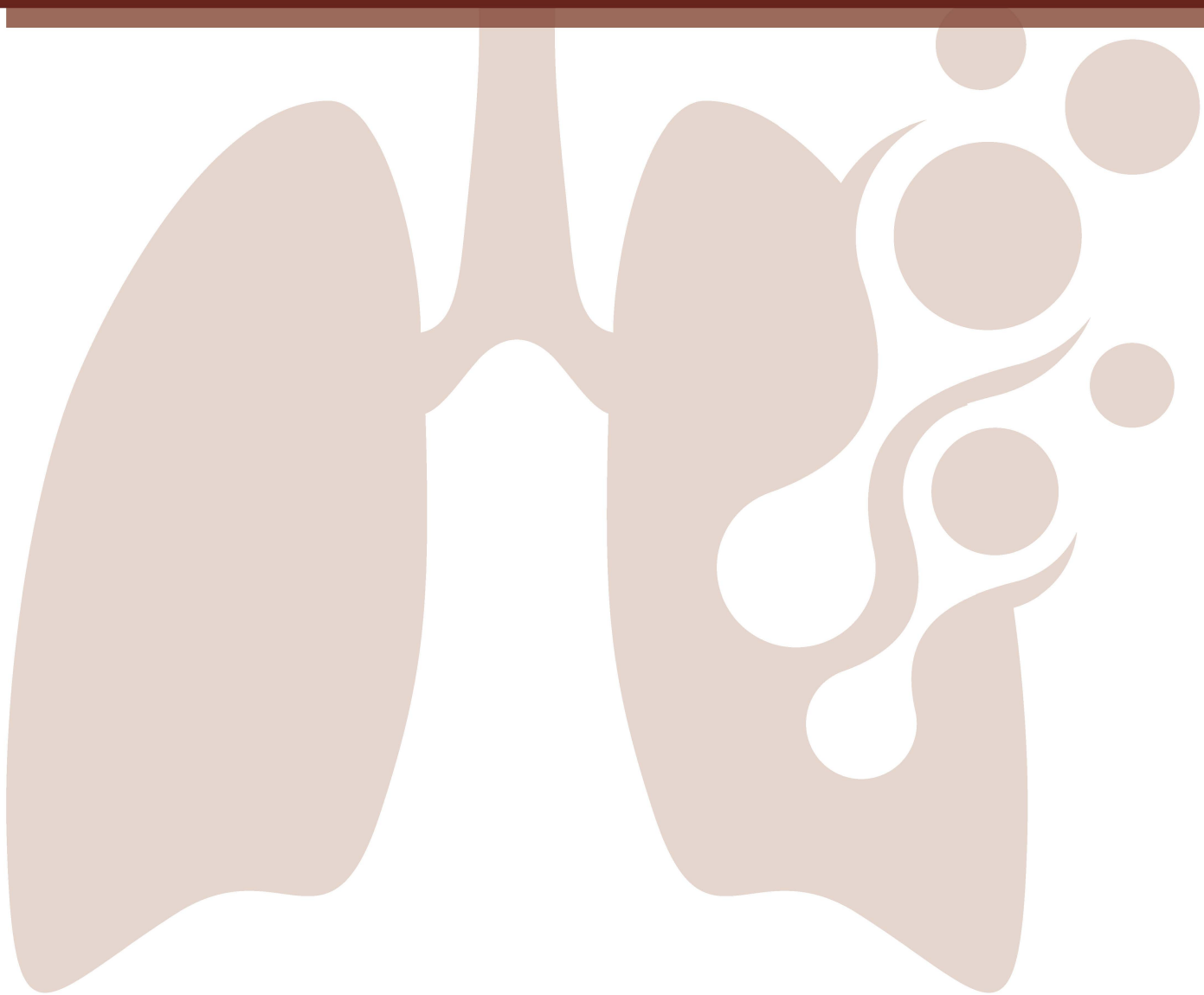
Drugs to prevent COVID-19

LIVING GUIDELINE

24 March 2023

World Health Organization



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World Health Organization (WHO)

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1. Summary: what is this living guideline?

Info Box

Clinical question: What is the role of drugs in preventing COVID-19?

Why does this matter? There is widespread interest in whether drug interventions can be used for the prevention of COVID-19, but there is uncertainty about which drugs, if any, are effective.

Recommendations: This second *Drugs to prevent COVID-19: living guideline* reiterates the previous strong recommendation against the use of hydroxychloroquine and includes a conditional recommendation against the use of tixagevimab-cilgavimab in individuals who do not have COVID-19 *(1)*.

How this guideline was created: This living guideline is from the World Health Organization (WHO) and provides up-to-date COVID-19 guidance to inform policy and practice worldwide. MAGIC Evidence Ecosystem Foundation (MAGIC) provides methodological support. A living systematic review with network analysis informs the recommendations. An international guideline development group (GDG) of content experts, clinicians, patients, an ethicist and methodologists produces recommendations following standards for trustworthy guideline development using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Understanding the recommendations: The living network meta-analysis (LNMA) informing this guideline included 12 trials (n=8379 participants) comparing hydroxychloroquine with standard care/placebo, and one trial (n=5197 participants) comparing tixagevimab-cilgavimab with standard care/placebo. When moving from evidence to the continued strong recommendation against the use of hydroxychloroquine, the GDG emphasized additional evidence suggesting no or little effect on mortality and hospital admission, and an increased risk of adverse effects. For the new conditional recommendation against the use of tixagevimab-cilgavimab, the GDG emphasized in vitro evidence reducing the applicability of available trial data. While trial results demonstrated modest reduction in the occurrence of laboratory-confirmed symptomatic COVID-19, lack of in vitro neutralization of new SARS-CoV-2 sub-lineages was considered to have rendered these results obsolete.

