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SARS-CoV-2-neutralising monoclonal antibodies to prevent COVID-19

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the effectiveness and safety of SARS-CoV-2-neutralising mAbs, including mAb fragments, to prevent infection with SARS-CoV-2 causing COVID-19; and to maintain the currency of the evidence, using a living systematic review approach.

BACKGROUND

Description of the condition

The clinical syndrome novel coronavirus disease 2019 (COVID-19) is a rapidly spreading infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; WHO 2020a). Declared a pandemic on 11 March 2020, COVID-19 is unprecedented in comparison to previous coronavirus outbreaks, such as severe acute respiratory syndrome (SARS) with 813 deaths by July 2003 (WHO 2003), and Middle East respiratory syndrome (MERS) with 882 deaths by January 2021 (WHO 2021a). Despite intensive international efforts to contain its spread, it has resulted in more than 105 million confirmed cases and more than 2.3 million deaths worldwide up to 7 February 2021 (WHO 2021b; WHO 2021c), impacting severely on healthcare facilities, healthcare workers, and medical equipment.

Since 23 March 2020, weekly hospitalisation rates in the USA fluctuated between 3 and 17.2 per 100,000 population, with a recent peak increase at the end of December 2020 (CDC 2021). COVID-19 case fatality ratios (number of deaths from COVID-19 divided by the number of cases of COVID-19) have varied widely between countries and reporting periods (from 0.0% to more than 25%) (Johns Hopkins 2021). However, these numbers may be misleading as they tend to overestimate the infection fatality ratio (the probability of dying for an infected individual) due to varying testing frequency, lags in reporting dates, and variations in case definitions, especially at the beginning of the pandemic when the main focus was on severe cases (WHO 2020b). A recent estimate of the infection fatality ratio of SARS-CoV-2 based on seroprevalence data from the general population of a country ranged from 0.00 to 1.54% for 51 different locations (corrected median: 0.23%; Ioannidis 2020).

The median incubation time is estimated to be between five and six days, and 97.5% of symptomatic cases develop symptoms within 11.5 days of exposure (Lauer 2020). Signs and symptoms can include sore throat, cough, fever, anosmia (loss of sense of smell), dysgeusia (distorted sense of taste), headache, fatigue, and myalgia or arthralgia (Struyf 2020). Other symptoms include shortness of breath, chills, nausea or vomiting, diarrhoea, nasal congestion, haemoptysis (coughing up blood), and conjunctival congestion (WHO 2020a). The proportion of infected people with mild disease is around 80% (Wu 2020), of whom 20% may remain completely asymptomatic (Buitrago-Garcia 2020). Fourteen per cent of infected people will experience severe disease, and 5% will develop critical disease with intensive care unit (ICU) admittance due to respiratory failure, septic shock or multiple organ dysfunction (Wu 2020).

Old age is a risk factor for developing infection and progressing to severe disease (WHO 2020a), with people aged over 80 years at highest risk of mortality. Other risk factors are smoking, cardiovascular disease, obesity, hypertension, diabetes, and chronic respiratory disease (Chen 2020; Huang 2020; WHO 2020a). Recent reports have suggested that people who are immune-compromised may not have an increased risk of being hospitalised with severe COVID-19 symptoms (D'Antiga 2020). However, evidence has been conflicting; people with malignancy and solid organ transplant recipients have been reported to have a potentially increased risk of severe COVID-19 (Fung 2020; Liang 2020). Strategies are being developed to prevent severe COVID-19 in these risk groups. Among these strategies is the possibility of using interventions for prophylaxis. The first study published on using hydroxychloroquine for post-exposure prophylaxis found no benefit from its use (Boulware 2020). Other studies are currently investigating interventions aimed at preventing severe disease in the aforementioned risk groups (NCT04836260; NCT04383548).

Description of the intervention

Monoclonal antibodies (mAbs) are laboratory-produced molecules derived from natural antibodies of hosts who have experienced or been injected with the antigen of interest, to substitute antibodies that are able to mimic a person's own immune attack (Bayer 2019). They are often used to help the body's immune system fight infection. More than 75 mAbs have already been licensed by the US Food and Drug Administration (FDA) to supplement host immunity for a spectrum of medical conditions, especially in oncology and immunology (Kaplon 2020; Lu 2020b). Palivizumab, a mAb against respiratory syncytial virus infection (RSV) for example, is recommended for prophylaxis in children at high risk of complications, and has shown to be effective in reducing the frequency of hospitalisations (Andabaka 2013). In animal models, the use of mAbs against HIV-1 has been shown to be effective in preventing virus acquisition, reducing viraemia, and increasing immunity (Jaworski 2020). During the Ebola outbreak in 2018 in the Democratic Republic of Congo, the mAbs ansuvimab (MAb114) and REGN-EB3 reduced mortality from Ebola virus disease (Mulangu 2019).

Ideally, mAbs intended for clinical practice should be easily mass produced, show high potency (high antigen-binding activity), be stable (prolonged shelf life), have a long half-life, and should not elicit a strong immune response (Marovich 2020). Immunogenicity varies by drug dosage, route of administration, possible contamination, structural features, and 'humanness' of the mAbs, as well as by patient characteristics, such as age, genetic background, and related diseases (Lu 2020b). The strategy of targeting a single epitope can, depending on the specific target, be utilised both for halting disease progression and as temporary prophylaxis for groups with increased antigen exposure, such as healthcare workers, or for those at increased risk of severe disease and mortality (Marston 2018). It is also possible that this may interrupt the chain of infection.

The administration of mAbs, in general, could cause immune reactions (e.g. acute anaphylaxis, serum sickness, generation of antibodies), specific target-related side effects (e.g. development of infections, cancer, autoimmune disease), or organ-specific events (e.g. cardiotoxicity) (Hansel 2010; Jaworski 2020). Organ-specific events are not expected to occur in the use of mAbs targeting a single epitope (Jaworski 2020). The most commonly reported treatment-emergent adverse events following bamlanivimab monotherapy and combination therapy of bamlanivimab and etesivimab for the treatment of people infected with SARS-CoV-2 were nausea, dizziness, diarrhoea, headache, pruritis, and vomiting. These events were similar for participants receiving placebo (Gottlieb 2021).

Alternatives to conventional mAbs are mAb fragments, such as nanobodies and microbodies. Due to their small size and high stability, mAb fragments can easily be synthesised and offer many advantages in terms of their production and neutralising activities (Custódio 2020; Hanke 2020), for instance allowing administration by inhalation (Gai 2021). In contrast, full-size antibodies are

very fragile and are mostly administered intravenously or subcutaneously (Jovčevska 2020). A number of antibody fragments are under clinical investigation; these cover a broad range of diseases, such as infectious diseases, breast cancer, lung diseases, inflammation and brain tumours (Jovčevska 2020).

While other passive antibody therapies, such as convalescent plasma or hyperimmune immunoglobulin, use antibodies derived from more than one type of white cell (polyclonal), mAbs and mAb fragments target only a single, predetermined epitope. Consequently, they generally cause fewer adverse events, such as serum sickness and anaphylaxis (Marston 2018). In contrast to convalescent plasma or hyperimmune immunoglobulin, mAbs and mAb fragments are comprehensively characterised in vitro. This enables precise control of dosage and, for example, composition of a mAb cocktail, which increases effectiveness. Furthermore, plasma products contain other plasma components, such as coagulation factors. For people with COVID-19, who are already at an increased risk for thromboembolic events, this might be potentially harmful (Driggin 2020).

