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The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral aetiology: a systematic review and exploratory meta-analysis

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ABSTRACT

Background

Administration of convalescent plasma, serum or hyperimmune immunoglobulin may be of clinical benefit for treatment of severe acute respiratory infections (SARI) of viral aetiology. We conducted a systematic review and exploratory meta-analysis to assess the overall evidence.

Methods

Healthcare databases and sources of grey literature were searched in July 2013. All records were screened against the protocol eligibility criteria using a three stage process. Data extraction and risk of bias assessments were undertaken.

Results

We identified 32 studies of SARS-CoV and severe influenza. Narrative analyses revealed consistent evidence for a reduction in mortality, especially when convalescent plasma is administered early after symptom onset. Exploratory *post hoc* meta-analysis showed a statistically significant reduction in the pooled odds of mortality following treatment compared to placebo or no therapy (odds ratio 0·25; 95% confidence interval 0·14 to 0·45; I^2 = 0%). Studies were commonly of low or very low quality, lacked control groups and at moderate or high risk of bias. Sources of clinical and methodological heterogeneity were identified.

Conclusions

Convalescent plasma may reduce mortality and appears safe. This therapy should be studied within the context of a well-designed clinical trial or other formal evaluation, including for treatment of MERS-CoV.

INTRODUCTION

As of 23 May 2014, the World Health Organization (WHO) had been informed of 635 laboratory-confirmed cases of Middle East Respiratory Syndrome coronavirus (MERS-CoV), of whom 193 (30%) have died.(1) The current approach to clinical management of MERS-CoV centres on general supportive care with provision of critical care and organ support where necessary.(2) It has recently been suggested that administration of convalescent plasma or hyperimmune immunoglobulin will yield a clinical effect for treatment of MERS-CoV.(3) However, numerous uncertainties remain since the clinical course, viral replication kinetics and host interactions are yet to be fully established.(4) Furthermore, the underlying evidence is based on studies of varying size and quality which describe clinical experience in treating other viral infections including Severe Acute Respiratory Syndrome coronavirus (SARS-CoV), Spanish influenza A(H1N1), avian influenza A(H5N1) and influenza A(H1N1)pdm09.(5–9)

We conducted a systematic review and exploratory meta-analysis to evaluate the clinical effectiveness of convalescent plasma, serum or hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral aetiology, to help inform clinical management of MERS-CoV.

METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.(10) The study protocol was registered with the National Institute for Health Research international prospective register of systematic reviews.(11)

The study eligibility criteria are available elsewhere.(11) Briefly, the study population of interest was human subjects of any age or sex, hospitalised due to severe acute respiratory infection (SARI) of laboratory confirmed or suspected viral aetiology. The intervention of interest was convalescent plasma, serum or hyperimmune immunoglobulin derived from convalescent plasma. Comparator treatments included placebo, sham therapy or no intervention; studies with no comparator group were

also included. Outcome measures were derived from the protocol research questions to ascertain the clinical effectiveness of therapy.(11)

Search strategy and study selection

Two reviewers (JM-J, MS-C) executed the search strategy in July 2013.. The sources of information searched and search construct are available elsewhere.(11) Adaptations were made for search interfaces which did not allow use of complex constructs. All search records were imported to EndNote® X5 software (Thomson Reuters, California, USA) or screened manually using paper records. Following the removal of duplicate entries, a three-stage screening process was followed to identify eligible records through the sequential examination of each title, abstract and full text. Two reviewers (JM-J, MS-C) screened each record, with provision for arbitration from a third reviewer (CRB).

Data collection

Data were collected independently by paired reviewers using a piloted form. Consensus agreement for each extracted data item was reached by discussion with provision for arbitration from a third reviewer (JM-J, MS-C, CRB). The data extraction form is available as an appendix to the study protocol.(11)

Risk of bias within studies

Risk of bias assessments were performed at the outcome measure level during data collection. The Cochrane Collaboration tool was used for experimental and prospective cohort studies,(12) the Newcastle-Ottawa scale for observational studies (excluding prospective cohort studies),(13) and a tool published by the US Agency for Healthcare Research and Quality for systematic reviews.(14) Records limited to abstracts were not assessed due to the paucity of information contained therein.

