-risk: women (no identified risk factor); Calcium supplementation has been shown to reduce the risk of development of preeclampsia in populations with low dietary calcium intake[11].

High-risk women with one or more risk factors are considered high risk for developing preeclampsia/eclampsia:

- history of preeclampsia/eclampsia (self or family members)
- chronic hypertension
- obesity and overweight
- chronic vascular or renal disease
- diabetes
- anaemia during pregnancy
- alcohol use

Preventive measures: Calcium 2 gm per day and Aspirin 150 mg daily commencing at 11–14 of gestation to be taken every night until either 36 weeks of gestation when delivery occurs, or when preeclampsia is diagnosed. Aspirin should be taken at bedtime[12].

Classification of pre-eclampsia

1. Preeclampsia without severe features
2. Preeclampsia with severe features

Preeclampsia with severe features: clinical features	
• Systolic BP >160mm Hg and diastolic BP >110mmHg • Persistent headache • Visual disturbances-scotomas/blurring of vision • Pulmonary oedema	• Right upper quadrant pain • Epigastric pain • Intrauterine growth restriction of the foetus • Oligohydramnios • Oliguria less than 500ml in 24 hours
Preeclampsia with severe features: laboratory results	
Lab investigation	Pointer of severe features
• Urinalysis HELLP syndrome	Proteinuria equal to or greater than 3gm per 24 hour urine collection or the equivalent in a test strip ≥2+. Proteinuria to creatinine ratio of ≥ 0.3mg
• Urea/Creatinine/Electrolytes	Serum creatinine >1.2mg/dl
• Total blood count	Thrombocytopenia less than 100,000/mm3
• Lactate Dehydrogenase	Lactate Dehydrogenase equal to or more than 600 IU
• Liver enzymes	Elevated serum transaminase levels more than twice the upper limit of normal (ALT, AST)

- HELLP syndrome describes a constellation of Haemolysis (anaemia with blood film evidence of haemolysis)
- Elevated Liver enzymes showing hepatic dysfunction (transaminases greater than twice the normal range)
- Low Platelets (platelet count of less than 100,000/dl)
- HELLP is associated with maternal mortality and severe morbidity including disseminated intravascular coagulopathy (DIC), liver hematoma, liver failure, and renal failure
- Cerebral haemorrhage
- Posterior reversible encephalopathy syndrome (PRES)
- Reversible Cerebral Vasoconstriction Syndrome
- Intrauterine growth restriction and foetal compromise
- Renal failure
- Placenta abruptio
- Pulmonary oedema
- Eclampsia

Foetal surveillance for women with preeclampsia

- Cardiotocograph (CTG) if >28 weeks gestation
- Ultrasound scan for assessment of:
  - Foetal growth
  - Amniotic fluid volume or deepest vertical pocket
  - Umbilical artery flow (Doppler)
  - Follow-up to assess foetal growth velocity

Management of Preeclampsia

Principles of Management of Preeclampsia
1. Prevent and treat convulsions 2. Blood pressure control 3. Fluid Management 4. Delivery

1. Prevention and treatment of convulsions

- Prophylactic treatment with Magnesium Sulphate is indicated for all patients with preeclampsia with severe features to prevent eclampsia.
- Airway, breathing, and circulation (the ABCs) during and after a convulsion
- Treat eclampsia with Magnesium Sulphate as a first-line agent
- Monitor for Magnesium Sulphate toxicity

Seizures refractory to Magnesium Sulphate therapy or with acute kidney injury: benzodiazepines e.g. Diazepam and/or Phenytoin may be considered.

Magnesium Sulphate: Administration and Monitoring

Signs of Magnesium Sulphate Toxicity

Combined intravenous (IV) and intramuscular (IM) regimen	Intravenous (IV) regimen
Loading dose - Total 14 gm **(IV 4 gm + IM 10 gm stat) given as follows** • 4 gm of 20% $MgSO_4$ IV bolus dose • Take a 20 mL syringe • Draw 4 gm of magnesium sulphate 50% (8 mL) • Add (dilute with) 12 mL sterile water or normal saline to the same syringe to make a 20% solution • Give this 4g $MgSO_4$ 20% solution IV over 5 – 20 minutes **NB: If IV 4g of 20% (100mls) is available, no need to dilute.** If unable to get IV access proceed with IM loading 10gms of 50% • Immediately followed by 10 gm of 50% MgSO4 IM (5 gm in each buttock) • Using two 20 mL syringes, draw 5 g of $MgSO_4$ 50% (10 ml) in EACH syringe • Add 1mL of 2% lignocaine to EACH of the two syringes. • Inject 1st syringe by deep IM injection into one buttock (5g $MgSO_4$) o Inject 2nd syringe by deep IM injection into the other buttock (5g $MgSO_4$) • If convulsions persists after 15 minutes: 2 gm of 20% $MgSO_4$ IV bolus over 5 minutes o Draw 2gms of 50% (4ml) + 6 mls of sterile water or normal saline **NB: this repeat dose should not affect the timing of the next maintenance dose**	Loading dose: 4gm as IV bolus dose o 20 mL syringe o 4 gm of magnesium sulphate 50% (8 mL) o Add (dilute with) 12 mL sterile water or normal saline to the same syringe to make a 20% solution o Give this 4g $MgSO_4$ 20% solution IV over 5 – 20 minutes **NB: If IV 4g of 20% (100mls) is available, no need to dilute** · If convulsion persists after 15 minutes: · 2 gm of 20 % MgSO4 IV bolus over 5 minutes o Take one 10 ml syringe o Draw 2gms of 50% IV (4mls) + 6 mls of sterile water or normal saline
Maintenance dose: Administer 4 hours after loading dose • 5 gm of 50% MgSO4 IM 4 hourly in alternate buttocks • Take one 10 ml syringe • Draw 5 gm (10mls) of 50% MgSO4 • Add 1 ml of 2% Lignocaine in each syringe • Give deep IM 4 hourly in alternate buttocks **Continue for 24 hours after the last convulsion or delivery whichever comes last**	**Maintenance dose** 1g/hour of 20% MgSO4 intravenous infusion up to 24 hours after the last convulsion or delivery whichever comes last.

MAGNESIUM SULPHATE TOXICITY: if any of these occur, withhold MgSo4		
Hourly respiration rate	≤ 16/minute	Respiratory depression
Patella reflexes	Absent	Muscle paresis
Urinary output	< 30 mL per hour over 4	Impaired renal function

Management of Magnesium Sulphate Toxicity

- If urine output < 30 ml/hour:
  - Withhold $MgSO_4$
  - IV Ringer's Lactate or Normal Saline infusion 1 litre over 8 hours
  - Monitor for pulmonary oedema
- If respiratory arrest occurs: Perform assisted ventilation
- The antidote of Magnesium Sulphate: Calcium Gluconate 1 gm (10% of 10 ml) IV slowly over 10 minutes.

Contraindications of Magnesium Sulphate

- Myasthenia gravis
- Impaired renal function

Other Benefits of Magnesium Sulphate

Magnesium sulphate is foetal neuroprotective. It prevents cerebral palsy following preterm birth.

2. Blood Pressure Control

- The goal is to lower the BP to prevent cerebrovascular and cardiac complications while maintaining uteroplacental blood flow.
- The goal is to maintain diastolic blood pressure at 100mmHg diastolic and between 140mmHg and 150mmHg systolic.
- First-line antihypertensives:
  - Labetalol 100mg BD, given orally or IV
  - IV Hydralazine 25 mg BD
- Second-line antihypertensives:
  - Methyldopa 250-500 mg orally
  - Nifedipine (slow release) 20 mg OD, given orally or IV
- Antihypertensives contraindicated in pregnancy are
  - Atenolol
  - Angiotensin-converting Enzyme (ACE) inhibitors e.g. Captopril and Enalapril
  - Angiotensin Receptor Blockers (ARBs) e.g. Candesartan and Losartan
  - Diuretics e.g. Aldactone, Hydrochlorothiazide and Lasix

Lasix should be avoided and only used for pulmonary oedema or any other justifiable indication.

Oral medication		
First-line		
Labetalol	100–400 mg	Initially: 100 mg BD Up to: 200 400 mg QID Daily Maximum: 2.4 gm
Hydralazine	25–50 mg	Initially:25 mg BD Up to 50–100 mg BD Daily Maximum: 200 mg
Nifedipine (immediate release)	10–20 mg	Initially:10–20 mg BD up to 40 mg BD Daily Maximum: 80 mg
Second-line		
Methyldopa	250–500 mg	Initially: 125–250 mg BD Up to 500 mg QID Daily Maximum: 2 g
Nifedipine (Slow Release)	20 mg	Initially. 20–30 mg daily Up to. 60–120 mg daily Maximum: 120 mg

3. Fluid Management

Despite peripheral oedema, patients with preeclampsia are intravascularly volume depleted with high peripheral vascular resistance. Therefore, diuretics should be avoided. Aggressive volume resuscitation may lead to pulmonary oedema. Pulmonary oedema occurs most frequently 48 - 72 hours postpartum (postpartum diuresis), probably due to the mobilization of extravascular fluid. Volume expansion has no demonstrated benefit. Patients should be fluid-restricted when possible, at least until the period of postpartum diuresis.

- Total fluids should generally be limited to 80mL/h or 1 mL/kg/h or 40 ml + the previous hour's urine output. Factor in the volume of IV drugs given.
- Careful measurement of fluid input and output is advisable, particularly in the immediate postpartum period. Many patients have a brief (6 hours) period of oliguria following delivery; this should be anticipated and not overcorrected.
- If fluids are required, preferably use Ringer's Lactate or Normal Saline at a rate of 80mls/ hour or 1ml/kg/hr. Avoid Dextrose or Dextrose- Saline infusion.

Delivery is the definitive treatment for antepartum preeclampsia and eclampsia.

Indications for delivery at any gestation

- Non-Reassuring Foetal Status
- Severe foetal growth restriction
- Gestational age>/=37 weeks
- Eclampsia
- Placental abruption
- Acute pulmonary oedema
- Deteriorating platelet count
- Persistent neurological symptoms
- Persistent epigastric pain
- IUFD
- HELLP Syndrome

Guidance on delivery based on severity

- Pre*ecl*ampsia
  - Delivery after 37 weeks gestation
  - Steroid foetal lung maturity (28-34 weeks)
- Severe preeclampsia
  - Delivery should be considered at 34 weeks' gestation
  - Steroids for foetal lung maturity
  - The severity of disease must be weighed against the risks of prematurity
- Eclampsia
  - Aim to deliver within 12 hours.
  - Vaginal delivery is indicated unless there is an indication for Caesarean section. Consider the progress of labour if the patient is in labour and Bishop's score before deciding for or against vaginal delivery.

Preeclampsia with severe features and eclampsia at 28 to 34 weeks

- If the foetus is less than 34 weeks of gestation and delivery can be deferred.
- Corticosteroids should be given, although after 24 hours the benefits of conservative management should be reassessed.
- Magnesium Sulphate should be given both for severe preeclampsia and neuroprotection.
- Conservative management at very early gestations may improve the perinatal outcome but must be carefully balanced with maternal well-being.
- The mode of delivery should be determined after considering the presentation of the foetus and the foetal condition, together with the likelihood of success of induction of labour after assessment of the cervix.

Postnatal Care

- There is a risk of seizures in the postpartum period especially the first 48 hours, but they can occur at any time up to 4 weeks after childbirth.
- Women who have received treatment for severe pre-eclampsia should be monitored in the hospital until at least the 3rd postnatal day and have 4 hourly blood pressure measurements.
- It is important to anticipate the need for antihypertensives in order to avoid delaying discharge and prevent severe hypertension. Prescribe oral antihypertensives to begin if BP > 150/100 on two occasions 30 minutes apart.
- Beta blockers (eg. Atenolol, Labetalol), alpha-adrenergic blockers (eg. Doxazosin), angiotensin converting enzyme (ACE) inhibitors (Enalapril, Captopril) and calcium antagonists (eg.

Nifedipine, Amlodipine) are all safe to use in a woman who is breastfeeding.

- Methyldopa should be discontinued postnatally due to the risk of postpartum depression.
- After days 3-4 women may be discharged when asymptomatic, provided the haematology and biochemistry results are normal or improving, and the blood pressure is <150/100 mmHg.
- Those on treatment should have a follow-up return date after 2 weeks or urgently at any time with the development of any danger signs.

Thresholds for reducing or stopping treatment: BP 130/80 mmHg reduce treatment, <120/70 mmHg stop treatment).

Measure BP every 1–2 days for up to 2 weeks after discharge, until antihypertensive treatment is stopped and there is no hypertension.

- After pre-eclampsia, blood pressure can take up to 3 months to return to normal. During this time, blood pressure should not be allowed to exceed 160/110 mmHg.
- All patients with severe pre-eclampsia who remain hypertensive or proteinuria □2+ should be referred for a clinic appointment 6-8 weeks post-delivery.
- Blood pressure and proteinuria assessment should be carried out at this appointment and an appropriate referral made if antihypertensive treatment is still required and/or significant proteinuria is confirmed.
- Postnatal review should include full debriefing of the events surrounding delivery, a review of ongoing antihypertensive treatment, contraception and any further investigations or medical referral which may be necessary.

Preconceptual counselling should be available for patients who had:

- Severe early onset of pre-eclampsia (<34 weeks)
- HELLP Syndrome
- IUGR
- Persistent hypertension requiring antihypertensives or > 1+ proteinuria 6-8 weeks postnatally[12].

Stabilization for Referral

When the woman requires delivery, transfer for foetal reasons is often considered. However, ex-utero transfer may be more appropriate. Minimum requirements before transfer:

- When the woman is ventilated, it is important to ensure ventilatory requirements are stable and oxygen saturations are being maintained.
- Blood pressure stabilised at <160/110 mmHg.
- Appropriate personnel are available for transport: a midwife, and an anaesthetist if the woman is ventilated.
- All basic investigations should have been performed and the results clearly recorded in the accompanying notes or telephone through.
- Foetal well-being has been assessed to be certain that transfer is in the foetal interest before delivery. Steroids should be given if the woman is pre term.
- Transfer has been discussed with appropriate specialist medical staff and all the relevant

people at the receiving unit e.g. the neonatal unit and neonatal medical staff, the resident obstetrician, the midwife in charge of delivery suite, intensive care unit and the intensive care anaesthetist (where appropriate).

Follow up

1. Patients with severe preeclampsia or eclampsia will need review and some de-briefing after delivery.
3. If the patient has a prolonged illness after delivery or has had any atypical symptoms, then she should be discussed with her consultant to decide if follow up or onward referral is needed.
4. If a woman had proteinuria throughout the antenatal period, then follow up should be arranged for about 6 weeks postpartum to ensure that renal function and blood pressure have resolved and there is no evidence of underlying renal disease.

Patient Education

Educate clients on:

- Completing prescribed medication and not to share medication
- When to come back to the health facility
  - if they develop: severe headaches, blurred vision or loss of vision, seizures, lower limb oedema
  - attending follow-up postnatal clinic and postpartum family planning and contraception services.

Chapter 4: PUERPERAL SEPSIS

(Childbirth Fever, Peripartum Sepsis)

Definition

Maternal sepsis is a life-threatening condition defined as organ dysfunction resulting from infection during pregnancy, childbirth, post-abortion, or post-partum period. Sepsis includes three essential components: infection, host response to infection and organ dysfunction. If not recognized early and treated in a timely manner, sepsis can progress to shock and death [13], [14].

The lack of institutional protocols and uncertainties about the antibiotic regimen of choice and correct timing of administration are critical areas that need to be addressed with antibiotic stewardship to avoid antimicrobial resistance.

Prevention

The following measures contribute to the prevention of puerperal sepsis.

1. Infection Prevention and Control (IPC) practices include hand hygiene, gloving, gowning, instruments decontamination and sterilization, and proper medical waste management.
2. Prophylaxis with obstetric procedures such as: C/S and assisted vaginal delivery.
3. Prevention of communicable diseases such as malaria, HIV.
4. Administration of tetanus toxoid.
5. Skilled birth attendance.
6. Recognition of sepsis post-abortion and in the puerperium
7. Appropriate management of sepsis

Risk Factors

Patient Factors

- Pre-existing conditions like Malnutrition, diabetes, obesity.
- Chronic renal disease, chronic hepatic disease, congestive heart failure, HIV.
- Diseases and infections including Renal or hepatic diseases, congestive heart failure, STI's/HIV, Vaginitis (purulent/aerobic), Severe anaemia and bacterial vaginosis.
- Multiple pregnancy
- Genetic background of the host

Intervention or Hospital Factors

- Retained placenta and Manual removal of the placenta
- Group B Streptococcus
- Assisted Reproductive Technology.
- Cervical cerclage
- Peripartum hysterectomy
- Blood transfusion
- Post abortion sepsis
- Caesarean section emergency and elective procedures compared to vaginal delivery.
- Multiple vaginal examinations

Group B Streptococus

Group B streptococcus is a gram-positive coccus that frequently colonizes the human genital and gastrointestinal tracts, and less frequently, the upper respiratory tract of children and adults. It is an important cause of illness in neonates, young infants, pregnant females, and adults with underlying medical conditions.

In pregnant and postpartum females, GBS is a frequent cause of asymptomatic bacteriuria, urinary tract infection, upper genital tract infection (i.e., intra-amniotic infection or chorioamnionitis), post-caesarean wound infection, postpartum endometritis, pneumonia, puerperal sepsis, and bacteraemia without a focus.

GBS accounts for 1 to 5 percent of UTIs during pregnancy and 5 to 10 percent of peripartum bacteraemia. It also can cause focal infection such as meningitis and endocarditis, albeit rarely. The serotype distribution of invasive GBS infection in pregnant females is similar to that of early-onset neonatal disease. GBS infection acquired from the colonized birth canal during labor or after membrane rupture can lead to miscarriage, stillbirth, prematurity or invasive neonatal disease.

Clinical Evaluation for Puerperal Sepsis

History and physical examination are essential in diagnosing sepsis.

History	Physical Examination
• Fever Chills and general malaise • Lower abdominal or perineal pain • Vomiting • Headache • Tender uterus • Sub- involution of the uterus • Purulent foul-smelling lochia loss • Evidence of mastitis, breast abscess, Infected Caesarean would or perineal wound • Signs of septic shock • Oedema, bloating or abdominal distension.	1. Temperature 38^{0}C 2. Vital signs (MEOWS Chart) 3. Examination for anaemia 4. Breast inspection and palpation 5. Respiratory system: tachypnoea, coarse crepitation, pleural effusion, 6. Cardiovascular system: Tachycardia, CCF, arrhythmias, heart murmurs, cardiomyopathy 7. Abdominal examination: sub-involution of uterus, tenderness, state of wound site, paralytic ileus 8. Perform bimanual examination – tears, laceration, lochia loss pattern and offensiveness. 9. Evidence of DVT

Laboratory Investigations for Puerperal Sepsis

Laboratory investigations are an integral part of recognizing and managing the source of sepsis appropriately

Investigations and reference ranges for puerperal sepsis are represented in the table below.

Investigation [33, 84 86]	Results in non-obstetric sepsis [33, 84 86]	Obstetric reference range (if relevant) [24]
Blood cultures – At least 2 sets, prior to antibiotic commencement as long as there is no delay. – Obtain samples from different sites – Cultures should also be obtained from IV access devices	May be positive for organism	
Other Cultures – Obtain cultures of additional sites as clinically indicated and as soon as possible Eg. urine MCS wound swab - episiotomy, caesarean placental swabs amniotic fluid sputum MCS naso-pharyngeal aspirate/swab cerebrospinal fluid vaginal swabs stool culture	May be positive for organism	
Arterial blood gases –detect acidosis, hypoxaemia, lactate as below		PaO_2 : 1st trimester: 93-100 mmHg 2nd trimester: 90-98mmHg 3rd trimester: 92-107mmHg $PaCO_2$: 25-33mmHg. Arterial pH: 7.4-7.47 HCO3 16-22mmol/L
Lactate - elevated levels in sepsis relate to tissue hypoperfusion and are associated with an increased sepsis mortality risk	≥ 2mmol/L associated with increased mortality	0.6-1.8 mmol/L
Full blood count	WCC >12 X10 9/L or <4 x10^9 /L Normal WCC count with > 10 % immature forms Thrombocytopenia is a severe sign of sepsis (Platelet count <100x10^9/L indicates organ dysfunction)	WCC 6-17 X 10^9 /L WCC in hours post-delivery between 9-15 X 10^9 (steroids also increase WCC) Platelets – lower limit of normal 150-420 x10^9/L

a) **The NEWS Scoring system:** National Early Warning Score systems that alert deteriorating adult patients in the hospital [15].

Physiological parameter	Score 3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–9'	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101 110	111 219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

- ***Low risk (aggregate score 1 to 4)*** – prompt assessment by ward nurse to decide on change to the frequency of monitoring or escalation of clinical care.
- ***Low to medium risk (score of 3 in any single parameter)*** – urgent review by ward-based doctor to determine the cause and to decide on change to the frequency of monitoring or escalation of clinical care.
- ***Medium risk (aggregate score 5 to 6)*** – urgent review by ward-based doctor or acute team nurse to decide on escalation to the critical care team.
- *High risk (aggregate score of 7 or over)* – emergency assessment by the critical care team, usually leading to patient transfer to higher-dependency care area.

Note: The recommendation for a NEWS 2 aggregate score of 0 (that is, no change to any parameter) is a minimum 12-hourly review and to continue routine monitoring.

Sepsis should be considered in any patient with a score equal to or greater than 5 in the presence of a known infection, symptoms and signs.

b) Sequential organ failure assessment (SOFA) score (omqSOFA) [16]

Assign 1 point for any of the following. A score >1 should prompt the clinician to consider sepsis and conduct further evaluation

- Systolic BP <90 mmHg
- Respiratory rate ≥25/min
- Mental status other than alert

c) The Obstetrical modified sequential score (omSOFA) [17]

System parameter	Score 0	1	2
Respiration: PaO_2/F_iO_2	≥400	300–<400	<300
Coagulation: platelets ($\times 10^3/\mu L$)	≥150	100–150	<100
Liver: bilirubin (μmol/L)	≤20	20–32	>32
Cardiovascular: MAP (mmHg)	≥70	<70	Vasopressors required
CNS	Alert	Rousable to voice	Rousable to pain
Renal: creatinine (μmol/L)	≤90	90–120	>120

Supportive management Of Puerperal Sepsis [18] . Golden hour – care bundles

- Obtain the blood cultures before administration of antibiotics.
- Administer broad spectrum antibiotics via parenteral route within one hour.
- Where a source of sepsis is localized refine antibiotic prescription based on microscopy, culture and sensitivity.
- Commence thromboprophylaxis.
- Commence resuscitation to stabilize the mother.
- Measure lactate level. Remeasure if initial lactate >2mmol/l.
- Begin rapid administration of crystalloids (30mls /Kg) for either hypotension or lactate =/>4mmol/l.
- Start vasopressors if the patient is hypotensive during or after fluid resuscitation, to maintain MAP =/>65mmHg.

Treatment of sepsis with an unknown source / Chorioamnionitis

Community-acquired sepsis

- Cefuroxime 1.5g IV every 8 hours or IV Ciprofloxacin or Levofloxacin
- Gentamicin 4-7mg/kg (1st dose) (80mg TDS)
- Metronidazole 500mg IV every 8 hours

If allergic to penicillin

- Clindamycin 600mg IV every 8 hours PLUS
- Gentamicin 4-7mg/kg (1st dose) IV (80mg TDS)
- Metronidazole 500mg IV every 8 hours

Hospital-acquired sepsis (Do an antibiotic sensitivity test)

- Piperacillin 4g + tazobactam 0.5g IV every 8 hours or Vancomycin 25-30mg/kg (Loading dose) IV
- Cefuroxime 1.5g IV every 8 hours
- Gentamicin 4-7mg/kg (1st dose) IV (80mg TDS)
- Metronidazole 500mg IV every 12 hours

Special Considerations

- Allergy to penicillin: Ciprofloxacin 400mg IV every 8 hours
- At risk of MRSA, add: Vancomycin 25-30mg/kg (Loading dose) IV
- At risk of GAS, add:

o Clindamycin 600mg IV every 8 hours

o Intravenous immunoglobulin (IVIG) 1-2g/kg up to 2 doses (IVIG is recommended for severe invasive streptococcal or staphylococcal infection if other therapies have failed).

Timing and mode of delivery in antepartum maternal sepsis

The timing of delivery will be determined by:

- The presence of intrauterine infection
- The nature of the maternal sepsis and response to initial resuscitation efforts
- The gestation of the pregnancy and fetal status

In case of intrauterine infection, an immediate caeserean delivery is indicated.

If there is extra uterine infection, efforts to treat maternal sepsis and prolong gestation should be considered at gestations remote from term, although it is reasonable to consider delivery in term pregnancies as a means of improving maternal resuscitation.

Fetal wellbeing should be monitored during maternal sepsis with the most gestation-appropriate method.

Complications of Puerperal Sepsis

Complications require critical care unit/referral to a tertiary facility:

Maternal:

a) Septic shock with multiple organ failure
b) Adult respiratory distress syndrome
c) Haemolysis
d) Enhanced infection spread and dissemination of the infection.
e) Disseminated intravascular coagulopathy (DIC)
f) Infertility
g) Chronic Pelvic Pain

Neonatal:

a) Prematurity,
b) Birth asphyxia,
c) Neonatal septicaemia

Chapter 5 OBSTRUCTED LABOUR

Definition

Obstructed labour, also known as labour dystocia, is the arrest of vaginal delivery of the foetus due to mechanical obstruction.

Risk Factors

i) Women of short stature, especially due to malnutrition
ii) Pelvic deformities secondary to osteomalacia, polio or fractures due to trauma
iii) Childhood pregnancy
iv) Underage marriage
v) Female genital mutilation
vi) History of obstructed labour, stillbirth or neonatal deaths
vii) History of caesarean section due to CPD or cervical dystocia or prolonged labour
viii) History of foetal macrosomia
ix) Delay in decision-making to seek care due to factors such as community decision-making processes, or distrust of health care personnel
x) Delays in accessing skilled care due to long distances, lack of transport and communication
xi) Traditional beliefs and practices regarding prolonged/obstructed labour
xii) Inadequately trained staff to recognize obstructed labour /Poor use of labour monitoring tools such as partograph.
xiii) Failure to act on risk factors
xiv) Delay in referral to a higher level of care

Prevention

At all stages of care, from preconception, through antenatal care and during labour and delivery, health care providers should look out for and identify patients at risk of obstructed labour, in order to plan for appropriate delivery:

A. **Community strategy:** preventive measures at community level are necessary to prevent risk factors, primary and secondary delays in access to care. These include:

i) Prevention of malnutrition
ii) Ensuring 100% immunization coverage
iii) CHV involvement in community education and mobilization
iv) Prevention of harmful cultural practices
v) Prevention of sexual and gender-based violence
vi) Prevention of adolescent pregnancies

B. **Preconception care:** identify women at risk of obstructed labour and counsel appropriately for Caesarean delivery early enough. These include:

i) Markedly short stature
ii) Pelvic deformities

C. **Antenatal care:** identify women whose previous obstetric history involved obstructed labour and plan accordingly:

i) History of obstructed labour, especially when coupled with stillbirth or neonatal death.

ii) History of caesarean section due to CPD, foetal macrosomia, cervical dystocia, or prolonged labour

iii) Women who have had corrective surgery for obstetric fistula

iv) Followed up in the obstetric specialist or high-risk clinic

v) Ultrasound/ Point of care ultrasound (POCUS) to estimate foetal weight

D. **Intrapartum care:** close monitoring of labour:

i) Correct diagnosis of labour

ii) Correct use of labour monitoring tools such as the partograph to prevent delays in intervention.

Diagnosis

A. **History**

i) Maternal age, parity, gravidity

ii) History of previous operative delivery

iii) History of previous still birth

iv) Duration of previous labour and outcome

v) Duration of current labour

vi) Duration of ruptured membranes

vii) History of analgesia use

B. Physical Examination

General examination

- Signs of physical and mental exhaustion.
- Signs of dehydration.
- Acetone breath due to ketoacidosis.
- Fever
- Signs of shock - rapid pulse, anuria or oliguria, cold extremities, pale complexion, low blood pressure.

N.B: Shock may be due to a ruptured uterus or sepsis.

Abdominal examination

- The presenting part may be palpable above the pelvic brim.
- There may be frequent and strong uterine contractions.
- Tetanic contractions uterus tightly moulded around the foetus.
- The border of upper and lower uterine segments becomes visible and/or palpable during a contraction: Bandl's ring seen as a depression across the abdomen at the level of the umbilicus.
- The uterus may stop contracting, indicating the possibility of a ruptured uterus
- The foetal parts may be easily palpable under the skin with uterine rupture.

Vaginal examination

- Oedema of the vulva.
- Foul-smelling meconium-stained liquor
- Absence of amniotic fluid
- Concentrated or blood-stained urine
- Hot and dry vagina
- Oedema of the cervix.
- Large caput succedaneum
- Severe moulding of the foetal head
- May have malpresentation such as shoulder presentation or prolapsed arm.

C. Partograph findings

a) Foetal heart rate of more than 170/minute or less than 110/minute indicating foetal distress
b) Foul-smelling or blood-stained liquor
c) Severe moulding of the foetal skull
d) The rate of cervical dilatation is slow or remains static in spite of adequate contractions
e) Maternal tachycardia
f) Maternal fever
g) Scanty urine with ketonuria

Management

A. Resuscitation

i. Oxygenation and management of acidosis: Administer oxygen by mask

ii. Rehydrate the patient: put up an intravenous infusion using a large bore cannula to maintain normal plasma volume, Ringers Lactate is preferable.

iii. Insert an indwelling urinary catheter using aseptic technique and monitor urine output and check for urinary ketosis.

iv. Administer broad-spectrum intravenous antibiotics intravenously; use first-line antibiotic regimen

v. Where possible, perform baseline blood gas analysis

vi. Foetal monitoring

B. Delivery of the baby

i) Cephalo-pelvic disproportion (CPD):

a. For a live foetus: emergency caesarean section.

b. If the foetus is dead: aim for embryotomy where possible. If this is not possible, defer to emergency caesarean section.

ii) Obstruction:

a. If the foetus is alive:

- Cervix fully dilated, and the head is at 0 station or below, deliver by assisted vacuum delivery.
- Cervix fully dilated with evidence of spontaneous symphysiotomy, deliver by assisted vacuum delivery.
- Cervix is not fully dilated, and the head is high, deliver by emergency Caesarean section.

b. Foetal demise: Deliver by embryotomy where applicable and competence is available. If not possible, deliver by Caesarean section.

C. Surgical interventions: Destructive obstetric procedures (embryotomy)

i) Destructive obstetric procedures for delivery (embryotomy) may be used to deliver the foetus where the foetus is no longer alive or in case of gross congenital abnormalities that are incompatible with life such as anencephaly

ii) Should be performed by a competent medical practitioner

iii) Maternal screening for suitability should be done, to exclude:

a. Extreme degree of contracted pelvis: true conjugate < 5.5 cm.

b. Partially dilated cervix.

c. Rupture or impending rupture of the uterus.

d. Obstructing pelvic tumours.

e. Cancer of the cervix with pregnancy

iv) Ensure informed consent from the patient

v) Ensure appropriate pre-operative anaesthetic review

vi) Ensure the appropriate equipment is available

vii) Procedure is performed in the operating theatre with the patient under general anaesthesia

viii) Bladder emptying

ix) May include craniotomy, decapitation, cleidotomy, evisceration or spondylotomy depending on the diagnosis

x) Complications to anticipate include:

   a. Uterine rupture

   b. Injuries to the genitourinary tract

xi) Retention of the indwelling urinary catheter to prevent fistula for at least 10 days.

xii) Post-operative care plan: antibiotics, analgesics, thromboprophylaxis, IV fluids, haematinic supplementation, consider family planning and early mobilization

xiii) Documentation

xiv) Debrief patient and psychological care and follow up

D. Surgical interventions: emergency Caesarean section

i) Ensure informed consent

ii) Appropriate pre-operative anaesthetic evaluation

iii) Bladder emptying

iv) Use of a classical, a J- or a U- incision should be applied in the case of presentation such as transverse lie with the foetal back inferiorly, a difficult breech or interlocking twins or congenital malformations such as anencephaly or large hydrocephalus.

v) Delivery of the placenta by controlled cord traction (CCT).

vi) Anticipate uterine tears, difficulty in achieving uterine haemostasis and uterine atony, hence PPH protocol to be in place intraoperatively

vii) Ensure appropriate competence for operative procedures such as compression sutures, B-Lynch procedures, uterine artery ligation, internal iliac artery ligation, and subtotal hysterectomy

viii) Use of non-braided sutures for closure, consideration of the use of Bogota bags and vacuum-assisted closures are necessary in the face of severe sepsis.

ix) Retention of the indwelling urinary catheter for at least 10 days to prevent fistula.

x) Post-operative care plan: choice of antibiotics, analgesics, IV fluids, and thromboprophylaxis. Further specialized care with regard to arising complications such as postpartum haemorrhage, genital tract trauma, sepsis and septic shock need for critical care post-operatively.

xi) Documentation of the procedures

xii) Debrief the patient

1. **Referral**

Patients who cannot be managed fully in the index health facility should be referred to an appropriate facility immediately. The referral procedure:

i. Perform resuscitation as above

ii. Insert a urinary catheter

iii. Collect blood samples for basic workup and preoperative management, label and ensure they accompany the patient: FBC, UECs, GXM, blood and swab cultures where necessary and possible

iv. Explain the reasons for referral and dangers of obstructed labour to the patient and the relatives

v. Write a detailed referral note including diagnosis and what has been done at referring facility. Include a copy of the partograph.

vi. Inform the receiving facility about the referral and refer immediately to a hospital with comprehensive obstetric care.

vii. A healthcare provider must continue to monitor the maternal and foetal condition in transit, ensuring the continuation of IV fluids and oxygen.

2. **Follow-up**

i) Management of complications arising out of the obstruction, such as uterine rupture, genital tract injury, post-partum haemorrhage, sepsis, anaemia, and obstetric fistula

ii) Ensure adequate patient education about the condition, treatment instituted, outcomes of the treatment, arising complications, post-discharge care and follow-up, and future pregnancy, including contraception care and delivery care

iii) Counselling and support to address peripartum foetal loss, complications, and post-partum depression where necessary

iv) Address lactation issues; support breastfeeding or suppress lactation

Chapter 6 EARLY PREGNANCY COMPLICATIONS

Definition

Early pregnancy complications occur during the first 28 weeks of pregnancy, at a time when the foetus is nonviable.

The risk factors include:

1. Blighted ovum: A blighted ovum, also called an anembryonic pregnancy, occurs when an early embryo never develops or stops developing, is resorbed and leaves an empty gestational sac. The reason is often unknown, but it may be due to chromosomal abnormalities in the fertilised egg.
2. Missed abortion is the unrecognised intrauterine death of the embryo or foetus without expulsion of the products of conception.
3. Intrauterine Foetal Death: when there is a foetal demise in utero.
4. Miscarriage -This is a spontaneous loss of a foetus before it can survive independently outside the uterus. It encompasses threatened abortion, inevitable abortion, and incomplete abortion - products of conception retained in the uterus after a miscarriage - and complete abortion.
5. Gestational Trophoblastic Disease (GTD) is a group of rare diseases in which abnormal trophoblast cells grow in the uterus after conception.

The commonest form is Hydatidiform mole. It is mostly benign but it may spread to nearby tissues (invasive mole). It may also become a malignant tumour, choriocarcinoma.

6. Any other medical condition that can risk the health or life of the pregnant woman.
7. Foetal anomalies incompatible with life.

Art 26(4) Constitution

Causes

- Genetic: aneuploidy (trisomy 16), monosomy X, polyploidy – 80-90% of 1st trimester pregnancy losses.
- Endocrine and metabolic factors: luteal phase defect, PCOS, diabetes, thyroid disease - 10-20% of abortions.
- Anatomical: unicornuate/bicornuate uterus, septate uterus, fibroid, synechiae >50% 2nd-trimester pregnancy losses.
- Immunological: autoimmune disorders eg antiphospholipid syndrome, SLE
- Infectious: Malaria, HIV, rubella, chlamydia, gonorrhoea, syphilis, bacterial vaginosis, listeria, brucella, toxoplasmosis, cytomegalovirus.
- Diabetes mellitus
- Toxicity: Cytotoxic drugs
- Emerging diseases like Zika, Ebola and Covid 19.
- Advanced maternal age. If above 40 years, the risk of miscarriage is 30%.

Prevention

Prevention of early pregnancy complications can be achieved by:

i. Preconception Care

ii. Antenatal care

iii. Skilled attendance at birth and postpartum care to prevent causes of early pregnancy complications in the next pregnancy e.g. gestational diabetes, preeclampsia.

iv. For risky and unintended pregnancy; early visit to a healthcare provider or healthcare facility for assistance.

v. Attend a health care facility for post-abortion care in case of a miscarriage.

Diagnosis

1. Clinical Assessment

i. Medical history: personal data, reasons for seeking medical care, obstetric history, gynaecological history, sexual history, surgical and medical history, drugs and allergies, family and social history.

ii. Physical Examination - general health assessment, central nervous system exam, respiratory and cardiovascular examination, abdominal examination, pelvic examination (speculum and bimanual examination).

iii. Investigations - Laboratory investigations and imaging. Pelvic ultrasound should be done to confirm various early pregnancy complications.

iv. Dating the pregnancy

- Gestational age (GA) refers to the length of pregnancy after the first day of the last menstrual period (LMP) and is usually expressed in weeks and days. This is also known as menstrual age.
- Conceptional age (CA) is the true foetal age and refers to the length of pregnancy from the time of conception.
- The Gestation age is usually preferred and can be confirmed by Bimanual Pelvic examination or by Pelvic ultrasound (transabdominal or transvaginal).

Ultrasound should be used where available to confirm foetal viability[19].

Identify a foetal heartbeat. If the heartbeat is present: Foetal viability is confirmed. If the heartbeat is not appreciated:

Option 1: No visible heartbeat on TVS, but there is a visible foetal pole:

- Measure the crown–rumps length (CRL).

➢ CRL is < 7.0 mm on TVS and no visible heartbeat: second scan at least 7 days after the first before making a diagnosis.

➢ CRL □ 7.0 mm on TVS and no visible heartbeat: seek a second opinion on foetal viability ± perform a second scan a minimum of 7 days after the first before making a diagnosis.

Option 2: No visible heartbeat when the crown–rump length is measured using a transabdominal ultrasound scan:

- Document the crown-rump length
- Perform a second scan a minimum of 14 days after the first before making a diagnosis.

Option 3: No visible foetal pole on TVS

- measure the mean gestational sac diameter
- The mean gestational sac diameter is < 25.0 mm on TVS and no visible foetal pole: perform a second scan a minimum of 7 days after the first before making a diagnosis.
- The mean gestational sac is ≥ 25mm and there is no visible foetal pole: seek a second opinion on foetal viability ± perform a second scan a minimum of 7 days after the first before making a diagnosis.

Rule out ectopic pregnancy and hydatidiform mole. In case the bleeding continues, counsel for evacuation

Management

Uterine evacuation can be carried out either by medical or surgical procedure, depending on the competence of the health professional, the level of facility, ability for linkage and referral, gestational age, previous Caesarean or other uterine scarring. The higher the gestation the higher the risk of complications.

Medical Uterine Evacuation Procedures

1. First Trimester

i. Early First Trimester (4 weeks-10 weeks) - under observation in the facility.

a. Misoprostol-only method

- Tab Misoprostol 800 mcg : oral, sublingual, buccal or vaginally 3 hourly for 3 doses.
- Review the client between 7 to 14 days after the procedure to assess completion of the process, provide contraceptive services, emotional support or management of any medical concerns.

b. Mifepristone and Misoprostol combination (Combipack)

- Mifepristone 200mg taken orally on the first day of treatment
- Misoprostol 800 mcg stat taken orally, sublingual, buccal and vaginally route from the second day of treatment.
- Review the client between 7 to 14 days after the procedure to assess completion of the process, provide contraceptive services, emotional support or management of any medical concerns.

ii. Late First Trimester (10 weeks -12 weeks)-Under facility observation

a. Mifepristone 200 mg orally stat. Then

- Misoprostol 600 mcg sublingually or 800 mcg vaginally 1-2 days after Mifepristone, then
- Misoprostol 400mcg sublingually or vaginally every three hours until complete expulsion.

b. Alternative: Mifepristone 200 mg orally followed 1-2 days later by Misoprostol 800 mcg buccally, sublingually, or vaginally. The dose of Misoprostol should be repeated until the expulsion of the products of conception. If expulsion has not occurred after 5 doses, review.

A review between 7 to 14 days after the procedure is recommended to assess completion, provide contraceptive services, emotional support or management of any medical concern

Misoprostol only

Gestational age	Misoprostol dosing
<12 weeks	Buccal, intravaginal*, sublingual: 800 mcg[¶]
≥12 weeks	Buccal, intravaginal*, sublingual: 400 mcg every 3 hours[Δ]

2. Second Trimester

Admit to a healthcare facility.

i. Early Second Trimester (13 weeks to 24 weeks)

a. Misoprostol-only method: Misoprostol 400 mcg is sublingually 3-hourly to a maximum of 5 doses or till complete expulsion of the products of conception. If unsuccessful, the client may rest for 12 hours and repeat Misoprostol as above.

b. Mifepristone and Misoprostol (Combipack method)

c. Mifepristone 200 mg is taken orally on the first day of treatment

Misoprostol 400mcg 3-hourly until the expulsion of the products of conception starting from the second day of treatment.

If unsuccessful, rest for 12 hours and repeat Misoprostol as above.

ii. Late Second Trimester (25 weeks to 28 weeks)

Mifepristone 200 mg taken orally on the first day of treatment and

Misoprostol 200 mcg taken by sublingual route 3 hourly till the expulsion of the foetus and placenta.

Give mifepristone followed by misoprostol when available as it is more effective.

An additional dose can be offered if the placenta is not expelled 30 minutes after foetal expulsion.

Surgical Uterine Evacuation Procedures

First-Trimester: Manual Vacuum Aspiration (MVA). This is performed during the first 12 weeks of pregnancy.

Cervical preparation:

- Mifepristone 200 mg orally 1-2 days prior to the procedure
- Misoprostol 400 ᴍg sublingually 1–2 hours prior to the procedure
- Misoprostol 400 ᴍg vaginally or buccally 2–3 hours prior to the procedure

1st Trimester Surgical Uterine Evacuation Procedures

Item	Manual Vacuum Aspiration	
Gestation age	Gestation age (4 weeks -8 weeks)	Gestation age (9 weeks -12 weeks
Outpatient Regimen	Prime the cervix with 200mcg of misoprostol sublingual and do the MVA 1-3 hours later. Use appropriate canula (Uterine size minus 2 is the formula to choose the canula)	Do as in column one but time for priming the cervix should be 3 hours. There is also need to use a small sponge holding forceps to remove placental tissue for completeness of procedure and avoid bleeding (use canula no.7 to 8 depending on gestation using the rule uterine size minus 2)
Inpatient Regimen	Not indicated unless the procedure is done under general anaesthesia	Not indicated unless the procedure is done under general anaesthesia
Follow up by clinician	One week after initial treatment. However, in case of complication or any concern she should call back, come back or go to the nearest health care facility for assistance	One week after initial treatment. However, in case of complication or any concern she should call back, come back or go to the nearest health care facility for assistance

Evidence that the MVA procedure is successful

- There is a gritty sensation from the cannula inside the uterus.
- A foam appearance in the syringe.
- Evidence of no POCs in the syringe after the last suction.

Second Trimester: Dilatation and Evacuation (D And E)

This is performed between 13 weeks and 16 weeks of gestation

a. Conditions for the performance of this procedure

It must be done by a skilled healthcare professional in a health facility with the necessary equipment and access to blood transfusion in case of emergency bleeding. The facility should have anaesthetic facilities or access to referral to a higher institution with specialized medical personnel to perform such procedures.

b. Cervical preparation

i. Mifepristone 200 mg 1 day before the procedure

ii. Misoprostol 400mcg sublingual 3 hourly on the second day for one or two doses before the procedure.

c. Dilatation and Evacuation (D and E) Technique

The client should empty the bladder, or the clinician should catheterize the client. Use specialized forceps (Sonopher or Bierer forceps) or straight sponge-holding forceps to remove the products of conception after draining the liquor. The procedure is completed by performing the MVA using cannula number 8 to clean up the uterus.

After completion of the procedure, the client is given a uterotonic injection such as Oxytocin 10 international units IM/IV complemented with bi-manual uterine massage to ensure that the uterus is well contracted and there is no bleeding before the client leaves the procedure couch.

If there is no uterotonic agent and the client is bleeding, she can be given 800mcg of misoprostol rectally. Uterine Balloon Tamponade can also be used in case of excessive bleeding, and the client can be given IV fluids and blood transfusion as preparations for referral are made if necessary.

d. Use of anti-D in Rhesus-negative women

This is recommended at a dose of 50mcg IM within 72 hours after evacuation of the uterus for first-trimester pregnancies.

e. Referral and follow up

This procedure must be done in a healthcare facility with a theatre, access to blood

Pain Management

i. Pain management for Medical Uterine Evacuation

- Offer pain medication to all women undergoing uterine evacuation.
- Nonsteroidal anti-inflammatory drugs (NSAIDs) are recommended either prophylactically or at the time cramping begins.
- Non-pharmacologic pain management measures may be helpful.
- Narcotic analgesics have not been demonstrated to be effective in relieving pain during the medical abortion process and are not recommended for routine use.
- Paracetamol is not useful and should not be used unless an allergy or contraindication to NSAIDs

ii. Pain management for Manual Vacuum Aspiration

- A combination of paracervical block and pre-procedure nonsteroidal anti-inflammatory drugs (NSAIDs) for pain management is recommended for all women.
- Additional measures such as narcotic analgesics, anxiolytics and non-pharmacologic pain management measures may be helpful.
- Intravenous conscious sedation, where available, may be offered.
- Paracetamol is not effective for vacuum aspiration pain management.
- General anaesthesia is not routinely recommended for vacuum aspiration pain management.

iii. Pain management during Dilatation and Evacuation

- A combination of paracervical block, nonsteroidal anti-inflammatory drugs (NSAIDs) and narcotic analgesics, with or without anxiolytics, is recommended.
- Intravenous conscious sedation, where available, should be offered.
- The increased risks of general anaesthesia must be weighed against the benefits

iv. Paracervical Block

- Paracervical block with local anaesthetic is an effective method of pain management and should be a part of all vacuum aspiration and dilatation and evacuation (D&E) procedures.
- Skilled healthcare professionals can safely and effectively provide paracervical anaesthesia.
- A paracervical block is ineffective for managing pain associated with foetal expulsion for medical abortion at or after 13 weeks gestation.
- A paracervical block of 20mL of 1% lidocaine, injected to a depth of 3cm is recommended. If 1% lidocaine is unavailable, 10mL of 2% lidocaine may be substituted, although evidence supporting the use of 2% lidocaine is sparse. A four-point paracervical injection technique should be used.

Prophylactic Antibiotics

Doxycycline 200 mg orally no more than 2 hours be- fore the procedure or Azithromycin 500 mg orally no more than 2 hours before the procedure
Doxycycline 200 mg orally within 1 hour before procedure

Referral And Follow-Up

Referral

When the condition cannot be adequately managed due to:

- Health system capacity
- Health care provider competency

Follow Up

All women undergoing uterine evacuation due to early pregnancy complications need follow up to

- Evaluate recovery
- Evaluate any further complications or issues arising after the discharge from the health care facility.
- Immediate post abortion family planning if eligible according to the medical eligibility criteria.
- For outpatient medical uterine evacuation clients are asked to go back to the facility after two weeks for review.

Post abortion Contraception

Post abortion contraception is recommended where the woman is not ready to have another pregnancy after the loss of the current pregnancy.

All hormonal methods are recommended from the day of commencement of the medical uterine evacuation and IUCD is given after confirmation of complete uterine evacuation following treatment.

For surgical uterine evacuation the woman can start any of the hormonal methods on the day of the evacuation and IUCD may also be given if there is no evidence of sepsis.

Conscientious Objection

The management of early pregnancy complication is an emergency procedure and hence conscientious objection does not apply in emergencies. However, incase a provider's conscience does not allow him or her to provide the service, the provider should refer the client to a colleague who will be able to assist the client.

Chapter 7 MATERNAL COLLAPSE

Definition

Maternal collapse is an acute event involving the cardiorespiratory systems and/or central nervous systems, resulting in a reduced or absent conscious level, at any stage in pregnancy and up to 6 weeks after birth [21]. This has the potential to lead to cardiac arrest and death.

Obstetric collapse in pregnancy is uncommon but contributes to maternal morbidity and mortality, particularly in women with non-obstetric conditions such as heart disease, respiratory disorders, and other medical conditions (indirect causes), as well as morbid obesity. Direct causes that include postpartum haemorrhage, hypertensive disease in pregnancy, puerperal sepsis, obstructed labour and unsafe abortion are common obstetric causes of maternal collapse. Some cases occur in women with no obvious clinical risk factors. Overall maternal survival is low or is associated with significant morbidity despite appropriate resuscitation.

Clinical Considerations

Consider a risk stratification to identify women at higher risk throughout the continuum of care and previous history of maternal collapse. Use a systematic approach to identify the cause, as there are many potential causes.

All staff should be aware that there are anatomical and physiological differences in the pregnant patient that may impede resuscitation, including:

i. **Cardiovascular System:** Aorto-caval compression by the gravid uterus. This results in reduced venous return and obstruction to the forward flow of blood into the aorta. The gravid uterus accounts for 10% of cardiac output, resulting in a significant shunt that further impairs effective cardiopulmonary resuscitation (CPR).

ii. **Respiratory System:** Reduced functional residual capacity (FRC) and increased oxygen consumption increase rates of desaturation and greatly hinder adequate oxygenation during CPR. In addition, patients are at increased risk of difficult and failed intubation.

iii. **Gastrointestinal System:** Increased risk of aspiration due to delayed gastric emptying.

iv. **Haematological:** Presence of anaemia in the mother, either physiological anaemia of pregnancy by 32 weeks or pathological.

NB: Among low-risk patients, maternal collapse can be the presenting condition.

Possible Causes of Maternal Collapse

CNS	Eclampsia
	Intracranial haemorrhage/ Infarcts/ Space occupying lesion
Embolism	Pulmonary
	Amniotic fluid
Haemorrhage	PPH
	Antepartum e.g. ectopic, abruption, previa
	Hepatic rupture
	Splenic artery rupture
Cardiovascular	Congestive Cardiac Failure, Aortic dissection, Arrhythmia Myocardial infarction, Cardiomyopathy
Sepsis	Localized and disseminated septicaemia
Drugs	Magnesium sulphate
	Local anaesthetic
	Other anaesthetic drug reactions e.g., spinal, epidural, opioids
	Illicit drugs
	Herbal medications
	Anaphylaxis
Metabolic	Hyponatremia e.g., oxytocin
	Hypoglycaemia e.g., Acute fatty liver
	Hyperkalaemia e.g., Diabetic ketoacidosis
Other	Airway obstruction especially during anaesthesia as well as other anaesthetic related complication trauma, metabolic and electrolyte disturbances.

Management

When maternal collapse is identified:

- Call for help. Ensure early involvement of senior experienced staff, including midwives, obstetricians, anaesthetists, and haematologists, to optimize outcomes.
- Multiple simultaneous actions are required by various categories of staff.
- Improved outcomes may result from the decision to perform a perimortem delivery (hysterotomy or caesarean section) in women with viable pregnancies. The evidence for this recommendation is limited and is noted as a good practice point.
- In a hospital setting, the procedure should be undertaken at the site of the cardiac arrest without moving to an operating theatre. The primary aim of perimortem caesarean section is to aid maternal survival, and not necessarily foetal survival.
- Rapid decision-making by senior staff is required when recommending a perimortem caesarean section.
- Clinical areas where pregnant women are seen should have a designated emergency pregnancy equipment box that is regularly monitored by the lead nursing staff, including the wards and the emergency departments.

Maternal collapse resuscitation should follow guidelines using the standard DR ABCDE approach, with some modifications for pregnancy.

The aims of the ABCDE approach are to:

- provide life-saving treatment
- break down complex clinical situations into more manageable parts
- serve as an assessment and treatment algorithm
- establish common situational awareness among all treatment providers
- buy time to establish a final diagnosis and treatment.