How the intervention might work

Treatment with mAbs is intended to reduce morbidity from severe COVID-19 by reducing the body's inflammatory response to infection. SARS-CoV-2 stems from the coronavirus family that is characterised by a positive-sense, single-stranded RNA (ribonucleic acid) (Lu 2020a). The spike proteins on its envelope, which give the virus its name, play a critical role in enabling it to enter a host cell by two mechanisms (Hoffmann 2020; Ou 2020). Firstly, the human angiotensin-converting enzyme 2 (ACE2) receptor on the spike protein binds to ACE2 proteins that are found throughout the body, but with higher expression in respiratory epithelial cells, type I and II alveolar cells in the lungs, oral cavity, kidney, testis, and intestines (Tolouian 2020). Secondly, this activates the S proteins' fusion machinery, which inserts into the cellular plasma membrane, brings the viral membrane into proximity, and fuses them to create a portal to deposit the virus RNA genome into the host cell, where it starts replicating (Glaunsinger 2020; Tolouian 2020). Dysregulation of ACE2 expression and its subsequent pathways play a crucial role in SARS-CoV-2 infection and may trigger excessive inflammation (the so-called 'cytokine storm') leading to acute respiratory distress syndrome (ARDS) in severe COVID-19 cases (de la Rica 2020).

Currently, due to the importance of this pathway in viral replication and symptom severity, the focus of research on SARS-CoV-2-neutralising mAbs is to block the binding of SARS-CoV-2 to the ACE2 receptor on human cells by targeting the receptor-binding domain (RBD) on the spike protein of the virus (Marovich 2020). This RBD-ACE2 interaction provides a clear therapeutic target for binding and prevention of infection. mAb fragments have the same ability as mAbs and bind to their antigens with high efficacy and specificity. In vitro, nanobodies have demonstrated the ability to inhibit the binding of the spike protein to ACE2 and potently neutralise SARS-CoV-2 (Hanke 2020; Lu 2021; Wrapp 2020). Proteins with an extracellular domain of ACE2 fusioned to the Fc domain of an immunoglobulin are called microbodies. They have been shown to inhibit the virus from attaching to the cells by trapping the spike protein (Glasgow 2020; Tada 2020). The possibility of administration by inhalation, directly at the infection site, could help control transmission of the virus (Gai 2021). In this review, we will focus on SARS-CoV-2-neutralising mAbs, including mAb fragments.

As of 9 February 2021, at least 132 SARS-CoV-2-neutralising mAbs and mAb fragments targeting the spike protein are in discovery, development, or testing phases. Twenty-five mAbs are in clinical trial phases (Chinese Antibody Society 2021; Yang 2020). The first SARS-CoV-2 specific mAb, LY-CoV555, has been tested in humans since June 2020. Many questions, besides their potential clinical effectiveness and most favourable timing of administration, remain to be addressed, such as their adverse events, the duration of protection, and possible mutations of the virus that lead to antibody resistance. Mutations in the spike protein of the virus may mean the viruses are no longer neutralised or cleared by the mAb, and may instead lead to increased severity of the infection, termed 'antibody-dependent enhancement (ADE)' (Lee 2020). Since December 2020, the emergence of three specific variants has caused concerns (WHO 2020c). These variants developed independently from each other. The variant B.1.1.7 (also known as 20I/501Y.V1 or VOC 202012/01) was first identified in the UK and has spread rapidly there, but it has also been identified in other countries. B.1.1.7 may be associated with increased transmissibility, and early evidence suggests an increase in disease severity (Muik 2021; Tang 2021). Another variant, B.1.351 (also known as 20H/501Y.V2), was initially identified in South Africa and might also be more transmissible. It is not suggested that this variant increases disease severity. The variant P.1 was first identified in Brazil and early evidence suggests that this variant might reduce antibody neutralisation (Wang 2021). Early in vitro findings suggest that bamlanivimab may efficiently neutralise the lineage B.1.1.7; however, no neutralising effect could be detected against variant B.1.351 (Widera 2021). Use of mAb cocktails, a mixture of several mAbs and mAb fragments targeting different epitopes on the receptor-binding domain (RBD), may be more efficient in retaining the ability to neutralise SARS-CoV-2 and prevent the emergence of escape variants (Baum 2020a; Koenig 2021).

Several reports of preclinical studies demonstrated in animal models that SARS-CoV-2-neutralising mAbs could also be effective as a preventive measure against SARS-CoV-2 infection by minimising viral replication and mitigating the severity of the disease (Alsoussi 2020; Hassan 2020; Rogers 2020; Zost 2020). Baum et al report on the efficacy of receiving REGN-COV2 as prophylaxis in a rhesus macaques animal model. Firstly, six animals were exposed to the virus through intranasal and intratracheal routes three days after intravenous administration of the antibody cocktail REGN-COV2. The impact of REGN-COV2 was assessed on days one, three, and five after exposure. Genomic RNA (gRNA) and subgenomic RNA (sgRNA), an indicator for viral replication, were measured. Despite similar RNA kinetics, sgRNA levels, and therefore viral replication, were lower in animals receiving REGN-COV2 when compared to placebo. Secondly, REGN-COV2 was administered in different dosages (high or low) to four rhesus macaques, before the animals were exposed to a higher SARS-CoV-2 infection dose than before. Animals treated with a high-dose antibody cocktail showed decreased viral replication, despite an increased infection dose. In animals treated with a low-dose antibody cocktail, the prophylactic effect was reduced (Baum 2020b).

Why it is important to do this review

To date, only two treatments have lowered mortality in severe or critically ill people: corticosteroids (WHO 2020d); and interleukin-6 inhibitors (Ghosn 2021). Interventions that prevent severe

COVID-19 are needed. Although many vaccines against SARS-CoV-2 are in development, production and distribution take time. Furthermore, vaccines do not guarantee immediate protection, and some weeks are required after vaccination to generate an effective immune response. Compared to mAbs, vaccines provide longer-lasting immunity (Marovich 2020). The administration of mAbs and mAb fragments provides immediate protection against infection and, if they are found to be effective and safe, they may serve as an additional preventive strategy against COVID-19 infections, especially for very young children, the elderly, and people with temporarily or permanently compromised immune systems.

Based on an interim analysis of two trials (NCT04427501; NCT04425629), the FDA issued an Emergency Use Authorization for bamlanivimab and REGN-CoV2. Both were authorised for the treatment of outpatients who have mild-to-moderate symptoms of COVID-19 and are at high risk of progression to severe disease (FDA 2021a). However, the FDA has recently withdrawn the Emergency Use Authorization for bamlanivimab, as bamlanivimab monotherapy is presumed to be ineffective against virus variants increasingly emerging in the USA (FDA 2021b). The efficacy and safety of SARS-CoV-2-neutralising mAbs is not yet well characterised, with only a few studies having been published (Gottlieb 2021; Lundgren 2020; Weinreich 2021).

