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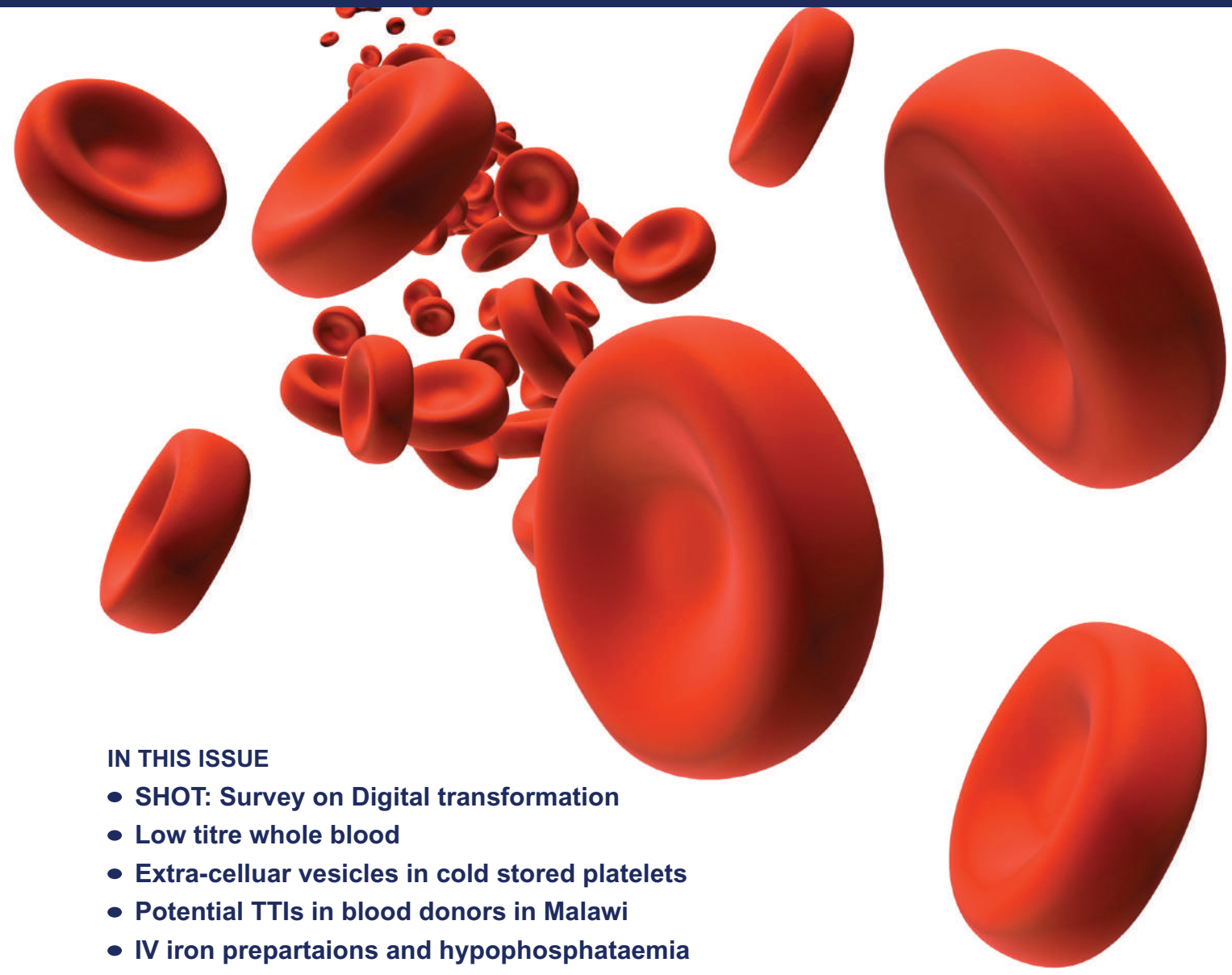

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Transfusion Medicine

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Aims

Transfusion Medicine will publish articles on transfusion medicine in its widest context, including blood transfusion practice (blood procurement, pharmaceutical, clinical, scientific, computing and documentary aspects), immunohaematology, immunogenetics, histocompatibility, medico-legal applications, and related molecular biology and biotechnology.
In addition to original articles, which may include brief communications and case reports, the journal will contain a regular educational section (based on invited reviews and state-of-the-art reports), technical section (including quality assurance and current practice guidelines), leading articles, letters to the editor, occasional historical articles and signed book reviews. Some lectures from Society meetings that are likely to be of general interest to readers of the Journal may be published at the discretion of the Editor and subject to the availability of space in the Journal.

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ORIGINAL ARTICLE

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SHOT UK Collaborative Reviewing and Reforming IT Processes in Transfusion (SCRIPT) survey: Laboratory information management systems: Are we ready for digital transformation?

Jennifer Davies [1,2,3] | Victoria Tuckley [1] | Alistair McGrann [1] | Megan Rowley [2] | Heather Clarke, Peter Baker [3] | Shruthi Narayan [3]

[1]Academic Department of Trauma & Orthopaedics, School of Medicine, University of Leeds, Leeds, UK

[2]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK

[3]Leeds Orthopaedic & Trauma Sciences, Leeds General Infirmary, University of Leeds, Leeds, UK

[4]Leeds Institute of Health Sciences, University of Leeds, Leeds, UK

[5]NIHR Leeds Biomedical Research Unit, Chapel Allerton Hospital, Leeds, UK

Correspondence
Michalis Panteli, Academic Department of Trauma & Orthopaedics, School of Medicine, University of Leeds, Clarendon Wing, Level D, Great George Street, Leeds LS1 3EX, West Yorkshire, UK.

Email: jennifer.davies56@nhs.net

Abstract

Objectives

To understand the use, functionality and interoperability of laboratory information management systems (LIMS) in UK transfusion laboratories.

Background

LIMS are widely used to support safe transfusion practice. LIMS have the potential to reduce the risk of laboratory error using algorithms. Reporting to Serious Hazards of Transfusion (SHOT), the United Kingdom (UK) haemovigilance scheme, has identified cases where the LIMS could have prevented errors but did not.

Methods and Materials

A survey was distributed to all SHOT-reporting organisations to understand the current state of LIMS in the UK, prevalence of expertise in transfusion IT, and barriers to progress.

Results

A variety of LIMS and version numbers are in use in transfusion laboratories, LIMS are not always updated due to resource constraints. Respondents identified interoperability and improved functionality as the main requirements for transfusion safety.

Conclusion

A nationally agreed set of minimum standards for transfusion LIMS is required for safe practice. Adequate resources, training and expertise should be provided to support the effective use and timely updates of LIMS. A single LIMS solution should be in place for transfusion laboratories working within a network and interoperability with other systems should be explored to further improve practice.

KEYWORDS

Haemovigilance, blood, medicine, transfusion

1 | INTRODUCTION

Severe acute respiratory infections caused by strains of influenza or coronavirus often lead to hospitalisation and sometimes death. Symptomatic infection with SARS CoV-2 (COVID-19) has surpassed the annual global burden of death due to influenza or coronaviruses.[1] Although there are several effective vaccines for COVID-19 therapeutic treatments are still required. Patients particularly at risk are those with disorders that affect the immune system, for example, haematological malignancies or those receiving drugs that suppress an immune response, for example, after organ transplantation.[2,3]

Passive antibody therapies, including monoclonal antibody combinations have proven effective for COVID-19[4] However, the cost of these therapies is prohibitive[5] and new SARS-CoV variants may become resistant to anti-virals developed in response to previous variants.[6] Alternative and affordable responses to emerging strains of virus are needed.

Convalescent plasma (CP) is typically collected from donors with confirmed diagnosis of infection at least 2 weeks after recovery.[7] CP contains neutralising antibodies specific to the infectious agent but may also contain other immune modulators and clotting factors that can be fractionated out to produce hyperimmune-immunoglobulin (hIVIG).[8]

CP containing high titres of polyclonal antibody (Ab), has been used to treat patients hospitalised with respiratory syndromes caused by viral infections. Many studies have been poorly controlled but such series suggested decreased mortality in H1N1 Influenza infections in 1918–1920 and in 2009/2010, SARS-CoV-1 infections in 2003 and most recently COVID-19. Recent systematic reviews lacked data from RCTs and analysis did not consider the titre used within trials.[9] Moreover, there are concerns that CP may cause harm, potentially causing severe transfusion reactions such as transfusion-associated acute lung injury (TRALI) or antibody dependent enhancement of the viral infection.[10]

Prior to the COVID-19 pandemic, studies investigating the effectiveness of CP for viral infections varied in quality and the outcomes reported may not have reflected current international guidelines.[11,12]

2 | OBJECTIVE

To evaluate the evidence for the safety and effectiveness of using convalescent plasma (CP) or hyperimmune immunoglobulin (hIVIG) to treat severe respiratory disease caused by coronaviruses or influenza.

3 | METHODS

The protocol for this review was prospectively registered on PROSPERO (CRD42020176392), and the review was carried out in accordance with Cochrane methodology and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13]

3.1 | Search strategy

We searched multiple electronic databases (MEDLINE, PubMed, The Cochrane Library, Embase, Epistemonikos), ClinicalTrials.gov and WHO International Clinical Trials Registry Platform for ongoing studies, without language restriction, for all publication types on 12th October 2020 (see Appendix A1 in Data S1). We updated our search on 28th June 2021, increasing the number of databases (Cochrane COVID-19 Study Register, Transfusion Evidence Library, Web of Science). We limited the update search to systematic reviews and RCTs due to the significant number of randomised trials available at this point. Ongoing studies identified in our searches were checked on 30th November 2021 and included if published in full (peer-reviewed) by this date. We hand searched reference lists of systematic reviews and included RCTs.[11]

3.2 | Selection criteria

For assessments of effectiveness, we included RCTs comparing transfusion of CP products to any control arm with participants of any age who were admitted to hospital with severe respiratory illness. For assessments of safety, we included all study designs where patients received CP or hIVIG.

Two reviewers (CK, AL, LJG, SV) independently screened title and abstract, and then full-text using Covidence.

Where a publication was in a non-English language, we used electronic translation tools and sought the help of native speakers where appropriate (Appendix A2 in Data S1).

3.3 | Data extraction

Two of four reviewers (CK, AL, LJG, JS) independently extracted data using Covidence and Excel. Reviewers who were involved with any original trials (AL, LE) were not involved in the data extraction for those trials.

Extracted data included: details of study participants (demographic and disease characteristics), details of interventions (including titre, volume, timing of CP/hIVIG), and outcomes.

Outcomes extracted: all-cause mortality up to 30 and 90 days; need for mechanical ventilation (MV) and non-invasive ventilation (NIV) at up to 30 days; duration of MV or NIV; length of hospital stay; length of intensive care unit (ICU) stay; duration of viral detection from admission up to 30 days; transfusion-related serious adverse events (SAEs).

In a deviation from our protocol, we also assessed SAEs up to 30 days due to substantial variability in the way that SAEs were reported. For papers from the 1918 to 1920 influenza pandemic, reporting style was substantially different and, if reported, there was no grading of AEs. We recorded any potential AE described in these publications.

Where data were not available for a particular timepoint, we extracted data to the nearest possible timepoint. We sought clarification from trial authors where necessary.

3.4 | Risk of bias assessment

Two review authors (CK, AL, LJG, JS) independently assessed all eligible studies for risk of bias (ROB), using the Cochrane ROB tools. ROB1 for RCTs[14] and ROBINS-I for observational studies according to the Cochrane Handbook for Systematic Reviews of Interventions.[15] Reviewers who had worked on a trial (AL, LE) did not participate in ROB assessments for those studies.

Observational studies assessed as having "critical" ROB were not included in quantitative analyses.

3.5 | Data analysis

Statistical analyses were undertaken in Review Manager 5.4,[16] R[17] and the *metafor* package in R.[18] For dichotomous outcomes, we used the Mantel–Haenszel method, or Peto OR for rare events. We calculated the pooled risk ratio (RR) with a 95% confidence interval (CI), using the random effects model in RevMan5.[16] We used Tau^2 and I^2 in the assessment of heterogeneity, according to the guidelines laid out in the Cochrane handbook.[19]

We have not combined RCTs and non-RCTs and so have reported the results separately.

We planned to analyse continuous outcomes using mean difference (MD) or standardised mean difference (SMD) where different scales had been used. Continuous outcomes reported as median (IQR/range) could not be meta-analysed or pooled and have been reported narratively within tables.

Information from observational studies was collated in tables and not meta-analysed. Certainty of the evidence (based on meta-analysable data only) was assessed using GRADEPro.[20]

3.5.1 | Subgroup and sensitivity analysis

We subgrouped included trials by the type of respiratory infection.

We also subgrouped COVID-19 studies by their use of high titre or low titre/unselected plasma (see Appendix A3 in Data S1) in response to emerging research that highlighted the wide variability in CP titres used in practice.

We intended to undertake sensitivity analyses based on selection bias to examine evidence from 'low risk' studies only. However, this was not necessary for the RCTs as all included RCTs were assessed as low (or unclear) risk for mortality endpoints within this domain.

3.5.2 | *Post hoc* analysis of seropositivity

We performed a *post hoc* analysis of trials where there were sufficient data to assess the impact of SARS-CoV-2 antibody status at baseline due to emerging evidence of greater effectiveness of passive antibody therapy (monoclonal antibodies) for patients who are antibody negative at baseline.[21] Meta-regression for *post hoc* analysis of seropositivity was performed using the metafor[18] package in R.

4 | RESULTS

Our search yielded 4826 references (Figure 1 PRISMA flow diagram; for excluded studies see Appendix A4 in Data S1).

4.1 | Study Characteristics

We identified 110 completed studies (Figure 1), including 30 RCTs (four for influenza, n = 578; and 26 for COVID-19 SARS-CoV-2, *n* = 18 204).[3,7,22–49] There were no RCTs or non-randomised controlled trials identified for MERS or SARS (SARS-CoV-1) (Appendix A Supplementary Table A1 in Data S1). We included 76 non-randomised studies (Appendix B in Data S1). Of these, eleven were controlled studies, of which only two were at less than "critical" ROB[50,51] (Appendix A Supplementary Table A2 in Data S1) We included 67 uncontrolled studies: 12 assessing influenza A; two on MERS-CoV; four on SARS-CoV, and 49 on COVID-19 (SARS-CoV-2).

We also identified 143 ongoing studies (Appendix C) which were either controlled trials or single arm studies, which listed at least one safety outcome in their intended primary or secondary outcomes.

Study size in the quantitative analyses ranged from 29 to 11 555 (34 to 308 for influenza).

Of the four RCTs assessing influenza: two included children (*n* = 24/236 < 18 years)[39,45]; three RCTs[39,45,47] included pregnant women (3/270 pregnant women).

Of the 26 RCTs and 2 non-randomised studies that assessed COVID-19: one RCT included children (*n* = 26/11558 < 18 years).[3] Three RCTs[29,34,44] did not report whether they included children. Three RCTs[3,29,35] included pregnant women (*n* = 36/12575 pregnant women). Eight RCTs[22,24,30–33,36,44] did not report whether they included pregnant women.

4.2 | Comparisons

We identified four comparisons within the data that could be combined in quantitative analysis:

(1) CP versus standard care (SoC) or biologically inactive placebo (saline) (20 RCTs): 19 RCTs compared CP to SoC,[3,7,22–25,27–31,33–36,38,39] one RCT[26] compared SoC with saline placebo, and two retrospective observational studies[50,51] compared CP patients with matched controls;

(2) CP versus biologically active control (FFP or IVIG) (6 RCTs): five RCTs compared CP to non-immune FFP,[40–43,45] and one compared CP with IVIG.[44]

(3) hIVIG versus control (3 RCTs) Of these, two compared hIVIG with SoC,[46,47] one compared hIVIG with saline placebo.[48]

(4) early CP versus deferred CP (1 RCT).[49]

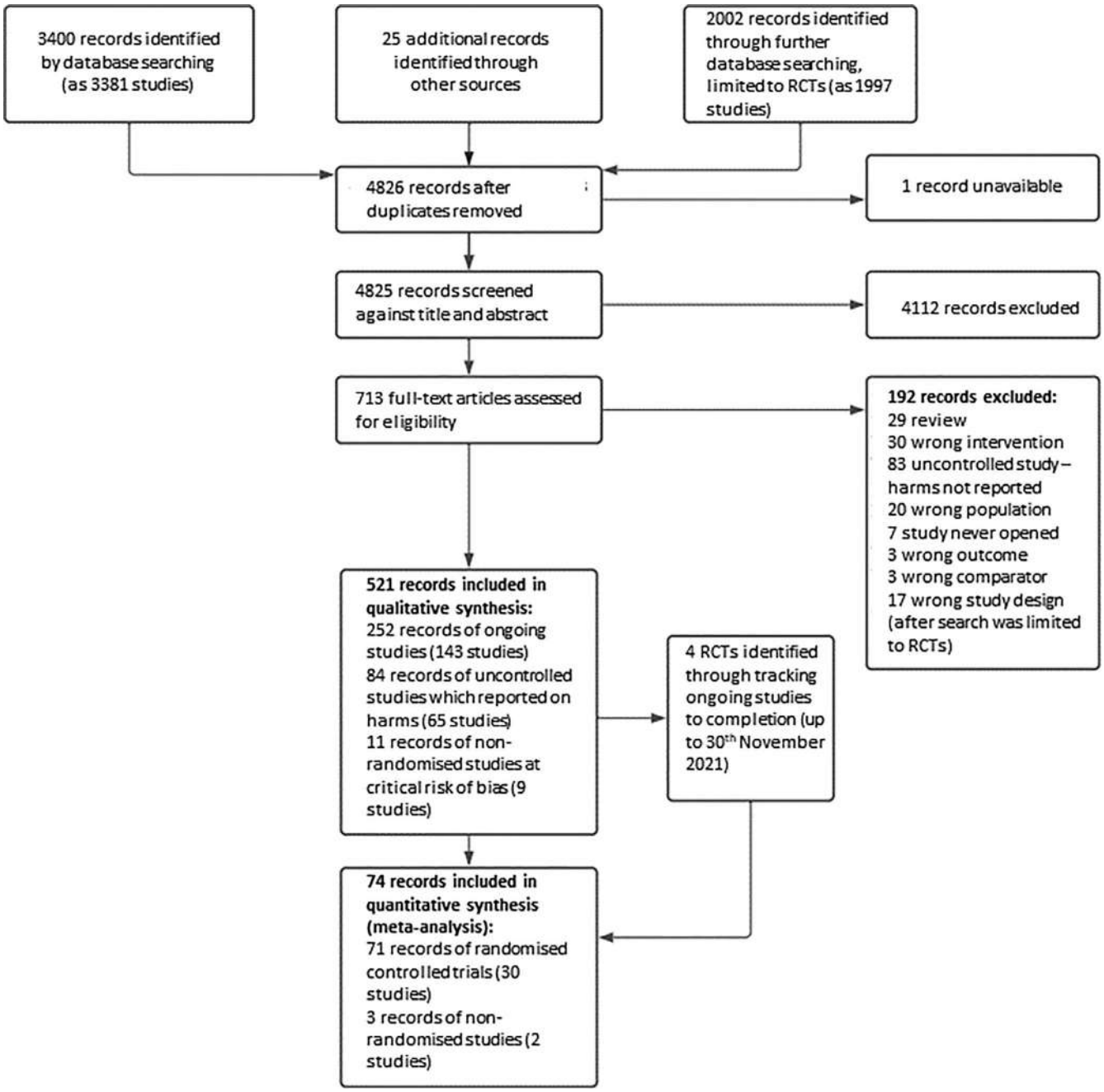

FIGURE 1 PRISMA flow diagram. Caption: The reasons for exclusion at each stage are shown with arrows to the right.

The comparators and baseline characteristics of participants in each of the thirty RCTs and two non-RCTs (retrospective observational studies)[50,51] within meta-analyses are summarised in Appendix A Table A1 in Data S1.

4.3 | Outcomes

We could only extract sufficient data to meta-analyse mortality and serious adverse events. We have presented remaining data from controlled studies in tables (Appendix A, Tables A3–A6 in Data S1). A summary of all outcomes reported is available in Appendix A5.

Most trials did not describe any method for dealing with competing risks when reporting their results. A competing risk is one which prevents the event of interest from occurring. Death is a competing risk for both (time to) mechanical ventilation and (time to) discharge. Devos 2021[28] approached competing risks using competing events analysis[52] to obtain cause-specific hazard ratios (HR). REMAP-CAP[30] used ordinal logistic regression by assigning each participant a category labelled with the number of ventilator-free days up to 21 days, with people who died up to day 90 being assigned −1, people who were on MV at

TABLE 1 Overview of meta-analysed results from patients hospitalised with severe respiratory infections

Comparison	30-day mortality		90-day mortality	Grade 3 or 4 transfusion related AEs	SAEs
Comparison 1: CP versus SoC or biologically inactive placebo (saline)	**All RCTs:** RR 0.99 (0.92 to 1.06) 15 RCTs[a], $n = 17\,266$ (37 children, 38 pregnant women) ⨁⨁⨁◯ $I^2 = 4\%$ $Tau^2 = 0.00$	**High Titre subgroup:** RR 0.98 (0.93 to 1.04) 9 RCTs[b], $n = 15\,954$ (26 children, 33 pregnant women) ⨁⨁⨁⨁ $I^2 = 0\%$ $Tau^2 = 0.00$	RR 0.92 (0.74 to 1.15) 6 RCTs[b], $n = 3210$ (8 pregnant women) ⨁⨁◯◯ $I^2 = 0\%$ $Tau^2 = 0.02$	*No transfusion in control group; results in intervention group are summarised in table A12*	RR 1.14 (0.92 to 1.41) 13 RCTs[a], $n = 16\,730$ (37 children, 38 pregnant women) ⨁◯◯◯ $I^2 = 56\%$ $Tau^2 = 0.07$
Comparison 2: CP versus biologically active control (FFP or IVIG)	RR 0.85 (0.56 to 1.29) 5 RCTs[a] $n = 700$ (13 children, 1 pregnant woman) ⨁◯◯◯ $I^2 = 33\%$ $Tau^2 = 0.07$		RR 0.99 (0.75 to 1.29) 2 RCTs[b], $n = 264$ ⨁◯◯◯ $I^2 = 0\%$ $Tau^2 = 0.00$	POR 0.43 (0.14 to 1.33) 6 RCTs[a], $n = 716$ (13 children, 1 pregnant woman) ⨁◯◯◯ $I^2 = 4\%$ $Chi^2 = 4.18$	RR 0.88 (0.65 to 1.19) 4 RCTs[b], $n = 523$ (13 children, 1 pregnant woman) ⨁⨁◯◯ $I^2 = 0\%$ $Tau^2 = 0.00$
Comparison 3: hIVIG versus control	RR 0.77 (0.34 to 1.73) 3 RCTs[c] $n = 392$ ⨁◯◯◯ $I^2 = 50\%$ $Tau^2 = 0.26$		*No RCTs reported mortality at 90 days in this comparison*	RD 0.00 (−0.08 to 0.08) 2 RCTs[a] $n = 84$ ⨁◯◯◯ $I^2 = 0\%$ $Tau^2 = 0.00$	RR 1.10 (0.76 to 1.58) 2 RCTs[a] $n = 342$ ⨁◯◯◯ $I^2 = n/a$ $Tau^2 = n/a$
Comparison 4: Early CP versus deferred CP	RR 2.68 (0.56 to 12.71) 1 RCT[b], $n = 58$ ⨁◯◯◯ $I^2 = n/a$ $Tau^2 = n/a$		*No RCTs reported mortality at 90 days in this comparison*	*Transfusion-related AEs were only reported for patients receiving CP; results are summarised in table A12*	*No RCTs reported SAEs in this comparison*

Note: Key: ⨁◯◯◯ very-low certainty evidence; ⨁⨁◯◯ low certainty evidence; ⨁⨁⨁◯ moderate certainty evidence; ⨁⨁⨁⨁ high certainty evidence.
Abbreviations: POR, Peto odds ratio; RD, risk difference; RR, risk ratio.
[a]Includes 1 RCT in influenza.
[b]All COVID-19.
[c]Includes 2 RCTs in influenza.

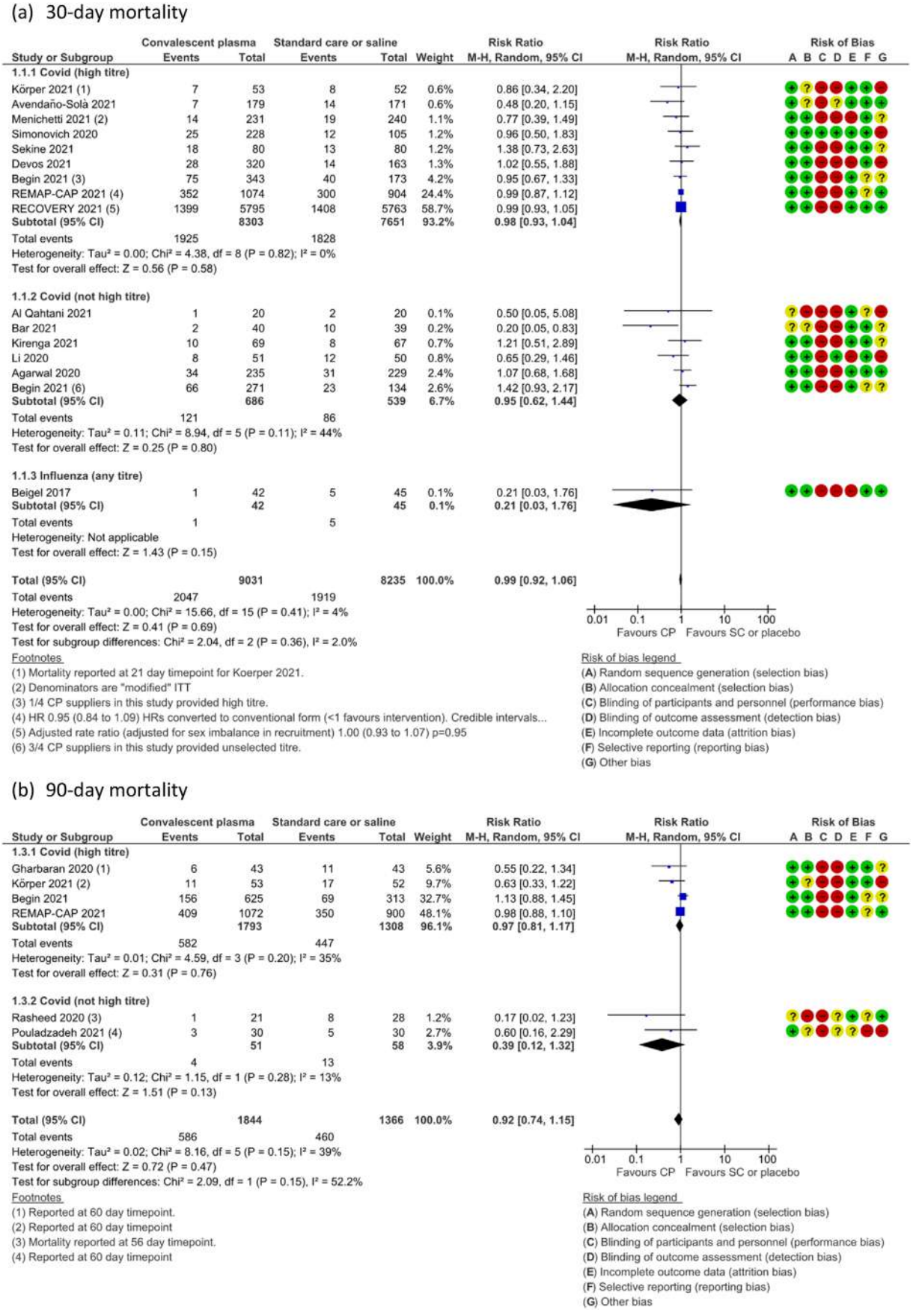

FIGURE 2 Forest plot of all-cause mortality, for comparison 1 (CP compared to SoC or a biologically inactive placebo) at up to (A) 30 days, and (B) 90 days

randomisation being assigned 0, and people who remained ventilator-free beyond day 21 being assigned 22. This is a useful way to compare the two groups while accounting for the very different possible outcomes but the resulting odds ratio (OR) and medians are difficult to interpret. No other trials used these methods and so we cannot combine the results but instead report the summary within Table A4 in Data S1.

Duration of viral detection was expressed as time (median IQR) to first negative test (2 RCTs).[23,36] One study,[25] reported the number of patients who had had two consecutive negative tests by day 30. See table A5 for viral detection data and table A6 for details of changes in viral loads.

4.4 | ROB in included studies

4.4.1 | RCTs (using Cochrane ROB1)

Nineteen RCTs were open-label, comparing CP to SoC, and were therefore assessed as having a high ROB for all outcomes except mortality, as knowledge of treatment allocation may have affected clinical decision-making. A summary of ROB judgements is available in Table A7 and Figure A1 in Data S1.

4.4.2 | Non-RCTs (using ROBINS-I)

Two non-RCTs[50,51] were assessed at serious RoB for selection bias and confounding at baseline. The remaining 9 studies[53–61] were at critical ROB due to baseline confounding or selection bias and were therefore not meta-analysed.

4.5 | Certainty of the evidence (GRADE)

Certainty of the evidence was GRADEd as very-low to high; primary reasons for downgrading were ROB and imprecision (wide confidence intervals and small sample size) (Tables A8–A11 in Data S1). We assessed publication bias through the generation of a funnel plot (Figure A2 in Data S1) for 30-day mortality in comparison 1, which suggests that some small studies have not been published. However, this was not significant enough to downgrade the certainty of the evidence because the analysis is dominated by two large, high-quality, and RCTs.

4.6 | Effect of the Intervention

See Table 1 for an overview of meta-analysed results.

4.6.1 | Comparison 1: CP versus SoC or biologically inactive placebo

Twenty RCTs and two retrospective studies assessed CP compared with SoC or a biologically inactive placebo.

All-cause mortality

30-day mortality data were available from 15 RCTs (30 days, 5 RCTs; 28 days, 9 RCTs; 21 days, 1 RCT) (Figure 2a); 90-day mortality data were available from 6 RCTs (56 days, 1 RCT; 60 days, 3 RCTs; 90 days, 2 RCTs) (Figure 2b).

Overall, CP did not reduce 30-day mortality (15 RCTs, n = 17 266; moderate-to-high certainty of evidence [Table A8 and footnotes in Data S1]) and there may be no effect on 90-day mortality (6 RCTs $n = 3210$; low certainty of evidence [Table A8]).

Two non-RCTs reported in-hospital mortality, and showed results consistent with the randomised evidence (2 studies, $n = 436$; very-low certainty evidence) (Figure A3A Table A8 in Data S1).

Improvement of clinical symptoms

Duration of NIV was reported in 4 studies (2 RCTs),[3,24,50,51] and duration of MV was reported by 11 studies (9 RCTs).[3,24,25,28–30,35,38,39,50,51] Two RCTs[27,31] reported any ventilatory support, but did not differentiate between MV, NIV, and passive oxygen support. One RCT[29] reported any ventilation, but also reported separately a composite outcome of patients who progressed to MV or death. Most studies reported the data as duration of support, either median (IQR) or mean (SD) (Table A4 in Data S1).

These outcomes were very variably reported, and many did not fully account for competing events, or report methods of analysis in sufficient detail. Based on what was reported, there was no apparent difference in duration of MV, NIV or ECMO support between the two groups.

Length of stay (LOS): hospital and ICU

Length of hospital stay was reported by 16 RCTs[7,23,25–28,30,31,38,39,42–47] and 1 non-RCT,[51] and length of ICU stay was reported by 9 RCTs[23,26,28,29,33,39,43,45,47] (Table A3 in Data S1). There was no evidence of an effect in length of hospital stay or length of ICU stay (Table A3 in Data S1).

Duration of viral detection from admission up to 30 days (viraemia, nasopharyngeal swabs, bronchoalveolar lavage, stool)

The 3 RCTs which reported time to negative test do not suggest any evidence of an effect (Table A5 in Data S1).

Adverse events

AEs due to transfusion were reported in 15 RCTs[3,7,22–39] (Table S10 in Data S1).

Seven RCTs reported no Grade 3 or 4 AEs due to transfusion.[22,24,26,27,31,35,39] Both non-RCTs reported AEs due to transfusion. All but one RCT[26] had SoC comparators, and therefore no transfusion-related SAEs are reported for the control group. Group comparison was not possible; results are summarised in Table A12 of in Data S1.

There was no evidence of an effect on reported SAEs[3,23–31,35,36,39] (13 RCTs, $n = 16\,730$, very-low certainty of evidence) (Figure A3B).

Data were not available on SAEs in seven RCTs.[7,22,32–34,37,38]

See forest plots Figure A3 in Data S1 and GRADE profile Table A8 in Data S1 for further detail.

4.6.2 | Comparison 2: CP versus biologically active control (FFP or IVIG)

RCTS assessed CP compared to FFP[40–43,45] or IVIG[44]

All-cause mortality

There was insufficient evidence to say whether or not there is a difference between groups in all-cause mortality at up to 30 days (5 RCTs $n = 700$; very-low certainty evidence, Figure A4A in Data S1), or at up to 90 days (2 RCTs, $n = 264$; very-low certainty evidence Figure A4B in Data S1). See forest plots Figures A4A and A4B in Data S1 and GRADE profile Table A9 in Data S1 for further detail.

Adverse events

Six RCTs reported transfusion-related Grade 3 or 4 AEs.[40–45] Events were rare (~2%) with no clear evidence of a difference (6 RCTs, $n = 716$; very-low certainty evidence. [Figure A4C in Data S1]). Four RCTs[40–42,45] reported SAEs up to 30 days, showing no evidence of an effect, although the rate of SAEs seems very low, given the severity of disease in hospitalised individuals (4 RCTs, $n = 523$; low certainty evidence, Figure A4D in Data S1). See forest plots Figure A4 and GRADE profile Table A9 in Data S1 for further detail.

Improvement of clinical symptoms

Duration of MV[40,43,45] and any ventilatory support[41] were reported as median (IQR) or mean (SD). Given the difficulties of dealing with competing events, and the small number of patients involved, it is very unclear if CP therapy had any effect on the duration of MV, NIV or ECMO support between the two groups. We have presented the data in Table A4 in Data S1 as reported by the individual studies.

Data were not available for LOS (hospital or ICU), and duration of viral load.

4.6.3 | Comparison 3: hyperimmune immunoglobulin versus control

Three assessed hIVIG compared with SoC or a biologically inactive placebo.

