Out for blood: causal inference in clinical transfusion research

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Chapter 4

Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a rapid review

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Cochrane Database Syst Rev. 2020 May 14;5(5):CD013600

Abstract

Background

Convalescent plasma and hyperimmune immunoglobulin may reduce mortality in patients with respiratory virus diseases, and are currently being investigated in trials as a potential therapy for coronavirus disease 2019 (COVID-19). A thorough understanding of the current body of evidence regarding the benefits and risks is required.

Objectives

To assess whether convalescent plasma or hyperimmune immunoglobulin transfusion is effective and safe in the treatment of people with COVID-19.

Search methods

The protocol was pre-published with the Center for Open Science and can be accessed here: osf.io/dwf53

We searched the World Health Organization (WHO) COVID-19 Global Research Database, MEDLINE, Embase, Cochrane COVID-19 Study Register, Centers for Disease Control and Prevention COVID-19 Research Article Database and trials registries to identify ongoing studies and results of completed studies on 23 April 2020 for case-series, cohort, prospectively planned, and randomised controlled trials (RCTs).

Selection criteria

We followed standard Cochrane methodology and performed all steps regarding study selection in duplicate by two independent review authors (in contrast to the recommendations of the Cochrane Rapid Reviews Methods Group).

We included studies evaluating convalescent plasma or hyperimmune immunoglobulin for people with COVID-19, irrespective of disease severity, age, gender or ethnicity.

We excluded studies including populations with other coronavirus diseases (severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS)) and studies evaluating standard immunoglobulins.

Data collection and analysis

We followed recommendations of the Cochrane Rapid Reviews Methods Group regarding data extraction and assessment.

To assess bias in included studies, we used the assessment criteria tool for observational studies, provided by Cochrane Childhood Cancer. We rated the certainty of evidence using the GRADE approach for the following outcomes: all-cause mortality at hospital discharge, improvement of clinical symptoms (7, 15, and 30 days after transfusion), grade 3 and 4 adverse events, and serious adverse events.

Main results

We included eight studies (seven case-series, one prospectively planned, single-arm intervention study) with 32 participants, and identified a further 48 ongoing studies evaluating convalescent plasma (47 studies) or hyperimmune immunoglobulin (one study), of which 22 are randomised.

Overall risk of bias of the eight included studies was high, due to: study design; small number of participants; poor reporting within studies; and varied type of participants with different severities of disease, comorbidities, and types of previous or concurrent treatments, including antivirals, antifungals or antibiotics, corticosteroids, hydroxychloroquine and respiratory support.

We rated all outcomes as very low certainty, and we were unable to summarise numerical data in any meaningful way. As we identified case-series studies only, we reported results narratively.

Effectiveness of convalescent plasma for people with COVID-19

The following reported outcomes could all be related to the underlying natural history of the disease or other concomitant treatment, rather than convalescent plasma.

All-cause mortality at hospital discharge

All studies reported mortality. All participants were alive at the end of the reporting period, but not all participants had been discharged from hospital by the end of the study (15 participants discharged, 6 still hospitalised, 11 unclear). Follow-up ranged from 3 days to 37 days post-transfusion. We do not know whether convalescent plasma therapy affects mortality (very low-certainty evidence).

Improvement of clinical symptoms (assessed by respiratory support)
Six studies, including 28 participants, reported the level of respiratory support required; most participants required respiratory support at baseline. All studies reported improvement in clinical symptoms in at least some participants. We do not know whether convalescent plasma improves clinical symptoms (very low-certainty evidence).

Time to discharge from hospital
Six studies reported time to discharge from hospital for at least some participants, which ranged from four to 35 days after convalescent plasma therapy.

Admission on the intensive care unit (ICU)
Six studies included patients who were critically ill. At final follow-up the majority of these patients were no longer on the ICU or no longer required mechanical ventilation.

Length of stay on the ICU
Only one study (1 participant) reported length of stay on the ICU. The individual was discharged from the ICU 11 days after plasma transfusion.

Safety of convalescent plasma for people with COVID-19

Grade 3 or 4 adverse events
The studies did not report the grade of adverse events after convalescent plasma transfusion. Two studies reported data relating to participants who had experienced adverse events, that were presumably grade 3 or 4. One case study reported a participant who had moderate fever (38.9 °C). Another study (3 participants) reported a case of severe anaphylactic shock. Four studies reported the absence of moderate or severe adverse events (19 participants). We are very uncertain whether or not convalescent plasma therapy affects the risk of moderate to severe adverse events (very low-certainty evidence).

Serious adverse events
One study (3 participants) reported one serious adverse event. As described above, this individual had severe anaphylactic shock after receiving convalescent plasma. Six studies reported that no serious adverse events occurred. We are very uncertain whether or not convalescent plasma therapy affects the risk of serious adverse events (very low-certainty evidence).

Authors' conclusions

We identified eight studies (seven case-series and one prospectively planned single-arm intervention study) with a total of 32 participants (range 1 to 10). Most studies assessed the risks of the intervention; reporting two adverse events (potentially grade 3 or 4), one of which was a serious adverse event. We are very uncertain whether convalescent plasma is effective for people admitted to hospital with COVID-19 as studies reported results inconsistently, making it difficult to compare results and to draw conclusions. We identified very low-certainty evidence on the effectiveness and safety of convalescent plasma therapy for people with COVID-19; all studies were at high risk of bias and reporting quality was low.

No RCTs or controlled non-randomised studies evaluating benefits and harms of convalescent plasma have been completed. There are 47 ongoing studies evaluating convalescent plasma, of which 22 are RCTs, and one trial evaluating hyperimmune immunoglobulin. We will update this review as a living systematic review, based on monthly searches in the above mentioned databases and registries. These updates are likely to show different results to those reported here.

Plain language summary

Plasma from people who have recovered from COVID-19 to treat individuals with COVID-19

Background

Coronavirus (COVID-19) is a highly infectious respiratory illness caused by a new strain of virus. The outbreak has spread rapidly on a global scale. People infected with this virus may not show signs of the disease, others may develop symptoms, including fever, cough, shortness of breath and sore throat. In some people the infection is more severe and can cause severe breathing difficulties, leading to hospitalisation, admission to intensive care or death. Currently, no vaccine or specific treatment is available.

People who have recovered from COVID-19 develop natural defences to the disease in their blood (antibodies). Antibodies are found in part of the blood called plasma. Plasma from blood donated from recovered patients, which contains COVID-19 antibodies, can be used to make two preparations. Firstly,

convalescent plasma, which is plasma that contains these antibodies. Secondly, hyperimmune immunoglobulin, which is more concentrated, and therefore contains more antibodies.

Convalescent plasma and hyperimmune immunoglobulin have been used successfully to treat other respiratory viruses. These treatments (given by a drip or injection) are generally well-tolerated, but unwanted effects can occur.

What did we want to find?

We wanted to know whether plasma from people who have recovered from COVID-19 is an effective treatment for people with COVID-19, and whether this treatment causes any unwanted effects.

Our methods

We searched major medical databases for clinical studies on treatment with convalescent plasma or hyperimmune immunoglobulin for people with COVID-19. Studies could be conducted anywhere in the world and include participants of any age, gender or ethnicity, with mild, moderate or severe COVID-19.

COVID-19 is spreading rapidly, so we needed to answer this question quickly. This meant that we shortened some steps of the normal Cochrane Review process - only one review author extracted data from studies and assessed study quality; normally two review authors would do this.

Key results

We included eight completed studies, with 32 participants who received convalescent plasma. None of the studies randomly allocated participants to different treatments (randomised trials produce the best evidence). None of the studies included a group of people who did not receive convalescent plasma, as a comparison group.

All participants in the studies were alive at the end of follow-up, but not all had been discharged from hospital. Follow-up varied from 3 to 37 days after treatment with convalescent plasma.

Six studies used the level of breathing support that participants required as a measure of recovery. Breathing support included oxygen therapy, mechanical ventilation and the need for a special machine that oxygenates the blood. All six studies reported clinical improvement in at least some of their participants,

but it remains uncertain whether this improvement was related to convalescent plasma, another treatment, or the natural progression of the disease.

Six studies reported time to discharge from hospital for some of their participants, all of whom received convalescent plasma. The time to discharge ranged from 4 to 35 days after convalescent plasma treatment.

Six studies included participants with severe COVID-19. Most had improved at final follow-up, but this improvement may have been due to another treatment, the natural progression of the disease or convalescent plasma treatment.

Two participants reported unwanted effects related to convalescent plasma. One participant developed a fever, and a second participant experienced anaphylactic shock (severe allergic reaction) early on in the transfusion.

Certainty of the evidence

Our certainty (confidence) in the evidence was very limited because the studies were not randomised and did not use reliable methods to measure their results. Furthermore, they had only a small number of participants, who received various treatments alongside convalescent plasma, and some had underlying health problems.

