

WHO Living guideline: Drugs to prevent COVID-19

INTERIM GUIDANCE
2 MARCH 2021



World Health
Organization



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1. Summary: what is this living guideline?

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

Target audience: The target audience is clinicians and health care decision-makers.

Current practice: Current use of drugs to prevent COVID-19 is variable, reflecting large-scale uncertainty. Numerous randomized trials of many different drugs are underway to inform practice. This first version of the *Drugs to prevent COVID-19: A WHO living guideline* contains new information and a recommendation on hydroxychloroquine (1). It follows the publication of six trials synthesized in a living network meta-analysis (NMA).

Recommendations: The panel made a strong recommendation against the use of hydroxychloroquine prophylaxis for individuals who do not have COVID-19 (high certainty evidence).

How this guideline was created: This living guideline is an innovation from the World Health Organization (WHO), driven by the urgent need for global collaboration to provide trustworthy and evolving COVID-19 guidance informing policy and practice worldwide. WHO has partnered with the non-profit Magic Evidence Ecosystem Foundation (MAGIC) for methodologic support and development and dissemination of living guidance for COVID-19 drugs to prevent and treat COVID-19. These guidelines are also published in the BMJ (2), supported by two living systematic reviews with network analysis that inform the recommendations (3, 4). An international Guideline Development Group (GDG) of content experts, clinicians, patients, an ethicist and methodologists produced recommendations following standards for trustworthy guideline development using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. No conflict of interest was identified for any panel member or other contributors to the guideline development process.

The latest evidence: The recommendation on hydroxychloroquine was informed by results from a systematic review and NMA that pooled data from six trials with 6059 participants who did not have COVID-19 and received hydroxychloroquine (3). Three trials enrolled participants who had a known exposure to infection.

The resulting GRADE evidence summary suggested that hydroxychloroquine has a small or no effect on mortality (odds ratio 0.70; 95% CI 0.24–1.99; absolute effect estimate 1 fewer death per 1000, 95% CI from 2 fewer – 3 more deaths per 1000 individuals; high certainty evidence) and on admission to hospital (odds ratio 0.87; 95% CI 0.42–1.77; absolute effect estimate 1 fewer per 1000, 95% CI 3 fewer – 4 more admissions to hospital per 1000 individuals; high certainty evidence). Hydroxychloroquine probably has a small or no effect on laboratory-confirmed SARS-CoV-2 infection (odds ratio 1.03; 95% CI 0.71–1.47; absolute effect estimate 2 more per 1000; 95% CI 18 fewer – 28 more infections per 1000 individuals; moderate certainty evidence). In contrast, hydroxychloroquine probably increases adverse events leading to discontinuation (odds ratio 2.34; 95% CI 0.93–6.08; absolute effect estimate 19 more per 1000, 95% CI 1 fewer – 70 more adverse events per 1000 individuals; moderate certainty evidence).

There was no indication of a credible subgroup effect based on known exposure to a person with SARS-CoV-2 infection or hydroxychloroquine dosing regimen (extremely low event rates precluded investigation of subgroup effects for mortality).

Understanding the recommendations: When moving from the evidence to the strong recommendation against the use of hydroxychloroquine to prevent COVID-19, the panel emphasized the evidence suggesting no or a small effect on mortality and hospital admission along with a probable increased risk of adverse effects. 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 should rather be oriented to evaluate other more promising prophylactic interventions.

Info Box

This first *Drugs to prevent COVID-19: A WHO living guideline* makes a strong recommendation against the use of hydroxychloroquine (1). The guideline was initiated after publication of six trials. Please see above for a summary of the guidance.

This is a living guideline, so the recommendation included here will be updated, and new recommendations will be added on other prophylactic interventions for COVID-19. The guideline is therefore 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), supported by the [living NMA 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:

- The [Therapeutics and COVID-19: living guideline](#), published 17 December 2020, which includes recommendations on drugs for patients with suspected or proven COVID-19 (5).
- The [COVID-19 Clinical management: living guidance](#), published 25 January 2021 and 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
MAGIC	Magic Evidence Ecosystem Foundation
NMA	network meta-analysis
PICO	population, intervention, comparator, outcome
RCT	randomized controlled trial
WHO	World Health Organization

3. Background

As of 16 February 2021, over 108 million people worldwide have been diagnosed with COVID-19, according to the WHO dashboard (7). The pandemic has so far claimed more than 2.3 million lives, and many areas of the world are experiencing a resurgence in cases.