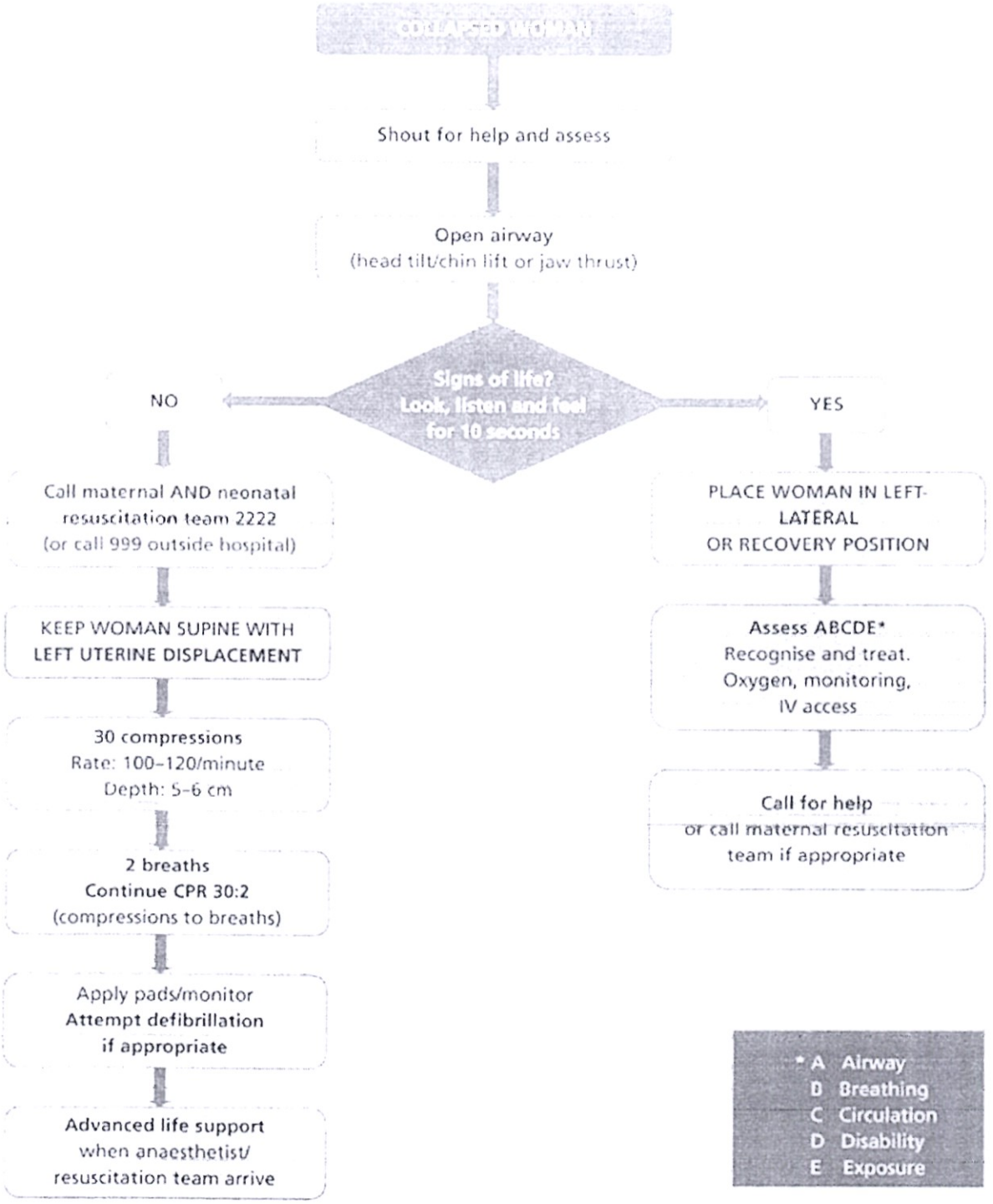
D	Signs of danger
R	Response
A	Airway Look for the signs of airway obstruction. Treat airway obstruction as a medical emergency. Give oxygen at high concentration.
B	Breathing Look listen and feel for signs of respiratory distress. Count the respiratory rate. Assess depth of each breath and chest expansion.
C	Circulation Look at the colour of hands and digits. Assess the limb temperature. Measure the capillary refill time. Count the patient pulse rate. Measure the patients' blood pressure. Auscultate the heart,
D	Disability/Defibrillation Determine level of consciousness – Alert, Voice Responsive, Pain Responsive, Unresponsive (AVPU) Recovery position Treat ABC Glucose for Hypoglycaemia
E	Exposure Body exposure Respect the patient's dignity and minimise the health loss

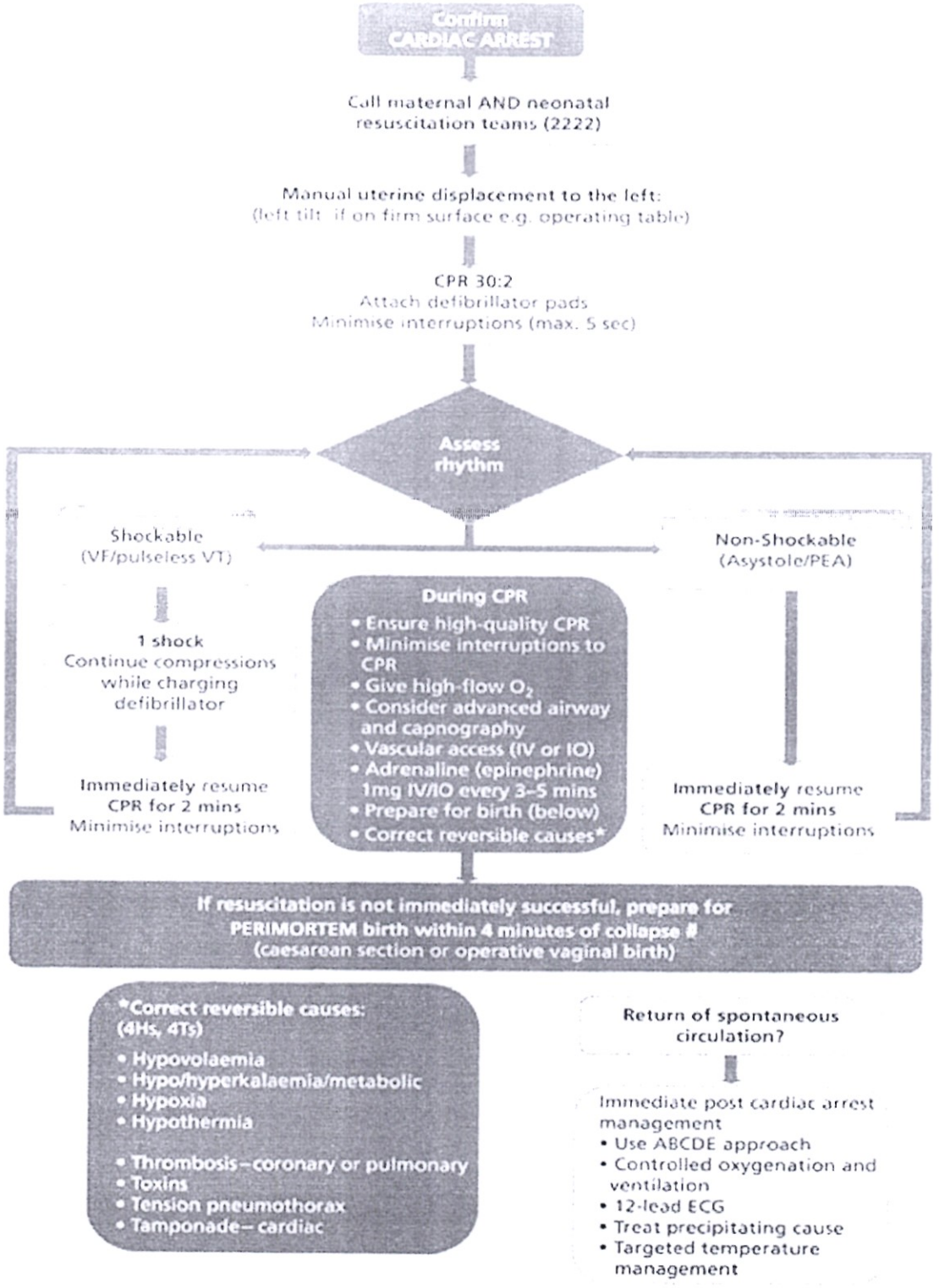
- Manual displacement of the uterus to the left is effective in relieving aortocaval compression in women above 20 weeks' gestation or where the uterus is palpable at or above the level of the umbilicus.
- A left lateral tilt of the woman from head to toe at an angle of 15–30° on a firm surface will relieve aortocaval compression in most pregnant women.
- Pregnant women are at an increased risk of aspiration.
- Difficult intubation is more likely in pregnancy.
- If the airway is clear and there is no breathing, chest compressions should commence immediately.
- Two wide-bore cannula (e.g., □ 16 gauge) should be inserted as soon as possible
- There should be an aggressive approach to volume replacement, although caution should be exercised in the context of pre-eclampsia or eclampsia.
- If available, abdominal ultrasound by a skilled operator may assist in the diagnosis of concealed haemorrhage.
- There should be no alteration in algorithm drugs or doses, or defibrillation energy levels used in the protocols.
- Continue resuscitation until the consultant obstetrician and consultant anaesthetist takes a decision to discontinue resuscitation.
- Referral should be supervised by an adequately skilled team with appropriate equipment.

Management by Cause

- Antepartum haemorrhage: In the case of maternal collapse secondary to antepartum haemorrhage, the foetus and placenta should be delivered promptly to allow control of the haemorrhage.
- Abruptio placentae: In the case of massive placental separation, caesarean section or hysterotomy may be indicated even if the foetus is dead to allow rapid control of the haemorrhage and sequelae. Intravenous tranexamic acid reduces mortality due to postpartum haemorrhage.
- Massive pulmonary embolism: treat according to national guidelines.
- Amniotic fluid embolism (AFL) is supportive rather than specific, as there is no proven effective therapy.
- Cardiac causes: After successful resuscitation, cardiac cases should be managed by a cardiology team.
- Septic shock should be managed in accordance with the national guidelines.
- Drug adverse effects:
  - The antidote to magnesium toxicity is 10 ml 10% calcium gluconate or 10 ml 10% calcium chloride given slowly by intravenous injection.
  - Local anaesthetic toxicity, immediately stop injecting. Lipid rescue should be used in cases of collapse secondary to local anaesthetic toxicity.
- Anaphylaxis: all potential causative agents should be removed, and the ABCDE approach to assessment and resuscitation followed.
- Involve other specialists depending on the cause e.g., neurologists, radiologists.

Algorithms for basic and advanced life support in pregnancy are presented below[22]:


COLLAPSED WOMAN
Shout for help and assess
Open airway
(head tilt/chin lift or jaw thrust)
Signs of life?
Look, listen and feel
for 10 seconds
NO
YES
Call maternal AND neonatal resuscitation team 2222
(or call 999 outside hospital)
KEEP WOMAN SUPINE WITH LEFT UTERINE DISPLACEMENT
30 compressions
Rate: 100–120/minute
Depth: 5–6 cm
2 breaths
Continue CPR 30:2
(compressions to breaths)
Apply pads/monitor
Attempt defibrillation
if appropriate
Advanced life support
when anaesthetist/
resuscitation team arrive
PLACE WOMAN IN LEFT-LATERAL
OR RECOVERY POSITION
Assess ABCDE*
Recognise and treat.
Oxygen, monitoring,
IV access
Call for help
or call maternal resuscitation
team if appropriate
* A Airway
B Breathing
C Circulation
D Disability
E Exposure


Confirm CARDIAC ARREST
Call maternal AND neonatal resuscitation teams (2222)
Manual uterine displacement to the left:
(left tilt if on firm surface e.g. operating table)
CPR 30:2
Attach defibrillator pads
Minimise interruptions (max. 5 sec)
Assess rhythm
Shockable (VF/pulseless VT)
Non-Shockable (Asystole/PEA)
1 shock
Continue compressions while charging defibrillator
Immediately resume CPR for 2 mins
Minimise interruptions
During CPR
• Ensure high-quality CPR
• Minimise interruptions to CPR
• Give high-flow O_2
• Consider advanced airway and capnography
• Vascular access (IV or IO)
• Adrenaline (epinephrine) 1mg IV/IO every 3–5 mins
• Prepare for birth (below)
• Correct reversible causes*
Immediately resume CPR for 2 mins
Minimise interruptions
If resuscitation is not immediately successful, prepare for PERIMORTEM birth within 4 minutes of collapse #
(caesarean section or operative vaginal birth)
*Correct reversible causes:
(4Hs, 4Ts)
• Hypovolaemia
• Hypo/hyperkalaemia/metabolic
• Hypoxia
• Hypothermia
• Thrombosis–coronary or pulmonary
• Toxins
• Tension pneumothorax
• Tamponade–cardiac
Return of spontaneous circulation?
Immediate post cardiac arrest management
• Use ABCDE approach
• Controlled oxygenation and ventilation
• 12-lead ECG
• Treat precipitating cause
• Targeted temperature management

Perimortem Caesarean Section or Hysterotomy (PMCS)

- In women over 28 weeks of gestation, if there is no response to correctly performed CPR within 4 minutes of maternal collapse or if resuscitation is continued beyond this, then PMCS should be undertaken to assist maternal resuscitation.
- It is recommended that this decision and delivery occur within 5 minutes of the collapse.
- PMCS should not be delayed by moving the woman. It should be performed where maternal collapse has occurred, and resuscitation is taking place.
- The most experienced clinician present should conduct the surgery using the incision, which will facilitate the most rapid access based on experience.
- Manual uterine displacement can be stopped immediately prior to incision. If
- resuscitation is successful, the uterus and abdomen should be closed in the usual way to control blood loss and minimize the risk of infection.
- Purpose of perimortem CS
- The gravid uterus impairs venous return and thus reduces cardiac output by approximately 60%, secondary to aortocaval compression.
- Delivery of the foetus and placenta reduces oxygen consumption, improves venous return and cardiac output, facilitates chest compressions, and makes ventilation easier.
- It also allows for internal chest compressions by inserting the hand through the open abdomen up to the diaphragm and compressing the posterior aspect of the heart against the chest wall. This improves cardiac output beyond that achieved in closed chest compressions.
- At less than 20 weeks of gestation there is no proven benefit from delivery of the foetus and placenta.
- PMCS should be considered a resuscitative procedure, to be performed primarily in the interests of maternal survival.

Follow Up: Referral and Linkage

The health care provider needs to have clear indication of their level of care at the Institution and as to whether it is a Basic/Comprehensive Obstetric unit and emergency preparedness. This should inform linkages from the community and between health Institutions and the provision of functional referral mechanisms.

Clear communication strategy (SBAR) from the referring health Institution using a hotline, accompanying skilled health personnel in a fully equipped ambulance and clear documentation of diagnosis, previous management provided, index triage as a continuum and the reason for referral (MoH 100).

Resuscitation

- Transfer to the critical care unit or refer.
- An emergency well-coordinated, orchestrated emergency drill and team. The team lead must take charge of the resuscitation.
- Daily checks of the resuscitation equipment and drugs.
- The most senior member of the clinical team should take charge of informing the family of key progress and outcomes throughout.
- Additionally, a team debrief should be carried out, whether or not the resuscitation is successful.
- Mandatory debriefing and counselling are recommended for the woman and the family.

Clinical Governance

- Accurate documentation is essential in all cases of maternal collapse.
- All cases of maternal collapse must be documented as clinical incidents.
- Mandatory formalized and recorded resuscitation and other emergency skills training are required for all relevant clinical staff at maternity units.
- The near miss and maternal mortality surveillance data must be audited [23].

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Appendix 1: Haemostasis Mnemonic for PPH Management

H	Ask for Help and Hands on uterus
A	Assess and resuscitate
E	Establish aetiology, ensure availability of blood and blood products
M	Massage uterus
O	Oxytocin infusion/prostaglandins – IV/IM/Rectal
S	Shift to theatre. aortic pressure/anti-shock garment/bimanual compression
T	Tamponade balloon/uterine packing after exclusion of tissue and trauma
A	Apply compression sutures: B-Lynch/modified
S	Systematic pelvic devascularization: uterine/ovaria/quadruple/internal iliac
I	Interventional radiology ± uterine artery embolization
S	Subtotal/total abdominal hysterectomy

Appendix 2: Medication used in prevention and management of PPH

Drug	Prevention (AMTSL)	Management	Caution	Contraindication
Oxytocin Inj	IM: 10 IU IV: 10 IU slowly over 1 minute	1st line 10IU IM and 20 IU in 1l Normal Saline at 60dpm, followed by 20IU in 1L Normal Saline at 60dpm	Not effective if cold chain outside 2°-8°C Avoid over 3l of fluid containing oxytocin	IV bolus
*Carbetocin Inj	Vaginal birth: 100 mcg. IM for vaginal births, slow IV at C/S		Single dose	IV bolus
Misoprostol	Per Rectal (PR) or Sublinngual (SL): 600mcg	1st line. If used for AMTSL, Add pR or sl:200mcg. If not used for AMTSL: 800mcg pR or sl	Adverse effects e.g vomiting, pyrexia, diarrhoea especially oral. Max 800mcg	Concurrent anticoagulant use
Ergometrine Inj	IM/ IV: 0.5 mg	2nd line 0.5mg IM repeat at 2hr to 4hr, Max 1g in 24hr	Not effective if cold chain outside 2°-8°C	Hypertension / PET, Heart disease
Prostaglandin F2 (Carboprost)		3rd line IM: 0.25mg IM every 15min	Not used for AMTSL Max 2mg	Asthma, Cardiovascular conditions.
Tranexamic Acid Inj		1g IV within 3 hours of delivery in all cases of PPH regardless of the cause.	Not for AMTSL, Administer < 3 hrs of delivery in addition to standard PPH Rx > 3hr post-delivery, TXA does not confer benefit and has risk	Thromboembolic event during pregnancy, History of coagulopathy, Active intravascular clotting, Hypersensitivity
*Carbetocin is used for prevention of PPH, given in active management of third stage of labour. No guidance for its use in treatment of PPH				

Appendix 3: PPH Emergency Kit

ITEM	AMOUNT	ITEM	AMOUNT
IV Cannula Gauge 16	4 pieces	Urine Bag	1 piece
Strapping	1 piece	Blood sample bottles – Purple, Yellow, Red top	4 pieces each
IV Giving Sets	2 pieces	Vaginal packs	10 pieces
Syringes: 5ml, 10ml, 20ml	2 pieces each	Gauze rolls	1 piece
Sterile gloves	5 pieces	Uterine Balloon Tamponade	1 piece
Gynaecological gloves	1 piece	Anti-Shock Garment	1 piece
Distilled water 10mls	5 pieces	Oxytocin 10IU At 2-8^{0}C	4 vials
Cotton balls	10 pieces	Misoprostol	4 tablets/ 800ug
IV Fluids Ringers Lactate, Normal Saline 500mls	2 pieces each	IV Tranexamic Acid	1 gram
Oxygen mask	1 piece	Ergometrine 0.5mg	1 vial
Blood giving set	1 piece	Sutures – Vicryl 2-0 Round	1 box
Urinary catheter Size 16	1 piece		

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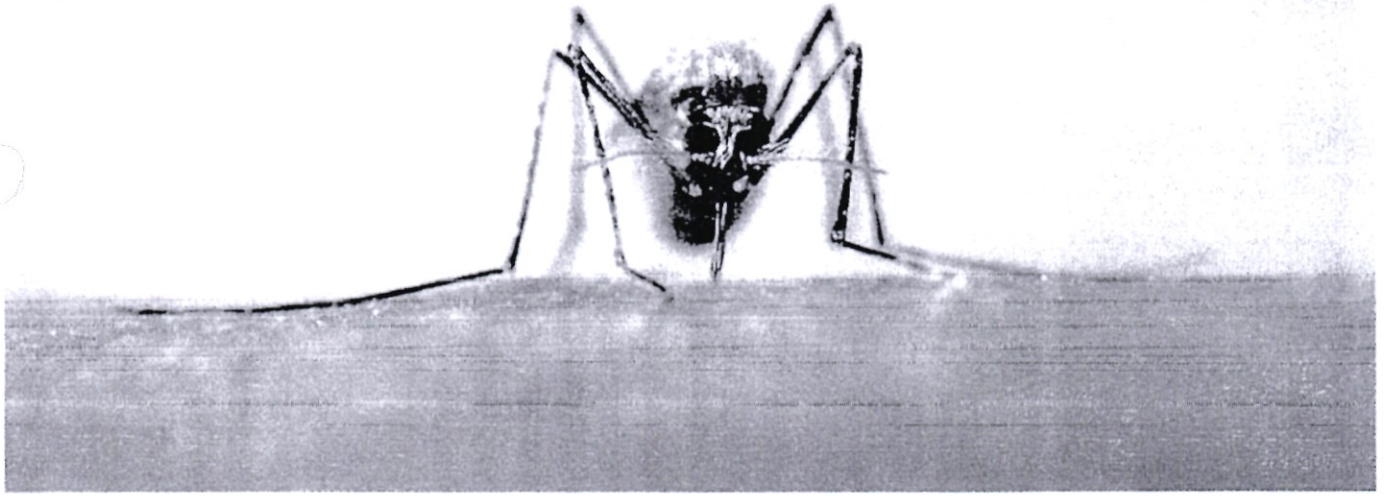
Kenya to Release Genetically Modified Mosquitoes to Fight Malaria



Malaria No More (https://www.malarianomore.org.uk/)

Mosquito.

The Accra Times (Accra) (https://theaccratimes.com/) 10 JULY 2024

By Gifty Danso

Nearly 3.42 million cases of malaria were confirmed in Kenya in 2022. Authorities believe leveraging genetic approaches can control the spread of malaria

Kenya's Medical Research Institute (Kemri) and the Imperial College of London are collaborating to introduce genetically modified (GM) mosquitoes to check the spread of malaria in that country.

Authorities in Kenya have emphasied the critical need to leverage advanced technologies to combat malaria, as the disease remains endemic. According to statistics, in 2022, nearly 3.42 million cases of malaria were confirmed in Kenya.

"It is therefore important to embrace new technology that can assist in controlling it," said Dr Martin Bundi, the acting Deputy Director of Research and Development at Kemri, although timelines for the initiative haven't been set yet.

The GM mosquitoes produced in a lab by the Centers for Disease Control carry two types of genes, which includes a self-limiting gene that prevents female mosquito offspring from surviving to adulthood and a fluorescent marker gene that glows under a special red light, local outlet the Nation reported.

"When the eggs hatch, they develop into adult mosquitoes. These mosquitoes mate with wild females. The genes are then passed on to offspring. The expected result of using GM mosquitoes is that the numbers of Aedes aegypti mosquitoes in an area decreases," the report said.

In May, Djibouti also carried out a similar exercise - becoming the first East African nation to release genetically modified mosquitoes in an effort to stop the spread of an invasive species that transmits malaria.

*Read the **original article (https://theaccratimes.com/kenya-to-release-genetically-modified-mosquitoes-to-fight-malaria/)** on **Accra Times (https://theaccratimes.com/)**.*

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Life & Times
The last British malaria outbreak

We inevitably associate malaria with tropical climates where the vector *Anopheles* mosquitoes are abundant. In 2017, there were an estimated 219 million cases worldwide, predominately in sub-Saharan Africa and India, resulting in 435 000 deaths.[1] Often forgotten is that malaria is widely believed to have been formerly endemic to the UK. The last outbreak involving locally acquired cases occurred between 1917 and 1921. Could vector-borne disease pose a threat today?

MALARIA IN THE UK

Febrile-like illnesses, probably malarial in origin, were historically common in lowland marshland areas.[2] Known variously as 'marsh fever', 'agues', or 'tertian fevers', these illnesses affected areas of low-lying Essex, Sussex, Kent, the Somerset levels, the Yorkshire Holderness, and the Lancashire Ribble Valley.[2] These were likely caused by *Plasmodium vivax* or *Plasmodium malariae*, and were probably transmitted by the native mosquito *Anopheles atroparvus*. By the 20th century, such indigenous malaria was becoming rare, banished by land drainage and better housing.

THE FIRST WORLD WAR: MALARIA VICTORIOUS

To break the Western Front deadlock of the First World War, a military front was opened in 1915 in Salonika in the Balkans. Malaria was endemic here; it proved the only victor. Throughout the campaign, 162 517 troops were admitted with malarial illness.[3] Troops repatriated back to the UK were stationed in field camps nationwide. Many had suffered malaria, or were incubating infection. An estimated 15 000 to 25 000 such infected troops returned to the UK,[4] many falling ill on their return. Unfortunately, and with amazing lack of foresight, one camp was situated on the Isle of Sheppey, Kent, an area notorious for marshland fevers and mosquito vectors.



Figure 1. GB War Office, anti-malaria brigade. Credit: Wellcome Collection. CC BY.

OUTBREAK

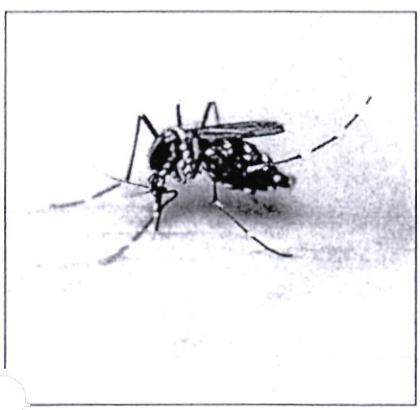
Large numbers of infected troops, stationed where mosquitoes were abundant, provided a ready source of infection from which an outbreak could become established. Locally acquired cases, seemingly triggered by the presence of these infected troops, were soon reported. A focus of infection was Kent, with 270 cases reported in 1917 and 1918.[4] Most were concentrated on the Isle of Sheppey, the Isle of Grain, and Sandwich. Troops and civilians living locally, who had never been abroad, contracted infection. However, the picture was confused: whether cases originated from returning infected troops, or were of truly native indigenous malaria already present in the area, was unclear.

Controlling the outbreak took considerable effort. Notification of malaria was made compulsory in 1919. Insecticides were used, and areas of standing water cleared (Figures 1 and 2). Reported cases continued until 1921. Writing afterwards, malaria specialist Percy Shute reported that there had been 481 indigenous cases between 1917 and 1921, all of the *Plasmodium vivax* form.[5] The last known indigenous case of malaria occurred as late as 1957.

CLIMATE CHANGE

Could mosquito-borne disease return? Improved housing, reduced exposure to vectors, and a lack of infected people, mean renewed outbreaks are unlikely. People do not live in field camps in the UK.

Tiger mosquito.



"To break the Western Front deadlock of the First World War, a military front was opened in 1915 in Salonika in the Balkans. Malaria was endemic here; it proved the only victor. Throughout the campaign, 162 517 troops were admitted with malarial illness."



Figure 2. GB War Office, anti-malaria detachment, Sandwich. Credit: Wellcome Collection. CC BY.

However, climate change may mean that new mosquito species, harbouring new diseases, appear.

Warmer conditions may have led to the urban-dwelling Asian tiger mosquito *Aedes albopictus* moving into Northern Europe; this is a most invasive coloniser and vector of chikungunya virus and dengue fever.[6] Previously unknown mosquitoes are being discovered in the UK, possibly because of climate change. For example, *Culex modestus*, a vector of West Nile virus, has been found in Kent and south eastern Essex recently.[7] Ports are now monitored for invasive mosquitoes.[7] As the 1917 outbreak demonstrates, inadvertent introductions easily occur.

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Florida mosquitoes: 750 million genetically modified insects to be released

20 August 2020

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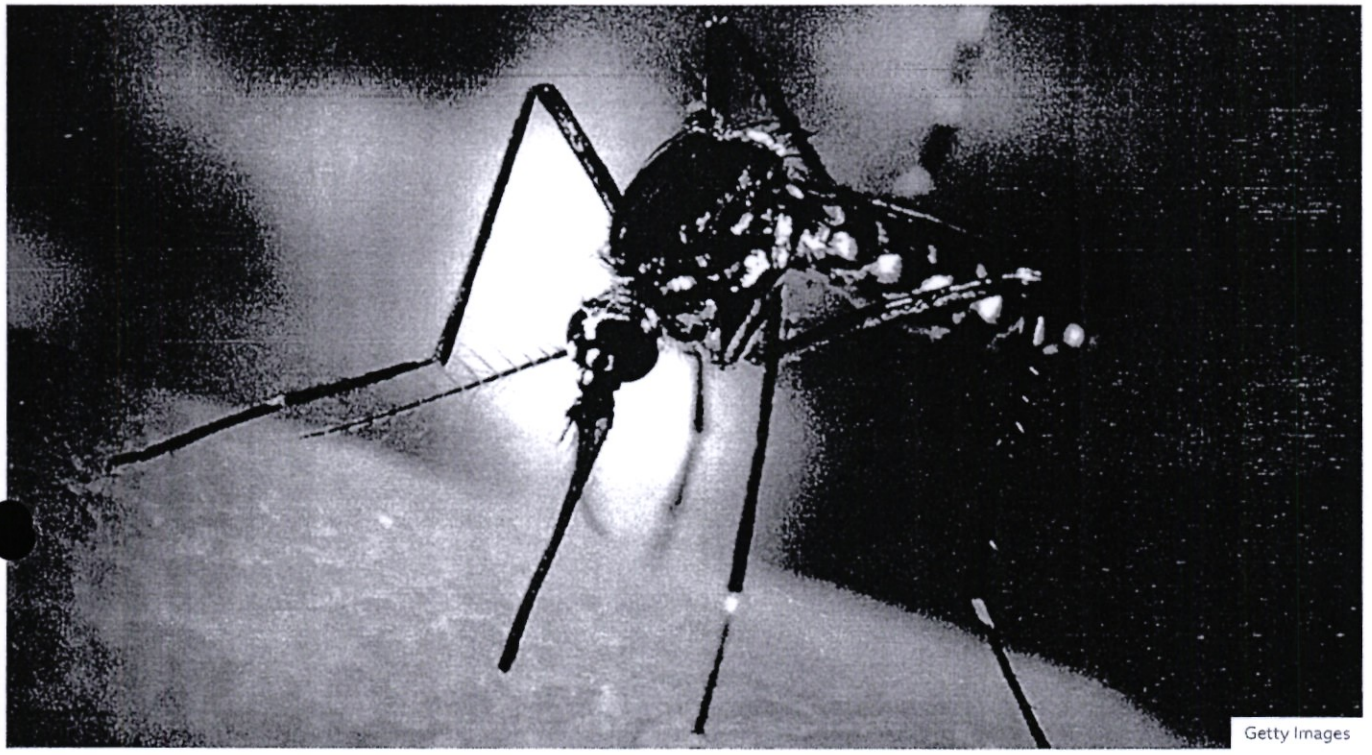

Getty Images

The aim is to reduce the population of Aedes aegypti mosquitoes

Local officials in Florida have approved the release of 750 million mosquitoes that have been genetically modified to reduce local populations.

The aim is to reduce the number of mosquitoes that carry diseases like dengue or the Zika virus.

The green-lighting of a pilot project after years of debate drew a swift outcry from environmental groups, who warned of unintended consequences.

One group condemned the plan as a public "Jurassic Park experiment".

Activists warn of possible damage to ecosystems, and the potential creation of hybrid, insecticide-resistant mosquitoes.

But the company involved says there will be no adverse risk to humans or the environment, and points to a slate of government-backed studies.

- Would it be wrong to eradicate mosquitoes?
- Florida polls split on GM mosquitoes
- Is the world ready for GM animals?

The plan to release the mosquitoes in 2021 in the Florida Keys, a string of islands, comes months after the modified mosquitoes were approved by federal regulators.
In May, the US Environmental Agency granted permission to the British-based, US-operated company Oxitec to produce the genetically engineered, male Aedes aegypti mosquitoes, which are known as OX5034.
Aedes aegypti mosquitoes are known to spread deadly diseases to humans such dengue, Zika, chikungunya and yellow fever.



A biologist in Brazil releases mosquitoes to combat a Zika outbreak

Only female mosquitoes bite humans because they need blood to produce eggs. So the plan is to release the male, modified mosquitoes who will then hopefully breed with wild female mosquitoes.

However the males carry a protein that will kill off any female offspring before they reach mature biting age. Males, which only feed on nectar, will survive and pass on the genes.

Over time, the aim is to reduce the population of Aedes aegypti mosquitoes in the area and thereby reduce the spread of disease to humans.

On Tuesday, officials in the Florida Keys Mosquito Control District (FKMCD) gave final approval to release 750 million of the modified mosquitoes over a two-year period.

The plan has many critics, including nearly 240,000 people who signed a petition on Change.org slamming Oxitec's plan to use US states "as a testing ground for these mutant bugs".

According to Oxitec's website, the company has found positive results conducting field trials in Brazil. It also plans to deploy them in Texas beginning in 2021 and has gained federal approval, but not state or local approval, according to reports.

In a statement denouncing the project, environmental group Friends of the Earth said: "The release of genetically engineered mosquitoes will needlessly put Floridians, the environment and endangered species at risk in the midst of a pandemic."

But an Oxitec scientist told AP news agency: "We have released over a billion of our mosquitoes over the years. There is no potential for risk to the environment or humans".

The Aedes aegypti is invasive to southern Florida, and are commonly found in urban areas where they live in standing pools of water. In many areas, including the Florida Keys, they have developed a resistance to pesticides.

You might also be interested in:



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Emergency Preparedness and Response

Important Updates on Locally Acquired Malaria Cases Identified in Florida, Texas, and Maryland

HAN HEALTH ALERT NETWORK

This is an official CDC HEALTH UPDATE

Distributed via the CDC Health Alert Network
August 28, 2023, 2:15 PM ET
CDCHAN-00496

Summary

The Centers for Disease Control and Prevention (CDC) is issuing this Health Alert Network (HAN) Health Update to share new information with clinicians, public health authorities, and the public about locally acquired malaria cases identified in the United States. On August 18, 2023, a single case of locally acquired malaria was reported in Maryland in the National Capital Region. This case was caused by the *Plasmodium falciparum (P. falciparum)* species and is unrelated to the es involving local transmission of *Plasmodium vivax (P. vivax)* malaria in Florida and Texas described in the HAN Health visory 494 issued on June 26, 2023. As an update to that report, to date, Florida has identified seven cases and Texas has identified one case of locally acquired *P. vivax* malaria, but there have been no reports of local transmission of malaria in Florida or Texas since mid-July 2023.

P. falciparum malaria can rapidly cause severe illness and even death if not quickly diagnosed, therefore rapid diagnosis and treatment is imperative. In addition to routinely considering malaria as a cause of febrile illness among patients with a history of international travel to areas where malaria is transmitted, clinicians should consider a malaria diagnosis in any person with an unexplained cause of fever, regardless of their travel history. The risk to the U.S. public for locally acquired mosquito-transmitted malaria remains very low. The most effective way to prevent malaria in the United States is for travelers to malaria-endemic areas to take appropriate steps to prevent acquiring malaria while traveling—including taking medications to prevent malaria—and ensuring early diagnosis and treatment of imported cases of malaria and preventing mosquito bites.

Background

CDC is collaborating with the Maryland Department of Health on the investigation of a single case of locally transmitted *alciparum* malaria identified in the National Capital Region this month. This follows the identification of two states' elated episodes of local transmission of malaria—seven cases of *P. vivax* within close geographic proximity in Florida, with the last case identified in mid-July 2023, and one case of *P. vivax* in Texas in June 2023. All patients received

treatment and are improving clinically. Surveillance for additional cases of malaria, as well as malaria-related mosquito surveillance and control, will continue in all three states for a period of 8 weeks following the most recent case in each state.

Before this year, locally acquired mosquito-borne malaria had not occurred in the United States since 2003, when eight cases of locally acquired *P. vivax* malaria were identified in Palm Beach County, FL (1). Despite recent cases, the risk of locally acquired malaria remains very low in the United States. However, *Anopheles* mosquito vectors, found throughout many regions of the country, are capable of transmitting malaria if they feed on a malaria-infected person (2). The risk of malaria transmission is higher in areas where local climatic conditions allow the *Anopheles* mosquito to survive during most of or the entire year and in locations with travelers from malaria-endemic areas. In addition to routinely considering malaria as a cause of febrile illness among patients with a history of international travel to areas where malaria is transmitted, clinicians should consider a malaria diagnosis in any person with an unexplained cause of fever, regardless of their travel history, particularly in patients with new anemia or thrombocytopenia. Clinicians practicing in areas of the United States where locally acquired malaria cases have occurred should follow guidance from their state and local health departments. Promptly diagnosing and treating people with malaria can prevent progression to severe disease or death and limit ongoing transmission to local *Anopheles* mosquitoes. Individuals can take steps to prevent mosquito bites and control mosquitoes at home to prevent malaria and other mosquito-borne illnesses.

Malaria is a serious and potentially fatal disease transmitted through the bite of an infective female anopheline mosquito. Though rare, malaria also can be transmitted congenitally from mother to fetus or to the neonate at birth, through blood transfusion or organ transplantation, or through unsafe needle-sharing practices. Malaria is caused by any of five species of protozoan parasite of the genus *Plasmodium*: *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, or *P. knowlesi*. Worldwide, more than 240 million cases of malaria occur each year (95% in Africa). Almost all cases of malaria in the United States are imported and occur in people traveling from countries with malaria transmission, many from sub-Saharan Africa or South Asia. Before the COVID-19 pandemic, approximately 2,000 cases of mostly travel-related malaria were diagnosed in the United States each year; approximately 300 people experienced severe disease (most *P. falciparum*), and 5 to 10 people with malaria died yearly (3). Most imported cases of malaria in the United States are diagnosed among travelers during summer and early fall seasons. In 2023, CDC expects international travel by U.S. residents to increase to pre-COVID-19 pandemic levels (4).

Clinical manifestations of malaria are non-specific and may include fever, chills, headache, myalgias, and fatigue. Nausea, vomiting, and diarrhea may also occur. For most people, symptoms begin 10 days to 4 weeks after infection, although a person may feel ill as early as 7 days or as late as 1 year after infection. If not treated promptly, malaria may progress to severe disease, a life-threatening stage in which mental status changes, seizures, renal failure, acute respiratory distress syndrome, and coma may occur. Malaria in pregnant people is associated with high risks of both maternal and perinatal morbidity and mortality. *P. falciparum* and *P. knowlesi* infections can cause rapidly progressive severe illness or death, while other species, including *P. vivax*, are less likely to cause severe disease. Laboratory abnormalities can include anemia, thrombocytopenia, hyperbilirubinemia, and elevated transaminases, varying from normal or mildly altered in uncomplicated disease to very abnormal in severe disease. *P. vivax* and *P. ovale* canremaindormant in the liver. Such infections require additional treatment; failure to treat the dormant hepatic stages may result in chronic infection, causing relapsing episodes. Relapses may occur after months or even years without symptoms.

Malaria is a medical emergency and should be treated accordingly. Patients suspected of having malaria should be urgently evaluated in a facility that is able to provide rapid diagnosis and treatment as soon as possible, within 24 hours of the patient's presentation. Order microscopic examination of thin and thick blood smears and a rapid diagnostic test (RDT), if available, to diagnose malaria as soon as possible. Hospitals should have a plan to rapidly diagnose and treat malaria as soon as possible, within 24 hours of the patient's presentation. Key recommendations on treatment are below. Additional information on diagnosing and treating malaria, including details of treating the dormant liver stages caused by certain species of *Plasmodium*, is available on the CDC website.

Recommendations for Clinicians

- Consider the diagnosis of malaria in any person with an unexplained cause of fever, regardless of international travel history, particularly if they have been to areas with recent locally acquired malaria.

- Routinely obtain a travel history and consider malaria in a symptomatic person who traveled to an area with malaria in the weeks to months preceding symptom onset
- Treatment recommendations for malaria vary by species and severity. Please refer to CDC's Malaria Diagnosis and Treatment Guidelines for U.S. Clinicians for specific detailed instructions.
  - Malaria is a medical emergency. If not diagnosed and treated promptly, illness may progress to severe disease, a life-threatening stage, in which mental status changes, seizures, renal failure, acute respiratory distress syndrome, and coma may occur. An algorithm for diagnosis and treatment of malaria is available here .
  - Patients suspected of having malaria should be urgently evaluated in a facility, such as an emergency department able to provide rapid diagnosis and treatment as soon as possible, within 24 hours of the patient's presentation.
  - Order microscopic examination of thin and thick blood smears and a rapid diagnostic test (RDT), if available, to diagnose malaria as soon as possible.
    - "BinaxNOW™ Malaria," a malaria RDT, is approved for use in the United States. RDTs are less sensitive than microscopy and cannot confirm each specific species of the malaria parasite or determine the parasite density.
    - Therefore, microscopy should also be obtained in conjunction with an RDT as soon as possible.
  - If blood smears or RDT are positive and species determination is not available, antimalarial treatment effective against chloroquine-resistant *P. falciparum* must be initiated immediately.
  - Artemether-lumefantrine (Coartem®) is the preferred option, if readily available, for the initial treatment of uncomplicated *P. falciparum* or unknown species of malaria acquired in areas of chloroquine resistance. Atovaquone-proguanil (Malarone®) is another recommended option. *P. vivax* infections acquired from regions other than Papua New Guinea or Indonesia should initially be treated with chloroquine (or hydroxychloroquine).
  - IV artesunate is the first-line drug for treatment of severe malaria in the United States. Artesunate for Injection™, manufactured by Amivas, is approved by the FDA for treating severe malaria and is commercially available. More information on how to acquire IV artesunate in the United States can be found here.
  - Species determination is important because *P. vivax* and *P. ovale* canremaindormant in the liver and require additional anti-relapse treatment; failure to treat the dormant hepatic parasites may result in chronic infection with relapsing episodes. Relapses may occur after months or even years without symptoms.
- After an urgent infectious disease consultation, if there are still questions about diagnosing and treating malaria, CDC malaria clinicians are on call 24/7 to provide advice to healthcare providers. Additional contact information can be found here.
- Suspected or confirmed locally acquired malaria is a public health emergency and should be reported immediately to your state, territorial, local, or tribal health department . Imported (or travel-associated malaria) is also reportable in all states through routine reporting methods.
- Discuss travel plans with patients; prescribe a CDC-recommended malaria chemoprophylaxis regimen and discuss mosquito bite prevention for those traveling to an international area with malaria; encourage patients to adhere to the regimen before, during, and after travel. Malaria chemoprophylaxis is not needed for domestic travel at this time.

Recommendations for Hospitals and Laboratories

- Have malaria diagnostic tests available (blood smear or BinaxNow™ rapid diagnostic test [RDT] followed by blood smear) and ensure that qualified personnel who can perform and interpret these tests are always available.
  - If malaria blood smear or RDT results are not readily available, refer patients for whom malaria is suspected to a higher level of care for prompt evaluation for malaria.
  - Bench aids for blood smear preparation, staining, diagnosis, and calculating the percent parasitemia are available here.
- Stock IV artesunate (Artesunate for Injection™) or have a plan in place for emergency procurement.
  - More information on how to acquire IV artesunate in the United States can be found here.
- Stock artemether-lumefantrine (Coartem®), the first-line drug in the United States for most cases of uncomplicated *P. falciparum* or unknown malaria species. Atovaquone-proguanil (Malarone®) is another recommended option.

Recommendations for Public Health Officials

- Public health officials who are concerned about potential cases of locally acquired malaria should contact CDC's Malaria Branch (malaria@cdc.gov; 770-488-7788) during regular business hours or CDC's Emergency Operations Center (eocreport@cdc.gov; 770-488-7100) outside of regular business hours for assistance with recommendations and testing.
- Consider the following strategies for rapid identification, prevention, and control:
  - Provide education to communities to prevent mosquito-borne illness, including how to prevent mosquito bites.
  - Support clinicians to identify hospitals that can rapidly diagnose and treat malaria.
  - Outreach to communities to provide education on the importance of precautions for malaria and other diseases before traveling internationally to an area where malaria occurs.
  - Perform mosquito surveillance and control activities.
- In areas of higher risk for local malaria transmission or with higher numbers of cases of imported malaria, consider
  - Assessing capacity of hospitals and laboratories to rapidly diagnose and treat malaria. This should include the ability to rapidly acquire and provide treatment (See Recommendations for Hospitals and Laboratories).
  - Coordinating with mosquito control programs to enhance mosquito surveillance.

Recommendations for the Public

- If you have traveled to an area where malaria occurs and develop fever, chills, headache, body aches, and fatigue, seek medical care and tell your healthcare provider that you have traveled.
- Take steps to prevent mosquito bites and control mosquitoes at home to protect yourself from any mosquito-borne illness.
- Before you travel, learn about the health risks and precautions for malaria and other diseases for your destination. If you are traveling internationally to an area where malaria occurs, talk to your healthcare provider about medicines to prevent you from getting malaria, and strategies to prevent mosquito bites.

For More Information

Malaria Prevention, Diagnosis, and Treatment

- CDC – Treatment of Malaria: Guidelines for Clinicians (United States)
- CDC – DPDx – Diagnostic Procedures
- Malaria – CDC Yellow Book 2024
- CDC – Malaria Information and Prophylaxis, by Country
- CDC – Parasites – Continuing Education – Malaria 101 for the Healthcare Provider
- CDC – Malaria – Travelers – Risk Assessment

Mosquito-Borne Disease Prevention

- Prevent Mosquito Bites – Mosquitoes | CDC

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The Centers for Disease Control and Prevention (CDC) protects people's health and safety by preventing and controlling diseases and injuries; enhances health decisions by providing credible information on critical health issues; and promotes healthy living through strong partnerships with local, national and international organizations.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

HAN Message Types

- **Health Alert:** Conveys the highest level of importance about a public health incident.
- **Health Advisory:** Provides important information about a public health incident.
- **Health Update:** Provides updated information about a public health incident.

###

This message was distributed to state and local health officers, state and local epidemiologists, state and local laboratory directors, public information officers, HAN coordinators, and clinician organizations.

###

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Last Reviewed: August 24, 2023

World Health Organization

Human papillomavirus and cancer

5 March 2024

العربية | 中文 | Français | Русский | Español

Key facts

- Human papillomavirus (HPV) is the name of a group of 200 known viruses. They do not cause concerns in most people, but infection with some high-risk types is common and can cause genital warts or cancer.
- In 90% of people the body controls the infection by itself. Persistent HPV infection with high-risk HPV types is the cause of cervical cancer and is associated with cancers of the vulva, vagina, mouth/throat, penis and anus *(1)*.
- In 2019, HPV caused an estimated 620 000 cancer cases in women and 70 000 cancer cases in men *(1)*.
- Prophylactic vaccination against HPV can prevent these cancers. In addition, HPV-screening and treatment of pre-cancer lesions is an effective way to prevent cervical cancer.

Overview

Human papillomavirus (HPV) is a common sexually transmitted infection. Almost all sexually active people will be infected at some point in their lives, usually without symptoms.

HPV can affect the skin, genital area and throat.

Condoms help prevent HPV but do not offer total protection because they do not cover all the genital skin.

HPV usually goes away on its own without treatment. Some HPV infections cause genital warts. Others can cause abnormal cells to develop, which go on to become cancer.

ncers from HPV can be prevented with vaccines.

The vaccine does not contain any live virus or DNA from the virus so it cannot cause cancer or other HPV-related illnesses. The HPV vaccine is not used to treat HPV infections or diseases caused by HPV, but instead to prevent the development of cancers.

Currently, cervical cancer is the only HPV-caused cancer for which screening tests are available. Screening tests are used to check for disease when there are no symptoms. The goal of screening for cervical cancer is to find precancerous cell changes before they become cancer and when treatment can prevent cancer from developing. Screening for cervical cancer is an important part of routine health care for people who have a cervix. This includes women and transgender men who still have a cervix.

Cervical cancer is the most common type of cancer caused by HPV, other less common ncers affecting men and women, including anal, vulvar, vaginal, mouth/throat and penile ancers.

Scope of the problem

The highest prevalence of cervical HPV among women is in sub-Saharan Africa (24%), followed by Latin America and the Caribbean (16%), eastern Europe (14%), and South-East Asia (14%) *(2)*. Prevalence in men is highly variable based on sexual trends.

Evidence showed that prevalence of the virus is higher among women living with HIV, men who have sex with men, immunocompromised individuals, people with co-infection with other sexually transmitted infections (STI), people who receive immunosuppressive medications and children who have been through sexual abuse.

obally, it is estimated that 620 000 new cancer cases in women and 70 000 new cancer cases in men were caused by HPV in 2019 *(1)*. Cervical cancer was the fourth leading cause of cancer and cancer deaths in women in 2022, with some 660 000 new cases and around 350 000 deaths worldwide *(3)*. Cervical cancers account for over 90% of HPV-related cancers in women *(1)*.

The highest rates of cervical cancer incidence and mortality are in low- and middle-income countries. This reflects major inequities driven by lack of access to national HPV vaccination, cervical screening and treatment services, and social and economic determinants.

Symptoms

Most people will not have any symptoms from an HPV infection. The immune system ually clears HPV from the body within a year or two with no lasting effects.

Some HPV infections cause small rough lumps (genital warts) that can appear on the vagina, penis or anus and rarely the throat. They may be painful, itchy or bleed or cause swollen glands.

HPV infection that does not go away on its own can cause changes to cervical cells, which lead to precancers that may become cervical cancer if left untreated. It usually takes 15–20 years for cervical cancer to develop after HPV infection.

The early changes in cervical cells and precancers mostly do not cause symptoms. Symptoms of cervical cancer may include bleeding between periods or after sexual intercourse or a foul-smelling vaginal discharge. These symptoms may be due to other diseases. People with these symptoms should speak to their healthcare provider.

Prevention

Being vaccinated is the best way to prevent HPV infection, cervical cancer and other HPV-related cancers. Screening can detect cervical precancers that can be treated before they develop into cancer.

HPV vaccines should be given to all girls aged 9–14 years, before they become sexually active.

The vaccine may be given as 1 or 2 doses. People with reduced immune systems should receive 2 or 3 doses. Check with your healthcare provider to determine what is best for you.

Using condoms during sex is an important way to prevent HPV infection. Voluntary male circumcision also reduces the risk of infection. Being a non-smoker or stopping smoking reduces the chances of developing persistent HPV infection.

Testing cells from a woman's cervix for HPV is used to screen women for cervical cancer. Women should be screened every 5–10 years starting at age 30. Women living with HIV should be screened every 3 years starting at age 25.

After a positive HPV test (or other screening method), a healthcare provider can look for changes on the cervix or precancers that could develop into cervical cancer if left untreated. Treatment of precancers prevents cervical cancer. Precancers rarely cause symptoms, which is why regular screening to check cervical health is important.

Learn more about vaccination of boys and older age groups: WHO position paper

reatment

There is currently no treatment for HPV infection. Treatments exist for genital warts, cervical precancers and cervical cancer.

Non-cancerous genital warts and precancerous lesions in the cervix, vagina, vulva, anus or penis can be removed or treated by ablation (freezing or heating) or with surgery.

Currently, cancer of the cervix (cervical cancer) is the only HPV-caused cancer for which screening tests are available.

Treatments for cancers caused by HPV (including cervical cancer) are more effective if diagnosed early. Treatment should begin quickly after diagnosis.

arn more about cervical precancer treatment here: WHO fact sheet on cervical cancer

Management pathways for invasive cancer care are important tools to ensure that a patient is referred promptly and supported as they navigate the steps to diagnosis and treatment decisions. A multidisciplinary team should ensure diagnosis and staging (histological testing, pathology, imaging) takes place prior to treatment decisions which could include surgery, radiotherapy and systemic therapy such as chemotherapy. Treatment decisions should be in line with national guidelines and interventions should be supported by holistic psychological, spiritual, physical and palliative care.

As low- and middle-income countries scale-up cervical screening, more cases of invasive cervical cancer will be detected, especially in previously unscreened populations. Therefore, referral and treatment strategies need to be implemented and expanded alongside prevention services.

WHO response

Giving the global public health burden of cervical cancer caused by HPV, the World Health Assembly (WHA. 73.2) adopted the Global strategy to accelerate the elimination of cervical cancer as a public health problem with the following targets:

- 90% of girls fully vaccinated with HPV vaccine by age 15;
- 70% of women are screened with a high-performance test by 35, and again by 45 years of age; and
- 90% of women identified with cervical disease receive treatment (90% of women with pre-cancer treated; 90% of women with invasive cancer managed).

Prevention of HPV-associated precancer and cancer is also a key element of WHO's Global health sector strategy on, respectively, HIV, hepatitis and sexually transmitted infections, 22–2030 and the resolution WHA74.5 (2021) on oral health includes actions on

outh/throat cancers.

The joint work of the WHO at global, regional and national level, alongside UN sister agencies delivers to:

1. increase political commitment to formulate policy and support implementation
2. offer contextualized technical assistance, lessons learned and best practices
3. develop norms and standards based on latest evidence
4. lead the global health ecosystem to achieve the targets and improve quality of care.

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Jørgensen et al. Systematic Reviews (2020) 9:43
https://doi.org/10.1186/s13643-019-0983-y

Systematic Reviews

RESEARCH Open Access

Benefits and harms of the human papillomavirus (HPV) vaccines: systematic review with meta-analyses of trial data from clinical study reports

Lars Jørgensen[1], Peter C. Gøtzsche[2,3] and Tom Jefferson[1*]

Abstract

Objective: To assess the benefits and harms of the human papillomavirus (HPV) vaccines.

Data sources: Clinical study reports obtained from the European Medicines Agency and GlaxoSmithKline from 2014 to 2017.

Eligibility criteria: Randomised trials that compared an HPV vaccine with a placebo or active comparator in healthy participants of all ages.

Appraisal and synthesis: Two researchers extracted data and judged risk of bias with the Cochrane tool (version 2011). Risk ratio (RR) estimates were pooled using random-effects meta-analysis.

Outcomes: Clinically relevant outcomes in intention to treat populations—including HPV-related cancer precursors irrespective of involved HPV types, treatment procedures and serious and general harms.

Results: Twenty-four of 50 eligible clinical study reports were obtained with 58,412 pages of 22 trials and 2 follow-up studies including 95,670 participants: 79,102 females and 16,568 males age 8–72; 393,194 person-years; and 49 months mean weighted follow-up. We judged all 24 studies to be at high risk of bias. Serious harms were incompletely reported for 72% of participants (68,610/95,670). Nearly all control participants received active comparators (48,289/48,595, 99%). No clinical study report included complete case report forms. At 4 years follow-up, the HPV vaccines reduced HPV-related carcinoma in situ (367 in the HPV vaccine group vs. 490 in the comparator group, RR 0.73 [95% confidence interval, CI, 0.53 to 1.00], number needed to vaccinate [NNV] 387, $P = 0.05$, $I^2 = 67\%$) and HPV-related treatment procedures (1018 vs. 1416, RR 0.71 [95% CI 0.63 to 0.80], NNV 75, $P < 0.00001$, $I^2 = 45\%$). The HPV vaccines increased serious nervous system disorders (exploratory analysis: 72 vs. 46, RR 1.49 [1.02 to 2.16], number needed to harm [NNH] 1325, $P = 0.040$, $I^2 = 0\%$) and general harms (13,248 vs. 12,394, RR 1.07 [95% CI 1.03 to 1.11], NNH 51, $P = 0.0002$, $I^2 = 77\%$) but did not significantly increase fatal harms (45 vs. 38, RR 1.19 [95% CI 0.65 to 2.19], $P = 0.58$, $I^2 = 30\%$) or serious harms (1404 vs. 1357, RR 1.01 [95% CI 0.94 to 1.08], $P = 0.79$, $I^2 = 0\%$).

(Continued on next page)

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Conclusion: At 4 years follow-up, the HPV vaccines decreased HPV-related cancer precursors and treatment procedures but increased serious nervous system disorders (exploratory analysis) and general harms. As the included trials were primarily designed to assess benefits and were not adequately designed to assess harms, the extent to which the HPV vaccines' benefits outweigh their harms is unclear. Limited access to clinical study reports and trial data with case report forms prevented a thorough assessment.

Systematic review registration: CRD42017056093. Our systematic review protocol was registered on PROSPERO in January 2017: https://www.crd.york.ac.uk/PROSPEROFILES/56093_PROTOCOL_20170030.pdf. Two protocol amendments were registered on PROSPERO on November 2017: https://www.crd.york.ac.uk/PROSPEROFILES/56093_PROTOCOL_20171116.pdf. Our index of the HPV vaccine studies was published in Systematic Reviews in January 2018: https://doi.org/10.1186/s13643-018-0675-z. A description of the challenges obtaining the data was published in September 2018: https://doi.org/10.1136/bmj.k3694.

Keywords: Human papillomavirus vaccine, Systematic review, Meta-analysis, Randomised clinical trial and Clinical study report

Introduction

The approved human papillomavirus (HPV) vaccines—GlaxoSmithKline's Cervarix™ and Merck Sharp and Dohme's Gardasil™ and Gardasil 9™—are considered safe and effective [1–3]. Recent evidence suggests that the vaccines have significant and long-lasting effects (> 12 years) on cervical cancer [4, 5], better effectiveness when vaccinated below the age of 17 [6], and are possibly able to substantially reduce the global incidence of cervical cancer [7]. However, there are important uncertainties regarding both the benefits and harms of the vaccines.

Uncertainties of the benefits of the HPV vaccines

The HPV vaccines' regulatory approvals were mainly based on per-protocol populations and surrogate outcomes of HPV-related lesions, e.g. 'cervical intraepithelial neoplasia or worse' (CIN2$^+$) infected with an HPV vaccine-specific HPV type, such as HPV types 16 and 18 that are associated with the majority of HPV-related cancers [8–10]. It was considered unfeasible and unethical to use HPV-related cancer as the primary outcome [11, 12], since it takes many years for cancer to develop after an HPV infection and also because cervical screening is an established secondary prevention method that leads to removal of precancerous lesions before they become cancerous. Up to 15% of HPV-related cervical cancers may not contain HPV [13], but HPV may be identified in more cases with newer and more sensitive analysis methods [14]. HPV-related lesions are often infected with more than one HPV type, some of which may not be targeted by the vaccines [15]. This makes it impossible to assess which HPV type caused the lesion. The regulatory vaccine approvals were not based on HPV-related lesions irrespective of HPV type in intention to treat populations, and factors such as antigenic changes and herd immunity may be important in the long-term perspective, as the approved HPV vaccines only target up to 9 of the 25 HPV types considered oncogenic [1].