Conclusion

We are very uncertain whether plasma from people who have recovered from COVID-19 is an effective treatment for people with COVID-19. The completed studies we found were poor quality and their results could be related to the natural progression of the disease, other treatments that the participants received, or to convalescent plasma. However, our searches found 48 ongoing studies: 47 evaluating convalescent plasma and 1 evaluating hyperimmune immunoglobulin, of which 22 are randomised. We will update this review with their results when these studies are completed.

Background

Description of the condition

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 11 March 2020, the World Health

Organization (WHO) declared the current COVID-19 outbreak a pandemic, with the outbreak resulting in almost 3.5 million cases and over 239,000 deaths worldwide (WHO 2020b; WHO 2020c). 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).

With a preliminary hospitalisation rate of 12.3 patients per 100,000 population in the USA, COVID-19 has taken a toll on healthcare capacity, and especially on intensive care unit (ICU) capacity (CDC 2020a). Early reports of the case fatality rate suggest that it ranges between of 0.7% to 4%, with higher rates also reported (WHO 2020a; WHO 2020c). However, these numbers should be interpreted with great care due to the data pertaining to the early emergency response, which due to shortage of test kits has led to selective testing of people with severe disease, underreporting of cases and delays from confirmation of a case to time of death (Kim 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). 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 the ICU with acute respiratory distress syndrome (ARDS), septic shock or multiple organ failure, or both (Team 2020; WHO 2020a). A risk factor for developing infection and progressing to severe disease is old age, with people aged over 80 years at highest risk of mortality. Other risk factors are cardiovascular disease, obesity, hypertension, diabetes, chronic respiratory disease, cancer and compromised immune status (Chen 2020; Huang 2020; Liang 2020; WHO 2020a; Wu 2020a).

SARS-CoV-2 is a positive-sense, single-stranded RNA (ribonucleic acid) virus with a large RNA genome. Although not much is known about the specific mechanisms underlying severe disease in COVID-19, there are indications that the virus is capable of inducing an excessive immune reaction in the host, with highly activated but decreased numbers of $CD4^+$ and $CD8^+$ T cells detected in the peripheral blood of people with COVID-19 (Xu 2020). Early reports also showed that people critically ill with COVID-19 frequently exhibit a hypercoagulable state and endothelial inflammation, which is hypothesised to lead to the high burden of thromboembolic

events seen in this population (Driggin 2020). Preliminary reports into the pathophysiology of SARS-CoV-2 have further indicated that the observed decrease in human angiotensin-converting enzyme 2 (ACE2) activity may play a role in causing the rapid deterioration of patient lung function (Tolouian 2020; Van de Veerdonk 2020). ACE2 is a protein that functions as the receptor facilitating entry of SARS-CoV-2 into the host cell, and is most abundant on type II alveolar cells in the lungs.

Description of the intervention

Convalescent plasma, convalescent serum and hyperimmune immunoglobulin prepared from convalescent plasma, are interventions that have been used in the past to treat conditions when no vaccine or pharmacological interventions were available. Diphtheria, pneumococcal pneumonia, hepatitis A and B, mumps, polio, measles and rabies are conditions where convalescent plasma has been shown to be effective (Eibl 2008).

A systematic review has shown that convalescent plasma may have clinical benefit for people with influenza and SARS (Mair-Jenkins 2015). This systematic review included observational studies and randomised controlled trials (RCTs) investigating the use of convalescent plasma, serum or hyperimmune immunoglobulin for treating severe acute respiratory infections of laboratory-confirmed or suspected viral aetiology, and included investigations with patients of any age and sex. Control interventions consisted of sham, or placebo, therapy and no therapy. The authors concluded that, although the included studies were generally small and of low quality, with a moderate to high risk of bias, the use of convalescent plasma may reduce mortality and appears safe (Mair-Jenkins 2015). The authors also suggested that the effectiveness of convalescent plasma in reducing hospital length of stay is dependent on early administration of the therapy, and use as prophylaxis is more likely to be beneficial than treating severe disease. However, the optimal timing and dosage of convalescent plasma therapy is unknown.

There is conflicting evidence about the effect of convalescent plasma or hyperimmune immunoglobulin for treating severe acute respiratory infections. Studies investigating the effectiveness of hyperimmune immunoglobulin for influenza have been contradictory, with some RCTs showing effectiveness (Hung 2013), whereas others show no benefit (Beigel 2017; Beigel 2019; Davey 2019).

Although convalescent plasma is generally thought to be a safe and well-tolerated therapy, adverse events can occur. Limited information is available about specific adverse events related to convalescent plasma therapy, but symptoms that have been reported are similar to those for other types of plasma blood

components, including fever or chills, allergic reactions, and transfusion-related acute lung injury (TRALI; Beigel 2019; Chun 2016; Luke 2006). Furthermore, the transfer of coagulation factors present in plasma products is potentially harmful for people with COVID-19, who are already at an increased risk of thromboembolic events (Driggin 2020). Plasma transfusions are also known to cause transfusion-associated circulatory overload (TACO). TACO and TRALI are especially important to consider, because COVID-19 patients with comorbidities, who might be eligible for experimental treatment with convalescent plasma therapy, are at an increased risk of these adverse events. There are risk-mitigation strategies that can be implemented to prevent TRALI. These include limiting donations from female donors, especially those with a history of pregnancy, and screening of donors for antibodies that are implicated in TRALI (Otrock 2017). In addition to the aforementioned adverse events, transfusion-transmitted infections, red blood cell alloimmunisation and haemolytic transfusion reactions have also been described following plasma transfusion, although they are less common (Pandey 2012). Pathogen inactivation can be implemented to decrease the risk of transmitting infections by transfusion (Rock 2011).

When compared to convalescent plasma, hyperimmune immunoglobulin has the advantage of preventing 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 hyperimmune immunoglobulin, but the safety profile of standard intravenous immunoglobulin is known and the adverse events reported here are also likely to occur in hyperimmune immunoglobulin therapy. Common adverse events of intravenous immunoglobulin that occur immediately after administration are: infusion site pain; swelling and erythaema; 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 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 convalescent plasma and hyperimmune immunoglobulin administration, is 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. Although antibody-dependent enhancement has not been demonstrated in COVID-19, it has been seen with previous coronavirus infections when the antibodies given targeted a different serotype of the virus (Wan 2020; Wang 2014). A mechanism for antibody-dependent enhancement in COVID-19 has recently been proposed, with non-neutralising antibodies to variable S domains potentially enabling an alternative infection pathway via Fc receptor-mediated uptake (Ricke 2020). Antibody-dependent enhancement is therefore a potentially harmful consequence of convalescent plasma and hyperimmune immunoglobulin therapy for COVID-19.

In summary, the benefits of the intervention, both for convalescent plasma or hyperimmune immunoglobulin, should be carefully considered in view of the risks of adverse events.

How the intervention might work

Convalescent plasma contains pathogen-specific neutralising antibodies, which can neutralise viral particles, and treatment with convalescent plasma or hyperimmune immunoglobulins 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 is postulated to increase the patient's own capacity to clear the initial inoculum (Casadevall 2020; Robbins 1995). This could lead to a reduction in mortality and fewer hospitalised patients progressing to the ICU. Furthermore, convalescent plasma may reduce the length of ICU stay in critically ill patients (Mair-Jenkins 2015), 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) patients who recovered from COVID-19 producing sufficient amounts of neutralising antibodies to protect against reinfection (Bao 2020; Wu 2020b). This implies that convalescent plasma from people who have recovered from SARS-CoV-2 infection is capable of conferring passive immunity. A recently reported case series also indicated

sufficient neutralising antibody titres in convalescent plasma to neutralise SARS-CoV-2 in five COVID-19 patients, who all recovered after treatment (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 2020).

Why it is important to do this review

There is a clear, urgent need for more information to guide clinical decision-making for COVID-19 patients. Pharmacological interventions have not yet proven to be effective, and current treatment consists of supportive care with extracorporeal membrane oxygenation in severe cases and oxygen supply in mild cases (CDC 2020b; WHO 2020d). A vaccine could aid in inducing immunity in the population and preventing transmission to those who are at risk for severe disease, but no vaccine is currently available, although multiple candidate vaccines are in development. Until these vaccines are available and distributed, convalescent plasma is a potential therapy for COVID-19 patients. Convalescent plasma, and hyperimmune immunoglobulin to a certain extent, can be prepared and made rapidly available by blood banks and hospitals 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 convalescent plasma for treatment of COVID-19.

A multitude of clinical trials investigating the safety and effectiveness of convalescent plasma or hyperimmune immunoglobulins 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 convalescent plasma for people with COVID-19, and an extensive review of the available literature is required.

Objectives

To assess whether convalescent plasma or hyperimmune immunoglobulin transfusion is effective and safe in the treatment of people with COVID-19.

Methods

Criteria for considering studies for this review

Types of studies

The protocol for this review was registered with the Center for Open Science (Piechotta 2020).

As planned at the protocol stage, we included prospective non-comparative study designs (e.g. case series), because there was no evidence from randomised controlled trials (RCTs), non-randomised studies of interventions (NRSIs), and only one prospective observational study available (please find further explanations in Appendix 1). We followed the suggestions specified in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019a), as far as possible, and applied the methodology outlined in the following sections. We considered studies including one or more participant(s) with coronavirus disease 2019 (COVID-19).

