Promoting the Quality of Medicines Plus (PQM+)

Scientific and technical information package for COVID-19 antivirals prescribed to prevent serious disease and death in high-risk populations infected with COVID-19

Nirmatrelvir tablets co-packaged with Ritonavir tablet; Molnupiravir capsule

August 2023

Package 1

USAID FROM THE AMERICAN PEOPLE

usp

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About PQM+

The Promoting the Quality of Medicines Plus (PQM+) Program is a six-year cooperative agreement between USAID and USP to sustainably strengthen medical product quality assurance systems in low- and middle-income countries. The program works to improve medical product quality through cross-sectoral and systems strengthening approaches and the application of international quality assurance standards across the pharmaceutical system. By sharing scientific expertise and providing technical support and leadership, PQM+ helps create resilient and robust local health systems that address diseases such as HIV/AIDS, tuberculosis, malaria, and neglected tropical diseases, as well as improve maternal, newborn, and child health.

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Acknowledgements

European Medicines Agency (EMA) authored documents are cited in their original form as published by EMA (either as a PDF or online publication).

U.S. Food and Drug Administration (FDA) authored documents are cited in their original form as published by U.S. FDA. Advisory committee briefing documents provided to the U.S. FDA by Pfizer and Merck Sharp & Dohme LLC are for public release and were published on the U.S. FDA website.

U.S. National Institutes of Health (NIH) documents were authored by the COVID-19 Treatment Guidelines Panel. Specifically, the Coronavirus Disease 2019 (COVID-19) Treatment Guidelines, National Institutes of Health available at https://www.covid19treatmentguidelines.nih.gov/. Accessed June 1, 2023. The COVID-19 Treatment Guidelines Panel regularly updates the recommendations in these guidelines as new information on the management of COVID-19 becomes available. The most recent version of the guidelines can be found on the COVID-19 Treatment Guidelines website (https://www.covid19treatmentguidelines.nih.gov/).

World Health Organization (WHO)-authored documents are cited in their original form as published by WHO (either as a PDF or online publication). Individual titles, place of publication, and year are contained in each original document except the one listed below. All documents were issued under License: CC BY-NC-SA 3.0 IGO

PQM+ would like to thank our implementing partner programs, Meeting Targets and Maintaining Epidemic Control (EpiC) and Reaching Impact, Saturation, and Epidemic Control (RISE), for their collaboration and support throughout the test-to-treat (T2T) program. We would also like to thank our collaborators from the national medicines regulatory authorities (NMRA) in each of the Test to Treat countries:

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Ministry of Health, Lesotho
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Acronyms

API	active pharmaceutical ingredients
EMA	European Medicines Agency
EUA	emergency use authorization
EUAL	emergency use assessment and listing
EUL	emergency use listing
FDA	U.S. Food and Drug Administration
NIH	U.S. National Institutes for Health
PHEIC	public health emergency of international concern
PQM+	Promoting the Quality of Medicines Plus
T2T	test-to-treat
USAID	U.S. Agency for International Development
USP	U.S. Pharmacopeial Convention
WHO	World Health Organization

Package 1. Document information (click each entry to link to document)

#	DOCUMENT TITLE	SOURCE
1.1	WHO declaration of the COVID-19 pandemic	WHO
1.2	WHO Emergency Use Listing Procedure (version 9, August 2022)	WHO
1.3	WHO Statement on the fifteenth meeting of the IHR (2005) Emergency Committee on the COVID-19 Pandemic (May 5, 2023)	WHO
1.4	Therapeutic Management of Non-hospitalized Adults with COVID-19 (July 21, 2023 update)	NIH
1.5	Drug Treatments for COVID-19: Living Systematic Review and Network Meta-Analysis	The BMJ
1.6	Liverpool Drug Interactions Group Drug-Drug Interactions with Key COVID-19 Therapies (May 31, 2023 update)	Liverpool Drug Interactions Group
1.7	Efficacy of Antiviral Agents Against the SARS-CoV-2 Omicron Subvariant BA.2	The New England Journal of Medicine
1.8	Remdesivir, Molnupiravir and Nirmatrelvir Remain Active Against SARS-CoV-2 Omicron and Other Variants of Concern	Antiviral Research
1.9	Efficacy of Antiviral Agents Against Omicron Subvariants BQ.1.1 and XBB	The New England Journal of Medicine
1.10	Impact of the Use of Oral Antiviral Agents on the Risk of Hospitalization in Community Coronavirus Disease 2019 Patients (COVID-19)	Clinical Infectious Diseases
1.11	Real-world effectiveness of early molnupiravir or nirmatrelvir-ritonavir in hospitalised patients with COVID-19 without supplemental oxygen requirement on admission during Hong Kong's omicron BA.2	The Lancet
1.12	Effectiveness, Tolerability and Prescribing Choice of Antiviral Molecules Molnupiravir, Remdesivir and Nirmatrelvir/r: A Real-World Comparison in the First Ten Months of Use	Viruses

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Document 1.1

WHO declaration of the COVID-19 pandemic

Document URL

https://www.who.int/news/item/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov)

License

World Health Organization

Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV)

30 January 2020 | Statement | Geneva, Switzerland | Reading time: 6 min (1737 words)

العربية | 中文 | Français | Русский | Español

The second meeting of the Emergency Committee convened by the WHO Director-General under the International Health Regulations (IHR) (2005) regarding the outbreak of novel coronavirus 2019 in the People's Republic of China, with exportations to other countries, took place on Thursday, 30 January 2020, from 13:30 to 18:35 Geneva time (CEST). The Committee's role is to give advice to the Director-General, who makes the final decision on the determination of a Public Health Emergency of International Concern (PHEIC). The Committee also provides public health advice or suggests formal Temporary Recommendations as appropriate.

Proceedings of the meeting

Members and advisors of the Emergency Committee were convened by teleconference

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The Director-General welcomed the Committee and thanked them for their support. He turned the meeting over to the Chair, Professor Didier Houssin.

Professor Houssin also welcomed the Committee and gave the floor to the Secretariat.

A representative of the department of compliance, risk management, and ethics briefed the Committee members on their roles and responsibilities.

Committee members were reminded of their duty of confidentiality and their responsibility to disclose personal, financial, or professional connections that might be seen to constitute a conflict of interest. Each member who was present was surveyed and no conflicts of interest were judged to be relevant to the meeting. There were no changes since the previous meeting.

The Chair then reviewed the agenda for the meeting and introduced the presenters.

Representatives of the Ministry of Health of the People's Republic of China reported on the current situation and the public health measures being taken. There are now 7711 confirmed and 12167 suspected cases throughout the country. Of the confirmed cases, 1370 are severe and 170 people have died. 124 people have recovered and been discharged from hospital.

The WHO Secretariat provided an overview of the situation in other countries. There are now 83 cases in 18 countries. Of these, only 7 had no history of travel in China. There has been human-to-human transmission in 3 countries outside China. One of these cases is severe and there have been no deaths.

At its first meeting, the Committee expressed divergent views on whether this event constitutes a PHEIC or not. At that time, the advice was that the event did not constitute a PHEIC, but the Committee members agreed on the urgency of the situation and suggested that the Committee should continue its meeting on the next day, when it reached the same conclusion.

This second meeting takes place in view of significant increases in numbers of cases and additional countries reporting confirmed cases.

Conclusions and advice

The Committee welcomed the leadership and political commitment of the very highest levels of Chinese government, their commitment to transparency, and the efforts made to investigate and contain the current outbreak. China quickly identified the virus and shared its sequence, so that other countries could diagnose it quickly and protect themselves, which has resulted in the rapid development of diagnostic tools.

The very strong measures the country has taken include daily contact with WHO and comprehensive multisectoral approaches to prevent further spread. It has also taken public health measures in other cities and provinces; is conducting studies on the severity and transmissibility of the virus, and sharing data and biological material. The country has also agreed to work with other countries who need their support. The measures China has taken are good not only for that country but also for the rest of the world.

The Committee acknowledged the leading role of WHO and its partners.

The Committee also acknowledged that there are still many unknowns, cases have now been reported in five WHO regions in one month, and human-to-human transmission has occurred outside Wuhan and outside China.

The Committee believes that it is still possible to interrupt virus spread, provided that countries put in place strong measures to detect disease early, isolate and treat cases, trace contacts, and promote social distancing measures commensurate with the risk. It is important to note that as the situation continues to evolve, so will the strategic goals and measures to prevent and reduce spread of the infection. The Committee agreed that the outbreak now meets the criteria for a Public Health Emergency of International Concern and proposed the following advice to be issued as Temporary Recommendations.

The Committee emphasized that the declaration of a PHEIC should be seen in the spirit of support and appreciation for China, its people, and the actions China has taken on the front lines of this outbreak, with transparency, and, it is to be hoped, with success. In line with the need for global solidarity, the Committee felt that a global coordinated effort is needed to enhance preparedness in other regions of the world that may need additional support for that.

Advice to WHO

The Committee welcomed a forthcoming WHO multidisciplinary technical mission to China, including national and local experts. The mission should review and support efforts to investigate the animal source of the outbreak, the clinical spectrum of the disease and its severity, the extent of human-to-human transmission in the community and in healthcare facilities, and efforts to control the outbreak. This mission will provide information to the international community to aid in understanding the situation and its impact and enable sharing of experience and successful measures.

The Committee wished to re-emphasize the importance of studying the possible source, to rule out hidden transmission and to inform risk management measures

The Committee also emphasized the need for enhanced surveillance in regions outside Hubei, including pathogen genomic sequencing, to understand whether local cycles of transmission are occurring.

WHO should continue to use its networks of technical experts to assess how best this outbreak can be contained globally.

WHO should provide intensified support for preparation and response, especially in vulnerable countries and regions.

Measures to ensure rapid development and access to potential vaccines, diagnostics, antiviral medicines and other therapeutics for low- and middle-income countries should be developed.

WHO should continue to provide all necessary technical and operational support to respond to this outbreak, including with its extensive networks of partners and collaborating institutions, to implement a comprehensive risk communication strategy, and to allow for the advancement of research and scientific developments in relation to this novel coronavirus.

WHO should continue to explore the advisability of creating an intermediate level of alert between the binary possibilities of PHEIC or no PHEIC, in a way that does not require reopening negotiations on the text of the IHR (2005).

WHO should timely review the situation with transparency and update its evidence-based recommendations.

The Committee does not recommend any travel or trade restriction based on the current information available.

The Director-General declared that the outbreak of 2019-nCoV constitutes a PHEIC and accepted the Committee's advice and issued this advice as Temporary Recommendations under the IHR.

To the People's Republic of China

Continue to:

• Implement a comprehensive risk communication strategy to regularly inform the population on the evolution of the outbreak, the prevention and protection measures for the population, and the response measures taken for its containment.

• Enhance public health measures for containment of the current outbreak.

• Ensure the resilience of the health system and protect the health workforce.

• Enhance surveillance and active case finding across China.

• Collaborate with WHO and partners to conduct investigations to understand the epidemiology and the evolution of this outbreak and measures to contain it.

• Share relevant data on human cases.

• Continue to identify the zoonotic source of the outbreak, and particularly the potential for circulation with WHO as soon as it becomes available.

• Conduct exit screening at international airports and ports, with the aim of early detection of symptomatic travellers for further evaluation and treatment, while minimizing interference with international traffic.

To all countries

It is expected that further international exportation of cases may appear in any country. Thus, all countries should be prepared for containment, including active surveillance, early detection, isolation and case management, contact tracing and prevention of onward spread of 2019-nCoVinfection, and to share full data with WHO. Technical advice is available on the WHO website.

Countries are reminded that they are legally required to share information with WHO under the IHR.

Any detection of 2019-nCoV in an animal (including information about the species, diagnostic tests, and relevant epidemiological information) should be reported to the World Organization for Animal Health (OIE) as an emerging disease.

Countries should place particular emphasis on reducing human infection, prevention of secondary transmission and international spread, and contributing to the international response though multisectoral communication and collaboration and active participation in increasing knowledge on the virus and the disease, as well as advancing research.

The Committee does not recommend any travel or trade restriction based on the current information available.

Countries must inform WHO about travel measures taken, as required by the IHR. Countries are cautioned against actions that promote stigma or discrimination, in line with the principles of Article 3 of the IHR.

The Committee asked the Director-General to provide further advice on these matters and, if necessary, to make new case-by-case recommendations, in view of this rapidly evolving situation.

To the global community

As this is a new coronavirus, and it has been previously shown that similar coronaviruses required substantial efforts to enable regular information sharing and research, the global community should continue to demonstrate solidarity and cooperation, in compliance with Article 44 of the IHR (2005), in supporting each other on the identification of the source of this new virus, its full potential for human-to-human transmission, preparedness for potential importation of cases, and research for developing necessary treatment.

Provide support to low- and middle-income countries to enable their response to this event, as well as to facilitate access to diagnostics, potential vaccines and therapeutics.

Under Article 43 of the IHR, States Parties implementing additional health measures that significantly interfere with international traffic (refusal of entry or departure of international travellers, baggage, cargo, containers, conveyances, goods, and the like, or their delay, for more than 24 hours) are obliged to send to WHO the public health rationale and justification within 48 hours of their implementation. WHO will review the justification and may request countries to reconsider their measures. WHO is required to share with other States Parties the information about measures and the justification received.

The Emergency Committee will be reconvened within three months or earlier, at the discretion of the Director-General.

The Director-General thanked the Committee for its work.

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Document 1.2

WHO EUL Procedure Updated

Document URL

https://cdn.who.int/media/docs/default-source/medicines/eulprocedure.pdf?s-fvrsn=55fe3ab8_8&download=true

Reference website URL

https://www.who.int/publications/m/item/emergency-use-listing-procedure

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World Health Organization

Emergency Use Listing Procedure

Version 9 August 2022

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Abbreviations

CTD	Common technical document
DOI	Declaration of Interest
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
EUAL	Emergency Use Assessment and Listing
EUL	Emergency Use Listing
EVD	Ebola Virus Disease
GCP	Good clinical practice
GLP	Good laboratory practice
GMOs	Genetically Modified Organisms
GMP	Good manufacturing practices
QMS	Quality Management Systems
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IVDs	In vitro diagnostics
LOQ	List of Questions
NRA	National regulatory authority
PEG	Product Evaluation Group
PHE	Public Health Emergency
PHEIC	Public Health Emergency of International Concern
PQT	Prequalification Team
PSUR	Periodic safety updated report
R&D	Research and Development
RPQ	Regulation and Prequalification Department
SRA	Stringent Regulatory Authority
TAG-EUL	Technical Advisory Group for Emergency Use Listing
TORs	Terms of Reference
TRS	Technical report series
WLA	WHO Listed Authority
WHO	World Health Organization

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1. Background

The World Health Organization (WHO) developed the Emergency Use Assessment and Listing (EUAL) mechanism in response to the 2014 – 2016 Ebola Virus Disease (EVD) outbreak. The EUAL is a risk-based procedure for assessing and listing unlicensed vaccines, therapeutics and in vitro diagnostics (IVDs) for use primarily during public health emergencies of international concern (PHEIC) but also in other public health emergencies if appropriate.

Two submissions for Ebola vaccines were received but none was listed. No therapeutic products that were in development were submitted during the 2014-2016 Ebola outbreak. Twenty- five applications for IVDs were received for Ebola assays of which seven were listed. Also, three out of thirty- three applications received for Zika assays were listed.

Based on the above experience, vaccine developers and national regulators identified the need to revise and simplify the procedure, in order to improve clarity on procedural aspects, and to avoid overlap or gaps in their respective functions.

Challenges encountered during the review of IVDs applications included poor quality of submissions and assay validation data, lack of international standards to guide the assessment, lack of reference preparations and panels for validating assays, missing ethical clearance related to the sourcing of these materials and concerns about the biosafety of IVDs. Manufacturers and regulators agreed that there was a need for better guidance on validation data required for IVDs in the EUAL process, as well as the availability of international reference materials and other validation materials.

2. Rationale for the revision of the EUAL

The WHO Informal Consultation on options to improve regulatory preparedness to address public health emergencies (Geneva, May 2017)[1] concluded that some aspects of the WHO EUAL procedure needed to be reconsidered and revised. The consensus was : a) the process should be reframed as the Emergency Use Listing (EUL) procedure ; b) the revised procedure should be used primarily during a Public Health Emergency of International Concern (PHEIC) [2], although the Director-General may authorize the use of this procedure for a public health emergency that does not meet the criteria of a PHEIC if s/he determines that this is in the best interest of public health.

[1] http://www.who.int/medicines/news/2017/PHEmeeting-reportIK-EG16_Nov_2017.pdf?ua=1

[2] The term Public Health Emergency of International Concern is defined in the IHR (2005) as "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". This definition implies a situation that: is serious, unusual or unexpected; carries implications for public health beyond the affected State's national border; and may require immediate international action.

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For the purpose of this document, a PHEIC or other public health emergency for which the use of this procedure is authorized are referred to as a "PHE" ; c) WHO should ensure that the use of an unlicensed product under the EUL framework is based on a pre-determined rationale and pre-determined criteria; d) the role of National Regulatory Authorities (NRAs) and the degree of reliance upon their assessments should be clear, and NRAs of potentially affected countries should be involved in the EUL procedure during public health emergencies, and; e) the EUL should also include plans for pre-emergency activities to allow a rapid listing decision once the emergency is declared.

Accordingly, this Emergency Use Listing (EUL) procedure, replaces the Emergency Use Assessment and Listing (EUAL) procedure.

3. Scope and purpose of the EUL procedure

The goal of the procedure is to define the steps that WHO will follow to establish eligibility of unlicensed products for assessment under this procedure, the essential information required, and the process to be used in conducting the assessment to determine whether an unlicensed product can be listed on a time limited basis, while further data is being gathered and evaluated.

The Prequalification Team has been assigned the role as EUL Secretariat, as this team possesses the required expertise in product evaluation and interacts with procurement organizations and NRAs (i.e. NRAs responsible for the regulatory oversight of products and NRAs from potential user countries).However it is very important to note that the EUL is not equivalent or an alternative to WHO prequalification, and should not be thought of as such. The EUL is a special procedure for unlicensed vaccines, medicines and in vitro diagnostics in the event of a PHE when the community/public health authorities may be willing to tolerate less certainty about the efficacy and safety of products, given the morbidity and/or mortality of the disease and the lack or paucity of treatment, diagnosis/detection or prevention options. It is intended to provide a time-limited listing (see section 5.2.3) for unlicensed products in an emergency context when limited data are available and the products are not yet ready for application for prequalification[3]. As part of the EUL, it is expected that the manufacturer will complete the development of the product and submit for licensure and WHO prequalification.

WHO has developed the EUL process to expedite the availability of unlicensed medical products needed in public health emergency situations, to assist interested UN procurement agencies and Member States in determining the acceptability of using specific products in the context of a public health emergency, based on an essential set of available quality, safety, and efficacy/immunogenicity/ performance data.

The EUL is not intended to interfere with ongoing clinical trials. This means that the clinical development should proceed as planned after the initial submission and subsequent updates.

[3] While EUL applies to unlicensed products, prequalification only considers products that have been licensed by the responsible NRA. See https://www.who.int/topics/prequalification/en/

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It should be noted that it is the sole prerogative of WHO Member States to use the EUL as the basis to authorize the use of an unlicensed vaccine/medicine/IVD at the national level.

This document I s intended to guide manufacturers who are willing to submit applications, with the goal of obtaining a listing of their product (s) for use during public health emergencies. Participation in the procedure is voluntary.

4. Eligibility of candidate products

The three product streams (vaccines, therapeutics and IVDs) each have specific requirements for products to be eligible for evaluation under the EUL procedure.

In order to qualify for assessment under this procedure, the following criteria must be met:

- The disease for which the product is intended is serious or immediately life threatening, has the potential of causing an outbreak, epidemic or pandemic and it is reasonable to consider the product for an EUL assessment, e.g., there are no licensed products for the indication or for a critical subpopulation (e.g., children);
- Existing products have not been successful in eradicating the disease or preventing outbreaks (in the case of vaccines and medicines);
- The product is manufactured in compliance with current Good Manufacturing Practices (GMP) in the case of medicines and vaccines and under a functional Quality Management System (QMS) in the case of IVDs, and;
- The applicant undertakes to complete the development of the product (validation and verification of the product in the case of IVDs) and apply for WHO prequalification once the product is licensed. For that purpose, the remaining clinical trials and other testing needed to complete the development of the product must already be underway at the time of the application for an EUL[4].

WHO may consider reviewing a candidate product for EUL that does not meet all of the requirements. In such situations, the application letter and documentation provided to WHO should justify the application of the product although it does not meet all eligibility requirements.

[4] A future prequalification application should incorporate all information submitted for the EUL plus any other information needed to complete a prequalification application

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5. Phases of the procedure

There are 3 phases of the EUL procedure:

- Pre-emergency phase;
- Emergency phase, and;
- Post-listing phase.

5.1. Pre-emergency phase

Past experiences with emergency situations have shown that a preparedness plan is key to a rapid response when the emergency is declared. The WHO Research & Development (R&D) Blueprint[5] was established based on this principle.

As products in development are added to the pipeline for each priority disease, there are several activities that can be planned and executed during the pre-emergency phase. This strategy is intended to concentrate -as much as possible- on the activities that can be done in advance, thus minimizing the time required for a final decision about possible listing of a product once the public health emergency is declared.

If pre-emergency activities have not been conducted, either at the time when a PHE occurs or whilst a PHE is in progress, they would be implemented during the emergency phase. In this situation, timelines for the process will be impacted.

The pre-emergency activities are divided into two types according to the objectives and the stakeholders involved:

- Establishment of an assessment platform.

This includes activities that are intended to establish a platform for collaboration between WHO, external experts, NRAs responsible for the oversight of the product and NRAs from potential user countries. Activities include establishment of a roster of experts to be called upon to set up the necessary advisory Groups at the different stages of the procedure, consultations, strategic planning and oversight of systems/procedures to support the implementation of the EUL.

- Eligibility and assessment of products

These aspects of the pre-emergency phase are related to the interactions with applicants. They include pre-submission meetings/activities, selection of products for assessment according to established eligibility criteria (See eligibility criteria below), assignment of an evaluation pathway, and assessment of submitted data (initial data and updates), with reports thereon. These aspects are part of the eligibility and assessment process and use the resources and output of the assessment platform.

[5] https://www.who.int/blueprint/about/en/

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The implementation of all these pre-emergency activities is intended to accelerate the decision-making process for possible listing when the public health emergency is declared. During the emergency phase, a recommendation for use (or non-use) will be issued and published by WHO.

5.1.1 Establishment of the assessment platform

5.1.1.1 Agreements with NRAs of record for information sharing

For vaccines, an agreement is required for information sharing between WHO and the NRA that is responsible for the regulatory oversight of the unlicensed product (NRA of record). This is consistent with the principles for use of the streamlined procedure for prequalification of vaccines. These agreements will allow WHO to rely on the NRA's assessment of quality, pre-clinical and clinical information and facilities. The NRA of record may also have issued an authorization for emergency use of the unlicensed product.

For medicines, reliance by WHO on the assessment by Stringent Regulatory Authorities/WHO Listed Authorities (SRAs/WLAs)[6] does not require an agreement for information sharing. Reports of the inspections conducted by the SRA/WLA that issued the authorization under extraordinary circumstances such as a public health emergency will also be considered to waive the requirement for an inspection by WHO. Reliance upon the SRA/WLA originally responsible for the regulatory oversight of a product, will determine whether the assessment pathway under the EUL procedure will be based on an abridged or a full review process. An abridged pathway to possible EUL listing may have an impact on the time required to complete the evaluation. (See "Selection of assessment pathways" below.)

5.1.1.2 Framework for interaction with NRAs and Ethics Committees of potentially affected countries

As priority diseases are identified and products are considered eligible for assessment, WHO will discuss with NRAs and Ethics Committees of potentially impacted countries, to define their level of participation during the pre-emergency, emergency and post listing phases for each specific product.

5.1.1.3. Establishment of a roster of experts to support the different phases of the procedure

A roster of experts will be established through a selection process by WHO's Regulation and Prequalification Department (RPQ) (former Regulation of Medicines and other Health Technologies Department).

Experts may be selected among suitably qualified members of existing ad hoc or standing advisory Groups, relevant WHO expert panels, including representatives from NRAs of

[6] WHO Listed Authority (level 4).

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manufacturing countries, NRAs responsible for the regulatory oversight of products, NRAs of potentially affected countries, academia and other relevant institutions. The pool of expertise should cover all technical/scientific areas to be considered during the pre-emergency, emergency and post-emergency phases, so that the required Groups (see 5.1.1.4) can be rapidly established when required for assessment and recommendations relevant to specific products.

The selected experts will be assessed for conflicts of interest and be required to enter into a confidentiality undertaking.

There are two types of Groups that will be established on an ad hoc basis from the roster of experts:

a) Product Evaluation Group (PEG)

This Product Evaluation Group (PEG) will be called during the pre-emergency phase of the procedure to: i) determine what sets of guidelines, requirements and scientific consensus guidelines -when available- will be used to assess a product; ii) evaluate applications of products that have met the EUL eligibility criteria and have passed the initial screening; iii) perform a risk-based assessment of the scientific data for a product, including quality, safety/efficacy/performance, and programmatic aspects; iv) prepare a report with the PEG's recommendations for submission to WHO. WHO may submit this report to the Advisory Committee for Emergency Listing (TAG-EUL) (See below) for consideration when a PHE is declared.

Should a submission be received once the PHE had been declared, the PEG will be convened in the emergency phase. Timelines for review and report will in this case be impacted but shortened as much as possible.

b) Technical Advisory Group for Emergency Use Listing (TAG-EUL):

This group will be established once a PHE has been declared (see emergency phase below).

Each PEG and each TAG-EUL will be coordinated by the Leader of the relevant Prequalification Team Group (Vaccines, Medicines, IVDs). (See Terms of Reference of PEG in Annex 1) .

5.1.1.4. Consensus on essential requirements on quality, safety, efficacy/immunogenicity/ performance and lot release (when applicable) for specific products

It is very likely that when the assessment of a product under the EUL procedure starts, there will be no official WHO standards or national regulatory guidelines that are fully applicable to a specific unlicensed product. The prioritization process for the development of product-specific WHO guidelines takes into account not only the priority list of diseases as per the R&D Blueprint but also several other competing global public health needs.

However, some WHO, international and national guidelines that are of a more general nature (i.e. cell substrates for vaccine production, virus inactivation and others) may be used for the assessment of products that are in development and for which there are no product-specific published WHO or NRA guidelines. Guidelines from WHO or NRAs, relevant international

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guidelines, as well as literature to support scientific consensus on aspects related to the specific type of product, will be considered and discussed by the Product Evaluation Group in order to decide which ones will be used to assess a specific product. The report will indicate the list of guidelines and other scientific literature that has been used by the PEG as the basis for the assessment.

5.1.1.5. Pre-submission activities/ meetings

If considered necessary or desirable by the applicant and WHO, a discussion may be held between the applicant and WHO before the actual evaluation process starts. These pre-submission exchanges may be done via a chosen method of communication, including face-to-face meetings. Pre-submission meetings should be scheduled as early as possible, with a predefined agenda addressing questions sent to WHO in advance by the applicant. Such meetings are important for discussing the availability of essential data required for specific products, expected timelines for submission and updates, monitoring of safety and effectiveness after deployment, and other relevant information. Additional meetings may be held during the assessment process, as required.

The procedural aspects of a pre-submission meeting are detailed in Annex 2.

5.1.1.6 Submission of applications

Applications:

The manufacturer must submit an application letter using the template set forth in Annex 3 hereto, duly completed, signed and dated by each applicant/manufacturer with the product, to WHO's Director of RPQ, with a copy to the relevant PQT Team Lead and the NRA responsible for the regulatory oversight of the unlicensed product. The application letter should include details of country and sites of manufacture, the presentations proposed for the product and information on whether or not the NRA has issued an authorization for emergency use or equivalent.

WHO will acknowledge receipt of the application letter by e-mail, with a copy to the relevant NRA. The acceptance of an application will also be confirmed by email, with a copy to the NRA. WHO will only respond with an official letter in those cases where the product cannot be accepted, including but not limited to because: the product does not meet the eligibility criteria. WHO will endeavour to advise the applicant and the NRA of a rejection of the application within 2 weeks of receipt of the official request.

Once the product has been accepted for review under the EUL procedure, the applicant will be required to submit a duly signed Letter of Agreement (as per the template in Annex 4) and the dossier in the appropriate format for each product stream. (See Annex 5).

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5.1.1.7 Assignment of Assessment pathway

Some national regulatory authorities have implemented pathways to assess products that are still in clinical development and authorize their use under extraordinary circumstances, such as a public health emergency. Where products submitted for EUL have undergone a previous assessment and/or obtained an extraordinary authorization by an NRA, it is not the intent of WHO to undertake duplicative work, if a review by WHO of the NRAs emergency mechanism deems it to be of a satisfactory standard.

The criteria for use of abridged review and full review for each type of product according to reliance on the NRA that has previously assessed the product (and, for vaccines, the manufacturer's previous WHO prequalification record), are detailed in Annex 6.

5.1.1.8 Assessment of initial information received

Once the product has been considered eligible for assessment under the EUL procedure, the PQT Team Lead of the relevant product stream will designate a focal person for the EUL assessment of a specific product.

The focal person will perform the screening of the submission to ensure that sufficient information is available to initiate the assessment by the PEG based on the essential data requirements (See Annex 5). If the screening indicates that the assessment cannot start due to lack of information, this will be communicated to the applicant. A complete dossier may be submitted any time afterwards.

In addition to the EUL dossier review process, a WHO inspection team will conduct a desk review of available inspection reports. As appropriate, the inspection team may also undertake on-site inspection of manufacturing and clinical sites, depending on the outcome of the desk review or if the PEG so recommends.

The focal person will coordinate the distribution of the submitted data package to the members of the PEG, provide specific instructions for the review as appropriate, and manage communications with the applicant.

A consolidated report of the PEG will indicate whether the information received is considered sufficient for a recommendation, or if additional information is needed prior to giving a recommendation. If the applicant has provided a timeline for additional results according to the product development plan, this will be indicated in the consolidated report.

The report of the PEG and all subsequent versions with updates (see below) will be submitted to WHO. WHO may submit this report to the Committee responsible for a final recommendation on possible listing (TAG-EUL) if/when a PHE is declared before additional data becomes available. The report will provide the TAG-EUL with a documented outcome of the evaluation of the quality, safety, efficacy/immunogenicity/performance of the product by the PEG based on currently available data. The report will also indicate when the next set of data is expected (for example, full report of phase II trials). (See Annex 7 for Assessment report templates.)

