



Drug treatments for mild or moderate covid-19: systematic review and network meta-analysis

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ABSTRACT

OBJECTIVE

To compare the effects of treatments for mild or moderate (that is, non-severe) coronavirus disease 2019 (covid-19).

DESIGN

Systematic review and network meta-analysis.

DATA SOURCES

Covid-19 Living Overview of Evidence Repository (covid-19 L-OVE) by the Epistemonikos Foundation, a public, living repository of covid-19 articles, from 1 January 2023 to 19 May 2024. The search also included the WHO covid-19 database (up to 17 February 2023) and six Chinese databases (up to 20 February 2021). The analysis included studies identified between 1 December 2019 and 28 June 2023.

STUDY SELECTION

Randomised clinical trials in which people with suspected, probable, or confirmed mild or moderate covid-19 were allocated to drug treatment or to standard care or placebo. Pairs of reviewers independently screened potentially eligible articles.

METHODS

After duplicate data abstraction, a bayesian network meta-analysis was conducted. Risk of bias was assessed by use of a modification of the Cochrane

risk of bias 2.0 tool, and the certainty of the evidence using the grading of recommendations assessment, development, and evaluation (GRADE) approach. For each outcome, following GRADE guidance, drug treatments were classified in groups from the most to the least beneficial or harmful.

RESULTS

Of 259 trials enrolling 166 230 patients, 187 (72%) were included in the analysis. Compared with standard care, two drugs probably reduce hospital admission: nirmatrelvir-ritonavir (25 fewer per 1000 (95% confidence interval 28 fewer to 20 fewer), moderate certainty) and remdesivir (21 fewer per 1000 (28 fewer to 7 fewer), moderate certainty). Molnupiravir and systemic corticosteroids may reduce hospital admission (low certainty). Compared with standard care, azithromycin probably reduces time to symptom resolution (mean difference 4 days fewer (5 fewer to 3 fewer), moderate certainty) and systemic corticosteroids, favipiravir, molnupiravir, and umifenovir probably also reduce duration of symptoms (moderate to high certainty). Compared with standard care, only lopinavir-ritonavir increased adverse effects leading to discontinuation.

CONCLUSION

Nirmatrelvir-ritonavir and remdesivir probably reduce admission to hospital, and systemic corticosteroids and molnupiravir may reduce admission to hospital. Several medications including systemic corticosteroids and molnupiravir probably reduce time to symptom resolution.

SYSTEMATIC REVIEW REGISTRATION

This review was not registered. The protocol is publicly available in the supplementary material.

Introduction

As of November 2024, more than seven million people have died with coronavirus disease 2019 (covid-19).¹ The evidence on covid-19 continues to evolve as global efforts to identify effective interventions for the prevention and treatment of covid-19 have resulted in more than 8000 completed or ongoing trials.²

Summarising the rapidly growing evidence base has proved challenging.³ Network meta-analysis,

WHAT IS ALREADY KNOWN ON THIS TOPIC

The evidence for drug treatments for covid-19 continues to evolve, with evidence suggesting different treatments are most effective at certain disease stages
This article focuses on patients with mild or moderate (non-severe) covid-19 from a network meta-analysis of covid-19 drug treatments

WHAT THIS STUDY ADDS

Network meta-analysis of 187 of 259 randomised trials (72%) comparing 40 different drug treatments in people with mild or moderate covid-19
Nirmatrelvir-ritonavir and remdesivir probably reduce hospital admission; molnupiravir and systemic corticosteroids may reduce hospital admission
Several drugs, including molnupiravir and systemic corticosteroids, probably reduce symptom duration, whereas nirmatrelvir-ritonavir and remdesivir may not

Box 1: Sources of latest evidence from this systematic review

- Author website “COVID-19 living network meta-analysis” (<https://www.covid19lnma.com>)
 - Interim updates will be available here.

Linked resources in *BMJ* Rapid Recommendations cluster

- Agarwal A, Hunt BJ, Stegeman M, et al. A living WHO guideline on drugs for covid-19 [update 13]. *BMJ* 2020;370:m3379, doi:10.1136/bmj.m3379.
 - Living WHO *BMJ* Rapid Recommendations guidance on drugs for covid-19.
- World Health Organization. Therapeutics and COVID-19. Living guideline. November 2023. (<https://www.who.int/teams/health-care-readiness-clinical-unit/covid-19/therapeutics>).
- MAGICapp (<https://app.magicapp.org/#/guideline/nBk01E>).
 - Expanded version of the WHO living guidelines with methods, processes, and results with multi-layered recommendations, evidence summaries, and decision aids for use on all devices.
- Siemieniuk RAC, Bartoszko JJ, Zeraatkar D, et al. Drug treatments for covid-19: living systematic review and network meta-analysis [update 4]. *BMJ* 2020;370:m2980, doi:10.1136/bmj.m2980.
 - Review and network meta-analysis of all available randomised trials that assessed drug treatments for covid-19 of all severities.

rather than pairwise meta-analysis, provides useful information about the comparative effectiveness of treatments that have not been tested head-to-head. The lack of such direct comparisons can otherwise limit our understanding of important comparisons, and the incorporation of indirect evidence can strengthen evidence in comparisons that were tested head-to-head.⁴

The current evidence supports two stages of covid-19 disease, an early phase marked by viral replication (non-severe disease) and a later inflammatory phase (severe disease).⁵ The different pathogenesis and resulting severity of symptoms at each of these stages suggest different interventions are most effective at certain stages of the disease.^{5 6} Consequently, our systematic review and network meta-analysis now addresses patients with mild or moderate covid-19 (also known as non-severe covid-19) separate from those with severe covid-19. In this publication, we compare the effects of drug treatments for mild or moderate covid-19. A separate publication will compare the effects of drug treatments for severe or critical covid-19, and together these two publications replace our previous living systematic review of covid-19 of all severities. Although we used living systematic review methods to conduct this review, no further updates or analyses are planned, and this publication represents our final analysis for mild or moderate covid-19. This systematic review and network meta-analysis will inform the World Health Organization living guidelines on covid-19 treatments.⁷ These guidelines were initiated and are dynamically updated to provide trustworthy, actionable, and living guidance to clinicians and patients soon after new and potentially practice-changing evidence becomes available (box 1).^{8 9} Drugs for prophylaxis¹⁰ and antibody based treatments¹¹ are addressed separately.