Uncertainties of the harms of the HPV vaccines

A Cochrane review from 2018 [3] and most large epidemiological studies [16–20] did not find serious or general harms associated with the HPV vaccines. The Cochrane review was mainly based on journal publications that often are influenced by reporting bias [21–24], and epidemiological studies are influenced by confounding [25].

Acknowledged rare serious harms include anaphylaxis and syncope [8–10]. Some case studies have reported rare neurological harms such as postural orthostatic tachycardia syndrome (POTS) [26, 27] and complex regional pain syndrome (CRPS) [28]. Cluster analyses of individual case safety reports from the World Health Organisation's (WHOs) VigiBase® revealed additional harms—often serious in nature—that overlapped with the symptomatology of POTS and CRPS [29]. Although the European Medicines Agency's (EMA) investigation of POTS and CRPS did not find an association with the HPV vaccines [2], EMA's investigation was based on the HPV vaccine manufacturers' own assessments [30], and about 30 cases of POTS and CRPS were not recognised in the HPV vaccine manufacturers' trials [31, 32]. Other reported rare harms have included chronic fatigue syndrome (CFS), Guillain–Barré syndrome (GBS) and premature ovarian failure (POF) [33–35].

Addressing the uncertainties of the HPV vaccines

To address the uncertainties of the benefits and harms of the HPV vaccines, we conducted a systematic review

with meta-analyses of trial data from clinical study reports. As of July 2017, about one third of the HPV vaccine studies had not been published and study results were not posted for about half of the completed studies on ClinicalTrials.gov [36]. Therefore, we based our review on study programmes in order to identify all trials [36] and on clinical study reports [37], as these reports provide vastly more information about a study than a corresponding journal publication [21–24].

Methods

Search strategy and study eligibility

Using a six-step process, we constructed and published an index of the HPV vaccine study programmes [36] that included 206 comparative prospective studies (see Fig. 1). Two researchers (LJ and TJ) conducted the six steps that included searches of trial registers, journal publication databases and correspondence with regulators and HPV vaccine manufacturers. It was not feasible to account for duplicate entries, as we indexed studies and searched databases that used different IDs for a unique study (e.g. register ID, study programme ID, manufacturer ID and publication ID) [36].

In May 2014, we requested the study programmes' corresponding clinical study reports from the European Medicines Agency (EMA; via its policy 0043) and obtained those reports that were freely available on GlaxoSmithKline's online trial register. We did not request clinical study reports from the manufacturers, as this would limit our ability to use and share the data [38]. In January 2017, we registered our systematic review protocol in PROSPERO (International prospective register of systematic reviews): CRD42017056093 [37].

We included those trials and their follow-up studies of the 206 comparative studies from our index that were randomised clinical phase II, III or IV trials. We aimed to include studies for which we obtained industry clinical study reports or similar non-industry reports. In the event of no clinical study report being available (for an otherwise eligible trial), we did not include data from the trial publication. We also aimed to include periodical safety update reports. PICO criteria (participants, interventions, comparisons and outcomes) were used to select trials that compared an HPV vaccine with a placebo (normal saline) or active comparator (adjuvant or non-HPV vaccine such as a hepatitis vaccine) in healthy participants (see Additional file 1 for our PRISMA checklist).

Data extraction and risk of bias assessment

One researcher performed trial selection and data extraction (LJ); a second researcher (TJ) checked the selection and extraction; a third researcher (PCG) arbitrated. Cochrane's tool (version 2011) was used for risk of bias assessments [25].

Outcome assessment

We assessed the following primary outcomes: all-cause mortality, deaths from and incidence of HPV-related cancers, incidence of histologically confirmed carcinoma in situ and moderate intraepithelial neoplasia, fatal harms, serious harms and harms of special interest (anaphylaxis, chronic fatigue syndrome [CFS], complex regional pain syndrome [CRPS], Guillain-Barré syndrome [GBS], postural orthostatic tachycardia syndrome [POTS], premature ovarian failure [POF] and syncope). Histological outcomes were assessed irrespective of which HPV types were involved.

Secondary outcomes included HPV-related external genital lesions and referral procedures, new onset diseases (reported in the included clinical study reports as 'medically significant conditions' and 'new medical history') and general harms (reported as 'solicited', 'unsolicited' and 'systemic adverse events'). We did not consider cytological, serological or virological outcomes or local harms due to their lower clinical importance.

The clinical study reports included over 3000 different types of harms that were classified with MedDRA (Medical Dictionary for Regulatory Activities) preferred terms. The harms were often incompletely and heterogeneously reported (see Table 1). We extracted and assessed all individual harms classified with MedDRA-preferred terms. We performed meta-analyses for the five most commonly occurring fatal and serious harms, the five fatal and serious harms that the HPV vaccines increased the most and the five fatal and serious harms that the HPV vaccines decreased the most. For new onset diseases and general harms, we performed meta-analyses for the three most common, increased and decreased harms for each category ('medically significant conditions' and 'new medical history'; and 'solicited', 'unsolicited' and 'systemic adverse events'). MedDRA-preferred terms and total harms were reported as the number of participants with one or more harms over the total number of participants.

To check for possible harm clustering on an organ system level, we meta-analysed the MedDRA-preferred terms in their respective system organ classes (for example, the MedDRA-preferred terms 'dizziness', 'pain' and 'syncope' were part of and therefore included in the MedDRA system organ class 'nervous system disorders'). Only Merck clinical study reports included aggregate numbers for participants with MedDRA system organ class harms, and only for new onset diseases ('new medical history') and general harms ('systemic adverse events'). For all GlaxoSmithKline clinical study reports and for serious harms for Merck clinical study reports, we pooled MedDRA-preferred terms in their respective system organ classes. A participant could potentially be included more than once in a separate analysis (e.g. if a participant experienced a serious 'headache' and serious

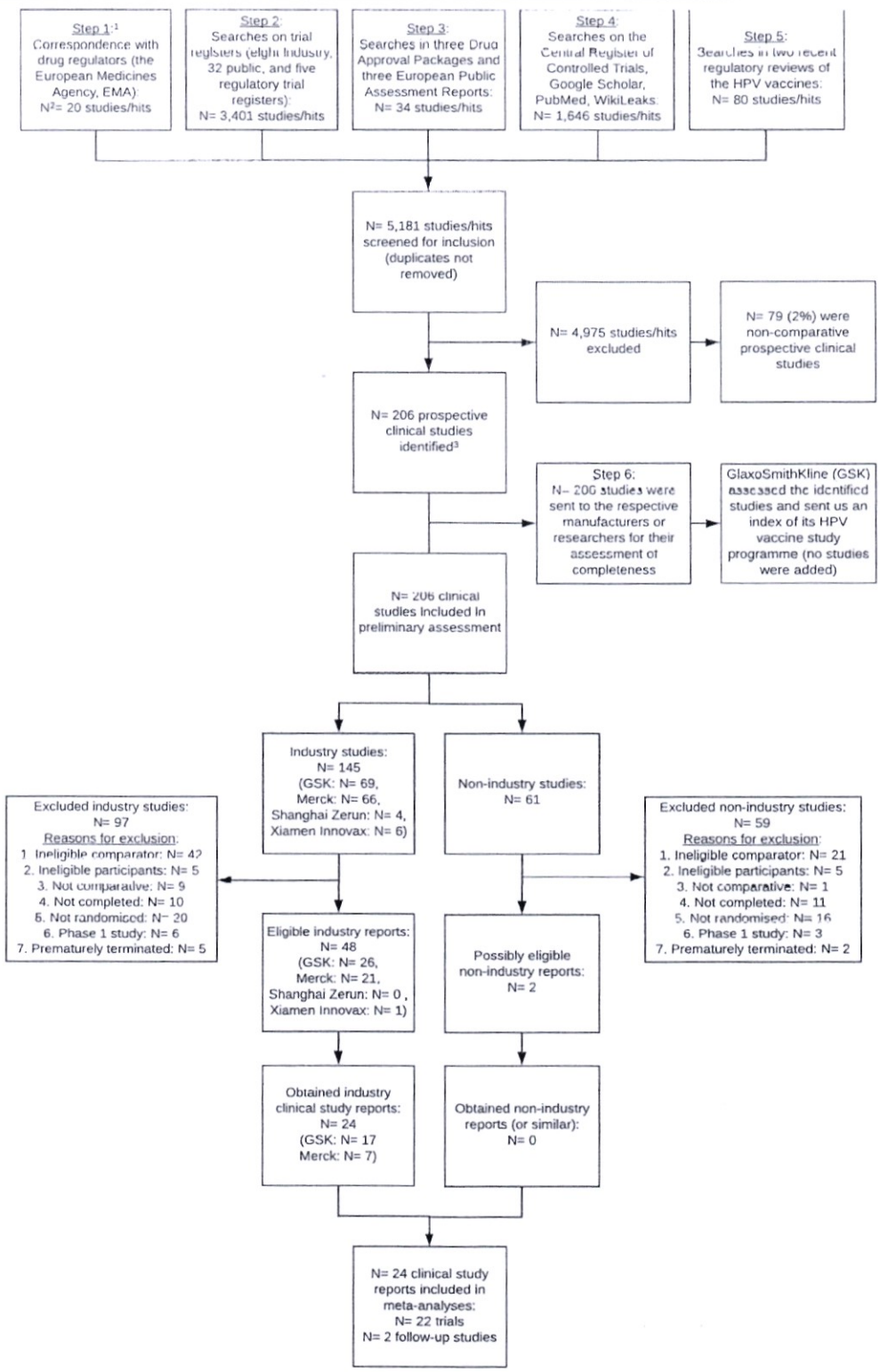

Fig. 1 Benefits and harms of the HPV vaccines: flowchart of the inclusion of clinical study reports. For details on the correspondence and searches conducted in steps 1 to 6, see Jørgensen et al. ([36]: Appendices 1 and 2). Two hundred six studies were identified according to our inclusion and classification criteria, see Jørgensen et al. ([36]: Methods). *N* = the number of studies/entries evaluated

Table 1 Benefits and harms of the HPV vaccines: reporting of harms in included HPV vaccine studies

Reporting of harms[a]	Total		GlaxoSmithKline		Merck Sharp and Dohme	
	Studies (*N* = 24)	Participants (*N* = 96,855)[a]	Studies (*N* = 17)	Participants (*N* = 66,235)[a]	Studies (*N* = 7)	Participants (*N* = 30,620)
Fatal harms						
Reported for the whole study period	23	64,679 (67%)	16	34,059 (51%)	7	30,620 (100%)
Reported for the whole study period for some[b] participants	1	32,176 (33%)	1	32,176 (49%)	0	0 (0%)
Serious harms[c]						
Reported for the whole study period	14	28,245 (30%)	14	28,245 (42%)	0	0 (0%)
No breakdown into MedDRA-preferred terms	3 (21%)	2586 (9%)	3 (21%)	2586 (9%)	0 (0%)	0 (0%)
Reported 0 to 14 days post-vaccination	7	30,620 (31%)	0	0 (0%)	7	30,620 (100%)
Reported for the 7-month vaccination period	2	5814 (6%)	2	5814 (9%)	0	0 (0%)
Reported for a subset or the serious harms judged vaccine-related by the trial investigators[b]	1	32,176 (33%)	1	32,176 (49%)	0	0 (0%)
New onset diseases[d]						
Reported as 'medically significant conditions' for the whole study period	15	65,741 (68%)	15	65,741 (99%)	0	0 (0%)
No breakdown into MedDRA-preferred terms	2 (13%)	33,216 (51%)	2 (13%)	33,216 (51%)	0 (0%)	0 (0%)
Reported as 'new medical history' for the whole study period	7	30,620 (31%)	0	0 (0%)	7	30,620 (100%)
Not reported/included in clinical study report	2	494 (1%)	2	494 (1%)	0	0 (0%)
General harms[e]						
Reported as 'solicited' and 'unsolicited' general harms 7 and 30 days post-vaccination	14	64,010 (66%)	14	64,010 (96%)	0	0 (0%)
Reported for a subset of participants[f]	2 (14%)	7791/50,820	2 (14%)	7791/50,820	0 (0%)	0 (0%)
Reported as 'systemic adverse events' 14 days post-vaccination	7	30,620 (31%)	0	0 (0%)	7	30,620 (100%)
No breakdown into MedDRA-preferred terms	3 (43%)	21,441 (70%)	0 (0%)	0 (0%)	3 (43%)	21,441 (70%)
Not reported/included in clinical study report	3	2225 (3%)	3	2225 (4%)	0	0 (0%)

[a]See Additional file 2 for details on the reporting of harms. Table 1 includes all 24 clinical study reports including the two follow-up studies HPV-023 (follow-up for trial HPV-001) of 433 participants and HPV-063 (follow-up for trial HPV-032) of 752 participants, i.e. 1185 participants (433 + 752) are included twice for the trials HPV-001 and HPV-032. The total denominator is 95,670 for the 22 included trials and 96,855 (95,670 + 1185) for the 24 included clinical study reports

[b]In one trial (HPV-040), 12% (3703/32,176) of participants were included in a subset population for fatal and serious harms reporting

[c](1) GlaxoSmithKline defined serious harms as "any untoward medical occurrence that a resulted in death and b was life-threatening, NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It did not refer to an event, which hypothetically might have caused death, if it were more severe. c. required hospitalisation or prolongation of existing hospitalisation, NOTE: In general, hospitalisation signified that the subject had been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occurred during hospitalisation were AEs [adverse events]. If a complication prolonged hospitalisation or fulfilled any other serious criteria, the event was serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE was to be considered serious. Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline was not considered an AE. d. resulted in disability/incapacity, NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition was not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or p[illegible]nt everyday life functions but did not constitute a substantial disruption. e. was a congenital anomaly/birth defect in the offspring of a study subject". (2) Merck Sharp and Dohme defined serious harms as "any adverse experience occurring at any dose that: Results in death; or that is life threatening (places the subject/patient, in the view of the investigator, at immediate risk of death from the experience as it occurred. [Note: This does not include an adverse experience that, had it occurred in a more severe form, might have caused death.]); or that results in a persistent or significant disability/incapacity (substantial disruption of one's ability to conduct normal life functions); or that results in or prolongs an existing inpatient hospitalisation (hospitalised is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation.); or ALSO: Other important medical events that may not result in death, not be life threatening, or not require hospitalisation may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardise the subject/patient and may require medical or surgical intervention to prevent one of the outcomes listed above"

[d](1) GlaxoSmithKline defined 'medically significant conditions' as "Adverse events prompting emergency room or physician visits that are not (1) related to common diseases or (2) routine visits for physical examination or vaccination, or SAEs [serious adverse events] that are not related to common diseases. Serious adverse events related to common diseases were reported but are not classified as medically significant conditions for analysis purposes. Common diseases include: upper respiratory infections, sinusitis, pharyngitis, gastroenteritis, urinary tract infections, cervicovaginal yeast infections, menstrual cycle abnormalities and injury". (2) Merck Sharp and Dohme did not provide a formal definition for 'new medical history' but described 'new medical history' as "all new reported diagnoses" in the clinical study report of trial V501-019

[e](1) GlaxoSmithKline defined 'solicited' general adverse events as "Adverse events to be recorded as endpoints in the clinical study [i.e. arthralgia, fatigue, headache, myalgia, pyrexia, rash and urticaria]. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period". (2) GlaxoSmithKline defined 'unsolicited' general adverse event as "Any AE [adverse event] reported in addition to those solicited during the clinical study. Also, any "solicited" symptom with onset outside the specified period of follow-up for solicited symptoms was reported as an unsolicited AE". (3) Merck Sharp and Dohme defined 'systemic adverse event' as "any systemic clinical adverse event that developed on the day of vaccination or during the 14 days after vaccination was recorded on the VRC [vaccination report card] along with the date it started and the last date it was present"

[f]The two trials HPV-008 and HPV-040 only reported general harms for 15% (7791/50,820) of included participants

'dizziness', the participant would be counted twice in the MedDRA system organ class analysis of serious nervous system disorders); we therefore consider these MedDRA system organ class analyses exploratory.

Post hoc exploratory outcome assessment

As we did not obtain complete case report forms or individual participant data for any trial, and as the trials' harm assessments had low internal and external validity (see Table 1 and the "Discussion" section), we performed post hoc exploratory outcome analyses where we (1) compared the clinical study report data with pharmacovigilance data; and (2) assessed signs and symptoms of POTS and CRPS (see protocol amendment on PROSPERO [39]).

1) We compared the three largest harm clusters reported from pharmacovigilance up to 1 January 2015 to the World Health Organisation's (WHO) VigiBase® [29] with the clinical study report data (for example, VigiBase's largest HPV vaccine harm cluster—'expected systemic reactions'—consists of the MedDRA-preferred terms headache, nausea, pyrexia, dizziness and vomiting). This was done to assess if the pharmacovigilance data were comparable to the clinical study report data. We used the individual harm cluster terms and found the corresponding MedDRA-preferred terms in the clinical study report data. The data were synthesised for those MedDRA-preferred terms included in each harm cluster.
2) POTS and CRPS are rare syndromes that are difficult to identify; as mentioned, about 30 cases of POTS and CRPS were not recognised in the HPV vaccine manufacturers' trials [31, 32], and there were no reports of POTS and CRPS in the clinical study reports (see Table 9 and the "Results" section). To assess whether signs and symptoms consistent with POTS and CRPS were present in the data, we asked a physician (Louise Brinth) with clinical expertise in POTS and CRPS to assess the reported MedDRA-preferred terms as 'definitely', 'probably', 'probably not' or 'definitely not' associated with the syndromes. As an example, the physician judged the MedDRA-preferred terms 'dizziness postural' and 'pain in extremity' to be 'definitely' associated with POTS and CRPS, respectively. The physician was blinded to the allocation groups and outcome data. The data was synthesised for those MedDRA-preferred terms that the physician judged 'definitely' associated with POTS or CRPS. (Note that the synthesis of two or more different MedDRA-preferred term categories may include a participant more than once in an analysis.)

Data synthesis and analysis

Risk ratios were meta-analysed with the random-effects inverse variance method. As small trials carry more weight with this method, we compared random-effects to a fixed-effect risk ratio for all outcomes. Absolute risk estimates were calculated as the number needed to vaccinate (NNV) or harm (NNH). Review Manager 5 was used for data synthesis and the intention to treat principle to calculate effect estimates. Sensitivity and subgroup analyses were conducted to investigate potential sources of heterogeneity by taking account of age, gender, risk of bias [25] and type of HPV vaccine and comparator.

Results

Characteristics of included trials

We identified 50 eligible studies: 43 industry trials, 5 industry follow-up studies and 2 non-industry trials (see Fig. 1). We obtained 24 clinical study reports of 58,412 pages from EMA and GlaxoSmithKline for 22 industry trials and 2 industry follow-up studies (17 Cervarix™, 5 Gardasil™, 1 Gardasil 9™ and 1 monovalent Merck HPV type 16 vaccine) with a total of 95,670 participants (79,102 females and 16,568 males age 8–72) and 393,194 person-years (see Tables 2 and 3 and Additional file 2). The 24 clinical study reports included 79% (95,670/121,441) of the total eligible sample of the 50 identified eligible studies. It is possible that for some of these eligible studies clinical study reports were never written but journal articles were published. The mean follow-up time was 49 months (weighted by sample size). About two fifths of the participants in the control groups received the aluminium-based adjuvants that were used in the HPV vaccines (18,192/48,595), three fifths received hepatitis vaccines that also contained the aluminium-based adjuvants that were used in the HPV vaccines—except for the hepatitis vaccine Aimmugen™—(29,500), and less than a thousand participants received carrier solution (597) or saline placebo (306).

Characteristics of potentially eligible studies

For the 26 remaining and potentially eligible studies (23 trials and three follow-up studies) for which no clinical study reports were obtained (or similar reports for the two non-industry trials), numbers of participants were identified for 20 of the 23 industry and 1 of the 2 non-industry trials. The trials included 25,632 and 139 participants, respectively, which were equal to 21% of the total eligible sample (25,771/121,441). These studies were not included in the review or analyses (see Additional file 3).

Risk of bias of included trials

All 22 trials and the 2 follow-up studies were at low risk of bias for 'sequence generation' and 'allocation concealment',

Table 2 Benefits and harms of the HPV vaccines: number of pages obtained of clinical study reports from the European Medicines Agency and GlaxoSmithKline

	HPV vaccine manufacturer	Study programme ID	Total pages obtained	European Medicines Agency	GlaxoSmithKline
1	GlaxoSmithKline	HPV-001	5813	5813	0
2	GlaxoSmithKline	HPV-003	799	0	799
3	GlaxoSmithKline	HPV-008	11,456	4263	7193
4	GlaxoSmithKline	HPV-013	8323	382	7941
5	GlaxoSmithKline	HPV-015	6290	543	5747
6	GlaxoSmithKline	HPV-023	936	0	936
7	GlaxoSmithKline	HPV-029	1543	0	1543
8	GlaxoSmithKline	HPV-030	1351	0	1351
9	GlaxoSmithKline	HPV-031	476	0	476
10	GlaxoSmithKline	HPV-032	2912	0	2912
11	GlaxoSmithKline	HPV-033	587	0	587
12	GlaxoSmithKline	HPV-035	451	0	451
13	GlaxoSmithKline	HPV-038	957	0	957
14	GlaxoSmithKline	HPV-040	2892	128	2764
15	GlaxoSmithKline	HPV-058	1745	0	1745
16	GlaxoSmithKline	HPV-063	1474	0	1474
17	GlaxoSmithKline	HPV-069	819	0	819
18	Merck Sharp and Dohme	V501 005	357	357	0
19	Merck Sharp and Dohme	V501-013	1797	1797	0
20	Merck Sharp and Dohme	V501-015	713	713	0
21	Merck Sharp and Dohme	V501-018	1014	1014	0
22	Merck Sharp and Dohme	V501-019	2645	2645	0
23	Merck Sharp and Dohme	V501-020	2595	2595	0
24	Merck Sharp and Dohme	V503-006	467	467	0
	Total pages obtained		58,412	20,717	37,695

and the majority were at low risk of bias for 'blinding of outcome assessors' (19/24) and 'blinding of participants and personnel' (16/24; see Figs. 2 and 3 and Additional file 2). However, due to the following reasons, we judged all studies to be at high risk of bias. Nearly all control participants (48,289/48,595, 99%) received an active comparator such as HPV vaccine aluminium-containing adjuvants or hepatitis vaccines. This distorted—to an unknown extent—the assessment of harms, as the trials tested an HPV vaccine vs. an active part of the same HPV vaccine (see reference [38] for additional clarification). Furthermore, serious harms were incompletely reported for 72% of the participants (68,610/95,670; see Table 1 and Additional file 2). All 24 clinical study reports contained redactions—especially of harms—and lacked significant parts such as serious harm narratives and case report forms (except for two reports: HPV-001 and HPV-008, which, however, included less than half of the participants' case report forms) [38]. These situations are not covered by Cochrane's risk of bias tool version 2011. Although not related to participant attrition, we judged the lack of serious harm narratives and case report forms as high risk of 'incomplete outcome data'. In addition, while not related to the availability of study protocols, we judged the redactions of the clinical study reports as high risk of 'selective outcome reporting'. We decided to conduct meta-analyses, since the high risk of bias mainly constituted situations that to our knowledge are not related to empirically verified bias mechanisms.

Benefits

Seven clinical study reports assessed histological outcomes of which four reported HPV-related cancer outcomes irrespective of involved HPV types. At 4 years follow-up, the HPV vaccines did not decrease HPV-related cancer (7 in the HPV vaccine groups vs. 3 in the comparator groups, risk ratio [RR] 1.68 [95% confidence interval, CI, 0.51 to 5.49], $P = 0.39$, $I^2 = 0\%$) or deaths hereof (2 vs. 1, RR 1.44 [95% CI 0.23 to 9.12], P

Table 3 Benefits and harms of the HPV vaccines: characteristics of included participants

Characteristics of included participants[a]	Total		HPV vaccine				Comparator		
	HPV vaccine (*N* = 47,075)	Comparator (*N* = 48,595)	Cervarix (*N* = 31,316)	Gardasil (*N* = 13,937)	Gardasil 9 (*N* = 618)	HPV 16 vaccine (*N* = 1204)	Placebo (*N* = 306)	Adjuvant[b] (*N* = 18,789)	Hepatitis vaccine[c] (*N* = 29,500)
Participation									
Randomised	47,075	48,595	31,316	13,937	618	1204	306	18,789	29,500
Received one (1) dose	47,012 (99%)	48,556 (99%)	31,291 (99%)	13,927 (99%)	615 (99%)	1193 (99%)	306 (100%)	18,750 (99%)	29,500 (100%)
Received two (2) doses	46,105 (98%)	47,725 (98%)	30,788 (98%)	13,564 (97%)	604 (98%)	1092 (91%)	304 (99%)	18,304 (97%)	29,117 (99%)
Received three (3) doses	45,079 (96%)	46,726 (96%)	30,073 (96%)	13,286 (95%)	597 (97%)	1019 (85%)	300 (98%)	17,906 (96%)	28,520 (97%)
Completed vaccination period	44,202 (94%)	45,862 (94%)	29,331 (94%)	13,156 (94%)	595 (97%)	993 (82%)	300 (98%)	17,809 (95%)	27,753 (94%)
Entered follow-up period	18,540 (39%)	18,059 (37%)	4090 (14%)	13,344 (96%)	Not applicable	1126 (94%)	Not applicable	17,590 (94%)	469 (2%)
Completed follow-up period	15,826 (34%)	14,601 (30%)	2929 (10%)	11,986 (86%)	Not applicable	835 (69%)	Not applicable	14,445 (77%)	156 (1%)
Gender									
Female	42,036 (89%)	37,066 (76%)	28,876 (92%)	11,338 (81%)	618 (100%)	1204 (100%)	306 (100%)	16,481 (88%)	20,279 (69%)
Age									
Mean age in years	20.3	20.2	21.2	21.4	19.0	20.0	19.0	22.9	20.5
Age group range in years	9–72	8–68	9–72	9–45	12–26	16–25	12–26	9–68	8–46
Race									
Asian	7589 (16%)	7295 (15%)	6232 (20%)	1248 (9%)	40 (6%)	69 (6%)	14 (5%)	2678 (14%)	4603 (16%)
Black	1426 (3%)	1492 (3%)	467 (2%)	862 (6%)	3 (1%)	94 (8%)	3 (1%)	1108 (6%)	381 (1%)
Hispanic	4492 (10%)	4378 (9%)	1787 (6%)	2616 (19%)	0 (0%)	89 (7%)	0 (0%)	3403 (18%)	975 (3%)
White	31,743 (67%)	33,558 (69%)	22,335 (70%)	7998 (56%)	483 (78%)	918 (76%)	231 (75%)	9960 (53%)	23,367 (79%)
Other	1625 (3%)	1576 (3%)	297 (1%)	1202 (9%)	92 (15%)	34 (3%)	58 (19%)	1343 (7%)	174 (1%)
Unknown	209 (1%)	296 (1%)	198 (1%)	11 (1%)	0 (0%)	0 (0%)	0 (0%)	297 (2%)	0 (0%)

[a]See Additional file 2 for details on the characteristics of included participants. Table 3 does not include data from the two follow-up studies HPV-023 (follow-up for trial HPV-001) of 433 participants and HPV-063 (follow-up for trial HPV-032) of 752 participants

[b]Adjuvant comparators included amorphous aluminium hydroxyphosphate sulphate (AAHS), aluminium hydroxide ($Al[OH]_3$) and Gardasil's carrier solution (yeast protein, sodium chloride, L-histidine, polysorbate 80 and sodium borate)

[c]Hepatitis vaccines included Aimmugen™ (hepatitis A vaccine), Engerix-B™ (hepatitis B vaccine), Havrix™ (hepatitis A vaccine) and Twinrix Paediatric™ (hepatitis A and B vaccine); see Additional file 2

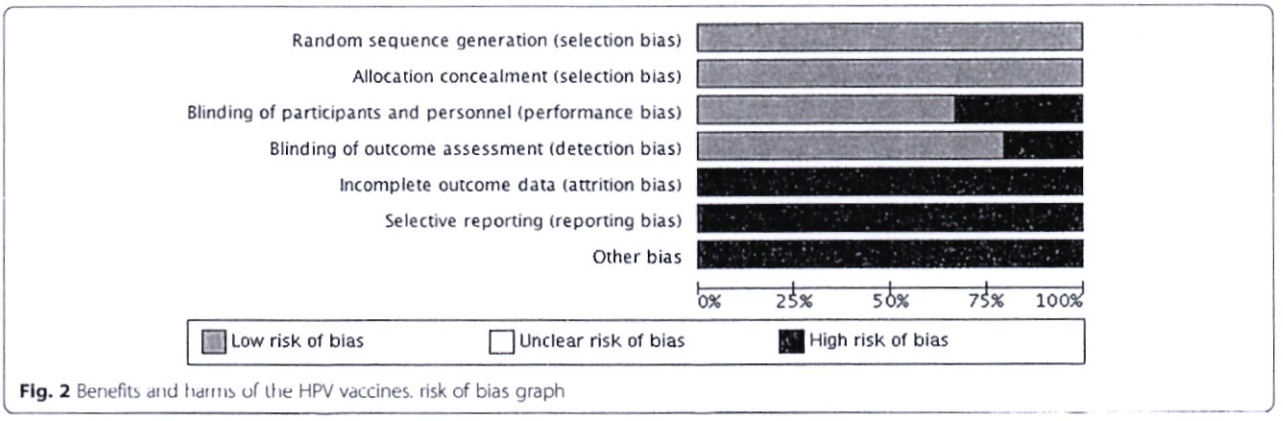

Fig. 2 Benefits and harms of the HPV vaccines. risk of bias graph

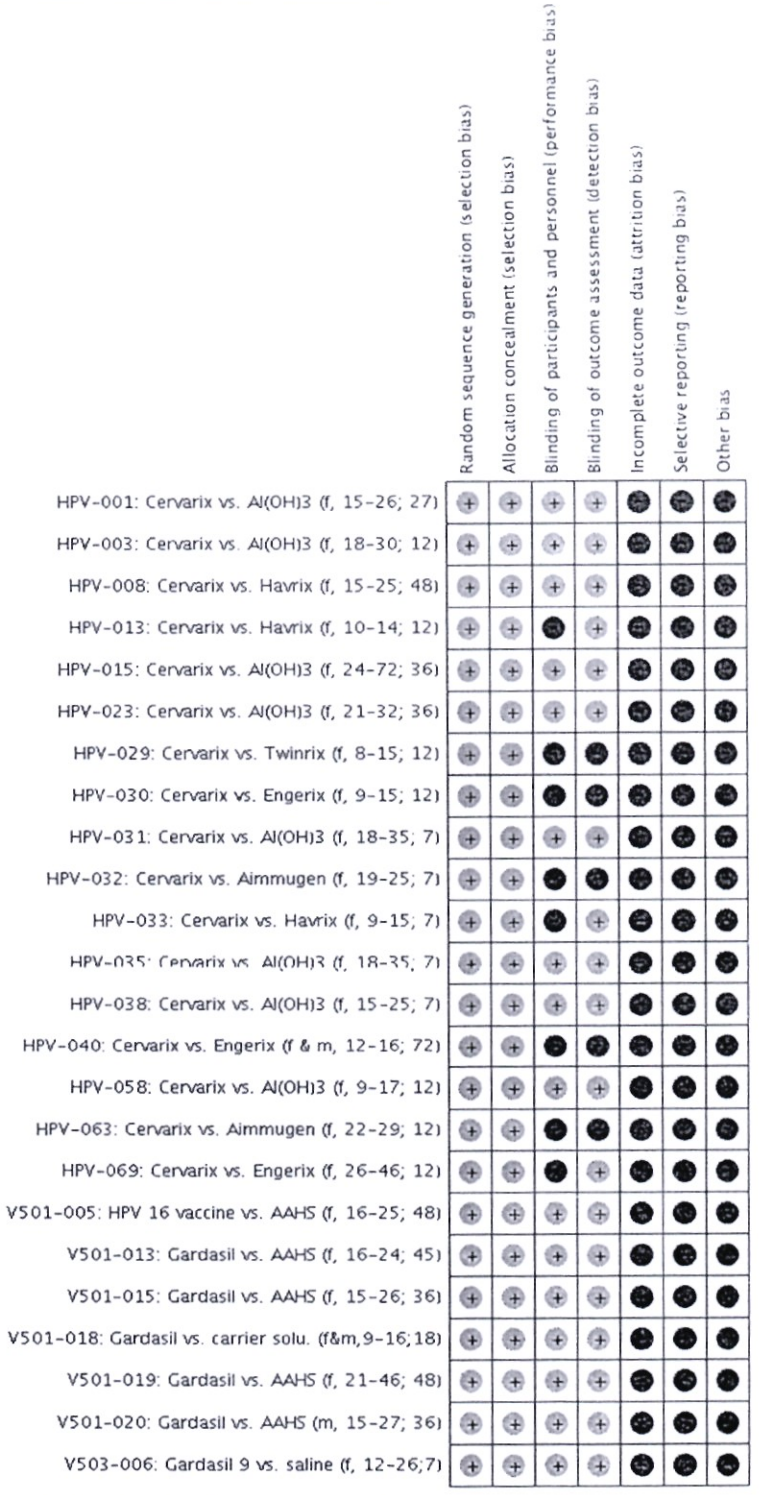

Fig. 3 Benefits and harms of the HPV vaccines: risk of bias summary (each study is noted as "manufacturer ID: type of HPV vaccine vs. type of comparator (included gender, age group; months of follow-up)", e.g. "HPV-001: Cervarix vs. $Al(OH)_3$ (f, 15-26; 27)")

Table 4 Benefits and harms of the HPV vaccines: summary of HPV-related outcomes

Summary of HPV-related outcomes[a]	HPV vaccine ($N = 47,075$)	Comparator ($N = 48,595$)	Risk ratio[c] [95% CI]
Cancer mortality			
Total	2	1	1.44 [0.23, 9.12]
Cervical	1 (50%)	0 (0%)	2.99 [0.12, 73.33]
Oropharyngeal	1 (50%)	1 (100%)	1.00 [0.10, 9.58]
Cancer incidence			
Total	7	3	1.68 [0.51, 5.49]
Anal	0 (0%)	0 (0%)	Not applicable
Cervical	3 (43%)	2 (67%)	1.41 [0.19, 10.21]
Oropharyngeal	1 (14%)	1 (33%)	1.00 [0.10, 9.58]
Penile	Not reported	Not reported	Not applicable
Vaginal	1 (14%)	0 (0%)	2.99 [0.12, 73.33]
Vulvar	2 (29%)	0 (0%)	3.01 [0.31, 28.89]
Not HPV-related	20	23	0.90 [0.49, 1.63]
Carcinoma in situ incidence			
Total	367	490	0.73 [0.53, 1.00]
Anal (AIN3)	Not reported	Not reported	Not applicable
Cervical	367 (100%)	490 (100%)	0.73 [0.53, 1.00]
Adenoid type (AIS)	9 (2%)	31 (6%)	0.32 [0.15, 0.66]
Squamous type (CIN3)	358 (98%)	459 (94%)	0.85 [0.61, 1.17]
Penile (PIN3)	Not reported	Not reported	Not applicable
Vaginal (VaIN3)	Not reported	Not reported	Not applicable
Vulvar (VIN3)	Not reported	Not reported	Not applicable
Moderate intraepithelial neoplasia incidence			
Total	538	763	0.81 [0.59, 1.11]
Anal (AIN2)	0 (0%)	0 (0%)	Not applicable
Cervical (CIN2)	538 (100%)	763 (100%)	0.81 [0.59, 1.11]
Penile (PIN2)	Not reported	Not reported	Not applicable
Vaginal (VaIN2)	Not reported	Not reported	Not applicable
Vulvar (VIN2)	Not reported	Not reported	Not applicable
Carcinoma in situ or worse incidence			
Total	372	498	0.79 [0.59, 1.05]
Anal ($AIN3^+$)	Not reported	Not reported	Not applicable
Cervical ($CIN3^+$, AIS included)	372 (100%)	498 (100%)	0.79 [0.59, 1.05]
Penile ($PIN3^+$)	Not reported	Not reported	Not applicable
Vaginal ($VaIN3^+$)	Not reported	Not reported	Not applicable
Vulvar ($VIN3^+$)	Not reported	Not reported	Not applicable
Moderate intraepithelial neoplasia or worse incidence			
Total	952	1239	0.78 [0.66, 0.91]
Anal ($AIN2^+$)	0 (0%)	0 (0%)	Not applicable
Cervical ($CIN2^+$)	892 (93%)	1144 (92%)	0.81 [0.68, 0.97]
Penile ($PIN2^+$)	3 (1%)	3 (1%)	1.00 [0.20, 4.95]
Vaginal ($VaIN2^+$)	17 (2%)	27 (2%)	0.64 [0.32, 1.27]
Vulvar ($VIN2^+$)	18 (2%)	36 (3%)	0.49 [0.18, 1.36]
Vaginal or vulvar ($VIN2^+$ or $VaIN2^+$)	22 (2%)	29 (2%)	0.76 [0.44, 1.32]

Table 4 Benefits and harms of the HPV vaccines: summary of HPV related outcomes *(Continued)*

Summary of HPV related outcomes[a]	HPV vaccine (*N* = 47,075)	Comparator (*N* = 48,595)	Risk ratio[c] [95% CI]
External genital lesion (EGL) incidence			
Total	289	582	0.56 [0.39, 0.82]
HPV-related referral procedures[b]			
Any	1941	2264	0.86 [0.81, 0.90]
Biopsy	2449	3021	0.74 [0.62, 0.88]
Endoscopy	4354	4965	0.88 [0.85, 0.91]
Treatment (surgical and non-surgical)	1018	1416	0.71 [0.63, 0.80]

[a]See Additional file 4 sections 1 to 8 for meta-analyses of HPV-related outcomes. It was not feasible to present this summary table for the 16 subgroups (based on age group, gender, type of HPV vaccine and comparator) of the 24 included clinical study reports
[b]Two trials (V501-013 and V501-015) reported 'any' procedure, while other trials reported individual outcomes, for example, 'biopsy'
[c]Risk ratios were calculated with the random-effects inverse variance method

= 0.70, I^2 = 0%); whereas they decreased HPV-related carcinoma in situ (367 vs. 490, RR 0.73 [95% CI 0.53 to 1.00], number needed to vaccinate [NNV] 387, $P = 0.05$, I^2 = 67%) and the composite surrogate outcome of HPV-related moderate intraepithelial neoplasia or worse (952 vs. 1239, RR 0.78 [95% CI 0.66 to 0.91], NNV 190, $P = 0.002$, I^2 = 53%). The HPV vaccines also decreased HPV-related external genital lesions (289 vs. 582, RR 0.56 [95% CI 0.39 to 0.82], NNV 47, $P = 0.003$, I^2 = 83%) and HPV-related treatment procedures such as cervical conisations (1018 vs. 1416, RR 0.71 [95% CI 0.63 to 0.80], NNV 75, $P < 0.00001$, I^2 = 45%) (see Table 4 and Additional file 4).

Harms

Serious harms

The HPV vaccines did not significantly increase fatal harms (45 vs. 38, RR 1.19 [95% CI 0.65 to 2.19], P = 0.58, I^2 = 30%) or serious harms (1404 vs. 1357, RR 1.01 [95% CI 0.94 to 1.08], $P = 0.79$, I^2 = 0%), and no individual fatal or serious harm classified with a MedDRA-preferred term was significantly increased or decreased by the HPV vaccines (see Table 5 and Additional file 4).

New onset diseases

The HPV vaccines increased new onset back pain (397 vs. 336, RR 1.15 [95% CI 1.00 to 1.33], NNH 589, P = 0.05, I^2 = 0%) but decreased new onset gynaecological chlamydia infection (1409 vs. 1512, RR 0.93 [95% CI 0.87 to 1.00], NNV 176, $P = 0.05$, I^2 = 0%) and vaginal infection (369 vs. 420, 0.87 [95% CI 0.76 to 1.00], NNV 150, $P = 0.05$, I^2 = 0%) (see Table 6 and Additional file 4).

General harms

The HPV vaccines increased general harms (13,248 vs. 12,394, RR 1.07 [95% CI 1.03 to 1.11], NNH 51, P = 0.0002, I^2 = 77%)—especially myalgia (3989 vs. 3047, RR 1.41 [95% CI 1.24 to 1.60], NNH 26, $P < 0.00001$, I^2 = 80%), fatigue (4933 vs. 4489, RR 1.13 [95% CI 1.08 to 1.18], NNH 67, $P < 0.00001$, I^2 = 22%) and headache (5561 vs. 5246, RR 1.06 [95% CI 1.02 to 1.11], NNH 83, $P = 0.009$, I^2 = 40%) (see Table 7 and Additional file 4).

Exploratory harm analyses

The HPV vaccines increased serious nervous system disorders grouped in the MedDRA system organ class (72 vs. 46, RR 1.49 [95% CI 1.02 to 2.16], number needed to harm [NNH] 1325, $P = 0.04$, I^2 = 0%) but decreased new onset vascular disorders grouped in the MedDRA system organ class (234 vs. 294, RR 0.80 [95% CI 0.67 to 0.94], NNV 439, $P = 0.009$, I^2 = 0%) (see Table 8 and Additional file 4).

Harms of special interest

Cases of anaphylaxis and syncope were evenly distributed. There were no cases of chronic fatigue syndrome (CFS), complex regional pain syndrome (CRPS), Guillain-Barré syndrome (GBS) or postural orthostatic tachycardia syndrome (POTS), but there was one case of premature ovarian failure (POF) in the HPV vaccine group (see Table 9 and Additional file 4).

Post hoc exploratory harm analyses of special interest

The data from the included clinical study reports that corresponded to the three largest harm clusters reported from pharmacovigilance were associated with general harms, but not serious harms or new onset diseases. The serious harms that were judged 'definitely associated' with POTS or CRPS by the blinded physician were increased by the HPV vaccines, both for POTS (56 vs. 26, RR 1.92 [95% CI 1.21 to 3.07], NNH 1073, $P = 0.006$, I^2 = 0%) and CRPS (95 vs. 57, RR 1.54 [95% CI 1.11 to 2.14], NNH 906, $P = 0.010$, I^2 = 0%). The new onset diseases that were judged 'definitely associated' with POTS were also increased by the HPV vaccines (3675 vs. 3352, RR 1.08 [95% CI 1.01 to 1.15], NNH 144, $P = 0.03$, I^2 = 29%) (see Table 9 and Additional file 4).

Table 5 Benefits and harms of the HPV vaccines: summary of fatal and serious harms

Summary of fatal and serious harms[a]	HPV vaccine (*N* = 47,075)	Comparator (*N* = 45,905)	Risk ratio[e] [95% CI]
Fatal harms			
Participants with fatal harms[b]	45	38	1.19 [0.65, 2.19]
Number of MedDRA-classified fatal harms[b]	79	51	Not applicable
Number of fatal harms judged HPV vaccine-related	0 (0%)	0 (0%)	Not applicable
Most common fatal harms (MedDRA-preferred terms, *n* = participants)			
Cardiorespiratory arrest	3	2	0.99 [0.13, 7.65]
Completed suicide	4	8	0.58 [0.15, 2.19]
Gunshot wound	2	3	0.74 [0.09, 5.85]
Homicide	2	2	0.95 [0.14, 6.50]
Road traffic accident	5	7	0.77 [0.24, 2.46]
Fatal harms most increased by the HPV vaccines (MedDRA-preferred terms, *n* = participants)			
Cardiac arrest	2	0	3.00 [0.31, 28.82]
Metastases to lung	2	0	3.00 [0.31, 28.82]
Renal failure acute	2	0	3.00 [0.31, 28.82]
Systemic lupus erythematosus	2	0	3.00 [0.31, 28.82]
Traumatic intracranial haemorrhage	2	0	3.00 [0.31, 28.82]
Fatal harms most decreased by the HPV vaccines (MedDRA-preferred terms, *n* = participants)[c]			
Completed suicide	4	8	0.58 [0.15, 2.19]
Gunshot wound	2	3	0.74 [0.09, 5.85]
Road traffic accident	5	7	0.77 [0.24, 2.46]
Serious harms			
Participants with serious harms[d]	1404	1357	1.01 [0.94, 1.08]
Participants that withdrew due to a serious harm	54 (4%)	49 (4%)	1.08 [0.72, 1.61]
Number of MedDRA-classified serious harms[d]	1741	1628	Not applicable
Number of serious harms judged HPV vaccine-related	46 (3%)	44 (3%)	Not applicable
Most common serious harms (MedDRA-preferred terms, *n* = participants)			
Abortion missed	33	41	0.81 [0.51, 1.27]
Abortion spontaneous	89	78	1.14 [0.84, 1.55]
Abortion spontaneous complete	63	62	1.01 [0.71, 1.44]
Abortion spontaneous incomplete	73	54	1.35 [0.95, 1.92]
Appendicitis	72	82	0.85 [0.62, 1.17]
Serious harms most increased by the HPV vaccines (MedDRA-preferred terms, *n* = participants)			
Abortion spontaneous	89	78	1.14 [0.84, 1.55]
Abortion spontaneous incomplete	73	54	1.35 [0.95, 1.92]
Pneumonia	26	15	1.64 [0.87, 3.09]
Pyelonephritis	31	17	1.70 [0.93, 3.10]
Tonsillitis	18	9	1.59 [0.72, 3.49]
Serious harms most decreased by the HPV vaccines (MedDRA-preferred terms, *n* = participants)			
Abortion missed	33	41	0.81 [0.51, 1.27]
Appendicitis	72	82	0.85 [0.62, 1.17]
Ligament rupture	5	12	0.44 [0.15, 1.29]
Ovarian cyst rupture	6	13	0.46 [0.18, 1.21]
Overdose	22	31	0.72 [0.42, 1.23]

[a]See Additional file 4 sections 9 and 10 for fatal and serious harm meta-analyses. The applied harm categories are MedDRA-preferred terms. It was not feasible to present this summary table for the 16 subgroups (based on age group, gender, type of HPV vaccine and comparator) of the 24 included clinical study reports
[b]The clinical study reports reported 130 individual MedDRA-classified fatal harms for 83 participants
[c]There were 20 different MedDRA-preferred term categories of fatal harms with the same non-significant difference, i.e. no fatal harm in the HPV vaccine group and one fatal harm in the comparator group
[d]The clinical study reports reported 3369 individual MedDRA-classified serious harms for 2761 participants, i.e. 1.2 serious harms per participant. Each MedDRA-classified serious harm was reported as the number of participants with a MedDRA-classified serious harm over the total number of participants
[e]Risk ratios were calculated with the random effects inverse variance method

Table 6 Benefits and harms of the HPV vaccines: summary of new onset diseases

Summary of new onset diseases[a]	HPV vaccine total ($N = 47,075$)	Comparator total ($N = 48,595$)	Risk ratio[f] total [95% CI]	Risk ratio[f] MSC [95% CI]	Risk ratio[f] NMH [95% CI]
Total					
Participants with new onset diseases[b]	14,258	14,014	0.99 [0.97, 1.02]	0.98 [0.90, 1.06]	1.00 [0.97, 1.03]
Follow-up[c]	2296	2365	0.98 [0.94, 1.01]	Not applicable	0.98 [0.94, 1.01]
Number of MedDRA-classified new onset diseases[b]	47,474	46,662	Not applicable	Not applicable	Not applicable
Medically significant conditions (MSC)[d]	7882 (17%)	7994 (17%)	Not applicable	Not applicable	Not applicable
New medical history (NMH)[e]	39,592 (83%)	38,668 (83%)	Not applicable	Not applicable	Not applicable
Most common new onset diseases (MedDRA-preferred terms, *n* = participants)					
MSC					
Depression	443	432	1.02 [0.89, 1.16]	1.02 [0.85, 1.23]	1.01 [0.84, 1.22]
Genitourinary tract gonococcal infection	149	162	0.92 [0.74, 1.15]	0.91 [0.73, 1.14]	1.15 [0.37, 3.52]
Gynaecological chlamydia infection	1409	1512	0.93 [0.87, 1.00]	0.95 [0.88, 1.03]	0.87 [0.76, 1.00]
NMH					
Vaginal candidiasis	1297	1359	0.95 [0.89, 1.02]	Not applicable	0.95 [0.89, 1.02]
Vaginitis bacterial	1185	1204	0.98 [0.91, 1.06]	Not applicable	0.98 [0.91, 1.06]
Urinary tract infection	1023	1086	0.93 [0.86, 1.01]	0.33 [0.01, 8.19]	0.93 [0.86, 1.02]
New onset diseases most increased by the HPV vaccines (MedDRA-preferred terms, *n* = participants)					
MSC					
Abdominal pain	433	374	1.21 [0.98, 1.50]	1.38 [1.00, 1.92]	1.17 [0.87, 1.57]
Back pain	397	336	1.15 [1.00, 1.33]	1.40 [1.05, 1.86]	1.08 [0.91, 1.28]
Headache	771	693	1.06 [0.92, 1.22]	1.29 [0.75, 2.24]	1.04 [0.93, 1.15]
NMH					
Amenorrhoea	394	359	1.09 [0.87, 1.37]	0.66 [0.38, 1.15]	1.17 [0.93, 1.48]
Headache	771	693	1.06 [0.92, 1.22]	1.29 [0.75, 2.24]	1.04 [0.93, 1.15]
Joint sprain	113	83	1.18 [0.80, 1.75]	0.60 [0.29, 1.22]	1.45 [0.94, 2.24]
New onset diseases most decreased by the HPV vaccines (MedDRA-preferred terms, *n* = participants)					
MSC					
Cystitis	480	502	0.93 [0.77, 1.09]	0.65 [0.44, 0.96]	0.99 [0.87, 1.13]
Gynaecological chlamydia infection	1409	1512	0.93 [0.87, 1.00]	0.95 [0.88, 1.03]	0.87 [0.76, 1.00]
Type 2 diabetes mellitus	31	47	0.89 [0.38, 2.09]	0.62 [0.32, 1.20]	3.00 [0.47, 19.02]
NMH					
Urinary tract infection	1023	1086	0.93 [0.86, 1.01]	0.33 [0.01, 8.19]	0.93 [0.86, 1.02]
Vaginal candidiasis	1297	1359	0.95 [0.89, 1.02]	Not applicable	0.95 [0.89, 1.02]
Vaginal infection	369	420	0.87 [0.76, 1.00]	Not applicable	0.87 [0.76, 1.00]

[a]See Additional file 4 section 11 for meta-analyses of new onset diseases. The applied harm categories are MedDRA-preferred terms. New onset diseases consist of 'medically significant conditions' (MSC) and 'new medical history' (NMH). Numbers for 'HPV vaccine' and 'comparator' are the total of MSC and NMH. We divided new onset diseases for MSC and NMH, since the definitions for MSC and NMH differed (see Table 1). It was not feasible to present this summary table for the 16 subgroups (based on age group, gender, type of HPV vaccine and comparator) of the 24 included clinical study reports

[b]The clinical study reports reported 94,136 individual MedDRA-preferred term classified new onset diseases for 28,272 participants, i.e. 3.3 new onset diseases per participant. New onset diseases were reported as the number of participants over the total number of participants

[c]'Follow-up' represents the trials V501-005, V501-019 and V501-020 that had dichotomized reporting of new medical history (NMH) into the vaccination period (day 0 to month 7) and follow-up period (from month 7 to the last day of follow-up). We included the vaccination periods for these trials in 'participants with new onset diseases' and included the follow-up periods in 'follow-up'

[d]GlaxoSmithKline defined 'medically significant conditions' as "Adverse events prompting emergency room or physician visits that are not (1) related to common diseases or (2) routine visits for physical examination or vaccination, or SAEs [serious adverse events] that are not related to common diseases. Serious adverse events related to common diseases were reported but are not classified as medically significant conditions for analysis purposes. Common diseases include: upper respiratory infections, sinusitis, pharyngitis, gastroenteritis, urinary tract infections, cervicovaginal yeast infections, menstrual cycle abnormalities and injury"

[e]Merck Sharp and Dohme did not provide a formal definition for 'new medical history' but described 'new medical history' as "all new reported diagnoses" in the clinical study report of trial V501-019

[f]Risk ratios were calculated with the random-effects inverse variance method

Table 7 Benefits and harms of the HPV vaccines: summary of general harms

Summary of general harms[a]	HPV vaccine total ($N = 47,075$)	Comparator total ($N = 48,595$)	Risk ratio[f] total [95% CI]	Risk ratio[f] SGAE [95% CI]	Risk ratio[f] UGAE [95% CI]	Risk ratio[f] SYAE [95% CI]
Total						
Participants with general harms[b]	13,248	12,394	1.07 [1.03, 1.11]	1.11 [1.06, 1.16][g]	1.11 [1.06, 1.16][g]	1.01 [0.98, 1.03]
Number of MedDRA-classified general harms[b]	37,999	31,916	Not applicable	Not applicable	Not applicable	Not applicable
Solicited general adverse events (SGAE)[c]	30,408 (80%)	25,300 (79%)	Not applicable	Not applicable	Not applicable	Not applicable
Unsolicited general adverse events (UGAE)[d]	3197 (8%)	3136 (10%)	Not applicable	Not applicable	Not applicable	Not applicable
Systemic adverse events (SYAE)[e]	4394 (12%)	3480 (11%)	Not applicable	Not applicable	Not applicable	Not applicable
Most common general harms (MedDRA-preferred terms, n = participants)						
SGAE and UGAE						
Fatigue	4933	4489	1.13 [1.08, 1.18]	1.14 [1.09, 1.19]	1.00 [0.15, 6.53]	0.92 [0.70, 1.20]
Headache	5561	5246	1.06 [1.02, 1.11]	1.08 [1.03, 1.14]	1.76 [1.26, 2.47]	0.98 [0.90, 1.07]
Myalgia	3989	3047	1.41 [1.24, 1.60]	1.42 [1.24, 1.63]	1.15 [0.24, 5.57]	1.33 [0.95, 1.85]
SYAE						
Headache	5561	5246	1.06 [1.02, 1.11]	1.08 [1.03, 1.14]	1.76 [1.26, 2.47]	0.98 [0.90, 1.07]
Pyrexia	1599	1386	1.12 [1.02, 1.22]	1.15 [1.06, 1.25]	1.47 [0.93, 2.34]	1.05 [0.80, 1.36]
Nasopharyngitis	339	277	1.17 [0.91, 1.50]	Not applicable	1.40 [0.94, 2.09]	0.95 [0.78, 1.16]
General harms most increased by the HPV vaccines (MedDRA-preferred terms, n = participants)						
SGAE and UGAE						
Fatigue	4933	4489	1.13 [1.08, 1.18]	1.14 [1.09, 1.19]	1.00 [0.15, 6.53]	0.92 [0.70, 1.20]
Headache	5561	5246	1.06 [1.02, 1.11]	1.08 [1.03, 1.14]	1.76 [1.26, 2.47]	0.98 [0.90, 1.07]
Myalgia	3989	3047	1.41 [1.24, 1.60]	1.42 [1.24, 1.63]	1.15 [0.24, 5.57]	1.33 [0.95, 1.85]
SYAE						
Myalgia	3989	3047	1.41 [1.24, 1.60]	1.42 [1.24, 1.63]	1.15 [0.24, 5.57]	1.33 [0.95, 1.85]
Nausea	213	148	1.21 [0.89, 1.65]	Not applicable	1.32 [0.35, 4.98]	1.25 [0.84, 1.86]
Pyrexia	1599	1386	1.12 [1.02, 1.22]	1.15 [1.06, 1.25]	1.47 [0.93, 2.34]	1.05 [0.80, 1.36]
General harms most decreased by the HPV vaccines (MedDRA-preferred terms, n = participants)						
SGAE and UGAE						
Influenza	119	120	0.91 [0.61, 1.36]	Not applicable	0.88 [0.39, 1.97]	0.94 [0.56, 1.58]
Cough	86	87	0.89 [0.65, 1.21]	Not applicable	0.83 [0.46, 1.49]	0.90 [0.60, 1.37]
Oropharyngeal pain	111	97	1.10 [0.80, 1.50]	Not applicable	0.91 [0.58, 1.43]	1.29 [0.75, 2.22]
SYAE						
Fungal infection	4	11	0.78 [0.09, 6.43]	Not applicable	3.01 [0.31, 28.83]	0.18 [0.04, 0.82]
Sinus headache	9	15	0.49 [0.21, 1.14]	Not applicable	Not applicable	0.49 [0.21, 1.14]
Joint injury	2	5	0.47 [0.11, 2.01]	Not applicable	3.01 [0.31, 28.83]	0.15 [0.03, 0.88]

[a]See Additional file 4 section 12 for meta-analyses of general harms for the 16 subgroups (based on age group, type of HPV vaccine and comparator) of the 24 included clinical study reports. The applied harm categories are MedDRA-preferred terms. The table contains general harms of 'solicited general adverse events' (SGAE), 'unsolicited general adverse events' (UGAE) and 'systemic adverse events' (SYAE). Numbers for 'HPV vaccine' and 'comparator' are the total of SGAE, UGAE and SYAE, but to avoid double counting of participants, UGAE (that accounted for less than 10% of the general harms) were dismissed from the total risk ratio for studies that reported SGAE and UGAE separately (SGAE and UGAE were not reported as pooled estimates for individual general harms classified with MedDRA-preferred terms; see Additional file 4). It was not feasible to present this summary table for the 16 subgroups (based on age group, type of HPV vaccine and comparator) of the 24 included clinical study reports

[b]The clinical study reports reported 69,915 individual MedDRA-classified general harms for 25,642 participants, i.e. 2.7 general harms per participant. General harms were reported as the number of participants with a MedDRA-classified general harm over the total number of participants

[c]GlaxoSmithKline defined 'solicited general adverse events' (SGAE) as "Adverse events to be recorded [from day 0 to day 6 after each vaccination] as endpoints [arthralgia, fatigue, headache, myalgia, pyrexia, rash and urticaria] in the clinical study"

[d]GlaxoSmithKline defined 'unsolicited general adverse events' (UGAE) as "Any AE [adverse event] reported in addition to those solicited during the clinical study. Also, any "solicited" symptom with onset outside the specified period of follow-up for solicited symptoms was reported as an unsolicited AE"

[e]Merck Sharp and Dohme defined 'systemic adverse events' (SYAE) as "any systemic clinical adverse event that developed on the day of vaccination or during the 14 days after vaccination was recorded on the VRC [vaccination report card]"

[f]Risk ratios were calculated with the random-effects inverse variance method

[g]The total numbers of participants with general harms in Cervarix studies were reported as 'solicited [SGAE] and unsolicited [UGAE]', i.e. the risk ratio is similar for SGAE and UGAE

Subgroup analyses

Younger HPV vaccinated participants were more protected against moderate HPV-related intraepithelial neoplasia or worse than older participants (age 15 to 29: 784 vs. 1079, RR 0.71 [95% CI 0.61 to 0.83]; age 21 to 72: 168 vs. 160, RR 1.04 [95% CI 0.84 to 1.29]; ratio of relative risk [RRR] 1.46 [1.12 to 1.91]) and also experienced fewer fatal harms than older participants (age 15 to 27: 24 vs. 32, RR 0.77 [95% CI 0.45, 1.33]; age 21 to 72: 21 vs. 6, RR 3.13 [95% CI 1.29 to 7.61]; RRR 0.25 [95% CI 0.09 to 0.70]), but there were no differences for serious nervous system disorders (age 10 to 35: 53 vs. 35, RR 1.46 [95% CI 0.95 to 2.25]; age 21 to 72: 19 vs. 11, RR 1.56 [95% CI 0.75 to 3.25]; RRR 0.93 [95% CI 0.40 to 2.19]), serious harms that were judged 'definitely associated' with of CRPS (age 9 to 35: 76 vs. 48, RR 1.48 [95% CI 1.03 to 2.12]; age 21 to 72: 19 vs. 9, RR 2.11 [95% CI 0.67 to 6.69]; RRR 0.70 [95% CI 0.21 to 2.34]) or serious harms that were judged 'definitely associated' with POTS (age 12 to 35: 43 vs. 21, RR 1.86 [95% CI 1.10, 3.15]; age 21 to 72: 13 vs. 5, RR 2.22 [95 CI 0.76 to 6.47]; RRR 0.84 [95% CI 0.25 to 2.76]) (see Additional file 4; note that the subgroup analyses used overlapping age groups due to the different age groups included in the trials). No significant subgroup differences were identified for subgroup analyses based on gender and control treatment.

