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Hyperimmune immunoglobulin for people with COVID-19 (Protocol)

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Hyperimmune immunoglobulin for people with COVID-19

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ABSTRACT

Objectives

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

Using a living systematic review approach, to assess whether hyperimmune immunoglobulin therapy is effective and safe in the treatment of people with COVID-19; and to maintain the currency of the evidence.

BACKGROUND

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Description of the condition

This review was previously part of a parent review addressing convalescent plasma and hyperimmune intravenous immunoglobulins (hereafter referred to as hyperimmune immunoglobulins or hIVIG) for people with COVID-19 (Piechotta 2021). The review has been split to address hIVIG and convalescent plasma separately. Therefore, parts of this background text are shared between the two reviews. Specific adaptations related to hyperimmune immunoglobulin have been made.

The clinical syndrome coronavirus disease 2019 (COVID-19) is a new, rapidly emerging zoonotic infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; WHO 2020a). On 22 March 2020, the World Health Organization (WHO) declared the current COVID-19 outbreak to be a pandemic, with the outbreak resulting in more than 181 million confirmed cases and over 3.9 million deaths worldwide (WHO 2020b; WHO 2021a). Although there are similarities with historic coronavirus epidemics, with severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) responsible for 813 and 858 deaths respectively, the scale and impact of the COVID-19 pandemic presents unprecedented challenges to health facilities and healthcare workers all over the world (WHO 2007; WHO 2019).

Approximately 5% of people with COVID-19, and 20% of those hospitalised, experience severe disease requiring intensive care (Wiersinga 2020). Early reports suggested case fatality rates between 0.7% and 4% (WHO 2020a; WHO 2020c). More recent reports estimate wide-ranging case fatality rates, as low as 0.0% in Singapore and up to 9.0% in Mexico (Johns Hopkins 2021). However, these numbers should be interpreted with great care due to testing availability, underreporting of cases, and delays from confirmation of a case to time of death (Kim 2020), and factors associated with ethnicity, underlying health conditions, access to health care, and socioeconomic status (Williamson 2020).

The median incubation period of SARS-CoV-2 was reported to be five days, with 97.5% of cases developing symptoms within 11.5 days of infection (Lauer 2020). Common signs and symptoms can include fever, dry cough, fatigue, and sputum production (WHO 2020a). Post-viral olfactory dysfunction is reported in 5% to 85% of cases, with loss of both smell and taste reported (Izquierdo-Dominguez 2020). Other less commonly reported signs and symptoms are shortness of breath, sore throat, headache, myalgia or arthralgia, chills, nausea or vomiting, nasal congestion, diarrhoea, haemoptysis, and conjunctival congestion (WHO 2020a). Of the reported cases, 80% are estimated to have a mild or asymptomatic course of infection, and an estimated 5% of cases are admitted to an intensive care unit (ICU) with acute respiratory distress syndrome (ARDS), septic shock, multiple organ failure, or all three conditions (NCPERE 2020; WHO 2020a). A risk factor for developing infection and progressing to severe disease is old age, with people aged over 80 years at the highest risk of mortality. Other risk factors are cardiovascular disease, obesity, hypertension, diabetes, chronic respiratory disease, cancer, and compromised immune status (Chen 2020a; Huang 2020; Liang 2020; WHO 2020a; Wu 2020a). Early 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, with people with malignancy and recipients of solid organ and allogeneic stem cell transplants reported to have an increased risk of severe COVID-19 disease (Fung 2020; Sharma 2021).

There are indications that the SARS-CoV-2 virus is capable of inducing an excessive immune reaction in the host, with highly activated but decreased numbers of T cells detected in the blood of people with COVID-19 (Xu 2020a). Early reports also showed that people critically ill with COVID-19 frequently exhibit an increased tendency to form blood clots, vascular inflammation, and elevated coagulation markers known as a hypercoagulable state (Maatman 2020). This hypercoagulable state is hypothesised to lead to the high burden of thromboembolic events seen in this population, with pulmonary embolism being the most common (Driggin 2020).

SARS-CoV-2 can infect people by binding to the angiotensin-converting enzyme 2 (ACE2), which functions as the viral receptor. ACE2 facilitates the entry of SARS-CoV-2 into the host cell and is most abundant on type II alveolar cells in the lungs (Tolouian 2020; Van de Veerdonk 2020).

Description of the intervention

Hyperimmune immunoglobulin (hIVIG) has been used to treat infections when no vaccine or pharmacological intervention is available. hIVIG is made from pools of human or animal donor serum with high neutralising titres (da Costa 2021). These hyperimmune sera contain polyclonal antibodies, which are concentrates of heterologous immunoglobulins, formed by intact IgG (immunoglobulin G, one of the five major classes of immunoglobulins) molecules or antigen-binding antibody fragments (da Costa 2021).

hIVIG provides passive immunisation with a level of therapeutic antibody that is more concentrated than convalescent plasma alone. Following an infection, antibodies are produced within B cell lineages exposed to antigens from the virus. These cells then produce immunoglobulins specific to different viral components. Preparations of hIVIG can be extracted from large amounts of pooled convalescent plasma, collected from people previously infected or vaccinated against the virus. Plasma may be obtained by separation of whole blood or by plasmapheresis. Alternatively, viral-specific antibodies can be injected with an adjuvant into a humanised animal modified to generate antibodies similar to those made naturally in humans.

Plasma from either source is then fractionated or extracted and purified to obtain the hIVIG preparation. Measures are then undertaken for viral inactivation or removal, which can include pasteurisation, solvent or detergent and low pH incubation and filtration. Regulatory oversight stipulates minimum viral reduction steps in the manufacturing process, which vary across countries (Bloch 2021). In 2020, a group of large plasma industry companies formed a plasma alliance to work together to develop hIVIG to be used in the treatment of COVID-19 (Farrugia 2020).

There is conflicting evidence about the effect of hIVIG for treating severe acute respiratory infections. Studies investigating the effectiveness of hIVIG for influenza have been contradictory, with at least one randomised controlled trial (RCT) showing effectiveness (Hung 2013), whereas another shows no benefit (Davey 2019). hIVIG

has also been used in treatment of coronaviruses (including SARS-CoV-1 and MERS-CoV) (da Costa 2021). In a systematic review, hIVIG has been found to be effective against cytomegalovirus in solid organ recipients (Bonaros 2008).

Apart from use in treatment of infections, hIVIG is also used to prevent infections in high-risk individuals or used as pre-exposure or post-exposure prophylaxis; for example, for varicella-zoster virus (PHE 2019).

A potential benefit of hIVIG over monoclonal antibody therapy is the diversity of antibodies obtained from a pool of donors. hIVIG may provide a wider range of specificity than monoclonal antibodies, be more effective in the setting of emerging variants, and provide a wide range of antiviral actions at relatively cheaper costs (Vandeberg 2021).