Methods

A protocol provides the detailed methods of this systematic review (supplementary material). We report this systematic review following the guidelines of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist for network meta-analyses.¹² The linked *BMJ* Rapid Recommendations guideline panels approved all decisions relevant to the eligibility of interventions and choice of outcomes.

Eligibility criteria

We included randomised clinical trials in people with suspected, probable, or confirmed mild or moderate covid-19 that compared drugs for treatment against one another or against no treatment, placebo, or standard care. We classified trials as addressing mild or moderate covid-19 based on the description of participants provided in the trials, using the following hierarchy: (1) WHO criteria (oxygen saturation $\geq 90\%$ on room air, respiratory rate ≤ 30 , and no respiratory distress, acute respiratory distress syndrome (ARDS), sepsis, or septic shock)⁸; (2) author definition; (3) infection not requiring respiratory support (such as supplemental oxygen, non-invasive ventilation, invasive ventilation). When authors classified participants receiving respiratory support as mild or moderate, we used respiratory support to classify participants instead of author definition.

We included trials regardless of publication status (peer reviewed, in press, preprint, conference abstracts, or unpublished data from authors) or language and included all drugs and Chinese medicines that were deemed of potential interest by a steering committee composed of clinicians (supplementary material).

The scope of this review did not include trials evaluating vaccination, blood products, and antibody-based antiviral therapies (such as virus specific monoclonal antibodies), nutrition, traditional Chinese herbal or alternative medicines that include more than one molecule or a molecule without specific molecular weighted dosing, and non-drug supportive care interventions. Trials that evaluated these interventions were identified and categorised separately.

Information sources

In collaboration with Epistemonikos, since 1 January 2023, we performed weekly searches using their Living Overview of the Evidence COVID-19 Repository (COVID-19 L-OVE).¹³ The database retrieves articles by conducting systematic searches in 42 databases, trial registries, and preprint servers and has been found to include 100% of covid-19 related randomised trials.¹⁴ Previously, and until 17 February 2023, we performed daily searches from Monday to Friday in the World Health Organization (WHO) covid-19 database— a comprehensive multilingual source of global literature on covid-19. Before its merge with the WHO covid-19 database on 9 October 2020, we performed daily searches from Monday to Friday in the US Centers for Disease Control and Prevention (CDC) COVID-19

Research Articles Downloadable Database.¹⁵ Previously, when searching the WHO covid-19 database or the CDC database, we filtered results through a validated and highly sensitive machine learning model to identify randomised trials.¹⁶ We tracked preprints of randomised trials for updates and through publication.

In addition, we searched six Chinese databases monthly: Wanfang, Chinese Biomedical Literature, China National Knowledge Infrastructure, VIP, Chinese Medical Journal Net (preprints), and ChinaXiv (preprints). Previous iterations describe the search strategies for these databases.¹⁷ Because they did not provide studies that meaningfully altered the evidence for any drug treatment, we stopped searching these databases on 20 February 2021.

We searched all English information sources from 1 December 2019 to 19 May 2024. The data synthesis includes articles retrieved by 28 June 2023 while articles found after this date, alongside a summary of their results are listed in the supplementary material.

Study selection

Using a systematic review software, Covidence,¹⁸ pairs of reviewers, following training and calibration exercises, independently screened all titles and abstracts, followed by full texts of trials that were identified as potentially eligible. A third reviewer adjudicated conflicts.

Data collection

For each eligible trial, pairs of reviewers, following training and calibration exercises, extracted data independently using a standardised, pilot tested data extraction form. Reviewers collected information on trial characteristics (trial registration, publication status, study status, design), patient characteristics (country, age, sex, smoking habits, comorbidities, setting and type of care, and severity of covid-19 symptoms), and outcomes of interest (means or medians and measures of variability for continuous outcomes and the number of participants analysed and the number of participants who experienced an event for dichotomous outcomes). Reviewers resolved discrepancies by discussion and, when necessary, with adjudication by a third party. Subsequently, a data cleaning team, made up of one to two experienced reviewers, reviewed all the extracted information for accuracy. We updated the data collected from included preprints as soon as the peer review publication became available.

Outcomes of interest were selected based on importance to patients¹⁹ and were informed by clinical expertise in the systematic review team and in the guideline panel responsible for the linked WHO living guidelines on covid-19 therapeutics.^{8 9 20} The panel includes unconflicted clinical and methodology experts, recruited to ensure global representation, and patient partners. We included the outcomes that the panel prioritised for decision making. The

process for outcome selection is described in the living guideline.⁸ Selected outcomes were aimed at limiting the progression of covid-19 disease and included mortality (closest to 90 days), use of mechanical ventilation (closest to 90 days), adverse events leading to discontinuation (within 28 days), admission to hospital, length of hospital stay, and time to symptom resolution or clinical improvement. For studies assessing anticoagulants, we also analysed incidence of venous thromboembolism and clinically important bleeding. In contrast to our previous living systematic review, for this iteration, we did not collect data on several outcomes which the guideline development group did not think were critical to decision making for a those with mild or moderate covid-19: viral clearance, time to viral clearance, intensive care unit length of stay, duration of mechanical ventilation, and days free from mechanical ventilation. While the last two outcomes are patient important outcomes, we did not include them because their impact on decision making for mild or moderate covid-19 is limited by their minimal baseline risk in such a population.

Mechanical ventilation includes both invasive and non-invasive mechanical ventilation. We used a hierarchy for the outcome mechanical ventilation in which we preferentially used the total number of patients who received mechanical ventilation over the study period. We used the number of patients ventilated at the time point that the largest number of the patients were ventilated, if the trial reported the number of patients ventilated at specific time points. We used author definitions for mechanical ventilation; when different forms were reported separately, we considered continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP) to be non-invasive mechanical ventilation. When reported separately, we did not consider high flow nasal cannula (HFNC) oxygen therapy to be non-invasive mechanical ventilation.

Risk of bias within individual studies

For each eligible trial, reviewers, following training and calibration exercises, used a revision of the Cochrane tool for assessing risk of bias in randomised trials (RoB 2.0)²¹ to rate trials as (1) at low risk of bias, (2) having some concerns—probably at low risk of bias, (3) having some concerns—probably at high risk of bias, or (4) at high risk of bias, across the following domains: bias arising from the randomisation process; bias owing to departures from the intended intervention; bias from missing outcome data; bias in measurement of the outcome; bias in selection of the reported results, including deviations from the registered protocol; and bias due to competing risks. Unlike previous iterations of our systematic reviews, we considered unblinded trials as probably at low risk of bias due to departures from intended interventions instead of probably high risk of bias, so long as there were no important imbalances in co-interventions.²² We judged trials to be at high risk of bias overall if one or more domains

were rated as probably high risk of bias or as high risk of bias and as low risk of bias if all domains were rated as probably low risk of bias or low risk of bias. Reviewers resolved discrepancies by discussion and, when not possible, with adjudication by a third party.

