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

Cite this as: *BMJ* 2020;370:m3379

<http://dx.doi.org/10.1136/bmj.m3379>

RAPID RECOMMENDATIONS

A living WHO guideline on drugs for covid-19

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ABSTRACT

UPDATES

This is the eleventh version (tenth update) of the living guideline, replacing earlier versions (available as data supplements). New recommendations will be published as updates to this guideline.

CLINICAL QUESTION

What is the role of drugs in the treatment of patients with covid-19?

CONTEXT

The evidence base for therapeutics for covid-19 is evolving with numerous randomised controlled trials (RCTs) recently completed and under way. This update adds new recommendations on fluvoxamine and colchicine in patients with non-severe covid-19; the former was informed by data from three RCTs with 2196 patients, and the latter by data from seven RCTs with 16484 patients. Alternatives are available for patients with non-severe covid-19 at highest risk of hospitalisation. In the absence of direct comparisons in trials, indirect comparisons from an accompanying living network meta-analysis have been used to inform use of one drug over another with a related mechanism of action. Choices will depend on availability of the drugs, routes of administration (only intravenous for remdesivir), co-administered medications, duration of treatment, time from onset of symptoms to starting treatment, and the given variant of SARS-CoV-2.

NEW RECOMMENDATIONS

- Fluvoxamine: a recommendation against its use, except in the context of a clinical trial in patients with non-severe illness.
 - Colchicine: a strong recommendation against its use in patients with non-severe illness.
- No recommendation was made for either drug in patients with severe or critical illness, given limited or no data.

UNDERSTANDING THE NEW RECOMMENDATIONS

In patients with non-severe illness, the recommendations against fluvoxamine and colchicine reflect the lack of a clear mechanism of action; evidence of little or no effect on risks of admission to hospital (low to moderate certainty evidence), mechanical ventilation, and mortality; and absence of reliable data on covid-19 related serious adverse events and harms. For fluvoxamine, known serious pharmacological interactions and the large proportion of drug discontinuations observed in included studies were also considered. For colchicine, known risks of drug interactions and the drug's narrow therapeutic window, particularly in patients with or at risk of hepatic and renal failure, were considered; colchicine toxicity can be severe, and sometimes fatal.

PRIOR RECOMMENDATIONS

- Recommended for patients with severe or critical covid-19—a strong recommendation for systemic corticosteroids; a strong recommendation for IL-6 receptor blockers (tocilizumab or sarilumab), in combination with corticosteroids; a strong recommendation for baricitinib as an alternative to IL-6 receptor blockers, in combination with corticosteroids; and a conditional recommendation for casirivimab-imdevimab, for those with seronegative status, (where rapid viral genotyping is available to confirm infection with a susceptible SARS-CoV-2 variant).
- Recommended for patients with non-severe covid-19 at highest risk of hospitalisation—a strong recommendation for nirmatrelvir/ritonavir; and conditional recommendations for molnupiravir, sotrovimab, casirivimab-imdevimab (where rapid viral genotyping is available to confirm infection with a susceptible SARS-CoV-2 variant), and for remdesivir.
- Not recommended for patients with non-severe covid-19—a conditional recommendation against systemic corticosteroids; and a strong recommendation against convalescent plasma.

- Not recommended for patients with non-severe covid-19 at low risk of hospitalisation—a conditional recommendation against nirmatrelvir/ritonavir.
- Not recommended for patients with severe or critical covid-19—a recommendation against convalescent plasma, except in the context of a clinical trial; and a conditional recommendation against ruxolitinib and tofacitinib.
- Not recommended, regardless of covid-19 disease severity—a strong recommendation against hydroxychloroquine; a strong recommendation against lopinavir/ritonavir; and a recommendation against ivermectin, except in the context of a clinical trial.

ABOUT THIS GUIDELINE

This living guideline from the World Health Organization (WHO) incorporates new recommendations on two drugs for non-severe covid-19. The Guideline Development Group (GDG) typically evaluates a therapy when WHO judges sufficient evidence is available to make a recommendation. While the GDG takes an individual patient perspective in making recommendations, it also considers resource implications, acceptability, feasibility, equity, and human rights. This guideline was developed according to standards and methods for trustworthy guidelines, making use of an innovative process to achieve efficiency in dynamic updating of recommendations. The methods are aligned with the WHO Handbook for Guideline Development and according to a pre-approved protocol (planning proposal) by the Guideline Review Committee (GRC). A box at the end of the article outlines key methodological aspects of the guideline process. MAGIC Evidence Ecosystem Foundation provides methodological support, including the coordination of living systematic reviews with network meta-analyses to inform the recommendations. The full version of the guideline is available online in MAGICapp and in PDF, with a summary version here in *The BMJ*.

FUTURE RECOMMENDATIONS

Recommendations on baricitinib, sotrovimab, and remdesivir are planned for the next update to this guideline.

Vaccines are linked to limiting hospitalisations, but limitations in global access and residual uncertainties remain regarding the duration of protection following vaccination or natural infection, and their efficacy against emerging SARS-CoV-2 variants. Therefore, the potential for drugs to treat people infected with covid-19 remains of interest. This living guideline responds to emerging evidence from randomised controlled trials (RCTs) on existing and new drug treatments for covid-19.

More than 5000 trials investigating covid-19 interventions have been registered or are ongoing (see section on emerging evidence and appendix 10 for drug-by-drug breakdown¹). Although most of these studies are small and of variable methodological quality, some large, international platform trials have provided robust evidence. Such trials can also adapt their design, recruitment strategies, and selection of interventions based on new insights. Examples include ACCT, RECOVERY, WHO SOLIDARITY, REMAP-CAP, and ACTIV, which recruit large numbers of patients in many countries.²⁻⁵ An overview of ongoing trials is available from the Infectious Diseases Data Observatory, through their living systematic review of covid-19

clinical trial registrations¹ and the World Health Organization (WHO) website (<https://www.covid-nma.com/dataviz/>).

However, existing and emerging evidence demonstrates remaining uncertainties concerning treatment effects for all outcomes of importance to patients. There is also a need for better evidence on values and preferences of patients with covid-19. Moreover, the rapidly evolving evidence landscape requires trustworthy interpretation and expeditious clinical practice guidelines to inform clinicians and health care decision-makers.

Several living network meta-analyses associated with this guideline incorporate emerging trial data and allow for analysis of comparative effectiveness of multiple covid-19 treatments.^{6,7} Box 1 includes these network meta-analyses and other related publications. To inform the living guidance, we also use additional relevant evidence on safety, prognosis, and patient values and preferences related to covid-19 treatments.

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

Versions of this guidance

- This article and infographic: Agarwal A, Rochweg B, Siemieniuk RAC, et al. A living WHO guideline on drugs for covid-19 [Update 10]. *BMJ* 2020;370:m3379, doi:10.1136/bmj.m3379
- WHO PDF: World Health Organization. *Therapeutics and COVID-19. Living guideline*. July 2022. <https://www.who.int/teams/health-care-readiness-clinical-unit/covid-19/therapeutics>
- MAGICapp (<https://app.magicapp.org/#/guideline/nBkO1E>)
 - Expanded version of the guideline, including methods, processes, and results with multi-layered recommendations, evidence summaries, and decision aids for use on all devices
 - MATCH-IT interactive decision support incorporating multiple treatment comparisons for recommended drugs in non-severe covid-19 at highest risk of hospitalisation: <https://magicevidence.org/match-it/220404dist-covid-meds/>

Linked research

- Siemieniuk RAC, Bartoszko JJ, Ge L, et al. Drug treatments for covid-19: living systematic review and network meta-analysis [Update 4]. *BMJ* 2021;370:m2980, doi:10.1136/bmj.m2980
 - Updated evidence available online: <https://www.covid19nma.com/>
- Siemieniuk RAC, Bartoszko JJ, Díaz Martínez JP, et al. Antibody and cellular therapies for treatment of covid-19: a living systematic review and network meta-analysis. *BMJ* 2021;374:n2231, doi:10.1136/bmj.n2231
- Zeraatkar D, Cusano E, Diaz Martinez JP, et al. Tocilizumab and sarilumab alone or in combination with corticosteroids for COVID-19: a systematic review and network meta-analysis. *medRxiv* 2021; doi:10.1101/2021.07.05.21259867v1
- Izcovich A, Siemieniuk RAC, Bartoszko JJ, et al. Adverse effects of remdesivir, hydroxychloroquine, and lopinavir/ritonavir when used for COVID-19: systematic review and meta-analysis of randomized trials. *medRxiv* 2020; doi:10.1101/2020.11.16.20232876v1
- Lamontagne F, Agoritsas T, Siemieniuk R, et al. A living WHO guideline on drugs to prevent covid-19. *BMJ* 2021;372:n526. doi:10.1136/bmj.n526

Treatments for covid-19

Overview of rapid recommendations


See an interactive version of this graphic online
<https://bit.ly/BMJrrcovid>


Population


This recommendation applies only to people with these characteristics:




Interventions


 Strong recommendations in favour

 Weak or conditional recommendations in favour

 Weak or conditional recommendations against

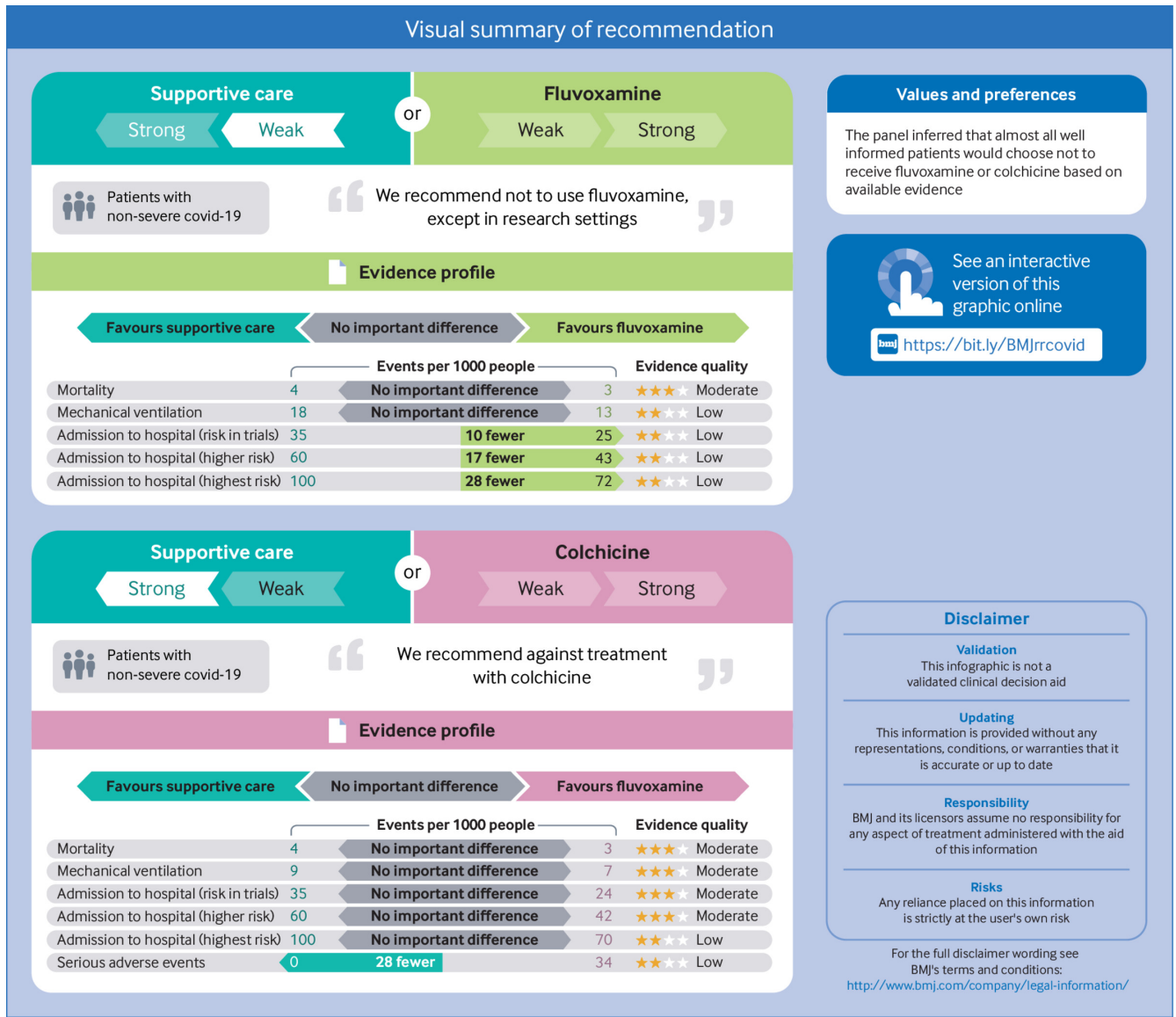
 Strong recommendations against

Disease severity

Non-severe	Severe	Critical
Absence of signs of severe or critical disease	Oxygen saturation <90% on room air Signs of pneumonia Signs of severe respiratory distress	Requires life sustaining treatment Acute respiratory distress syndrome Sepsis Septic shock
Nirmatrelvir and ritonavir	Corticosteroids IL-6 receptor blockers or Baricitinib Depending on availability as well as clinical and contextual factors	
Molnupiravir Requires mitigation strategies to reduce potential harms		
Sotrovimab		
Remdesivir		
Casirivimab and imdevimab  Evidence of limited efficacy against Omicron BA1 variant	Casirivimab and imdevimab For those with seronegative status for SARS-CoV-2 antibodies	
Corticosteroids	Ruxolitinib and tofacitinib Should be considered only if neither baricitinib nor IL-6 receptor blockers are available	
	Ivermectin Only in research settings	
Fluvoxamine Only in research settings	Convalescent plasma Only in research settings	
Colchicine		
Convalescent plasma		
	Hydroxychloroquine	
	Lopinavir-ritonavir	