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5.1.1.9 Submission of updates

After the initial submission of the application with all the required information for initial assessment, applicants should promptly submit any additional information on the development of the product to WHO, particularly if it may affect the product's benefit/risk assessment.

The applicant should – as much as possible- provide tentative timelines for the submission of additional/supplementary information based on the expected dates of completion/planned interim analyses of studies currently ongoing/or being initiated soon.

Submission of updates/additional data should clearly follow the section numbering system of the initial submission (see Essential Data Requirements in Annex 5).

5.2 Emergency phase activities

5.2.1 Expert Groups

The TAG-EUL for the evaluation of a specific product or group of products for a specific disease will be established by WHO upon declaration of a PHE. In some cases, WHO may establish the TAG-EUL while the PHE declaration procedure is still pending. Members of the TAG-EUL will be selected by WHO from the established roster of experts. The focal point designated by the Team Lead of the relevant PQ product stream may provide the TAG-EUL members with the report prepared by the relevant PEG and any other information considered critical for the deliberations and decisions. (See Terms of Reference of the TAG-EUL in Annex 1)

5.2.2 WHO decision on emergency use listing

This procedure includes provisions to concentrate most of the activities related to the submission and assessment of available data during the pre-emergency phase. Therefore, optimally the TAG-EUL will have all the necessary information to deliberate and issue a recommendation to WHO on whether or not a product should be listed, and if so, under what conditions for use, in a short period of time. The TAG-EUL may request further information from the applicant before making a recommendation. The recommendation of the TAG-EUL will be used by WHO to decide whether or not the product can be granted an EUL.

5.2.3 Publication of review outcomes and communications

Upon making a decision whether or not to grant a recommendation (acceptance or non-acceptance) for emergency use listing of the evaluated product, WHO will (without prejudice to any confidential information of the applicant/manufacturer) publish information about the product in a public report available on a dedicated portal of the WHO website. This may include negative assessment outcomes.

As WHO is responsible for the EUL assessment process, the ownership of the reports arising from or relating to the EUL assessment process lies with WHO. Thus, WHO shall be entitled to use and

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publish such reports, subject always, however, to the protection of any commercially sensitive confidential information of the manufacturer. Confidential information in this context means:

- confidential intellectual property, know-how, and trade secrets (including, e.g. formulas, processes or information contained or embodied in a product, unpublished aspects of trademarks, patents, etc.); and
- commercial confidences (e.g. structures and development plans of a company).

Subject to the protection of commercially sensitive confidential information, WHO will publish on the WHO website and make publicly available the following information in connection with the prequalification assessment process:

- the names of products and of manufacturers that have applied for EUL, the product code(s) submitted for EUL and the EUL status of each application;
- a WHO EUL public report summarizing the findings of the EUL assessment; and
- any negative outcomes of the EUL assessment.

In addition, WHO reserves the right to share full reports with the relevant authorities of any interested Member State of the Organization and interested United Nations agencies.

Furthermore, at any time during the EUL assessment process, WHO will have the right to use, publish, issue, share with national regulatory authorities (NRAs) and other relevant authorities of WHO Member States and/or with United Nations agencies and other relevant intergovernmental organizations, and/or make publicly available any outcomes, reports, notices and/or results—whether in draft or final form, and whether positive or negative—arising from or relating to the EUL assessment process and/or any listed product and/or any confidential information (as defined above) to which WHO may gain access in the course of the EUL assessment process. WHO's aforementioned rights will be exercised in accordance with the provisions of this EUL procedure regarding the protection of any commercially sensitive information of the applicant/manufacturer.

The validity of an emergency use listing in the context of a PHE will generally be for 12 months.

All decisions to list a product in the EUL will be reassessed at 12 months intervals (or sooner, if further data become available that could alter the original decision). When deemed necessary, the emergency use listing can be extended. Products may be taken off the EUL list earlier, if new data become available that change the benefit-risk balance of the product or immediately upon termination of the PHE.

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5.3 Activities after a product has been listed, deployed and used

5.3.1 Post listing monitoring

After a product has been listed, WHO will take into consideration reports on safety surveillance, efficacy/effectiveness/performance monitoring, quality complaints and other relevant data that may impact the validity of the listing status.

The sources of such information will inter alia be based on existing surveillance mechanisms in affected countries (as discussed with relevant NRAs during the pre-emergency phase) and on post-listing surveillance commitments of the manufacturer, set as conditions for the listing.

WHO reserves the right to issue an information notice for procurement agencies and relevant programs, if at any time, WHO deems that the EUL holder is not responding to a post-listing quality/safety issue in a timely and/or scientifically sound manner. If quality/safety issues are identified post listing, WHO may seek advice from the TAG-EUL. If a quality/safety issue cannot be resolved to WHO's satisfaction, WHO reserves the right to restrict or revoke the emergency use listing of the product.

5.3.2. Post-listing changes

Once a product has been listed under the EUL procedure, the development of the product must -whenever possible- continue to completion for marketing authorization and be submitted to WHO for prequalification, once licensure has been obtained.

The applicant must promptly inform WHO of all changes regarding formulation, manufacturing process, testing methods, specifications, facilities and any other aspects that might (a) result in a change of the safety and/or efficacy and/or performance of the product or (b) change the basis for the listing recommendation. Such changes to the product must follow the procedure for submission of updates described in 5.1.1.9.

Changes to products listed based on an abridged procedure must be accepted for emergency use by the original NRA responsible for the oversight of the product, and WHO must be notified of the accepted changes.

6. Resolution of Disputes

Any and all claims or disputes arising from or in connection with this EUL procedure, including, but not limited to, any rejection of an application, any assessment hereunder and/or any decision whether or not to grant an EUL recommendation for an evaluated product (hereinafter, collectively, "Disputes") must be submitted in writing to WHO's Director of RPQ, with a copy to the relevant PQT Team Lead.

WHO's Director of RPQ, or one of his/her authorized representatives, will acknowledge in writing receipt of the relevant Dispute and will conduct an investigation into the Dispute within

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30 days of receipt. Following the investigation, WHO's Director of RPQ, or one of his/her authorized representatives, will provide a written response to the applicant/manufacturer that submitted the Dispute. If the applicant/manufacturer is dissatisfied with the written response, then it must object in writing to WHO within 30 days of the date of WHO's aforementioned written response. In the event that the applicant/manufacturer does not object to WHO in writing within such 30 day period, then the content of WHO's written response (including, without limitation, any findings or decisions contained therein) will be final and can no longer be challenged by the applicant/manufacturer in any way. However, if the applicant/manufacturer does object to WHO in writing within such 30 day period, then the Dispute will be referred to WHO's Director-General for his or her decision which will be final and binding on the parties.

7. Privileges and Immunities of WHO

By virtue of WHO's status as a Specialized Agency of the United Nations, WHO, its officials and experts performing missions for WHO (including, e.g. assessors and inspectors) enjoy privileges and immunities under national and international laws and conventions, including without limitation: (i) the Convention on the Privileges and Immunities of the Specialized Agencies, adopted by the General Assembly of the United Nations on 21 November 1947 (the "1947 Convention"), and (ii) the United States' International Organizations Immunities Act of 1945 and Executive Order 9698 relating thereto (collectively, the "IOIA"). Nothing contained in or in connection with this EUL procedure and/or any assessment process hereunder will constitute or be deemed as a waiver of any of the privileges or immunities which WHO, its officials and/or experts performing missions for WHO enjoy pursuant to the 1947 Convention, the IOIA or otherwise under any national or international law, convention or agreement, and/or as submitting WHO, its officials and/or experts aforesaid to any national court jurisdiction.

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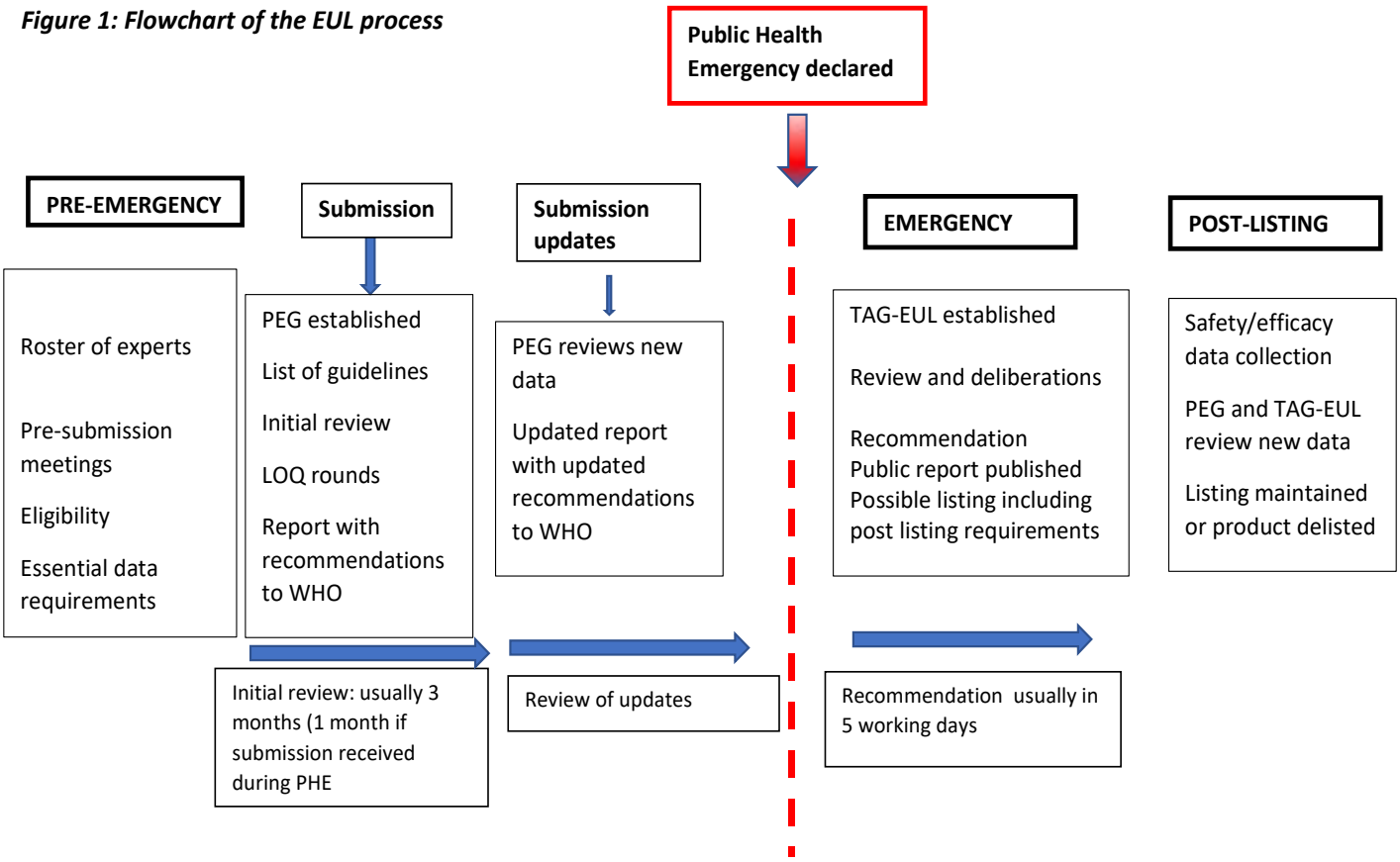
Table 1: list of activities during the three phases of the EUL

Activity	Pre-emergency	Emergency	Post-listing
Agreements between WHO and relevant NRAs	✓		
Establishment of roster of experts by WHO	✓		
Assessment by WHO of eligibility of specific products	✓	✓	
Development of consensus by the PEG on requirements	✓	✓	
Pre-submission meetings between WHO and applicant	✓	✓	
Assignment of assessment pathway by WHO	✓	✓	
Establishment of Experts Groups (PEG and TAG-EUL) by WHO	✓	✓	
Assessment of submission by PEG	✓	✓	
Assessment of PEG report by TAG-EUL		✓	
Submission of updates by manufacturer	✓	✓	✓
Decision on listing by WHO		✓	
Post listing monitoring			✓
Decision by WHO on whether to extend listing		✓	✓
Possible post-listing changes by WHO			✓

Emergency Use Listing Procedure

Figure 1: Flowchart of the EUL process



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Annex 1: Terms of Reference for Experts and Advisory Groups (PEG and TAG-EUL)

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Terms of Reference for the Product Evaluation Group (PEG)

Background

In the context of the World Health Organization (WHO) procedure for emergency use listing (EUL) of medical products , the WHO PQ Secretariat will require advice from an independent evaluation group known as the Product Evaluation Group (PEG).

There will be three PEGs, one for each product stream under the EUL (vaccines, medicines and IVDs) :

- **PEG-V**: for evaluation of vaccines, which will be selected, convened and coordinated by the WHO Vaccine PQ Team Lead
- **PEG-M**: for evaluation of medicines, which will be selected, convened and coordinated by the WHO Medicines PQ Team Lead
- **PEG-D**: for evaluation of Diagnostics, which will be selected, convened and coordinated by the WHO In Vitro Diagnostics PQ Team Lead.

The experts will be selected from a pre-established roster, according to the requirements for evaluation under the EUL procedure.

The PEG will have the functions described below.

Members must respect the impartiality and independence required of WHO. In performing their work, they may not seek or accept instructions from any Government or from any authority external to the Organization. They must be free of real, potential or apparent conflict of interest. To this end, proposed members will be required to complete a declaration of interest form and their appointment, or continuation of their appointment, will be subject to the evaluation of completed forms by the WHO Secretariat, determining that their participation would not give rise to a real, potential or apparent conflict of interest.

Information and documentation to which members may gain access in performing PEG related activities will be considered as confidential and proprietary to WHO and/or parties collaborating with WHO, including in particular, but not limited to, the applicants. PEG members shall not purport to speak on behalf of, or represent, the PEG or WHO to any third party, and treat the deliberations of the PEG as strictly confidential. All proposed members will be required to commit to an appropriate confidentiality undertaking and agree to provisions on ownership. To this end, each member will be required to enter into a Memorandum of Agreement with WHO.
Experts selected for the PEG from the pre-established roster will be required to commit to make every effort to be available on a short notice to perform their PEG related responsibilities.

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Functions

The functions of the PEG are:

a) To assess what published guidelines, requirements/recommendations and international guidance documents are available from WHO and regulatory agencies that are relevant for the evaluation of a product.

b) To conduct a search for relevant publications with evidence of scientific consensus with regards to safety, immunogenicity or clinical efficacy of a product.

c) To agree on a set of guidelines, requirements/recommendations and other parameters that will be used to evaluate a product or group of products

d) To screen submissions for completeness of the information required

e) To review the quality, clinical and performance information of the unlicensed medical product (See Annex 5 for information required, after the product has been determined to be eligible for EUL assessment)

f) To make a recommendation to WHO on the risk/benefit balance (positive/negative) of the product, should a PHE occur which justifies the need for the product before additional data is provided as the development of the product advances. This recommendation should be based on a review of the available data and the Applicant's response to the PEG List Of Questions (LOQs).

The report and recommendation by the PEG will be based on the following:

a) Complete application submitted by the applicant to the WHO PQ Team

b) Responses from the applicant to the LOQs prepared after the initial review (if applicable)

c) Additional information or updates submitted by the applicant at any point, and

d) Other information related to the product that the committee deems important for the review

The report of the PEG should follow the template in Annex 7 and will be submitted by the Chair to WHO (PQ Team Lead for the product stream).

The Chair may assign reviewers from among the PEG members for specific reviews.

If after initial review of the submission, the PEG decides to address additional questions to the applicant, the Chair will prepare a consolidated LOQ that will be sent to all members for consensus. This LOQ will be submitted to the WHO PQ Team focal person who will forward it to the applicant. There will be no direct communications between the PEG (or any of its members) and the applicant.

Once the responses are received, they will be reviewed by the PEG and there may be more rounds of questions until all responses are considered satisfactory by the PEG or until no more responses can be obtained from the applicant. The PEG will then complete its report, with a recommendation as provided above.

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Membership

PEG members shall serve in their personal capacities, as temporary advisers to WHO, and will be selected to represent the broad range of disciplines relevant to the product under review. As such, they need to enter into the standard Memorandum of Agreement for Temporary Advisers with WHO.

1) PEG-V

The PEG-V consists of a maximum of 10 members from the established roster of experts and should include the following areas of expertise:

- production and quality control;
- quality systems, quality risk management and GMP;
- non-clinical and clinical assessment
- pharmacovigilance
- infectious disease specialists

Note: One of two experts may be selected for each area of expertise

2) PEG-M

The PEG-V consists of a maximum of 10 members from the established roster of experts and should include the following areas of expertise:

a) regulators with the relevant expertise in the assessment of:

- pharmaceutical quality data (production, quality control and GMP)
- toxicological/pre-clinical data
- pharmacokinetic and modelling/simulation data
- clinical efficacy and safety data
- pharmacovigilance measures

b) Infectious disease specialists (clinician, non-regulator), paediatricians and, depending on the nature of the disease also other clinical specialists.

3) PEG-D

The PEG-D consists of a maximum of 10 members from the established roster of experts and should include the following areas of expertise:

- Quality management system
- Validation and verification studies and labelling of IVDs
- Infectious disease specialists
- Laboratory scientist with expertise in diagnosis of the disease

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Term

All PEG members will commit to serve on an ad hoc basis until the evaluation of the product in question has been completed, including post listing data. WHO may terminate a member's membership at any time prior to his/her term.

Chair

A Chair will be selected by the WHO PQ Secretariat from among the PEG members.

The Chair is responsible for:

- chairing the meeting(s) of the PEG;
- managing communications with the WHO PQ Secretariat (including submitting adopted reports to the PQ focal person)
- managing the process of review, consolidation of any LOQs and preparation and approval of agendas and reports;
- ensuring compliance with time frames.

Operation

Schedule of the PEG activities

The WHO PQ Secretariat will act as secretariat to the PEG and will facilitate the documentation and minutes for the PEG meetings. As such, the WHO PQ Secretariat will distribute a submission to the members of the PEG, convene virtual or face-to-face meetings for deliberations and assist the Chair in the preparation of proposed agendas and reports.

The WHO PQ Secretariat will not participate in the deliberations and taking of decisions by the PEG.

Once the PQ focal point has provided the Chair and other members of the PEG with the submission, the experts will normally have 3 months to review the information received and prepare a report. If additional information is required, each expert will prepare questions to be added to the LOQ and submit these to the Chair. In case the submission is received after a PHE has been declared, the timeline will be reduced to 1 month, provided the submission is complete. The Chair may coordinate a discussion among PEG members as required. The Chair will consolidate the LOQ and will send it to the PQ focal person. Once the responses are received, each expert will report to the Chair if the answers are satisfactory or if there are inadequacies. There may be more than one round of LOQs, until no further information is required or forthcoming from the applicant. Based on the information available, the Chair will prepare a consolidated report (template in Annex 7) and will circulate to all PEG members for adoption. The PEG will adopt its reports and develop its recommendations by consensus. Any dissenting views will be noted in the report.

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The timeline to submit the consolidated report of the PEG to WHO will depend on the number of questions, the time the applicant takes to respond, and the volume of information sent in the responses, among other factors.

If new data becomes available, the WHO PQ focal person will call the same PEG to review the information and update its report accordingly.

Management of communications

The PQ focal person will manage all communications between the PQ Secretariat and the PEG, and with the applicant, respectively.

For each review the focal person will:

a) provide the Chair and other members of the PEG with the submission received and electronic copies of all relevant WHO recommendations and guidelines as well as relevant guidance documents from regulatory bodies, relevant scientific meeting reports and scientific publications;

b) communicate to the applicant that the submission will be reviewed by the PEG according to the EUL procedure. The timeline for completion will depend on the need for clarifications and additional information requested by the PEG;

c) facilitate the arrangements for teleconferences, face to face meetings and any other means of communication among members of the PEG;

d) monitor progress with the PEG Chair;

e) submit LOQs to the Applicant, and forward responses submitted by the applicant to the PEG;

f) assist the PEG Chair in the preparation of draft agendas and reports, receive the final report with recommendations from the PEG Chair, and formally close the review. Should no additional data become available before a public health emergency occurs that justifies the use of the product, WHO may submit, the final report to the TAG-EUL. If additional data are submitted (i.e. updates on clinical trial results, completion of validation of processes and tests, etc.), the PEG will be requested to update its final report and submit the updated final report to WHO, through the Chair. The report shall be prepared using a standardized format (Annex 7) that will include an executive summary, the assessment of the information reviewed, List of Questions and responses and the final recommendation.

All PEG recommendations are advisory to WHO, who retains full control over any subsequent decisions and actions, including whether or not to publish the findings and recommendations of the PEG in a WHO EUL public report and whether or not to submit the report of the PEG to the TAG-EUL.

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Terms of Reference for the Technical Advisory Group for Emergency Use Listing (TAG-EUL)

Background

In the context of the World Health Organization (WHO) procedure for emergency use listing of medical products, the WHO PQ Secretariat will require advise from an independent advisory group known as the Technical Advisory Group for Emergency Use Listing (TAG-EUL).

There will be three TAG-EULs, one for each product stream under the EUL (vaccines, medicines and IVDs):

- TAG-EUL-V: for listing of vaccines, and will be selected, convened and coordinated by the Vaccine PQ Team Lead
- TAG-EUL-M: for listing of medicines and will be selected, convened and coordinated by the Medicines PQ Team Lead
- TAG-EUL-D: for listing of Diagnostics and will be selected, convened and coordinated by the In Vitro Diagnostics PQ Team Lead.

The experts will be selected from a pre-established roster, according to the requirements for evaluation under the EUL procedure.

Members must respect the impartiality and independence required of WHO. In performing their work, they may not seek or accept instructions from any Government or from any authority external to the Organization. They must be free of real, potential or apparent conflict of interest. To this end, proposed members will be required to complete a declaration of interest form and their appointment, or continuation of their appointment, will be subject to the evaluation of completed forms by the WHO Secretariat, determining that their participation would not give rise to a real, potential or apparent conflict of interest.

Information and documentation to which members may gain access in performing TAG-EUL related activities will be considered as confidential and proprietary to WHO and/or parties collaborating with WHO, including in particular, but not limited to, the applicants. TAG-EUL members shall not purport to speak on behalf of, or represent, the TAG-EUL or WHO to any third party, and treat the deliberations of the TAG-EUL ad strictly confidential. All proposed members will be required to commit to an appropriate confidentiality undertaking and agree to provisions on ownership. To this end, each member will be required to enter into a Memorandum of Agreement with WHO.

Functions

The function of the TAG-EUL is to provide a recommendation on whether or not an unlicensed medical product should be listed for emergency use under the EUL procedure once a PHE occurs, and if so, under what conditions.

In formulating its recommendation, the TAG-EUL will use any information deemed critical by WHO for consideration by the TAG-EUL. This may include the report on quality, safety and

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efficacy or performance, prepared by the Product Evaluation Group (PEG), including the initial evaluation and any updates based on additional information submitted by the applicant

The TAG-EUL will furthermore consider any emergency program needs when applicable, as well as any additional information which the TAG-EUL may request from the PQ Team or the applicant through the PQ focal person.

The report prepared by the TAG-EUL should follow the template in Annex 7 and will be submitted by the Chair to WHO/PQ team Lead for the product stream.

Membership

1) TAG-EUL-V

The TAG-EUL-V consists of members from the established roster of experts and should include:

- one member with expertise in the epidemiology of the disease that should be prevented with the vaccine in question;
- one member with regulatory expertise relating to vaccine evaluation and risk management plans;
- one or more members from the NRA of the affected countries
- one member from the PEG-V with expertise in quality assessment
- one member from the PEG-V with expertise in clinical assessment
- one or more members (non-expert) from the affected region who are informed and representative of the local community viewpoint may be included at the discretion of WHO .

2) TAG-EUL-M

The TAG-EUL-M consists of members from the established roster of experts and should include:

- one member with expertise in the epidemiology of the disease or condition of interest.
- one member with regulatory expertise relating to the product and potential risk management plans
- one or more members from the NRA of the affected countries
- one member from the PEG-M with expertise in quality assessment
- one member from the PEG-M with expertise in clinical assessment
- one or more members (non-expert) from the affected region who are informed and representative of the local community viewpoint may be included at the discretion of WHO.

3) TAG-EUL-D

The TAG-EUL-V consists of members from the established roster of experts and should include:

- one member with expertise in quality management systems for IVDs
- one member with expertise in validation and verification studies and labelling

Term

All TAG-EUL members will commit to serve on an ad hoc basis until the process of developing the required recommendation has been completed.

Chair

A Chair will be selected by the WHO PQ Secretariat from among the TAG-EUL members.

The Chair is responsible for:

- chairing the meeting (s) of the TAG-EUL
- managing communications with the WHO PQ Secretariat (including submitting adopted reports to the PQ focal person);
- managing the process of review and preparation and approval of agendas, records and reports;
- assuring compliance with time frames;

Operation

Schedule of the TAG-EUL activities

The WHO PQ Secretariat will convene the members of the TAG-EUL on short notice in a virtual or face to face meeting and provide them with the information deemed critical by WHO for consideration by the TAG-EUL. This may include the consolidated report prepared by the PEG for the specific product and any other data considered relevant for the discussions.

The TAG-EUL should in principle submit its recommendation to WHO within five (five) working days after the virtual or face to face meeting. If additional information is requested, a recommendation should in principle be issued within three days of receipt of this information.

The Chair will prepare a consolidated report (template in Annex 7) and will circulate to all TAG-EUL members for adoption. The TAG-EUL will adopt its reports and develop its recommendations by consensus. Any dissenting views will be noted in the report.

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Management of communications between the WHO PQ Secretariat and the TAG-EUL

A focal person, designated by the WHO PQ Secretariat, will manage all communications between the PQ Secretariat and the TAG-EUL and the PQ Secretariat and the applicant respectively.

For each review the WHO PQ focal person will:

- provide the TAG-EUL Chair with the information deemed critical by WHO for consideration by the TAG-EUL. This may include the consolidated report prepared by the PEG for the specific product and any other data considered relevant for the discussions;
- communicate to the applicant that the submission will be reviewed by the TAG-EUL according to the EUL procedure and the expected timeline for completion;
- facilitate the arrangements for teleconferences, face-to-face meetings and any means of communication among members of the TAG-EUL;
- monitor progress, with the TAG-EUL Chair, of each review;
- manage communications with the applicant as required;
- assist the TAG-EUL Chair in the preparation of draft agendas and reports and receive the final report with the recommendations from the TAG-EUL Chair and formally close the review. The report shall be prepared using a standardized format (Annex 7) that will include the recommendation (positive or negative) and a summary justification.

All TAG-EUL recommendations are advisory to WHO, who retains full control over any subsequent decisions and actions. WHO also retains full control over the publication of the reports of the TAG-EUL, including whether or not to publish to share them with Members States and UN procurement agencies.

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Memorandum of Agreement - Terms and Conditions for Temporary Advisers

I, the undersigned, in accepting to act as a Temporary Adviser to the World Health Organization (WHO), agree to the following:

1. RELATIONSHIP BETWEEN THE PARTIES

The execution of the work as Temporary Adviser does not create any employer/employee relationship as between WHO, on the one hand, and me and/or persons claiming under me, on the other hand. Thus, WHO shall not be liable to me or any other person whatsoever for any damage, loss, accident, injury, illness and/or death sustained by me in connection with, or as a result of, my assignment as Temporary Adviser to WHO, including travel.

2. TRAVEL COSTS, PER DIEM AND INCIDENTALS

I understand that my travel, per diem and incidentals will be paid by WHO, in accordance with WHO rules described in Annex 1 attached hereto.

3. CONFLICT OF INTERESTS

I agree to truthfully complete the Declaration of Interests for WHO Experts and disclose any circumstances that may give rise to a real, potential or apparent conflict of interest in relation to my work as Temporary Adviser. I will ensure that the disclosed information is correct and will truthfully declare that no other situation of real, potential or apparent conflict of interest is known to me. I undertake to promptly inform WHO of any change in these circumstances, including if an issue arises during the course of my work as Temporary Adviser. I understand and agree that this Memorandum of Agreement may be cancelled by WHO if WHO determines that the information disclosed by me in the Declaration of Interests requires modification or cancellation of the invitation extended to me to serve as Temporary Adviser to WHO.

4. INSURANCE

I agree that the insurance arrangements set forth below are being made by WHO without any prejudice whatsoever to section 1 above. Thus, I agree that WHO shall not be liable for any damage, loss, accidents, injury, illness and/or death sustained by me in connection with, or as a result of, my assignment as Temporary Adviser to WHO, including travel.

While travelling, my baggage and personal effects will be insured by WHO up to an amount of US$ 5000 (five thousand United States dollars). This insurance covers all hand baggage carried by me with the exception of documents, travel tickets, currency/cash/travellers cheques, stamps, stamped paper, identity papers, household goods and *objets d'art* (art works). Personal computers and accessories are also not included in WHO's personal baggage insurance cover unless it is noted on the travel authorization that a personal computer is required during the journey. Laptops must be hand-carried on board airplanes and not checked as registered baggage. Fees to replace stolen travel tickets, credit cards and official documents may be claimed under the insurance policy.

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Annex 2: Pre-submission meetings

Introduction

Pre-submission meetings are an important element in the pre-emergency phase of the EUL procedure. They provide an opportunity for the applicant to meet the WHO/PQT team that is responsible for the determination of eligibility of their product, and the initial assessment of their submission.

A pre-submission meeting allows WHO/PQT to have an overview of the product and a) ensure that the applicant has substantial information for a submission, b) provide general guidance on how to proceed with the application and dossier, and c) provide guidance on identified issues that should be dealt with prior to submission. At the same time, it is an opportunity for the applicant to: a) introduce and discuss the intended dossier, b) raise questions and gain valuable feedback and c) address issues prior to submission. The pre-submission meeting aims at enabling an applicant to submit a dossier that may proceed more quickly through the screening and subsequent stages of assessment.

A pre-EUL submission meeting should be planned as early as possible. The meeting should have a defined agenda and clear objectives to avoid as much as possible the need for further clarifications after the meeting.

To request a pre-submission meeting, the applicant must send the completed Pre-submission Meeting Request Form (see below) to the Prequalification Team Coordinator with copy to the relevant Team Lead. The Team Lead will reply to the applicant with a proposed date for the meeting as appropriate and the deadline to submit the information package. The applicant must send the list of proposed participants (up to a maximum of 10 participants per applicant) not later than 15 days before the meeting. The information package should be sent not later than 10 business days before the proposed meeting date.

The PQ Team Lead may invite members of the roster of experts to join the PQ team for the pre-submission meeting.

The Meeting

Meetings are organized by the PQT Team Lead and will be held at WHO premises or by audio/video conference. The time allocated will not exceed 3 hours, depending on the agenda prepared by PQT based on the information package received, the planned presentations and the questions submitted in advance by the applicant.