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.

There are 2610 registered or ongoing trials investigating various interventions for COVID-19 (see Section 8) (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?

This first version of the *Drugs to prevent COVID-19: A WHO living guideline* addresses the use of hydroxychloroquine to prevent COVID-19. It follows the publication of a systematic review and NMA that pooled data from six trials with 6059 participants who did not have COVID-19 and received hydroxychloroquine (3, 9-14). Three trials enrolled participants who had a known exposure to a person with SARS-CoV-2 infection.

In response to the release of trial data, the WHO GDG developed recommendations on hydroxychloroquine, an anti-inflammatory agent that works through blocking of Toll-like receptors reducing dendritic cell activation. It is used to treat rheumatoid arthritis and systemic lupus erythematosus. It has an antiviral effect against many viruses in vitro, including SARS-CoV-2, but a clinically useful antiviral effect has not been shown for any viral infection.

3.2 Who made this guideline?

As detailed in Section 4, the WHO convened a standing GDG with 27 clinical content experts, 4 patient-partners and 1 ethicist, headed by a clinical chair (Dr Michael Jacobs) 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. The 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 on 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 (15). It accommodates dynamic updating of evidence and recommendations that can focus 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 here 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 the MAGICapp online formats and additional tools, such as the infographics, is to make it easier to navigate and make use of the guideline in busy 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](#)) (15).

4. Methods: how this guideline was created

The *Drugs to prevent COVID-19: A WHO living guideline* 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 (16).

Related guidelines

This guideline is related to the [Therapeutics and COVID-19: living guideline](#), published 17 December 2020, which includes recommendations on drugs for patients with suspected or proven COVID-19 (5, 17).

The [COVID-19 Clinical management: living guidance](#), published 25 January 2021 and available also on the 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 guideline development process to WHO publication, within 1 month, while maintaining standards and methods for trustworthy guidelines ([WHO Handbook for guideline development](#)) (16, 18).

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 the recommendations. To do so, various processes occurred 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 NMA, 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 9), 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 the high-quality evidence synthesis living systematic review;
- relevance to a global audience.

Step 2: Convening the GDG

The pre-selected expert panel (see Section 9) convened on two occasions. The first meeting, held on 14 January 2021, focused on development of clinical questions in PICO formats, prioritization of patient-important outcomes and proposed subgroup analyses. The second meeting, held on 21 January 2021, served to clarify methodological concepts relevant to guidelines for prophylactic interventions before reviewing the evidence summary from the living NMA and creating a recommendation for hydroxychloroquine. No conflict of interest was identified for any panel member according to WHO standards, with individual biographies available on the WHO website (web link).

Step 3: Evidence synthesis

Following a request by the WHO Therapeutics Steering Committee and coordinated by the Guidance Support Collaboration Committee, the living systematic review team conducted an independent systematic review and NMA to evaluate prophylactic interventions for COVID-19. The systematic review team is multidisciplinary and made up of systematic review experts, clinical experts, clinical epidemiologists and biostatisticians. The team has expertise in GRADE methodology and rating certainty of evidence specifically in NMAs. The NMA team was informed of the deliberations from the initial GDG meeting in order to guide the NMA, specifically focusing on the outcomes and subgroups prioritized by the panel.

Step 4: Final recommendation

The GRADE approach provided the framework for establishing evidence certainty and generating both the direction and strength of recommendations (19, 20). Voting procedures were established at the outset, in case consensus was not reached, but these procedures were not necessary for this recommendation which reached consensus amongst the panel. A simple majority would provide the direction of the recommendation and 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) (21);
- quality/certainty of the evidence (19, 22);
- values and preferences of patients (23);
- resources and other considerations (including considerations of feasibility, applicability, equity) (23);
- 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 (if the panel members disagree regarding the evidence assessment or strength of recommendations, voting occurs according to established methods).

Step 5: External and internal review

The WHO guideline was then reviewed by pre-specified external reviewers (see Section 9) and then approved by the WHO Guideline Review Committee.

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.