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

This eleventh version of the WHO living guideline addresses the use of fluvoxamine and colchicine in non-severe covid-19. These drugs are less costly and more readily available than other therapeutic alternatives and have therefore received considerable interest during the pandemic. In light of this, coupled with a growing evidence base from newer trials, WHO decided to create recommendations. The trials were analysed in a mini-network meta-analysis and are included in a parallel update to the living network meta-analysis on drug treatments for covid-19.⁶

Other therapeutics in progress for this WHO living guideline include therapeutic anticoagulation. Recommendations for baricitinib, sotrovimab, monoclonal antibodies, and in severe and critical covid-19, remdesivir, are being updated, given availability of new evidence.

How to use this guideline and associated resources

This is a living guideline. The recommendations and evidence included here will be updated, and new recommendations will be

added for other treatments for covid-19. The infographic provides a summary of the recommendations. Readers can find more detailed information in the full version of the WHO guideline (see [box 1](#) for links to MAGICapp and the PDF version).

Who do the recommendations apply to?

This guideline applies to all patients with covid-19. Recommendations may differ based on the severity of covid-19, according to WHO severity definitions ([box 2](#)).⁸ These definitions avoid reliance on access to healthcare to define patient subgroups.

Box 2: WHO definitions of illness severity for covid-19

- *Critical covid-19*—Defined by the criteria for acute respiratory distress syndrome (ARDS), sepsis, septic shock, or other conditions that would normally require the provision of life-sustaining therapies such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy.
- *Severe covid-19*—Defined by any of:
 - Oxygen saturation <90% on room air*
 - Signs of pneumonia

- Signs of severe respiratory distress (in adults, accessory muscle use, inability to complete full sentences, respiratory rate > 30 breaths per minute; and, in children, very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger signs including inability to breastfeed or drink, lethargy, convulsions, or reduced level of consciousness).
- *Non-severe covid-19*—Defined as the absence of any criteria for severe or critical covid-19.

*The Guideline Development Group (GDG) noted that the oxygen saturation threshold of 90% to define severe covid-19 was arbitrary and should be interpreted cautiously when defining illness severity. For example, clinicians must use their judgment to determine whether a low oxygen saturation is a sign of severity or is normal for a given patient with chronic lung disease. Similarly, clinicians may interpret a saturation of 90-94% on room air as abnormal in a patient with normal lungs, or as an early sign of severe disease in a patient with a downward clinical trajectory. Generally, in cases where there is any doubt, the GDG suggested erring on the side of considering disease as severe.

How to use the recommendations

Selecting therapeutic agents

Two years into the pandemic, there are several effective treatments to choose between. When moving from evidence to recommendations for these drugs, the Guideline Development Group (GDG) considered a combination of the evidence regarding relative benefits and harms, values and preferences, practical issues, resource considerations, and feasibility and equity considerations (box 3). The GDG notes that these issues have to be considered when re-using or adapting the recommendations in national or local contexts. Some therapies can be used in combination (such as corticosteroids and IL-6 receptor blockers for severe or critical covid-19) while others are to be used as alternative monotherapies (such as for patients with non-severe covid-19 at highest risk of hospitalisation).

Box 3: Resources, access, and equity issues when choosing therapeutics

Several drugs may be unavailable or impractical for use in some contexts. Additional obstacles to access in low and middle income countries (LMICs) may include cost and availability, and limited access to services such as diagnostic testing and treatments within the first five days of symptoms, which may further limit access to interventions. Health inequities may be exacerbated if patients at higher risk receive the intervention. See the full version of the guideline (box 1) for more information.

WHO aims to provide a stimulus to engage all possible mechanisms to improve global access to diagnostic tests and effective interventions and how countries can address such challenges; such as the integration of a covid-19 clinical care pathway and establishing services to offer intravenous treatments.

At a time of drug shortage, it may be necessary to prioritise use through clinical triage such as selecting patients with the highest baseline risk for mortality (for instance, those with critical illness over those with severe illness), in whom the absolute benefit of treatment is greatest. Other suggestions for prioritisation, which lack direct evidence, include focusing on patients with an actively deteriorating clinical course and avoiding treatment in patients with established multi-organ failure (in whom the benefit is likely to be small).

An interactive decision support tool incorporates the multiple treatment comparisons for patients with non-severe covid-19: <https://magicvidence.org/match-it/220404dist-covid-meds/>. Choices will also depend on availability of the drugs, routes of administration, co-administered medications, durations of treatment, covid-19 variant, feasibility, and time from onset of symptoms (as different therapeutics vary in efficacy depending on

when in the illness course they are started). Efficacy may also vary in function of specific SARS-CoV-2 variants; for example, previously recommended monoclonal antibodies may be less effective for the omicron BA.1/BA.2 variant.

Identifying patients with non-severe illness at highest risk of hospitalisation

Several recommendations for therapeutics in patients with non-severe covid-19 apply to those at highest risk of hospitalisation, defined as beyond 10% risk of being hospitalised for covid-19. These patients should achieve what the GDG agreed would represent what most patients would value as an important benefit: a 6% absolute reduction in hospital admission (see box on how this guideline was created). Reliably identifying those at highest risk is challenging because of the changing global context, with evolution of the virus and patterns of vaccination, thus raising the importance of validation of models to local contexts. A living systematic review of 232 risk prediction models for covid-19, recently updated, identified two promising risk prediction tools before circulation of the omicron variant: these tools concur that typical characteristics of people at highest risk include older age, immunosuppression, and/or presence of chronic diseases, with lack of vaccination as an additional risk factor.⁹

Uncertainties

Uncertainties exist regarding covid-19 therapeutics and emerging evidence which may both inform clinical decision-making as well as future research. The recommendations therefore need to be used in light of these uncertainties. Specific uncertainties are listed with the relevant drug, but many uncertainties are common across therapeutics:

- For drugs recommended in non-severe illness: the lack of accurate clinical prediction guides to establish the individual patient risk of hospitalisation in order to best identify patients that would most benefit from interventions; data regarding emergence of resistance and efficacy against new variants; safety and efficacy in children and in immunocompromised, vaccinated, or pregnant patients and other specific subgroups of patients; optimal duration of therapies; head-to-head comparisons of recommended treatments; and relative effectiveness of combination therapy.
- For drugs recommended in severe or critical illness: safety and efficacy in children and in immunocompromised, vaccinated, or pregnant patients and other specific subgroups of patients; long term mortality and functional outcomes in covid-19 survivors; and immunity and the risk of a subsequent infection, which may affect the risk of death after 28 days.

The recommendations

Fluvoxamine (Update 10, published 14 July 2022)

Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI), approved as an antidepressant. It increases concentrations of serotonin in the synaptic cleft. Indirect evidence from non-covid-19 disease models have suggested possible anti-inflammatory properties, and mechanistic studies have suggested host-directed antiviral properties. There are currently no published preclinical studies that directly demonstrate a mechanism in covid-19. The clinical evidence underpinning the recommendations (focused on the benefits and short term harms from trial data) is outlined in box 4.

Box 4: Fluvoxamine data for non-severe covid-19 (<https://app.maggi-capp.org/#/guideline/nBkO1E/rec/jmYxpV>)

The living network meta-analysis for fluvoxamine was informed by three trials, which enrolled 2208 patients with non-severe covid-19 in outpatient settings. The largest trial (n=1480) exclusively enrolled patients in Brazil. All three trials were registered, and two were published in a peer reviewed journal at the time of data synthesis. None of the included studies enrolled children. See more trial details in the updated living network meta-analysis on drug treatments for covid-19.⁶

The trial data on fluvoxamine provided low certainty evidence for a reduction in admission to hospital (odds ratio (OR) 0.70 (95% confidence interval 0.34 to 1.23); absolute difference in highest risk group, 28 fewer admissions per 1000 patients (95% CI 64 fewer to 20 more)). Moderate certainty evidence showed probably little or no difference in mortality (OR 0.68 (0.33 to 1.32); absolute difference 1 fewer death per 1000 patients (3 fewer to 1 more)), and low certainty evidence suggested the same in mechanical ventilation (OR 0.73 (0.38 to 1.40); absolute difference 5 fewer per 1000 patients (11 fewer to 7 more)). Effects of fluvoxamine on adverse events leading to drug discontinuation and time to symptom resolution are unknown.

Based on data from the TOGETHER trial, no credible subgroup effects were observed on the primary outcome by age (children v adults v older adults) or time from symptom onset (0-3 days v 4-7 days). Planned subgroup analyses for disease severity, age and chronic conditions, serological status, and vaccination status were precluded by lack of available data.

See MAGIcapp for details about the evidence and certainty ratings, and additional details regarding pre-specified subgroup analyses.

Recommendation 1: For patients with non-severe covid-19, we recommend not to use fluvoxamine, except in the context of a clinical trial (recommended only in a research setting).

Understanding the recommendation

Insufficient evidence of benefit, coupled with a lack of a clear mechanism of action and known drug interactions, drove the recommendation against use in clinical care.

Balance of benefits and harms—There was low to moderate certainty evidence suggesting little or no effect on hospitalisation, mortality, or mechanical ventilation, and an absence of reliable data on serious adverse effects attributable to the drug. Fluvoxamine is known for substantial pharmacological interactions. In the largest trial, markedly more patients discontinued treatment in the fluvoxamine group than in the placebo group. Acknowledging that its evaluation of the certainty of the evidence may differ from other published meta-analyses, GDG members pointed out that early stopping due to apparent benefit may have biased the results of the largest trial. They argued that, although the stopping rules were pre-specified, the decision to stop the trial was based on the effect estimate on a composite outcome of questionable importance; meanwhile the number of important events was lower and vulnerable to bias. The GDG also raised concerns regarding the uncertain applicability of this trial conducted in a single country.

Values and preferences—The GDG inferred that almost all well informed patients would choose not to receive fluvoxamine therapy for covid-19 based on available evidence. The GDG did not believe that other considerations, such as feasibility, acceptability, equity, and cost, would affect this specific recommendation. Specifically, the GDG did not consider the potential role of fluvoxamine as an antidepressant for this guideline of medications for covid-19.

Applicability—None of the included studies enrolled children, and the applicability of this recommendation to children is therefore uncertain. However, the GDG did not see a reason to assume that

children with covid-19 would respond any differently to treatment with fluvoxamine.