A large number of clinical studies have been initiated to investigate the safety and effectiveness of SARS-CoV-2-neutralising mAbs. However, some of these studies plan to include people who will receive mAbs for prophylaxis either before or after potentially being exposed to SARS-CoV-2 (pre-exposure or post-exposure prophylaxis). Promising data from an interim analysis of an ongoing phase 3 study comparing the mAb cocktail REGN-CoV2 (casirivimab and imdevimab) with placebo in healthy, seronegative people living in a household with a SARS-CoV-2 infected individual were reported in a press release, but the final analysis remains to be seen (Regeneron 2021). Other pharmacological approaches to prevent COVID-19 are also being investigated (Scarabel 2021). One systematic review focused on hydroxychloroquine for COVID-19 prophylaxis; this did not show it to be beneficial for preventing COVID-19, compared to placebo or no prophylaxis (Lewis 2021). A protocol for a Cochrane Review assessing the safety and efficacy of convalescent plasma and hyperimmune immunoglobulin to prevent SARS-CoV-2 infection has recently been published (Valk 2021).

The current systematic review will fill existing gaps by identifying, describing, evaluating, and meta-analysing all evidence for SARS-CoV-2-neutralising mAbs, including mAb fragments, used as prophylaxis for SARS-CoV-2 infections. To provide a frequently updated status, we are planning to create this as a living systematic review.

OBJECTIVES

To assess the effectiveness and safety of SARS-CoV-2-neutralising mAbs, including mAb fragments, to prevent infection with SARS-CoV-2 causing COVID-19; and to maintain the currency of the evidence, using a living systematic review approach.

METHODS

Criteria for considering studies for this review

Types of studies

To assess the effectiveness and safety of SARS-CoV-2-neutralising mAbs, including mAb fragments, to prevent infection with SARS-CoV-2, we aim to include RCTs, as this study design, if performed appropriately, provides the best evidence for experimental therapies in highly-controlled therapeutic settings. We will include non-standard RCT designs, such as cluster-randomised trials (using methods as recommended in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020a)), and cross-over trials. We will only consider results from the first period of a cross-over trial (i.e. before participants crossed over) because COVID-19 is not a chronic condition and its exact course and long-term effects are yet to be defined.

We will include the following formats if there is sufficient information available on study design, characteristics of participants, interventions, and outcomes, or if we can obtain this via contact with study authors.

- Full-text publications
- Preprint articles
- Abstract publications
- Results published in trials registries

We have decided to include preprints and conference abstracts to have a complete overview of the ongoing research activity. We will not apply any limitation with respect to the length of follow-up.

Types of participants

We will include studies examining participants without exposure, or with potential exposure to SARS-CoV-2, but who do not have a confirmed diagnosis of COVID-19 (virus antigens or RNA detected). We will not exclude any studies based on age, gender, ethnicity, or setting. We will exclude studies that evaluate mAbs to prevent infection from other coronavirus diseases (e.g. SARS or MERS), or other viral diseases, such as influenza. If studies enrolled populations with mixed viral diseases, we will only include these if trial authors provide subgroup data for participants with COVID-19.

Treatment of individuals who have SARS-CoV-2 infection with SARS-CoV-2-neutralising mAbs is covered in another review (Kreuzberger 2021).

Types of interventions

We will include the following interventions.

- SARS-CoV-2-neutralising mAbs, including mAb fragments
- 'Antibody cocktails' that include SARS-CoV-2-neutralising mAbs

We will include the following comparisons for studies with a control arm.

- Any mAb therapy compared with a control intervention, for example, vaccinations, drug treatments (including but not limited to hydroxychloroquine, remdesivir), standard or hyperimmune immunoglobulin, convalescent plasma, other prevention strategies (e.g. protective clothing, face masks,

social distancing), complementary medicine (e.g. quercetin, elderberry, zinc) or others.
- Any mAb therapy compared with no treatment or placebo.

Co-interventions are allowed, but these must be comparable between intervention groups.

We will also include studies that compare several mAbs or mAb fragments with each other and another treatment, placebo or no treatment, as well as studies that compare several doses of one type of mAb or mAb fragments with another treatment, placebo or no treatment.

We will explicitly exclude mAbs or mAb fragments that are not specifically designed to treat COVID-19 (e.g. nivolumab, tocilizumab, canakinumab).

Types of outcome measures

We will evaluate core outcomes as predefined by the Core Outcome Set for studies evaluating public health, primary and secondary care interventions for prevention of COVID-19 transmission (COMET 2020). The study to define outcomes is still ongoing (study completion was planned for September 2020). The outcomes listed below are therefore subject to change.

Primary outcomes

Effectiveness of SARS-CoV-2-neutralising mAbs to prevent infection with SARS-CoV-2

- Infection with SARS-CoV-2 (confirmed by positive reverse transcription polymerase chain reaction (RT-PCR) test) within 30 days.
- Development of clinical COVID-19 symptoms, assessed with the WHO Clinical Progression Scale (WHO 2020e), within 30 days:
  - uninfected;
  - ambulatory mild disease;
  - hospitalised with moderate disease;
  - hospitalised with severe disease;
  - death.

Secondary outcomes

Effectiveness of SARS-CoV-2-neutralising mAbs to prevent infection with SARS-CoV-2

- All-cause mortality at day 28, day 60, longest follow-up, and time-to-event
- Admission to hospital within 30 days
- Admission to the intensive care unit (ICU) within 30 days
- Quality of life, assessed with standardised scales; e.g. the World Health Organization Quality of Life assessment instrument (WHOQOL-100; WHO 2020f), at up to seven days, up to 30 days, and longest follow-up available.

Safety of SARS-CoV-2-neutralising mAbs to prevent infection with SARS-CoV-2

- Number of participants with adverse events until end of follow-up
- Number of participants with serious adverse events until end of follow-up

Timing of outcome measurement

In case of time-to-event analysis, e.g. for mortality, we will include the outcome measure based on the longest follow-up time. We will also collect information on outcomes from all other time points reported in the publications.

We will include adverse events and serious adverse events occurring until end of follow-up. If sufficient data are available, we will group the measurement time points of eligible outcomes, for example, adverse events and serious adverse events, into those measured directly after treatment (up to 7 days after treatment), medium-term outcomes (up to 15 days after treatment) and longer-term outcomes (more than 30 days after treatment).

Search methods for identification of studies

This review is part of a COVID-19 living systematic review project evaluating the effectiveness and safety of SARS-CoV-2-neutralising mAbs. Our search addresses:

- SARS-CoV-2-neutralising mAbs to prevent infection with SARS-CoV-2; and
- SARS-CoV-2-neutralising mAbs to treat people with COVID-19 (for the Cochrane Review by Kreuzberger 2021).

We will carry out weekly searches for completed and ongoing studies in all languages in order to limit language bias. We will check weekly for newly emerging mAbs and changing terminology regarding mAbs included in the search strategy, and adapt the strategy where necessary.

Electronic searches

For the identification of studies on the effectiveness and safety of SARS-CoV-2-neutralising mAbs, we designed search strategies in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2020). The review team's Information Specialist (IM) developed the search strategy, based on input from clinicians, and Carolyn Dorée peer-reviewed it. Due to the international urgency for research on therapies for COVID-19, we assume that the abstracts of clinical trials would have been published in English. If the full-text publication is published in a language that lies outside the abilities of our team (English, German, Dutch, French, Italian, Malay and Spanish), we will involve Cochrane TaskExchange to identify people who are able to translate (taskexchange.cochrane.org). We will search the following databases from 1 January 2020:

- Cochrane COVID-19 Study Register (covid-19.cochrane.org; Appendix 1)*;
- MEDLINE (via Ovid; Appendix 2);
- Embase (via Ovid; Appendix 3);
- PubMed (for epublications ahead of print only; Appendix 4);
- Epistemonikos, L*OVE List Coronavirus disease (COVID-19) (app.iloveevidence.com/loves; Appendix 5);
- World Health Organization COVID-19 Global literature on coronavirus disease (bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov; Appendix 6).