Benefits of hIVIG in comparison to convalescent plasma include lower volume, a higher concentration of antibody titre, the possibility of administration as an intramuscular injection (instead of intravenous infusion), and more convenience in storage and shipping conditions, allowing for more ease of transport (Bloch 2021). When compared to convalescent plasma, hIVIG also has the advantage of preventing the transfer of potentially harmful coagulation factors that are present in plasma products. The amount and antibody concentration can be more accurately dosed compared to convalescent plasma, and hyperimmune immunoglobulin can be prepared in a consistent manner (Hung 2013).

Not many studies have reported on adverse events of hIVIG, but the safety profile of standard intravenous immunoglobulin is known, and the adverse events reported here are also likely to occur in hIVIG therapy. These include: infusion site pain; swelling and erythema; and immediate systemic reactions, such as head and body aches, chills, and fever (Stiehm 2013). Other, less common, early adverse reactions to immunoglobulin therapy are pulmonary complications, such as pulmonary embolism, pulmonary oedema, and pleural effusion, with transfusion-related acute lung injury (TRALI) also reported (Baudel 2020; Stiehm 2013). Anaphylactic and anaphylactoid reactions to immunoglobulin therapy are rare (Brennan 2003; Stiehm 2013). Delayed adverse events of immunoglobulin therapy, which occur within hours to days of initiation of immunoglobulin therapy, are persistent headaches (common), aseptic meningitis, renal failure, thromboembolic events, and haemolytic reactions (Sekul 1994; Stiehm 2013). Transmission of infectious agents has been described after administration of intravenous immunoglobulin, but this risk is considered to be low (Stiehm 2013). Other severe adverse events that occur late after administration are lung disease, enteritis, and dermatological disorders (Stiehm 2013).

A theoretical risk related to virus-specific antibodies, which are transferred with hIVIG administration, is an antibody-dependent enhancement of infection (Morens 1994). Here, virus-binding antibodies facilitate the entry and replication of virus particles into monocytes, macrophages, and granulocytic cells, and thereby increase the risk of more severe disease in the infected host. Antibody-dependent enhancement has not been demonstrated in people who have recovered and become reinfected with COVID-19, and there have been no reports of antibody-dependent enhancement in studies on monoclonal antibodies, convalescent plasma, or following COVID-19 vaccination. However, antibody-dependent enhancement has been seen with previous coronavirus infections when the antibodies given targeted a different serotype of the virus (Wan 2020; Wang 2014). The circulation of COVID-19 variants could increase the risk of antibody-dependent enhancement when the intervention contains antibodies targeting parts of the virus that are different from the original strain. Antibody-dependent enhancement is therefore a potentially harmful consequence of hIVIG therapy for COVID-19.

Further definitions of the terms used in this description can be found in the glossary of abbreviations and medical terms (Appendix 1).

In summary, the benefits of the intervention should be carefully considered in view of the risks of adverse events.

How the intervention might work

Hyperimmune immunoglobulin contains pathogen-specific neutralising antibodies, which can neutralise viral particles, and treatment with hIVIG confers passive immunity to recipients. The duration of conferred protection can differ depending on the timing of administration, ranging from weeks to months after treatment (Casadevall 2020).

By neutralising SARS-CoV-2 particles, early treatment with convalescent plasma, and by extrapolation hIVIG, is postulated to increase the individual's own capacity to clear the initial infection (Casadevall 2020; Robbins 1995). This could lead to a reduction in mortality and fewer hospitalised people progressing to the ICU, thus helping to lift pressure from global healthcare systems and increasing ICU capacity.

Preliminary evidence in humans and rhesus macaques has shown that reinfection with SARS-CoV-2 is not likely, with most (but not all) individuals who recovered from COVID-19 producing sufficient amounts of neutralising antibodies to protect against reinfection (Bao 2020; Wu 2020b). This implies that hIVIG made from convalescent plasma of people who have recovered from SARS-CoV-2 infection may be capable of conferring passive immunity. Retrospective studies also observed a potential correlation between the level of antibody titres in convalescent plasma and recovery after treatment (Joyner 2021; Shen 2020). It is important to note, however, that research in other coronavirus species has shown that immunity may not be long-lasting, with two to three years of protection estimated from work with SARS and MERS (Mo 2006; Payne 2016). Furthermore, there are indications that the severity of infection has an impact on antibody titres, with less severe disease leading to lower neutralising antibody response in people with SARS and COVID-19 (Ho 2005; Zhao 2020a). And, it is unclear exactly how often reinfection occurs, with the burden of reinfection likely to be underestimated, while at the same time a number of case reports of severe reinfection have been published (Iwasaki 2021).

Why it is important to do this review

There is a clear, urgent need for more information to guide clinical decision-making for people with COVID-19. Pharmacological treatment options are being investigated in many ongoing trials: currently, only treatment of dexamethasone and tocilizumab is proven to be effective in reducing mortality (Ghosn 2021; Horby 2020), and remdesivir and REGN-COV2 (the brand name of Regeneron Pharmaceuticals antibody cocktail Casirivimab/

imdevimab) are shown to reduce time to recovery (Beigel 2020; Horby 2021). The current treatment further consists of supportive care with extracorporeal membrane oxygenation in severe cases and oxygen supply in less severe cases (CDC 2020; WHO 2020d; WHO 2020f). Despite these treatments, people hospitalised with COVID-19 are still at a high risk of mortality. hIVIG could potentially be used alongside these treatments in ambulatory or hospitalised settings, if it proves to be effective and safe.

While our recent systematic review showed that convalescent plasma for the treatment of moderate to severe COVID-19 does not reduce mortality and has little to no impact on measures of clinical improvement (Piechotta 2021), we remain very uncertain about the efficacy of convalescent plasma in people with asymptomatic or mild disease. Therefore, it is important to continue to assess the possible effect of hIVIG and other antibody therapies on people with COVID-19, particularly in the early phase, and their potential role in specific subgroups of individuals.

Mass vaccination programmes have been underway since late 2020 (WHO 2020b). Until these vaccines are globally distributed, hIVIG may be a potential therapy for people with COVID-19. Even with effective vaccines, not everyone can be effectively vaccinated; for example, people who are temporarily or permanently immune-compromised, and very young children. hIVIG can be prepared and made available when enough potential donors have recovered from the infection, using readily available materials and methods (Bloch 2020). However, its safety and efficacy are not well-characterised, and there are costs associated with pursuing the use of hIVIG for treatment of COVID-19.

Several clinical trials investigating the safety and effectiveness of hIVIG have been announced, and their results will need to be interpreted with care. Thus, there needs to be a thorough understanding of the current body of evidence regarding the use of hIVIG for people with COVID-19, and an extensive review of the available literature is required.

OBJECTIVES

Using a living systematic review approach, to assess whether hyperimmune immunoglobulin therapy is effective and safe in the treatment of people with COVID-19; and to maintain the currency of the evidence.

METHODS

Criteria for considering studies for this review

Types of studies

The main description of methods is based on the standard template of the Cochrane Haematology review group and is in line with the parent review of this series, addressing convalescent plasma and hyperimmune immunoglobulins for people with COVID-19 (Piechotta 2021). We made specific adaptations related to the research question, we updated the methods slightly in light of the evolving research knowledge.