All-cause mortality

There was insufficient evidence to say whether or not there is an effect on mortality compared to control at up to 30 days (3 RCTs $n = 392$; very-low certainty evidence) (Table 1, Figure A5A, Table A10 in Data S1). There were no data for 90-day mortality.

Adverse events

Two RCTs reported transfusion-related AEs; neither reported any AEs due to transfusion in either group (2 RCTs, $n = 84$; very-low certainty evidence, Figure A5B in Data S1). Two RCTs reported SAES (2 RCTs $n = 342$; very-low certainty evidence. [Figure A5C in Data S1]). See forest plots Figure A5 and GRADE profile Table A10 in Data S1 for further detail.

Improvement of clinical symptoms

One RCT in influenza[48] reported on duration of MV and NIV. However, the data were presented using an ordinal scale that was not mappable to our outcomes or other trial results, and we were unable to extract the data.

Data were not available for LOS (hospital or ICU), and duration of viral load.

4.6.4 | Comparison 4: early CP versus deferred CP

One RCT assessed early CP compared to deferred CP.

All-cause mortality

There was insufficient evidence to say whether there is a difference in 30-day mortality between early CP and deferred CP (1 RCT $n = 58$; very-low certainty of evidence) (Figure A6 in Data S1). There were no data for 90-day mortality. See forest plots Figure A6 and GRADE profile Table A11 in Data S1 for further detail.

Adverse events

There were three Grade 3 or 4 transfusion-related AEs within 24 h, all in the early CP group: (1 RCT $n = 58$, very-low certainty evidence) (Table A12 in Data S1). SAEs were not reported. See forest plots and GRADE profile Table A11 in Data S1 for further detail.

Improvement of clinical symptoms

Duration of MV and NIV was reported as median (IQR). We have presented the data in Table A4 in Data S1 as reported by the RCT. Both groups had similar duration of ventilatory support. It is unclear if the authors accounted for competing events.

Data were not available for LOS (hospital or ICU), and duration of viral load.

4.7 | Results from uncontrolled studies (for safety only)

We identified 73 non-randomised or uncontrolled studies [49 case reports or case series] that assessed the use of CP or hIVIG in respiratory viral infection and reported AEs: 12 in influenza A, 2 in MERS-CoV, and 4 in SARS-CoV-1, and 67 in SARS-CoV-2 (COVID-19). Of the influenza studies, 10 were from the 1918 to 1920 pandemic. Fifty-one studies reported that no AEs were observed (37/49 case reports or case series). Eighteen studies reported transfusion-related AEs, and four studies reported other SAEs. These data are presented in Appendix B in Data S1.

4.8 | Post hoc subgroup analysis: seropositivity at baseline

Three RCTs,[3,30,62] including the two largest, reported 30-day mortality for subgroups defined by seropositivity at baseline. These results are shown in Figure 3.

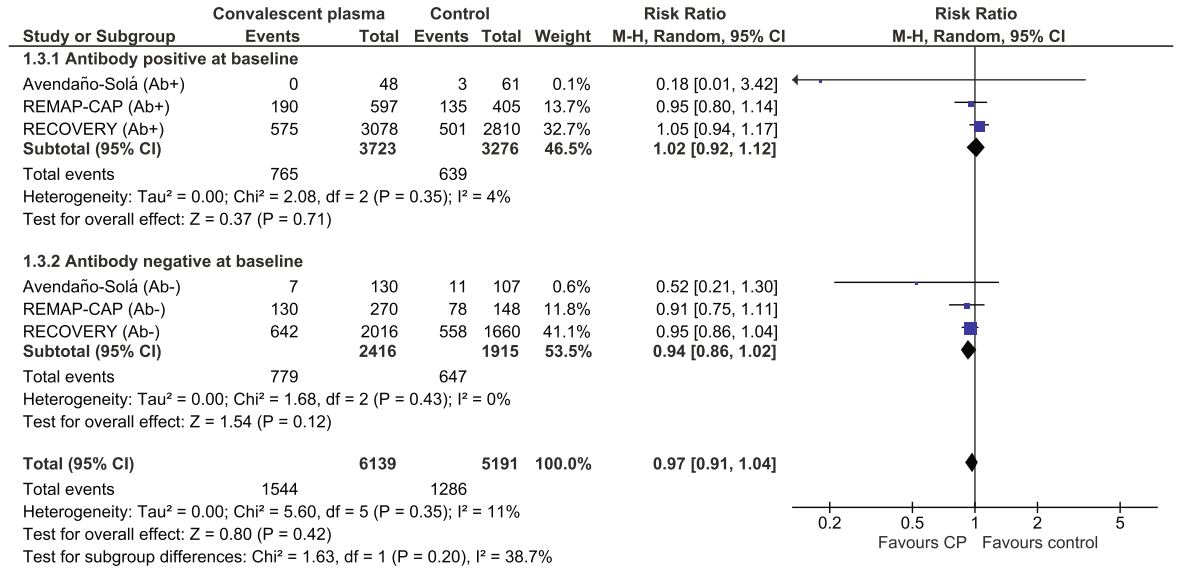

FIGURE 3 Subgrouped by seropositivity at baseline: RCTs reporting 30-day mortality for comparison 1 (CP compared to SoC or a biologically inactive placebo)

With almost all the information coming from the two large, high-quality RCTs,[3,30] the pooled estimates from these three RCTs are: RR 1.02 (0.92 to 1.12) for people who are seropositive at baseline and 0.94 (0.86 to 1.02) for those who are seronegative. The test for interaction (subgroup difference) gives a *p*-value of 0.20 with very little heterogeneity either within or between groups.

We explored this further using meta-regression on the group of trials comparing high titre CP with SoC which reported the proportion seropositive at baseline and 30-day mortality. This analysis produced near identical results with an estimated RR at 0% seropositivity of 0.93 (0.85, 1.01) and 1.02 (0.93, 1.12) at 100% seropositivity (See Appendix A6 in Data S1. Mortality results are summarised in Table A14 in Data S1).

5 | DISCUSSION

The objective of this review was to determine the safety and effectiveness of CP or hIVIG from CP to treat patients with serious respiratory disease due to influenza or coronavirus infection. In order to increase the relevance of our findings to the COVID-19 pandemic we used the core outcome set[63] for assessing treatments for patients infected with SARS-CoV-2. We aimed to use high-quality evidence from RCTs to assess safety and effectiveness. We also used all other study designs to describe serious harms reported following transfusion with CP or hIVIG.

5.1 | Main findings

We were able to meta-analyse 32 studies for our primary outcome of 30-day mortality (30 RCTs and 2 non-RCTs). We found little evidence of any difference between the groups in either benefits or harms for patients hospitalised with a severe viral respiratory infection requiring hospital admission. Most evidence was of low or very-low certainty. The only high-certainty evidence was for the COVID high-titre subgroup in the outcome all-cause mortality at up to 30 days in CP versus SoC (Table 1).

Adverse events were variably reported. No RCTs reported a high number of transfusion-related AEs (proportion 0% to 5.67%[22–24,26,27,31,35,38,39,43,44,46,47]) (very-low to low certainty evidence). There was no evidence of an increase in harms compared with standard plasma.

5.2 | Quality (certainty) of the evidence

Where meta-analysis was possible, we used GRADE to assess our certainty in the result (Table 1). Certainty in the evidence was assessed as very-low to low certainty for all outcomes apart from mortality data in the comparison CP versus standard care.

Evidence was downgraded for serious ROB (lack of blinding, baseline imbalance, randomisation processes, missing data and unclear reporting of outcomes) and imprecision (wide confidence intervals around the effect estimate, and small sample sizes for the outcome of interest). Some of the sources of potential bias (such as patient and personnel blinding) would be hard to overcome in future trials due to the issues in finding an ethical control infusion: even saline is problematic, with the risk of volume overload, and ease with which it can be differentiated from plasma.

SAEs were also downgraded for inconsistency as the heterogeneity was significant between studies, this is likely to be due to the variation in reporting of the SAEs. This may be in part due to differing regulatory environments and different classifications of CP, requiring

varying levels of AE reporting including the need to use a grading system (e.g., MedDRA[64]).

We included lower-level evidence for the assessment of safety outcomes. However, we were unable to perform quantitative analyses, and so have only presented these data as reported in Appendix B in Data S1.

There were very few endpoints reported consistently enough for meta-analysis. The difficulty in defining endpoints, especially time-to-event endpoints,[65] is discussed further in Appendix A6 in Data S1.

5.3 | Strengths and Limitations of this review

We have attempted to minimise potential bias in the review process, using Cochrane methods and PRISMA guidelines for reporting. We conducted a comprehensive search: searching data sources to ensure that all relevant studies would be captured, using multiple databases and reference lists of included studies. We included conference proceedings and included a search of clinical trial registries. We also attempted to contact authors for additional data and for clarification of their data.

There were no restrictions for the language in which the paper was originally published. We pre-specified outcomes prior to analysis and have explained the rationale for including one additional outcome (any SAEs).

We undertook duplicate screening, data extraction, and assessment of bias. Additionally, the clinical advisor (LE) was consulted for disagreements, or need for clarification.

The limitations of this review mostly arose due to gaps in the evidence base, which are discussed more fully in the next section.

5.4 | Interpretation and context

A recent analysis of individual patient data (IPD) pooled from eight RCTs[9] IPD reported an OR for mortality of 0.85 at day 28 (95% credible interval, 0.62 to 1.18; posterior probability of OR <1 of 84%). These results are broadly comparable and in agreement with our own aggregate analyses for 30-day mortality. However, it should be noted that the IPD analysis included two RCTs[66,67] published after our 30th November 2021 cut-off, but did not include the two largest RCTs of CP RECOVERY[3] and REMAP-CAP[30] which we have analysed, and which together contribute 83% of sample size contributing to our analysis of 30-day mortality for CP versus SoC.

A limitation of the current evidence base is that of the 30 RCTs and two non-randomised studies included in our meta-analysis, 26 studies (24 RCTs) excluded children and 16 RCTs excluded pregnant women, with 1 RCT[39] admitting pregnant women only on the second round of recruitment. Given that children and pregnant women are both considered to be at increased risk of serious disease and death from many severe respiratory viral infections, their exclusion from trials is concerning. Of the 144 ongoing studies we identified, most trials will exclude children and pregnant women. Many ongoing studies have an upper age cut-off (of 65, 70 or 80 years), despite older age being one of the biggest risk factors for COVID-19.

The precision of our meta-analysis was affected by the different titres of CP-neutralising antibodies between trials (Table A1 in Data S1). We tried to address this by subgrouping studies based on the CP-titre reported, and whether it was considered high enough according to FDA criteria (see Appendix A3 in Data S1). However, several studies used local assays that could not be correlated with an FDA reference method. Since we conducted our first search, several variants of SARS-CoV-2 have arisen worldwide and may require much higher antibody titres measured using ELISA assays.[68] Much higher titre CP, from vaccinated convalescent donors, may be active against future variants[69] indicating that new COVID CP trials should aim to use very high titre CP standardised using internationally recognised methods.

Similarly, between trials, there was heterogeneity of patient groups and severity of illness on admission to hospital (Table 1). The RCTs in COVID may not have used the same criteria to categorise trial participants at enrolment and trials designed to treat different patient groups based on comorbidities and immune states were absent. Several COVID-19 studies reported clinical improvement using the WHO ordinal scale. However, the scale was revised several times over the course of 2020–2021, going from an 8-point scale[70] to a 10-point scale at its latest revision[71] which have made comparisons between trials difficult.

The results of our post hoc subgroup analysis by seropositivity at baseline are very similar to the results reported by RECOVERY alone. We have not found stronger evidence of this potential interaction than that reported by RECOVERY (with a similar trend also reported by REMAP-CAP, especially for organ support-free days) but similarly, we have not found any reason to discount the possibility that there is a small but important interaction, with immunocompromised individuals potentially benefitting more. This hypothesis is consistent with the REGN-COV2 RECOVERY trial,[21] which has shown no benefit of monoclonal antibodies for seropositive patients who either have advanced disease or who are immunocompetent. The very high baseline risk of immunocompromised individuals might translate very small relative risks into substantial absolute risk differences. REMAP-CAP has recently reopened for immunocompromised people to test this hypothesis.[72]

5.5 | Implications for research and practice

There is currently no evidence for a benefit of CP in an unselected population of patients hospitalised with coronaviruses or influenza. It is likely that the titre of the CP and the immune response of the recipient may both be important factors affecting response to treatment.

Studies should use CP of a high enough titre to elicit a biological response, and report the actual titre used as well as the minimum as described in the protocol. Matching variants between donor and recipient may not be feasible, but viral variants circulating at the time of collection of plasma and during the study should be recorded.

Studies should assess and publish antibody status (seropositivity) at baseline in both intervention and control groups, and identify and

report immunocompromised patients separately, to establish whether certain groups of patients are more likely to benefit from this intervention.

There are difficulties in designing truly blinded RCTs of CP or hIVIG (see Reference 73 for review). There are ethical problems with using a placebo which is assumed to have no clinical benefit, but has known harms.[74] One RCT[26] used a saline placebo, with potential concerns about volume overload, and six RCTs used a biologically active control, (FFP in 5 RCTs,[40–43,45] and IVIG in one[44]) which raises additional concerns about transfusion reactions.

Unless reported explicitly by investigators, it was difficult to distinguish the AEs experienced following transfusion from the symptoms of severe respiratory disease.[75] This limited the number of RCTs that we could include in our meta-analysis of AEs due to transfusion. There was also substantial variability in the way that AEs were recorded and reported in these studies. It was not always possible to determine the severity of AEs, and different studies used different criteria for SAEs. In some cases, it was hard to determine if SAE reporting was per event or per patient, making it extremely difficult to compare rates of AEs between studies. Blood components in the UK are not classified as medicines and so require a different grading system for reporting AEs to countries that classify CP as a medicine, e.g. Germany. A consensus on how AEs associated with blood products are reported in RCTs would help to address this problem.

6 | CONCLUSION

This review has highlighted several issues regarding study design and reporting which should be addressed in current and future research. A minimum titre should be established and ensured for a positive biological response to the therapy. Further research on the impact of CP/hIVIG in patients who have not produced antibodies to the virus prior to hospital admission or who are immunocompromised would be useful to target therapies at groups who will potentially benefit the most.

AUTHOR CONTRIBUTIONS

Catherine Kimber: screening and full text assessment, retrieved full text publications, data extraction, risk of bias assessment, entered data into RevMan and undertook subgroup analyses, performed GRADE assessments, interpreted the results, contributed to the development of the manuscript. **Abigail A. Lamikanra:** screening and full text assessment, retrieved full text publications, data extraction, risk of bias assessment, performed GRADE assessments, interpreted the results, contributed to the development of the manuscript. **Louise J. Geneen:** screening and full text assessment, retrieved full text publications, data extraction, risk of bias assessment, entered data into RevMan and undertook subgroup analyses, performed GRADE assessments, interpreted the results, contributed to the development of the manuscript. **Josie Sandercock:** data extraction, risk of bias assessment, and undertook all metaregression analyses, performed GRADE assessments, interpreted the results, contributed to the development of the manuscript. **Carolyn Doree:** developed and performed all search strategies and de-duplication, retrieved full text publications, contributed to the development of the manuscript. **Sarah J. Valk:** screening and full text assessment, retrieved full text publications, contributed to the development of the manuscript. **Lise J. Estcourt:** developed the initial idea of the review, developed, wrote, and registered the protocol, interpreted the results, and contributed to the development of the manuscript.

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ORCID

Catherine Kimber https://orcid.org/0000-0002-7796-9931
Abigail A. Lamikanra https://orcid.org/0000-0002-9287-2177
Louise J. Geneen https://orcid.org/0000-0001-6759-0437
Josie Sandercock https://orcid.org/0000-0001-7337-8635
Carolyn Dorée https://orcid.org/0000-0001-6955-7497
Sarah J. Valk https://orcid.org/0000-0003-3964-2505
Lise J. Estcourt https://orcid.org/0000-0003-4309-9162

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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ORIGINAL ARTICLE

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Low-titer group O whole blood in military ground ambulances: Lessons from the Israel Defense Forces initial experience

Tomer Talmy[1,2] | Michael Malkin[1,2] | Akiva Esterson[1] | Mark H. Yazer[3] | Anat Sebbag[1] | Avi Shina[1,2] | Eilat Shinar[4] | Elon Glassberg[1,5,6] | Sami Gendler[1] | Ofer Almog[1,2]

[1]Israel Defense Forces, Medical Corps, Ramat Gan, Israel

[2]Department of Military Medicine, Faculty of Medicine, Hebrew University, Jerusalem, Israel

[3]Department of Pathology, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

[4]Magen David Adom, National Blood Services, Ramat Gan, Israel

[5]The Azrieli Faculty of Medicine, Bar-Ilan University, Safed, Israel

[6]The Uniformed Services University of the Health Sciences, Bethesda, Maryland, USA

Correspondence
Tomer Talmy, Israel Defense Forces, Medical Corps, Surgeon General's Headquarters, Ramat Gan 5262000, Israel.
Email: ttalmy@gmail.com

Abstract

Background: Cold-stored low-titer group O whole blood (LTOWB) has become increasingly utilised in both prehospital and in-hospital settings for resuscitation of traumatic haemorrhage. However, implementing the use of LTOWB to ground medical teams has been limited due to logistic challenges.

Methods: In 2022, the Israel Defense Forces (IDF) started using LTOWB in ambulances for the first time in Israel. This report details the initial experience of this roll-out and presents a case-series of the first patients treated with LTOWB.

Results: Between January–December 2022, seven trauma patients received LTOWB administered by ground IDF intensive care ambulances after presenting with profound shock. Median time from injury to administration of LTOWB was 35 min. All patients had evidence of severe bleeding upon hospital arrival with six undergoing damage control laparotomy and all but one surviving to discharge.

Conclusions: The implementation of LTOWB in ground medical units is in its early stages, but continued experience may demonstrate its feasibility, safety, and effectiveness in the prehospital setting. Further research is necessary to fully understand the indications, methodology, and benefits of LTOWB in resuscitating severely injured trauma patients in this setting.

KEYWORDS

damage control resuscitation, low titer group O whole blood, prehospital, prehospital transfusion, whole blood

1 | INTRODUCTION

Haemorrhage is the leading cause of preventable death in the setting of trauma.[1–3] Timely and balanced resuscitation, as embodied by the principles of damage-control resuscitation (DCR), confers a survival benefit for the haemorrhaging trauma patient.[4–6] The concept of DCR, dictating balanced ratios of packed red blood cells (PRBCs), plasma and platelets—reconstituting the makeup of whole blood, was devised to combat the early coagulopathy of trauma,[5] affecting more than 25% of trauma patients by the time they arrive to the hospital, and conferring a significant increase in mortality.[7,8]

Tomer Talmy and Michael Malkin contributed equally to this study and are co-first authors.

Sami Gendler and Ofer Almog contributed equally to this study and are co-last authors.

Recently, cold-stored low-titer group O whole blood (LTOWB) has become increasingly utilised in resuscitation of both paediatric and adult trauma patients with several suggested advantages over component therapy.[9–11] LTOWB provides physiological ratios of blood components in one bag, that does not require reconstitution, and is associated with fewer donor exposures than component therapy.[12–14] Additional benefits of whole blood include the higher haematocrit, reduced volume of citrate-containing preservative and improved coagulation activity as compared with balanced component therapy.[15,16] However, the use of LTOWB in prehospital settings is met with significant deployment and logistic challenges, and has therefore been used in limited settings, primarily among helicopter emergency medical services.[17,18] In October 2017, the American Association of Blood Banks (AABB)[19] approved the use of whole blood as a standard product for patients with severe bleeding, but its use in ground ambulances has remained very limited.[20,21]

The use of blood products in the prehospital setting has become a fundamental part of remote damage-control resuscitation (RDCR), considering the potential benefit of their use close to the point-of-injury.[22] Since 2018, the Israel Defense Forces Medical Corps (IDF-MC) has instituted a whole blood program, utilising cold-stored LTOWB in its Airborne MedEvac Unit, demonstrating initial safety and logistic feasability.[23] In 2022, recognising the benefits of early transfusion of whole blood, the IDF-MC deployed whole blood in ground ambulances for the first time in Israel. Herein, we report on the initial experience, and present a case-series of the first patients receiving LTOWB by ground ambulance teams.

2 | STUDY DESIGN AND METHODS

2.1 | Setting and design

The IDF-MC provides prehospital trauma care to both civilians and soldiers injured in military or civilian circumstances (i.e., road traffic collision, falls) occurring in proximity to IDF bases. IDF-MC intensive care unit (ICU) ambulances are staffed with paramedic-led teams and provide both point-of-injury and en-route care. These teams are stationed along Israel's borders with varying transport times (Approximately between 30 and 90 min, depending on region). In most military scenarios, these ICU ambulances are tasked with rapidly evacuating patients to the hospital following hand-over from teams providing point-of-injury care. Since the IDF does not operate military hospitals, patients requiring further care are transferred to civilian hospitals, as part of the national health system.

In 2022, the IDF-MC initiated the deployment of low titer cold-stored O RhD-positive whole blood (LTOWB) to several ICU ambulances, replacing the previous IDF-MC's standard fluid of choice for trauma resuscitation—freeze-dried plasma (FDP).[24] Each of the ICU ambulances were equipped with two units of LTOWB, replaced upon expiry or use. We retrospectively reviewed the IDF Trauma Registry (IDF-TR) to identify cases of whole blood administration by ground ICU ambulance teams, between January and December 2022. In our analysis, we excluded cases of patients administered whole blood for the indication of traumatic cardiac arrest. The IDF-MC Institutional Review Board approved this study (Protocol #: 1948–2018). This manuscript was written and formatted according to the STROBE guidelines for cohort studies.[25]

2.2 | Products and logistics

All LTOWB units to be used in the IDF were supplied by Magen David National Blood Services (MDABS), Israel's national blood bank, from whole blood donations of male–only O Rh + volunteer donors, with a volume of 450 ± 50 mL, as previously described.[23] All whole blood units are collected in CPDA-1, with a maximal expiration of 35-days. Each unit undergoes an automated screening procedure, and only units with a titer of Anti-A or Anti-B of <1:100 were classified as LTOWB during the study period. Units identified as LTOWB are tagged and do not undergo separation into components, creating an inventory for use by the IDF as well as by several civilian hospitals. Currently, platelet-sparing leukocyte reduction is not utilised during unit processing as quality control tests performed during the validation of the filtration procedure revealed a significant reduction in the platelet content of the final LTOWB product. Units are supplied to the IDF ICU ambulance teams upon demand, to be used within 21 days from the time of collection. LTOWB units can be issued within 3 days after collection, due to preparation and transport times to the remote military units. Units not utilised during this period are returned to MDABS laboratories, to be discarded. During transport in the ICU ambulances, units are stored in a Crēdo ProMed Cooler™ (Pelican BioThermal, Plymouth, MN), and transferred to monitored, alarm-equipped medical refrigerators (Horizon Series™ HLR105, Helmer Scientific, Noblesville, IN) when the team is on-base.

2.3 | Training and administration protocol

For the initial rollout, several ICU ambulances were selected to be equipped with LTOWB. Paramedics manning these teams, underwent dedicated instruction and certification for the administration of LTOWB by a medical officer from the IDF Trauma and Combat Medicine Branch. The instructional sessions included an overview of the rationale for use of whole blood, indications, administration protocols, storage principles and diagnosis and treatment of adverse events, in accordance with the corresponding clinical practice guideline (CPG).[26] Thereafter, paramedics were required to achieve a passing score in a multiple-choice examination assessing the principles of LTOWB through a series of knowledge-based questions and clinical vignettes. Administration of whole blood by IDF paramedics was predicated on approval of an on-call physician (Board-certified specialist in emergency medicine/anaesthesia/general surgery), abiding by the indications for volume resuscitation as detailed below. Each use was subject to immediate reporting and recording on both casualty cards and our prehospital trauma registry.

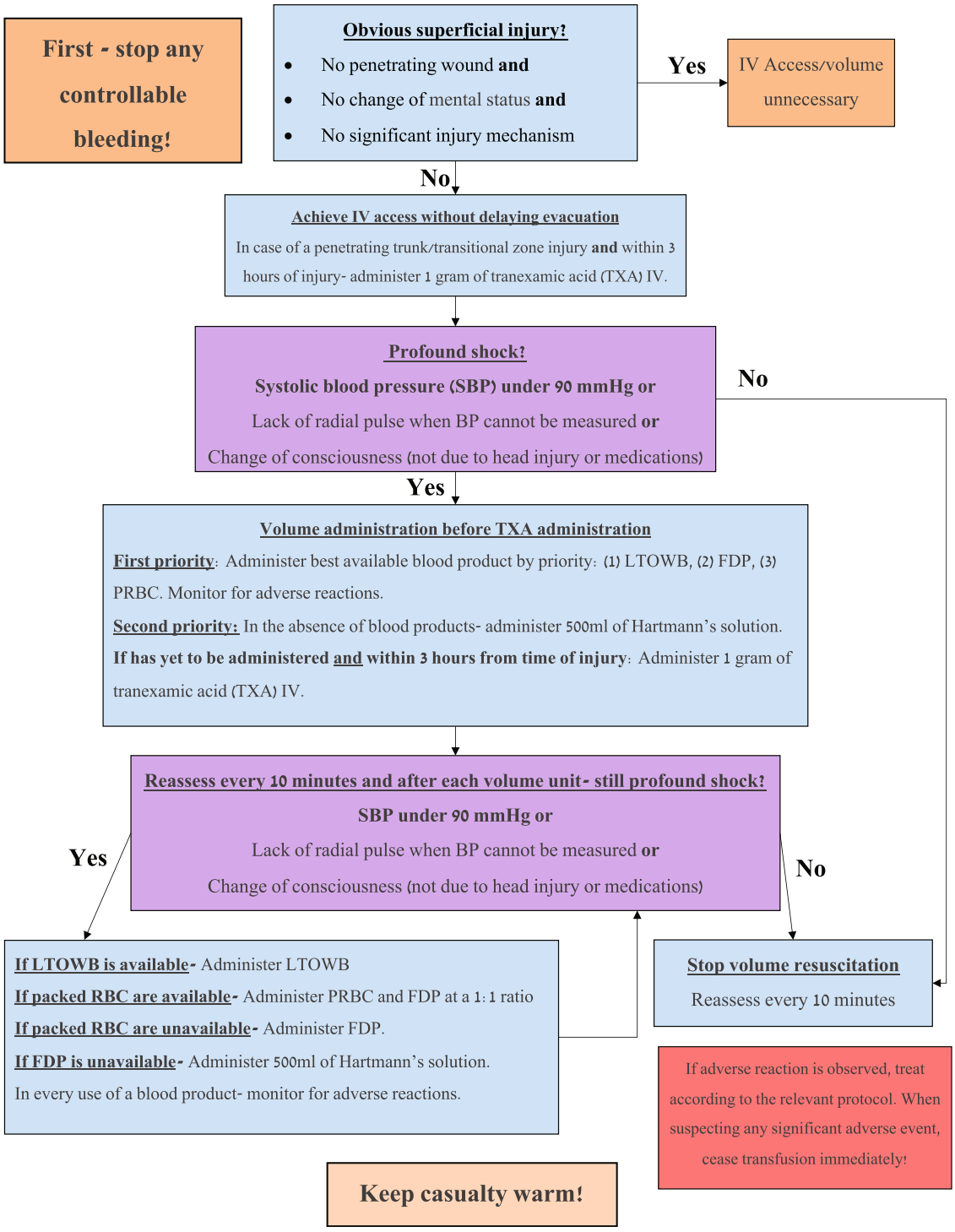

FIGURE 1 Israel Defense Forces Medical Corps standard operating procedure for remote damage control resuscitation (RDCR). BP, blood pressure; FDP, freeze-dried plasma; LTOWB, low titer group O whole blood; PRBC, packed red blood cells; SBP, systolic blood pressure.

2.4 | Whole blood administration CPG

The IDF-MC CPGs for Remote Damage Control Resuscitation[26] instruct use of the best available resuscitation fluid in patients deemed to present with one or more signs of profound shock (Figure 1). The primary indication is a systolic blood pressure measurement of ≤90 mmHg in a trauma patient. If blood pressure is unmeasurable due to clinical presentation or technical reasons, unpalpable radial pulse or altered mental status, estimated not to result from head injury or medication administration, are used as indications. Administration of fluids through a blood warmer (Warrior, QinFlow Ltd.) is recommended via both the intravenous or

TABLE 1 Description and characteristics of patients treated with LTOWB by Israel Defense Forces ICU ambulances.

Case	Age	Sex	Injury setting	Trauma mechanism	Injury description	Initial vital signs	Assessment and initial treatment	Whole blood indication	Access method	Time from injury to whole blood administration	Time from injury to hospital arrival	In-hospital care	Outcome
1	21	Male	Military	Gunshot wound	Multiple gunshot wounds to abdomen, right thigh and left calf	GCS – 15 Pulse – 110 BPM Blood pressure – Unmeasurable SaO_2–89%	Fully conscious, patent airway. Applied tourniquet proximal to left calf wound. Developed tachycardia of 150 BPM, GCS of 11 and was pale and clammy upon transfer to the MICU. Later administered 1 g of IV TXA and 25 mg of IV ketamine.	Altered mental status with unmeasurable blood pressure following penetrating trauma	14G IV access Through blood warmer	40 min	60 min	Endotracheal intubation, massive transfusion protocol, damage control laparotomy and vascular shunt in left thigh.	Survived to discharge, 8-day ICU stay
2	28	Male	Military	Gunshot wound	Multiple gunshot wounds to right lower abdomen, mid-scapular region and right posterior thigh.	GCS – 15 Pulse – 120 BPM Blood pressure - 90/60 mmHg SaO_2–100%	Fully conscious, patent airway. No palpable radial pulse, pale and clammy. Repeat blood pressure read 85 mmHg systolic. Later administered 25 mg of IV ketamine.	Profound hypotension following penetrating trauma	18G IV access Without blood warmer	23 min	32 min	Two units of uncross-matched PRBC, rushed for a damage control laparotomy with cross clamping of the aorta and several enterotomies.	Survived to discharge, 7-day ICU stay
3	49	Male	Military	Gunshot wound	Multiple gunshot wounds to the groin, thigh and gluteal area	GCS – 12 Pulse – 81 BPM Blood pressure – 91/50 mmHg SaO_2–84%	Obtunded, patent airway. No palpable radial pulse, pale and clammy. Repeat blood pressure read	Altered mental status and hypotension following penetrating trauma	18G IV access Through blood warmer	40 min	66 min	Upon arrival, HR of 75 BPM and blood pressure of 100/60. Underwent exploratory laparotomy	Survived to discharge, 1-day ICU stay

(Continues)

TABLE 1 (Continued)

Case	Age	Sex	Injury setting	Trauma mechanism	Injury description	Initial vital signs	Assessment and initial treatment	Whole blood indication	Access method	Time from injury to whole blood administration	Time from injury to hospital arrival	In-hospital care	Outcome
							85 mmHg systolic. Later administered 1 g of IV TXA and 25 mg of IV ketamine.					with primary repair of small bowel perforations following identification of free air in abdominal CT. Internal fixation of compound fracture in right femur.	
4	35	Female	Civilian – Motor Vehicle Accident	Blunt trauma in motor vehicle accident (Passenger)	Deformation of right forearm, bruise on abdominal wall complaining of pain in back and arms.	GCS – 15 Pulse – 88 BPM Blood pressure – Unmeasurable SaO_2–95%	Fully conscious at first, patent airway. After several minutes, tachycardic with reduced alertness (GCS 10), administered oxygen via face mask. Later administered 1 g of TXA IV, 25 mg of IV ketamine and a unit of freeze-dries plasma upon reassessment following LTOWB administration.	Altered mental status and unmeasurable blood pressure following blunt trauma	18G IV access Through blood warmer	21 min	41 min	Upon arrival HR of 120, blood pressure 60/30 mmHg. Started on massive transfusion protocol and rushed for exploratory damage control laparotomy. Underwent resection or repair of several small bowel lacerations.	Survived to discharge, 14-day ICU stay, 73 day hospital stay
5	59	Male	Military	Gunshot wound	Single gunshot wound to abdomen	GCS – 13 Pulse – 134 BPM	Obtunded, patent airway, tachypneic.	Altered mental status and unmeasurable	Through 15G intraosseous access (NIO	34 min	42 min	Upon admission, HR of 80, BP of 111/68 and	Died during ICU stay.

TABLE 1 (Continued)

Case	Age	Sex	Injury setting	Trauma mechanism	Injury description	Initial vital signs	Assessment and initial treatment	Whole blood indication	Access method	Time from injury to whole blood administration	Time from injury to hospital arrival	In-hospital care	Outcome
						Blood pressure – Unmeasurable SaO_2 – Unmeasurable	No palpable radial pulse, pale and clammy with decreased breath sounds in right hemithorax. Monitored pulse of 134 BPM. Later administered 1 g of TXA IV and received needle application in right hemithorax.	blood pressure following penetrating trauma	Adult™, Persys Medical, Houston, TX) Without blood warmer			GCS of 15, diagnosed with grade 5 liver laceration. Underwent primary arterial embolization but died during ICU stay.	
6	16	Male	Civilian – Motor Vehicle Accident	Blunt trauma in motor vehicle accident (Passenger)	Diffuse blunt injuries, laceration above eyebrow, subcutaneous hematomas in abdomen and flank	GCS – 11 Pulse – 147 BPM Blood pressure – 97/72 SaO_2 – Unmeasurable	Obtunded, responsive to pain, tachypneic. No palpable radial pulse, blood pressure unmeasurable with increase in monitored pulse to 150 BMP after several minutes. Later administered 1 g of TXA IV and 25 mg of IV ketamine.	Altered mental status and unmeasurable blood pressure following blunt trauma	18G IV access Through blood warmer	52 min	85 min	Upon arrival, HR of 110, BP of 90/42, rushed for exploratory damage control laparotomy with severe bleeding from liver laceration. Later underwent fixation of acetabular and sacroiliac joint fractures.	Survived to discharge, 7-day ICU stay, 21 day hospital stay
7	18	Male	Military	Gunshot wound	Multiple gunshot wounds to the abdomen	GCS – 14 Pulse – 170 BPM Blood pressure – Unmeasurable	Obtunded, responsive to voice, tachypneic.	Altered mental status and unmeasurable blood	18G IV access Through blood warmer	35 min	53 min	Upon admission, obtunded with GCS of 12, heart rate	Survived to discharge, 10-day ICU stay

(Continues)

TABLE 1 (Continued)

Case	Age	Sex	Injury setting	Trauma mechanism	Injury description	Initial vital signs	Assessment and initial treatment	Whole blood indication	Access method	Time from injury to whole blood administration	Time from injury to hospital arrival	In-hospital care	Outcome
					and gluteal area	SaO_2 – Unmeasurable	No palpable radial pulse, monitored pulse of 170 BPM, blood pressure unmeasurable. Later administered 1 g of TXA IV.	pressure following penetrating trauma				of 150 BPM, started on massive transfusion protocol and received endotracheal intubation. Rushed for damage control laparotomy with resection of several small bowel segments. Additional laparotomy the following day due to hemodynamic instability.	