Summary measures and synthesis of results

Odds ratios, case fatality rates (CFRs), absolute difference in CFR and difference in means were calculated as summary statistics with 95% confidence intervals (CIs). Study characteristics and outcome measures were tabulated. A recognised framework for narrative synthesis was adopted.(15) Due to potential concerns with clinical heterogeneity, analyses were stratified by viral aetiology for each research question in accordance with the protocol.(11)

An exploratory, *post hoc*, random effects model meta-analysis was conducted to describe the pooled odds ratio of mortality irrespective of SARI aetiology following treatment with convalescent plasma or serum compared to placebo or no therapy. Results were adjusted by adding 0.5 to each cell of the contingency table where no deaths occurred in the exposed group of individual studies.(12) Meta-analysis of crude CFRs using a random effects model was undertaken. Statistical heterogeneity was ascertained using the I^2 statistic and meta-analyses were abandoned where this reached 85%.(16) Sensitivity analyses were undertaken to investigate the impact of excluding studies where five or less patients were in the exposed group. Publication bias was assessed through construction of funnel plots and using Egger's test.

All statistical analyses were conducted using Stata® software version 12·1 (StataCorp, College Station, TX, USA) except for meta-analysis of pooled proportions where we used StatsDirect® software version 2·8·0 (StatsDirect Ltd, Altrincham, Cheshire, UK). Statistical significance was assumed at the 5% level.

RESULTS

Study selection

The search process yielded a total of 3,406 records (Figure 1). After sifting 1,449 unique records against the protocol eligibility criteria, we identified 32 studies from 50 reports (Table S1). Three studies could not be obtained(17–19) although results from a study by Bass *et al.* (1919)(17) were

reported elsewhere(20) which enabled their inclusion. French (n = 1), German (n = 2) and Korean (n = 2) records were screened by single reviewers due to a lack of multilingual collaborators.

Study characteristics

The study characteristics are summarised in Table S2. Three systematic reviews met our protocol eligibility criteria.(7,21,22) Data on 1,327 patients from six case studies,(23–28) 20 case series,(8,17,20,29–45) two case comparison studies,(46,47) and one prospective cohort(48) were included. We identified 13 observational studies published between 1918 and 1920 which studied 980 patients clinically diagnosed with influenza pneumonia or Spanish influenza A (H1N1).(17,20,33–35,38–44,47) It is unclear whether some of these studies recruited patients with secondary bacterial pneumonia. Sixteen observational studies which met our protocol eligibility criteria were published between 2003 and 2011. Four studies reported outcomes for 29 patients infected with avian influenza A(H5N1),(23,26,27,36) four studies reported outcomes for 104 patients infected with influenza A(H1N1)pdm09,(24,30,37,48) and eight studies reported outcomes for 214 SARS patients.(8,25,28,29,31,32,45,46) The clinical status of patients at the time of treatment administration varied as did concomitant treatments and comorbidities. Convalescent plasma was used in all observational studies of SARS-CoV, influenza A(H1N1)pdm09 and avian influenza A(H5N1) (Table S2). For Spanish influenza A(H1N1), two observational studies used convalescent plasma and 11 used convalescent serum (Table S2). No studies met our protocol eligibility criteria which used hyperimmune immunoglobulin. The use of sham treatments or placebos was not reported.

Risk of bias within studies

Two systematic reviews were at low risk of bias(7,21) whilst one was at moderate to low risk of bias across most domains (Table 1).(22) Data extraction was judged to be a moderate source of bias in all systematic reviews. Search strategies were also a moderate source of bias in two systematic reviews as grey literature and non-peer reviewed sources were not considered.(7,22)

The risks of bias of two outcomes in a single prospective cohort study were considered to be moderate (Table 2).(48) The lack of randomised treatment allocation may have introduced systematic error and the viral load outcome was at high risk of bias due to incomplete follow-up of patients.

Figure 2 summarises the risk of bias assessments for 44 outcomes from 25 observational studies. Studies reported outcomes that were either at moderate risk (11 outcomes) or moderate to high risk of selection bias (33 outcomes). The majority of studies lacked a comparator group and 28 studies were at high or very high risk of reporting bias. This suggests the observational study data included are at moderate to high risk of bias.

