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Additional material is published online only. To view please visit the journal online

Cite this as: *BMJ* 2021;372:n526

<http://dx.doi.org/10.1136/bmj.n526>

RAPID RECOMMENDATIONS

A living WHO guideline on drugs to prevent covid-19

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ABSTRACT

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. The first version of this living guideline focuses on the evidence for hydroxychloroquine. Subsequent updates will cover other drugs being investigated for their role in the prevention of covid-19.

RECOMMENDATION

The guideline development panel made a strong recommendation against the use of hydroxychloroquine for individuals who do not have covid-19 (high certainty).

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) provided methodological support. A living systematic review with network analysis informed the recommendations. An international guideline development panel 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.

UNDERSTANDING THE NEW RECOMMENDATION

The linked systematic review and network meta-analysis (6 trials and 6059 participants) found that hydroxychloroquine had a small or no effect on mortality and admission to hospital (high certainty evidence). There was a small or no effect on laboratory confirmed SARS-CoV-2 infection (moderate certainty evidence) but probably increased adverse events leading to discontinuation (moderate certainty evidence). The panel judged that almost all people would not consider this drug worthwhile. In addition, the panel decided that contextual factors such as resources, feasibility, acceptability, and equity for

countries and healthcare systems were unlikely to alter the recommendation. The panel considers that this drug is no longer a research priority and that resources should rather be oriented to evaluate other more promising drugs to prevent covid-19.

UPDATES

This is a living guideline. New recommendations will be published in this article and signposted by update notices to this guideline.

READERS NOTE

This is the first version of the living guideline for drugs to prevent covid-19. It complements the WHO living guideline on drugs to treat covid-19. When citing this article, please consider adding the update number and date of access for clarity.

Drugs could be used as prophylaxis to prevent covid-19 developing in those who are free from disease. Such drugs complement vaccines that, through developing immune responses to SARS-CoV-2, reduce the risk of developing covid-19 and its consequences. Drugs to prevent covid-19 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 those at higher risk of death and poor outcomes if infected. There are 2610 trials investigating various drug interventions for covid-19 (see section on emerging evidence).¹ This rapidly evolving evidence landscape requires trustworthy interpretation and expeditious clinical practice guidelines to inform clinicians, patients, governments, ministries and health administrators.

This living guideline uses emerging evidence from RCTs on drugs to prevent covid-19 and complements the living WHO guideline on drugs to treat covid-19.² The living network meta-analysis associated with this guideline will incorporate new trial data and allow for analysis of comparative effectiveness.³ Details of the network meta-analysis and other related publications are listed in [box 1](#). We will also use additional relevant evidence on long term safety, prognosis, and patient values and preferences related to covid-19 treatments to inform the living guidance.

Box 1: Linked resources in this BMJ Rapid Recommendations cluster

- Lamontagne F, Agoritsas T, Siemieniuk R, et al. A living WHO guideline on drugs to prevent covid-19 [Version 1]. *BMJ* 2021;372:n526, doi:10.1136/bmj.n526
- World Health Organization. *Drugs to prevent COVID-19: A WHO living guideline*. 2021. <https://apps.who.int/iris/bitstream/handle/10665/339877/WHO-2019-nCoV-prophylaxes-2021.1-eng.pdf>
- MAGICapp (<https://app.magicapp.org/#/guideline/L6RxYL>)
 - Expanded version of the methods, processes, and results with multilayered recommendations, evidence summaries, and decision aids for use on all devices
- Bartoszko JJ, Siemieniuk R, Kum E, et al. Prophylaxis against covid-19: living systematic review and network meta-analysis (in peer-review)
 - Preprint data is available at *MedRxiv*: <https://www.medrxiv.org/content/10.1101/2021.02.24.21250469v1>

What triggered this version of the guideline?

This first version addresses the use of hydroxychloroquine to prevent covid-19. It follows six trials with 6059 participants pooled into a systematic review and network meta-analysis (NMA) that suggested hydroxychloroquine was unlikely to be of use in preventing covid-19.³⁻⁹ In response, the WHO guideline panel developed recommendations on hydroxychloroquine for prevention of covid-19.