Random-effects vs. fixed-effect

We found similar results with the fixed-effect model but with narrower confidence intervals, as the between-trial variance is not included in this model.

Discussion

Our systematic review of 24 clinical study reports with 95,670 participants showed that the HPV vaccines within 4 years of follow-up decreased HPV-related carcinoma in situ, which have a high likelihood of progressing to cancer [1], and HPV-related treatment procedures, but the vaccines also increased serious nervous system disorders (exploratory analysis) and general harms. Younger participants who are those primarily intended to receive HPV vaccination [1] were more protected against HPV-related neoplasia and had fewer fatal harms.

Strengths

Our review was based on study programmes, randomised trials reported in clinical study reports, clinically important pre-specified outcomes, intention to treat analyses, absolute risk estimates and a conservative statistical method based on the random-effects model. There was no heterogeneity for serious nervous system disorders or for the post hoc exploratory harm analyses of serious signs and symptoms judged 'definitely associated' with POTS and CRPS by a blinded physician with clinical expertise.

Limitations

Insufficient trial data access, incomplete reporting, data fragmentation and limited trial follow-up periods were major limitations. It took 3 years to obtain an incomplete subset of the eligible clinical study reports; a process which we have documented in detail elsewhere [38]. Our review is therefore limited by reporting bias—the bias that we aimed to reduce [37]. We did not obtain any periodical safety update reports before our data lock. The inclusion of the remaining participants from the 26 studies with no available clinical study reports included a fifth of the total eligible participants, which could have influenced our review, as some of our results had P values around our cut-off of 0.05 and confidence intervals that were wide.

We performed multiple comparisons: 166 meta-analyses of which 31 (19%) showed statistical significance for the total risk ratio estimate. With our P value cut-off of 0.05, about eight (166*0.05) or a fourth (8/31) of the significant results are likely to have occurred by chance. We did not use Bonferroni (or similar) corrections [40], as one of our primary outcomes was serious harms, which were affected by incomplete reporting (see Table 1) and lack of saline placebo controls (see Additional file 2).

The 24 included clinical study reports only included one Gardasil 9 trial (V503–006) that was small and did not investigate histological outcomes. Many countries are currently implementing Gardasil 9 as a two-dose regimen in their vaccination programme instead of Cervarix or Gardasil [1]. Two doses of Gardasil 9 may induce fewer harms than three doses, but Gardasil 9 may induce more harms than Gardasil. For example, in the clinical study report that we obtained of phase 3 multicentre trial V503-001/NCT00543543 (not eligible for our systematic review) of 7106 and 7109 healthy females age 16–26 randomised to receive three doses Gardasil 9 or Gardasil, there were more serious harms (233 vs. 183, RR 1.27 [95% CI 1.05 to 1.54], NNH 151, $P = 0.010$; reported from day 0 to 390) and general harms ('systemic adverse events': 2086 vs. 1929, RR 1.08 [95% CI 1.03 to 1.14], NNH 75, $P = 0.003$; reported 0–14 days post-vaccination) in the Gardasil 9 group. A 0.5-ml dose of Gardasil 9 contains more virus-like particles (270 μg vs. 100 μg) and aluminium-containing adjuvant (500 μg vs. 225 μg) compared to a 0.5-ml dose of Gardasil, which could explain the harm differences. Although Gardasil 9 targets five more HPV types than Gardasil, Gardasil 9 did not decrease CIN2$^+$ more than Gardasil during trial V503-001's 42-month follow-up (325 vs. 326, RR 1.00 [95% CI 0.86 to 1.16], $P = 0.97$).

A substantial part of our results should be interpreted carefully due to high heterogeneity. We expected the high heterogeneity for several results (e.g. for HPV-related carcinoma in situ), as the included trials comprised 16

Table 8 Benefits and harms of the HPV vaccines: summary of exploratory harm analyses by MedDRA system organ class

Summary of exploratory harm analyses by MedDRA system organ class[a]	Fatal harms			Serious harms			New onset diseases[b]			General harms[c]		
	HPV vaccine ($N = 47,075$)	Comparator ($N = 48,595$)	Risk ratio[d] [95% CI]	HPV vaccine ($N = 47,075$)	Comparator ($N = 48,595$)	Risk ratio[d] [95% CI]	HPV vaccine ($N = 47,075$)	Comparator ($N = 48,595$)	Risk ratio[d] [95% CI]	HPV vaccine ($N = 47,075$)	Comparator ($N = 48,595$)	Risk ratio[d] [95% CI]
Blood and lymphatic system disorders	0	0	Not applicable	11	12	0.97 [0.44, 2.18]	424	421	1.00 [0.88, 1.15]	17	10	1.33 [0.56, 3.15]
Cardiac disorders	3	5	2.45 [0.87, 6.87]	28	21	1.12 [0.49, 2.55]	108	86	1.09 [0.67, 1.78]	6	5	0.89 [0.26, 2.99]
Congenital, familial and genetic disorders	0	0	Not applicable	1	9	0.32 [0.09, 1.13]	50	67	0.74 [0.51, 1.06]	0	1	0.55 [0.02, 13.40]
Ear and labyrinth disorders	0	0	Not applicable	4	6	0.68 [0.19, 2.45]	154	139	1.04 [0.78, 1.39]	54	40	1.10 [0.71, 1.69]
Endocrine disorders	1	0	2.83 [0.12, 69,36]	7	4	1.60 [0.48, 5.35]	189	207	0.91 [0.74, 1.10]	1	1	0.72 [0.04, 11.85]
Eye disorders	0	0	Not applicable	6	4	1.51 [0.42, 5.37]	296	326	0.89 [0.76, 1.04]	40	39	0.84 [0.53, 1.33]
Gastrointestinal disorders	1	0	2.83 [0.12, 69,36]	107	92	1.12 [0.85, 1.48]	2226	2141	1.05 [0.95, 1.16]	4085	3735	1.09 [1.01, 1.17]
General disorders	0	0	Not applicable	13	9	1.45 [0.60, 3.50]	563	483	1.14 [1.01, 1.28]	6401	5842	1.10 [1.04, 1.17]
Hepatobiliary disorders	1	1	0.94 [0.06, 15.06]	52	48	1.03 [0.70, 1.52]	126	143	0.86 [0.61, 1.22]	2	1	2.00 [0.18, 22.00]
Immune system disorders	1	0	2.83 [0.12, 69,36]	9	14	0.68 [0.30, 1.58]	371	398	0.92 [0.78, 1.08]	35	24	1.25 [0.75, 2.18]
Infections and infestations	8	5	1.51 [0.49, 4.61]	400	367	1.04 [0.80, 1.37]	8970	9025	0.98 [0.96, 1.00]	1141	965	1.14 [1.00, 1.30]
Injury, poisoning and procedural complications	16	18	0.84 [0.43, 1.64]	199	224	0.85 [0.64, 1.13]	1205	1209	0.94 [0.82, 1.06]	142	122	1.03 [0.81, 1.33]
Investigations	0	0	Not applicable	1	2	0.69 [0.11 4.40]	1438	1429	1.00 [0.94, 1.07]	7	4	1.34 [0.41, 4.41]
Metabolism and nutrition disorders	1	1	0.94 [0.06, 15.06]	19	11	1.44 [0.72 2.89]	342	355	0.95 [0.82, 1.10]	17	15	0.98 [0.49, 1.96]
Musculoskeletal and connective tissue disorders	2	0	4.71 [0.23, 98.09]	35	31	1.07 [0.66 1.74]	1263	1213	1.02 [0.94, 1.10]	6005	4683	1.34 [1.21, 1.49]
Neoplasms benign, malignant and unspecified	13	4	3.06 [1.00, 9.39]	68	56	1.20 [0.84, 1.71]	466	421	1.09 [0.96, 1.25]	2	2	0.71 [0.14, 3.51]
Nervous system disorders	4	1	3.77 [0.42, 33.71]	72	46	1.49 [1.02, 2.16]	1410	1305	1.06 [0.97, 1.16]	5967	5422	1.09 [1.04, 1.14]
Pregnancy, puerperium and perinatal conditions	0	0	Not applicable	458	426	1.08 [0.94, 1.23]	726	714	1.02 [0.92, 1.12]	1	0	2.91 [0.12, 68.66]

Table 8 Benefits and harms of the HPV vaccines: summary of exploratory harm analyses by MedDRA system organ class *(Continued)*

Summary of exploratory harm analyses by MedDRA system organ class[a]	Fatal harms			Serious harms			New onset diseases[b]			General harms[c]		
	HPV vaccine (*N* = 47,075)	Comparator (*N* = 48,595)	Risk ratio[d] [95% CI]	HPV vaccine (*N* = 47,075)	Comparator (*N* = 48,595)	Risk ratio[d] [95% CI]	HPV vaccine (*N* = 47,075)	Comparator (*N* = 48,595)	Risk ratio[d] [95% CI]	HPV vaccine (*N* = 47,075)	Comparator (*N* = 48,595)	Risk ratio[c] [95% CI]
Psychiatric disorders	4	8	0.47 [0.14, 1.56]	80	87	0.92 [0.68, 1.25]	961	959	0.99 [0.91, 1.08]	49	53	0.90 [0.61 1.33]
Renal and urinary disorders	2	1	1.88 [0.17, 20.77]	19	17	1.07 [0.57, 2.01]	404	395	1.01 [0.88, 1.16]	12	6	1.32 [0.48 3.59]
Reproductive system and breast disorders	2	0	4.71 [0.23, 98.09]	72	78	0.90 [0.65, 1.24]	3453	3463	0.99 [0.95, 1.04]	213	158	1.13 [0.92 1.38]
Respiratory, thoracic and mediastinal disorders	3	2	1.41 [0.24, 8.45]	44	34	1.26 [0.8 , 1.97]	795	771	1.00 [0.91, 1.11]	464	394	1.02 [0.89 1.18]
Skin and subcutaneous tissue disorders	1	0	2.83 [0.12, 69.36]	12	7	1.48 [0.60, 3.63]	1173	1176	0.99 [0.88, 1.12]	997	771	1.21 [1.03 1.44]
Social circumstances	2	2	0.94 [0.13, 6.69]	2	2	0.95 [0.14, 6.50]	46	42	0.95 [0.62, 1.47]	1	1	1.00 [0.10 9.60]
Surgical and medical procedures	0	0	Not applicable	6	5	1.15 [0.36, 3.67]	1313	1340	0.97 [0.90, 1.04]	0	0	Not applicable
Vascular disorders	4	3	1.26 [0.28, 5.61]	16	16	0.96 [0.47, 1.99]	234	294	0.80 [0.67, 0.94]	11	12	0.68 [0.28 1.63]

[a]See Additional file 4 sections 9 to 12 for meta-analyses of MedDRA system organ classes. Only Merck clinical study reports aggregated data for MedDRA system organ classes per participant and only for new onset diseases ('new medical history') and general harms ('systemic adverse events'). A participant may have been counted more than once in the MedDRA system organ class analyses of GlaxoSmithKline clinical study reports and in analyses of fatal and serious harms; we therefore consider these analyses exploratory. Risk ratios for GlaxoSmithKline and Merck studies are provided separately in Additional file 4. It was not feasible to present this summary table for the 16 subgroups (based on age group, gender, type of HPV vaccine and comparator) of the 24 included clinical study reports. To avoid double counting of participants in the total risk ratio estimate we only included the new onset diseases reported in the vaccination period for the trials V501-005, V501-019 and V501-020, and we only included solicited adverse events when studies also reported unsolicited adverse events (see Additional file 4)

[b]New onset diseases were compiled of the harm categories 'medically significant conditions' (for Cervarix) and 'new medical history' (for Gardasil, Gardasil 9 and the HPV 16 vaccine)

[c]General harms were compiled of the harm categories 'solicited general adverse events', 'unsolicited general adverse events' (for Cervarix) and 'systemic adverse events' (for Gardasil, Gardasil 9 and the HPV 16 vaccine). To avoid double counting of participants, 'unsolicited general adverse events' were dismissed from the total risk ratio for studies that reported SGAE and UGAE separately

[d]Risk ratios were calculated with the random-effects inverse variance method

Table 9 Benefits and harms of the HPV vaccines: summary of harms of special interest and post hoc exploratory harm analyses

Summary of harms of special interest and post hoc exploratory harm analyses[a]	Serious harms			New onset diseases[d]			General harms[e]		
	HPV vaccine ($N = 47,075$)	Comparator ($N = 48,595$)	Risk ratio[f] [95% CI]	HPV vaccine ($N = 47,075$)	Comparator ($N = 48,595$)	Risk ratio[f] [95% CI]	HPV vaccine ($N = 47,075$)	Comparator ($N = 48,595$)	Risk ratio[f] [95% CI]
Harms of special interest (MedDRA-preferred terms, n = participants)									
Anaphylaxis	2	4	0.59 [0.13, 2.82]	11	8	1.18 [0.48, 2.91]	0	0	Not applicable
Chronic fatigue syndrome (CFS)	0	0	Not applicable	0	0	Not applicable	0	0	Not applicable
Chronic regional pain syndrome (CRPS)	0	0	Not applicable	0	0	Not applicable	0	0	Not applicable
Guillain-Barré syndrome (GBS)	0	0	Not applicable	0	0	Not applicable	0	0	Not applicable
Postural orthostatic tachycardia syndrome (POTS)	0	0	Not applicable	0	0	Not applicable	0	0	Not applicable
Premature ovarian failure (POF)	0	0	Not applicable	1	0	3.00 [0.12, 73.48]	0	0	Not applicable
Syncope	4	3	0.94 [0.23, 3.81]	62	60	1.03 [0.58, 1.84]	7	7	0.77 [0.25, 2.34]
Post hoc exploratory analyses of VigiBase® harm clusters[b]									
Expected systemic reactions	25	11	1.96 [0.96, 3.98]	1465	1358	1.03 [0.93, 1.14]	10,926	9948	Not applicable[g]
Allergic/hypersensitivity reactions	2	2	0.96 [0.14, 6.52]	284	279	1.05 [0.82, 1.35]	1912	1469	1.30 [1.18, 1.45]
Vasovagal reactions	9	5	1.31 [0.50, 3.46]	232	212	1.06 [0.78, 1.44]	173	123	1.20 [0.93, 1.55]
Post hoc exploratory analyses of CRPS and POTS[c]									
Harms judged as 'definitely associated' with CRPS	95	57	1.54 [1.11, 2.14]	5079	4790	1.04 [0.98, 1.10]	27,899	23,223	Not applicable[g]
Harms judged as 'definitely associated' with POTS	56	26	1.92 [1.21, 3.07]	3675	3352	1.08 [1.01, 1.15]	18,207	16,288	Not applicable[g]

[a]See Additional file 4 sections 13 and 14 for meta-analyses of the harms of special interest and post hoc exploratory harm analyses. There was no applicable fatal harm of special interest. It was not feasible to present this summary table for the 16 subgroups (based on age group, gender, type of HPV vaccine and comparator) of the 24 included clinical study reports. As we did not obtain complete case report forms or individual participant data, we could not assign harms to individual participants

[b]As the included studies' harm assessments were at risk of low internal and external validity (see Table 1 and the "Discussion" section), we compared the three largest harm clusters reported from pharmacovigilance up to 1 January 2015 to the World Health Organisation's (WHO) VigiBase with the clinical study report data. We did this to see if the pharmacovigilance data were similar to the study data. VigiBase's largest HPV vaccine harm cluster (expected systemic reactions) consists of 'headache, nausea, pyrexia, dizziness and vomiting'. VigiBase's second largest HPV vaccine harm cluster (allergic/hypersensitivity reactions) consists of 'pruritis, urticaria, rash and erythema'. VigiBase's third largest HPV vaccine harm cluster (vasovagal reactions) consists of 'syncope, dizziness, loss of consciousness, pallor and seizure'. As we synthesised individual MedDRA-preferred term classified harms, our post hoc exploratory analyses of VigiBase harm clusters may therefore include a participant more than once in each separate analysis

[c]We asked a physician with clinical expertise in POTS and CRPS to assess the reported MedDRA terms as 'definitely', 'probably', 'probably not' or 'definitely not' associated with the syndromes. The physician was blinded to the allocation groups and outcome data. The data was synthesised for those MedDRA-preferred terms that the physician judged 'definitely' associated with POTS or CRPS. As we synthesised individual MedDRA-preferred terms, our post hoc exploratory analyses of CRPS and POTS may include a participant more than once in each separate analysis

[d]New onset diseases were compiled of the harm categories 'medically significant conditions' (for Cervarix) and 'new medical history' (for the HPV 16 vaccine, Gardasil and Gardasil 9)

[e]General harms were compiled of the harm categories 'solicited general adverse events', 'unsolicited general adverse events' (for Cervarix) and 'systemic adverse events' (for Gardasil, Gardasil 9 and the HPV 16 vaccine)

[f]Risk ratios were calculated with the random-effects inverse variance method

[g]Some numerators exceeded the denominators making the result nonsensical. Therefore, we did not perform meta-analyses

different subgroups—based on the type of HPV vaccine, comparator, age and gender. All meta-analyses were divided according to the 16 subgroups to provide heterogeneity measures (see Additional file 4), but the nationality of the participants and regional practices of HPV related screening and treatment procedures may also have contributed to the heterogeneity.

Limitations of benefit assessment

Only 10 HPV-related cancers occurred in the follow-up periods. Extended follow-up was not possible for 75% of the comparator participants (36,344/48,595), as they were offered HPV vaccination at trial completion.

We only included benefit results of intention to treat analyses, which also included participants that were enrolled after they had been infected with HPV. The HPV vaccines have no documented effect on HPV-related neoplasia caused by previous infections [1]. Our benefit results may therefore be skewed toward the null compared to real-life settings where mainly 12-year-old adolescents—that are expected to not be previously HPV-infected—are HPV vaccinated. Getting vaccinated before sexual debut is likely to improve the HPV vaccines' benefits, but no included trial investigated histological outcomes for participants that were vaccinated under the age of 15.

Three trials—HPV-008, V501-013 and V501-015 that contained 38% (36,266/95,670) of the analysed participants—were stopped early when HPV type 16/18-related cervical intraepithelial neoplasia or worse ($CIN2^+$) was significantly reduced for their HPV vaccine per-protocol populations. On average, trials stopped early for benefits exaggerate effects by 29% compared to completed trials of the same intervention [41]. When the three trials were excluded from our $CIN2^+$ meta-analysis, $CIN2^+$ was not significantly decreased (184 vs. 200, RR 0.85 [95% CI 0.54 to 1.33], $P = 0.47$, $I^2 = 77\%$; see Additional file 4).

One clinical study report (HPV-015) only reported $CIN2^+$, although there were three cases of HPV-related cancers in the HPV vaccine group and one in the comparator group (see Additional file 4). These cancers were listed as serious harms and were not mentioned elsewhere in the clinical study report. For transparency, it would have been more appropriate to report each histological outcome (cancer, carcinoma in situ, moderate intraepithelial neoplasia, etc.) than only a composite surrogate outcome such as $CIN2^+$.

No trial tested the HPV vaccines' protection against cervical cancer without using cervical screening. This may reduce external validity, as some studies show that HPV-vaccinated women may tend to avoid cervical screening [42]; although other studies have not shown a clear tendency [43]. The trial personnel often performed cervical screening together with colposcopy every 6 months, and the included participants were often women aged 15–26. In clinical practice, cervical screening is usually performed every 3 to 5 years and recommended after age 25 [44], as most $CIN2^+$ lesions in women under age 30 regress spontaneously, which may justify active surveillance rather than immediate intervention [45].

No trial used mandatory biopsies, which may reduce internal validity. For example, the precursor lesion of cervical adenocarcinoma is difficult to detect on colposcopy, but easier to recognise on a biopsy [46]. The incidence of cervical adenocarcinoma is increasing and may more often be HPV negative compared to cervical squamous carcinoma [46], but only 5% (40/857) of the reported cervical carcinoma in situ cases in the included studies were adenocarcinoma in situ (see Table 4).

We did not pre-specify genital warts as an outcome, but the HPV vaccines reduced external genital lesions and there is strong evidence that the HPV vaccines—especially Gardasil and Gardasil 9 that target the HPV types 6 and 11—decrease the incidence of genital warts [47].

Limitations of harm assessment

Only Merck clinical study reports reported aggregate numbers for participants with MedDRA system organ classified harms, and only for new onset diseases and general harms. The synthesis of MedDRA system organ classes for all GlaxoSmithKline clinical study reports and for serious harms for Merck clinical study reports may therefore include a participant more than once. As a result, we consider these analyses exploratory.

Serious harms were incompletely reported for 72% of the participants (68,610/95,670; see Table 1 and Additional file 2). There were 2.8 times more serious harms reported in the clinical study reports that reported serious harms for the whole trial period (1838/27,493 vs. 923/38,356). As an example, trial HPV-008 of Cervarix that had reported all serious harms during its 48 months follow-up reported 10 times more participants with serious harms compared to V501-015 of Gardasil that only reported serious harms 14 days post-vaccination (1664/18,644 vs. 102/12,167). In the cluster-randomised trial, HPV-040, 88% (28,473 of 32,176) of the participants were not included for serious harms reporting (see Table 1 and Additional file 2).

The use of active comparators may have underestimated harms related to the HPV vaccines [38]. The aluminium-containing comparators were used, as they provided a similar appearance to that of the HPV vaccines, which enhanced blinding and decreased the risk of performance and detection bias. A single trial—V503-006, of Gardasil 9—used a saline placebo in 306

participants who had previously been vaccinated with Gardasil. It is unlikely that those who had experienced harms following previous Gardasil vaccination would have participated in the Gardasil 9 trial, so the trial's harm results are not reliable. The trial's blinding procedure was adequate to ensure low risk of performance and detection bias and could have been used in other trials (see Additional file 2).

Although the manufacturers consider the aluminium-containing comparators to be safe, 52% of the participants (49,301/95,670) were only included in the trials if they had never received the aluminium-containing comparators before. GlaxoSmithKline state that their aluminium-containing comparator induces myalgia ("higher incidences of myalgia might namely be attributable to the higher content of aluminium in the HPV vaccine [450 micrograms $Al(OH)_3$] than the content of aluminium in the HAV [hepatitis A] vaccine [225 micrograms $Al(OH)_3$]" [48]), which we found was increased by the HPV vaccines (see Table 7).

The clinical study reports, their informed consent forms and corresponding journal publications (for example, V501-013 [49] and V501-015 [50]) often used the term placebo (which is a substance with no active effect) to describe the active aluminium-based comparators.

Two thirds of the participants (63,468/95,670) were only included in the trials if they had no history of immunological or nervous system disorders (see Additional file 2). Such disorders are not listed as warnings or contraindications on the package inserts of the approved HPV vaccines [8–10]. The degree of harms might therefore be higher in clinical practice than in the trials. The HPV vaccines did not increase the three largest HPV vaccine-related VigiBase® harms clusters for serious harms and new onset diseases (see the "Methods" section, Table 9 and Additional file 4), which may reflect the differences between real-life and the trials' settings and entry criteria.

The exploratory analyses of MedDRA system organ classes may have included a participant more than once. For serious nervous system disorders, this is unlikely, as there were only 118 participants with such disorders (reported as individual MedDRA-preferred terms) for 61,331 participants (see Additional file 4). We note, however, that the serious nervous system disorders consisted of very heterogenous harms, for example, 'anoxic encephalopathy', 'moyamoya disease' and 'vertebral artery dissection'.

The serious harm analyses of MedDRA-preferred terms associated with POTS and CRPS may also have included a participant more than once, although this is unlikely as there only were 82 participants with a POTS sign/symptom for 60,058 participants and 152 participants with a CRPS sign/symptom for 60,915 participants. The selection of MedDRA-preferred terms associated with POTS and CRPS was subjective, not verified by other assessors and included some signs/symptoms that do not align well with the diagnostic criteria of POTS or CRPS [51, 52], for example, 'constipation', 'vision blurred' and 'vomiting'. Other blinded assessors would possibly assign MedDRA-preferred terms differently, as there were over 3000 different included MedDRA-preferred terms. The post hoc exploratory POTS and CRPS analyses were based on randomised trial data where serious harms were underreported and likely underestimated, but since no complete serious harm narratives or complete case report forms were available, the analyses could not take symptom duration, symptom clustering or the diagnostic criteria into account. Therefore, the analyses do not prove that the HPV vaccines cause POTS and CRPS, but they do provide a signal, which makes it important to carry out independent analyses of POTS and CRPS based on the complete data set with individual participant data.

Similar studies

In May 2018, a Cochrane review of the HPV vaccines that included 26 trials with 73,428 female participants concluded that the HPV vaccines decrease precursors to cervical cancer and do not increase serious or general harms [3]. The Cochrane review had similar inclusion criteria to our review, but it was mainly based on journal publications and only included phase II and III trials. In comparison, we identified 50 possibly eligible studies for which we obtained clinical study reports for 22 trials and two follow-up studies and included 30% more participants (95,670) than the Cochrane review. We found that the HPV vaccines decrease precursors to HPV-related cancer and treatment procedures but increase serious nervous system disorders (exploratory analyses) and general harms. Another recent review on males [53] and most large epidemiological studies have found no serious harms associated with the HPV vaccines [16–20].

Conclusion

At 4 years follow-up, the HPV vaccines decreased HPV-related precursors to cervical cancer and treatment procedures but increased serious nervous system disorders (exploratory analysis) and general harms. As the included trials were primarily designed to assess benefits and not adequately designed to assess harms, the extent to which the benefits outweigh the harms is unclear. Limited access to clinical study reports and trial data with case report forms prevented a thorough assessment. An independent assessment of the complete individual participant data is needed. If granted access to the

complete data set with individual participant data, we will update this systematic review. A large industry-independent multicentre trial of two doses of Gardasil 9 vs. saline placebo would likely be informative in identifying a more accurate benefit-harm balance, but we recognise that such a trial will be considered unethical in most settings.

Additional files

Additional file 1: Benefits and harms of the HPV vaccines—PRISMA 2009 checklist. (DOCX 31 kb)

Additional file 2: Benefits and harms of the HPV vaccines—characteristics of included studies. (DOCX 121 kb)

Additional file 3: Benefits and harms of the HPV vaccines—list of excluded studies. (DOCX 63 kb)

Additional file 4: Benefits and harms of the HPV vaccines—meta-analyses. (PDF 26103 kb)

Abbreviations

AIN: Anal intraepithelial neoplasia; CFS: Chronic fatigue syndrome; CIN: Cervical intraepithelial neoplasia; CRPS: Chronic regional pain syndrome; EGL: External genital lesion; EMA: European Medicines Agency; FDA: Food and Drug Administration; GBS: Guillain-Barré syndrome; GSK: GlaxoSmithKline; HPV: Human papillomavirus; ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; MedDRA: Medical Dictionary for Regulatory Activities; Merck: Merck and Co., Inc. or Merck Sharp and Dohme outside the USA and Canada; MSC: Medically significant condition; NMH: New medical history; NNH: Number needed to harm; NNV: Number needed to vaccinate; PICO: Patient, intervention, comparator and outcome; PIN: Penile intraepithelial neoplasia; POF: Premature ovarian failure; POTS: Postural orthostatic tachycardia syndrome; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO: International Prospective Register of Systematic Reviews; SGAE: Solicited general adverse event; SYAE: Systemic adverse event; UGAE: Unsolicited general adverse event; VaIN: Vaginal intraepithelial neoplasia; VIN: Vulvar intraepithelial neoplasia; WHO: World Health Organisation

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Availability of data and materials

The datasets generated and analysed during the current systematic review are available from the first author (LJ) upon request.

Authors' contributions

LJ wrote the first draft. LJ and TJ contributed to the conception of the review, the design of the review, the collection and assembly of data, the analysis and interpretation of the data, the drafting of the article, the critical revision of the article for important intellectual content and the final approval of the article. PCG contributed to the conception of the review, the critical revision of the article for important intellectual content and the final approval of the article. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable

Competing interests

All authors have completed the ICMJE uniform disclosure form. LJ declares no support from any organisation for the submitted work, no financial relationships with any organisations that might have an interest in the submitted work, no other relationships or activities that could appear to have influenced the submitted work. PCG spoke by video link about the HPV vaccines at the IFICA (International Federation for Injured Children and Adults, www.ificaeurope.org) conference in 2018 but received no fee or reimbursement for this. PCG and TJ were co-signatories of a complaint to the European Ombudsman on maladministration in relation to the EMA investigation of possible harms from HPV vaccines. PCG does not regard this as a competing interest. TJ was a co-recipient of a UK National Institute for Health Research grant (HTA-10/80/01 update and amalgamation of two Cochrane Reviews: neuraminidase inhibitors for preventing and treating influenza in healthy adults and children—https://www.journalslibrary.nihr.ac.uk/programmes/hta/108001#/). TJ is also in receipt of a Cochrane Methods Innovations Fund grant to develop guidance on the use of regulatory data in Cochrane reviews. TJ is occasionally interviewed by market research companies about phase I or II pharmaceutical products. In 2011–2014, TJ acted as an expert witness in a litigation case related to the antiviral oseltamivir, in two litigation cases on potential vaccine-related damage and in a labour case on influenza vaccines in healthcare workers in Canada. He has acted as a consultant for Roche (1997–1999), GSK (2001–2002), Sanofi-Synthelabo (2003) and IMS Health (2013). In 2014–2016, TJ was a member of three advisory boards for Boehringer Ingelheim. TJ was a member of an independent data monitoring committee for a Sanofi Pasteur clinical trial on an influenza vaccine.

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Human papillomavirus vaccine-associated premature ovarian insufficiency and related adverse events: data mining of Vaccine Adverse Event Reporting System

Li Gong[1,2], Huan-huan Ji[1], Xue-wen Tang[3], Ling-yun Pan[4], Xiao Chen[5] & Yun tao Jia[1]✉

We detected disproportionate reports of premature ovarian insufficiency (POI) and related events, including amenorrhea, menstruation irregular, FSH increased, and premature menopause, following human papillomavirus (HPV) vaccine from FDA Vaccine Adverse Event Reporting System (VAERS). The signal was detected by the methods of Bayesian Confidence Propagation Neural Network (BCPNN) and Multi-item Gamma Poisson Shrinker (MGPS). When both methods detected a positive result, a signal was generated. Besides, time-scan map is drawn based on the IC value and 95%CI of BCPNN, if the IC curve showed a steady upward trend and the 95%CI narrowed, the signal was stable and strong association.The results showed that there were not POI reports of HPV vaccine, but VAERS received a total of 2, 389, 27 POI related events for HPV2, HPV4, HPV9 respectively from the year of marketed to 2018. No signal was detected for HPV2. HPV4-POI ralated events were all detected as signals by two methods. There was only one signal of menstruation irregular for HPV9. Time scan of HPV4-POI ralated events showed those signals were stability and strong association, but not for HPV9. Our results only represent statistical association between HPV vaccine and POI related events, causal relationship needs further investigation.

Human papillomavirus (HPV) is the most common viral infection of the reproductive tract and is the cause of a range of conditions in both men and women and cervical cancer is caused by certain types of HPV. It was estimated that 569,847 new cervical cancer in 2018, of which 311,365 deaths around the world[1]. Continuous infection of high-risk HPV types is highly associated with the development of cervical cancer, and administration HPV vaccine can effectively prevent cervical cancer. Three prophylactic HPV vaccines are currently available worldwide, including HPV bivalent recombinant vaccine (HPV2), HPV quadrivalent recombinant vaccine (HPV4), HPV 9-valent recombinant vaccine (HPV9).

Premature ovarian insufficiency (POI), also known as premature menopause or premature ovarian failure[2], is a clinical syndrome defined by loss of ovarian activity before the age of 40, which is characterized by menstrual disturbance (amenorrhea or oligomenorrhea) with raised gonadotrophins and low estradiol [3]. Women with POI have a little chance of spontaneous pregnancy, and no interventions could increase ovarian activity and natural conception rates [3]. With the widespread of HPV vaccine, there were an increasing number of reports and studies

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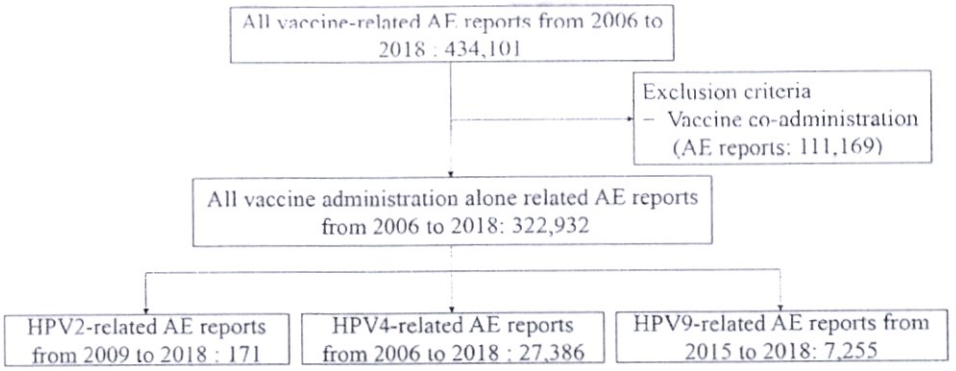

Figure 1. Flow diagram of case inclusion in this study.

on HPV vaccine-POI combination. For example, case reports and case series study reported a possible link about adolescent POI following HPV4 [4], but a population-based retrospective cohort study found no elevated risk of POI after HPV4 administration [5]. Although these observations were not identified the possible risk for HPV vaccine-POI association, we connot exclude HPV vaccination has a role in pathogenesis of POI [6]. So far, there are no reports and studies of HPV2 and HPV9-POI combination, and whether various HPV vaccines associated with POI is still inconclusive.

Published adverse reactions about HPV vaccines were mainly available form clinical trials, which might not reflect the full safety characteristics of HPV vaccines because of strict trial design, relatively small sample size and short duration of follow-up. Large-scale adverse event spontaneous reporting system is an important data source for identifying and discovering new or rare adverse reactions and after marketing. Signal detection from spontaneous reporting system (SRS) is carried out by many regulatorty authorities, such as the US Food and Drug Administration (FDA) [7], the World Health Organization Uppsala Montoring Centre (WHO-UMC) [8], the Netherlands Pharmacovigilance Centre Lareb. [9], to evaluate possible association between vaccine/drug and event combination, which including detection of novel signal, strengthening or weaking of existing signal and providing evidence for or against exicting safety concern not evaluated by data mining.

Published researches have supported or opposed the possible association between HPV4 vaccination and POI. We designed this study to evaluate the statistical association and detect the signal of POI and related events of three HPV vaccines, and to provide evidence for or against exicting HPV4-associated POI concern based on the data mining and signal detection method. The research data was obtained from the Vaccine Adverse Event Reporting System (VAERS).

Results

Descriptive analysis. Between 2009 and 2018, VAERS received a total of 275,595 vaccinated alone reports, including 171 for HPV2; from 2006 to 2018, there were 322,932 single use reports, of which 27,386 were HPV4; 143,909 were extracted from 2015 to 2018 and 7,255 for HPV9 (Fig. 1). In the adverse event reports of each HPV vaccinated alone, reports of amenorrhea, irregular menstruation, FSH increased, and premature menopause were extracted, and there were 2 reports for HPV2, 389 for HPV4, and 27 for HPV9.

For the types of the reporter, it was mainly come from healthcare provider (HPV2 accounting for 100.00%, HPV4 for 54.76%, HPV9 for 29.63%), suggesting that the report was authentic and professional. The healthcare providers include physician, physician assistant, medical assistant, certified medical assistant, nurse, registered nurse, licensed practical nurse, nurse practitioner, health professional, healthcare worker, doctor of pharmacy, pharmacist, pharmacy technician, physical therapist.

The age distribution was mainly concentrated on 9–18 years old (HPV2 accounting for 100.00%, HPV4 for 50.64%, HPV9 for 55.56%), and the proportion of less than 40 years old is 100.00%, 77.12%, and 70.37%, respectively for HPV2, HPV4 and HPV9. For serious adverse event (SAE), there are 0, 55 and 1 reports for HPV2, HPV4 and HPV9 respectively. The general characteristics and composition of each HPV adverse event reports are shown in Table 1.

Signal detection. Signal detection was performed on POI related events of three HPVs. The results are shown in Table 2. The number of HPV2 reports did not reach the test standard, and no signal was detected. HPV4-associated amenorrhea, menstruation irregular, FSH increased, premature menopause were positive results by two methods, suggesting statistically significant elevated risk of HPV4-associated POI and related events. For HPV9, irregular menstruation was detected as signal, but the other 3 adverse events did not detect positive result by MGPS.

Diagram of time scan. A time-scan map is drawn for the HPV-associated POI related events to show the change tendency of the signal over time. When the lower 95% confidence interval (CI) limit of the IC for the HPV vaccine AE combinations changes from a negative a positive value, the signal appears. When the curve of IC shows a steady upward trend and the 95%CI narrowed, it indicates that the signal tends to be stable and

	HPV2	HPV4	HPV9
Total reports	2	389	27
Type of reports			
Healthcare provider	2(100.00%)	213(54.76%)	8(29.63%)
Manufacturer	/	34(8.74%)	1(3.70%)
Patient/parent	/	34(8.74%)	4(14.81%)
Other/unknown	/	108(27.76%)	14(51.85%)
Age groups (years)			
< 9	/	1(0.26%)	0
9–18	2(100.00%)	197(50.64%)	15(55.56%)
19–26	/	97(24.94%)	4(14.81%)
27–40	/	5(1.29%)	0
> 40	/	1(0.26%)	0
Unknown serious adverse event	/	88(22.62%)	8(29.63%)
Death	/	1(0.26%)	0
Life-threatening	/	11(2.83%)	0
Hospitalized	/	14(3.60%)	0
Prolonged hospitalization	/	4(1.03%)	0
Disability	/	25(6.43%)	1(3.70%)

Table 1. General characteristics and composition of adverse event reports.

Events	Amenorrhea			Menstruation irregular			FSH increased			Premature menopause		
HPV	N	BCPNN (IC-2SD)	MGPS (EB05)	N	BCPNN (IC-2SD)	MGPS (EB05)	N	BCPNN (IC-2SD)	MGPS (EB05)	N	BCPNN (IC-2SD)	MGPS (EB05)
HPV2	2	–	–	0	–		0	–	–	0	–	–
HPV4	138	2.95	8.80	239	2.97	6.92	6	0.82	7.17	33	2.30	6.90
HPV9	8	0.56	1.96	15	1.47	2.55	1	–	–	4	−0.04	1.55

Table 2. The results of signal detection for POI related events.

strong association [10]. The results are shown in Figs. 2–3, of which Fig. 2 show the HPV4- associated POI related events and Fig. 3 for HPV9.

The time scan of HPV4-associated amenorrhea and menstruation irregular shown in Fig. 2a and b, which have a similar feature. From the diagrams in Fig. 2a and b, we can see the value of IC increase markedly and the lower 95%CI limit above zero in 2007 as the number of reports of HPV4-associated POI related events increasing, which indicates the two signal first appeared in 2007 and earlier than some case reports and researches. From 2007 to 2018, the interval of the IC becomes smaller, which means a stable signal and strong association.

Figure 2c shows the time scan of HPV4-associated FSH increased. The lower 95%CI limit always below zero, because few reports are received in VAERS from 2006 to 2015. As the reports increasing, this makes the value of IC increasing and the lower 95%CI limit above zero in 2016, which means the signal first generated in 2016. From 2016 to 2018, the bars around the IC are smaller, which shows the signal is stable and a strong statistical association.

For the HPV4-associated premature menopause (Fig. 2d), because no reports are accepted about this association, the IC curve decreases from 2006 to 2008, apart from a slight increasing after 2009 when the adverse event was reported. In 2013, there are 11 reports received of this event, then the IC increasing rapidly and the lower 95%CI limit changing from a negative to a positive value which shows the signal first be found in 2013. From 2013 to 2018, the time scan map indicates a trend to a highly association and stable signal.

The time scans of HPV9-associated AEs are shown in Fig.3. In our research, only menstruation irregular was detected as signal by 2 methods and was a strong statistical association with the IC increasing, but the large 95% CI diminished possibility of a relationship between HPV9 and menstruation irregular. This signal was firt appeared in 2015. The combinations of HPV9-amenorrhea, FSH increased and premature menopause were not detected as a signal, and the time scans indicated a low possible association.

Discussion

To our knowledge, this is the first signal detection research in which POI and related events were evaluated as a potential HPV vaccine adverse event. For the general characteristics of the reports, the reporter of healthcare providers accounted for 54.76% in HPV4, for 29.63% in HPV9, indicating that reports mainly accessed by professional staff. The patient age composition mainly concentrated on adolescent of 9–18 years old (HPV4 50.64%,

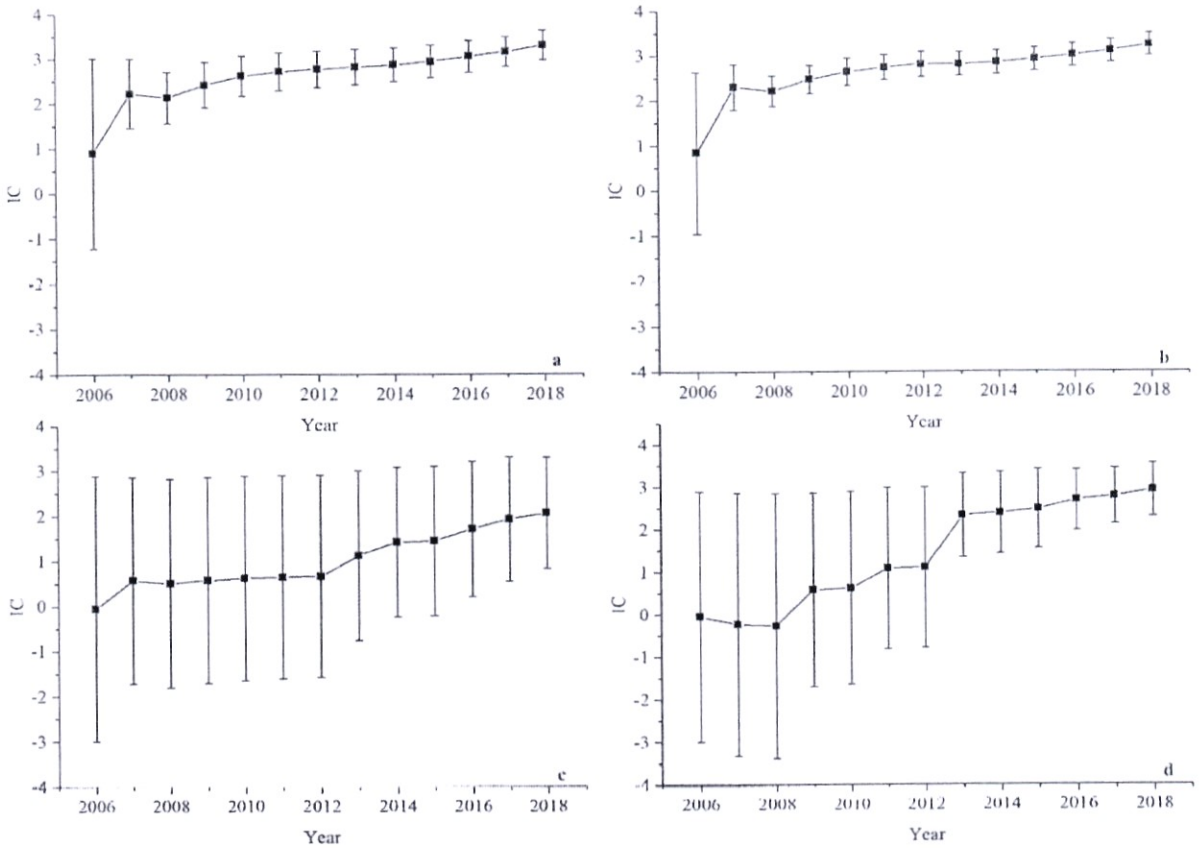

Figure 2. Time scans of IC for HPV4-associated POI raleted events from the year 2006 to 2018: (**a**) HPV4-amenorrhea association, (**b**) HPV4-menstruation irregular association, (**c**) HPV4-FSH increased association, (**d**) HPV4-premature menopause association.

HPV9 55.56%) and reproductive-age women between 19 and 26 years old (HPV4 24.94%, HPV9 14.81%), within the age for ovarian development and fertility. In addition, more than 70% of patients were younger than 40 years old, consistent with the epidemiological characteristics and diagnostic criteria of POI [3]. SAE reports were few in this database, mainly in disability (6.43% for HPV4; 3.70% for HPV9). Although two methods, BCPNN and MGPS, were used to improve the signal detection, some positive signals might have been missed due to the low sensitivity of Bayesian method.

The American Society of Reproductive Medicine classified POI into occultation period, biochemical abnormality period and clinical abnormal period according to FSH level, menstrual status and fertility. The fertility is reduced with the increase of FSH as early manifestation, and finally develops into irregular menstruation or amenorrhea [11]. Amenorrhea, FSH increased, and menstruation irregular are the symptoms and examination indicators of POI that serve as early warning on the development of POI for healthcare providers to identify POI early. Although POI is often used as synonyms of menopause, they are not equivalent. Thus, we conducted signal detection for amenorrhea, FSH increased, menstruation irregular, and premature menopause to assessing the sataistical risk of POI caused by HPV vaccines.

The signal detection results showed: (a) HPV2 did not yield any signal; (b) HPV4 was associated with amenorrhea, FSH increased, menstrual irregularities and premature menopause, indicating HPV4 with a sataistical risk of POI and related events; (c) irregular menstruation was detected as signal for HPV9 only. The diagrams of time scan showed: (a) because there was no signal for HPV2, no time scan figure was done for it; (b) the time scan of HPV4-associated POI related events showed that the signals were stable and strong association; (c) time scan of HPV9-POI related events indicated that the value of IC increasing but with a large 95% CI bars, suggesting the unstable signals. It was worth noting that the signals only represented a statistical relationship between HPV vaccines and adverse events, did not represent a causal relationship.

The possible pathogenesis between POI and HPV vaccines were multifactorial, such as autoimmune response prompted by HPV vaccines [12] and the adjuvant adverse effect of vaccine [13]. A possible relationship between POI and HPV vaccination has been proposed in view of the temporal vaccine-event association [12]. POI is a clinical disorder with complicated aetiology, and 5–30% of POI cases have an autoimmune mechanism [14]. But the pathogenesis of HPV vaccine as a tigger factor for autoimmune disease is difficult to assess and did not found conclusive evidence [12]. In immunology, according to defined by the National Cancer Institute, an adjuvant is an agent which might stimulate and increase the immune response to a vaccine, the aluminum salt was the most common adjuvant in human vaccines [15], and aluminum salt is the adjuvant in HPV2, HPV4 and HPV9. The

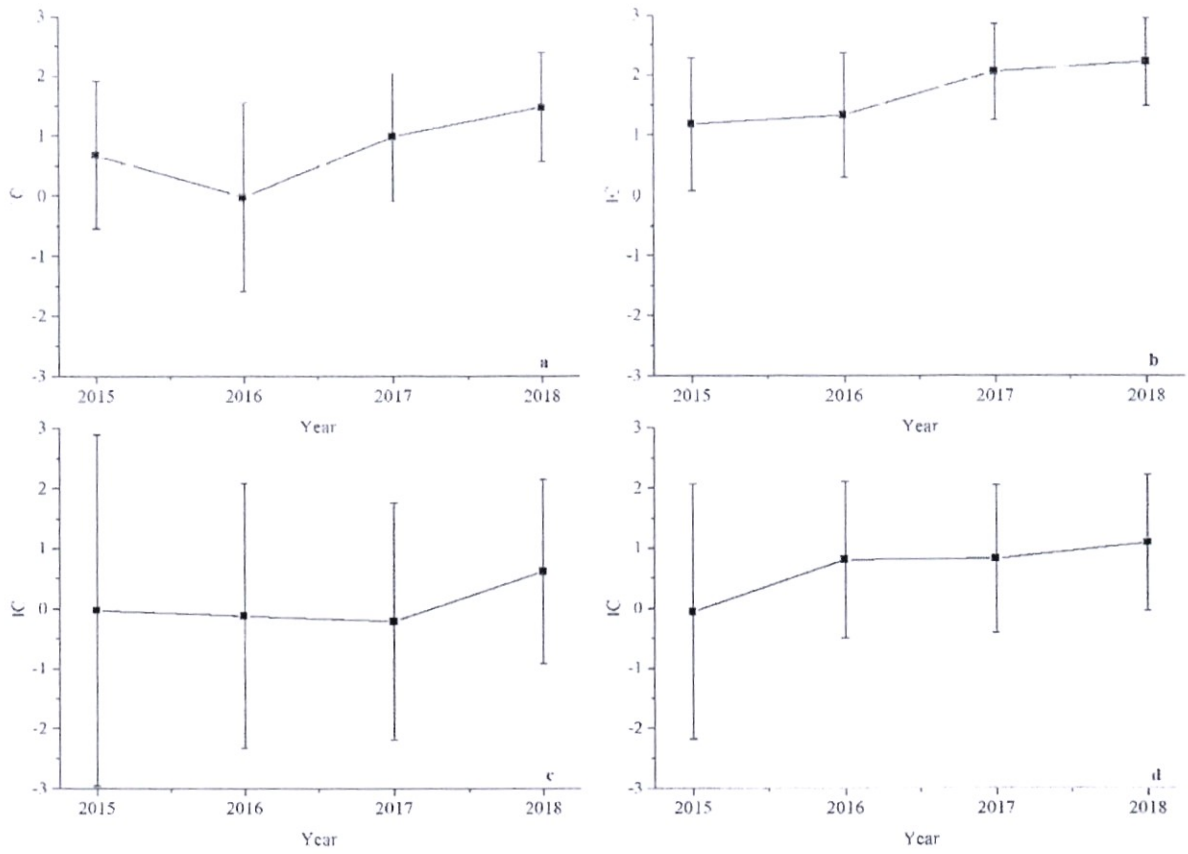

Figure 3. Time scans of IC for HPV9-associated POI related events from the year 2015 to 2018. (**a**) HPV9-amenorrhea association, (**b**) HPV9 menstruation irregular association, (**c**) HPV9 FSH increased association, (**d**) HPV9-premature menopause association.

adjuvant of aluminum salt could enhance or prolong antigen-specific immune response, but it may have potential adverse effect. According to animal experiments, aluminum could accumulate in the ovary, damage the structure of the ovary and decrease ovarian weight, which suppressed the concentrations of estrogen, progestogen, FSH, luteinizing hormone and resulted in abnormal development of ovarian follicles, and the reproductive function of female rats was inhibited by aluminum exposure [16,17].