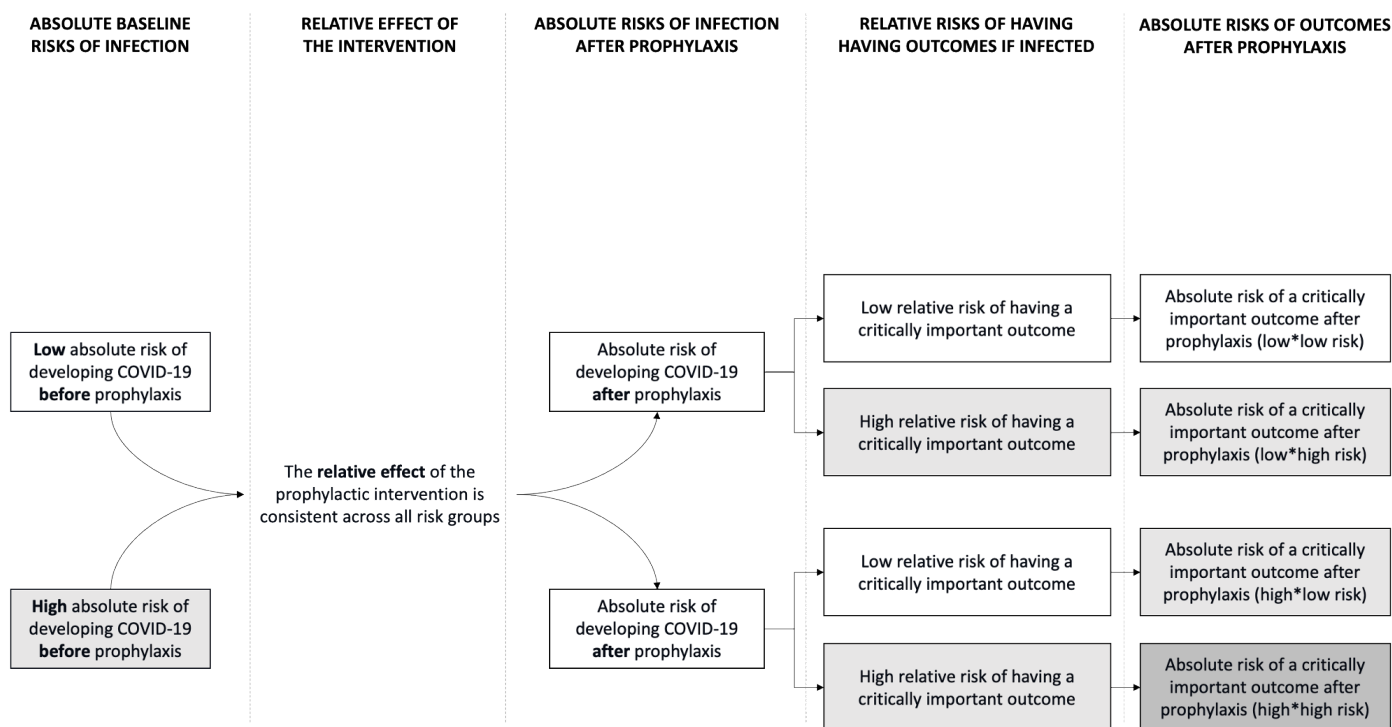
Subgroup comparisons for evidence pertaining to prophylactic interventions

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 (24). 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. 1 illustrates how this modelling may result in different absolute risks of experiencing a critically important outcome after prophylaxis.

Fig. 1. Determination of varying absolute risks of critically important outcomes based on modelling



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

5. The latest evidence

This section outlines what information the GDG panel requested and used in making their recommendation for hydroxychloroquine prophylaxis.

Benefits and harms

The GDG panel requested an update of the living NMA of RCTs of prophylactic interventions for COVID-19.

The GDG members prioritized outcomes (rating from 1 [not important] to 9 [critical]) taking a patient's perspective (Table 1). The panel's questions were structured using the PICO format (see evidence profile under the recommendations).

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.

For hydroxychloroquine, the evidence summary was based on six trials and 6059 participants for which the NMA provided relative estimates of effect for patient-important outcomes (9-14) (Table 2). Three trials enrolled participants who had a known exposure to a person with SARS-CoV-2 infection and three others enrolled participants without a known exposure.