Updates and access: This is a living guideline; therefore, recommendations may be updated, and new recommendations for other prophylactic interventions for COVID-19 may be added. The guideline is written, disseminated, and updated in a format and structure aiming to make it user-friendly and easy to navigate while accommodating for dynamically updated evidence and recommendations, focusing on what is new while keeping existing recommendations within the guideline.

Please visit the WHO website for the latest version of the guidance *(1)*, also available in the BMJ as Rapid Recommendations *(2)*, and supported by the LNMA on COVID-19 prophylaxis, a major evidence source for the guidelines *(3)*.

This guideline is related to two other WHO living guidelines for COVID-19:

- *Therapeutics and COVID-19: living guideline*, last updated 13 January 2023, also available on MAGICapp, which includes recommendations on drugs for patients with COVID-19 *(4)(5)*.
- *Clinical management of COVID-19: living guideline*, last updated 13 January 2023, also available on MAGICapp, includes recommendations on a broad list of topics related to non-pharmacological clinical management of COVID-19 *(6)*.

2. Abbreviations

CI	confidence interval
COVID-19	coronavirus disease 2019
GDG	guideline development group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
LNMA	living network meta-analysis
MAGIC	Magic Evidence Ecosystem Foundation
PICO	population, intervention, comparator, outcome
RCT	randomized controlled trial
WHO	World Health Organization

3. Background

As of 7 March 2023, over 759 million people worldwide have been diagnosed with COVID-19, according to estimates from the WHO dashboard *(7)*. The pandemic has so far claimed more than 6.7 million lives.

This living guideline responds to emerging evidence from randomized controlled trials (RCTs) on prophylactic interventions for COVID-19. These interventions aim to prevent the disease developing in those who are free from disease. Interventions could target whole populations, those at higher risk of becoming infected with SARS-CoV-2 due to their work, social circumstances or a particular exposure, or target those at higher risk of death and poor outcomes.

As of 6 February 2023, there are 14 225 registered or ongoing trials investigating various interventions for COVID-19 (see Section 7) *(8)*. This rapidly evolving evidence landscape requires trustworthy interpretation and expeditious clinical practice guidelines to inform clinicians, patients, governments, ministries and health administrators.

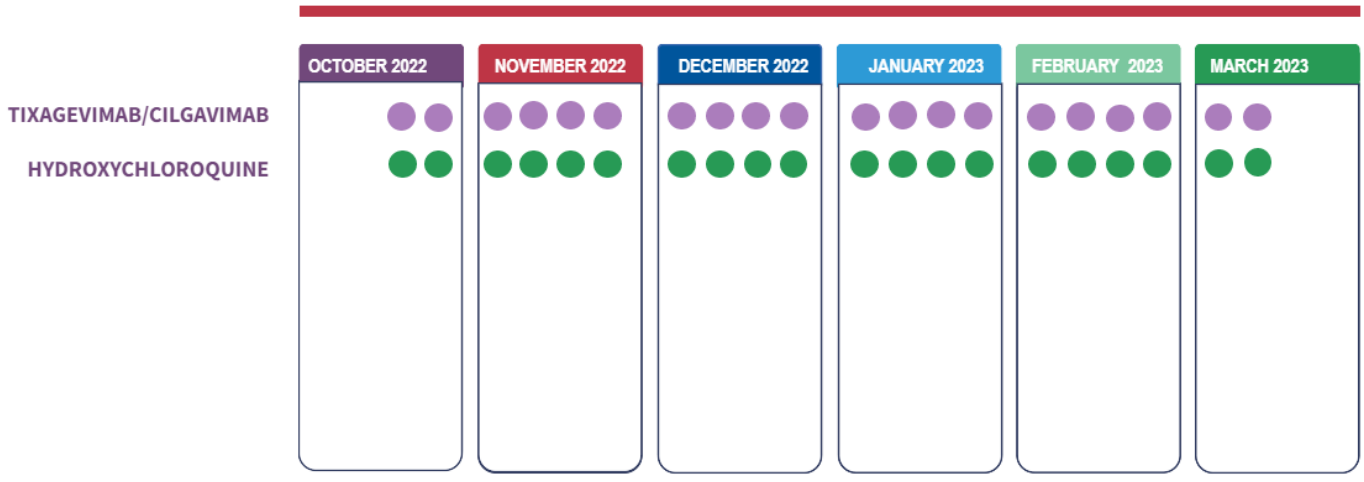
3.1 What triggered this version of the guideline and what is coming next?

This second version of the guideline on drugs to prevent COVID-19 addresses the use of hydroxychloroquine and tixagevimab-cilgavimab in individuals who do not have COVID-19 *(1)*. It follows the publication of the LNMA *(3)* that pooled data from 12 trials (n=8379 participants) comparing hydroxychloroquine with standard care/placebo *(9)(10)(11)(12)(13)(14)(15)(16)(17)(18)(19)(20)*, and one trial (n=5197 participants) comparing tixagevimab-cilgavimab with standard care/placebo *(21)*.

The publication of one clinical trial of tixagevimab-cilgavimab suggesting potential benefits associated with the prophylactic use of these monoclonal antibodies and the subsequent emergence of in vitro evidence suggesting that these clinical trial data were potentially obsolete triggered the creation of a new recommendation on tixagevimab-cilgavimab prophylaxis *(22)*. In turn, correspondence following the publicatIon of the previous version of the guideline justified re-examining whether new evidence reinforced or contradicted the recommendatIon against hydroxychloroquine prophylaxis *(23)*.

Fig. 1 shows the drugs in progress for this WHO living guideline, also communicated through the WHO portal. Each dot represents a week of time. In deciding which drugs to cover, the WHO considers multiple factors, including the extent of available evidence to inform recommendations, and makes a judgment on whether and when additional evidence might be anticipated. The WHO has a standing Steering Committee (see Section 4) to evaluate possibilities for new drug recommendations and updates to existing drug recommendations.