Three studies were not assessed for risk of bias because they presented insufficient data.(17,29,45)

Results of individual studies and data synthesis

Table 3 summarises our narrative synthesis and Table S3 shows results of the individual studies which included an all-cause mortality outcome. Meta-analyses, sensitivity analyses and assessments of publication bias by viral aetiology proved unfeasible due to a paucity of suitable data. There were no data available to address study questions relating to organ failure and sepsis, or hospital readmission and recurrence of severe disease.

Mortality

SARS-CoV

Table 3 and S3 summarise eight observational studies at moderate to high risk of bias that reported improved mortality after patients received convalescent plasma in varying doses.(8,25,28,29,31,32,45,46) A retrospective case comparison study showed a CFR reduction after plasma treatment which reached statistical significance (absolute reduction in CFR of 23%; 95% CI 6% to 42%; p = 0·049).(46) A second study with a comparator group described a cluster of 29 SARS-CoV cases, where one patient received convalescent plasma and survived (absolute reduction in CFR 7%; 95% CI -2% to 17%; p = 0·93).(32,49) Three small studies reported treatment of five patients

with no deaths, and a case series by Cheng *et al.* (2005) reported a CFR of 12·5% (10/80) following treatment (Table S3).(8,9,25,28,31,45,50) Within this series, a subgroup analysis of 30 patients found that those treated when PCR positive but seronegative for SARS-CoV were more likely to be discharged within 22 days of admission than those who were seropositive at the time of plasma infusion (67% vs. 20%; p = 0·001). A further subgroup analysis of 48 patients found convalescent plasma treatment before day 14 from onset of symptoms improved the likelihood of discharge within 22 days of admission (58% vs. 16%; p < 0·001); this remained significant after adjusting for age, viral status, time of administration and lactate dehydrogenase level suggesting early treatment with convalescent plasma may be beneficial. However, allocation of treatment was mostly based on the physician's decision and availability of plasma and this study was at high risk of bias.

Pandemic influenza A(H1N1)pdm09

Four observational studies(24,30,37,48) and one systematic review(22) reported data on severe cases of influenza A(H1N1)pdm09 treated with convalescent plasma (Table 3 and Table S3). Hung *et al.*(2011)(48) carried out a prospective cohort study where patients received a single 500ml dose of convalescent plasma with a neutralising antibody titre (NAT) >1:160. Univariate analysis showed a significant absolute reduction in CFR of 35% (95% CI 14% to 56%, p = 0·01) after treatment. Multivariable analysis also showed a significant reduction in relative risk of mortality (odds ratio [OR] 0·20; 95% CI 0·06 to 0·69; p = 0·011), although the factors adjusted for were not clearly stated. Both groups received other treatments such as neuraminidase inhibitors and steroids (Table S2). This non-randomised study was at moderate risk of bias. A small study by Chan *et al.*(2010)(30) at moderate risk of bias reported exclusively on patients receiving extracorporeal membrane oxygenation (ECMO) and showed a non-significant absolute reduction in CFR of 33% (95% CI -20% to 87%) after convalescent plasma treatment.

Avian influenza A(H5N1)

Table S3shows the results of a case series at high risk of bias where 2 of 26 patients received convalescent plasma with a non-significant absolute reduction in CFR of 70% (95% CI 52% to 89%;

p = 0·11).(36) Three case reports reported recovery after treatment with convalescent plasma.(23,26,27) The dose of convalescent plasma varied across each study, and the NAT concentration was reported for only one case (titre = 1:80).(26) All studies were at high to moderate risk of bias and had patients who were given other therapies concomitantly (including steroids and antivirals) which could have impacted on the reported clinical effect.