Note: Data ascertained from review of cases in the IDF-TR and hospital records of patients receiving whole blood.

Abbreviations: AW, airway; BPM, beats per minute; CT, computed tomography; GCS, Glasgow coma scale; ICU, intensive care unit; IV, intravenous; PRBC, packed red blood cells; SaO_2, oxygen saturation; TXA, tranexamic acid.

intraosseous routes. Administration of 1 g of tranexamic acid (TXA) is also indicated for patients with profound shock (If presenting within 3 h from injury). Following the completion of each unit, patients are reassessed for signs of profound shock. If signs of profound shock remain, an additional unit of the best available fluid is indicated. The hierarchy of products currently available to IDF-MC teams includes LTOWB, followed by FDP, packed red blood cells and crystalloids if no blood products are available. Additionally, the IDF CPG for prehospital cardiac arrest resulting from trauma[27] also instruct initiation of volume resuscitation with the best available product.

2.5 | Data sources, variables, measures and analysis

The IDF Trauma Registry (IDF-TR) is a prehospital trauma registry established in 1997 to document point-of-injury and en-route care of trauma patients treated by IDF advanced life support (ALS) teams.[28] Data recorded in the registry is based on casualty cards filled during treatment and additional data entered by ALS providers as part of the after-action report for each incident. Data entry undergoes quality assurance review by a team at the IDF-MC Trauma and Combat Medicine Branch, which maintains the database. For select cases of interest (i.e., severely wounded patients, novel treatment administered etc.), data regarding the in-hospital diagnoses, treatment and outcomes are provided by civilian hospital trauma coordinators and integrated into the registry. In this study, cases identified in the IDF-TR of ground ambulance LTOWB administration were extracted for manual review of both categorised and free-text case data by two of the authors (T. T, M. M). Variables of interest documented in the registry were recorded in dedicated Excel spreadsheets (i.e., patient age, sex, trauma mechanism, vital signs etc.) for further statistical analyses. Continuous variables are presented as medians and interquartile ranges (IQR) and categorical variables as *n* (%). Statistical analyses and were performed using R (version 4.0.3; R Foundation, Vienna, Austria).

3 | RESULTS

3.1 | Patient demographics and injury setting

Overall, 10 cases of ground ambulance LTOWB administration were identified in the IDF-TR between January and December 2022. During this time-period, 23 patients treated by other IDF-MC ALS teams, not equipped with whole blood, were administered freeze-dried plasma, and 11 patients were administered LTOWB by the IDF Airborne MedEvac Unit. In three instances of LTOWB administration by ground teams, the indication was traumatic cardiac arrest prior to ALS team arrival, and these were excluded from the analysis. Of the seven patients administered LTOWB for profound shock, six were males with a median age of 28 (IQR 19.5–42) years. Five of the patients were injured in military circumstances, all from gunshot wounds, while two sustained blunt injuries in civilian road traffic collisions. Table 1 describes the characteristics, presentation, and outcomes of the patients included in the case-series.

3.2 | Prehospital presentation, treatment, whole blood indication and hospital outcomes

The median initial heart rate at presentation was 120 (IQR 99–141), systolic blood pressure was unmeasurable for four patients (Range 90–97 among measured) and digital pulse oximetry unmeasurable for three patients. The median Glasgow Coma Scale at presentation was 14 (IQR 12.5–15). LTOWB was administered after a hypotensive measurement (≤90 mmHg) in two cases. In the remaining five cases, the indication for volume resuscitation was altered mental status, in the absence of head injury or premedication with unmeasurable blood pressure. Whole blood was administered through intravenous access in 6/7 cases and was administered through a blood warmer in 5/7 cases. The median time from injury to LTOWB administration was 35 (IQR 28.5–40) minutes, and median time from injury to hospital arrival 53 (IQR 41.5–63) minutes. In only one case, a second unit of volume resuscitation (With the highest priority blood product available to the team) was indicated following reassessment and prior to hospital arrival. In this case, a unit of freeze-dried plasma was administered, as the team had only one unit of non-expired whole blood on hand. Additionally, 1 g of IV tranexamic acid was administered in 6/7 cases. No adverse events were recorded after whole blood administration.

Upon hospital arrival, six of seven patients underwent damage control laparotomy and three were started on a massive transfusion protocol (Table 1). All patients except one survived to discharge following ICU admission. One patient, a 59-year-old male with a grade 5 liver laceration, died during ICU stay following angioembolization. Table 2 presents the vital signs and laboratory measures of the LTOWB recipients upon hospital admission.

4 | DISCUSSION

This small case series presents the initial experience of the IDF-MC in deploying LTOWB in ground ambulances, for the first time in Israel. This series demonstrates that administration of LTOWB by paramedic-lead ICU ambulance teams is feasible, and based on current evidence, could be safe and potentially improve outcomes of patients with severe traumatic haemorrhage. The hospital data of patients in this case-series demonstrates that they were indeed seriously wounded, suffered from severe bleeding, and that prehospital LTOWB transfusion was indeed indicated.

Although currently limited, our experience with LTOWB comes at a crucial time in the debate over prehospital utilisation of blood products. The benefits of whole blood (albeit – fresh whole blood), demonstrated in several observational studies,[29,30] along with its increased utilisation in civilian settings[9–11,17] have raised the prospects of

TABLE 2 Laboratory measures upon admission of patients treated with LTOWB by Israel Defense Forces ICU ambulances.

Case	Age	Gender	Injury setting	Trauma mechanism	SBP in the ED (mmHg)	DBP in the ED (mmHg)	HR in the ED (BPM)	Hb (g/dL)	PLT (K/microL)	Fibrinogen (mg/dl)	INR	pH	Base excess (mmol/L)	Lactate (mmol/L)	Ionised calcium (mmol/L)
1	21	Male	Military	Gunshot wound	99	68	152	14.4	185	238	1.28	7.27	−7.7	6.2	0.79
2	28	Male	Military	Gunshot wound	90	62	117	15.3	219	248	1.02	7.35	−7	4.3	1.21
3	49	Male	Military	Gunshot wound	100	60	75	13.1	228	591	1.01	7.3	−0.7	4	1.07
4	35	Female	Civilian – Motor Vehicle Accident	Blunt trauma in motor vehicle accident (Passenger)	60	30	120	11.6	332	139.6	1.25	6.9	−24.1	2.86	1.07
5	59	Male	Military	Gunshot wound	N/A	N/A	N/A	10.9	110	573	1.79	6.99	−21.1	17	1.05
6	16	Male	Civilian – Motor Vehicle Accident	Blunt trauma in motor vehicle accident (Passenger)	90	42	110	9.1	451	N/A	N/A	N/A	N/A	N/A	N/A
7	18	Male	Military	Gunshot wound	N/A	N/A	150	13.3	211	925	1.34	6.89	−19	32.4	1.09

Note: Data ascertained from review of cases in the IDF-TR and hospital records of patients receiving whole blood.
Abbreviations: BPM, beats per minute; DBP, diastolic blood pressure; ED, emergency department; Hb, haemoglobin; HR, heart rate; INR, international normalised ratio; PLT, platelets; SBP, systolic blood pressure.

deploying whole blood in the prehospital military setting. The recently published RePHILL[31] trial, has brought into question the benefits of prehospital PRBC and plasma. Of note is that the study population, setting and outcomes of the RePHILL trial differ substantially from our current report. Specifically, our cohort is characterised by a higher proportion of penetrating injuries and shorter times to blood administration and transport times as compared with the RePHILL trial, along with utilisation of whole blood units as opposed to PRBC and plasma. Based on the current evidence on the benefits and safety of whole blood,[9,10,17,22,23,29,32–34] we chose to implement its use in the prehospital setting, with the aim of continuing to evaluate our data along with growing evidence on its use.

Five of the patients in this study suffered from single or multiple gunshot wounds, resulting in severe bleeding and signs of profound shock, and six underwent damage control laparotomy. As compared with previous publications on the use of whole blood for trauma resuscitation, this case-series seems to be more reflective of combat injuries observed on the battlefield. Perkins et al.[35] compared the use of fresh-whole blood versus platelets, with penetrating trauma accounting for more than 90% of injuries in both groups. In contrast, observational studies performed in the civilian setting have evaluated the use of whole blood predominantly for blunt injuries.[17,36,37] Additionally, in the initial report on use of LTOWB in the IDF Airborne MedEvac unit by Levin et al.,[23] less than 30% of patients had penetrating injury. The in-hospital diagnoses and outcomes in this current case-series further emphasise the severity of injuries in this small cohort. Thus, we expect that based on the initial rollout in ICU ambulances, continued use of LTOWB may yield more reliable measures of the benefits and safety among patient populations with combat injuries.

Time to whole blood administration may play a key role in determining its efficacy and potential effect on mortality.[22] The Joint Trauma System consensus statement on whole blood calls for its availability within 30 min of injury.[38] In our initial experience, median time to administration was 35 min from injury. Delays in LTOWB administration in our setting may be attributed to several possible causes: complexity of casualty extraction in military circumstances, difficulties in obtaining vascular access and the need to obtain authorization from an on-call physician before proceeding. As noted, five of seven patients described were injured in military scenarios, and extraction from the point-of-injury may have delayed initial assessment by the ICU team. Establishment of peripheral intravenous access may be challenging in patients with shock,[39] as has been mostly demonstrated in the context of septic shock.[40] As a result, the use of intraosseous access can be considered an alternative for patients requiring emergent vascular access such as in the case of hypovolemic shock. While intravenous access is often preferred as the initial route,[39] flow rates of whole blood through the intraosseous route have been demonstrated as being sufficient and recommend its use could potentially expedite time to transfusion.[41] Accordingly, we plan on evaluating the use of additional intraosseous access devices and techniques for whole blood transfusion. Investigation of the cases presented in this report did not reveal an instance of delay due to on-call physician unavailability. However, when envisioning the potential use of LTOWB in wartime scenarios, "on-call" physician authorization may not be feasible and therefore, establishing strict criteria and indications for administration among unexperienced providers is vital, with other products such as FDP serving as alternatives in certain instances.

The current IDF-MC guidelines for volume resuscitation dictate that hypotension, as determined by a systolic blood pressure ≤90 mmHg is the primary measure indicating volume resuscitation. In four cases, volume resuscitation was indicated due to altered mental status and unmeasurable blood pressure. Considering the potential risk for adverse events upon blood product administration, we believe that indications for volume resuscitation, specifically in the context of inexperienced ALS providers, must rely on objective measures such as systolic blood pressure. However, we recognise that in patients with profound shock, blood pressure measurement may sometimes be challenging or inaccurate, specifically during en-route care.[42] Although review of the cases presented here revealed that early volume resuscitation was warranted in all cases, one must consider the possibility of trauma patients who could potentially benefit from LTOWB, who did not fulfil the current criteria. Importantly, administration of whole blood by paramedic-led teams requires policy change,[20] and we thus instituted several stopgaps to ensure proper and indicated administration. Balancing the risks and benefits of whole blood administration could be informed by research evaluating the sensitivity and specificity of prehospital signs dictating hemorrhagic shock, and investigations of additional measures to reliably assess volume status such as point-of-care ultrasound or point of care lactate measurement.[43,44]

The thresholds for storage time and Anti-A and Anti-B titers utilised in this deployment were stringent, as to reduce the risk of adverse events or potentially diminishing efficacy of LTOWB during this preliminary rollout. Although use of these thresholds was implemented as to reduce the likelihood of adverse transfusion-related reactions or reduced hemostatic activity,[45] the low antibody (<1:100 titer) and storage-time (14-days from receipt by the ICU ambulances) thresholds may be currently unsuitable for larger-scale operational use. First, use of cold-stored whole blood is reliant on the inventory of the National Blood Services, which would presumably be overburdened in times of war, supplying routine hospital requirements as well as the treatment of civilian war-related trauma injuries. Second, maintenance of the cold chain and timely replacement of blood units within the currently determined expiry window may also be hindered by austere operational circumstances. Therefore, further laboratory and clinical data must be collected and analysed to determine if a more permissive approach, with regards to titter and storage, may be possible. Efforts have now been initiated to reduce the duration of the supply-chain with the aim of increasing the expiry window to 21 days in the ICU ambulances. An additional concern underlying the deployment of cold-stored LTOWB to ground units is the waste and discarding of valuable blood units. Levin et al.[23] documented a utilisation rate of 2% in the IDF Airborne MedEvac whole blood deployment, indicative of large amounts of discarded products. As such,

novel approaches, such as the rotation of whole blood units as pioneered by the Southwest Texas Regional Advisory Council,[21] may warrant adoption to the military and national settings, aiming to maximise usage of products.

An additional topic which warrants discussion in the context of our patient population is the use of Rhesus D positive (RhD+) LTOWB on a universal basis. In this current case-series, 35-year-old woman received a unit of Rh + LTOWB during prehospital treatment, following severe blunt trauma in a motor vehicle accident. Given her hospital presentation in severe hemorrhagic shock (Blood pressure 60/30, rushed for damage control laparotomy), the single unit of LTOWB administered during prehospital transport may have contributed greatly to her survival. As has been thoroughly discussed by McGinity and colleagues,[46] the primary concern with uncrossmatched use of RhD+ blood is anti-D alloimmunization and subsequent hemolytic disease of the fetus and newborn among women of childbearing age. Selleng et al.[47] demonstrated that the risk of alloimmunization among RhD- trauma patients receiving Rh + transfusions is far inferior to that of RhD- healthy volunteers.[47] McGinity et al.[46] expanded on the risk–benefit analysis of RhD+ transfusions, stating that sex differences in injury epidemiology further exemplify the low risks of child-bearing age alloimmunization within whole blood programs. These reservations on the potential risk, joined with the suggested benefits of whole blood for severe traumatic haemorrhage may favour the universal use of more readily available, Rh + units, to reduce mortality and improve availability of LTOWB.[48,49] Despite the latter, rollout of RhD+ LTOWB in military organisations, such as the IDF which does not exclude females from any combat role, warrants additional discussion and consideration as the evidence on the topic continues to amount.

The use of LTOWB in the IDF ground units is in its infancy and will continue to evolve in the coming years. Continued experience with treatment of trauma patients with LTOWB in both aeromedical and ground units may prove feasibility, safety and potential efficacy. The initial experience with ground deployment and treatment of predominantly military-related injuries as presented here, could contribute to the end goal of bringing whole blood resuscitation far-forward, to austere, remote combat environments, as well as to civilian prehospital national emergency medical services. This experience will enable further refinement of guidelines and techniques for whole blood transfusion among prehospital providers. Future studies are required to better characterise the indications, safety, and benefits of whole blood in resuscitating severely injured trauma patients in the prehospital setting.

AUTHOR CONTRIBUTIONS

TT, MM, SG and OA conceptualized the study and its design. TT performed the statistical analysis. TT and MM collected the clinical data and drafted the initial manuscript. AE performed data collection and revised the manuscript. MH, AS, ES, EG, SG and OA provided critical revisions of the manuscript. All authors approved the final version of the manuscript and are accountable for the accuracy and integrity of the work.

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CONFLICT OF INTEREST STATEMENT

The authors have no competing interests. This work was conducted as part of the Israel Defense Forces Medical Corps Trauma and Combat Medicine Branch's efforts for quality control and improvement in trauma care, and did not receive any designated funding.

PATIENT CONSENT STATEMENT

The Israel Defense Forces Institutional Review Board waived the requirement for informed consent considering the retrospective nature of this study.

ORCID

Tomer Talmy https://orcid.org/0000-0002-7440-8864
Michael Malkin https://orcid.org/0000-0002-9769-1893
Mark H. Yazer https://orcid.org/0000-0001-6740-2758
Eilat Shinar https://orcid.org/0000-0002-5658-248X
Sami Gendler https://orcid.org/0000-0002-2772-9550
Ofer Almog https://orcid.org/0000-0002-0293-681X

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ORIGINAL ARTICLE

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Comparing transfusion practice at multiple hospitals using electronically collected and analysed data

Ross D'Souza [1] | Amanpreet Singh Dhesi [1] | Kate Pendry [2] | Andrew Charlton [2] | Sophie Staples [3] | Nicholas A. Watkins [3] | Michael F. Murphy [1,2,3]

[1]Academic Department of Trauma & Orthopaedics, School of Medicine, University of Leeds, Leeds, UK

[2]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK

[3]Leeds Orthopaedic & Trauma Sciences, Leeds General Infirmary, University of Leeds, Leeds, UK

[4]Leeds Institute of Health Sciences, University of Leeds, Leeds, UK

[5]NIHR Leeds Biomedical Research Unit, Chapel Allerton Hospital, Leeds, UK

Correspondence
Michalis Panteli, Academic Department of Trauma & Orthopaedics, School of Medicine, University of Leeds, Clarendon Wing, Level D, Great George Street, Leeds LS1 3EX, West Yorkshire, UK.

Email: mike.murphy@nhsbt.nhs.uk

Abstract

Background

Comparisons of transfusion practice between organisations are time-consuming using manual methods for data collection. We performed a feasibility study to determine whether large-scale transfusion data from three English hospitals could be combined to allow comparisons of transfusion practice.

Methods

Clinical, laboratory and transfusion data from patients discharged between 1 April 2016 and 31 March 2017 were extracted from Patient Administration Systems (PAS), Laboratory Information Management Systems (LIMS), and electronic transfusion systems at three NHS hospitals, which are academic medical centres based in large cities outside London. A centralised database and business intelligence software were used to compare the data.

Results

The dataset contained 748 982 episodes of patient care with 91 410 blood components transfused. The study confirms the results of previous studies finding peaks in the ages of transfusion in the 0–4 years age range, in women of childbearing ages, and in males over 60 years. The number of components transfused per 1000 bed days was used as a standardised comparator. Red cell utilisation was 42.4, 40.4 and 49.5 units/1000 bed days and platelet utilisation 11.69, 7.76, and 11.66 units/1000 bed days. 60.5% (6848/11 310) of Group O D negative red cell units were transfused to non-group O D negative recipients. An analysis of component usage highlighted variations in practice, for example platelet usage for cardiac surgery varied from 2.4% to 7.3% across the three hospitals.

Conclusion

This feasibility study demonstrates that large electronic datasets from hospitals can be combined to identify areas for targeted interventions to improve transfusion practice.

KEYWORDS
Haemovigilance, blood, medicine, transfusion

1 | INTRODUCTION

Severe acute respiratory infections caused by strains of influenza or coronavirus often lead to hospitalisation and sometimes death. Symptomatic infection with SARS CoV-2 (COVID-19) has surpassed the annual global burden of death due to influenza or coronaviruses.[1] Although there are several effective vaccines for COVID-19 therapeutic treatments are still required. Patients particularly at risk are those with disorders that affect the immune system, for example, haematological malignancies or those receiving drugs that suppress an immune response, for example, after organ transplantation.[2,3]

Passive antibody therapies, including monoclonal antibody combinations have proven effective for COVID-19[4] However, the cost of these therapies is prohibitive[5] and new SARS-CoV variants may become resistant to anti-virals developed in response to previous variants.[6] Alternative and affordable responses to emerging strains of virus are needed.

Convalescent plasma (CP) is typically collected from donors with confirmed diagnosis of infection at least 2 weeks after recovery.[7] CP contains neutralising antibodies specific to the infectious agent but may also contain other immune modulators and clotting factors that can be fractionated out to produce hyperimmune-immunoglobulin (hIVIG).[8]

CP containing high titres of polyclonal antibody (Ab), has been used to treat patients hospitalised with respiratory syndromes caused by viral infections. Many studies have been poorly controlled but such series suggested decreased mortality in H1N1 Influenza infections in 1918–1920 and in 2009/2010, SARS-CoV-1 infections in 2003 and most recently COVID-19. Recent systematic reviews lacked data from RCTs and analysis did not consider the titre used within trials.[9] Moreover, there are concerns that CP may cause harm, potentially causing severe transfusion reactions such as transfusion-associated acute lung injury (TRALI) or antibody dependent enhancement of the viral infection.[10]

Prior to the COVID-19 pandemic, studies investigating the effectiveness of CP for viral infections varied in quality and the outcomes reported may not have reflected current international guidelines.[11,12]

2 | OBJECTIVE

To evaluate the evidence for the safety and effectiveness of using convalescent plasma (CP) or hyperimmune immunoglobulin (hIVIG) to treat severe respiratory disease caused by coronaviruses or influenza.

3 | METHODS

The protocol for this review was prospectively registered on PROSPERO (CRD42020176392), and the review was carried out in accordance with Cochrane methodology and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13]

3.1 | Search strategy

We searched multiple electronic databases (MEDLINE, PubMed, The Cochrane Library, Embase, Epistemonikos), ClinicalTrials.gov and WHO International Clinical Trials Registry Platform for ongoing studies, without language restriction, for all publication types on 12th October 2020 (see Appendix A1 in Data S1). We updated our search on 28th June 2021, increasing the number of databases (Cochrane COVID-19 Study Register, Transfusion Evidence Library, Web of Science). We limited the update search to systematic reviews and RCTs due to the significant number of randomised trials available at this point. Ongoing studies identified in our searches were checked on 30th November 2021 and included if published in full (peer-reviewed) by this date. We hand searched reference lists of systematic reviews and included RCTs.[11]

3.2 | Selection criteria

For assessments of effectiveness, we included RCTs comparing transfusion of CP products to any control arm with participants of any age who were admitted to hospital with severe respiratory illness. For assessments of safety, we included all study designs where patients received CP or hIVIG.

Two reviewers (CK, AL, LJG, SV) independently screened title and abstract, and then full-text using Covidence.

Where a publication was in a non-English language, we used electronic translation tools and sought the help of native speakers where appropriate (Appendix A2 in Data S1).

3.3 | Data extraction

Two of four reviewers (CK, AL, LJG, JS) independently extracted data using Covidence and Excel. Reviewers who were involved with any original trials (AL, LE) were not involved in the data extraction for those trials.

Extracted data included: details of study participants (demographic and disease characteristics), details of interventions (including titre, volume, timing of CP/hIVIG), and outcomes.

Outcomes extracted: all-cause mortality up to 30 and 90 days; need for mechanical ventilation (MV) and non-invasive ventilation (NIV) at up to 30 days; duration of MV or NIV; length of hospital stay; length of intensive care unit (ICU) stay; duration of viral detection from admission up to 30 days; transfusion-related serious adverse events (SAEs).

In a deviation from our protocol, we also assessed SAEs up to 30 days due to substantial variability in the way that SAEs were reported. For papers from the 1918 to 1920 influenza pandemic, reporting style was substantially different and, if reported, there was no grading of AEs. We recorded any potential AE described in these publications.

Where data were not available for a particular timepoint, we extracted data to the nearest possible timepoint. We sought clarification from trial authors where necessary.

3.4 | Risk of bias assessment

Two review authors (CK, AL, LJG, JS) independently assessed all eligible studies for risk of bias (ROB), using the Cochrane ROB tools. ROB1 for RCTs[14] and ROBINS-I for observational studies according to the Cochrane Handbook for Systematic Reviews of Interventions.[15] Reviewers who had worked on a trial (AL, LE) did not participate in ROB assessments for those studies.

Observational studies assessed as having "critical" ROB were not included in quantitative analyses.

3.5 | Data analysis

Statistical analyses were undertaken in Review Manager 5.4,[16] R[17] and the *metafor* package in R.[18] For dichotomous outcomes, we used the Mantel–Haenszel method, or Peto OR for rare events. We calculated the pooled risk ratio (RR) with a 95% confidence interval (CI), using the random effects model in RevMan5.[16] We used Tau^2 and I^2 in the assessment of heterogeneity, according to the guidelines laid out in the Cochrane handbook.[19]

We have not combined RCTs and non-RCTs and so have reported the results separately.

We planned to analyse continuous outcomes using mean difference (MD) or standardised mean difference (SMD) where different scales had been used. Continuous outcomes reported as median (IQR/range) could not be meta-analysed or pooled and have been reported narratively within tables.

Information from observational studies was collated in tables and not meta-analysed. Certainty of the evidence (based on meta-analysable data only) was assessed using GRADEPro.[20]

3.5.1 | Subgroup and sensitivity analysis

We subgrouped included trials by the type of respiratory infection.

We also subgrouped COVID-19 studies by their use of high titre or low titre/unselected plasma (see Appendix A3 in Data S1) in response to emerging research that highlighted the wide variability in CP titres used in practice.

We intended to undertake sensitivity analyses based on selection bias to examine evidence from 'low risk' studies only. However, this was not necessary for the RCTs as all included RCTs were assessed as low (or unclear) risk for mortality endpoints within this domain.

3.5.2 | *Post hoc* analysis of seropositivity

We performed a *post hoc* analysis of trials where there were sufficient data to assess the impact of SARS-CoV-2 antibody status at baseline due to emerging evidence of greater effectiveness of passive antibody therapy (monoclonal antibodies) for patients who are antibody negative at baseline.[21] Meta-regression for *post hoc* analysis of seropositivity was performed using the metafor[18] package in R.

4 | RESULTS

Our search yielded 4826 references (Figure 1 PRISMA flow diagram; for excluded studies see Appendix A4 in Data S1).

4.1 | Study Characteristics

We identified 110 completed studies (Figure 1), including 30 RCTs (four for influenza, n = 578; and 26 for COVID-19 SARS-CoV-2, *n* = 18 204).[3,7,22–49] There were no RCTs or non-randomised controlled trials identified for MERS or SARS (SARS-CoV-1) (Appendix A Supplementary Table A1 in Data S1). We included 76 non-randomised studies (Appendix B in Data S1). Of these, eleven were controlled studies, of which only two were at less than "critical" ROB[50,51] (Appendix A Supplementary Table A2 in Data S1) We included 67 uncontrolled studies: 12 assessing influenza A; two on MERS-CoV; four on SARS-CoV, and 49 on COVID-19 (SARS-CoV-2).

We also identified 143 ongoing studies (Appendix C) which were either controlled trials or single arm studies, which listed at least one safety outcome in their intended primary or secondary outcomes.

Study size in the quantitative analyses ranged from 29 to 11 555 (34 to 308 for influenza).

Of the four RCTs assessing influenza: two included children (*n* = 24/236 < 18 years)[39,45]; three RCTs[39,45,47] included pregnant women (3/270 pregnant women).

Of the 26 RCTs and 2 non-randomised studies that assessed COVID-19: one RCT included children (*n* = 26/11558 < 18 years).[3] Three RCTs[29,34,44] did not report whether they included children. Three RCTs[3,29,35] included pregnant women (*n* = 36/12575 pregnant women). Eight RCTs[22,24,30–33,36,44] did not report whether they included pregnant women.

4.2 | Comparisons

We identified four comparisons within the data that could be combined in quantitative analysis:

(1) CP versus standard care (SoC) or biologically inactive placebo (saline) (20 RCTs): 19 RCTs compared CP to SoC,[3,7,22–25,27–31,33–36,38,39] one RCT[26] compared SoC with saline placebo, and two retrospective observational studies[50,51] compared CP patients with matched controls;

(2) CP versus biologically active control (FFP or IVIG) (6 RCTs): five RCTs compared CP to non-immune FFP,[40–43,45] and one compared CP with IVIG.[44]

(3) hIVIG versus control (3 RCTs) Of these, two compared hIVIG with SoC,[46,47] one compared hIVIG with saline placebo.[48]

(4) early CP versus deferred CP (1 RCT).[49]

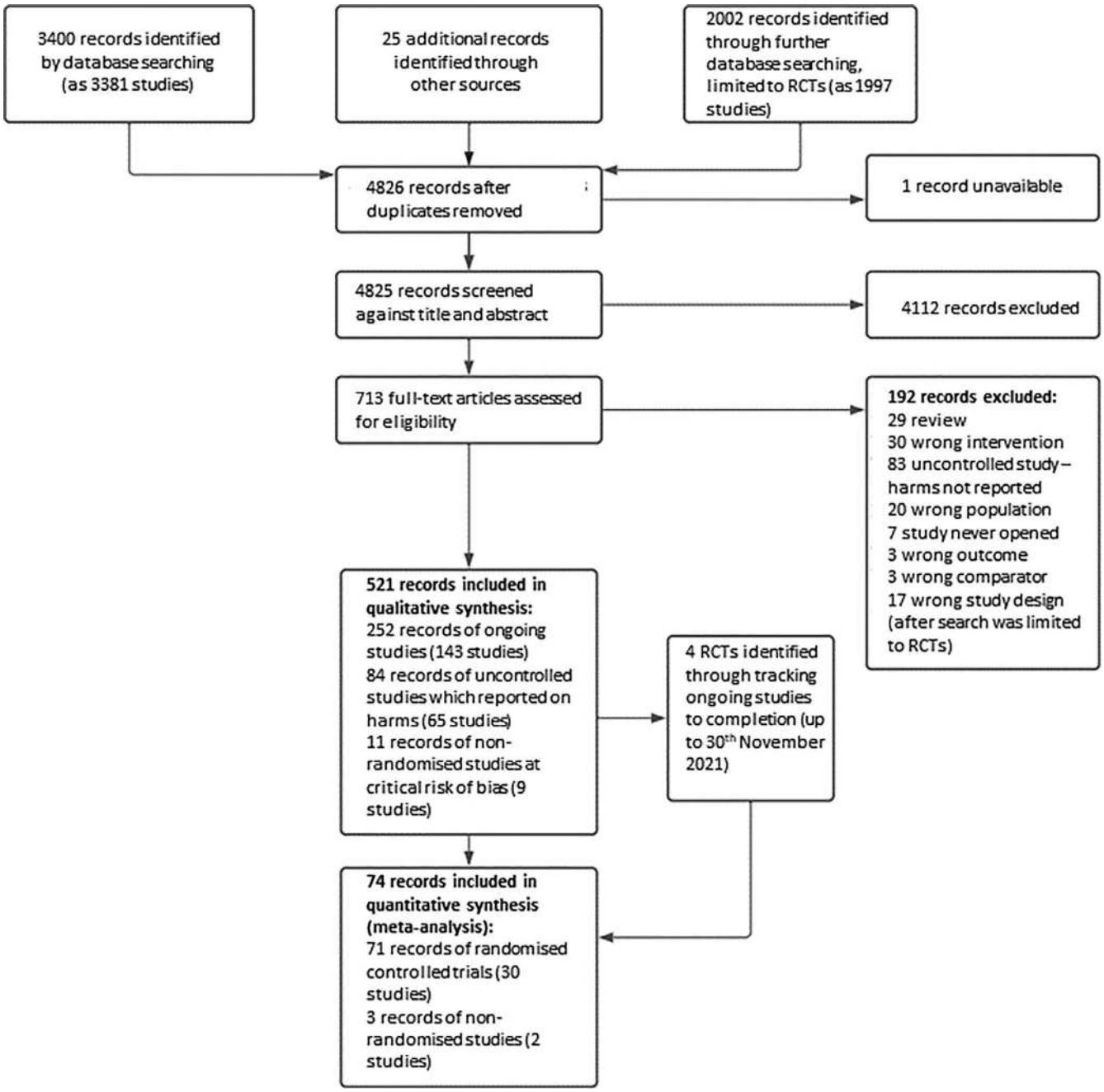

FIGURE 1 PRISMA flow diagram. Caption: The reasons for exclusion at each stage are shown with arrows to the right.

The comparators and baseline characteristics of participants in each of the thirty RCTs and two non-RCTs (retrospective observational studies)[50,51] within meta-analyses are summarised in Appendix A Table A1 in Data S1.

4.3 | Outcomes

We could only extract sufficient data to meta-analyse mortality and serious adverse events. We have presented remaining data from controlled studies in tables (Appendix A, Tables A3–A6 in Data S1). A summary of all outcomes reported is available in Appendix A5.

Most trials did not describe any method for dealing with competing risks when reporting their results. A competing risk is one which prevents the event of interest from occurring. Death is a competing risk for both (time to) mechanical ventilation and (time to) discharge. Devos 2021[28] approached competing risks using competing events analysis[52] to obtain cause-specific hazard ratios (HR). REMAP-CAP[30] used ordinal logistic regression by assigning each participant a category labelled with the number of ventilator-free days up to 21 days, with people who died up to day 90 being assigned −1, people who were on MV at

TABLE 1 Overview of meta-analysed results from patients hospitalised with severe respiratory infections

Comparison	30-day mortality		90-day mortality	Grade 3 or 4 transfusion related AEs	SAEs
Comparison 1: CP versus SoC or biologically inactive placebo (saline)	**All RCTs:** RR 0.99 (0.92 to 1.06) 15 RCTs[a], $n = 17\,266$ (37 children, 38 pregnant women) ⨁⨁⨁◯ $I^2 = 4\%$ $Tau^2 = 0.00$	**High Titre subgroup:** RR 0.98 (0.93 to 1.04) 9 RCTs[b], $n = 15\,954$ (26 children, 33 pregnant women) ⨁⨁⨁⨁ $I^2 = 0\%$ $Tau^2 = 0.00$	RR 0.92 (0.74 to 1.15) 6 RCTs[b], $n = 3210$ (8 pregnant women) ⨁⨁◯◯ $I^2 = 0\%$ $Tau^2 = 0.02$	*No transfusion in control group; results in intervention group are summarised in table A12*	RR 1.14 (0.92 to 1.41) 13 RCTs[a], $n = 16\,730$ (37 children, 38 pregnant women) ⨁◯◯◯ $I^2 = 56\%$ $Tau^2 = 0.07$
Comparison 2: CP versus biologically active control (FFP or IVIG)	RR 0.85 (0.56 to 1.29) 5 RCTs[a] $n = 700$ (13 children, 1 pregnant woman) ⨁◯◯◯ $I^2 = 33\%$ $Tau^2 = 0.07$		RR 0.99 (0.75 to 1.29) 2 RCTs[b], $n = 264$ ⨁◯◯◯ $I^2 = 0\%$ $Tau^2 = 0.00$	POR 0.43 (0.14 to 1.33) 6 RCTs[a], $n = 716$ (13 children, 1 pregnant woman) ⨁◯◯◯ $I^2 = 4\%$ $Chi^2 = 4.18$	RR 0.88 (0.65 to 1.19) 4 RCTs[b], $n = 523$ (13 children, 1 pregnant woman) ⨁⨁◯◯ $I^2 = 0\%$ $Tau^2 = 0.00$
Comparison 3: hIVIG versus control	RR 0.77 (0.34 to 1.73) 3 RCTs[c] $n = 392$ ⨁◯◯◯ $I^2 = 50\%$ $Tau^2 = 0.26$		*No RCTs reported mortality at 90 days in this comparison*	RD 0.00 (−0.08 to 0.08) 2 RCTs[a] $n = 84$ ⨁◯◯◯ $I^2 = 0\%$ $Tau^2 = 0.00$	RR 1.10 (0.76 to 1.58) 2 RCTs[a] $n = 342$ ⨁◯◯◯ $I^2 = n/a$ $Tau^2 = n/a$
Comparison 4: Early CP versus deferred CP	RR 2.68 (0.56 to 12.71) 1 RCT[b], $n = 58$ ⨁◯◯◯ $I^2 = n/a$ $Tau^2 = n/a$		*No RCTs reported mortality at 90 days in this comparison*	*Transfusion-related AEs were only reported for patients receiving CP; results are summarised in table A12*	*No RCTs reported SAEs in this comparison*

Note: Key: ⨁◯◯◯ very-low certainty evidence; ⨁⨁◯◯ low certainty evidence; ⨁⨁⨁◯ moderate certainty evidence; ⨁⨁⨁⨁ high certainty evidence.
Abbreviations: POR, Peto odds ratio; RD, risk difference; RR, risk ratio.
[a]Includes 1 RCT in influenza.
[b]All COVID-19.
[c]Includes 2 RCTs in influenza.