The manufacturer will record meeting minutes, including summary of information presented, the questions raised and the responses, as well as follow up actions if applicable. These will be sent to WHO within 15 days for final review and comments.

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Pre-submission meeting request form
EUL ASSESSMENTS

Please complete each section of this application form and submit electronically as a Word document to the PQ Team Lead as appropriate.

Vaccines: whoeul@who.int

Medicines: prequalassessment@who.int

IVDs: diagnostics@who.int

Attachments in electronic format that are 8MB or less in size can be sent by email with the completed pre-submission meeting request form, including a proposed agenda for the meeting. Attachments in electronic format that are larger than 8MB should be submitted on CD/DVD, or else be printed and sent by courier or surface mail to the relevant PQ Group Lead, WHO Prequalification Team, World Health Organization, 20 avenue Appia, 1211 Geneva, Switzerland.

Contact Details

Applicant (name of manufacturer)	
Contact person responsible for this application	
Contact person's job title/position	
Contact details (Including full postal address, phone, fax, email)	

Meeting Details

Type of meeting requested

Face-to-face ☐ Teleconference ☐

Brief statement of the intended dossier (INN/strength/dosage form), or IVD type/analyte detected, etc. and the expected date for submission to WHO for EUL

Specific objectives/outcomes expected from the meeting

Preliminary proposed agenda including estimated time needed for each agenda item (up to a maximum of 3 hours for the entire meeting) and designated speaker(s)

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List of specific questions by technical area

List of all individuals (including titles) who will attend the proposed meeting from the applicant's organization and/or consultants (up to a maximum of 10 proposed participants).

Proposed date(s) and time(s) for the meeting

Additional information is attached: Yes ☐ No ☐

Additional information will be forwarded separately: Yes ☐ No ☐

Completed by: Date:

For WHO internal use Only

Internal Reference	
Scheduled date and time of meeting	
Location	

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Annex 3: Application letter model

[Name of the Director of PQT]

World Health Organization

Team Lead **[product stream]** assessment Prequalification Team

Regulation of Medicines and other Health Products

CH-1211 GENEVA 27

SWITZERLAND

Date

Product: [name of the product]

Subject: Letter of application for Emergency Use Listing (EUL) of [name of product]

Contact person: [name of applicant's contact person]

Title

Tel:

Email:

Dear [name of Team Lead]

Following our pre-submission meeting on [date of pre-submission meeting], we hereby confirm that [name of the company] intends to submit the dossier for EUL assessment on [intended date of submission].

{name of product] is a [type of product, presentation].

The target in indication for [name of product] is [description of intended use].

The product has been granted [authorization of emergency use] by [name of National Regulatory Authority, Country].

[Signature, name, title and date]

CC: Name of the relevant PQT Team Lead

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Annex 4: Letter of Agreement

WHO Emergency Use Listing Procedure - Letter of Agreement
Product name: [insert full product name]
Application number: [insert application number]

Dear [insert salutation and last name],

This letter is with reference to the application dated [insert day / month / year] submitted by [insert full legal name of applicant] (hereinafter **"you"** or the **"applicant"** the World Health Organization (WHO) for the assessment of the **[insert full name of product]** product under the WHO Emergency Use Listing (EUL) Procedure (such applica is hereinafter referred to as your **"application"**).

Your application been given the following WHO reference number: **[insert application number]**. Please use this reference number in all future communications pertaining to this application. Receipt of this letter does not reflect a decision on EUL li of the **[insert full name of product]** product. This letter should not be used to inform procurement, as it does not constitute an endorsement or WHO EUL listing of the final product.

Please be advised that the signature and completion (duly and in full) of this let agreement by the applicant is a prerequisite for WHO proceeding with the EUL assessm of your application concerning the **[insert full name of product]** product. The EUL assessment of your application *will not proceed* until this letter of agreement has been and fully signed, completed and dated by the applicant, and returned to WHO, as indic in this letter.

With respect to your application under the EUL Procedure, by signing this letter of agreement, the following points are hereby accepted and agreed to by the applicant:

1. The applicant confirms that it has read, agrees with, and will adhere to and com with all of the provisions, terms and conditions of the EUL Procedure and of this letter of agreement.

2. The applicant represents, warrants and shall ensure that all of the applicant's suppliers, service providers, manufacturers and other contractors for the produ (hereinafter collectively referred to as **"Contractors"**) have been legally bound b and have agreed to adhere to and comply with, all of the provisions, terms and conditions of the EUL Procedure and of this letter of agreement.

3. The applicant confirms that it is the manufacturer of, and that it has intellectual property ownership of or has obtained all necessary rights to, the product subm for assessment under the EUL Procedure (the **"product"**). If the applicant has concluded any agreements or otherwise established any arrangements with an third party (including, without limitation, with any Contractors) regarding the production and/or distribution of the product, then the applicant: (a) must clea

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state the same in the information package presented to WHO in the pre-submission meeting, and (b) shall ensure that all such third parties comply with the obligations under paragraph 2 above. In addition, the applicant is responsible for obtaining all consents, cooperation, assistance and information from any such third party (including, without limitation, any Contractor) as are necessary or reasonably requested by WHO in connection with the EUL process.

4. *For in vitro diagnostics only*:

   4a) The applicant understands and agrees, and shall ensure that each Contractor understands and agrees, that WHO reserves the right to require the product to undergo a performance evaluation conducted by an independent laboratory commissioned by WHO and/or to require the product to undergo blinded testing of a performance panel as requested by WHO. Any such performance evaluation testing shall be conducted using the protocol and technical criteria established by WHO. For the avoidance of doubt, WHO may exercise its aforementioned rights at any time during the EUL assessment process and/or after the product has been granted EUL recommendation.

   4b) The applicant understands and agrees, and shall ensure that each Contractor understands and agrees, that in the event WHO exercises any of its rights described under paragraph 4a) above, then the applicant shall provide, and shall ensure that each Contractor provides, sufficient quantities (as determined by WHO) from different lots of the product, as required by WHO, for the relevant performance evaluation and/or blind panel testing, as applicable, of the product; and such quantities of the product shall be provided at no charge to WHO and/or any relevant evaluating laboratories collaborating with it. The applicant further understands and agrees, and shall ensure that each Contractor understands and agrees, that the product submitted for the performance evaluations and/or blind panel testing, as applicable: (i) shall be identical to the product described in this letter; (ii) shall have a minimum shelf-life of six months at the time of delivery to the laboratory; and (iii) shall be sent **Free Domicile** in accordance with detailed shipping instructions which shall be given to the applicant in due time. If necessary, the applicant shall also make available, and shall ensure that each Contractor also makes available, any special equipment needed to perform the performance evaluation of the product at no charge to the WHO and/or any relevant evaluating laboratories collaborating with it (customs declaration and payment of customs duties, transport, etc., shall be taken care of by the applicant).

5. The applicant understands and agrees, and shall ensure that each Contractor understands and agrees, that WHO will have absolute, exclusive, unfettered control over the manner in which the EUL assessment is carried out, including the publication of the results of the EUL assessment, regardless of the outcome.

6. The applicant also understands and agrees, and shall ensure that each Contractor understands and agrees, that WHO reserves the right to use, publish, issue, share

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with national regulatory authorities (NRAs) and other relevant authorities of WHO Member States and/or with United Nations agencies and other relevant intergovernmental organizations, and/or make publicly available any outcomes, reports, notices and/or results—whether in draft or final form, and whether positive or negative—arising from or relating to the EUL assessment process and/or any listed product and/or any confidential information (as defined in the EUL Procedure) to which WHO may gain access in the course of the EUL process. WHO's aforementioned rights shall be exercised in accordance with the provisions of the EUL Procedure, including but not limited to its provisions regarding the protection of any commercially sensitive information of the applicant and/or any of the manufacturers.

7. The applicant acknowledges and agrees, and shall ensure that each Contractor acknowledges and agrees, that WHO shall have the right to share with the applicant any reports, documents and/or correspondence regarding any inspections conducted by or on behalf of WHO in connection with the EUL assessment of the product. In this respect, it shall be the applicant's sole responsibility to promptly ensure that appropriate confidentiality obligations/arrangements are agreed to and put in place among the applicant and its Contractors to enable WHO to fully exercise its aforementioned right.

8. For the sake of good order, the applicant acknowledges and agrees, and shall ensure that each Contractor acknowledges and agrees, that it is not in WHO's mandate to issue any approvals, certificates or licenses for medical products. As that responsibility lies with the regulatory authority of each country, it is thus the sole prerogative of national authorities to decide whether or not to allow the emergency use of an unlicensed product in their country. Furthermore, the applicant acknowledges and agrees, and shall ensure that each Contractor acknowledges and agrees, that WHO does not, as a matter of policy, endorse any specific commercial product over others. The purpose of the WHO EUL of medical products is to provide guidance to interested UN agencies and WHO Member States in determining the acceptability of using a specific product in the context of a public health emergency. In this regard, the applicant acknowledges and agrees, and shall ensure that each Contractor acknowledges and agrees, that the results of the EUL assessment, the participation in the WHO EUL process, the inclusion of any product in the EUL list and/or the WHO name and emblem, shall not be used by or on behalf of the applicant or any Contractors for any commercial and/or promotional purposes.

9. The applicant understands and agrees, and shall ensure that each Contractor understands and agrees, that by virtue of WHO's status as a Specialized Agency of the United Nations, WHO, its officials and experts performing missions for WHO (including, e.g., inspectors) enjoy privileges and immunities under national and international laws and conventions, including without limitation: (i) the Convention on the Privileges and Immunities of the Specialized Agencies, adopted by the General Assembly of the United Nations on 21 November 1947 (the **"1947 Convention"**), and (ii) the Unites States' International Organizations Immunities Act of 1945 and Executive Order 9698 relating thereto (collectively, the **"IOIA"**). Nothing contained in or in connection with this EUL procedure and/or any assessment process hereunder

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will constitute or be deemed as a waiver of any of the privileges or immunities which WHO, its officials and/or experts performing missions for WHO enjoy pursuant to the 1947 Convention, the IOIA or otherwise under any national or international law, convention or agreement, and/or as submitting WHO, its officials and/or experts aforesaid to any national court jurisdiction.

10. Any and all claims or disputes arising from or in connection with this EUL procedure, including, but not limited to, any rejection of an application, any assessment hereunder and/or any decision whether or not to grant an EUL recommendation for an evaluated product (hereinafter, collectively, **"Disputes"**) must be submitted in writing to WHO's Director of RPQ, with a copy to the relevant PQT Team Lead. WHO's Director of RPQ, or one of his/her authorized representatives, will acknowledge in writing receipt of the relevant Dispute and will conduct an investigation into the Dispute within 30 days of receipt. Following the investigation, WHO's Director of RPQ, or one of his/her authorized representatives, will provide a written response to the applicant/manufacturer that submitted the Dispute. If the applicant/manufacturer is dissatisfied with the written response, then it must object in writing to WHO within 30 days of the date of WHO's aforementioned written response. In the event that the applicant/manufacturer does not object to WHO in writing within such 30 day period, then the content of WHO's written response (including, without limitation, any findings or decisions contained therein) will be final and can no longer be challenged by the applicant/manufacturer in any way. However, if the applicant/manufacturer does object to WHO in writing within such 30 day period, then the Dispute will be referred to WHO's Director-General for his or her decision which will be final and binding on the parties.

11. The applicant should please: (i) arrange for this letter of agreement to be duly and fully signed, completed and dated by a duly authorized representative of the applicant, and (ii) **by no later than [insert date of letter plus 30 calendar days],** return the original of this letter of agreement once fully signed (i.e., once duly and fully signed, completed and dated by a duly authorized representative of the applicant) to WHO's attention by pre-paid registered mail or pre-paid international courier. An electronic copy of this letter of agreement once fully signed should also be sent to WHO by e-mail to **[insert email for relevant WHO/PQ product team]**.

Thank you in advance for your collaboration.

Yours sincerely,

[Name of WHO Signatory]
[Title of WHO Signatory]
Prequalification Unit
Regulation and Prequalification Department

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By signing in the spaces provided below, each of the applicant and the manufacturers agrees to the terms of this Letter of Agreement, dated [insert day / month / year], with WHO reference number: [insert reference number of application]

Agreed to and accepted by and on behalf of the applicant: [insert full legal name of the applicant]

Commercial name of product: **[insert full name of the product]**

Signature of duly authorized representative of the applicant: . . . . . .

Name of duly authorized representative of the applicant: . . . . . .

Title of duly authorized representative of the applicant: . . . . . .

Date: . . . . . .

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Annex 5: Essential data requirements for EUL for vaccines, medicines and in vitro diagnostics

Since the expectation is that the manufacturing/quality control and clinical development of the product submitted for EUL will continue to product licensure and ultimately be submitted for prequalification, the submission for EUL of medicines and vaccines should follow the ICH CTD format. In the CTD dossier, sections for which no information is available at the time of the initial submission should be indicated as "data or information not available", "study ongoing" or "not applicable" as the case may be.

For IVDs, the dossier structure to be used for the submissions has been developed by the IVD PQT. Applicants should follow the dossier structure requirements laid down in documents *PQDx_018 Instructions for compilation of a product dossier* and *PQDx_049 Product dossier checklist*. The instructions for compilation of a product dossier and the product dossier checklist can be found on the PQ website: http://www.who.int/diagnostics_laboratory/evaluations/PQDxInfo/en/

For IVDs, the dossier content requirements may differ depending on the analyte being detected and clarification of specific data requirements will require discussion between the applicant and WHO in advance of submission.

Vaccines

Clarification of specific data requirements will require discussion between the applicant and WHO. Applicants are highly encouraged to contact WHO as early as possible to discuss specifics of the application.

A. Manufacturing and quality control Data:

1. Full characterization of cell banks according to WHO Technical Report Series (TRS) 978, and any subsequent updates.
2. Full characterization of master and working seed organism(s), based on reference to the most appropriate WHO TRS.
3. Process validation (based on quality risk assessment for the development stage) and demonstration of consistency of production at the production scale used for the lots to be distributed. If deemed appropriate by WHO data on clinical batches with a commitment to complete validation on production batches and to submit the data as part of lot release review may be considered.

   N.B., if full characterization is not possible at the time of submission, adequate justification must be submitted as to why not, and a plan must be presented to address the data gaps. Validation of potency tests and other critical assays. If novel test methods have been developed, full description of the test development and qualification must be presented.
4. Justified specifications for starting material, intermediates, and final products.

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5. Stability data for the vaccine produced at the scale produced for the lots to be supplied. If available, accelerated stability data must be included. For vaccines being assessed for emergency use, WHO and the Advisory Committee for the Emergency Use Listing (TAG-EUL-V – see below), when convened, will consider programmatic suitability and may consider candidate vaccines with characteristics that would not be accepted for prequalification.

    a) Vaccines requiring storage at less than -20°C are generally not accepted for prequalification. However, under this emergency procedure, such vaccines can be considered. Upon receipt of such an application, WHO staff responsible for emergency response vaccine deployment will be informed by the WHO EUL Secretariat, and will be requested to evaluate and consider whether recipient countries will require assistance with regards to infrastructure for vaccine storage and distribution at required temperatures.

    b) Routinely, if a vaccine presented for prequalification requires storage below +2°C during its shelf-life period, it should have a minimum period of storage between +2°C and +8°C of 6 months. Under this emergency procedure, vaccines with a shelf life at +2 to +8°C of less than 6 months may be considered. The application should include stability data at +2 to +8°C to determine the minimum acceptable storage period at +2 to +8°C. Upon receipt of such an application, WHO staff responsible for emergency response vaccine deployment will be informed by the WHO EUL Secretariat, and will be requested to evaluate and consider whether recipient countries will require assistance with regards to infrastructure for vaccine storage and distribution at required temperatures. Routinely, multi-dose vaccines for prequalification should contain adequate preservative, unless they are live-attenuated vaccines (where the preservative may have an adverse effect on the viability of the microbe). However, if a multi-dose vaccine submitted under this emergency procedure does not contain a preservative, information/plans on how such a vaccine could be safely managed in the field should be submitted.

6. Inspection report(s) from the responsible NRA or from the WHO inspection team showing compliance with GMP requirements – if available, and;

7. Process changes: by the time of submission, it is likely that the manufacturing process is not finalized and that numerous changes will have to be applied after the first listing. These changes should be submitted as updates as indicated in section 5.1.1.9.

B. Non-clinical and Clinical Data:

Non-clinical data demonstrating acceptable safety, immunogenicity, and efficacy – if available- in the most appropriate animal model. The applicant must justify the choice of animal model. If the non-clinical package is not complete at the time of submission, the applicant must submit adequate justification for the lack of complete data and a plan and timeline for submitting those data.

Clinical data demonstrating the appropriate dose to be used and initial acceptable safety and immunogenicity in the population in which the vaccine will be used in the context of the public health emergency

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Preliminary data showing some efficacy– if available. If preliminary human data showing some efficacy are not available for the vaccine under consideration and if not imminently available for other vaccines being concurrently developed, WHO will consider whether the preponderance of evidence from the non-clinical, and early human studies justifies considering the immunogenicity data as a potential surrogate that is thought to be reasonably predictive of clinical efficacy. In such cases, the emergency use listing can proceed, provided there are trials underway that will ultimately provide confirmation that immunogenicity is a surrogate. Safety and immunogenicity data from other vaccines made by the manufacturer using the same product platform may be considered as supportive data for review if applicable.

Note: products developed under the animal rule will also be considered for review.

C. Plan for monitoring and reporting of adverse events

Since the vaccines listed under the EUL procedure have not been licensed for use in routine immunization settings, post marketing data would not be available at the time of application, Therefore, the manufacturer should discuss with WHO in pre-submission meetings, the plans to ensure the collection and analysis of information on the safety and effectiveness of the product during the period when the EUL listing would be in effect and for a reasonable time following such period. WHO encourages applicants to discuss proposals for active data collection and follow-up mechanisms to capture adverse event information under the EUL during the pre-submission meetings.

D. Labelling:

1. Summary of product characteristic (information for healthcare provider)
2. Patient information leaflet
3. Container labelling
4. Any other instructional materials provided to the user.
5. A plan to help assure that prospective recipients and healthcare providers are adequately informed about the uncertainties regarding both the potential benefits and risks.

Note: When the product is listed, the labelling should clearly indicate that that product is for emergency use only.

E. Environmental Risk Assessment (ERA)

If the product contains a Genetically Modified Organism, the applicant must submit a completed Environmental Risk Assessment report.

Medicines

Clarification of specific data requirements will require discussion between the applicant and WHO. Applicants are highly encouraged to contact WHO as early as possible to discuss specifics of the application.

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A. Manufacturing and Quality Data:

1. Information on the active ingredient(s) and finished product, including characterization (including known and potential impurities), composition, preparation, controls (specifications, analytical methods and their validation).

2. A list of intended changes for scale up, if any, along with a discussion on impact of these changes on the quality and safety/efficacy profile of the product.

3. Stability data.

4. Inspection report(s) from an SRA/WLA or from a WHO prequalification inspection showing compliance with GMP requirements for other, but similar products. Based on the acceptability of the SRA/WLA report, WHO may or may not need to perform its own assessment of GMP compliance.

B. Non-clinical and Clinical Data:

1. All relevant *in vitro* and *in vivo* pharmacodynamic (PD) data, *e.g.*, on microbiologic/virologic activity (including any modelling performed).
2. Data on efficacy and safety in *in-vitro* tests and in animal model(s) under well-controlled and documented conditions. The preferred model depends on the disease and may vary according to the medicine's mechanism of action. The applicant must justify the choice of animal model.
    a) Evidence of efficacy should include improved survival and/or reduced morbidity of animals in the preferred model under relevant conditions. Surrogate markers, validated or reasonably expected to predict efficacy, would be supportive.
    b) All available evidence of the medicine's activity *in vitro* and in other animals, together with pharmacokinetics and efficacy in humans, also against other diseases should be submitted
3. A rationale should be provided for the proposed dosing in humans, with reference to drug exposures shown to be safe and effective in suitable models. Ideally, human pharmacokinetic data should be available, demonstrating similar levels of the drug following administration at the proposed dose, compared to blood levels found to be safe and efficacious in the relevant animal model.
4. If human pharmacokinetic trials or studies in other indications at the exposure level proposed for treatment of the PHE disease have been conducted, assessment of safety using standard parameters (e.g., adverse events, clinical laboratory monitoring, etc.) will be done. This safety evaluation may be supplemented by any other non-clinical and clinical data at different exposure levels.
5. If available, clinical data demonstrating safety and efficacy at the proposed dose for PHE field use should be submitted.

C. Labelling

1. Summary of product characteristics (information for health care provider)

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2. Patient information leaflet
3. Primary and secondary labelling
4. Any other instructional materials provided to the user.
5. A plan to help ensure that prospective recipients and health care providers are adequately informed about the uncertainties regarding both the potential benefits and risks.

Note: When the product is listed, the labelling should clearly indicate that that product is for emergency use only.

In Vitro Diagnostics

Clarification of specific data requirements will require discussion between the applicant and WHO. Applicants are highly encouraged to contact WHO as early as possible to discuss specifics of the application.

A. QMS Review

A review of the manufacturer's quality management system (QMS) documentation and specific manufacturing documents is the first step in the process. At the conclusion of this step, WHO may either decide to proceed or to request further documentation, or to terminate the application. The decision to proceed with the assessment process will be made if there is sufficient evidence that the applicant is the manufacturer, that there is evidence of an adequate QMS in place, and that the requisite manufacturing capability exists.

- Evidence of implementation of a manufacturing quality management system (e.g., ISO 13485 certificate and most recent regulatory (or certification body) audit report, quality manual, exclusions or non-applications, list of valid quality management documentation, management review report);
- Details of the production workflow including QC points (in process and final release activities);
- Critical supplier list including supplied products (components/raw materials) and services;
- If the product was approved for Research Use Only (RUO), details on the experience with the product;
- Details on the manufacturing capacity (existing inventory, minimum time to provide finished product, maximum batch/lot size).
- Procedure/s relevant to control of non-conforming goods, including but not limited to procedures for corrective and preventative actions, recalls, field safety notices etc.

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B. Product dossier review

The second step is the assessment of the documentary evidence of safety and performance. It is acknowledged that many of the required studies to meet full regulatory requirements may not have been performed for IVDs undergoing EUL assessment. Based on the submitted documentation, a risk- based judgment will be made on whether there is a favourable benefit/risk profile. An initial evidence base that includes studies using banked specimens from previous studies, relevant studies in the literature, and studies using contrived specimens to supplement testing of clinical specimens including representative analytes may be acceptable in the absence of complete analytical and/or clinical performance studies, if this evidence base provides a reasonable assurance of safety and performance.

The outcome of this step will determine if the application will proceed to step 3, whether further documentation should be requested, or whether the application should be terminated.

The below sections should be submitted by the applicant, following the requirements laid down in documents *PQDx_018 Instructions for compilation of a product dossier* and *PQDx_049 Product dossier checklist*:

1. ***Product Information***

   a) Regulatory versions of this product7

   b) Product description including variants (configurations) and accessories

   c) Essential principles checklist

   d) Risk analysis and control summary

2. ***Design and Manufacturing Information***

   a) Product design

   - Design overview
   - Formulation and composition
   - Biological safety
   - Documentation of design changes

   b) Manufacturing processes

[7] The submitted version is defined by all of the documentation related to development, manufacture and intended use, labelling and post-market surveillance of the product and all the documented evidence supporting the safety and performance claims associated with that submission. If any aspect of this documentation differs in any way between the submissions to different regulatory authorities or assessment bodies (United States Food and Drug Administration, Health Canada, a Notified Body for CE marking, etc.) it is considered to be a different regulatory version.

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- Overview of manufacture
- Sites of manufacture

c) Key suppliers

3) Product Performance Specification, and Associated Validation and Verification Studies

a) Analytical performance

a.1. Stability of specimens

a.2. Validation of specimens

a.3. Metrological traceability of calibrators and control material values

a.4. Accuracy of measurement

a.4.1. Trueness

a.4.2. Precision (repeatability & reproducibility)

a.5. Analytical sensitivity (LOD & LOQ)

a.6. Analytical specificity

a.7. High dose hook effect

a.8. Measuring range of the assay

a.9. Validation of assay cut-off

a.10. Validation of assay procedure

a.11. Usability/human factors

a.12. Stability of the IVD

a.12.1 Claimed shelf-life[8]

a.12.2 In-use stability (open pack or open vial stability)

a.12.3 Shipping stability

b) Clinical evidence

b.1. Clinical/diagnostic sensitivity

b2. Clinical/diagnostic specificity

[8] Accelerated studies or extrapolated data from real time data are acceptable for initial shelf life claim but need to be followed up with real time stability studies.

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C. **Plan for monitoring and reporting of adverse events/incidents/non-conforming goods and processes**

In some jurisdictions, minimizing potential harm of an IVD listed for emergency use is achieved by active post-market surveillance. However, it cannot always be assumed that, in the public health emergency settings this EUL process serves, there are sufficient resources and institutions in place for any consistent effective surveillance. It will be critical for the manufacturer to detail which post-emergency-use-listing safety monitoring activities are planned if the EUL is granted.

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Annex 6: Criteria for selection of assessment pathways

a) Vaccines

For vaccines, the initial EUL assessment will use similar principles as those used for prequalification and take into account agreements with NRAs to share reports, past inspections of the manufacturer's facilities, the assessment of the manufacturer's quality systems and any record of performance of the manufacturer and its product (s).

The following criteria will be followed to determine the assessment approach

Table 1: Assignment of assessment category for vaccines

	Manufacturer with PQd vaccines	**Manufacturer without PQd vaccines**
Vaccine approved for emergency use by a stringent NRA/WLA for the target disease and agreement in place between WHO and the NRA for the exchange of information	A	C
Vaccine not approved for emergency use by a stringent NRA/WLA for the target disease or no agreement in place with the NRA	B	C

Table 2: Vaccines assessment approach for each category

Category	***Assessment approach***
A	*Abridged assessment, consisting of initial assessment of:* *- Report(s) from the responsible SRA/WLA (Summary basis for the emergency use approval or equivalent)* *- Programmatic aspects **
B**	*Abridged assessment, consisting of initial assessment of:* - Application (see content above) - Programmatic aspects
C	*WHO will conduct a full initial review of:* - Application (see content above) - Inspection report (conducted by WHO) - Programmatic aspects

* Programmatic aspects include: indication, dosage, conservative, storage temperature, autodisable syringe, etc.

** *Company has prequalified products, therefore, they have been inspected by WHO*

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a) Medicines

Table 3: Medicines assessment approach

	Assessment approach	**Inspection**
Product authorized for emergency use by an SRA/WLA for the target disease	Abridged assessment based on the SRA/WLA report	Desk review of available SRA/WLA inspection reports, and/or if required, inspection by WHO.
Product not approved for emergency use by an SRA/WLA for the target disease	Full assessment by WHO of the submitted dossier information. The review will also consider available assessment reports written by NRAs.[9]	Inspection by WHO and/or desk review of available WHO, SRA/WLA, or PIC/s member inspectorate reports[10]

b) In vitro diagnostics

Table 4: IVDs assessment approach

	Assessment approach	**Inspection**
Product assessed through another emergency mechanism of an acceptable standard?	Abridged initial assessment of reports	Desk review of the QMS
Product not assessed through another emergency mechanism of an acceptable standard?	Full initial assessment by WHO of the submitted documentary evidence	Desk review of the QMS and/or inspection if required

[9] Reports from some non-SRA/WLAs might be useful

[10] Inspections reports covering other but similar products.

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Abridged IVD EUL assessment

For IVDs, some submissions for WHO EUL may have undergone a previous assessment through other emergency mechanisms, for example, the US FDA Emergency Use Authorization (EUA) process. Where this is the case, it is not the intent of WHO to undertake duplicative work, if the review of the other emergency mechanism is deemed to be of a satisfactory standard. The ability to waive aspects of the EUL assessment in these circumstances can be applied to any of the two steps of the review.

However, WHO EUL is designed to provide a minimum level of assurance of the quality, safety, and performance of unlicensed products for the primary purpose of use in the setting of a current PHE. This focus means that WHO may still undertake some extra assessment activities if deemed necessary or request the dossier that was assessed previously through other emergency mechanisms.

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Annex 7: Template of Assessment reports

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Assessment Report

Product Evaluation Group - Vaccines (PEG-V)

Emergency Use Listing

Product

Manufacturer

WHO/PQT Focal Person	
PEG Chair	
PEG Reviewers	
Date of this report	

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1. Executive summary

1.1 The product

Description of the product, location of production, stage of clinical development.

1.2. Authorizations granted by the NRA responsible for the regulatory oversight of the product

Details of any kind of authorization for use granted for the unlicensed product for emergency use, or exceptional circumstances, etc.

1.3. Recommendation

Based on the review of the available data and the Applicant's response to the PEG LOQs on quality, safety and efficacy, this Committee considers that should a PHE occur justifying the need for the product before additional data on (quality), (safety) (efficacy) is provided as the development of the product advances, the risk-benefit balance of this product is

Positive
Negative

The major objections are related to the following deficiencies (indicate all that apply if the outcome is negative):

a) Quality

b) safety

c) efficacy/immunogenicity

d) GMP, GLP, GCP compliance

e) Other

2. Guidelines used for the assessment

List of guidelines from WHO and regulatory bodies, WHO recommendations, international guidance documents, scientific reports and publications and any other relevant documents that the PEG has agreed to use as a set of parameters to assess the information submitted for the product.

3. Scientific review of the submission

3.1. Quality assessment

3.1.1. Summary of reviewed information

3.1.2. Rounds of questions and answers from the applicant

3.1.3. Conclusion

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3.2. Non-Clinical assessment

3.2.1. Summary of reviewed information

3.2.2. Rounds of questions and answers from the applicant

3.2.3. Conclusion

3.3. Clinical assessment

3.3.1. Summary of reviewed information

3.3.2. Rounds of questions and answers from the applicant

3.3.3. Conclusion

3.4. GMP/GLP/GCP compliance

3.4.1. Summary of reviewed information

3.4.2. Rounds of questions and answers from the applicant

3.4.3. Conclusion

3.5. Proposed labelling

Summary of reviewed information

Rounds of questions and answers from the applicant

Conclusion

3.6. Benefit-risk assessment

3.7. Proposed post listing measures

4. Final remarks

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Assessment Report

Product Evaluation Group - Medicines (PEG-M)

Emergency Use Listing

Product

Manufacturer

WHO/PQT Focal Person	
PEG Chair	
PEG Reviewers	
Date of this report	

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1. Executive summary

1.1. The product

Description of the product, location of production, stage of clinical development.