Spanish influenza A(H1N1)

A systematic review and meta-analysis by Luke *et al.*(2006)(21) showed treatment with convalescent plasma, serum, or blood was associated with a significant absolute reduction in pooled CFR of 21% (95% CI 15% to 27%). Statistical heterogeneity was low (I^2 = 29·3%) although interventions were clinically heterogeneous. Of the six studies included in the meta-analysis, two reported use of convalescent whole blood; however, these studies only contributed 84 (25%) patients in the treatment group. Where timing of treatment was recorded, patients who received early treatment (<4 days from pneumonia onset) had a CFR of 19% (28/148) compared with 59% (49/83) in those treated later.(21)

Only two studies of convalescent serum reported a comparator group.(38,47) Both reported absolute reductions in CFR after treatment - 19% (95% CI 11% to 48%) and 22% (95% CI 11% to 32%); the latter reached statistical significance (p = 0·008). The remaining studies observed a CFR ranging from 0% (0/2) to 48% (12/25) after treatment (Table S3). A significant absolute reduction in CFR was observed in a case series of 157 cases, 46 of whom received convalescent plasma (absolute reduction in CFR 18%; 95% CI 8% to 30%; p = 0·0075).(33) A further study of patients treated with convalescent plasma reported a CFR of 50% (7/14).(41)

The majority of studies on Spanish influenza A(H1N1) were found to have high risk of bias due to the use of now archaic research methods and a risk of wartime censorship and publication bias.(21)

Exploratory post hoc meta-analysis

Meta-analysis pooled data from eight comparative studies: two SARS-CoV,(32,46) two influenza A(H1N1)pdm09,(30,48) one avian influenza A(H5N1)(36) and three Spanish influenza A(H1N1) studies.(33,38,47) There was a statistically significance lower risk of mortality in the group treated with convalescent plasma or serum (Figure 3; pooled OR 0·25; 95% CI 0·14 to 0·45; $p < 0·001$; $I^2 = 0\%$). Examination of the funnel plot and Egger's test showed no evidence of publication bias. Sensitivity analyses excluding studies with five or fewer cases demonstrated little variation in the pooled odds ratio or change in statistical heterogeneity (Figure 4).

Meta-analysis of crude CFR in treated patients was rejected due to excessive statistical heterogeneity ($I^2 = 85\%$). Sensitivity analysis excluding studies with five or fewer cases did not account for this and was similarly abandoned ($I^2 = 91\%$).

Hospital length of stay

Convalescent plasma treatment was associated with a significant increase in the proportion of SARS-CoV patients discharged within 22 days of admission in one centre (absolute difference 54%; 95% CI 25% to 85%; $p = 0·004$) after excluding patients with co-morbidities from the analysis (Table 3).(46) A further SARS-CoV case series(31) reported 47% (15/33) of patients were discharged by day 22, and initiation of therapy was significantly earlier among patients discharged by that time (mean number of days from symptom onset 11·67 vs. 16·04 ; $p < 0·001$). Both studies were at moderate to high risk of selection bias and confounding by indication. A case comparison study at moderate risk of bias(30) reported no significant difference in length of hospital stay between treatment and control patients with severe pandemic influenza A(H1N1) who required ECMO (Table 3).

Duration of critical care support

A retrospective observational study(30) reported convalescent plasma treatment made non-significant reductions to length of time spent in ICU, days of mechanical ventilation, or number of days of ECMO for six patients with severe pandemic influenza A (H1N1)pdm09 (Table 3). Two other case

reports of pandemic influenza A (H1N1)pdm09(24) and avian influenza A(H5N1)(27) also suggested convalescent plasma may have aided clinical improvement and reduced the duration of mechanical ventilation.

Viral antibody levels

We identified limited evidence relating to levels of viral antibodies after convalescent plasma treatment; studies did not utilise a comparator and were at high risk of bias. Peaks in SARS-CoV antibody levels occurred within three to five days following a single dose of convalescent plasma in three healthcare workers (Table 3).(8) However, it is likely that other treatments such as IVIG, ribavirin and steroids may have influenced the relationship between plasma and antibody levels. A case report of a patient with avian influenza A(H5N1) also found that virus specific antibodies appeared between day 7 and 16 following administration of convalescent plasma.(23)

Viral load

Viral load of SARS-CoV in the respiratory tract decreased at a higher rate in those who received convalescent plasma in a subgroup analysis of 44 influenza A(H1N1)pdm09 patients within a prospective cohort study (Table 3);(48) viral loads were significantly lower 3, 5, and 7 days post ICU admission. However, there was a high risk of selection bias for this outcome and concomitant treatments including oseltamivir, zanamivir and corticosteroids may have confounded the results.