Practical issues—The GDG made a recommendation against using fluvoxamine for treatment of patients with covid-19 outside the setting of a clinical trial, and therefore practical considerations are less relevant for this drug.

Resource implications, acceptability, feasibility, equity, and human rights—Fluvoxamine is relatively inexpensive compared with other drugs used for covid-19, and widely available, including in low income settings. Its use would risk diverting attention and resources away from interventions that are more likely to provide a benefit.

Specific uncertainties, emerging evidence, and future research—The current evidence does not justify using fluvoxamine to treat covid-19. However, the recommendation does not imply that fluvoxamine is proven to be ineffective. Decisions to further investigate the effects of fluvoxamine for covid-19 will likely hinge on how stakeholders perceive the opportunity cost of investigating the effects of fluvoxamine over other candidate therapies. The GDG discussions highlighted the following knowledge gaps:

- What are the effects of fluvoxamine in patients who have a combination of non-severe covid-19 that is at risk of deteriorating and significant symptoms of anxiety?
- What are the side effects of fluvoxamine therapy in patients with non-severe covid-19 at risk of deteriorating?
- What proportion of patients with non-severe covid-19 at risk of deteriorating would be ineligible due to risk of pharmacological interactions?

The GDG surmised that, in the future, investigators would have to carefully consider whether fluvoxamine could still be compared with placebo or no treatment given that effective treatments are available. If the rationale to further investigate fluvoxamine is its advantageous cost and availability, non-inferiority designs may be considered.

Colchicine (Update 10, published 14 July 2022)

Colchicine is an anti-inflammatory drug used to treat gout, recurrent pericarditis, familial Mediterranean fever, and other inflammatory conditions. Proposed mechanisms for its anti-inflammatory effect include a reduction in neutrophil chemotaxis, inflammasome signalling inhibition, and decreased production of cytokines such as interleukin 1b. No published animal models evaluating colchicine in SARS-CoV-2 infection are published at the time of guideline publication. The clinical evidence underpinning the recommendations (focused on the benefits and short term harms from trial data) is outlined in [box 5](#).

Box 5: Colchicine data for non-severe covid-19 (<https://app.maggi-capp.org/#/guideline/nBkO1E/rec/nVNW9e>)

The systematic review for colchicine included 13 trials that enrolled 18 172 patients. All but three trials were registered. None of the studies enrolled children. A single trial of 4488 participants, which contributed almost all of the evidence on hospitalisations, was stopped prematurely. See more trial details in the updated living network meta-analysis on drug treatments for covid-19.⁶

The trial data on colchicine provided moderate certainty evidence for little or no impact on mortality (OR 0.84 (95% confidence interval 0.50 to 1.17); absolute difference 1 fewer deaths per 1000 patients (2 fewer to 1 more)) and mechanical ventilation (OR 0.75 (0.37 to 1.26); absolute difference 2 fewer per 1000 patients (6 fewer to 2 more)); and low certainty evidence for no impact on admission to hospital in patients at highest risk (OR 0.68 (0.27 to 1.57); absolute difference 30 fewer admissions per

1000 patients (71 fewer to 49 more)). Low certainty evidence suggested colchicine may increase the risk of serious adverse effects leading to drug discontinuation (absolute difference 34 more per 1000 patients (0 to 59 more)).

The planned subgroup analyses for colchicine versus standard care did not show different relative effects for disease severity and age (children, adults, older adults); no data were reported to inform a subgroup analysis for time from illness onset.

See MAGICapp for details about the evidence and certainty ratings, and pre-specified subgroup analyses.

Recommendation 1: For patients with non-severe covid-19, we recommend against treatment with colchicine (strong recommendation).

Understanding the recommendation

The lack of benefits on hospitalisations, mortality, and mechanical ventilation, combined with possible harms and toxicity, drove the strong recommendation against the use of colchicine in patients with non-severe covid-19.

Balance of benefits and harms—In patients with non-severe covid-19, colchicine has little or no impact on mortality or mechanical ventilation (moderate certainty). It is unclear whether it affects hospitalisations or adverse effects leading to drug discontinuation. The GDG discussed the risk of drug interactions and colchicine's narrow therapeutic window, particularly in patients with or at risk of hepatic and renal failure. Colchicine toxicity can be severe and sometimes fatal. The planned subgroup analyses for colchicine versus standard care did not show different relative effects for disease severity or age (children, adults, older adults), with no data reported from illness onset.

Values and preferences—The GDG inferred that almost all well informed patients would choose not to receive colchicine.

Applicability—The applicability of this recommendation to children is currently uncertain because none of the included studies enrolled children. However, the GDG did not consider that children with covid-19 would respond any differently to treatment with colchicine.

Practical issues—The GDG made a strong recommendation against using colchicine for treatment of patients with non-severe covid-19, and therefore practical considerations are less relevant.

Resource implications, acceptability, feasibility, equity, and human rights—These considerations did not affect this specific recommendation. Although colchicine is relatively inexpensive compared with other drugs used for covid-19, and widely available, including in low income settings, the evidence does not justify the use of colchicine for non-severe covid-19 anywhere. Although the cost of colchicine may be low, the GDG raised concerns regarding the risk of diverting attention and resources away from interventions that are more likely to provide a benefit.

Specific uncertainties, emerging evidence, and future research—The GDG considered it unlikely that future studies would identify subgroups of patients who would benefit from colchicine.

Nirmatrelvir/ritonavir (Update 9, published 22 April 2022)

Overview

Nirmatrelvir is a SARS-CoV protease inhibitor which prevents viral replication. Nirmatrelvir/ritonavir is administered orally in combination with ritonavir, a HIV protease inhibitor, which boosts its pharmacokinetics. Through its impact on metabolism and clearance, ritonavir is a perpetrator of many drug-drug interactions during active treatment and possibly for several days after treatment

completion. While these may be more easily managed with short durations of treatment, twice daily administration involves doubling ritonavir dose relative to most modern antiretroviral regimens.

The antiviral effect of nirmatrelvir has been demonstrated through in vitro animal studies and human models.^{10–12} Nirmatrelvir retains activity against the omicron BA1 variant in vitro, but clinical data are currently unavailable.¹³ There remains uncertainty regarding risk of emergence of resistance; in vitro studies have suggested acquired mutations in the protease sequence may significantly reduce nirmatrelvir activity, though variably so depending on type and number of mutations.¹⁰

Evidence—For patients with non-severe covid-19, data were derived from two trials (EPIC-SR and EPIC-HR) that enrolled 3100 non-hospitalised patients. See MAGICapp for detailed description of the mechanism of action, evidence, and subgroup analyses underpinning the recommendations (<https://app.magicapp.org/#/guideline/nBk01E/rec/LwrMyv> and <https://app.magicapp.org/#/guideline/nBk01E/rec/Lrv03R>).

Recommendation 1: For patients with non-severe covid-19 at highest risk of hospitalisation, we recommend treatment with nirmatrelvir/ritonavir (strong recommendation).

Understanding the recommendation

Only a minority of patients who are at highest risk are likely to achieve sufficient benefit in reduced admission to hospital. Nirmatrelvir/ritonavir likely represents a superior choice for these patients because it may have greater efficacy in preventing hospitalisation than available alternatives, has fewer concerns with respects to harms than molnupiravir, and is easier to administer than intravenous remdesivir and antibodies.

Balance of benefits and harms—Beyond the important benefits in reducing hospital admission in patients at highest risk of hospital admission, treatment may have little or no impact on mortality; data regarding effects on time to symptom resolution or mechanical ventilation are limited. Treatment does not increase the likelihood of serious adverse effects leading to drug discontinuation, though diarrhoea and altered taste were noted to occur more often with treatment relative to placebo. The GDG also acknowledged the paucity of information related to emergence of resistance.

Values and preferences—The GDG inferred that almost all well informed patients at highest risk of hospitalisation would choose to receive nirmatrelvir/ritonavir.

Applicability—Given included RCTs enrolled only non-pregnant adults, the GDG concluded that nirmatrelvir/ritonavir should not be offered to children or to breastfeeding or pregnant women with covid-19.

Practical issues—As per the large trials informing the recommendation, nirmatrelvir/ritonavir is administered as 300 mg/100 mg orally every 12 hours for five days. Administration should be as early as possible in the course of the disease. In the included studies, nirmatrelvir/ritonavir was administered within five days of disease onset. Through its impact on metabolism and clearance, ritonavir is a perpetrator of many drug-drug interactions, warranting serious consideration by clinicians. The Liverpool covid-19 drug interaction checker may constitute a valuable tool for management of drug interactions with nirmatrelvir/ritonavir.¹⁴ Additional considerations regarding practical issues are summarised in MAGICapp.

Resource implications, acceptability, feasibility, equity, and human rights—Nirmatrelvir/ritonavir is unlikely to be available for all

individuals who, given the option, would choose to receive the treatment.

Recommendation 2: For patients with non-severe covid-19 at low risk of hospitalisation, we suggest no nirmatrelvir/ritonavir (conditional or weak recommendation).

Understanding the recommendation

Most patients with non-severe covid-19 at low risk of hospitalisation will experience trivial benefits with use of nirmatrelvir/ritonavir. The GDG inferred that most such patients would be uninterested in taking the drug for these trivial benefits. However, there are likely to be an appreciable number of individuals who place a high value on very small reductions in the risk of hospitalisation and would thus choose to use nirmatrelvir/ritonavir; therefore, a conditional (rather than a strong) recommendation was made. The benefits and harms and other factors the GDG considered are comprehensively described in the full version of the guideline (see [box 1](#)).

Specific uncertainties, emerging evidence, and future research (across disease severities)

No drug-specific uncertainties: see broadly applicable uncertainties section in “How to use this guideline” (above)

Remdesivir (Update 9, published 22 April 2022, replaces earlier recommendation)

Overview

Remdesivir is a nucleoside analogue which interacts with the SARS-CoV-2 polymerase to elicit delayed chain termination during RNA genome synthesis. The drug was repurposed for SARS-CoV-2.

Update—An initial conditional (weak) recommendation was made on 20 November 2020, suggesting not to use remdesivir for patients with covid-19 regardless of illness severity. This was based on data from the four RCTs available at the time, with 7333 participants hospitalised for covid-19. In the 10th iteration of the guideline, a new recommendation was made for the use of remdesivir for patients with non-severe illness.

Evidence—For patients with non-severe covid-19, data were derived from five trials enrolling 2731 non-hospitalised patients, of which data was available for 2710 patients. See MAGICapp for detailed description of the mechanism of action, evidence, and subgroup analyses underpinning the recommendation (<https://app.magicapp.org/#/guideline/nBk01E/rec/nBMO8R>).

Recommendation 1: We suggest treatment with remdesivir for patients with non-severe covid-19, conditional to those at highest risk of hospitalisation (conditional or weak recommendation).

Understanding the recommendation

The GDG emphasised the benefits on decreased need for hospitalisation, along with little or no serious adverse effects attributable to the drug. Feasibility, costs, access, and complexity of administration were also carefully considered and led to the conditional recommendation for use only in patients at highest risk of hospitalisation.

Balance of benefits and harms—In highest risk patients with non-severe illness, moderate certainty evidence showed that remdesivir probably provides an important reduction in hospital admissions, and may have little or no effect on mortality. The impact of remdesivir on mechanical ventilation and time to symptom resolution is very uncertain. Treatment probably does not increase the likelihood of serious adverse effects leading to drug discontinuation.

Values and preferences—The GDG inferred that almost all well informed patients with a low risk of hospitalisation would decline remdesivir, and only those at highest risk would choose to receive treatment.

Applicability—Only one included trial enrolled children (aged 12 years and older) with small numbers included; the applicability of this recommendation to children therefore remains uncertain. In the absence of trial data for children aged ≤ 12 years with weight < 40 kg, the use of remdesivir in these children is not recommended. Uncertainty also remains with regard to administration of remdesivir to pregnant or lactating women. The decision regarding use should be made between the pregnant individual and their healthcare provider while discussing whether the potential benefit justifies the potential risk to the mother and fetus.

The GDG also had concerns regarding whether the drug would retain efficacy against emerging variants of concern, such as omicron BA-1 or BA-2. Surveillance is needed for SARS-CoV-2 strains with reduced susceptibility to remdesivir, and further research examining the role of combination therapy in severely immunocompromised patients. In the absence of further data, the GDG did not have reason to believe the activity against known variants would be diminished.