To assess the effectiveness and safety of hyperimmune immunoglobulins for the treatment of COVID-19, we will include RCTs, as such studies, if performed appropriately, give the best evidence for experimental therapies in highly controlled therapeutic settings. For RCT data, we will use the methods recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021a, hereafter referred to as the *Cochrane Handbook*), as specified in the description of the methods. If we identify non-standard RCT designs, such as cluster-randomised trials and cross-over trials, we plan to include those, and apply the methods recommended in Chapter 23 of the *Cochrane Handbook* (Higgins 2021b). We will consider only the results from the first cycle of cross-over RCTs.

We will include full-text publications, pre-print articles, abstract publications, and results published in trials registries, if sufficient information is available on study design, characteristics of participants, interventions, and outcomes. We will not apply any limitation with respect to the length of follow-up.

Types of participants

We will include individuals with a suspected or confirmed diagnosis of COVID-19, with no age, gender, or ethnicity restrictions.

We will include trials that included participants with any disease severity. We will perform separate analyses for populations with ambulatory mild disease and for hospitalised participants with moderate to severe disease, according to the latest WHO clinical progression score (see Table 1; WHO 2020e).

We will exclude studies including populations with other coronavirus diseases (SARS or MERS). We will also exclude studies of populations with mixed viral diseases (e.g. influenza) unless the trial authors provide subgroup data for people with COVID-19.

Types of interventions

We will include the following interventions.

- Human hyperimmune immunoglobulin therapy.
- Hyperimmune animal sera containing polyclonal antibodies.

These include polyclonal immunoglobulin therapies containing full-length antibodies or fragment antibodies, and may be sourced from convalescent humans or immunised animals (including bovine, equine, rabbit, chicken, or other animal sources).

We will not include studies on: standard immunoglobulin (from non-convalescent donors) except as comparator; monoclonal antibodies; nanobodies; and microbodies.

We will not include studies of hIVIG used in healthy individuals to prevent COVID-19.

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

- Hyperimmune immunoglobulin therapy versus control treatment; for example, drug treatments (including but not limited to hydroxychloroquine and remdesivir). Co-interventions are allowed but must be comparable between intervention groups.
- Hyperimmune immunoglobulin therapy versus standard care or placebo (i.e. saline solution).

Types of outcome measures

We evaluated core outcomes, as predefined by the Core Outcome Measures in Effectiveness Trials (COMET) Initiative for people

with COVID-19 (COMET 2020), and additional outcomes that have been prioritised by consumer representatives, referees of previous versions of this review (Piechotta 2021), and the German guideline panel for inpatient therapy of people with COVID-19.

We defined outcome sets for two populations: individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease, and individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease, according to the WHO clinical progression scale (WHO 2020e).

Primary outcomes

These critical outcomes will be included in the summary of findings table.

Individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease

- All-cause mortality at day 28, day 60, time-to-event, and at hospital discharge
- Clinical status, at day 28, day 60, and up to longest follow-up, including the following:
  - Worsening of clinical status: participants with clinical deterioration (new need for invasive mechanical ventilation) or death.
  - Improvement of clinical status: participants discharged alive. Participants should be discharged without clinical deterioration or death.
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100, a standardised scale for assessing quality of life) at up to 7 days, up to 28 days, and longest follow-up available
- Adverse events (any grade, grade 1-2, grade 3-4), defined as the number of participants with any event and including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, transfusion-associated circulatory overload (TACO), transfusion-associated dyspnoea (TAD), acute transfusion reactions, headache, thromboembolic events)
- Serious adverse events, defined as the number of participants with any event

Individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease

- All-cause mortality at day 28, day 60, time-to-event, and at longest follow-up
- Admission to hospital or death within 28 days
- Symptom resolution:
  - All initial symptoms resolved (asymptomatic) at day 14, day 28, and up to longest follow-up
  - Duration to symptom resolution
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to 7 days, up to 28 days, and longest follow-up available
- Adverse events (any grade, grade 1-2, grade 3-4), defined as the number of participants with any event and including the potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions, headache, thromboembolic events)
- Serious adverse events, defined as the number of participants with any event

Secondary outcomes

These important outcomes will not be included in the summary of findings table.

Individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease

- Clinical status at day 28, day 60, and up to longest follow-up, including:
  - Worsening of clinical status:
    - ☐ New need for invasive mechanical ventilation;
    - ☐ New need for non-invasive mechanical ventilation or high flow;
    - ☐ New need for oxygen by mask or nasal prongs.
  - Improvement of clinical status:
    - ☐ Weaning or liberation from invasive mechanical ventilation in surviving patients;
    - ☐ Ventilator free days;
    - ☐ Duration to liberation from invasive mechanical ventilation;
    - ☐ Liberation from supplemental oxygen in surviving patients;
    - ☐ Duration to liberation from supplemental oxygen.
- Need for dialysis at up to 28 days
- Admission to the intensive care unit (ICU) on day 28
- Duration of hospitalisation
- Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 14 days

Individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease

- Clinical status at day 28 and up to longest follow-up, including:
  - Worsening of clinical status (moderate to severe COVID-19 symptoms):
    - ☐ Need for invasive mechanical ventilation;
    - ☐ Need for non-invasive mechanical ventilation or high flow;
    - ☐ Need for hospitalisation with the need for oxygen by mask or nasal prongs;
    - ☐ Need for hospitalisation without oxygen therapy.
- Viral clearance, assessed with RT-PCR for SARS-CoV-2 at baseline, up to 3, 7, and 14 days

Timing of outcome measurement

For time-to-event outcomes, such as mortality, discharge from hospital, and improvement of clinical symptoms, we will include outcome measures representing the longest follow-up time available.

We will include all other outcome categories for the observational periods that the study publications report. We will include those adverse events occurring during active treatment, and long-term adverse events as well. If sufficient data are available, we plan to 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 (15 days after treatment) and longer-term outcomes (over 30 days after treatment).

Search methods for identification of studies

Electronic searches

We will search electronic databases according to methods suggested in the *Cochrane Handbook* (Lefebvre 2021). Studies reported in all languages are eligible, in order to limit language bias. If studies are published in languages other than those our review team can accommodate (English, Dutch, German, French, Italian, Malay, and Spanish), we will involve Cochrane Task Exchange to identify people within Cochrane to translate these studies.

As publication bias might influence all subsequent analyses and conclusions, we will search all potentially relevant trials registries in detail to detect ongoing as well as completed, but not yet published, studies. If outcome data are not available elsewhere, we will extract any outcome data found in the trial registry entry.

We will search the following databases and sources from 1 January 2019.

Databases of medical literature

- MEDLINE (Ovid, from 1 January 2019; Appendix 2)
- Embase (Ovid, from 1 January 2019; Appendix 3)
- Cochrane COVID-19 Study Register (covid-19.cochrane.org; from inception; Appendix 4)*
- PubMed (for e-publications ahead of print only; from 1 January 2019; Appendix 5)
- World Health Organization COVID-19 Global literature on coronavirus disease (https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/; from inception) without references of MEDLINE and PubMed; Appendix 6)
- Epistemonikos, L*OVE List Coronavirus disease (COVID-19) (app.iloveevidence.com/loves; from inception; Appendix 7)

*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. Complete data sources and search methods for the register are available at: community.cochrane.org/about-covid-19-study-register. The register contains study reports from several sources, including:

- daily searches of PubMed;
- daily searches of ClinicalTrials.gov;
- 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).