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

Types of participants

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

We excluded studies including populations with other coronavirus diseases (severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS)). We also excluded studies including populations with mixed virus diseases (e.g. influenza), unless the trial authors provided subgroup data for people with COVID-19.

Types of interventions

We included the following interventions.

- Convalescent plasma from people who recovered from SARS-CoV-2 infection
- Hyperimmune immunoglobulin therapy

We did not include studies on standard immunoglobulin.

In future updates we plan to include the following comparisons for studies with a control arm.

- Convalescent plasma versus standard care or placebo

- Convalescent plasma therapy versus control treatment, for example, drug treatments (including but not limited to hydroxychloroquine, remdesivir). Co-interventions will be allowed, but must be comparable between intervention groups.
- Convalescent plasma therapy versus hyperimmune immunoglobulin
- Hyperimmune immunoglobulin versus standard care or placebo
- Hyperimmune immunoglobulin versus control treatment, for example, drug treatments (including but not limited to hydroxychloroquine, remdesivir). Co-interventions will be allowed, but must be comparable between intervention groups.

Types of outcome measures

We evaluated core outcomes as pre-defined by the Core Outcome Measures in Effectiveness Trials Initiative for Covid-19 patients (COMET 2020).

Primary outcomes

Effectiveness of convalescent plasma for people with COVID-19

- All-cause mortality at hospital discharge
- Time to death

Secondary outcomes

Effectiveness of convalescent plasma for people with COVID-19

- Improvement of clinical symptoms, assessed by need for respiratory support at up to 7 days; 8 to 15 days; 16 to 30 days:
  - oxygen by mask or nasal prongs
  - oxygen by non-invasive ventilation (NIV) or high-flow
  - intubation and mechanical ventilation
  - mechanical ventilation plus high-flow oxygen
  - extracorporeal membrane oxygenation (ECMO)
- 30-day and 90-day mortality
- Time to discharge from hospital
- Admission on the ICU
- Length of stay on the ICU

Safety of convalescent plasma for people with COVID-19

- Number of participants with grade 3 and grade 4 adverse events, including potential relationship between intervention and adverse reaction (e.g. TRALI,

transfusion-transmitted infection, TACO, transfusion-associated dyspnoea (TAD), acute transfusion reactions)
- Number of participants with serious adverse events

Timing of outcome measurement

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

We included all other outcome categories for the observational periods that the study publications reported. We included those adverse events occurring during active treatment and had planned to include long-term adverse events as well. If sufficient data had been available, we planned 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 seven 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

We searched for studies in all languages in order to limit language bias. However, we prioritised articles in languages that our review team could accommodate (these are English, Dutch, German, French, Italian, Malay and Spanish). We did not seek translators for this version of the review. We tagged all references in additional languages as 'awaiting classification' and will seek translators via Cochrane TaskExchange in an update of this review.

Electronic searches

We designed and tested search strategies for electronic databases according to methods suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2019), CD developed them and Cochrane Haematology's Information Specialist (IM) peer reviewed them. In this emerging field, we expected that at least the abstract would be in English. If studies are published in other languages than those our review team could accommodate (English, Dutch, German, French, Italian, Malay and Spanish), we plan to involve Cochrane TaskExchange to identify people within Cochrane to translate these studies for an update of this review.

As publication bias might influence all subsequent analyses and conclusions, we searched all potential relevant trials registries in detail to detect ongoing as well as completed studies, but not yet published studies. Nowadays, it is mandatory

to provide results at least in the trials registry. In case results were not published elsewhere, we had planned to extract and analyse these data. However, no outcome data have yet been added to the trials registries (also stated in Differences between protocol and review).

We searched the following databases and sources, from 1 January 2019 to 23 April 2020.

- Databases of medical literature
  - WHO COVID-19 Global Research Database (search.bvsalud.org/global-research-on-novel-coronavirus-2019-ncov/advanced/?lang=en), searched 23 April 2020; Appendix 2
  - MEDLINE (Ovid, 1 January 2019 to 23 April 2020), Appendix 3
  - Embase (Ovid, 1 January 2019 to 23 April 2020), Appendix 4
  - PubMed (for epublications ahead of print only; searched 23 April 2020), Appendix 5
  - Center for Disease Control and Prevention COVID-19 Research Article Database (www.cdc.gov/library/researchguides/2019novelcoronavirus/databasesjournals.html; downloaded 22 April 2020), Appendix 6
  - Cochrane COVID-19 Study Register (covid-19.cochrane.org; searched 23 April 2020), Appendix 7
- Trials registries and registry platforms to identify ongoing studies and results of completed studies
  - ClinicalTrials.gov - COVID-19 Subset (clinicaltrials.gov/ct2/results?cond=COVID-19; searched 23 April 2020), Appendix 8
  - WHO International Clinical Trials Registry Platform (ICTRP) - COVID-19 Subset (www.who.int/ictrp/en); searched 23 April 2020), Appendix 9

Searching other resources

In an update of this rapid review we plan to:

- handsearch the reference lists of all identified studies, relevant review articles and current treatment guidelines for further literature; and
- contact experts in the field, drug manufacturers and regulatory agencies in order to retrieve information on unpublished studies.

Data collection and analysis

Selection of studies

Two out of four review authors (SJV, KLC, VP, NS) independently screened the results of the search strategies for eligibility for this review by reading the abstracts using Covidence software. We coded the abstracts as either 'retrieve'

or 'do not retrieve'. In the case of disagreement or if it was unclear whether we should retrieve the abstract or not, we obtained the full-text publication for further discussion. Two review authors assessed the full-text articles of selected studies. If the two review authors were unable to reach a consensus, they consulted a third review author to reach a final decision.

We documented 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 list all articles that we excluded after full-text assessment and the reasons for their exclusion in the Characteristics of excluded studies table.

Data extraction and management

One review author (SJV or KLC) performed all data extractions and assessments. Two other review authors (VP, NS) verified the accuracy and (where applicable) the plausibility of extractions and assessment.

One review author (VP or NS) assessed eligible studies obtained in the process of study selection (as described above) for methodological quality and risk of bias, the other review author verified the 'Risk of bias' assessment.

One review author (SJV or KLC) extracted data using a customised data extraction form developed in Microsoft Excel (Microsoft Corporation 2018); please see Differences between protocol and review). Another review author (NS) verified the accuracy and (where applicable) the plausibility of extractions and assessment. We conducted data extraction according to the guidelines proposed by Cochrane (Li 2019). If the review authors were unable to reach a consensus, we consulted a third review author (VP).

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

We extracted the following information.

- General information: author, title, source, publication date, country, language, duplicate publications
- Quality assessment: study design, confounding, definition of risk estimates, selection bias, attrition bias, detection bias, reporting bias
- 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, previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation)
- Interventions: convalescent plasma therapy or hyperimmune immunoglobulin therapy, concomitant therapy, duration of follow-up
  - For studies including a control group: comparator (type)
- Outcomes
  - Effectiveness of convalescent plasma for people with COVID-19:
    - all-cause mortality at hospital discharge
    - time to death
    - improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8 to 15 days; 16 to 30 days
    - 30-day and 90-day mortality
    - time to discharge from hospital
    - admission on the ICU
    - length of stay on the ICU
  - Safety of convalescent plasma for people with COVID-19:
    - number of participants with grade 3 and grade 4 adverse events, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions)
    - number of participants with serious adverse events

Assessment of risk of bias in included studies

If RCT data had been available, we had planned to use the Risk of Bias 2.0 (RoB 2) tool to analyse the risk of bias in the underlying study results (Sterne 2019). If non-randomised studies of interventions (NRSIs) data had been available, we had planned to use the Risk Of Bias in Non-randomised Studies - of Interventions (ROBINS-I) tool (Sterne 2016). Please refer to Appendix 1 for detailed information regarding how we had planned to assess the risk of bias of RCTs and NRSIs.

Non-controlled, prospectively planned studies

As specified in the Types of studies section we only included non-controlled prospective studies because we did not identify any controlled studies.

One review author (VP or NS) assessed eligible studies for methodological quality and risk of bias (using the 'Risk of bias' assessment criteria for observational studies tool provided by Cochrane Childhood Cancer (see Table 1; Mulder 2019). A second review author (VP or NS) verified the accuracy and the plausibility. Any 'Risk of bias' judgements were performed and presented per outcome per study.

The quality assessment strongly depends upon information on the design, conduct and analysis of the trial. The two review authors (VP, NS) resolved any disagreements regarding the quality assessments by discussion, in case of disagreement they would have consulted a third review author (SJV or KLC).

We assessed the following domains of bias.

- Internal validity
  - Unrepresentative study group (selection bias)
  - Incomplete outcome assessment/follow-up (attrition bias)
  - Outcome assessors unblinded to investigated determinant (detection bias)
  - Important prognostic factors or follow-up not taken adequately into account (confounding)
- External validity
  - Poorly defined study group (reporting bias)
  - Poorly defined follow-up (reporting bias)
  - Poorly defined outcome (reporting bias)
  - Poorly defined risk estimates (analyses)

For every criterion, we made a judgement using one of three response options.