How to use this guideline

This is a living guideline, so the recommendations included here will be updated, and new recommendations will be added for other prophylactic drugs for covid-19. The infographic provides a summary of the recommendations and includes links to the MAGICapp for more details on the evidence and rationale for the recommendation, as well as patient decision aids. **Box 2** outlines key methodological aspects of the guideline process.

Box 2: How this living guideline was created (see MAGICapp for full details <https://app.magicapp.org/public/guideline/L6RxYL>)

This guideline was developed by WHO and the MAGIC Evidence Ecosystem Foundation (MAGIC) with support from *The BMJ*. It is driven by an urgent need for trustworthy and living guidance to rapidly inform policy and practice worldwide during the covid-19 pandemic. WHO has partnered with MAGIC for their methodological support in the development and dissemination of living guidance for covid-19 drug treatments and prophylaxis, in the form of *BMJ* Rapid Recommendations, to provide patients, clinicians, and policy makers with up to date, evidence based, and user friendly guidelines.

Standards, methods, and processes for living and trustworthy guidance

The guideline development panel produced the recommendations following standards for trustworthy guideline development using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach, in compliance with the *WHO Handbook for Guideline Development* 2nd Edition,¹⁰ the Institute of Medicine, and the Guideline International Network (G-I-N).¹¹ Details are provided in the WHO guideline and MAGICapp (**box 1**).

Selection and support of the guideline development panel

For the hydroxychloroquine prophylaxis recommendation, WHO convened an international guideline development panel with 32 individuals, of whom 27 were content experts (clinicians, methodologists, scientists, and one ethicist) and four were patients who had survived covid-19. The methods chair (methodological expertise) and a clinical chair (content expertise) guided the panel discussions. Panel members were invited by WHO, after consultation with the methods chair and MAGIC, with the

aim of achieving gender, geography, expertise, and patient representation balance in the panel. No relevant conflict of interest was identified for any panel member.

As recommended by the WHO handbook, the panel aimed to create a recommendation based on consensus but elected, at the beginning of the first panel meeting, to call a vote if a consensus could not be reached. Before discussions started, the panel determined that a simple majority would provide the direction of the recommendation and that 80% would be required to make a strong recommendation.

Guideline perspective, outcomes, and values and preferences

The target audience for this guidance consists primarily of clinicians and healthcare decision makers. The panel considered an individual patient perspective but also took account of contextual factors (such as resources, feasibility, acceptability, equity) to accommodate a global context and the realities of different countries and healthcare systems. In the absence of empirical evidence on values and preferences guiding decisions for covid-19 prophylactic interventions, the panel members relied on their own judgments of how well-informed individuals would value benefits, harms, and burdens of prophylactic interventions. The panel included four patient representatives who had lived experience of covid-19. The panel concluded that:

- Mortality would be the outcome most important to individuals, followed by need for hospital admission, laboratory confirmed 19SARS-CoV-2 infection, 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 effects, if they do exist, are small, and the possibility of important harm remains.

The panel acknowledged, however, that values and preferences could vary. There may 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 if they are not yet ill. 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.