Living systematic review considerations

We will carry out weekly searches for completed and ongoing studies. We will check weekly for newly emerging hyperimmune immunoglobulins, and review search methods and strategies approximately monthly, to ensure they reflect any terminology changes in the topic area, or in the databases. We will adapt the strategy where necessary.

Searching other resources

We will handsearch the reference lists of all identified studies. We will also contact experts in the field, drug manufacturers, and regulatory agencies in order to retrieve information on unpublished studies.

Living systematic review considerations

The signal for updating this review will stem from weekly monitoring of the published relevant RCTs via the database search, as described under “Electronic searches”. Once the decision to update the review has been made, the methods mentioned in this section will be incorporated in the review update.

Data collection and analysis

Selection of studies

Using Covidence software, two review authors (from among SJV, KLC, VP, CK, CI, and NS) will independently screen for eligibility the results of the search strategies, by reading the abstracts. We will code the abstracts as either 'retrieve' or 'do not retrieve'. In the case of disagreement, or if it is unclear whether we should retrieve the abstract or not, we will obtain the full-text publication 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 a third review author 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 numbers of retrieved references and the numbers of included and excluded studies. We will list all studies excluded after full-text assessment, and the reasons for their exclusion, in the Characteristics of excluded studies table.

Living systematic review considerations

Two review authors will screen records derived from weekly searches to identify new studies.

Data extraction and management

Two review authors (from among SJV, KLC, VP, CK, and CI) 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 to reach a final decision.

Two review authors (from among SJV, KLC, CK, CI, and VP) will extract data using a customised data extraction form, developed in Microsoft Excel (Microsoft Corporation 2018). Another review author (CI, VP, or NS) will verify the accuracy and (where applicable) the plausibility of extractions and assessment. We will conduct data extraction according to the guidelines proposed by Cochrane (Li 2021). If the review authors are unable to reach a consensus, we will consult a third review author. All extracted data will be summarised in tables or appendices.

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.

- General information: author, title, source, publication date, country, language, duplicate publications.
- Quality assessment: study design, confounding, definition of risk estimates, bias arising from the randomisation process: due to deviations from the intended interventions; due to missing outcome data; in measurement of the outcome; and in selection of the reported results.
- 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, disease, severity of disease, additional diagnoses, baseline serostatus, previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation), whether the donors were tested by nasal swabs or whether the plasma was tested.
- Interventions: hyperimmune immunoglobulin therapy, concomitant therapy, duration of follow-up, donors' disease severity, methods of hyperimmune immunoglobulin preparation, whether hyperimmune immunoglobulin dosage was adjusted based on batch-dependent neutralising antibody levels.
  * For studies including a control group: comparator (type).
- Outcomes: as specified in Types of outcome measures.

Living systematic review considerations

Two review authors will extract, evaluate, and integrate studies identified through the weekly searches.

Assessment of risk of bias in included studies

We will use the risk of bias 2 (RoB 2) tool to analyse the risk of bias in the underlying study results (Sterne 2019). Of interest for this review is the effect of the assignment to the intervention (the intention-to-treat (ITT) effect), and we will perform all assessments with RoB 2 to this effect. The outcomes that we will address are those specified for inclusion in 'Summary of findings and assessment of the certainty of the evidence'.

Two review authors (from among SJV, KLC, VP, CK, CI and NS) will independently assess the risk of bias for each study result. In case of discrepancies between their judgements or 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* (Higgins 2021c).

- 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-RCTs, we plan to 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 2016), and in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021b).

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 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 unfulfilled 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 unfulfilled 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 these levels of bias:

- low risk of bias;
- some concerns;
- high risk of bias.

Subsequently, we will derive a risk of bias rating for each pre-specified outcome in each study in accordance with the following suggestions.

- 'Low risk of bias': we judged the trial to be at low risk of bias for all domains for this result.
- 'Some concerns': we judged 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 on the riskofbiasinfo.org website); we will add our judgements to the analysis for each assessed study and outcome; and we will store our detailed RoB 2 assessments as supplementary online material. We will use the overall risk of bias judgement, derived from the RoB 2 Excel tool, to inform our GRADE decision on downgrading for risk of bias.

Measures of treatment effect

For continuous outcomes, we will record the mean, standard deviation, and total number of participants in both the treatment and control groups. For dichotomous outcomes, we will record the number of events and total number of participants in both the treatment and control groups.

For continuous outcomes using 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.

If available, we will extract and report hazard ratios (HRs) for time-to-event outcomes (e.g. discharge from hospital). If HRs are not available, we will make every effort to estimate the HR as accurately as possible using the available data and a purpose-built method based on the Parmar and Tierney approach (Parmar 1998; Tierney 2007). If sufficient studies provided HRs, we will use HRs rather than risk ratios (RRs) or MDs in a meta-analysis.

For dichotomous outcomes, we plan to report the pooled RR and risk difference (RD) with the associated 95% CIs (Deeks 2019). If the number of observed events is small (less than 5% of sample per group), and if studies have balanced treatment groups, we plan to report the Peto odds ratio (OR) with 95% CI (Deeks 2019).

Unit of analysis issues

As recommended in Chapter 6 of the *Cochrane Handbook* (Higgins 2021d), for studies with multiple treatment groups, we plan to combine arms if they can be regarded as subtypes of the same intervention.

When arms cannot be pooled this way, we plan to compare each arm with the common comparator separately. For pair-wise meta-analysis, we plan to split the 'shared' group into two or more groups with smaller sample sizes, and include two or more (reasonably independent) comparisons. For this purpose, for dichotomous outcomes, both the number of events and the total number of participants will be divided up, and for continuous outcomes, the total number of participants will be divided up with unchanged means and standard deviations (SDs).

Dealing with missing data

When we identify missing data at the study level, we will contact principal investigators and request these data. If, after this, data are still missing, we will consult with content experts to judge whether data are missing at random (e.g. if missing outcomes were balanced across study arms, reasons for lost to follow-up are common and reasonable) or not. If we judge data to be missing at random, we will perform a complete case analysis and exclude the participants with missing outcome data from the analysis (Guyatt 2017). When we judge data to be not missing at random, and we identify no supporting evidence that the results were not biased by missing outcome data, we will not make any assumptions about the missing outcome data. We will conduct sensitivity analyses to assess the impact of missing data on the overall effect. We will discuss the potential impact of its absence on the results.

Assessment of heterogeneity

We will assess heterogeneity of treatment effects between trials using a Chi^2 test with a significance level at P less than 0.1, and visual examination. We will use the I^2 statistic (Higgins 2003), to quantify possible heterogeneity (I^2 > 30% to signify moderate heterogeneity, I^2 > 75% to signify considerable heterogeneity; Deeks 2019). If heterogeneity is above 80%, we will explore potential causes through subgroup analyses. If we find a reason for heterogeneity, we will not perform a meta-analysis, but we will comment on results from all studies and present these in tables.