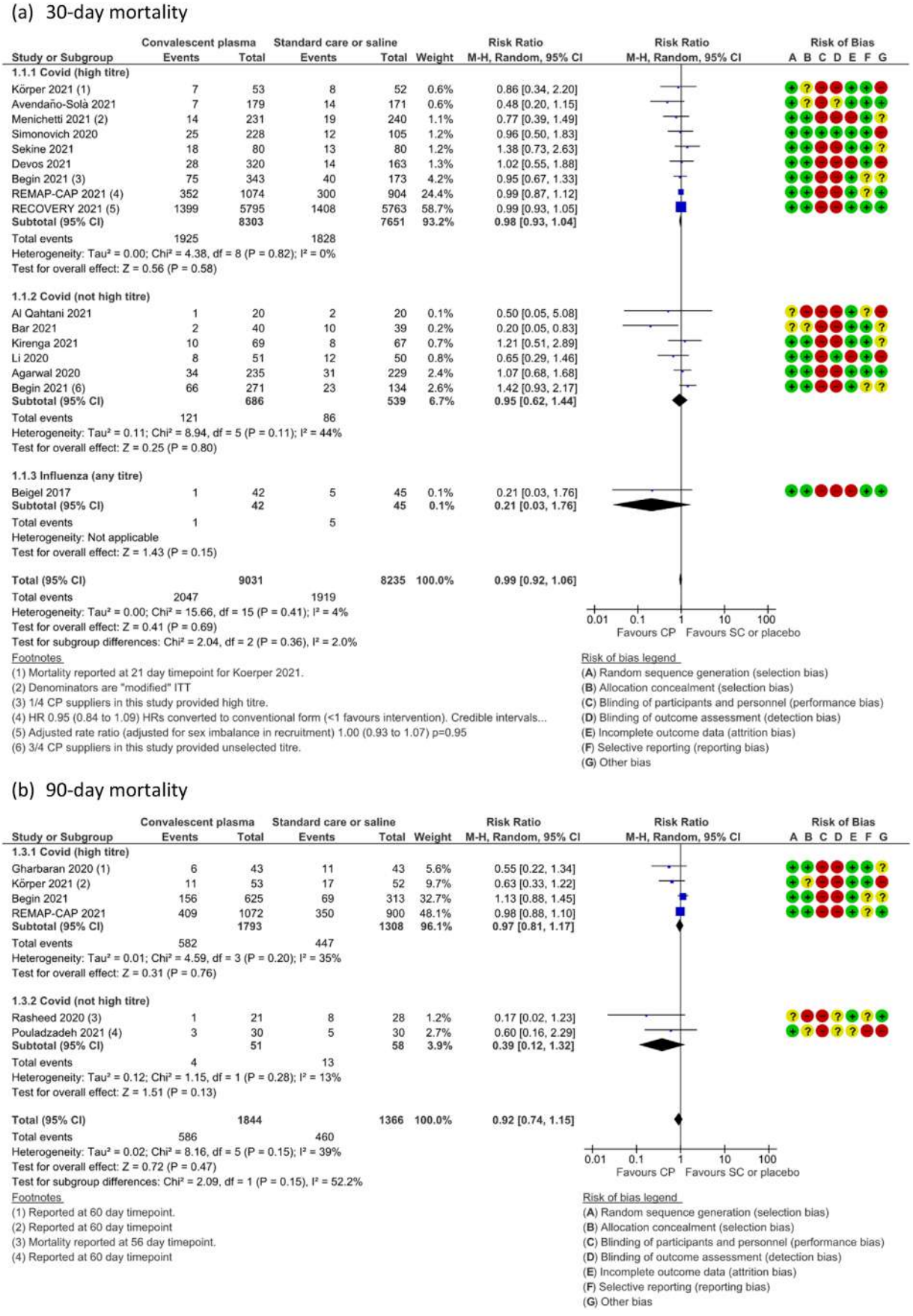

FIGURE 2 Forest plot of all-cause mortality, for comparison 1 (CP compared to SoC or a biologically inactive placebo) at up to (A) 30 days, and (B) 90 days

randomisation being assigned 0, and people who remained ventilator-free beyond day 21 being assigned 22. This is a useful way to compare the two groups while accounting for the very different possible outcomes but the resulting odds ratio (OR) and medians are difficult to interpret. No other trials used these methods and so we cannot combine the results but instead report the summary within Table A4 in Data S1.

Duration of viral detection was expressed as time (median IQR) to first negative test (2 RCTs).[23,36] One study,[25] reported the number of patients who had had two consecutive negative tests by day 30. See table A5 for viral detection data and table A6 for details of changes in viral loads.

4.4 | ROB in included studies

4.4.1 | RCTs (using Cochrane ROB1)

Nineteen RCTs were open-label, comparing CP to SoC, and were therefore assessed as having a high ROB for all outcomes except mortality, as knowledge of treatment allocation may have affected clinical decision-making. A summary of ROB judgements is available in Table A7 and Figure A1 in Data S1.

4.4.2 | Non-RCTs (using ROBINS-I)

Two non-RCTs[50,51] were assessed at serious RoB for selection bias and confounding at baseline. The remaining 9 studies[53–61] were at critical ROB due to baseline confounding or selection bias and were therefore not meta-analysed.

4.5 | Certainty of the evidence (GRADE)

Certainty of the evidence was GRADEd as very-low to high; primary reasons for downgrading were ROB and imprecision (wide confidence intervals and small sample size) (Tables A8–A11 in Data S1). We assessed publication bias through the generation of a funnel plot (Figure A2 in Data S1) for 30-day mortality in comparison 1, which suggests that some small studies have not been published. However, this was not significant enough to downgrade the certainty of the evidence because the analysis is dominated by two large, high-quality, and RCTs.

4.6 | Effect of the Intervention

See Table 1 for an overview of meta-analysed results.

4.6.1 | Comparison 1: CP versus SoC or biologically inactive placebo

Twenty RCTs and two retrospective studies assessed CP compared with SoC or a biologically inactive placebo.

All-cause mortality

30-day mortality data were available from 15 RCTs (30 days, 5 RCTs; 28 days, 9 RCTs; 21 days, 1 RCT) (Figure 2a); 90-day mortality data were available from 6 RCTs (56 days, 1 RCT; 60 days, 3 RCTs; 90 days, 2 RCTs) (Figure 2b).

Overall, CP did not reduce 30-day mortality (15 RCTs, n = 17 266; moderate-to-high certainty of evidence [Table A8 and footnotes in Data S1]) and there may be no effect on 90-day mortality (6 RCTs $n = 3210$; low certainty of evidence [Table A8]).

Two non-RCTs reported in-hospital mortality, and showed results consistent with the randomised evidence (2 studies, $n = 436$; very-low certainty evidence) (Figure A3A Table A8 in Data S1).

Improvement of clinical symptoms

Duration of NIV was reported in 4 studies (2 RCTs),[3,24,50,51] and duration of MV was reported by 11 studies (9 RCTs).[3,24,25,28–30,35,38,39,50,51] Two RCTs[27,31] reported any ventilatory support, but did not differentiate between MV, NIV, and passive oxygen support. One RCT[29] reported any ventilation, but also reported separately a composite outcome of patients who progressed to MV or death. Most studies reported the data as duration of support, either median (IQR) or mean (SD) (Table A4 in Data S1).

These outcomes were very variably reported, and many did not fully account for competing events, or report methods of analysis in sufficient detail. Based on what was reported, there was no apparent difference in duration of MV, NIV or ECMO support between the two groups.

Length of stay (LOS): hospital and ICU

Length of hospital stay was reported by 16 RCTs[7,23,25–28,30,31,38,39,42–47] and 1 non-RCT,[51] and length of ICU stay was reported by 9 RCTs[23,26,28,29,33,39,43,45,47] (Table A3 in Data S1). There was no evidence of an effect in length of hospital stay or length of ICU stay (Table A3 in Data S1).

Duration of viral detection from admission up to 30 days (viraemia, nasopharyngeal swabs, bronchoalveolar lavage, stool)

The 3 RCTs which reported time to negative test do not suggest any evidence of an effect (Table A5 in Data S1).

Adverse events

AEs due to transfusion were reported in 15 RCTs[3,7,22–39] (Table S10 in Data S1).

Seven RCTs reported no Grade 3 or 4 AEs due to transfusion.[22,24,26,27,31,35,39] Both non-RCTs reported AEs due to transfusion. All but one RCT[26] had SoC comparators, and therefore no transfusion-related SAEs are reported for the control group. Group comparison was not possible; results are summarised in Table A12 of in Data S1.

There was no evidence of an effect on reported SAEs[3,23–31,35,36,39] (13 RCTs, $n = 16\,730$, very-low certainty of evidence) (Figure A3B).

Data were not available on SAEs in seven RCTs.[7,22,32–34,37,38]

See forest plots Figure A3 in Data S1 and GRADE profile Table A8 in Data S1 for further detail.

4.6.2 | Comparison 2: CP versus biologically active control (FFP or IVIG)

RCTS assessed CP compared to FFP[40–43,45] or IVIG[44]

All-cause mortality

There was insufficient evidence to say whether or not there is a difference between groups in all-cause mortality at up to 30 days (5 RCTs $n = 700$; very-low certainty evidence, Figure A4A in Data S1), or at up to 90 days (2 RCTs, $n = 264$; very-low certainty evidence Figure A4B in Data S1). See forest plots Figures A4A and A4B in Data S1 and GRADE profile Table A9 in Data S1 for further detail.

Adverse events

Six RCTs reported transfusion-related Grade 3 or 4 AEs.[40–45] Events were rare (~2%) with no clear evidence of a difference (6 RCTs, $n = 716$; very-low certainty evidence. [Figure A4C in Data S1]). Four RCTs[40–42,45] reported SAEs up to 30 days, showing no evidence of an effect, although the rate of SAEs seems very low, given the severity of disease in hospitalised individuals (4 RCTs, $n = 523$; low certainty evidence, Figure A4D in Data S1). See forest plots Figure A4 and GRADE profile Table A9 in Data S1 for further detail.

Improvement of clinical symptoms

Duration of MV[40,43,45] and any ventilatory support[41] were reported as median (IQR) or mean (SD). Given the difficulties of dealing with competing events, and the small number of patients involved, it is very unclear if CP therapy had any effect on the duration of MV, NIV or ECMO support between the two groups. We have presented the data in Table A4 in Data S1 as reported by the individual studies.

Data were not available for LOS (hospital or ICU), and duration of viral load.

4.6.3 | Comparison 3: hyperimmune immunoglobulin versus control

Three assessed hIVIG compared with SoC or a biologically inactive placebo.

All-cause mortality

There was insufficient evidence to say whether or not there is an effect on mortality compared to control at up to 30 days (3 RCTs $n = 392$; very-low certainty evidence) (Table 1, Figure A5A, Table A10 in Data S1). There were no data for 90-day mortality.

Adverse events

Two RCTs reported transfusion-related AEs; neither reported any AEs due to transfusion in either group (2 RCTs, $n = 84$; very-low certainty evidence, Figure A5B in Data S1). Two RCTs reported SAES (2 RCTs $n = 342$; very-low certainty evidence. [Figure A5C in Data S1]). See forest plots Figure A5 and GRADE profile Table A10 in Data S1 for further detail.

Improvement of clinical symptoms

One RCT in influenza[48] reported on duration of MV and NIV. However, the data were presented using an ordinal scale that was not mappable to our outcomes or other trial results, and we were unable to extract the data.

Data were not available for LOS (hospital or ICU), and duration of viral load.

4.6.4 | Comparison 4: early CP versus deferred CP

One RCT assessed early CP compared to deferred CP.

All-cause mortality

There was insufficient evidence to say whether there is a difference in 30-day mortality between early CP and deferred CP (1 RCT $n = 58$; very-low certainty of evidence) (Figure A6 in Data S1). There were no data for 90-day mortality. See forest plots Figure A6 and GRADE profile Table A11 in Data S1 for further detail.

Adverse events

There were three Grade 3 or 4 transfusion-related AEs within 24 h, all in the early CP group: (1 RCT $n = 58$, very-low certainty evidence) (Table A12 in Data S1). SAEs were not reported. See forest plots and GRADE profile Table A11 in Data S1 for further detail.

Improvement of clinical symptoms

Duration of MV and NIV was reported as median (IQR). We have presented the data in Table A4 in Data S1 as reported by the RCT. Both groups had similar duration of ventilatory support. It is unclear if the authors accounted for competing events.

Data were not available for LOS (hospital or ICU), and duration of viral load.

4.7 | Results from uncontrolled studies (for safety only)

We identified 73 non-randomised or uncontrolled studies [49 case reports or case series] that assessed the use of CP or hIVIG in respiratory viral infection and reported AEs: 12 in influenza A, 2 in MERS-CoV, and 4 in SARS-CoV-1, and 67 in SARS-CoV-2 (COVID-19). Of the influenza studies, 10 were from the 1918 to 1920 pandemic. Fifty-one studies reported that no AEs were observed (37/49 case reports or case series). Eighteen studies reported transfusion-related AEs, and four studies reported other SAEs. These data are presented in Appendix B in Data S1.

4.8 | Post hoc subgroup analysis: seropositivity at baseline

Three RCTs,[3,30,62] including the two largest, reported 30-day mortality for subgroups defined by seropositivity at baseline. These results are shown in Figure 3.

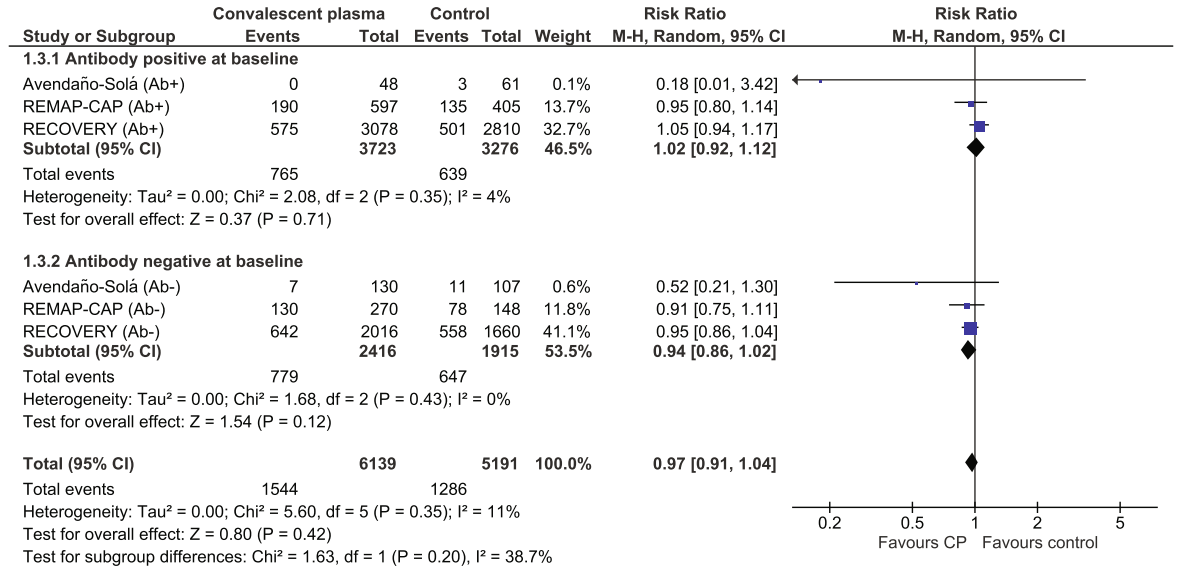

FIGURE 3 Subgrouped by seropositivity at baseline: RCTs reporting 30-day mortality for comparison 1 (CP compared to SoC or a biologically inactive placebo)

With almost all the information coming from the two large, high-quality RCTs,[3,30] the pooled estimates from these three RCTs are: RR 1.02 (0.92 to 1.12) for people who are seropositive at baseline and 0.94 (0.86 to 1.02) for those who are seronegative. The test for interaction (subgroup difference) gives a *p*-value of 0.20 with very little heterogeneity either within or between groups.

We explored this further using meta-regression on the group of trials comparing high titre CP with SoC which reported the proportion seropositive at baseline and 30-day mortality. This analysis produced near identical results with an estimated RR at 0% seropositivity of 0.93 (0.85, 1.01) and 1.02 (0.93, 1.12) at 100% seropositivity (See Appendix A6 in Data S1. Mortality results are summarised in Table A14 in Data S1).

5 | DISCUSSION

The objective of this review was to determine the safety and effectiveness of CP or hIVIG from CP to treat patients with serious respiratory disease due to influenza or coronavirus infection. In order to increase the relevance of our findings to the COVID-19 pandemic we used the core outcome set[63] for assessing treatments for patients infected with SARS-CoV-2. We aimed to use high-quality evidence from RCTs to assess safety and effectiveness. We also used all other study designs to describe serious harms reported following transfusion with CP or hIVIG.

5.1 | Main findings

We were able to meta-analyse 32 studies for our primary outcome of 30-day mortality (30 RCTs and 2 non-RCTs). We found little evidence of any difference between the groups in either benefits or harms for patients hospitalised with a severe viral respiratory infection requiring hospital admission. Most evidence was of low or very-low certainty. The only high-certainty evidence was for the COVID high-titre subgroup in the outcome all-cause mortality at up to 30 days in CP versus SoC (Table 1).

Adverse events were variably reported. No RCTs reported a high number of transfusion-related AEs (proportion 0% to 5.67%[22–24,26,27,31,35,38,39,43,44,46,47]) (very-low to low certainty evidence). There was no evidence of an increase in harms compared with standard plasma.

5.2 | Quality (certainty) of the evidence

Where meta-analysis was possible, we used GRADE to assess our certainty in the result (Table 1). Certainty in the evidence was assessed as very-low to low certainty for all outcomes apart from mortality data in the comparison CP versus standard care.

Evidence was downgraded for serious ROB (lack of blinding, baseline imbalance, randomisation processes, missing data and unclear reporting of outcomes) and imprecision (wide confidence intervals around the effect estimate, and small sample sizes for the outcome of interest). Some of the sources of potential bias (such as patient and personnel blinding) would be hard to overcome in future trials due to the issues in finding an ethical control infusion: even saline is problematic, with the risk of volume overload, and ease with which it can be differentiated from plasma.

SAEs were also downgraded for inconsistency as the heterogeneity was significant between studies, this is likely to be due to the variation in reporting of the SAEs. This may be in part due to differing regulatory environments and different classifications of CP, requiring

varying levels of AE reporting including the need to use a grading system (e.g., MedDRA[64]).

We included lower-level evidence for the assessment of safety outcomes. However, we were unable to perform quantitative analyses, and so have only presented these data as reported in Appendix B in Data S1.

There were very few endpoints reported consistently enough for meta-analysis. The difficulty in defining endpoints, especially time-to-event endpoints,[65] is discussed further in Appendix A6 in Data S1.

5.3 | Strengths and Limitations of this review

We have attempted to minimise potential bias in the review process, using Cochrane methods and PRISMA guidelines for reporting. We conducted a comprehensive search: searching data sources to ensure that all relevant studies would be captured, using multiple databases and reference lists of included studies. We included conference proceedings and included a search of clinical trial registries. We also attempted to contact authors for additional data and for clarification of their data.

There were no restrictions for the language in which the paper was originally published. We pre-specified outcomes prior to analysis and have explained the rationale for including one additional outcome (any SAEs).

We undertook duplicate screening, data extraction, and assessment of bias. Additionally, the clinical advisor (LE) was consulted for disagreements, or need for clarification.

The limitations of this review mostly arose due to gaps in the evidence base, which are discussed more fully in the next section.

5.4 | Interpretation and context

A recent analysis of individual patient data (IPD) pooled from eight RCTs[9] IPD reported an OR for mortality of 0.85 at day 28 (95% credible interval, 0.62 to 1.18; posterior probability of OR <1 of 84%). These results are broadly comparable and in agreement with our own aggregate analyses for 30-day mortality. However, it should be noted that the IPD analysis included two RCTs[66,67] published after our 30th November 2021 cut-off, but did not include the two largest RCTs of CP RECOVERY[3] and REMAP-CAP[30] which we have analysed, and which together contribute 83% of sample size contributing to our analysis of 30-day mortality for CP versus SoC.

A limitation of the current evidence base is that of the 30 RCTs and two non-randomised studies included in our meta-analysis, 26 studies (24 RCTs) excluded children and 16 RCTs excluded pregnant women, with 1 RCT[39] admitting pregnant women only on the second round of recruitment. Given that children and pregnant women are both considered to be at increased risk of serious disease and death from many severe respiratory viral infections, their exclusion from trials is concerning. Of the 144 ongoing studies we identified, most trials will exclude children and pregnant women. Many ongoing studies have an upper age cut-off (of 65, 70 or 80 years), despite older age being one of the biggest risk factors for COVID-19.

The precision of our meta-analysis was affected by the different titres of CP-neutralising antibodies between trials (Table A1 in Data S1). We tried to address this by subgrouping studies based on the CP-titre reported, and whether it was considered high enough according to FDA criteria (see Appendix A3 in Data S1). However, several studies used local assays that could not be correlated with an FDA reference method. Since we conducted our first search, several variants of SARS-CoV-2 have arisen worldwide and may require much higher antibody titres measured using ELISA assays.[68] Much higher titre CP, from vaccinated convalescent donors, may be active against future variants[69] indicating that new COVID CP trials should aim to use very high titre CP standardised using internationally recognised methods.

Similarly, between trials, there was heterogeneity of patient groups and severity of illness on admission to hospital (Table 1). The RCTs in COVID may not have used the same criteria to categorise trial participants at enrolment and trials designed to treat different patient groups based on comorbidities and immune states were absent. Several COVID-19 studies reported clinical improvement using the WHO ordinal scale. However, the scale was revised several times over the course of 2020–2021, going from an 8-point scale[70] to a 10-point scale at its latest revision[71] which have made comparisons between trials difficult.

The results of our post hoc subgroup analysis by seropositivity at baseline are very similar to the results reported by RECOVERY alone. We have not found stronger evidence of this potential interaction than that reported by RECOVERY (with a similar trend also reported by REMAP-CAP, especially for organ support-free days) but similarly, we have not found any reason to discount the possibility that there is a small but important interaction, with immunocompromised individuals potentially benefitting more. This hypothesis is consistent with the REGN-COV2 RECOVERY trial,[21] which has shown no benefit of monoclonal antibodies for seropositive patients who either have advanced disease or who are immunocompetent. The very high baseline risk of immunocompromised individuals might translate very small relative risks into substantial absolute risk differences. REMAP-CAP has recently reopened for immunocompromised people to test this hypothesis.[72]

5.5 | Implications for research and practice

There is currently no evidence for a benefit of CP in an unselected population of patients hospitalised with coronaviruses or influenza. It is likely that the titre of the CP and the immune response of the recipient may both be important factors affecting response to treatment.

Studies should use CP of a high enough titre to elicit a biological response, and report the actual titre used as well as the minimum as described in the protocol. Matching variants between donor and recipient may not be feasible, but viral variants circulating at the time of collection of plasma and during the study should be recorded.

Studies should assess and publish antibody status (seropositivity) at baseline in both intervention and control groups, and identify and

report immunocompromised patients separately, to establish whether certain groups of patients are more likely to benefit from this intervention.

There are difficulties in designing truly blinded RCTs of CP or hIVIG (see Reference 73 for review). There are ethical problems with using a placebo which is assumed to have no clinical benefit, but has known harms.[74] One RCT[26] used a saline placebo, with potential concerns about volume overload, and six RCTs used a biologically active control, (FFP in 5 RCTs,[40–43,45] and IVIG in one[44]) which raises additional concerns about transfusion reactions.

Unless reported explicitly by investigators, it was difficult to distinguish the AEs experienced following transfusion from the symptoms of severe respiratory disease.[75] This limited the number of RCTs that we could include in our meta-analysis of AEs due to transfusion. There was also substantial variability in the way that AEs were recorded and reported in these studies. It was not always possible to determine the severity of AEs, and different studies used different criteria for SAEs. In some cases, it was hard to determine if SAE reporting was per event or per patient, making it extremely difficult to compare rates of AEs between studies. Blood components in the UK are not classified as medicines and so require a different grading system for reporting AEs to countries that classify CP as a medicine, e.g. Germany. A consensus on how AEs associated with blood products are reported in RCTs would help to address this problem.

6 | CONCLUSION

This review has highlighted several issues regarding study design and reporting which should be addressed in current and future research. A minimum titre should be established and ensured for a positive biological response to the therapy. Further research on the impact of CP/hIVIG in patients who have not produced antibodies to the virus prior to hospital admission or who are immunocompromised would be useful to target therapies at groups who will potentially benefit the most.

AUTHOR CONTRIBUTIONS

Catherine Kimber: screening and full text assessment, retrieved full text publications, data extraction, risk of bias assessment, entered data into RevMan and undertook subgroup analyses, performed GRADE assessments, interpreted the results, contributed to the development of the manuscript. **Abigail A. Lamikanra:** screening and full text assessment, retrieved full text publications, data extraction, risk of bias assessment, performed GRADE assessments, interpreted the results, contributed to the development of the manuscript. **Louise J. Geneen:** screening and full text assessment, retrieved full text publications, data extraction, risk of bias assessment, entered data into RevMan and undertook subgroup analyses, performed GRADE assessments, interpreted the results, contributed to the development of the manuscript. **Josie Sandercock:** data extraction, risk of bias assessment, and undertook all metaregression analyses, performed GRADE assessments, interpreted the results, contributed to the development of the manuscript. **Carolyn Doree:** developed and performed all search strategies and de-duplication, retrieved full text publications, contributed to the development of the manuscript. **Sarah J. Valk:** screening and full text assessment, retrieved full text publications, contributed to the development of the manuscript. **Lise J. Estcourt:** developed the initial idea of the review, developed, wrote, and registered the protocol, interpreted the results, and contributed to the development of the manuscript.

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ORCID

Catherine Kimber https://orcid.org/0000-0002-7796-9931
Abigail A. Lamikanra https://orcid.org/0000-0002-9287-2177
Louise J. Geneen https://orcid.org/0000-0001-6759-0437
Josie Sandercock https://orcid.org/0000-0001-7337-8635
Carolyn Dorée https://orcid.org/0000-0001-6955-7497
Sarah J. Valk https://orcid.org/0000-0003-3964-2505
Lise J. Estcourt https://orcid.org/0000-0003-4309-9162

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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ORIGINAL ARTICLE

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Prevalence and incidence of transfusion-transmissible infections among blood donors in Malawi: A population-level study

Emmanuel Singogo[1] | Maganizo Chagomerana[1] | Collin Van Ryn[2] | Robert M'bwana[3] | Andrew Likaka[3] | Bridon M'baya[3] | Sydney Puerto-Meredith[1] | Effie Chipeta[4] | Victor Mwapasa[5] | Adamson Muula[5] | Cavan Reilly[2] | Mina C. Hosseinipour[1,6] | Malawi BLOODSAFE Program

[1]UNC Project, Lilongwe, Malawi

[2]Department of Biostatistics, University of Minnesota Twin Cities, Minneapolis, Minnesota, USA

[3]Malawi Blood Transfusion Service, Blantyre, Malawi

[4]Centre for Reproductive Health, Kamuzu University of Health Sciences, Blantyre, Malawi

[5]School of Global and Public Health, Kamuzu University of Health Sciences, Blantyre, Malawi

[6]Division of Infectious Diseases, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, North Carolina, USA

Correspondence
Emmanuel Singogo, UNC Project, Lilongwe, Malawi.
Email: emmsingo@gmail.com; esingogo@unclilongwe.org

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Abstract

Background: Voluntary non-remunerated blood donors (VNRBDs) are essential to sustain national blood supplies. Expanding testing capacity for the major transfusion-transmitted infections (TTI) is crucial to ensure safe blood products. Understanding trends in TTIs can inform prioritisation of resources.

Methods: We conducted a retrospective cohort data analysis of routine blood donation data collected from VNRBDs by the Malawi Blood Transfusion Service from January 2015 to October 2021. Variables included age, occupation; and screening results of TTIs (HIV, Hepatitis B and C, and syphilis). We estimated both prevalence and incidence per person-year for each TTI using longitudinal and spatial logistic regression models.

Results: Of the 213 626 donors, 204 920 (95.8%) donors were included in the final analysis. Most donors (77.4%) were males, baseline median age was 19.9 (IQR 18.0, 24.1), 70.9% were students, and over 80.0% were single at first donation. Overall TTI prevalence among donors was 10.7%, with HBV having the highest prevalence (3.4%), followed by syphilis (3.3%), then HIV (2.4%) and HCV (2.4%). Incidence per 1000 person-years for syphilis was 20.1 (19.0, 21.3), HCV was 18.4 (17.3, 19.5), HBV was 13.7 (12.8, 14.7), and HIV was 11.4 (10.6, 12.3). We noted geographical variations with the northern region having lower rates of both prevalence and incidence compared to central and southern regions.

Conclusion: The individual TTI prevalence and incidence rates from this study are consistent with Southern African regional estimates. By identifying geographical variations of TTI prevalence and incidence, these findings could potentially inform prioritisation of blood collection efforts to optimise blood collection processes.

KEYWORDS
blood transfusion, BLOODSAFE Project, cohort data analysis, incidence, prevalence, spatial modelling, transfusion transmissible infections

1 | INTRODUCTION

The World Health Organisation (WHO) is credited for expanding blood transfusion services in the last two decades.[1] This has led to an increased recruitment of voluntary donors and also improved and expanded testing capacity for the major transfusion-transmitted infections, especially in developing countries in Africa. Many transfusion safety studies indicate that the rates of transfusion transmissible infections (TTIs) among donors still remain high.[1–3] With high rates of TTIs, there is a need to conduct targeted blood donation campaigns to minimise exclusions of blood units.

Despite an increase in implementing regionally coordinated training initiatives, and adopting tiered accreditation process, a general decline in funding over the last decade for transfusion safety has strained the sustainability and further improvement of blood transfusion-related services in Africa.[4–6]

In Malawi, the Malawi Blood Transfusion Service (MBTS) is leading the effort to provide safe blood products for the entire country by collecting blood from voluntary non-remunerated donors (VNRBDs), and ensures quality screening for TTIs. Since its inception 2004, MBTS has not been able to meet the annual national demand which is currently estimated at 120000 blood units.[7] Therefore, several hospitals continue to supplement or rely entirely on blood units collected from replacement donors.[8] MBTS has collected up to 50% of the estimated annual blood collection.

Volunteer donors are the cornerstone of the program and strategies to promote regular donation practices are pursued to ensure a steady blood supply. Currently, MBTS hosts community engagement events promoting blood donation, maintains >1000 regular donors, and benefits from significant uptake of donation by secondary school students through school programs. Proper evaluation and use of routinely collected program data has helped to improve expanded programs, such as HIV prevention and treatment programs in sub-Saharan Africa (SSA), despite the challenges with data completeness.[9,10] An earlier epidemiological evaluation of the MBTS blood donor database was conducted using data covering the period 2011–2015. This evaluation is now old, did not include spatial analysis and only considered prevalence and not incidence of TTIs.[11] Therefore, to further support surveillance of TTIs, we conducted a comprehensive evaluation of epidemiology of HIV, syphilis, hepatitis B and C using routinely collected blood donation data to assess TTI prevalence and incidence over the past 7 years among blood donors in Malawi.

2 | MATERIALS AND METHODS

2.1 | Subjects studied

We conducted a retrospective cohort data analysis of routine blood donation data collected by the MBTS from January 2015 to October 2021. The study population was all voluntary nonremunerated blood donors who donated blood at a MBTS facility or MBTS sponsored blood drive in the period from January 2015 to October 2021. The exclusion criteria for blood donation are extensive and include, among others, health requirements; restrictions on those who engage in behaviour that increase risk for TTIs; age requirements (16–65 years); past medical history suggestive of HIV, hepatitis or syphilis; past or present history of renal, cardiovascular, central nervous system and metabolic disorders such as insulin dependent diabetes; haemoglobin below 12.5 g/dL and weight below 42 kgs. Only individuals who satisfied the national blood donation eligibility criteria were accepted as blood donors, allowed to donate blood and were therefore included in this study.

2.2 | Ethics statement

This study was approved by the National Health Sciences Research Council (NHSRC (Protocol #:20/07/257). It was conducted as part of the BLOODSAFE Project being implemented in Malawi, Kenya and Ghana. The NIH-established Data Safety and Monitoring Board (DSMB) and the Data Coordinating Center (DCC) at University of Minnesota approved the protocol and monitored the study progress.

2.3 | Data collection procedures and management

MBTS captures and enters individual-level data, with every donor assigned a unique identification number that is used at subsequent donation visits. Blood donation data collected by MBTS are entered and stored in the MBTS database and all donations made by each donor are uniquely identifiable and linked to each donor for that particular donation visit.