1.2. Authorizations granted by the NRA responsible for the regulatory oversight of the product

Details of any kind of authorization for use granted for the unlicensed product for emergency use, or exceptional circumstances, etc.

1.3. Recommendation

Based on the review of the available data and the Applicant's response to the PEG LOQs on quality, safety and efficacy, this Committee considers that should a PHE occur justifying the need for the product before additional data on (quality), (safety) (efficacy) is provided as the development of the product advances, the risk-benefit balance of this product is

Positive
Negative.

The major objections are related to the following deficiencies (indicate all that apply if the outcome is negative):

a) Quality

b) Safety

c) Efficacy

d) GMP, GLP, GCP compliance

e) Other

2. Guidelines used for the assessment

List of guidelines from WHO and regulatory bodies, WHO recommendations, international guidance documents, scientific reports and publications and any other relevant documents that the PEG has agreed to use as a set of parameters to assess the information submitted for the product.

3. Scientific review of the submission

3.1 Quality assessment

3.1.1. Summary of reviewed information

3.1.2. Rounds of questions and answers from the applicant

3.1.3. Conclusion

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3. 2. Non-Clinical assessment

3.2.1. Summary of reviewed information

3.2.2. Rounds of questions and answers from the applicant

3.2.3. Conclusion

3.3. Clinical assessment

3.3.1. Summary of reviewed information

3.3.2. Rounds of questions and answers from the applicant

3.3.3. Conclusion

3.4. GMP/GLP/GCP compliance

3.4.1. Summary of reviewed information

3.4.2. Rounds of questions and answers from the applicant

3.4.3. Conclusion

3.5. Proposed labelling

3.5.1. Summary of reviewed information

3.5.2. Rounds of questions and answers from the applicant

3.5.3. Conclusion

3.6. Benefit-risk assessment

3.7. Proposed post listing measures

4. Final remarks

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Assessment Report

Product Evaluation Group - IVDs (PEG-D)

Emergency Use Listing

Product

Manufacturer

WHO/PQT Focal Person	
PEG Chair	
PEG Reviewers	
Date of this report	

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1. Executive summary

1.1. The product

Description of the product, location of production, stage of clinical development.

1.2. Authorizations granted by the NRA responsible for the regulatory oversight of the product

Details of any kind of authorization for use granted for the unlicensed product for emergency use, or exceptional circumstances, etc.

1.3. Recommendation

Based on the review of the available data and the Applicant's response to the PEG LOQs on quality, safety and performance, this Committee considers that should a PHE occur justifying the need for the product before additional data on (quality), (safety) (performance) is provided as the development of the product advances, the risk-benefit balance of this product is

Positive
Negative.

The major objections are related to the following deficiencies (indicate all that apply if the outcome is negative):

a) Labelling
    - Labels
    - Instructions for use

b) Product Performance Specifications, and Associated Validation and Verification Studies
    - Non-clinical evidence (analytical performance)
    - Clinical evidence

c) Quality management systems (QMS) requirements

2. Guidelines used for the assessment

List of guidelines from WHO and regulatory bodies, WHO recommendations, scientific reports and publications and any other relevant documents that the PEG has agreed to use as a set of parameters to assess the information submitted for the product.

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3. Scientific review of the submission

3.1. Labelling

3.2. Product information

3.3. Product Performance Specifications, and Associated Validation and Verification Studies

- Specimen type
- Analytical performance characteristics/non-clinical evidence
- Clinical evidence (clinical or diagnostic sensitivity and specificity)
- Intended testing population

3.4. Quality management system (QMS) requirements

3.5. Benefit-risk assessment

3.6. Proposed post listing measures

4. Final remarks

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Assessment Report

Advisory Group for EUL (TAG-EUL)

Emergency Use Listing

Product

Manufacturer

WHO/PQT Focal Person	
TAG-EUL Chair	
TAG-EUL members	
Date of this report	

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1. The product

Description of the product, location of production, stage of clinical development.

2. Authorizations granted by the NRA responsible for the regulatory oversight of the product

Details of any kind of authorization for use granted for the unlicensed product for emergency use, or exceptional circumstances, etc.

3. Information assessed by the PEG

4. Recommendation

Based on information and documentation submitted to the TAG-EUL (which includes [the report prepared by the PEG], [additional information from the applicant] and ……), and based on the deliberations among the members of this Committee, the Committee considers that since a PHE has been declared justifying the need for the product for emergency use, the risk-benefit balance of this product is:

Positive
Negative

Rationale for the decision: ……..

Therefore, the recommendation from this Group to WHO is to:

List

Not list

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Assessment Report Templates

List of acronyms

GCP	Good Clinical Practices
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
LOQ	List of Questions
NRA	National Regulatory Authority
PEG	Product Evaluation Group
QMS	Quality Management Systems

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Annex 8 Notes and disclaimers - EUL List of candidate products

General notes

- The medical products included in this list are unlicensed products, i.e. they have not been granted a marketing authorization by a national regulatory authority. This list is exclusively intended to assist interested UN procurement agencies and Member States in determining the acceptability of using a specific unlicensed product in the context of a public health emergency (PHE). The products included in this list have been evaluated based on a minimum set of available quality, safety, and efficacy data or performance and an agreed plan for their further development. It is the sole prerogative of national authorities to decide whether or not to allow the emergency use of an unlicensed products in their country. This list is updated regularly. Unlicensed products may be added to the list as and when (following the voluntary participation by relevant manufacturers) the available data on such products are evaluated and, if necessary, relevant sites are inspected by WHO, and are - at the time of evaluation - found to meet the requirements outlined in the EUL Procedure for a recommendation for the use of such products in the context of a PHE. WHO cannot in respect of any listed product represent that these requirements will continue to be met. WHO may suspend or remove products from the list based on information that may subsequently become available to it.
- The list is not an exhaustive list of products that may be used in a PHE. It reflects those unlicensed products which have been submitted to WHO for evaluation by interested parties.
- The fact that certain unlicensed products and suppliers are not included in the list does not mean that if evaluated, they would not be found to meet the above-mentioned requirements
- Inclusion in the list does not imply any approval or endorsement by WHO of the products and manufacturing sites in question (which is the sole prerogative of national authorities).
- This list may not be used by manufacturers and suppliers for commercial or promotional purposes.

Listing of products in the EUL list based on emergency approval by stringent regulatory authorities/WHO listed authorities

WHO may recognize the emergency evaluation and approval of products by regulatory authorities that apply stringent standards for quality, similar to those recommended by WHO, such as, but not limited to, the US Food and Drug Administration (USFDA), the European Medicines Agency (EMA) and Health Canada (HCnda).

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Suggestions relating to procurement

- Any interested UN procurement agency and Member States intending to use the EUL list of unlicensed vaccines for procurement and/or use should ensure that only products from the manufacturing sites mentioned in this list are supplied to it.

Disclaimer to the WHO EUL List Vaccines

1. Inclusion in this list does not constitute an endorsement of the products listed. WHO explicitly disclaims any warranty of the fitness of any listed unlicensed product for a particular purpose, including in regard to its safety and/or efficacy and/or performance.

2. WHO does not furthermore warrant or represent that:

a. the list is complete or error free; and/or that

b. the listed unlicensed products which have been found to meet the requirements outlined in the EUL Procedure for use in the context of a PHE will continue to do so; and/or that the unlicensed products listed have obtained emergency use approval for their specified use or any other use in any country of the world, or that their emergency use is otherwise in accordance with the national laws and regulations of any country, including without limitation, any patent laws.

3. In addition, WHO wishes to alert organizations and Members States relying on the EUL list that the improper storage, handling and transportation of medical products may affect their quality, safety, efficacy and performance.

4. WHO disclaims any and all liability and responsibility for any injury, death, loss, damage or other prejudice of any kind whatsoever that may arise as a result of or in connection with the procurement, distribution and use of any unlicensed product included in the list.

5. WHO disclaims any and all liability and responsibility for any loss, damage, liability or other prejudice of any kind whatsoever that may arise as a result of or in connection with any assessment and recommendation under the EUL procedure.

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Authors

The first proposed draft of the revised procedure was prepared by Liliana Chocarro-Consultant - WHO and presented to the EUL drafting group coordinated by Carmen Rodriguez – WHO: Regina Lehnert, Consultant – WHO; Raymond Corrin, Consultant – WHO; Ryoko Miyazaki-Krause – WHO; Elisabeth Pluut – WHO; Irena Prat – WHO; Mathias Stahl - WHO; Ute Ströher – WHO; Wondi Worku – WHO.

The final draft was circulated among other WHO units and posted on the WHO biologicals web site for public consultation. Comments were compiled and discussed among the drafting group and the final version prepared by Liliana Chocarro on the basis of comments received from all contributors and from the drafting group.

Acknowledgments

Acknowledgements are due to the following organizations and experts for their comments on the draft Emergency Use Listing Procedure: Bill and Melinda Gates Foundation; Coalition for Epidemic Preparedness Innovations; International Federation of Pharmaceutical Manufacturers & Associations; PATH; Office of the Assistant Secretary for Preparedness and Response within the United States Department of Health and Human Services; Global Health Security Initiative Medical Countermeasures Task Force including the Italian Ministry of Health – Italian Medicines Agency, the Public Health Agency of Canada and HHS; United States Food and Drug Administration; WHO - MSF Access Campaign; WHO Polio department; WHO Legal Office and David Wood independent contractor.

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Document 1.3

WHO COVID-19 pandemic declaration

Document URL

https://www.who.int/news/item/05-05-2023-statement-on-the-fifteenth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-coronavirus-disease-(covid-19)-pandemic

License

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World Health Organization

Statement on the fifteenth meeting of the IHR (2005) Emergency Committee on the COVID-19 pandemic

5 May 2023 | Statement | Reading time: 7 min (1792 words)

العربية | 中文 | Français | Русский | Español

The WHO Director-General has the pleasure of transmitting the Report of the fifteenth meeting of the International Health Regulations (2005) (IHR) Emergency Committee regarding the coronavirus 2019 disease (COVID-19) pandemic, held on Thursday 4 May 2023, from 12:00 to 17:00 CET.

During the deliberative session, the Committee members highlighted the decreasing trend in COVID-19 deaths, the decline in COVID-19 related hospitalizations and intensive care unit admissions, and the high levels of population immunity to SARS-CoV-2. The Committee's position has been evolving over the last several months. While acknowledging the remaining uncertainties posted by potential evolution of SARS-CoV-2, they advised that it is time to transition to long-term management of the COVID-19 pandemic.

The WHO Director-General concurs with the advice offered by the Committee regarding the ongoing COVID-19 pandemic. He determines that COVID-19 is now an established and ongoing health issue which no longer constitutes a public health emergency of international concern (PHEIC).

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The WHO Director-General considered the advice provided by the Committee regarding the proposed Temporary Recommendations and issued them as per the below statement. The WHO Director-General will convene an IHR Review Committee to advise on Standing Recommendations for the long-term management of the SARS-CoV-2 pandemic, taking into account the 2023-2025 COVID-19 Strategic Preparedness and Response Plan. During this transition, States Parties are advised to continue following the issued Temporary Recommendations. The Director-General expressed his sincere gratitude to the Chair, the Members, and the Advisors of the Committee for their engagement and advice during the last three years.

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Proceedings of the meeting

The WHO Director-General, Dr Tedros Adhanom Ghebreyesus, welcomed Members and Advisors of the Emergency Committee, who were convened by videoconference. He noted that the number of weekly reported deaths and hospitalizations continue to decrease, but expressed concern that surveillance reporting to WHO has declined significantly, that there continues to be inequitable access to life-saving interventions, and that pandemic fatigue continues to grow. The Director-General announced the publication of the 2023-2025 COVID-19 Strategic Preparedness and Response Plan which is designed to guide countries in transitioning to long-term management of COVID-19. This plan outlines important actions for countries to consider for five areas: collaborative surveillance, community protection, safe and scalable care, access to countermeasures, and emergency coordination. The Director-General thanked Professor Houssin for his leadership in guiding the Committee over the last three years and each of the Committee Members and Advisors for their expertise, dedication, and commitment.

The Office of Legal Counsel's representative briefed the Committee Members and Advisors on their roles, responsibilities, and mandate under the relevant articles of the IHR. The Ethics Officer from the Department of Compliance, Risk Management, and Ethics reminded Members and Advisers of their duty of confidentiality as to the meeting discussions and the work of the Committee, as well as their individual responsibility to disclose to WHO in a timely manner any interests of a personal, professional, financial, intellectual, or commercial nature that may give rise to a perceived or direct conflict of interest. No conflicts of interest for the attending Members and Advisors were identified.

The Chair of the Emergency Committee, Professor Didier Houssin, introduced the objectives of the meeting: to provide views to the WHO Director-General on whether the COVID-19 pandemic continues to constitute a PHEIC and to review Temporary Recommendations to States Parties.

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While the global risk assessment remains high, there is evidence of reducing risks to human health driven mainly by high population-level immunity from infection, vaccination, or both; consistent virulence of currently circulating SARS-CoV-2 Omicron sub-lineages compared to previously circulating Omicron sub-lineages; and improved clinical case management. These factors have contributed to a significant global decline in the weekly number of COVID-19 related deaths, hospitalizations, and admissions to intensive care units since the beginning of the pandemic. While SARS-CoV-2 continues to evolve, the currently circulating variants do not appear to be associated with increased severity.

WHO provided updates on the status of global vaccination and considerations of implications for the potential termination of a PHEIC. The Committee was informed that, globally, 13.3 billion doses of COVID-19 vaccines have been administered. Currently, 89% of health workers and 82% of adults over 60 years have completed the primary series (the initial one or two doses recommended as per the vaccine schedule), although coverage in these priority groups varies in different regions.

As requested by the Committee, the WHO Secretariat provided overviews of the status of integration of COVID-19 surveillance into the Global Influenza Surveillance and Response System and opportunities to streamline this; the process for issuing Standing Recommendations under the IHR; and the potential regulatory implications for Emergency Use Listed (EUL) when a PHEIC is terminated. As the Director-General will continue to authorize the use of EUL procedure, the termination of the PHEIC should not affect access to vaccines and diagnostics that have already received an EUL. States Parties will still be able to access these vaccines and diagnostics (provided the manufacturers continue production). COVAX will also continue to provide funded doses and delivery support throughout 2023 in line with demand. This continuity can enable a smooth transition from EUL to prequalification of vaccines and diagnostics. As the large majority of therapeutics used to treat COVID-19 are repurposed medicines already licensed for other indications, the termination of a PHEIC should not affect their regulatory status.

Deliberative Session on the Status of the PHEIC

The Committee considered the three criteria of a PHEIC: whether COVID-19 continues to constitute 1) an extraordinary event, 2) a public health risk to other States through the international spread, and 3) potentially requires a coordinated international response. They discussed the current status of the COVID-19 pandemic. They acknowledged that, although SARS-CoV-2 has been and will continue circulating widely and evolving, it is no longer an unusual or unexpected event. The Committee recognized that the Director-General may decide to convene an IHR Emergency Committee on COVID-19 in the future if the situation requires.

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The COVID-19 PHEIC has prompted countries to enhance their functional capacities, particularly related to emergency coordination, collaborative surveillance, clinical care, and risk communications and communication engagement. The world has made significant and impressive global progress since the declaration of the PHEIC in January 2020. Reaching the point where COVID-19 can be considered as no longer constituting a PHEIC should be seen as accolade to international coordination and commitment to global health.

As it has during past meetings, the Committee deliberated the potential benefits and issues posed by maintaining the PHEIC. While the PHEIC has been a valuable instrument to support the global response to COVID-19, the Committee agreed that the time is right to move towards the long-term management of SARS-CoV-2 as an ongoing health issue.

Moving forward, the Committee suggested that the Director-General consider convening an IHR Review Committee to advise on Standing Recommendations to for long-term risks posed by SARS-CoV-2 taking into account the 2023-2025 COVID-19 Strategic Preparedness and Response Plan. At the same time, the Committee recognized that Member States are currently negotiating the Pandemic Prevention, Preparedness, and Response Accord, discussing amendments to the IHR, and considering the ten proposals to build a safer world together by strengthening the Global Architecture for Health Emergency Preparedness, Response, and Resilience (HEPR).

They thanked the WHO Secretariat and States Parties for their sustained commitment and technical expertise, and emphasized that this is not the time to stop work or dismantle systems. The Committee stressed that it will be critical to address the gaps recognised during the pandemic. They highlighted the need to strengthen health systems, continue active risk communications and community engagement, implement a One Health approach to preparedness and response, and integrate COVID-19 surveillance and response activities into routine health programmes. The Committee advocated that WHO, partners, and States Parties dedicate sustained attention and resources to preparedness and resilience for emerging threats.

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Temporary Recommendations issued by the WHO Director-General to all States Parties

1. Sustain the national capacity gains and prepare for future events to avoid the occurrence of a cycle of panic and neglect. States Parties should consider how to improve country readiness for future outbreaks. In alignment with WHO guidance, States Parties should update respiratory

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pathogen pandemic preparedness plans incorporating learnings from national and sub-national After Action Reviews. States Parties should continue to restore health programmes adversely affected by the COVID-19 pandemic.

- Preparedness and resilience for Emerging Threats;
- Strengthening pandemic preparedness planning for respiratory pathogens: policy brief;
- WHO COVID-19 policy briefs;
- Emergency Response Reviews

2. Integrate COVID-19 vaccination into life course vaccination programmes. States Parties should maintain efforts to increase COVID-19 vaccination coverage for all people in the high-priority groups (as defined by the SAGE Roadmap of April 2023) with WHO recommended vaccines and continue to actively address vaccine acceptance and demand issues with communities.

- Global COVID-19 Vaccination Strategy in a Changing World (July 2022 update);
- SAGE Roadmap (Updated March 2023);
- Good practice statement on the use of variant-containing COVID-19 vaccines;
- Continued collaboration with IVAC and others to summarise VE studies, Behavioural and social drivers of vaccination: tools and practical guidance for achieving high uptake.

3. Bring together information from diverse respiratory pathogen surveillance data sources to allow for a comprehensive situational awareness. States Parties should maintain reporting of mortality and morbidity data as well as variant surveillance information to WHO. Surveillance should incorporate information from an appropriate mix of representative sentinel populations, event-based surveillance, human wastewater surveillance, sero-surveillance, and surveillance of selected animal populations known to be at risk of SARS-COV-2. States Parties should leverage the Global Influenza Surveillance and Response System (GISRS) and support the establishment of the WHO Global Coronavirus Laboratory Network (CoViNet).

- Public health surveillance for COVID-19

4. Prepare for medical countermeasures to be authorized within national regulatory frameworks to ensure long-term availability and supply. States Parties should strengthen their regulatory authorities to support long-term authorization and use of vaccines, diagnostics, and therapeutics.

- Therapeutics and COVID-19: living guideline;
- COVID-19 Clinical Care Pathway;
- Emergency Use Listing procedures;
- Prequalification procedures for vaccines;
- Prequalification procedures for in vitro diagnostics

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5. Continue to work with communities and their leaders to achieve strong, resilient, and inclusive risk communications and community engagement (RCCE) and infodemic management programmes. State Parties should adapt RCCE and infodemic management strategies and interventions to local contexts.

6. Continue to lift COVID-19 international travel related health measures, based on risk assessments, and to not require any proof of vaccination against COVID-19 as a prerequisite for international travel.

- Interim position paper: considerations regarding proof of COVID-19 vaccination for international travellers;
- Policy considerations for implementing a risk-based approach to international travel in the context of COVID-19

7. Continue to support research to improve vaccines that reduce transmission and have broad applicability; to understand the full spectrum, incidence and impact of post COVID-19 condition and the evolution of SARS-COV-2 in immunocompromised populations; and to develop relevant integrated care pathways.

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Document 1.4

Therapeutic Management of Non-hospitalized Adults with COVID-19 (July 21, 2023 update)

Document URL

https://files.covid19treatmentguidelines.nih.gov/guidelines/section/section_141.pdf

Reference website URL

https://www.covid19treatmentguidelines.nih.gov/management/clinical-management-of-adults/nonhospitalized-adults--therapeutic-management/?utm_

License

Not applicable

Therapeutic Management of Nonhospitalized Adults With COVID-19

Last Updated: July 21, 2023

Symptom management should be initiated for all nonhospitalized adults with mild to moderate COVID-19. For adults who are at high risk of progression to severe disease, several antiviral therapeutic options are available to reduce the risk of hospitalization or death. The COVID-19 Treatment Guidelines Panel's (the Panel) recommendations on the use of these drugs for the treatment of COVID-19 are outlined in this section.

The main goal of therapeutic management for nonhospitalized patients is to prevent progression to severe disease, hospitalization, or death. Other goals may include accelerating symptom recovery, viral clearance, and prevention of long-term sequelae. Current data on the impact of therapy on these secondary goals are limited.

Several factors affect the selection of the best treatment option for a specific patient. These factors include the clinical efficacy and availability of the treatment option, the feasibility of administering parenteral medications, the potential for significant drug-drug interactions, the patient's pregnancy status, the time from symptom onset, and the in vitro activities of the available products against the currently circulating SARS-CoV-2 variants and subvariants.

Most of the data that support the use of the recommended treatment options come from clinical trials that enrolled individuals who were at high risk of disease progression and who had no pre-existing immunity from COVID-19 vaccination or prior SARS-CoV-2 infection. Accordingly, the proportion of hospitalizations and deaths in the placebo arms of these trials was high compared to what has been seen more recently in populations where most people are vaccinated or have had prior SARS-CoV-2 infection. Although these trials demonstrated the efficacy of using antiviral drugs in high-risk populations, it is difficult to know their precise effectiveness in the current setting because of the low rates of hospitalization and death among those who have been vaccinated.

Nevertheless, some patients continue to have an increased risk of disease progression, and it is in those people that therapies are most likely to be beneficial. Patients who are at the highest risk are older patients (i.e., those aged >50 years and especially those aged ≥65 years) and patients who are unlikely to have an adequate immune response to COVID-19 vaccines due to a moderate to severe immunocompromising condition or the receipt of immunosuppressive medications. Other risk factors include lack of vaccination or incomplete vaccination; a prolonged amount of time since the most recent vaccine dose (e.g., >6 months); and conditions such as obesity, diabetes, and chronic respiratory, cardiac, or kidney disease.[1]

People who are members of racial and ethnic minority groups have higher rates of hospitalization and death from COVID-19 than people who are White.[2] Disparities in the use of antiviral treatments in patients who are not White have been reported; therefore, attention to equitable access is critical.[3,4]

The Panel's recommendations reflect the available data on the benefits of using antiviral therapies to prevent progression to severe COVID-19. The Panel will consider the potential benefits of available therapies for other outcomes, such as symptom recovery, as those data emerge.

Table 2a outlines the Panel's recommendations for the therapeutic management of nonhospitalized adults with COVID-19. For recommended doses of the agents listed in Table 2a, see Table 4e.

Who Do Not Require Supplemental Oxygen

Patient Disposition	Panel's Recommendations
All Patients	• Symptom management should be initiated for all patients **(AIII)**. • The Panel **recommends against** the use of **dexamethasone**[a] or other systemic corticosteroids in the absence of another indication **(AIIb)**.
Patients Who Are at High Risk of Progressing to Severe COVID-19[b,c]	*Preferred therapies. Listed in order of preference:* • **Ritonavir-boosted nirmatrelvir (Paxlovid)**[d] **(AIIa)**; see footnote on drug interactions[e] • **Remdesivir**[d,f] **(BIIa)** *Alternative therapy. For use when the preferred therapies are not available, feasible to use, or clinically appropriate:* • **Molnupiravir**[d,g,h] **(CIIa)**
Each recommendation in the Guidelines receives a rating for the strength of the recommendation (A, B, or C) and a rating for the evidence that supports it (I, IIa, IIb, or III). See Guidelines Development for more information.	

[a] There is currently a lack of safety and efficacy data on the use of dexamethasone in outpatients with COVID-19. Using systemic glucocorticoids in outpatients with COVID-19 may cause harm.

[b] For a list of risk factors, see the CDC webpage Underlying Medical Conditions Associated With Higher Risk for Severe COVID-19. When deciding whether to prescribe antiviral treatment to a patient who has been vaccinated, clinicians should be aware of the conditions associated with a high risk of disease progression. These conditions include older age, a prolonged amount of time since the most recent vaccine dose (e.g., >6 months), and a decreased likelihood of an adequate immune response to vaccination due to a moderate to severe immunocompromising condition or the receipt of immunosuppressive medications. The number and severity of risk factors also affects the level of risk.

[c] For a discussion of potential treatment options for patients who are immunocompromised and have prolonged COVID-19 symptoms and evidence of ongoing viral replication, see below and Special Considerations in People Who Are Immunocompromised.

[d] If a patient requires hospitalization after starting treatment, the full treatment course can be completed at the health care provider's discretion.

[e] Ritonavir-boosted nirmatrelvir has significant drug-drug interactions. Clinicians should carefully review a patient's concomitant medications and evaluate potential drug-drug interactions. See Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications for more information.

[f] Administration of remdesivir requires an IV infusion once daily for 3 days.

[g] Molnupiravir appears to have lower efficacy than the other options recommended by the Panel. Therefore, it should be considered when the other options are not available, feasible to use, or clinically appropriate.

[h] The Panel **recommends against** the use of **molnupiravir** for the treatment of COVID-19 in pregnant patients unless there are no other options and therapy is clearly indicated **(AIII)**.

Key: CDC = Centers for Disease Control and Prevention; IV = intravenous; the Panel = the COVID-19 Treatment Guidelines Panel

Symptom Management

Treatment of symptoms includes using over-the-counter antipyretics, analgesics, or antitussives for fever, headache, myalgias, and cough. Patients should be advised to drink fluids regularly to avoid dehydration. Rest is recommended as needed during the acute phase of COVID-19, and ambulation and other forms of activity should be increased according to the patient's tolerance. Patients should be educated about the variability in time to symptom resolution and complete recovery. When possible, patients with symptoms of COVID-19 should be triaged via telehealth visits to determine whether they require COVID-19–specific therapy and in-person care **(AIII)**.

and in-person monitoring of these patients should be considered **(AIII)**. Patients with persistent or progressive dyspnea, especially those who have an oxygen saturation measured by pulse oximetry ≤94% on room air at sea level or have symptoms that suggest high acuity (e.g., chest pain or tightness, dizziness, confusion, other mental status changes), should be referred to a health care provider for an in-person evaluation **(AIII)**.

Rationale for the Panel's Recommendations

The Panel's recommendations for the antiviral agents that are used to treat nonhospitalized patients with mild to moderate COVID-19 who are at high risk of clinical progression are based on the results of clinical trials. The Panel **recommends against** using anti-SARS-CoV-2 monoclonal antibodies for the treatment of COVID-19 **(AIII)** because the dominant Omicron subvariants in the United States are not expected to be susceptible to these products. See Anti-SARS-CoV-2 Monoclonal Antibodies for more information.

The Panel favors the use of ritonavir-boosted nirmatrelvir (Paxlovid) in most high-risk, nonhospitalized patients with mild to moderate COVID-19. When ritonavir-boosted nirmatrelvir is not clinically appropriate (e.g., because of significant drug-drug interactions), the Panel recommends using remdesivir. Ritonavir-boosted nirmatrelvir has high efficacy; has been shown to reduce hospitalization and death when administered to high-risk, unvaccinated, nonhospitalized patients within 5 days of symptom onset;[5] and is an oral medication, whereas remdesivir requires intravenous (IV) administration.

The Panel's recommendation for remdesivir is based on a Phase 3, randomized, placebo-controlled trial that reported high clinical efficacy in high-risk patients with COVID-19 who were unvaccinated.[6] However, in some settings, daily IV administration of remdesivir for 3 days may be a logistical challenge.

The Panel recommends **molnupiravir** as a therapeutic option when the other recommended antiviral treatment options are not available, feasible to use, or clinically appropriate **(CIIa)**. Molnupiravir appears to have lower clinical efficacy than the other treatment options, although no randomized studies have compared these therapies directly. The rationale for each of the Panel's recommendations is discussed below.

Currently, data on the use of combinations of antiviral agents for the treatment of COVID-19 are limited.[6] Clinical trials are needed to determine whether combination therapy has a role in the treatment of COVID-19.

Strategies for the Use of Ritonavir-Boosted Nirmatrelvir

Because ritonavir is a strong cytochrome P450 3A4 inhibitor and a P-glycoprotein inhibitor, it may increase blood concentrations of certain concomitant medications and increase the potential for serious drug toxicities. Therefore, the Food and Drug Administration (FDA) prescribing information and Emergency Use Authorization (EUA) fact sheet include a boxed warning for significant drug-drug interactions with ritonavir-boosted nirmatrelvir.[7,8] Clinicians should consider both the potential benefits of treatment with ritonavir-boosted nirmatrelvir and the potential risks related to drug-drug interactions.

Many drug-drug interactions between ritonavir-boosted nirmatrelvir and concomitant medications **can be safely managed** (e.g., with certain statins, calcium channel blockers, or direct oral anticoagulants). If a significant drug-drug interaction is identified, prescribers should consider consulting with a pharmacist.

The following resources are available to assist in identifying and managing drug-drug interactions:

- Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications

- The University of Waterloo/University of Toronto drug interaction guide
- The FDA prescribing information, EUA fact sheet, and checklist for ritonavir-boosted nirmatrelvir

The use of ritonavir-boosted nirmatrelvir may be challenging in patients with severe renal impairment and in patients receiving certain transplant-related immunosuppressants or chemotherapy. The FDA prescribing information and EUA fact sheet state that until more data are available, ritonavir-boosted nirmatrelvir is not recommended in patients with an estimated glomerular filtration rate (eGFR) of <30 mL/min.[8] Although data on dose adjustments are limited, some groups have proposed dosing adjustments in patients with an eGFR of <30 mL/min or for patients receiving hemodialysis.[9-12]

The decision to prescribe ritonavir-boosted nirmatrelvir to patients receiving calcineurin and mammalian target of rapamycin inhibitors should always be made in consultation with the patient's specialist providers. Among reports submitted to the FDA Adverse Events Reporting System, the most commonly reported concomitant medications resulting in serious adverse reactions, including fatal events, were calcineurin inhibitors (e.g., tacrolimus).[13] Ritonavir-boosted nirmatrelvir may be prescribed to select patients if an expert in managing the interaction is available and close therapeutic drug monitoring is logistically feasible. Otherwise, an alternative therapy for COVID-19 should be considered. See the American Society of Transplantation statement for additional information.

Interactions between ritonavir-boosted nirmatrelvir and chemotherapeutic agents should also be managed in consultation with the patient's specialist providers. For guidance on managing these interactions, refer to the FDA prescribing information and EUA fact sheet for ritonavir-boosted nirmatrelvir and the prescribing information for the chemotherapeutic agent.[7,8] The University Health Network/Kingston Health Sciences Centre provides an additional resource for evaluating drug-drug interactions between ritonavir-boosted nirmatrelvir and chemotherapeutic agents.