Our study detected the signals of HPV4-associated POI related events and the signal of menstruation irregular for HPV9. Although our results were different from other reseauches, such as Naleway [5] and Pellegrino [6], which did not obversed an elevated risk of POI after HPV4 administration but they suspected presenting of a rare risk factor of determining the adverse event [6], our results provided a signal evidence in the view of pharmacovigilance. Furthermore, long-term reproductive safety studies are surely needed. HPV4 and HPV9 have the same preparation process and adjuvants except for the different viral subtypes. Short-term of marketed and lack of long-term safety data may be attribute to the difference in signals between the both. In addition, no studies have shown that the difference in adverse events due to different virus subtypes.

However, data mining and signal detection of VAERS has several limitations. First, the major limitations of our study are that it is unclear whether these AEs caused by disease, and lack of the data of medical history, medication history and menstrual history. Therefore, disease-oriented adverse events could be detected as signals. Second, VAERS is subject to various biased such as missing data, over-reporting, under-reporting. Third, because there is no specific value of FSH in VAERS and each report is only one FSH test result without continuous result, the FSH increase signal may bias to POI. Fourth, since combined vaccination may inhibit or enhance the immune response [18], this study only includes the reports of vaccination alone and excluding data from co-vaccination. But it resulted in a reduction in sample size and it is also a bias in our study. According to the clinical trials for HPV4 and HPV9 co-vaccination with other vaccines, they found that it is safety in vaccination combination, but lack of the data of post-marketed [19,20].

Conclusions

AE reports in VAERS were reviewed to analysis the safety profiles of HPV vaccine-associated POI and related events. From the results of signal detection, it was suggesting that HPV4 have statistically signaificant association with POI, including amenorrhea, menstruation irregular, FSH increased and premature menopause, and HPV9 have potential statistical risk in menstruation irregular. However, it should be noted that our research data is accessed from VAERS and results are affected by the quantity and quality of AE reports, and studying POI as an

	Reports with the target AE	All other AEs	Total
Reports with the target vaccine	a	b	a+b
All other vaccines	c	d	c+d
Total	a+c	b+d	a+b+c+d

Table 3. Two-by-two contingency table for disproportionality analysis.

Method	Criterion
BCPNN[22]	a ≥ 3; IC-SD > 0
MGPS[23,24]	a ≥ 3; EB05 ≥ 2

Table 4. Signal detection standards of each method.

HPV vaccine adverse event is challenging for many reasons. Finally, further research and cauaslity investigation between HPV vaccine and POI are strongly suggested in the future.

Methods

Data sources. VAERS is a passive surveillance system created by the Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC) to receive adverse event (AE) reports that may be possible associated with vaccines. The primary purpose of VAERS is to find early signal and generate hypotheses about possible new vaccine adverse events that do not be found during pre-market trails. VAERS is a free and open database, and VAERS data is accessible by two ways: downloading raw data in comma-separated value (CSV) files from https://vaers.hhs.gov/data/datasets.html, or using the CDC WONDER online search tool. The raw data in VAERS is presented by calendar year and updated monthly. The downloaded data include 3 separated data files, which are VAERSDATA, VAERSSYMTOMS, VAERSVAX, and each file have a unique ID for one report [21]. In our study, we downloaded raw data from VAERS wepsite and extract data using ID.

In VAERSVAX file, HPV vaccine was encoded as HPVX, HPV2, HPV4, HPV9, so the search terms of this study were defined as HPV2, HPV4 and HPV9. The search time was set to the year of vaccine launch until 2018, with HPV2 from January 2009 to December 2018, HPV4 from January 2006 to December 2018, and HPV9 from January 2015 to December 2018. In order to avoid the impact of co-vaccination, this study only included adverse event reports of HPV vaccination alone. We used EXCEL 2016 to screen and extract data on target vaccine-adverse event reports, including: number of reports, age, the type of reporter, and serious adverse events.

The definition of POI and related event. Medical Dictionary for Regulatory Activities (MedDRA) is a collection of international medical terminology prepared by the International Council for Harmonization (ICH) for the standardization and unification of adverse event report. MedDRA contains 5 hierarchical structures, which are Lowest Level Term (LLT), Preferred Term (PT), High Level Terms (HLT), High Group Terms (HLGT), System Organ Classes (SOC). Adverse events in VAERS reports are coded using the MedDRA of PT. We searched adverse events in MedDRA 19.0. Since MedDRA 19.0 did not include the term of POI, we redefined POI and related events according to definition and diagnostic criteria from ESHRE Guideline [3], which are oligomenorrhea/amenorrhea for at least 4 months, an elevated follicle stimulating hormone (FSH) level more than 25 IU/L on two occasion more than 4 weeks apart. We defined 3 related events: amenorrhea, irregular menstruation (including oligomenorrhea and delayed menstruation), and FSH increased to evaluate the association between HPV and POI. Considering that the two terms of POI and premature menopause are often used interchangeably [5], we also included the event of premature menopause into the study.

Signal detection. The signals of disproportionality reports were detected by Bayesian methods, including Bayesian Confidence Propagation Neural Network (BCPNN)[22] and Multi-item Gamma Poisson Shrinker (MGPS)[23,24]. The basis of those methods is based on two-by-two contingency table (Table 3).

The theory is to organize the reports of HPV-associated POI and related events in VAERS into the four analysis units of the vaccine-AE combination, including target vaccine-target AE, target vaccine-other AEs, other vaccine target AE, other vaccines other AEs. Then, we conducted statistical and disproportionalily analysis. In order to reduce the generation of false positive signals, our study used both BCPNN and MGPS methods to detect signals. When the results of both methods were positive, a signal was detected. The signal detection standards of each method are shown in Table 4.

In addition, this study will plot the time scan for HPV-associated POI and related events of information component(IC) and 95% CI, in order to reflect the change tendency of the target vaccine-target adverse event association in the database as the number of reports increasing over time, and verify the signal stability and association strength. When the IC curve is steady upward trend and the 95% CI narrowed, the signal is stable and strong association.

Data availability

The datasets generated and analysed during our study were available in the VAERS repository, https://vaers.hhs.gov/data/datasets.html.

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Author contributions

All the authors were involved in the study. Study design: L.G., H.J. and Y.J. Data collection and collation: L.G., H.J., X.T. and L.P. Analysis and interpretation of data: L.G., H.J., X.T., L.P. and Y.J. Writing the manuscript: L.G., H.J., X.C. and Y.J. All the authors took part in the discussions of the results and contributed to the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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Case Report

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Adolescent Premature Ovarian Insufficiency Following Human Papillomavirus Vaccination: A Case Series Seen in General Practice

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Abstract

Three young women who developed premature ovarian insufficiency following quadrivalent human papillomavirus (HPV) vaccination presented to a general practitioner in rural New South Wales, Australia. The unrelated girls were aged 16, 16, and 18 years at diagnosis. Each had received HPV vaccinations prior to the onset of ovarian decline. Vaccinations had been administered in different regions of the state of New South Wales and the 3 girls lived in different towns in that state. Each had been prescribed the oral contraceptive pill to treat menstrual cycle abnormalities prior to investigation and diagnosis. Vaccine research does not present an ovary histology report of tested rats but does present a testicular histology report. Enduring ovarian capacity and duration of function following vaccination is unresearched in preclinical studies, clinical and postlicensure studies. Postmarketing surveillance does not accurately represent diagnoses in adverse event notifications and can neither represent unnotified cases nor compare incident statistics with vaccine course administration rates. The potential significance of a case series of adolescents with idiopathic premature ovarian insufficiency following HPV vaccination presenting to a general practice warrants further research. Preservation of reproductive health is a primary concern in the recipient target group. Since this group includes all prepubertal and pubertal young women, demonstration of ongoing, uncompromised safety for the ovary is urgently required. This matter needs to be resolved for the purposes of population health and public vaccine confidence.

Keywords

premature ovarian failure, amenorrhea, human papillomavirus vaccination, ovarian insufficiency, menopause

Introduction

Premature ovarian insufficiency (POI) has been defined as hypergonadotropic hypogondism developing before age 40 years due to follicle depletion or dysfunction.[1] Oocyte depletion may be due to low initial numbers or accelerated loss. The function of the ovary may fluctuate in this state before failure, hence the recent preferred usage of the term POI (terminology used in this article will be consistent with references). POI with possible ovarian failure is a devastating diagnosis for a young woman's health and hopes of motherhood. The condition is important to identify and its causes are important to investigate and research for the preservation of future well-being. The physical, psychological, reproductive, and social impact is significant and will be greater when the condition develops in very young women and adolescents. Life expectancy may be reduced because of skeletal and organ effects. This impact will increase where diagnosis is delayed or the condition and its causes inadequately treated. Causation is unknown in 74% to 90% of cases[2,3] and the background age-specific incidence of idiopathic premature ovarian failure (POF) in early to mid-adolescence is so rare as to be also unknown, with the annual incidence reported as 10/100 000 person-years up to age 30 years.[4] The development of idiopathic POI and POF in a series of young teenagers after receiving the quadrivalent human papillomavirus (HPV) vaccine therefore has no age-specific background rates for comparison.

Each quadrivalent HPV vaccine is a recombinant protein particulate vaccine, containing 20, 40, 40, 20 μg of the major

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capsid (L1) protein of HPV types 6, 11, 16, and 18 respectively, 225 μg aluminum hydroxyphosphate sulfate, 9.65 mg sodium chloride, 780 μg; L-histidine, 50 μg polysorbate 80, and 35 μg sodium borate ("Gardasil," "HPV4," "4vHPV"). It is recommended to young women for its protective role against the 2 most common HPV oncogenic types, HPV 16 and HPV 18. This vaccine could potentially prevent 70% of cervical cancer.[5] Protection against 2 other HPV types (6 and 11) causing genital warts is included in HPV4. Since 30% of cervical cancer may still occur in vaccinated individuals, papanicolaou smears to the seventh decade are still required. Prior to vaccine introduction, the incidence and mortality rate of cervical cancer were steadily declining. These rates more than halved in the decade prior to 2000 in the 20- to 69-year age group in Australia and 578 new cases were diagnosed in 2000.[6] The incidence was highest in remote areas,[7] with the risk of death from cervical cancer for an Indigenous woman in Australia 6 times that of a non-Indigenous woman. In 1989, it was estimated that cervical cancer pap screening could potentially prevent 90% of squamous malignancies.[8] Increasing success of the Australian National Cervical Screening Programme has been moving toward this capacity with prevention of 70% of squamous cell cancers in 1998,[9] up from 46% in 1989. In 2002, the Australian incidence of cervical cancer was 6.2 per 100 000 women[8] and the mortality rate 1.7 per 100 000 women. In 2011 in Australia, there were 229 deaths from cancer of the cervix.[10] Five-year relative survival is 72.1%.[11]

A consideration of vaccine benefit versus vaccine risk requires high-quality safety evidence. This case series is therefore presented for its possible significance to young women's health and fecundity. The limited capacity of existing HPV4 research to attest to ovarian safety together with factors that impede vaccine adverse event reporting could affect the quality of information supplied to informed consent. This second case series of adolescent POI/POF increases evidence suggesting that the hypothesis of an association between HPV vaccine and premature ovarian demise needs to be tested.

Background

Early symptoms and signs of POI vary and a delay in presentation and diagnosis of POI is common. It has been observed that 92% of women with idiopathic POF describe an altered menstrual cycle as their initial symptom.[12] A total of 58% have described amenorrhea lasting 3 months or longer as the presenting symptom and 29% have described oligomenorrhea as the presenting symptom. Polymenorrhea, infertility, metrorrhagia, and vasomotor symptoms were less common presentations. In all, 25% of karyotypically normal women with noniatrogenic POF took more than 5 years from onset of a menstrual cycle abnormality for the diagnosis to be established. The median duration to diagnosis was 2 years. Overall, 57% of women with POF required 3 or more clinician visits prior to laboratory testing and 61% of women reported seeing 3 or more clinicians prior to diagnosis. Noninvestigation of new menstrual pattern abnormalities in young women may be due to a low perception of importance by the patient or low perceived importance by the physician. It has been observed that 39% of women developing amenorrhea consult a doctor.[13] Similarly, clinicians appreciate that some 4% of reproductive-aged women may miss 3 periods each year.[14,15]

Since the incidence of POF increases with age, we need finer gradations of incidence for very young teens at 13 and 14 years of age in whom this condition following HPV4 has been reported.[16,17] The unknown prevalence of idiopathic premature ovarian failure in the early to mid-teenage HPV4 vaccine target group renders adverse event analysis methods such as "rapid cycle" vaccine event analysis inapplicable.[18]

Premature ovarian insufficiency has serious health implications. A Swedish study of 22 000 postmenopausal women suggests those entering menopause aged 40 to 45 years have a 40% increased risk of cardiac failure than those entering menopause at age 50 to 54 years.[19] For every year delay in the onset of menopause the rate of cardiac failure was lowered 2%. The cardiac implications for teenagers entering menopause have yet to be defined. Altered ovulatory and menstrual patterns also lead to accelerated loss of bone density and increased wrist and hip fractures in later life.[20] POF is one of the greatest risk factors for osteoporosis.[21] Furthermore, lowered bone mineral density begins with diminished ovarian function before the onset of amenorrhea[22] and suboptimal bone density in teens is a factor in the development of osteoporosis.[23] Other health implications of POI will differ by cause.

Published case reports have considered a possible link between quadrivalent human papillomavirus vaccine and premature ovarian failure.[17,24] Declining menstrual function in girls aged 14, 15, and 20 years followed HPV4 vaccination and preceded POF in the previous case series. The formerly published *BMJ* case report of a 16-year-old with irregular menses gradually progressing to oligomenorrhea, amenorrhea, and POF after HPV4 was the first such case presenting to this practitioner and is therefore summarized as "Case 1" below.

This case series presents 3 young women who consulted a primary care general practice in rural New South Wales, Australia. Two experienced a duration of cycle disruption progressing to amenorrhea and 1 had an unknown prodrome to amenorrhea due to oral contraceptive pill (OCP) usage. These symptoms followed HPV4 vaccination. The girls are not known to be related and reside 40 to 500 km apart (1 patient was holidaying). Vaccination batches that were identified were dissimilar and administered in locations 3, 500, and 570 km from this attending practitioner.

Case 1

This case has previously been published in the *BMJ Case Reports*.[24] It was the initial presenting case diagnosed in this

series. Therapeutic Goods Administration of Australia adverse event report reference number is 285383.

Menarche at age 13 years in 2007 was followed by light periods, which became heavier and regularized over the next 12 months. HPV4 was administered in February, May, and August of 2008 (Department of Health New South Wales. 2011). Cycles became irregular early in 2009 and become scant and infrequent in 2010. Menstruation ceased in January 2011 and hot flushes commenced. There was no past history of significant illness or surgery. She was a nonsmoker, took no medications, and had no history of injury. Body mass index was 22.6 kg/m^2. There was no family history of premature menopause. At her initial consultation for oligomenorrhea becoming amenorrhea, she was prescribed the OCP without investigation. She was not sexually active.

She declined the OCP and consulted a second clinician. Investigations revealed that follicle-stimulating hormone was 108 U/L (menopausal range 20-140 U/L); luteinizing hormone was 31 U/L (menopausal range 10-65 U/L); estradiol was low at 63 pmol/L (normal follicular range >110 pmol/L, menopausal range = 40-200 pmol/L). Progesterone was 1.1 nmol/L (menopausal range <2.2 nmol/L). Anti-Müllerian hormone was <1.0. There were no antiovarian antibodies or antiadrenal antibodies detected. Thyroid peroxidase antibodies were 2 IU/mL and thyroglobulin antibodies were 44 IU/mL (levels up to 100 IU/mL can occur in normal subjects). A pelvic ultrasound was reported normal. Full blood count, renal, liver and thyroid function, and prolactin were normal. Premature ovarian failure was diagnosed at age 16 years. Some irregular anovulatory pattern bleeds occurred before commencement of hormone replacement therapy.

Karyotype was 46XX. Galactosemia testing was negative. Fragile X testing was normal.

This girl was counseled about the need for bone strength preservation. Her bone mineral density testing suggested femoral neck to be in the low range for age, height, and weight at 0.766 g/cm^2 and lumbar spine bone mineral density to be normal for height and weight but lower than the expected range for age at 0.903 g/cm^2. She is considering ovarian tissue cryopreservation.

Case 2

An 18-year-old young woman presented with 6 months amenorrhea. Menarche had occurred at age 11 years. She suffered from mild cerebral palsy (possibly due to low birth weight of 1.88 kg at 38 weeks' gestation), mild asthma, Asperger's syndrome, anxiety, and epileptic events from age 14 to 15 years, considered secondary to cerebral palsy. She had a ruptured appendix at age 12 years. There was no other significant past history; no drug usage; she did not smoke or drink alcohol, and had not become sexually active. Sertraline was used for treatment of anxiety from 2009 to 2010 followed by fluoxetine. There was a family history of osteoarthritis and osteopenia and of pancreatic cancer; no family history of premature menopause. The OCP was commenced at age 12 years. The attending gynecologist recorded "although her periods were reasonably normal, she was put on the pill (20 µg ethinyloestradiol and 100 µg levonorgestrol) the next year because coping with her periods made her anxiety and depression symptoms worse." Her first HPV4 vaccination was administered at age 12 years and 9 months; the second vaccination near her 13th birthday, and the third vaccination at age 13 years and 5 months. The first HPV4 vaccination was given concomitantly with hepatitis B vaccination in the other arm. OCP usage continued for 2 years to age 14 years. It was briefly ceased at age 14 and this was followed by 3 months amenorrhea. OCP was then resumed without further investigation. At age 18 years, the OCP was again ceased and amenorrhea again ensued.

Follicle-stimulating hormone 1 month later was elevated at 44.5 IU/L (menopausal range is 25-130 IU/L). Luteinizing hormone was 29.2 IU/L (basal range 2.0-12, midcycle peak range 8.0-90, postmenopausal range 5.0-62 IU/L). Estradiol was 157 pmol/L. She continued amenorrheic and presented again for investigation 6 months later. At this time, follicle-stimulating hormone remained elevated at 34 IU/L. Luteinizing hormone was elevated at 46 IU/L. Estrodiol (Oest2) was 413 pmol/L and progesterone 2 nmol/L. Anti-Müllerian hormone was 1.5 pmol/L (14.0-30.0 pmol/L normal; levels <14 pmol/L suggest diminished ovulatory reserve) tested by Beckman Coulter Gen II ELISA assay. Anti-Müllerian hormone repeated 6 months later was <1 pmol/L and estradiol was <37 pmol/L. At this time and at age 18 years POI was diagnosed.

Full blood count, iron levels, liver function, blood glucose, and renal function were normal. Thyroid-stimulating hormone was normal 0.4 mIU/L (normal 0.3-3.5 mIU/L) and thyroid antibodies were normal. Prolactin was normal 294 mIU/L. Testosterone 0.9 nmol/L (normal 0.2-1.8 nmol/L); free androgen index 2.6 (normal 0.3-4.0); iron studies were normal. There were no antiadrenal or antiovarian antibodies detected. Morning cortisol was 218 nmol/L (normal range 160-650) nmol/L, ACTH 14 ng/L (normal range 9-51 ng/L), growth factor-1 27 nmol/L (normal range 21-76 nmol/L). Pelvic ultrasound performed at the time when the anti-Müllerian hormone level was 1.5 showed a normal uterus with an endometrial echo of 8.2 mm. Transvaginal ultrasound was declined and the left ovary was not visualized. The right ovary was 3.1 cm^3 in size and there was a 9-mm follicle within it. Brief menstrual bleeds then occurred for 4 months before amenorrhea resumed.

Testing for Fragile X revealed 2 normal-sized triplet alleles 23 and 37 cytosine–guanine–guanine n repeats (the normal zone is <44). Testing for galactosemia showed a normal Gal-1-P uridyl transferase-RC at 0.31 U/g hemoglobin (normal range 0.26-0.52 U/g). Records reported a vitamin B_{12} deficiency at age 16 years, but levels of vitamin B_{12} were within normal limits at 275 pmol/L (normal range 135-650 pmol/L). Karyotype was established as 46XX.

This young woman elected to undergo right ovary cryopreservation through Monash IVF in the hope that future developments, such as stimulation of ovarian stem cells, may be of later benefit. She was not deemed a suitable candidate for gonadotropin stimulation for oocyte preservation due to the undetectable anti-Müllerian hormone level. The pathologist described the macroscopic appearance of the ovary as "cystic and disrupted." Microscopic histology of three right ovarian biopsies reported fibrovascular connective tissue with no primordial follicles in the ovarian cortex of sample one. Ovarian sample 2 reported a cystic follicle and a cystic corpus luteum but no primordial follicles within surrounding parenchyma. Ovarian sample 3 reported "fibrofatty connective tissue only. No ovarian parenchyma is identified." Summary: "Levels through all tissue containing ovarian parenchyma show a single primordial follicle. No other follicular structures are identified." No samples contained evidence of atypia or malignancy (Sullivan Nicolaides Pathology. Brisbane, Queensland, Australia). Personal communication with the reporting pathologist confirmed no lymphoid or granulomatous inflammation and suggested the ovarian appearance was "consistent with that of a woman in her late forties."

She has been counseled about bone density preservation and the need for hormone replacement therapy. This case was notified to the Therapeutic Goods Administration (TGA) of Australia in January 2014 (reference number 333136) as diagnosed POI. Its listing as "amenorrhoea" on the TGA database in May 2014 was later altered to POF (July 2014).

Case 3

Menarche had commenced at age 10 years, and was followed by regular menses. The first 2 HPV4 vaccinations were received at age 14 years and the third vaccine after turning 15 years in 2008 (Department of Health New South Wales. School vaccination programme. Vaccinations administered February 18, May 23, and October 24 in 2008). The patient reports "prior to this, my periods were like clockwork." The period due after the third vaccination dose was 2 weeks late and was the first late period she had experienced. The next period occurred 2 months later. The next and final menstruation occurred 9 months later, approximately 1 year after completion of the third HPV4 vaccination. Hot flushes developed and 10 kg weight gain was noted over the next year. Previously present acne improved. Pelvic ultrasound was unremarkable apart from a 3.7-mm endometrial width and the absence of visible ovarian follicles. She had not become sexually active, had no history of drug or alcohol usage and there was no history of trauma, surgery or of significant past illness. There was no family history of premature menopause. She was allergic to benzoyl peroxide. POF was diagnosed just before her 17th birthday.

At age 15 years, initial testing was undertaken: testosterone was 1.1 nmol/L (normal range <2.6), sex hormone binding globulin 41 nmol/L (normal range 20-118 nmol/L), free androgen index 2.7% (normal range <7.2%). There is no significant further testing until nearly 17 years of age: prolactin 160 mIU/L (normal range 40-570 mIU/L), thyroid-stimulating hormone 1.1 mIU/L (normal range 0.5-4.5 mIU/L), dihydroepiandrostenedione (DHEA-S) 3.5 μmol/L (normal range 3.6-9.8 μmol/L), androstenedione 1.8 nmol/L (normal range 1.0-11.5 nmol/L), testosterone <0.7 nmol/L (normal range <3.2 nmol/L), serum hormone binding globulin 32 nmol/L (normal range 30-90 nmol/L), free androgen index <2.2%, luteinizing hormone 32.8 IU/L (midcycle range 17.7-47.5; postmenopausal range >9.3 IU/L), follicle-stimulating hormone 73.8 IU/L (midcycle range 9.6-24.1; postmenopausal >50 IU/L), estradiol <100 pmol/L (midcycle range 500-1500; postmenopausal <100 pmol/L). Estradiol (radioimmune assay) <10 pmol/L. Repeated hormone levels 7 weeks later revealed luteinizing hormone 42.9 IU/L, follicle-stimulating hormone 61.8 IU/L, and estradiol 18 pmol/L. Antiovarian antibodies were negative <1:10 and antiadrenal antibodies were negative. Anti-Müllerian hormone level was unrecordable. Bone mineral density scan was reported normal at age 17 years and 1 month (*z*-score 0.9 for lumbar spine and 1.4 for "whole body").

When reviewed in the Department of Clinical Endocrinology at Westmead Hospital, New South Wales, it was determined that she would not respond to gonadotropin stimulation for oocyte collection for cryopreservation. She has been counseled about the need for bone preservation and is currently on hormone replacement therapy. This case was reported to the Therapeutic Goods Administration of Australia in April 2014. No response was received and the case was renotified to the TGA in June 2014 and to the New South Wales Chief Medical Officer. Reference number and notification response are awaited. Consultation for ovarian cryopreservation has commenced.

Discussion

Consideration of the possible significance of this second case series of idiopathic POI/POF after HPV4 requires review of preclinical and clinical safety studies identified at licensing[25] and review of larger postlicensing safety studies. A summarized report of existing HPV4 research in relation to the very young ovary was presented by this author at the 18th World Congress of Controversies in Obstetrics, Gynecology and Infertility in October 2013[26] and to the Brighton Collaboration Journal Club (as author response to review of *BMJ* September 2012 Case Report).[27]

Preclinical Studies

Safety assessment of a new vaccine begins with preclinical studies for toxic effects in rodents. After diagnosis of case 1, and in response to a query from this patient, rodent ovarian histology after HPV4 vaccination testing was sought.

No histology report of the vaccine-tested rodent ovary was available under Freedom of Information Request to the Therapeutic Goods Administration of Australia.[28] There is no cellular observation available on tested rodents' ovaries beyond a numbering of corpora lutea present on the ovary at caesarian section.[29] Five-week-old tested rats conceived only 1 litter before euthanasia.

It is unfortunate that available toxicology studies only provide histology of the male rodent reproductive system after HPV4 vaccine[30,31] and not of the female rodent reproductive tract or ovaries. Vaccine-tested rat ovary histology reports would have been useful to consult to better understand any possible link between cases of teenage premature ovarian insufficiency and rat vaccine effects.

Published Sprague-Dawley rat testing for HPV4 vaccine fertility safety comprised 2 control groups and 2 vaccine groups.[32] Control group 1 was given a formulation of phosphate-buffered saline as placebo (the chemical formulation selected is not stated). Control group 2 consisted of the carrier solution components of Gardasil. It contained "aluminum (0.45 mg per mL), sodium chloride (18.7 mg/mL), sodium borate (70 mg/mL [sic]), L-histidine (1.55 mg/mL), and polysorbate 80 (100 μg/mL)." Vaccine group 1 consisted of rats only given the vaccine after their first mating and resultant conception. Vaccine group 2 rats received 2 vaccine doses 5 and 2 weeks prior to first mating/conception and at 6 days after conception and on lactation day 7.

Twenty-two rats within each of these 4 groups were assigned to caesarian section, and 22 from each group were assigned to give live birth before postweaning euthanasia. In the caesarian section data,[32,33] the total number of corpora lutea present in the group of 22 rats not vaccinated before mating, of whom all 22 fell pregnant at mating, was 366. The total number of corpora lutea present in 22 rats who received the first and second vaccinations before mating, of whom 20 fell pregnant at mating, was 326. The ratio of corpora lutea per rat that did fall pregnant was 16.30 (±2.5 SD) for those receiving 2 vaccinations before mating, and for those not vaccinated prior to mating was 16.63 (±2.3 SD). While these were only small differences of corpora lutea numbers, it is not known whether administration of the complete 3-dose vaccination course to test fertility may have shown a more significant disparity. The overall fecundity index of rats who received two thirds of the vaccination course prior to mating was 95%, the lowest of the 4 groups and very slightly lower than the fecundity index of 98% in rats who received no vaccination prior to mating. In controls 1 and 2, the fecundity index was 97% and 98%, respectively. In preclinical fertility studies submitted at licensing, no rats were tested with the complete vaccination course, with representative interval administration, prior to mating. The study concludes that vaccine rodent fertility testing conferred "a safety margin of 200-fold by body weight for adolescents." "Guidance for Industry" research guidelines state "where possible we recommend that you administer the maximum human dose (eg, 1 human dose = 1 rabbit dose) regardless of body weight."[34] The reason for omission of the third vaccination dose prior to measuring the rats' capacity to conceive is unclear.

The 200-fold safety prediction was derived from the 0.25 kg weight of a rat compared with the "average body weight of an adolescent girl (50 kg)." The HPV4 target girl group is aged from 9 years and administration in Australia is to girls aged 12 and 13 years under the National Immunization Programme. The 50th centile weight of 9-year-olds is 28 kg, of 12-year-olds is 42 kg, and of 13-year-olds is 46 kg.[35] Australian age-specific weights therefore also reduce modeled calculations of fertility safety.

Long-term fecundity studies of vaccinated female rodents' duration of reproductive lifespan, recorded numbers of litters and pup numbers in subsequent litters was also requested under the original freedom of information application but were unavailable.

Clinical Studies

Research consideration of ongoing female fertility was similarly absent from phases II and III clinical safety studies. The capacity of safety studies to assess ovarian function, particularly of the target age group, was reduced by several factors. The phase II and phase III studies identified as safety studies at the time of licensing[25] by the Vaccine and Related Biological Products Advisory Committee (VRBPAC) to the Food and Drug Administration are study protocols V501 007,[36] 016,[37] 018,[38] and 013,[39] and 015,[5] respectively. Only protocols 016 and 018 studied safety in the young female vaccine target group. Mean ages in these groups were 12.6 and 11.9 years, respectively. It is not clear what proportion of these were postmenarche.

In protocol 016, 240 girls (aged 10-15 years) were left in the study at 12 months, comprising 47.4% of screened healthy participant younger girls. Immune response data were collected through month 7, and safety data through to month 12. More than 52% were lost from the 12-month safety follow-up instituted as a protocol amendment. Loss of the majority of participants to safety observation significantly compromised this trial as a safety study of younger adolescents forming the vaccine's target group. One girl in this study experienced vaginal hemorrhages meeting Serious Adverse Event Criteria[40] after second and third vaccinations. These were initially deemed vaccine related, but subsequently considered by gynecological review[37] to have been related to a preexisting condition not excluded at general health screening. Protocol 018 fully vaccinated 587 girls. A total of 52.3% of enrolled girls were aged 9 to 12 years. It is not clear what proportions of girls in these target group safety studies could potentially have reported menstrual cycle patterns or aberrations of patterns. Similarly, health interviews with the participants 18 months after the first vaccination may not have been able to determine menstrual abnormalities while cycles are commencing or establishing ovulatory patterns.

Given the masking effects of hormonal contraception on ovarian function it is relevant that contraceptive hormone usage was reported at 58% to 60% of vaccine recipients in safety trials at baseline interview in phase III studies.[41] This rose to 68% to 83% of participants in the 2 substudies of protocol 013.[42(p143)] In all, 75% to 82% used hormonal contraception within 15 days of any vaccination in trial 007,[42(p216)] and more than two thirds recorded concomitant hormonal contraception usage within 14 days of any vaccination in protocol 015.[42(p244)] Phase III studies' participants, mostly 16 years and older, were required to use effective contraception for at least 7 months. A major review of the HPV4 vaccine safety profile reports: "new medical conditions were not considered adverse events if they occurred post month 7, or were not considered by the investigator to be vaccine related."[43]

The design of safety studies with use of a vaccine report card further restricted the recording and reporting of menstrual dysfunction. The largest safety study, phase III study protocol 015, enrolled older females predominantly aged 16 to 23 years (1 was 15 years old, 46 were older than 23 years) of whom 5916 completed the 3-dose HPV4 vaccination period and 5953 completed placebo dosages.[42(p58)] A subgroup selected from among these formed the Detailed Safety Cohort. It followed 448 recipients of at least 1 vaccination and 447 control recipients, asking them to record nonserious adverse events (NSAEs) for 2 weeks after each vaccination on a vaccine report card. Serious adverse events (SAEs) in the 2 weeks following each vaccination were also recorded.[5] Participants not included in the NSAE substudy were solicited only for SAEs occurring within 2 weeks after each vaccination.[42(p52)] All SAEs that were considered to be potentially related to administration of the vaccine were to be reported throughout the study. However, menstrual cycle disruption, oligomenorrhea, and amenorrhea will not signal as SAEs by definition. SAEs are defined as life-threatening, resulting in death, permanent disability, congenital anomaly, hospitalization, prolongation of hospitalization, or necessitating medical or surgical intervention to prevent one of these outcomes.[44] The use of a vaccine report card to record other adverse events occurring within 2 weeks of each vaccination has limited ability to detect diminishing menstrual cycles. This is a weakness in the safety design of clinical trials. It would not have detected the menstrual cycle decline evident in the cases of premature ovarian insufficiency presented in this series. Protocol 018 VRC prompted for additional information such as headaches, rashes, muscle/joint pain, and diarrhea that occurred within 14 days but not menstrual aberration.

When the Center for Biologics Evaluation and Research requested an analysis of autoimmune conditions over the entire safety database, the sponsor noted that "there were subjects with additional new medical conditions that were not reported in the Clinical Study Reports for 011 and 012 [within protocol 013]. These included two subjects with amenorrhea."[12(p198)]

Longer term follow-up beyond the vaccination interval was limited to SAEs. Protocol 015 mean follow-up was 3 years from first vaccination for SAEs. The second largest study, protocol 013, fully vaccinated 2582 women[42(p136)] and vaccine report cards recorded NSAEs for 2 weeks after each injection. Lack of long-term follow-up is identified as a limitation of this study.[39,42(p136)]

Underrepresentation of the vaccine's target age group, incomplete and short-term follow-up, definitional limitations, hormone usage, fortnight restrictions of vaccine report card documentation and the decision not to report new medical conditions as adverse events which occurred post month seven from first vaccination compromised safety studies' observation of ovarian health.

Vaccine Components Used as Safety Study Controls

The choice of placebo affects the validity and quality of scientific information available from placebo-controlled studies. The control in any experiment should lack the factor being tested. The placebo that formed the control selected for phase III safety studies of Gardasil (older girls) was the aluminum adjuvant present in the vaccine solution, amorphous aluminum hydroxyphosphate sulfate. The selection of aluminum as a control in vaccine studies is at variance with the scientific principles of a control. The placebo in the only controlled study of very young girls was the remainder of the vaccine carrier solution: "The placebo used in this study contained identical components to those in the vaccine, with the exception of HPV L1 VLPs and aluminum adjuvant."[38] It contained 50 μg polysorbate 80 (polyoxyethylene sorbitan mono-oleate also known as Tween 80), 35 μg borax, 9.56 mg sodium chloride, and 0.78 mg L-histidine.

Safety studies identified at licensing did not compare HPV4 with normal saline controls. The second placebo contained several substances together with saline. The researchers' reference to the "carrier solution" placebo conflicts with the licensing review. The Center for Biologics Evaluation and Research states, "Protocol 018 provides saline placebo-controlled safety data for subjects 9 to 15 years. This is of particular interest because the other studies used alum placebo as a safety comparison."[42(p330)] Subsequent reviews of safety studies also claim a saline placebo was the comparator of younger girl safety studies and variously refer to this placebo control as "non-aluminum containing (saline) placebo"[43] and "saline placebo."[45] Gardasil Product Information itself refers to the control as a "saline placebo."[46] Published safety studies only compared HPV4 vaccine with its own components. This may be significant since injected substances in both placebo control arms have either a suggested association with autoimmune ovarian damage[17] or known direct ovarian toxicity.[47]

Completed vaccine and placebo courses each administered 675 µg of aluminum to older girl safety study participants; or components including 150 µg polysorbate 80 to all 9- to 15-year-old safety study participants.

When polysorbate 80 ("Tween 80") was injected into newborn rats, it caused similar ovarian damage to injected diethylstilbocstrol. Rat ovary effects occurred at all doses tested over a tenfold range.[47] Since this study provides a relevant ovary histology report of a substance in HPV4 it bears detailed consideration. 1%, 5%, or 10% solutions of polysorbate 80 at 0.1 mL per rat were injected into rats at 4, 5, 6, and 7 days after birth. The oestrous cycle was examined at weeks 10, 14, and 18 of age. Findings were compared with control rats given no treatment; negative controls given water injections; and a "positive" control group given a formulation of 50 µg diethylstilboestrol. Rats injected with polysorbate 80 had an oestrous cycle ranging from 9 to 14 days, compared with 4.3 days average length throughout the test in untreated controls and 9.4 days in diethylstilboestrol injected rats. Postmortem conducted at 20 weeks of age on "Tween"/polysorbate 80 tested rats reported

1. All Tween-treated groups showed a statistically significant ($P < .001$) decrease in the relative weight of the ovaries in comparison with the untreated control. The relative weight (% of body weight) was slightly lower in the 1% Tween 80–treated groups than in the 10% Tween 80–treated groups.
2. In the group of 6 rats given the lowest dose of Tween 80 "in two rats the uterus was enlarged and had a marked vascular pattern."
3. The 5 rats given diethylstilboestrol showed "microscopically degenerated follicles in the ovaries with complete absence of corpora lutea. Findings in the ovaries similar to those in the positive control [diethylstilbestrol control] group were also observed in all of the groups given Tween 80."
4. Abnormal histological findings in the cells lining the uterus were observed in all 17 rats given Tween 80 and resembled the abnormal histology observed in diethylstilboestrol-treated rats, which had high cylindrical epithelial cells and some mitoses. The study concluded, "4-day administration of Tween 80 to female rats during the period crucial for the development and function of reproductive organs accelerates the maturation of these organs." As well as a prolonged oestrous cycle researchers also noted induction of persistent vaginal oestrous. This was slightly more marked in the 1% solution of Tween 80 than in the 5% or 10% solutions. Statistically significant increased weight of the adrenals ($P \leq .05$) was also noted in the 1% polysorbate injected rats.

No dose response curve was identified. This chemical is present in orally ingested medicines and foods, but did not affect rat reproduction when subject to digestive processes at up to 5% of their oral intake. It did decrease rat reproduction at 20% of their oral intake.[48] It is not known whether some protection may be conferred by digestive processes to smaller loads of polysorbate 80 that is not present in the parenteral route of administration to young female rats. This research highlights 4 issues. First, the scientific role of control groups and placebo selection. Second, a possible confounding effect of polysorbate 80 used as placebo in younger girls' HPV4 safety trials. A potential ovarian toxin in both control and vaccine arms could obscure the already limited ability to observe risk differences of adverse menstrual events. Third, the absence of crucial histological reporting of the rodent ovary after HPV4 vaccination containing 150 µg polysorbate 80. Fourth, whether clinical investigators of vaccine safety considered the potential ovarian effects of this vaccine component when determining a "likelihood" relationship between menstrual aberration and the study vaccine. Safety trial investigators determined the relationship of both Vaccine report card documented adverse events and new medical conditions before month 7 to vaccination, based on criteria of "likely cause," exposure, time course, and rechallenge. Licensing bodies asserting "no biological plausibility"[49,50] of ovary effects arising from vaccine constituents accept a null hypothesis at odds with existing research. This may also reflect research investigator considerations of "likelihood."

Histologically evident toxic ovarian effects of polysorbate 80 evidenced 5 months after serial injections into very young rats have not been compared with the histological effect of the HPV4 vaccine course containing 150-µg dosage. The relevance of polysorbate 80 ovarian damage to the cases presented here is unresearched and unknown and assurances of "no biologically plausible" link between HPV4 vaccine and ovarian effects cannot be given.

The role of the aluminum adjuvant as a safety study placebo also requires consideration. The development of an "autoimmune/inflammatory syndrome induced by adjuvants" (ASIA) has been postulated by some immunologists to be implicated in the development of premature ovarian failure.[17] The 3 young women in the previous published case series of POF following HPV4 had associated symptomatology which fulfilled criteria for this syndrome. These criteria include clinical signs (such as neurological, sleep, or cognitive disturbances, myalgia, arthralgia, fatigue, and fever) with a major feature of prior exposure to external stimuli such as infection, vaccine or vaccine adjuvants, and possible other autoimmune phenomena.[51] Existence of this syndrome is under dispute, but proponents suggest autoimmunity may be induced in this context in genetically predisposed individuals. Antiovarian antibodies were found in the 15-year-old girl diagnosed with POF in that series. A possible autoimmune implication of injected aluminum reinforces the scientific principle that placebos should not contain the factor being tested. Respect owed to this principle is further endorsed by findings that "the structure of the ovary

was disrupted" in rats exposed to subchronic ingestion of aluminum chloride.[52] Other associations with this aluminum salt included reduced levels of alkaline phosphatase, acid phosphates, and ATPase and lowered protein expression of follicle-stimulating hormone receptor and luteinizing hormone receptor. The selection of aluminum as the safety comparator may have confused safety trial outcomes. Its use as a placebo is therefore questionable.

Postlicensing studies

Two large safety studies, sentinel cohort follow-up, reviews of existing research, and vaccine adverse event reporting systems have reported on postmarketing vaccine safety.

The first of the 2 largest post marketing studies sought to evaluate vaccine safety "during the course of routine clinical care" by reviewing presentations at emergency departments and hospitalizations from within a cohort of 189 629 vaccinees.[55] This group included 44 000 females who had completed 3 vaccinations. Eleven- to 12-year-olds comprised 4.3% of the total vaccine group. Emergency department visits are not the consultation context for seeking medical management of altered menstrual cycles, oligomenorrhea, or amenorrhea. These conditions rarely require hospitalization. This study had no capacity to evaluate ongoing ovarian health or safety. Further analysis of these emergency department presentations/hospitaliza-tions to review the risk of 16 autoimmune conditions did not include ovarian dysfunction or failure.

The largest and most recent published cohort study from Denmark and Sweden of 997 585 girls measured incident hospital diagnosed autoimmune, neurological, and thromboembolic events.[54] Menstrual cycle aberrations indicative of ovarian malfunction were not included and, again, do not usually present to emergency and hospital settings. This study of approximately 1 million girls sheds no light on reproductive function or egg-bearing capacity.

The sentinel study of 577 girls from protocol V501 018 was to provide the first long-term data of vaccinated adolescents. It assessed safety by monitoring for serious adverse experiences and pregnancy outcomes.[45,55] The Nordic extension of the long-term follow-up of protocol V501 015[45] addressed the hypothesis that Gardasil will remain effective for 14 years after vaccination. This long-term follow-up study will connect with National Hospital Registers in participating countries and cancer registries searching for adverse events such as deaths, hospitalizations, cancers and other safety outcomes. It has the capacity to search health-related registries to find "safety events of interest," comparing adverse event rates to those in the age-matched general population. Ovarian function is not recorded in its research focus. Furthermore, data search of ovarian insufficiency if undertaken may be impeded by evidenced delays to diagnosis within 5 years,[12] OCP usage and lack of incidence statistics in an age-matched population.

Postlicensure monitoring is relied on to detect rarer adverse events. The Vaccine Safety Datalink[56] has reviewed associations between HPV4 vaccination and outcomes prespecified as Guillan-Barre, stroke, venous thromboembolism, appendicitis, seizures, syncope, allergic reactions, and anaphylaxis. Ovarian dysfunction was not studied and rare events need background incidence rates for comparison. Monitored outcomes were those with relatively acute onset, which could "represent a biologically plausible association with vaccination." Rapid cycle analysis of vaccine safety datalink information requires comparison between vaccinated and unvaccinated groups.[57] The Clinical Immunization Safety Assessment Network reviews SAEs reported to the Vaccine Adverse Event Reporting System (VAERS) following immunization and have therefore reported on deaths, venous thromboembolism, neurological, and allergic outcomes.

The VAERS[58] accessed August 2013 noted 104 cases of amenorrhea following HPV4. Less than 9% had a reported return of menses. Only 1 girl out of 105 amenorrhea notifications had a follicle-stimulating hormone level recorded. This was "elevated at 72" (no units given). No notifications had an anti-Müllerian hormone level reported. A comparison of adverse events following immunization reported to VAERS with adverse events following immunization reported to the World Health Organization "Vigibase" reveals similar proportions of notifications.[59] As with all passive reporting systems, reliance is placed on voluntary reporting accessing the reporting process. These reports often derive from a population of unknown size. It is not possible, therefore, to determine the incidence of these events or to assess causality. The chief function of adverse event reports and of case reporting is to generate hypotheses for further study.

Considerations

The great quantity of research concerning HPV4 vaccine does not necessarily establish a comprehensive, qualitative safety assurance. The administration of vaccines to all well prepubertal and peripubertal young persons necessitates a consideration of reproductive health that has not been met in the context of ovarian health. Selection of large numbers of participants may not produce the best data if the vaccine target group is underrepresented, or if research for adverse events is focused on hospitalizations and emergency settings rather than routine primary care settings—the context for many disease category presentations. Regardless of vast data, pre- and postlicensing studies have not assessed ovarian safety. Neither vaccine target age group study considered the proportion of girls postmenarche. Research reviews have not always analyzed safety study design quality. An Australian review of this vaccine's safety research spoke of "impressive clinical trial results" conducted before licensing.[60] However, younger person safety studies comprised 2 phase II studies of which only 1 had a "control" group, with

very small numbers of young females receiving all 3 vaccinations. One of these 2 studies had lost more than half to 12 month follow-up even though these 10- to 15-year-olds were to be followed for 1 year after first vaccination for safety related data.[37] Only 40.4% of boys studied, 205 in total, completed 12-month safety follow up in this designated safety study in which one 15-year-old boy died suddenly 27 days after his second vaccination.[37] With no clinical findings at autopsy, the investigator determined his death was unrelated to the study vaccine "because of the lack of any plausible or temporal relationship."

Other considerations await research. The relevance of claimed detection of HPV L1 gene DNA sequences in Gardasil vials in separate studies is unknown.[61,62] A recent report states "preliminary data showed the presence of contaminating HPV L1 DNA in all tested different batches of Gardasil® Vaccine from France. Our observations confirm independently and extend the previous observations by Lee SH." Researchers concluded "the persistence in muscle tissue of residual HPV DNA fragments is uncertain after intramuscular injection and requires further investigation for vaccine safety."

The occurrence of increased adverse vaccine events in girls who had not previously been exposed to the HPV vaccine viral types before vaccination also has unknown relevance. Food and Drug Administration summary of safety trials reported most adverse events occurring in girls naïve to the injected vaccine HPV types prior to vaccination.[42(p288, p432)] Those who were polymerase chain reaction (PCR) negative and seronegative to all 4 vaccine HPV types at baseline reported the highest incidence of systemic adverse events, the highest proportion of "moderate to severe" systemic adverse events and the highest incidence of headache after Gardasil when compared with groups who evidenced prior HPV type exposure at baseline. The difference in adverse event recording between those naïve to the HPV 6, 11, 16, 18 types and those who had been previously exposed was most marked in the "Detailed Safety Cohort" of protocol 015 (United States).[42(p93)] In all, 63.8% of previously unexposed (seronegative/PCR negative) vaccine recipients recorded clinical adverse events after any injection. This compared with 51.5% of previously exposed (seropositive or PCR positive) recipients. The disparity within control groups was less marked. The Detailed Safety Cohort analysis records adverse clinical events in 60.4% of HPV naïve recipients of the aluminum control compared with 56.1% of HPV-exposed recipients. In the vaccine cohort, the disparity between the rates of clinical adverse events recorded in those who were naïve to HPV types 6, 11, 16, 18 prior to vaccination and those who were not naïve increased with each successive dose. The greatest difference was observed after dose 3, when 27.9% of naïve recipients had clinical adverse events recorded, compared with 16.8% of those who evidenced previous exposure to HPV types 6, 11, 16 and 18. Where only one HPV type was present in the tested vaccine, phase II study 005 of HPV 16 L1 VLP, there were no increased clinical adverse events in the sexually naïve. None of the 3 girls in the case series discussed was sexually active. The relevance of this status is not known. Since the preferred target group of the HPV4 vaccination program is virgins, and this group is less represented in safety studies, further clarification is appropriate.

These cases presented to a part-time general practitioner in a 5-doctor general practice. Cases 1 and 2 lived in different towns 40 km apart. Case 3 had been diagnosed elsewhere but her case had not been notified to the TGA. Her presentation, while holidaying, was stimulated by her awareness of case 1 in medical literature and by identification of the township of the author. The third case had passed unnoticed in the context of preceding HPV vaccination. The number of girls in the population who may have a similar unnotified diagnosis is not knowable. The pattern of ovarian demise here is not clear, but a gradual process is apparent. Lack of diagnosis in cases 1 and 2 prompted investigation in preference to further issuing of oral contraceptive prescriptions. OCP prescribing would delay appropriate diagnosis and management as well as notification of a possible adverse event. Therapeutic management was commenced with a more appropriate level of hormone replacement, attention to calcium, vitamin D, exercise, bone mineral density, and subsequent monitoring for autoimmune conditions that may be associated. Psychological health will also be monitored given the physiological and emotional effects of this diagnosis. Depressive symptoms were not found in these patients. Anxiety symptoms have been found in premature ovarian failure and psychosocial stress has scored higher during the year before cessation of menses.[63]

Diagnosis of idiopathic POI in mid-adolescence raises questions around future childbearing. Because of unrecordable anti-Müllerian hormone levels, 2 of these cases were not considered suitable for oocyte collection and cryopreservation. Recent studies of mouse oogonial stem cells have suggested the possibility of in vitro propagation and of future egg generation in vivo. Ovary tissue cryopreservation is being considered for future assistance in fertility preservation.[64]

Future Research

Further research would consider a delayed onset of ovarian decline as suggested in this case series. The starting point of these girls' anti-Müllerian hormone levels is not known, but the decline in case 2 from 1.5 to <1 in 6 months may reflect the gradual decline that has possibly taken 5 years to complete. Anti-Müllerian hormone levels are a biomarker of ovarian reserve, with 1 study suggesting peak levels at 15.8 years and a decline commencing after age 25 years.[65] Their measurement may have a role to play in researching and monitoring ovarian demise and toxicity, since anti-Müllerian hormone levels strongly correlate with the existing antral follicle count and are therefore a quantitative measure of

ovarian reserve.[66] Rodent ovarian histology—similar to the manufacturer's rodent testis histology report postvaccination—is also required. The delayed onset evidenced by this case series could also inform belated rodent ovary and fecundity studies to observe rodent ovaries and reproductive capacity at intervals after completed vaccination through their reproductive life span. Rodent fertility studies did not evaluate the standard vaccine course prior to conception, or the cumulative effect over time of 3 serial vaccinations, or the possibility of a delayed effect on reproductive capacity. Further research is needed to determine whether fecundity and fertility indices in rats are affected by the completed dosages administered to young teens as per industry guidelines.

Cohort studies of menstrual patterns in vaccinated and unvaccinated individuals are also required with timed anti-Müllerian hormone sampling. All such research should be wholly independent of commercial interests and manufacturer.

Conclusion

It is not known whether idiopathic POI developing progressively in young teens following HPV4 is related to this vaccination. Case reports do not and cannot establish causation. It is known that safety research before and after licensing has inadequate capacity to determine ovarian safety. Small numbers of young persons represented in research, hormonal usage in older females' studies, vaccine report card limitations, omission of a true placebo, inconsistent rodent toxicity studies, limitations of SAEs recording, subjective investigator decisions of likelihood and failure to record new conditions arising after month 7 as vaccine-related have weakened safety research. Diagnosis of premature ovarian insufficiency and failure is delayed in the general population and notified teenage amenorrhea is similarly underinvestigated in VAERS documentation. This primary care issue reduces the effectiveness of postmarketing surveillance. POF/POI notifications would be further compromised by OCP treatment of uninvestigated amenorrhea and hormonal contraception levels in the general population. Analysis of adverse event reporting is impeded by lack of background age-specific teen incidence figures. Long-term follow-up data after HPV vaccination has not surveyed ovarian function, recorded, measured, or analyzed symptoms or signs of dysfunction. Disparagement of adverse event reporting by licensing bodies' instruction to health providers that "there is no biologically plausible way in which HPV vaccine could cause infertility" lacks science and compromises safety monitoring by undermining "reporting efficiency"[67] safety signaling and informed consent. Public reassurance that "studies have not found ovarian failure to be associated with HPV vaccination"[68] in the absence of sound research may be harmful to vaccine confidence. Edward Jenner, considered the father of vaccines, was known to say "let's not speculate, let's do the experiment." Further studies are required to make any claims of ovary complications. Principles of informed consent, population health, and vaccine confidence require careful, rigorous and independent research to establish ovarian safety following HPV vaccination.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Cervical Cancer Elimination Initiative

Cervical cancer is preventable and curable, as long as it is detected early and managed effectively. Yet it is the 4th most common form of cancer among women worldwide, with the disease claiming the lives of almost 350 000 women in 2022.

Few diseases reflect global inequities as much as cancer of the cervix. Nearly 94% of the deaths in 2022 occurred in low- and middle-income countries. This is where the burden of cervical cancer is greatest, because access to public health services is limited and screening and treatment for the disease have not been widely implemented.

An ambitious, concerted and inclusive strategy has been developed to guide the elimination of cervical cancer as a public health problem.

A global strategy

In May 2018, the WHO Director-General announced a global call for action to eliminate cervical cancer, underscoring renewed political will to make elimination a reality and calling for all stakeholders to unite behind this common goal.

In August 2020 the World Health Assembly adopted the Global Strategy for cervical cancer elimination.

Now is the time to act to eliminate cervical cancer as a public health problem.

chieving elimination

To eliminate cervical cancer, all countries must reach and maintain an incidence rate of below 4 per 100 000 women. Achieving that goal rests on three key pillars and their corresponding targets:

- vaccination: 90% of girls fully vaccinated with the HPV vaccine by the age of 15;
- screening: 70% of women screened using a high-performance test by the age of 35, and again by the age of 45;
- treatment: 90% of women with pre-cancer treated and 90% of women with invasive cancer managed.

Each country should meet the 90–70–90 targets by 2030 to get on the path to eliminate cervical cancer within the next century.

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Amoth appointed as WHO Executive Board chairperson

Amoth succeeds Dr Harsh Vardhan from India as new WHO Executive Board Chairman.

by SHARON MAOMBO
Business Writer

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In Summary

•Amoth's appointment was announced on Wednesday during the 149th meeting of the WHO Executive board in Geneva.