Practical issues—Remdesivir is administered via intravenous infusion as a three-day regimen, in keeping with the large trials informing the recommendation; 200 mg is administered intravenously on day 1, followed by 100 mg given intravenously on days 2 and 3. Administration should be as early as possible in the course of the disease, with monitoring for allergic, infusion related, or other adverse outcomes. In the included studies, remdesivir was administered within seven days of disease onset. Additional considerations regarding practical issues are summarised in MAGICapp.

Resource implications, acceptability, feasibility, equity, and human rights—The infusion schedule represents a feasibility challenge in the outpatient settings. Furthermore, remdesivir is unlikely to be available for all individuals who, given the option, would choose to receive the treatment. See [box 3](#) for concerns about costs, availability, and health inequities.

Specific uncertainties, emerging evidence, and future research—Resistance to remdesivir under selective pressure has been observed in vitro and in a previous case study, associated with a mutation (E802D) within the sequence coding for the polymerase. The clinical importance of this if remdesivir were widely used in patients with non-severe covid-19 is unclear,^{15,16} as further described in the full version of the guideline (see [box 1](#)).

Molnupiravir (Update 8, published 01 March 2022)

Overview

Molnupiravir is an antiviral administered orally. It was re-purposed as an antiviral for covid-19 because it inhibits replication of SARS-CoV-2 with an in vitro potency broadly similar to remdesivir.^{17,18} This inhibitory effect has been shown in animal studies, both at higher and lower doses, with possibly greater efficacy when combined with favipiravir (compared with either drug alone).^{19–21} The drug is active against alpha and beta variants in vivo based on studies in hamsters and human cell models, and delta and omicron variants in vitro (no data in vivo).^{22–24} In vitro and animal studies have suggested the possibility of carcinogenesis; no human data with long term follow-up are available regarding this. There is also residual uncertainty regarding other long term harms; the efficacy of the drug against variants, particularly those with higher replication or transmission rates; the possibility of a selective

pressure for resistant mutations at an individual level, with the potential to spread at a population level; and the emergence of new variants related to random mutagenesis arising from molnupiravir's mechanism of action. These issues are comprehensively described in the full version of the guideline (see [box 1](#)).

Evidence—For patients with non-severe covid-19, data were derived from six trials that enrolled 4827 patients, of which the LNMA team had access to data for 4796 patients. See MAGICapp for detailed description of the mechanism of action, evidence, and subgroup analyses underpinning the recommendation (<https://app.magicapp.org/#/guideline/nBk01E/rec/E85WNb>).

Recommendation 1: We suggest treatment with molnupiravir for patients with non-severe covid-19, conditional to those at highest risk of hospitalisation (conditional or weak recommendation).

Understanding the recommendation

Only a minority of patients who are at highest risk are likely to achieve sufficient benefit. Especially given the safety concerns related to molnupiravir, the WHO and the GDG recognise the need to mitigate risks, both for individual patients and at the population level.

Balance of benefits and harms—Molnupiravir probably provides benefits on admission to hospital and time to symptom resolution (both moderate certainty) and may have a small effect on mortality (low certainty), without an increase in short term adverse effects (high certainty). Absolute benefits depend on the prognosis of the individual patient. The GDG also considered potential long term harms of molnupiravir, including risk of malignancy based on preclinical data (very low certainty), in what they ultimately considered to be a close balance between benefits and harms.

Values and preferences—The GDG inferred that almost all well informed patients with a low risk of hospitalisation would decline molnupiravir, and only those at highest risk would choose to receive treatment.

Applicability—

- Children. Due to evidence of impact on growth plate thickness and decreased bone formation in some animal studies, molnupiravir should not be used in children.
- Pregnancy, breastfeeding, and conception. Since molnupiravir elicited embryo-fetal lethality and teratogenicity in offspring when given to pregnant animals, it should not be used in pregnant or breastfeeding women. If pregnancy status is unclear, one should perform a pregnancy test before starting molnupiravir treatment. Women and people who can get pregnant should be counselled regarding reducing the risk of conception (such as using birth control) during treatment and for at least four days after the last dose of molnupiravir.
- Uncertainty remains regarding consequences to children conceived by fathers receiving or having recently received molnupiravir, and whether spermatogenesis may be especially prone to mutagenic effects. Men who might father a child should use birth control during treatment and for at least three months after the last dose of molnupiravir.
- Mitigation strategies at the population level include active sequence monitoring of SARS-CoV-2 detected in clinical respiratory samples for patients receiving therapy and active pharmacovigilance programmes.

Practical issues—As per large trials informing the recommendation, molnupiravir is dosed as 800 mg orally every 12 hours for five days. Administration should be as early as possible in the course of the disease. In the included studies, molnupiravir was administered within five days of symptom onset.

Resource implications, feasibility, equity, and human rights—Molnupiravir is unlikely to be available for all individuals who, given the option, would choose to receive the treatment.

Specific uncertainties, emerging evidence, and future research

- Need for clinical data to investigate safety and applicability concerns (including in children, lactating or pregnant women, and men; and long term impact on mutagenesis and cancer risk).

Janus kinase (JAK) inhibitors (Update 7, published 14 January 2022)

Overview

JAK inhibitors inhibit intracellular signalling in response to numerous interleukins, interferons, colony stimulating factors, and hormones. As a consequence, they interfere with many cellular responses, including antiviral responses, angiotensin-converting enzyme 2 (ACE2) expression, T cell function and differentiation, and macrophage activation. Baricitinib, ruxolitinib, and tofacitinib are three of at least nine JAK inhibitors. Their inherent differences, as well as variation in dosing and administration and pharmacokinetics, limit class-wide recommendations, and the GDG decided to make separate recommendations for individual drugs.

Update—No changes were made to the JAK inhibitors recommendations in this eleventh version of the guideline; however, we are aware of recent publication of RECOVERY trial that supports our previous recommendation and are currently reviewing.

Evidence—For patients with covid-19, data were derived from three trials that enrolled 2659 inpatients for baricitinib, two trials that enrolled 475 inpatients for ruxolitinib, and one trial that enrolled 289 inpatients for tofacitinib. See MAGICapp for detailed description of the mechanism of action, evidence, and subgroup analyses underpinning the recommendation (<https://app.magicapp.org/#/guideline/nBk01E/rec/E5AOaN>).

Recommendation 1: We recommend treatment with baricitinib for patients with severe or critical covid-19 (strong recommendation).

Understanding the recommendation

Evidence of improved survival and decreased length of hospital stay, coupled with no evidence of serious adverse events, drove the strong recommendation for baricitinib. The GDG acknowledged that some serious adverse events such as invasive fungal infections may not have been accurately captured during the relatively short follow-up period in the included trials.

The GDG carefully considered whether to make a recommendation or to wait for new data (RECOVERY trial data was not available at the time). However, given that moderate to high certainty evidence already showed benefits with baricitinib, the GDG made an immediate strong recommendation for use of the drug, with readiness to update the recommendation as necessary once RECOVERY trial data are publicly available.

The GDG has previously made a strong recommendation for the use of interleukin-6 (IL-6) receptor blockers (tocilizumab or sarilumab) in patients with severe or critical covid-19. Based on their mechanism of action as immune modulators, both baricitinib and IL-6 receptor

blockers should have fairly similar benefits. Combining them may unacceptably increase harms, including secondary bacterial and fungal infections. In the absence of evidence of incremental benefit, the GDG advises that clinicians do not administer the drugs together.

Balance of benefits and harms—In patients with severe or critical illness, baricitinib probably reduces mortality and duration of mechanical ventilation (both moderate certainty), and reduces hospital length of stay (high certainty). Treatment probably results in little or no increase in harm, specifically drug discontinuation (moderate certainty). Some serious adverse events such as fungal infections may not have been accurately captured during the relatively short follow-up in the included trials. This risk may vary in different parts of the world according to the local prevalence of infections such as tuberculosis. This risk may also be less pertinent, given the short course of baricitinib used for the treatment of covid-19.

Values and preferences—The GDG inferred that almost all well informed patients with severe or critical covid-19 would choose to receive baricitinib due to the likely reduction in mortality, and moderate certainty evidence of little or no increase in serious adverse events.

Applicability—None of the included RCTs for baricitinib enrolled children, or pregnant or lactating women; therefore, the applicability of this recommendation remains uncertain. The GDG did not have reason to believe that patients in these groups with covid-19 would respond differently; decisions regarding the use of JAK inhibitors in these groups should be guided by discussion between the individual and their healthcare provider.

Practical issues—Baricitinib is administered orally once daily as tablets; it can be crushed, dispersed in water, or given via a nasogastric tube. Based on trials informing the recommendation, the recommended dose is 4 mg daily orally in adults with normal renal function for a duration of 14 days or until hospital discharge, whichever is first.

Dose adjustments may be needed for patients with leucopenia, renal impairment, or hepatic impairment, all of which should be monitored during treatment, and for patients taking strong organic anion transporter 3 (OAT3) inhibitors such as probenecid, where drug interactions warrant dose reductions.

Baricitinib, like IL-6 receptor blockers, should be initiated at the same time as systemic corticosteroids; there are currently no data to suggest that specific timing during hospitalisation or the course of illness is beneficial.

Resource implications, feasibility, equity, and human rights—Compared with some other candidate treatments for covid-19, baricitinib is expensive. The recommendation does not take into account cost effectiveness.

Recommendation 2: We suggest not to use ruxolitinib or tofacitinib for patients with severe or critical covid-19 (conditional or weak recommendation).

Understanding the recommendation

Low to very low certainty evidence for mortality and duration of mechanical ventilation and a possible increase in serious adverse events, particularly for tofacitinib, drove the weak recommendation not to use ruxolitinib or tofacitinib in patients with severe or critical covid-19. Clinicians should consider using ruxolitinib or tofacitinib only if neither baricitinib nor IL-6 receptor blockers (tocilizumab or sarilumab) are available. The GDG emphasised the need for more

trial evidence to better inform the recommendations; this is anticipated through ongoing trials for these JAK inhibitors.

Benefits and harms—Low to very low certainty evidence from small trials failed to demonstrate benefits for mortality or duration of mechanical ventilation, and suggested tofacitinib may increase adverse events leading to drug discontinuation. When more evidence is available, the GDG acknowledged that these drugs may prove to have similar benefits as baricitinib.

Values and preferences—Most well informed patients would decline ruxolitinib or tofacitinib. However, a minority might choose to receive one or the other drug if neither baricitinib nor IL-6 receptor blockers are available, given the possibility of benefit has not been excluded, and a class effect of JAK inhibitors might exist.

Applicability—None of the included RCTs enrolled children; therefore, the applicability of this recommendation to children remains uncertain. Uncertainty also remains with regards to the administration of ruxolitinib or tofacitinib to pregnant or lactating women.

Practical issues—Both drugs are administered orally twice daily as tablets and can be dispersed in water or administered via nasogastric tube.

The GDG referred to treatment regimens in the included trials, available via MAGICapp, in the absence of other available information. If ruxolitinib or tofacitinib is administered, like with IL-6 receptor blockers, it should be given with systemic corticosteroids; specific timing during hospitalisation or in the context of the course of illness is not specified.

Resource implications, equity, and human rights—Efforts to ensure access to drugs should focus on those that are currently recommended.

Specific uncertainties, emerging evidence, and future research (for all JAK inhibitors)

- Incremental benefit for patients receiving baricitinib and IL-6 blockers together, rather than either drug individually.
- Impact of tofacitinib and ruxolitinib relative to that of baricitinib.

Sotrovimab (Update 7, published 14 January 2022)

Overview

Sotrovimab is a single human monoclonal antibody that binds to a highly conserved epitope in the SARS-CoV-2 spike protein, preventing the virus from entering cells. Monoclonal antibodies such as sotrovimab and casirivimab-imdevimab are expected to have similar benefits against the SARS-CoV-2 virus. However, their action against the spike protein may render them less effective against emerging variants of the virus such as omicron, where the spike protein is altered.