*The Cochrane COVID-19 Study Register is a specialised register built within the Cochrane Register of Studies (CRS) and is maintained by Cochrane Information Specialists. The register contains study reports from several sources, including:

- daily searches of PubMed;
- daily searches of ClinicalTrials.com;
- weekly searches of Embase.com;
- weekly searches of the WHO International Clinical Trials Registry Platform (ICTRP);
- monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL).

Complete data sources and search methods for the register are available at: community.cochrane.org/about-covid-19-study-register.

To track ongoing research efforts and address the potential influence of publication bias on our conclusions, we will search relevant trial registries to find ongoing and completed, but not yet published, studies. If results are uploaded into the trials registry that have not yet been published elsewhere, we will integrate these data for the current review and add or replace data in future updates of this review in case of publication.

To identify prospectively registered platform trials for prevention of SARS-CoV-2 infection that may add a mAb arm during the course of the study, such as the COVER HCW trial (NCT04561063), we will search these trials (Appendix 7), list them in the section 'Studies awaiting classification' and regularly check whether they have added additional treatment arms that include mAbs.

Searching other resources

- We will check the reference lists of:
  - all identified studies;
  - relevant review articles; and
  - current treatment guidelines for further literature.
- We will conduct forwards citation searching on the included studies via Google Scholar and use the 'Similar articles' feature on PubMed.
- We will contact experts in the field, drug manufacturers and regulatory agencies in order to retrieve information on unpublished studies.
- We will compare our results with results from projects that aim to track COVID-19 intervention research, i.e.
  - www.covid-trials.org
  - covid-nma.com/dataviz
  - chineseantibody.org/covid-19-track

Data collection and analysis

Selection of studies

Two review authors (NK, ET, KLC, NS, or CH) will independently screen the results of the search strategies for eligibility for this review by reading the abstracts using Covidence software (Covidence). Following the living review approach, we will screen any new citations retrieved by the weekly searches immediately. We will obtain the full-text publications of any abstracts that both review authors find eligible, and also of those that they disagree upon or rate as uncertain, for further discussion. Two review authors will assess the full-text articles of selected studies. If the two review authors are unable to reach a consensus, we will consult all review authors who are involved in study selection to reach a final decision.

We will document the study selection process in a flow chart, as recommended in the PRISMA statement (Moher 2009), and show the total number of retrieved references, and the numbers of included and excluded studies. We will list all studies that we excluded after full-text assessment and the reasons for their exclusion in the 'Characteristics of excluded studies' section.

Data extraction and management

We will conduct data extraction according to the guidelines proposed by Cochrane (Li 2020). Two review authors (NK, KLC, or CH) will extract data independently and in duplicate, using a customised data extraction form developed in Microsoft Excel. We will solve disagreements by discussion. Should no agreement be obtained, we will involve a third review author to solve the disagreement.

Two review authors (NK, KLC, or CH) will independently assess eligible studies obtained in the process of study selection (as described above) for methodological quality and risk of bias. If the review authors are unable to reach a consensus, we will consult a third review author.

We will collate multiple reports of one study so that the study, and not the report, is the unit of analysis.

We will extract the following information, if reported.

- General information: author, title, source, publication date, country, language, duplicate publications
- Study characteristics: trial design, setting and dates, source of participants, inclusion/exclusion criteria, comparability of groups, treatment cross-overs, compliance with assigned treatment, length of follow-up
- Participant characteristics: age, gender, ethnicity, number of participants recruited/allocated/evaluated, additional diagnoses, severity of disease, previous treatments, concurrent treatments, complementary medicine (e.g. quercetin, elderberry, zinc)
- Interventions: type of mAbs or mAb fragments, target of mAbs or mAb fragments, dose, frequency, timing, duration and route of administration, setting (e.g. inpatient, ambulant), duration of follow-up
- Control intervention: concomitant prevention strategies, dose, frequency, timing, duration and route of administration, setting, duration of follow-up
- Outcomes: as specified under Types of outcome measures

Assessment of risk of bias in included studies

We will use the Risk of Bias 2.0 (RoB 2) tool to analyse the risk of bias of study results (Sterne 2019). Of interest for this review is the effect of the assignment to the intervention (the intention-to-treat (ITT) effect); thus, we will perform all assessments with RoB 2 on this effect. The outcomes that we will asses are those specified for inclusion in the summary of findings table.

Two review authors (KLC, CH, NK) will independently assess the risk of bias for each outcome. In case of discrepancies among their judgements and inability to reach consensus, we will consult a third review author to reach a final decision. We will assess the following types of bias as outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020b).

- Bias arising from the randomisation process
- Bias due to deviations from the intended interventions
- Bias due to missing outcome data
- Bias in measurement of the outcome
- Bias in selection of the reported result

For cluster-randomised trials, we will add an additional domain to assess bias arising from the timing of identification and recruitment of participants in relation to timing of randomisation, as recommended in the archived RoB 2 guidance for cluster-randomised trials (Eldridge 2021), and in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020a).

To address these types of bias, we will use the signalling questions recommended in RoB 2 and make a judgement using the following options.

- 'Yes': if there is firm evidence that the question is fulfilled in the study (i.e. the study is at low or high risk of bias for the given the direction of the question).
- Probably yes': a judgement has been made that the question is fulfilled in the study (i.e. the study is at low or high risk of bias given the direction of the question).
- 'No': if there is firm evidence that the question is unfilled in the study (i.e. the study is at low or high risk of bias for the given the direction of the question).
- 'Probably no': a judgement has been made that the question is unfilled in the study (i.e. the study is at low or high risk of bias given the direction of the question).
- 'No information': if the study report does not provide sufficient information to allow any judgement.

We will use the algorithms proposed by RoB 2 to assign each domain one of the following levels of bias.

- Low risk of bias
- Some concerns
- High risk of bias

Subsequently, we will derive an overall risk of bias rating for each prespecified outcome in each study in accordance with the following suggestions.

- 'Low risk of bias': we judge the trial to be at low risk of bias for all domains for this result.
- 'Some concerns': we judge the trial to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.
- 'High risk of bias': we judge the trial to be at high risk of bias in at least one domain for the result, or we judge the trial to have some concerns for multiple domains in a way that substantially lowers confidence in the results.

We will use the RoB 2 Excel tool to implement RoB 2 (available from riskofbias.info), and will store and present our detailed RoB 2 assessments as supplementary online material.

Measures of treatment effect

For continuous outcomes, we will record the mean, standard deviation and total number of participants in both treatment and control groups. Where continuous outcomes use the same scale, we will perform analyses using the mean difference (MD) with 95% confidence intervals (CIs). For continuous outcomes measured with different scales, we will perform analyses using the standardised mean difference (SMD). For interpreting SMDs, we will re-express SMDs in the original units of a particular scale with the most clinical relevance and impact (e.g. clinical symptoms with the WHO Clinical Progression Scale (WHO 2020e)).