Data synthesis

We conducted network meta-analysis using a bayesian framework.²³ Any additional data syntheses will be posted on our website (www.covid19lnma.com).

Summary measures

We summarised the effect of drug treatments on dichotomous outcomes using the odds ratio and corresponding 95% credible interval. Owing to the low number of events in most studies, we summarised adverse effects leading to discontinuation using risk differences. Because we expected similar durations across randomised trials for continuous outcomes, we used the mean difference and corresponding 95% credible interval for days for length of hospital stay. Because we expected substantial variation between studies for time to symptom resolution, we performed the analyses using the ratio of means and corresponding 95% credible interval before calculating the mean difference in days.²⁴

Treatment nodes

We grouped treatments into common nodes based on molecule and included different doses and durations in the same node unless there was evidence to suggest that the effects differed. We created a separate node for intervention arms in which participants received a combination of drugs. For anticoagulants, we grouped treatments into nodes based on intensity (eg, full dose anticoagulation, intermediate dose anticoagulation).²⁵ The *networkplot* command of Stata version 15.1 (StataCorp, College Station, TX) provided the software for drawing network plots with thickness of lines between nodes and size of the nodes weighted based on the number of studies per comparison or treatment.²⁶

Statistical analysis

We conducted pairwise meta-analyses and network meta-analyses using a bayesian framework with random effects models for all outcomes.²³ We used a plausible prior for the variance parameter and a uniform prior for the effect parameter suggested in a previous study based on empirical data.²⁷ For all analyses, we used three Markov chains with 100 000 iterations after an initial burn-in of 10 000 and a thinning of 10. We used node splitting models to assess local incoherence and to obtain indirect estimates.²⁸ All network meta-analyses were performed using the *gemtc* package and all pairwise meta-analyses using the *bayesmeta* package in R version 3.6.3 (RStudio, Boston, MA).^{23 29}

In our prior living iteration of this network meta-analysis, some treatment nodes with few total participants and few total events resulted in highly implausible and extremely imprecise effect estimates.

To maximise the probability of providing useful results, we therefore included only nodes with at least 100 patients or at least 20 events.

Certainty of the evidence

We assessed the certainty of evidence using the grading of recommendations assessment, development and evaluation (GRADE) approach for network meta-analysis using semi-automated spreadsheets.^{4 30-32} For each outcome, two people with experience in using GRADE rated each domain for each comparison independently and resolved discrepancies by consensus. We rated the certainty for each comparison and outcome as high, moderate, low, or very low, based on considerations of risk of bias, inconsistency, indirectness, publication bias, intransitivity, incoherence (difference between direct and indirect effects), and imprecision.³¹ To minimise value judgments, our target of certainty rating was any non-zero effect, regardless of the magnitude (that is, we used a minimally contextualised approach with the null effect as the threshold of interest).³³ When point estimates were close to the null effect (between the threshold for a small but important effect and the null), we changed our target of certainty rating to assess our certainty on little to no effect (that is, the effect is in the range between the threshold for small benefit and the threshold for small harm).³⁴ We decided on the small effect threshold based on a survey of the authors, and present the thresholds for each outcome.

Interpretation of results

To facilitate interpretation of the results, we calculated absolute effects for outcomes in which the summary measure was an odds ratio or ratio of means. For the outcomes of mortality, admission to hospital, and time to symptom resolution, we inferred baseline risk in the standard care group for each outcome according to the WHO covid-19 living guideline moderate risk group.⁸ For all other outcomes, we used the median from all studies in which participants received standard of care to calculate the baseline risk for each outcome. We calculated absolute effects using the transitive risks model using the *R2jags* package in R.^{35 36}

For each outcome, we classified treatments in groups from the most to the least effective using the minimally contextualised framework, which focuses on the treatment effect estimates and the certainty of the evidence.³⁷

We interpreted and communicated the results using standardised language to reflect the certainty of the evidence.³⁸

Subgroup and sensitivity analysis

We performed subgroup analyses for specific drug treatments of interest at the direction of the WHO living guideline panel. Previous iterations included subgroup analyses for ivermectin, interleukin-6 receptor antagonists, corticosteroids, hydroxychloroquine, lopinavir-ritonavir, and remdesivir. To conduct