The following data elements were collected and included analysis: donor identifier, donation date, sex, date of birth, marital status, donation location, donation district, occupation, and results from tests for TTIs (HIV, Hepatitis B and C and syphilis). Districts are the primary subnational administrative units and are collected from a fixed list, hence these were used for all spatial analyses (we have data for 28 districts). Other variables were derived from these variables such as categorization of whether the donor is a first-time donor (FT) or is a repeat regular donor (RPT); and whether there was TTI seroconversion among repeat/regular donors.

Data were extracted as a comma separated values (CSV) file and was imported into R Software for further cleaning, management and preparation before being analysed in R Software. During data cleaning, we removed duplicate records and excluded any donation record that had inconclusive test results for any of the four TTIs under

consideration. Donors who had reactive results during the previous visit were not allowed to donate again. For data cleaning purposes, we removed any donation record that was made after a positive TTI result to avoid two or more positive results for the same TTI. In addition, we removed any record or donor without any testing result. After this data cleaning process, 344 622 unique donation records from 204 920 unique donors (96% of original data) were retained for analysis.

2.4 | Laboratory testing

HIV serology was done using Green screen ULTRA HIV antigen–antibody enzyme immunoassay (EIA) reagents (Bio-Rad, France) via the Evolis semi-automated platform. From August 2015, supplementary testing with Determine antibody rapid test kits (Allere, Japan) was added for those found positive with the EIA algorithm but in 2016 the EIA reagents were replaced with chemiluminiscence immunoassays from Abbot (Germany) on the Architect i2000 platform.

HBV serology was done using Monalisa HBsAg ULTRA EIA (Bio-Rad, France) reagents detecting HBV surface antigen (HBsAg) on the Evolis semi-automated platform were used until the last quarter of 2016 calendar year when they were replaced with CLIA Abbott (German) reagents (detecting the same markers) on the Architect i2000 platform.

HCV serology was done using Monalisa anti-HCV EIA (Bio-Rad France) antibody reagents on the Evolis semi-automated platform were used until the last quarter of 2016 calendar year where they were replaced with chemiluminiscence Immunoassays Abbott (Germany) anti-HCV reagents on the Architect i2000 platform.

Syphilis serology was done using Bio-Rad (France) manual Treponema Pallidum Haemaglutination Assay (TPHA) reagents. Micro plates were used until the last quarter of 2016 calendar year when they were replaced with chemiluminiscence immunoassays from Abbott (Germany) reagents detecting the same markers on the Architect i2000 platform.

All the algorithms for testing HIV, HBV, HCV and syphilis involved repeating in duplicate all initial positives and interpreting results based on the concordant two of the three. Concordant TTI reactive results were then used to calculate seroprevalence and incidence.

2.5 | Statistical analysis

Descriptive analyses were conducted for donor characteristics, including age in years, sex, first-time donation status, repeat donor status, marital status, occupation and district (of first donation). For consistency, First-time (FT) donors were defined as those with only one donation record in the dataset. Repeat (RPT) donors were defined as those with two or more donations during the study period. For data summaries, we used counts and percentages for binary and categorical variables, and medians (with first and third quartiles) for continuous variables. The frequencies and percent of missing or unknown data were also presented for each characteristic.

Seroprevalence was determined as the proportion of individual blood donors who tested reactive among all donors tested for each of the four TTIs. A binary response was constructed for each individual TTI (HIV, HCV, HBV and syphilis) and overall TTI reactivity was considered if any individual TTI was reactive. To determine annual prevalence for each TTI and for overall TTIs respectively, we estimated the seroprevalence for each individual TTI (HIV, HCV, HBV and syphilis) and for overall TTIs and their corresponding 95% confidence intervals for each year.

To determine factors which are predictive of TTI test outcome, multiple logistic regression models were fit that accounted for donations coming from the same donor using an independence correlation structure and generalised estimating equations. These models were fit to all donations. The models included fixed effects for age (categorised into three levels: 16–25, 26–35 and over 35), sex, student status, marital status (categorised as single, married and other), year of donation, and district where the donation took place. In the model, the reference points were chosen as follows: a category with a smaller n was chosen as reference for age, sex, student status except for marital status where we wanted to compare between *married* and *single*; while for calendar year, the first year was chosen and for a district, the district at the centre of the country was chosen.

To estimate the prevalence of each TTI and any TTI overall, spatial logistic regression models were fit to the district level TTI rates which averaged over all years. The spatial component was modelled using a stationary isotropic exponential correlation function. The centroids of the 28 districts in Malawi were computed and used to measure the spatial proximity (and therefore the correlation) of geographical regions. Parameter estimates were obtained using Monte Carlo maximum likelihood.[12] These models were used to predict the prevalence in each district and 95% confidence intervals (CIs) were produced to summarise the uncertainty of the estimates. The PrevMap package for R was used to estimated prevalence.[12]

We also defined seroconversion as new case of TTI reactivity for an individual donor after returning a nonreactive result in the previous donation visit. We estimated the incidence of each TTI as well as overall incidence for each district using a Poisson regression model. Incidence was defined as the number of new seroconversions per 1000 Person-Years (PYs). For categorical variables, we fitted survival models and used a logrank test (*survival package*) to compare the number of seroconversions. For each TTI (HIV, HCV, HBV and syphilis), maps were used to plot both crude and spatially-smoothed estimated incidence at the district-level in order to highlight districts with higher and lower incidence.

Less than 5% of the data records were missing and were dropped from the final analyses using complete-case analysis. All analyses were conducted with the statistical software package R using the following packages: *rgeos*, *rgdal* and *geoR* for manipulation of spatial objects in R, *PrevMap* package for geostatical modelling, and *ggplot* package for plotting. We also reported 95% CI for each estimate and assessed significance of results using $p < 0.05$.

3 | RESULTS

3.1 | Characteristics of blood donors

Of the 213 626 donors who donated over the 7-year period, data for 204 920 (95.8%) donors were included in the final analysis. Among the 204 920 donors, 77.4% were males, and 30.4% donated twice or more (Table 1). At baseline, median age was 19.9 (IQR 18.0, 24.1), 70.9% were students, and over 80% of donors were single.

3.2 | Trends over time in the number of blood donations

The number of donations were at peak during school calendar months. The number of donations varied over time from a low of 21 520 (18% of national need) in 2016 to a high of 62 717 (52% of national need) in 2019 (Table 2), with the proportion of first-time donors increasing from 11.3% in 2015 to 18.1% in 2018 but later decreased to 14.6% in 2020 (Table 1). Donations were lower during the years of the COVID-19 pandemic with a 16% reduction in 2020

TABLE 1 Characteristics of donors in the MBTS dataset.

Characteristics	One-time donors	Repeat donors	Overall
N donations on record	133 681 (26.4)	373 406 (73.6)	507 087
N donations during study period	133 681 (38.8)	210 941 (61.2)	344 622
N donors	133 681 (65.2)	71 239 (34.8)	204 920
Sex			
Female	32 536 (24.3)	13 876 (19.5)	46 412 (22.6)
Male	101 145 (75.7)	57 363 (80.5)	158 508 (77.4)
Age in years	20.1 (18.1, 25)	19.5 (17.8, 22.9)	19.9 (18, 24.1)
Age category			
16–25	103 058 (77.1)	58 869 (82.6)	161 927 (79)
26–25	18 244 (13.6)	8163 (11.5)	26 407 (12.9)
≥36	12 379 (9.3)	4207 (5.9)	16 586 (8.1)
Occupation			
Unknown	8824 (6.6)	2064 (2.9)	10 888 (5.3)
Student	89 242 (66.8)	56 143 (78.8)	145 385 (70.9)
Other	35 615 (26.6)	13 032 (18.3)	48 647 (23.7)
Marital status			
Divorced	630 (0.5)	182 (0.3)	812 (0.4)
Married	25 275 (18.9)	7553 (10.6)	32 828 (16)
Separated	277 (0.2)	75 (0.1)	352 (0.2)
Single	107 160 (80.2)	63 278 (88.8)	170 438 (83.2)
Widow	339 (0.3)	151 (0.2)	490 (0.2)
Donation per donor	1	3 (2, 5)	1 (1, 2)
Time between donations (months)	–	6 (4, 12)	–
Regular donor at any time since 2015	–	49 303 (69.2)	–
Lapsed donor at any time since 2015	–	27 611 (38.8)	–
Year of first donation			
<2015	0 (0)	20 092 (28.2)	20 092 (9.8)
2015	15 157 (11.3)	6659 (9.3)	21 816 (10.6)
2016	8041 (6)	2720 (3.8)	10 761 (5.3)
2017	20 528 (15.4)	10 460 (14.7)	30 988 (15.1)
2018	24 197 (18.1)	12 300 (17.3)	36 497 (17.8)
2019	21 690 (16.2)	9847 (13.8)	31 537 (15.4)
2020	19 457 (14.6)	6246 (8.8)	25 703 (12.5)
2021	24 611 (18.4)	2915 (4.1)	27 526 (13.4)

Note: Descriptive statistics are presented as *N* (%) or Median (Q1, Q3).

TABLE 2 Comparison of TTI screening results across all donations by selecting demographic factors.

		HIV screening		Hep. B screening		Hep. C screening		Syphilis screening		All TTI screening	
Characteristics	***N* (%)**	**%Reactive**	**Adj. OR (95% CI)**	**%Reactive**	**Adj. OR (95% CI)**	**%Reactive**	**Adj. OR (95% CI)**	**%Reactive**	**Adj. OR (95% CI)**	**%Reactive**	**Adj. OR (95% CI)**
Age at donation											
16–25	267 422 (77.6)	1.2	0.79 (0.7, 0.89)	2	1.07 (0.96, 1.19)	1.5	1.42 (1.24, 1.63)	1.6	0.7 (0.63, 0.78)	6	0.93 (0.87, 0.99)
26–35	48 342 (14)	2.5	1.04 (0.94, 1.16)	2.7	1.08 (0.98, 1.19)	1.4	1.02 (0.89, 1.16)	3.3	0.9 (0.83, 0.98)	9.2	1 (0.94, 1.06)
≥36	28 858 (8.4)	2.6	Ref.	2.8	Ref.	1.7	Ref.	4	Ref.	10.2	Ref.
Sex											
Female	66 630 (19.3)	1.4	Ref.	1.6	Ref.	1.1	Ref.	1.8	Ref.	5.7	Ref.
Male	277 992 (80.7)	1.5	0.97 (0.89, 1.04)	2.3	1.37 (1.28, 1.47)	1.6	1.47 (1.35, 1.60)	2.1	1.04 (0.98, 1.11)	7.1	1.16 (1.13, 1.23)
Student status											
Non-student	84 265 (28.2)	2.3	Ref.	2.7	Ref.	1.7	Ref.	3.6	Ref.	9.5	Ref.
Student	247 402 (71.8)	1.1	0.55 (0.51, 0.61)	1.8	0.66 (0.61, 0.72)	1.4	0.81 (0.74, 0.89)	1.4	0.45 (0.42, 0.49)	5.6	0.59 (0.56, 0.61)
Marital status											
Single	288 896 (83.8)	1.3	Ref.	2	Ref.	1.4	Ref.	1.7	Ref.	6.1	Ref.
Married	53 163 (15.4)	2.7	1.09 (0.99, 1.2)	3.1	1.12 (1.03, 1.22)	2	1.35 (1.21, 1.51)	3.6	0.96 (0.88, 1.04)	10.4	1.08 (1.03, 1.14)
Other	2563 (0.7)	2.9	1.49 (1.15, 1.93)	3	1.32 (1.03, 1.7)	1.5	1.11 (0.79, 1.57)	4.6	1.48 (1.21, 1.82)	10.6	1.35 (1.16, 1.56)
Year of donation											
2015	41 230 (12)	1.7	Ref.	3	Ref.	0.8	Ref.	2	Ref.	7	Ref.
2016	21 520 (6.2)	1.4	0.83 (0.73, 0.96)	2.9	0.98 (0.89, 1.08)	0.9	1.26 (1.06, 1.51)	2	0.99 (0.88, 1.12)	6.8	0.99 (0.93, 1.05)
2017	48 401 (14)	2.2	1.37 (1.24, 1.51)	3	0.97 (0.9, 1.05)	1.2	1.5 (1.31, 1.73)	2.8	1.39 (1.27, 1.53)	8.6	1.22 (1.16, 1.28)
2018	61 518 (17.9)	1.4	0.87 (0.78, 0.97)	2.4	0.77 (0.71, 0.84)	2.3	2.81 (2.47, 3.2)	2.3	1.15 (1.05, 1.26)	7.9	1.11 (1.06, 1.17)
2019	62 717 (18.2)	1.2	0.76 (0.68, 0.85)	1.7	0.57 (0.52, 0.62)	1.6	2.05 (1.8, 2.35)	1.7	0.86 (0.78, 0.94)	6	0.83 (0.79, 0.88)
2020	52 814 (15.3)	1.5	0.8 (0.72, 0.89)	1.6	0.47 (0.43, 0.52)	2.1	2.61 (2.29, 2.98)	2.2	0.95 (0.87, 1.05)	6.8	0.87 (0.83, 0.92)
2021	56 422 (16.4)	1.2	0.72 (0.64, 0.8)	1.3	0.39 (0.35, 0.43)	1.1	1.25 (1.08, 1.44)	1.6	0.79 (0.72, 0.88)	4.9	0.65 (0.61, 0.68)
District											
Dedza	3895 (1.1)	1.3	Ref.	2.2	Ref.	2	Ref.	1.8	Ref.	7.1	Ref.
Dowa	5789 (1.7)	2.2	1.49 (1.06, 2.09)	2.3	0.95 (0.72, 1.27)	2.7	1.25 (0.93, 1.68)	2.8	1.31 (0.97, 1.77)	9.3	1.18 (1, 1.39)
Kasungu	11 506 (3.3)	2	1.52 (1.11, 2.09)	2.8	1.24 (0.96, 1.6)	3.8	1.9 (1.46, 2.46)	2.4	1.21 (0.91, 1.61)	10.4	1.45 (1.25, 1.68)
Lilongwe	72 017 (20.9)	2	1.12 (0.84, 1.5)	2.6	0.91 (0.72, 1.15)	1.8	0.85 (0.66, 1.09)	2.5	0.93 (0.72, 1.21)	8.2	0.9 (0.78, 1.03)
Mchinji	6236 (1.8)	2.2	1.75 (1.25, 2.45)	3.1	1.37 (1.04, 1.81)	2.6	1.36 (1.01, 1.82)	2.3	1.28 (0.94, 1.75)	9.6	1.39 (1.18, 1.64)
Nkhota-kota	4442 (1.3)	1.1	0.99 (0.66, 1.5)	2.7	1.37 (1.02, 1.84)	3	1.5 (1.1, 2.04)	1.9	1.25 (0.89, 1.75)	8.3	1.3 (1.09, 1.55)
Ntcheu	9827 (2.9)	1.5	1.1 (0.78, 1.54)	1.9	0.83 (0.63, 1.09)	1.9	1 (0.75, 1.33)	1.9	1.02 (0.76, 1.36)	6.9	0.94 (0.8, 1.1)
Ntchisi	1580 (0.5)	1.8	1.71 (1.04, 2.81)	1.8	1.03 (0.66, 1.62)	2.5	1.37 (0.92, 2.06)	1.6	1.02 (0.64, 1.64)	7	1.18 (0.92, 1.51)
Salima	5624 (1.6)	2.2	1.36 (0.96, 1.93)	4.1	1.57 (1.2, 2.05)	3.2	1.57 (1.18, 2.1)	3.1	1.31 (0.97, 1.77)	11.4	1.42 (1.21, 1.66)

(Continues)

TABLE 2 (Continued)

Characteristics	N (%)	HIV screening		Hep. B screening		Hep. C screening		Syphilis screening		All TTI screening	
		%Reactive	Adj. OR (95% CI)	%Reactive	Adj. OR (95% CI)	%Reactive	Adj. OR (95% CI)	%Reactive	Adj. OR (95% CI)	%Reactive	Adj. OR (95% CI)
Chitipa	5382 (1.6)	0.7	0.61 (0.38, 0.98)	0.9	0.44 (0.3, 0.65)	0.4	0.24 (0.15, 0.39)	0.5	0.34 (0.22, 0.53)	2.5	0.37 (0.29, 0.47)
Karonga	7095 (2.1)	0.7	0.55 (0.36, 0.83)	2.1	0.95 (0.7, 1.29)	1.2	0.67 (0.47, 0.95)	1.3	0.79 (0.56, 1.11)	5.1	0.73 (0.61, 0.88)
Mzimba	15 113 (4.4)	1	0.81 (0.58, 1.12)	1.8	0.77 (0.59, 1.01)	1.2	0.63 (0.47, 0.83)	1.2	0.63 (0.46, 0.85)	5	0.68 (0.58, 0.79)
Mzuzu	19 710 (5.7)	0.9	0.65 (0.47, 0.89)	1.4	0.54 (0.42, 0.7)	0.8	0.48 (0.36, 0.64)	1.2	0.58 (0.43, 0.77)	4.2	0.52 (0.45, 0.61)
Nkhata-Bay	2740 (0.8)	1.3	1.17 (0.75, 1.81)	2.7	1.34 (0.94, 1.92)	3.9	2.14 (1.55, 2.96)	1.8	1.15 (0.77, 1.73)	8.9	1.42 (1.16, 1.74)
Rumphi	6505 (1.9)	1.1	0.89 (0.61, 1.31)	1.8	0.78 (0.58, 1.06)	1.2	0.62 (0.43, 0.89)	1.2	0.68 (0.48, 0.97)	5.1	0.71 (0.59, 0.85)
Balaka	12 059 (3.5)	1.4	1.08 (0.78, 1.5)	2.2	0.97 (0.75, 1.26)	1.6	0.81 (0.61, 1.07)	2.1	1.1 (0.82, 1.46)	6.8	0.93 (0.8, 1.09)
Blantyre	80 594 (23.4)	1.4	0.91 (0.68, 1.22)	1.8	0.65 (0.52, 0.83)	1	0.48 (0.37, 0.62)	2	0.84 (0.65, 1.09)	5.8	0.67 (0.58, 0.76)
Chikwawa	5239 (1.5)	1.5	0.99 (0.68, 1.44)	2.7	1.08 (0.81, 1.44)	1.7	0.82 (0.59, 1.14)	3.3	1.53 (1.13, 2.07)	8.5	1.05 (0.89, 1.25)
Chiradzulu	7235 (2.1)	1.3	1.16 (0.81, 1.66)	2	0.87 (0.65, 1.16)	1	0.52 (0.37, 0.75)	1.5	0.94 (0.68, 1.31)	5.5	0.82 (0.69, 0.97)
Machinga	4937 (1.4)	1.6	1.36 (0.93, 1.97)	2.9	1.32 (0.99, 1.77)	2	1.06 (0.76, 1.47)	2.1	1.34 (0.97, 1.85)	8.1	1.22 (1.02, 1.45)
Mangochi	7850 (2.3)	1.2	0.95 (0.66, 1.36)	2.3	1.05 (0.79, 1.39)	1.6	0.85 (0.63, 1.15)	1.7	1.01 (0.74, 1.39)	6.4	0.93 (0.79, 1.1)
Mulanje	6184 (1.8)	1.6	1.4 (0.98, 2.01)	2.1	0.94 (0.7, 1.27)	1.6	0.91 (0.65, 1.27)	2.7	1.72 (1.27, 2.34)	7.6	1.17 (0.98, 1.38)
Mwanza	4031 (1.2)	1.2	1.14 (0.76, 1.73)	1.2	0.6 (0.4, 0.89)	1.3	0.65 (0.44, 0.95)	1.4	0.93 (0.64, 1.36)	4.8	0.75 (0.61, 0.92)
Neno	2761 (0.8)	0.8	0.73 (0.44, 1.23)	1.4	0.67 (0.42, 1.06)	1.5	0.75 (0.49, 1.16)	1.1	0.69 (0.43, 1.1)	4.6	0.68 (0.53, 0.87)
Nsanje	6960 (2)	0.6	0.56 (0.36, 0.87)	1.4	0.64 (0.46, 0.87)	0.7	0.35 (0.24, 0.51)	1.2	0.81 (0.57, 1.14)	3.8	0.56 (0.47, 0.68)
Phalombe	3603 (1)	0.9	0.89 (0.56, 1.39)	2.1	0.99 (0.7, 1.41)	0.8	0.42 (0.27, 0.66)	1.3	0.86 (0.57, 1.3)	5	0.75 (0.6, 0.93)
Thyolo	13 813 (4)	1.2	0.83 (0.6, 1.16)	1.8	0.76 (0.58, 0.99)	0.8	0.41 (0.3, 0.56)	2.9	1.42 (1.08, 1.86)	6.4	0.82 (0.71, 0.96)
Zomba	11 895 (3.5)	2	1.37 (1.0, 1.87)	2.7	1.2 (0.93, 1.56)	2.2	1.04 (0.79, 1.37)	3.2	1.5 (1.14, 1.97)	9.5	1.24 (1.07, 1.44)

Note: Odds ratios are adjusted for all factors presented and were estimated by GEE logistic models which accounted for repeated measures.

TABLE 3 Sample proportions of donors testing positive for HIV, syphilis, hep B and hep C along with model-based spatially-smoothed estimates and their corresponding 95% confidence intervals.

	HIV			Syphilis			Hep B			Hep C			Any TTI		
District	Sample proportion	Estimated prevalence	95% CI	Sample proportion	Estimated Prevalence	95% CI	Sample proportion	Estimated prevalence	95% CI	Sample proportion	Estimated prevalence	95% CI	Sample proportion	Estimated prevalence	95% CI
Balaka	0.024	0.024	(0.021, 0.027)	0.035	0.034	(0.025, 0.043)	0.037	0.034	(0.029, 0.04)	0.027	0.027	(0.018, 0.035)	0.114	0.112	(0.091, 0.133)
Blantyre	0.029	0.029	(0.027, 0.03)	0.04	0.038	(0.028, 0.047)	0.035	0.033	(0.028, 0.037)	0.018	0.021	(0.015, 0.027)	0.113	0.111	(0.091, 0.131)
Chikwawa	0.021	0.021	(0.017, 0.025)	0.049	0.044	(0.032, 0.056)	0.04	0.032	(0.027, 0.038)	0.026	0.021	(0.014, 0.029)	0.126	0.121	(0.098, 0.145)
Chiradzulu	0.022	0.023	(0.02, 0.027)	0.025	0.026	(0.018, 0.034)	0.034	0.033	(0.028, 0.038)	0.016	0.02	(0.014, 0.025)	0.094	0.095	(0.076, 0.114)
Chitipa	0.01	0.011	(0.008, 0.014)	0.009	0.013	(0.009, 0.018)	0.015	0.026	(0.02, 0.031)	0.007	0.013	(0.007, 0.018)	0.038	0.048	(0.037, 0.06)
Dedza	0.016	0.019	(0.015, 0.023)	0.022	0.023	(0.016, 0.031)	0.027	0.033	(0.028, 0.039)	0.024	0.028	(0.018, 0.038)	0.085	0.088	(0.07, 0.106)
Dowa	0.027	0.026	(0.022, 0.03)	0.035	0.034	(0.025, 0.043)	0.029	0.033	(0.028, 0.039)	0.032	0.032	(0.022, 0.043)	0.115	0.112	(0.091, 0.134)
Karonga	0.011	0.011	(0.009, 0.014)	0.02	0.022	(0.016, 0.029)	0.029	0.027	(0.022, 0.032)	0.017	0.015	(0.009, 0.021)	0.073	0.078	(0.062, 0.094)
Kasungu	0.027	0.026	(0.023, 0.03)	0.031	0.031	(0.022, 0.039)	0.038	0.033	(0.027, 0.039)	0.05	0.037	(0.024, 0.049)	0.137	0.13	(0.107, 0.154)
Lilongwe	0.027	0.027	(0.026, 0.029)	0.035	0.034	(0.025, 0.042)	0.037	0.034	(0.028, 0.04)	0.024	0.028	(0.019, 0.038)	0.115	0.113	(0.092, 0.133)
Machinga	0.024	0.024	(0.019, 0.028)	0.034	0.033	(0.023, 0.042)	0.044	0.036	(0.029, 0.042)	0.029	0.026	(0.017, 0.036)	0.123	0.119	(0.096, 0.142)
Mangochi	0.018	0.019	(0.016, 0.023)	0.027	0.028	(0.02, 0.036)	0.036	0.035	(0.029, 0.041)	0.027	0.028	(0.018, 0.038)	0.103	0.102	(0.083, 0.122)
Mchinji	0.029	0.029	(0.024, 0.033)	0.03	0.03	(0.021, 0.039)	0.04	0.034	(0.028, 0.04)	0.033	0.031	(0.02, 0.043)	0.125	0.121	(0.098, 0.144)
Mulanje	0.022	0.021	(0.018, 0.025)	0.039	0.037	(0.026, 0.047)	0.029	0.032	(0.027, 0.037)	0.021	0.019	(0.013, 0.025)	0.106	0.105	(0.084, 0.125)
Mwanza	0.025	0.025	(0.019, 0.03)	0.029	0.029	(0.02, 0.039)	0.024	0.031	(0.026, 0.037)	0.028	0.025	(0.016, 0.033)	0.1	0.1	(0.079, 0.122)
Mzimba	0.016	0.016	(0.014, 0.019)	0.018	0.02	(0.014, 0.025)	0.026	0.029	(0.024, 0.035)	0.019	0.024	(0.015, 0.032)	0.076	0.08	(0.064, 0.095)
Mzuzu	0.016	0.017	(0.014, 0.019)	0.02	0.022	(0.016, 0.028)	0.025	0.029	(0.024, 0.034)	0.014	0.021	(0.014, 0.028)	0.073	0.077	(0.062, 0.092)
Neno	0.02	0.024	(0.019, 0.029)	0.025	0.026	(0.017, 0.036)	0.027	0.032	(0.027, 0.037)	0.031	0.026	(0.017, 0.034)	0.097	0.098	(0.076, 0.121)
Nkhata-Bay	0.02	0.018	(0.014, 0.022)	0.025	0.026	(0.018, 0.035)	0.035	0.03	(0.024, 0.035)	0.051	0.027	(0.018, 0.036)	0.118	0.114	(0.091, 0.138)
Nkhota-Kota	0.015	0.017	(0.013, 0.021)	0.027	0.027	(0.019, 0.035)	0.037	0.033	(0.027, 0.039)	0.037	0.034	(0.022, 0.046)	0.11	0.108	(0.087, 0.129)
Nsanje	0.012	0.014	(0.011, 0.017)	0.024	0.026	(0.018, 0.033)	0.027	0.031	(0.025, 0.037)	0.014	0.017	(0.01, 0.024)	0.075	0.08	(0.063, 0.097)
Ntcheu	0.023	0.023	(0.02, 0.027)	0.033	0.032	(0.023, 0.041)	0.031	0.033	(0.028, 0.039)	0.031	0.028	(0.019, 0.038)	0.112	0.11	(0.089, 0.131)
Ntchisi	0.022	0.023	(0.017, 0.028)	0.021	0.024	(0.015, 0.032)	0.023	0.033	(0.027, 0.038)	0.032	0.034	(0.023, 0.045)	0.089	0.092	(0.07, 0.113)
Phalombe	0.018	0.021	(0.016, 0.025)	0.022	0.024	(0.016, 0.032)	0.037	0.034	(0.028, 0.039)	0.015	0.02	(0.013, 0.027)	0.087	0.09	(0.071, 0.11)
Rumphi	0.017	0.016	(0.013, 0.019)	0.018	0.021	(0.014, 0.027)	0.026	0.027	(0.022, 0.033)	0.016	0.017	(0.011, 0.024)	0.074	0.078	(0.062, 0.095)
Salima	0.026	0.025	(0.021, 0.029)	0.04	0.037	(0.027, 0.047)	0.052	0.036	(0.029, 0.042)	0.04	0.033	(0.022, 0.045)	0.144	0.136	(0.111, 0.162)
Thyolo	0.019	0.019	(0.017, 0.022)	0.046	0.042	(0.031, 0.053)	0.028	0.032	(0.027, 0.037)	0.013	0.018	(0.012, 0.023)	0.101	0.101	(0.082, 0.12)
Zomba	0.029	0.028	(0.024, 0.031)	0.047	0.043	(0.032, 0.054)	0.039	0.034	(0.029, 0.04)	0.03	0.024	(0.017, 0.031)	0.136	0.129	(0.106, 0.152)

compared to 2019. The number of donations improved from 2020 to 2021 but was still down 10% from the peak in 2019 (Table 2).

3.3 | Epidemiology of any TTI

The overall TTIs seroprevalence among donors was 10.7%, with hepatitis B (HBV) having the highest prevalence (3.4%; 95% CI: 3.3, 3.5), followed by syphilis (3.3%; 95% CI: 3.2, 3.4), HIV (2.4%; 95% CI: 2.3, 2.4) and hepatitis C (2.4%; 95% CI: 2.3, 2.4). The incidence per 1000 person-years for HIV was 11.4 (95% CI: 10.6, 12.3), HBV was 13.7 (95% CI: 12.8, 14.7), hepatitis C (HCV) was 18.4 (95%CI: 17.3, 19.5), and syphilis was 20.1 (95% CI: 19.0, 21.3).

The prevalence of reactive tests for overall TTIs decreased over time (Table 2). The highest rate was in 2017 with 8.6% of donations testing reactive and the lowest rate was in 2021 with 4.9% of donations testing reactive. Males had significantly higher rates than females (OR = 1.18, 95% CI: 1.13, 1.23) and students were less likely to test reactive than non-students (OR = 0.59, 95% CI: 0.56, 0.61). Married donors were more likely to test reactive than single donors (OR = 1.08, 95% CI: 1.03, 1.14). Repeat donors had significantly lower risk of TTI reactivity compared to one-time donors (age and sex adjusted OR: 0.45, 95% CI: 0.43, 0.46).

The mean prevalence of all TTIs varied between districts from 3.8% (Chitipa in the northern region) to 13.7% (Kasungu in central region). The geostatistical model performed very little smoothing. The estimated prevalences from the geostatistical model varied from 4.8% (Chitipa, 95% CI: 3.7%–6.0%) to 13.0% (Kasungu, 95% CI: 10.7%–15.4%) as seen in Table 3.

Overall, 3635 seroconversions of any TTI were observed among 62 367 donors over 59133.1 person-years (PYs), resulting in a cumulative incidence rate (CIR) of 61.5 (59.5, 63.5) per 1000 PYs. There was some smoothing by the spatial model but it did not change the overall distribution of mean district-level TTI incidence, which was highest in Mchinji (102 per 1000 PYs), Kasungu and Nkhota-kota (in central region) and Mwanza, Neno (in southern region) and lowest in Chitipa (CIR of 22 per 1000 PYs). For all four TTIs, the northern region had lower incidence rates compared to other regions (Figure 2). The overall TTI incidence rate was higher in male and non-student donors, and decreased with increasing age (Table 4).

3.4 | Prevalence and Incidence of HIV among blood donors

The prevalence of HIV among donors varied over time with a high of 2.6% in 2017 and a low of 1.4% in 2021 with no consistent trend. Results from multiple logistic regression models indicate that donations from those who were aged 16–25 were less likely to test reactive for HIV than those aged 26–35 and the age group of those over 35 (OR = 0.79, 95% CI: 0.70, 0.89). Also, students were significantly less likely to test reactive for HIV compared to non-students (OR = 0.55, 95% CI: 0.51, 0.61). However, there was not a significant difference between male and female donors (OR = 0.97, 95% CI: 0.89, 1.04), and also no significant difference between those who were single compared to those who were married (OR = 1.09, 95% CI: 0.99, 1.20).

The mean district-level prevalence of HIV over the study period varied from 1% (Chitipa) to 2.9% (Mchinji, Blantyre, Zomba). The geostatistical model did very little smoothing of the district level prevalences (see Figure 1). The estimated prevalences from the geostatistical model varied from 1.1% (Chitipa, 95% CI: 0.8%–1.4%) to 2.9% (Blantyre, 95% CI: 2.7%–3.0%, and Mchinji, 95% CI: 2.4%–3.3%) as seen in Table 3. HIV prevalence varied significantly by district.

The mean district-level HIV incidence rate was 11.4 per 1000 PYs (10.6, 12.3), with a total of 675 new HIV seroreactive cases among donors who donated more than once during the study period. The spatial smoothing did not change the pattern, with seroconversion (incidence) rates higher in Mwanza (in the south), Ntchisi, Salima and Dowa (in central region), and lowest in Nkhata-bay and Karonga in the north (Figure 2).

TABLE 4 Overall TTI incidence by demographic characteristics of blood donors.