Assessment of reporting biases

As mentioned above, we will search trials registries to identify completed studies that have not been published elsewhere, to minimise or determine publication bias. We will include studies irrespective of their publication status, as recommended in Chapter 3 of the *Cochrane Handbook* (McKenzie 2021).

We will 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 studies (Page 2021). We will consider a P value of less than 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 meta-analysis. We will perform separate analyses for populations with ambulatory mild disease and for hospitalised participants with moderate to severe disease, according to the latest WHO clinical progression score (WHO 2020e). We will perform analyses according to the recommendations in Chapter 10 of the *Cochrane Handbook* (Deeks 2019). We will not conduct meta-analyses that include different study designs. We will conduct separate meta-analyses for each comparison.

We will use the RevMan Web 2020 software for analyses (RevMan Web 2020). 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 for included studies, true effects would be related, but would not be the same. For binary outcomes, we will base the estimation of the between-study variance using the Mantel-Haenszel method. We will use the inverse variance method for continuous outcomes, outcomes that include data from cluster-RCTs, or outcomes where HRs are available. We plan to explore heterogeneity above 80% with subgroup analyses. If we cannot find a cause for the heterogeneity or if study outcomes are too clinically heterogeneous to be combined, we will not perform a meta-analysis, but comment on the results in a narrative analysis, with the results from all studies presented in tables.

Living systematic review considerations

Whenever new evidence (studies, data, or information) that meets the review inclusion criteria is identified, we will immediately assess the risk of bias and extract the data and incorporate it in the synthesis, as appropriate. We will not adjust the meta-analyses to account for multiple testing, given the methods related to frequent updating of meta-analyses are under development (Simmonds 2017).

Subgroup analysis and investigation of heterogeneity

We will perform subgroup analyses of the following characteristics for the outcome of mortality.

- Severity of condition (divided into moderate and severe disease; divided into participants receiving invasive mechanical ventilation at baseline or not).
- Duration since symptom onset (divided into up to 7 days and more than 7 days).
- Antibodies in recipients detected at baseline; that is, seropositive or seronegative (divided into detected in a

maximum of 20% of recipients versus detected in at least 80% of recipients).
- Age of participants (divided into applicable age groups; e.g. children; 18 to 65 years, 65 years and older).
- Pre-existing conditions (diabetes, respiratory disease, hypertension, immunosuppression).
- SARS-CoV-2 variants (e.g. B1.1.7, B.1.351, P.1, and other variants that may occur in the future).
- Concentration of neutralising antibodies in the therapy (i.e. with known concentration of neutralising antibodies by taking into account batch-dependent neutralising antibody levels, or with unknown concentration).

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

Sensitivity analysis

We will perform sensitivity analyses for the following.

- 'Risk of bias' assessment components (studies with a low risk of bias or some concerns versus studies with a high risk of bias).
- Impact of completed, but not published, studies.
- Impact of premature termination of studies.
- Impact of studies that include individuals with suspected COVID-19.
- Fixed-effect model meta-analysis.
- Impact of missing outcome data.

Summary of findings and assessment of the certainty of the evidence

We will use the GRADE approach to assess the certainty of the evidence for the following outcomes, and we will prepare one summary of findings table per population.

Individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease

- All-cause mortality; all-cause mortality at hospital discharge most favourable. If not reported, all-cause mortality day 60, followed by day 28, or time-to-event estimate, will be included in the summary of findings table.
- Worsening of clinical status at day 28:
  * Participants with clinical deterioration (new need for invasive mechanical ventilation) or death.
- Improvement of clinical status at day 28:
  * Participants discharged alive. Participants should be discharged without clinical deterioration or death.
- Quality of life, including fatigue and functional independence; assessed with standardised scales (e.g. WHOQOL-100) at longest follow-up available
- Any adverse events during the study period
- Serious adverse events during the study period

Individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease

- All-cause mortality; all-cause mortality at longest follow-up and greater than 60 days most favourable. If not reported, all-cause mortality day 60, followed by day 28, or time-to-event estimate, will be included in the summary of findings table.
- Admission to hospital or death within 28 days
- Symptom resolution:
  * All initial symptoms resolved (asymptomatic) at day 14;
  * Duration to symptom resolution. Quality of life, including fatigue and functional independence; assessed with standardised scales (e.g. WHOQOL-100) at longest follow-up available
- Any adverse events during the study period
- Serious adverse events during the study period

We will follow the current GRADE guidance in its entirety for these assessments, as recommended in Chapter 14 of the *Cochrane Handbook* (Schünemann 2021). We will use GRADEpro GDT software to create a summary of findings table (Schünemann 2021). For RCTs, 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 assess the certainty of the evidence for non-controlled non-randomised studies of interventions (NRSIs) as reported in the GRADE guidance 3, starting from low-certainty evidence (Balshem 2011). For time-to-event outcomes, we will calculate absolute effects at specific time points, as recommended in the GRADE guidance 27 (Skoetz 2020). We will phrase the findings and certainty of the evidence as suggested in the informative statement guidance (Santesso 2020). For binary data, we will report relative and absolute risk differences.

Methods for future updates - living systematic review considerations

We will update our searches to monitor newly published results of RCTs on hyperimmune immunoglobulins on a weekly basis. Two review authors will screen, extract, evaluate, and integrate information following the guidance for Cochrane living systematic reviews (Brooker 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 of the critical outcomes.
- The credibility (e.g. GRADE rating) of one or more of the critical outcomes.
- New settings, populations, interventions, comparisons, or outcomes studied.

When review methods will be reviewed

We will check the review 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 or outcomes, or new review methods, become available).

The conditions under which the review will no longer be maintained as a living systematic review (LSR)

In our regular review of the scope, we will decide whether to continue or stop updating the review. Decisions to stop may be that the conclusions for our main outcomes and populations of interest are unlikely to change with future studies included in the review,

no new evidence is expected, or the review question is no longer a priority for policy and practice.

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ADDITIONAL TABLES

Table 1. WHO clinical progression scale

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalised: moderate disease	Hospitalised; no oxygen therapy[a]	4
	Hospitalised; oxygen by mask or nasal prongs	5

Table 1. WHO clinical progression scale *(Continued)*

Hospitalised: severe disease	Hospitalised; oxygen by non-invasive mechanical ventilation or high flow	6
	Intubation and mechanical ventilation; $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$	7
	Invasive mechanical ventilation; $pO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors	8
	Invasive mechanical ventilation; $pO_2/FiO_2 < 150$ and vasopressors, dialysis or ECMO	9
Dead	Dead	10

World Health Organization (WHO) clinical progression scale from: WHO 2020e
[a]If hospitalised for isolation only, record status as for ambulatory patient.
Abbreviations: ECMO: extracorporeal membrane oxygenation; FiO_2: fraction of inspired oxygen; pO_2: partial pressure of oxygen; SpO_2: oxygen saturation

APPENDICES

Appendix 1. Glossary of abbreviations and medical terms

Abbreviations

ACE2 - angiotensin-converting enzyme 2, a protein on the surface of many cells in the body