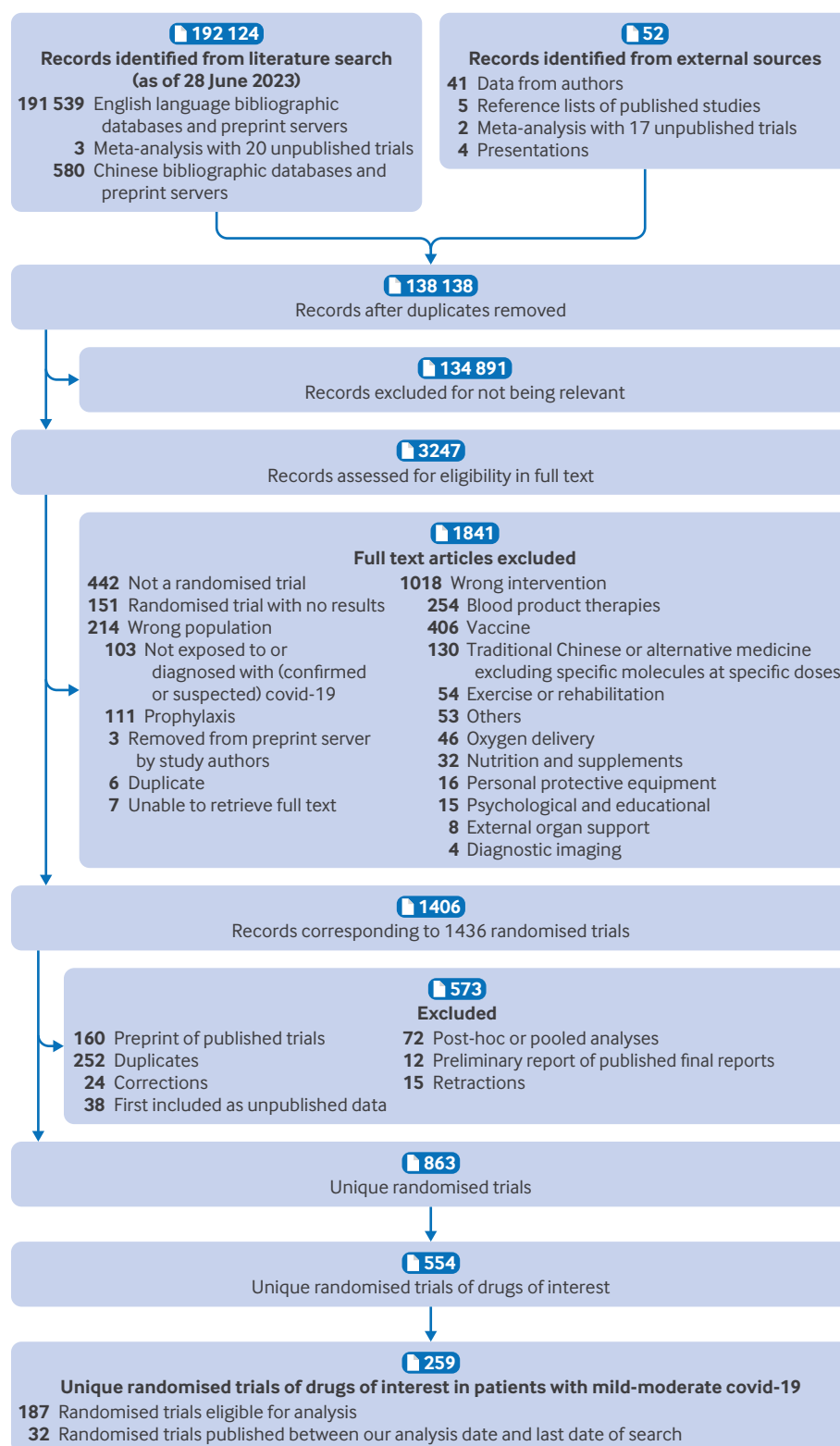


Fig 1 | Study selection

these analyses, we used bayesian hierarchical meta-regression with study as a random effect. Where possible, we performed within rather than between trial analyses. We did not perform any sensitivity analyses.

Patient and public involvement

As part of the WHO living guideline and *BMJ* Rapid Recommendations initiative, patients were involved in outcome selection and the generation of parallel recommendations.⁷⁻⁹

Table 1 | Study characteristics. Data are number (%) of studies unless stated otherwise

Characteristic	No (%) of studies
Registered	234/259 (90.3)
Publication status:	
Preprint	24/259 (9.3)
Published	217/259 (83.8)
Unpublished	18/259 (6.9)
Median (IQR) No of patients	157 (73-470)
Country of study:	
USA	48/259 (18.5)
Brazil	33/259 (12.7)
India	32/259 (12.4)
UK	28/259 (10.8)
China	25/259 (9.7)
Intensity of care:	
Outpatient	108/259 (41.7)
Inpatient	129/259 (49.8)

Results

After screening 138 138 titles and abstracts and 3247 full texts, we identified 863 unique randomised trials. Of those, 259 randomised trials evaluated drug treatments of interest in patients with mild or moderate covid-19 as of 28 June 2023 (fig 1). The supplementary material includes a table of excluded studies from full text screening along with their reason of exclusion. Of the 259 trials, 217 (84%) have been published in peer reviewed journals, 24 (9%) are preprints, and 18 (7%) remain unpublished as abstracts, data from meta-analyses, data from authors, or data from presentations (table 1). Most trials were registered (234/259; 90%), and half evaluated treatment in patients admitted to hospital with covid-19 (128/259; 50%). The majority (at least 80%) of patients in 221 of the 259 included studies had confirmed covid-19 infection. Trials were most commonly conducted in the USA, Brazil, India, UK, and China. Researchers evaluated 108 different drug treatments.

Between 28 June 2023 (data analysis date) and until 19 May 2024, we identified 150 eligible records, of which 51 evaluated treatments of interest in patients with mild or moderate covid-19. Of these 51 records, 12 (24%)³⁹⁻⁵⁰ were associated with already included studies and provided no additional data, seven (14%)⁵¹⁻⁵⁷ would be excluded from analysis because they do not report outcomes of interest or investigated treatments with fewer than 100 patients, while the remaining 32 (63%)⁵⁸⁻⁸⁹ reported relevant data. The supplement lists and describes the results of these 32 studies and compares them to our current findings.

Several trials (35/259; 13%) could not be included in the analysis because both arms would have been classified within the same treatment node (7/35; 20%)⁹⁰⁻⁹⁶ or they reported no outcomes of interest (28/35; 80%).⁹⁷⁻¹²⁴ Ultimately, we analysed 187 (187/259; 72%) trials that reported on treatments with at least 100 patients or 20 events. Thirty seven trials reported on treatments that did not meet this threshold and therefore were not included in the analysis.¹²⁵⁻¹⁶¹ Table 1 presents a summary of the characteristics of the 259 included studies across all included studies. Additional study characteristics and

risk of bias assessments for each study are available in the supplementary material.

Of the 187 randomised trials included in the analyses, nine (5%) did not have publicly accessible protocols or registrations. Of those with publicly accessible protocols or registrations, 73 (39%) reported results for one or more of our outcomes of interest that were not prespecified in protocols or registrations. Three studies had discrepancies in the reporting of the time point at which an outcome was assessed.

Sixty five studies were initially posted as preprints and subsequently published after peer review. The supplementary material presents the differences between study preprint and peer reviewed publications. Twenty-eight studies (28/65; 43%) had discrepancies in outcome reporting between the preprint and peer-reviewed publication, 29 studies (29/65; 45%) had discrepancies with patient baseline characteristics, and eight studies (8/65; 12%) had discrepancies in reporting that led to changes in risk of bias ratings. No substantive differences were found for 22 studies (22/65; 34%).

Risk of bias in included studies

The supplementary material presents the assessment of risk of bias of the included studies for each outcome: 114 studies (114/187; 61%) were judged at low risk or probably low risk of bias in all domains for at least one outcome.

Effects of the interventions

The supplementary material presents the network plots depicting the drug treatments included in the network meta-analysis of each outcome. Figure 2 presents a summary of the effects of the interventions on the outcomes. The supplementary material also presents relative and absolute effect estimates and certainty of the evidence for all comparisons and outcomes. We did not detect statistical incoherence in any of the network meta-analyses. All analyses reached convergence based on trace plots and a Brooks-Gelman-Rubin statistic less than 1.05.