Strategies for the Use of Remdesivir

Advanced planning (e.g., reserving infusion slots, identifying alternative infusion sites) may be needed to increase access to IV remdesivir. IV remdesivir can be administered in skilled nursing facilities, home health care settings, and outpatient facilities such as infusion centers. If treatment facilities cannot provide a 3-day course of remdesivir IV infusions to all eligible patients, prioritizing patients who will benefit the most from the therapy becomes necessary. The prioritization scheme below is based on 4 key elements: age, vaccination status, immune status, and clinical risk factors. For a list of risk factors, see the Centers for Disease Control and Prevention (CDC) webpage Underlying Medical Conditions Associated With Higher Risk for Severe COVID-19. The groups are listed by tier in descending order of priority.

Tier	Risk Group
1	• Immunocompromised individuals not expected to mount an adequate immune response to COVID-19 vaccination or SARS-CoV-2 infection due to their underlying conditions,[a] regardless of vaccine status; *or* • Unvaccinated individuals at the highest risk of severe disease (anyone aged ≥75 years or anyone aged ≥65 years with additional risk factors).
2	• Unvaccinated individuals not included in Tier 1 who are at risk of severe disease (anyone aged ≥65 years or anyone aged <65 years with clinical risk factors)
3	• Vaccinated individuals at risk of severe disease (anyone aged ≥65 years or anyone aged <65 years with clinical risk factors)[b]

[a] See the CDC website COVID-19 Vaccines for People Who Are Moderately or Severely Immunocompromised for a discussion of immunocompromising conditions.

within this tier who are in this situation should be prioritized for treatment. See the CDC webpage Stay Up to Date with COVID-19 Vaccines for more information.

See Prioritization of Anti-SARS-CoV-2 Therapies for the Treatment of COVID-19 in Nonhospitalized Patients When There Are Logistical Constraints for more information.

Patients Who Are Immunocompromised and Have Prolonged Symptoms and Evidence of Ongoing Viral Replication

For patients who are immunocompromised and have prolonged COVID-19 symptoms and evidence of ongoing viral replication (e.g., those with a low cycle threshold value, as measured by a reverse transcription polymerase chain reaction result or with a positive rapid antigen test result) despite receiving a course of antiviral therapy, the optimal management is unknown. Case reports and case series have documented the treatment of these patients with additional antiviral treatments, prolonged courses of antiviral treatments, high-titer COVID-19 convalescent plasma (CCP), or combination therapy.[14-18] The data for these approaches are not definitive, but some Panel members would use 1 or more of the following treatment options:

- Longer and/or additional courses of ritonavir-boosted nirmatrelvir
- Longer and/or additional courses of remdesivir
- High-titer CCP from a vaccinated donor who recently recovered from COVID-19 likely caused by a SARS-CoV-2 variant similar to the variant causing the patient's illness

The ritonavir-boosted nirmatrelvir that was packaged in accordance with the EUA is the only ritonavir-boosted nirmatrelvir available at this time. For information on how to request expanded access use of ritonavir-boosted nirmatrelvir (e.g., for a course of treatment longer than 5 days), see "May health care providers prescribe Paxlovid for uses not authorized under EUA?" in this Frequently Asked Questions document from the FDA.

For further discussion of these potential treatment options, see Special Considerations in People Who Are Immunocompromised.

Additional Information on Ritonavir-Boosted Nirmatrelvir

Nirmatrelvir is an orally bioavailable protease inhibitor that is active against M^{PRO}, a viral protease that plays an essential role in viral replication.[19] The FDA has approved ritonavir-boosted nirmatrelvir for the treatment of mild to moderate COVID-19 in nonhospitalized adults who are at high risk of progressing to severe COVID-19.[8] Ritonavir-boosted nirmatrelvir is currently only available from EUA supplies, and its use must be consistent with the terms and conditions of the EUA.

Patients should complete the 5-day treatment course of ritonavir-boosted nirmatrelvir, which was shown to be efficacious in the EPIC-HR trial.[5] If a patient requires hospitalization after starting treatment, the full 5-day treatment course of ritonavir-boosted nirmatrelvir should be completed unless there are drug-drug interactions that preclude its use.

In the EPIC-HR trial, ritonavir-boosted nirmatrelvir reduced the risk of hospitalization or death by 89% compared to placebo in unvaccinated, nonhospitalized adults with laboratory-confirmed SARS-CoV-2 infection.[5] This efficacy is comparable to the efficacies reported in similar patient populations for remdesivir (87% relative reduction)[5,8] and greater than the efficacy reported for molnupiravir in this setting (31% relative reduction).[20]

Because ritonavir-boosted nirmatrelvir has the potential for significant drug-drug interactions with

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Interactions Between Ritonavir-Boosted Nirmatrelvir [Paxlovid] and Concomitant Medications). However, because ritonavir-boosted nirmatrelvir is the only highly effective oral antiviral available for the treatment of COVID-19, drug-drug interactions that can be safely managed should not preclude the use of this medication.

For more information on the use of ritonavir-boosted nirmatrelvir, see Ritonavir-Boosted Nirmatrelvir (Paxlovid). See Viral Rebound and Symptom Recurrence below for information regarding SARS-CoV-2 viral rebound in patients who have completed treatment with ritonavir-boosted nirmatrelvir.

Additional Information on Remdesivir

Remdesivir is a nucleotide prodrug of an adenosine analog that inhibits SARS-CoV-2 replication. It is approved by the FDA for the treatment of COVID-19 in adults and children aged ≥28 days and weighing ≥3 kg who are hospitalized with COVID-19 and for those with mild to moderate COVID-19 who are not hospitalized and are at high risk of progressing to severe disease. In the PINETREE trial, nonhospitalized patients with mild to moderate COVID-19 who were unvaccinated and at high risk of progressing to severe disease received 3 days of IV remdesivir or placebo. Use of remdesivir resulted in an 87% relative reduction in the risk of hospitalization or death.[21-23]

Remdesivir should be administered in a setting where severe hypersensitivity reactions, such as anaphylaxis, can be managed. Patients should be monitored during the infusion and observed for at least 1 hour after the infusion as clinically appropriate.

For more information, see Remdesivir.

Additional Information on Molnupiravir

Molnupiravir is the oral prodrug of beta-D-N4-hydroxycytidine, a ribonucleoside that has shown antiviral activity against SARS-CoV-2 in vitro and in clinical trials.[24-26] The FDA issued an EUA for molnupiravir for the treatment of mild to moderate COVID-19 in nonhospitalized patients aged ≥18 years who are at high risk of disease progression and for whom alternative treatment options are not accessible or clinically appropriate.

The MOVe-OUT trial enrolled nonhospitalized adults who were unvaccinated and at high risk of progression to severe disease in the pre-Omicron era. The study found that molnupiravir reduced the rate of hospitalization or death by 31% compared to placebo.[8,27] A secondary analysis of MOVe-OUT trial data revealed that patients who received molnupiravir and progressed to hospitalization were less likely to need respiratory interventions than patients who received placebo and progressed to hospitalization.[28]

The PANORAMIC trial enrolled participants during a period when the Omicron variant was circulating.[29] The participants were nonhospitalized adults with COVID-19 who were at high risk of progressing to severe disease, and 94% had received at least 3 doses of a COVID-19 vaccine. The study found that the use of molnupiravir plus usual care did not reduce the primary composite outcome of hospitalization or death compared to usual care alone. The rates of this composite outcome were low (1%) in both arms. Molnupiravir plus usual care was superior to usual care alone for several secondary clinical endpoints. For example, patients who received molnupiravir plus usual care reported recovering from COVID-19 an estimated 4 days earlier than those who received usual care alone. However, because the PANORAMIC trial was an open-label study and the patients knew whether they were receiving molnupiravir or not, this may have affected their reported symptoms. As a result, these findings are less reliable than those from a placebo-controlled trial.

the Panel recommends using molnupiravir as an alternative therapy when ritonavir-boosted nirmatrelvir and remdesivir are not available, feasible to use, or clinically appropriate, because molnupiravir appears to have lower clinical efficacy than these other options.

Molnupiravir is a mutagenic ribonucleoside antiviral agent, and there is a theoretical risk that the drug will be metabolized by the human host cell and incorporated into the host DNA, leading to mutations. The available genotoxicity data and the 5-day duration of treatment led the FDA to conclude that molnupiravir has a low risk for genotoxicity.[8]

The Panel **recommends against** the use of **molnupiravir** for the treatment of COVID-19 in pregnant patients unless there are no other options and therapy is clearly indicated **(AIII)**. People who engage in sexual activity that may result in conception should use effective contraception during and following treatment with molnupiravir.

Fetal toxicity has been reported in animal studies of molnupiravir.[8] However, when other therapies are not available, pregnant patients with COVID-19 who are at high risk of progressing to severe disease may reasonably choose molnupiravir after being fully informed of the risks, particularly if they are beyond the time of embryogenesis (i.e., >10 weeks' gestation). See Pregnancy, Lactation, and COVID-19 Therapeutics for more information.

For more information, see Molnupiravir.

Viral Rebound and Symptom Recurrence

Observational studies and the EPIC-HR and MOVe-OUT trials have described SARS-CoV-2 viral rebound and the recurrence of COVID-19 symptoms in some patients who have completed treatment with ritonavir-boosted nirmatrelvir or molnupiravir.[8,30-33] The frequency, mechanism, and clinical implications of these events are unclear. Viral rebound and the recurrence of COVID-19 symptoms can also occur in the absence of treatment.[8,30-32,34]

To date, the recurrence of COVID-19 symptoms and virus detection following the use of antiviral therapies has not been associated with progression to severe COVID-19. Therefore, concerns about the recurrence of symptoms or viral rebound **should not** be a reason to avoid using antiviral therapies.[33,35-37] The FDA EUA fact sheets for ritonavir-boosted nirmatrelvir and molnupiravir do not authorize treatment courses that are longer than 5 days, and there are insufficient data on the efficacy of administering a second course.[37]

Immunomodulators

The Panel **recommends against** the use of **dexamethasone** or other systemic corticosteroids to treat outpatients with mild to moderate COVID-19 who do not require hospitalization or supplemental oxygen **(AIIb)**. Patients with COVID-19 who are receiving **dexamethasone** or another corticosteroid for an underlying condition should continue this therapy as directed by their health care provider **(AIII)**.

Medicare and FDA data show a significant increase in the number of prescriptions for systemic corticosteroids among nonhospitalized patients with COVID-19[38] despite a lack of safety and efficacy data on the use of systemic corticosteroids in this setting. Systemic glucocorticoids may cause harm in nonhospitalized patients with COVID-19. Results from 1 randomized controlled trial and 1 observational cohort study did not demonstrate a clinical benefit of dexamethasone among hospitalized patients who did not require supplemental oxygen,[39] and dexamethasone may potentially cause harm in these patients.[40]

In the RECOVERY trial, the use of dexamethasone had no effect on mortality among hospitalized

1.55).[39] A large observational study of patients at Veterans Affairs hospitals reported no survival benefit for dexamethasone among patients with COVID-19 who did not require supplemental oxygen. Instead, these patients had an increased risk of 90-day mortality (HR 1.76; 95% CI, 1.47–2.12).[39] However, hospitalized patients with COVID-19 are likely to have an increased risk of mortality compared to nonhospitalized patients, which is a limitation of observational trial data.

Concomitant Medication Management

In general, a patient's usual medication and/or supplement regimen should be continued after the diagnosis of COVID-19 (see Considerations for Using Concomitant Medications in Patients With COVID-19). Angiotensin-converting enzyme (ACE) inhibitors; angiotensin receptor blockers (ARBs); statin therapy; nonsteroidal anti-inflammatory drugs; and oral, inhaled, and intranasal corticosteroids that are prescribed for comorbid conditions should be continued as directed (**AIIa** for ACE inhibitors and ARBs; **AIII** for other medications). Patients should be advised to avoid the use of nebulized medications in the presence of others to avoid potential aerosolization of SARS-CoV-2.[41] In patients with HIV, antiretroviral therapy should not be switched or adjusted for the theoretical purpose of preventing or treating SARS-CoV-2 infection **(AIII)**. For more information, see Special Considerations in People With HIV.

When a patient is receiving an immunomodulating medication, the prescribing clinician or an expert in the subspecialty should be consulted about the risks and benefits associated with a temporary dose reduction or discontinuation. These risks and benefits will depend on the medication's indication and the severity of the underlying condition (see Special Considerations in People Who Are Immunocompromised).

Before prescribing ritonavir-boosted nirmatrelvir, clinicians should carefully review the patient's concomitant medications, including over-the-counter medications and herbal supplements, to evaluate potential drug-drug interactions.

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Drug Treatments for COVID-19: Living Systematic Review and Network Meta-Analysis

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Drug treatments for covid-19: living systematic review and network meta-analysis

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ABSTRACT

OBJECTIVE

To compare the effects of treatments for coronavirus disease 2019 (covid-19).

DESIGN

Living systematic review and network meta-analysis.

DATA SOURCES

WHO covid-19 database, a comprehensive multilingual source of global covid-19 literature, up to 3 December 2021 and six additional Chinese databases up to 20 February 2021. Studies identified as of 1 December 2021 were included in the analysis.

STUDY SELECTION

Randomised clinical trials in which people with suspected, probable, or confirmed covid-19 were randomised to drug treatment or to standard care or placebo. Pairs of reviewers independently screened potentially eligible articles.

METHODS

After duplicate data abstraction, a bayesian network meta-analysis was conducted. Risk of bias of the included studies was assessed using a modification of the Cochrane risk of bias 2.0 tool, and the certainty of the evidence using the grading of recommendations assessment, development, and evaluation (GRADE) approach. For each outcome, interventions were classified in groups from the most to the least beneficial or harmful following GRADE guidance.

RESULTS

463 trials enrolling 166 581 patients were included; 267 (57.7%) trials and 89 814 (53.9%) patients are new from the previous iteration; 265 (57.2%) trials evaluating treatments with at least 100 patients or 20 events met the threshold for inclusion in the analyses. Compared with standard care, three drugs reduced mortality in patients with mostly severe disease with at least moderate certainty: systemic corticosteroids (risk difference 23 fewer per 1000 patients, 95% credible interval 40 fewer to 7 fewer, moderate certainty), interleukin-6 receptor antagonists when given with corticosteroids (23 fewer per 1000, 36 fewer to 7 fewer, moderate certainty), and Janus kinase inhibitors (44 fewer per 1000, 64 fewer to 20 fewer, high certainty). Compared with standard care, two drugs probably reduce hospital admission in patients with non-severe disease: nirmatrelvir/ritonavir (36 fewer per 1000, 41 fewer to 26 fewer, moderate certainty) and molnupiravir (19 fewer per 1000, 29 fewer to 5 fewer, moderate certainty). Remdesivir may reduce hospital admission (29 fewer per 1000, 40 fewer to 6 fewer, low certainty). Only molnupiravir had at least moderate quality evidence of a reduction in time to symptom resolution (3.3 days fewer, 4.8 fewer to 1.6 fewer, moderate certainty); several others showed a possible benefit. Several drugs may increase the risk of adverse effects leading to drug discontinuation; hydroxychloroquine probably increases the risk of mechanical ventilation (moderate certainty).

CONCLUSION

Corticosteroids, interleukin-6 receptor antagonists, and Janus kinase inhibitors probably reduce mortality and confer other important benefits in patients with severe covid-19. Molnupiravir and nirmatrelvir/ritonavir probably reduce admission to hospital in patients with non-severe covid-19.

SYSTEMATIC REVIEW REGISTRATION

This review was not registered. The protocol is publicly available in the supplementary material.

READERS' NOTE

This article is a living systematic review that will be updated to reflect emerging evidence. Updates may occur for up to two years from the date of original publication. This is the fifth version of the original article published on 30 July 2020 (*BMJ* 2020;370:m2980), and previous versions can be found as data supplements. When citing this paper please consider adding the version number and date of access for clarity.

Introduction

As of 23 March 2022, more than 475 million people have been infected with severe acute respiratory syndrome coronavirus virus 2 (SARS-CoV-2), the virus responsible for coronavirus disease 2019 (covid-19); of these, more than six million have died.[1] Despite global efforts to identify effective interventions for the prevention and treatment of covid-19, which have resulted in approximately 3000 trials completed or

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underway,[2] evidence for effective treatment remains limited.

Summarising the rapidly growing evidence base has been a challenge.[3] Living systematic reviews deal with the main limitation of traditional reviews—that of providing an overview of the relevant evidence only at a specific time.[4] This is crucial in the context of covid-19, in which the best evidence is constantly changing. The ability of a living network meta-analysis to present a complete, broad, and updated view of the evidence makes it the best type of evidence synthesis to inform the development of practice recommendations. Network meta-analysis, rather than pairwise meta-analysis, provides useful information about the comparative effectiveness of treatments that have not been tested head to head. The lack of such direct comparisons is certain to limit inferences in the covid-19 setting. Moreover, the incorporation of indirect evidence can strengthen evidence in comparisons that were tested head to head.[5]

In this living systematic review and network meta-analysis we compare the effects of drug treatments for covid-19. This review is part of the *BMJ* Rapid Recommendations project, a collaborative effort from the MAGIC Evidence Ecosystem Foundation (www.magicproject.org) and *The BMJ*.[6] This living systematic review and network meta-analysis informs World Health Organization and *BMJ* Rapid Recommendations on covid-19 treatments, initiated to provide trustworthy, actionable, and living guidance to clinicians and patients soon after new and potentially practice-changing evidence becomes available (box 1).[7 8] This living network meta-analysis is the fifth version. The previous versions are available in the supplementary material. Drugs for prophylaxis[9] and antibody-based treatments[10] are addressed separately.

Box 1: Linked resources in this *BMJ* Rapid Recommendations cluster

- Agarwal A, Rochwerg B, Siemieniuk RAC, et al. A living WHO guideline on drugs for covid-19 [Update 10]. *BMJ* 2020;370:m3379, doi:10.1136/bmj.m3379
  - Living WHO *BMJ* Rapid Recommendations guidance on drugs for covid-19
- World Health Organization. *Therapeutics and COVID-19. Living guideline*. July 2022. https://www.who.int/teams/health-care-readiness-clinical-unit/covid-19/therapeutics.
- Siemieniuk RAC, Bartoszko JJ, Zeraatkar D, et al. Drug treatments for covid-19: living systematic review and network meta-analysis [Update 4]. *BMJ* 2020;370:m2980, doi:10.1136/bmj.m2980
  - Review and network meta-analysis of all available randomised trials that assessed drug treatments for covid-19
- MAGICapp (https://app.magicapp.org/#/guideline/nBkO1E)
  - Expanded version of the methods, processes, and results with multilayered recommendations, evidence summaries, and decision aids for use on all devices
- Author website "COVID-19 living network meta-analysis." https://www.covid19lnma.com
  - Interim updates will be available here

Methods

A protocol provides the detailed methods of this systematic review, including all updates (see supplementary file). We report this living systematic review following the guidelines of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist for network meta-analyses.[11] A living systematic review is a cumulative synthesis that is updated regularly as new evidence becomes available.[12] The linked *BMJ* Rapid Recommendations guideline panels approved all decisions relevant to data synthesis.

Eligibility criteria

We included randomised clinical trials in people with suspected, probable, or confirmed covid-19 that compared drugs for treatment against one another or against no intervention, placebo, or standard care. We included trials regardless of publication status (peer reviewed, in press, or preprint) or language. No restrictions were applied based on severity of illness or setting, and we included trials of Chinese medicines if the drug comprised one or more specific molecules with a defined molecular weight dosing.

We excluded randomised trials evaluating vaccination, blood products and antibody-based antiviral therapies (such as virus-specific monoclonal antibodies), nutrition, traditional Chinese herbal or alternative medicines that include more than one molecule or a molecule without specific molecular weighted dosing, and non-drug supportive care interventions. Trials that evaluated these interventions were identified and categorised separately.

Information sources

We perform daily searches from Monday to Friday in the World Health Organization (WHO) covid-19 database for eligible studies—a comprehensive multilingual source of global literature on covid-19. Prior to its merge with the WHO covid-19 database on 9 October 2020, we performed daily searches from Monday to Friday in the US Centers for Disease Control and Prevention (CDC) COVID-19 Research Articles Downloadable Database for eligible studies.[13] The database includes, but is not limited to the following 25 bibliographic and grey literature sources: Medline (Ovid and PubMed), PubMed Central, Embase, CAB Abstracts, Global Health, PsycInfo, Cochrane Library, Scopus, Academic Search Complete, Africa Wide Information, CINAHL, ProQuest Central, SciFinder, the Virtual Health Library, LitCovid, WHO covid-19 website, CDC covid-19 website, Eurosurveillance, China CDC Weekly, Homeland Security Digital Library, ClinicalTrials.gov, bioRxiv (preprints), medRxiv (preprints), chemRxiv (preprints), and SSRN (preprints).

The daily searches are designed to match the update schedule of the database and to capture eligible studies the day of or the day after publication. To identify randomised trials, we filtered search results through a validated and highly sensitive machine learning model.[14] We tracked preprints of randomised trials for updates and through publication: when data were discrepant, we used the most recent data.

In addition, we search six Chinese databases: Wanfang, Chinese Biomedical Literature, China National Knowledge Infrastructure, VIP, Chinese Medical Journal Net (preprints), and ChinaXiv (preprints). We adapted the search terms for covid-19 developed by the CDC to the Chinese language. For the Chinese literature search, we also included search terms for randomised trials. The supplementary file includes the Chinese literature search strategy. We stopped searching the Chinese databases on 20 February 2021 because they had not provided studies that meaningfully altered the evidence for any intervention.

We monitor living evidence retrieval services on an ongoing basis. These included the Living Overview of the Evidence (L-OVE) COVID-19 Repository by the Epistemonikos Foundation[15] and the Systematic and Living Map on COVID-19 Evidence by the Norwegian Institute of Public Health, in collaboration with the Cochrane Canada Centre at McMaster University.[16]

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We searched all English information sources from 1 December 2019 to 3 December 2021, and the Chinese literature from conception of the databases to 20 February 2021.

Study selection

Using a systematic review software, Covidence,[17] pairs of reviewers, following training and calibration exercises, independently screened all titles and abstracts, followed by full texts of trials that were identified as potentially eligible. A third reviewer adjudicated conflicts.

Data collection

For each eligible trial, pairs of reviewers, following training and calibration exercises, extracted data independently using a standardised, pilot tested data extraction form. Reviewers collected information on trial characteristics (trial registration, publication status, study status, design), patient characteristics (country, age, sex, smoking habits, comorbidities, setting and type of care, and severity of covid-19 symptoms for studies of treatment), and outcomes of interest (means or medians and measures of variability for continuous outcomes and the number of participants analysed and the number of participants who experienced an event for dichotomous outcomes). Reviewers resolved discrepancies by discussion and, when necessary, with adjudication by a third party. We updated the data collected from included preprints as soon as the peer review publication became available.

Outcomes of interest were selected based on importance to patients[18] and were informed by clinical expertise in the systematic review team and in the linked guideline panel responsible for the WHO-*BMJ* Rapid Recommendations.[19 7 8] The panel includes unconflicted clinical and methodology experts, recruited to ensure global representation, and patient partners. All panel members rated outcomes from 1 to 9 based on importance to individual patients (9 being most important), and we included any outcome rated 7 or higher by any panel member. Selected outcomes included mortality (closest to 90 days), mechanical ventilation (total number of patients, over 90 days), adverse events leading to discontinuation (within 28 days), admission to hospital, length of hospital stay, duration of mechanical ventilation, and time to symptom resolution or clinical improvement. In contrast to previous iterations, for this iteration, we did not include several outcomes which the GDG did not think were critical to decision making: viral clearance (closest to 7 days, 3 days either way), time to viral clearance, intensive care unit (ICU) length of stay, and days free from mechanical ventilation (within 28 days).

Mechanical ventilation includes both invasive and non-invasive mechanical ventilation. We used a hierarchy for the outcome mechanical ventilation in which we preferentially used the total number of patients who received mechanical ventilation over the study. We used the number of patients ventilated at the time point that the largest number of the patients were ventilated, if the trial reported the number of patients ventilated at specific timepoints. We used author definitions for mechanical ventilation; when separate, continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP) were considered non-invasive mechanical ventilation.

Risk of bias within individual studies

For each eligible trial, reviewers, following training and calibration exercises, used a revision of the Cochrane tool for assessing risk of bias in randomised trials (RoB 2.0)[20] to rate trials as either at i) low risk of bias, ii) some concerns—probably low risk of bias, iii) some concerns—probably high risk of bias, or iv) high risk of bias, across the following domains: bias arising from the randomisation process; bias owing to departures from the intended intervention; bias from missing outcome data; bias in measurement of the outcome; bias in selection of the reported results, including deviations from the registered protocol; bias due to competing risks; and bias arising from early termination for benefit. We rated trials at high risk of bias overall if one or more domains were rated as probably high risk of bias or as high risk of bias and as low risk of bias if all domains were rated as probably low risk of bias or low risk of bias. Reviewers resolved discrepancies by discussion and, when not possible, with adjudication by a third party.

Data synthesis

We conducted the network meta-analysis using a bayesian framework.[21] In this report, we conducted a network meta-analysis of drug treatments for covid-19 that included all patients, regardless of severity of disease.

Summary measures

We summarised the effect of interventions on dichotomous outcomes using the odds ratio and corresponding 95% credible interval. For continuous outcomes, we used the mean difference and corresponding 95% credible interval in days for ICU length of stay, length of hospital stay, and duration of mechanical ventilation because we expected similar durations across randomised trials. For time to symptom resolution, we first performed the analyses using the relative effect measure ratio of means and corresponding 95% credible interval before calculating the mean difference in days because we expected substantial variation between studies.[22]

Treatment nodes

Treatments were grouped into common nodes based on molecule and not on dose or duration. For intervention arms with more than one drug, we created a separate node. Chloroquine and hydroxychloroquine were included in the same node for covid-19 specific effects and separated for disease independent adverse effects. We drew network plots using the *networkplot* command of Stata version 15.1 (StataCorp, College Station, TX), with thickness of lines between nodes and size of the nodes based on the inverse of the variance of the direct comparison.[23]

Statistical analysis

For most outcomes, we conducted network meta-analyses and pairwise meta-analyses using a bayesian framework with the same priors for the variance and effect parameters.[21] In previous versions, we used fixed effects for some outcomes because data was sparse or dominated by a single trial. As per our protocol, we used random effects for all outcomes. We used a plausible prior for variance parameter and a uniform prior for the effect parameter suggested in a previous study based on empirical data.[24] For all analyses, we used three Markov chains with 100 000 iterations after an initial burn-in of 10 000 and a thinning of 10. We used node splitting models to assess local incoherence and to obtain indirect estimates.[25] All network meta-analyses were performed using the *gemtc* package of R version 3.6.3 (RStudio, Boston, MA)[26] and all pairwise meta-analyses using the *bayesmeta* package.[21]

In the first iteration of this living network meta-analysis, some treatment nodes with few total participants and few total events resulted in highly implausible and extremely imprecise effect estimates. We therefore decided to include only treatments that included at least 100 patients or had at least 20 events, based on our impression of the minimum number of patients/events to possibly provide meaningful results.

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Certainty of the evidence

We assessed the certainty of evidence using the grading of recommendations assessment, development and evaluation (GRADE) approach for network meta-analysis.[5 27 28] Two people with experience in using GRADE rated each domain for each comparison separately and resolved discrepancies by consensus. We rated the certainty for each comparison and outcome as high, moderate, low, or very low, based on considerations of risk of bias, inconsistency, indirectness, publication bias, intransitivity, incoherence (difference between direct and indirect effects), and imprecision.[28] We rated down for risk of bias if the interpretation of the effect would change if only studies at low risk of bias would have been considered. For example, if the credible interval of the pooled effect from studies at low risk of bias would have crossed the threshold for imprecision, we rated down for risk of bias. Judgments of imprecision for this systematic review were made using a minimally contextualised approach, with a null effect as the threshold of importance.[29] The minimally contextualised approach considers only whether credible intervals include the null effect and thus does not consider whether plausible effects, captured by credible intervals, include both important and trivial effects.[29] To evaluate certainty of no benefit (or no effect), we used a 2% risk difference threshold of the 95% credible interval for mortality and mechanical ventilation. In other words, if the entire 95% credible interval was within 2% of the null effect, we would not rate down for imprecision. We decided on this preliminary threshold based on a survey of the authors. Interim updates and additional study data will be posted on our website (www.covid19lnma.com).

Interpretation of results

To facilitate interpretation of the results, we calculated absolute effects for outcomes in which the summary measure was an odds ratio or ratio of means. When available, we inferred baseline risk in the usual care group for each outcome from representative observational data (supplementary material). For mortality, we used data from the CDC on patients who were hospitalised with covid-19.[30 31] For mechanical ventilation, duration of invasive mechanical ventilation, length of hospital stay, and ICU length of stay we used baseline risks from the International Severe Acute Respiratory and Emerging Infection COVID-19 database.[32] For all other outcomes, we used the median from all studies in which participants received standard of care to calculate the baseline risk for each outcome, with each study weighed equally. We calculated absolute effects using the transitive risks model[33] using *R2jags* package in R.[34]

For each outcome, we classified treatments in groups from the most to the least effective using the minimally contextualised framework, which focuses on the treatment effect estimates and the certainty of the evidence.[35]

Subgroup and sensitivity analysis

Subgroup analyses were performed for specific interventions of interest at the direction of the linked WHO living guideline panel. Previous iterations included subgroup analyses for ivermectin, interleukin-6 receptor antagonists, corticosteroids, hydroxychloroquine, lopinavir-ritonavir, and remdesivir. The panel requested subgroup analyses by age (children *v* non-elderly adults *v* elderly), severity (non-severe *v* severe and critical), and risk of bias. We performed bayesian hierarchical meta-regression with study as a random effect. Where possible, we performed within rather than between trial analyses.

Patient and public involvement

Patients were involved in outcome selection, interpretation of results, and the generation of parallel recommendations, as part of the *BMJ* Rapid Recommendations initiative.