Update—The GDG is currently assessing to what extent the increasingly predominant omicron BA2 variant is substantially reducing the clinical efficacy of sotrovimab, at this stage demonstrated through preclinical in vitro data.

Evidence—For patients with non-severe covid-19, data were derived from one trial that enrolled 1057 non-hospitalised patients with symptomatic covid-19 for five days or less since symptom onset, and at least one risk factor for illness progression; data was available for 1044 patients. See MAGICapp for detailed description of the mechanism of action, evidence, and subgroup analyses

underpinning the recommendation (<https://app.magicapp.org/#/guideline/nBkO1E/rec/LA69PM>).

Recommendation: We suggest treatment with sotrovimab for patients with non-severe covid-19, conditional to those at highest risk of hospitalisation (conditional or weak recommendation).

Understanding the recommendation

Although there is moderate certainty evidence of a substantial relative risk reduction in hospitalisation, only a minority of patients who are at highest risk are likely to achieve sufficient benefit to compensate for the risks and other disadvantages of this therapy. Other limitations, in addition to a lack of reliable tools to identify high risk patients, including delivering a parenteral therapy to patients who are typically cared for in the community, and limited availability of the drug.

The GDG advised that clinicians do not administer multiple monoclonal antibodies (including casirivimab-imdevimab) together, given an absence of supporting evidence and low likelihood mechanistically of incremental benefit.

The GDG then considered how to choose between the two drugs. No trials provide head-to-head comparisons. With alpha and delta variants, there may be little or no difference in the agents' impact on critical outcomes, according to an indirect comparison from the network meta-analysis. Now and in the future, the choice of monoclonal antibodies will depend on emerging evidence regarding effectiveness with different variants and their availability, as well as clinical and contextual factors. Of note, the trials included in the living network meta-analysis were conducted before the emergence of the omicron variant.

Preclinical evidence has recently emerged suggesting that casirivimab-imdevimab lacks neutralisation activity against the omicron variant *in vitro*.²⁵ Sotrovimab has been reported to retain activity against omicron in pseudo-virus assays, but with higher concentrations being required for neutralisation.²⁶ More data are required to ascertain whether efficacy against the omicron variant will be maintained at the studied doses of monoclonal antibodies, and recommendations will be updated when additional data becomes available.

Balance of benefits and harms—In patients with non-severe illness, sotrovimab probably reduces hospitalisation, with little or no impact on mortality (both moderate certainty) and mechanical ventilation (low certainty). There is little or no increase in infusion reactions (high certainty). Indirect comparison data with casirivimab-imdevimab versus sotrovimab provides moderate certainty evidence of little or no difference on mortality, mechanical ventilation and hospitalisation, and high certainty of no difference in infusion reactions.

Values and preferences—The GDG inferred that almost all well informed patients with a low risk of hospitalisation would decline sotrovimab, and only those at highest risk would choose to receive treatment.

Applicability—The included trial enrolled only non-pregnant adults; the applicability to children and pregnant women remains uncertain. The GDG had no reason to believe that children or pregnant women with covid-19 would respond differently to treatment with sotrovimab. However, for children, the risk of hospitalisation is generally extremely low; the GDG therefore inferred that, in the absence of immunosuppression or another major risk factor, children should not receive the intervention.

The GDG did not provide a recommendation for sotrovimab in severe or critical illness. A recently published RCT randomised 546 adults hospitalised with covid-19 to two neutralising monoclonal antibody therapies (sotrovimab and B212-196 plus B212-198) or placebo.²⁷ The results did not demonstrate benefits from these antibodies therapies, including a subgroup analysis on patients with seropositive versus seronegative status. Although the role of sotrovimab in severe or critical covid-19 is not supported by the new trial, it was not assessed by the GDG, as they focused on patients with non-severe covid-19 where evidence was available at the time of recommendation development; this trial, and any other new evidence that is publicly available, will be fully considered by the GDG for future recommendations for sotrovimab.

Practical issues—The authorised regimen for sotrovimab is one single intravenous infusion of 500 mg over 30 minutes, administered as soon as possible after a positive viral test for SARS-CoV-2 and within 10 days of symptom onset. Sotrovimab is available as a concentrated solution and must be diluted before administration. Patients should be clinically monitored during the infusion and observed for at least one hour after the infusion is completed.

Additional considerations regarding practical issues are summarised in MAGICapp.

Resource implications, equity, human rights, acceptability, and feasibility—Sotrovimab is unlikely to be available for all individuals who, given the option, would choose to receive the treatment. Additional challenges include the requirement for intravenous administration to patients who would normally be treated at home.

Specific uncertainties, emerging evidence, and future research

- Efficacy and safety for severe or critical seronegative covid-19 patients

Convalescent plasma (Update 6, published 6 December 2021)

Overview

Treatment with convalescent plasma involves the transfer of endogenously produced neutralising antibodies present within the plasma from previously infected and recovered patients into patients with active infection. The concentrations (titre) of neutralising antibodies present within convalescent plasma are highly variable between donors, and various methodologies to measure antibody levels are available.

Evidence—Data were derived from 16 trials enrolling 16 236 patients across illness severities, of which four RCTs with 1602 patients informed estimates for outcomes in non-severe illness. See MAGICapp for detailed description of the mechanism of action, evidence, and subgroup analyses underpinning the recommendation (<https://app.magicapp.org/#/guideline/nBkO1E/section/LG5NRE>).

Recommendation 1: We recommend not to use convalescent plasma for patients with non-severe covid-19 (strong recommendation).

Understanding the recommendation

The GDG noted that, although not demonstrated in the evidence summary, there remains a potential for harms with blood product transfusion. Most importantly, given there was no benefit demonstrated for any of the critical or important outcomes for non-severe covid-19, the GDG did not see any justification for the resources (including time and cost) that would be associated with administration of convalescent plasma.

Balance of benefits and harms—In patients with non-severe illness, convalescent plasma does not have an important impact on mortality (high certainty). Convalescent plasma probably does not affect mechanical ventilation (moderate certainty). There were no data evaluating the risk of hospitalisation with convalescent plasma; the impact is therefore very uncertain. Convalescent plasma probably does not result in important increases in risks of transfusion-related acute lung injury, transfusion-associated circulatory overload (both moderate certainty), or allergic reactions (low certainty).

Values and preferences—Applying the agreed values and preferences, the GDG inferred that almost all well informed patients with non-severe covid-19 would choose against receiving convalescent plasma.

Acceptability and applicability—Although blood transfusion is acceptable to most, there is a subset of the population who will not accept allogenic blood transfusions. There are also regulatory challenges in most jurisdictions related to blood product transfusions. The included RCTs enrolled non-pregnant women and men. The GDG did not have reason to believe that children or pregnant women with covid-19 would respond any differently to treatment with convalescent plasma; the GDG therefore inferred that children and pregnant women should not receive the intervention either.

Practical issues—Issues include, though are not limited to, the identification and recruitment of potential donors, collection of plasma, storage and distribution of plasma, and infusion of convalescent plasma into recipients.

Resource implications, feasibility, equity, and human rights—The GDG noted that convalescent plasma use is associated with significant resource requirements, including identification of potential donors, testing of donors to ensure adequate titres of anti-SARS-CoV-2 antibodies, collection of donor plasma, storage of plasma, transportation of plasma to recipient location, and administration of plasma. These resources and feasibility issues are compounded for those with non-severe illness, who are most often outpatients. Also, this process is costly and time consuming. Given the number of patients with non-severe illness and the low event rate in this subgroup of patients, mobilising the use of convalescent plasma on a large scale would be of questionable feasibility.

Recommendation 2: We recommend not to use convalescent plasma for patients with severe or critical covid-19, except in the context of a clinical trial (recommended only in research settings).

Understanding the recommendation

Given relative benefits and harms, the GDG agreed further research addressing these patient-important outcomes would be valuable for patients with severe or critical illness. A recommendation to use a drug only in the setting of clinical trials is appropriate when there is low certainty evidence, and future research has potential to reduce uncertainty about the effects of the intervention, and for doing so at a reasonable cost.

Balance of benefits and harms—In patients with severe or critical covid-19, convalescent plasma may not result in an important impact on mortality, mechanical ventilation, time to symptom improvement, length of hospital stay, or ventilator-free days (all low or very low certainty). Convalescent plasma probably does not result in important increases in risks of transfusion-related acute lung injury, transfusion-associated circulatory overload (both moderate certainty), or allergic reactions (low certainty). However, there is always potential for harms with blood product transfusions.

Values and preferences—Applying the agreed values and preferences, the GDG inferred that almost all well informed patients would choose against receiving convalescent plasma outside the research setting.

Specific uncertainties, emerging evidence, and future research

- Effects of high titre convalescent plasma on mortality and other patient-important outcomes.
- Effects in patients with seronegative antibody status.

Casirivimab-imdevimab (neutralising monoclonal antibodies) (Update 5, published 23 September 2021, updated 01 March 2022)

Update to initial recommendation (part of eighth update of guideline)

Following the publication of the conditional recommendation for casirivimab-imdevimab, additional pre-clinical evidence has emerged. There is a substantial body of in vitro data, and a confirmatory in vivo evaluation, demonstrating lack of efficacy of casirivimab-imdevimab against the omicron BA1 variant. As a result, casirivimab-imdevimab is no longer recommended for covid-19 treatment except in cases where rapid viral genotyping is available and confirms infection with a SARS-CoV-2 variant (such as delta) that is susceptible to the neutralising activity of this combination of monoclonal antibodies. The text below reflects the initial assessment made by the GDG, adding issues relevant to the omicron variant.

Overview

Casirivimab and imdevimab are two fully human antibodies (REGN10933 and REGN10987) that bind to the SARS-CoV-2 spike protein and have demonstrated antiviral activity in animal models. It has been postulated that administration of a combination of casirivimab and imdevimab might have differential effects in patients who have produced their own anti-SARS-CoV-2 spike protein antibodies (hereafter seropositive) compared with those who have not (hereafter seronegative); it was hypothesised that effects might be larger for, or restricted to, seronegative individuals who have not yet mounted an effective natural antibody response.

There is a predicted lack of efficacy for casirivimab and imdevimab with the omicron variant; other monoclonal antibodies such as sotrovimab, however, may retain some efficacy.²⁸

Evidence—For patients with non-severe illness, data were derived from four RCTs with 4722 patients, all coming from a larger adaptive randomised master trial. For patients with severe or critical illness, one large trial (RECOVERY) enrolling 9785 patients, most of whom received corticosteroids, informed estimates. See MAGICapp for detailed description of the mechanism of action, evidence, and subgroup analyses underpinning the recommendation (<https://app.magicapp.org/#/guideline/nBkO1E/section/LG5NRE>).

Recommendation 1: We suggest treatment with casirivimab-imdevimab for patients with non-severe covid-19, conditional to those at highest risk of hospitalisation and where viral genotyping can confirm a susceptible SARS-CoV-2 variant (that is, excluding omicron BA1) (conditional or weak recommendation).

Understanding the updated recommendation

Although there is moderate certainty evidence of a substantial relative risk reduction in hospitalisation, only a minority of patients at highest risk hospitalisation and with infection with a SARS-CoV-2

variant susceptible to this drug combination (that is, a variant other than omicron BA1) are likely to achieve important benefit. Limited availability and need for parenteral administration for a group of patients who are typically cared for in the community present important challenges.

Balance of benefits and harms—In non-severely ill patients without the omicron BA1 variant, casirivimab-imdevimab probably reduces the risk of hospitalisation and duration of symptoms (both moderate certainty); however, the absolute benefit will be trivial in absolute terms for all but those at highest risk, for whom the intervention should be reserved. The lack of an empirically developed and validated risk prediction tool for establishing patients' risk of hospitalisation represents the major source of indirectness for which the GDG rated down the certainty of the evidence. Casirivimab-imdevimab is unlikely to have serious adverse effects (high certainty), including allergic reactions (moderate certainty). We found no evidence of subgroup effects with age or time from onset of illness for any outcomes.

Values and preferences—The GDG inferred that almost all well informed patients at typical low risk of hospitalisation would decline casirivimab-imdevimab, and only those at higher risk would choose to receive treatment.