ARDS – acute respiratory distress syndrome, severe inflammation of the lungs following infection or injury

GRADE - Grading of Recommendations, Assessment, Development and Evaluation, a method of assessing the level of certainty about clinical evidence

hIVIG – hyperimmune intravenous immunoglobulin, the intervention of interest in this review

IgG - immunoglobulin G, one of the five major classes of immunoglobulins

MERS - Middle East respiratory syndrome, a coronavirus disease related to COVID-19

NRSI - non-randomised study of an intervention, a trial which compares two or more groups, but patients are not assigned to the groups randomly

pH - power of hydrogen, a standard scale for measuring acidity

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses, a standard set of items that should appear within a systematic review

REGN-COV2 – brand name of Regeneron Pharmaceuticals antibody cocktail Casirivimab/imdevimab, used to treat COVID-19

RoB 2 - Risk of bias 2, a tool for assessing the methodological quality of included studies

SARS – severe acute respiratory syndrome, a coronavirus disease related to COVID-19

SARS-CoV-2 - severe acute respiratory syndrome coronavirus 2, the virus that causes COVID-19

TACO - transfusion-associated circulatory overload, a serious transfusion reaction, defined as acute or worsening swelling in the lungs during transfusion, or up to 12 hours afterwards. Alongside this, there can be cardiovascular changes which are caused by the transfusion and not by a patient's underlying condition.

TAD - transfusion-associated dyspnoea, difficulty in breathing caused by the body reacting to transfusion

TRALI - transfusion-related acute lung injury, a serious transfusion reaction defined as a new and sudden lung injury, occurring within six hours of transfusion

WHO – World Health Organization, the United Nations agency dedicated to health promotion

WHOQOL-100 - a 100-question standardised scale for assessing quality of life

Medical terms relating to hIVIG

Antibody-dependent enhancement - a phenomenon where antibody treatment may cause the symptoms caused by the virus to be more severe

Antibody titre - the level of concentration of antibodies in blood or plasma

Antigen-binding antibody fragments / fragment antibodies - antibodies that have been manipulated in a laboratory to make a smaller molecule

Anaphylactic reaction - a serious allergic reaction involving the IgE-producing cells in the immune system

Anaphylactoid reaction - a serious allergic reaction not involving the IgE-producing cells in the immune system

T cells - cells in the immune system produced in the thymus

Coagulation factors - proteins in the blood which control bleeding

Convalescent plasma - plasma from a person who has recovered from COVID-19, containing the antibodies they made to the disease

Erythema - skin redness caused by inflammation of small blood vessels

Granulocytic cells - a type of immune cell which secretes enzymes during infection

Haemolytic reaction - a serious reaction to transfusion, where the recipient's body destroys the donated cells

Hyperimmune animal sera - a product containing antibodies extracted and produced from animals immunised with live virus

Macrophages - a type of white blood cell which removes dead cells

Microbodies - antibodies that have been manipulated in a laboratory to be smaller and more consistent

Monoclonal antibody therapy - a type of antibody originating from identical B-cells, produced in a laboratory

Monocytes - the largest type of white blood cell

Nanobodies - antibodies that have been manipulated in a laboratory to be smaller and more consistent

Pathogen-specific neutralising antibodies - antibodies to a specific illness, which prevent virus cells from entering healthy cells in the body

Pleural effusion - build up of fluid around the lungs

Polyclonal antibodies - a mixture of several antibodies, which originate from different B-cells, and is prepared in a laboratory

Post-exposure prophylaxis - a treatment given to someone who has come into contact with COVID-19 but does not have the disease, to prevent them from becoming ill

Pre-exposure prophylaxis - a treatment given to someone who does not have COVID-19 but might come into contact with it in the future, to prevent them from becoming ill

Pulmonary embolism - a blood clot in the lungs

Pulmonary oedema - fluid in the lungs

Seronegative - the patient does not have detectable antibodies to the virus in their blood

Seropositive - the patient has detectable antibodies to the virus in their blood

Standard intravenous immunoglobulin - a product produced from donated plasma, containing antibodies

Transfusion-transmitted infection - an infection caused by bacteria, virus, or parasite in a donated blood product

Appendix 2. Search strategy MEDLINE

#	Searches
1	Coronavirus Infections/ or Coronavirus/
2	SARS-CoV-2/ or COVID-19/
3	("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.
4	((corona* or corono*) adj1 (virus* or viral* or virinae*)).tw,kf.
5	"severe acute respiratory syndrome coronavirus 2".tw,kf,nm.
6	(anti-flu* or anti-influenza* or antiflu* or antinfluenza*).tw,kf.
7	or/1-6
8	Plasma/
9	Immunoglobulins/
10	Immunoglobulins, Intravenous/
11	Immune Sera/
12	((convalesc* or recovered or cured or rehabilitat* or survivor* or survived or virus-positive or virus neutrali* or virus inactivated or antibod* or high-titre* or high-titer*) adj6 (plasma or blood or serum or sera)).mp.
13	((plasma adj1 therap*) or gamma-globulin* or "γ-Globulin" or hyper-Ig).tw,kf.
14	(hyperimmune* or hyper-immune*).mp.
15	(high-dos* adj3 (plasma or immunoglobulin* or IVIG* or immune globulin* or globulin* or IgG)).tw,kf.
16	(plasma adj5 (immun* or antibod* or exchange* or donor* or donat* or transfus* or infus*)).mp.
17	((convalesc* or recovered or cured or rehabilitat* or survivor* or survived or virus-positive or virus inactivated or antibody-positive) adj5 (donor* or donat*)).mp.
18	(serum or sera or serotherap* or sero-therap*).tw,kf.
19	exp Immunization, Passive/
20	(passiv* adj3 (antibod* transfer* or immunization* or immunotherap* or immuno-therap* or vaccin*)).tw,kf.
21	((immunoglobulin* or immune globulin*) adj2 (therap* or treatment* or neutrali?ing or prevent* or protect* or prophylax*)).tw,kf.
22	hIVIG.tw,kf.
23	(XAV-19 or SAB-185 or equine or INM005 or CSL760).tw,kf.
24	(IGY-110 or IGY110 or GIGA-2050 or GIGA2050).tw,kf.
25	(GC5131 or 5131A).tw,kf.
26	(((anti-coronavirus or anticoronavirus) adj1 immunoglobulin*) or ITAC).tw,kf.
27	("Hyperimmune anti-COVID-19 IVIG" or C-IVIG or CIVIG).tw,kf.
28	(equine polyclonal antibod* or EpAbs).tw,kf.
29	Flebogamma.tw,kf.
30	or/8-29
31	7 and 30

32 "Covid-19 Serotherapy".px.

33 (Flu-IVIG or ((anti-flu* or anti-influenza* or antiflu* or antinfluenza*) adj5 plasma)).mp.

34 or/31-33

35 exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/

36 ((control and (group* or study)) or (time and factors) or program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp.

37 or/35-36

38 (animals/ not humans/) or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/

39 hi.fs. or case report.mp.

40 or/38-39

41 37 not 40

42 randomized controlled trial.pt.