- High risk of bias
- Low risk of bias
- Unclear risk of bias

Measures of treatment effect

Please refer to Appendix 1 for information regarding how we had planned to measure the treatment effects of RCTs and NRSIs.

Uncontrolled studies

For uncontrolled studies we did not carry out an analysis using quantitative data from indirect controls, as we are aware of the difficulties of indirect comparisons of participant groups with varying baseline characteristics, especially in the absence of individual patient data. Because authors of one-arm, non-comparative studies, often discuss their findings using information from other intervention and observational studies as implicit controls, we discussed our findings extensively in the context of what is known about the outcome of 'comparable' patients receiving other experimental treatments but not convalescent plasma therapy or hyperimmune immunoglobulin therapy. We did not meta-analyse the data but provided information from individual studies within tables.

Unit of analysis issues

As we identified uncontrolled studies only, meta-analysis was not appropriate. Instead, we narratively described and presented results per study in tables.

Please refer to Appendix 1 for information regarding how we had planned to combine studies with multiple treatment groups.

Dealing with missing data

Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* suggests a number of potential sources for missing data, which we will need to take into account: at study level, at outcome level and at summary data level (Higgins 2019b). In the first instance, it is of the utmost importance to differentiate between data 'missing at random' and 'not missing at random'.

We will request missing data from the study authors in an update of this review. If, after this, data are still missing, we will have to make explicit assumptions of 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

As we identified uncontrolled studies only, meta-analysis was not appropriate. Instead, we narratively described and presented results per study in tables.

Please refer to Appendix 1 for information regarding how we had planned to assess heterogeneity.

Assessment of reporting biases

As mentioned above, we searched trials registries to identify completed studies that have not been published elsewhere, to minimise or determine publication bias.

In an update of this review, we intend to explore potential publication bias by generating a funnel plot and statistically testing this by conducting a linear regression test (Sterne 2019), for meta-analyses involving at least 10 studies. We will consider $P < 0.1$ as significant for this test.

Data synthesis

Please refer to Appendix 1 for information regarding how we had planned to synthesise data from RCTs and NRSIs.

We did not meta-analyse data from uncontrolled trials, as there might be no additional benefit in meta-analysing data without a control group. We reported outcome data of each included trial within tables.

As data did not allow quantitative assessment, we presented outcome data individually per study within tables.

Subgroup analysis and investigation of heterogeneity

In an update of this review, we plan to perform subgroup analyses of the following characteristics.

- Age of participants (divided into applicable age groups, e.g. children; 18 to 65 years, 65 years and older)
- Severity of condition
- Pre-existing conditions (diabetes, respiratory disease, hypertension, immunosuppression)

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

Sensitivity analysis

In an update of this review, we will perform only one sensitivity analysis for the following.

- 'Risk of bias' assessment components (low risk of bias versus high risk of bias)

To assess the influence of study quality on an outcome, we will perform sensitivity analyses per outcome, comparing studies with at least one domain of high risk of bias to those without high risk of bias.

- Influence of completed, but not published studies
- Influence of premature termination of studies

Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach to assess the certainty of the evidence for the following outcomes (please find the rationale for the amendment of graded outcomes in the Differences between protocol and review).

- All-cause mortality at hospital discharge
- Time to death
- Clinical improvement (assessed by need for respiratory support) at the following time points
  - 7 days post-convalescent plasma transfusion
  - 15 days post-convalescent plasma transfusion

- 30 days post-convalescent plasma transfusion
- Grade 3 and 4 adverse events
- Serious adverse events

We used GRADEpro GDT software to create an 'evidence profile'. We will also use the GRADEpro GDT software to create a 'Summary of findings' table, as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* when results of controlled trials are available (Schünemann 2019).

Results

Description of studies

Results of the search

We identified 1267 potentially relevant references. After removing duplicates, we screened 1039 references based on their titles and abstracts, and we excluded 956 references that were irrelevant because they did not meet the prespecified inclusion criteria. We evaluated the remaining 83 references and screened the full texts, or, if these were not available, abstract publications or trials registry entries. Of these, we classified two studies as awaiting classification for this review (Qiu 2020; Tu 2020).

We identified 56 potentially eligible studies within 57 citations: eight completed studies (Ahn 2020; Duan 2020; Pei 2020; Shen 2020; Tan 2020; Ye 2020; Zhang 2020a; Zhang 2020b), and 48 ongoing studies (ChiCTR2000029757; ChiCTR2000029850; ChiCTR2000030010; ChiCTR2000030039; ChiCTR2000030179; ChiCTR2000030627; ChiCTR2000030702; ChiCTR2000030841; ChiCTR2000030929; ChiCTR2000031501; EUCTR2020-001310-38; IRCT20151228025732N53; IRCT20200310046736N1; IRCT20200325046860N1; IRCT20200404046948N1; IRCT20200409047007N1; IRCT20200413047056N1; NCT04264858; NCT04292340; NCT04321421; NCT04327349; NCT04332380; NCT04332835; NCT04333251; NCT04333355; NCT04338360; NCT04340050; NCT04342182; NCT04343261; NCT04343755; NCT04344535; NCT04345289; NCT04345523; NCT04345679; NCT04345991; NCT04346446; NCT04346589; NCT04347681; NCT04348656; NCT04348877; NCT04352751; NCT04353206; NCT04354831; NCT04355767; NCT04355897; NCT04356482; NCT04356534; NCT04357106). See PRISMA flow diagram (Figure 1; Moher 2009).

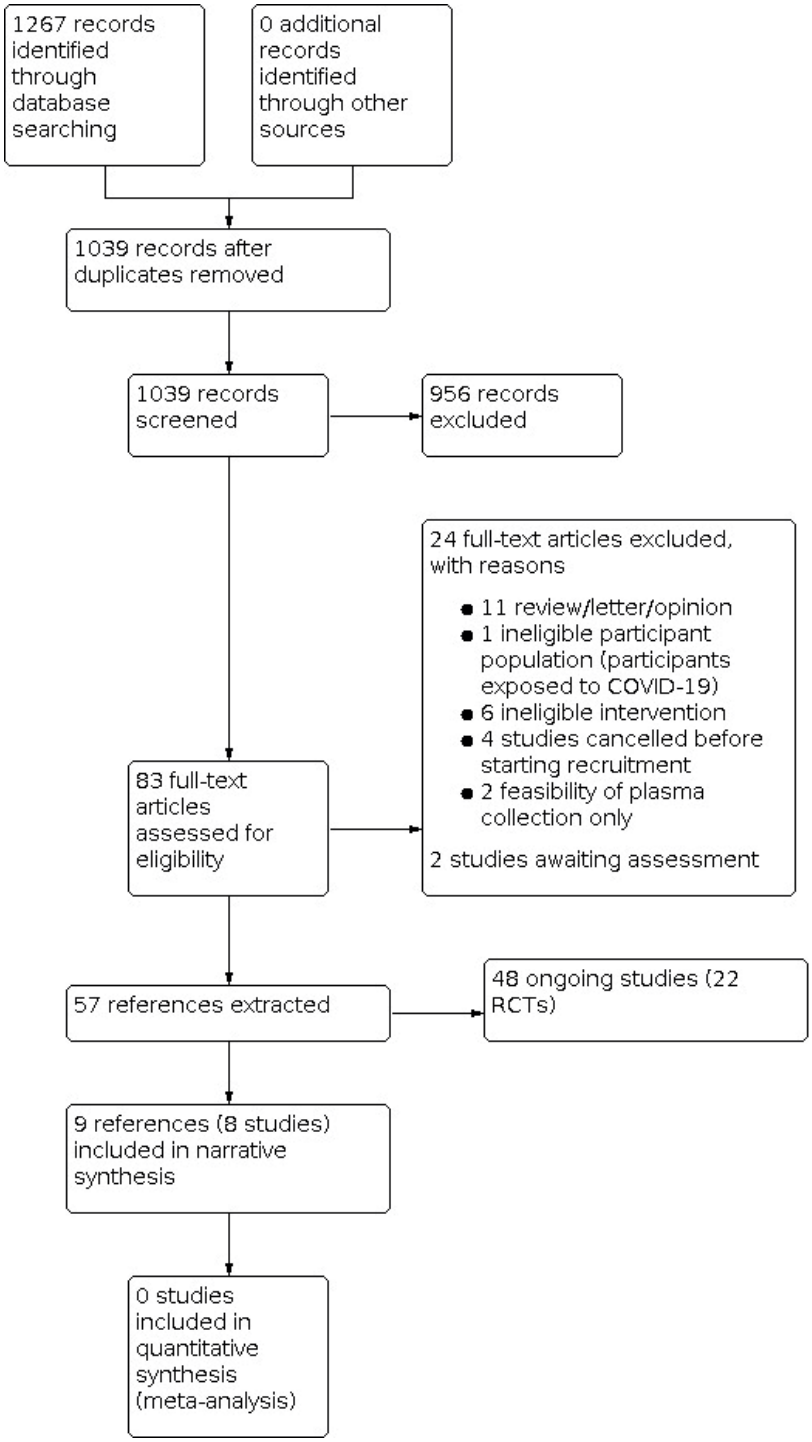

Figure 1.