Table 2. Summary of trial characteristics informing the hydroxychloroquine recommendation (trials = 6, total patients = 6059)

Geographic regions	North America	4 trials, 3265 participants
	Europe	2 trials, 2794 participants
	Asia	0 trials, 0 patients
	Middle East	
	South America Australasia	
Exposure to the virus	Known exposure	3 trials, 4175 participants
	No known exposure	3 trials, 1884 participants
Age	Mean age (range of means)	43.6 (33–48.7)
Sex	Mean % of men (range of means)	37.2 (26.8–48.8)
Dose on day 1	Mean dose on day 1 in mg (range of means)	706.6 (400–1400)
Total cumulative dose	Median cumulative dose in mg (range of cumulative dose)	5200 (3200–33 600)
Duration of therapy	Median number of days (range)	35 (5–172)
Type of risk	Close contact	3 trials, 4175 participants
	Healthcare workers (considered without a known exposure)	3 trials, 1884 participants
Number of participants	Median, range	825 (132–2525)

Subgroup analyses

The GDG requested subgroup analyses based on known vs. unknown exposure to a person with SARS-CoV-2 infection and hydroxychloroquine dosing regimen.

The panel discussed the relevance of seeking potential subgroup effects for all outcomes but recognized that these analyses would not be possible for mortality given the extremely low number of deaths in studies evaluating prophylactic interventions.

The pairwise subgroup analyses were performed using a Bayesian analysis which incorporated meta-regression using study as a random effect. The panel used a pre-specified framework incorporating the ICEMAN tool to assess the credibility of subgroup findings (24). With evidence summaries showing moderate to high certainty of no important benefit for hydroxychloroquine in any subgroup on any outcome, the panel decided not to stratify patients based on differing baseline risks for the patient-important outcomes.

Baseline risk estimates (prognosis of patients with COVID-19): informing absolute estimates of effect

The baseline risks were calculated from data from the control groups of trials included in the NMA, which also yielded the estimate of relative effects of prophylactic interventions (3). The evidence summaries that informed the guideline recommendation reported the anticipated absolute effects of hydroxychloroquine 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 on treatment decisions 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 four patient-representatives 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, laboratory-confirmed COVID-19, and adverse effects leading to discontinuation.
- Most individuals would be reluctant to use a medication for which the evidence left high uncertainty regarding effects on the outcomes listed above, particularly when evidence suggested treatment effects, if they do exist, are small, and the possibility of important harm remains.

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.

6. Who do the recommendations apply to?

Info Box

This *Drugs to prevent COVID-19: A WHO 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 any specific recommendations for individuals with known exposure to a person with SARS-CoV2 infection, or for different drug doses.

7. Recommendations for prophylaxis

7.1 Hydroxychloroquine

Recommendation against

New

We recommend against administering hydroxychloroquine prophylaxis to individuals who do not have COVID-19 (strong recommendation, high certainty evidence).

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

Evidence to decision

Benefits and harms

Substantial net benefits of the recommended alternative

Used prophylactically, hydroxychloroquine has a small or no effect on death and hospital admission (high certainty), and probably has a small or no effect on laboratory-confirmed COVID-19 (moderate certainty). It probably increases the risk of adverse effects leading to discontinuation of the drug (moderate 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

For key outcomes of mortality and hospital admission, the panel had high certainty that hydroxychloroquine had no or a small effect. The certainty was moderate for the outcome of laboratory-confirmed COVID-19 due to serious risk of bias (lack of blinding in one trial), and also for adverse effects due to serious imprecision (in this case the panel assessed the certainty that the null effect could be excluded).

Preference and values

We expect few to want the intervention

Given the evidence, the panel inferred that almost all well-informed individuals would decline hydroxychloroquine.

Resources and other considerations

Important negative issues

Hydroxychloroquine is relatively inexpensive and is widely available, including in low-income 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 (25).

Justification

When moving from the evidence to the strong recommendation against the use of hydroxychloroquine to prevent COVID-19, the panel emphasized the evidence suggesting no or a small effect on mortality and hospital admission along with a probable increased risk of adverse effects. 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.

Subgroup analyses

The panel did not find any evidence of a subgroup effect as a function of known exposure to infection or by dose of hydroxychloroquine. Of note, for trials that enrolled participants without a known exposure to infection, 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 infection, 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. Although hydroxychloroquine has been used in pregnant women with systemic autoimmune diseases, such as systemic lupus erythematosus, pregnant women may have even more reasons than other individuals to be reluctant to use hydroxychloroquine for COVID-19 prophylaxis.

Uncertainties

Please see Section 8 for residual uncertainties. The panel felt that it was unlikely future studies would identify a subgroup of individuals likely to benefit from hydroxychloroquine prophylaxis.