Applicability—Available trials only enrolled adults; the applicability of this recommendation to children is therefore uncertain. The GDG did not have reason to believe that children with covid-19 would respond any differently to treatment. However, given the risk of hospitalisation in children is extremely low, the GDG inferred that, in the absence of immunosuppression or another significant risk factor, children should not receive the intervention. Lack of data precluded the GDG from making specific recommendations for other special populations, such as pregnant women.

Practical issues—Casirivimab-imdevimab should be administered through an intravenous line containing a sterile in-line or add-on 0.2 µm filter. Following infusion, patients should undergo monitoring for allergic reactions; although available trials have not convincingly shown that casirivimab-imdevimab results in allergic reactions, the possibility remains.

Resource implications, acceptability, feasibility, equity, and human rights—Major feasibility challenges include the requirement for parenteral administration.

Casirivimab-imdevimab is unlikely to be available for all individuals who would choose to receive treatment.

The trials used different doses of the monoclonal antibody combination, and health systems will face the choice of which dose to use; this can be informed, in part, by system values and preferences. If one's priority is to ensure giving as many people as possible the opportunity to benefit from treatment, one might use the lowest effective dose offered in the studies of non-severe patients, 1200 mg total dose (600 mg of each antibody). If one's priority is to ensure effectiveness in every individual who receives treatment and minimise the risk of emergence of resistance, one might use a higher total dose of 2400 mg (1200 mg of each antibody).

Similar considerations apply to choosing between intravenous and subcutaneous administration, the former used in the four trials included in the living network meta-analysis, and the latter used in a recent trial; one may balance priorities of maximum effectiveness and faster ability to achieve maximum drug concentrations with intravenous therapy, with widespread accessibility with subcutaneous therapy. Volumes that can be

administered subcutaneously are limited to the lowest dose, which is a total dose of 1200 mg (600 mg of each antibody).

Recommendation 2: We suggest treatment with casirivimab-imdevimab for patients with severe or critical covid-19, conditional to those with seronegative status and where viral genotyping can confirm a susceptible SARS-CoV-2 variant (that is, excluding omicron BA1) (conditional or weak recommendation).

Understanding the recommendations

In patients with severe or critical illness, the conditional recommendation in favour reflects the likelihood that benefits are restricted to patients who have seronegative status and without the omicron BA1 variant. In order to translate trial findings into clinical practice, assessment of serological status will need to be integrated into a clinical decision pathway before treatment is administered.

Balance of benefits and harms—A credible subgroup effect based on RECOVERY trial data demonstrated that casirivimab-imdevimab probably reduces mortality and may reduce need for mechanical ventilation in patients with seronegative status (moderate and low certainty, respectively). Impact on duration of hospitalisation is very uncertain (very low certainty).

In all patients with severe or critical covid-19, casirivimab-imdevimab may not have an impact on mortality (low certainty), and the impact on mechanical ventilation and duration of hospitalisation is very uncertain (very low certainty). Aside from the credible subgroup effect for serological status, we found no evidence of subgroup effects on age, time from onset of illness, and severity in patients with severe or critical covid-19.

Values and preferences—The GDG inferred that most, if not all, well informed patients with severe or critical covid-19 and seronegative status would choose to receive casirivimab-imdevimab. Other patients—those with seropositive status or whose status is uncertain—are likely to decline the intervention.

Applicability—None of the included randomised trials, including RECOVERY, enrolled children; therefore, the applicability of this recommendation to children is uncertain. Fortunately, very few children become critically ill with covid-19. For those who do and have seronegative status, it is possible they may benefit from casirivimab-imdevimab. Lack of data precluded the GDG from making specific recommendations for other special populations, such as pregnant women.

Practical issues—Same as prior recommendation (see above).

Resource implications, acceptability, feasibility, equity, and human rights—Challenges include cost, availability, and serologic testing to identify patients with seronegative status.

Dosing of casirivimab-imdevimab differed in trials for non-severe covid-19; a single intravenous dose of 8000 mg was used in the RECOVERY trial for severe or critical covid-19. Clinical trials and pharmacokinetic studies in non-severe covid-19 have provided supporting data for similar effects on decreasing the need for hospitalisation with total doses of 1200 mg, 2400 mg, 4000 mg, and 8000 mg. Thus, using doses lower than used in the RECOVERY trial (8000 mg total dose) for treatment of severely and critically ill patients may achieve the same benefit; on the other hand, it is theoretically plausible but untested that pharmacokinetic differences in patients with severe or critical illness, when compared with non-severe illness, may reduce drug exposure. This would increase the risk of suboptimal drug exposure in some individuals, which, in turn, could increase the risk of therapeutic failure and

the emergence of viral resistance. In the absence of clinical data on treatment of severe or critical covid-19 patients with doses lower than 8000 mg, the choice of dose depends on system values and preferences, with due consideration to maximising effectiveness and minimising emergence of resistance with higher doses, compared with lower doses maximising accessibility in the face of low drug availability and high cost.

Specific uncertainties, emerging evidence, and future research

No specific uncertainties: see uncertainties section in “How to use this guideline” (above)

Interleukin-6 (IL-6) receptor blockers (Update 4, published 6 July 2021)

Overview

IL-6 receptor blockers tocilizumab and sarilumab are monoclonal antibodies approved for use in rheumatoid arthritis. Elevated IL-6 concentrations are associated with severe outcomes in covid-19, including respiratory failure and death. IL-6 receptor blockers antagonise membrane-bound and soluble forms of the IL-6 receptor, blocking the cytokine’s activation and regulation of the immune response to infection.

WHO has made a strong recommendation for JAK inhibitors, specifically baricitinib, in patients with severe or critical covid-19. An IL-6 receptor blocker and baricitinib should not be given together and should be viewed as alternatives (see discussion for JAK inhibitors above).

Evidence—In addition to the linked network meta-analysis, this recommendation was also informed by an independent prospective meta-analysis from the WHO Rapid Evidence Appraisal for covid-19 group.²⁹ The network meta-analysis included 30 RCTs with 10 618 participants, and these data were used by the GDG for all outcomes other than mortality. We used the prospective meta-analysis for mortality because it included additional data that was unpublished at the time. The prospective meta-analysis pooled data from 22 RCTs with 10 156 participants.²⁹ See MAGICapp for detailed description of the mechanism of action, evidence, and subgroup analyses underpinning the recommendation (<https://app.magicapp.org/#/guideline/nBk01E/section/LG5NRE>).

Recommendation: We recommend treatment with IL-6 receptor blockers (tocilizumab or sarilumab) for patients with severe or critical covid-19 (strong recommendation).

Understanding the recommendation

Of note, corticosteroids have previously been strongly recommended in patients with severe or critical covid-19, and we recommend that patients meeting these severity criteria should now receive both corticosteroids and IL-6 receptor blockers, alternatively baricitinib (see above).

Balance of benefits and harms—IL-6 receptor blockers reduce mortality and need for mechanical ventilation (both high certainty), and may reduce durations of mechanical ventilation and hospitalisation (both low certainty).

There was uncertainty about the risk of serious adverse effects (very low certainty). There may be little or no increased risk of bacterial infections. However, the GDG had some concerns that, given the short term follow-up of most trials and the challenges associated with accurately capturing adverse events such as bacterial or fungal infections, that the evidence summary may under-represent the risks of treatment with IL-6 receptor blockers. Furthermore, the trials of IL-6 receptor blockers that inform this recommendation

were mostly performed in high-income countries, where the risk of infectious complications may be less than in some other parts of the world; the generalisability of the data on these adverse events is therefore unclear.

Values and preferences—The GDG inferred that almost all well informed patients with severe or critical covid-19 infection would want to receive IL-6 receptor blockers, given the reduction in mortality and mechanical ventilation, despite low certainty around evidence for serious adverse events. A minority of the GDG felt that a significant proportion of patients might decline the intervention due to the uncertainties around harms, and taking into account the small reduction in mortality.

Applicability—None of the included RCTs enrolled children or pregnant women. Although this resulted in uncertain applicability, the GDG did not have reason to believe that children or pregnant women with COVID-19 would respond any differently to treatment with IL-6 receptor blockers.

Practical issues—IL-6 receptor blockers require intravenous administration but only require one, or at most two, doses. See MAGICapp for practical information, including considerations if IL-6 receptor blockers are considered in children and pregnant women.

Resource implications, acceptability, feasibility, equity, and human rights—IL-6 receptor blockers require intravenous administration but only require one, or at most two, doses.

Compared with other treatments for covid-19, IL-6 receptor blockers are expensive and may be inaccessible. The recommendation does not consider cost-effectiveness. Given limited availability of the drug, one may consider the relative effects (odds ratio 0.87) for reduction in mortality with IL-6 receptor blockers result in 28 fewer deaths per 1000 patients (95% confidence interval 9 to 47 fewer deaths) in critically ill patients, compared with 12 fewer deaths per 1000 patients (4 to 19 fewer deaths) in severely ill patients.

Finally, sarilumab is not indicated for use in children; therefore, there could be a preference for tocilizumab in this subgroup.

Specific uncertainties, emerging evidence, and future research

- Safety data, including nosocomial infections.
- Immunity and the risk of subsequent infection, which may affect the risk of death after 28 days.
- Outcomes by different IL-6 receptor blocker dosing, and optimal timing of drug initiation.

Ivermectin (Update 3, published 31 March 2021)

Overview

Ivermectin is an antiparasitic agent that interferes with nerve and muscle function of helminths through binding glutamate-gated chloride channels. The treatment is relatively inexpensive and accessible internationally. We currently lack persuasive evidence of a mechanism of action for ivermectin in covid-19; any observed clinical benefit would be unexplained.

We are aware of a few new, relatively small trials published since our recommendation was made, and that one key trial has since been retracted, given concerns about research fraud.^{30 31} However, the updated evidence summary from the living network meta-analysis is consistent with our previous recommendation. This updated evidence summary will be fully considered by the GDG in an upcoming iteration of the guideline.

Evidence—The living systematic review and network meta-analysis pooled data from 16 trials with 2407 participants. Of the included trials, 75% examined patients with non-severe illness, and 25% included patients with both severe and non-severe illness. See MAGICapp for detailed description of the mechanism of action, evidence, and subgroup analyses underpinning the recommendation (<https://app.magicapp.org/#/guideline/nBkO1E/section/LG5NRE>).

Recommendation: We recommend not to use ivermectin for patients with covid-19, regardless of illness severity, except in the context of a clinical trial (recommended only in research settings).

Understanding the recommendation

Very low certainty evidence was a critical factor in the recommendation.

Balance of benefits and harms—Certainty of evidence for mortality was deemed very low, despite a point estimate and confidence interval that seemed to suggest benefit with ivermectin; similar judgments were made for other outcomes, including mechanical ventilation, hospital admission, duration of hospitalisation, and viral clearance.

Ivermectin may have little or no effect on time to clinical improvement (low certainty) and may increase the risk of adverse events leading to drug discontinuation (low certainty). A recommendation to only use a drug in the setting of clinical trials is appropriate when there is very low certainty evidence, and when future research has large potential for reducing uncertainty about the effects of the intervention and at a reasonable cost.

Subgroup analyses indicated no effect modification based on dose. We were unable to examine subgroups based on age or severity of illness due to insufficient trial data. Therefore, we assumed similar effects across all subgroups.

Values and preferences—The GDG inferred that almost all well informed patients would not want to receive ivermectin, given available evidence left a very high degree of uncertainty in effects on critical outcomes and the possibility of harms, such as adverse events associated with treatment.

Applicability—None of the included trials enrolled children or pregnant women; the applicability of the evidence to these subgroups is therefore uncertain, though there is no rationale to suggest they would respond differently.

Resource implications, acceptability, feasibility, equity, and human rights—Although the cost of ivermectin may be low per patient, the GDG raised concerns about diverting attention and resources away from care likely to provide a benefit, such as corticosteroids in patients with severe covid-19, and other supportive care interventions. Also, use of ivermectin for covid-19 would divert supply away from pathologies for which it is clearly indicated, potentially contributing to drug shortages, especially for helminth control and elimination programmes. If corticosteroids are used in the treatment of covid-19, empiric treatment with ivermectin may still be considered in strongyloidiasis-endemic areas, albeit not for treatment of covid-19 itself.