Study flow diagram

Included studies

We included eight studies describing 32 participants in this review (Ahn 2020; Duan 2020; Pei 2020; Shen 2020; Tan 2020; Ye 2020; Zhang 2020a; Zhang 2020b). The eight included studies were all uncontrolled studies, seven studies were case series (Ahn 2020; Pei 2020; Shen 2020; Tan 2020; Ye 2020; Zhang 2020a; Zhang 2020b), and one was a prospectively registered single-arm intervention study (Duan 2020). Of the eight included studies, seven originated from China (Duan 2020; Pei 2020; Shen 2020; Tan 2020; Ye 2020; Zhang 2020a; Zhang 2020b), and one from South Korea (Ahn 2020). In seven of the eight studies, convalescent plasma was transfused in critically ill individuals (Ahn 2020; Duan 2020; Pei 2020; Shen 2020; Ye 2020; Zhang 2020a; Zhang 2020b). One study described a person with moderate disease severity (Pei 2020), and one study described a hospitalised participant with moderate disease severity (Tan 2020).

The dose, volume and timing of convalescent plasma varied greatly between studies. The total volume of convalescent plasma transfused varied between 200 mL and 2400 mL, with participants receiving between one to eight doses of plasma. Antibody titres were reported in four studies (Duan 2020; Pei 2020; Shen 2020; Zhang 2020b). Characteristics of the donors of convalescent plasma also varied between studies, although reporting was not complete. Out of the eight studies, only six reported information on plasma donors (Ahn 2020; Duan 2020; Pei 2020; Shen 2020; Ye 2020; Zhang 2020b). Most donors were male, but Pei 2020 included a female donor with a previous history of pregnancy. The age of the donors varied: Ahn 2020 included donors in their twenties; Shen 2020 included donors aged between 18 and 60 years; Duan 2020 included donors with a median age of 42 years; and Zhang 2020b included donors aged between 30 and 50. Some studies provided information on previously reported symptoms and disease severity of convalescent plasma donors (Ahn 2020; Duan 2020; Zhang 2020b). Ahn 2020 reported that the two included donors had been admitted to hospital with fever, cough and pneumonia. Duan 2020 reported that donors had been admitted to hospital, but no other information on severity of illness was available. Zhang 2020b reported that all six donors had fever and cough during the course of disease and were admitted to the hospital. In the five studies that reported assessment of donor recovery, all donors were symptom-free and completely recovered from coronavirus disease 2019 (COVID-19) prior to donating plasma (Ahn 2020; Duan 2020; Shen 2020; Ye 2020; Zhang 2020b). Four studies required a negative SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) test prior to convalescent plasma donation (Duan 2020; Shen 2020; Ye 2020; Zhang 2020b), with three studies requiring two consecutive negative results as a requirement for donation (Duan 2020; Ye 2020; Zhang 2020b). Four

studies used an enzyme-linked immunosorbent assay (ELISA) to quantify neutralising antibodies (Duan 2020; Pei 2020; Shen 2020; Zhang 2020b), with limited information available on the type of ELISA that was used. One study additionally used a plaque reduction neutralisation assay to assess the neutralising activity of the plasma (Duan 2020).

We had also planned to include studies on hyperimmune immunoglobulin therapy in this rapid review. However we did not identify any eligible studies.

Please refer to the Characteristics of included studies for more detailed information.

Ongoing studies

Of the 48 ongoing studies, 22 are RCTs (ChiCTR2000029757; ChiCTR2000030010; ChiCTR2000030179; ChiCTR2000030627; ChiCTR2000030702; ChiCTR2000030929; EUCTR2020-001310-38; IRCT20200310046736N1; IRCT20200404046948N1; IRCT20200409047007N1; IRCT20200413047056N1; NCT04332835; NCT04333251; NCT04342182; NCT04344535; NCT04345289; NCT04345991; NCT04345523; NCT04355767; NCT04346446; NCT04348656; NCT04356534).

Of these, 16 are expected to be completed in 2020 (ChiCTR2000030010; ChiCTR2000030179; ChiCTR2000030627; ChiCTR2000030702; ChiCTR2000030929; IRCT20200310046736N1; IRCT20200404046948N1; IRCT20200409047007N1; IRCT20200413047056N1; NCT04332835; NCT04342182; NCT04345523; NCT04345991; NCT04346446; NCT04348656; NCT04356534), and plan to evaluate between 15 and 1200 participants.

Two further large RCTs are planned to be completed in 2021: NCT04344535, randomising 500 participants and NCT04345289, evaluating 1500 participants.

Please refer to Characteristics of ongoing studies for more detailed information.

Excluded studies

We excluded 24 studies that did not match our inclusion criteria:

- 11 were a review of the literature, a letter or an opinion (Bloch 2020; Casadevall 2020; Chen 2020; Jawhara 2020; Roback 2020; Syal 2020; Tanne 2020; Tiberghien 2020; Wong 2020; Yoo 2020; Zhao 2020b);

- six studies were performed with an intervention other than convalescent plasma or hyperimmune immunoglobulin (Cao 2020; Díez 2020; Hu 2020; NCT04261426; Shi 2020; Xie 2020);
- four studies were cancelled by the investigator before recruiting participants into the study (ChiCTR2000030312; ChiCTR2000030381; ChiCTR2000030442; NCT04325672);
- two studies pertained to feasibility of collection of convalescent plasma only (NCT04344015; NCT04344977);
- one study included the wrong participant population (participants exposed to COVID-19; NCT04323800).

Risk of bias in included studies

Overall, we rated the risk of bias within and across studies to be serious. In addition to the high risk of bias due to the non-randomised study design, we assessed the internal and external validity as outlined in the 'Risk of bias' assessment criteria for observational studies tool provided by the Cochrane Childhood Cancer Group (see Additional Table 1; Mulder 2019). The full judgement per trial and category is presented in Figure 2 and the support for judgement in the Characteristics of included studies.

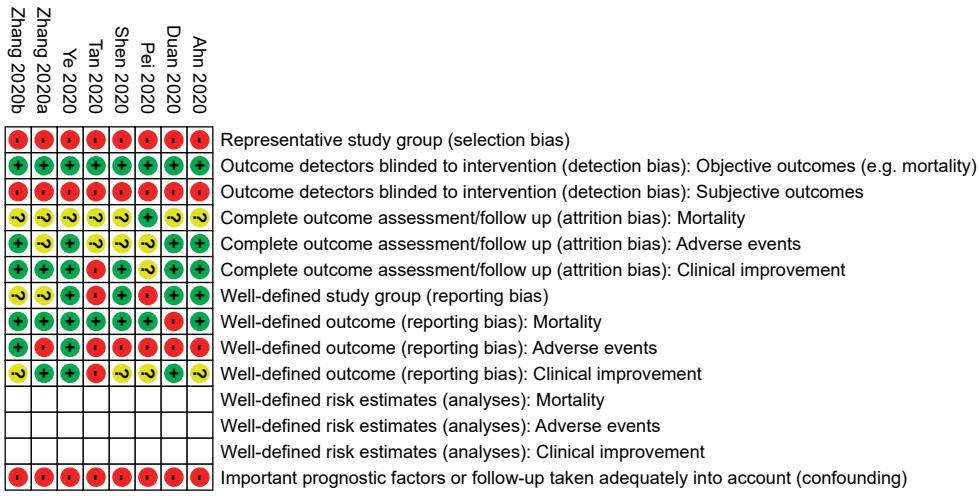

Figure 2.

'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study

Allocation

All studies were at high risk of selection bias. We considered study groups not to be representative, as all studies included low numbers of participants (1 to 10 participants) with no control groups.

Blinding

All studies were unblinded and therefore at high risk of performance and detection bias for subjective outcomes. All outcomes apart from all-cause mortality are subjective to a greater or lesser extent and therefore at risk of bias.

Incomplete outcome data

We assessed attrition bias in terms of whether studies (equally) assessed outcomes for all participants. We evaluated attrition bias for three outcome categories.

Mortality

All studies assessed this outcome until discharge from hospital or the latest point of follow-up. We judged the risk for attrition bias to be unclear for seven studies (Ahn 2020; Duan 2020; Shen 2020; Tan 2020; Ye 2020; Zhang 2020a; Zhang 2020b), because some participants were either still hospitalised or it was unclear whether participants had been discharged. Therefore the outcome for these participants is unknown.

We judged the risk for attrition bias to be low for one study (Pei 2020), as all participants had been free of disease and were discharged from the hospital.

Adverse events

We judged the risk of attrition bias to be low for four studies (Ahn 2020; Duan 2020; Ye 2020; Zhang 2020b), because they assessed and reported adverse events for all participants.