Further studies reported that viral load became rapidly undetectable in the blood of three SARS-CoV patients(8) and respiratory specimens of an influenza A(H1N1)pdm09 patient(24) after treatment. Similar decreases in serum and respiratory viral load were observed in three cases of avian influenza A(H5N1) with virus becoming undetectable after two to three days post convalescent plasma treatment for two of the cases and between the 7th and 16th days of treatment for the third case (Table S3).(23,26,36)

Severe adverse events & treatment complications

No studies reported a serious adverse event and few studies reported information about treatment complications, although minor complications may be underreported in the literature. Two observational studies (8,46) concerned with SARS-CoV reported that treatments did not cause harm when administered to patients. One study involving influenza A(H1N1)pdm09 reported that no adverse events were observed in the treatment group.(48)

Three studies from 1918-1920 (of 101 to 157 influenza patients) reported minor infusion complications including chills, increased temperature (34,44) and sweats.(33) A study of 14 patients did not report chills or any serious complications. Methodology and reporting of these studies reflect the period of time they were conducted and are at high risk of bias.

DISCUSSION

Our analyses suggest that convalescent plasma may have a clinically relevant impact in reducing the rate of mortality and viral load in patients with SARI of viral aetiology. *Post hoc* pooled meta-analysis across all viral aetiologies showed a statistically significant 75% reduction in odds of mortality in those who were treated with convalescent plasma or serum. We found no evidence of serious adverse events or complications due to therapy and limited evidence of a reduction in use of critical care resources and length of stay in hospital.

It is interesting to note the evidence for a survival benefit after early administration. A recent multicentre, prospective, double-blind, randomised control trial compared the use of hyperimmune immunoglobulin (derived from influenza A(H1N1)pdm09 convalescent plasma) to intravenous immunoglobulin manufactured before the 2009 pandemic.(5) Although excluded per protocol, a multivariate subgroup analysis of 22 patients in this study who received treatment within five days of symptom onset demonstrated that hyperimmune immunoglobulin had a protective effect (OR 0·14; 95% CI 0·02 to 0·92).(5) Evidence from studies of SARS-CoV(31) and Spanish influenza

A(H1N1)(21) showed a survival benefit following convalescent plasma treatment within 14 days and four days of symptom onset, respectively. These findings suggest that early initiation of treatment may be of critical importance to reducing mortality in SARI patients of viral aetiology.

Limitations

A lack of high quality studies and paucity in the volume of literature limited our analyses. Observational studies were predominately case reports or series, had no control groups and at moderate to high risk of bias. Findings were commonly at high risk of confounding by indication. Whilst selection or reporting bias may favour the intervention, recruiting patients who are clinically deteriorating or moribund would bias the result in the opposite direction. Adequate methodological or statistical measures were infrequently used to control bias and confounding, and we identified numerous sources of clinical and methodological heterogeneity. We cannot be assured that all Spanish influenza A(H1N1) studies were included since our protocol did not include hand searching of literature from 1918-1920. Whilst our *post hoc* meta-analyses were undertaken to help inform clinical decision making, the theoretical rationale for pooling mortality data from different viral aetiologies remains to be fully established. The results obtained must be considered experimental and interpreted with an appropriate level of caution.

Implications for practice

We did not identify any reports of convalescent plasma use for MERS-CoV patients. The evidence for a reduction in mortality associated with convalescent plasma is strongest for SARS and influenza A(H1N1)pdm09. Whilst it is clinically rational to consider novel therapies for critically ill patients, there is evidence that maximum benefit from convalescent plasma might be realised through early initiation of therapy. However, many treatment protocols currently mention convalescent plasma as a treatment of last resort. If this treatment is considered for MERS-CoV patients with SARI it should ideally only be administered in acute centers able to manage potential treatment-related complications such as transfusion related acute lung injury. We consider this a precautionary approach due to the limited clinical experience of administering convalescent plasma to this patient group.

Further research needs

Improved knowledge regarding the mode of action of convalescent plasma and the virologic and immunologic kinetics of novel respiratory infections which cause SARI (such as MERS-CoV) are needed. This would help clarify the potential benefits and harms of treatment, identify optimal dosage and ascertain whether repeated treatments are relevant factors for clinical practice. Randomised controlled trials or observational studies which adopt a standardised minimum dataset are needed to better evaluate convalescent plasma as a therapeutic option for MERS-CoV before this can be fully recommended or refinements made over current usage other than our current recommendation for early use. WHO and the International Severe Acute Respiratory and Emerging Infection Consortium are currently developing a clinical trial protocol to investigate the effectiveness of passive immunotherapy for SARI patients.