For dichotomous outcomes, we will record the number of events and the total number of participants in both treatment and control groups. We will report the pooled risk ratio (RR) with a 95% CI (Deeks 2020). If the number of observed events is small (less than 5% of sample per group), and if studies have balanced treatment groups, we will report the Peto odds ratio (OR) with 95% CI (Deeks 2020).

If available, we will extract and report hazard ratios (HRs) for time-to-event outcomes (e.g. time to death). If HRs are not available, we will make every effort to estimate the HR as accurately as possible from available data using the methods proposed by Parmar 1998 and Tierney 2007. If sufficient studies provide HRs, we will use HRs rather than RRs or MDs in a meta-analysis, as they provide more information.

Unit of analysis issues

The aim of this review is to summarise trials that analyse data at the level of the individual. We also accept cluster-randomised trials for inclusion and we will use the methods recommended in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020a): whenever primary study authors used an analysis that accounts for clustering, such as multilevel or generalised models, we will directly incorporate the effect estimate using inverse-variance meta-analysis. If authors did not account for clustering, we will estimate the effective sample size or inflated standard error from the non-accounted effect estimate, the number of clusters, and the intraclass correlation coefficient for inclusion in meta-analysis (Higgins 2020a). From cross-over trials, we will only consider results from the first period before cross-over.

Studies with multiple treatment groups

As recommended in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020c), for studies with multiple treatment groups of the same intervention (i.e. dose, route of administration), we will evaluate if study arms are sufficiently homogeneous to be combined. When it is not feasible to pool arms, we will compare each arm with the common comparator separately. For pair-wise meta-analysis, we will split the 'shared' group into two or more groups with smaller sample size, and include two or more (reasonably independent) comparisons. For this purpose, for dichotomous outcomes, we will divide both the number of events and the total number of participants; for continuous outcomes, we will divide the total number of participants and leave the means and SDs unchanged.

Dealing with missing data

Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* suggests a number of potential sources for missing data, which we will take into account: at study level, at outcome level and at summary data level (Deeks 2020). At all levels, it is important to differentiate between data 'missing at random', which

may often be unbiased, and 'not missing at random', which may bias study, and thus review, results.

If data are missing, we will request these data from the principal investigators. If, after this, data are still missing, we will have to make explicit assumptions about any methods the included studies used. For example, we will assume that the data were missing at random or we will assume that missing values had a particular value, such as a poor outcome.

Assessment of heterogeneity

We will assess heterogeneity of treatment effects between trials using a Chi^2 test with a significance level at $P < 0.1$. We will use the I^2 statistic to quantify possible heterogeneity (I^2 statistic between 30% and 60% may signify moderate heterogeneity, I^2 statistic between 50% and 90% may signify substantial heterogeneity, and $I^2 > 75\%$ may signify considerable heterogeneity; Deeks 2020). If heterogeneity is above $I^2 > 75\%$, we will explore potential causes through sensitivity and subgroup analyses. If we cannot find a reason for heterogeneity, we will not perform a meta-analysis but will comment on results from all studies and present these in tables.

Assessment of reporting biases

As mentioned above, we will search trial registries to identify completed trials that have not been published elsewhere, to minimise or determine publication bias. We intend to explore potential publication bias by generating a funnel plot and statistically testing this by conducting a linear regression test for meta-analyses involving at least 10 trials (Sterne 2019). We will consider $P < 0.1$ as significant for this test.

Data synthesis

If the clinical and methodological characteristics of individual studies are sufficiently homogeneous, we will pool the data in a meta-analysis. We will conduct separate meta-analyses for different mAbs, as each mAb will be a different molecule with a different target epitope or polytope. We will perform analyses according to the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2020). We will conduct separate meta-analyses for each proposed comparison, that is, separate meta-analyses for different comparators, except if a group of drugs has been shown to be sufficiently homogeneous (e.g. corticosteroids). We will treat placebo and no treatment as the same intervention, as well as standard of care at different institutions and time points.

We will use the Review Manager Web (RevMan Web) software for analyses (RevMan Web 2021). One review author will enter the data into the software, and a second review author will check the data for accuracy. We will use the random-effects model for all analyses as we anticipate that true effects will be related, but will not be the same for included studies. If we cannot perform a meta-analysis, we will comment on the results narratively and present the results from all studies in tables. If meta-analysis is possible, we will assess the effects of potential biases in sensitivity analyses (see Sensitivity analysis). For binary outcomes, we will base the estimation of the between-study variance on the calculation performed using the Mantel-Haenszel method. We will use the inverse variance method for continuous outcomes, outcomes that include data from cluster-randomised trials, or outcomes where HRs are available.

Subgroup analysis and investigation of heterogeneity

To explore heterogeneity, we will perform subgroup analyses of the following characteristics.

- Age of participants (divided into applicable age groups, e.g. children; 18 to 65 years; older than 65 years)
- Pre-existing condition versus without any pre-existing condition
- Variants of SARS-CoV-2 detected in case of infection

We will use the tests for interaction in RevMan Web to test for differences between subgroup results.

Sensitivity analysis

We will perform sensitivity analyses to examine the influence of the following characteristics for our primary outcomes.

- Risk of bias assessment components
- Preprints of COVID-19 interventions
- Premature termination of studies

Summary of findings and assessment of the certainty of the evidence

Summary of findings table

We will only create summary of findings tables and evaluate GRADE for interventions evaluated in RCTs. We will create a separate table per mAb type and mAb fragment type. We will only present summary of findings tables for the three most clinically important mAbs. We will present informal summary of findings tables for the remaining mAbs and mAb fragments in the Additional tables section.

We will use GRADEpro GDT software to create the summary of findings tables, as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2020).

For time-to-event outcomes, we will calculate absolute effects at specific time points, as recommended in the GRADE guidelines 27 (Skoetz 2020).

According to Chapter 14 of the updated *Cochrane Handbook for Systematic Reviews of Interventions*, the "most critical and/or important health outcomes, both desirable and undesirable" should be included in the summary of findings tables (Schünemann 2020). We will include outcomes prioritised according to the Core Outcome Set for studies evaluating public health, primary and secondary care interventions for prevention of COVID-19 transmission (COMET 2020). These are:

- Infection with SARS-CoV-2 (positive RT-PCR test) within 30 days
- Development of clinical COVID-19 symptoms, assessed with the WHO Clinical Progression Scale (WHO 2020e), within 30 days
- All-cause mortality at longest follow-up and greater than 60 days (or most favourable time-to-event estimate). If not reported, we will include all-cause mortality at day 60 followed by day 28.
- Admission to hospital within 30 days
- Quality of life, assessed with standardised scales (e.g. WHOQOL-100; WHO 2020f), at longest follow-up
- Number of participants with adverse events until end of follow-up

- Number of participants with serious adverse events until end of follow-up

Assessment of the certainty in the evidence

We will use the GRADE approach to assess the certainty in the evidence for the outcomes listed in the previous section.

The GRADE approach uses five domains (risk of bias, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty in the body of evidence for each prioritised outcome. We will follow the current GRADE guidance for these assessments in their entirety, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions*, Chapter 14 (Schünemann 2020).

We will use the overall risk of bias judgement, derived from the RoB 2 Excel tool, to inform our decision on downgrading for risk of bias. We will phrase the findings and certainty in the evidence as suggested in the guidance on informative statements (Santesso 2020).