Sources of evidence

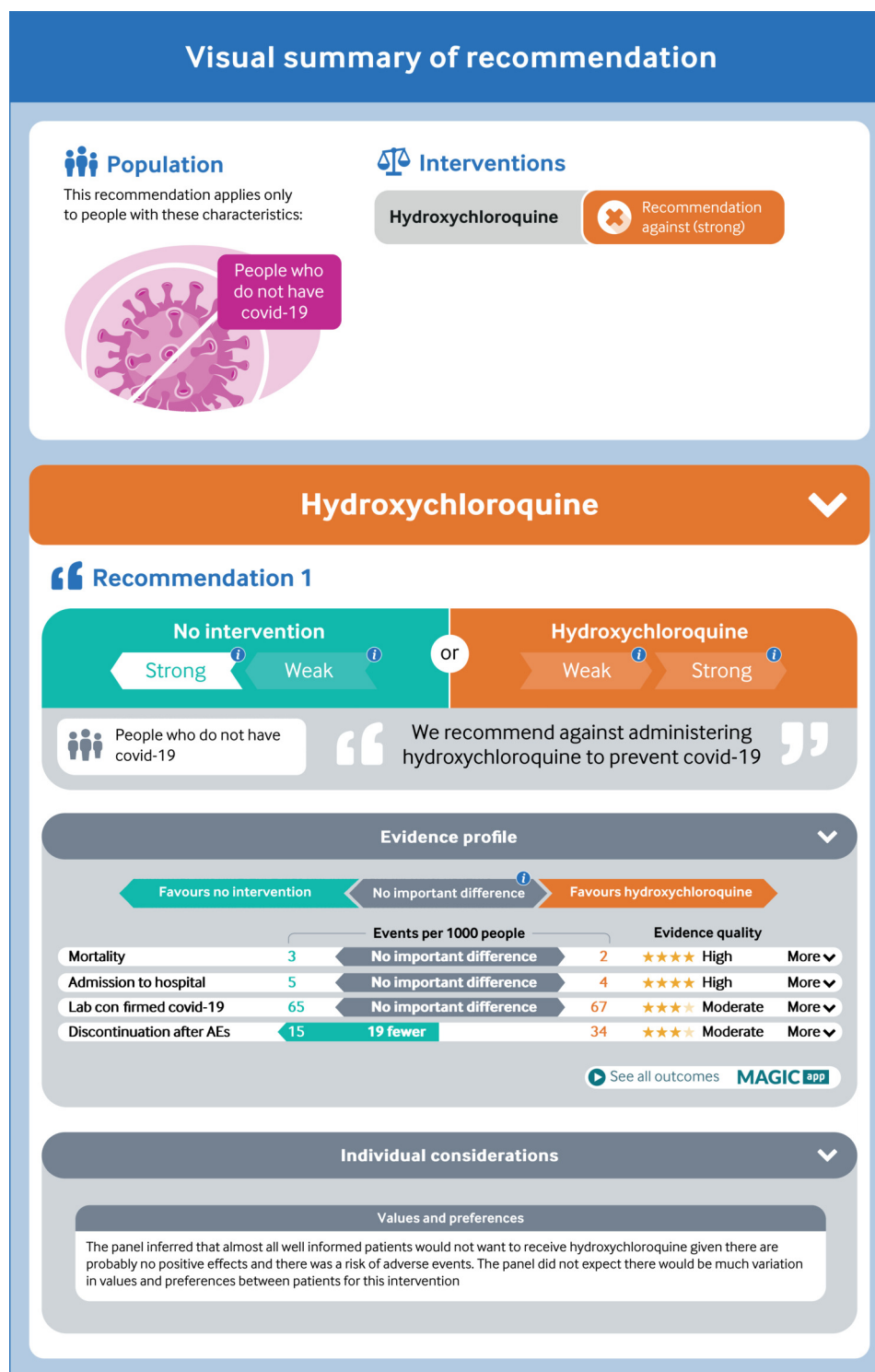
To create recommendations, the panel relied on evidence synthesised in a living network meta-analysis, led by MAGIC collaborators.³ While the investigators responsible for the meta-analyses rated the certainty of the evidence, this was re-assessed independently by the guideline panel.

Derivation of absolute effects for drug treatments

The baseline risks were calculated from data from the control groups of trials included in the network meta-analysis, which also yielded the estimate of relative effects of prophylactic interventions.¹ 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 randomised 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.

Special considerations for recommendations on prophylaxis

As detailed in the full WHO guideline (see **box 1**), the panel considered the implications of very low risks of critical outcomes such as death in trials of prophylactic interventions. The panel opted to consider the magnitude of effect (for example, trivial, small, moderate, or large effect) when rating certainty. The panel considered two prespecified subgroup analyses based on known exposure to SARS-CoV-2 infection and dose of hydroxychloroquine.



