WHO Living guideline: Drugs to prevent COVID-19

INTERIM GUIDANCE
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Contents

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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* adresses 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 epidemiologistsg 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