Fig. 1. COVID-19 prophylaxes under assessment as of March 2023



3.2 Who made this guideline?

As detailed in Section 4, the WHO convened a standing GDG with 33 clinical content experts and one patient-partner, headed by a clinical chair (Dr Miriam Stegemann) and a methods chair (Dr Francois Lamontagne). WHO selected GDG members to ensure global geographical representation, gender balance, and appropriate technical and clinical expertise. No panel member had a conflict of interest.

The MAGIC Evidence Ecosystem Foundation (MAGIC) provided methodological experts with high-level expertise in standards and

methods for systematic reviews and guideline development, including GRADE; in addition, MAGIC offered innovations in processes (BMJ Rapid Recommendations) and platforms (MAGICapp) for developing living guidance in user-friendly formats. Methodological experts were not involved in the formulation of recommendations.

3.3 How to use this guideline?

This is a living guideline from the WHO. Recommendations will be updated, and new recommendations will be added for other prophylactic interventions for COVID-19.

The guideline is written, disseminated and updated in MAGICapp, with a format and structure aiming to make it user-friendly and easy to navigate *(24)*. It accommodates dynamic updating of evidence and recommendations that focuses on what is new while keeping existing recommendations, as appropriate, within the guideline. Section 4 outlines key methodological aspects of the living guideline process including special considerations relevant to the special area of scientific evaluation of prophylactic interventions.

The guideline is available in MAGICapp in online, multilayered formats and via:

- WHO website in PDF format *(1)*
- WHO Academy App (via AppStore and Google Play)
- BMJ Rapid Recommendations with infographics *(2)*

The purpose of MAGICapp online formats and additional tools, such as the infographics, is to facilitate easy navigation and access to relevant evidence and guidance in clinical practice. The online multilayered formats are designed to allow end-users to find recommendations first and then drill down to find supporting evidence and other information pertinent to applying the recommendations in practice, including tools for shared decision-making (clinical encounter decision aids) *(24)*.

4. Methods: how this guideline was created

This guideline on drugs to prevent COVID-19 is developed according to standards and methods for trustworthy guidelines, making use of an innovative process to achieve efficiency in dynamic updating of recommendations *(1)*. The methods are aligned with the *WHO Handbook for guideline development* and according to a pre-approved protocol (planning proposal) by the WHO Guideline Review Committee *(25)*.

Related guidelines
This guideline is related to the *Therapeutics and COVID-19: living guideline*, last updated on 13 January 2023, and available on MAGICapp, which includes recommendations on drugs for patients with COVID-19 *(5)(26)*.

The *Clinical management of COVID-19: living guideline*, published 13 January 2023, and available on MAGICapp, includes recommendations on a broad list of topics related to non-pharmacological clinical management of COVID-19 *(6)*.

Timing
This guidance aims to be trustworthy and living, dynamically updated and globally disseminated once new evidence warrants a change in recommendations for COVID-19 prophylactic interventions. We aim for an ambitious timeframe from trials that trigger the guideline development process to WHO publication within 1 month, while maintaining standards and methods for trustworthy guidelines (*WHO Handbook for guideline development*) *(25)(27)*.

Stepwise approach
Here we outline the stepwise approach we take to improve efficiency and timeliness of the living, trustworthy guidance, in the development and dissemination of recommendations. To do so, various processes occurr simultaneously.

Step 1: Evidence monitoring and mapping and triggering of evidence synthesis
Comprehensive daily monitoring of all emerging RCTs occurs on a continuous basis, within the context of the living systematic review and LNMA, using experienced information specialists, who look at all relevant information sources for new RCTs addressing interventions for the prevention of COVID-19. Once practice-changing evidence is identified, the WHO Therapeutics Steering Committee triggers the guideline development process. With the Guidance Support Collaboration Committee (see Section 8), PICO development and construction of evidence summaries addressing the intervention of interest are initiated.

The trigger for producing or updating specific recommendations is based on the following:

- likelihood to change practice;
- sufficient RCT data on prophylactic interventions to inform high-quality evidence synthesis;
- relevance to a global audience.

Step 2: Evidence synthesis
Following a request by the WHO Therapeutics Steering Committee and coordinated by the Guidance Support Collaboration Committee, the LNMA team conducted an independent review to summarize evidence regarding prophylactic interventions for COVID-19, including drugs of interest. The LNMA team is multidisciplinary and composed of systematic review experts, clinical experts and biostatisticians. The team has expertise in GRADE methods and rating certainty of evidence in LNMAs. To inform their evidence synthesis process, the LNMA team was informed of the outcomes and subgroups prioritized by the panel.

Step 3: Convening the GDG
The pre-selected clinical expert panel (see Section 8) convened on 16 December 2022 to discuss methodological concepts relevant to guidelines for prophylactic interventions, review evidence summaries pertaining to hydroxychloroquine and tixagevimab-cilgavimab, and develop recommendations. No conflict of interest was identified for any panel member according to WHO standards, with individual biographies available on the WHO website.

Step 4: Final recommendations
The GRADE approach provided the framework for establishing evidence certainty and generating both the direction and strength of recommendations *(28)(29)*. Recommendations were developed and agreed upon with a consensus-based approach, with voting procedures pre-established to address cases where consensus was not reached. Established procedures included that a simple majority would provide the direction of the recommendation, and that 80% would be required to make a strong recommendation.

The following key factors were used to formulate transparent and trustworthy recommendations:

- absolute benefits and harms for all critically important outcomes through structured evidence summaries (e.g. GRADE summary of findings tables) *(30)*;

- quality/certainty of the evidence *(28)(31)*;
- values and preferences of patients *(32)*;
- resources and other considerations (including considerations of feasibility, applicability, equity) *(32)*.