Conclusion

Available evidence suggests convalescent plasma is likely to reduce mortality in SARI of a viral aetiology with larger treatment effects if commenced early after symptom onset. However, this is based on predominately low quality, uncontrolled studies. Our review supports the use of convalescent plasma in critically ill MERS-CoV patients as part of a well-designed clinical trial or other formal evaluation.

AUTHOR CONTRIBUTIONS

Conceived and designed the study protocol: JM-J, MS-C, KB, PC, FMK, WSL, SM, KR, JSN-V-T, CRB.

Execution of the search strategy and screening: JM-J, MS-C.

Risk of bias assessments and data extraction: JM-J, MS-C, PC, FMK, SM, JSN-V-T.

Data analysis or interpretation: JM-J, MS-C, JSN-V-T, CRB.

Drafting of the manuscript: JM-J, MS-C, JSN-V-T, CRB.

Contribution of intellectual content to the manuscript: KB, PC, FMK, WSL, SM, KR.

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Convalescent Plasma Study Group

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Potential conflicts of interest

JM-J, MS-C, KB, PC, FMK, SM, KR, JSN-V-T, CRB have no potential conflicts of interest to declare. WSL has received funding from the National Institute for Health Research (NIHR) to set up a pandemic influenza clinical trial, and has received unrestricted funding from Pfizer for a study in adult pneumonia. The University of Nottingham Health Protection Research Group (JSN-V-T, CRB) is an official WHO Collaborating Centre for pandemic influenza and research. It receives limited funding from WHO in support for specific activities.

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DISCLAIMER

The authors alone are responsible for the views expressed in this article and they do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

LEGEND TO FIGURES

Figure 1. PRISMA diagram

Figure 2. Summary of outcome level risk of bias assessments in eligible observational studies using the Newcastle Ottawa tool (excluding prospective cohort studies; 44 outcomes from 25 studies)

Figure 3. Forest plot of pooled odds ratios of mortality following treatment with convalescent plasma or convalescent serum (n = 8 studies)

Figure 4. Forest plot of pooled odds ratios of mortality following treatment with convalescent plasma or convalescent serum excluding studies with fewer than five patients (n = 5 studies)

SUPPLEMENTARY MATERIAL

See the associated file "*Mair-Jenkins et al supplementary data JID.docx*".