43 controlled clinical trial.pt.

44 randomi?ed.ab.

45 placebo.ab.

46 drug therapy.fs.

47 randomly.ab.

48 trial.ab.

49 groups.ab.

50 or/42-49

51 exp animals/ not humans/

52 50 not 51

53 clinical trial, phase iii/

54 ("Phase 3" or "phase3" or "phase III" or P3 or "PIII").ti,ab,kw.

55 (53 or 54) not 51

56 52 or 55

57 34 and (41 or 56)

58 limit 57 to yr="2019 -Current"

Appendix 3. Search strategy Embase

#	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 (anti-flu* or anti-influenza* or antiflu* or antifluenza*).tw,kw.

10 or/1-9

11 Plasma Transfusion/

12 exp Immunoglobulin/

13 ((convalesc* or recovered or cured or survivor* or survived or rehabilitat* or virus-positive or virus-neutrali* or virus inactived or antibody-rich or high-tire* or high-titer*) adj6 (plasma or blood or serum or sera)).mp.

14 ((plasma adj1 therap*) or gamma-globulin or "y-Globulin" or hyper-lg).tw,kw.

15 (plasma adj5 (immun* or antibod* or exchange* or donor* or donat* or transfus* or infus*)).mp.

16 (hyperimmune* or hyper-immune*).mp.

17 (high-dos* adj3 (plasma or immunoglobulin* or IVIG* or immune globulin* or globulin* or IgG)).tw,kw.

18 ((convalesc* or recovered or cured or rehabilitat* or survivor* or survived or virus-positive or virus inactivated or antibody-positive) adj5 (donor* or donat*)).mp.

19 (serum or sera or serotherap* or sero-therap*).tw,kw.

20 passive immunization/

21 (passiv* adj3 (antibod* transfer* or immuni?ation* or immunotherap* or immuno-therap* or immunit* transfer* or vaccin*)).tw,kw.

22 passive immunit*.tw,kw.

23 ((immunoglobulin* or immune globulin*) adj2 (therap* or treatment* or neutrali?ing or prevent* or protect* or prophylax*)).tw,kw.

24 hIVIG.tw,kw.

25 (CSL760 or INM005 or XAV-19 or SAB-185 or equine).tw,kw.

26 (IgY-110 or IgY110 or GIGA-2050 or GIGA2050).tw,kw.

27 (GC5131 or 5131A).tw,kw.

28 (((anti-coronavirus or anticoronavirus) adj1 immunoglobulin*) or ITAC).tw,kw.

29 ("Hyperimmune anti-COVID-19 IVIG" or C-IVIG or CIVIG).tw,kw.

30 (equine polyclonal antibod* or EpAbs).tw,kw.

31 flebogamma.tw,kw.

32 or/11-31

33 (Flu-IVIG or ((anti-flu* or anti-influenza* or antiflu* or antinfluenza*) adj5 plasma)).mp.

34 Clinical study/

35 (cross sectional adj (study or studies)).tw.

36 exp longitudinal study/

37 exp prospective study/

38 exp follow up/

39 cohort*.tw.

40 exp case control study/

41 (case* and control*).tw.

42 or/34-41

43 Randomized controlled trial/

44 Controlled clinical study/

45 random*.ti,ab.

46 randomization/

47 intermethod comparison/

48 placebo.ti,ab.

49 (compare or compared or comparison).ti.

50 (open adj label).ti,ab.

51 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.

52 double blind procedure/

53 parallel group$1.ti,ab.

54 (crossover or cross over).ti,ab.

55 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant $1)).ti,ab.

56 (controlled adj7 (study or design or trial)).ti,ab.

57 (volunteer or volunteers).ti,ab.

58 trial.ti.

59 or/43-58

60 phase 3 clinical trial/

61 ("Phase 3" or "phase3" or "phase III" or P3 or "PIII").tw,kw.

62 or/60-61

63 (10 and 32) or 33

64 63 and (42 or 59 or 62)

65 limit 64 to yr="2019 -Current"

Appendix 4. Search strategy Cochrane COVID-19 Study Register

plasma OR convalesc* OR serum OR sera OR donor* OR donation* OR serotherapy OR "sero-therapy" OR "flu-IVIG" OR antiflu* OR "anti-flu" OR hyperimmune* OR hyper-immune* OR IVIG OR immunoglobulin OR "immune-globulin" OR globulin OR "gamma-globulin" OR "γ-Globulin" OR "hyper-Ig" OR immunization OR immunisation OR immunotherap* OR CSL760 OR INM005 OR equine OR "XAV-19" OR "SAB-185" OR hIVIG OR equine OR INOSARS OR "GIGA-2050" or GIGA2050 OR "IGY-110" OR IGY1109 OR "GC5131" OR "5131A" OR ITAC OR "C-IVIG" OR CIVIG OR flebogamma OR EpAbs

Limits: treatment and management

Appendix 5. Search strategy PubMed

#1 "2019 ncov"[Title/Abstract] OR "2019nCoV"[Title/Abstract] OR "corona virus"[Title/Abstract] OR "corona viruses"[Title/Abstract] OR "Coronavirus"[Title/Abstract] OR "coronaviruses"[Title/Abstract] OR "COVID"[Title/Abstract] OR "COVID19"[Title/Abstract]

OR "ncov 2019"[Title/Abstract] OR "SARS-CoV2"[Title/Abstract] OR "SARS-CoV-2"[Title/Abstract] OR "SARSCoV2"[Title/Abstract] OR "SARSCoV-2"[Title/Abstract] OR "COVID-19"[MeSH Terms] OR "Coronavirus"[MeSH Terms:noexp] OR "SARS-CoV-2"[MeSH Terms] OR "COVID-19"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept]

#2 ("convalesc*"[Title/Abstract] OR "recovered"[Title/Abstract] OR "cured"[Title/Abstract] OR "rehabilitat*"[Title/Abstract] OR "survivor*"[Title/Abstract] OR "survived"[Title/Abstract] OR "virus-positive"[Title/Abstract] OR "virus neutrali*"[Title/Abstract] OR "virus inactivated"[Title/Abstract] OR "antibod*"[Title/Abstract] OR "high titre*"[Title/Abstract] OR "high titer*"[Title/Abstract]) AND ("plasma"[Title/Abstract] OR "blood"[Title/Abstract] OR "donor*"[Title/Abstract] OR "donat*"[Title/Abstract])

#3 ("plasma"[Title] AND ("immun*"[Title/Abstract] OR "transfus*"[Title/Abstract] OR "infus*"[Title/Abstract]))

#4 ("high dos*"[Title/Abstract] AND ("plasma"[Title/Abstract] OR "immunoglobulin*"[Title/Abstract] OR "ivig*"[Title/Abstract] OR "immune globulin*"[Title/Abstract] OR "globulin*"[Title/Abstract] OR "IgG"[Title/Abstract])