For each outcome, effect estimates and confidence intervals, with a measure of certainty in the evidence, were presented in summary of findings tables. Recommendations were rated as either conditional or strong, as defined by GRADE.

Step 5: External and internal review
The WHO guideline was then reviewed by pre-specified external reviewers and subsequently approved by the WHO Guideline Review Committee.

Benefits and harms
The GDG members prioritized outcomes (rating from 1 [not important] to 9 [critical]) taking a patient perspective (Table 1). The panel's questions were structured using the PICO format (see summary of findings tables under recommendations in Section 6).

Table 1. Panel outcome rating from a patient perspective

Outcome	Min	Max	Median	Mean	SD
Death	3	9	9	8.4	1.55
Infection (lab-confirmed)	2	9	7	6.74	1.84
Infection (suspected or probable, or lab-confirmed)	1	9	6	5.95	2.14
Admission to hospital	5	9	7.5	7.35	1.11
Adverse effects leading to discontinuation	2	9	7	6.75	1.56
Time to resolution or clinical improvement	3	9	5	5	1.73

SD = standard deviation.
Note: 1: not important, 9: critically important.

Baseline risk estimates (prognosis of patients with COVID-19): informing absolute estimates of effect
Baseline risks were calculated from data from the control groups of trials included in the LNMA, which also yielded the estimate of relative effects of prophylactic interventions. The evidence summaries that informed the guideline recommendation reported the anticipated absolute effects of prophylactic medications compared with usual care across all patient-important outcomes, with explicit judgments of certainty in the evidence for each outcome. For mortality, the event rate among all participants randomized to standard care or placebo was used to calculate the baseline risk. For all other outcomes, the median event rate in the standard care or placebo arms was used, with each study weighted equally.

Values and preferences
There were insufficient published data to provide the panel with an informative systematic review of studies describing individuals' experiences or values and preferences for COVID-19 prophylactic interventions. The panel members therefore relied on their own judgments of what well-informed individuals would value after carefully balancing the benefits, harms and burdens of prophylactic interventions and their subsequent preferences. The panel included one patient partner who had lived experience with COVID-19.

The panel agreed that the following values and preferences would be representative of those of typical well-informed patients:

- Mortality would be the outcome most important to individuals, followed by need for hospital admission, adverse effects leading to discontinuation, and laboratory-confirmed SARS-CoV-2 infection.
- Most patients would be reluctant to use an intervention for which the evidence left high uncertainty regarding effects on outcomes they consider important, or when evidence suggested a low certainty of benefit. When beneficial effects, if present, would be very small, almost all patients would decline to use such an intervention.
- The panel also considered optimal resource use at a public health level. The panel placed a low value on allocating substantial resources for uncertain benefit and, conversely, a high value on preserving resources for interventions with a high certainty of benefit.

The panel acknowledged, however, that values and preferences are likely to vary. There will be individuals inclined to use a prophylactic intervention when an important benefit cannot be ruled out, particularly when the underlying condition is potentially fatal. On the other hand, other individuals will have a high threshold of likely benefit before opting to take medications prophylactically. Although the panel

focused on an individual patient perspective, the members also considered a population perspective in which feasibility, acceptability, equity and cost are important considerations, particularly when a very large number of otherwise healthy individuals might need to be treated before preventing one outcome.

4.1 Special methodological considerations for recommendations on prophylactic interventions

Implications of very low event rates

Prophylactic interventions are administered to prevent the occurrence of an illness among individuals who are not yet sick. A minority will develop the illness and, of those, a minority will develop complications from the illness. Accordingly, the number of critically important events (e.g. death) in studies evaluating prophylactic interventions is typically very low. For that reason, researchers may choose to measure the effectiveness of prophylactic interventions by measuring their impact on outcomes that are more common albeit less critically important for patients, such as the development of the illness. In those instances, a more practical outcome is chosen because it is considered a surrogate for a critically important outcome. For example, if a study yielded evidence suggesting that an intervention reduces the risk of developing COVID-19, it is plausible that the same intervention would also reduce the risk of death from COVID-19. However, this would be less certain than if the study had measured mortality directly and would justify downgrading for indirectness.

What is the guideline panel rating concerning certainty of evidence?

When rating certainty of the evidence for an individual outcome with GRADE, the panel is rating how certain we are that the true effect lies within a particular range or on one side of a threshold. If there are no serious concerns about risk of bias, inconsistency, indirectness, or publication bias, the confidence interval will represent a reasonable estimate of a certainty range, that is the range of reasonably believable effects of the intervention. Guideline panels and guideline users may consider that the same range of plausible treatment (e.g. 95% CI from 5 fewer to 5 more events per 1000) is highly precise if the panel's focus is to exclude a large treatment effect corresponding, say, to a reduction of 20 or more events per 1000 individuals, but not precise enough to exclude any effect at all. The panel's focus depends on what audiences would find most useful. If the focus is on whether there is any effect at all (i.e. a non-null effect) guidelines may be minimally contextualized; however, if the focus is on the magnitude of effect (i.e. trivial, small, moderate or large), then the panel's approach must be contextualized (see below).

Contextualization in these guidelines

Given the low event rates in studies evaluating prophylactic interventions (discussed above), a large number of healthy individuals would have to take a prophylactic medication, and therefore expose themselves to risks and other disadvantages, to prevent one event from occurring. Accordingly, the panel opted for a partially contextualized approach whereby certainty will be rated for a magnitude of effect (e.g. trivial, small, moderate, or large effect). Here, the panel is responsible for balancing the magnitude of a plausible effect that justifies delivering prophylactic interventions in light of the disadvantages associated with treating a very large number of otherwise healthy individuals.