•Accepting his new position, the DG said the appointment is a boost to Kenya. Amoth succeeds Dr Harsh Vardhan from India.

by SHARON MAOMBO
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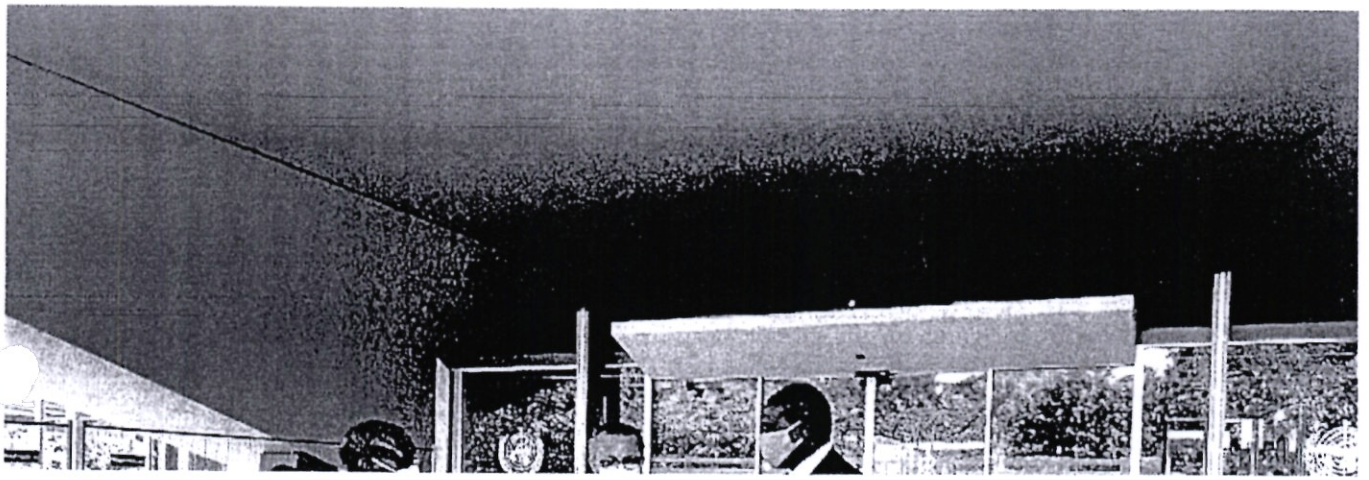



Amb. Mailu Cleopa, (Permanent Representativeof Kenya to the UN and Other International Organizations), Dr. Tedros Adhanom (Director General of the WHO), and the Ag. DG Patrick Amoth during formal briefing meeting with the WHA Secretariat-headed by the DG WHO Image: COURTESY

Acting Director-General of Health Patrick Amoth has been appointed Chairperson of the World Health Organisation (WHO) Executive Board.

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Amoth's appointment was announced on Wednesday during the 149th meeting of the WHO Executive board in Geneva.

Accepting his new position, the DG said the appointment is a boost to Kenya. Amoth succeeds Dr Harsh Vardhan from India.

serve as Chairperson of the Executive Board" Amoth said.

He added, "This is not an honour that the Republic of Kenya takes lightly and I commit, on behalf of the Government of Kenya, to undertake the duties and responsibilities entrusted to this office with utmost commitment and humility.

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He was elected Vice President of the Executive Board of the WHO for a two-year term in My 2020.

The Executive Board consists of 34 members who are entitled to elect the chairperson.

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Member.

Kenya's Ambassador in Geneva Dr. Cleopa Mailu is the alternate member. These Members are elected for three years and may be re-elected.

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Ref.: C.L.2.2022

Proposal for amendments to the International Health Regulations (2005)

The Director-General of the World Health Organization presents his compliments to States Parties to the International Health Regulations (2005) ((IHR (2005)) and has the honour to transmit the text of the proposal for amendments of the IHR (2005) received from the United States of America pursuant to paragraph 1 of Article 55 of the IHR (2005).

In accordance with paragraph 2 of Article 55 of the IHR (2005), this letter constitutes a formal communication of the text of the amendments proposed by the United States of America.

The Director-General of the World Health Organization takes this opportunity to renew to States Parties to the IHR (2005) the assurance of his highest consideration.

GENEVA, 20 January 2022

ENCLS.: (2)

THE PERMANENT MISSION
OF THE
UNITED STATES OF AMERICA
TO THE
UNITED NATIONS AND OTHER INTERNATIONAL ORGANIZATIONS
IN GENEVA

No. 4-22

The Permanent Mission of the United States of America to the United Nations Office and Other International Organizations in Geneva presents its compliments to the World Health Organization (WHO) and refers to the International Health Regulations (IHR) (2005). In accordance with Article 55(1) of the IHR (2005), the United States of America is proposing amendments to the IHR (2005). The Mission, by means of this note, and in accordance with Article 55(2) of the IHR (2005), respectfully requests the Director-General of the WHO to communicate the text of the attached proposed IHR amendments to all States Parties at least four months before the Seventy-fifth World Health Assembly. We are also transmitting via this note a letter to WHO Director-General Tedros Adhanom Ghebreyesus from the Assistant Secretary for Global Affairs of the United States Department of Health and Human Services, Loyce Pace, reiterating the critical importance of strengthening the IHR (2005) along with other efforts to strengthen the ability of the WHO and Member States to prevent, detect, and respond to future public health emergencies of international concern.

The Permanent Mission of the United States of America avails itself of this opportunity to renew to the WHO the assurances of its highest consideration.

Enclosed:

1. Letter from HHS Assistant Secretary Loyce Pace
2. Proposed IHR amendments

Geneva, 18 January 2022

World Health Organization

Submission of the United States of America
Proposed Amendments to the International Health Regulations (2005)
Articles 5, 6, 9, 10, 11, 12, 13, 15, 18, 48, 49, 53, 59

Explanation of changes: The proposed new text is shown in **bold underline**, and proposed deletions to existing text is shown in ~~strikethrough~~. All other text would remain unchanged.

Article 5: Surveillance

1. Each State Party shall develop, strengthen and maintain, as soon as possible but no later than five years from the entry into force of these Regulations for that State Party, the capacity to detect, assess, notify and report events in accordance with these Regulations, as specified in Annex 1. **This capacity will be periodically reviewed through the Universal Health Periodic Review mechanism. Should such review identify resource constraints and other challenges in attaining these capacities, WHO and its Regional Offices shall, upon the request of a State Party, provide or facilitate technical support and assist in mobilization of financial resources to develop, strengthen and maintain such capacities.**

New 5. WHO shall develop early warning criteria for assessing and progressively updating the national, regional, or global risk posed by an event of unknown causes or sources and shall convey this risk assessment to States Parties in accordance with Articles 11 and 45 where appropriate. The risk assessment shall indicate, based on the best available knowledge, the level of risk of potential spread and risks of potential serious public health impacts, based on assessed infectiousness and severity of the illness.

Article 6: Notification

1. Each State Party shall assess events occurring within its territory by using the decision instrument in Annex 2 **within 48 hours of the National IHR Focal Point receiving the relevant information.** Each State Party shall notify WHO, by the most efficient means of communication available, by way of the National IHR Focal Point, and within 24 hours of assessment of public health information, of all events which may constitute a public health emergency of international concern within its territory in accordance with the decision instrument, as well as any health measure implemented in response to those events. If the notification received by WHO involves the competency of the International Atomic Energy Agency (IAEA), **the Food and Agriculture Organization (FAO), the World Organisation for Animal Health (OIE), the UN Environment Programme (UNEP) or other relevant entities,** WHO shall immediately notify the ~~IAEA~~ **relevant entities**.

2. Following a notification, a State Party shall continue to communicate to WHO**, by the most efficient means of communication available,** timely, accurate and sufficiently detailed public health information available to it on the notified event, where possible including **genetic sequence data,** case definitions, laboratory results, source and type of the risk, number of cases and deaths, conditions affecting the spread of the disease and the health measures employed; and report, when necessary, the difficulties faced and support needed in responding to the potential public health emergency of international concern.

Article 9: Other reports

1. WHO may take into account reports from sources other than notifications or consultations and shall assess these reports according to established epidemiological principles and then communicate information on the event to the State Party in whose territory the event is allegedly occurring. ~~Before taking any action based on such reports, WHO shall consult with and attempt to obtain verification from the State Party in whose territory the event is allegedly occurring in accordance with the procedure set forth in Article 10. To this end,~~ WHO shall make the information received available to the States Parties and only where it is duly justified may WHO maintain the confidentiality of the source. This information will be used in accordance with the procedure set forth in Article 11.

Article 10: Verification

1. **Within 24 hours of receiving information,** WHO shall request~~, in accordance with Article 9,~~ verification from a State Party of reports from sources other than notifications or consultations of events which may constitute a public health emergency of international concern allegedly occurring in the State's territory. In such cases, WHO shall inform the State Party concerned regarding the reports it is seeking to verify.

2. Pursuant to the foregoing paragraph ~~and to Article 9~~, each State Party, when requested by WHO, shall verify and provide:

(a) within 24 hours, an initial reply to, or acknowledgement of, the request from WHO;

(b) within 24 hours, available public health information on the status of events referred to in WHO's request; and

(c) information to WHO in the context of an assessment under Article 6, including relevant information as described in **paragraphs 1 and 2 of** that Article.

3. When WHO receives information of an event that may constitute a public health emergency of international concern, it shall offer **within 24 hours** to collaborate with the State Party concerned in assessing the potential for international disease spread, possible interference with international traffic and the adequacy of control measures. Such activities may include collaboration with other standard-setting organizations and the offer to mobilize international assistance in order to support the national authorities in conducting and coordinating on-site assessments.

3bis. Within 24 hours of receiving a WHO offer of collaboration, the State Party may request additional information supporting the offer. WHO shall provide such information within 24 hours. When 48 hours have elapsed since the initial WHO offer of collaboration, failure by the State Party to accept the offer of collaboration shall constitute rejection for the purposes of sharing available information with States Parties under Paragraph 4 of this section.

4. If the State Party does not accept the offer of collaboration **within 48 hours,** WHO **shall** ~~may~~, when justified by the magnitude of the public health risk, **immediately** share with other States Parties the information available to it, whilst encouraging the State Party to accept the offer of collaboration by WHO~~, taking into account the views of the State Party concerned~~.

Article 11: Provision of information by WHO

1. Subject to paragraph 2 of this Article, WHO shall send to all States Parties and, as appropriate, to relevant intergovernmental organizations, as soon as possible and by the most efficient means available, in confidence, such public health information which it has received under Articles 5 to 10 inclusive**, or which is available in the public domain,** and which is necessary to enable States Parties to respond to a public health risk. WHO **shall** communicate information to other States Parties that might help them in preventing the occurrence of similar incidents.

2. WHO shall use information received under Articles 6, ~~and~~ 8 and ~~paragraph 2 of Article~~ 9 for verification, assessment and assistance purposes under these Regulations and, unless otherwise agreed with the States Parties referred to in those provisions, shall ~~not~~ make this information generally available to other States Parties, **when** ~~until such time as~~:

(a) the event is determined to constitute a public health emergency of international concern in accordance with Article 12; or

(b) information evidencing the international spread of the infection or contamination has been confirmed by WHO in accordance with established epidemiological principles; or

(c) there is evidence that:

(i) control measures against the international spread are unlikely to succeed because of the nature of the contamination, disease agent, vector or reservoir; or

(ii) the State Party lacks sufficient operational capacity to carry out necessary measures to prevent further spread of disease; or

(d) the nature and scope of the international movement of travellers, baggage, cargo, containers, conveyances, goods or postal parcels that may be affected by the infection or contamination requires the immediate application of international control measures; or

(e) WHO determines it is necessary that such information be made available to other States Parties to make informed, timely risk assessments.

3. WHO shall **inform** ~~consult with~~ the State Party in whose territory the event is occurring as to its intent to make information available under this Article.

4. When information received by WHO under paragraph 2 of this Article is made available to States Parties in accordance with these Regulations, WHO **shall** make it available to the public if other information about the same event has already become publicly available and there is a need for the dissemination of authoritative and independent information.

New 5. WHO shall annually report to the Health Assembly on all activities under this Article, including instances of sharing information that has not been verified by a State Party on whose territory an event that may constitute a public health emergency of international concern is or is allegedly occurring with States Parties through alert systems.

Article 12: Determination of a public health emergency of international concern, ***public health emergency of regional concern, or intermediate health alert***

1. The Director-General shall determine, on the basis of information received, in particular from the State Party within whose territory an event is occurring, whether an event constitutes a public health emergency of international concern in accordance with the criteria and the procedure set out in these Regulations.

2. If the Director-General considers, based on an assessment under these Regulations, that a **potential or actual** public health emergency of international concern is occurring, the Director-General shall **notify all States Parties and seek to** consult with the State Party in whose territory the event arises regarding this preliminary determination **and may, in accordance with the procedure set forth in Article 49, seek the views of the Committee established under Article 48 (hereinafter the "Emergency Committee").** If the Director-General determines ~~and the State Party are in agreement regarding this determination~~ **that the event constitutes a public health emergency of international concern**, the Director-General shall, in accordance with the procedure set forth in Article 49, seek the views of the ~~Committee established under Article 48 (hereinafter the~~ "Emergency Committee") on appropriate temporary recommendations.

3. ~~If, following the consultation in paragraph 2 above, the Director-General and the State Party in whose territory the event arises do not come to a consensus within 48 hours on whether the event constitutes a public health emergency of international concern, a determination shall be made in accordance with the procedure set forth in Article 49~~.

4. In determining whether an event constitutes a public health emergency of international concern, the Director-General shall consider:

(a) Information provided by the State Party**, by other States Parties, available in the public domain, or otherwise available under Articles 5-10;**

(b) The decision instrument contained in Annex 2;

(c) The advice of the Emergency Committee;

(d) Scientific principles as well as available scientific evidence and other relevant information; and

(e) An assessment of the risk to human health, of the risk of international spread of disease and of the risk of interference with international traffic.

5. If the Director-General, following consultations with the **Emergency Committee and relevant** States Parties ~~within whose territory the public health emergency of international concern has occurred~~, considers that a public health emergency of international concern has ended, the Director-General shall take a decision in accordance with the procedure set out in Article 49.

New 6. Where an event has not been determined to meet the criteria for a public health emergency of international concern but the Director-General has determined it requires heightened international awareness and a potential international public health response, the Director-General, on the basis of information received, may determine at any time to issue an intermediate public health alert to States Parties and may consult the Emergency Committee in a manner consistent with the procedure set out in Article 49.

New 7. A Regional Director may determine that an event constitutes a public health emergency of regional concern and provide related guidance to States Parties in the region either before or after notification of an event that may constitute a public health emergency of international concern is made to the Director-General, who shall inform all States Parties.

Article 13: Public health response

3. ~~At the request of a State Party~~, WHO shall **offer assistance** ~~collaborate~~ **to a State Party** in the response to public health risks and other events by providing technical guidance and assistance and by assessing the effectiveness of the control measures in place, including the mobilization of international teams of experts for on-site assistance, when necessary. **The State Party shall accept or reject such an offer of assistance within 48 hours and, in the case of rejection of such an offer, shall provide to WHO its rationale for the rejection, which WHO shall share with other States Parties.**

4. If WHO, in consultation with the States Parties concerned as provided in Article 12, determines that a public health emergency of international concern is occurring, it **shall** ~~may~~ offer, in addition to the support indicated in paragraph 3 of this Article, further assistance to the State Party, including an assessment of the severity of the international risk and the adequacy of control measures. Such collaboration may include the offer to mobilize international assistance in order to support the national authorities in conducting and coordinating on-site assessments. When requested by the State Party, WHO shall provide information supporting such an offer. **The State Party shall accept or reject such an offer of assistance within 48 hours and, in the case of rejection of such an offer, shall provide to WHO its rationale for the rejection, which WHO shall share with other States Parties. Regarding on-site assessments, in compliance with its national law, a State Party shall make reasonable efforts to facilitate short-term access to relevant sites; in the event of a denial, it shall provide its rationale for the denial of access.**

Article 15: Temporary recommendations

2. Temporary recommendations may include **the deployment of expert teams, as well as** health measures to be implemented by the State Party experiencing the public health emergency of international concern, or by other States Parties, regarding persons, baggage, cargo, containers, conveyances, goods and/or postal parcels to prevent or reduce the international spread of disease and avoid unnecessary interference with international traffic.

Article 18: Recommendations with respect to persons, baggage, cargo, containers, conveyances, goods and postal parcels

New 3. In developing temporary recommendations, the Director-General shall consult with relevant international agencies such as ICAO, IMO and WTO in order to avoid unnecessary interference with international travel and trade, as appropriate. Additionally, temporary recommendations should allow

for the appropriate exemption of essential health care workers and essential medical products and supplies from travel and trade restrictions.

New 4: In implementing health measures pursuant to these Regulations, including Article 43, States Parties shall make reasonable efforts, taking into account relevant international law, to ensure that:

(a) Contingency plans are in place to ensure that health care worker movement and supply chains are facilitated in a public health emergency of international concern;

(b) Travel restrictions do not unduly prevent the movement of health care workers necessary for public health responses;

(c) Trade restrictions make provision to protect supply chains for the manufacture and transport of essential medical products and supplies; and

(d) The repatriation of travellers is addressed in a timely manner, given evidence-based measures to prevent the spread of diseases.

Article 48: Terms of reference and composition

2. The Emergency Committee shall be composed of experts selected by the Director-General from the IHR Expert Roster and, when appropriate, other expert advisory panels of the Organization**, as well as Regional Directors from any impacted region**. The Director-General shall determine the duration of membership with a view to ensuring its continuity in the consideration of a specific event and its consequences. The Director-General shall select the members of the Emergency Committee on the basis of the expertise and experience required for any particular session and with due regard to the principles of equitable **age, gender, and** geographical representation, **and require training in these Regulations before participation.** ~~At least one member~~ **Members** of the Emergency Committee should **include** ~~be an~~ **at least one** expert nominated by ~~a~~ **the** State Party within whose territory the event arises**, as well as experts nominated by other affected States Parties. For the purposes of Articles 48 and 49, an "affected State Party" refers to a State Party either geographically proximate or otherwise impacted by the event in question.**

Article 49: Procedure

3 bis. If the Emergency Committee is not unanimous in its findings, any member shall be entitled to express his or her dissenting professional views in an individual or group report, which shall state the reasons why a divergent opinion is held and shall form part of the Emergency Committee's report.

3 ter. The composition of the Emergency Committee and its complete reports shall be shared with Member States.

4. The Director-General shall invite **affected States Parties, including** the State Party in whose territory the event arises, to present ~~its~~ **their** views to the Emergency Committee. To that effect, the Director-General shall notify **States Parties of** ~~to it~~ the dates and the agenda of the meeting of the Emergency Committee with as much advance notice as necessary. The State Party **in whose territory the event arises** ~~concerned, however~~, may not seek a postponement of the meeting of the Emergency Committee for the purpose of presenting its views thereto.

…

7. **Affected** States Parties ~~in whose territories the event has occurred~~ may propose to the Director-General the termination of a public health emergency of international concern and/or the temporary recommendations, and may make a presentation to that effect to the Emergency Committee.

New Chapter IV (Article 53 bis-quater): The Compliance Committee

53 bis Terms of reference and composition

1. The State Parties shall establish a Compliance Committee that shall be responsible for:

(a) Considering information submitted to it by WHO and States Parties relating to compliance with obligations under these Regulations;

(b) Monitoring, advising on, and/or facilitating assistance on matters relating to compliance with a view to assisting States Parties to comply with obligations under these Regulations;

(c) Promoting compliance by addressing concerns raised by States Parties regarding implementation of, and compliance with, obligations under these Regulations; and

(d) Submitting an annual report to each Health Assembly describing:

(i) The work of the Compliance Committee during the reporting period;

(ii) The concerns regarding non-compliance during the reporting period; and

(iii) Any conclusions and recommendations of the Committee.

2. The Compliance Committee shall be authorized to:

(a) Request further information on matters under its consideration;

(b) Undertake, with the consent of any State Party concerned, information gathering in the territory of that State Party;

(c) Consider any relevant information submitted to it;

(d) Seek the services of experts and advisers, including representatives of NGOs or members of the public, as appropriate; and

(e) Make recommendations to a State Party concerned and/or WHO regarding how the State Party may improve compliance and any recommended technical assistance and financial support.

3. The Members of the Compliance Committee shall be appointed by States Parties from each Region, comprising six government experts from each Region. The Compliance Committee shall be appointed for four-year terms and meet three times per year.

53 ter. Conduct of business

1. The Compliance Committee shall strive to make its recommendations on the basis of consensus.

2. The Compliance Committee may request the Director-General to invite representatives of the United Nations and its specialized agencies and other relevant intergovernmental organizations or nongovernmental organizations in official relations with WHO to designate representatives to attend the Committee sessions, where appropriate to address a specific issue under consideration. Such representatives, with the consent of the Chairperson, make statements on the subjects under discussion.

53 quater Reports

1. For each session, the Compliance Committee shall prepare a report setting forth the Committee's views and advice. This report shall be approved by the Compliance Committee before the end of the session. Its views and advice shall not commit WHO, States Parties, or other entities and shall be formulated as advice to the relevant State Party.

2. If the Compliance Committee is not unanimous in its findings, any member shall be entitled to express his or her dissenting professional views in an individual or group report, which shall state the reasons why a divergent opinion is held and shall form part of the Committee's report.

3. The Compliance Committee's report shall be submitted to all States Parties and to the Director-General, who shall submit reports and advice of the Compliance Committee, to the Health Assembly or the Executive Board, as well as any relevant committees, for consideration, as appropriate.

Article 59: Entry into force; period for rejection or reservations

1. The period provided in execution of Article 22 of the Constitution of WHO for rejection of, or reservation to, these Regulations ~~or an amendment thereto~~, shall be 18 months from the date of the notification by the Director-General of the adoption of these Regulations ~~or of an amendment to these Regulations~~ by the Health Assembly. Any rejection or reservation received by the Director-General after the expiry of that period shall have no effect.

1 bis. The period provided in execution of Article 22 of the Constitution of WHO for rejection of, or reservation to, an amendment to these Regulations shall be six months from the date of the notification by the Director-General of the adoption of an amendment to these Regulations by the Health Assembly. Any rejection or reservation received by the Director-General after the expiry of that period shall have no effect.

2. These Regulations shall enter into force 24 months after the date of notification referred to in paragraph 1 of this Article, **and amendments to these Regulations shall enter into force six months after the date of notification referred to in paragraph 1bis of this Article,** except for:

(a) a State that has rejected these Regulations or an amendment thereto in accordance with Article 61;

(b) a State that has made a reservation, for which these Regulations shall enter into force as provided in Article 62;

(c) a State that becomes a Member of WHO after the date of the notification by the Director-General referred to in paragraph 1 of this Article, and which is not already a party to these Regulations, for which these Regulations shall enter into force as provided in Article 60; and

(d) a State not a Member of WHO that accepts these Regulations, for which they shall enter into force in accordance with paragraph 1 of Article 64.

3. If a State is not able to adjust its domestic legislative and administrative arrangements fully with these Regulations **or amendments thereto** within the periods set out in paragraph 2 of this Article**, as applicable,** that State shall submit within the period specified in paragraph 1 of this Article a declaration to the Director-General regarding the outstanding adjustments and achieve them no later than 12 months after the entry into force of these Regulations **or the amendments thereto** for that State Party.

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INTERNATIONAL HEALTH REGULATIONS

(2005)

THIRD EDITION



World Health Organization

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FOREWORD

A central and historic responsibility for the World Health Organization (WHO) has been the management of the global regime for the control of the international spread of disease. Under Articles 21(a) and 22, the Constitution of WHO confers upon the World Health Assembly the authority to adopt regulations "designed to prevent the international spread of disease" which, after adoption by the Health Assembly, enter into force for all WHO Member States that do not affirmatively opt out of them within a specified time period.

The International Health Regulations ("the IHR" or "Regulations") were adopted by the Health Assembly in 1969[1], having been preceded by the International Sanitary Regulations adopted by the Fourth World Health Assembly in 1951. The 1969 Regulations, which initially covered six "quarantinable diseases" were amended in 1973[2] and 1981[3], primarily to reduce the number of covered diseases from six to three (yellow fever, plague and cholera) and to mark the global eradication of smallpox.

In consideration of the growth in international travel and trade, and the emergence or re-emergence of international disease threats and other public health risks, the Forty-eighth World Health Assembly in 1995 called for a substantial revision of the Regulations adopted in 1969[4]. In resolution WHA48.7, the Health Assembly requested the Director-General to take steps to prepare their revision, urging broad participation and cooperation in the process.

After extensive preliminary work on the revision by WHO's Secretariat in close consultation with WHO Member States, international organizations and other relevant partners, and the momentum created by the emergence of severe acute respiratory syndrome (the first global public health emergency of the 21st century)[5], the Health Assembly established an Intergovernmental Working Group in 2003 open to all Member States to review and recommend a draft revision of the Regulations to the Health Assembly[6]. The IHR (2005) were adopted by the Fifty-eighth World Health Assembly on 23 May 2005[7]. They entered into force on 15 June 2007.

The purpose and scope of the IHR (2005) are "to prevent, protect against, control and provide a public health response to the international spread of disease in ways that are commensurate with and restricted to public health risks, and which avoid unnecessary interference with international traffic and trade." The IHR (2005) contain a range of innovations, including: (a) a scope not limited to any specific disease or manner of transmission, but covering "illness or medical condition, irrespective of origin or source, that presents or could present significant harm to humans"; (b) State Party obligations to develop certain minimum core public health capacities; (c) obligations on States Parties to notify WHO of events that may constitute a public health emergency of international concern according to defined criteria; (d) provisions authorizing WHO to take into consideration unofficial reports of public health events and to obtain verification from States Parties concerning such events; (e) procedures for the determination by the Director-General of a "public health emergency of international concern" and issuance of corresponding temporary recommendations, after taking into account the views of an Emergency Committee; (f) protection of the human rights of persons and travellers; and (g) the

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[1] See WHO Official Records, No. 176, 1969, resolution WHA22.46 and Annex I.
[2] See WHO Official Records, No. 209, 1973, resolution WHA26.55.
[3] See document WHA34/1981/REC/1 resolution WHA34.13; see also WHO Official Records, No. 217, 1974, resolution WHA27.45, and resolution EB67.R13, Amendment of the International Health Regulations (1969).
[4] See resolution WHA48.7.
[5] See resolution WHA56.29.
[6] See resolution WHA56.28.
[7] See resolution WHA58.3.

establishment of National IHR Focal Points and WHO IHR Contact Points for urgent communications between States Parties and WHO.

By not limiting the application of the IHR (2005) to specific diseases, it is intended that the Regulations will maintain their relevance and applicability for many years to come even in the face of the continued evolution of diseases and of the factors determining their emergence and transmission. The provisions in the IHR (2005) also update and revise many of the technical and other regulatory functions, including certificates applicable to international travel and transport, and requirements for international ports, airports and ground crossings.

Addition to the foreword of the second edition

The second edition contained the text of the IHR (2005), the text of World Health Assembly resolution WHA58.3, the version of the Health Part of the Aircraft General Declaration that entered into force on 15 July 2007, appendices containing a list of States Parties and State Party reservations and other communications in connection with the IHR (2005).

Addition to the foreword of the third edition

This third edition contains the first amendment to the IHR (2005): a revision to Annex 7 adopted by the Sixty-seventh World Health Assembly in 2014. The amendment provides that the period of protection from vaccination with an approved vaccine against infection with Yellow Fever, and the validity of the related certificate, will be for the life of the person vaccinated rather than a period of ten years as previously required. In accordance with the WHO Constitution and the IHR (2005), this amendment entered into force for all States Parties on 11 July 2016. There were no reservations or rejections concerning the amendment submitted by any State Party within the period required by the IHR (2005). This edition also updates Appendix 1 containing the list of IHR (2005) States Parties (to include Liechtenstein and South Sudan).

As of the Sixth-ninth World Health Assembly in 2016, three Review Committees have been convened under the IHR (2005) and reported through the Director-General to the Health Assembly with conclusions and recommendations on key aspects of the functioning and implementation of the Regulations. The reports of the three Review Committees are available in the six official languages on the WHO website at http://www.who.int/ihr.

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REVISION OF THE INTERNATIONAL HEALTH REGULATIONS

The Fifty-eighth World Health Assembly,

Having considered the draft revised International Health Regulations[1];

Having regard to articles 2(*k*), 21(*a*) and 22 of the Constitution of WHO;

Recalling references to the need for revising and updating the International Health Regulations in resolutions WHA48.7 on revision and updating of the International Health Regulations, WHA54.14 on global health security: epidemic alert and response, WHA55.16 on global public health response to natural occurrence, accidental release or deliberate use of biological and chemical agents or radionuclear material that affect health, WHA56.28 on revision of the International Health Regulations, and WHA56.29 on severe acute respiratory syndrome (SARS), with a view to responding to the need to ensure global public health;

Welcoming resolution 58/3 of the United Nations General Assembly on enhancing capacity building in global public health, which underscores the importance of the International Health Regulations and urges that high priority should be given to their revision;

Affirming the continuing importance of WHO's role in global outbreak alert and response to public health events, in accordance with its mandate;

Underscoring the continued importance of the International Health Regulations as the key global instrument for protection against the international spread of disease;

Commending the successful conclusion of the work of the Intergovernmental Working Group on Revision of the International Health Regulations,

1. ADOPTS the revised International Health Regulations attached to this resolution, to be referred to as the "International Health Regulations (2005)";

2. CALLS UPON Member States and the Director-General to implement fully the International Health Regulations (2005), in accordance with the purpose and scope set out in Article 2 and the principles embodied in Article 3;

3. DECIDES, for the purposes of paragraph 1 of Article 54 of the International Health Regulations (2005), that States Parties and the Director-General shall submit their first report to the Sixty-first World Health Assembly, and that the Health Assembly shall on that occasion consider the schedule for the submission of further such reports and the first review on the functioning of the Regulations pursuant to paragraph 2 of Article 54;

4. FURTHER DECIDES that, for the purposes of paragraph 1 of Article 14 of the International Health Regulations (2005), the other competent intergovernmental organizations or international bodies with which WHO is expected to cooperate and coordinate its activities, as appropriate, include the following: United Nations, International Labour Organization, Food and Agriculture Organization, International Atomic Energy Agency, International Civil Aviation Organization, International Maritime Organization, International Committee of the Red Cross, International Federation of Red

[1] See document A58/4.

Cross and Red Crescent Societies, International Air Transport Association, International Shipping Federation, and *Office International des Epizooties*;

5. URGES Member States:

(1) to build, strengthen and maintain the capacities required under the International Health Regulations (2005), and to mobilize the resources necessary for that purpose;

(2) to collaborate actively with each other and WHO in accordance with the relevant provisions of the International Health Regulations (2005), so as to ensure their effective implementation;

(3) to provide support to developing countries and countries with economies in transition if they so request in the building, strengthening and maintenance of the public health capacities required under the International Health Regulations (2005);

(4) to take all appropriate measures for furthering the purpose and eventual implementation of the International Health Regulations (2005) pending their entry into force, including development of the necessary public health capacities and legal and administrative provisions, and, in particular, to initiate the process for introducing use of the decision instrument contained in Annex 2;

6. REQUESTS the Director-General:

(1) to give prompt notification of adoption of the International Health Regulations (2005) in accordance with paragraph 1 of Article 65 thereof;

(2) to inform other competent intergovernmental organizations or international bodies of adoption of the International Health Regulations (2005) and, as appropriate, to cooperate with them in the updating of their norms and standards and to coordinate with them the activities of WHO under the International Health Regulations (2005) with a view to ensuring application of adequate measures for the protection of public health and strengthening of the global public-health response to the international spread of disease;

(3) to transmit to the International Civil Aviation Organization (ICAO) the recommended changes to the Health Part of the Aircraft General Declaration,[1] and, after completion by ICAO of its revision of the Aircraft General Declaration, to inform the Health Assembly and replace Annex 9 of the International Health Regulations (2005) with the Health Part of the Aircraft General Declaration as revised by ICAO;

(4) to build and strengthen the capacities of WHO to perform fully and effectively the functions entrusted to it under the International Health Regulations (2005), in particular through strategic health operations that provide support to countries in detection and assessment of, and response to, public health emergencies;

(5) to collaborate with States Parties to the International Health Regulations (2005), as appropriate, including through the provision or facilitation of technical cooperation and logistical support;

(6) to collaborate with States Parties to the extent possible in the mobilization of financial resources to provide support to developing countries in building, strengthening and maintaining the capacities required under the International Health Regulations (2005);

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[1] Document A58/41 Add.2.

(7) to draw up, in consultation with Member States, guidelines for the application of health measures at ground crossings in accordance with Article 29 of the International Health Regulations (2005),

(8) to establish the Review Committee of the International Health Regulations (2005) in accordance with Article 50 of the Regulations;

(9) to take steps immediately to prepare guidelines for implementation and evaluation of the decision instrument contained in the International Health Regulations (2005), including elaboration of a procedure for review of its functioning, which shall be submitted to the Health Assembly for its consideration pursuant to paragraph 3 of Article 54 of the Regulations;

(10) to take steps to establish an IHR Roster of Experts and to invite proposals for its membership, pursuant to Article 47 of the International Health Regulations (2005).

INTERNATIONAL HEALTH REGULATIONS (2005)

PART I – DEFINITIONS, PURPOSE AND SCOPE, PRINCIPLES AND RESPONSIBLE AUTHORITIES

Article 1 Definitions

1. For the purposes of the International Health Regulations (hereinafter "the IHR" or "Regulations"):

"affected" means persons, baggage, cargo, containers, conveyances, goods, postal parcels or human remains that are infected or contaminated, or carry sources of infection or contamination, so as to constitute a public health risk;

"affected area" means a geographical location specifically for which health measures have been recommended by WHO under these Regulations;

"aircraft" means an aircraft making an international voyage;

"airport" means any airport where international flights arrive or depart;

"arrival" of a conveyance means:

(a) in the case of a seagoing vessel, arrival or anchoring in the defined area of a port;

(b) in the case of an aircraft, arrival at an airport;

(c) in the case of an inland navigation vessel on an international voyage, arrival at a point of entry;

(d) in the case of a train or road vehicle, arrival at a point of entry;

"baggage" means the personal effects of a traveller;

"cargo" means goods carried on a conveyance or in a container;

"competent authority" means an authority responsible for the implementation and application of health measures under these Regulations;

"container" means an article of transport equipment:

(a) of a permanent character and accordingly strong enough to be suitable for repeated use;

(b) specially designed to facilitate the carriage of goods by one or more modes of transport, without intermediate reloading;

(c) fitted with devices permitting its ready handling, particularly its transfer from one mode of transport to another; and

(d) specially designed as to be easy to fill and empty;

"container loading area" means a place or facility set aside for containers used in international traffic;

"contamination" means the presence of an infectious or toxic agent or matter on a human or animal body surface, in or on a product prepared for consumption or on other inanimate objects, including conveyances, that may constitute a public health risk;

"conveyance" means an aircraft, ship, train, road vehicle or other means of transport on an international voyage;

"conveyance operator" means a natural or legal person in charge of a conveyance or their agent;

"crew" means persons on board a conveyance who are not passengers;

"decontamination" means a procedure whereby health measures are taken to eliminate an infectious or toxic agent or matter on a human or animal body surface, in or on a product prepared for consumption or on other inanimate objects, including conveyances, that may constitute a public health risk;

"departure" means, for persons, baggage, cargo, conveyances or goods, the act of leaving a territory;

"deratting" means the procedure whereby health measures are taken to control or kill rodent vectors of human disease present in baggage, cargo, containers, conveyances, facilities, goods and postal parcels at the point of entry;

"Director-General" means the Director-General of the World Health Organization;

"disease" means an illness or medical condition, irrespective of origin or source, that presents or could present significant harm to humans;

"disinfection" means the procedure whereby health measures are taken to control or kill infectious agents on a human or animal body surface or in or on baggage, cargo, containers, conveyances, goods and postal parcels by direct exposure to chemical or physical agents;

"disinsection" means the procedure whereby health measures are taken to control or kill the insect vectors of human diseases present in baggage, cargo, containers, conveyances, goods and postal parcels;

"event" means a manifestation of disease or an occurrence that creates a potential for disease;

"*free pratique*" means permission for a ship to enter a port, embark or disembark, discharge or load cargo or stores; permission for an aircraft, after landing, to embark or disembark, discharge or load cargo or stores; and permission for a ground transport vehicle, upon arrival, to embark or disembark, discharge or load cargo or stores;

"goods" mean tangible products, including animals and plants, transported on an international voyage, including for utilization on board a conveyance;

"ground crossing" means a point of land entry in a State Party, including one utilized by road vehicles and trains;

"ground transport vehicle" means a motorized conveyance for overland transport on an international voyage, including trains, coaches, lorries and automobiles;

"health measure" means procedures applied to prevent the spread of disease or contamination; a health measure does not include law enforcement or security measures;

"ill person" means an individual suffering from or affected with a physical ailment that may pose a public health risk;

"infection" means the entry and development or multiplication of an infectious agent in the body of humans and animals that may constitute a public health risk;

"inspection" means the examination, by the competent authority or under its supervision, of areas, baggage, containers, conveyances, facilities, goods or postal parcels, including relevant data and documentation, to determine if a public health risk exists;

"international traffic" means the movement of persons, baggage, cargo, containers, conveyances, goods or postal parcels across an international border, including international trade;

"international voyage" means:

(a) in the case of a conveyance, a voyage between points of entry in the territories of more than one State, or a voyage between points of entry in the territory or territories of the same State if the conveyance has contacts with the territory of any other State on its voyage but only as regards those contacts;

(b) in the case of a traveller, a voyage involving entry into the territory of a State other than the territory of the State in which that traveller commences the voyage;

"intrusive" means possibly provoking discomfort through close or intimate contact or questioning;

"invasive" means the puncture or incision of the skin or insertion of an instrument or foreign material into the body or the examination of a body cavity. For the purposes of these Regulations, medical examination of the ear, nose and mouth, temperature assessment using an ear, oral or cutaneous thermometer, or thermal imaging; medical inspection; auscultation; external palpation; retinoscopy; external collection of urine, faeces or saliva samples; external measurement of blood pressure; and electrocardiography shall be considered to be non-invasive;

"isolation" means separation of ill or contaminated persons or affected baggage, containers, conveyances, goods or postal parcels from others in such a manner as to prevent the spread of infection or contamination;

"medical examination" means the preliminary assessment of a person by an authorized health worker or by a person under the direct supervision of the competent authority, to determine the person's health status and potential public health risk to others, and may include the scrutiny of health documents, and a physical examination when justified by the circumstances of the individual case;

"National IHR Focal Point" means the national centre, designated by each State Party, which shall be accessible at all times for communications with WHO IHR Contact Points under these Regulations;

"Organization" or "WHO" means the World Health Organization;

"permanent residence" has the meaning as determined in the national law of the State Party concerned;

"personal data" means any information relating to an identified or identifiable natural person;

"point of entry" means a passage for international entry or exit of travellers, baggage, cargo, containers, conveyances, goods and postal parcels as well as agencies and areas providing services to them on entry or exit;

"port" means a seaport or a port on an inland body of water where ships on an international voyage arrive or depart;

"postal parcel" means an addressed article or package carried internationally by postal or courier services;

"public health emergency of international concern" means an extraordinary event which is determined, as provided in these Regulations:

(i) to constitute a public health risk to other States through the international spread of disease and

(ii) to potentially require a coordinated international response;

"public health observation" means the monitoring of the health status of a traveller over time for the purpose of determining the risk of disease transmission;

"public health risk" means a likelihood of an event that may affect adversely the health of human populations, with an emphasis on one which may spread internationally or may present a serious and direct danger;

"quarantine" means the restriction of activities and/or separation from others of suspect persons who are not ill or of suspect baggage, containers, conveyances or goods in such a manner as to prevent the possible spread of infection or contamination;

"recommendation" and "recommended" refer to temporary or standing recommendations issued under these Regulations;

"reservoir" means an animal, plant or substance in which an infectious agent normally lives and whose presence may constitute a public health risk;

"road vehicle" means a ground transport vehicle other than a train;

"scientific evidence" means information furnishing a level of proof based on the established and accepted methods of science;

"scientific principles" means the accepted fundamental laws and facts of nature known through the methods of science;

"ship" means a seagoing or inland navigation vessel on an international voyage;

"standing recommendation" means non-binding advice issued by WHO for specific ongoing public health risks pursuant to Article 16 regarding appropriate health measures for routine or periodic application needed to prevent or reduce the international spread of disease and minimize interference with international traffic;

"surveillance" means the systematic ongoing collection, collation and analysis of data for public health purposes and the timely dissemination of public health information for assessment and public health response as necessary;

"suspect" means those persons, baggage, cargo, containers, conveyances, goods or postal parcels considered by a State Party as having been exposed, or possibly exposed, to a public health risk and that could be a possible source of spread of disease;

"temporary recommendation" means non-binding advice issued by WHO pursuant to Article 15 for application on a time-limited, risk-specific basis, in response to a public health emergency of international concern, so as to prevent or reduce the international spread of disease and minimize interference with international traffic;

"temporary residence" has the meaning as determined in the national law of the State Party concerned;

"traveller" means a natural person undertaking an international voyage;

"vector" means an insect or other animal which normally transports an infectious agent that constitutes a public health risk;

"verification" means the provision of information by a State Party to WHO confirming the status of an event within the territory or territories of that State Party;

"WHO IHR Contact Point" means the unit within WHO which shall be accessible at all times for communications with the National IHR Focal Point.

2. Unless otherwise specified or determined by the context, reference to these Regulations includes the annexes thereto.

Article 2 Purpose and scope

The purpose and scope of these Regulations are to prevent, protect against, control and provide a public health response to the international spread of disease in ways that are commensurate with and restricted to public health risks, and which avoid unnecessary interference with international traffic and trade.

Article 3 Principles

1. The implementation of these Regulations shall be with full respect for the dignity, human rights and fundamental freedoms of persons.

2. The implementation of these Regulations shall be guided by the Charter of the United Nations and the Constitution of the World Health Organization.

3. The implementation of these Regulations shall be guided by the goal of their universal application for the protection of all people of the world from the international spread of disease.

4. States have, in accordance with the Charter of the United Nations and the principles of international law, the sovereign right to legislate and to implement legislation in pursuance of their health policies. In doing so they should uphold the purpose of these Regulations.

Article 4 Responsible authorities

1. Each State Party shall designate or establish a National IHR Focal Point and the authorities responsible within its respective jurisdiction for the implementation of health measures under these Regulations.

2. National IHR Focal Points shall be accessible at all times for communications with the WHO IHR Contact Points provided for in paragraph 3 of this Article. The functions of National IHR Focal Points shall include:

(a) sending to WHO IHR Contact Points, on behalf of the State Party concerned, urgent communications concerning the implementation of these Regulations, in particular under Articles 6 to 12; and

(b) disseminating information to, and consolidating input from, relevant sectors of the administration of the State Party concerned, including those responsible for surveillance and reporting, points of entry, public health services, clinics and hospitals and other government departments.

3. WHO shall designate IHR Contact Points, which shall be accessible at all times for communications with National IHR Focal Points. WHO IHR Contact Points shall send urgent communications concerning the implementation of these Regulations, in particular under Articles 6 to 12, to the National IHR Focal Point of the States Parties concerned. WHO IHR Contact Points may be designated by WHO at the headquarters or at the regional level of the Organization.

4. States Parties shall provide WHO with contact details of their National IHR Focal Point and WHO shall provide States Parties with contact details of WHO IHR Contact Points. These contact details shall be continuously updated and annually confirmed. WHO shall make available to all States Parties the contact details of National IHR Focal Points it receives pursuant to this Article.

PART II – INFORMATION AND PUBLIC HEALTH RESPONSE

Article 5 Surveillance

1. Each State Party shall develop, strengthen and maintain, as soon as possible but no later than five years from the entry into force of these Regulations for that State Party, the capacity to detect, assess, notify and report events in accordance with these Regulations, as specified in Annex 1.

2. Following the assessment referred to in paragraph 2, Part A of Annex 1, a State Party may report to WHO on the basis of a justified need and an implementation plan and, in so doing, obtain an extension of two years in which to fulfil the obligation in paragraph 1 of this Article. In exceptional circumstances, and supported by a new implementation plan, the State Party may request a further extension not exceeding two years from the Director-General, who shall make the decision, taking into account the technical advice of the Committee established under Article 50 (hereinafter the "Review Committee"). After the period mentioned in paragraph 1 of this Article, the State Party that has obtained an extension shall report annually to WHO on progress made towards the full implementation.

3. WHO shall assist States Parties, upon request, to develop, strengthen and maintain the capacities referred to in paragraph 1 of this Article.

4. WHO shall collect information regarding events through its surveillance activities and assess their potential to cause international disease spread and possible interference with international traffic. Information received by WHO under this paragraph shall be handled in accordance with Articles 11 and 45 where appropriate.

Article 6 Notification

1. Each State Party shall assess events occurring within its territory by using the decision instrument in Annex 2. Each State Party shall notify WHO, by the most efficient means of communication available, by way of the National IHR Focal Point, and within 24 hours of assessment of public health information, of all events which may constitute a public health emergency of international concern within its territory in accordance with the decision instrument, as well as any health measure implemented in response to those events. If the notification received by WHO involves the competency of the International Atomic Energy Agency (IAEA), WHO shall immediately notify the IAEA.

2. Following a notification, a State Party shall continue to communicate to WHO timely, accurate and sufficiently detailed public health information available to it on the notified event, where possible including case definitions, laboratory results, source and type of the risk, number of cases and deaths, conditions affecting the spread of the disease and the health measures employed; and report, when necessary, the difficulties faced and support needed in responding to the potential public health emergency of international concern.

Article 7 Information-sharing during unexpected or unusual public health events

If a State Party has evidence of an unexpected or unusual public health event within its territory, irrespective of origin or source, which may constitute a public health emergency of international concern, it shall provide to WHO all relevant public health information. In such a case, the provisions of Article 6 shall apply in full.

Article 8 Consultation

In the case of events occurring within its territory not requiring notification as provided in Article 6, in particular those events for which there is insufficient information available to complete the decision instrument, a State Party may nevertheless keep WHO advised thereof through the National IHR Focal Point and consult with WHO on appropriate health measures. Such communications shall be treated in accordance with paragraphs 2 to 4 of Article 11. The State Party in whose territory the event has occurred may request WHO assistance to assess any epidemiological evidence obtained by that State Party.

Article 9 Other reports

1. WHO may take into account reports from sources other than notifications or consultations and shall assess these reports according to established epidemiological principles and then communicate information on the event to the State Party in whose territory the event is allegedly occurring. Before taking any action based on such reports, WHO shall consult with and attempt to obtain verification from the State Party in whose territory the event is allegedly occurring in accordance with the procedure set forth in Article 10. To this end, WHO shall make the information received available to the States Parties and only where it is duly justified may WHO maintain the confidentiality of the source. This information will be used in accordance with the procedure set forth in Article 11.

2. States Parties shall, as far as practicable, inform WHO within 24 hours of receipt of evidence of a public health risk identified outside their territory that may cause international disease spread, as manifested by exported or imported:

(a) human cases;

(b) vectors which carry infection or contamination; or

(c) goods that are contaminated.

Article 10 Verification

1. WHO shall request, in accordance with Article 9, verification from a State Party of reports from sources other than notifications or consultations of events which may constitute a public health emergency of international concern allegedly occurring in the State's territory. In such cases, WHO shall inform the State Party concerned regarding the reports it is seeking to verify.

2. Pursuant to the foregoing paragraph and to Article 9, each State Party, when requested by WHO, shall verify and provide:

(a) within 24 hours, an initial reply to, or acknowledgement of, the request from WHO;

(b) within 24 hours, available public health information on the status of events referred to in WHO's request; and

(c) information to WHO in the context of an assessment under Article 6, including relevant information as described in that Article.

3. When WHO receives information of an event that may constitute a public health emergency of international concern, it shall offer to collaborate with the State Party concerned in assessing the potential for international disease spread, possible interference with international traffic and the adequacy of control measures. Such activities may include collaboration with other standard-setting organizations and the offer to mobilize international assistance in order to support the national authorities in conducting and coordinating on-site assessments. When requested by the State Party, WHO shall provide information supporting such an offer.

4. If the State Party does not accept the offer of collaboration, WHO may, when justified by the magnitude of the public health risk, share with other States Parties the information available to it, whilst encouraging the State Party to accept the offer of collaboration by WHO, taking into account the views of the State Party concerned.

Article 11 Provision of information by WHO

1. Subject to paragraph 2 of this Article, WHO shall send to all States Parties and, as appropriate, to relevant intergovernmental organizations, as soon as possible and by the most efficient means available, in confidence, such public health information which it has received under Articles 5 to 10 inclusive and which is necessary to enable States Parties to respond to a public health risk. WHO should communicate information to other States Parties that might help them in preventing the occurrence of similar incidents.

2. WHO shall use information received under Articles 6 and 8 and paragraph 2 of Article 9 for verification, assessment and assistance purposes under these Regulations and, unless otherwise agreed with the States Parties referred to in those provisions, shall not make this information generally available to other States Parties, until such time as:

(a) the event is determined to constitute a public health emergency of international concern in accordance with Article 12; or

(b) information evidencing the international spread of the infection or contamination has been confirmed by WHO in accordance with established epidemiological principles; or

(c) there is evidence that:

(i) control measures against the international spread are unlikely to succeed because of the nature of the contamination, disease agent, vector or reservoir; or

(ii) the State Party lacks sufficient operational capacity to carry out necessary measures to prevent further spread of disease; or

(d) the nature and scope of the international movement of travellers, baggage, cargo, containers, conveyances, goods or postal parcels that may be affected by the infection or contamination requires the immediate application of international control measures.

3. WHO shall consult with the State Party in whose territory the event is occurring as to its intent to make information available under this Article.

4. When information received by WHO under paragraph 2 of this Article is made available to States Parties in accordance with these Regulations, WHO may also make it available to the public if other information about the same event has already become publicly available and there is a need for the dissemination of authoritative and independent information.

Article 12 Determination of a public health emergency of international concern

1. The Director-General shall determine, on the basis of the information received, in particular from the State Party within whose territory an event is occurring, whether an event constitutes a public health emergency of international concern in accordance with the criteria and the procedure set out in these Regulations.

2. If the Director-General considers, based on an assessment under these Regulations, that a public health emergency of international concern is occurring, the Director-General shall consult with the State Party in whose territory the event arises regarding this preliminary determination. If the Director-General and the State Party are in agreement regarding this determination, the Director-General shall, in accordance with the procedure set forth in Article 49, seek the views of the Committee established under Article 48 (hereinafter the "Emergency Committee") on appropriate temporary recommendations.

3. If, following the consultation in paragraph 2 above, the Director-General and the State Party in whose territory the event arises do not come to a consensus within 48 hours on whether the event constitutes a public health emergency of international concern, a determination shall be made in accordance with the procedure set forth in Article 49.

4. In determining whether an event constitutes a public health emergency of international concern, the Director-General shall consider:

(a) information provided by the State Party;

(b) the decision instrument contained in Annex 2;

(c) the advice of the Emergency Committee;

(d) scientific principles as well as the available scientific evidence and other relevant information; and

(e) an assessment of the risk to human health, of the risk of international spread of disease and of the risk of interference with international traffic.

5. If the Director-General, following consultations with the State Party within whose territory the public health emergency of international concern has occurred, considers that a public health emergency of international concern has ended, the Director-General shall take a decision in accordance with the procedure set out in Article 49.

Article 13 Public health response

1. Each State Party shall develop, strengthen and maintain, as soon as possible but no later than five years from the entry into force of these Regulations for that State Party, the capacity to respond promptly and effectively to public health risks and public health emergencies of international concern as set out in Annex 1. WHO shall publish, in consultation with Member States, guidelines to support States Parties in the development of public health response capacities.

2. Following the assessment referred to in paragraph 2, Part A of Annex 1, a State Party may report to WHO on the basis of a justified need and an implementation plan and, in so doing, obtain an extension of two years in which to fulfil the obligation in paragraph 1 of this Article. In exceptional circumstances and supported by a new implementation plan, the State Party may request a further extension not exceeding two years from the Director-General, who shall make the decision, taking into account the technical advice of the Review Committee. After the period mentioned in paragraph 1 of this Article, the State Party that has obtained an extension shall report annually to WHO on progress made towards the full implementation.

3. At the request of a State Party, WHO shall collaborate in the response to public health risks and other events by providing technical guidance and assistance and by assessing the effectiveness of the control measures in place, including the mobilization of international teams of experts for on-site assistance, when necessary.

4. If WHO, in consultation with the States Parties concerned as provided in Article 12, determines that a public health emergency of international concern is occurring, it may offer, in addition to the support indicated in paragraph 3 of this Article, further assistance to the State Party, including an assessment of the severity of the international risk and the adequacy of control measures. Such collaboration may include the offer to mobilize international assistance in order to support the national authorities in conducting and coordinating on-site assessments. When requested by the State Party, WHO shall provide information supporting such an offer.

5. When requested by WHO, States Parties should provide, to the extent possible, support to WHO-coordinated response activities.

6. When requested, WHO shall provide appropriate guidance and assistance to other States Parties affected or threatened by the public health emergency of international concern.

Article 14 Cooperation of WHO with intergovernmental organizations and international bodies

1. WHO shall cooperate and coordinate its activities, as appropriate, with other competent intergovernmental organizations or international bodies in the implementation of these Regulations, including through the conclusion of agreements and other similar arrangements.

2. In cases in which notification or verification of, or response to, an event is primarily within the competence of other intergovernmental organizations or international bodies, WHO shall coordinate its activities with such organizations or bodies in order to ensure the application of adequate measures for the protection of public health.

3. Notwithstanding the foregoing, nothing in these Regulations shall preclude or limit the provision by WHO of advice, support, or technical or other assistance for public health purposes.

PART III – RECOMMENDATIONS

Article 15 Temporary recommendations

1. If it has been determined in accordance with Article 12 that a public health emergency of international concern is occurring, the Director-General shall issue temporary recommendations in accordance with the procedure set out in Article 49. Such temporary recommendations may be modified or extended as appropriate, including after it has been determined that a public health emergency of international concern has ended, at which time other temporary recommendations may be issued as necessary for the purpose of preventing or promptly detecting its recurrence.

2. Temporary recommendations may include health measures to be implemented by the State Party experiencing the public health emergency of international concern, or by other States Parties, regarding persons, baggage, cargo, containers, conveyances, goods and/or postal parcels to prevent or reduce the international spread of disease and avoid unnecessary interference with international traffic.

3. Temporary recommendations may be terminated in accordance with the procedure set out in Article 49 at any time and shall automatically expire three months after their issuance. They may be modified or extended for additional periods of up to three months. Temporary recommendations may not continue beyond the second World Health Assembly after the determination of the public health emergency of international concern to which they relate.

Article 16 Standing recommendations

WHO may make standing recommendations of appropriate health measures in accordance with Article 53 for routine or periodic application. Such measures may be applied by States Parties regarding persons, baggage, cargo, containers, conveyances, goods and/or postal parcels for specific, ongoing public health risks in order to prevent or reduce the international spread of disease and avoid unnecessary interference with international traffic. WHO may, in accordance with Article 53, modify or terminate such recommendations, as appropriate.

