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Antibody and cellular therapies for treatment of covid-19: a living systematic review and network meta-analysis

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ABSTRACT

OBJECTIVE

To evaluate the efficacy and safety of antiviral antibody therapies and blood products for the treatment of novel coronavirus disease 2019 (covid-19).

DESIGN

Living systematic review and network meta-analysis, with pairwise meta-analysis for outcomes with insufficient data.

DATA SOURCES

WHO covid-19 database, a comprehensive multilingual source of global covid-19 literature, and six Chinese databases (up to 21 July 2021).

STUDY SELECTION

Trials randomising people with suspected, probable, or confirmed covid-19 to antiviral antibody therapies, blood products, or standard care or placebo. Paired reviewers determined eligibility of trials independently and in duplicate.

METHODS

After duplicate data abstraction, we performed random effects bayesian meta-analysis, including network meta-analysis for outcomes with sufficient data. We assessed risk of bias using a modification of the Cochrane risk of bias 2.0 tool. The certainty of the evidence was assessed using the grading of recommendations assessment, development, and evaluation (GRADE) approach. We meta-analysed interventions with ≥100 patients randomised or ≥20 events per treatment arm.

RESULTS

As of 21 July 2021, we identified 47 trials evaluating convalescent plasma (21 trials), intravenous immunoglobulin (IVIg) (5 trials), umbilical cord mesenchymal stem cells (5 trials), bamlanivimab (4 trials), casirivimab-imdevimab (4 trials), bamlanivimab-etesevimab (2 trials), control plasma (2 trials), peripheral blood non-haematopoietic enriched stem cells (2 trials), sotrovimab (1 trial), anti-SARS-CoV-2 IVIg (1 trial), therapeutic plasma exchange (1 trial), XAV-19 polyclonal antibody (1 trial), CT-P59 monoclonal antibody (1 trial) and INM005 polyclonal antibody (1 trial) for the treatment of covid-19. Patients with non-severe disease randomised to antiviral monoclonal antibodies had lower risk of hospitalisation than those who received placebo: casirivimab-imdevimab (odds ratio (OR) 0.29 (95% CI 0.17 to 0.47); risk difference (RD) −4.2%; moderate certainty), bamlanivimab (OR 0.24 (0.06 to 0.86); RD −4.1%; low certainty), bamlanivimab-etesevimab (OR 0.31 (0.11 to 0.81); RD −3.8%; low certainty), and sotrovimab (OR 0.17 (0.04 to 0.57); RD −4.8%; low certainty). They did not have an important impact on any other outcome. There was no notable difference between monoclonal antibodies. No other intervention had any meaningful effect on any outcome in patients with non-severe covid-19. No intervention, including antiviral antibodies, had an important impact on any outcome in patients with severe or critical covid-19, except casirivimab-imdevimab, which may reduce mortality in patients who are seronegative.

CONCLUSION

In patients with non-severe covid-19, casirivimab-imdevimab probably reduces hospitalisation; bamlanivimab-etesevimab, bamlanivimab, and sotrovimab may reduce hospitalisation. Convalescent plasma, IVIg, and other antibody and cellular interventions may not confer any meaningful benefit.

SYSTEMATIC REVIEW REGISTRATION

This review was not registered. The protocol established a priori is included as a data supplement.

FUNDING

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READERS' NOTE

This article is a living systematic review that will be updated to reflect emerging evidence. Interim updates and additional study data will be posted on our website (www.covid19lnma.com).

Introduction

Global cases of coronavirus disease 2019 (covid-19) continue to rise. As of 14 September 2021, more than 225 million people have been infected with severe acute respiratory syndrome coronavirus virus 2 (SARS-CoV-2), and total deaths have surpassed 4.6 million.[1] Because covid-19 represents a significant threat to global health, coordinated international efforts to identify evidence based therapies have resulted in over 2900 registered clinical trials. Approximately 12% of these trials are investigating cellular or antibody-based therapies such as convalescent plasma, intravenous immunoglobulins (IVIg), or antiviral antibodies.[2]

Given their favourable toxicity profile and historical (though variable) mortality benefit when used in patients with SARS-CoV-1, 1918 pandemic Spanish influenza A, influenza H1N1, influenza H5N1, respiratory syncytial virus, and Ebola virus disease, these harvested and manufactured antiviral antibodies represent attractive therapeutic options for covid-19.[3-6] Indeed, based on this historical evidence combined with early clinical trial data, several countries have issued authorisation for emergency use of convalescent plasma for the treatment of hospitalised patients with covid-19. Several countries have also authorised the use of antiviral monoclonal antibodies of covid-19.[7]

Unlike drugs, stem cells, convalescent plasma, and IVIg cannot be manufactured; thus, production is limited by the number of donors. Since these products have established therapeutic applications in the treatment of congenital and acquired diseases,[8] one can, in the absence of clear evidence for use in covid-19, anticipate challenges related to resource allocation. In contrast, monoclonal antibodies are very easily scalable once they are identified, but production can be time consuming.[9] Therefore, in the midst of a global pandemic in which resource management is fundamental, timely summaries of available evidence and associated guidelines are crucial.[10]