Methods for future updates

Living systematic review considerations

Our Information Specialist (IM) will provide us with the new records each week, which two review authors will screen, extract, evaluate, and integrate following the guidance on Cochrane living systematic reviews (Living Evidence Network 2019).

We will manually check platform trials that were previously identified and listed as 'studies awaiting classification' for additional treatment arms.

We will wait until the accumulating evidence changes one or more of the following components of the review before republishing the review.

- The findings of one or more prioritised outcomes
- The credibility (e.g. GRADE rating) of one or more prioritised outcomes
- New settings, populations, interventions, comparisons, or outcomes studied

We will review the Cochrane Review's scope and methods approximately monthly, or more frequently if appropriate, in light of potential changes in COVID-19 research (for example, when additional comparisons, interventions, subgroups, outcomes, or new review methods become available).

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APPENDICES

Appendix 1. Search strategy: Cochrane Covid-19 Study Register

"Ly-3832479" OR Ly3832479 OR "LY-3832479" OR LY3832479 OR "LY-CoV016" OR "REGN-COV2" OR "REGEN-COV2" OR REGN10933 OR REGN10987 OR REGEN10933 OR REGEN10987 OR casirivimab OR imdevimab OR "LY-3819253" OR LY3819253 OR "LY-CoV555" OR Bamlanivimab OR Banlanivimab OR "VIR-7831" OR VIR7831 OR GSK4182136 OR "GSK-4182136" OR sotrovimab OR AZD7442 OR "AZD-7442" OR AZD8895 OR "AZD-8895" OR tixagevimab OR "COV2-2196" OR COV22196 OR AZD1061 OR "AZD-1061" OR cilgavimab OR "COV2-2130" OR COV22130 OR DXP593 OR "DXP-593" OR "BGB-DXP-593" OR BGBDXP593 OR JS016 OR "JS-016" OR etesevimab OR TY027 OR "TY-027" OR CTP59 OR "CTP-59" OR "CT-P59" OR regdanvimab OR STI1499 OR "STI-1499" OR "COVI-shield" OR COVIshield OR "COVI-guard" OR COVIguard OR BRII196 OR "BRII-196" OR SCTA01 OR "SCTA-01" OR MW33 OR "MW-33" OR BRII198 OR "BRII-198" OR HFB30132A OR "HFB-30132A" OR ADM03820 OR "ADM-03820" OR HLX70 OR "HLX-70" OR STI2020 OR "STI-2020" OR COVIAMG OR "COVI-AMG" OR DZIF10c OR "DZIF-10c" OR BI767551 OR "BI-767551" OR "COV2-2381" OR COV22381 OR "ABBV-47D11" OR 47D11 OR ABBV47D11 OR "COR-101" OR COR101 OR "STE90-C11" OR "DXP-604" OR DXP604 OR "BGB-DXP604" OR BGBDXP604 OR "BGB-DXP-604" OR "chicken egg antibody" OR "egg yolk antibody" OR IgY* OR "VIR-7832" OR VIR7832 OR GSK4182137 OR "GSK-4182137" OR IDB003 OR MD65 OR "MTX-COVAB"

Appendix 2. Search strategy: MEDLINE via Ovid

#	Searches
1	"spike protein, SARS-CoV-2".mp.
2	Coronavirus Infections/ or Coronavirus/
3	SARS-CoV-2/ or COVID-19/
4	("2019 nCoV" or 2019nCoV or coronavir* or coronovir* or COVID or COVID19 or HCoV* or "nCov 2019" or "SARS CoV2" or "SARS CoV 2" or SARSCoV2 or "SARSCoV 2").tw,kf.
5	"severe acute respiratory syndrome coronavirus 2".tw,kf,nm.
6	((corona* or corono*) adj1 (virus* or viral* or virinae*)).tw,kf.
7	or/2-6
8	*Antibodies, Monoclonal/
9	Antibodies, Neutralizing/
10	Antibodies, Viral/
11	((antibod* or mAb* or nAb*) adj2 (therap* or treatment* or neutrali?ing or prevent* or protect* or prophylax*)).tw,kf.
12	Spike Glycoprotein, Coronavirus/
13	Binding, Competitive/
14	(compet* adj1 bind*).tw,kf.
15	("spike protein*" or "s protein*" or "Spike (S) protein").mp.
16	((cocktail* or mixture* or combination*) adj3 (mAb* or antibod* or nAb*)).tw,kf.
17	(LY3832479* or LY-CoV016* or LY-3832479* or LYCoV016* or JS016* or JS-016* or etesevimab*).mp.
18	(REGN-COV2* or REGN-COV-2* or REGN10933* or REGN10987* or REGN-10933* or REGN-10987* or REGEN-COV2* or REGEN-COV-2* or REGEN10933* or REGEN10987* or REGEN-10933* or REGEN-10987* or casirivimab* or imdevimab*).mp.
19	(LY3819253* or LY-3819253* or LY-CoV555* or LYCoV555* or bamlanivimab* or banlanivimab*).mp.
20	(VIR7831* or VIR-7831* or GSK4182136* or GSK-4182136* or sotrovimab*).mp.

21 (AZD7442* or AZD-7442* or AZD8895* or AZD-8895* or tixagevimab* or COV2-2196 or COV22196* or AZD1061* or AZD-1061* or cilgavimab* or COV2-2130* or COV22130*).mp.

22 (DXP-593* or DXP593* or BGB-DXP593* or BGBDXP593* or BGB-DXP-593*).mp.

23 (TY027* or TY-027*).mp.

24 (CTP59* or CTP-59* or CT-p59 or regdanvimab*).

25 (STI1499* or STI-1499* or covi-shield* or covishield* or COVI-GUARD* or COVIguard*).mp.

26 (BRII196* or BRII-196*).mp.

27 (SCTA01* or SCTA-01*).mp.

28 (MW33* or MW-33*).mp.

29 (BRII198* or BRII-198*).mp.

30 (HFB30132A* or HFB-30132A*).mp.

31 (ADM03820* or ADM-03820*).mp.

32 (HLX70* or HLX-70*).mp.

33 (STI2020* or STI-2020* or COVIAMG* or COVI-AMG*).mp.

34 (DZIF10c* or DZIF-10c* or BI767551* or BI-767551*).mp.

35 (COV2-2381* or COV22381*).mp.

36 (ABBV-47D11* or 47D11* or ABBV47D11*).mp.

37 (COR-101* or COR101* or STE90-C11*).mp.

38 (DXP-604* or DXP604* or BGB-DXP604* or BGBDXP604* or BGB-DXP-604*).mp.

39 (Chicken egg antibod* or egg yolk antibod* or IgY*).mp.

40 (VIR-7832 or VIR7832 or GSK4182137* or GSK-4182137*).mp.

41 (IDB003 or MD65 or MTX-COVAB).mp.

42 or/8-41

43 7 and 42

44 (exp Animals/ or exp Animal Experimentation/ or exp Models, Animal/) not Humans/

45 43 not 44

46 limit 45 to yr="2020-Current"

Appendix 3. Search strategy: Embase via Ovid

#	Searches
1	coronavirinae/ or coronaviridae/ or coronaviridae infection/
2	coronavirus disease 2019/
3	Coronavirus infection/
4	sars-related coronavirus/
5	"Severe acute respiratory syndrome coronavirus 2"/
6	((corona* or corono*) adj1 (virus* or viral* or virinae*)).tw,kw.