Admission to hospital

The network meta-analysis included 75 trials¹⁶²⁻²³⁴ with 75 968 participants addressing 24 different drug treatments. The supplementary material contains the network plots and complete network meta-analysis results including the certainty of the evidence. The most common treatments were standard care or placebo (74 trials, 37 321 participants), ivermectin (11 trials, 3821 participants), and hydroxychloroquine (10 trials, 1766 participants).

Based on our classification from most to least effective, nirmatrelvir-ritonavir (odds ratio compared with standard care (OR_{SC}) 0.15 (95% credible interval (95% CI) 0.07 to 0.32), moderate certainty) is probably the best at reducing hospital admission, while remdesivir (OR_{SC} 0.25 (0.07 to 0.77), moderate certainty) probably provides an intermediate benefit for this outcome (fig 2). Systemic corticosteroids (OR_{SC}

	Admission to hospital	Mortality	Mechanical ventilation	Adverse events‡	Venous thrombo-embolism	Clinically important bleeding	Length of hospital stay	Time to symptom resolution
Baseline risk*	0.03 per 1000	0.003 per 1000	0.02 per 1000	-	0.008 per 1000	0.003 per 1000	-	9 days
Minimal important difference†	10 per 1000	10 per 1000	15 per 1000	20 per 1000	20 per 1000	20 per 1000	1 day	1 day
(Hydroxy)chloroquine	-1.97 (-11.61 to 11.38)	0.15 (-1.03 to 1.59)	8.72 (-4.34 to 28.73)	10.09 (-2.84 to 23.95)			-0.610 (-2.180 to 0.570)	-0.690 (-1.810 to 0.560)
ACEi/ARB		0.77 (-1.06 to 3.63)	-1.59 (-10.07 to 11.64)				-0.170 (-1.820 to 1.620)	
Aspirin	-5.31 (-17.83 to 13.57)	-0.53 (-1.6 to 0.95)	-2.27 (-10.54 to 9.67)	1.28 (-8.46 to 14.87)			0.000 (-2.330 to 2.320)	0.700 (-2.410 to 4.820)
Aspirin, statins		2.05 (-1.56 to 9.66)	18.22 (-9.05 to 74.9)	-1.59 (-17.48 to 13.62)			0.330 (-2.020 to 2.680)	
Multivitamin	-13.0 (-27.32 to 26.47)	623.08 (-3.0 to 997.0)	-19.62 (-20.0 to -16.18)					
Azithromycin	3.07 (-12.27 to 27.31)	0.08 (-1.1 to 1.98)§	-4.53 (-17.69 to 29.53)					-4.060 (-5.270 to -2.580)
Azithromycin, hydroxychloroquine	845.18 (84.09 to 970.0)	0.76 (-2.97 to 14.53)						
Colchicine	-5.88 (-14.17 to 4.47)	-1.08 (-1.87 to 0.24)§	-8.08 (-13.96 to 3.45)§	0.75 (-7.39 to 11.78)			0.500 (-1.500 to 2.510)	-1.570 (-3.190 to 0.390)
Corticosteroids (systemic)	-15.99 (-23.93 to -2.63)	0.17 (-1.48 to 1.98)	-3.53 (-12.38 to 11.02)	-0.01 (-14.28 to 14.53)				-3.480 (-5.320 to -1.050)
Doubase C		167.67 (-3.0 to 997.0)						
Doxycycline		6.32 (-1.26 to 45.41)§	-7.56 (-18.33 to 21.3)				-1.330 (-2.630 to -0.030)§	0.150 (-2.770 to 3.970)
Doxycycline, ivermectin		-2.98 (-3.0 to -2.94)		9.91 (-11.64 to 31.62)				-1.590 (-4.050 to 1.710)
Ensirelvir		145.0 (-3.0 to 996.99)		4.17 (-15.14 to 22.85)				
Favipiravir	3.2 (-11.63 to 25.18)	16.13 (-0.39 to 73.63)	11.31 (-7.21 to 45.57)	8.05 (-2.2 to 18.54)			-0.630 (-2.050 to 0.730)	-2.170 (-3.150 to -1.080)
Fluvoxamine	-7.44 (-16.41 to 4.56)	-0.75 (-2.11 to 1.72)	-3.37 (-12.32 to 11.49)	36.68 (-6.66 to 79.88)				-0.090 (-2.910 to 3.600)
Fluvoxamine, inhaled corticosteroids	1.12 (-21.84 to 52.47)	835.08 (0.96 to 997.0)	845.59 (1.31 to 980.0)	6.6 (-9.16 to 22.68)				
HIV reverse transcriptase inhibitor	18.75 (-22.29 to 142.63)			1.93 (-16.33 to 22.44)				0.540 (-2.550 to 4.590)
IL6 receptor antagonists		213.37 (-3.0 to 996.99)						
Inhaled and intranasal corticosteroid	47.38 (-16.46 to 231.54)	96.97 (-3.0 to 997.0)						
Inhaled corticosteroids	-8.86 (-24.35 to 22.72)	148.38 (-3.0 to 997.0)	3.29 (-12.28 to 34.32)	-9.73 (-30.26 to 10.18)				-0.290 (-1.940 to 1.640)
Interferon alpha		867.5 (16.67 to 997.0)	91.59 (-16.12 to 621.08)				0.130 (-2.210 to 2.480)	-1.060 (-3.770 to 2.580)
Interferon beta (nebulised)		0.08 (-2.8 to 10.04)						
Interferon beta (subcutaneous)	-4.99 (-19.5 to 20.49)	-0.7 (-2.21 to 2.14)	-0.68 (-12.94 to 22.18)				0.790 (-1.580 to 3.120)	
Interferon lambda (subcutaneous)	-10.21 (-20.69 to 7.24)	-1.75 (-2.97 to 2.87)	-0.91 (-15.86 to 34.48)					0.110 (-2.310 to 3.150)
Intermediate-dose anticoagulation		-0.81 (-1.95 to 0.99)	-8.21 (-14.62 to 1.74)		-0.08 (-6.74 to 17.03)	1.38 (-2.51 to 12.11)		0.160 (-2.760 to 4.000)
Ivermectin	-4.02 (-11.4 to 5.35)	-0.69 (-1.64 to 0.59)	-6.52 (-12.14 to 1.12)	5.74 (-1.1 to 16.07)			-0.400 (-1.800 to 0.950)	-0.690 (-1.660 to 0.370)
JAK inhibitors		-0.66 (-2.0 to 1.53)	-12.46 (-17.53 to -2.98)					
Lopinavir-ritonavir	-2.57 (-16.79 to 20.62)	1.11 (-0.49 to 3.81)	2.81 (-10.45 to 27.33)	41.46 (15.1 to 68.29)			1.770 (0.340 to 3.190)§	4.440 (-0.580 to 12.540)¶
Molnupiravir	-9.82 (-16.66 to -2.28)	-2.23 (-2.78 to -1.19)	-10.96 (-17.36 to 1.69)	-0.5 (-8.59 to 6.08)				-2.340 (-3.450 to -1.070)
Nicosamide		1.82 (-2.52 to 16.56)						-2.070 (-4.110 to 0.510)
Nirmatrelvir-ritonavir	-24.99 (-27.86 to -20.19)	-2.25 (-2.8 to -1.15)	-0.92 (-12.37 to 17.65)	-5.6 (-18.05 to 8.63)			-0.500 (-2.620 to 1.430)	0.200 (-2.960 to 4.420)
P2Y12 inhibitor		-2.01 (-2.79 to -0.39)						
Prophylactic-dose anticoagulation	2.45 (-9.05 to 17.76)	-0.42 (-2.15 to 2.89)	12.99 (-7.78 to 54.25)	0.08 (-11.62 to 13.81)	-7.1 (-8.26 to -4.17)	7.6 (0.27 to 29.03)§		
Remdesivir	-20.93 (-27.79 to -6.69)	-0.71 (-1.75 to 0.87)	-5.82 (-12.53 to 3.0)	9.3 (-5.8 to 25.4)			0.640 (-1.040 to 2.340)	-0.560 (-2.890 to 2.370)
Serine protease inhibitors	-2.85 (-21.12 to 34.46)	844.0 (-0.15 to 997.0)		15.53 (-23.16 to 53.74)				-0.120 (-1.590 to 1.580)
Statins		1.41 (-1.81 to 8.39)	13.7 (-10.93 to 66.38)	3.1 (-15.03 to 20.16)			0.000 (-2.340 to 2.350)	
Therapeutic-dose anticoagulation	90.33 (-22.39 to 442.64)	-0.24 (-1.88 to 2.81)	5.04 (-7.49 to 25.13)		-5.97 (-8.21 to 0.23)	5.01 (-1.62 to 21.0)		
Umifenovir		1.79 (-2.57 to 16.59)						-2.410 (-3.850 to -0.710)
Vitamin D		0.77 (-1.77 to 5.85)	2.74 (-11.74 to 30.5)	1.13 (-29.83 to 31.86)			-1.570 (-3.310 to 0.030)	
VV116		313.73 (-3.0 to 997.0)		-13.07 (-39.58 to 14.62)				0.360 (-3.800 to 6.590)