Clinical question/PICO

Population: Individuals who do not have COVID-19
Intervention: Hydroxychloroquine
Comparator: Standard care

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care Hydroxychloroquine	Certainty of the evidence (Quality of evidence)	Plain text summary
Mortality	Odds Ratio 0.7 (CI 95% 0.24 - 1.99) Based on data from 4849 patients in 4 studies. (Randomized controlled)	3 per 1000 2 per 1000 Difference: 1 fewer per 1000 (CI 95% 2 fewer - 3 more)	High	Hydroxychloroquine has a small or no effect on mortality.
Admission to hospital	Odds Ratio 0.87 (CI 95% 0.42 - 1.77) Based on data from 5659 patients in 5 studies. (Randomized controlled)	5 per 1000 4 per 1000 Difference: 1 fewer per 1000 (CI 95% 3 fewer - 4 more)	High	Hydroxychloroquine has a small or no effect on hospital admission.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Plain text summary
		Standard care	Hydroxychloroquine		
Lab-confirmed COVID-19 diagnosis	Odds Ratio 1.03 (CI 95% 0.71 - 1.47) Based on data from 5294 patients in 6 studies.	65 per 1000	67 per 1000	Moderate Due to serious risk of bias ¹	Hydroxychloroquine probably has a small or no effect on lab- confirmed COVID-19 diagnosis.
Adverse events leading to discontinuation	Odds Ratio 2.34 (CI 95% 0.93 - 6.08) Based on data from 3616 patients in 4 studies.	15 per 1000	34 per 1000	Moderate Due to serious imprecision ²	Hydroxychloroquine probably increases adverse events leading to discontinuation.

8. 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, laboratory-confirmed COVID-19) given the consistent results in trials across subgroups and location.

Emerging evidence

The unprecedented volume of planned and ongoing studies for COVID-19 interventions (2610 randomized controlled trials as of 18 February 2021) 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).

Concerning hydroxychloroquine or chloroquine prophylaxis, more than 80 trials planning to enroll at least 100 000 participants are registered or ongoing (8). The high certainty evidence that has emerged regarding the lack of effect of hydroxychloroquine prophylaxis suggests that funders and researchers should reconsider the initiation or continuation of these trials.

9. Authorship, contributions and acknowledgements

WHO would like to thank the collaborative efforts of all those involved to make this process rapid, efficient, trustworthy and transparent, including extensive in-kind support from the Magic Evidence Ecosystem Foundation (MAGIC) and their partner, the BMJ, to develop and disseminate this living guideline for prevention of COVID-19, based on a living systematic review and network analysis from investigators at McMaster University, Canada.

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 Guideline Development Group (GDG).

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

We would like to acknowledge the Guidance Support Collaboration Committee which provided the coordination between WHO and MAGIC to allow the rapid development of the WHO guideline and its dissemination: Thomas Agoritsas (MAGIC, University Hospitals of Geneva); Janet Diaz (WHO); Fiona Godlee (BMJ); Gordon H Guyatt (McMaster University, Canada); Navjoyt Ladher (BMJ); Francois Lamontagne (Université de Sherbrooke, Canada); Srinivas Murthy (University of British Columbia, Canada); Bram Rochweg (McMaster University, Canada); Per Olav Vandvik (MAGIC, University of Oslo, Norway). Though members of this group represent various stakeholders in the process of development and dissemination of the WHO guideline, the roles of each stakeholder were transparent and kept independent and thus these sessions used to share updates and enhance coordination.

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No conflict of interest was identified for any member. For members involved in the living systematic review see next paragraph. For MAGIC members, all completed WHO conflict of interest forms and also BMJ forms for their co-authorship in the guideline appearing in the BMJ (2).

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No conflict of interest was identified for any member, as reported in the ICMJE disclosure forms completed for the submission of the manuscript to BMJ (in peer-review, published at MedRxiv) (3).

External reviewers

Special thanks are extended to the external reviewers for their insights: Yaseen Arabi (King Saud Bin Abdulaziz University for Health Sciences, Saudi Arabia); Richard Kojan (Alliance for International Medical Action); Bhargavir Rao (Médecins Sans Frontières).

No conflict of interest was identified for the external reviewers, based on completed WHO declaration forms.

Infographic

Special thanks to the BMJ for providing the infographic for this guideline.

Funding

No specific funding was provided for this guideline, with MAGIC providing pro bono contributions and support to WHO in the context of the COVID-19 pandemic.

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