Results

After screening 79 601 titles and abstracts and 1438 full texts, 463 unique randomised trials were identified that evaluated drug treatments as of 3 December 2021 (fig 1). A table of excluded full texts is provided in the supplementary file. Searches of living evidence retrieval services identified 219 publications of eligible randomised trials, which were reconciled with our formal search strategy when necessary. Three hundred and six randomised trials have been published in peer reviewed journals, 109 are preprints and 48 remain unpublished as either abstracts, data from meta-analyses, data from authors or data from presentations. The supplement describes the 43 randomised trials that were identified after the data analysis (1 December 2021) and that will be considered in the next update of the data analysis. Of the remaining trials, most were registered (373/420; 89%), nearly three quarters evaluated treatment in patients admitted to hospital with covid-19 (312/420; 74%), and one fifth evaluated treatment in outpatients with covid-19 (86/420; 20%). The United States, Iran, Brazil, India, and China were the five countries in which randomised trials were most commonly conducted. One hundred and eighty one different drug treatments were evaluated.

Several trials could not be included in the analysis because both arms would have been classified within the same treatment node, they evaluated different durations or doses of the same drug, had insufficient data, or reported no outcomes of interest. Ultimately, we analysed 265 (63%) trials that reported on treatments with at least 100 patients or 20 events. Table 1 presents the characteristics of the 420 included studies. Additional study characteristics, outcome data, and risk of bias assessments for each study are available in the supplementary file.

Of the randomised trials included in the analyses, eight did not have publicly accessible protocols or registrations. Of the trials with publicly accessible protocols or registrations, 79 reported results for one or more of our outcomes of interest that were not prespecified in protocols or registrations. No other discrepancies in the reporting of outcomes of interest were noted. One trial did not stratify reporting of outcomes for those who were truly randomised versus those who were allocated by preference; the authors shared outcome data with us among patients who were truly randomised.

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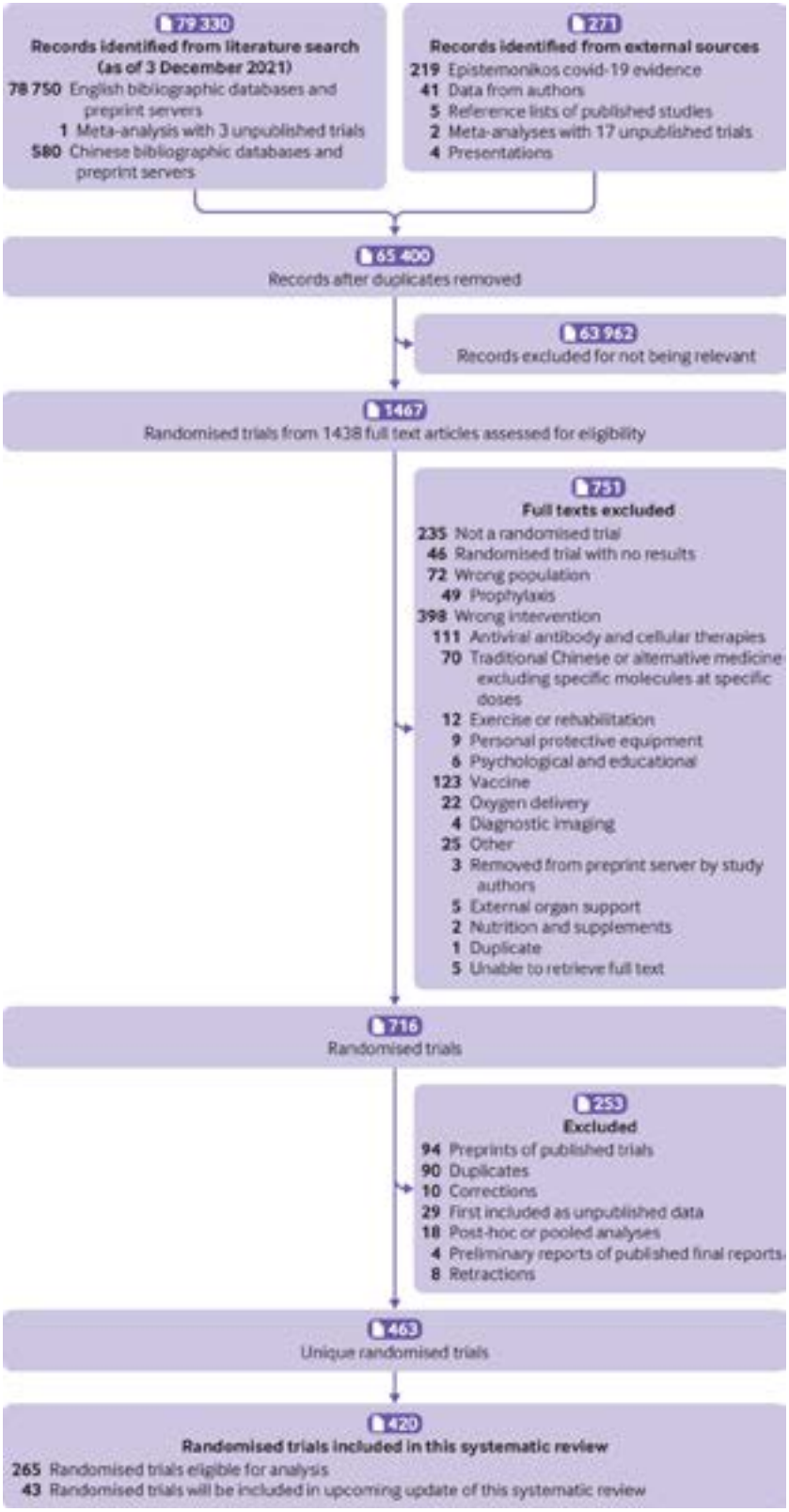

Fig 1 | Study selection

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Table 1 | Study characteristics

Characteristic	Value
No (%) of studies registered	373 (88.8)
No (%) of studies by publication status:	
Preprint	96 (22.9)
Published	278 (66.1)
Unpublished	46 (11.0)
Median (IQR) No of patients	101 (50-238)
No (%) of studies by country:	
United States	73 (17.4)
Iran	67 (16.0)
Brazil	52 (12.4)
India	43 (10.2)
China	41 (10.0)
No (%) of studies by intensity of care:	
Outpatient	86 (20.5)
Inpatient	312 (74.3)
ICU	24 (5.7)
No (%) of studies by illness severity:	
Mild/moderate	89 (21.2)
Severe/critical	42 (10.0)
Median (IQR) percentage of patients mechanically ventilated at baseline	2.8 (0.0-33.0)

Seventy five studies were initially posted as preprints and subsequently published after peer review. The supplementary material presents the differences between study preprint and peer reviewed publications. Thirty two studies had discrepancies in outcome reporting between the preprint and peer-reviewed publication, 32 studies had discrepancies with patient baseline characteristics, and 14 studies had discrepancies in reporting that led to changes in risk of bias ratings. No substantive differences were found for 26 studies.

All analyses reached convergence based on trace plots and a Brooks-Gelman-Rubin statistic less than 1.05, except comparisons including umifenovir for mortality because no patients randomised to either of these drugs died, interleukin-6 inhibitors and doxycycline with ivermectin for adverse events, proxalutamide for hospital admission, and sulodexide for clinically important bleeding.

Risk of bias in included studies

The supplementary material presents the assessment of risk of bias of the included studies for each outcome: 121 studies were judged at low risk of bias in all domains for at least one outcome.

Effects of the interventions

The supplementary material presents the network plots depicting the interventions included in the network meta-analysis of each outcome. Figure 2 presents a summary of the effects of the interventions on the outcomes. The supplementary file also presents detailed relative and absolute effect estimates and certainty of the evidence for all comparisons and outcomes. We did not detect statistical incoherence in any of the network meta-analyses.

Mortality

Two hundred and sixty seven trials with 138 345 participants met the threshold of analysing treatments with a minimum of 100 patients or 20 events and were included in the network meta-analysis (supplementary file). Supplementary figure S1 on bmj.com shows the network plot for mortality, with each edge representing a direct comparison between two interventions. Fifty seven different interventions were included: the most common were standard care/placebo (252 trials, 69 448 participants), colchicine (7 trials, 8194 participants), aspirin (3 trials, 7716 participants), hydroxychloroquine (35 trials, 4955 participants), remdesivir (9 trials, 5044 participants), lopinavir-ritonavir (11 trials, 4153 participants), interleukin-6 receptor antagonists with corticosteroids (32 trials, 4153 participants), and corticosteroids (13 trials, 3076 participants).

Interventions with at least moderate certainty of benefit included: systemic corticosteroids (odds ratio 0.80, 95% credible interval 0.65 to 0.94; moderate certainty), interleukin-6 receptor antagonists when given with systemic corticosteroids (0.80, 0.69 to 0.94; moderate certainty), and Janus kinase inhibitors (0.63, 0.47 to 0.83; high certainty) (fig 2). Notable interventions that did not suggest benefit included aspirin (0.93, 0.69 to 1.20; low certainty), azithromycin (0.98, 0.78 to 1.25, low certainty), colchicine (0.93, 0.65 to 1.16; low certainty), fluvoxamine (0.68, 0.33 to 1.32; low certainty), full-dose anticoagulation (0.96, 0.78 to 1.16; low certainty), hydroxychloroquine (1.08, 0.92 to 1.27; moderate certainty), interleukin-6 receptor antagonists without concurrent corticosteroids (1.09, 0.91 to 1.31; moderate certainty), ivermectin (0.63, 0.37 to 1.05; low certainty), lopinavir-ritonavir (1.06, 0.88 to 1.28; low certainty), and remdesivir (odds ratio 0.91, 0.73 to 1.11; low certainty).

Mechanical ventilation

One hundred and forty trials with 93 968 participants met the threshold of analysing treatments with a minimum of 100 patients or 20 events and were included in the network meta-analysis (supplementary appendix). Forty four interventions were included: the most common interventions were standard care (132 trials, 47 865 participants), colchicine (5 trials, 6313 participants), aspirin (2 trials, 5157 participants), remdesivir (7 trials, 3981 participants), lopinavir-ritonavir (7 trials, 3628 participants), hydroxychloroquine (15 trials, 3474 participants), azithromycin (6 trials, 3400 participants), interleukin-6 receptor antagonists with systemic corticosteroids (11 trials, 2399 participants), and corticosteroids (9 trials, 1171 participants).

Compared with standard care, interventions that reduce risk of mechanical ventilation include interleukin 6 receptor antagonists when given with systemic corticosteroids (0.79, 0.63 to 0.98; moderate certainty) and interleukin-6 receptor antagonists without corticosteroids (0.58, 0.35 to 0.97; high certainty) (fig 2). Other interventions may reduce risk of mechanical ventilation including corticosteroids (odds ratio 0.79, 0.58 to 1.05; low certainty), Janus kinase inhibitors (0.78, 0.56 to 1.04; moderate certainty), and remdesivir (0.79, 0.60 to 1.01; low certainty).

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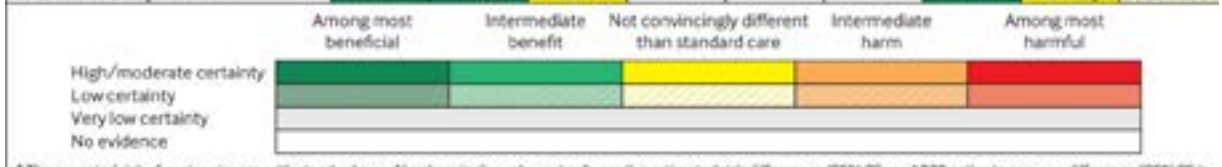
	Mortality	Mechanical ventilation	Adverse events‡	Admission to hospital	Venous thrombo-embolism	Clinically important bleeding	Length of hospital stay	Time to symptom resolution	Duration of mechanical ventilation
Baseline risk*	130 per 1000	116 per 1000	0 per 1000	43 per 1000	32 per 1000	17 per 1000	12.8 days	9.9 days	14.7 days
Minimal important difference†	10 per 1000	15 per 1000	20 per 1000	10 per 1000	10 per 1000	20 per 1000	1 day	1 day	1 day
(Acetyl) cysteine	-17 (-74 to 66)	-16 (-64 to 53)	0 (-24 to 23)				0.1 (-2.7 to 3.0)§		
(Hydroxy) chloroquine	10 (-9 to 30)	28 (3 to 58)	13 (2 to 24)	0 (-21 to 23)			2.0 (0.0 to 3.9)	-1.2 (-2.3 to 0.1)	
ACEI/ARB	-15 (-53 to 35)	1 (-36 to 46)	4 (-19 to 27)				-0.5 (-3.6 to 2.6)		
Antihepaciviral	-23 (-52 to 10)	-27 (-64 to 22)	0 (-9 to 8)				-1.2 (-4.4 to 2.0)	-2.7 (-4.2 to -0.9)	
Aspirin	-7 (-35 to 21)	-8 (-43 to 32)	9 (-6 to 24)	-42 (-43 to -41)	838 (12 to 9668)	21 (-14 to 121)	-0.7 (-5.6 to 4.2)		
Aspirin, statins	68 (-52 to 255)	69 (-49 to 251)	0 (-9 to 9)				0.3 (-1.0 to 1.7)§		
Azithromycin	-2 (-25 to 25)	-6 (-35 to 26)	-2 (-24 to 20)	6 (-18 to 48)			0.2 (-3.5 to 3.9)	-4.2 (-5.5 to -2.8)	
Azithromycin, hydroxychloroquine	-28 (-88 to 61)	76 (-10 to 191)	5 (-13 to 23)	14 (-25 to 89)			0.4 (-0.8 to 1.5)§		
Azithromycin, hydroxychloroquine, oseltamivir	164 (-54 to 517)		55 (12 to 99)				6.8 (-1.1 to 14.8)	2.7 (-2.0 to 9.2)	
Azithromycin, lopinavir-ritonavir			-1 (-24 to 23)						
Azithromycin, NSAID	24 (-85 to 225)	-56 (-115 to 156)							
Azithromycin, NSAID, corticosteroid	-27 (-107 to 147)	-8 (-107 to 269)							
Cefepime	373 (-130 to 870)							-3.2 (-5.4 to -0.3)	
Ceftazidime	372 (-130 to 870)							-2.7 (-5.1 to 0.4)	
Clarithromycin								-5.4 (-6.7 to -3.5)	
Colchicine	-8 (-39 to 18)	-21 (-51 to 11)	25 (-10 to 59)	-6 (-27 to 30)			-0.5 (-3.8 to 2.8)		
Colchicine, emtricitabine, tenofovir, statins	-49 (-90 to 15)	-29 (-75 to 45)	32 (3 to 61)				0.1 (-7.1 to 7.3)		
Colchicine, statins	-20 (-72 to 56)	10 (-54 to 104)	14 (-8 to 35)				-0.0 (-7.2 to 7.2)		
Corticosteroids (systemic)	-23 (-40 to -7)	-22 (-45 to 4)					1.0 (-2.1 to 4.2)		-1.4 (-3.4 to 0.6)
Doxycycline	243 (-33 to 669)	-44 (-105 to 102)					-1.3 (-2.6 to -0.0)§	0.2 (-3.1 to 4.4)	
Doxycycline, ivermectin	-125 (-130 to -83)		10 (-7 to 27)					-1.8 (-4.5 to 1.9)	
Doxycycline, lopinavir-ritonavir			-5 (-27 to 17)						
Electrolyzed saline	-99 (-127 to -30)		27 (-8 to 62)	-26 (-38 to -1)				-4.2 (-6.2 to -1.4)	
Emtricitabine, tenofovir	-25 (-77 to 53)	-18 (-69 to 61)	22 (-2 to 46)				1.0 (-6.3 to 8.2)		
Favipiravir	34 (-41 to 141)	47 (-23 to 142)	5 (-9 to 20)				-1.2 (-2.4 to -0.1)§	-3.0 (-4.2 to -1.6)	
Favipiravir, hydrochloroquine	2 (-72 to 117)	16 (-54 to 124)					1.0 (-1.8 to 3.8)§	3.3 (-2.3 to 11.5)	
Fluvoxamine	-34 (-81 to 35)	-25 (-68 to 39)		-12 (-27 to 9)					
Full-dose anticoagulant	-5 (-26 to 18)	-34 (-75 to 24)	-3 (-29 to 22)	-11 (-35 to 46)	-16 (-22 to -7)	20 (6 to 40)	0.3 (-1.4 to 1.9)§		-0.3 (-1.5 to 0.9)
GM-CSF inhibitor	-26 (-54 to 6)	-3 (-62 to 89)					0.0 (-1.1 to 1.1)§	-0.9 (-2.7 to 1.3)	
IL1 inhibitors	-29 (-64 to 18)	-18 (-61 to 42)	2 (-8 to 12)				-1.0 (-2.2 to 0.2)§	-1.6 (-4.0 to 1.4)	
IL6 receptor antagonists with corticosteroids (systemic)	-23 (-36 to -7)	-22 (-39 to -2)	-4 (-13 to 4)				-4.9 (-7.8 to -1.9)	-1.5 (-3.7 to 1.7)§	-1.0 (-2.2 to 0.2)



* The expected risk of each outcome with standard care. Numbers in the coloured cells are the estimated risk differences (95% CI) per 1000 patients or mean difference (95% CI) in days when compared to standard care
† Minimal important differences were used to support judgements of imprecision
‡ Median rate of adverse events in standard care arm is 0 per 1,000. Therefore, this outcome was analysed as a risk difference
ACEI/ARB: Angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; GM-CSF inhibitor: Granulocyte macrophage colony-stimulating factor inhibitor; IL6 receptor antagonists: Interleukin-6 receptor antagonists; IL1 inhibitors: Interleukin-1 inhibitors; JAKi: Janus kinases inhibitors; NSAID: Non-steroidal anti-inflammatory drugs; SGLT2 inhibitors: Sodium-glucose co-transporter 2 inhibitors; Synthetic VIP: Synthetic vasoactive intestinal peptide
§ Best estimate of effect was obtained from direct evidence.

Fig 2 | Summary of effects compared with standard care

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	Mortality	Mechanical ventilation	Adverse events‡	Admission to hospital	Venous thrombo-embolism	Clinically important bleeding	Length of hospital stay	Time to symptom resolution	Duration of mechanical ventilation
Baseline risk*	130 per 1000	116 per 1000	0 per 1000	43 per 1000	32 per 1000	17 per 1000	12.8 days	9.9 days	14.7 days
Minimal important difference†	10 per 1000	15 per 1000	20 per 1000	10 per 1000	10 per 1000	20 per 1000	1 day	1 day	1 day
IL6 receptor antagonists without corticosteroids (systemic)	11 (-11 to 34)	-44 (-72 to -5)	-2 (-13 to 9)				0.1 (-3.7 to 3.9)	1.0 (-2.0 to 4.8)	-1.6 (-3.3 to 0.1)
Inhaled corticosteroids		11 (-67 to 140)						-0.1 (-3.0 to 3.7)	
Interferon alfa (subcutaneous)	816 (221 to 870)	195 (-94 to 820)					0.1 (-1.0 to 1.2)§	-1.2 (-4.2 to 2.9)	
Interferon beta (subcutaneous)	2 (-28 to 33)	3 (-28 to 41)	0 (-30 to 31)				-0.1 (-3.4 to 3.1)	-1.3 (-3.0 to 0.6)	1.2 (-0.3 to 2.7)
Interferon beta (subcutaneous), lopinavir-ritonavir	110 (20 to 223)	57 (-8 to 139)	291 (216 to 366)				5.0 (3.3 to 6.7)§	-0.1 (-2.6 to 3.1)	
Intermediate-dose anticoagulant	19 (-31 to 83)	19 (-61 to 144)			19 (-10 to 67)	-3 (-14 to 24)			
Intranasal corticosteroids	-116 (-130 to -35)		-8 (-25 to 9)	0 (-29 to 56)				0.3 (-3.6 to 5.6)	
Intranasal hypertonic polymer spray				43 (-24 to 203)					
Ivermectin	-41 (-77 to 7)	2 (-50 to 75)	3 (-4 to 9)	-18 (-32 to 7)			-0.2 (-3.8 to 3.4)	-1.8 (-3.5 to 0.3)	
JAK inhibitors	-44 (-64 to -20)	-23 (-47 to 4)	5 (-6 to 16)				-1.1 (-1.9 to -0.4)§	-0.7 (-2.5 to 1.5)	-3.2 (-5.9 to -0.5)
Lopinavir-ritonavir	7 (-13 to 29)	12 (-13 to 39)	49 (27 to 72)	-8 (-31 to 36)			0.4 (-2.2 to 3.0)	-0.8 (-2.5 to 1.3)	
Melatonin	-119 (-130 to -87)								
Methylene blue	-57 (-93 to -5)						-4.4 (-9.6 to 0.8)§		
Molnupiravir	-116 (-130 to -76)	179 (-116 to 884)	0 (-1.2 to 1.2)†	-19 (-29 to -5)				-3.3 (-4.8 to -1.6)	
Nitazoxanide	-40 (-112 to 110)		2 (-7 to 10)	-14 (-35 to 32)				0.9 (-2.6 to 5.7)	
Omega 3	-108 (-128 to -55)								
Nirmatrelvir/ritonavir	-129 (-130 to -125)		-19 (-38 to 0)	-36 (-41 to -26)					
Probiotics	25 (-98 to 293)		0 (-13 to 13)	709 (-43 to 957)				-2.6 (-5.0 to 0.6)	
Proxalutamide	-111 (-119 to -101)	-107 (-113 to -97)	-2 (-17 to 14)	-41 (-43 to -37)				-7.9 (-8.7 to -6.9)	
Recombinant human granulocyte colony-stimulating factor	-98 (-124 to -43)	-95 (-107 to -75)					-0.7 (-2.3 to 1.0)§	-0.6 (-3.6 to 3.5)	
Remdesivir	-10 (-31 to 12)	-22 (-42 to 1)	6 (-6 to 17)	-29 (-40 to -6)			-0.5 (-3.6 to 2.5)	-1.2 (-2.9 to 0.6)	-1.2 (-3.9 to 1.4)
Serine protease inhibitors	-31 (-95 to 85)	160 (-33 to 497)	-16 (-63 to 33)				-0.3 (-1.7 to 1.0)§	-0.2 (-2.8 to 3.0)	
SGLT2 inhibitors	-28 (-67 to 23)	-17 (-58 to 38)	-17 (-48 to 13)						
Statins	44 (-67 to 219)	36 (-65 to 202)	4 (-8 to 17)				-0.5 (-2.0 to 0.6)§		
Sulodexide	-65 (-119 to 48)	-44 (-105 to 93)	14 (-44 to 73)	-17 (-33 to 15)	25 (-29 to 227)	-14 (-17 to 3)			
Synthetic VIP	23 (-50 to 132)								
Tyrosine kinase inhibitors	-67 (-100 to -19)	-60 (-94 to -3)	62 (19 to 105)				0.7 (-1.0 to 2.3)§		
Umifenovir	-30 (-83 to 53)		5 (-24 to 34)				-1.2 (-3.5 to 1.1)§	-0.2 (-2.8 to 3.0)	
Vitamin C	-38 (-85 to 30)	22 (-42 to 112)					-0.1 (-4.8 to 4.6)	-0.7 (-3.0 to 2.2)	
Vitamin D	-42 (-68 to 27)		-1 (-26 to 24)				-1.4 (-2.8 to -0.2)§		

‖ The expected risk of each outcome with standard care. Numbers in the coloured cells are the estimated risk differences (95% CI) per 1000 patients or mean difference (95% CI) in days when compared to standard care
† Minimal important differences were used to support judgements of imprecision
‡ Median rate of adverse events in standard care arm is 0 per 1,000. Therefore, this outcome was analysed as a risk difference
ACEI/ARB: Angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; GM-CSF inhibitor: Granulocyte-macrophage colony-stimulating factor inhibitor; IL6 receptor antagonists: interleukin-6 receptor antagonists; IL1 inhibitors: interleukin-1 inhibitors; JAK: Janus kinases inhibitors; NSAID: Non-steroidal anti-inflammatory drugs; SGLT2 inhibitors: Sodium-glucose co-transporter 2 inhibitors; Synthetic VIP: Synthetic vasoactive intestinal peptide
§ Best estimate of effect was obtained from direct evidence.

Fig 2 | contd. Summary of effects compared with standard care

Adverse events leading to discontinuation

Ninety nine trials with 31 840 participants met the threshold of analysing treatments with a minimum of 100 patients or 20 events and were included in the network meta-analysis (supplementary appendix). Fourty four interventions were included: the most common interventions were standard care (95 trials, 13 795 participants), molnupiravir (6 trials, 2442 participants), interleukin-6

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receptor antagonists with corticosteorids (6 trials, 1696 participants), remdesivir (6 trials, 1445 participants), and hydroxychloroquine (14 trials, 1257 participants). The drugs with a high risk of adverse effects included hydroxychloroquine (13 more per 1000, 2 more to 24 more; low certainty), lopinavir-ritonavir (49 more per 1000, 27 more to 72 more; moderate certainty), and tyrosine kinase inhibitors (62 more per 1000, 19 more to 105 more; moderate certainty). Several drugs did not have a higher risk of discontinuation for adverse effects than standard care/placebo (fig 2).

Admission to hospital

Thirty five randomised trials with 21 306 participants met the threshold of analysing treatments with a minimum of 100 patients or 20 events and were included in the network meta-analysis (supplementary appendix). Nineteen interventions were included: the most common interventions were standard care (36 trials, 10 492 participants), molnupiravir (5 trials, 2385 participants), colchicine (1 trial, 2235 participants), and fluvoxamine (3 trials, 1093 participants). Molnupiravir (odds ratio 0.54, 0.30 to 0.90; moderate certainty), nirmatrelvir/ritonavir (0.13, 0.04 to 0.40; moderate certainty), and remdesivir (0.25, 0.07 to 0.86; low certainty) probably reduce hospitalisation. There was insufficient evidence to know if any other interventions reduce hospitalisation (fig 2).

Venous thromboembolism

Eleven trials that randomised 6195 participants to five different interventions reported venous thromboembolism. Full dose anticoagulation may reduce odds of venous thromboembolism compared with prophylactic dose anticoagulation (odds ratio 0.50, 0.32 to 0.78; low certainty). The impacts of aspirin, intermediate dose anticoagulation, and sulodexide are less certain.

Clinically important bleeding

Thirteen trials randomised 6732 participants to five different interventions. Full dose anticoagulation may increase the odds of clinically important bleeding compared with prophylactic dose anticoagulation (odds ratio 2.15, 1.35 to 3.52; low certainty). The impacts of aspirin, intermediate dose anticoagulation, and sulodexide are less certain.

Length of hospital stay

One hundred and thirteen trials with 91 270 participants met the threshold of analysing treatments with a minimum of 100 patients and were included in the network meta-analysis (supplementary appendix). Thirty eight interventions were studied: the most common interventions were standard care (107 trials, 48 098 participants), colchicine (6 trials, 5809 participants), remdesivir (6 trials, 4340 participants), hydroxychloroquine (15 trials, 3347 participants), azithromycin (4 trials, 2795 participants), corticosteroids (6 trials, 2694 participants), Janus kinase inhibitors (6 trials, 1778 patients), and interleukin-6 receptor antagonists with systemic corticosteroids (7 trials, 1506 participants).

Compared with standard care, hospitalisation was shorter in patients who received interleukin-6 receptor antagonists with systemic corticosteroids (mean difference −4.7 days, −8.9 to −0.5; moderate certainty) and Janus kinase inhibitors (−1.1 days, −1.9 to −0.4; moderate certainty). Interleukin-6 receptor antagonists probably do not reduce length of hospital stay when given without systemic corticosteroids (0.0 days, −1.2 to 1.2; moderate certainty). Evidence was low or very low certainty for all other interventions (fig 2).

Duration of mechanical ventilation

Twenty eight trials with 3947 participants met the threshold of analysing treatments with a minimum of 100 patients and were included in the network meta-analysis (supplementary appendix). Eight interventions were included: the most common were standard care (28 trials, 1989 participants), interferon beta (2 trials, 502 participants), full dose anticoagulation (1 trial, 308 participants), interleukin-6 receptor antagonists (7 trials, 251 participants), and remdesivir (3 trials, 201 participants). Janus kinase inhibitors probably reduce the duration of mechanical ventilation (−3.2 days, −5.9 to −0.5; high certainty). There was no convincing evidence that any of the other interventions reduce duration of mechanical ventilation (fig 2).

Time to symptom resolution

Seventy nine trials including 26 119 participants met the threshold of analysing treatments with a minimum of 100 patients and were included in the network meta-analysis. Thirty four interventions were studied: the most common interventions were standard care (73 trials, 11 674 participants), Janus kinase inhibitors (4 trials, 1585 participants), molnupiravir (3 trials, 1536 participants), remdesivir (4 trials, 1497 participants), and inhaled corticosteroids (2 trials, 1031 participants). Molnupiravir probably reduces time to symptom resolution (ratio of means 0.66, 0.52 to 0.83; mean difference −3.3 days, −4.8 to −1.6; moderate certainty). No other intervention had at least moderate certainty evidence of benefit or harm (fig 2).

Subgroups and sensitivity analyses

Previous iterations of this living systematic review explored subgroup effects for remdesivir, lopinavir-ritonavir, hydroxychloroquine, corticosteroids, ivermectin, and interleukin-6 receptor antagonists. An additional network meta-analysis limited to interventions of interest for patients with non-severe disease up to 2 February 2022 showed that nirmatrelvir/ritonavir and molnupiravir may reduce mortality (supplementary material). Findings for other outcomes were not meaningfully different from the full network. Among patients with non-severe disease, we did not identify any subgroup effects for molnupiravir, nirmatrelvir/ritonavir, fluvoxamine, or remdesivir.

Discussion

This living systematic review and network meta-analysis provides a comprehensive overview of the evidence for drug treatments of covid-19 up to 1 December 2021 and a comprehensive list of drug trials to 3 December 2021. There are now more than 400 randomised trials examining many different interventions for treating covid-19, and as a result, the certainty in evidence for multiple interventions is improved.

For patients with severe covid-19, three anti-inflammatory drugs probably reduce mortality: systemic corticosteroids, interleukin-6 receptor antagonists (when given with systemic corticosteroids), and Janus kinase inhibitors. Interleukin-6 receptor antagonists, when co-administered with systemic corticosteroids, also probably reduce mechanical ventilation and length of hospital stay. When they are provided without systemic corticosteroids, interleukin-6 receptor antagonists might not reduce mortality or length of hospital stay. The subgroup effect is consistent with evidence from other meta-analyses.[36] A single dose of either sarilumab and tocilizumab appears to be similarly efficacious.[37]

Janus kinase inhibitors probably reduce mortality, length of hospital stay, and duration of mechanical ventilation. The evidence supporting janus kinase inhibitors comes primarily from studies

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that used baricitinib. The RECOVERY trial, which randomized 8156 patients to baricitinib or standard care, was published after our analyses were completed.[38] The RECOVERY trial confirmed that baricitinib reduces mortality. It was also the first study to show that janus kinase inhibitors may have added benefit in patients also receiving interleukin-6 receptor antagonists and systemic corticosteroids.