Among most beneficial

Intermediate benefit

Not convincingly different
than standard care

Harmful

 High/moderate certainty
 Low certainty
 Very low certainty
 No evidence

*Expected risk of each outcome with standard care. Numbers in coloured cells are estimated risk differences (95% CI) per 1000 patients or mean difference (95% CI) in days when compared to standard care

† Minimal important differences were used to support judgements of imprecision

‡ This outcome was analysed as a risk difference due to low number of events

§ Best estimate of effect was obtained from direct evidence

¶ Best estimate of effect was obtained from indirect evidence

ACEi/ARB: Angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; HIV reverse transcriptase inhibitor: human immunodeficiency viruses reverse transcriptase inhibitor; IL6 receptor antagonists: interleukin-6 receptor antagonists; JAK inhibitors: Janus kinases inhibitors

Fig 2 | Summary of effects of drug treatments compared with standard care for mild and moderate covid-19

0.43 (0.20 to 0.90), low certainty) and molnupiravir (OR_{sc} 0.66 (0.44 to 0.92), low certainty) may also provide an intermediate benefit. Colchicine (OR_{sc} 0.79 (0.52 to 1.15), moderate certainty), fluvoxamine (OR_{sc} 0.73 (0.44 to 1.15), moderate certainty), hydroxychloroquine (OR_{sc} 0.91 (0.61 to 1.39), moderate certainty), ivermectin (OR_{sc} 0.85 (0.61 to 1.18), moderate certainty), and prophylactic-dose anticoagulation (OR_{sc} 1.06 (0.69 to 1.62), moderate certainty) are probably not convincingly different from standard care.

Mortality

The network meta-analysis included 161 trials^{162-172 174-192 194-208 210 213-219 222-226 229-323} with 104 831 participants, addressing 40 different drug treatments (supplementary material). The most common treatments were standard care or placebo (155 trials, 51 298 participants), hydroxychloroquine (22 trials, 3119 participants), and ivermectin (21 trials, 4790 participants).

Based on our classification, aspirin (OR_{sc} 0.8 (0.48 to 1.29), high certainty), azithromycin (OR_{sc} 1.03 (0.63 to 1.66), high certainty), colchicine (OR_{sc} 0.64 (0.38 to 1.08), high certainty), hydroxychloroquine (OR_{sc} 1.06 (0.68 to 1.55), high certainty), ivermectin (OR_{sc} 0.75 (0.48 to 1.18), high certainty), lopinavir-ritonavir (OR_{sc} 1.30 (0.84 to 2.17), high certainty), and remdesivir (OR_{sc} 0.75 (0.43 to 1.28), high certainty) are not convincingly different from standard care (fig 2). Evidence was low or very low certainty for all other drug treatments, and no treatment suggested a benefit.

Mechanical ventilation

The network meta-analysis included 74 trials^{164 167 168 171 172 175 181-183 189 190 194 197-200 203 204 213 214 216 217 221 223 226 230 232 236 241-244 247 253 254 256 257 260 263-265 269 270 273 278 280 282-285 290 291 293 297-299 302 303 305 306-308 311 315 317 320 321 324-326} with 43 566 participants, addressing 28 different drug treatments (supplementary material). The most common treatments were standard care or placebo (73 trials, 21 329 participants), ivermectin (13 trials, 2511 participants), and favipiravir (8 trials, 702 participants).