This living systematic review complements the published living systematic review and network meta-analysis comparing the effects of drug treatments[11] and prophylaxis[12] for covid-19. A living systematic review is dynamic and captures all relevant data published over time.[13] Network meta-analysis, which combines direct and indirect evidence to compare interventions, can provide robust information regarding the relative efficacy of interventions that may not have been compared head-to-head due to feasibility or other constraints.[14]

The present living systematic review and network meta-analysis is part of the *BMJ* Rapid Recommendations project, a collaboration between the MAGIC Evidence Ecosystem Foundation (www.magicproject.org) and *The BMJ*. This living network meta-analysis will inform a collaborative living guideline from the World Health Organization, BMJ, and MAGIC Evidence Ecosystem Foundation.[15] Data will inform WHO and *BMJ* Rapid Recommendations[15-17] to deliver trustworthy and potentially practice-changing evidence to both clinicians and patients.

Methods

A protocol provides the detailed methods of this systematic review, including all updates (see supplementary data on bmj.com). We report this living systematic review following the guidelines of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist for pairwise[18 19] and network meta-analyses.[20] A living systematic review is a cumulative synthesis that is updated regularly as new evidence becomes available.[21] The WHO living guideline panel provided guidance on decisions relevant to data synthesis.

Eligibility criteria

We included randomised trials in people with suspected, probable, or confirmed covid-19 that compared blood products and covid-19-specific antiviral antibodies against one another or against no intervention, placebo, or standard care. We included trials regardless of publication status (peer reviewed, in press, or preprint) or language. No restrictions were applied based on severity of illness or setting.

We excluded randomised trials evaluating vaccines, pharmacologic drugs, nutrition, traditional Chinese herbal medicines, and non-drug supportive care interventions. We identified and separately categorised trials including patients with covid-19 that evaluated these interventions. Randomised trials evaluating drug treatments[11] and prophylaxis[12] for covid-19 were synthesised in separate living network meta-analyses. We excluded non-randomised trials.

Information sources

We perform daily searches from Monday to Friday in the WHO global literature on covid-19 database. Before its merging with the WHO global literature on 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 for eligible studies.[22] The database includes 25 bibliographic and grey literature sources: Medline (Ovid and PubMed), PubMed Central, Embase, CAB Abstracts, Global Health, PsycInfo, Cochrane Library, Scopus, Academic Search Complete, Africa Wide Information, CINAHL, ProQuest Central, SciFinder, the Virtual Health Library, LitCovid, WHO covid-19 website, CDC covid-19 website, Eurosurveillance, China CDC Weekly, Homeland Security Digital Library, ClinicalTrials.gov, bioRxiv (preprints), medRxiv (preprints), chemRxiv (preprints), and SSRN (preprints).

The daily searches are designed to match the update schedule of the database and to capture eligible studies the day of or the day after publication. To identify randomised controlled trials, we filter the results from the WHO database through a validated and highly sensitive machine learning model.[23] We track preprints of randomised controlled trials until publication and update data to match that in the peer reviewed publication when discrepant, and reconcile corrections and retractions if they exist.

In addition, we searched six Chinese databases: Wanfang, Chinese Biomedical Literature, China National Knowledge Infrastructure, VIP, Chinese Medical Journal Net (preprints), and ChinaXiv (preprints). We adapted the search terms for covid-19 developed by the CDC to the Chinese language. For the Chinese literature search, we also included search terms for randomised trials. The supplementary data include the Chinese literature search strategy.

We monitor living evidence retrieval services on an ongoing basis. These included the Living Overview of the Evidence (L-OVE) covid-19 Repository by the Epistemonikos Foundation[24] and the Systematic and Living Map on covid-19 Evidence by the Norwegian Institute of Public Health, in collaboration with the Cochrane Canada Centre at McMaster University.[25]

We searched WHO information sources from 1 December 2019 to 21 July 2021, and the Chinese literature from inception to 20 February 2021.

Study selection

Using a systematic review software, Covidence,[26] pairs of reviewers, following training and calibration exercises, independently screen all titles and abstracts, followed by full texts of trials that were identified as potentially eligible. A third reviewer adjudicates conflicts.

Data collection

For each eligible trial, pairs of reviewers, following training and calibration exercises, extract data independently using a standardised, pilot tested data extraction form. Reviewers collect information on trial characteristics (trial registration, publication status, study status, design), patient characteristics (country, age, sex, smoking habits, comorbidities, setting and type of care, severity of covid-19 symptoms, timing of therapy relative to symptom onset), donor characteristics (selection criteria, sex, severity of disease), 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 resolve discrepancies by discussion and, when necessary, with adjudication by a third party.