Article 17 Criteria for recommendations

When issuing, modifying or terminating temporary or standing recommendations, the Director-General shall consider:

(a) the views of the States Parties directly concerned;

(b) the advice of the Emergency Committee or the Review Committee, as the case may be;

(c) scientific principles as well as available scientific evidence and information;

(d) health measures that, on the basis of a risk assessment appropriate to the circumstances, are not more restrictive of international traffic and trade and are not more intrusive to persons than reasonably available alternatives that would achieve the appropriate level of health protection;

(e) relevant international standards and instruments;

(f) activities undertaken by other relevant intergovernmental organizations and international bodies; and

(g) other appropriate and specific information relevant to the event.

With respect to temporary recommendations, the consideration by the Director-General of subparagraphs (e) and (f) of this Article may be subject to limitations imposed by urgent circumstances.

Article 18 Recommendations with respect to persons, baggage, cargo, containers, conveyances, goods and postal parcels

1. Recommendations issued by WHO to States Parties with respect to persons may include the following advice:

- no specific health measures are advised;
- review travel history in affected areas;
- review proof of medical examination and any laboratory analysis;
- require medical examinations;
- review proof of vaccination or other prophylaxis;
- require vaccination or other prophylaxis;
- place suspect persons under public health observation;
- implement quarantine or other health measures for suspect persons;
- implement isolation and treatment where necessary of affected persons;
- implement tracing of contacts of suspect or affected persons;
- refuse entry of suspect and affected persons;
- refuse entry of unaffected persons to affected areas; and
- implement exit screening and/or restrictions on persons from affected areas.

2. Recommendations issued by WHO to States Parties with respect to baggage, cargo, containers, conveyances, goods and postal parcels may include the following advice:

- no specific health measures are advised;
- review manifest and routing;
- implement inspections;
- review proof of measures taken on departure or in transit to eliminate infection or contamination;
- implement treatment of the baggage, cargo, containers, conveyances, goods, postal parcels or human remains to remove infection or contamination, including vectors and reservoirs;
- the use of specific health measures to ensure the safe handling and transport of human remains;
- implement isolation or quarantine;

– seizure and destruction of infected or contaminated or suspect baggage, cargo, containers, conveyances, goods or postal parcels under controlled conditions if no available treatment or process will otherwise be successful; and

– refuse departure or entry.

PART IV – POINTS OF ENTRY

Article 19 General obligations

Each State Party shall, in addition to the other obligations provided for under these Regulations:

(a) ensure that the capacities set forth in Annex 1 for designated points of entry are developed within the timeframe provided in paragraph 1 of Article 5 and paragraph 1 of Article 13;

(b) identify the competent authorities at each designated point of entry in its territory; and

(c) furnish to WHO, as far as practicable, when requested in response to a specific potential public health risk, relevant data concerning sources of infection or contamination, including vectors and reservoirs, at its points of entry, which could result in international disease spread.

Article 20 Airports and ports

1. States Parties shall designate the airports and ports that shall develop the capacities provided in Annex 1.

2. States Parties shall ensure that Ship Sanitation Control Exemption Certificates and Ship Sanitation Control Certificates are issued in accordance with the requirements in Article 39 and the model provided in Annex 3.

3. Each State Party shall send to WHO a list of ports authorized to offer:

(a) the issuance of Ship Sanitation Control Certificates and the provision of the services referred to in Annexes 1 and 3; or

(b) the issuance of Ship Sanitation Control Exemption Certificates only; and

(c) extension of the Ship Sanitation Control Exemption Certificate for a period of one month until the arrival of the ship in the port at which the Certificate may be received.

Each State Party shall inform WHO of any changes which may occur to the status of the listed ports. WHO shall publish the information received under this paragraph.

4. WHO may, at the request of the State Party concerned, arrange to certify, after an appropriate investigation, that an airport or port in its territory meets the requirements referred to in paragraphs 1 and 3 of this Article. These certifications may be subject to periodic review by WHO, in consultation with the State Party.

5. WHO, in collaboration with competent intergovernmental organizations and international bodies, shall develop and publish the certification guidelines for airports and ports under this Article. WHO shall also publish a list of certified airports and ports.

Article 21 Ground crossings

1. Where justified for public health reasons, a State Party may designate ground crossings that shall develop the capacities provided in Annex 1, taking into consideration:

(a) the volume and frequency of the various types of international traffic, as compared to other points of entry, at a State Party's ground crossings which might be designated; and

(b) the public health risks existing in areas in which the international traffic originates, or through which it passes, prior to arrival at a particular ground crossing.

2. States Parties sharing common borders should consider:

(a) entering into bilateral or multilateral agreements or arrangements concerning prevention or control of international transmission of disease at ground crossings in accordance with Article 57; and

(b) joint designation of adjacent ground crossings for the capacities in Annex 1 in accordance with paragraph 1 of this Article.

Article 22 Role of competent authorities

1. The competent authorities shall:

(a) be responsible for monitoring baggage, cargo, containers, conveyances, goods, postal parcels and human remains departing and arriving from affected areas, so that they are maintained in such a condition that they are free of sources of infection or contamination, including vectors and reservoirs;

(b) ensure, as far as practicable, that facilities used by travellers at points of entry are maintained in a sanitary condition and are kept free of sources of infection or contamination, including vectors and reservoirs;

(c) be responsible for the supervision of any deratting, disinfection, disinsection or decontamination of baggage, cargo, containers, conveyances, goods, postal parcels and human remains or sanitary measures for persons, as appropriate under these Regulations;

(d) advise conveyance operators, as far in advance as possible, of their intent to apply control measures to a conveyance, and shall provide, where available, written information concerning the methods to be employed;

(e) be responsible for the supervision of the removal and safe disposal of any contaminated water or food, human or animal dejecta, wastewater and any other contaminated matter from a conveyance;

(f) take all practicable measures consistent with these Regulations to monitor and control the discharge by ships of sewage, refuse, ballast water and other potentially disease-causing matter which might contaminate the waters of a port, river, canal, strait, lake or other international waterway;

(g) be responsible for supervision of service providers for services concerning travellers, baggage, cargo, containers, conveyances, goods, postal parcels and human remains at points of entry, including the conduct of inspections and medical examinations as necessary;

(h) have effective contingency arrangements to deal with an unexpected public health event; and

(i) communicate with the National IHR Focal Point on the relevant public health measures taken pursuant to these Regulations.

2. Health measures recommended by WHO for travellers, baggage, cargo, containers, conveyances, goods, postal parcels and human remains arriving from an affected area may be reapplied on arrival, if there are verifiable indications and/or evidence that the measures applied on departure from the affected area were unsuccessful.

3. Disinsection, deratting, disinfection, decontamination and other sanitary procedures shall be carried out so as to avoid injury and as far as possible discomfort to persons, or damage to the environment in a way which impacts on public health, or damage to baggage, cargo, containers, conveyances, goods and postal parcels.

PART V – PUBLIC HEALTH MEASURES

Chapter I – General provisions

Article 23 Health measures on arrival and departure

1. Subject to applicable international agreements and relevant articles of these Regulations, a State Party may require for public health purposes, on arrival or departure:

(a) with regard to travellers:

(i) information concerning the traveller's destination so that the traveller may be contacted;

(ii) information concerning the traveller's itinerary to ascertain if there was any travel in or near an affected area or other possible contacts with infection or contamination prior to arrival, as well as review of the traveller's health documents if they are required under these Regulations; and/or

(iii) a non-invasive medical examination which is the least intrusive examination that would achieve the public health objective;

(b) inspection of baggage, cargo, containers, conveyances, goods, postal parcels and human remains.

2. On the basis of evidence of a public health risk obtained through the measures provided in paragraph 1 of this Article, or through other means, States Parties may apply additional health measures, in accordance with these Regulations, in particular, with regard to a suspect or affected traveller, on a case-by-case basis, the least intrusive and invasive medical examination that would achieve the public health objective of preventing the international spread of disease.

3. No medical examination, vaccination, prophylaxis or health measure under these Regulations shall be carried out on travellers without their prior express informed consent or that of their parents or guardians, except as provided in paragraph 2 of Article 31, and in accordance with the law and international obligations of the State Party.

4. Travellers to be vaccinated or offered prophylaxis pursuant to these Regulations, or their parents or guardians, shall be informed of any risk associated with vaccination or with non-vaccination and with the use or non-use of prophylaxis in accordance with the law and international obligations of the

State Party. States Parties shall inform medical practitioners of these requirements in accordance with the law of the State Party.

5. Any medical examination, medical procedure, vaccination or other prophylaxis which involves a risk of disease transmission shall only be performed on, or administered to, a traveller in accordance with established national or international safety guidelines and standards so as to minimize such a risk.

Chapter II – Special provisions for conveyances and conveyance operators

Article 24 Conveyance operators

1. States Parties shall take all practicable measures consistent with these Regulations to ensure that conveyance operators:

(a) comply with the health measures recommended by WHO and adopted by the State Party;

(b) inform travellers of the health measures recommended by WHO and adopted by the State Party for application on board; and

(c) permanently keep conveyances for which they are responsible free of sources of infection or contamination, including vectors and reservoirs. The application of measures to control sources of infection or contamination may be required if evidence is found.

2. Specific provisions pertaining to conveyances and conveyance operators under this Article are provided in Annex 4. Specific measures applicable to conveyances and conveyance operators with regard to vector-borne diseases are provided in Annex 5.

Article 25 Ships and aircraft in transit

Subject to Articles 27 and 43 or unless authorized by applicable international agreements, no health measure shall be applied by a State Party to:

(a) a ship not coming from an affected area which passes through a maritime canal or waterway in the territory of that State Party on its way to a port in the territory of another State. Any such ship shall be permitted to take on, under the supervision of the competent authority, fuel, water, food and supplies;

(b) a ship which passes through waters within its jurisdiction without calling at a port or on the coast; and

(c) an aircraft in transit at an airport within its jurisdiction, except that the aircraft may be restricted to a particular area of the airport with no embarking and disembarking or loading and discharging. However, any such aircraft shall be permitted to take on, under the supervision of the competent authority, fuel, water, food and supplies.

Article 26 Civilian lorries, trains and coaches in transit

Subject to Articles 27 and 43 or unless authorized by applicable international agreements, no health measure shall be applied to a civilian lorry, train or coach not coming from an affected area which passes through a territory without embarking, disembarking, loading or discharging.

Article 27 Affected conveyances

1. If clinical signs or symptoms and information based on fact or evidence of a public health risk, including sources of infection and contamination, are found on board a conveyance, the competent authority shall consider the conveyance as affected and may:

(a) disinfect, decontaminate, disinsect or derat the conveyance, as appropriate, or cause these measures to be carried out under its supervision; and

(b) decide in each case the technique employed to secure an adequate level of control of the public health risk as provided in these Regulations. Where there are methods or materials advised by WHO for these procedures, these should be employed, unless the competent authority determines that other methods are as safe and reliable.

The competent authority may implement additional health measures, including isolation of the conveyances, as necessary, to prevent the spread of disease. Such additional measures should be reported to the National IHR Focal Point.

2. If the competent authority for the point of entry is not able to carry out the control measures required under this Article, the affected conveyance may nevertheless be allowed to depart, subject to the following conditions:

(a) the competent authority shall, at the time of departure, inform the competent authority for the next known point of entry of the type of information referred to under subparagraph (b); and

(b) in the case of a ship, the evidence found and the control measures required shall be noted in the Ship Sanitation Control Certificate.

Any such conveyance shall be permitted to take on, under the supervision of the competent authority, fuel, water, food and supplies.

3. A conveyance that has been considered as affected shall cease to be regarded as such when the competent authority is satisfied that:

(a) the measures provided in paragraph 1 of this Article have been effectively carried out; and

(b) there are no conditions on board that could constitute a public health risk.

Article 28 Ships and aircraft at points of entry

1. Subject to Article 43 or as provided in applicable international agreements, a ship or an aircraft shall not be prevented for public health reasons from calling at any point of entry. However, if the point of entry is not equipped for applying health measures under these Regulations, the ship or aircraft may be ordered to proceed at its own risk to the nearest suitable point of entry available to it, unless the ship or aircraft has an operational problem which would make this diversion unsafe.

2. Subject to Article 43 or as provided in applicable international agreements, ships or aircraft shall not be refused *free pratique* by States Parties for public health reasons; in particular they shall not be prevented from embarking or disembarking, discharging or loading cargo or stores, or taking on fuel, water, food and supplies. States Parties may subject the granting of *free pratique* to inspection and, if a source of infection or contamination is found on board, the carrying out of necessary disinfection, decontamination, disinsection or deratting, or other measures necessary to prevent the spread of the infection or contamination.

3. Whenever practicable and subject to the previous paragraph, a State Party shall authorize the granting of *free pratique* by radio or other communication means to a ship or an aircraft when, on the basis of information received from it prior to its arrival, the State Party is of the opinion that the arrival of the ship or aircraft will not result in the introduction or spread of disease.

4. Officers in command of ships or pilots in command of aircraft, or their agents, shall make known to the port or airport control as early as possible before arrival at the port or airport of destination any cases of illness indicative of a disease of an infectious nature or evidence of a public health risk on board as soon as such illnesses or public health risks are made known to the officer or pilot. This information must be immediately relayed to the competent authority for the port or airport. In urgent circumstances, such information should be communicated directly by the officers or pilots to the relevant port or airport authority.

5. The following shall apply if a suspect or affected aircraft or ship, for reasons beyond the control of the pilot in command of the aircraft or the officer in command of the ship, lands elsewhere than at the airport at which the aircraft was due to land or berths elsewhere than at the port at which the ship was due to berth:

(a) the pilot in command of the aircraft or the officer in command of the ship or other person in charge shall make every effort to communicate without delay with the nearest competent authority;

(b) as soon as the competent authority has been informed of the landing it may apply health measures recommended by WHO or other health measures provided in these Regulations;

(c) unless required for emergency purposes or for communication with the competent authority, no traveller on board the aircraft or ship shall leave its vicinity and no cargo shall be removed from that vicinity, unless authorized by the competent authority; and

(d) when all health measures required by the competent authority have been completed, the aircraft or ship may, so far as such health measures are concerned, proceed either to the airport or port at which it was due to land or berth, or, if for technical reasons it cannot do so, to a conveniently situated airport or port.

6. Notwithstanding the provisions contained in this Article, the officer in command of a ship or pilot in command of an aircraft may take such emergency measures as may be necessary for the health and safety of travellers on board. He or she shall inform the competent authority as early as possible concerning any measures taken pursuant to this paragraph.

Article 29 Civilian lorries, trains and coaches at points of entry

WHO, in consultation with States Parties, shall develop guiding principles for applying health measures to civilian lorries, trains and coaches at points of entry and passing through ground crossings.

Chapter III – Special provisions for travellers

Article 30 Travellers under public health observation

Subject to Article 43 or as authorized in applicable international agreements, a suspect traveller who on arrival is placed under public health observation may continue an international voyage, if the traveller does not pose an imminent public health risk and the State Party informs the competent authority of the point of entry at destination, if known, of the traveller's expected arrival. On arrival, the traveller shall report to that authority.

Article 31 Health measures relating to entry of travellers

1. Invasive medical examination, vaccination or other prophylaxis shall not be required as a condition of entry of any traveller to the territory of a State Party, except that, subject to Articles 32, 42 and 45, these Regulations do not preclude States Parties from requiring medical examination, vaccination or other prophylaxis or proof of vaccination or other prophylaxis:

(a) when necessary to determine whether a public health risk exists;

(b) as a condition of entry for any travellers seeking temporary or permanent residence;

(c) as a condition of entry for any travellers pursuant to Article 43 or Annexes 6 and 7; or

(d) which may be carried out pursuant to Article 23.

2. If a traveller for whom a State Party may require a medical examination, vaccination or other prophylaxis under paragraph 1 of this Article fails to consent to any such measure, or refuses to provide the information or the documents referred to in paragraph 1(a) of Article 23, the State Party concerned may, subject to Articles 32, 42 and 45, deny entry to that traveller. If there is evidence of an imminent public health risk, the State Party may, in accordance with its national law and to the extent necessary to control such a risk, compel the traveller to undergo or advise the traveller, pursuant to paragraph 3 of Article 23, to undergo:

(a) the least invasive and intrusive medical examination that would achieve the public health objective;

(b) vaccination or other prophylaxis; or

(c) additional established health measures that prevent or control the spread of disease, including isolation, quarantine or placing the traveller under public health observation.

Article 32 Treatment of travellers

In implementing health measures under these Regulations, States Parties shall treat travellers with respect for their dignity, human rights and fundamental freedoms and minimize any discomfort or distress associated with such measures, including by:

(a) treating all travellers with courtesy and respect;

(b) taking into consideration the gender, sociocultural, ethnic or religious concerns of travellers; and

(c) providing or arranging for adequate food and water, appropriate accommodation and clothing, protection for baggage and other possessions, appropriate medical treatment, means of necessary communication if possible in a language that they can understand and other appropriate assistance for travellers who are quarantined, isolated or subject to medical examinations or other procedures for public health purposes.

Chapter IV – Special provisions for goods, containers and container loading areas

Article 33 Goods in transit

Subject to Article 43 or unless authorized by applicable international agreements, goods, other than live animals, in transit without transhipment shall not be subject to health measures under these Regulations or detained for public health purposes.

Article 34 Container and container loading areas

1. States Parties shall ensure, as far as practicable, that container shippers use international traffic containers that are kept free from sources of infection or contamination, including vectors and reservoirs, particularly during the course of packing.

2. States Parties shall ensure, as far as practicable, that container loading areas are kept free from sources of infection or contamination, including vectors and reservoirs.

3. Whenever, in the opinion of a State Party, the volume of international container traffic is sufficiently large, the competent authorities shall take all practicable measures consistent with these Regulations, including carrying out inspections, to assess the sanitary condition of container loading areas and containers in order to ensure that the obligations contained in these Regulations are implemented.

4. Facilities for the inspection and isolation of containers shall, as far as practicable, be available at container loading areas.

5. Container consignees and consignors shall make every effort to avoid cross-contamination when multiple-use loading of containers is employed.

PART VI – HEALTH DOCUMENTS

Article 35 General rule

No health documents, other than those provided for under these Regulations or in recommendations issued by WHO, shall be required in international traffic, provided however that this Article shall not apply to travellers seeking temporary or permanent residence, nor shall it apply to document requirements concerning the public health status of goods or cargo in international trade pursuant to applicable international agreements. The competent authority may request travellers to complete contact information forms and questionnaires on the health of travellers, provided that they meet the requirements set out in Article 23.

Article 36 Certificates of vaccination or other prophylaxis

1. Vaccines and prophylaxis for travellers administered pursuant to these Regulations, or to recommendations and certificates relating thereto, shall conform to the provisions of Annex 6 and, when applicable, Annex 7 with regard to specific diseases.

2. A traveller in possession of a certificate of vaccination or other prophylaxis issued in conformity with Annex 6 and, when applicable, Annex 7, shall not be denied entry as a consequence of the disease to which the certificate refers, even if coming from an affected area, unless the competent authority has verifiable indications and/or evidence that the vaccination or other prophylaxis was not effective.

Article 37 Maritime Declaration of Health

1. The master of a ship, before arrival at its first port of call in the territory of a State Party, shall ascertain the state of health on board, and, except when that State Party does not require it, the master shall, on arrival, or in advance of the vessel's arrival if the vessel is so equipped and the State Party requires such advance delivery, complete and deliver to the competent authority for that port a Maritime Declaration of Health which shall be countersigned by the ship's surgeon, if one is carried.

2. The master of a ship, or the ship's surgeon if one is carried, shall supply any information required by the competent authority as to health conditions on board during an international voyage.

3. A Maritime Declaration of Health shall conform to the model provided in Annex 8.

4. A State Party may decide:

(a) to dispense with the submission of the Maritime Declaration of Health by all arriving ships; or

(b) to require the submission of the Maritime Declaration of Health under a recommendation concerning ships arriving from affected areas or to require it from ships which might otherwise carry infection or contamination.

The State Party shall inform shipping operators or their agents of these requirements.

Article 38 Health Part of the Aircraft General Declaration

1. The pilot in command of an aircraft or the pilot's agent, in flight or upon landing at the first airport in the territory of a State Party, shall, to the best of his or her ability, except when that State Party does not require it, complete and deliver to the competent authority for that airport the Health Part of the Aircraft General Declaration which shall conform to the model specified in Annex 9.

2. The pilot in command of an aircraft or the pilot's agent shall supply any information required by the State Party as to health conditions on board during an international voyage and any health measure applied to the aircraft.

3. A State Party may decide:

(a) to dispense with the submission of the Health Part of the Aircraft General Declaration by all arriving aircraft; or

(b) to require the submission of the Health Part of the Aircraft General Declaration under a recommendation concerning aircraft arriving from affected areas or to require it from aircraft which might otherwise carry infection or contamination.

The State Party shall inform aircraft operators or their agents of these requirements.

Article 39 Ship sanitation certificates

1. Ship Sanitation Control Exemption Certificates and Ship Sanitation Control Certificates shall be valid for a maximum period of six months. This period may be extended by one month if the inspection or control measures required cannot be accomplished at the port.

2. If a valid Ship Sanitation Control Exemption Certificate or Ship Sanitation Control Certificate is not produced or evidence of a public health risk is found on board a ship, the State Party may proceed as provided in paragraph 1 of Article 27.

3. The certificates referred to in this Article shall conform to the model in Annex 3.

4. Whenever possible, control measures shall be carried out when the ship and holds are empty. In the case of a ship in ballast, they shall be carried out before loading.

5. When control measures are required and have been satisfactorily completed, the competent authority shall issue a Ship Sanitation Control Certificate, noting the evidence found and the control measures taken.

6. The competent authority may issue a Ship Sanitation Control Exemption Certificate at any port specified under Article 20 if it is satisfied that the ship is free of infection and contamination, including vectors and reservoirs. Such a certificate shall normally be issued only if the inspection of the ship has been carried out when the ship and holds are empty or when they contain only ballast or other material, of such a nature or so disposed as to make a thorough inspection of the holds possible.

7. If the conditions under which control measures are carried out are such that, in the opinion of the competent authority for the port where the operation was performed, a satisfactory result cannot be obtained, the competent authority shall make a note to that effect on the Ship Sanitation Control Certificate.

PART VII – CHARGES

Article 40 Charges for health measures regarding travellers

1. Except for travellers seeking temporary or permanent residence, and subject to paragraph 2 of this Article, no charge shall be made by a State Party pursuant to these Regulations for the following measures for the protection of public health:

(a) any medical examination provided for in these Regulations, or any supplementary examination which may be required by that State Party to ascertain the health status of the traveller examined;

(b) any vaccination or other prophylaxis provided to a traveller on arrival that is not a published requirement or is a requirement published less than 10 days prior to provision of the vaccination or other prophylaxis;

(c) appropriate isolation or quarantine requirements of travellers;

(d) any certificate issued to the traveller specifying the measures applied and the date of application; or

(e) any health measures applied to baggage accompanying the traveller.

2. States Parties may charge for health measures other than those referred to in paragraph 1 of this Article, including those primarily for the benefit of the traveller.

3. Where charges are made for applying such health measures to travellers under these Regulations, there shall be in each State Party only one tariff for such charges and every charge shall:

(a) conform to this tariff;

(b) not exceed the actual cost of the service rendered, and

(c) be levied without distinction as to the nationality, domicile or residence of the traveller concerned.

4. The tariff, and any amendment thereto, shall be published at least 10 days in advance of any levy thereunder.

5. Nothing in these Regulations shall preclude States Parties from seeking reimbursement for expenses incurred in providing the health measures in paragraph 1 of this Article:

(a) from conveyance operators or owners with regard to their employees; or

(b) from applicable insurance sources.

6. Under no circumstances shall travellers or conveyance operators be denied the ability to depart from the territory of a State Party pending payment of the charges referred to in paragraphs 1 or 2 of this Article.

Article 41 Charges for baggage, cargo, containers, conveyances, goods or postal parcels

1. Where charges are made for applying health measures to baggage, cargo, containers, conveyances, goods or postal parcels under these Regulations, there shall be in each State Party only one tariff for such charges and every charge shall:

(a) conform to this tariff;

(b) not exceed the actual cost of the service rendered; and

(c) be levied without distinction as to the nationality, flag, registry or ownership of the baggage, cargo, containers, conveyances, goods or postal parcels concerned. In particular, there shall be no distinction made between national and foreign baggage, cargo, containers, conveyances, goods or postal parcels.

2. The tariff, and any amendment thereto, shall be published at least 10 days in advance of any levy thereunder.

PART VIII – GENERAL PROVISIONS

Article 42 Implementation of health measures

Health measures taken pursuant to these Regulations shall be initiated and completed without delay, and applied in a transparent and non-discriminatory manner.

Article 43 Additional health measures

1. These Regulations shall not preclude States Parties from implementing health measures, in accordance with their relevant national law and obligations under international law, in response to specific public health risks or public health emergencies of international concern, which:

(a) achieve the same or greater level of health protection than WHO recommendations; or

(b) are otherwise prohibited under Article 25, Article 26, paragraphs 1 and 2 of Article 28, Article 30, paragraph 1(c) of Article 31 and Article 33,

provided such measures are otherwise consistent with these Regulations.

Such measures shall not be more restrictive of international traffic and not more invasive or intrusive to persons than reasonably available alternatives that would achieve the appropriate level of health protection.

2. In determining whether to implement the health measures referred to in paragraph 1 of this Article or additional health measures under paragraph 2 of Article 23, paragraph 1 of Article 27, paragraph 2 of Article 28 and paragraph 2(c) of Article 31, States Parties shall base their determinations upon:

(a) scientific principles;

(b) available scientific evidence of a risk to human health, or where such evidence is insufficient, the available information including from WHO and other relevant intergovernmental organizations and international bodies; and

(c) any available specific guidance or advice from WHO.

3. A State Party implementing additional health measures referred to in paragraph 1 of this Article which significantly interfere with international traffic shall provide to WHO the public health rationale and relevant scientific information for it. WHO shall share this information with other States Parties and shall share information regarding the health measures implemented. For the purpose of this Article, significant interference generally means refusal of entry or departure of international travellers, baggage, cargo, containers, conveyances, goods, and the like, or their delay, for more than 24 hours.

4. After assessing information provided pursuant to paragraph 3 and 5 of this Article and other relevant information, WHO may request that the State Party concerned reconsider the application of the measures.

5. A State Party implementing additional health measures referred to in paragraphs 1 and 2 of this Article that significantly interfere with international traffic shall inform WHO, within 48 hours of implementation, of such measures and their health rationale unless these are covered by a temporary or standing recommendation.

6. A State Party implementing a health measure pursuant to paragraph 1 or 2 of this Article shall within three months review such a measure taking into account the advice of WHO and the criteria in paragraph 2 of this Article.

7. Without prejudice to its rights under Article 56, any State Party impacted by a measure taken pursuant to paragraph 1 or 2 of this Article may request the State Party implementing such a measure to consult with it. The purpose of such consultations is to clarify the scientific information and public health rationale underlying the measure and to find a mutually acceptable solution.

8. The provisions of this Article may apply to implementation of measures concerning travellers taking part in mass congregations.

Article 44 Collaboration and assistance

1. States Parties shall undertake to collaborate with each other, to the extent possible, in:

(a) the detection and assessment of, and response to, events as provided under these Regulations;

(b) the provision or facilitation of technical cooperation and logistical support, particularly in the development, strengthening and maintenance of the public health capacities required under these Regulations;

(c) the mobilization of financial resources to facilitate implementation of their obligations under these Regulations; and

(d) the formulation of proposed laws and other legal and administrative provisions for the implementation of these Regulations.

2. WHO shall collaborate with States Parties, upon request, to the extent possible, in:

(a) the evaluation and assessment of their public health capacities in order to facilitate the effective implementation of these Regulations;

(b) the provision or facilitation of technical cooperation and logistical support to States Parties; and

(c) the mobilization of financial resources to support developing countries in building, strengthening and maintaining the capacities provided for in Annex 1.

3. Collaboration under this Article may be implemented through multiple channels, including bilaterally, through regional networks and the WHO regional offices, and through intergovernmental organizations and international bodies.

Article 45 Treatment of personal data

1. Health information collected or received by a State Party pursuant to these Regulations from another State Party or from WHO which refers to an identified or identifiable person shall be kept confidential and processed anonymously as required by national law.

2. Notwithstanding paragraph 1, States Parties may disclose and process personal data where essential for the purposes of assessing and managing a public health risk, but State Parties, in accordance with national law, and WHO must ensure that the personal data are:

(a) processed fairly and lawfully, and not further processed in a way incompatible with that purpose;

(b) adequate, relevant and not excessive in relation to that purpose;

(c) accurate and, where necessary, kept up to date; every reasonable step must be taken to ensure that data which are inaccurate or incomplete are erased or rectified; and

(d) not kept longer than necessary.

3. Upon request, WHO shall as far as practicable provide an individual with his or her personal data referred to in this Article in an intelligible form, without undue delay or expense and, when necessary, allow for correction.

Article 46 Transport and handling of biological substances, reagents and materials for diagnostic purposes

States Parties shall, subject to national law and taking into account relevant international guidelines, facilitate the transport, entry, exit, processing and disposal of biological substances and diagnostic specimens, reagents and other diagnostic materials for verification and public health response purposes under these Regulations.

PART IX – THE IHR ROSTER OF EXPERTS, THE EMERGENCY COMMITTEE AND THE REVIEW COMMITTEE

Chapter I – The IHR Roster of Experts

Article 47 Composition

The Director-General shall establish a roster composed of experts in all relevant fields of expertise (hereinafter the "IHR Expert Roster"). The Director-General shall appoint the members of the IHR Expert Roster in accordance with the WHO Regulations for Expert Advisory Panels and Committees (hereinafter the "WHO Advisory Panel Regulations"), unless otherwise provided in these Regulations. In addition, the Director-General shall appoint one member at the request of each State Party and, where appropriate, experts proposed by relevant intergovernmental and regional economic integration organizations. Interested States Parties shall notify the Director-General of the qualifications and fields of expertise of each of the experts they propose for membership. The Director-General shall periodically inform the States Parties, and relevant intergovernmental and regional economic integration organizations, of the composition of the IHR Expert Roster.

Chapter II – The Emergency Committee

Article 48 Terms of reference and composition

1. The Director-General shall establish an Emergency Committee that at the request of the Director-General shall provide its views on:

(a) whether an event constitutes a public health emergency of international concern;

(b) the termination of a public health emergency of international concern; and

(c) the proposed issuance, modification, extension or termination of temporary recommendations.

2. The Emergency Committee shall be composed of experts selected by the Director-General from the IHR Expert Roster and, when appropriate, other expert advisory panels of the Organization. The Director-General shall determine the duration of membership with a view to ensuring its continuity in the consideration of a specific event and its consequences. The Director-General shall select the members of the Emergency Committee on the basis of the expertise and experience required for any particular session and with due regard to the principles of equitable geographical representation. At least one member of the Emergency Committee should be an expert nominated by a State Party within whose territory the event arises.

3. The Director-General may, on his or her own initiative or at the request of the Emergency Committee, appoint one or more technical experts to advise the Committee.

Article 49 Procedure

1. The Director-General shall convene meetings of the Emergency Committee by selecting a number of experts from among those referred to in paragraph 2 of Article 48, according to the fields of expertise and experience most relevant to the specific event that is occurring. For the purpose of this Article, "meetings" of the Emergency Committee may include teleconferences, videoconferences or electronic communications.

2. The Director-General shall provide the Emergency Committee with the agenda and any relevant information concerning the event, including information provided by the States Parties, as well as any temporary recommendation that the Director-General proposes for issuance.

3. The Emergency Committee shall elect its Chairperson and prepare following each meeting a brief summary report of its proceedings and deliberations, including any advice on recommendations.

4. The Director-General shall invite the State Party in whose territory the event arises to present its views to the Emergency Committee. To that effect, the Director-General shall notify to it the dates and the agenda of the meeting of the Emergency Committee with as much advance notice as necessary. The State Party concerned, however, may not seek a postponement of the meeting of the Emergency Committee for the purpose of presenting its views thereto.

5. The views of the Emergency Committee shall be forwarded to the Director-General for consideration. The Director-General shall make the final determination on these matters.

6. The Director-General shall communicate to States Parties the determination and the termination of a public health emergency of international concern, any health measure taken by the State Party concerned, any temporary recommendation, and the modification, extension and termination of such recommendations, together with the views of the Emergency Committee. The Director-General shall inform conveyance operators through States Parties and the relevant international agencies of such temporary recommendations, including their modification, extension or termination. The Director-General shall subsequently make such information and recommendations available to the general public.

7. States Parties in whose territories the event has occurred may propose to the Director-General the termination of a public health emergency of international concern and/or the temporary recommendations, and may make a presentation to that effect to the Emergency Committee.

Chapter III – The Review Committee

Article 50 Terms of reference and composition

1. The Director-General shall establish a Review Committee, which shall carry out the following functions:

(a) make technical recommendations to the Director-General regarding amendments to these Regulations;

(b) provide technical advice to the Director-General with respect to standing recommendations, and any modifications or termination thereof;

(c) provide technical advice to the Director-General on any matter referred to it by the Director-General regarding the functioning of these Regulations.

2. The Review Committee shall be considered an expert committee and shall be subject to the WHO Advisory Panel Regulations, unless otherwise provided in this Article.

3. The Members of the Review Committee shall be selected and appointed by the Director-General from among the persons serving on the IHR Expert Roster and, when appropriate, other expert advisory panels of the Organization.

4. The Director-General shall establish the number of members to be invited to a meeting of the Review Committee, determine its date and duration, and convene the Committee.

5. The Director-General shall appoint members to the Review Committee for the duration of the work of a session only.

6. The Director-General shall select the members of the Review Committee on the basis of the principles of equitable geographical representation, gender balance, a balance of experts from developed and developing countries, representation of a diversity of scientific opinion, approaches and practical experience in various parts of the world, and an appropriate interdisciplinary balance.

Article 51 Conduct of business

1. Decisions of the Review Committee shall be taken by a majority of the members present and voting.

2. The Director-General shall invite Member States, the United Nations and its specialized agencies and other relevant intergovernmental organizations or nongovernmental organizations in official relations with WHO to designate representatives to attend the Committee sessions. Such representatives may submit memoranda and, with the consent of the Chairperson, make statements on the subjects under discussion. They shall not have the right to vote.

Article 52 Reports

1. For each session, the Review Committee shall draw up a report setting forth the Committee's views and advice. This report shall be approved by the Review Committee before the end of the session. Its views and advice shall not commit the Organization and shall be formulated as advice to the Director-General. The text of the report may not be modified without the Committee's consent.

2. If the Review Committee is not unanimous in its findings, any member shall be entitled to express his or her dissenting professional views in an individual or group report, which shall state the reasons why a divergent opinion is held and shall form part of the Committee's report.

3. The Review Committee's report shall be submitted to the Director-General, who shall communicate its views and advice to the Health Assembly or the Executive Board for their consideration and action.

Article 53 Procedures for standing recommendations

When the Director-General considers that a standing recommendation is necessary and appropriate for a specific public health risk, the Director-General shall seek the views of the Review Committee. In addition to the relevant paragraphs of Articles 50 to 52, the following provisions shall apply:

(a) proposals for standing recommendations, their modification or termination may be submitted to the Review Committee by the Director-General or by States Parties through the Director-General;

(b) any State Party may submit relevant information for consideration by the Review Committee;

(c) the Director-General may request any State Party, intergovernmental organization or nongovernmental organization in official relations with WHO to place at the disposal of the Review Committee information in its possession concerning the subject of the proposed standing recommendation as specified by the Review Committee;

(d) the Director-General may, at the request of the Review Committee or on the Director-General's own initiative, appoint one or more technical experts to advise the Review Committee. They shall not have the right to vote;

(e) any report containing the views and advice of the Review Committee regarding standing recommendations shall be forwarded to the Director-General for consideration and decision. The Director-General shall communicate the Review Committee's views and advice to the Health Assembly;

(f) the Director-General shall communicate to States Parties any standing recommendation, as well as the modifications or termination of such recommendations, together with the views of the Review Committee;

(g) standing recommendations shall be submitted by the Director-General to the subsequent Health Assembly for its consideration.

PART X – FINAL PROVISIONS

Article 54 Reporting and review

1. States Parties and the Director-General shall report to the Health Assembly on the implementation of these Regulations as decided by the Health Assembly.

2. The Health Assembly shall periodically review the functioning of these Regulations. To that end it may request the advice of the Review Committee, through the Director-General. The first such review shall take place no later than five years after the entry into force of these Regulations.

3. WHO shall periodically conduct studies to review and evaluate the functioning of Annex 2. The first such review shall commence no later than one year after the entry into force of these Regulations. The results of such reviews shall be submitted to the Health Assembly for its consideration, as appropriate.

Article 55 Amendments

1. Amendments to these Regulations may be proposed by any State Party or by the Director-General. Such proposals for amendments shall be submitted to the Health Assembly for its consideration.

2. The text of any proposed amendment shall be communicated to all States Parties by the Director-General at least four months before the Health Assembly at which it is proposed for consideration.

3. Amendments to these Regulations adopted by the Health Assembly pursuant to this Article shall come into force for all States Parties on the same terms, and subject to the same rights and obligations, as provided for in Article 22 of the Constitution of WHO and Articles 59 to 64 of these Regulations.

Article 56 Settlement of disputes

1. In the event of a dispute between two or more States Parties concerning the interpretation or application of these Regulations, the States Parties concerned shall seek in the first instance to settle

the dispute through negotiation or any other peaceful means of their own choice, including good offices, mediation or conciliation. Failure to reach agreement shall not absolve the parties to the dispute from the responsibility of continuing to seek to resolve it.

2. In the event that the dispute is not settled by the means described under paragraph 1 of this Article, the States Parties concerned may agree to refer the dispute to the Director-General, who shall make every effort to settle it.

3. A State Party may at any time declare in writing to the Director-General that it accepts arbitration as compulsory with regard to all disputes concerning the interpretation or application of these Regulations to which it is a party or with regard to a specific dispute in relation to any other State Party accepting the same obligation. The arbitration shall be conducted in accordance with the Permanent Court of Arbitration Optional Rules for Arbitrating Disputes between Two States applicable at the time a request for arbitration is made. The States Parties that have agreed to accept arbitration as compulsory shall accept the arbitral award as binding and final. The Director-General shall inform the Health Assembly regarding such action as appropriate.

4. Nothing in these Regulations shall impair the rights of States Parties under any international agreement to which they may be parties to resort to the dispute settlement mechanisms of other intergovernmental organizations or established under any international agreement.

5. In the event of a dispute between WHO and one or more States Parties concerning the interpretation or application of these Regulations, the matter shall be submitted to the Health Assembly.

Article 57 Relationship with other international agreements

1. States Parties recognize that the IHR and other relevant international agreements should be interpreted so as to be compatible. The provisions of the IHR shall not affect the rights and obligations of any State Party deriving from other international agreements.

2. Subject to paragraph 1 of this Article, nothing in these Regulations shall prevent States Parties having certain interests in common owing to their health, geographical, social or economic conditions, from concluding special treaties or arrangements in order to facilitate the application of these Regulations, and in particular with regard to:

(a) the direct and rapid exchange of public health information between neighbouring territories of different States;

(b) the health measures to be applied to international coastal traffic and to international traffic in waters within their jurisdiction;

(c) the health measures to be applied in contiguous territories of different States at their common frontier;

(d) arrangements for carrying affected persons or affected human remains by means of transport specially adapted for the purpose; and

(e) deratting, disinsection, disinfection, decontamination or other treatment designed to render goods free of disease-causing agents.

3. Without prejudice to their obligations under these Regulations, States Parties that are members of a regional economic integration organization shall apply in their mutual relations the common rules in force in that regional economic integration organization.

Article 58 International sanitary agreements and regulations

1. These Regulations, subject to the provisions of Article 62 and the exceptions hereinafter provided, shall replace as between the States bound by these Regulations and as between these States and WHO, the provisions of the following international sanitary agreements and regulations:

(a) International Sanitary Convention, signed in Paris, 21 June 1926;

(b) International Sanitary Convention for Aerial Navigation, signed at The Hague, 12 April 1933;

(c) International Agreement for dispensing with Bills of Health, signed in Paris, 22 December 1934;

(d) International Agreement for dispensing with Consular Visas on Bills of Health, signed in Paris, 22 December 1934;

(e) Convention modifying the International Sanitary Convention of 21 June 1926, signed in Paris, 31 October 1938;

(f) International Sanitary Convention, 1944, modifying the International Sanitary Convention of 21 June 1926, opened for signature in Washington, 15 December 1944;

(g) International Sanitary Convention for Aerial Navigation, 1944, modifying the International Sanitary Convention of 12 April 1933, opened for signature in Washington, 15 December 1944;

(h) Protocol of 23 April 1946 to prolong the International Sanitary Convention, 1944, signed in Washington;

(i) Protocol of 23 April 1946 to prolong the International Sanitary Convention for Aerial Navigation, 1944, signed in Washington;

(j) International Sanitary Regulations, 1951, and the Additional Regulations of 1955, 1956, 1960, 1963 and 1965; and

(k) the International Health Regulations of 1969 and the amendments of 1973 and 1981.

2. The Pan American Sanitary Code, signed at Havana, 14 November 1924, shall remain in force with the exception of Articles 2, 9, 10, 11, 16 to 53 inclusive, 61 and 62, to which the relevant part of paragraph 1 of this Article shall apply.

Article 59 Entry into force; period for rejection or reservations

1. The period provided in execution of Article 22 of the Constitution of WHO for rejection of, or reservation to, these Regulations or an amendment thereto, shall be 18 months from the date of the notification by the Director-General of the adoption of these Regulations or of an amendment to these Regulations by the Health Assembly. Any rejection or reservation received by the Director-General after the expiry of that period shall have no effect.

2. These Regulations shall enter into force 24 months after the date of notification referred to in paragraph 1 of this Article, except for:

(a) a State that has rejected these Regulations or an amendment thereto in accordance with Article 61;

(b) a State that has made a reservation, for which these Regulations shall enter into force as provided in Article 62;

(c) a State that becomes a Member of WHO after the date of the notification by the Director-General referred to in paragraph 1 of this Article, and which is not already a party to these Regulations, for which these Regulations shall enter into force as provided in Article 60; and

(d) a State not a Member of WHO that accepts these Regulations, for which they shall enter into force in accordance with paragraph 1 of Article 64.

3. If a State is not able to adjust its domestic legislative and administrative arrangements fully with these Regulations within the period set out in paragraph 2 of this Article, that State shall submit within the period specified in paragraph 1 of this Article a declaration to the Director-General regarding the outstanding adjustments and achieve them no later than 12 months after the entry into force of these Regulations for that State Party.

Article 60 New Member States of WHO

Any State which becomes a Member of WHO after the date of the notification by the Director-General referred to in paragraph 1 of Article 59, and which is not already a party to these Regulations, may communicate its rejection of, or any reservation to, these Regulations within a period of twelve months from the date of the notification to it by the Director-General after becoming a Member of WHO. Unless rejected, these Regulations shall enter into force with respect to that State, subject to the provisions of Articles 62 and 63, upon expiry of that period. In no case shall these Regulations enter into force in respect to that State earlier than 24 months after the date of notification referred to in paragraph 1 of Article 59.

Article 61 Rejection

If a State notifies the Director-General of its rejection of these Regulations or of an amendment thereto within the period provided in paragraph 1 of Article 59, these Regulations or the amendment concerned shall not enter into force with respect to that State. Any international sanitary agreement or regulations listed in Article 58 to which such State is already a party shall remain in force as far as such State is concerned.

Article 62 Reservations

1. States may make reservations to these Regulations in accordance with this Article. Such reservations shall not be incompatible with the object and purpose of these Regulations.

2. Reservations to these Regulations shall be notified to the Director-General in accordance with paragraph 1 of Article 59 and Article 60, paragraph 1 of Article 63 or paragraph 1 of Article 64, as the case may be. A State not a Member of WHO shall notify the Director-General of any reservation with its notification of acceptance of these Regulations. States formulating reservations should provide the Director-General with reasons for the reservations.

3. A rejection in part of these Regulations shall be considered as a reservation.

4. The Director-General shall, in accordance with paragraph 2 of Article 65, issue notification of each reservation received pursuant to paragraph 2 of this Article. The Director-General shall:

(a) if the reservation was made before the entry into force of these Regulations, request those Member States that have not rejected these Regulations to notify him or her within six months of any objection to the reservation, or

(b) if the reservation was made after the entry into force of these Regulations, request States Parties to notify him or her within six months of any objection to the reservation.

States objecting to a reservation should provide the Director-General with reasons for the objection.

5. After this period, the Director-General shall notify all States Parties of the objections he or she has received with regard to reservations. Unless by the end of six months from the date of the notification referred to in paragraph 4 of this Article a reservation has been objected to by one-third of the States referred to in paragraph 4 of this Article, it shall be deemed to be accepted and these Regulations shall enter into force for the reserving State, subject to the reservation.

6. If at least one-third of the States referred to in paragraph 4 of this Article object to the reservation by the end of six months from the date of the notification referred to in paragraph 4 of this Article, the Director-General shall notify the reserving State with a view to its considering withdrawing the reservation within three months from the date of the notification by the Director-General.

7. The reserving State shall continue to fulfil any obligations corresponding to the subject matter of the reservation, which the State has accepted under any of the international sanitary agreements or regulations listed in Article 58.

8. If the reserving State does not withdraw the reservation within three months from the date of the notification by the Director-General referred to in paragraph 6 of this Article, the Director-General shall seek the view of the Review Committee if the reserving State so requests. The Review Committee shall advise the Director-General as soon as possible and in accordance with Article 50 on the practical impact of the reservation on the operation of these Regulations.

9. The Director-General shall submit the reservation, and the views of the Review Committee if applicable, to the Health Assembly for its consideration. If the Health Assembly, by a majority vote, objects to the reservation on the ground that it is incompatible with the object and purpose of these Regulations, the reservation shall not be accepted and these Regulations shall enter into force for the reserving State only after it withdraws its reservation pursuant to Article 63. If the Health Assembly accepts the reservation, these Regulations shall enter into force for the reserving State, subject to its reservation.

Article 63 Withdrawal of rejection and reservation

1. A rejection made under Article 61 may at any time be withdrawn by a State by notifying the Director-General. In such cases, these Regulations shall enter into force with regard to that State upon receipt by the Director-General of the notification, except where the State makes a reservation when withdrawing its rejection, in which case these Regulations shall enter into force as provided in Article 62. In no case shall these Regulations enter into force in respect to that State earlier than 24 months after the date of notification referred to in paragraph 1 of Article 59.

2. The whole or part of any reservation may at any time be withdrawn by the State Party concerned by notifying the Director-General. In such cases, the withdrawal will be effective from the date of receipt by the Director-General of the notification.

Article 64 States not Members of WHO

1. Any State not a Member of WHO, which is a party to any international sanitary agreement or regulations listed in Article 58 or to which the Director-General has notified the adoption of these Regulations by the World Health Assembly, may become a party hereto by notifying its acceptance to the Director-General and, subject to the provisions of Article 62, such acceptance shall become effective upon the date of entry into force of these Regulations, or, if such acceptance is notified after that date, three months after the date of receipt by the Director-General of the notification of acceptance.

2. Any State not a Member of WHO which has become a party to these Regulations may at any time withdraw from participation in these Regulations, by means of a notification addressed to the Director-General which shall take effect six months after the Director-General has received it. The State which has withdrawn shall, as from that date, resume application of the provisions of any international sanitary agreement or regulations listed in Article 58 to which it was previously a party.

Article 65 Notifications by the Director-General

1. The Director-General shall notify all States Members and Associate Members of WHO, and also other parties to any international sanitary agreement or regulations listed in Article 58, of the adoption by the Health Assembly of these Regulations.

2. The Director-General shall also notify these States, as well as any other State which has become a party to these Regulations or to any amendment to these Regulations, of any notification received by WHO under Articles 60 to 64 respectively, as well as of any decision taken by the Health Assembly under Article 62.

Article 66 Authentic texts

1. The Arabic, Chinese, English, French, Russian and Spanish texts of these Regulations shall be equally authentic. The original texts of these Regulations shall be deposited with WHO.

2. The Director-General shall send, with the notification provided in paragraph 1 of Article 59, certified copies of these Regulations to all Members and Associate Members, and also to other parties to any of the international sanitary agreements or regulations listed in Article 58.

3. Upon the entry into force of these Regulations, the Director-General shall deliver certified copies thereof to the Secretary-General of the United Nations for registration in accordance with Article 102 of the Charter of the United Nations.

ANNEX 1

A. CORE CAPACITY REQUIREMENTS FOR SURVEILLANCE AND RESPONSE

1. States Parties shall utilize existing national structures and resources to meet their core capacity requirements under these Regulations, including with regard to:

(a) their surveillance, reporting, notification, verification, response and collaboration activities; and

(b) their activities concerning designated airports, ports and ground crossings.

2. Each State Party shall assess, within two years following the entry into force of these Regulations for that State Party, the ability of existing national structures and resources to meet the minimum requirements described in this Annex. As a result of such assessment, States Parties shall develop and implement plans of action to ensure that these core capacities are present and functioning throughout their territories as set out in paragraph 1 of Article 5 and paragraph 1 of Article 13.

3. States Parties and WHO shall support assessments, planning and implementation processes under this Annex.

4. At the local community level and/or primary public health response level

The capacities:

(a) to detect events involving disease or death above expected levels for the particular time and place in all areas within the territory of the State Party; and

(b) to report all available essential information immediately to the appropriate level of health-care response. At the community level, reporting shall be to local community health-care institutions or the appropriate health personnel. At the primary public health response level, reporting shall be to the intermediate or national response level, depending on organizational structures. For the purposes of this Annex, essential information includes the following: clinical descriptions, laboratory results, sources and type of risk, numbers of human cases and deaths, conditions affecting the spread of the disease and the health measures employed; and

(c) to implement preliminary control measures immediately.

5. At the intermediate public health response levels

The capacities:

(a) to confirm the status of reported events and to support or implement additional control measures; and

(b) to assess reported events immediately and, if found urgent, to report all essential information to the national level. For the purposes of this Annex, the criteria for urgent events include serious public health impact and/or unusual or unexpected nature with high potential for spread.

6. At the national level

Assessment and notification. The capacities:

(a) to assess all reports of urgent events within 48 hours; and

(b) to notify WHO immediately through the National IHR Focal Point when the assessment indicates the event is notifiable pursuant to paragraph 1 of Article 6 and Annex 2 and to inform WHO as required pursuant to Article 7 and paragraph 2 of Article 9.

Public health response. The capacities:

(a) to determine rapidly the control measures required to prevent domestic and international spread;

(b) to provide support through specialized staff, laboratory analysis of samples (domestically or through collaborating centres) and logistical assistance (e.g. equipment, supplies and transport);

(c) to provide on-site assistance as required to supplement local investigations;

(d) to provide a direct operational link with senior health and other officials to approve rapidly and implement containment and control measures;

(e) to provide direct liaison with other relevant government ministries;

(f) to provide, by the most efficient means of communication available, links with hospitals, clinics, airports, ports, ground crossings, laboratories and other key operational areas for the dissemination of information and recommendations received from WHO regarding events in the State Party's own territory and in the territories of other States Parties;

(g) to establish, operate and maintain a national public health emergency response plan, including the creation of multidisciplinary/multisectoral teams to respond to events that may constitute a public health emergency of international concern; and

(h) to provide the foregoing on a 24-hour basis.

B. CORE CAPACITY REQUIREMENTS FOR DESIGNATED AIRPORTS, PORTS AND GROUND CROSSINGS

1. At all times

The capacities:

(a) to provide access to (i) an appropriate medical service including diagnostic facilities located so as to allow the prompt assessment and care of ill travellers, and (ii) adequate staff, equipment and premises;

(b) to provide access to equipment and personnel for the transport of ill travellers to an appropriate medical facility;

(c) to provide trained personnel for the inspection of conveyances;

(d) to ensure a safe environment for travellers using point of entry facilities, including potable water supplies, eating establishments, flight catering facilities, public washrooms,

appropriate solid and liquid waste disposal services and other potential risk areas, by conducting inspection programmes, as appropriate; and

(e) to provide as far as practicable a programme and trained personnel for the control of vectors and reservoirs in and near points of entry.

2. For responding to events that may constitute a public health emergency of international concern

The capacities:

(a) to provide appropriate public health emergency response by establishing and maintaining a public health emergency contingency plan, including the nomination of a coordinator and contact points for relevant point of entry, public health and other agencies and services;

(b) to provide assessment of and care for affected travellers or animals by establishing arrangements with local medical and veterinary facilities for their isolation, treatment and other support services that may be required;

(c) to provide appropriate space, separate from other travellers, to interview suspect or affected persons;

(d) to provide for the assessment and, if required, quarantine of suspect travellers, preferably in facilities away from the point of entry;

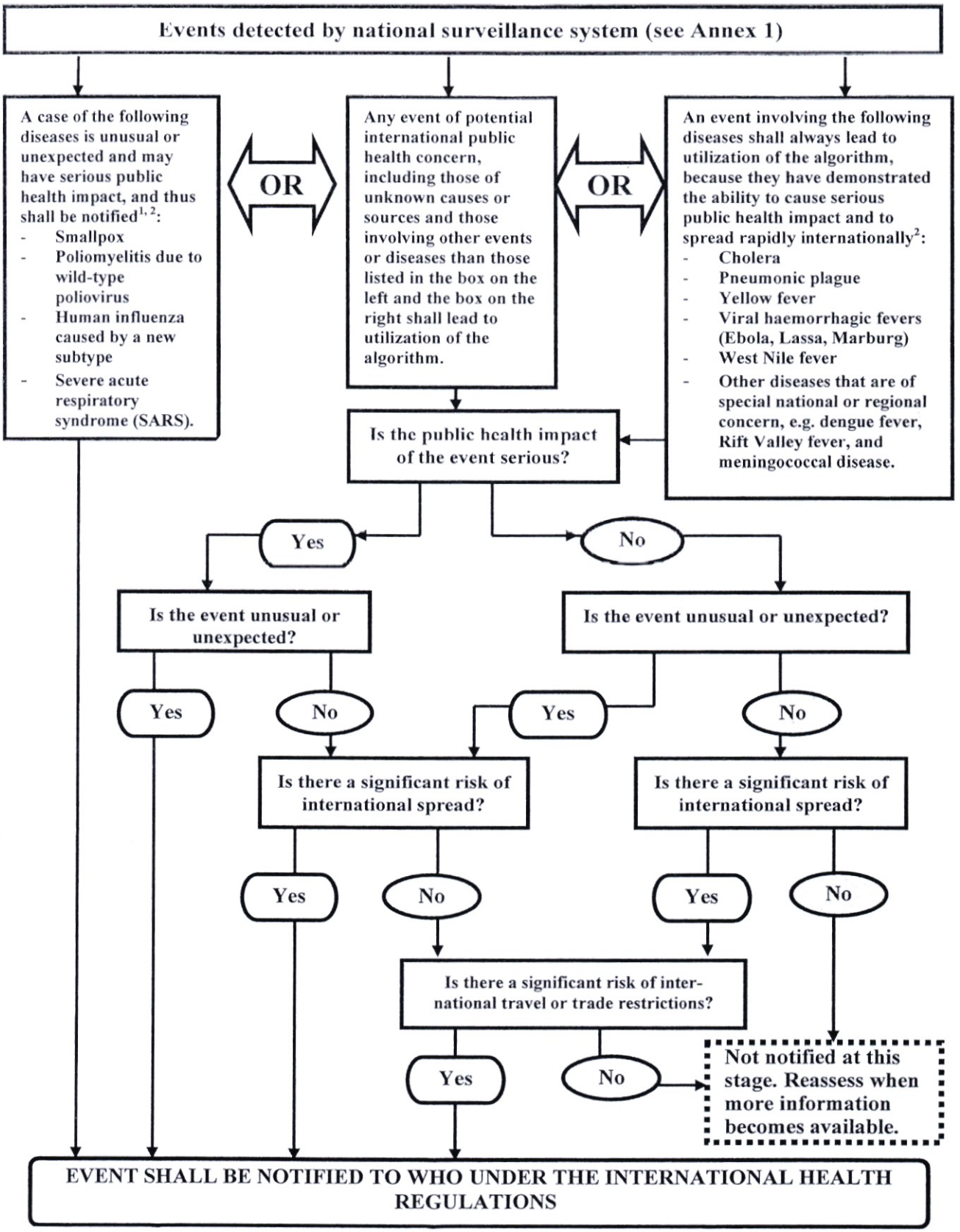
(e) to apply recommended measures to disinsect, derat, disinfect, decontaminate or otherwise treat baggage, cargo, containers, conveyances, goods or postal parcels including, when appropriate, at locations specially designated and equipped for this purpose;

(f) to apply entry or exit controls for arriving and departing travellers; and

(g) to provide access to specially designated equipment, and to trained personnel with appropriate personal protection, for the transfer of travellers who may carry infection or contamination.