#5 "serum"[Title] OR "sera"[Title] OR "immunization, passive"[MeSH Terms] OR "hyperimmune"[Title/Abstract] OR "hyperimmunity"[Title/Abstract] OR "serotherap*"[Title/Abstract] OR "sero therap*"[Title/Abstract] OR "therapeutic plasma"[Title/Abstract] OR "plasma therapy"[Title/Abstract] OR "immune plasma"[Title/Abstract] OR "plasma exchange"[Title/Abstract] OR "gamma globulin*"[Title/Abstract] OR "gamma-Globulin"[Title/Abstract] OR "hyper-Ig"[Title/Abstract]

#6 ("passiv*"[Title/Abstract] AND (("antibod*"[All Fields] AND "transfer*"[All Fields]) OR "immunisation*"[All Fields] OR "vaccin*"[Title/Abstract] OR "immunization*"[All Fields] OR "immunotherap*"[All Fields] OR "immuno therap*"[All Fields] OR "vaccin*"[All Fields])

#7 ("immunoglobulin*"[Title] OR "immune globulin*"[Title]) AND ("therap*"[Title/Abstract] OR "treat*"[Title/Abstract] OR "prevent*"[Title/Abstract] OR "protect*"[Title/Abstract] OR "prophylax*"[Title/Abstract]))

#8 ("equine*"[Title/Abstract] OR "hivig*"[Title/Abstract] OR "c ivig*"[Title/Abstract] OR "XAV-19"[Title/Abstract] OR "5131A"[Title/Abstract] OR "equine polyclonal antibod*"[Title/Abstract] OR "EpAbs"[Title/Abstract] OR "flebogamma*"[Title/Abstract] OR (("anti-coronavirus"[Title/Abstract] OR "anticoronavirus"[Title/Abstract]) AND "immunoglobulin*"[Title/Abstract]))

#9 (("anti-coronavirus"[Title/Abstract] OR "anticoronavirus"[Title/Abstract]) AND "immunoglobulin*"[Title/Abstract])

#10 #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9

#11 (("anti flu*"[Title/Abstract] OR "anti influenza*"[Title/Abstract] OR "antiflu*"[Title/Abstract] OR "antinfluenza*"[Title/Abstract]) AND ("plasma*"[Title/Abstract])) OR ("flu ivig*"[Title/Abstract])

#12 #1 AND #10

#13 #11 OR #12

#14 ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])

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

#16 #13 NOT #14

#17 #15 AND #16 Filters: from 2020/1/1 - 3000/12/12

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

Advanced search; search fileds: title, abstract, subject

Search 1: (plasma OR convalesc* OR serum OR sera OR donor* OR donation* OR serotherapy OR "sero-therapy" OR "flu-IVIG" OR antiflu* OR "anti-flu" OR hyperimmune* OR hyper-immune* OR IVIG) AND (random* OR placebo OR RCT)

Search 2: (immunoglobulin OR immune-globulin OR globulin OR gamma-globulin OR γ-Globulin OR hyper-Ig) AND (random* OR placebo OR RCT)

Search 3: (immunization OR immunisation OR immunotherap*) AND (random* OR placebo OR RCT)

Search 4: (CSL760 OR INM005 OR equine OR "XAV-19" OR "SAB-185" OR hIVIG) AND (random* OR placebo OR RCT)

Search 5: (INOSARS OR "GIGA-2050" OR "GIGA2050" OR "IGY-110" OR "IGY1109" OR GC5131 OR 5131A OR ITAC OR C-IVIG OR CIVIG OR flebogamma OR EpAbs) AND (random* OR placebo OR RCT)

Appendix 7. Search strategy - Epistemonikos, L*OVE List Coronavirus disease (COVID-19)

by pico search: population: Covid-19: intervention: passive immunization

Prevention or treatment: passive immunization: convalescent plasma: primary studies: RCTs

Prevention or treatment: passive immunization: Immunoglobulin therapy: primary studies: RCTs

Prevention or treatment: passive immunization: heterologous antibodies: primary studies: RCTs

HISTORY

Date	Event	Description
30 August 2020	New search has been performed	Two RCTs, eight controlled NRSIs and nine non-controlled NRSIs included
30 August 2020	New citation required and conclusions have changed	Additional safety data included (more than 20,000 participants)
3 June 2020	New citation required and conclusions have changed	We included results from one RCT and three controlled NRSIs and added further safety data from non-controlled NRSIs.
31 May 2020	New search has been performed	We included eight new studies.

CONTRIBUTIONS OF AUTHORS

CK: clinical expertise, study selection, data extraction and assessment, and conception and writing of the manuscript

SJV: clinical expertise, study selection, data extraction and assessment, and conception and writing of the manuscript

KLC: clinical expertise, study selection, data extraction and assessment, and conception and writing of the manuscript

VP: methodological expertise, study selection, data extraction and assessment, and conception and writing of the manuscript

CI: methodological expertise, study selection, data extraction and assessment, and writing of the manuscript

IM: development of the search strategy

EMW: clinical expertise and advice

AL: clinical expertise and advice

DJR: clinical expertise and advice

ZM: clinical expertise and advice

CS-O: clinical expertise and advice

LJE: clinical expertise, and conception and writing of the manuscript

NS: methodological expertise, study selection, data extraction and assessment, and conception and writing of the manuscript

DECLARATIONS OF INTEREST

CK: none known

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

KLC: HSANZ Leukaemia Foundation PhD scholarship to support studies at Monash University. This is not related to the work in this review.

VP: none known

CI: none known

IM: none known

EMW: I have received funding support from the Australian Medical Research Future Fund for a trial of convalescent plasma. I was not involved in bias assessment, data extraction or interpretation, but served as a content expert.

AL: none known

DJR: investigator on the REMAP-CAP and RECOVERY trial. I was not involved in bias assessment, data extraction or interpretation, but served as a content expert.

ZM: I have received funding support from the Australian Medical Research Future Fund for a trial of convalescent plasma. I was not involved in bias assessment, data extraction or interpretation, but served as a content expert.

CS-O: is a member of the BEST Collaborative Clinical Study Group and Associate Editor for *Transfusion Medicine* journal. I was not involved in bias assessment, data extraction or interpretation, but served as a content expert.

LJE: co-lead of the COVID-19 immunoglobulin domain of the REMAP-CAP trial and investigator on the RECOVERY trial. I was not involved in bias assessment, data extraction or interpretation, but served as a content expert.

NS: none known

SOURCES OF SUPPORT

Internal sources

- Sanquin Blood Supply, Netherlands

  Center for Clinical Transfusion Research
- University Hospital of Cologne, Germany

  Cochrane Cancer, Department I of Internal Medicine
- Monash University, Australia

  Transfusion Research Unit, Department of Epidemiology and Preventive Medicine
- NHS Blood and Transplant, UK

  NHS Blood and Transplant
- Leukaemia Foundation and HSANZ, Australia

  Haematology Society of Australia and New Zealand (HSANZ)

External sources

- European Union's Horizon 2020 research and innovation programme, Belgium

  SUPPORTing high-quality evaluation of covid-19 convalescent plasma throughout EUROPE (Support-E)

NOTES

This review was previously part of 'Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review' (Piechotta 2021). The methodology for this review was developed concurrently with 'SARS-CoV-2-neutralising monoclonal antibodies for the treatment of COVID-19' (Kreuzberger 2021).