Outcomes of interest were selected based on the clinical expertise of our systematic review team and by a guideline panel developing WHO and *BMJ* Rapid Recommendations. Selected outcomes include mortality (closest to 90 days), mechanical ventilation (total number of patients, over 90 days), adverse events leading to discontinuation (within 28 days), viral clearance (closest to 7 days ±3 days), transfusion-related acute lung injury (TRALI; total number of patients, within 28 days), transfusion-associated circulatory overload (TACO; total number of patients, within 28 days), infusion reactions (total number of patients, within 28 days), duration of hospitalisation, intensive care unit (ICU) length of stay, time to symptom resolution or clinical improvement, and time to viral clearance. Viral clearance at seven days and time to viral clearance were included because both may be surrogates for transmissibility.[27]

Risk of bias within individual studies

For each eligible trial and outcome, reviewers, following training and calibration exercises, use a revision of the Cochrane tool for assessing risk of bias in randomised trials (RoB 2.0)[28] to rate trials as (*a*) at low risk of bias; (*b*) some concerns, probably at low risk of bias; (*c*) some concerns, probably at high risk of bias; or (*d*) 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; bias due to competing risks; and bias arising from early termination for benefit. We rate trials at high risk of bias overall if one or more domains were rated as (c) some concerns, probably high risk of bias or as (d) high risk of bias, and as low risk of bias overall if all domains were rated as (*b*) some concerns, probably low risk of bias or (*a*) low risk of bias. Reviewers resolve discrepancies by discussion and, when necessary, with adjudication by a third party.

Data synthesis

We performed bayesian random-effects network meta-analysis for outcomes with sufficient data, and synthesise all other outcomes using pairwise bayesian random-effects meta-analyses if there was only one comparison for a specific outcome.[29]

Severity of illness

For efficacy outcomes, we analysed patients with severe disease and non-severe disease separately. We changed our analysis plan after development of the initial protocol at the request of the linked WHO Guideline Development Group because several antiviral based therapies may have different effects in patients with non-severe disease than in patients with severe or critical disease. Severity was defined using the WHO severity scale.[30] Non-severe disease includes patients who have oxygen saturation >90% without supplementary oxygen, a respiratory rate of <30 breaths per minute, and without other clinical signs of severe respiratory distress.

Summary measures

We summarised the effect of interventions on dichotomous outcomes using odds ratios and their corresponding 95% credible interval (CI). For outcomes with extremely rare events, we summarised the effect of interventions using risk difference and 95% CI. For continuous outcomes, specifically duration of hospital stay, we used the mean difference and corresponding 95% CI because we expect similar durations across randomised trials. For time to symptom resolution, time to viral clearance, and duration of mechanical ventilation, we performed the analyses using ratio of means and corresponding 95% CI before calculating the mean difference in days, as we expect substantial between-study.[31] To mitigate highly implausible results or extreme imprecision, we limited our analyses to interventions with at least 100 participants or 20 events across studies.[11]

Treatment nodes

Treatments were grouped into nodes based on intervention, not dose or duration. We created network plots using the *networkplot* command of Stata version 15.1 (StataCorp, College Station, TX, USA). Thickness of lines between nodes and the size of nodes were based on the inverse variance of the direct comparison.[32]

Statistical analysis

We performed a random-effects bayesian meta-analysis using the *bayesmeta* package[29] in RStudio version 3.5.3 (R Studio, Boston, MA, USA). As suggested in an empirical study, we used a plausible prior for the variance parameter and a uniform prior for the effect parameter.[33] For outcomes where the median risk of an event in the control group was 0 (that is, TACO, TRALI, adverse events leading to discontinuation), we performed network meta-analysis with risk difference and fixed effects rather than odd ratios and random effects. Network meta-analysis was performed using the R package *gemtc*. We used three Markov chains with 100 000 iterations after an initial burn-in of 10 000 and a thinning of 10. Node splitting models were used to obtain indirect estimates and to assess local heterogeneity.[34] We did not perform any adjustments for interventions with zero events. The R code used is available publicly at https://github.com/covid19lnma/covid19_lnma/.

Certainty of the evidence

We assessed the certainty of evidence using the grading of recommendations assessment, development, and evaluation (GRADE) approach,[35-37] including specific guidance for network meta-analyses.[14] Two methodologists with experience in using GRADE rated each domain for each comparison independently, resolving discrepancies by discussion. We rated the certainty for each comparison and outcome as high, moderate, low, or very low, taking into consideration risk of bias, inconsistency, indirectness, publication bias, imprecision, incoherence (differences between direct and indirect effect estimates), and intransitivity (differences in study characteristics that may modify the treatment effect in the direct comparisons that form the basis for the indirect estimate).[14 36] We used a minimally contextualised approach with a null effect threshold to rate the certainty that there is a benefit or a harm.[38] When the point estimate is between the null effect and the minimally important difference, we rated the certainty that there is a trivial to no effect.[38] In the absence of data from quantitative studies of patient values, the review team chose thresholds of small but important effects by consensus: 1% for mortality, 2% for mechanical ventilation, 1% for hospitalisation, 1 day for duration of hospitalisation, and 2% for all adverse effects.[38]

Presentation and interpretation of results

To facilitate interpretation of results of dichotomous outcomes, we calculated absolute effects per 1000 patients. To inform the risk of mortality in the standard care group in patients with severe or critical disease, we used data from the CDC on hospitalised patients with covid-19.[39 40] For mechanical ventilation and duration of hospitalisation, we used baseline risks as reported from the International Severe Acute Respiratory and Emerging Infections

Consortium (ISARIC) covid-19 database.[41] For all other outcomes, we used the median event rate in the standard care arm, weighing each study equally.

Results for all comparisons are also presented in an interactive format online (https://www.covid19lnma.com), which will be updated regularly as new data arises.