We judged the risk of attrition bias to be unclear for the other four studies (Pei 2020; Shen 2020; Tan 2020; Zhang 2020a), because it was unclear whether they had assessed adverse events for all participants or whether they had selectively reported outcomes. Pei 2020 reported one serious adverse event occurring in one participant, however did not report whether they had assessed or observed other adverse events. Shen 2020 did not provide any information regarding the safety of plasma transfusion. Tan 2020 reported that their participant experienced moderate fever after the transfusion, however did not report whether other adverse events occurred. Zhang 2020a described that they had observed no adverse events for one of their participants after plasma transfusion, but did not provide any information regarding the occurrence of adverse events for the other participants. They stated in the conclusions that they had not observed any serious adverse events.

Clinical improvements
We judged the risk of bias to be low for six studies (Ahn 2020; Duan 2020; Shen 2020; Ye 2020; Zhang 2020a; Zhang 2020b), because they assessed and reported clinical improvements for all participants.

We judged the risk of attrition bias to be high for one study (Tan 2020), because it was unclear why the participant was still hospitalised and they did not report clinical improvements.

Pei 2020 did not report the course of disease after convalescent plasma transfusion so we judged it at unclear risk of bias for this domain.

Selective reporting

We assessed reporting bias in terms of whether the study group and intervention were well-defined and whether the outcomes were equally reported for all participants and the length of follow-up was mentioned.

Well-defined study group and intervention
We judged the risk of reporting bias to be low for four studies (Ahn 2020; Duan 2020; Shen 2020; Ye 2020), because both the study population and intervention were well described.

Zhang 2020a described the study population, but reported only limited information on the intervention. Zhang 2020b provided clear information on the intervention, but scarcely described the participant. We therefore judged the risk of reporting bias to be unclear for these two studies.

We judged the risk of bias to be high for two studies (Pei 2020; Tan 2020), which only reported limited information on the study population and the intervention. However, Pei 2020 was a preprint only, and claimed that the patient characteristics would be provided in the supplementary material once published.

Well-defined outcomes
We evaluated reporting bias for three outcome categories.

Mortality
We judged the risk for reporting bias to be low for seven studies (Ahn 2020; Pei 2020; Shen 2020; Tan 2020; Ye 2020; Zhang 2020a; Zhang 2020b), because all reported information for this outcome per participant until discharge from hospital or the latest point of follow-up.

We judged the risk for reporting bias to be high for Duan 2020 because the follow-up was unclear and it was unclear whether all participants were free of disease and discharged.

Adverse events

We judged the risk of reporting bias to be low for two studies (Ye 2020; Zhang 2020b), because observation period and results were reported for all participants.

We judged the risk of reporting bias to be high for the other six studies (Ahn 2020; Duan 2020; Pei 2020; Shen 2020; Tan 2020; Zhang 2020a), because it was unclear whether adverse events had not been (equally) assessed for all participants or whether outcomes were selectively reported. Pei 2020 reported one serious adverse event occurring in one participant, however did not report whether they had assessed or observed other adverse events. Shen 2020 did not provide any information regarding the safety of plasma transfusion. Tan 2020 reported that their participant experienced moderate fever after the transfusion, however did not report whether other adverse events occurred. Zhang 2020a described they had not observed any adverse events for one of their participants after plasma transfusion, but did not provide any information regarding the occurrence of adverse events for the other participants. They stated in the conclusions that they had not observed any serious adverse events.

Clinical improvements

Reporting of clinical improvements was very heterogeneous across studies.

We judged the risk of reporting bias to be low for three studies (Duan 2020; Ye 2020; Zhang 2020a), which clearly described clinical improvements and periods of follow-up per participant.

We judged the risk of reporting bias to be unclear for three studies (Ahn 2020; Shen 2020; Zhang 2020b), because of the following reasons. Reporting and follow-up was unclear for one participant of Ahn 2020, two participants of Shen 2020 probably were still on the intensive care unit (ICU) but it was unclear, and Zhang 2020b did not provide details but the participant was transferred to another ward.

We judged the risk of reporting bias to be high for Tan 2020 because neither clinical symptoms nor clinical improvement were reported in detail, but the participant was still in hospital.

Pei 2020 did not report the course of disease after convalescent plasma transfusion so we judged it at unclear risk of bias for this domain.

Other potential sources of bias

We further considered confounding and poorly-defined risk estimates as potential sources of bias.

Confounding

All studies were at high risk of confounding because none of the studies adjusted for confounding factors, including concomitant treatments.

Poorly-defined risk estimates

None of the studies performed any analyses.

Effects of interventions

In the 'Evidence profile' (Additional Table 2), we present certainty of the evidence for the outcomes that were prioritised in the protocol (Piechotta 2020).

Effectiveness of convalescent plasma for people with COVID-19

As no RCTs or well conducted non-randomised studies evaluating benefits and harms of convalescent plasma have yet been completed, we are not sure if the following results are related to convalescent plasma therapy; they could also be related to the underlying natural history of the disease or other concomitant treatments.

All-cause mortality at hospital discharge

All-cause mortality at hospital discharge cannot be fully evaluated, as not all of the participants had been discharged at the end of follow-up. None of the studies reported any deaths during their study periods, meaning that all 32 participants were alive at the end of follow-up. Participants were followed until discharge from hospital or from three (Duan 2020), to 37 days (Shen 2020), after transfusion. Two participants of Shen 2020 and one participant each of Ahn 2020, Ye 2020, Zhang 2020a, and Zhang 2020b were still hospitalised. The participant in Zhang 2020a still remained on the ICU. Further, it was unclear, whether all 11 participants of Duan 2020 and Tan 2020 had been discharged from hospital.

Time to death

All participants were alive at the end of follow-up (3 to 37 days).

Improvement of clinical symptoms (assessed by need for respiratory support)
The effect of convalescent plasma on improvement of clinical symptoms was reported in six included studies (Ahn 2020; Duan 2020; Shen 2020; Ye 2020; Zhang 2020a; Zhang 2020b), including 24 participants on respiratory support at baseline, and four participants who did not require respiratory support. The results of these studies can be found in Additional Table 3. We grouped them according to the prespecified time points; day 7, day 15, and day 30 after the plasma transfusion, and summarised baseline information and clinical status at the longest time of follow-up for each study.

Six studies reported on improvement of clinical symptoms, but we could not extract all information about timing of improvement and types of respiratory support from all the studies.

Ahn 2020 described two critically ill people with COVID-19 requiring intubation and mechanical ventilation. The two participants received a tracheotomy and one participant was reportedly successfully weaned from the ventilator by day 18 after convalescent plasma therapy. For the other participant, the date of cessation of respiratory support was not evident from the publication, but tracheotomy and weaning from mechanical ventilation were reported during the study period.

Duan 2020 reported decreased need for respiratory support in four out of 10 participants within three days of convalescent plasma transfusion. One other participant was reported to require only intermittent oxygenation after previously receiving continuous low-flow oxygenation via nasal cannula. The study also reported on two individuals who required no respiratory support preceding convalescent plasma therapy. No information on improvement of clinical symptoms for other time points was available.

Shen 2020 reported a case series that included five participants who were described as critically ill at baseline, with four participants in need of mechanical ventilation and intubation and one participant receiving extracorporeal membrane oxygenation (ECMO). Of these five participants, three were discharged from hospital at the end of the study period, and two were in a stable condition, intubated and receiving mechanical ventilation.

Ye 2020 included six participants, four of whom required oxygen at baseline (one via nasal cannula, with the other modes not specified in the publication). Two individuals did not require respiratory support before convalescent plasma

was administered. All four participants previously requiring respiratory support experienced alleviation of symptoms after convalescent plasma therapy, with none of them requiring respiratory support at the end of the study follow-up. The study reports information on respiratory support but lacks information on the type of support received by the participants, and the timing of this outcome is not part of the presented data for all participants.

Zhang 2020a reported in detail the clinical characteristics and timing of convalescent plasma therapy for four people with COVID-19. One participant was on non-invasive ventilation (NIV) and high-flow oxygenation, one participant was mechanically ventilated and intubated at baseline, and two participants received ECMO. Three out of the four participants were discharged at the end of the study period, and all participants were reported to have recovered from the infection eventually. For one participant it was unclear whether oxygen support was still required by the end of the study period.

Zhang 2020b described one participant who was mechanically ventilated and intubated before receiving convalescent plasma therapy. At day 11 after convalescent plasma therapy, the participant was removed from mechanical ventilation. Whether the participant required other types of respiratory support was not reported.

30-day and 90-day mortality

All participants were alive at the end of follow-up. Participants were followed until discharge from hospital or three (Duan 2020), to 37 days (Shen 2020), after transfusion.

Time to discharge from hospital

The time to discharge was reported for at least some of the participants in six studies (Ahn 2020; Pei 2020; Shen 2020; Ye 2020; Zhang 2020a; Zhang 2020b). The day of discharge after convalescent plasma therapy ranged from 4 days to 35 days. Only one study (3 participants) reported time to discharge from hospital for all participants (Pei 2020). Please refer to Additional Table 4 for further information regarding each trial and participant.