Specific uncertainties, emerging evidence, and future research

No specific uncertainties: see uncertainties section in “How to use this guideline” (above).

Hydroxychloroquine (Update 2, published 17 December 2020)

Evidence—The recommendation addressing hydroxychloroquine was informed by results from the living network meta-analysis, pooling data from 30 RCTs with 10 921 participants. See MAGICapp for detailed description of the evidence and subgroup analyses underpinning the recommendation (<https://app.magicapp.org/#/guideline/nBkO1E/section/j197zj>).

Recommendation: We recommend not to use hydroxychloroquine or chloroquine for patients with covid-19, regardless of illness severity (strong recommendation).

Understanding the recommendation

Balance of benefits and harms—Hydroxychloroquine and chloroquine probably do not reduce mortality or mechanical ventilation (both moderate certainty) and may have no effect on duration of hospitalisation (low certainty). The evidence does not exclude the potential for a small increased risk of death and mechanical ventilation with hydroxychloroquine. The effect on other less important outcomes, including time to symptom resolution, admission to hospital, and viral clearance, remains uncertain.

Hydroxychloroquine may increase the risk of diarrhoea and nausea or vomiting (both low certainty), a finding consistent with evidence from its use in other conditions. Diarrhoea and vomiting may increase the risk of hypovolaemia, hypotension, and acute kidney injury, especially in settings where healthcare resources are limited. Whether and to what degree hydroxychloroquine increases the risk of cardiac toxicity, including life-threatening arrhythmias, when used in patients with covid-19 is uncertain (very low certainty).

Subgroup analyses indicated no effect modification based on severity of illness, age, cumulative dose, or predicted day 3 serum trough concentrations. Therefore, we assumed similar effects in all subgroups.

We also reviewed evidence comparing the use of hydroxychloroquine plus azithromycin versus hydroxychloroquine alone. There was no evidence that the addition of azithromycin modified the effect of hydroxychloroquine for any outcome (very low certainty).

Values and preferences—Applying the agreed values and preferences, the GDG inferred that almost all well informed patients would not want to receive hydroxychloroquine.

Applicability—None of the included trials enrolled children or adolescents; the applicability to this subgroup is therefore uncertain.

Resource implications, feasibility, equity, and human rights—Hydroxychloroquine and chloroquine are relatively inexpensive compared with other drugs used for covid-19 and are already widely available, including in low-income settings. Although the cost may be low per patient, the GDG raised concerns about diverting attention and resources away from care likely to provide a benefit such as corticosteroids in patients with severe covid-19 and other supportive care interventions.

Specific uncertainties, emerging evidence, and future research

Although some uncertainty remains, the GDG felt that further research was unlikely to uncover a subgroup of patients who would benefit from hydroxychloroquine on the most important outcomes (mortality, mechanical ventilation) given the consistent results in trials across illness severity and location.

Lopinavir-ritonavir (Update 2, published 17 December 2020)

Evidence—The recommendation was informed by data from seven RCTs with 7429 participants. See MAGICapp for detailed description of the evidence and subgroup analyses underpinning the recommendation (<https://app.magicapp.org/#/guideline/nBkO1E/section/EgyLXL>).

Recommendation: We recommend not to use lopinavir-ritonavir for patients with covid-19, regardless of illness severity (strong recommendation).

Balance of benefits and harms—Lopinavir-ritonavir probably has little or no effect on mortality and mechanical ventilation (both moderate certainty); effects on time to clinical improvement and other patient-important outcomes were uncertain (low or very low certainty). Treatment probably increases the risk of diarrhoea and nausea or vomiting (both moderate certainty), a finding consistent with the indirect evidence evaluating its use in patients with HIV infection. Diarrhoea and vomiting may increase the risk of hypovolaemia, hypotension, and acute kidney injury, especially in settings where healthcare resources are limited. There was an uncertain effect on viral clearance and acute kidney injury.

Subgroup analysis indicated no effect modification based on severity of illness or age. As there was no evidence of a statistical subgroup effect, we did not formally evaluate credibility. Although the trials did not report subgroup effects by time from symptom onset, many of the trials enrolled patients early in the illness course. The GDG therefore felt that the evidence applies to all patients with covid-19.

Values and preferences—Applying the agreed values and preferences, the GDG inferred that almost all well informed patients would not want to receive lopinavir-ritonavir given that the evidence suggested there was probably no effect on mortality or need for mechanical ventilation and there was a risk of adverse events including diarrhoea and nausea or vomiting.

Resource implications, feasibility, equity, and human rights—Although the cost of lopinavir-ritonavir is not as high as some other investigational drugs for covid-19 and the drug is generally available in most healthcare settings, the GDG raised concerns about opportunity costs and the importance of not drawing attention and resources away from best supportive care or the use of corticosteroids in severe covid-19.

Specific uncertainties, emerging evidence, and future research

Although some uncertainty remains, the GDG felt that further research was unlikely to uncover a subgroup of patients who would benefit from lopinavir-ritonavir on the most important outcomes (mortality, mechanical ventilation) given the consistent results in trials across illness severity and location.

Systemic corticosteroids (Original publication, published 4 September 2020)

Evidence—The GDG reviewed evidence from eight RCTs (7184 patients) evaluating systemic corticosteroids versus usual care in treatment of covid-19, seven of which reported mortality data by subgroup of illness severity. Mortality data from one trial, GLUCOCOVID, were not incorporated in the summary of finding for mortality because the mortality outcome data were not available by subgroup. See MAGICapp for detailed description of the evidence and subgroup analyses underpinning the recommendation and practical information on how to administer systemic corticosteroids (<https://app.magicapp.org/#/guideline/nBkO1E/section/nByvRL>).

Update—Whereas the recommendations remain unchanged, the evidence summary available via MAGICapp for corticosteroids was updated before the fifth iteration of the living guideline. The baseline risk estimates for mortality are now based on the WHO SOLIDARITY trial (as for other drugs in this guideline)⁴ rather than the initial ISARIC cohort study that likely overestimates current mortality risks at the global level.³² This update was also needed to inform the baseline risk for mortality in the evidence summary informing the strong recommendation for IL-6 inhibitors in addition to standard care for patients with severe or critical covid-19, where corticosteroids provide a relative reduction in mortality by 21%.

Recommendation 1: We recommend treatment with systemic corticosteroids for patients with severe or critical covid-19 (strong recommendation).

Balance of benefits and harms—Ultimately, the GDG made its recommendation on the basis of a 28-day mortality reduction of 3.4% in severe or critical covid-19 combined (moderate certainty). Systemic corticosteroids probably reduce the need for mechanical ventilation (moderate certainty).

Overall, the GDG has reasonable certainty that the adverse effects, when considered together, are sufficiently limited in importance and frequency, and suggested that corticosteroids administered in these doses for 7-10 days are not associated with an increased risk of adverse events, beyond likely increasing the incidence of hyperglycaemia and hyponatremia (both moderate certainty). In contrast with new agents proposed for covid-19, clinicians have vast experience administering systemic corticosteroids, and the GDG was reassured by their overall safety profile.

Values and preferences—The GDG took an individual patient perspective to values and preferences but, given the burden of the pandemic for healthcare systems globally, also placed a high value on resource allocation and equity. The benefits of corticosteroids on mortality were deemed of critical importance to patients, with little or no anticipated variability in their preference to be offered treatment if severely ill from covid-19.

Applicability—Applicability is less clear for populations that were under-represented in the considered trials, such as children, patients with tuberculosis, and those who are immunocompromised. In considering potential contraindications to short term systemic corticosteroids in such patients, clinicians must determine if they warrant depriving a patient of a potentially lifesaving therapy. Clinicians should exercise caution in use of corticosteroids in patients with diabetes or underlying immunocompromise. The GDG was confident that clinicians using these guidelines would be aware of additional potential side effects and contraindications to systemic corticosteroid therapy, which may vary geographically in function of endemic microbiological flora.

Acceptability and practical issues—The ease of administration, the relatively short duration of a course of systemic corticosteroid therapy, and the generally benign safety profile of systemic corticosteroids administered for up to 7-10 days led the GDG to conclude that the acceptability of this intervention was high. Practical issues are summarised in detail on MAGICapp.

Resource implications, feasibility, equity, and human rights—Systemic corticosteroids are low cost, easy to administer, and readily available globally. Dexamethasone and prednisolone are among the most commonly listed medicines in national essential medicines lists; listed by 95% of countries. Accordingly, systemic corticosteroids are among a relatively small number of interventions for covid-19 that have the potential to reduce inequities and improve equity in

health. Those considerations influenced the strength of this recommendation.

Recommendation 2: We suggest not to use systemic corticosteroids for patients with non-severe covid-19 (conditional or weak recommendation).

Balance of benefits and harms—Systemic corticosteroids may increase the risk of 28-day mortality (low certainty).

Values and preferences—The conditional recommendation was driven by likely variation in patient values and preferences. The GDG judged that most individuals with non-severe illness would decline systemic corticosteroids. However, many may want them after shared decision making with their treating physician.

Applicability—Several specific circumstances were considered.

- Systemic corticosteroids should not be stopped for patients with non-severe covid-19 who are already treated with systemic corticosteroids for other reasons (such as patients with chronic obstructive pulmonary disease or chronic autoimmune disease).
- If the clinical condition of patients with non-severe covid-19 worsens (that is, increase in respiratory rate, signs of respiratory distress or hypoxaemia) they should receive systemic corticosteroids (see recommendation 1).
- Pregnancy: antenatal corticosteroid therapy may be administered for pregnant women at risk of preterm birth from 24 to 34 weeks' gestation when there is no clinical evidence of maternal infection and adequate childbirth and newborn care are available. In cases where the woman presents with mild or moderate covid-19, the clinical benefits of antenatal corticosteroid might outweigh the risks of potential harm to the mother. In this situation, the balance of benefits and harms for the woman and the preterm newborn should be discussed with the woman to ensure an informed decision, as this assessment may vary depending on the woman's clinical condition, her wishes and those of her family, and available healthcare resources.
- Endemic infections that may worsen with corticosteroids should be considered. For example, for *Strongyloides stercoralis* hyper-infection associated with corticosteroid therapy, diagnosis or empiric treatment may be considered in endemic areas if steroids are used.

Resource implications, feasibility, equity, and human rights—To help guarantee access to systemic corticosteroids for patients with severe or critical covid-19, it is reasonable to avoid their administration to patients who, given the current evidence, do not seem to derive any benefit from this intervention.

Specific uncertainties, emerging evidence, and future research

Remaining uncertainties include effects on:

- Patients with non-severe covid-19 (that is, pneumonia without hypoxaemia).
- Immunity and the risk of a subsequent infection, which may affect the risk of death after 28 days.
- By different steroid preparation, dosing, and optimal timing of drug initiation.

How this living guideline was created (see MAGICapp for full details <https://app.magicapp.org/#/guideline/nBk01E>)

Standards, methods, and processes for living and trustworthy guidance

The Guideline Development Group (GDG) 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*,³³ the Institute of Medicine, and the Guideline International Network (G-I-N).³⁴

Selection and support of the GDG

WHO convened a Guideline Development Group (GDG) with content experts (clinicians, methodologists, scientists) and patients who previously had covid-19. The methods chair (methodological expertise) and a clinical chair (content expertise) guided the GDG discussions. GDG members were invited by WHO, with the aim of achieving gender, geography, expertise, and patient representation balance as well as relevant technical and clinical expertise. The WHO technical unit collected and managed declarations of interests (DOIs) and found no GDG member, chair, or systematic review team member to have a conflict of interest. The GDG aimed to create a recommendation based on consensus with a provision for voting that proved unnecessary for this recommendation.

Guideline perspective, outcomes, and values and preferences

The target audience for this guidance consists of clinicians, patients, and healthcare decision makers. The GDG defined covid-19 by clinical severity (box 2). The GDG considered an individual patient perspective, but also took account of contextual factors (such as resources, feasibility, acceptability, and equity) to accommodate global re-use and adaptation for countries and healthcare systems, and to recognise system challenges in implementing recommendations.