Characteristic		Total donors	No. of new cases	Person time (years)	Incidence per year (95% CI)	*p*-Value
Overall		62 367	3635	59133.1	0.0615 (0.0595, 0.0635)	N/A
Sex						
	Female	12 066	484	11374.3	0.0426 (0.0388, 0.0465)	<0.001
	Male	50 301	3151	47758.8	0.0660 (0.0637, 0.0683)	
Age						
	16–25	51 931	2801	45709.4	0.0613 (0.0500, 0.0636)	<0.001
	26–35	6772	568	8681.6	0.0654 (0.0602, 0.0710)	
	≥36	3664	266	47,42.1	0.0561 (0.0496, 0.0633)	
Marital status						
	Married	6880	499	7806.4	0.0639 (0.0584, 0.0698)	0.05
	Single	55 487	3136	51326.7	0.0611 (0.0590, 0.0633)	
Occupation						
	Student	49 636	2700	45397.3	0.0595 (0.0573, 0.0618)	0.7
	Non-student	12 731	935	13735.8	0.0681 (0.0638, 0.0726)	

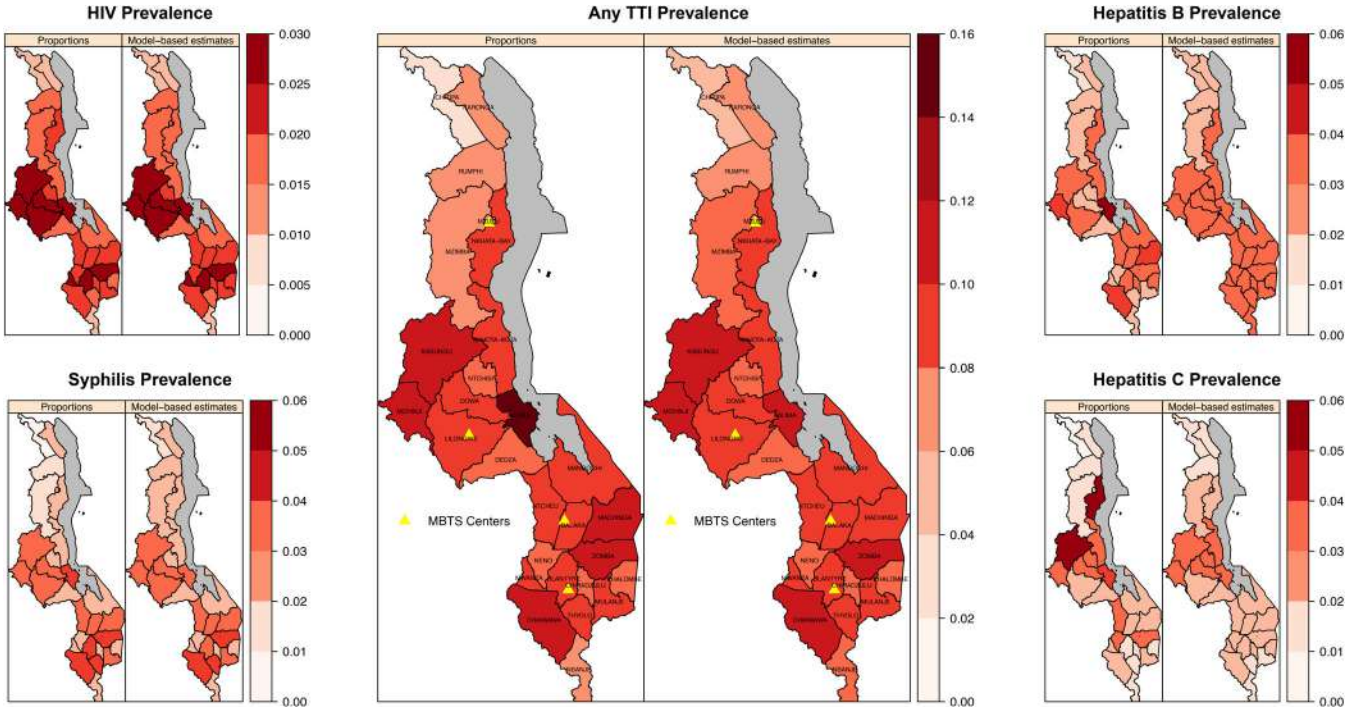

FIGURE 1 Sample proportions and model-based spatially smoothed estimates of donors testing reactive for any TTI, HIV, syphilis, hepatitis B and hepatitis C.

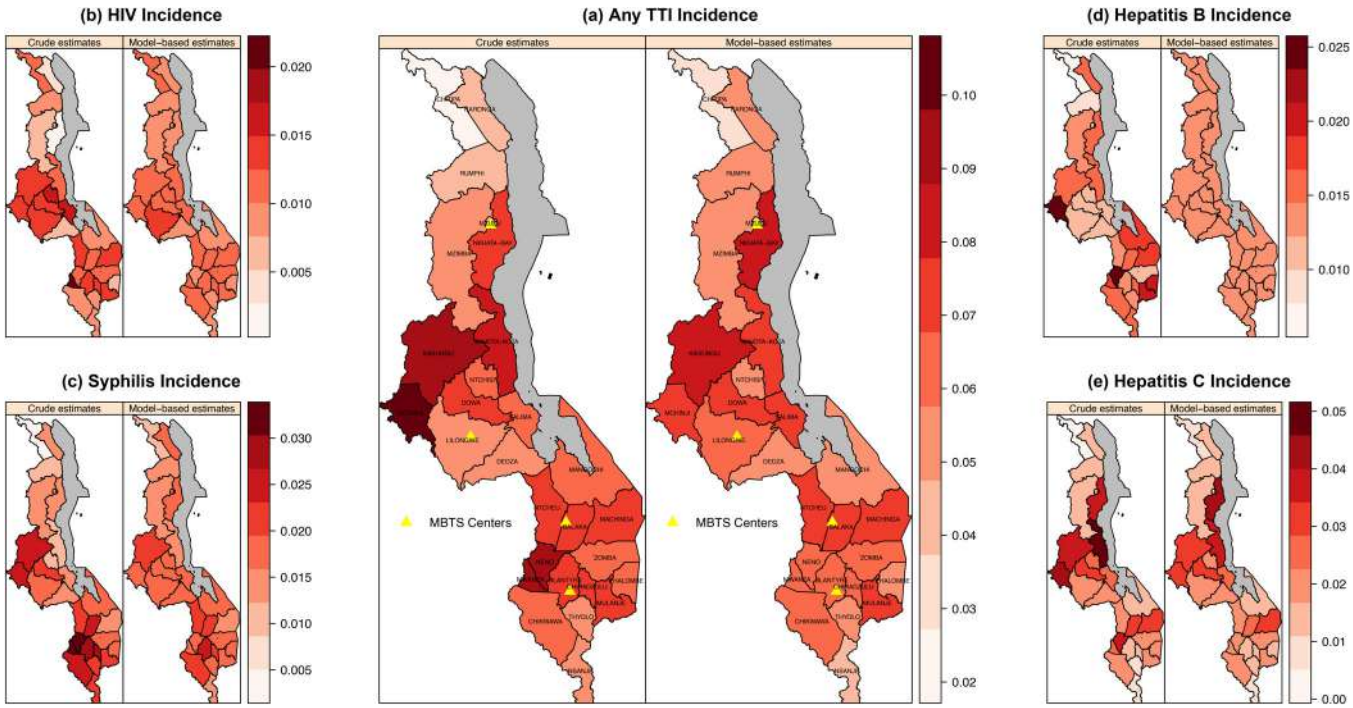

FIGURE 2 Crude incidence and model-based spatially smoothed estimates of incidence for any TTI, HIV, syphilis, hepatitis B and hepatitis C.

3.5 | Prevalence and incidence of hepatitis B among donors

The prevalence of hepatitis B among donors steadily declined from 3.4% in 2015 to 1.5% in 2021. While the multiple logistic regression model did not identify a difference in the years immediately after 2015, all years from 2018 forward had significantly lower prevalence rates than in 2015. There was no difference in terms of age but donations from males had a significantly higher odds of testing reactive (OR = 1.37, 95% CI: 1.28, 1.47). Donations from students were less

likely to test reactive (OR = 0.66, 95% CI: 0.61, 0.72). Donations from married donors were more likely to test reactive than from single donors (OR = 1.12, 95% CI: 1.03, 1.22).

The mean district-level prevalence of hepatitis B over the study period varied from 1.5% (Chitipa) to 5.2% (Salima). In contrast to what was observed with HIV, the geostatistical model performed extensive smoothing and detected 2 major regions: a region of low prevalence in the north and a region of higher prevalence in the south (Figure 1). The estimated prevalences from the geostatistical model varied from 2.6% (Chiptia, 95% CI: 2.0%–3.1%) to 3.6% (Machinga, 95% CI: 2.9%–4.2% and Salima, 95% CI: 2.9%–4.2%) as seen in Table 3. All of the 95% prediction intervals overlapped indicating that after adjustment for spatial proximity there are no significant differences among the districts in hepatitis B rates.

A total of 809 new cases of hepatitis B were observed during the study period. The mean district-level incidence rate of hepatitis B was 13.7 per 1000 Pys (12.8, 14.7). The spatial smoothing removed the initial geographical patterns observed in crude estimates (Figure 2).

3.6 | Prevalence and incidence of hepatitis C among blood donors

The prevalence of hepatitis C among donors varied over the study period with the lowest level of 0.9% in 2015 and a peak of 2.7% in 2018. While there was a significant decline to 2.0% in 2019, 2.5% tested reactive in 2020. This returned to the low level of 1.3% in 2021. In multiple logistic regression models, many of these year to year differences were significant. These models also identified a significantly higher rate among those 16–25 compared to those over 35 (OR = 1.42, 95% CI: 1.24, 1.63). The percentage was significantly higher among males (OR = 1.47, 95% CI: 1.35, 1.60) and significantly lower among students (OR = 0.81, 95% CI: 0.74, 0.89). Married donors were more likely to test reactive than single donors (OR = 1.35, 95% CI: 1.21, 1.51).

The mean district-level prevalence of hepatitis C over the study period varied from 0.7% (Chitipa) to 5.1% (Nkhata-Bay). The geostatistical model performed some spatial smoothing and identified a spatial gradient that goes from a high prevalence region in the west central portion of the country to lower prevalence regions in the north and the south (Figure 1). The estimated prevalences from the geostatistical model varied from 1.3% (Chitipa, 95% CI: 0.7%–1.8%) to 3.7% (Kasungu, 95% CI: 2.4%–4.9%) as seen in Table 3. As these prediction intervals indicate, there are some significant differences among districts in terms of the rate of hepatitis C reactivity.

There were a total of 1088 new cases of hepatitis C seroreactivity among repeat donors. The mean district-level incidence rate of hepatitis C was 18.4 (17.3, 9.5). There was little spatial smoothing, the patterns remaining the same with the rates higher in Nkhotakota (in central), lowest in Chitipa and Karonga in the north region (Figure 2).

3.7 | Prevalence and incidence of syphilis among blood donors

The lowest level of reactive syphilis tests was observed in the final year at 1.6% in 2021. The highest rate was in 2017 at 2.8% and there was no discernible trend over the study period. Many of the year to year differences were statistically significant in logistic regression models. Both of the younger age groups had significantly lower rates than the group of donors aged greater than 35 (OR = 0.70, 95% CI: 0.63, 0.78 for 16–25 compared to over 35, and OR = 0.9, 95% CI: 0.83, 0.98 for 26–35 compared to over 35). The percentage testing reactive was similar across the sexes (OR = 1.04, 95% CI: 0.98, 1.11) but students were less likely to test reactive compared to non-students (OR = 0.45, 95% CI: 0.42, 0.49). There was no difference by marital status.

The mean district-level prevalence of syphilis over the study period varied from 0.9% (Chitipa) to 4.9% (Chikwawa). The geostatistical model performed very little spatial smoothing for syphilis as can be seen in Figure 1, however it smoothed all estimates more towards the district-level mean compared to the results from the model for HIV. The estimated prevalences from the geostatistical model varied from 1.3% (Chitipa, 95% CI: 0.9%–1.8%) to 4.4% (Chikwawa, 95% CI: 3.2%–5.6%) as seen in Table 3. These prediction intervals indicate that there are many districts with different rates of syphilis among donors.

A total of 1188 new cases of syphilis were observed during the study period. The mean district-level incidence rate of syphilis was 20.1 per 1000 Pys (19.0, 21.3). The geospatial model did little smoothing, with the incidence rates higher in Neno (in the south), and lowest in Chitipa and Karonga (Figure 2).

4 | DISCUSSION

Our study is an extension of a previous study in Malawi on seroprevalence of HIV, syphilis, hepatitis B and C utilising blood donation data from 2011 to 2015.[11] But, it is the first study to report incidence of TTIs among blood donors in Malawi. Our analysis showed that the seroprevalence and incidence of overall TTI reactivity was 6.8% and 62 per 1000 PYs respectively. The overall TTI incidence rate was higher in male and non-student donors, and decreased with increasing age. We also observed geographical variations in the distribution of overall TTI reactivity, HIV, syphilis and hepatitis C. The observed patterns on overall TTIs must be interpreted with caution as risk factors for individual TTIs differ from one TTI to another. The patterns observed are mostly influenced by different TTIs for different risk factors.

The overall TTIs are important for estimating national blood needs and estimating the country's blood donation potential. High overall TTI seroprevalence results in wastage of consumables for blood collection and staff time. The reported prevalence is for blood donors who have passed pre-donation screening. The common practice when estimating blood donation potential is to reduce the number of potential blood donors by the population-level prevalence of

TTIs. However, when estimating blood needs, the overall TTI prevalence (any TTI reactivity) in the blood donor population itself must be factored in to avoid underestimating what must be collected in order to meet national needs for usable units of blood. Since we expect TTI levels to be lower than the general population (donors are younger and are screened for TTI risk), using the general population prevalence could lead to overestimation of TTI rates and setting donation targets needlessly high.

HIV prevalence in this cohort was 1.5% compared to a national HIV prevalence of 8.9% in the general adult population (15 years and older) in Malawi.[13] Studies in other countries in the sub-Saharan Africa reported similar HIV prevalence in blood donor populations; Tanzania[15] (1.7%), DRC[16] (1.6%), Malawi[11] (1.9%), except for Lidenge et al.[17] in Tanzania who reported prevalence as high as 4.2%. In this cohort, younger blood donors (16–25 yrs) and student donors had lower risk of HIV reactivity, and HIV prevalence significantly decreased from 2015. The HIV cumulative incidence rate in our cohort was estimated at 1.14% over 7 years (approx. 0.16% per year) which is lower compared to the 0.21% per year from the recent nationwide population HIV survey done between 2020 and 2021. The lower prevalence and incidence of HIV infections among blood donors could be attributed to enhanced screening procedures that are used before donation as they discourage those with risk factors for TTIs from donating blood. In addition, donors are a self-selected population and only those who perceive themselves as low risk for infections come forward for donation.

Syphilis seroprevalence among blood donors in Malawi was 2.1% which is similar to 2% from antenatal national program data in Malawi[8] and which was also similar to 2019 estimates from retrospective studies from Malawi and Tanzania.[11,15] There was no clear pattern of syphilis prevalence over the years but the rates were significantly higher in 2017 and 2018 compared to 2015 rates. Student as well as donors younger than 36 years had a reduced risk of syphilis reactivity, echoing the results by an earlier study.[11] However, we did not find any gender differences in risk of syphilis reactivity as reported in an earlier study in Malawi.[11] The syphilis incidence in this cohort was 20 per 1000 PYs (equivalent to annual incidence of 0.29%). Considering the pre-donation screening (with a questionnaire) in blood donors, the similar prevalence with pregnant women, who do not undergo pretesting screening should be surprising. The same pattern is not observed in other sexually transmitted infections such as HIV where prevalence in blood donors is lower than in pregnant women at 1.5% and 6% (ANC data, 2022)[16] respectively. The similar prevalence of syphilis in these two population groups is most likely due to the screening tests used in both groups as they detect IgG antibodies which persist in circulation for up to 20 year after the infection has been resolved.

The overall seroprevalence of Hepatitis B was 2.1% while year to year prevalence steadily declined from 3.4% in 2015 to 1.5% in 2021. Hepatitis B prevalence also showed a decline trend over the period 2011–2015.[12] The sustained decline despite change of test kits could be due to the protective effect of introducing routine hepatitis B vaccination into the vaccination schedule for Malawi that occurred in 2002.[18] During the study period, two studies from Tanzania also reported high prevalence rates of 4.1% in 2019[15] and 7.3% in 2020.[17] Based on our recent unpublished systematic review looking at prevalence of TTIs in Southern African Development Community (SADC) region, hepatitis B was the most prevalent TTI in the region (pooled estimates: HBV prevalence = 3.0%; 95% CI: 2.0–5.0; and HIV, HCV, and Syphilis was 2.0%, 1.0% 2.0% respectively).[19] Male donors and also married or divorced donors were at increased risk of HBV reactivity. Other studies in the region also reported these significant gender and marital status differences among first-time donors.[20,21] The predominance of young unmarried donors in our blood donor population and the similar HIV and syphilis risk among male and female donors suggests that the sexual route may not be responsible for the higher HBV risk in male blood donors. Close shaves in barbershops and traditional circumcision could be responsible for the observed pattern although our geospatial modelling did not show geographical hotspots in regions which practice traditional circumcisions. The HBV incidence in our study was 13 per 1000 PYs which was lower than the incidence reported in DRC.[22]

Hepatitis C prevalence was higher than what was reported in the earlier study (1.5% in 2021 vs. 1% in 2015, $p < 0.001$).[11] Younger donors (16–25), male and married donors had significantly higher risk of HCV reactivity. The HCV prevalence peaked at a high of 2.7% in 2018 and dropped thereafter. Hepatitis C results reported in this study needs to be interpreted with caution. With no confirmatory testing, Abbott reagents may have detected more false positives than BioRad. In an earlier study, M'baya et al.[10] have discussed extensively the issue of false positives of the enzyme immunoassays and their implications. Like other infections, students had lower risk of HCV reactivity. When comparing rates in the SADC region, two studies from DRC[21] and another from Tanzania[17] reported higher prevalence rates but other studies in Tanzania,[15] South Africa[23] and Madagascar[24] reported similar or lower rates compared to Malawi. Hepatitis C virus transmission is mainly through the parenteral route and commonly via intravenous drug use, unsterile medical procedures and unsafe blood transfusions.[25] Unlike HBV infection where a small percentage of infections develop clinical disease, a higher proportion of HCV infections produce clinical disease which usually progresses to chronic liver disease. The lack of risk factors for HCV infection in the predominantly-student blood donor population and low burden of both clinical hepatitis and chronic liver disease in Malawi supports findings of other studies in Malawi and beyond, of high false HCV reactive results on EIA-based laboratory testing algorithms which do not include confirmatory testing.[26-29]

Geographical patterns emerged across the country in crude analyses for prevalence and incidence estimates. For prevalence maps, use of geostatistical modelling did very little smoothing for any TTI, HIV and syphilis with the pattern remaining the same as in the crude estimates. Also for incidence, spatial smoothing did not alter the general pattern of district-level incidence for overall TTI, HIV, syphilis and hepatitis C. This shows a disproportionate burden of the TTIs across the country. For both prevalence and incidence maps, HIV and syphilis tended to follow similar geographical patterns probably as a

consequence of their mainly sexual route of transmission. In the last two decades, studies have continually reported increasing rates of HIV and syphilis co-infections.[30-32] As such, many national standard HIV care programs encourage regular syphilis serology testing.[29] For example, in Malawi all women attending an antenatal clinic are screened for both HIV and syphilis as part of standard HIV care. The use of spatial methods in mapping TTIs in national blood donor programs is not common in SSA region but these methods have been widely applied in other program settings for general population such as HIV programs,[33,34] TB program[35] and malaria programs.[36,37] The use of spatial tools have evidently been crucial in helping the program frontline staff and policy makers to prioritise areas where there is high burden.

Like any other studies, our study has some limitations. First, the testing algorithm did not include confirmatory testing which might have inflated the prevalence and incidence due to false reactives. Seroprevalence and incidence rates observed in Malawian blood donor population were similar to those reported in previous studies in Malawi and other countries.[38] Second, we used a routine program dataset that had incomplete data for 2016 blood donation figures compared to the annual program report,[39] likely due to the database migration to a new system. We did not have a comprehensive list of donor characteristics, hence we did not conduct an exhaustive assessment of other risk factors for the TTIs which may have influenced our findings. However, for the factors included in the study, our results were similar to results reported in other studies from the region. Lastly, there are concerns about utility of routine longitudinal program data (accuracy, reliability and completeness). Despite these concerns, routine data have been used to potentially inform and facilitate recruitment in randomised and to customise program implementation.[40-42]

In conclusion, the TTI prevalence and incidence rates among blood donors from this study are consistent with estimates from other countries in sub-Saharan Africa.[14,20,38] We were able to identify subgroups of blood donors at high risk of testing reactive for a TTI and this risk was lower if a donor was a repeat donor. By identifying geographical variations of TTI prevalence and incidence, these findings could potentially inform further studies to identify hotspots within districts with high burden of disease which could be sparingly targeted for blood collection activities to optimise usage of resources. As countries are putting in place strategies and interventions to improve safety of blood transfusions, it is important that TTI surveillance studies are strengthened to ensure effective monitoring of more prevalent TTIs.

AUTHOR CONTRIBUTIONS

Conceptualization and research proposal: Emmanuel Singogo, Bridon M'baya, Mina Hosseinpour, Maganizo Chagomerana. *Funding acquisition*: Mina Hosseinipour, Bridon M'baya, Emmanuel Singogo, Effie Chipeta. *Methodology*: Emmanuel Singogo, Bridon M'baya, Mina Hosseinpour, Maganizo Chagomerana, Cavan Reilly, Collin Van Ryn. *Formal analysis*: Emmanuel Singogo, Bridon M'baya, Mina Hosseinpour, Maganizo Chagomerana, Cavan Reilly, Collin Van Ryn, Robert M'bwana. *Manuscript writing and review*: Emmanuel Singogo, Bridon M'baya, Mina Hosseinpour, Maganizo Chagomerana, Cavan Reilly, Collin Van Ryn, Robert M'bwana, Sydney Puerto-Meredith, Effie Chipeta, Victor Mwapasa, Adamson Muula, Andrew Likaka.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Due to confidentiality agreements, data used in this analysis can be made available upon request to bona fide researchers subject to a non-disclosure agreement. Details of the data and how to request access are available through the corresponding author.

ORCID

Emmanuel Singogo https://orcid.org/0000-0002-2015-335X

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SHORT COMMUNICATION

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How do we translate gaps and unmet needs of blood management for thalassemia into a collaborative implementation framework?

Chanin Limwongse [1] | Ponlapat Rojnuckarin [1] | Pawinee Kupatawintu [1] | Aphisit Thongthaisin [2] | Parichart Permpikul [1,2] | Suporn Chuncharunee [1,2]

[1]Academic Department of Trauma & Orthopaedics, School of Medicine, University of Leeds, Leeds, UK

[2]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK

[3]Leeds Orthopaedic & Trauma Sciences, Leeds General Infirmary, University of Leeds, Leeds, UK

[4]Leeds Institute of Health Sciences, University of Leeds, Leeds, UK

[5]NIHR Leeds Biomedical Research Unit, Chapel Allerton Hospital, Leeds, UK

Correspondence
Michalis Panteli, Academic Department of Trauma & Orthopaedics, School of Medicine, University of Leeds, Clarendon Wing, Level D, Great George Street, Leeds LS1 3EX, West Yorkshire, UK.

Email: mike.murphy@nhsbt.nhs.uk

Abstract

Background and Objective

The mainstay of management for thalassemia is regular blood transfusions. However, gaps and unmet needs of blood services for thalassemia are still not clearly identified and addressed in Thailand, a country prevalent with thalassemia. What can be a collaborative implementation framework that helps advance practices and policies relating to blood management for thalassemia?

Methods

The first Blood & Beyond Roundtable Discussion was held in July 2022 to gather the current situation, gaps, and unmet needs of blood services for thalassemia from multidisciplinary experts and thalassemic patients. The Implementation Guide as suggested by the Centre for Effective Services was applied as a tool to consolidate information from the discussions and construct the collaborative implementation framework.

Results

The National Blood Center and hospitals in Thailand followed the missions specified in the National Blood Policy and the standard guidelines to ensure the best practice of blood management for thalassemia. However, there were six gaps and unmet needs identified from the discussions. After all discussion points were mapped onto the framework, an implementation plan comprised of five specific activities became clear and actionable.

Conclusion

Without the complete information from both experts and patients, the implementation plan would not have been successfully constructed. The method that we employed to translate all information into the framework can be adapted by other countries to develop their own specific framework efficiently.

KEYWORDS

Haemovigilance, blood, medicine, transfusion

1 | INTRODUCTION

Severe acute respiratory infections caused by strains of influenza or coronavirus often lead to hospitalisation and sometimes death. Symptomatic infection with SARS CoV-2 (COVID-19) has surpassed the annual global burden of death due to influenza or coronaviruses.[1] Although there are several effective vaccines for COVID-19 therapeutic treatments are still required. Patients particularly at risk are those with disorders that affect the immune system, for example, haematological malignancies or those receiving drugs that suppress an immune response, for example, after organ transplantation.[2,3]

Passive antibody therapies, including monoclonal antibody combinations have proven effective for COVID-19[4] However, the cost of these therapies is prohibitive[5] and new SARS-CoV variants may become resistant to anti-virals developed in response to previous variants.[6] Alternative and affordable responses to emerging strains of virus are needed.

Convalescent plasma (CP) is typically collected from donors with confirmed diagnosis of infection at least 2 weeks after recovery.[7] CP contains neutralising antibodies specific to the infectious agent but may also contain other immune modulators and clotting factors that can be fractionated out to produce hyperimmune-immunoglobulin (hIVIG).[8]

CP containing high titres of polyclonal antibody (Ab), has been used to treat patients hospitalised with respiratory syndromes caused by viral infections. Many studies have been poorly controlled but such series suggested decreased mortality in H1N1 Influenza infections in 1918–1920 and in 2009/2010, SARS-CoV-1 infections in 2003 and most recently COVID-19. Recent systematic reviews lacked data from RCTs and analysis did not consider the titre used within trials.[9] Moreover, there are concerns that CP may cause harm, potentially causing severe transfusion reactions such as transfusion-associated acute lung injury (TRALI) or antibody dependent enhancement of the viral infection.[10]

Prior to the COVID-19 pandemic, studies investigating the effectiveness of CP for viral infections varied in quality and the outcomes reported may not have reflected current international guidelines.[11,12]

2 | OBJECTIVE

To evaluate the evidence for the safety and effectiveness of using convalescent plasma (CP) or hyperimmune immunoglobulin (hIVIG) to treat severe respiratory disease caused by coronaviruses or influenza.

3 | METHODS

The protocol for this review was prospectively registered on PROSPERO (CRD42020176392), and the review was carried out in accordance with Cochrane methodology and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13]

3.1 | Search strategy

We searched multiple electronic databases (MEDLINE, PubMed, The Cochrane Library, Embase, Epistemonikos), ClinicalTrials.gov and WHO International Clinical Trials Registry Platform for ongoing studies, without language restriction, for all publication types on 12th October 2020 (see Appendix A1 in Data S1). We updated our search on 28th June 2021, increasing the number of databases (Cochrane COVID-19 Study Register, Transfusion Evidence Library, Web of Science). We limited the update search to systematic reviews and RCTs due to the significant number of randomised trials available at this point. Ongoing studies identified in our searches were checked on 30th November 2021 and included if published in full (peer-reviewed) by this date. We hand searched reference lists of systematic reviews and included RCTs.[11]

3.2 | Selection criteria

For assessments of effectiveness, we included RCTs comparing transfusion of CP products to any control arm with participants of any age who were admitted to hospital with severe respiratory illness. For assessments of safety, we included all study designs where patients received CP or hIVIG.

Two reviewers (CK, AL, LJG, SV) independently screened title and abstract, and then full-text using Covidence.

Where a publication was in a non-English language, we used electronic translation tools and sought the help of native speakers where appropriate (Appendix A2 in Data S1).

3.3 | Data extraction

Two of four reviewers (CK, AL, LJG, JS) independently extracted data using Covidence and Excel. Reviewers who were involved with any original trials (AL, LE) were not involved in the data extraction for those trials.

Extracted data included: details of study participants (demographic and disease characteristics), details of interventions (including titre, volume, timing of CP/hIVIG), and outcomes.

Outcomes extracted: all-cause mortality up to 30 and 90 days; need for mechanical ventilation (MV) and non-invasive ventilation (NIV) at up to 30 days; duration of MV or NIV; length of hospital stay; length of intensive care unit (ICU) stay; duration of viral detection from admission up to 30 days; transfusion-related serious adverse events (SAEs).

In a deviation from our protocol, we also assessed SAEs up to 30 days due to substantial variability in the way that SAEs were reported. For papers from the 1918 to 1920 influenza pandemic, reporting style was substantially different and, if reported, there was no grading of AEs. We recorded any potential AE described in these publications.

Where data were not available for a particular timepoint, we extracted data to the nearest possible timepoint. We sought clarification from trial authors where necessary.

3.4 | Risk of bias assessment

Two review authors (CK, AL, LJG, JS) independently assessed all eligible studies for risk of bias (ROB), using the Cochrane ROB tools. ROB1 for RCTs[14] and ROBINS-I for observational studies according to the Cochrane Handbook for Systematic Reviews of Interventions.[15] Reviewers who had worked on a trial (AL, LE) did not participate in ROB assessments for those studies.

Observational studies assessed as having "critical" ROB were not included in quantitative analyses.

3.5 | Data analysis

Statistical analyses were undertaken in Review Manager 5.4,[16] R[17] and the *metafor* package in R.[18] For dichotomous outcomes, we used the Mantel–Haenszel method, or Peto OR for rare events. We calculated the pooled risk ratio (RR) with a 95% confidence interval (CI), using the random effects model in RevMan5.[16] We used Tau^2 and I^2 in the assessment of heterogeneity, according to the guidelines laid out in the Cochrane handbook.[19]

We have not combined RCTs and non-RCTs and so have reported the results separately.

We planned to analyse continuous outcomes using mean difference (MD) or standardised mean difference (SMD) where different scales had been used. Continuous outcomes reported as median (IQR/range) could not be meta-analysed or pooled and have been reported narratively within tables.

Information from observational studies was collated in tables and not meta-analysed. Certainty of the evidence (based on meta-analysable data only) was assessed using GRADEPro.[20]

3.5.1 | Subgroup and sensitivity analysis

We subgrouped included trials by the type of respiratory infection.

We also subgrouped COVID-19 studies by their use of high titre or low titre/unselected plasma (see Appendix A3 in Data S1) in response to emerging research that highlighted the wide variability in CP titres used in practice.

We intended to undertake sensitivity analyses based on selection bias to examine evidence from 'low risk' studies only. However, this was not necessary for the RCTs as all included RCTs were assessed as low (or unclear) risk for mortality endpoints within this domain.

3.5.2 | *Post hoc* analysis of seropositivity

We performed a *post hoc* analysis of trials where there were sufficient data to assess the impact of SARS-CoV-2 antibody status at baseline due to emerging evidence of greater effectiveness of passive antibody therapy (monoclonal antibodies) for patients who are antibody negative at baseline.[21] Meta-regression for *post hoc* analysis of seropositivity was performed using the metafor[18] package in R.

4 | RESULTS

Our search yielded 4826 references (Figure 1 PRISMA flow diagram; for excluded studies see Appendix A4 in Data S1).

4.1 | Study Characteristics

We identified 110 completed studies (Figure 1), including 30 RCTs (four for influenza, n = 578; and 26 for COVID-19 SARS-CoV-2, *n* = 18 204).[3,7,22–49] There were no RCTs or non-randomised controlled trials identified for MERS or SARS (SARS-CoV-1) (Appendix A Supplementary Table A1 in Data S1). We included 76 non-randomised studies (Appendix B in Data S1). Of these, eleven were controlled studies, of which only two were at less than "critical" ROB[50,51] (Appendix A Supplementary Table A2 in Data S1) We included 67 uncontrolled studies: 12 assessing influenza A; two on MERS-CoV; four on SARS-CoV, and 49 on COVID-19 (SARS-CoV-2).

We also identified 143 ongoing studies (Appendix C) which were either controlled trials or single arm studies, which listed at least one safety outcome in their intended primary or secondary outcomes.

Study size in the quantitative analyses ranged from 29 to 11 555 (34 to 308 for influenza).

Of the four RCTs assessing influenza: two included children (*n* = 24/236 < 18 years)[39,45]; three RCTs[39,45,47] included pregnant women (3/270 pregnant women).

Of the 26 RCTs and 2 non-randomised studies that assessed COVID-19: one RCT included children (*n* = 26/11558 < 18 years).[3] Three RCTs[29,34,44] did not report whether they included children. Three RCTs[3,29,35] included pregnant women (*n* = 36/12575 pregnant women). Eight RCTs[22,24,30–33,36,44] did not report whether they included pregnant women.

4.2 | Comparisons

We identified four comparisons within the data that could be combined in quantitative analysis:

(1) CP versus standard care (SoC) or biologically inactive placebo (saline) (20 RCTs): 19 RCTs compared CP to SoC,[3,7,22–25,27–31,33–36,38,39] one RCT[26] compared SoC with saline placebo, and two retrospective observational studies[50,51] compared CP patients with matched controls;

(2) CP versus biologically active control (FFP or IVIG) (6 RCTs): five RCTs compared CP to non-immune FFP,[40–43,45] and one compared CP with IVIG.[44]

(3) hIVIG versus control (3 RCTs) Of these, two compared hIVIG with SoC,[46,47] one compared hIVIG with saline placebo.[48]

(4) early CP versus deferred CP (1 RCT).[49]

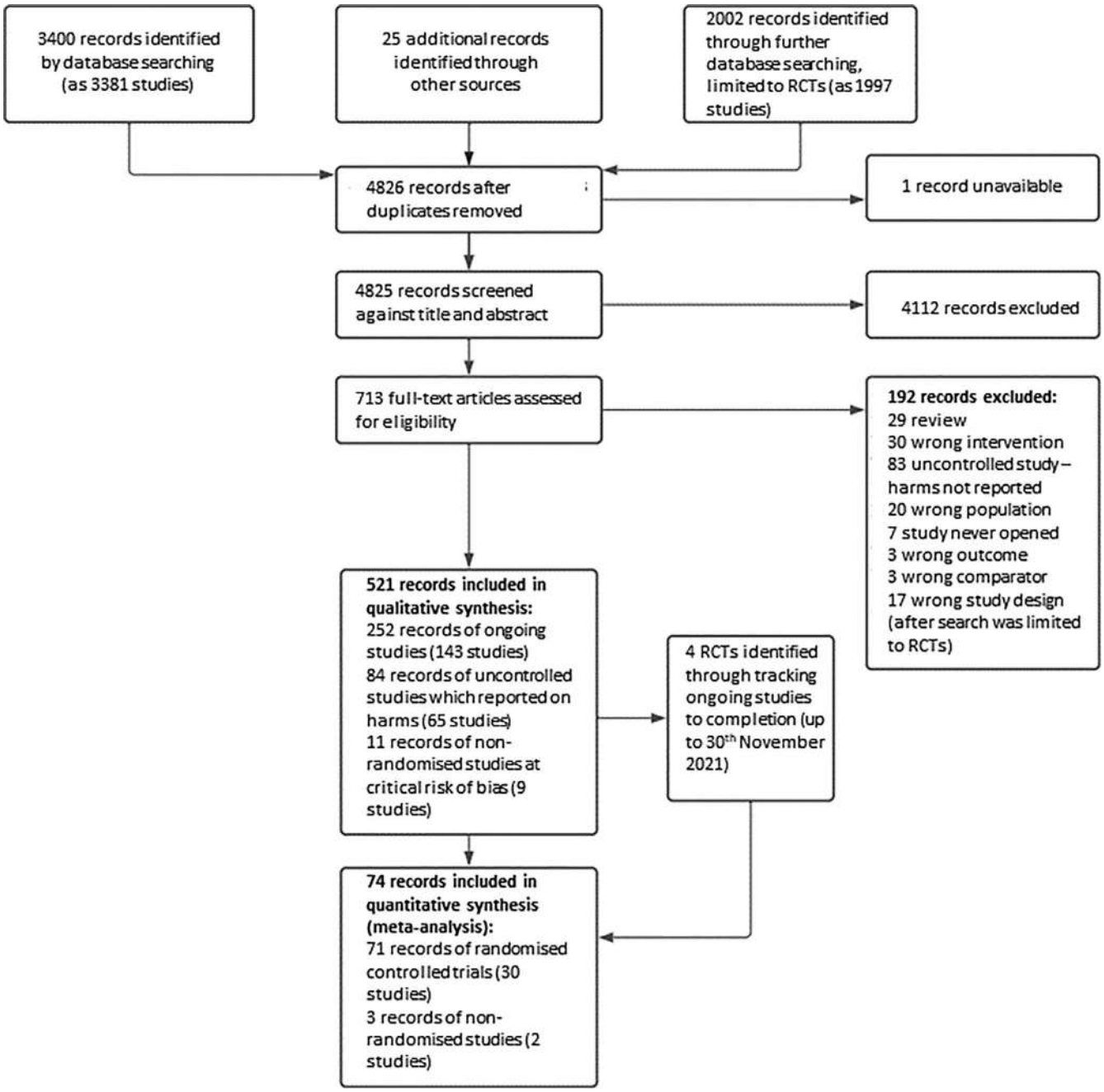

FIGURE 1 PRISMA flow diagram. Caption: The reasons for exclusion at each stage are shown with arrows to the right.