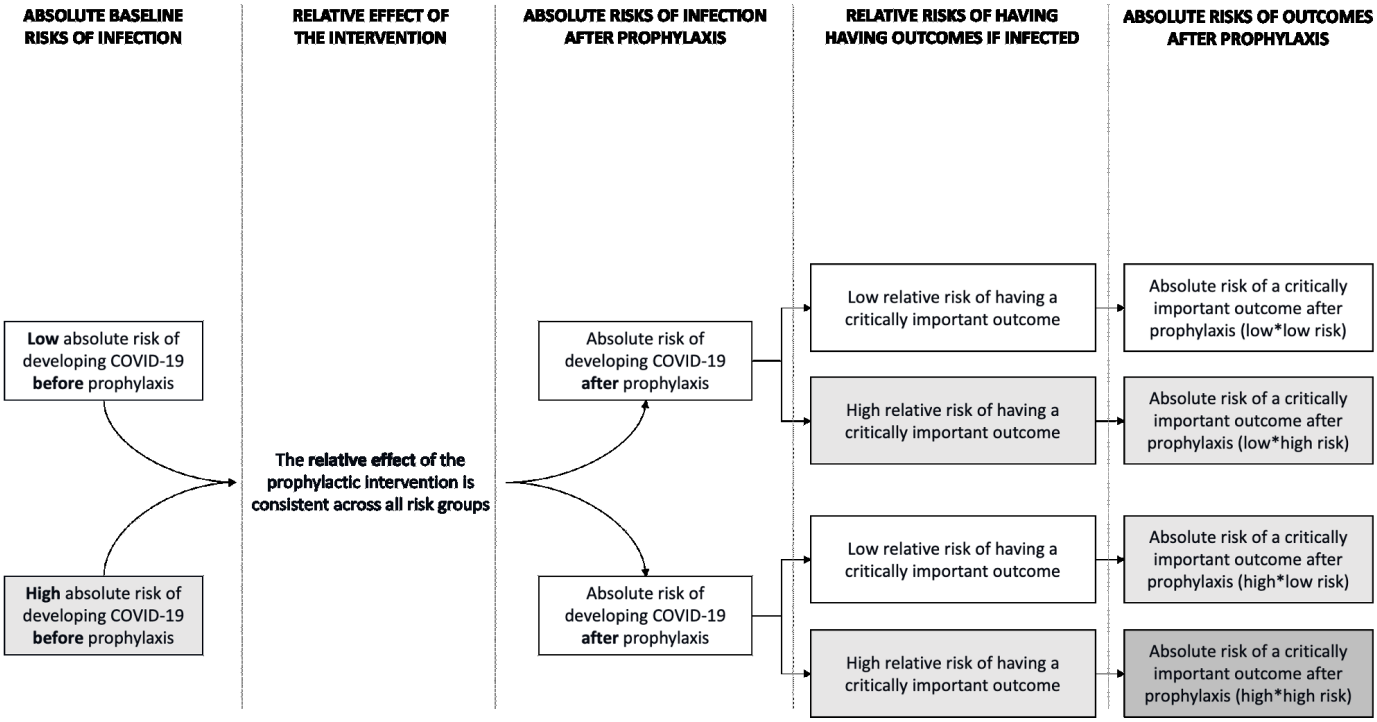
Subgroup comparisons for evidence pertaining to prophylactic interventions

When evaluating the effect of an intervention, guideline panels examine its absolute effects on critically important outcomes, which is calculated by multiplying a risk ratio with a population's baseline risk. When ascertaining whether subgroup effects exist, guideline panels may first look for differences in relative effects between subgroups. An intervention that increases the risk of an event in one subgroup but reduces the risk in another subgroup is an example of a relative subgroup effect. When evaluating the credibility of subgroup effects, the WHO panel applied pre-specified criteria *(33)*. For guidelines on prophylactic interventions, the panel chose to systematically conduct two default subgroup analyses in search of potential differences in relative effects. For the outcome of laboratory-confirmed infection, the panel examined whether the effect of prophylactic interventions varied as a function of a known exposure to a person with SARS-CoV-2 infection (as opposed to no known exposure). They also examined if the effect on adverse events leading to discontinuation of the drug varies as a function of the dose. Additional subgroup analyses looking for differences in relative effects may be requested a priori by the panel in updates of this living guideline for other prophylactic interventions.

Whether or not differences in relative effects exist, the effect of a beneficial intervention may vary considerably in absolute terms across subgroups. This is particularly true of prophylactic interventions since their impact on critically important outcomes depends on an individual's risk both of developing the illness and of a critically important outcome if ill.

Assuming there is no difference in relative effects, this approach entails modelling the absolute risk of laboratory-confirmed infection in at least two populations with different baseline risks of developing COVID-19 and then, in each stratum, modelling the risk of experiencing a critically important outcome in at least two populations with different risks of having that particular outcome. Fig. 2 illustrates how this modelling may result in different absolute risks of experiencing a critically important outcome after prophylaxis.

Fig. 2. Determination of varying absolute risks of critically important outcomes based on modelling



Note: The asterisk (*) in the final column refers to multiplication.

Impact of in vitro evidence of virus neutralization

There has been substantial interest in how the panel evaluates the effectiveness of anti-SARS-CoV-2 monoclonal antibodies as evidence emerges about their in vitro neutralization efficacy *(34)*.

As for any other medication, the evaluation of clinical effectiveness hinges on RCT data fed into the LNMA underpinning the guideline *(3)*. However, the rapid evolution of SARS-CoV-2 sublineages specifically impacted the recommendations for monoclonal antibodies, given the concerns of significantly reduced virus neutralization efficacy, which is the primary mechanism of action.