Based on our classification, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (ACEi/ARB) (OR_{sc} 0.87 (0.49 to 1.59), high certainty), aspirin (OR_{sc} 0.86 (0.47 to 1.50), high certainty), colchicine (OR_{sc} 0.59 (0.30 to 1.18), high certainty), and ivermectin (OR_{sc} 0.66 (0.40 to 1.07), high certainty) are not convincingly different from standard care (fig 2). Moderate certainty evidence found that the following interventions were probably not convincingly different from standard care: JAK inhibitors, systemic corticosteroids, favipiravir, fluvoxamine, hydroxychloroquine, subcutaneous interferon β , lopinavir-ritonavir, molnupiravir, nirmatrelvir-ritonavir, prophylactic-dose anticoagulation, and vitamin D. Evidence was low or very low certainty for all other drug treatments.

Adverse events leading to discontinuation

The network meta-analysis included 81 trials^{164 169 170 173 176 178 179 181 184 187 188 189 191 192 194 196 198-201 204 208-213 215 221-224 227 229-232 238 240 242 246 248 250 251 253 256 259-261 264 269 271 276-283 287 295 296 297 299 305 307 309 310 312 313 317 319 325 327 328-332} with 34 727 participants, addressing 23 different drug treatments (supplementary material). The most common treatments were standard care or placebo (78 trials, 15 995 participants), favipiravir (13 trials, 1626 participants), and ivermectin (12 trials, 1529 participants). Based on our classification, high certainty evidence found lopinavir-ritonavir to be harmful compared with standard care (41 more per 1000 (15 more to 68 more)) and ivermectin to be not convincingly different from standard care (6 more per 1000 (1 fewer to 16 more)) (fig 2). Moderate certainty evidence found that the following intervention were probably not convincingly different from standard care: aspirin, aspirin combined with statins, colchicine, systemic corticosteroids, doxycycline combined with ivermectin, ensitrelvir, favipiravir, fluvoxamine combined with inhaled corticosteroids, inhaled corticosteroids, molnupiravir, nirmatrelvir-ritonavir, prophylactic-dose anticoagulation, and serine protease inhibitors.

Venous thromboembolism

Ten trials^{164 168 169 180 181 210 289 290 292 308} with 5386 participants allocated to four different drug treatments reported venous thromboembolism (supplementary material). Based on our classification, prophylactic-dose anticoagulation is probably not convincingly different from standard care (OR_{sc} 0.12 (0.02 to 0.50), moderate certainty) (fig 2). Evidence was low certainty for all other drug treatments, and no treatment suggested a benefit.

Clinically important bleeding

Ten trials^{164 168-180 181 210 289 290 292 308} with 5298 participants allocated to four different drug treatments reported clinically important bleeding (supplementary material). Based on our classification, prophylactic-dose anticoagulation (OR_{sc} 3.28 (1.08 to 9.90), moderate certainty), intermediate-dose anticoagulation (OR_{sc} 1.08 (0.25 to 4.67), moderate certainty), and therapeutic-dose anticoagulation (OR_{sc} 1.98 (0.53 to 7.49), moderate certainty) are probably not convincingly different from standard care (fig 2).

Length of hospital stay

The network meta-analysis included 29 trials^{189 193 196 217 236 238 243 244 247 251 253-255 260 270 279 282-284 297 299 306 311 317 320 321 324} with 11 642 participants, addressing 16 different drug treatments (supplementary material). The most common treatments were standard care or placebo (29 trials, 5592 participants), hydroxychloroquine (5 trials, 656 participants), ACEi/ARB (4 trials, 463 participants), and ivermectin (4 trials, 424 participants).

Based on our classification, doxycycline probably reduces length of hospital stay (mean difference compared with standard care (MD_{sc} -1.33 days (95% CI -2.63 to -0.03), moderate certainty) (fig 2). ACEi/ARB (MD_{sc} -0.17 (-1.82 to 1.62), moderate certainty), favipiravir (MD_{sc} -0.63 (-2.05 to 0.73), moderate certainty), subcutaneous interferon β (MD_{sc} 0.79 (-1.58 to 3.12), moderate certainty), ivermectin (MD_{sc} -0.40 (-1.80 to 0.95), moderate certainty), and nirmatrelvir-ritonavir (MD_{sc} -0.50 (-2.62 to 1.43), moderate certainty) are probably not convincingly different from standard care. Lopinavir-ritonavir increases duration of hospital admission (MD_{sc} 1.77 days (0.34 to 3.19), high certainty).

Time to symptom resolution

The network meta-analysis included 70 trials^{162 163 167 170 171 173-175 178 179 191-193 195-197 200 202 204-206 211 216-218 221 223 224 228 231 232 234 237 241-246 248 250-252 258 261 262 264 266 277 285 287 290 293 297 305 309 311 312 317 318 326 328 329 332-338} with 48 497 participants, addressing 24 different drug treatments (supplementary material). A description of how symptom resolution was defined in each trial can be found in the supplementary material. The most common treatments were standard care or placebo (67 trials, 23 063 participants), ivermectin (11 trials, 3144 participants), and hydroxychloroquine (11 trials, 756 participants).

Based on our classification from most to least effective, azithromycin is probably the best at reducing time to symptom resolution (MD_{sc} -4.06 days (-5.27 to -2.58), moderate certainty) (fig 2). Several interventions also suggested an intermediate benefit: molnupiravir (MD_{sc} -2.34 (-3.45 to -1.07), high certainty), systemic corticosteroids (MD_{sc} -3.48 (-5.32 to -1.05), moderate certainty), favipiravir (MD_{sc} -2.17 (-3.15 to -1.08), moderate certainty), and umifenovir (MD_{sc} -2.41 (-3.85 to -0.71), moderate certainty). The results suggest that the remaining interventions may be not convincingly different from standard care (fig 2).

Subgroups and sensitivity analyses

We have conducted subgroup analyses in previous iterations which did not yield important results.¹⁷ Consequently, as this analysis includes a narrower population for which we did not observe consistent, serious heterogeneity, and as the guideline panel did not request any subgroup analyses, we did not conduct any for this iteration. We did not perform any sensitivity analyses.

Discussion

Summary of findings

This systematic review and network meta-analysis provides a comprehensive overview of the evidence for drug treatments for mild or moderate covid-19 up to 28 June 2023. This includes more than 250 randomised trials specific to non-severe patients and analyses results from 40 different interventions for treating covid-19. We have also identified 32 records⁵⁸⁻⁸⁹ (with relevant data) that would be eligible as of 19 May 2024

(supplementary material). These 32 records would inform 75 outcomes across 25 comparisons. These comparisons include five new treatments: leritrelvir, simnotrelvir, GST-HG171 combined with ritonavir, fluoxetine, and bemnifosbuvir. The preliminary analysis across these 75 outcomes is largely consistent with our results (supplementary material); however, it is limited by the lack of risk of bias assessments and certainty of the evidence assessments, which are only included for the results of our network meta-analysis.