The comparators and baseline characteristics of participants in each of the thirty RCTs and two non-RCTs (retrospective observational studies)[50,51] within meta-analyses are summarised in Appendix A Table A1 in Data S1.

4.3 | Outcomes

We could only extract sufficient data to meta-analyse mortality and serious adverse events. We have presented remaining data from controlled studies in tables (Appendix A, Tables A3–A6 in Data S1). A summary of all outcomes reported is available in Appendix A5.

Most trials did not describe any method for dealing with competing risks when reporting their results. A competing risk is one which prevents the event of interest from occurring. Death is a competing risk for both (time to) mechanical ventilation and (time to) discharge. Devos 2021[28] approached competing risks using competing events analysis[52] to obtain cause-specific hazard ratios (HR). REMAP-CAP[30] used ordinal logistic regression by assigning each participant a category labelled with the number of ventilator-free days up to 21 days, with people who died up to day 90 being assigned −1, people who were on MV at

TABLE 1 Overview of meta-analysed results from patients hospitalised with severe respiratory infections

Comparison	30-day mortality		90-day mortality	Grade 3 or 4 transfusion related AEs	SAEs
Comparison 1: CP versus SoC or biologically inactive placebo (saline)	**All RCTs:** RR 0.99 (0.92 to 1.06) 15 RCTs[a], $n = 17\,266$ (37 children, 38 pregnant women) ⨁⨁⨁◯ $I^2 = 4\%$ $Tau^2 = 0.00$	**High Titre subgroup:** RR 0.98 (0.93 to 1.04) 9 RCTs[b], $n = 15\,954$ (26 children, 33 pregnant women) ⨁⨁⨁⨁ $I^2 = 0\%$ $Tau^2 = 0.00$	RR 0.92 (0.74 to 1.15) 6 RCTs[b], $n = 3210$ (8 pregnant women) ⨁⨁◯◯ $I^2 = 0\%$ $Tau^2 = 0.02$	*No transfusion in control group; results in intervention group are summarised in table A12*	RR 1.14 (0.92 to 1.41) 13 RCTs[a], $n = 16\,730$ (37 children, 38 pregnant women) ⨁◯◯◯ $I^2 = 56\%$ $Tau^2 = 0.07$
Comparison 2: CP versus biologically active control (FFP or IVIG)	RR 0.85 (0.56 to 1.29) 5 RCTs[a] $n = 700$ (13 children, 1 pregnant woman) ⨁◯◯◯ $I^2 = 33\%$ $Tau^2 = 0.07$		RR 0.99 (0.75 to 1.29) 2 RCTs[b], $n = 264$ ⨁◯◯◯ $I^2 = 0\%$ $Tau^2 = 0.00$	POR 0.43 (0.14 to 1.33) 6 RCTs[a], $n = 716$ (13 children, 1 pregnant woman) ⨁◯◯◯ $I^2 = 4\%$ $Chi^2 = 4.18$	RR 0.88 (0.65 to 1.19) 4 RCTs[b], $n = 523$ (13 children, 1 pregnant woman) ⨁⨁◯◯ $I^2 = 0\%$ $Tau^2 = 0.00$
Comparison 3: hIVIG versus control	RR 0.77 (0.34 to 1.73) 3 RCTs[c] $n = 392$ ⨁◯◯◯ $I^2 = 50\%$ $Tau^2 = 0.26$		*No RCTs reported mortality at 90 days in this comparison*	RD 0.00 (−0.08 to 0.08) 2 RCTs[a] $n = 84$ ⨁◯◯◯ $I^2 = 0\%$ $Tau^2 = 0.00$	RR 1.10 (0.76 to 1.58) 2 RCTs[a] $n = 342$ ⨁◯◯◯ $I^2 = n/a$ $Tau^2 = n/a$
Comparison 4: Early CP versus deferred CP	RR 2.68 (0.56 to 12.71) 1 RCT[b], $n = 58$ ⨁◯◯◯ $I^2 = n/a$ $Tau^2 = n/a$		*No RCTs reported mortality at 90 days in this comparison*	*Transfusion-related AEs were only reported for patients receiving CP; results are summarised in table A12*	*No RCTs reported SAEs in this comparison*

Note: Key: ⨁◯◯◯ very-low certainty evidence; ⨁⨁◯◯ low certainty evidence; ⨁⨁⨁◯ moderate certainty evidence; ⨁⨁⨁⨁ high certainty evidence.
Abbreviations: POR, Peto odds ratio; RD, risk difference; RR, risk ratio.
[a]Includes 1 RCT in influenza.
[b]All COVID-19.
[c]Includes 2 RCTs in influenza.

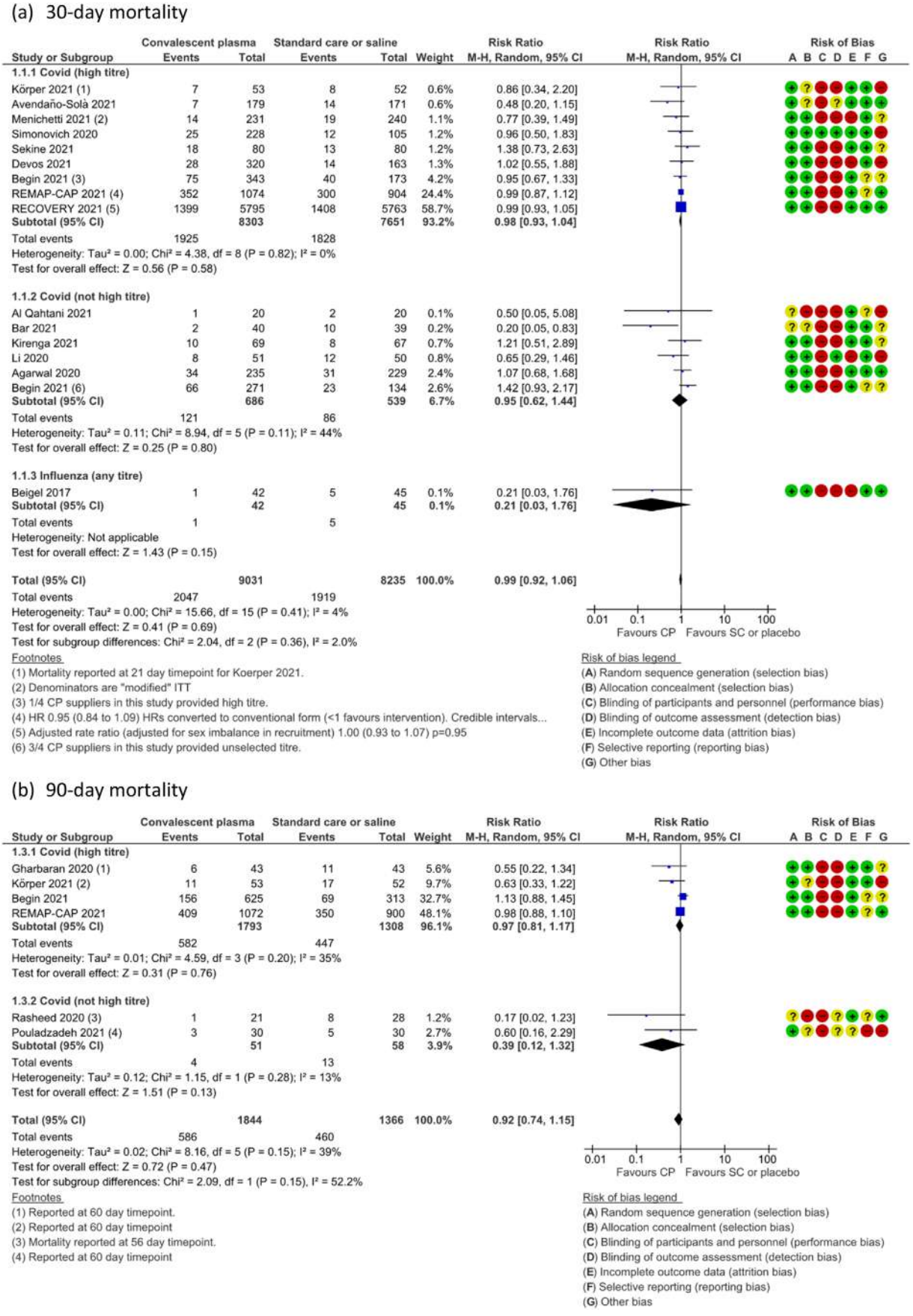

FIGURE 2 Forest plot of all-cause mortality, for comparison 1 (CP compared to SoC or a biologically inactive placebo) at up to (A) 30 days, and (B) 90 days

randomisation being assigned 0, and people who remained ventilator-free beyond day 21 being assigned 22. This is a useful way to compare the two groups while accounting for the very different possible outcomes but the resulting odds ratio (OR) and medians are difficult to interpret. No other trials used these methods and so we cannot combine the results but instead report the summary within Table A4 in Data S1.

Duration of viral detection was expressed as time (median IQR) to first negative test (2 RCTs).[23,36] One study,[25] reported the number of patients who had had two consecutive negative tests by day 30. See table A5 for viral detection data and table A6 for details of changes in viral loads.

4.4 | ROB in included studies

4.4.1 | RCTs (using Cochrane ROB1)

Nineteen RCTs were open-label, comparing CP to SoC, and were therefore assessed as having a high ROB for all outcomes except mortality, as knowledge of treatment allocation may have affected clinical decision-making. A summary of ROB judgements is available in Table A7 and Figure A1 in Data S1.

4.4.2 | Non-RCTs (using ROBINS-I)

Two non-RCTs[50,51] were assessed at serious RoB for selection bias and confounding at baseline. The remaining 9 studies[53–61] were at critical ROB due to baseline confounding or selection bias and were therefore not meta-analysed.

4.5 | Certainty of the evidence (GRADE)

Certainty of the evidence was GRADEd as very-low to high; primary reasons for downgrading were ROB and imprecision (wide confidence intervals and small sample size) (Tables A8–A11 in Data S1). We assessed publication bias through the generation of a funnel plot (Figure A2 in Data S1) for 30-day mortality in comparison 1, which suggests that some small studies have not been published. However, this was not significant enough to downgrade the certainty of the evidence because the analysis is dominated by two large, high-quality, and RCTs.

4.6 | Effect of the Intervention

See Table 1 for an overview of meta-analysed results.

4.6.1 | Comparison 1: CP versus SoC or biologically inactive placebo

Twenty RCTs and two retrospective studies assessed CP compared with SoC or a biologically inactive placebo.

All-cause mortality

30-day mortality data were available from 15 RCTs (30 days, 5 RCTs; 28 days, 9 RCTs; 21 days, 1 RCT) (Figure 2a); 90-day mortality data were available from 6 RCTs (56 days, 1 RCT; 60 days, 3 RCTs; 90 days, 2 RCTs) (Figure 2b).

Overall, CP did not reduce 30-day mortality (15 RCTs, n = 17 266; moderate-to-high certainty of evidence [Table A8 and footnotes in Data S1]) and there may be no effect on 90-day mortality (6 RCTs $n = 3210$; low certainty of evidence [Table A8]).

Two non-RCTs reported in-hospital mortality, and showed results consistent with the randomised evidence (2 studies, $n = 436$; very-low certainty evidence) (Figure A3A Table A8 in Data S1).

Improvement of clinical symptoms

Duration of NIV was reported in 4 studies (2 RCTs),[3,24,50,51] and duration of MV was reported by 11 studies (9 RCTs).[3,24,25,28–30,35,38,39,50,51] Two RCTs[27,31] reported any ventilatory support, but did not differentiate between MV, NIV, and passive oxygen support. One RCT[29] reported any ventilation, but also reported separately a composite outcome of patients who progressed to MV or death. Most studies reported the data as duration of support, either median (IQR) or mean (SD) (Table A4 in Data S1).

These outcomes were very variably reported, and many did not fully account for competing events, or report methods of analysis in sufficient detail. Based on what was reported, there was no apparent difference in duration of MV, NIV or ECMO support between the two groups.

Length of stay (LOS): hospital and ICU

Length of hospital stay was reported by 16 RCTs[7,23,25–28,30,31,38,39,42–47] and 1 non-RCT,[51] and length of ICU stay was reported by 9 RCTs[23,26,28,29,33,39,43,45,47] (Table A3 in Data S1). There was no evidence of an effect in length of hospital stay or length of ICU stay (Table A3 in Data S1).

Duration of viral detection from admission up to 30 days (viraemia, nasopharyngeal swabs, bronchoalveolar lavage, stool)

The 3 RCTs which reported time to negative test do not suggest any evidence of an effect (Table A5 in Data S1).

Adverse events

AEs due to transfusion were reported in 15 RCTs[3,7,22–39] (Table S10 in Data S1).

Seven RCTs reported no Grade 3 or 4 AEs due to transfusion.[22,24,26,27,31,35,39] Both non-RCTs reported AEs due to transfusion. All but one RCT[26] had SoC comparators, and therefore no transfusion-related SAEs are reported for the control group. Group comparison was not possible; results are summarised in Table A12 of in Data S1.

There was no evidence of an effect on reported SAEs[3,23–31,35,36,39] (13 RCTs, $n = 16\,730$, very-low certainty of evidence) (Figure A3B).

Data were not available on SAEs in seven RCTs.[7,22,32–34,37,38]

See forest plots Figure A3 in Data S1 and GRADE profile Table A8 in Data S1 for further detail.

4.6.2 | Comparison 2: CP versus biologically active control (FFP or IVIG)

RCTS assessed CP compared to FFP[40–43,45] or IVIG[44]

All-cause mortality

There was insufficient evidence to say whether or not there is a difference between groups in all-cause mortality at up to 30 days (5 RCTs $n = 700$; very-low certainty evidence, Figure A4A in Data S1), or at up to 90 days (2 RCTs, $n = 264$; very-low certainty evidence Figure A4B in Data S1). See forest plots Figures A4A and A4B in Data S1 and GRADE profile Table A9 in Data S1 for further detail.

Adverse events

Six RCTs reported transfusion-related Grade 3 or 4 AEs.[40–45] Events were rare (~2%) with no clear evidence of a difference (6 RCTs, $n = 716$; very-low certainty evidence. [Figure A4C in Data S1]). Four RCTs[40–42,45] reported SAEs up to 30 days, showing no evidence of an effect, although the rate of SAEs seems very low, given the severity of disease in hospitalised individuals (4 RCTs, $n = 523$; low certainty evidence, Figure A4D in Data S1). See forest plots Figure A4 and GRADE profile Table A9 in Data S1 for further detail.

Improvement of clinical symptoms

Duration of MV[40,43,45] and any ventilatory support[41] were reported as median (IQR) or mean (SD). Given the difficulties of dealing with competing events, and the small number of patients involved, it is very unclear if CP therapy had any effect on the duration of MV, NIV or ECMO support between the two groups. We have presented the data in Table A4 in Data S1 as reported by the individual studies.

Data were not available for LOS (hospital or ICU), and duration of viral load.

4.6.3 | Comparison 3: hyperimmune immunoglobulin versus control

Three assessed hIVIG compared with SoC or a biologically inactive placebo.

All-cause mortality

There was insufficient evidence to say whether or not there is an effect on mortality compared to control at up to 30 days (3 RCTs $n = 392$; very-low certainty evidence) (Table 1, Figure A5A, Table A10 in Data S1). There were no data for 90-day mortality.

Adverse events

Two RCTs reported transfusion-related AEs; neither reported any AEs due to transfusion in either group (2 RCTs, $n = 84$; very-low certainty evidence, Figure A5B in Data S1). Two RCTs reported SAES (2 RCTs $n = 342$; very-low certainty evidence. [Figure A5C in Data S1]). See forest plots Figure A5 and GRADE profile Table A10 in Data S1 for further detail.

Improvement of clinical symptoms

One RCT in influenza[48] reported on duration of MV and NIV. However, the data were presented using an ordinal scale that was not mappable to our outcomes or other trial results, and we were unable to extract the data.

Data were not available for LOS (hospital or ICU), and duration of viral load.

4.6.4 | Comparison 4: early CP versus deferred CP

One RCT assessed early CP compared to deferred CP.

All-cause mortality

There was insufficient evidence to say whether there is a difference in 30-day mortality between early CP and deferred CP (1 RCT $n = 58$; very-low certainty of evidence) (Figure A6 in Data S1). There were no data for 90-day mortality. See forest plots Figure A6 and GRADE profile Table A11 in Data S1 for further detail.

Adverse events

There were three Grade 3 or 4 transfusion-related AEs within 24 h, all in the early CP group: (1 RCT $n = 58$, very-low certainty evidence) (Table A12 in Data S1). SAEs were not reported. See forest plots and GRADE profile Table A11 in Data S1 for further detail.

Improvement of clinical symptoms

Duration of MV and NIV was reported as median (IQR). We have presented the data in Table A4 in Data S1 as reported by the RCT. Both groups had similar duration of ventilatory support. It is unclear if the authors accounted for competing events.

Data were not available for LOS (hospital or ICU), and duration of viral load.

4.7 | Results from uncontrolled studies (for safety only)

We identified 73 non-randomised or uncontrolled studies [49 case reports or case series] that assessed the use of CP or hIVIG in respiratory viral infection and reported AEs: 12 in influenza A, 2 in MERS-CoV, and 4 in SARS-CoV-1, and 67 in SARS-CoV-2 (COVID-19). Of the influenza studies, 10 were from the 1918 to 1920 pandemic. Fifty-one studies reported that no AEs were observed (37/49 case reports or case series). Eighteen studies reported transfusion-related AEs, and four studies reported other SAEs. These data are presented in Appendix B in Data S1.

4.8 | Post hoc subgroup analysis: seropositivity at baseline

Three RCTs,[3,30,62] including the two largest, reported 30-day mortality for subgroups defined by seropositivity at baseline. These results are shown in Figure 3.

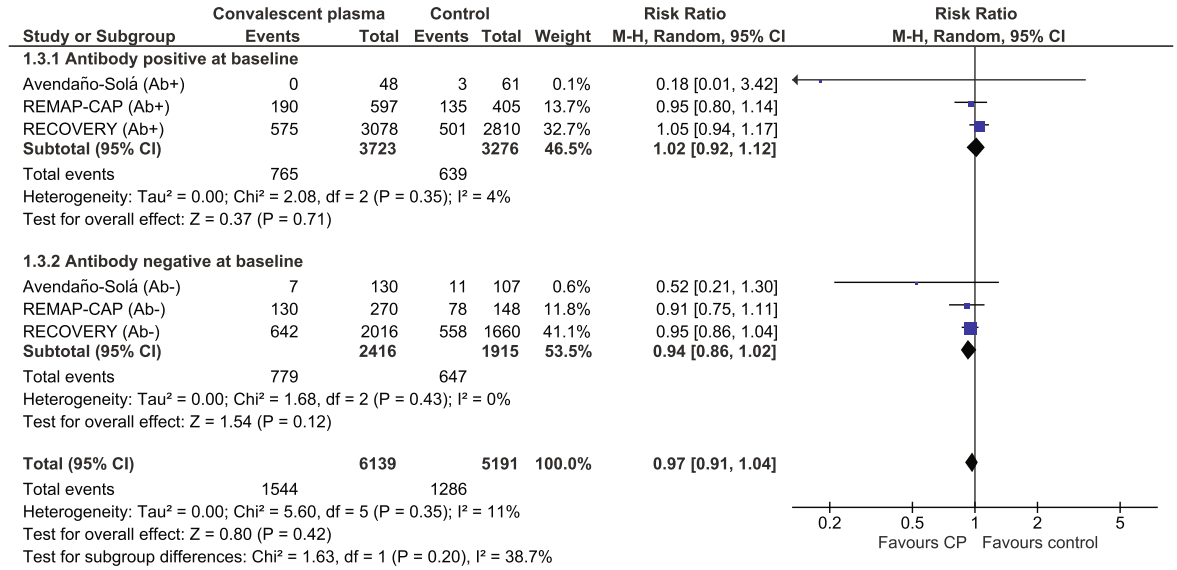

FIGURE 3 Subgrouped by seropositivity at baseline: RCTs reporting 30-day mortality for comparison 1 (CP compared to SoC or a biologically inactive placebo)

With almost all the information coming from the two large, high-quality RCTs,[3,30] the pooled estimates from these three RCTs are: RR 1.02 (0.92 to 1.12) for people who are seropositive at baseline and 0.94 (0.86 to 1.02) for those who are seronegative. The test for interaction (subgroup difference) gives a *p*-value of 0.20 with very little heterogeneity either within or between groups.

We explored this further using meta-regression on the group of trials comparing high titre CP with SoC which reported the proportion seropositive at baseline and 30-day mortality. This analysis produced near identical results with an estimated RR at 0% seropositivity of 0.93 (0.85, 1.01) and 1.02 (0.93, 1.12) at 100% seropositivity (See Appendix A6 in Data S1. Mortality results are summarised in Table A14 in Data S1).

5 | DISCUSSION

The objective of this review was to determine the safety and effectiveness of CP or hIVIG from CP to treat patients with serious respiratory disease due to influenza or coronavirus infection. In order to increase the relevance of our findings to the COVID-19 pandemic we used the core outcome set[63] for assessing treatments for patients infected with SARS-CoV-2. We aimed to use high-quality evidence from RCTs to assess safety and effectiveness. We also used all other study designs to describe serious harms reported following transfusion with CP or hIVIG.

5.1 | Main findings

We were able to meta-analyse 32 studies for our primary outcome of 30-day mortality (30 RCTs and 2 non-RCTs). We found little evidence of any difference between the groups in either benefits or harms for patients hospitalised with a severe viral respiratory infection requiring hospital admission. Most evidence was of low or very-low certainty. The only high-certainty evidence was for the COVID high-titre subgroup in the outcome all-cause mortality at up to 30 days in CP versus SoC (Table 1).

Adverse events were variably reported. No RCTs reported a high number of transfusion-related AEs (proportion 0% to 5.67%[22–24,26,27,31,35,38,39,43,44,46,47]) (very-low to low certainty evidence). There was no evidence of an increase in harms compared with standard plasma.

5.2 | Quality (certainty) of the evidence

Where meta-analysis was possible, we used GRADE to assess our certainty in the result (Table 1). Certainty in the evidence was assessed as very-low to low certainty for all outcomes apart from mortality data in the comparison CP versus standard care.

Evidence was downgraded for serious ROB (lack of blinding, baseline imbalance, randomisation processes, missing data and unclear reporting of outcomes) and imprecision (wide confidence intervals around the effect estimate, and small sample sizes for the outcome of interest). Some of the sources of potential bias (such as patient and personnel blinding) would be hard to overcome in future trials due to the issues in finding an ethical control infusion: even saline is problematic, with the risk of volume overload, and ease with which it can be differentiated from plasma.

SAEs were also downgraded for inconsistency as the heterogeneity was significant between studies, this is likely to be due to the variation in reporting of the SAEs. This may be in part due to differing regulatory environments and different classifications of CP, requiring

varying levels of AE reporting including the need to use a grading system (e.g., MedDRA[64]).

We included lower-level evidence for the assessment of safety outcomes. However, we were unable to perform quantitative analyses, and so have only presented these data as reported in Appendix B in Data S1.

There were very few endpoints reported consistently enough for meta-analysis. The difficulty in defining endpoints, especially time-to-event endpoints,[65] is discussed further in Appendix A6 in Data S1.

5.3 | Strengths and Limitations of this review

We have attempted to minimise potential bias in the review process, using Cochrane methods and PRISMA guidelines for reporting. We conducted a comprehensive search: searching data sources to ensure that all relevant studies would be captured, using multiple databases and reference lists of included studies. We included conference proceedings and included a search of clinical trial registries. We also attempted to contact authors for additional data and for clarification of their data.

There were no restrictions for the language in which the paper was originally published. We pre-specified outcomes prior to analysis and have explained the rationale for including one additional outcome (any SAEs).

We undertook duplicate screening, data extraction, and assessment of bias. Additionally, the clinical advisor (LE) was consulted for disagreements, or need for clarification.

The limitations of this review mostly arose due to gaps in the evidence base, which are discussed more fully in the next section.

5.4 | Interpretation and context

A recent analysis of individual patient data (IPD) pooled from eight RCTs[9] IPD reported an OR for mortality of 0.85 at day 28 (95% credible interval, 0.62 to 1.18; posterior probability of OR <1 of 84%). These results are broadly comparable and in agreement with our own aggregate analyses for 30-day mortality. However, it should be noted that the IPD analysis included two RCTs[66,67] published after our 30th November 2021 cut-off, but did not include the two largest RCTs of CP RECOVERY[3] and REMAP-CAP[30] which we have analysed, and which together contribute 83% of sample size contributing to our analysis of 30-day mortality for CP versus SoC.

A limitation of the current evidence base is that of the 30 RCTs and two non-randomised studies included in our meta-analysis, 26 studies (24 RCTs) excluded children and 16 RCTs excluded pregnant women, with 1 RCT[39] admitting pregnant women only on the second round of recruitment. Given that children and pregnant women are both considered to be at increased risk of serious disease and death from many severe respiratory viral infections, their exclusion from trials is concerning. Of the 144 ongoing studies we identified, most trials will exclude children and pregnant women. Many ongoing studies have an upper age cut-off (of 65, 70 or 80 years), despite older age being one of the biggest risk factors for COVID-19.

The precision of our meta-analysis was affected by the different titres of CP-neutralising antibodies between trials (Table A1 in Data S1). We tried to address this by subgrouping studies based on the CP-titre reported, and whether it was considered high enough according to FDA criteria (see Appendix A3 in Data S1). However, several studies used local assays that could not be correlated with an FDA reference method. Since we conducted our first search, several variants of SARS-CoV-2 have arisen worldwide and may require much higher antibody titres measured using ELISA assays.[68] Much higher titre CP, from vaccinated convalescent donors, may be active against future variants[69] indicating that new COVID CP trials should aim to use very high titre CP standardised using internationally recognised methods.

Similarly, between trials, there was heterogeneity of patient groups and severity of illness on admission to hospital (Table 1). The RCTs in COVID may not have used the same criteria to categorise trial participants at enrolment and trials designed to treat different patient groups based on comorbidities and immune states were absent. Several COVID-19 studies reported clinical improvement using the WHO ordinal scale. However, the scale was revised several times over the course of 2020–2021, going from an 8-point scale[70] to a 10-point scale at its latest revision[71] which have made comparisons between trials difficult.

The results of our post hoc subgroup analysis by seropositivity at baseline are very similar to the results reported by RECOVERY alone. We have not found stronger evidence of this potential interaction than that reported by RECOVERY (with a similar trend also reported by REMAP-CAP, especially for organ support-free days) but similarly, we have not found any reason to discount the possibility that there is a small but important interaction, with immunocompromised individuals potentially benefitting more. This hypothesis is consistent with the REGN-COV2 RECOVERY trial,[21] which has shown no benefit of monoclonal antibodies for seropositive patients who either have advanced disease or who are immunocompetent. The very high baseline risk of immunocompromised individuals might translate very small relative risks into substantial absolute risk differences. REMAP-CAP has recently reopened for immunocompromised people to test this hypothesis.[72]

5.5 | Implications for research and practice

There is currently no evidence for a benefit of CP in an unselected population of patients hospitalised with coronaviruses or influenza. It is likely that the titre of the CP and the immune response of the recipient may both be important factors affecting response to treatment.

Studies should use CP of a high enough titre to elicit a biological response, and report the actual titre used as well as the minimum as described in the protocol. Matching variants between donor and recipient may not be feasible, but viral variants circulating at the time of collection of plasma and during the study should be recorded.

Studies should assess and publish antibody status (seropositivity) at baseline in both intervention and control groups, and identify and

report immunocompromised patients separately, to establish whether certain groups of patients are more likely to benefit from this intervention.

There are difficulties in designing truly blinded RCTs of CP or hIVIG (see Reference 73 for review). There are ethical problems with using a placebo which is assumed to have no clinical benefit, but has known harms.[74] One RCT[26] used a saline placebo, with potential concerns about volume overload, and six RCTs used a biologically active control, (FFP in 5 RCTs,[40–43,45] and IVIG in one[44]) which raises additional concerns about transfusion reactions.

Unless reported explicitly by investigators, it was difficult to distinguish the AEs experienced following transfusion from the symptoms of severe respiratory disease.[75] This limited the number of RCTs that we could include in our meta-analysis of AEs due to transfusion. There was also substantial variability in the way that AEs were recorded and reported in these studies. It was not always possible to determine the severity of AEs, and different studies used different criteria for SAEs. In some cases, it was hard to determine if SAE reporting was per event or per patient, making it extremely difficult to compare rates of AEs between studies. Blood components in the UK are not classified as medicines and so require a different grading system for reporting AEs to countries that classify CP as a medicine, e.g. Germany. A consensus on how AEs associated with blood products are reported in RCTs would help to address this problem.

6 | CONCLUSION

This review has highlighted several issues regarding study design and reporting which should be addressed in current and future research. A minimum titre should be established and ensured for a positive biological response to the therapy. Further research on the impact of CP/hIVIG in patients who have not produced antibodies to the virus prior to hospital admission or who are immunocompromised would be useful to target therapies at groups who will potentially benefit the most.

AUTHOR CONTRIBUTIONS

Catherine Kimber: screening and full text assessment, retrieved full text publications, data extraction, risk of bias assessment, entered data into RevMan and undertook subgroup analyses, performed GRADE assessments, interpreted the results, contributed to the development of the manuscript. **Abigail A. Lamikanra:** screening and full text assessment, retrieved full text publications, data extraction, risk of bias assessment, performed GRADE assessments, interpreted the results, contributed to the development of the manuscript. **Louise J. Geneen:** screening and full text assessment, retrieved full text publications, data extraction, risk of bias assessment, entered data into RevMan and undertook subgroup analyses, performed GRADE assessments, interpreted the results, contributed to the development of the manuscript. **Josie Sandercock:** data extraction, risk of bias assessment, and undertook all metaregression analyses, performed GRADE assessments, interpreted the results, contributed to the development of the manuscript. **Carolyn Doree:** developed and performed all search strategies and de-duplication, retrieved full text publications, contributed to the development of the manuscript. **Sarah J. Valk:** screening and full text assessment, retrieved full text publications, contributed to the development of the manuscript. **Lise J. Estcourt:** developed the initial idea of the review, developed, wrote, and registered the protocol, interpreted the results, and contributed to the development of the manuscript.

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ORCID

Catherine Kimber https://orcid.org/0000-0002-7796-9931
Abigail A. Lamikanra https://orcid.org/0000-0002-9287-2177
Louise J. Geneen https://orcid.org/0000-0001-6759-0437
Josie Sandercock https://orcid.org/0000-0001-7337-8635
Carolyn Dorée https://orcid.org/0000-0001-6955-7497
Sarah J. Valk https://orcid.org/0000-0003-3964-2505
Lise J. Estcourt https://orcid.org/0000-0003-4309-9162

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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SHORT COMMUNICATION

TRANSFUSION MEDICINE WILEY

Hypophosphatemia related to intravenous iron therapy with ferric carboxymaltose: A case series

Nigel Wei-Peng Seng [1] | Jason Bae Barco [1] | Marc Hai-Liang Wong [2] | Kai-Xiong Lim, Wee-Ming Peh [2] | Frederick Hong-Xiang Koh[1,2]

[1]Academic Department of Trauma & Orthopaedics, School of Medicine, University of Leeds, Leeds, UK

[2]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK

[3]Leeds Orthopaedic & Trauma Sciences, Leeds General Infirmary, University of Leeds, Leeds, UK

[4]Leeds Institute of Health Sciences, University of Leeds, Leeds, UK

[5]NIHR Leeds Biomedical Research Unit, Chapel Allerton Hospital, Leeds, UK

Correspondence
Michalis Panteli, Academic Department of Trauma & Orthopaedics, School of Medicine, University of Leeds, Clarendon Wing, Level D, Great George Street, Leeds LS1 3EX, West Yorkshire, UK.

Email: frederickkohhx@gmail.com

Abstract

Objectives

This case series would like to highlight hypophosphatemia related to ferric carboxymaltose and its adverse clinical consequences.

Background

Intravenous iron supplementation is a good alternative to oral iron replacement in iron deficiency anaemia due to its ability to correct iron deficit with minimal infusions without incurring the gastrointestinal side effects of oral iron replacement. Ferric carboxymaltose is one common formula for intravenous iron supplementation. However, an increasingly recognised adverse side-effect of intravenous ferric carboxymaltose is hypophosphatemia. There has been increasing reports and studies highlighting hypophosphatemia related to intravenous iron therapy. Though initially thought to be transient and asymptomatic, recent studies have shown that persistent hypophosphatemia in iron therapy can result in debilitating disease including myopathy, fractures and osteomalacia.

Methods

A retrospective analysis of all patients who had ferric carboxymaltose was performed.

Results

We highlight 3 cases where hyposphatemia affected the clinical outcomes.

Conclusion

With the increased use of IV iron it is important to be aware of the high potential for hypophosphatemia secondary to ferric carboxymaltose..