Subgroup and sensitivity analysis

We plan to conduct subgroup analyses based on high versus low risk of bias studies. Additionally, for convalescent plasma, we plan to perform subgroup analyses based on antibody titres and time of infusion relative to disease progression. We hypothesise that treatment with convalescent plasma will be more efficacious when transfusion occurs earlier in the disease course, and when plasma from patients with more severe illness is used. In the future, additional subgroup analyses may be conducted based on direction from the linked guidelines panels. When there is statistical evidence of a subgroup effect, we will assess its credibility using the Instrument to assess the Credibility of Effect Modification Analyses in randomised controlled trials and meta-analyses (ICEMAN) tool.[42]

Patient and public involvement

Patients will be involved in the interpretation of results and the generation of parallel recommendations, as part of the *BMJ* Rapid Recommendations initiative in the future. So far, patients have not been involved for this first iteration.

Results

After screening 52350 titles and abstracts and 1029 full texts, 47 unique randomised controlled trials that evaluated antiviral antibody or cellular treatments were identified as of 21 July 2021 (fig 1).[43-88] A table of excluded full texts is provided in the supplementary data on bmj.com. Searches of living evidence retrieval services identified 11 publications of eligible randomised trials, which were reconciled with our formal search strategy when necessary.[22-25 45 49 56 64 66-68 75 83 86 88] Thirty randomised controlled trials were published in a peer reviewed journal, 16 were preprints, and one was an abstract. Thirty seven trials enrolled hospitalised patients, and 10 enrolled outpatients. All of the trials were registered and published in English. Fourteen different antiviral antibody or cellular treatments were evaluated for the treatment of covid-19: convalescent plasma (21 trials), intravenous immunoglobulin (IVIG) (5 trials), umbilical cord mesenchymal stem cells (5 trials), bamlanivimab (LY-CoV555; 4 trials), casirivimab-imdevimab (REGEN-COV; 4 trials), bamlanivimab-etesevimab (2 trials), control plasma (2 trials), peripheral blood non-haematopoietic enriched stem cells (2 trials), sotrovimab (1 trial), anti-SARS-CoV-2 IVIG (1 trial), therapeutic plasma exchange (1 trial), XAV-19 polyclonal antibody (1 trial), CT-P59 monoclonal antibody (1 trial), and INM005 polyclonal antibody (1 trial).

Table 1 presents the characteristics of the included studies. The supplementary data on bmj.com present additional study characteristics, outcome data, and risk of bias assessments for each study.

Table 1 | Characteristics of studies included in review of antibody and cellular therapies for treatment of covid-19. Values are numbers (percentages) of studies unless specified otherwise

Study characteristics	
Registered	47 (100%)
Publication status:	
Preprint	16 (34%)
Published	30 (64%)
Unpublished	1 (2%)
Median (IQR) No of patients	105.0 (58-431)
Country:	
United States	16 (34%)
India	5 (11%)
Brazil	4 (9%)
China	3 (6%)
United Kingdom	3 (6%)
Intensity of care:	
Outpatient	10 (21%)
Inpatient	37 (79%)
ICU	3 (6%)
Severity of illness:	
Mild/moderate	9 (19%)
Severe/critical	24 (51%)
Median (IQR) percentage of patients receiving mechanical ventilation	10.0 (0-56.0)

IQR = interquartile range. ICU = intensive care unit

One randomised trial was identified after the data analysis: Dilogo 2021[53] (registration No NCT04457609), a trial of umbilical cord mesenchymal stromal cells versus placebo in 40 participants. It will be included in the next update.

Twelve preprints were subsequently published after peer review. The supplementary data present the differences between study preprint and peer-reviewed publications. Six studies had discrepancies in outcome reporting between the preprint and peer-reviewed publication. Five studies had discrepancies with patient baseline characteristics. Two studies had discrepancies in reporting that led to changes in risk of bias ratings. We found no substantiative differences for three studies.

Risk of bias in included studies

The supplementary data present the assessment of risk of bias of the included studies for each outcome. Twelve trials[50 54 56 60 65 67 72 86] proved at low risk of bias for all domains. All other studies proved at probably high or high risk of bias for at least one domain.

Effects of the interventions

Figure 2 presents a summary of the effects of interventions on important efficacy and safety outcomes. The supplementary data include network plots and forest plots of pairwise meta-analyses for all outcomes, as well as detailed relative and absolute effect estimates and the certainty of evidence for all comparisons and outcomes.

Non-severe disease

Admission to hospital—Six trials including 8444 patients reported on admission to hospital (supplementary data). Patients randomised

to four monoclonal antibody combinations had a lower risk of hospitalisation: casirivimab-imdevimab (odds ratio (OR) 0.29 (95% CI 0.17 to 0.47); moderate certainty), bamlanivimab (OR 0.24 (0.06 to 0.86); low certainty), bamlanivimab-etesevimab (OR 0.31 (0.11 to 0.81); low certainty), and sotrovimab (OR 0.17 (0.04 to 0.57), low certainty) (fig 2). The certainty of all evidence was rated down due to imprecision (serious for casirivimab-imdevimab and very serious for the others because there were few events in the studies). The effect of CT-P59 monoclonal antibody was less certain (OR 0.48 (0.14 to 1.60), low certainty).