It was unclear, whether all participants of Duan 2020 and Tan 2020 had been discharged from the hospital.

Admission on the ICU

This outcome was not reported in a consistent way in the included studies. Ye 2020, Zhang 2020a and Zhang 2020b reported the number of participants on the ICU at baseline (Additional Table 5). These were none of six (Ye 2020), four of four (Zhang 2020a), and one of one (Zhang 2020b), respectively. The other studies did not report the number of participants on the ICU at baseline, however Ahn 2020, Duan 2020, Pei 2020, and Shen 2020 reported the number of participants that were mechanically ventilated, and so presumably on the ICU (please see Additional Table 5). The participant reported in Tan 2020 presented with moderate symptoms only, and so presumably was not on the ICU.

Length of stay on the ICU

We could not evaluate the length of stay on the ICU as none of the included studies reported this outcome in a consistent way. Zhang 2020a reported that one participant was still on the ICU at the end of follow-up, the other three participants had been discharged from the ICU. Zhang 2020b reported that their participant could be released from the ICU 11 days after plasma transfusion to a general ward; 18 days after admission on the ICU. Based on the reported clinical course of disease presumably one participant of Ahn 2020 and two participants of Shen 2020 were also still on the ICU at the end of follow-up (please see Table 5). However, this was not clearly reported.

Safety of convalescent plasma for people with COVID-19

Number of participants with adverse events of possibly grade 3 or grade 4 severity

Seven studies reported assessment of adverse events (Ahn 2020; Duan 2020; Pei 2020; Tan 2020; Ye 2020; Zhang 2020a; Zhang 2020b), however, Zhang 2020a only reported for one of their participants that no adverse event had been observed. It was unclear whether the other three participants did or did not experience any adverse events.

Six studies therefore reported the presence or absence of adverse events for all participants. Two studies reported adverse events that were possibly grade 3 or 4 severity but they did not report the degree of severity (see Additional Table 6). Tan 2020, a case study, reported that their participant experienced moderate fever (38.9 °C) after convalescent plasma transfusion. One of the three participants in Pei 2020 had severe anaphylactic shock after receiving 30 mL of plasma from a female donor with a history of pregnancy. Four other studies reported no

adverse events that were possibly of grade 3 or grade 4 severity (19 participants; Ahn 2020; Duan 2020; Ye 2020; Zhang 2020b).

Number of participants with serious adverse events
Seven studies assessed and reported serious adverse events (Ahn 2020; Duan 2020; Pei 2020; Tan 2020; Ye 2020; Zhang 2020a; Zhang 2020b). One participant in Pei 2020 (3 participants) experienced a serious adverse event (see Additional Table 7). As described above, this individual had severe anaphylactic shock after receiving convalescent plasma from a female donor with a history of pregnancy. No serious adverse events occurred in six studies (24 participants).

Discussion

Summary of main results
The aim of this review was to assess the effectiveness and safety of convalescent plasma and hyperimmune immunoglobulin in the treatment of coronavirus disease 2019 (COVID-19) illness.

We included eight studies in this review - seven case-series and one prospectively planned, single-arm intervention study, all evaluating convalescent plasma (32 participants in total). There were no completed studies evaluating hyperimmune immunoglobulin. We identified 47 ongoing studies evaluating convalescent plasma and one ongoing study evaluating hyperimmune immunoglobulin. Twenty-two of the ongoing studies on convalescent plasma are randomised.

Effectiveness of convalescent plasma for people with COVID-19

As no RCTs or high-quality, non-randomised studies evaluating benefits and harms of convalescent plasma are completed yet, we do not know whether the following results are related to the underlying natural history of the disease, other concomitant treatment, or convalescent plasma.

All-cause mortality at hospital discharge
All studies reported mortality, and all participants were alive at the end of reporting, but not all of the participants had been discharged from hospital at the end of follow-up. We do not know whether convalescent plasma has any effect on all-cause mortality (very low-certainty evidence).

Improvement of clinical symptoms (as assessed by respiratory support)
Six studies reported on the level of respiratory support required in participants; most participants required respiratory support at baseline. All studies reported improvement in clinical symptoms in at least some of their participants. We do not know whether convalescent plasma improves clinical symptoms or whether this improvement was due to other interventions, or the natural history of the disease (very low-certainty evidence).

Time to discharge from the hospital
Six studies reported time to discharge from hospital for at least some of their participants. The day of discharge after convalescent plasma therapy ranged from 4 to 35 days.

Admission on the intensive care unit (ICU)
Six studies included participants who were critically ill. The majority of these participants were no longer on the ICU or no longer required mechanical ventilation at final follow-up.

Length of stay on the ICU
None of the studies clearly reported this outcome.

Safety of convalescent plasma for people with COVID-19

Adverse events
Two studies reported participants who had experienced adverse events, presumably of grade 3 or 4 (they did not report degree of severity). One case study reported a participant who had moderate fever (38.9 °C) after the transfusion of convalescent plasma. The other study (3 participants) reported a case of severe anaphylactic shock after convalescent plasma transfusion. Four studies reported that no participants experienced moderate or severe adverse events (19 participants). We are very uncertain whether convalescent plasma therapy affects the risk of moderate to severe adverse events (very low-certainty evidence).

Serious adverse events
One study with three participants reported one serious adverse event. This participant had severe anaphylactic shock after receiving convalescent plasma. Six studies reported that no serious adverse events occurred. We are very uncertain whether convalescent plasma therapy affects the risk of serious adverse events (very low-certainty evidence).

Overall completeness and applicability of evidence

We found eight published non-randomised, uncontrolled studies (seven case-series, one prospectively planned study) evaluating convalescent plasma in adults, most with severe COVID-19. These studies included 32 participants (ranging from 1 to 10 participants). Most of these participants had already received different treatment options either solely or in combination. These included antivirals, antifungals or antibiotics, corticosteroids, hydroxychloroquine and respiratory support (extracorporeal membrane oxygenation (ECMO), mechanical ventilation or oxygen). Therefore, the participant population might have been too small and heterogeneous to generalise results.

We identified 48 ongoing studies, of which 22 are designed as RCTs. Of these ongoing studies, 47 evaluate convalescent plasma and one evaluates hyperimmune immunoglobulin. Sixteen RCTs are planned to be completed in 2020. The publication of the results of these studies will necessitate an update of this review. The conclusions of the updated review could differ from those of the present review, and may allow for a better judgement regarding the effectiveness and safety of convalescent plasma therapy.

Certainty of the evidence

It is important to note that the outcome measures are heterogeneous with wide variation in reporting across the included studies. Only one study was prospectively planned (Duan 2020), a non-randomised and uncontrolled study, evaluating 10 participants. However, this study reported a very short follow-up only (three days after convalescent plasma was given). The other seven small case-series studies were not registered. These study designs lead to high risk of bias, both in terms of selection and detection bias. Studies were not adjusted for potential confounders (e.g. severity of disease, comorbidities, previous or concomitant COVID-19 treatment). Currently, there is no standard instrument available to assess risk of bias for this type of study. We used the form developed by the Cochrane Childhood Cancer Group (Additional Table 1; Mulder 2019).

As we included eight small observational studies only (32 participants altogether), the results are very imprecise and very inconsistent, with very high risk of bias. Therefore, the certainty of the evidence is very low for all prioritised outcomes.

Potential biases in the review process

To avoid potential bias in the review, we had planned to include the best available evidence. However, as COVID-19 is a novel disease, results from RCTs and non-

RCTs are not yet available. In fact, we could only identify uncontrolled studies, reporting on a small number of participants. To increase the informative value of our review, we are tracking all registered trials and will update this review on a monthly basis as more evidence becomes available.

Two experienced Information Specialists developed a sensitive search strategy, to identify all ongoing and completed studies. We searched all relevant databases and trials registries, and in contrast to the recommendations of the Cochrane Rapid Reviews Methods Group, we decided to conduct all review steps regarding the study selection in duplicate by two independent review authors. We are confident that we identified all relevant published and ongoing studies and will monitor them closely in the future.

Unlike standard Cochrane methodology, only one review author performed data extraction and 'Risk of bias' and GRADE assessments for this rapid review. To minimise bias in these steps, at least one other review author verified the accuracy and (where applicable) the plausibility of extractions and assessment.

Although we have very limited confidence in the available evidence, we are not aware of any deficiencies in our review process. However, we are certain that the results are likely to be substantially different and conclusions may change as soon as high-certainty evidence becomes available.

Agreements and disagreements with other studies or reviews

This systematic review identified very low-certainty evidence on the safety and effectiveness of convalescent plasma for people with COVID-19.