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Who do the recommendations apply to?

This 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-CoV-2 infection or for different drug doses.

The guidance

Hydroxychloroquine

Hydroxychloroquine is an immunomodulator that blocks 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.

The recommendation was informed by the linked systematic review and network meta-analysis that included six trials and 6059 participants.^{3–9} 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.

Understanding the recommendation on hydroxychloroquine

We recommend against the use of hydroxychloroquine as prophylaxis in individuals who do not have covid-19 (strong recommendation; high certainty evidence).

Balance of benefit and harm—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 SARS-CoV-2 infection (moderate certainty). It probably increases the risk of adverse effects leading to discontinuation of the drug (moderate certainty). There were no subgroup effects according to known exposure to a person with SARS-CoV-2 infection or hydroxychloroquine dose regimen on the outcomes of hospital admission, laboratory confirmed covid-19, and adverse effects leading to discontinuation. Extremely low event rates precluded investigation of subgroup effects for mortality and in the absence of other subgroup effects, the panel assumed similar relative effects on mortality across subgroups.

Values and preferences—Applying the agreed values and preferences (box 2), the guideline development panel inferred that almost all well-informed patients would decline hydroxychloroquine.

Resource implications, feasibility, equity, and human rights—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.¹²

Uncertainties, emerging evidence, and future research

Uncertainties

The panel felt that further research was unlikely to uncover a subgroup of patients who benefit from hydroxychloroquine prophylaxis on the most important outcomes (mortality, admission to hospital) given the consistent results of trials completed to date.

Emerging evidence

The unprecedented volume of planned and ongoing studies for covid-19 interventions (2610 randomised controlled trials as of 18 February 2021) implies that further evidence will emerge to inform policy and practice.¹ 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 registrations¹), the WHO website, and other repositories such as the COVID-NMA initiative.

Future research

Concerning hydroxychloroquine or chloroquine prophylaxis, more than 80 trials planning to enrol at least 100 000 participants are registered or ongoing.¹ 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.

How patients were involved in the creation of this article

The guideline development panel included four patients who have had covid-19. Their perspectives were crucial in considering the values and preferences associated with hydroxychloroquine prophylaxis.

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• World Health Organisation (WHO) Secretariat for Therapeutics and COVID-19

• External reviewers for WHO

We also thank

• The living systematic review and network meta-analysis team, led by investigators Reed Siemieniuk and Romina Brignardello-Petersen at McMaster University, Canada

• BMJ editorial team with Navjoyt Ladher (head of education), Will Stahl-Timmins (data graphics designer) and Greg Cotton (technical editor) of this living guideline publication in *The BMJ*

• Alistair MacLean, Brittany Maguire, Philippe Guerin, and Sumayyah Rathan for providing up to date corticosteroid data from the Infectious Diseases Data Observatory (IDDO) living systematic review for covid-19 clinical trial registration (<https://www.iddo.org/research-themes/covid-19/live-systematic-clinical-trial-review>).

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Main infographic: Summary of recommendations and evidence

Appendix. Table of registered ongoing trials for hydroxychloroquine or chloroquine

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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.

Competing interests: All guideline panel members have completed the WHO interest disclosure form. All authors have completed the *BMJ* Rapid Recommendations interest of disclosure form. The WHO, MAGIC, and *The BMJ* judged that no panel member had any financial conflict of interest. Professional and academic interests are minimised as much as possible, while maintaining necessary expertise on the panel to make fully informed decisions. MAGIC and *The BMJ* assessed declared interests from other co-authors of this publication and found no conflicts of interests.

Provenance and peer review: This publication was commissioned by *The BMJ* in partnership with WHO and the MAGIC Evidence Ecosystem Foundation, in the context of the *BMJ* Rapid Recommendations. Pre-publication internal and external peer-review managed by WHO, and internal review at *The BMJ*. Post-publication review through rapid responses on bmj.com and through MAGICapp.

We thank all the following collaborators who contributed to this endeavour, as detailed in the WHO guidance (see link in box 1)