Mortality—Eleven trials including 10 683 patients reported mortality closest to 90 days (supplementary data). The risk of mortality is very low in patients with non-severe disease; as a result, no intervention was found to result in an important reduction in mortality. The effects of the interventions are: casirivimab-imdevimab (OR 0.58 (95% CI 0.26 to 1.22); moderate certainty), bamlanivimab (OR 0.46 (0.01 to 27.79); low certainty), bamlanivimab-etesevimab (OR 0.05 (0.00 to 1.01); low certainty), sotrovimab (OR 0.33 (0.01 to 10.16), low certainty), CT-P59 (OR 0.51 (0.01 to 30.40); low certainty), and convalescent plasma (OR 0.83 (0.43 to 1.46); moderate certainty) (fig 2).

Mechanical ventilation—Six trials including 5775 patients reported need for mechanical ventilation (supplementary data). The risk of mechanical ventilation is very low in patients with non-severe disease. No intervention was found to result in an important reduction in mechanical ventilation: casirivimab-imdevimab (OR 0.21 (95% CI 0.02 to 1.20); very low certainty), sotrovimab (OR 0.20 (0.01 to 5.07); very low certainty), and convalescent plasma (OR 0.71 (0.18 to 1.77); very low certainty).

Time to symptom resolution—Four trials including 5646 patients reported time to symptom resolution (supplementary data). Casirivimab-imdevimab (ratio of means 0.72 (95% CI 0.58 to 0.92); moderate certainty) probably reduces duration of symptoms. The credible interval included no effect for bamlanivimab (ratio of means 0.92 (95% CI 0.64 to 1.32); low certainty), bamlanivimab-etesevimab (ratio of means 0.89 (0.68 to 1.16); moderate certainty), and CT-P59 (ratio of means 0.66 (0.42 to 1.05); moderate certainty).

Viral clearance at 7 days (±3 days)—Four trials including 1274 patients reported viral clearance (supplementary data). None of the interventions appeared to increase viral clearance at seven days: bamlanivimab (OR 0.90 (95% CI 0.28 to 3.06); low certainty), bamlanivimab-etesevimab (OR 1.31 (0.37 to 4.71); low certainty), CT-P59 (OR 1.67 (0.53 to 5.21); low certainty), and convalescent plasma (OR 2.05 (0.92 to 5.31); very low certainty).

Time to viral clearance—Two trials including 877 patients reported time to viral clearance (supplementary data). None of the monoclonal antibodies tested appeared to reduce time to viral clearance, as measured by nasopharyngeal PCR: bamlanivimab (ratio of means 1.01 (95% CI 0.39 to 2.69); low certainty), bamlanivimab-etesevimab (ratio of means 0.88 (0.34 to 2.36); low certainty), and CT-P59 (ratio of means 0.95 (0.35 to 2.56); low certainty).

Severe disease

Mortality—Nineteen trials including 24 229 patients reported mortality (supplementary data). None of the interventions tested appeared to reduce mortality: casirivimab-imdevimab (OR 0.94 (95% CI 0.58 to 1.52); very low certainty), convalescent plasma (OR 0.92 (0.70 to 1.12); low certainty), and IVIg (OR 0.70 (0.39 to 1.16); very low certainty). The RECOVERY trial found a credible subgroup effect suggesting that casirivimab-imdevimab may reduce mortality in patients without detectable antibodies at the time of randomisation.[63]

Mechanical ventilation—Eight trials including 840 patients reported need for mechanical ventilation (supplementary data). Neither convalescent plasma (OR 0.92 (95% CI 0.46 to 1.68); very low certainty) nor IVIg (OR 0.67 (0.29 to 1.45); very low certainty) reduced mechanical ventilation.

Duration of hospitalisation—Twenty trials including 24 529 patients reported duration of hospitalisation (supplementary data). Neither convalescent plasma (mean difference −0.7 days (95% CI −2.3 to 1.0); low certainty) nor IVIg (mean difference −2.1 days (−5.8 to 1.6); very low certainty) reduced duration of hospitalisation.

Duration of mechanical ventilation—No interventions included at least 100 patients and thus no network meta-analysis was conducted.

Ventilator-free days—Three trials including 2857 patients reported ventilator-free days (supplementary data). Convalescent plasma may not affect ventilator-free days (mean difference −0.7 days (95% CI −1.8 to 0.4); low certainty).

Time to symptom resolution—One trial including 333 patients reported time to symptom resolution.[89] The study found that convalescent plasma may not affect time to complete resolution of physical function (subhazard ratio 0.89 (95% CI 0.66 to 1.18)) or time to improvement of two categories in the WHO ordinal scale (hazard ratio 1.00 (0.76 to 1.32)).

ICU length of stay—Two trials including 914 patients reported ICU length of stay. One of these trials analysed at least 100 patients in each arm.[64] Convalescent plasma may not affect ICU length of stay (mean difference 0.6 days (95% CI −0.44 to 1.64); low certainty).