7 ("2019 nCoV" or 2019nCoV or coronavir* or coronovir* or COVID or COVID19 or HCoV* or "nCov 2019" or "SARS CoV2" or "SARS CoV 2" or SARSCoV2 or "SARSCoV 2").tw,kw.

8 "Severe acute respiratory syndrome coronavirus 2".mp.

9 or/1-8

10 Antibodies, Monoclonal/

11 Antibodies, Neutralizing/

12 Antibodies, Viral/

13 ((antibod* or mAb* or nAb*) adj2 (therap* or treatment* or neutrali?ing or prevent* or protect* or prophylax*)).tw,kw.

14 Spike Glycoprotein, Coronavirus/

15 Binding, Competitive/

16 (compet* adj1 bind*).tw,kw.

17 ("spike protein*" or "s protein*" or "Spike (S) protein").mp.

18 ((cocktail* or mixture* or combination*) adj3 (mAb* or antibod* or nAb*)).tw,kw.

19 (LY3832479* or LY-CoV016* or LY-3832479* or LYCoV016* or JS016* or JS-016* or etesevimab*).mp.

20 (REGN-COV2* or REGN-COV-2* or REGN10933* or REGN10987* or REGN-10933* or REGN-10987* or REGEN-COV2* or REGEN-COV-2* or REGEN10933* or REGEN10987* or REGEN-10933* or REGEN-10987* or casirivimab* or imdevimab*).mp.

21 (LY3819253* or LY-3819253* or LY-CoV555* or LYCoV555* or bamlanivimab* or banlanivimab*).mp.

22 (VIR7831* or VIR-7831* or GSK4182136* or GSK-4182136* or sotrovimab*).mp.

23 (AZD7442* or AZD-7442* or AZD8895* or AZD-8895* or tixagevimab* or COV2-2196 or COV22196* or AZD1061* or AZD-1061* or cilgavimab* or COV2-2130* or COV22130*).mp.

24 (DXP-593* or DXP593* or BGB-DXP593* or BGBDXP593* or BGB-DXP-593*).mp.

25 (TY027* or TY-027*).mp.

26 (CTP59* or CTP-59* or regdanvimab*).mp.

27 (STI1499* or STI-1499* or COVI-shield* or COVIshield* or COVI-GUARD* or COVIguard*).mp.

28 (BRII196* or BRII-196*).mp.

29 (SCTA01* or SCTA-01*).mp.

30 (MW33* or MW-33*).mp.

31 (BRII198* or BRII-198*).mp.

32 (HFB30132A* or HFB-30132A*).mp.

33 (ADM03820* or ADM-03820*).mp.

34 (HLX70* or HLX-70*).mp.

35 (STI2020* or STI-2020* or COVIAMG* or COVI-AMG*).mp.

36 (DZIF10c* or DZIF-10c* or BI767551* or BI-767551*).mp.

37 (COV2-2381* or COV22381*).mp.

38 (ABBV-47D11* or 47D11* or ABBV47D11*).mp.

39 (COR-101* or COR101* or STE90-C11*).mp.

40 (DXP-604* or DXP604* or BGB-DXP604* or BGBDXP604* or BGB-DXP-604*).mp.

41 (Chicken egg antibod* or egg yolk antibod* or IgY*).mp.

42 (VIR-7832* or VIR7832* or GSK4182137* or GSK-4182137*).mp.

43 (IDB003 or MD65 or MTX-COVAB).mp.

44 or/10-43

45 (exp animal/ or nonhuman/) not exp human/

46 Animal experiment/ not (human experiment/ or human/)

47 or/45-46

48 9 and 44

49 48 not 47

50 limit 49 to yr="2020 -Current"

Appendix 4. Search strategy: PubMed (ahead of print only)

#1 2019 nCoV[tiab] OR 2019nCoV[tiab] OR corona virus[tiab] OR corona viruses[tiab] OR coronavirus[tiab] OR coronaviruses[tiab] OR COVID[tiab] OR COVID19[tiab] OR nCov 2019[tiab] OR SARS-CoV2[tiab] OR SARS CoV-2[tiab] OR SARSCoV2[tiab] OR SARSCoV-2[tiab] OR "COVID-19"[Mesh] OR "Coronavirus"[Mesh:NoExp] OR "SARS-CoV-2"[Mesh] OR "COVID-19"[nm] OR "severe acute respiratory syndrome coronavirus 2"[nm]

#2 (antibod*[Title/Abstract] OR mAb[Title/Abstract] OR mAbs[Title/Abstract] OR nAb[Title/Abstract] OR nAbs[Title/Abstract]) AND (therap*[Title/Abstract] OR treat*[Title/Abstract] OR neutrali*[Title/Abstract] OR prevent*[Title/Abstract] OR protect*[Title/Abstract] OR prophylax*[Title/Abstract])

#3 (compet*[Title/Abstract] AND bind*[Title/Abstract])

#4 (cocktail*[Title/Abstract] OR mixture*[Title/Abstract] OR combination*[Title/Abstract]) AND (mAb[Title/Abstract] OR mAbs[Title/Abstract] OR antibod*[Title/Abstract] OR nAb[Title/Abstract] OR nAbs[Title/Abstract])

#5 "spike protein*"[Title/Abstract] OR "s protein*"[Title/Abstract] OR "Spike (S) protein"[Title/Abstract]

#6 (LY-3832479 OR LY3832479 OR LY-CoV016 OR REGN-COV2 OR REGN10933 OR REGN10987 OR REGN-10933 OR REGN-10987 OR REGEN10933 OR REGEN10987 OR REGEN-10933 OR REGEN-10987 OR REGN-CoV2* OR REGN-CoV-2* OR REGEN-CoV2* OR REGEN-CoV-2* OR casirivimab OR imdevimab OR LY-3819253 OR LY3819253 OR LY-CoV555 OR Bamlanivimab OR Banlanivimab OR VIR-7831 OR VIR7831 OR GSK4182136 OR GSK-4182136 OR sotrovimab OR AZD7442 OR AZD-7442 OR AZD1061 OR AZD-1061 OR AZD8895 OR AZD-8895 OR tixagevimab OR cilgavimab OR DXP593 OR DXP-593 OR BGB-DXP-593 OR BGBDXP593 OR JS016 OR JS-016 OR LY-CoV016 OR etesevimab OR TY027 OR TY-027 OR CTP59 OR regdanvimab OR STI1499 OR STI-1499 OR COVI-shield OR COVIshield OR COVI-guard OR COVIguard OR BRII196 OR BRII-196 OR SCTA01 OR SCTA-01 OR MW33 OR MW-33 OR BRII198 OR BRII-198 OR HFB30132A OR HFB-30132A OR ADM03820 OR ADM-03820 OR HLX70 OR HLX-70 OR STI2020 OR STI-2020 OR COVIAMG OR COVI-AMG OR DZIF10c OR DZIF-10c OR BI767551 OR BI-767551 COV2-2381 OR COV22381 OR ABBV-47D11 OR 47D11 OR ABBV47D11 OR COR-101 OR COR101 OR STE90-C11 OR DXP-604 OR DXP604 OR BGB-DXP604 OR BGBDXP604 OR BGB-DXP-604 OR „chicken egg antibod*" OR "egg yolk antibod*" OR IgY OR IgYs OR VIR-7832 OR VIR7832 OR GSK4182137 OR GSK-4182137 OR IDB003 OR MTX-COVAB OR MD65 OR TATX-03 OR NOVOAB-20)

#7 ("spike protein, SARS-CoV-2"[nm])

#8 #1 AND (#2 OR #3 OR #4 OR #5 OR #6 OR #7)

#9 ("animals"[mh] NOT "humans"[mh])

#10 (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb])

#11 #8 NOT #9 AND #10 Filters: from 2020/1/1 - 3000/12/12

Appendix 5. Search strategy: Epistemonikos, L*OVE List Coronavirus disease (COVID-19)

app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d?utm=epdb_en

the Coronavirus disease (COVID-19) L*OVE for Prevention or treatment > Pharmacological interventions > Targeted therapies > Anti-SARS-CoV-2 Mab > primary studies.