Advised by methods and pharmacology experts, the GDG concluded that in vitro evidence could render clinical trial data obsolete if there was high certainty that circulating sublineages were not neutralized by the anti-SARS-CoV-2 monoclonal antibodies evaluated in clinical trials (see Section 6) *(34)*.

Notwithstanding, the GDG reiterated the necessity of clinical trial evidence to prove clinical effectiveness. Accordingly, although in vitro data may indicate previously effective anti-SARS-CoV-2 monoclonal antibodies are obsolete for current sublineages, new monoclonal antibodies would nonetheless have to be evaluated in clinical trials before being used clinically.

5. Who do the recommendations apply to?

Info Box

This living guideline applies to all individuals who do not have COVID-19.

In the case of hydroxychloroquine, the GDG concluded that there was no justification for separate recommendations for subgroups and that this recommendation was applicable irrespective of known exposure to individuals with SARS-CoV-2 infection or across different drug doses.

In the case of tixagevimab-cilgavimab, given the in vitro evidence suggesting lack of neutralization efficacy for new circulating Omicron sublineages, the GDG concluded that prophylactic use of tixagevimab-cilgavimab should be strictly restricted to situations where there could be high certainty that the circulating sublineages exhibit in vitro neutralization activities equivalent to those circulating in populations and regions when and where the supporting clinical trial was conducted. Moreover, even in the presence of these unlikely circumstances, there was no justification for separate recommendations for subgroups and that this recommendation was applicable irrespective of known exposure to SARS-CoV2, or for different drug doses. Only a minority of high-risk patients who have not been vaccinated or who are severely immunocompromised may choose to consider using tixagevimab-cilgavimab.

6. Recommendations for prophylaxis

6.1 Hydroxychloroquine

Strong recommendation against

Updated

We recommend against administering hydroxychloroquine prophylaxis to individuals who do not have COVID-19 (strong recommendation)

Remark: This recommendation applies to individuals with any baseline risk of developing COVID-19 and any hydroxychloroquine dosing regimen.

Practical Info

Given the strong recommendation against using hydroxychloroquine prophylaxis for individuals who do not have COVID-19, practical considerations were felt to be less relevant here.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

Used prophylactically, hydroxychloroquine has no or little effect on death and hospital admission (high certainty), and has no or little effect on laboratory-confirmed SARS-CoV-2 infection (high certainty). It increases the risk of adverse effects leading to discontinuation of the drug (high certainty).

There was no subgroup effect according to known exposure to a person with SARS-CoV-2 infection or hydroxychloroquine dose regimen (extremely low event rates precluded investigation of subgroup effects for mortality). The panel therefore assumed similar relative effects across subgroups.

Certainty of the Evidence

High

Certainty was high for all key outcomes.

Values and preferences

We expect few to want the intervention

Given the high certainty of the evidence, the panel inferred that almost all informed individuals would choose not to have the intervention and would decline hydroxychloroquine.

Resources and other considerations

Important negative issues

Hydroxychloroquine is relatively inexpensive and is widely available, including in low-resource settings. Although the cost may be low per patient, the overall cost of delivering a prophylactic intervention on a large scale may be significant. Moreover, the panel raised concerns about diverting hydroxychloroquine stocks away from patients with other conditions for whom this medication is indicated *(36)*.

Justification

When moving from the evidence to the strong recommendation against the use of hydroxychloroquine to prevent COVID-19-related outcomes, the panel emphasized the evidence suggesting no or little effect on mortality and hospital admission along with an increased risk of adverse effects. For a more detailed discussion about how high certainty of no or little effect may be achieved with low event rates and the steps separating administration of a prophylactic intervention from the occurrence of an important clinical endpoint, please refer to the discussion on special methodological considerations relevant to this guideline (section 4.1). Of note, when updating this recommendation, the panel considered data on mortality from 12 trials (n=8379) randomizing participants to hydroxychloroquine or standard care/placebo *(9)(10)(11)(12)(13)(14)(15)(16)(17)(18)(19)(20)*. This strengthened the panel's certainty that prophylactic interventions, in the populations studied in these clinical trials,

will not lead to large reductions in mortality given their risk of death is very small. Although certain subgroups of vulnerable individuals may have been under-represented in previous hydroxychloroquine prophylaxis trials, the panel maintained its view that, given the existing evidence, it would be extremely unlikely that hydroxychloroquine would lead to a meaningful mortality reduction even in those subgroups, and highly unlikely that future trials would successfully enrol individuals that previous trials have not been able to enrol thus far. In light of this evidence, the panel did not anticipate important variability when it comes to patient values and preferences. In addition, the panel decided that contextual factors such as resources, feasibility, acceptability and equity for countries and health care systems were unlikely to alter the recommendation. The panel acknowledged that a strong recommendation against hydroxychloroquine to prevent COVID-19 indicates that this area is no longer a research priority and that resources devoted to clinical research should rather be oriented to evaluate other more promising prophylactic interventions. Notwithstanding, the panel also reiterated that a strong recommendation signifies that its members believed that *almost all well-informed* individuals would choose not to receive hydroxychloroquine prophylaxis, which implies that there may be exceptions.

Subgroup analyses
The panel did not find any evidence of a subgroup effect as a function of known exposure to SARS-CoV-2 infection or by dose of hydroxychloroquine. Of note, for trials that enrolled participants without a known exposure, the weekly dose of hydroxychloroquine was used as the variable of interest to account for longer term prophylaxis; for trials that enrolled participants following a known exposure to SARS-CoV-2, the cumulative dose was used as the variable of interest to reflect shorter term prophylaxis. As no subgroup effect modification was found, the strong recommendation is applicable across risk groups and dose regimens of hydroxychloroquine.