Adverse effects

Adverse effects leading to intervention discontinuation—Ten trials including 7895 patients reported adverse effects leading to treatment discontinuation (supplementary data). Certainty was very low for convalescent plasma and IVIg. Bamlanivimab (RD −2 per 1000 (95% CI −13 to 9); moderate certainty) and casirivimab-imdevimab (RD −2 per 1000 (−4 to 0); moderate certainty) probably do not result in an important increase in adverse effects leading to discontinuation.

Infusion reactions—Nineteen trials including 31 708 patients reported infusion reactions (supplementary data). Convalescent plasma probably causes infusion reactions, but the absolute risk is very low (OR 3.25 (95% CI 1.27 to 9.30); RD 6 per 1000 (1 to 18); moderate certainty). The credible interval included no effect for the other interventions: bamlanivimab (OR 1.84 (95% CI 0.74 to 5.26); moderate certainty of no important increase), bamlanivimab-etesevimab (OR 1.68 (0.17 to 12.94); low certainty), casirivimab-imdevimab (OR 2.41 (0.57 to 13.07); low certainty), CT-P59 (OR 0.20 (0.00 to 3.67); low certainty), and sotrovimab (OR 0.39 (0.01 to 6.49); low certainty).

Transfusion-associated circulatory overload (TACO)—Four trials including 1442 patients reported TACO (supplementary data). The risk of TACO with convalescent plasma may be small (RD 5 per 1000 (95% CI −1 to 12); low certainty).

Transfusion-related acute lung injury (TRALI)—Four trials including 1365 patients reported TRALI (supplementary data). The risk of TRALI from convalescent plasma may be small (RD no difference per 1000 (95% CI −5 to 6); low certainty).

Discussion

Our living systematic review and network meta-analysis provides an overview of all trials administering blood products for treatment of covid-19 up to 21 July 2021. Currently, trials have only focused on treatment of covid-19 with the monoclonal antibodies bamlanivimab, bamlanivimab-etesevimab, casirivimab-imdevimab, CT-P59, and sotrovimab, as well as convalescent plasma and intravenous immunoglobulin (IVIg).

Monoclonal antibodies appear to be more effective in patients with non-severe disease than in patients with severe disease. In patients with non-severe disease, patients randomised to any of the monoclonal antibodies had a lower risk of hospitalisation than those randomised to placebo. However, only casirivimab-imdevimab had moderate certainty for this outcome. The impact on other patient-important outcomes was less certain because few patients with non-severe disease died or required mechanical ventilation. An alternative view of this evidence is that there is at least moderate certainty that antiviral monoclonal antibodies do not confer an important reduction in mortality or mechanical ventilation among all patients with non-severe covid-19 because the risk of death is very low regardless of the interventions used.

Our review did not find evidence that any of the blood products or antiviral antibodies had an impact on outcomes in patients with severe or critical covid-19. However, a subgroup analysis from the RECOVERY trial opens the possibility that antiviral monoclonal antibodies may reduce mortality in patients who do not have detectable antibodies against the SARS-CoV-2 spike protein.[63] The subgroup effect is of moderate credibility according to ICEMAN criteria.[42]

Operationalising this subgroup effect is difficult, given that rapid antibody testing is not currently widely available. If the subgroup effect is true, it is possible that casirivimab-imdevimab may increase mortality in patients with severe covid-19 who have detectable antibody response. The linked WHO guideline panel therefore made a recommendation against using casirivimab-imdevimab in patients with severe covid-19 and unknown serostatus.[16]

The randomised trials included in our review generally did not enrol patients with contemporary SARS-COV-2 variants, including the delta variant. Antiviral antibody-based therapies may be less effective against some newer variants.[90] The B.1.617 variant, for example, is resistant to bamlanivimab, and several health authorities have recommended against its use as monotherapy—thus prompting the combination product with etesevimab.[91]

Our review did not find evidence that convalescent plasma confers any benefit to patients with covid-19 of any severity. Evidence was consistent between trials, except one, that limited donors to those with higher neutralising titres and enrolled high risk patients with non-severe disease.[71] This finding has not yet been replicated and is inconsistent with the body of evidence on convalescent plasma; therefore whether or not high titre convalescent plasma confers any benefit remains uncertain.

We are aware of a living Cochrane review that addresses the use of convalescent plasma or hyperimmune immunoglobin for patients with covid-19.[92] The results of their meta-analysis—though based on only nine randomised trials—are consistent with our conclusions: currently, there is uncertainty about the efficacy of convalescent plasma for covid-19. One recent systematic review on interventions in outpatients with covid-19 included nine trials and concluded that bamlanivimab-etesevimab probably reduces progression to severe disease, and insufficient information about other interventions.[93] To our knowledge, our review is the most comprehensive published to date on this topic.

Strengths and limitations of this review

Our living systematic review is conducted by a multidisciplinary team of clinical and methodological experts who have undergone extensive training and calibration exercises for each part of the review process. We utilised a comprehensive literature search without any restrictions on language or publication status, explicit eligibility criteria, and limited meta-analysis of interventions that were randomised to at least 100 patients (or had ≥20 events) to avoid spurious or imprecise findings with network meta-analysis. We used the GRADE approach to rate the certainty of the evidence.