Appendix 6. Search strategy: World Health Organization COVID-19 Global literature on coronavirus disease

Advanced search: search fields: title, abstract, subject

search 1: "Ly-3832479" OR Ly3832479 OR "LY-3832479" OR LY3832479 OR "LY-CoV016" OR "REGN-COV2" OR "REGEN-COV2" OR REGN10933 OR REGN10987 OR REGEN10933 OR REGEN10987 OR casirivimab OR imdevimab

search 2: "LY-3819253" OR LY3819253 OR "LY-CoV555" OR Bamlanivimab OR Banlanivimab OR "VIR-7831" OR VIR7831 OR GSK4182136 OR "GSK-4182136" OR sotrovimab

search 3: AZD7442 OR "AZD-7442" OR AZD8895 OR "AZD-8895" OR tixagevimab OR "COV2-2196" OR COV22196 OR AZD1061 OR "AZD-1061" OR cilgavimab OR "COV2-2130" OR COV22130

search 4: DXP593 OR "DXP-593" OR "BGB-DXP-593" OR BGBDXP593 OR JS016 OR "JS-016" OR etesevimab OR TY027 OR "TY-027" OR CTP59 OR "CTP-59" OR "CT-P59" OR regdanvimab

search 5: STI1499 OR "STI-1499" OR "COVI-shield" OR COVIshield OR "COVI-guard" OR COVIguard OR BRII196 OR "BRII-196" OR SCTA01 OR "SCTA-01" OR MW33 OR "MW-33" OR BRII198 OR "BRII-198"

search 6: HFB30132A OR "HFB-30132A" OR ADM03820 OR "ADM-03820" OR HLX70 OR "HLX-70" OR STI2020 OR "STI-2020" OR COVIAMG OR "COVI-AMG" OR DZIF10c OR "DZIF-10c" OR BI767551 OR "BI-767551"

search 7: "COV2-2381" OR COV22381 OR "ABBV-47D11" OR 47D11 OR ABBV47D11 OR "COR-101" OR COR101 OR "STE90-C11" OR "DXP-604" OR DXP604 OR "BGB-DXP604" OR BGBDXP604 OR "BGB-DXP-604"

search 8: "chicken egg antibody" OR "egg yolk antibody" OR IgY* OR "VIR-7832" OR VIR7832 OR GSK4182137 OR "GSK-4182137" OR IDB003 OR MD65 OR "MTX-COVAB"

Appendix 7. Search strategy: Cochrane Covid-19 Study Register for platform trials

Cochrane COVID-19 Study Register via the Cochrane Register of Studies crsweb.cochrane.org/

1	(adaptive clinical trial):PT AND INREGISTER
2	(adaptive NEAR7 (trial OR stud*)) AND INREGISTER
3	(adaptive NEAR5 (design)) AND INREGISTER
4	master protocol AND INREGISTER
5	"cohort multiple randomized controlled trial*" AND INREGISTER
6	"cohort multiple randomised controlled trial*" AND INREGISTER
7	"cmRCT" AND INREGISTER
8	(("multi-factorial" OR multifactorial) NEAR7 (trial OR stud*)) AND INREGISTER
9	(network NEAR2 trial) AND INREGISTER
10	(network NEAR2 stud*):ti AND INREGISTER
11	(additional NEAR2 (arm* OR drug* OR agent* OR treatment* OR intervention*)): TI,AB AND INREGISTER
12	"candidate agents": TI,AB AND INREGISTER
13	(new NEAR2 (arm* OR drug*)): TI,AB AND INREGISTER
14	(different NEXT (agent* OR drug* OR treatment*)): TI,AB AND INREGISTER
15	(multiple NEXT (agent* OR treatment* OR intervention*)): TI,AB AND INREGISTER
16	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15

CONTRIBUTIONS OF AUTHORS

CH: methodological expertise, and conception and writing of the protocol

SJV: clinical expertise, and conception and writing of the protocol

VP: methodological expertise, and conception and writing of the protocol

KLC: clinical expertise, and conception and writing of the protocol

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IM: development of the search strategy

SS: conception of the protocol

ET: methodological expertise

MP: clinical expertise and advice

EMW: clinical expertise and advice

CS-O: clinical expertise and advice

DJR: clinical expertise and advice

ZM: clinical expertise and advice

NS: methodological expertise and advice, and conception and writing of the protocol

NK: methodological expertise, and conception and writing of the protocol

DECLARATIONS OF INTEREST

CH: none known

SJV: is receiving a PhD scholarship from the not-for-profit Sanquin blood bank.

VP: none known

KLC: none known

LJE: is a consultant haematologist for NHS Blood and Transplant.

IM: none known

SS: is funded by the Federal Ministry of Education and Research, Germany (NaFoUniMedCovid19, funding number: 01KX2021; part of the project "COVIM", which was paid to the institution). I have participated in a study on kinetics of the neutralising antibody response to SARS-CoV-2 (www.biorxiv.org/content/10.1101/2021.01.26.428207v1). In this review, I will not be involved in risk of bias assessment, data extraction or interpretation, but will serve as content expert.

ET: none known

MP: none known

EMW: none known

CS-O: has declared to be employed by the not-for-profit Sanquin blood bank.

DJR: is a consultant haematologist for NHS Blood and Transplant.

ZM: is a haematologist at Monash University.

NS: none known

NK: is funded by the Federal Ministry of Education and Research, Germany (NaFoUniMedCovid19, funding number: 01KX2021; part of the project "COVIM", which was paid to the institution).

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Internal sources

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- NHS Blood and Transplant, UK
- Monash University Australia, Australia

  Transfusion Research Unit, Department of Epidemiology and Preventive Medicine
- Haematology Society of Australia and New Zealand, Australia

  Leukaemia Foundation and HSANZ Australia

External sources

- Federal Ministry of Education and Research, Germany

  NaFoUniMedCovid19 (funding number: 01KX2021); part of the project 'COVIM'
- CEOsys, Germany

  The CEOsys project is funded under a scheme issued by the Network of University Medicine (Nationales Forschungsnetzwerk der Universitätsmedizin (NUM)) by the Federal Ministry of Education and Research of Germany (Bundesministerium für Bildung und Forschung (BMBF))

NOTES

Parts of the review's background and methods sections are reproduced from templates of Cochrane Haematology and two similar protocols published by Valk 2021 and Kreuzberger 2021.