KEYWORDS

Hypophosphatemia, ferric carboxymaltose , blood, medicine, transfusion

1 | INTRODUCTION

The incidence of hip fractures continues to increase, along with the global expansion of aging population observed secondary to improved healthcare and quality of life.[1] Subtrochanteric fractures are defined as fractures encountered between the inferior border of lesser trochanter and 5 cm distal to it.[2] They represent a complex subset of injuries surrounding the hip, which are most commonly managed with intramedullary (IM) nailing.[3,4] However, their moderate blood supply and being subjected to high concentration of stresses[5-8] meant these

have long been the standard method to assess iron status. However, haemoglobin levels can remain sufficient for some time, even when iron stores are dwindling; this is known as iron deficiency non-anaemia.[1]

In contrast to haemoglobin, serum ferritin levels reflect the amount of stored iron.[1] Therefore, they are increasingly used to assess individuals' iron stores when these are at risk, for instance after traumatic blood loss, during pregnancy, or in blood donors.[3] Sanquin, the national blood service in the Netherlands, started measuring ferritin levels in each new donor, and subsequently after every fifth donation, in October 2017. Donating blood has a substantial impact on ferritin levels. Ferritin levels are lower among blood donors than in the general population: cross-sectional studies report lower ferritin levels in donors with a higher number of whole blood donations and a large randomised trial showed that ferritin levels indeed decline with more frequent blood donations.[4,5] Among new donors, large variation in ferritin levels is observed.[4] It is well established that individual characteristics such as sex and age are relevant: women in general, but pre-menopausal women in particular, have considerably lower ferritin levels than men.[4,6,7] Higher body mass index (BMI) is associated with higher ferritin levels.[8] In recent decades, many other factors that affect iron status have been identified: diet,[9,10] genetics,[11,12] ethnicity,[13] and iron supplementation, which is mostly studied among blood donors.[14,15]

Ferritin is also a known acute-phase protein that is elevated in inflammatory conditions, complicating its diagnostic value in individuals with conditions such as inflammatory bowel disease or chronic heart failure.[16] This could also explain the association between BMI and ferritin levels, as adipose tissue is known to promote systemic inflammation.[17] Additionally, exposure to environmental pollutants has been linked to disordered iron homeostasis,[18,19] and ambient particle matter (PM) concentration is correlated with ferritin levels.[19] The biological mechanism behind this is still unclear, but it is postulated that iron attaches to the PM rather than to cell nuclei, effectively creating a functional deficiency.[18,19] In turn, mechanisms start upregulating iron uptake and recycling in an attempt to meet the iron requirement of the cells, thereby altering iron homeostasis. Another suggested mechanism is that when pollutants enter the lungs, iron is transported away from the surface of the lung tissue and stored in ferritin complexes, in order to avoid chemical reactions between iron and the pollutant.[18] Other potential environmental determinants are neighbourhood characteristics, including population density and socio-economic status, which are consistently shown to be related to body weight[20] and blood parameters.[21]

Previous studies on ferritin levels have focused on studying the association with variables in a limited setting, for example, characteristics such as age and BMI, donation-related variables, or environmental pollutants. In this paper, we propose a novel framework that integrates multiple settings, using a structural equation model. By grouping relevant explanatory variables into constructs, we describe relationships with ferritin on a more general level. This enhances the insight into various mechanisms that influence ferritin levels, which is valuable to those who use these as a diagnostic tool. We explore associations between ferritin levels and individual characteristics, donation behaviour and environmental factors, in a large group of newly registered and active whole blood donors.

2 | METHODS

For this cross-sectional study, data collected by Sanquin and the Geoscience and health cohort consortium (GECCO) were analysed. Sanquin is by law the only blood service in the Netherlands, collecting over 400 000 whole-blood donations each year, with collection sites geographically well-distributed throughout the country. Several eligibility criteria exist to ensure the safety of the donors and recipients and the quality of the blood product. Donors must be aged between 18 and 79 years old, and a pre-donation screening visit takes place before the first 500 ml whole blood donation, which includes blood sampling for blood type and infectious disease testing, as well as initial haemoglobin and ferritin measurements. We will refer to these prospective donors, who have not donated yet, as 'new donors'.

Before every donation, a donor screening is performed, including a donor health questionnaire and measurements of blood pressure, pulse rate and haemoglobin levels to assess whether the donor is eligible to donate. Haemoglobin levels need to be at least 7.8 mmol/L for women and 8.4 mmol/L for men. This is measured by point-of-care testing with a photometer (HemoCue, Angelholm, Sweden). Ferritin levels, are measured in serum samples, using the Architect i2000 (Abbott Diagnostics, Chicago, IL), after the pre-donation screening visit and after every fifth whole blood donation. As such, ferritin measurements are only available in case of successful whole blood donations, and for new donors whose venous samples are taken as part of the pre-donation screening visit.

2.1 | Data

This study included all new and active whole blood donors who gave consent to the use of their data for scientific research (consent given by >99% of all donors) and for whom ferritin measurements were available between 1 October 2017 and 31 December 2019. If multiple ferritin measurements were available for a donor, only the first measurement was used. Information on donors and donation histories was extracted from the blood bank information system (ePROGESA, MAK-SYSTEM International Group, Paris, France). Variables used were sex, age, height, weight, time since previous successful donation, the number of successful donations in the previous 2 years, donor status (new or active donor), and ferritin levels. BMI was calculated from self-reported donor height and weight. Sanquin does not register donor ethnicity, but Duffy negative phenotype was included to function as a proxy for sub-Saharan African descent.

Environmental exposure variables of various characteristics were obtained from the Geoscience and health cohort consortium (GECCO).[22] The exposure data were operationalised based on publicly

TABLE 1 Grouping of variables into constructs for each model

Variable	Model A	Model B	Model C	Model D
Age	Individual characteristics	Individual characteristics	Individual characteristics	Individual characteristics
Weight				
Height				
BMI				
Duffy phenotype				
Time since previous donation[a]	Donation history	Donation history		
Number of previous donations[a]				
Population density	Environment	Environment	Environment	Environment
Temperature				
Socio-economic status				
Ozone	Pollution		Pollution	
PM2.5				
PM10				
Soot				
NO_2				

Note: All models contain the same observed variables but differ in how these are grouped into latent constructs.
[a]Only available for active donors.

available data. Data from 30 weather stations in the Netherlands—obtained from the Royal Netherlands Meteorological Institute (KNMI)—were used to estimate temperature at a spatial resolution of 1 km. Three options for the measurement level were considered (minimum, average, and maximum daily temperature), as well as three time spans (day, week or month before donation), resulting in nine options in total. The combination that showed the highest correlation with ferritin was included in the final model.

Daily concentrations for particulate matter (PM) 2.5, PM10, NO_2, ozone and soot levels were obtained via the Dutch National Institute for Public Health and the Environment (RIVM), for the years 2017–2019. These variables were imputed on a spatial resolution of 1 by 1 km. Neighbourhood socio-economic status (SES) scores and population density from 2017–2019 were acquired from Statistics Netherlands (CBS), both available on 6-digit postal code level. SES scores are based on percentiles of income, education level and vocational history of households, with a score of 0 being exactly the national average, and positive scores being above average. All spatio-temporal variables were matched with donor and donation data based on donation date and donor postal code. Lastly, the date and time of each donation were included as potential factors to account for seasonal and diurnal variation, as they are known to affect haemoglobin levels and may also affect ferritin levels.

To check for a possible confounding effect of smoking on environmental variables, we analysed the correlation between the percentage of smokers per municipality (data from Statistics Netherlands) and all environmental variables described in the above paragraph.

There were no missing data for environmental datasets from the RIVM and CBS. Donors with no ferritin measurement were excluded from the analysis. There were no missing data for the other donor or donation level variables.

2.2 | Statistical analysis

Structural equation modelling (SEM) was used to investigate which variables relate to serum ferritin and to what extent. Briefly, observed variables and latent constructs are distinguished in SEM. Latent constructs cannot be measured or observed directly, but are inferred from the observed variables. One or more hypothesized sets of relationships and correlations between variables and constructs are specified a priori and shown in a path diagram. For each relationship, a parameter is estimated that indicates its strength. Estimates are obtained by numeric optimization of a fit criterion, using maximum likelihood estimation. A more detailed overview of this method is provided in Appendix A.

We compared four ways to divide the 15 variables included in the analysis into latent constructs, as shown in Table 1. Date and time of the donation were added to the model separate of the constructs, and as such are not included in Table 1. Model A contains four latent constructs, and in models B, C and D different sets of constructs are combined. Confirmatory factor analysis (CFA) was used to test the validity of the specified measurement models, that is, the hypothesized relationships between the latent constructs and their observed variables. The overall fit of the models was assessed by the Tucker-Lewis Index (TLI) and the root mean square error of approximation (RMSEA). A rule of thumb is to exclude variables for which the absolute value of the standardised factor loading is below 0.4, but at sample sizes larger than 300, if the overall model fit is good, exclusion is not necessary and should be judged separately for each variable based on sensible background knowledge.[23]

Pairwise residual correlations between observed variables were calculated to identify whether any covariances needed to be added to the model. Of the four specified models, we continued our analysis with the best fit according to CFA, based on the TLI and RMSEA.

TABLE 2 Distribution of explanatory variables by donor status and sex

	New donors		Active donors	
	Women	Men	Women	Men
N	40 172	19 424	39 085	39 233
Age (years)	26 (21–37)	28 (23–37)	47 (31–58)	53 (39–62)
Height (cm)	170 (166–175)	183 (178–188)	170 (166–175)	183 (178–188)
Weight (kg)	68 (62–77)	82 (74–90)	70 (64–80)	85 (78–93)
BMI (kg/m^2)	24 (21–26)	24 (22–27)	24 (22–27)	25 (23–27)
Time since previous donation (days)	NA	NA	154 (132–217)	139 (71–147)
Number of previous donations[a]	NA	NA	3 (2–4)	5 (4–7)
Population density (inhabitants per km^2)	1173 (425–2617)	1246 (477–2936)	827 (322–1855)	814 (320–1824)
Duffy phenotype (proportion)	0.25	0.17	0.28	0.16
Temperature (°C)[b]	11.4 (6.4–16.6)	11.7 (6.6–16.7)	10.4 (6.0–16.0)	10.4 (5.9–16.0)
Socio-economic status	0.04 (−0.21 to 0.22)	0.02 (−0.24 to 0.22)	0.10 (−0.10 to 0.25)	0.12 (−0.07 to 0.26)
Ozone (μg/m^3)	46.9 (45.6–48.8)	46.8 (45.5–48.7)	47.2 (45.9–49.2)	47.2 (45.9–49.1)
PM2.5 (μg/m^3)	10.7 (9.7–11.6)	10.7 (9.8–11.6)	10.5 (9.6–11.5)	10.6 (9.7–11.6)
PM10 (μg/m^3)	18.2 (16.8–19.3)	18.2 (16.9–19.3)	18.0 (16.6–19.0)	18.0 (16.7–19.1)
Soot (μg/m^3)	0.66 (0.54–0.78)	0.66 (0.55–0.78)	0.63 (0.52–0.75)	0.65 (0.54–0.76)
NO_2 (μg/m^3)	17.6 (14.9–21.6)	17.8 (15.1–21.8)	16.8 (14.2–19.7)	16.9 (14.3–19.6)
Ferritin (ng/ml)	47 (28–75)	118 (79–170)	30 (17–47)	34 (20–56)

Note: Data are presented as medians (interquartile range) due to non-normal distributions of the variables.
[a]Within 2 years before the ferritin measurement.
[b]The maximum temperature recorded on the day of donation.

To the model with the best fit, we added the structural component, which contains the relationships between the latent variables and ferritin, the outcome variable. A multiple group SEM was carried out with parameters estimated separately for male and female donors, and for new and active donors. Because the assumption of normality of the explanatory variables does not hold in our data, a different estimator than the default maximum likelihood estimator was used: the 'mean and covariance adjusted weighted least squares estimator', which is robust against violations of the normality assumptions in a multivariate setting.[24]

The same model was fitted in all four groups, although the variables belonging to the *donation history* construct (see Table 1) are not available for new donors, as they do not (yet) have a donation history. The overall fit of the SEM model was assessed using the TLI and RMSEA, as well as the R^2 measure.

All analyses were conducted using *R* programming language and environment for statistical computing version 4.0.3,[25] with package *zoo*[26] for pre-processing environmental data, and *lavaan*[27] for CFA and SEM analyses. Path diagrams were created with yEd Live Graph Editor.[28]

3 | RESULTS

3.1 | Sample composition

Table 2 shows descriptive statistics of the study population by sex and donor status. The size of each of the groups was comparable, except for the group of new male donors, which was only half the size of the other groups. Between new and active donors, age differed considerably, new donors being younger than active donors by 17 years on average ($p < 0.001$ using a two-sample *t*-test). In both new and active donors, men were older (by 6 years on average, $p < 0.001$) and heavier (by 13 kg on average, $p < 0.001$) than women. *p*-values were obtained using two-sample *t*-tests. The time since last donation is higher in women than in men, and the number of prior donations is higher in men than in women. These differences are due to differences in the minimum required donation interval: for women, there must be 122 days between two donations with a maximum of 3 donations per year, while for men, the minimum is 57 days between two donations with a maximum of 5 donations per year. Differences in ferritin levels between the groups are as expected from previous studies: men have higher ferritin levels than women, and repeat donors have lower ferritin levels than new donors.

For pollution and environmental variables, there was little difference between the groups, any differences between new and active donors were most likely due to the different age and geographical distribution of the groups. None of these differences were statistically significant.

We found a weak correlation between the percentage of smokers and SES score (Pearson's $r = -0.4$) and a moderate correlation between the percentage of smokers and population density (Pearson's $r = 0.5$). No correlation was found for any of the other environmental variables.

3.2 | Model selection

CFA did not provide support for the *environment* construct as defined by the three variables *temperature*, *population density* and *socio-economic status*. These variables did not share a high proportion of their variance and consequently there was no convergent validity, effectively ruling out models A and C. In models B and D, variables *Duffy phenotype*, *temperature*, *SES* and *height* were omitted due to very low factor loadings (<0.05). The factor loading for variable *age* was also low (0.35) but this variable was not excluded, as it is expected that this factor loading would be small, considering the other variables in the construct (*weight* and *BMI*) are much more closely related. All other factor loadings were above the suggested threshold of 0.6. All latent constructs (individual characteristics, donation history and environment) showed convergent and discriminant validity in models B and D. Variables *time* and *day of year*, which were added to the model outside the constructs, were also dropped due to very low factor loadings (<0.05).

The presence of a *donation history* construct was the only difference between models B and D, and since new donors do not yet have a donation history, the models only differed for active donors. Model B had a TLI of 0.961 and RMSEA of 0.063, while model D had a TLI of 0.932 and RMSEA of 0.083. Based on these fit measures, model B fit the data best, and was therefore used in the remainder of the analyses.

Based on inspection of the pairwise residual correlations between all observed variables, two covariance terms were added to the model: one for *PM2.5* and *PM10* (residual correlation 0.092–0.102, depending on sex/donor status), and one for *age* and *population density* (residual correlation −0.151 to −0.149, depending on sex/donor status). We also added one covariance term for *weight* and *BMI*, as BMI was calculated using weight and was therefore inherently dependent.

3.3 | Parameter estimates

Figure 1 shows the structure of the final model and the parameter estimates for new donors. Parameter estimates were similar for both sexes, but factor loadings for variables belonging to the *individual characteristics* construct were higher for women than for men, indicating more shared variance. Factor loadings in the *environment* construct did not differ between sexes, showing that the covariance structure of those variables was not dependent on sex. The parameter estimates for the regression coefficients show the relative importance of each latent construct for the outcome variable. Table 3 shows the percentage of variance in ferritin levels that is explained by each construct for each model, adding up to the total percentage of variance explained.

Figure 2 shows the final model for active donors. As in new donors, factor loadings in the *individual characteristics* construct were higher for women than for men, and they were also higher for new donors than for active donors. The relative importance

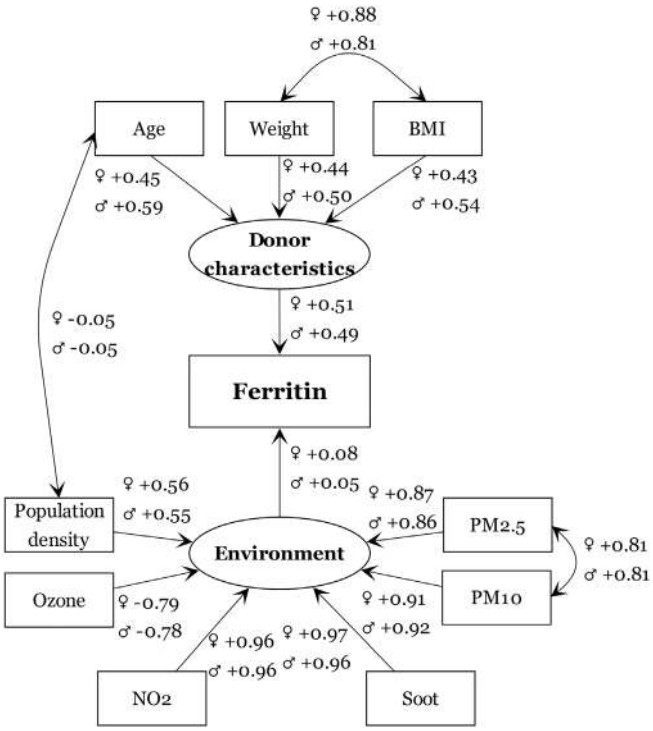

FIGURE 1 Final structural equation model for ferritin determinants in new donors, with parameters estimated separately for men and women. All parameter estimates are standardised so that the variance of each observed variable and latent construct equals 1

TABLE 3 Relative contribution to explanation of variance of ferritin levels per model

	New donors		Active donors	
Construct	**Women**	**Men**	**Women**	**Men**
Individual characteristics	23%	23%	20%	17%
Donation history	NA	NA	14%	25%
Environment	2%	2%	5%	4%
Total % of variance explained	25%	25%	39%	46%

of individual characteristics and donation history was opposite for both sexes: for men, donation history was correlated with ferritin levels more strongly than individual characteristics (0.66 vs. 0.45), while this was reversed for women (0.43 vs. 0.61). The regression coefficient of the *environment* construct is 0.15 for women and 0.10 for men. The *environment* construct explains twice as much variation in ferritin levels in active donors as in new donors.

As for overall model fit, with a TLI of 0.981 and 0.979 and RMSEA of 0.052 and 0.042, for new and active donors respectively, both models fit very well when compared to commonly used thresholds (TLI > 0.95, RMSEA < 0.06).[29] R^2 was calculated separately by sex: for new donors, R^2 was 0.251 for men and 0.252 for women, and for active donors, 0.458 for men and 0.393 for women.

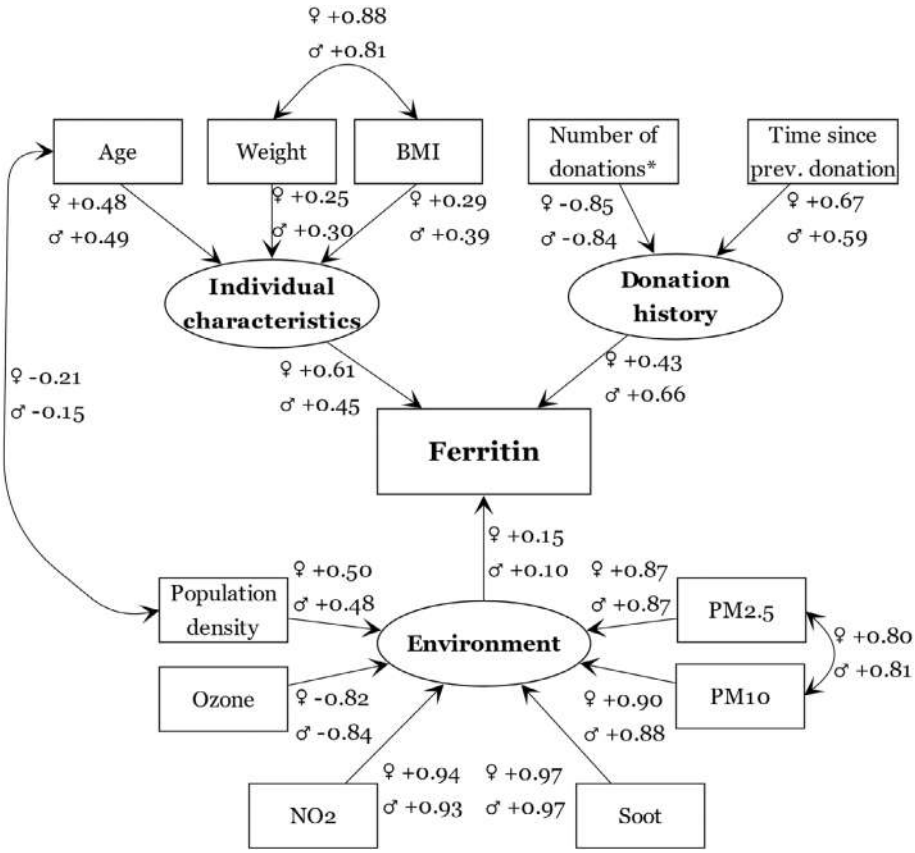

FIGURE 2 Final structural equation model for ferritin determinants in active donors, with parameters estimated separately for men and women. All parameter estimates were standardised so that the variance of each observed variable and latent construct equals 1

4 | DISCUSSION

This study investigated the impact of individual and environmental determinants on ferritin levels in Dutch individuals, using SEM. The model was able to explain 25% of ferritin level variance in new donors for both sexes, and 46% and 39% in active donors for male and female donors, respectively.

We found the construct composed of individual characteristics (age, weight, and BMI) to be the most important determinant of ferritin in female active donors, followed by donation history (time since previous donation, number of donations in the past 2 years). For male active donors, this was the opposite: donation history was a more important determinant than individual characteristics. In both sexes, environmental factors are associated with ferritin levels, albeit to a lesser degree than individual characteristics and donation history.

The relationship between ferritin levels and anthropometric characteristics is well-documented, and the positive correlations we found for ferritin with age, weight and BMI are consistent with those found in other studies.[4,15,30] Men have much higher ferritin levels than women in general and show a larger decrease in ferritin levels after repeated donations. As a result, ferritin levels in active donors are similarly low for women and men.[4] The *donation history* construct explained more variance in ferritin levels in men than in women. Although often not explicitly mentioned, this discrepancy is also found in previous studies, with stronger relationships between variables regarding donation history and ferritin for men than for women.[15] A reasonable explanation for this is that men commonly display more variation in donation history variables due to the possibility of more frequent donations: in many blood services, men are allowed to donate more often than women and are usually less frequently deferred for low haemoglobin levels.[31]

From previous epidemiological studies, we know that environmental factors may play a role in iron metabolism, and that certain pollutants can disrupt iron homeostasis.[32] Our study shows that although environmental factors are less strongly associated with ferritin levels than individual characteristics and donation history, their effects are far from negligible. Because of the wide reach of environmental exposures over geographic areas, even a relatively small influence on individuals can result in a large effect on the population level. As this study includes only data from the Netherlands, which is a relatively small country, associations between environmental variables and ferritin levels were not very strong, as was expected. Repeating this study on a larger, or even global, scale may result in finding a more substantial effect.

Higher values for all but one environmental factor (ozone) were positively correlated with higher ferritin levels. These findings support the hypothesis that air pollution causes higher ferritin levels. The underlying mechanism may be that when certain pollutants enter the lungs, iron is transported away from the lung tissue surface and stored in ferritin complexes to avoid chemical reactions between iron and the pollutant.[18,33] This would imply that using serum ferritin as a proxy for total body iron is less reliable when there is significant air pollution.

The *environment* construct was more strongly associated with ferritin level in active donors than in new donors. In new donors, environmental factors explain 2% of variance in ferritin levels, while in active donors this increases to 4%–5% depending on sex. This indicates that environmental factors are more important for ferritin recovery after blood loss than for naive ferritin level. A plausible explanation for this difference is that since both exposure to air pollution and donating blood causes significant disruptions to iron homeostasis, these disruptions may interact and together have a larger effect than simply additive.

SEM is a technique well-suited to test hypotheses on how different factors interact and correlate with a specific outcome like ferritin levels, especially when there are many factors to consider. Compared to multiple (linear) regression, more complex models can be tested, and for each variable measurement error is taken into account.[34] Moreover, the percentage of variance explained by groups of related variables can be calculated and compared. The stratified approach in this study also adds to the model validity: parameter estimates can be compared across groups, allowing discovery of implausible results. Our analyses show that the convergent validity of the *individual characteristics* construct is lower for active donors than for new donors. This may indicate that new donors are a more homogenous group than active donors, which is likely due to the more narrow age range of new donors. Other strengths of this study are its large sample size and collection of data throughout the country.

Two main limitations of this study should be noted: its generalizability and its restricted scope. One might be tempted to generalise the results of new donors to the general Dutch population, as these donors have never donated blood before. However, even new donors form a very specific, generally healthier subgroup of the general population, which means that selection bias has likely been introduced. We can speculate that less healthy individuals would show a higher rate of inflammation, which may cause higher serum ferritin levels. On the other hand, iron deficient or anaemic individuals are likely underrepresented in our sample. As this selection bias most likely reduced variance in ferritin levels, this may have attenuated our results.

Regarding the scope, data on some other potentially important determinants of ferritin levels were not available in this study, the two most important being genetics and diet.[9,10] Several genetic polymorphisms that have an effect on iron pathways have been identified, and these are likely to play a role in the recovery speed of ferritin levels after blood donation.[12,35–37] Dietary behaviour, and in particular heme iron intake, is also a determinant of iron status in donors.[9,15] Information on iron supplementation was also not available for this study. Sanquin does not prescribe oral supplementation of iron to donors, and only a small minority (8.7%) uses iron supplements.[9] Information on donors' smoking status is also expected to add value to the model. Had these determinants been available for our analysis, the proportion of variance explained in donor ferritin levels would likely have increased.

This study presents a model to explain variance in ferritin levels in individuals with or without donation history, based on three types of determinants. The model explained a relatively large part of the variance, especially in active donors. Individual characteristics and donation history form the most important determinants of ferritin levels. Although environmental factors accounted for less variance than the individual and donation history constructs, their contribution is meaningful and statistically significant. When clinicians or researchers use serum ferritin as a proxy for total body iron, they should be aware of this potentially confounding effect.

For blood services that are considering implementing ferritin testing for their donors, these results are of particular value. The results can be of use while the blood service is deciding on a sensible threshold for donation: rather than implementing a one-size-fits-all threshold, environmental conditions in the country can be taken into account. If there is a high level of air pollution, ferritin levels are likely to be overestimated, and thus a higher threshold for donation may be desired. It could even be taken further to make ferritin thresholds more tailored to a specific donor, by taking into account a donor's individual characteristics.

AUTHOR CONTRIBUTIONS

Rosa de Groot, Katja van den Hurk, and Jeroen Lakerveld conceptualised the study; Mart Janssen and Marieke Vinkenoog designed the methodology; Marieke Vinkenoog, Rosa de Groot, and Jeroen Lakerveld curated data; Marieke Vinkenoog did the formal analysis and wrote the original draft; all authors reviewed and edited the manuscript; Jeroen Lakerveld, Katja van den Hurk, and Mart Janssen supervised the study.

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CONFLICT OF INTEREST

The authors have no competing interests.

DATA AVAILABILITY STATEMENT

Data collected on prospective and active donors by Sanquin Blood Supply Foundation will not be shared due to privacy reasons. The authors are open to research questions from other researchers; proposals for joint research projects may be made to the corresponding author via e-mail. The environmental exposure data provided by the GECCO institute is based on publicly available data, and can be requested via a data access request form available on the website: www.gecco.nl.

ORCID

Marieke Vinkenoog https://orcid.org/0000-0001-5653-8078
Mart Janssen https://orcid.org/0000-0002-1682-7817

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APPENDIX A

A.1 | STRUCTURAL EQUATION MODELLING OVERVIEW

Structural equation modelling (SEM) comprises a set of statistical methods that enables researchers to assess the support for hypothesized relationships between variables of interest. Its purpose is to account for variation and covariation of the variables in the model. Many different techniques are included in SEM, this appendix explains the approach taken in this particular study. In SEM, observed variables and latent constructs are distinguished. Observed variables are variables in the traditional sense, which are observations in the data set that have been

collected by the researcher. Latent constructs are theoretical concepts that cannot be measured, but must be inferred from the observed variables; a well-known example is the latent construct *intelligence* that cannot be measured directly, but can be inferred from observed variables such as scores for an IQ test. Intuitively, observed variables that belong to a latent construct represent the same underlying concept, and latent constructs form in a way a dimensionality reduction of the observed variables. Mathematically, latent constructs represent shared variance of the observed variables related to the construct they belong to.

SEM is composed of two main model components: the measurement model, which shows how observed variables are divided among latent constructs, and the structural model, which shows the relationships between latent constructs and outcome variable(s). First, the measurement model is specified, and test its validity using confirmatory factor analysis (CFA). Often, several measurement models are tested and compared to see which division into latent constructs best fits the data. When the measurement model is considered to have a good fit, the structural part of the model is added, and the model fit is assessed for the full SEM model.

A.1.1. | Measurement model

The validity of the latent constructs must be measured in two ways: each construct must have convergent and discriminant validity. Convergent validity occurs when the observed variables belonging to the latent construct share a high proportion of their variance. This is assessed by the factor loadings of the observed variables onto the latent construct: the higher the (absolute value of the) factor loading, the stronger the indication that this variable belongs to this construct. Very generally speaking, factor loadings greater than 0.4 are acceptable for including a variable within a construct, but this threshold depends greatly on the hypothesized interpretation of the latent variable. Variables with low factor loadings are excluded from the construct.

The discriminant validity of a latent construct is a measure for how well the construct can be distinguished from the other constructs in the model. It is measured by the covariances between latent constructs. A high covariance between two constructs can indicate that these constructs are (partly) overlapping, and thus have no discriminant validity.

If convergent and discriminant validity are satisfactory, model fit indices can be calculated for the measurement model. Commonly used indices are the chi-square test, comparative fit index (CFI), Tucker-Lewis index (TLI) and root mean square error of approximation (RMSEA). The CFI and TLI are both relative measures of fit, and compare the fit of the tested model against a null model, which in CFA means that the means and variances of each variable are freely estimated, but no correlations are included. CFI and TLI are on a scale from 0 to 1, with higher values indicating a better fit of the hypothesized model relative to the null model. The TLI is always more conservative (lower value) than the CFI, because the TLI includes a harsher penalty for the number of parameters estimated. Because the two fit indices are highly correlated, only one should be reported. We chose the TLI because of its more elegant penalty for complexity. Values higher than 0.95 indicate good fit.

The RMSEA is an absolute measure of fit that is not sensitive to large sample sizes, unlike the chi-square test. It uses the covariance matrix of the entire data set and of the fitted hypothesized model, and calculates the differences between these two. This results in a measure between 0 and 1, with lower values indicating smaller differences and better model fit. Cut-offs of 0.08, 0.05, and 0.01 indicate mediocre, good, and excellent fits, respectively.

If multiple measurement models are compared, as in this study, the best fitting model is selected, based on the fit indices described above. If these indicate sufficient model fit, the analysis can be continued with inspection of residual correlation between observed variables. If the pairwise residual correlation between two variables is high (absolute value of 0.1 or higher is a common cut-off), this indicates that these two variables share more variance than is currently captured in the model. If this occurs, the researcher needs to decide whether a covariance term for these two variables should be included in the model. However, this should only be done if there is sufficient theoretical support for an interpretable correlation between these variables. Otherwise there is a risk of overfitting the model to the data; after all, in confirmatory factor analysis we build upon a set of relationships that are hypothesized by the researcher. It is not a data-driven method of finding the best set of relationships. If such an approach is desired, exploratory factor analysis (EFA) can be applied instead of CFA.

A.1.2. | Structural model

The structural component is added to the model once the latent constructs are defined, variables with low factor loadings are removed, and necessary covariance terms are added. The structural component consists of the relationships between latent constructs, or between latent constructs and outcome variable(s). With this, we now have three types of parameters for which an estimate must be calculated:

1. Factor loadings (observed variable → latent construct).
2. Covariances (observed variable ↔ observed variable).
3. Regression coefficients (latent construct → latent construct or outcome variable).

Each parameter adds one degree of freedom to the model, and the number of parameters determines the identifiability of the model. Parameter estimates can only be obtained when the number of free parameters (the number of 'unknowns') is equal to or smaller than the number of independent elements in the covariance matrix of the data (the number of 'knowns'), which is equal to $k(k+1)/2$, where k is the number of observed variables in the model. If there are more unknowns than knowns, the model is under-identified and no solution can be found. If the numbers are the same, the model is just identified, and a unique solution can be obtained. If there are fewer unknowns than knowns, we have an over-identified model, which means that

there is no unique solution but multiple, and we can select the best solution based on fit measures. An over-identified model is desired.

In most software packages parameter estimates are obtained by a maximum likelihood estimator by default, but alternative estimators can be chosen as well. In this study most observed variables did not follow a normal distribution, which violates maximum likelihood estimator assumptions. Therefore, the diagonally weighted least squares (DWLS) method was used instead, which is more robust and provides more accurate parameter estimates in case the normality assumption is violated.

If the model is over-identified, fit measures can be reported along with the parameter estimates. Again, TLI and RMSEA are used to assess model fit, with the same thresholds as seen in the CFA (TLI > 0.9, RMSEA < 0.08). If the model fit is acceptable the parameter estimates can be interpreted. The interpretation of the parameter estimates depends on the specification of the model. By default, one factor loading in each latent construct is set to 1, to fix the scale of the latent construct. However, in order to compare factor loadings across constructs it is useful to consider standardized parameter estimates. The variance of the latent construct is then set to 1 and factor loadings are interpreted in terms of a change in variance. In this study, we look only at the standardized parameter estimates, as we are interested in the relative importance of each observed variable and latent construct.

Factor loadings indicate how much variance of an observed variable is shared with the variance of its latent construct. Higher absolute values indicate more shared variance, and the sign of the factor loading specifies the direction of the association. Covariance terms provide the same information for two observed variables, which can belong to the same construct or to different constructs. If they belong to the same construct, a high covariance term indicates that these two variables share more variance with each other than can be explained by the latent construct. Regression coefficients indicate how much variance of the outcome variable is explained by the variance of the latent construct. To find the relative effect of a single observed variable on the outcome variable, its factor loading must be multiplied by the regression coefficient that connects the latent construct to the outcome.