For patients with non-severe covid-19, two antivirals probably reduce admission to hospital: nirmatrelvir-ritonavir and remdesivir. Low certainty evidence suggests systemic corticosteroids and molnupiravir may also reduce hospital admission. For those admitted to hospital, moderate certainty evidence found doxycycline probably reduces their length of stay. Additionally, several drug treatments probably hasten symptom resolution, including azithromycin, molnupiravir, systemic corticosteroids, favipiravir, and umifenovir. High certainty evidence found lopinavir-ritonavir to increase adverse effects leading to discontinuation and increase duration of hospital stay (perhaps as a result of the side effects).

According to our classification no drug was convincingly different from standard care for the outcomes of mortality, mechanical ventilation, venous thromboembolism, and clinically important bleeding; however, rating the certainty using a different target may provide important insights. For example, some interventions suggested little or no effect. For mortality, low certainty evidence suggested nirmatrelvir-ritonavir, and molnupiravir may provide little or no benefit. For mechanical ventilation, moderate certainty evidence suggested JAK inhibitors probably provide little or no benefit. Moderate certainty evidence suggested prophylactic-dose anticoagulation probably provides little or no benefit for venous thromboembolism and probably results in little or no increase of clinically important bleeding.

Several interventions do not seem to result in a benefit for any patient important outcomes, including ACEi/ARB, aspirin, colchicine, fluvoxamine, hydroxychloroquine, ivermectin, and lopinavir-ritonavir. Lopinavir-ritonavir increases the risk of adverse effects leading to drug discontinuation and increases length of hospital stay.

Strengths and limitations of this review

Our review includes studies from various stages of the pandemic, with many trials being conducted earlier, before the deployment of vaccines and when covid-19 had worse outcomes. To ensure that our results remain applicable, we consulted with the WHO guideline panel to choose baseline risks (non-severe, moderate risk) most reflective of this population.⁸ Additionally, while our included studies include patients infected with different covid-19 variants, we do not believe this is likely to importantly affect our results as, to our knowledge, there is no substantial evidence that viral subtype is an effect modifier of any of our included

drugs.³³⁹ Some of the included drugs have downsides that this review did not capture; however, further details can be found in the guideline.⁸ For example, molnupiravir could be carcinogenic,³⁴⁰ nirmatrelvir-ritonavir has many critical drug-drug interactions, and remdesivir is administered intravenously. Thus, while this review provides an overview of the evidence, individual considerations (such as patient values and preferences, contraindications, drug-drug interactions, and drug-specific adverse events not included in this review) must be taken into account when deciding whether to use any medication.

Our search strategy and eligibility criteria were comprehensive, without restrictions on language of publication or publication status. To ensure expertise in all areas, our team is composed of clinical and methods experts who have undergone training and calibration exercises for all stages of the review process. To minimise problems with counterintuitive results, we anticipated challenges that arise in network meta-analysis when data are sparse.³⁴¹ Many of the results for comparisons with sparse data were uninformative and sometimes implausible. For that reason, we decided to restrict our analysis to treatments for which at least 100 people were randomised or for which there were at least 20 events. Despite our best effort with this restriction, we observed that the use of a bayesian framework and random effects models for analysis resulted in several estimates of effect having wide confidence intervals, particularly for comparisons in which there were few studies and infrequent outcomes. Although we considered conducting sensitivity analyses using different statistical methods, we judged that the wide confidence intervals appropriately reflected the statistical uncertainty in those cases and decided against switching our analysis methods.

As implied above, the main limitation of the evidence is that there are few events (and thus serious imprecision) for many of the drugs for many outcomes. Partly, the low number of events for some outcomes was because our systematic review was restricted to patients with mild or moderate covid-19, who are less likely to experience outcomes such as admission to hospital, mortality, and mechanical ventilation. As a result (and not only because of the method of analysis), many credible intervals are imprecise, which reduced the certainty of the evidence. Additionally, data for some outcomes, especially time to symptom resolution, are limited by the different measurement and reporting methods between studies.

The inclusion of preprints in our network meta-analysis might limit our results due to errors and the reporting limitations of preprints. Differences between preprints and peer reviewed publications have thus far been limited to additional baseline patient information, clarification on study design, and outcomes reported in the peer reviewed publications (supplementary material). We believe that none of these changes would have resulted in a meaningful change to pooled effect estimates or certainty for any outcome.³⁴²

Our systematic review and network meta-analysis has continued to inform the development of the WHO living guidelines and *BMJ* Rapid Recommendations.^{8,9} However, these have an important difference in the methods for assessing the certainty of the evidence. In this systematic review and network meta-analysis, we use a minimally contextualised approach for rating the certainty of the evidence, whereas the WHO guideline panels use a fully contextualised approach in which thresholds of importance of magnitudes of effects depend on all other outcomes and factors involved in the decision.³³ The contextualisation explains differences in the certainty of the evidence between the two, driven by different judgments on imprecision. One example is molnupiravir, for which the WHO guideline panel concluded with moderate certainty evidence—as opposed to our low certainty evidence—for a reduction in hospital admission in patients with non-severe covid-19.

Comparison with other studies

We are aware of two other similar efforts addressing covid-19.^{343 344} Our intention is different in that our results fully inform clinical decision making for the associated living WHO guideline.⁸ We also use different analytical methods, which we believe are best suited for this evidence. It is also important to evaluate the reproducibility and replicability of findings from different scientific approaches. We are aware of three network meta-analyses investigating treatments specific to non-severe covid-19; however, the most recent of these included studies up to April 2022 and each looked at only a specific subset of treatment comparisons.³⁴⁵⁻³⁴⁷

This is the first and only version of this systematic review and network meta-analysis that considered only patients with non-severe covid-19. We will perform separate network meta-analyses for patients with severe covid-19. Although not planned, any updates will be published on www.covid19lnma.com, the primary resource to go to between the intermittent publications in *The BMJ* (box 1).

Conclusions

Evidence from this systematic review and network meta-analysis of drug treatments for non-severe covid-19 suggests nirmatrelvir-ritonavir and remdesivir probably reduce admission to hospital while systemic corticosteroids and molnupiravir may reduce hospital admissions. Azithromycin, corticosteroids, favipiravir, molnupiravir, and umifenovir probably reduce duration of symptoms. For most other interventions, the evidence remains uncertain regarding their impact on patient-important outcomes or indicates they are probably not beneficial.

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Supplementary material