The trials included participants from North and South America and Europe who either had a known exposure to a person with SARS-CoV-2 infection or who were considered at risk given their professional occupations (e.g. health care workers).

Applicability
Regarding special populations, none of the included RCTs enrolled children, and therefore the applicability of this recommendation to children is currently uncertain. However, the panel had no reason to think that children would respond any differently to prophylactic hydroxychloroquine. There were similar considerations in regards to pregnant women, with no data directly examining this population, but no rationale to suggest they would respond differently to other adults. Hydroxychloroquine crosses the placental barrier and there are concerns that it may lead to retinal damage in neonates.

Clinical Question/ PICO

Population: Individuals at risk of COVID-19
Intervention: Hydroxychloroquine
Comparator: Standard care

Summary

The Table shows the characteristics of the RCTs evaluating hydroxychloroquine compared with standard care/placebo included in the LNMA informing the recommendation *(3)*. The GDG was informed by 12 trials (n=8379 participants) when they made this recommendation in December 2022 *(9)(10)(11)(12)(13)(14)(15)(16)(17)(18)(19)(20)*. The most recent LNMA publication *(3)* contains an additional trial comparing hydroxychloroquine to active interventions *(35)*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Hydroxychloroquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality	Based on data from 6822 participants in 7 studies. (Randomized controlled)	3 per 1000 Difference:	3 per 1000 **0 fewer per 1000** (CI 95% 3 fewer — 2 more)	High	Hydroxychloroquine has little or no effect on mortality.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Hydroxychloroquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Admission to hospital	Based on data from 7432 participants in 10 studies. (Randomized controlled)	3 per 1000 Difference:	1 per 1000 **2 fewer per 1000** (CI 95% 6 fewer — 2 more)	High	Hydroxychloroquine has little or no effect on hospital admission.
Laboratory-confirmed SARS-CoV-2 infection	Odds ratio 0.95 (CI 95% 0.62 — 1.32) Based on data from 8379 participants in 12 studies.	62 per 1000 Difference:	59 per 1000 **3 fewer per 1000** (CI 95% 24 fewer — 19 more)	High	Hydroxychloroquine has little or no effect on laboratory-confirmed COVID-19 infection.
Adverse events leading to discontinuation	Based on data from 6153 participants in 9 studies.	22 per 1000 Difference:	28 per 1000 **6 more per 1000** (CI 95% 2 more — 10 more)	High	Hydroxychloroquine has a small increase in adverse effects leading to discontinuation.

6.2 Tixagevimab-cilgavimab

Conditional recommendation against

New

We suggest not to use tixagevimab-cilgavimab in individuals who do not have COVID-19 (conditional recommendation).

Remark: This recommendation applies to all individuals who do not have COVID-19.

Practical Info

Given the conditional recommendation against using tixagevimab-cilgavimab prophylaxis for individuals who do not have COVID-19, practical considerations were felt to be less relevant here.

Evidence To Decision

Benefits and harms

The panel reviewed clinical trial evidence, available via the LNMA *(3)*, in parallel with subsequent in vitro data on virus neutralization efficacy of tixagevimab-cilgavimab (see section 6.2.1). The panel noted that while the clinical trial results suggested prophylactic use of tixagevimab-cilgavimab reduced the occurrence of laboratory-confirmed symptomatic COVID-19 (i.e. individuals were only tested if they developed symptoms). Tixagevimab-cilgavimab were not associated with reductions in hospital admissions or deaths. Moreover, the panel also concluded that these modest benefits represent the

best-case scenario obtained under bygone conditions since new SARS-CoV-2 sublineages have since replaced the former Omicron sublineages that could be neutralized by tixagevimab-cilgavimab.

Certainty of the Evidence

Having concluded that recently emerged in vitro evidence rendered the clinical trial results obsolete, the panel abstained from rating the certainty of the underlying evidence.

Values and preferences

The GDG inferred that, in the absence of compelling evidence of clinical effectiveness for the currently circulating SARS-CoV-2 sublineages, the majority of informed individuals would choose not to receive tixagevimab-cilgavimab.

Resources and other considerations

The panel placed a low value on minor health benefits associated with a costly intervention of limited availability and requiring parenteral administration. Conversely, the panel placed a high value on preserving resources for interventions with a high certainty of benefit and noted the availability of effective therapeutic options.

The conditional recommendation against the use of tixagevimab-cilgavimab is supported by the requirement for expertise to offer such prophylaxis, and the availability of oral antiviral therapies recommended for treatment.

Justification

When moving from the evidence to the conditional recommendation against the use of tixagevimab-cilgavimab to prevent COVID-19-related outcomes, the panel emphasized in vitro evidence reducing the applicability of tixagevimab-cilgavimab prophylaxis trial data to the point of precluding any certainty rating. In this context, all panel members agreed on the direction of the recommendation, but not on the strength of the recommendation. Approximately half of the panel voted for a strong recommendation also because they believed that it would be extremely unlikely for previous SARS-CoV-2 sublineages to re-emerge. Moreover, in the event that new sublineages might be neutralized by tixagevimab-cilgavimab as former sublineages were, in vitro neutralization, a *sine qua non* condition for clinical effectiveness, would not guarantee clinical effectiveness. Panel members who voted for a conditional recommendation underscored that it nonetheless remained theoretically possible that former sublineages would continue to cause COVID-19 in certain regions and that, assuming that real-time monitoring of the prevalence of SARS-CoV-2 sublineages was available, a significant number of extremely vulnerable individuals may chose to receive prophylactic tixagevimab-cilgavimab. All panel members agreed that any prophylactic use of this intervention should be restricted to extremely vulnerable individuals, i.e. those who highly unlikely to mount an immune response following COVID-19 vaccination and who, due to a limited physiological reserve, are at increased risk of developing severe manifestations of COVID-19.