For patients with non-severe covid-19, three antivirals probably reduce admission to hospital: molnupiravir, nirmatrelvir/ritonavir, and remdesivir. Molnupiravir and nirmatrelvir/ritonavir may also slightly reduce the risk of death. Based on this review, the WHO has recently suggested using one of these antivirals rather than no antiviral.[7] These drugs were all studied in people who were at increased risk of hospitalisation: they had not received a SARS-CoV-2 vaccine and had other risk factors for disease progression. The absolute benefit should therefore be substantially smaller in patients who are vaccinated against SARS-CoV-2 or who do not have risk factors for disease progression. Each of the antivirals has some drawbacks that were not captured in this overview. For example, molnupiravir could be carcinogenic, nirmatrelvir/ritonavir has a large number of critical drug-drug interactions, and remdesivir is administered intravenously.

Full dose anticoagulation, compared with prophylactic dose anticoagulation, may reduce the risk of venous thromboembolism by approximately 16 per 1000 patients and increase the risk of clinically important bleeding by approximately 20 per 1000 patients. There did not seem to be a difference in other outcomes such as mortality or mechanical ventilation.

Several interventions do not seem to have important benefit on any patient-important outcomes, including angiotensin-converting enzyme inhibitors, aspirin, azithromycin, colchicine, hydroxychloroquine, inhaled corticosteroids, intranasal corticosteroids, interferon beta, ivermectin, lopinavir-ritonavir, umifenovir, and vitamin C. Hydroxychloroquine may increase the risk of mechanical ventilation, adverse effects leading to drug discontinuation, and length of hospital stay.

Compared with the fourth iteration, there are several important updates (box 2). We now have evidence from several large scale international trials on azithromycin, interleukin-6 inhibitors, molnupiravir, nirmatrelvia/ritonavir, Janus kinase inhibitors, full dose anticoagulation, and colchicine.

Box 2: Summary of changes since last iteration

- Two hundred and sixty seven trials and 89 814 participants are new from the previous iteration
- Additional evidence for Janus kinase inhibitors suggests that they probably reduce mortality in patients with severe covid-19
- Additional evidence suggests that colchicine probably does not have any important benefit (the previous iteration suggested that it might)
- New evidence suggests that the antivirals molnupiravir and nirmatrelvir/ritonavir probably reduce hospitalisation in patients with non-severe covid-19, while remdesivir might

Strengths and limitations of this review

Our search strategy and eligibility criteria were comprehensive, without restrictions on language of publication or publication status. To ensure expertise in all areas, our team is composed of clinical and methods experts who have undergone training and calibration exercises for all stages of the review process. To minimise problems with counterintuitive results, we anticipated challenges that arise in network meta-analysis when data are sparse.[39] Many of the results for comparisons with sparse data were uninformative and were sometimes implausible. For that reason, we decided to report evidence on treatments for which at least 100 people were randomised or for which there were at least 20 events.

The primary limitation of the evidence for most interventions is lack of blinding, which might introduce bias through differences in co-interventions between randomised groups. We chose to consider the treatment arms that did not receive an active experimental drug (that is, placebo or standard care) within the same node: it is possible that the unblinded standard care groups received systematically different co-interventions than groups randomised to receive a placebo. Direct comparisons in which the evidence is dominated by unblinded studies were rated down, consistent with GRADE, for risk of bias and that is reflected in the rating of the quality of evidence from the network estimate.[40] Many of the data also had reporting concerns. For some outcomes, the method in which the researchers measured and reported outcomes proved inconsistent across studies. This led the team to propose a hierarchy for the outcome mechanical ventilation, as described in the methods.

The living nature of our systematic review and network meta-analysis could conceivably (at least temporarily) amplify publication bias, because studies with promising results are more likely to be published and are published sooner than studies with negative results. The inclusion of preprints, many of which have negative results, might reduce this risk. However, the inclusion of preprints in our network meta-analysis might introduce bias from simple errors and the reporting limitations of preprints. We include preprints because of the urgent need for information and because so many of the studies on covid-19 are published first as preprints. So far, differences between preprints and peer reviewed publications have mostly been limited to additional baseline patient information, clarification on study design, and outcomes reported in the peer reviewed publications. None of these changes would have resulted in a meaningful change to pooled effect estimates or certainty for any outcome.[41]

Our living systematic review and network meta-analysis will continue to inform the development of the WHO living guidelines and *BMJ* Rapid Recommendations.[6 19] An important difference in the methods for assessing the certainty of the evidence does, however, exist between the two. In this living systematic review and network meta-analysis, we use a minimally contextualised approach for rating the certainty of the evidence, whereas the guideline panels use a fully contextualised approach in which the thresholds of importance of magnitudes of effects depend on all other outcomes and factors involved in the decision.[29] The contextualisation explains differences in the certainty of the evidence between the two. We used observational data to inform the absolute risk estimates for some outcomes; differences in baseline risk can impact GRADE assessments for imprecision.

To date, we are aware of two other similar efforts to ours.[42 43] Our intention is different in that the results fully inform clinical decision making for the associated living guidance.[6] We also include a more comprehensive search for the evidence and several differences in analytical methods, which we believe are best suited for this evidence. For example, some others use fixed rather than random effects meta-analysis and provide estimates for pairwise comparisons only. It is also important to evaluate the reproducibility and replicability of findings from different scientific approaches.

This is the final version of this particular living systematic review and network meta-analysis. Mounting evidence suggests that

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antivirals (such as molnupiravir and nirmatrelvir) are most effective in the early stages of covid-19 when patients have non-severe disease, whereas anti-inflammatories (such as corticosteroids) seem to be most effective in the later disease stages. Therefore, going forward, we will perform separate living network meta-analyses for non-severe covid-19 and severe covid-19. Updates will continue to be published on covid19lnma.com.

Conclusions

Evidence from this living systematic review and network meta-analysis suggests that systemic corticosteroids, interleukin-6 receptor antagonists, and Janus kinase inhibitors reduce mortality and have other important benefits in patients with severe covid-19. Molnupiravir, nirmatrelvir/ritonavir, and remdesivir probably reduce hospitalisation in patients with non-severe covid-19. All other interventions either are probably not beneficial, or the evidence remains highly uncertain regarding their impacts on patient-important outcomes.

What is already known on this topic

- Despite huge efforts to identify effective drug interventions for coronavirus disease 2019 (covid-19), evidence for effective treatment remains limited

What this study adds

- This living systematic review and network meta-analysis provides a comprehensive overview and assessment of the evidence published as of 3 December 2021
- The certainty of the evidence for most interventions is low or very low, including ivermectin
- In patients with severe covid-19, systemic corticosteroids, interleukin-6 receptor antagonists, and Janus kinase inhibitors probably reduce mortality
- In patients with non-severe covid-19, molnupiravir, nirmatrelvir/ritonavir, and remdesivir probably reduce hospital admission

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RACS affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Dissemination to participants and related patient and public communities: The infographic and MAGICapp decision aids (available at www.magicapp.org/) were created to facilitate conversations between healthcare providers and patients or their surrogates. The MAGICapp decision aids were co-created with people who have lived experience of covid-19.

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Data sharing: No additional data available.

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Web appendix: Supplementary material for update 4 of this review

Fig S1. Network plot for mortality. The size of the circles is proportional to the number of patients randomised to that intervention and the size of the lines is proportional to the inverse of the standard error of the effect estimate

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Document 1.6

Liverpool Drug Interactions Group Drug-Drug Interactions with Key COVID-19 Therapies (May 31, 2023 update)

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Document 1.7

Efficacy of Antiviral Agents against the SARS-CoV-2 Omicron Subvariant BA.2

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Document 1.8

Remdesivir, Molnupiravir and Nirmatrelvir remain active against SARS-CoV-2 Omicron and other variants of concern

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Remdesivir, Molnupiravir and Nirmatrelvir remain active against SARS-CoV-2 Omicron and other variants of concern

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A B S T R A C T

We assessed the *in vitro* antiviral activity of remdesivir and its parent nucleoside GS-441524, molnupiravir and its parent nucleoside EIDD-1931 and the viral protease inhibitor nirmatrelvir against the ancestral SARS-CoV2 strain and the five variants of concern including Omicron. VeroE6-GFP cells were pre-treated overnight with serial dilutions of the compounds before infection. The GFP signal was determined by high-content imaging on day 4 post-infection. All molecules have equipotent antiviral activity against the ancestral virus and the VOCs Alpha, Beta, Gamma, Delta and Omicron. These findings are in line with the observation that the target proteins of these antivirals (respectively the viral RNA dependent RNA polymerase and the viral main protease Mpro) are highly conserved.

One and a half year after the start of the global COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), multiple variants have emerged. These can be harmless or slightly beneficial for the virus, causing for example increased transmission, virulence, or immune escape (Davies et al., 2021; Sabino et al., 2021; Mahase, 2021). SARS-CoV-2 genetic diversification was initially considered slow when the virus was spreading in early 2020. The first official *variant*, a single spike D614G mutation found in early European lineages, was linked to more efficient transmission (Volz et al., 2021) and rapidly spread to become the dominant viral strain worldwide. Late 2020, multiple variants emerged that spiked regional epidemics. Five 'variants of concern' (VOC) have been identified (Alpha, Beta, Gamma, Delta and Omicron). All have characteristic mutations (www.ecdc.europa.eu/en/covid-19/variants-concern). The spike (S) glycoprotein appears especially prone to accumulate mutations (Saputri et al., 2020) and all of the circulating VOCs have some mutations that favor evasion from the host immune response (Khateeb et al., 2021). Numerous spike-protein based vaccines were developed and vaccination programs are running at full speed. However, studies of sera and emerging real-world evidence indicate that Omicron escapes the immunity whether from previous infection or vaccination (Cohen, 2021).

Several direct-acting antivirals against SARS-CoV-2 have been approved or are advancing in clinical development. They can be divided in two classes, monoclonal antibodies (mAbs) directed against the Spike protein and small molecules interfering with the viral replication machinery. mAbs are administered intravenously but studies are underway to explore intramuscular or subcutaneous administration which would overcome the requirement of a hospital setting for dosing. (Kumar et al., 2021). Recent cell culture data indicates that the SARS-CoV-2 variant of concern (VOC) Omicron is not susceptible to most of the approved mAbs making it unlikely that their clinical efficacy will be maintained (Alexander Wilhelm et al., 2021; VanBlargan et al., 2022).

The direct-acting small-molecule SARS-CoV-2 antivirals that have received approval or emergency use authorization do not target the variable spike-protein but target either the conserved viral RNA-dependent RNA polymerase (RdRp) or the conserved viral main protease (Mpro or 3CL protease). Remdesivir, a monophosphoramidate prodrug of the nucleoside GS-441524, originally developed to treat Ebola virus infections, inhibits the RdRp of SARS-CoV-2. It was the first antiviral approved or authorized for emergency use to treat COVID-19 in several countries. Remdesivir improves clinical outcomes in patients hospitalized with moderate-to-severe disease and it prevents disease

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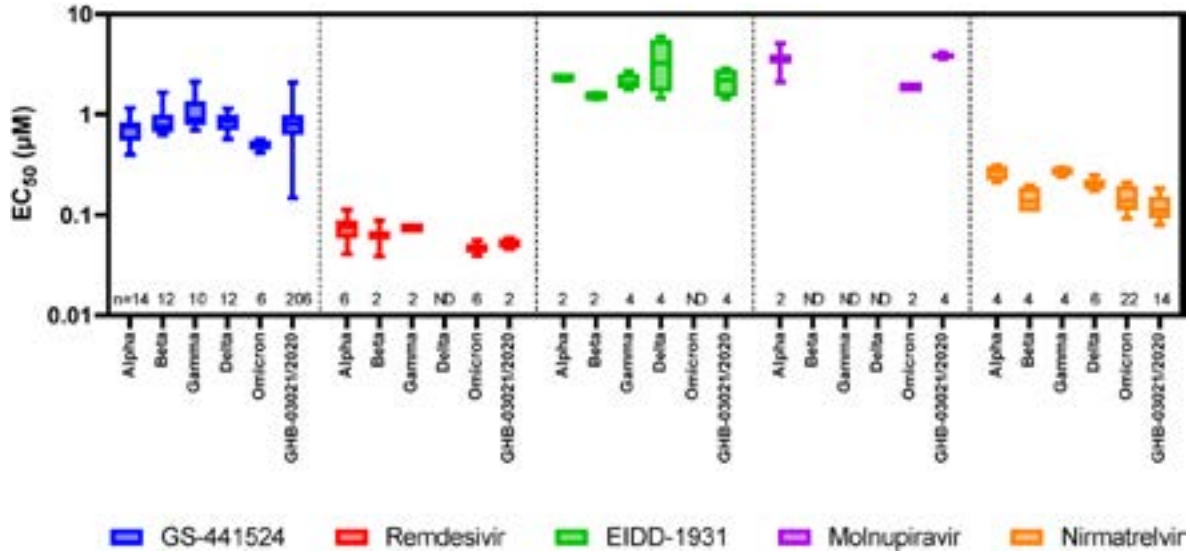

Fig. 1. Activity of various antivirals upon infection of VeroE6-GFP cells with different SARS-CoV-2 VOC. VeroE6-GFP cells were pre-treated overnight with serial dilutions of the compounds. The next day, cells were infected with SARS-CoV-2 at a multiplicity of infection (MOI) of 0.001 tissue culture infectious dose ($TCID_{50}$) per cell. The number of fluorescent pixels of GFP signal, determined by high-content imaging on day 4 post-infection, was used as read-out. The percentage of inhibition was calculated by subtracting background (number of fluorescent pixels in the untreated infected control wells) and normalizing to the untreated-uninfected control wells (also background subtracted). The 50% effective concentration (EC_{50}, the concentration of compound required for fifty percent recovery of cell-induced fluorescence) was determined using logarithmic interpolation. These experiments were performed in the presence of the Pgp-inhibitor CP-100356 (0.5 µM) in order to limit compound efflux. This graph was created using Graphpad Prism 9.2.0. The boxes extend from the 25th to 75th percentiles while the whiskers indicate the minimal and maximal values. The numbers above the X-axis indicate the number of measurements for each condition. While we determined the EC_{50} of remdesivir, molnupiravir and nirmatrelvir on Omicron we did not determine the EC_{50} on all VOC for all compounds tested. Due to time constrains we only used historical data from our database for the other VOCs and thus some of the values are depicted as "ND" ("Not Determined"). For the same reason, we included EIDD-1931 to allow comparison with molnupiravir as both compounds are intracellularly converted to the same antiviral molecule and thus have the same EC_{50}. The individual EC_{50}s values of this study are available at Mendeley Data (https://doi.org/10.17632/bmjc74dyjs.1).

progression in outpatients (Beigel et al., 2020; Gottlieb et al., 2021). While remdesivir requires intravenous administration, an oral prodrug of GS-441524 is being developed (Cox et al., 2021). Molnupiravir (MK-4482 or EIDD-2801), a prodrug of the nucleoside analogue EIDD-1931 (β-D-N4-hydroxycytidine), is another inhibitor of the viral RdRp and was originally developed against different RNA viruses such as influenza (Painter et al., 2021). A phase 2a clinical trial of molnupiravir in patients with COVID-19 shows accelerated SARS-CoV-2 RNA clearance and elimination of infectious virus (Fischer et al., 2021). This orally bioavailable drug was recently authorized in the UK for use in people who have mild to moderate COVID-19 and who have at least one risk factor for developing severe illness. Also, the U.S. FDA issued an emergency use authorization (EUA) in infected adults who are at high risk for progression to severe COVID-19, and for whom alternative COVID-19 treatment options are not accessible or clinically appropriate.

Another target for antiviral drugs is the viral main protease Mpro (or 3CL protease), a cysteine protease which cleaves the two polyproteins (pp1a and pp1ab) of SARS-CoV-2 at multiple locations, resulting in the various non-structural proteins, which are key for viral replication. Nirmatrelvir (PF-07321332), is an irreversible inhibitor of SARS-CoV-2 Mpro that is co-formulated with ritonavir allowing an oral route of administration (known as Paxlovid). When treatment is initiated during the first days after symptom onset, it results in roughly a 90% protection against severe COVID-19 and hospitalization (Owen et al., 2021). Even though the Mpro-gene can be slightly affected by evolutionary mutations, the antiviral potency does not seem to be compromised (Sven Ullrich et al., 2021).

We here assess the *in vitro* antiviral effect of GS-441524, remdesivir, EIDD-1931, molnupiravir and nirmatrelvir against the various SARS-CoV-2 VOCs, including Omicron.

The SARS-CoV-2 antiviral assay is based on the previously established SARS-CoV assay(Ivens et al., 2005). Upon infection the fluorescence of VeroE6-GFP cell cultures declines due to a cytopathogenic effect. In the presence of an antiviral compound, the cytopathogenicity is inhibited and the fluorescent signal maintained. To this end VeroE6-GFP cells (kindly provided by Marnix Van Loock, Janssen Pharmaceutica, Beerse, Belgium), were used as described previously (Do et al., 2021; Rana Abdelnabi et al., 2021). Since VeroE6 cells show a high efflux of some chemotypes, the antiviral assays were performed in the presence of the P-glycoprotein (Pgp) efflux inhibitor CP-100356 (0.5 µM)(Hoffman et al., 2020). A SARS-CoV-2 strain grown from the first Belgian patient sample (GHB-03021/2020), was used as ancestral strain as it is closely related to the prototypic Wuhan-Hu-1 2019-nCoV (GenBank accession number MN908947.3) (Boudewijns et al., 2020). All the other isolates were obtained from patients in Belgium and more information can be found in GISAID (Alpha = EPI_ISL_791333; Beta = EPI_ISL_896474; Gamma = EPI_ISL_1091366; Delta = EPI_ISL_2425097; Omicron = EPI_ISL_6794907). The multiplicity of infection (MOI) was kept constant for the different VOC to allow comparison of the potency.

Our *in vitro* results show that GS-441524, remdesivir, EIDD-1931, molnupiravir and nirmatrelvir retain their activity against all current VOCs including Omicron (Fig. 1). The maximal change of the median EC_{50}s over the different VOC is for each compound < 3x (1.8x for GS-441524, 1.6x for remdesivir, 2.5x for the series EIDD-1931 and molnupiravir and 2.5x for nirmatrelvir). In our experience these results are within the normal range of measurement error. For example, the ratio between the 95% and 5% percentile of the EC_{50}s of GS-441524 on GHB-03021/2020 is 2.9x (n = 206; calculated using Graphpad v9.2.0). So only differences in EC_{50}s of >3x and with statistical significance should be considered as meaningful differences using this methodology. The individual EC50s values of this study are available at Mendeley Data (https://doi.org/10.17632/bmjc74dyjs.1).

The fact that these antivirals retain their activity on the different SARS-CoV-2 VOCs is in accordance with the observation that the target proteins of these antivirals are highly conserved. For the RdRp there are only two amino acid changes (P323L in all VOCs and G671S in Delta;

position 4715/5063 in ORF1ab or 314/662 in ORF1b respectively) when compared with the ancestral lineage (NC_045512). As these are distant from the active site, a different susceptibility towards remdesivir or molnupiravir is not to be expected. For the Mpro there are also two amino acid changes described (K90R in Beta and P132H in Omicron; position 3353 and 3395 in ORF1ab respectively). Alike for the RdRp, these mutations are not located near the active site of the Mpro and hence no difference in susceptibility for nirmatrelvir is expected.

These results indicate that when more VOCs arise, due to antigenic drift, there is a high probability that they will remain sensitive towards current (and likely also future) antivirals that do not target the spike. It is therefore of utmost importance to develop more pan-corona antivirals as they will be an essential armor and complement vaccines in the strategy to control the current pandemic (Torneri et al., 2020).

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Efficacy of Antiviral Agents against Omicron Subvariants BQ.1.1 and XBB

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Document 1.10

Impact of the Use of Oral Antiviral Agents on the Risk of Hospitalization in Community Coronavirus Disease 2019 Patients (COVID-19)

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Document 1.11

Real-world effectiveness of early molnupiravir or nirmatrelvir-ritonavir in hospitalised patients with COVID-19 without supplemental oxygen requirement on admission during Hong Kong's omicron BA.2 wave: a retrospective cohort study

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Effectiveness, Tolerability and Prescribing Choice of Antiviral Molecules Molnupiravir, Remdesivir and Nirmatrelvir/r: A Real-World Comparison in the First Ten Months of Use

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Effectiveness, Tolerability and Prescribing Choice of Antiviral Molecules Molnupiravir, Remdesivir and Nirmatrelvir/r: A Real-World Comparison in the First Ten Months of Use

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Abstract: In 2022, three antiviral drugs—molnupiravir, remdesivir and nirmatrelvir/ritonavir—were introduced for treatment of mild-to-moderate COVID-19 in high-risk patients. The aim of this study is the evaluation of their effectiveness and tolerability in a real-life setting. A single-center observational study was set up, with the involvement of 1118 patients, with complete follow-up data, treated between the 5th of January and the 3rd of October 2022 at Santa Maria Goretti's hospital in Latina, Central Italy. A univariable and a multivariable analysis were performed on clinical and demographic data and composite outcome, the persistence of symptoms at 30 days and time to negativization, respectively. The three antivirals showed a similar effectiveness in containing the progression of the infection to severe COVID-19 and a good tolerability in the absence of serious adverse effects. Persistence of symptoms after 30 days was more common in females than males and less common in patients treated with molnupiravir and nirmatrelvir/r. The availability of different antiviral molecules is a strong tool and, if correctly prescribed, they can have a significant role in changing the natural history of infection for frail persons, in which vaccination could be not sufficient for the prevention of severe COVID-19.

Keywords: antivirals; molnupiravir; remdesivir; nirmaltrelvir/ritonavir; early therapy; COVID-19; SARS-CoV2

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1. Introduction

In the early history of the SARS-CoV-2 pandemic, limited therapeutic possibilities were available. However, thanks to the strong global effort of the international scientific community, some new strategies were developed. In particular, at the very beginning, molecules already employed for treating other diseases, such as hydroxychloroquine, chloroquine, lopinavir–ritonavir and ivermectin [1], but also bioactive natural products and small-molecule inhibitors, were used in order to treat patients with severe COVID-19 [2,3].

Since January 2022, three antiviral drugs against SARS-CoV-2 were introduced in Italy, molnupiravir (MP), remdesivir (RDV) and nirmaltrelvir/ritonavir (NMV/r), available for patients with SARS-CoV-2 infection with a high risk of progression to severe illness. Specifically, MP was introduced on the 29 December 2021 (Agenzia Italiana del Farmaco, AIFA note n°1644/2021); RDV was introduced as a three-day scheme for non-hospitalized

patients on the 7 January 2022 (AIFA note n°92/2020); and NMV/r was introduced on 1 February 2022 (AIFA note n°15/2022) [4].

These three antivirals act with different mechanisms of action. In particular, RDV and MP are both prodrugs and act as viral RNA-dependent RNA polymerase (RdRp) inhibitors, interfering with the genomic replication, but with different mechanisms.

In fact, MP is converted into an active nucleoside b-D-N4-hydroxycytidine by esterases present in the plasma [5], inhibiting SARS-CoV-2 replication by a mechanism known as "lethal mutagenesis" and preventing viral propagation by fostering error accumulation in a process referred to as "error catastrophe" [cit], while RDV (GS-5734) is a phosphoramidite prodrug of an adenosine monophosphate analog, metabolized into its pharmacologic analog adenosine triphosphate, acting as a non-obligate chain terminator [6].

NMV/r is a viral protease inhibitor that binds the enzymatic catalytic cysteine residue (Cys145), blocking the viral assembly; ritonavir acts as a pharmacologic booster of nirmatrelvir, inhibiting the CYP3A4 enzyme in order to maintain high plasmatic levels of nirmatrelvir itself [7].

Registration studies, such as "MoveOut" for MP, "Pinetree" for RDV and "Epic-Hr" for NMV/r, have shown similar and good tolerability for the three drugs, but different results in terms of efficacy defined as no progression to death or hospitalization [8–10]. In fact, RDV and NMV/r were associated with greater efficacy compared to placebo, reporting a relative reduction in death and hospitalization by 89% and 88%, respectively. MP reported a relative reduction in death and hospitalization by 30%.

However, these studies presented some limits. First of all, people with mild-to-moderate SARS-CoV-2 infection were enrolled during the prevalence of the Delta variant of SARS-CoV-2, but in clinical practice, the antiviral drugs were used during the prevalence of the Omicron variant [8–10]. Furthermore, among the people who received antiviral treatment, a high portion did not match the clinical characteristics required to be a candidate for early treatment. In particular, people enrolled had a median age of 40, had no more than one comorbidity, were not vaccinated, and patients affected by immunodeficiency were not considered in these studies.

Considering these limitations, along with the low number of studies that compare the three drugs [11–13], this study has the aim of comparing the three molecules in a real-life setting, evaluating their impact in an everyday clinical practice. In other terms, this study has the purpose of evaluating and comparing the three drugs in terms of effectiveness and tolerability, in order to understand which of them could be more suitable for the peculiar clinical features of each patient and offer a personalized treatment.

2. Materials and Methods

2.1. Study Design

This is a single-center observational real-world study (RWS) of a cohort of patients with a confirmed diagnosis of SARS-CoV-2, through a positive nasopharyngeal swab (NPS). Only non-hospitalized patients with mild-to-moderate COVID-19 disease and one or more risk factors for progression to severe illness, as defined by the European Medicines Agency (EMA) [14] and AIFA guidelines [4], were considered eligible for early treatment. According to the aforementioned guidelines, risk factors include: body mass index (BMI) >30, diabetes mellitus (DM), chronic kidney failure (CKD), immunodeficiency, neurological diseases, cardiovascular diseases, lung diseases, age >65, hospitalization for other diseases, chronic hepatopathy, active oncological diseases and haemoglobinopathies.

Patients treated with early RDV (three-day scheme) who were hospitalized for other diseases different from COVID-19 illness or were in the emergency room were excluded from the study in order to make the three groups of treatment more homogeneous, including only outpatients. In fact, inpatients showed a different baseline from outpatients in terms of severity of comorbidities and clinical symptoms not directly related to SARS-CoV-2 infection, which had an impact on the progression of COVID-19 disease.

2.2. Study Setting

A clinic for early COVID-19 was set up at Santa Maria Goretti Hospital, in Latina, Central Italy, at the beginning of March 2021, and was dedicated to providing early treatment for COVID-19 to high-risk outpatients. From the 5 January, when all three antivirals were available, to the 3 October 2022, 3206 patients were treated, when VOCs (variants of concern) Omicron BA.1, BA.2, BA.4 and BA.5 were prevalent in Italy [15].

Patients were considered suitable for therapy if they tested positive for SARS-CoV-2 (NPS) and had at least one risk factor for severe COVID-19, as indicated by AIFA [4]. There were three main possible ways of recruitment: referral by general practitioner (GP), hospital specialists, or self-referral by a phone regional system, as shown in Figure 1. After receiving the application, patients suitable for the enrollment were reached by telephone for an opening counseling considering their clinical features, such as weight and height, to calculate filtrate glomerular rate (FGR), and social conditions. Firstly, general clinical conditions and COVID-19-related symptoms were investigated, in order to stratify risk, then polypharmacy was evaluated, especially potential interactions with NMV/r since it cannot be prescribed if patients' home therapy includes drugs such as new oral anticoagulants (e.g., Apixaban), atypical antipsychotic drugs (e.g., Quetiapine) and other drugs [16]. Oral therapy with MP or NMV/r was also not considered if patients were dysphagic, preferring intravenous therapy with RDV, in absence of FGR lower than 30 mL/min or alanine aminotransferase (ALT) five times higher than normal levels. When the choice of hospital intravenous administration of RDV was made, and if the patient could not come to the clinic on their own, the hospital provided ambulance transportation.

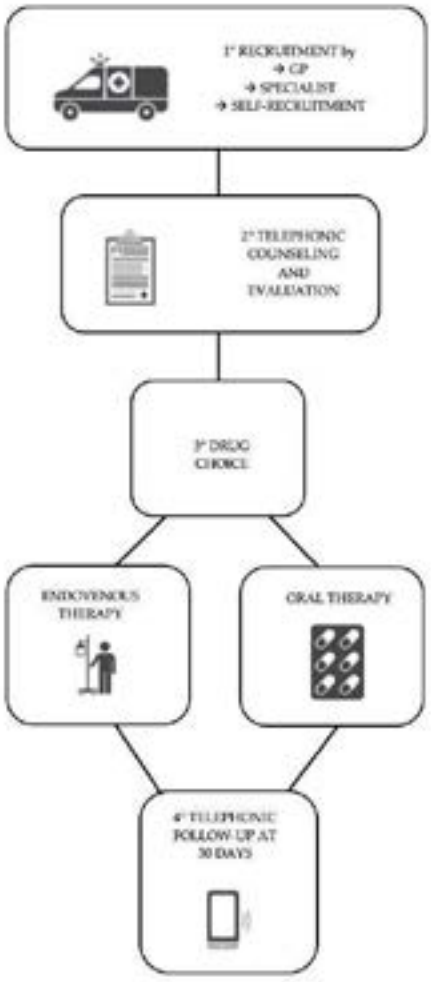

Figure 1. Patients' recruitment algorithm.

Only after acquiring patients' consensus was the adequate molecule prescribed with the right posology. If an oral antiviral was chosen, it was collected by a patient's relative. Meanwhile, patients treated with RDV were evaluated at the clinic by a medical and nurse team and its 2 h administration was done while monitoring vital signs. In the following days, higher risk patients were monitored by a telemedicine system and the ones who showed any signs of worsening were invited to the emergency department and admitted when needed.

After 30 days from the start of therapy, a telephone follow-up was performed and clinical data about the effect of the three molecules were collected. In particular, we evaluated the persistence of symptoms (e.g., dyspnea, arthromyalgia, fever, cough, rhinitis, gastrointestinal problems, asthenia), evolution of illness (pneumonia, acute respiratory distress syndrome (ARDS), hospitalization or death), time to negativization and eventual adverse effects. In more details we considered ARDS as established by the Berlin definition [17], based on a pO_2/FiO_2 ratio <300.

Patients also received a diary in which they could annotate, for 30 days, the presence of COVID-19-related symptoms, adverse effects and vital signs. Patients treated with parenteral RDV reported the presence of side effects through interviews; in other cases, clinicians who were present during the administration of the drug directly observed early adverse reactions. In a minority of cases, if telephonic follow-up could not be performed, clinical data were collected by consulting a regional platform of COVID-19 positivity or medical records of hospitalization.

The EMA and AIFA's guidelines for excluding patients from one treatment rather than another were strictly followed.