With respect to limitations, our prespecified thresholds for imprecision were not based on empirical data and are determined based on consensus within the review team. Thus, judgments about the certainty of the evidence may differ if people have different thresholds for what they consider an important effect.

The main limitation of the evidence is lack of blinding in most of the included trials of blood products, including convalescent plasma, and the possible differential administration of cointerventions and supportive therapies between the intervention and standard care arms. Thus, consistent with GRADE guidance, we rated down the certainty of the evidence due to risk of bias for all affected outcomes.[94]

Given that ours is a living systematic review, the risk of publication bias may be amplified, since trials with more positive or promising results are likely to be published sooner than those with insignificant findings.

We will periodically update this review as we identify more eligible trials through our systematic search and perform network meta-analysis if data permits. This review will be accompanied by an interactive infographic, and updated results and additional study data will be available on our website https://www.covid19lnma.com.

Conclusions

In patients with non-severe covid-19, the antiviral monoclonal antibodies casirivimab-imdevimab probably reduce risk of hospitalisation; bamlanivimab, bamlanivimab-etesevimab, and sotrovimab may reduce hospitalisation. Casirivimab-imdevimab may reduce the risk of mortality in patients with severe covid-19 who do not have detectable antibodies to the SARS-CoV-2 spike protein, but casirivimab-imdevimab and all other interventions do not appear to have any impact when given to all patients with severe covid-19. Low rates of adverse events leading to discontinuation, transfusion-related acute lung injury (TRALI), and transfusion-associated circulatory overload (TACO) make it difficult to make conclusions about the safety of antiviral monoclonal antibodies and convalescent plasma. Additional high quality data are needed to evaluate the efficacy and safety of antiviral antibodies and blood products for the treatment of covid-19.

What is already known on this topic

- Effective and safe interventions for coronavirus disease 2019 (covid-19) remain elusive, especially in patients with non-severe disease

What this study adds

- This living systematic review and network meta-analysis provides a comprehensive overview the evidence for antibody and cellular therapies used for treatment of covid-19 to 21 July 2021

- Casirivimab-imdevimab probably reduces hospitalisation in patients with non-severe covid-19
- Casirivimab-imdevimab may reduce mortality in patients with severe or critical disease who do not have detectable antibodies
- Bamlanivimab, bamlanivimab-etesevimab, and sotrovimab may reduce hospitalisation
- Convalescent plasma and intravenous immunoglobulins may not have any important impact in patients with covid-19

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RACS affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Dissemination to participants and related patient and public communities: The infographic and MAGICapp decision aids (available at www.magicapp.org/) were created to facilitate conversations between healthcare providers and patients or their surrogates. The MAGICapp decision aids were co-created with people who have lived experience of covid-19.

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Supplementary material: Details of search strategies, excluded studies, study charcteristics, risk of bias assessments, network plots, complete network meta-analysis results and protocol

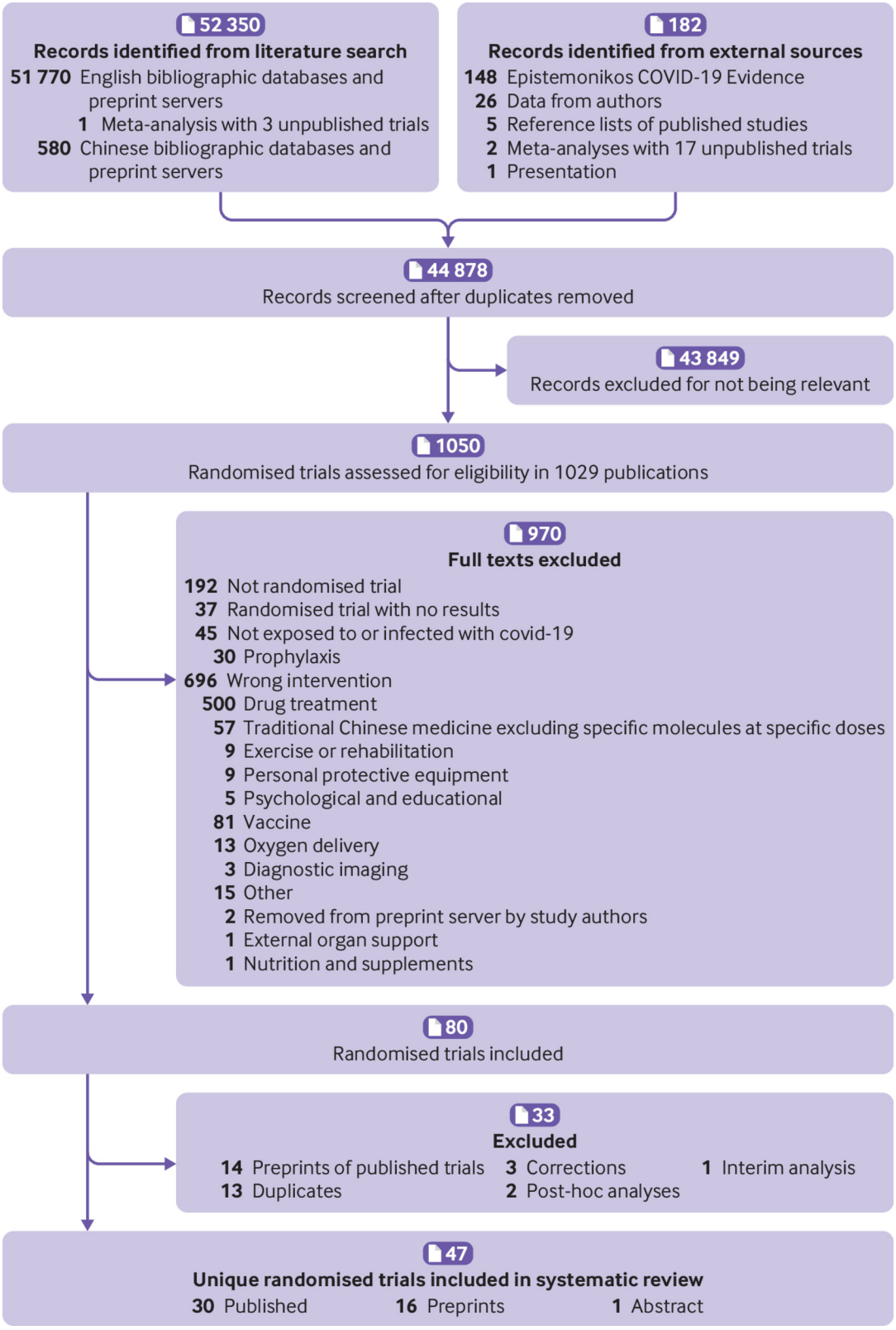
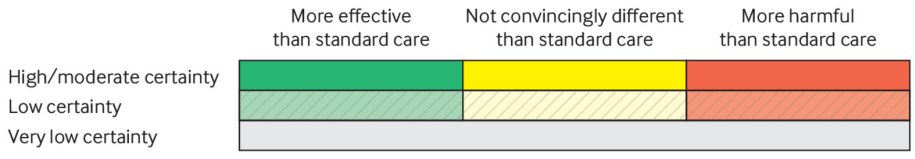