There were insufficient published data to provide the GDG with an evidence-based description of patient experiences, or values and preferences regarding treatment decisions for covid-19 drug treatments. The GDG therefore relied on their own judgments of what well informed patients would value after carefully balancing the benefits, harms, and burdens of treatment. These judgments on values and preferences were also informed through the experiences of former patients with covid-19, represented in the GDG.

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

- Most patients would be reluctant to use a treatment for which the evidence left high uncertainty regarding effects on the outcomes they consider important. This was particularly so when evidence suggested treatment effects, if they exist, are small and the possibility of important harm remains.
- In an alternative situation with larger benefits and less uncertainty regarding both benefits and harms, more patients would be inclined to choose the treatment.

Sources of evidence

To create recommendations, the GDG relied on evidence synthesised in two living network meta-analyses coordinated by MAGIC.^{6 7}

Derivation of absolute effects for drug treatments

For patients with non-severe illness, we used the median of the control arm of the RCTs that contributed to the evidence. For patients with severe or critical illness, the GDG identified the control arm of the WHO SOLIDARITY trial, performed across a wide variety of countries and geographical regions, as representing the most relevant source of evidence for baseline risk estimates for mortality and mechanical ventilation.⁴ Systemic corticosteroids now represent standard of care in patients with severe or critical covid-19 (see strong recommendation issued by WHO in September 2020). Therefore, the baseline risk estimates in the evidence summaries for JAK inhibitors, convalescent plasma and IL-6 receptor blockers were adjusted for treatment effects of corticosteroids for the outcome of mortality and mechanical ventilation.⁴ For other outcomes, we used the median of the control arm of the RCTs that contributed to the evidence. Baseline risks, and thus absolute effects, may vary significantly geographically and over time. Thus, users of this guideline may prefer estimating absolute effects by using local event rates. Recommended combinations of treatments are based on direct comparisons from trials demonstrating additional benefit, such as adding baricitinib or interleukin-6 receptor blockers to systemic corticosteroids

in patients with severe or critical covid-19. In patients with non-severe covid-19 the absence of direct comparisons from RCTs necessitate indirect comparisons from the living network meta-analysis to inform judgments made about alternative treatment options.

How patients were involved in the creation of this article

The GDG included four patients who previously had covid-19. Their perspectives were crucial in considering the values and preferences associated with the various treatments.

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- a co-senior author
- Funding: Bill & Melinda Gates Foundation, Norwegian Directorate of Public Health and Germany provided funding for this guideline, with MAGIC providing pro-bono contributions and support to WHO in the context of the covid-19 pandemic.
- Competing interests: All GDG 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 GDG member or co-chair had any financial conflict of interest. Professional and academic interests are minimised as much as possible, while maintaining necessary expertise on the GDG to make fully informed decisions. MAGIC and *The BMJ* assessed declared interests from other co-authors of this publication and found no relevant 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)
- 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 of Greg Cotton (technical editor), Cat Chatfield (head of education), and Will Stahl-Timmins (data graphics designer) for their work on this living guideline publication in *The BMJ*
 - Lien Tran, Lorenzo Arena, Kasia Stepniewska, and Philippe Guerin for providing up to date data on registered and ongoing trials from the Infectious Diseases Data Observatory (IDDO) living systematic review of covid-19 clinical trial registrations (<https://www.iddo.org/covid-19/live-systematic-review-trials>). Data extraction is supported by Fiona Caldwell, Vitalis Feteh, Gerald Makuka, Roland Ngu, and Chinwe Ogbonna-Njoku.
 - Andrew Owen (University of Liverpool, UK) for contributions on pharmacological considerations and analyses
- Maguire BJ, Guérin PJ. A living systematic review protocol for COVID-19 clinical trial registrations. *Wellcome Open Res* 2020;5. doi: 10.12688/wellcomeopenres.15821.1 PMID: 32292826
 - Angus DC, Derde L, Al-Beidh F, et al. Writing Committee for the REMAP-CAP Investigators. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. *JAMA* 2020;324:29. doi: 10.1001/jama.2020.17022 PMID: 32876697
 - Horby P, Lim WS, Emberson JR, et al. RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med* 2021;384:704. doi: 10.1056/NEJMoa2021436 PMID: 32678530
 - Pan H, Peto R, Henao-Restrepo AM, et al. WHO Solidarity Trial Consortium. Repurposed antiviral drugs for Covid-19 - Interim WHO Solidarity Trial results. *N Engl J Med* 2021;384:511. doi: 10.1056/NEJMoa2023184 PMID: 33264556
 - Lundgren JD, Grund B, Barkauskas CE, et al. ACTIV-3/TICO LY-CoV555 Study Group. A neutralizing monoclonal antibody for hospitalized patients with Covid-19. *N Engl J Med* 2021;384:14. doi: 10.1056/NEJMoa2033130 PMID: 33356051
 - Siemieniuk RA, Bartoszko JJ, Ge L, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. *BMJ* 2020;370. doi: 10.1136/bmj.m2980 PMID: 32732190
 - Siemieniuk RAC, Bartoszko JJ, Diaz Martinez JP, et al. Antibody and cellular therapies for treatment of covid-19: a living systematic review and network meta-analysis. *BMJ* 2021;374. doi: 10.1136/bmj.n2231 PMID: 34556486
 - World Health Organization. Clinical management of COVID-19: interim guidance. 2020. <https://www.who.int/publications/item/clinical-management-of-covid-19>.
 - Wynants L, Van Calster B, Collins GS, et al. Prediction models for diagnosis and prognosis of covid-19: systematic review and critical appraisal. *BMJ* 2020;369. doi: 10.1136/bmj.m1328 PMID: 32265220
 - United States Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for PAXLOVID. 2022. <https://www.fda.gov/media/155050/download>.
 - Owen DR, Allerton CMN, Anderson AS, et al. An oral SARS-CoV-2 M^{PRO} inhibitor clinical candidate for the treatment of COVID-19. *Science* 2021;374:93. doi: 10.1126/science.abl4784 PMID: 34726479
 - Abdelnabi R, Foo CS, Jochmans D, et al. The oral protease inhibitor (PF-07321332) protects Syrian hamsters against infection with SARS-CoV-2 variants of concern. *Nat Commun* 2022;13. doi: 10.1038/s41467-022-28354-0 PMID: 35169114
 - Vangeel L, Chiu W, De Jonghe S, et al. Remdesivir, molnupiravir and nirmatrelvir remain active against SARS-CoV-2 omicron and other variants of concern. *Antiviral Res* 2022;198:105252. doi: 10.1016/j.antiviral.2022.105252 PMID: 35085683
 - University of Liverpool. COVID-19 drug interactions. <https://www.covid19-druginteractions.org/checker>.
 - Szemiel AM, Merits A, Orton RJ, et al. In vitro selection of remdesivir resistance suggests evolutionary predictability of SARS-CoV-2. *PLoS Pathog* 2021;17:e1009929. doi: 10.1371/journal.ppat.1009929 PMID: 34534263
 - Gandhi S, Klein J, Robertson AJ, et al. De novo emergence of a remdesivir resistance mutation during treatment of persistent SARS-CoV-2 infection in an immunocompromised patient: a case report. *Nat Commun* 2022;13. doi: 10.1038/s41467-022-29104-y PMID: 35301314
 - Sheahan TP, Sims AC, Zhou S, et al. An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple coronaviruses in mice. *Sci Transl Med* 2020;12:eabb5883. doi: 10.1126/scitranslmed.abb5883 PMID: 32253226
 - Tao S, Zandi K, Bassit L, et al. Comparison of anti-SARS-CoV-2 activity and intracellular metabolism of remdesivir and its parent nucleoside. *Curr Res Pharmacol Drug Discov* 2021;2:100045. doi: 10.1016/j.cphar.2021.100045 PMID: 34870151
 - Rosenke K, Hansen F, Schwarz B, et al. Orally delivered MK-4482 inhibits SARS-CoV-2 replication in the Syrian hamster model. *Research Square* 2020. doi: 10.21203/rs.3.rs-86289/v1
 - Cox RM, Wolf JD, Plemper RK. Therapeutically administered ribonucleoside analogue MK-4482/EIDD-2801 blocks SARS-CoV-2 transmission in ferrets. *Nat Microbiol* 2021;6:8. doi: 10.1038/s41564-020-00835-2 PMID: 33273742
 - Abdelnabi R, Foo CS, Kaptein SJF, et al. The combined treatment of molnupiravir and favipiravir results in a potentiation of antiviral efficacy in a SARS-CoV-2 hamster infection model. *EBioMedicine* 2021;72:103595. doi: 10.1016/j.ebiom.2021.103595 PMID: 34571361
 - Abdelnabi R, Foo CS, De Jonghe S, Maes P, Weynand B, Neyts J. Molnupiravir inhibits replication of the emerging SARS-CoV-2 variants of concern in a hamster infection model. *J Infect Dis* 2021;224:53. doi: 10.1093/infdis/jiab361 PMID: 34244768
 - Prince T, Donovan-Banfield I, Goldswain H, et al. Antiviral activity of molnupiravir precursor NHC against variants of concern (VOCs) and its therapeutic window in a human lung cell model. *bioRxiv* 2021. doi: 10.1101/2021.11.23.469695
 - Vangeel L, De Jonghe S, Maes P, et al. Remdesivir, molnupiravir and nirmatrelvir remain active against SARS-CoV-2 omicron and other variants of concern. *bioRxiv* 2021. doi: 10.1101/2021.12.27.474275
 - Wilhelm A, Widera M, Grikscheit K, et al. Reduced neutralization of SARS-CoV-2 omicron variant by vaccine sera and monoclonal antibodies. *medRxiv* 2021. doi: 10.1101/2021.12.07.21267432
 - Cathart AL, Havenar-Daughton C, Lempp FA, et al. The dual function monoclonal antibodies VIR-7831 and VIR-7832 demonstrate potent in vitro and in vivo activity against SARS-CoV-2. *bioRxiv* 2021. doi: 10.1101/2021.03.09.434607.
 - Self WH, Sandkovsky U, Reilly CS, et al. ACTIV-3/Therapeutics for Inpatients with COVID-19 (TICO) Study Group. Efficacy and safety of two neutralising monoclonal antibody therapies, sotrovimab and BRIL-196 plus BRIL-198, for adults hospitalised with COVID-19 (TICO): a randomised controlled trial. *Lancet Infect Dis* 2021. doi: 10.1016/S1473-3099(21)00751-9. doi: 10.1016/S1473-3099(21)00751-9 PMID: 34706189
 - World Health Organization. Enhancing readiness for omicron (B.1.1.529): technical brief and priority actions for member states. 2021. <https://www.who.int/publications/m/item/enhancing-readiness-for-omicron-%28b.1.1.529%29-technical-brief-and-priority-actions-for-member-states>.
 - Shankar-Hari M, Vale CL, Godolphin PJ, et al. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association between administration of IL-6 antagonists and mortality among patients hospitalized for COVID-19: a meta-analysis. *JAMA* 2021;326:518. doi: 10.1001/jama.2021.11330 PMID: 34228774
 - Elgazzar A, Hany B, Youssef SA, et al. Efficacy and safety of ivermectin for treatment and prophylaxis of COVID-19 pandemic. *Research Square* 2021. .
 - Reardon S. Flawed ivermectin preprint highlights challenges of COVID drug studies. *Nature* 2021;596:4. doi: 10.1038/d41586-021-02081-w PMID: 34341573
 - Docherty AB, Harrison EM, Green CA, et al. SARIC4C investigators. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. *BMJ* 2020;369. doi: 10.1136/bmj.m1985 PMID: 32444460
 - World Health Organization. Handbook for guideline development. 2008. https://www.who.int/publications/guidelines/handbook_2nd_ed.pdf?ua=1.
 - Qaseem A, Forland F, Macbeth F, Ollenschläger G, Phillips S, van der Wees P. Board of Trustees of the Guidelines International Network. Guidelines International Network: toward international standards for clinical practice guidelines. *Ann Intern Med* 2012;156:31. doi: 10.7326/0003-4819-156-7-201204030-00009 PMID: 22473437

Main infographic: Summary of recommendations and evidence