Noting that similar in vitro evidence led to a strong recommendatIon against the therapeutic use of human monoclonal antibodies, the panel noted that while there exists no alternative for prophylaxis, while patients who develop COVID-19 have other therapeutic options.

Clinical Question/ PICO

Population: Individuals at risk of COVID-19
Intervention: Tixagevimab + cilgavimab
Comparator: Standard care/placebo

Summary

The Table shows the characteristics of the RCT evaluating tixagevimab-cilgavimab compared with standard care/placebo included in the LNMA informing the recommendation [3].

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care/ placebo	**Intervention** Tixagevimab + cilgavimab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality	Based on data from 5197 participants in 1 studies. (Randomized controlled)	2 per 1000 Difference:	1 per 1000 **1 fewer per 1000** (CI 95% 30 fewer — 28 more)		
Laboratory-confirmed SARS-CoV-2 infection	Odds ratio 0.23 (CI 95% 0.07 — 0.74) Based on data from 5172 participants in 1 studies. (Randomized controlled)	65 per 1000 Difference:	17 per 1000 **48 fewer per 1000** (CI 95% 62 fewer — 17 fewer)		
Admission to hospital	Based on data from 5197 participants in 1 studies. (Randomized controlled)	4 per 1000 Difference:	0 per 1000 **4 fewer per 1000** (CI 95% 35 fewer — 27 more)		
Serious adverse events	Based on data from 5197 participants in 1 studies. (Randomized controlled)	37 per 1000 Difference:	37 per 1000 **0 fewer per 1000** (CI 95% 11 fewer — 10 more)		

6.2.1 Mechanism of action

Tixagevimab (COV2-2196, AZD8895) and cilgavimab (COV2-2130, AZD1061) are a combination (Evusheld, AZD7442) of human monoclonal antibodies that bind to nonoverlapping regions of the receptor-binding domain (RBD) of the SARS-CoV-2 Spike protein *(37)*. Both antibodies are Fc-engineered IgGs, whereby amino acid substitutions increase pharmacokinetic half-life by 2 to 4-fold, but also reduce recruitment of effector functions *(38)*. The combination of tixagevimab and cilgavimab administered prophylactically as intravenous infusion prevented infection animal models by ancestral SARS-CoV-2 *(39)* but animal data for currently circulating variants are unavailable. Resistance to both antibodies occurred when historical variants were placed under a selective pressure in vitro *(40)*. Cilgavimab selected for N74K, R346I, K444Q/E/R and S686G, tixagevimab selected for G476D and N487D, and the combination selected for R346G, E484K, and F486V. Unlike sotrovimab and casirivimab-imdevimab, tixagevimab-cilgavimab is administered intramuscularly, which provides lower serum concentrations than when equivalent doses are administered intravenously. In vitro neutralization of BA.1 Omicron was compromised for both tixagevimab and cilgavimab *(41)(42)*, but for subsequent earlier Omicron sublineages, the activity of cilgavimab (but not tixagevimab) was partially restored *(43)*. For more recent variants including BA.2.75.2, BQ.1, BQ.1.1, and XBB lineages, the in vitro neutralization of both antibodies is compromised *(22)(44)(45)(46)(47)*.

7. Uncertainties, emerging evidence and future research

Ongoing uncertainties and opportunities for future research

Hydroxychloroquine
The panel felt that further research was unlikely to uncover a subgroup of patients that benefit from hydroxychloroquine prophylaxis on the most important outcomes (mortality, admission to hospital and laboratory-confirmed SARS-CoV-2 infection).

Tixagevimab-cilgavimab

While the panel unanimously supported the direction of the recommendation, there was substantial discussion on the strength of the recommendatIon for tixagevimab-cilgavimab and, ultimately, the 14 GDG members who voted for a strong recommendation were outnumbered by the 17 who supported a conditional recommendation.

All members of the panel acknowledged that the available in vitro data suggests that the results of the published clinical trials are now, at best, highly uncertain. However, the panel was split regarding the certainty with which guideline users could rule out that the prevailing SARS-CoV-2 sublineages in their region would be resistant to tixagevimab-cilgavimab neutralization. Those who voted for a strong recommendation pointed out that emerging sublineages tended to rapidly replace older sublineages all over the globe and that regional real-time monitoring of circulating SARS-CoV-2 sublineages was onerous and unrealistic in most geographical areas. Notwithstanding, those who voted for a conditional recommendation argued that, provided that these conditions could be satisfied, some highly vulnerable patients may choose to receive tixagevimab-cilgavimab.

The panel inferred that restricting use of tixagevimab-cilgavimab to clinical trials would be futile considering the large number of participants required to demonstrate clinical effectiveness.

Emerging evidence

The unprecedented volume of planned and ongoing studies for COVID-19 interventions implies that further evidence will emerge to inform policy and practice. An overview of registered and ongoing trials for COVID-19 therapeutics and prophylaxis is available from the Infectious Diseases Data Observatory, through their living systematic review of COVID-19 clinical trial registrations, the WHO website and other repositories, such as the COVID-NMA initiative *(8)*.

8. Authorship, contributions and acknowledgements

WHO would like to thank the collaborative efforts of all those involved in making this process rapid, efficient, trustworthy and transparent.

WHO Therapeutics Steering Committee
The committee includes representatives from various WHO departments at headquarters and the regions and has been approved by the WHO Director of the Country Readiness Department and the WHO Chief Scientist. The WHO Secretariat meets on a regular basis to discuss when to trigger guideline updates based on evidence updates from the WHO rapid review team and other sources of evidence and selects the members of the GDG.

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The WHO Therapeutics Steering Committee is fully responsible for decisions about guidance production and convening the GDG.

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