Fig 1 | Study selection for inclusion in review of antibody and cellular therapies for treatment of covid-19

	Mortality	Mechanical ventilation	Admission to hospital	Viral clearance at 7 days	Adverse events*	Infusion reactions*	TRALI*	TACO*	Duration of hospital-isation	Time to symptom resolution	Time to viral clearance	Ventilator free days	ICU length of stay
Non severe disease													
Standard care†	3 per 1000	6 per 1000	60 per 1000	160 per 1000					14 days	9 days	24 days		
Bamlanivimab	-2 (-3 to 82)‡		-41 (-57 to -6)	2 (-113 to 216)						-1 (-3 to 3)	4 (-15 to 43)		
Bamlanivimab, etesevimab	-3 (-3 to 0)‡		-38 (-54 to -9)	57 (-100 to 319)						-1 (-3 to 1)	1 (-16 to 35)		
Casirivimab, imdevimab	-1 (-3 to 1)‡	-4 (-6 to 2)	-42 (-50 to -30)							-2 (-4 to -1)			
Convalescent plasma	-1 (-2 to 2)‡	-1 (-5 to 4)		132 (-15 to 348)					-4 (-10 to 1)				
CT-P59 monoclonal antibody	-2 (-3 to 90)‡	4 (-7 to 231)‡	-24 (-52 to 37)	94 (-72 to 352)						-3 (-5 to 0)	3 (-16 to 40)		
Sotrovimab	-2 (-3 to 29)‡	-6 (-6 to -4)‡	-48 (-58 to -25)										
Severe or critical disease													
Standard care†	220 per 1000	300 per 1000							12 days			14 days	4 days
Casirivimab, imdevimab	-7 (-79 to 82)												
Control plasma	118 (-41 to 307)												
Convalescent plasma	-14 (-56 to 20)	-14 (-135 to 115)							-1 (-2 to 1)			-1 (-2 to 0)	1 (-2 to 0)‡
Intravenous immunoglobulin	-53 (-119 to 29)	-70 (-190 to 80)							-2 (-6 to 2)				
All severities													
Standard care†					0 per 1000	3 per 1000	0 per 1000	0 per 1000					
Bamlanivimab					-2 (-12 to 9)	3 (-1 to 10)							
Bamlanivimab, etesevimab						5 (-2 to 27)							
Casirivimab, imdevimab					-2 (-4 to 0)	6 (-1 to 29)							
Control plasma						8 (-2 to 45)							
Convalescent plasma					2 (-31 to 34)	6 (1 to 18)	0 (-5 to 6)	5 (-1 to 12)					
CT-P59 monoclonal antibody						-1 (-2 to 7)							
Intravenous immunoglobulin					25 (-14 to 64)								
Puried equine anti-RBD					0 (-16 to 16)								
Sotrovimab						0 (-2 to 14)							



* Based on directm (pairwise) estimate of effect rather than network estimate

† Expected risk of each outcome with standard care is reported in grey row. Numbers incoloured cells areestimated risk differences (95% CI) per 1000 patients or mean difference (95% CI) in days when compared to standard care

‡ Because we expected that there would be no effect modification, this outcome was not analyzed according to disease severity

Fig 2 | Summary of effects compared with standard care of antibody and cellular therapies for treatment of covid-19