A recent systematic review and meta-analysis found low-certainty evidence for the use of convalescent plasma for treating people with infections with different aetiologies (Mair-Jenkins 2015). The authors reported a systematic review and meta-analysis of the literature on the use of convalescent plasma and hyperimmune immunoglobulin in treating severe acute respiratory infections of viral aetiology, and found that this treatment is likely to be both safe and effective in preventing mortality. The study identified a 75% reduction in the odds of mortality in their exploratory post hoc meta-analysis across all viral aetiologies. The studies included in this review were performed with people treated with convalescent plasma for severe acute respiratory syndrome (SARS) and influenza. The limited number of identified studies and the low quality of included, mainly uncontrolled studies restricted the authors' ability to analyse extensively the risks and benefits of convalescent plasma therapy. Recommendations from the

authors were to investigate the use of convalescent plasma and hyperimmune immunoglobulin in large, well-designed clinical trials or other formal evaluations to obtain better-certainty evidence, and to evaluate the optimal treatment regimen.

Results from several large RCTs on the use of convalescent plasma and hyperimmune immunoglobulin in treating severe influenza have recently been made public (Beigel 2017; Beigel 2019; Davey 2019; Hung 2013). However, the results from these studies are inconsistent, with some studies showing a beneficial effect of convalescent plasma for treating people with severe influenza, whereas other studies show no benefit. The studies were well designed and reported in detail the timing of the intervention and relevant outcomes. One trial reported effectiveness of hyperimmune immunoglobulin, but only in a post hoc analysis of a subgroup of participants treated within five days of symptom onset (Hung 2013). In a different trial, for the subgroup analysis of people with influenza B, the effect of hyperimmune immunoglobulin also resulted in a demonstrable clinical and virological benefit (Davey 2019). Different mechanisms in the human immune system and their role in responding to different circulating influenza strains might further explain why the results of clinical trials of convalescent plasma and hyperimmune immunoglobulin for influenza varied (Davey 2019). Influenza A immunity is reported to carry over to the next years, known as heterosubtypic immunity (Kreijtz 2011), and the current outbreak of COVID-19 can, in that sense, not be compared with seasonal influenza. Notwithstanding these dissimilarities which might explain why the aforementioned influenza studies were not successful in clearly demonstrating benefit, the possibility of a null effect of convalescent plasma over a suitable comparator cannot be ruled out with the currently available evidence on COVID-19.

The adverse events associated with plasma transfusions are well characterised. Critically ill patients receiving plasma transfusions have an especially high risk of TACO, which is the leading cause of transfusion-related mortality (Pandey 2012). Many countries have now introduced risk mitigation strategies to decrease the risk of TRALI. In the UK in 2018 there was only one confirmed case of TRALI.

In this systematic review of the literature, which mainly identified studies that included people with COVID-19 with critical illness, we identified one potentially grade 3 adverse event and one potentially grade 4 adverse event (which also qualified as a serious adverse event). With the information available at this moment from published trials registry entries, it is apparent that the majority of clinical trials are enrolling people with COVID-19 who have progressed to moder-

ate or severe disease. Despite there being some evidence from other infectious diseases that early therapy might be more effective (Mair-Jenkins 2015), targeting this population is justifiable given the evident lack of effective interventions for COVID-19. The population that is eligible for treatment in these trials with convalescent plasma is potentially at high risk of transfusion reactions, and when treating critically ill people with COVID-19, their status should be carefully monitored.

Authors' conclusions

Implications for practice

The currently available evidence on the safety and effectiveness of convalescent plasma and hyperimmune immunoglobulin for treatment of people with COVID-19 is of very low certainty. Thus, any conclusions that are drawn based on these data are of limited value and these conclusions are subject to change as more reliable results become available. For the primary outcomes, the included studies reported that all participants were alive at the end of follow-up. Clinical improvement assessed through the need for respiratory support was reported by most studies, but details on timing and type of respiratory support were not clear for all studies. Other outcomes that were reported in a subset of the included studies were length of stay on the intensive care unit (ICU) and time to discharge from hospital, but reporting of these outcomes was not complete. Two studies reported adverse events that were potentially grade 3 and grade 4, of which one was a serious adverse event. More thorough investigations, preferably well-designed clinical trials, are needed in order to assess the benefits and risks of convalescent plasma therapy for people with COVID-19.

Implications for research

In this systematic review of the literature, we identified seven case-series studies and one prospectively planned, single-arm intervention study. We encountered difficulties while extracting data from these studies because there were major differences in the way these studies reported participant characteristics, details on the intervention, and outcomes. Future publications could benefit from more standardised reporting, especially of timing of intervention and clinically relevant outcomes, like days until discharge from hospital and improvement of clinical symptoms. We support the adoption of a reporting guideline in this rapidly evolving field of research.

Randomised controlled trials (RCTs) or at least non-randomised trials with a control group are needed to confirm the findings of this review. As there are 47 ongoing studies evaluating convalescent plasma and one ongoing study evaluating hyperimmune immunoglobulin, of which 22 are randomised, we will screen search results monthly and publish updates as a living systematic review in the near future. It might well be that this update will show different results than those published in this rapid review.

Acknowledgements

This review was published in collaboration with the Cochrane Editorial and Methods Department. We particularly thank Sarah Hodgkinson (Associate Editor, Editorial and Methods Dept), Analysis of Review Group Output (ARGO) for their comments on the Abstract, Clare Dooley (Managing Editor), and Denise Mitchell (Copy Editor) for their excellent support. Thanks also to the Cochrane Editorial and Methods Department team, for their valuable comments on the review and timely management of the editorial process.

We thank Robin Featherstone (Information Specialist, Editorial and Methods Department) for commenting on the search strategy and Gerald Gartlehner and Adrienne Stevens for their advice on rapid review methodology. We thank Susan J Brunskill for her support in identifying included and ongoing studies.

We thank all external peer reviewers who read and commented on this review. We thank Miquel Lozano (MD, PhD Clinic University Hospital, University of Barcelona, Spain), and Michael James Ankcorn (Virology Department, Northern General Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, UK), who greatly helped to improve this review.

History

Review first published: Issue 5, 2020

Contributions of authors

SJV: clinical expertise and conception and writing of the review
VP: methodological expertise and conception and writing of the review

KLC: clinical expertise and conception and writing of the review
CD: development of the search strategy
IM: development of the search strategy
EMW: clinical expertise and advice
AL: clinical expertise and advice
CK: clinical expertise and advice
ZM: clinical expertise and advice
CS-O: clinical expertise and advice
LJE: clinical and methodological expertise and conception and writing of the review
NS: methodological expertise and advice and conception and writing of the review

Declarations of interest

SJV: none known
VP: none known
KLC: HSANZ Leukaemia Foundation PhD scholarship to support studies at Monash University. This is not related to the work in this review.
CD: none known
IM: none known
EMW: I have sought funding support from Australian Medical Research Future Fund for a trial of convalescent plasma. I will not be involved in bias assessment, data extraction or interpretation, but will serve as a content expert.
AL: none known
CK: none known
ZM: I have sought funding support from Australian Medical Research Future Fund for a trial of convalescent plasma. I will not be involved in bias assessment, data extraction or interpretation, but will serve as a content expert.
CS-O: is a member of the BEST Collaborative Clinical Study Group. I will not be involved in bias assessment, data extraction or interpretation, but will serve as a content expert.
LJE: co-lead of the COVID-19 immunoglobulin domain of the REMAP-CAP trial. I will not be involved in bias assessment, data extraction or interpretation, but will serve 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

External sources
· No sources of support supplied

Differences between protocol and review

Types of outcome measures
We revised the secondary outcome 'Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8 to 15 days; 16 to 30 days' and added to the fourth bullet point: 'plus high-flow oxygen', to differentiate from the third bullet point. It now reads:

Improvement of clinical symptoms, assessed by need for respiratory support at up to 7 days; 8 to 15 days; 16 to 30 days:
o oxygen by mask or nasal prongs
o oxygen by NIV (non-invasive ventilation) or high flow
o intubation and mechanical ventilation
o mechanical ventilation plus high-flow oxygen
o extracorporeal membrane oxygenation (ECMO)

Electronic searches
As publication bias might influence all subsequent analyses and conclusions, we searched all potential relevant trials registries in detail to detect ongoing as well as completed studies, but not yet published studies. Nowadays, it is mandatory to provide results at least in the trials registry. In case results were not published

elsewhere, we had planned to extract and analyse these data. However, no outcome data had yet been added to the trials registries.

Data extraction and management

We had planned to extract data using a standardised data extraction form developed in Covidence. However, we could not adapt the standardised form to our needs. Therefore we generated a customised data extraction form in Microsoft Excel (Microsoft Corporation 2018).

Summary of findings and assessment of the certainty of the evidence

At protocol stage we had planned to assess the certainty of the evidence for our primary outcomes (all-cause mortality at hospital discharge and time to death), only. However, as none of the included studies reported any deaths during their study periods, we decided to assess the certainty of the evidence also for prioritised secondary outcomes (clinical improvement, grade 3 and 4 adverse events, and serious adverse events) to increase the informative value on effectiveness and safety of convalescent plasma therapy.

Some passages in this protocol, especially in the methods section, are from the standard template of Cochrane Haematology.

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The Additional Tables and Appendices for this chapter can be found here: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013600/appendices#CD013600-sec-0097"