ANNEX 2

DECISION INSTRUMENT FOR THE ASSESSMENT AND NOTIFICATION OF EVENTS THAT MAY CONSTITUTE A PUBLIC HEALTH EMERGENCY OF INTERNATIONAL CONCERN



[1] As per WHO case definitions.

[2] The disease list shall be used only for the purposes of these Regulations.

EXAMPLES FOR THE APPLICATION OF THE DECISION INSTRUMENT FOR THE ASSESSMENT AND NOTIFICATION OF EVENTS THAT MAY CONSTITUTE A PUBLIC HEALTH EMERGENCY OF INTERNATIONAL CONCERN

The examples appearing in this Annex are not binding and are for indicative guidance purposes to assist in the interpretation of the decision instrument criteria.

DOES THE EVENT MEET AT LEAST TWO OF THE FOLLOWING CRITERIA?

Is the public health impact of the event serious?	**I. Is the public health impact of the event serious?**
	1. *Is the number of cases and/or number of deaths for this type of event large for the given place, time or population?*
	2. *Has the event the potential to have a high public health impact?* THE FOLLOWING ARE EXAMPLES OF CIRCUMSTANCES THAT CONTRIBUTE TO HIGH PUBLIC HEALTH IMPACT: ✓ Event caused by a pathogen with high potential to cause epidemic (infectiousness of the agent, high case fatality, multiple transmission routes or healthy carrier). ✓ Indication of treatment failure (new or emerging antibiotic resistance, vaccine failure, antidote resistance or failure). ✓ Event represents a significant public health risk even if no or very few human cases have yet been identified. ✓ Cases reported among health staff. ✓ The population at risk is especially vulnerable (refugees, low level of immunization, children, elderly, low immunity, undernourished, etc.). ✓ Concomitant factors that may hinder or delay the public health response (natural catastrophes, armed conflicts, unfavourable weather conditions, multiple foci in the State Party). ✓ Event in an area with high population density. ✓ Spread of toxic, infectious or otherwise hazardous materials that may be occurring naturally or otherwise that has contaminated or has the potential to contaminate a population and/or a large geographical area.
	3. *Is external assistance needed to detect, investigate, respond and control the current event, or prevent new cases?* THE FOLLOWING ARE EXAMPLES OF WHEN ASSISTANCE MAY BE REQUIRED: ✓ Inadequate human, financial, material or technical resources – in particular: – insufficient laboratory or epidemiological capacity to investigate the event (equipment, personnel, financial resources); – insufficient antidotes, drugs and/or vaccine and/or protective equipment, decontamination equipment, or supportive equipment to cover estimated needs; – existing surveillance system is inadequate to detect new cases in a timely manner.
	IS THE PUBLIC HEALTH IMPACT OF THE EVENT SERIOUS? **Answer "yes" if you have answered "yes" to questions 1, 2 or 3 above.**

Is the event unusual or unexpected?	II. Is the event unusual or unexpected?
	4. *Is the event unusual?* THE FOLLOWING ARE EXAMPLES OF UNUSUAL EVENTS: ✓ The event is caused by an unknown agent or the source, vehicle, route of transmission is unusual or unknown. ✓ Evolution of cases more severe than expected (including morbidity or case-fatality) or with unusual symptoms. ✓ Occurrence of the event itself unusual for the area, season or population.
	5. *Is the event unexpected from a public health perspective?* THE FOLLOWING ARE EXAMPLES OF UNEXPECTED EVENTS: ✓ Event caused by a disease/agent that had already been eliminated or eradicated from the State Party or not previously reported.
	IS THE EVENT UNUSUAL OR UNEXPECTED? **Answer "yes" if you have answered "yes" to questions 4 or 5 above.**

Is there a significant risk of international spread?	III. Is there a significant risk of international spread?
	6. *Is there evidence of an epidemiological link to similar events in other States?*
	7. *Is there any factor that should alert us to the potential for cross border movement of the agent, vehicle or host?* THE FOLLOWING ARE EXAMPLES OF CIRCUMSTANCES THAT MAY PREDISPOSE TO INTERNATIONAL SPREAD: ✓ Where there is evidence of local spread, an index case (or other linked cases) with a history within the previous month of: – international travel (or time equivalent to the incubation period if the pathogen is known); – participation in an international gathering (pilgrimage, sports event, conference, etc.); – close contact with an international traveller or a highly mobile population. ✓ Event caused by an environmental contamination that has the potential to spread across international borders. ✓ Event in an area of intense international traffic with limited capacity for sanitary control or environmental detection or decontamination.
	IS THERE A SIGNIFICANT RISK OF INTERNATIONAL SPREAD? **Answer "yes" if you have answered "yes" to questions 6 or 7 above.**

Risk of international restrictions?	IV. Is there a significant risk of international travel or trade restrictions?
	8. *Have similar events in the past resulted in international restriction on trade and/or travel?*
	9. *Is the source suspected or known to be a food product, water or any other goods that might be contaminated that has been exported/imported to/from other States?*
	10. *Has the event occurred in association with an international gathering or in an area of intense international tourism?*
	11. *Has the event caused requests for more information by foreign officials or international media?*
	IS THERE A SIGNIFICANT RISK OF INTERNATIONAL TRADE OR TRAVEL RESTRICTIONS? **Answer "yes" if you have answered "yes" to questions 8, 9, 10 or 11 above.**

States Parties that answer "yes" to the question whether the event meets any two of the four criteria (I-IV) above, shall notify WHO under Article 6 of the International Health Regulations.

ANNEX 3

MODEL SHIP SANITATION CONTROL EXEMPTION CERTIFICATE/SHIP SANITATION CONTROL CERTIFICATE

Port of ..... Date .....

This Certificate records the inspection and 1) exemption from control or 2) control measures applied

Name of ship or inland navigation vessel .....Flag ..... Registration/IMO No. .....

At the time of inspection the holds were unladen/laden with ..... tonnes of ..... cargo

Name and address of inspecting officer .....

Ship Sanitation Control Exemption Certificate

Areas, [systems, and services] inspected	Evidence found[1]	Sample results[2]	Documents reviewed
Galley			Medical log
Pantry			Ship's log
Stores			Other
Hold(s)/cargo			
Quarters:			
- crew			
- officers			
- passengers			
- deck			
Potable water			
Sewage			
Ballast tanks			
Solid and medical waste			
Standing water			
Engine room			
Medical facilities			
Other areas specified - see attached			
Note areas not applicable, by marking N/A.			

Ship Sanitation Control Certificate

Control measures applied	Re-inspection date	Comments regarding conditions found

No evidence found. Ship/vessel is exempted from control measures.

Control measures indicated were applied on the date below.

Name and designation of issuing officer ..... Signature and seal ..... Date .....

[1] (a) Evidence of infection or contamination, including: vectors in all stages of growth; animal reservoirs for vectors; rodents or other species that could carry human disease, microbiological, chemical and other risks to human health; signs of inadequate sanitary measures. (b) Information concerning any human cases (to be included in the Maritime Declaration of Health).

[2] Results from samples taken on board. Analysis to be provided to ship's master by most expedient means and, if re-inspection is required, to the next appropriate port of call coinciding with the re-inspection date specified in this certificate.

Sanitation Control Exemption Certificates and Sanitation Control Certificates are valid for a maximum of six months, but the validity period may be extended by one month if inspection cannot be carried out at the port and there is no evidence of infection or contamination.

ATTACHMENT TO MODEL SHIP SANITATION CONTROL EXEMPTION CERTIFICATE/SHIP SANITATION CONTROL CERTIFICATE

Areas/facilities/systems inspected[1]	Evidence found	Sample results	Documents reviewed	Control measures applied	Re-inspection date	Comments regarding conditions found
Food						
Source						
Storage						
Preparation						
Service						
Water						
Source						
Storage						
Distribution						
Waste						
Holding						
Treatment						
Disposal						
Swimming pools/spas						
Equipment						
Operation						
Medical facilities						
Equipment and medical devices						
Operation						
Medicines						
Other areas inspected						

[1] Indicate when the areas listed are not applicable by marking N/A.

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ANNEX 4

TECHNICAL REQUIREMENTS PERTAINING TO CONVEYANCES AND CONVEYANCE OPERATORS

Section A Conveyance operators

1. Conveyance operators shall facilitate:

(a) inspections of the cargo, containers and conveyance;

(b) medical examinations of persons on board;

(c) application of other health measures under these Regulations; and

(d) provision of relevant public health information requested by the State Party.

2. Conveyance operators shall provide to the competent authority a valid Ship Sanitation Control Exemption Certificate or a Ship Sanitation Control Certificate or a Maritime Declaration of Health, or the Health Part of an Aircraft General Declaration, as required under these Regulations.

Section B Conveyances

1. Control measures applied to baggage, cargo, containers, conveyances and goods under these Regulations shall be carried out so as to avoid as far as possible injury or discomfort to persons or damage to the baggage, cargo, containers, conveyances and goods. Whenever possible and appropriate, control measures shall be applied when the conveyance and holds are empty.

2. States Parties shall indicate in writing the measures applied to cargo, containers or conveyances, the parts treated, the methods employed, and the reasons for their application. This information shall be provided in writing to the person in charge of an aircraft and, in case of a ship, on the Ship Sanitation Control Certificate. For other cargo, containers or conveyances, States Parties shall issue such information in writing to consignors, consignees, carriers, the person in charge of the conveyance or their respective agents.

ANNEX 5

SPECIFIC MEASURES FOR VECTOR-BORNE DISEASES

1. WHO shall publish, on a regular basis, a list of areas where disinsection or other vector control measures are recommended for conveyances arriving from these areas. Determination of such areas shall be made pursuant to the procedures regarding temporary or standing recommendations, as appropriate.

2. Every conveyance leaving a point of entry situated in an area where vector control is recommended should be disinsected and kept free of vectors. When there are methods and materials advised by the Organization for these procedures, these should be employed. The presence of vectors on board conveyances and the control measures used to eradicate them shall be included:

(a) in the case of aircraft, in the Health Part of the Aircraft General Declaration, unless this part of the Declaration is waived by the competent authority at the airport of arrival;

(b) in the case of ships, on the Ship Sanitation Control Certificates; and

(c) in the case of other conveyances, on a written proof of treatment issued to the consignor, consignee, carrier, the person in charge of the conveyance or their agent, respectively.

3. States Parties should accept disinsecting, deratting and other control measures for conveyances applied by other States if methods and materials advised by the Organization have been applied.

4. States Parties shall establish programmes to control vectors that may transport an infectious agent that constitutes a public health risk to a minimum distance of 400 metres from those areas of point of entry facilities that are used for operations involving travellers, conveyances, containers, cargo and postal parcels, with extension of the minimum distance if vectors with a greater range are present.

5. If a follow-up inspection is required to determine the success of the vector control measures applied, the competent authorities for the next known port or airport of call with a capacity to make such an inspection shall be informed of this requirement in advance by the competent authority advising such follow-up. In the case of ships, this shall be noted on the Ship Sanitation Control Certificate.

6. A conveyance may be regarded as suspect and should be inspected for vectors and reservoirs if:

(a) it has a possible case of vector-borne disease on board;

(b) a possible case of vector-borne disease has occurred on board during an international voyage; or

(c) it has left an affected area within a period of time where on-board vectors could still carry disease.

7. A State Party should not prohibit the landing of an aircraft or berthing of a ship in its territory if the control measures provided for in paragraph 3 of this Annex or otherwise recommended by the Organization are applied. However, aircraft or ships coming from an affected area may be required to land at airports or divert to another port specified by the State Party for that purpose.

8. A State Party may apply vector control measures to a conveyance arriving from an area affected by a vector-borne disease if the vectors for the foregoing disease are present in its territory.

ANNEX 6

VACCINATION, PROPHYLAXIS AND RELATED CERTIFICATES

1. Vaccines or other prophylaxis specified in Annex 7 or recommended under these Regulations shall be of suitable quality; those vaccines and prophylaxis designated by WHO shall be subject to its approval. Upon request, the State Party shall provide to WHO appropriate evidence of the suitability of vaccines and prophylaxis administered within its territory under these Regulations.

2. Persons undergoing vaccination or other prophylaxis under these Regulations shall be provided with an international certificate of vaccination or prophylaxis (hereinafter the "certificate") in the form specified in this Annex. No departure shall be made from the model of the certificate specified in this Annex.

3. Certificates under this Annex are valid only if the vaccine or prophylaxis used has been approved by WHO.

4. Certificates must be signed in the hand of the clinician, who shall be a medical practitioner or other authorized health worker, supervising the administration of the vaccine or prophylaxis. The certificate must also bear the official stamp of the administering centre; however, this shall not be an accepted substitute for the signature.

5. Certificates shall be fully completed in English or in French. They may also be completed in another language, in addition to either English or French.

6. Any amendment of this certificate, or erasure, or failure to complete any part of it, may render it invalid.

7. Certificates are individual and shall in no circumstances be used collectively. Separate certificates shall be issued for children.

8. A parent or guardian shall sign the certificate when the child is unable to write. The signature of an illiterate shall be indicated in the usual manner by the person's mark and the indication by another that this is the mark of the person concerned.

9. If the supervising clinician is of the opinion that the vaccination or prophylaxis is contraindicated on medical grounds, the supervising clinician shall provide the person with reasons, written in English or French, and where appropriate in another language in addition to English or French, underlying that opinion, which the competent authorities on arrival should take into account. The supervising clinician and competent authorities shall inform such persons of any risk associated with non-vaccination and with the non-use of prophylaxis in accordance with paragraph 4 of Article 23.

10. An equivalent document issued by the Armed Forces to an active member of those Forces shall be accepted in lieu of an international certificate in the form shown in this Annex if:

(a) it embodies medical information substantially the same as that required by such form; and

(b) it contains a statement in English or in French and where appropriate in another language in addition to English or French recording the nature and date of the vaccination or prophylaxis and to the effect that it is issued in accordance with this paragraph.

MODEL INTERNATIONAL CERTIFICATE OF VACCINATION OR PROPHYLAXIS

This is to certify that [name] ....., date of birth ....., sex .....,

nationality ....., national identification document, if applicable .....

whose signature follows .....

has on the date indicated been vaccinated or received prophylaxis against:

(name of disease or condition) .....

in accordance with the International Health Regulations.

Vaccine or prophylaxis	Date	Signature and professional status of supervising clinician	Manufacturer and batch No. of vaccine or prophylaxis	Certificate valid from ..... until	Official stamp of administering centre
1.					
2.					

This certificate is valid only if the vaccine or prophylaxis used has been approved by the World Health Organization.

This certificate must be signed in the hand of the clinician, who shall be a medical practitioner or other authorized health worker, supervising the administration of the vaccine or prophylaxis. The certificate must also bear the official stamp of the administering centre; however, this shall not be an accepted substitute for the signature.

Any amendment of this certificate, or erasure, or failure to complete any part of it, may render it invalid.

The validity of this certificate shall extend until the date indicated for the particular vaccination or prophylaxis. The certificate shall be fully completed in English or in French. The certificate may also be completed in another language on the same document, in addition to either English or French.

ANNEX 7

REQUIREMENTS CONCERNING VACCINATION OR PROPHYLAXIS FOR SPECIFIC DISEASES[1]

1. In addition to any recommendation concerning vaccination or prophylaxis, the following diseases are those specifically designated under these Regulations for which proof of vaccination or prophylaxis may be required for travellers as a condition of entry to a State Party:

Vaccination against yellow fever.

2. Recommendations and requirements for vaccination against yellow fever:

(a) For the purpose of this Annex:

(i) the incubation period of yellow fever is six days;

(ii) yellow fever vaccines approved by WHO provide protection against infection starting 10 days following the administration of the vaccine;

(iii) this protection continues for the life of the person vaccinated; and

(iv) the validity of a certificate of vaccination against yellow fever shall extend for the life of the person vaccinated, beginning 10 days after the date of vaccination.

(b) Vaccination against yellow fever may be required of any traveller leaving an area where the Organization has determined that a risk of yellow fever transmission is present.

(c) If a traveller is in possession of a certificate of vaccination against yellow fever which is not yet valid, the traveller may be permitted to depart, but the provisions of paragraph 2(h) of this Annex may be applied on arrival.

(d) A traveller in possession of a valid certificate of vaccination against yellow fever shall not be treated as suspect, even if coming from an area where the Organization has determined that a risk of yellow fever transmission is present.

(e) In accordance with paragraph 1 of Annex 6 the yellow fever vaccine used must be approved by the Organization.

(f) States Parties shall designate specific yellow fever vaccination centres within their territories in order to ensure the quality and safety of the procedures and materials employed.

(g) Every person employed at a point of entry in an area where the Organization has determined that a risk of yellow fever transmission is present, and every member of the crew of a conveyance using any such point of entry, shall be in possession of a valid certificate of vaccination against yellow fever.

(h) A State Party, in whose territory vectors of yellow fever are present, may require a traveller from an area where the Organization has determined that a risk of yellow fever transmission is present, who is unable to produce a valid certificate of vaccination against

[1] Amended by the Sixty-seventh World Health Assembly as to subparagraphs (iii) and (iv) of Section 2(a) in WHA67.13, 24 May 2014. This amendment entered into force for all IHR (2005) States Parties as of 11 July 2016.

yellow fever, to be quarantined until the certificate becomes valid, or until a period of not more than six days, reckoned from the date of last possible exposure to infection, has elapsed, whichever occurs first.

(i) Travellers who possess an exemption from yellow fever vaccination, signed by an authorized medical officer or an authorized health worker, may nevertheless be allowed entry, subject to the provisions of the foregoing paragraph of this Annex and to being provided with information regarding protection from yellow fever vectors. Should the travellers not be quarantined, they may be required to report any feverish or other symptoms to the competent authority and be placed under surveillance.

ANNEX 8

MODEL OF MARITIME DECLARATION OF HEALTH

To be completed and submitted to the competent authorities by the masters of ships arriving from foreign ports

Submitted at the port of ..... Date .....

Name of ship or inland navigation vessel ..... Registration/IMO No .....arriving from ..... sailing to .....

(Nationality)(Flag of vessel) ..... Master's name .....

Gross tonnage (ship) .....

Tonnage (inland navigation vessel) .....

Valid Sanitation Control Exemption/Control Certificate carried on board? Yes ..... No ..... Issued at ..... date .....

Re-inspection required? Yes ..... No .....

Has ship/vessel visited an affected area identified by the World Health Organization? Yes ..... No .....

Port and date of visit .....

List ports of call from commencement of voyage with dates of departure, or within past thirty days, whichever is shorter:

.....

Upon request of the competent authority at the port of arrival, list crew members, passengers or other persons who have joined ship/vessel since international voyage began or within past thirty days, whichever is shorter, including all ports/countries visited in this period (add additional names to the attached schedule):

(1) Name .....joined from: (1) .....(2) .....(3) .....

(2) Name .....joined from: (1) .....(2) .....(3) .....

(3) Name joined from: (1) (2) .....(3) .....

Number of crew members on board .....

Number of passengers on board .....

Health questions

(1) Has any person died on board during the voyage otherwise than as a result of accident? Yes .... No .....
If yes, state particulars in attached schedule. Total no. of deaths .....

(2) Is there on board or has there been during the international voyage any case of disease which you suspect to be of an infectious nature? Yes..... No..... If yes, state particulars in attached schedule.

(3) Has the total number of ill passengers during the voyage been greater than normal/expected? Yes .... No .....
How many ill persons? .....

(4) Is there any ill person on board now? Yes ..... No ..... If yes, state particulars in attached schedule.

(5) Was a medical practitioner consulted? Yes ..... No ..... If yes, state particulars of medical treatment or advice provided in attached schedule.

(6) Are you aware of any condition on board which may lead to infection or spread of disease? Yes ..... No .....
If yes, state particulars in attached schedule.

(7) Has any sanitary measure (e.g. quarantine, isolation, disinfection or decontamination) been applied on board? Yes ..... No .....
If yes, specify type, place and date .....

(8) Have any stowaways been found on board? Yes ..... No ..... If yes, where did they join the ship (if known)? .....

(9) Is there a sick animal or pet on board? Yes ..... No .....

Note: In the absence of a surgeon, the master should regard the following symptoms as grounds for suspecting the existence of a disease of an infectious nature:

(a) fever, persisting for several days or accompanied by (i) prostration; (ii) decreased consciousness; (iii) glandular swelling; (iv) jaundice; (v) cough or shortness of breath; (vi) unusual bleeding; or (vii) paralysis.

(b) with or without fever: (i) any acute skin rash or eruption; (ii) severe vomiting (other than sea sickness); (iii) severe diarrhoea; or (iv) recurrent convulsions.

I hereby declare that the particulars and answers to the questions given in this Declaration of Health (including the schedule) are true and correct to the best of my knowledge and belief.

Signed .....

Master

Countersigned .....

Ship's Surgeon (if carried)

Date .....

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ATTACHMENT TO MODEL OF MARITIME DECLARATION OF HEALTH

Name	Class or rating	Age	Sex	Nationality	Port, date joined ship/vessel	Nature of illness	Date of onset of symptoms	Reported to a port medical officer?	Disposal of case[1]	Drugs, medicines or other treatment given to patient	Comments

[1] State: (1) whether the person recovered, is still ill or died; and (2) whether the person is still on board, was evacuated (including the name of the port or airport), or was buried at sea.

ANNEX 9

THIS DOCUMENT IS PART OF THE AIRCRAFT GENERAL DECLARATION, PROMULGATED BY THE INTERNATIONAL CIVIL AVIATION ORGANIZATION

HEALTH PART OF THE AIRCRAFT GENERAL DECLARATION[1]

Declaration of Health

Name and seat number or function of persons on board with illnesses other than airsickness or the effects of accidents, who may be suffering from a communicable disease (a fever - temperature 38°C/100 °F or greater - associated with one or more of the following signs or symptoms, e.g. appearing obviously unwell; persistent coughing; impaired breathing; persistent diarrhoea; persistent vomiting; skin rash; bruising or bleeding without previous injury; or confusion of recent onset, increases the likelihood that the person is suffering a communicable disease) as well as such cases of illness disembarked during a previous stop .....
.....

Details of each disinsecting or sanitary treatment (place, date, time, method) during the flight. If no disinsecting has been carried out during the flight, give details of most recent disinsecting
.....
.....

Signature, if required, with time and date _____

Crew member concerned

[1] This version of the Aircraft General Declaration entered into force on 15 July 2007. The full document may be obtained from the website of the International Civil Aviation Organization at http://www.icao.int.

APPENDIX 1

STATES PARTIES TO THE INTERNATIONAL HEALTH REGULATIONS (2005) [1]

Except as otherwise indicated, the International Health Regulations (2005) entered into force on 15 June 2007 for the following States:

Afghanistan, Albania, Algeria, Andorra, Angola, Antigua and Barbuda, Argentina, Armenia, Australia, Austria, Azerbaijan, Bahamas, Bahrain, Bangladesh, Barbados, Belarus, Belgium, Belize, Benin, Bhutan, Bolivia (Plurinational State of), Bosnia and Herzegovina, Botswana, Brazil, Brunei Darussalam, Bulgaria, Burkina Faso, Burundi, Cabo Verde, Cambodia, Cameroon, Canada, Central African Republic, Chad, Chile, China[2], Colombia, Comoros, Congo, Cook Islands, Costa Rica, Côte d'Ivoire, Croatia, Cuba, Cyprus, Czech Republic, Democratic People's Republic of Korea, Democratic Republic of the Congo, Denmark, Djibouti, Dominica, Dominican Republic, Ecuador, Egypt, El Salvador, Equatorial Guinea, Eritrea, Estonia, Ethiopia, Fiji, Finland, France, Gabon, Gambia, Georgia, Germany, Ghana, Greece[2], Grenada, Guatemala, Guinea, Guinea-Bissau, Guyana, Haiti, Holy See, Honduras, Hungary, Iceland, India (8 August 2007)[2], Indonesia, Iran (Islamic Republic of)[2], Iraq, Ireland, Israel, Italy, Jamaica, Japan, Jordan, Kazakhstan, Kenya, Kiribati, Kuwait, Kyrgyzstan, Lao People's Democratic Republic, Latvia, Lebanon, Lesotho, Liberia, Libya, Liechtenstein (28 March 2012), Lithuania, Luxembourg, Madagascar, Malawi, Malaysia, Maldives, Mali, Malta, Marshall Islands, Mauritania, Mauritius, Mexico, Micronesia (Federated States of), Monaco, Mongolia, Montenegro (5 February 2008), Morocco, Mozambique, Myanmar, Namibia, Nauru, Nepal, Netherlands, New Zealand, Nicaragua, Niger, Nigeria, Niue, Norway, Oman, Pakistan, Palau, Panama, Papua New Guinea, Paraguay, Peru, Philippines, Poland, Portugal[2], Qatar, Republic of Korea, Republic of Moldova, Romania, Russian Federation, Rwanda, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Samoa, San Marino, Sao Tome and Principe, Saudi Arabia, Senegal, Serbia, Seychelles, Sierra Leone, Singapore, Slovakia, Slovenia, Solomon Islands, Somalia, South Africa, South Sudan (16 April 2013), Spain, Sri Lanka, Sudan, Suriname, Swaziland, Sweden, Switzerland, Syrian Arab Republic, Tajikistan, Thailand, The former Yugoslav Republic of Macedonia, Timor-Leste, Togo, Tonga[2], Trinidad and Tobago, Tunisia, Turkey[2], Turkmenistan, Tuvalu, Uganda, Ukraine, United Arab Emirates, United Kingdom of Great Britain and Northern Ireland, United Republic of Tanzania, United States of America (18 July 2007)[2], Uruguay, Uzbekistan, Vanuatu, Venezuela (Bolivarian Republic of), Viet Nam, Yemen, Zambia, Zimbabwe.

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[1] At 16 April 2013.

[2] Indicates that a State Party has submitted, to the Director-General of WHO, documentation related to the International Health Regulations (2005), which has been circulated by the Director-General to all Member States of WHO as well as to other States eligible to become Parties to the Regulations pursuant to Article 64 thereof.

APPENDIX 2

RESERVATIONS AND OTHER STATE PARTY COMMUNICATIONS IN CONNECTION WITH THE INTERNATIONAL HEALTH REGULATIONS (2005) [1, 2]

I. RESERVATIONS AND UNDERSTANDINGS

INDIA

I am directed to refer to Reservations in respect of India mentioned in Annexure-II to IHR 1969 (Revised upto 1983) {copy enclosed} and to request you to notify the following Reservations in respect of India for notification under Article 62 of the recently circulated IHR 2005 :-

Proposed Reservation to IHR 2005:-

1. The Government of India reserves the right to consider the whole territory of a country as infected with yellow fever whenever yellow fever has been notified under Article 6 and other relevant articles in this regard of IHR (2005). The Government of India reserves the right to continue to regard an area as infected with yellow fever until there is definite evidence that yellow fever infection has been completely eradicated from that area.
2. Yellow Fever disease will be treated as disease of Public health emergency of international concern and all health measures being applied presently like disinsection of conveyance, vaccination requirements and quarantine of passengers and crew (as may be required) (as per Article 7, 9.2(b), 42 and relevant annexures) will be continued as has been stipulated under Annex-II of IHR-1969 (Revised in 1983).

UNITED STATES OF AMERICA

The Mission, by means of this note, informs the Acting Director-General of the World Health Organization that the Government of the United States of America accepts the IHRs, subject to the reservation and understandings referred to below.

The Mission, by means of this note, and in accordance with Article 22 of the Constitution of the World Health Organization and Article 59(1) of the IHRs, submits the following reservation on behalf of the Government of the United States of America:

The Government of the United States of America reserves the right to assume obligations under these Regulations in a manner consistent with its fundamental principles of federalism. With respect to obligations concerning the development, strengthening, and maintenance of the core capacity requirements set forth in Annex 1, these Regulations shall be implemented by the Federal Government

[1] At 16 April 2013.

[2] This Appendix reproduces the relevant parts of the communications submitted by States in connection with the original adoption in 2005 and entry into force of the IHR (2005), which have been edited by the Secretariat of WHO, or translations thereof. There were no rejections, reservations or other such communications submitted within the required period in connection with the amendment to Annex 7 which entered into force on 11 July 2016. Copies of the original communications are available at http://www.who.int/ihr.

of the state governments, as appropriate and in accordance with our Constitution, to the extent that the implementation of these obligations comes under the legal jurisdiction of the Federal Government. To the extent that such obligations come under the legal jurisdiction of the state governments, the Federal Government shall bring such obligations with a favorable recommendation to the notice of the appropriate state authorities.

The Mission, by means of this note, also submits three understandings on behalf of the Government of the United States of America. The first understanding relates to the application of the IHRs to incidents involving natural, accidental or deliberate release of chemical, biological or radiological materials:

In view of the definitions of "disease," "event," and "public health emergency of international concern" as set forth in Article 1 of these Regulations, the notification requirements of Articles 6 and 7, and the decision instrument and guidelines set forth in Annex 2, the United States understands that States Parties to these Regulations have assumed an obligation to notify to WHO potential public health emergencies of international concern, irrespective of origin or source, whether they involve the natural, accidental or deliberate release of biological, chemical or radionuclear materials.

The second understanding relates to the application of Article 9 of the IHRs:

Article 9 of these Regulations obligates a State Party "as far as practicable" to notify the World Health Organization (WHO) of evidence received by that State of a public health risk occurring outside of its territory that may result in the international spread of disease. Among other notifications that could prove to be impractical under this article, it is the United States' understanding that any notification that would undermine the ability of the U.S. Armed Forces to operate effectively in pursuit of U.S. national security interests would not be considered practical for purposes of this Article.

The third understanding relates to the question of whether the IHRs create judicially enforceable private rights. Based on its delegation's participation in the negotiations of the IHRs, the Government of the United States of America does not believe that the IHRs were intended to create judicially enforceable private rights:

The United States understands that the provisions of the Regulations do not create judicially enforceable private rights.

II. OBJECTIONS TO RESERVATIONS AND UNDERSTANDINGS

IRAN (Islamic Republic of)

The Permanent Mission of the Islamic Republic of Iran to the United Nations Office and other International Organizations in Geneva presents its compliments to the World Health Organization and with reference to note verbale No. C.L.2.2007 dated 17 January 2007 concerning the Reservation and Understandings of the Government of the United States of America on the International Health Regulations (IHR), has the honor to convey the official objection of the Government of the Islamic Republic of Iran to the same Reservation and Understandings, based on the following:

According to the IHR, while "States may make reservations to these Regulations", "such reservations shall not be incompatible with the object and purpose of these regulations". Furthermore, in accordance with the IHR, "the implementation of these Regulations shall be guided by the goal of their universal application for the protection of all people of the world from the international spread of disease".

The Government of the Islamic Republic of Iran believes that, by giving more prominence to federalism than its obligations under the IHR, the reserving Government attempts to evade its due responsibilities and obligations. The aforementioned Government, by adopting a selective approach, provides its states with the option of exempting themselves from full compliance with the provisions of the IHR. Since implementation of the IHR largely depends on the development, strengthening and maintenance of the core capacity requirements set forth in Annex 1, reservation of such a general nature leads to undermining the IHR foundations as well as its integrity and universal applicability. Such reservation is considered to be incompatible with the object and purpose of these Regulations and is, therefore, unacceptable.

Moreover, the understandings and interpretations assumed by a government, too, should not affect the obligations to be undertaken by that government and must not be incompatible with the object and purpose of the Regulations.

As regards to the first Understanding of the reserving Government, it must be recalled that the majority of W.H.O. Member States participating in the IHR negotiations, categorically rejected the inclusion of the related interpretation within the provisions of the IHR. Their rejections were prompted to avoid confusion over respective obligations of the State Parties under the IHR and to preempt overlapping of the competencies and duplication of work among the relevant intergovernmental organizations or international bodies. Article 6.1 and 14.2 of the IHR address such concerns.

The second Understanding attempts to dilute the obligations of the U.S. Government under the IHR. It is an attempt to place national interests above the treaty obligations by excluding the U.S. Armed Forces from the IHR bindings. The universal applicability of the IHR for the protection of all peoples of the world from the international spread of diseases leaves no room for exempting the American Armed Forces, in particular those operating abroad. Such an exemption could not be conceded to, taking into account the nature, direction and possible public health consequences of the U.S. Armed Forces operations. It should be recalled that during IHR negotiations, the majority of W.H.O. Member States strongly rejected the above exclusion proposed by the U.S. Government. It is, therefore, in violation of the U.S. obligations under the IHR and is incompatible with the object and purpose of these regulations, to which the Government of the Islamic Republic of Iran strongly objects.

The Government of the Islamic Republic of Iran reiterates that it does not consider the Reservation and the two Understandings stated by the U.S. Government, as legally binding.

III. DECLARATIONS AND STATEMENTS

CHINA[1]

1. The Government of the People's Republic of China decides that the *International Health Regulations (2005)* (hereinafter referred to as "the IHR") applies to the entire territory of the People's Republic of China, including the Hong Kong Special Administrative Region, the Macau Special Administrative Region and the Taiwan Province.

2. The Ministry of Health of the People's Republic of China is designated as China's National Focal Point, pursuant to Paragraph 1 of Article 4 of the IHR. The local health administrative authorities are the health authorities responsible for the implementation of the IHR in their respective

[1] English translation provided by the Government.

jurisdictions. The General Administration of Quality Supervision, Inspection and Quarantine of the People's Republic of China and its local offices are the competent authorities of the points of entry referred to in Article 22 of the IHR.

3. To meet the needs of applying the IHR, the Government of the People's Republic of China is revising the *Frontier Health and Quarantine Law of the People's Republic of China*. It has incorporated the development, enhancement and maintenance of the core capability-building for rapid and effective response to public health hazards and public health emergencies of international concern into its program of establishing a national health emergency response system during the 11th Five-year Plan for National Economic and Social Development. It is formulating the technical standards for the surveillance, reporting, assessment, determination and notification of public health emergencies of international concern. It has established an inter-agency information-sharing and coordination mechanism for implementing the IHR. And it has conducted cooperation and exchanges with relevant states parties on the implementation of the IHR.

4. The Government of the People's Republic of China endorses and will implement the resolution of the 59th World Health Assembly calling upon its member states to comply immediately, on a voluntary basis, with provisions of the IHR considered relevant to the risk posed by the avian influenza and pandemic influenza.

GREECE

Reply dated 24 January 2007 to the statement made by the Republic of Turkey on 14 December 2006

The Permanent Mission of Greece to the United Nations Office and other International Organizations in Geneva presents its compliments to the Director General of the World Health Organization and, with reference to the latter's Note Verbale under ref.no. C.L.3.2007, dated January 17th, 2007, and the Note Verbale enclosed therein of the Permanent Mission of the Republic of Turkey ref. no 520.20/2006/BMCO DT/12201, dated December 14th, 2006, has the honour to draw the attention of the Director General to the fact that the correct title of the Montreux Convention regarding the regime of the straights of the Dardanelles, the Marmara sea and the Bosporus is: "The Convention Regarding the Regime of the Straights signed at Montreux on July 20th, 1936".

Furthermore, concerning the reference made in the aforementioned Note Verbale of the Permanent Mission of Turkey to the maritime traffic regulations unilaterally adopted in Turkey in 1998, we would like to remind the Director General that they are in contravention to the provisions of the International Law of the Sea, the Montreux Convention and the relevant rules and Recommendations of the International Maritime Organization adopted on June 1st, 1994.

Reply dated 16 April 2007 to the Note Verbale from the Permanent Mission of Turkey dated 1 March 2007

A. Firstly, it should be noted that there is no substantive link between the content of the Turkish statement contained in Note Verbale 520.20/BMCO DT/12201 dated 14th December 2006 and the new International Health Regulations. In fact, the Turkish statement seeks to elicit tacit acceptance or recognition of the national regulations, adopted by Turkey, concerning maritime traffic through the Straits.

However, these regulations were adopted unilaterally and were not approved by the International Maritime Organization or the parties of the Montreux Convention of 1936 which governs the issue.

Concerning its precise content, the statement goes on to assert that Turkey rightly points out that as far as the implementation of the new International Health Regulations for maritime traffic in the Straits is concerned, this should be done in accordance with the provisions of the Montreux Convention of 1936 regarding the regime of the Straits. It is, however, self-evident that the new Health Regulations do not influence the existing international regime of navigation through the Straits, neither could they do so, as there is no connection of substance between them.

The Turkish statement goes on to assert that the Turkish Maritime Traffic Regulations of 1998 will also be taken into account. This means that the Turkish Authorities will enforce the International Health Regulations subject to certain ill-defined national modifications, which are in fact themselves in contravention of the international obligations Turkey has undertaken under the Montreux Convention.

Furthermore, the Turkish Authorities reserve the right to also take into account any further revision of their national traffic regulations, to be adopted in the same unilateral way in the future. In fact, this would seem simply that, in so far as the Straits are concerned, Turkey may implement the new International Heath Regulations as it sees fit.

The reference, therefore, to national legislation and to any future revisions of this legislation, while irrelevant to the subject at hand, is nonetheless problematic because it seeks to subject international conventional obligations to national rules and regulations.

B. Furthermore, the Turkish Regulations concerning traffic in the Straits are themselves not in conformity with:

- The 1936 Montreux Convention: this Convention enshrines full freedom of navigation (articles 1 and 2) through the Straits without any restrictions whatsoever (apart from sanitary control) and without any formalities, irrespective of the kind of cargo or the timing of the transit. Thus, the Turkish Regulations by, amongst other things, imposing a compulsory reporting system (Reg. 6, 25 and al.) and, particularly, by providing for the possibility of the total suspension of traffic (Reg.20) are incompatible with the Montreux Convention.

- The IMO Rules and Regulations: Paragraphs 1.2 and 1.3 foresee that only in the case where a vessel is unable to comply with the Traffic Separation Scheme do the Turkish Authorities have the right to temporarily suspend two-way traffic and to regulate the resulting one way traffic. The IMO Rules and Regulations on no account foresee a total suspension of traffic in the Straits. The Turkish Regulations, on the other hand, provide for the possibility to completely suspend traffic in general for a wide variety of reasons.

- The international law of the sea regarding navigation through international straits: such law encourages cooperation in order to ensure the safe transit of vessels through the Straits and in order to protect the environment. The Turkish Regulations, however, were adopted unilaterally, in contravention of the law of the sea and the relevant law of treaties.

C. As to the Turkish Note dated 1st March 2007 (Ref. No: 520.20/2007/BMCO DT/1711), the information contained there in is inaccurate on several points. More specifically, the said Turkish Note states:

- that the Turkish Regulations "have been put into effect taking into account Turkey's obligations and rights arising from the Montreux Convention", whereas the latter contains and rights arising from the Montreux Convention", whereas the latter contains no provision which authorizes Turkey to unilaterally issue traffic regulations.

- that Turkey "informed IMO of the safety measures taken in the Straits", whereas Turkey has consistently refused to officially submit its national regulations to IMO for discussion and examination, alleging that it is a matter of exclusive Turkish jurisdiction.

- that "...Traffic Separation Schemes and Reporting System... were adopted by IMO together with some other rules in 1995", whereas only Traffic Separation Schemes were adopted by that Organization, together with the relevant IMO Rules and Recommendations. The Reporting System included in the Turkish Regulations was never adopted by IMO.

- that "...the maritime Safety Committee of the IMO confirmed at its 71st session that the routing system and the associated IMO Rules and Recommendations... had contributed significantly to an increase in safety ..." in an attempt to create the impression that the IMO is referring to the Turkish Regulations, whereas it is only referring to the measures adopted within the IMO itself.

In the light of the above, Greece considers the statement made by Turkey in its Note Verbale 520.20/2006/BMCO DT/12201 dated 14th December 2006 as irrelevant to the International Health Regulations, thus having no legal effect as to the latter's implementation. Furthermore, Greece reiterates the point made in her Note Verbale no. (331) 6395/6/AS 168 dated 24 January 2007 as to the importance of using the correct terminology when referring to international instruments such as the Montreux Convention.

PORTUGAL

Declaration of the Presidency of the Council of the European Union (EU) on the reservation of the Government of the United States of America concerning the International Health Regulations

The International Health Regulations (IHR) are a very effective tool for reinforcing the connection between the surveillance systems and in establishing rapid reaction mechanisms. The EC and its 27 Member States have strongly supported the revised IHR, which recently came into force, and we will continue this support for the implementation of the IHR in full and without restrictions.

The EC and its 27 Member States take note of the above mentioned reservation and declare that they understand it to mean that, in accordance with the principle that a Party may not invoke the provisions of its internal law as justification for its failure to perform its international obligations, this reservation in no way intends to question the obligations stemming from the IHR. The EC and its 27 Member States understand that the Federal Government of the United States of America fully recognises those obligations and that it will exercise every effort to ensure that the provisions of the IHR are fully implemented and given full effect by the pertinent authorities in the United States of America.

Declaration of the Presidency of the Council of the European Union (EU) on the statement of the Government of Turkey concerning the International Health Regulations

The International Health Regulations (IHR) are a very effective tool for reinforcing the connection between the surveillance systems and in establishing rapid reaction mechanisms. The EC and its 27 Member States have strongly supported the revised IHR, which recently came into force, and we will continue this support for the implementation of the IHR in full and without restrictions.

The EC and its 27 Member States take note of Turkey's intention to implement the provisions of the IHR in accordance with the Convention regarding the regime of the Straits, signed at Montreux on 20 July 1936.

The EC and its 27 Member States understand the desire of the Turkish authorities to respect their international obligations, such as the Montreux Convention regarding traffic in the Straits. In this respect they would like to refer to Article 57 of the IHR, which provides that States parties recognize that the IHR and other relevant international agreements should be interpreted so as to be compatible. The provisions of the IHR shall not affect the rights and obligations of any State party deriving from other international agreements.

Concerning the reference by Turkey to internal legislation which has no direct bearing on the implementation of the IHR, the EC and its 27 Member States understand that Turkey will ensure that the application of its internal legislation fully respects the letter and spirit of the IHR and the regime of freedom of navigation in the Straits as established by the Montreux Convention.

Declaration of the Presidency of the Council of the European Union (EU) on the reservation of the Government of India concerning the International Health Regulations

The International Health Regulations (IHR) are a very effective tool for reinforcing the connection between the surveillance systems and in establishing rapid reaction mechanisms. The EC and its 27 Member States have strongly supported the revised IHR, which recently came into force, and we will continue this support for the implementation of the IHR in full and without restrictions.

The EC and its 27 Member States understand the willingness of the Government of India to apply strong measures in order to keep the territory of India free of yellow fever. The EC and its 27 Member States recognise the challenges in ensuring the surveillance and protection of such a large territory, considering the existence of factors (e.g. presence of aedes) which may facilitate the spread of contamination.

The EC and its 27 Member States nevertheless expect that this reservation will be implemented in a reasonable way, considering the potentially unnecessary interference it could have with international traffic and trade from the largest part of the geographical territory of the EC in the case of a yellow fever outbreak in an outermost region of the EU or in a non-European part of a Member State of the EC (e.g. Guyana, Antilles). The fact that the Government of India considers yellow fever to be a notifiable disease should not trigger disproportionate control measures.

The commitment of the EC and its 27 Member States to ensure the rapid and comprehensive implementation of the IHR will reinforce the measures already implemented to maintain the whole territory of the EC free of yellow fever.

TURKEY

Statement made by the Republic of Turkey on 14 December 2006

Turkey will implement the provisions of the International Health Regulations in accordance with the Convention regarding the regime of the Turkish Straits, signed at Montreux on 20 July 1936, as well as by taking into account Turkish 1998 Maritime Traffic Regulations for the Turkish Straits and any future revisions to be made thereto.

Reply dated 1 March 2007 to the Note Verbale from the Permanent Mission of Greece dated 24 January 2007

The Maritime Traffic Regulations for the Turkish Straits have been put into effect taking into account Turkey's obligations and rights arising from the Montreux Convention. The said Regulations do not contain any element that is in contravention of international law or International Maritime Organization's (IMO) Rules and Recommendations and are being implemented accordingly.

The measures taken in the Turkish Straits in accordance with the said Regulations are aimed at improving the safety of navigation, human life, cultural and environmental heritage. Moreover, the safety measures are needed vis-à-vis the risks and dangers of passage of the increased number of tanker traffic in the Straits.

Turkey has duly informed IMO of the safety measures taken in the Straits. Besides, Traffic Separation Schemes and Reporting System, established within the framework of the Turkish Straits Regulations, were adopted by IMO together with some other rules in 1995.

Furthermore, the Maritime Safety Committee of the IMO confirmed at its 71st session on May 1999 that the routeing system and the associated IMO Rules and Recommendations relating to the Turkish Straits have proven to be effective and successful and had contributed significantly to an increase in safety and a reduction of the risk of collisions.

The Turkish Straits Vessel Traffic Services which have been functioning since 31 December 2003 within the framework of the Montreux Convention, IMO Rules and the Turkish Straits Regulations, provide traffic arrangements successfully with high standard technical equipment and qualified expert personnel.

Accordingly, the arguments in the above-mentioned Note of the Permanent Mission of Greece are unfounded and the statement of Turkey registered in our Note dated 14 December 2006 (Ref. no: 520.20/2006/BMCO DT/12201) remains unchanged and valid.

Reply dated 18 May 2007 to the Note Verbale from the Permanent Mission of Greece dated 16 April 2007

The Permanent Mission of the Republic of Turkey to the United Nations Office at Geneva and other International Organizations in Switzerland presents its compliments to the Director-General of the World Health Organization (WHO) and with reference to the latter's Note dated 9 May 2007 (Ref. no: C.L.22.2007) and the Note enclosed therein of the Permanent Mission of Greece dated 16 April 2007 (Ref. no: 6395(3160)/22/AS 783) has the honour to inform the Director-General of the following.

The Permanent Mission of the Republic of Turkey would like to underline that the statement in this Mission's Note of December 14, 2006 (No: 520.20/BMCO DT/12201) was a factual representation of the state of affairs.

Furthermore, the Permanent Mission would like to point out that the arguments and assertions raised in the Greek Delegation's above-mentioned Note are unfounded. Turkey's position on the Maritime Traffic Regulations for the Turkish Straits is also acknowledged by the International Maritime Organization (IMO) and remains unchanged. In fact, Turkish Straits Vessel Traffic Services (TSVTS) center is effectively providing traffic information, navigational assistance and traffic organization under the existing regulations to all vessels passing through the Straits.

As to the terminology used when referring to the Montreux Convention, the Permanent Mission, with all due respect to the wording of the said Convention, would like to emphasize the fact that the Straits subject of the said Convention are the "Turkish Straits", namely, the "Strait of İstanbul" and the "Strait of Çanakkale".

IV. DECLARATIONS UNDER ARTICLE 59, PARAGRAPH 3, OF THE IHR (2005)

TONGA

Following their adoption by the World Health Assembly in May 2005, the International Health Regulations (IHR) 2005 will enter into force on 15 June 2007.

The Kingdom of Tonga supports the important contribution the IHR 2005 will make to the strengthening of national and global systems for the protection of public health from the spread of disease.

The Kingdom of Tonga understands that in order to be effective, the IHR 2005 will need to operate at various levels within each country, as well as between countries internationally and the World Health Organization. With this in mind, Tonga has, with support from regional partners including WHO, taken a number of steps to prepare for the entry into force of the new regime. However, it is not possible to confirm that all the required adjustments will be able to be achieved by 15 June 2007.

Therefore, on behalf of the Kingdom of Tonga, and in accordance with paragraph 3 of Article 59 of the IHR 2005, I declare that the following adjustments may not be completed by June 2007.

The outstanding adjustments are as follows:

1. Complete the review of the Public Health Act 1992 to ensure legislative consistency with the IHR 2005;

2. Strengthen existing systems for the regular, national reporting of notifiable diseases, including the reporting of any events of potential public health significance, irrespective of their source;

3. Various enhancements to border health protection functions, including improved reporting and response capacities for public health events at Fua'amotu Airport and surveillance and control of vector/reservoir species at Fua'amotu airport and the seaport at Nuku'alofa.

The Kingdom of Tonga is, and will remain, committed to playing its part in the collective actions that contribute to the protection of public health for all people of the world. It is my intention that the outstanding adjustments will be achieved by 31 December 2007, and certainly no later than 15 June 2008.

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The purpose and scope of the International Health Regulations (2005) are "to prevent, protect against, control and provide a public health response to the international spread of disease in ways that are commensurate with and restricted to public health risks, and which avoid unnecessary interference with international traffic and trade". Because the IHR (2005) are not limited to specific diseases but apply to new and ever-changing public health risks, they are intended to have long-lasting relevance in the international response to the emergence and spread of disease. The IHR (2005) also provide the legal basis for important health documents applicable to international travel and transport and sanitary protections for the users of international airports, ports, and ground crossings.

This third edition contains the text of the IHR (2005), the text of World Health Assembly resolution WHA58.3, the amended version of Annex 7 (concerning period of protection of vaccination against yellow fever, and validity of related certificates) that entered into force on 11 July 2016, the Health Part of the Aircraft General Declaration that entered into force on 15 July 2007, and appendices containing an updated list of States Parties and State Party reservations and other communications in connection with the IHR (2005).

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BUSINESS TODAY

HEALTH

Dr Patrick Amoth Is CS Nakhumicha's Choice as New Health Director General

JUSTUS KIPRONO

Jun 22, 2024



Dr Patrick Amoth. (Photo: Web)

Cabinet Secretary (CS) of the Ministry of Health, Susan Nakhumicha, has nominated Dr Patrick oth, a consultant obstetrician and gynaecologist – a specialist doctor who manages conditions that affect the female reproductive system, to be the Director General of Health.

Generally, the Director General of Health is a technical advisor to the government on all matters relating to health within the healthcare sector to enhance the health and well-being of all Kenyans.

The post requires Parliament confirmation, but Dr Amoth, who is one of the country's leading experts on health care and regulatory issues, is not expected to face serious opposition.

The Public Service Commission (PSC) has been advertising and re-advertising that position since then, but the whole process has been stalling due to structural developments and changes brought about by devolution in Kenya's 2010 Constitution.

On why Dr Amoth had not been appointed directly as the Director General of Health despite his over 27 years of professional health experience, a senior high-ranking official at the health ministry speaking to Nation said: "This has nothing to do with Dr Amoth as a person but with the system. If you remember, when the ministry got devolved, it meant that the organisational structures had to change so that the entire government aligns itself in view of the new Constitution."

CS Nakhumicha, when reorganising the Ministry of Health in April last year, announced that Dr Amoth would continue holding the office in an acting capacity effective April 19, 2023.

But since PSC has put up the advert for the DG's job again, the CS has clarified that Dr Amoth is fit to apply despite still being active in office as Acting Director General of Health.

"So we have to advertise for the job. The advert does not exclude Amoth from applying. I have nfidence, given the experience he has. He (Amoth) should emerge as the best," CS Nakhumicha d.

Formerly, Dr Amoth headed the Department of Health Sector Coordination and Intergovernmental Affairs before working as a Chief Medical Specialist and Senior Deputy Director of Medical Services at Mama Lucy Kibaki Hospital Nairobi.

In 2021, he was appointed as the World Health Organisation (WHO) Executive Board chairperson by the Union's Health Minister, Dr Harsh Vardhan, during the 149th Session of the WHO Executive Board.

Dr Amoth holds a Bachelor in Medicine and Bachelor in Surgery Degree from the University of Nairobi (UON), as well as a Master of Medicine in Obstetrics and Gynecology from the same institution.

Additionally, he has a Diploma in Health Systems Management from Galilee College in Israel.

Nation Media Group to Lay Off Hundreds of Workers

REPUBLIC OF KENYA

PARLIAMENT
THIRTEENTH PARLIAMENT – THIRD SESSION

APPROVAL HEARING FOR DR. PATRICK OMWANDA AMOTH, NOMINEE FOR APPOINTMENT TO THE POSITION OF DIRECTOR GENERAL FOR HEALTH

INVITATION TO SUBMIT MEMORANDA

WHEREAS, Article 118(1)(b) of the Constitution requires Parliament to facilitate public participation and involvement in the legislative and other business of Parliament and its Committees;

AND WHEREAS, the Honourable Speakers of the Houses of Parliament received communication from the Cabinet Secretary, Ministry of Health, submitting the name of **Dr. Patrick Omwanda Amoth** as the successful candidate for appointment to the position of Director General for Health;

NOTING THAT, section 16(2) of the Health Act, Cap. 241, requires that the nominee be vetted by Parliament and appointed by the Cabinet Secretary.

AND WHEREAS, following receipt of the nomination, the Speakers of the Houses of Parliament referred the matter to the National Assembly Departmental Committee on Health and the Senate Standing Committee on Health, respectively, for the joint consideration of the Committees;

IT IS NOTIFIED that in accordance with section 6(9) of the Public Appointments (Parliamentary Approval) Act, Cap.7F, the Committees invite interested members of the public to submit any representations, by **written statements on oath (Affidavits),** with supporting evidence, on the suitability of the nominee for appointment to the position of Director General for Health.

The representations may be hand-delivered to the **Office of the Clerk of the National Assembly** and the **Office of the Clerk of the Senate, P.O. Box 41842-001000, Main Parliament Building, Nairobi**; or emailed to cna@parliament.go.ke and clerk.senate@parliament.go.ke, to be received on or before **Friday, 19th July, 2024** at **5.00 pm**.

SAMUEL NJOROGE, CBS
CLERK OF THE NATIONAL ASSEMBLY

J.M. NYEGENYE, CBS
CLERK OF THE SENATE