2.3. Patient Characteristics

The demographic data collected were age and sex; clinical data were SARS-CoV-2 vaccinal status (date of the last dose), comorbidities, home therapy, necessity of transport to hospital, persistence of COVID-19-related symptoms after 30 days, progression to severe illness (pneumonia, ARDS) or death (COVID-19 and no COVID-19), time to negativization and adverse effects.

For comorbidities, a focus on immunocompromised patients was conducted, and they were further subdivided into groups based both on their disease or therapy: hematological, solid tumors, HIV infection, transplant patients, autoimmune diseases which require chronic immunosuppressive therapy (rheumatological and neurological ones, prevalently) and any other immunosuppressant comorbidities (e.g., diabetes mellitus).

2.4. Outcome

The aim of this study is to compare the three antiviral drugs in terms of effectiveness, tolerability and prescribing choice, considering these endpoints:

- composite endpoint (pneumonia, ARDS, COVID-19 and non-COVID-19-related death) in all the patients and in the immunocompromised subgroup;
- persistence of symptoms at 30 days (assessed by phone call);
- NPS negativization (according to the date reported in the regional platform of COVID-19 patients).

We also evaluated the percentage of the most common adverse effects for the three molecules, such as diarrhea, fever, nausea and vomiting, post-infusion tachycardia, hypertension, rash, headache, mucositis, hypotension, dizziness, metallic taste, inappetence, increased liver markers, abdominal pain and fatigue.

To study the persistence of symptoms at 30 days, according to the criteria established by the National Institute for Health and Care Excellence (NICE) and the World Health Organization (WHO), we studied which demographic and clinical features could influence the presence of post–acute COVID-19 syndrome, defined as a set of signs and symptoms that emerge during or after an infection consistent with COVID-19, persist for more than 12 weeks and are not explained by an alternative diagnosis [18,19]. More precisely, many

experts, including the NICE panel, agree with subdividing into two categories the immediate outcome: a post COVID-19 subacute phase of ongoing symptoms that lasts from 4 to 12 weeks after the onset of illness, and a chronic-phase or long COVID-19, defined as symptoms and abnormalities that last more than 12 weeks after the onset of illness and are not explained by other causes [18,19].

2.5. Statistical Analysis

Data are expressed as mean and standard deviation (SD) or median and interquartile range (IQR) for numerical variables according to their distribution, and as counts and percentages for categorical variables. Comparison between treatment groups was performed using a chi squared test or Kruskal–Wallis test, as appropriate. Multivariable logistic regression models were estimated to establish the influence of covariates (age, sex, treatment, immunodeficiency, neurological diseases, chronic kidney disease, liver dysfunction, vaccination) on the outcomes (composite endpoint, persistence of symptoms at 30 days). A multivariable linear regression model was defined to evaluate the impact of the covariates on time until negativization. Model selection was performed using a stepwise procedure based on the Akaike Information Criterion.

P values < 0.05 were considered to be significant. Confidence intervals were at the 95% level. All analyses were performed using R software (version 4.2.2, R Foundation for Statistical Computing, Vienna, Austria).

3. Results

From 5 January to 3 October 2022, a total of 1118 patients were treated, 230 were treated with RDV, 499 with MP and 389 with NMV/r, as shown in Table 1.

Table 1. Univariable analysis of demographic and clinical data of patients. MP: molnupiravir; RDV: remdesivir; NMV/r: nirmatrelvir/ritonavir; CKD: chronic kidney disease.

Total Patients 1118	**RDV** ***n* = 230**	**MP** ***n* = 499**	**NMV/r** ***n* = 398**	***p*-Value**
Age median (min, max)	66 (18, 98)	78 (21, 103)	64 (17, 104)	<0.001
Sex n (%)	116 (50.4)	247 (49.5)	167 (42.9)	0.089
Incomplete vaccinal status n (%)	32 (13.9)	26 (5.2)	24 (6.2)	<0.001
Immunodeficiency n (%)	94 (40.9)	97 (19.4)	129 (33.2)	<0.001
Cardiovascular disease n (%)	130 (56.5)	367 (73.5)	175 (45)	<0.001
Neurological disease n (%)	9 (3.9)	67 (13.4)	23 (5.9)	<0.001
CKD n (%)	78 (3.5)	48 (9.6)	13 (3.3)	<0.001

3.1. Demographic and Clinical Data of the Three Populations

Age analysis shows that MP was prescribed more often in older patients in comparison to the other two groups of treatment, as shown in Table 1.

Considering the variable sex, no statistically significant difference was observed between the three groups of patients.

Among risk factors, it was observed that in patients affected by immunodeficiency, RDV was preferred, while in patients with neurological and cardiovascular diseases and CKD, MP was preferred.

Among patients with altered immunological status, those who suffered from hematologic disease were mostly treated with RDV or NMV/r, with a statistically significant difference versus MP ($p = 0.016$), as shown in Table 2.

Table 2. Univariable analysis of immunodeficient patients' subgroup. Others: diabetes mellitus, cardiovascular disease, Down's syndrome and other rare diseases (Proteus syndrome, Shwachman–Diamond syndrome).

Total Patients 320	**RDV** ***n* = 94**	**MP** ***n* = 97**	**NMV/r** ***n* = 129**	***p*-Value**
Hematologic disease n (%)	20 (21.3)	8 (8.2)	28 (21.7)	0.016
Solid tumor n (%)	30 (31.9)	44 (45.4)	49 (38)	0.160
Organ transplant n (%)	7 (7.4)	1 (1.0)	0 (0.0)	0.001
HIV infection n (%)	5 (5.3)	6 (6.2)	5 (3.9)	0.722
Immunosuppressive therapy n (%)	30 (31.9)	22 (22.7)	36 (27.9)	0.357
Other n (%)	19 (20.2)	32 (33.0)	26 (20.2)	0.048

Patients who received organ transplant were mostly treated with RDV, with a statistically significant difference between MP and NMV/r ($p = 0.001$).

Finally, MP was associated more frequently with patients affected by cardiovascular disease and diabetes mellitus (Other in Table 2), confirming the descriptive clinical data analysis about comorbidities of all treated patients.

3.2. Analysis of End Points

A multivariate analysis was performed with a multivariable logistic regression model to analyze the differences between the three groups of treatment.

The primary endpoint was the clinical progression, defined as the above composite outcome in all patients treated and in the immunocompromised subgroup. Secondary endpoints were the persistence of symptoms at 30 days and the negativization period.

Regarding clinical evolution, progression to pneumonia, ARDS, COVID-19 or non-COVID-19-related death appears to be very low. This was similar for all three drugs (progression was observed in the 2.8% of patients treated with MP, 1.3% of those treated with NMV/r and 3% of patients treated with RDV). There were four documented COVID-19-related deaths: three in the MP-treated group and one in the RDV-treated group (Table 3).

A statistically significant difference in terms of time to negativization was observed (Table 3). In particular, a shorter time was observed in the NMV/r group (median 8 days, IQR 7–10) compared with the other two molecules.

From the univariate analysis among the immunocompromised subgroup, no statistically significant difference was found between the three groups of treatment in terms of clinical progression of SARS-CoV-2 infection to severe patterns of disease and in terms of all-cause mortality (COVID-19 and non-COVID-19), as shown in Table 4.

A difference statistically significant in time to negativization emerged between the NMV/r's group ($p < 0.001$) of treatment and the other two groups. In fact, as Table 4 below shows, NMV/r seems to be related to early negativization of NPS in immunocompromised patients as well (median days 8, IQR 7–10 in NMV/r vs. median days 10, IQR 9-13 both in RDV and MP).

Table 3. Results of univariable analysis of patients' clinical evolution by the two endpoints: composite outcome and symptoms at 30 days. * Composite outcome: pneumonia, ARDS, COVID-19 Death, Non-COVID-19 Death. IQR: interquartile range.

Totals Patients 1118	**RDV** ***n* = 230**	**MP** ***n* = 499**	**NMV/r** ***n* = 389**	***p*-Value**
OUTCOME				
Clinical Progression *	3 (1.3)	14 (2.8)	5 (1.3)	0.194
Time to negativization Median [(IQR)]	10 [9–12]	10 [8–13]	8 [7–10]	<0.001
All cause mortality (COVID-19 and no COVID-19) n (%)	2 (0.9)	7 (1.4)	4 (1)	0.785
COVID-19 mortality n (%)	1 (0.4)	3 (0.6)	0 (0)	0.261
Symptoms at 30 days n (%)	59 (25.7)	56 (11.2)	62 (15.9)	<0.001

Table 4. Results of univariable analysis of immunocompromised subgroup by the endpoints: composite outcome (clinical progression), all-cause mortality (COVID-19 and non-COVID-19) and time to negativization. * Composite outcome: pneumonia, ARDS, COVID-19 Death, Non-COVID-19 Death. IQR: interquartile range.

Totals Patients 320	**RDV** ***n* = 94**	**MP** ***n* = 97**	**NMV/r** ***n* = 129**	***p*-Value**
OUTCOME				
Clinical Progression * n (%)	2 (2.1)	5 (5.2)	4 (3.1)	0.499
All–cause mortality (COVID-19 and no COVID-19) n (%)	1 (1.1)	2 (2.1)	4 (3.1)	0.587
Time to negativization Median [(IQR)]	10 [9–13]	10 [9–13]	8 [7–10]	<0.001

Age, comorbidities such as immunodeficiency (OR = 6.14; IC = 2.29, 17.20), CKD (OR = 7.98, IC = 1.56, 14.26) and neurological issues (OR = 4.65; IC = 1.48, 13.38) seem to be related to a high risk of progression of COVID-19 illness. Complete vaccination appears to be a protective factor (OR = 0.22; IC = 0.06, 1.07) (Figure 2).

Furthermore, patients treated with MP and NMV/r showed a significantly lower persistence of symptoms at 30 days compared to the group treated with RDV, as the univariate analysis pointed out (MP vs. RDV OR = 0.46; IC = 0.30, 0.71, NMV/r vs. RDV OR = 0.56; IC = 0.37, 0.85) (Figure 3). Additionally, in general, females (OR = 1.68; IC = 1.20, 2.37) and patients who suffer from pulmonary diseases seem to be more affected by long-term symptoms (OR = 1.65; IC = 1.13, 2.39).

As illustrated in Figure 4, time to negativization seems to be shorter in patients treated with NMV/r than in patients who received MP or NMV/r as medications. This is confirmed by the multivariable analysis, as shown in Figure 4; not only NMV/r (beta = −1.84; IC = −2.70, −0.98) but also vaccination (beta = −1,93; IC = −3.13, −0.74) seem to be a protective factor for shorter time to negativization. On the other hand, age (beta = 0.02; IC = 0.00, 0.04) seems to be a risk factor for longer time to negativization.

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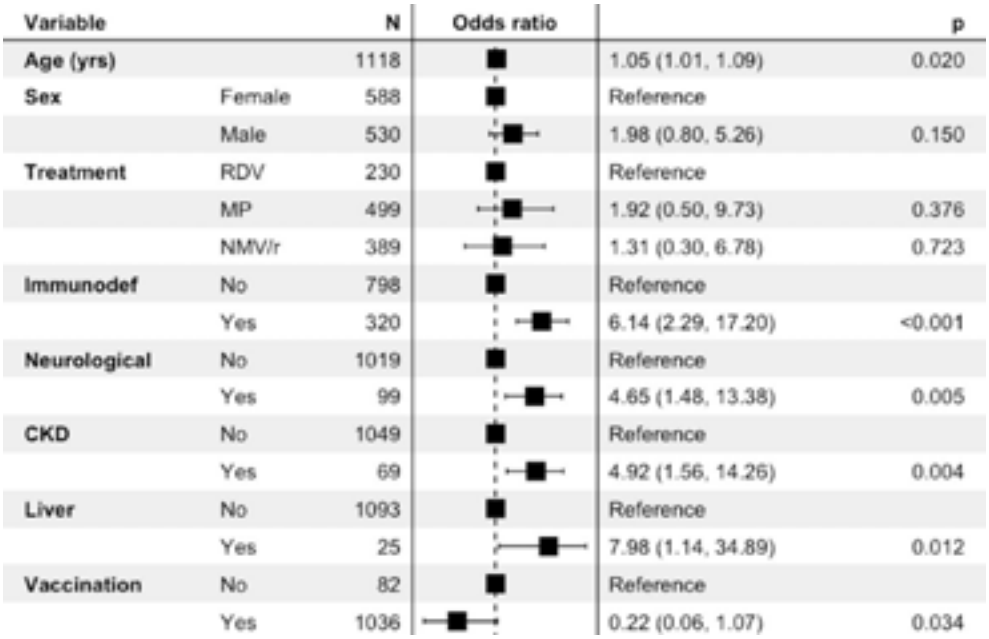

Figure 2. Logistic regression multivariate analysis of composite outcome (pneumonia, ARDS, COVID-19 Death, Non-COVID-19 Death) YRS: years; RDV: remdesivir; MP: molnupiravir; NMV/r: nirmatrelvir/ritonavir; CKD: chronic kidney disease.

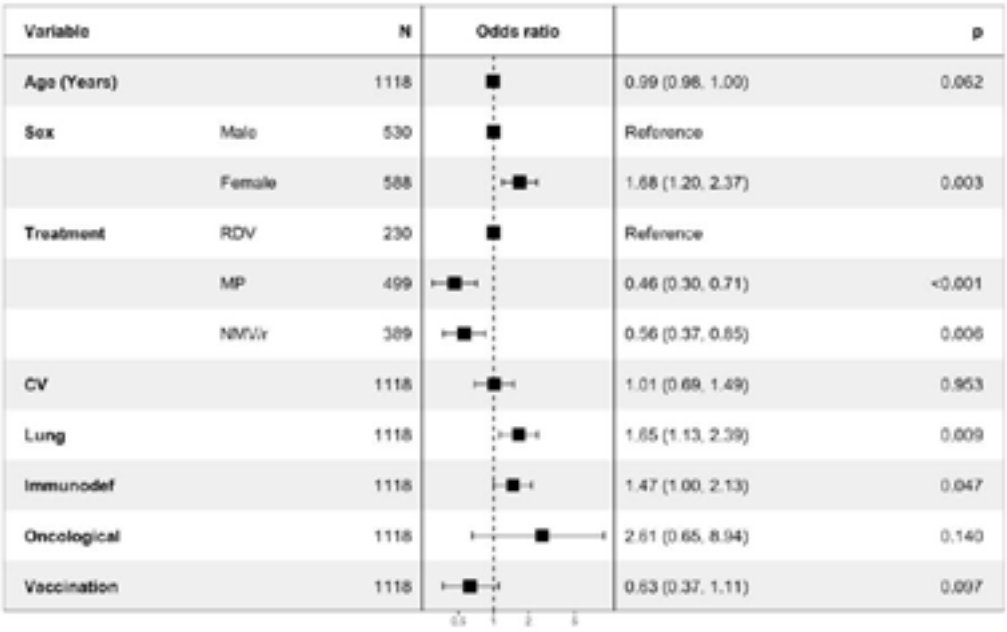

Figure 3. Logistic regression analysis of persistence of symptoms at 30 days. RDV: remdesivir; MP: molnupiravir; NMV/r: nirmatrelvir/ritonavir; CV: cardiovascular disease; Immunodef: immunodeficiency.

3.3. Adverse Effects

Although no severe adverse effects, according to the EMA definition [20], were reported in the three groups of treatment, RDV showed the fewest number of events (14.8%); MP and NMV/r, on the other hand, showed a number of events in 22.5% and 54% of cases, respectively (Figure 5), mainly diarrhea and metallic taste (Figure 6). Only 13 patients voluntarily interrupted early treatment with antiviral drugs: five patients treated with MP, for diarrhea and urticarial rash onset, six with NMV/r, complaining of nausea and vomiting, and two with RDV. However, it must be pointed out that these latter were not for the onset of adverse effects but rather because one patient decided on his own to not

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continue the treatment and the other one was converted to a five-day scheme therapy with RDV after a thorax CT scan documented COVID-19-related bilateral interstitial pneumonia.

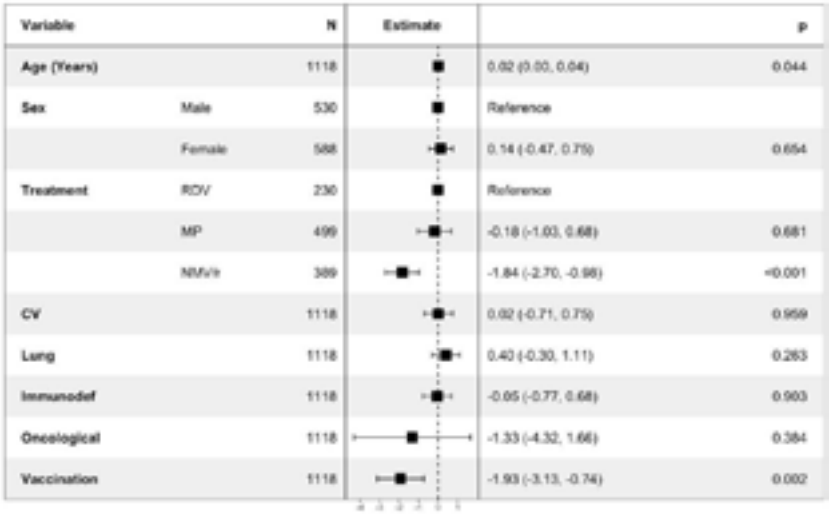

Figure 4. Linear regression analysis of time to negativization. RDV: remdesivir; MP: molnupiravir; NMV/r: nirmatrelvir/ritonavir; CV: cardiovascular disease; Immunodef: immunodeficiency.

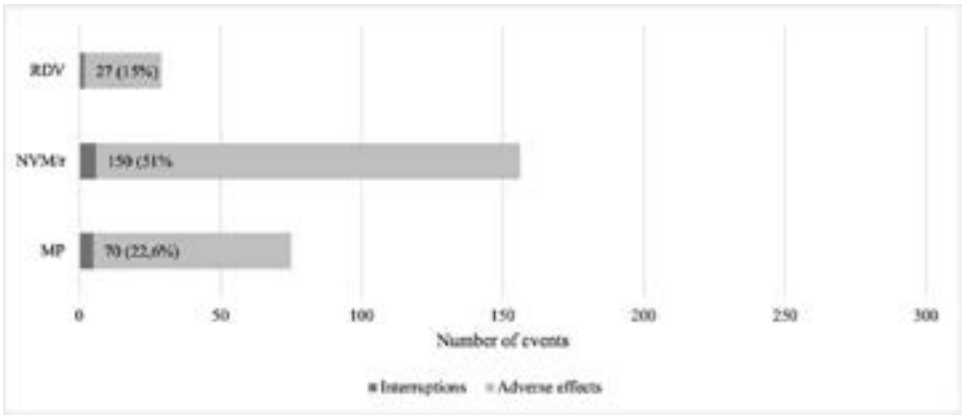

Figure 5. Frequency of self-reported adverse effects and interruptions in the three groups of treatment. MP: molnupiravir, NVM/r: nirmatrelvir/ritonavir, RDV: remdesivir. MP vs. RDV *p*-Value 0.0001; NVM/r vs. RDV *p*-Value 0.0001.

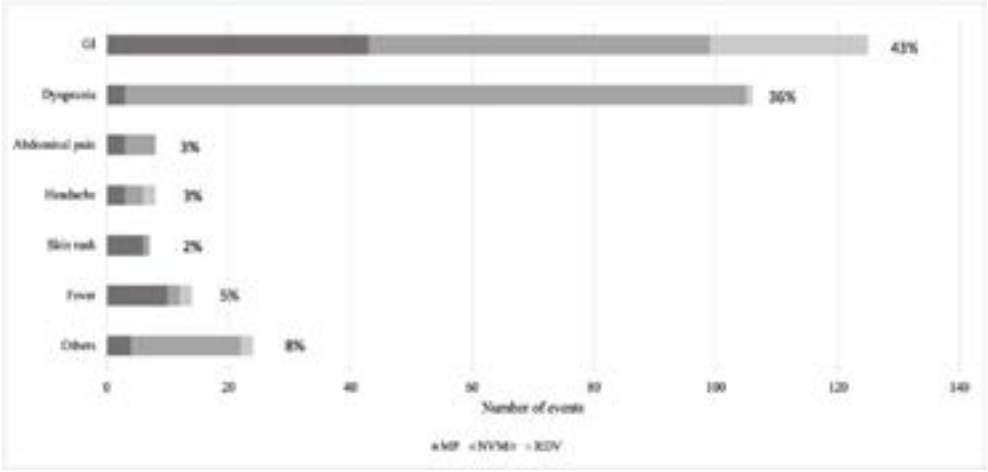

Figure 6. Adverse effects reported by patients GI: gastrointestinal. MP: molnupiravir, NMV/r: nirmatrelvir/r, RDV: remdesivir.

4. Discussion

This study suggests that the heterogeneity of antiviral drugs available for the prevention of severe SARS-CoV-2 infection in high-risk patients plays a key role in terms of patient management, offering the possibility to choose the most suitable drug for every single patient while ensuring similar clinical outcomes and significant containment of disease progression.

Considering the results of this study, elderly patients preferred to be treated with MP, instead of NMV/r or RDV, probably because of conspicuous drug interactions with NMV/r that impede the prescription of this molecule in this age range. Furthermore, MP's prescription is more consistent in patients with comorbidities such as cardiovascular diseases, neurological diseases and CKD that require chronic therapy with drugs that cannot be safely associated with NMV/r [16] nor modified in their posology. On the other hand, CKD could be associated with high levels of creatinine and low FGR that excludes the possible prescription of RDV or NMV/r without any risk. Similar results were obtained through a multicenter observational study—the FEDERATE cohort—confirming the importance of the availability of MP as an alternative drug that could be prescribed in high-risk patients, including in the early treatment of COVID-19 in people who could otherwise be excluded because of important contraindications to NMV/r or RDV [13].

The cohort of patients involved in this study was mostly vaccinated with a complete vaccination cycle; the RDV group contained the largest group of patients with an incomplete vaccination cycle (13.9%). Some hypotheses can be made in order to explain this result: patients who refused vaccination or did not complete it may be more confident with a therapy with a longer post-marketing period at the time of the study, with a direct 3 h medical supervision during treatment and also a shorter time of administration. However, it must be pointed out that we did not perform any questionnaires to evaluate patients' preferences, and so this remains a mere supposition.

Among the three antiviral drugs, there were no statistically significant differences between the three groups of treatment, concerning both evolution to pneumonia/ARDS and death, as other research has established [11–13]. Risk analysis in our study underlines that immunodeficiency and liver disease presented the higher risk of progression (OR 6.14 and 7.98; IC 95%, respectively), followed by CKD and neurological diseases (OR 4.92 and 4.65, respectively), confirming evidence deriving from several other studies [10]. Immunodeficiency remains a challenge for the COVID-19 pandemic, especially in the Omicron era; in fact, VOCs Omicron, despite their lower pathogenic role compared to other strains (e.g., Delta), are more transmittable and have high power of immune-escape, even from vaccine-induced immunity, which remains the first line of prevention of severe disease in immunodeficient patients [21]. Other studies also underlined the aggressivity of Omicron variants, associated with an increased risk of severe clinical patterns in immunocompromised patients [13,22]. In this setting, some scientists have proposed a new approach with new antivirals, better association of two antivirals, or a combination of antiviral and monoclonal antibodies (mAbs) [23–25]. Among monoclonal antibodies, tixagevimab–cilgavimab (Evusheld), which has shown efficacy in prophylaxis of SARS-CoV-2 infection in immunocompromised patients both in clinical trials [26] and RWS [27], also has a possible therapeutic role if administered alone or in association with antiviral molecules to immunocompromised patients infected by SARS-CoV-2 [28]. Unfortunately, in vitro studies demonstrated a significant and many-fold increase of the minimal inhibitory concentration against more recent omicron variants for all mAbs available [29,30]. However, emerging data showed a significant clinical impact of these mAbs, and other studies are necessary in order to understand their role in the future and their possible synergy with antiviral drugs.

Other studies have assessed the necessity of a "tailored and standardized" therapeutic approach in the cases of immunocompromised in- and outpatients with SARS-CoV-2 infection [31], with a particular attention on patients with B-cell depletion due not only to primary severe immunodeficiency but also to biological therapy with Rituximab (anti-CD20

mAb) or in treatment with Fingolimod; in fact, if not properly detected and treated these patients have a COVID-19 case fatality rate of 40% [31,32].

Some good evidence was obtained from this study. In fact, in the immunocompromised subgroup (treated with a monotherapy regimen—only one of the three antivirals, not in combination with mAbs), the three antiviral molecules seem to have the same behavior from a clinical and therapeutic point of view that they show in immunocompetent patients, affected by other comorbidities not referable to an altered immunological status (Table 4). This result suggests the importance of the availability of antiviral molecules as a powerful therapeutic presidium that could be strengthened if associated with proper and effective mAbs.

Concerning the second endpoint, patients affected by lung diseases (OR = 1.65; IC = 1.13, 2.39) seem to be associated with a major risk of persistence of symptoms at 30 days, probably because of the chronic lung dysfunction that could impede a rapid recovery from respiratory COVID19-related symptoms. Moreover, male sex seems to be associated with a lower risk of having 30-day symptoms.

Despite that, it is important to keep investing in studies and research about risk factors and comorbidities associated with persistent COVID19-related symptoms, in order to find out the way to manage specific groups of patients during the acute infection to prevent post-COVID-19 syndrome. Previous studies have shown in general that women showing a major persistence of symptoms at 30 days is a common finding. In particular, they underline how women reported symptoms that constrained daily activities more than men [33], and that female patients were more likely to have headaches, myalgia and abdominal symptoms, and less likely to have abnormal breathing and cognitive deficits than male patients [33].

Concerning antivirals, the risk of COVID19-related symptoms at 30 days was significantly decreased for patients treated with MP and NMV/r compared to the group treated with RDV.

Considering then the persistence of symptoms at 30 days and the study of Post COVID-19 syndrome, the University of Oxford and the National Institute for Health and Care Researches have recently set up a clinical study called PANORAMIC. The study aims to find out in which patients the new antivirals acted properly, preventing the need of hospital admission and increased recovery speed. In particular, this study is open to anyone with ongoing COVID-19 symptoms and a positive PCR test [34]. In the near future, a lot of new data will be collected about long COVID-19 and new clinical strategies could be pointed out for the management of some categories of patients.

The endpoint time to negativization seems to be influenced positively by treatment with NMV/r and by vaccination (Figure 4), confirming the strength of anti-SARS- CoV-2 vaccine and its ability to induce a good immunological response with adequate antibody production, which is necessary to put in place as an early efficient weapon against SARS-CoV-2 infection.

Vaccination remains the most powerful presidium against severe COVID-19 illness, despite the availability of antiviral drugs, and it is fundamental to prevent the progression to severe COVID-19 disease and has changed the natural history of SARS-CoV-2 infection. However, another study has affirmed that vaccination did not reduce the risk of anxiety/depression, headache, abdominal symptoms, chest/throat pain, abnormal breathing and cognitive symptoms in patients who suffered from long-COVID, but that certain symptoms, notably fatigue and myalgia, were less common in the vaccinated population [35].

Regarding the same effectiveness of the three antivirals in containing the progression of COVID-19 disease, this study suggests that in the Omicron era, early therapy has a strong impact on the natural history of the infection [36,37] and confirms the importance of real world studies (RWS) as instruments to validate the results of clinical trials. Antivirals play a key role in the Omicron era, especially NMV/r, which showed a potential therapeutic efficacy against this novel variant in previous in vitro studies. Despite the biological mutation of Omicron, both in RNA-dependent RNA-polymerase (RpRd)—the therapeutic target of RDV and MP—and the SARS-CoV-2 major protease inhibitor—the target of

NMV/r [18,19]—these drugs maintain therapeutic efficacy, confirmed by several real world studies [13,38–41].

The absence of severe adverse effects [13] in the three groups of treatment underlines the possibility of a safe prescription that could reassure patients who show reticence to the consumption of the antiviral drugs. In the group treated with MP, the most common adverse effect was diarrhea, limited to the days of consumption of the drug. Other reviews and RWSs have demonstrated that gastrointestinal discomfort (nausea and diarrhea) and headache was mostly reported by patients treated with MP [5]. Dysgeusia, referred to as a metallic taste by patients, was associated in our study mainly to NMV/r and was very frequent and transitory, as in other studies [5,42,43]. The mechanism for this adverse effect is not clear but a study pointed out that ritonavir, and protease inhibitors in general, could have a role in modifying the taste perception of a variety of taste compounds, influencing patients' compliance with medical treatment regimens [44]. The biological mechanisms involved in this phenomenon seem to be related to adverse sensory properties of the drug itself and to biochemical disruption of normal taste and smell signals caused by medications. In general, geriatric patients complain of dysgeusia more than younger ones, possibly because of polypharmacy [45]. In our study we did not perform blood test analysis because of the real-life nature of the study in a cohort of outpatients. A gastroenterologic study investigated the possible liver toxicity of MP and NMV/r, affirming that there is a minimal risk of drug-induced liver injury (DILI); in fact, compared to no antiviral treatment, both MP and NMV/r did not increase the risk of elevated liver enzymes or DILI [46].

A final mention must be made of the recent discontinuation of MP as established by AIFA on the 15th of March (AIFA DG/85/2023) [47], after the EMA recommended the refusal of its marketing authorization [48]. In fact, the Agency's opinion was that it was not possible to conclude that MP could reduce the risk of any outcomes in adults at risk of severe disease and that its balance of benefits and risks in the treatment of COVID-19 could not be established. However, we must stress that this is not what we observed in our RWE study, and also in other studies [49], and that we confirmed the absence of safety issues related to MP as remarked on both by EMA and AIFA.

5. Limitation of the Study

The main limitation of this study is the retrospective nature of the study and the absence of an untreated control group.

Furthermore the data collection of our study is mostly based on phone call follow-up, so the evaluation of symptoms at 30 days are self-reported and they were not objectified by physical and instrumental examination or laboratory tests. Although patients who reported important persistent symptoms were invited for a medical consultation at our post-COVID-19 clinic.

Finally, it must be considered that no specific objectification with NPS for time to negativization was provided by our clinic, in fact it was self-referred from the patients themselves and it has to be considered as an estimate and, whenever possible, it was double-checked by verifying the date reported in the local regional platform.

6. Conclusions

In conclusion, our real-world evidence study compared antiviral treatments for early COVID-19 in a high risk population demonstrating a low rate of progression in all treatment groups without differences. Each patient received the best drug considering comorbidities, personal choice and polypharmacy, and side effects were limited and discontinuation was rare. A strong network and a rapid communication between GPs and hospital teams remains essential, in order to detect high risk patients early and reach the maximum effectiveness of treatment. The best option for the severe immunocompromised population remains to be addressed in future studies.

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