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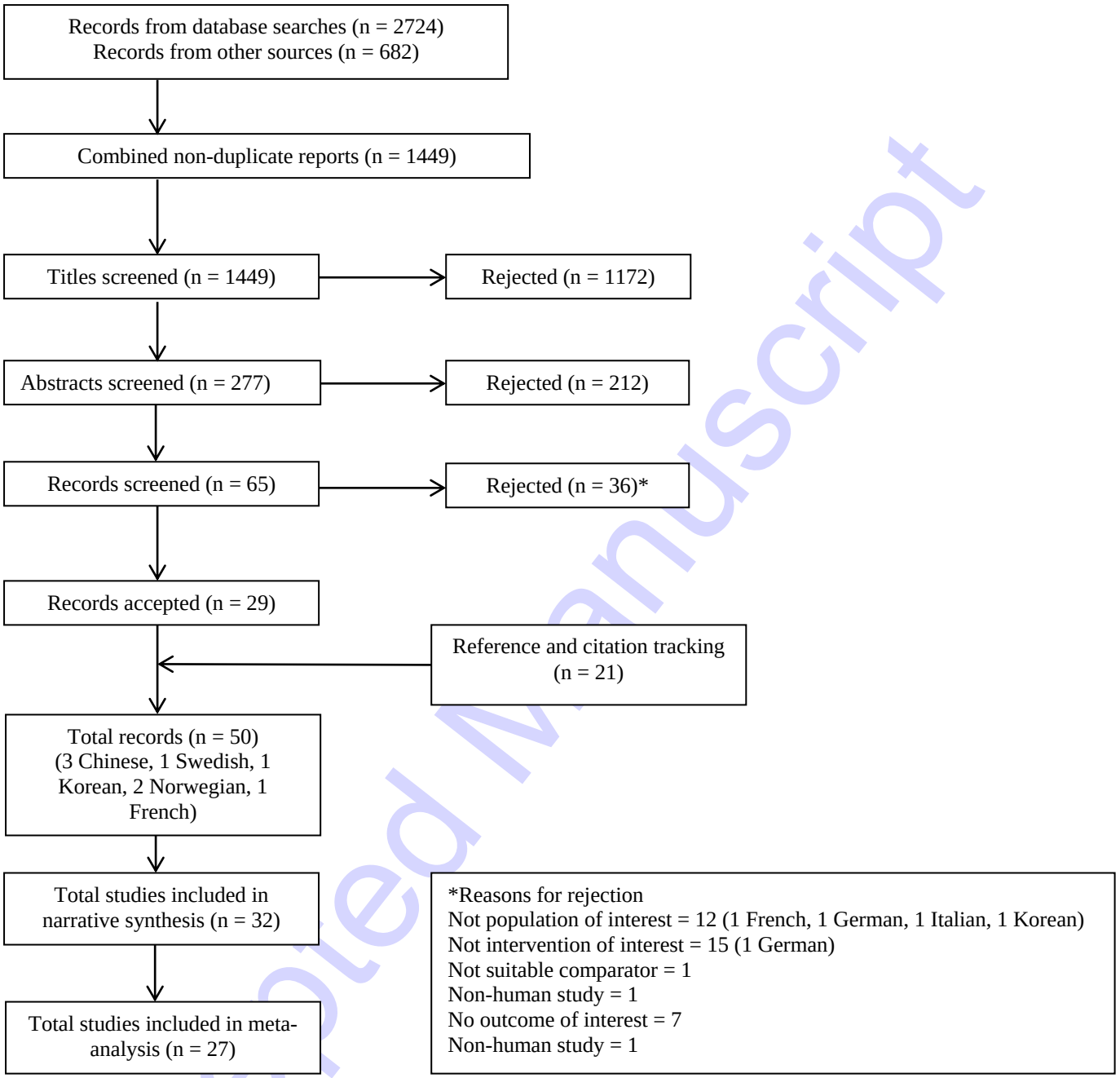
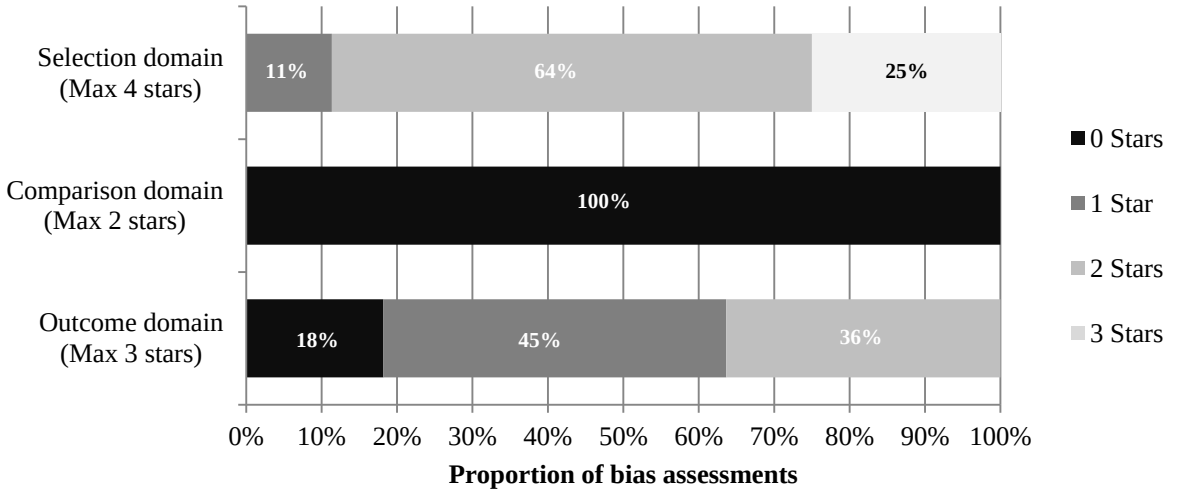
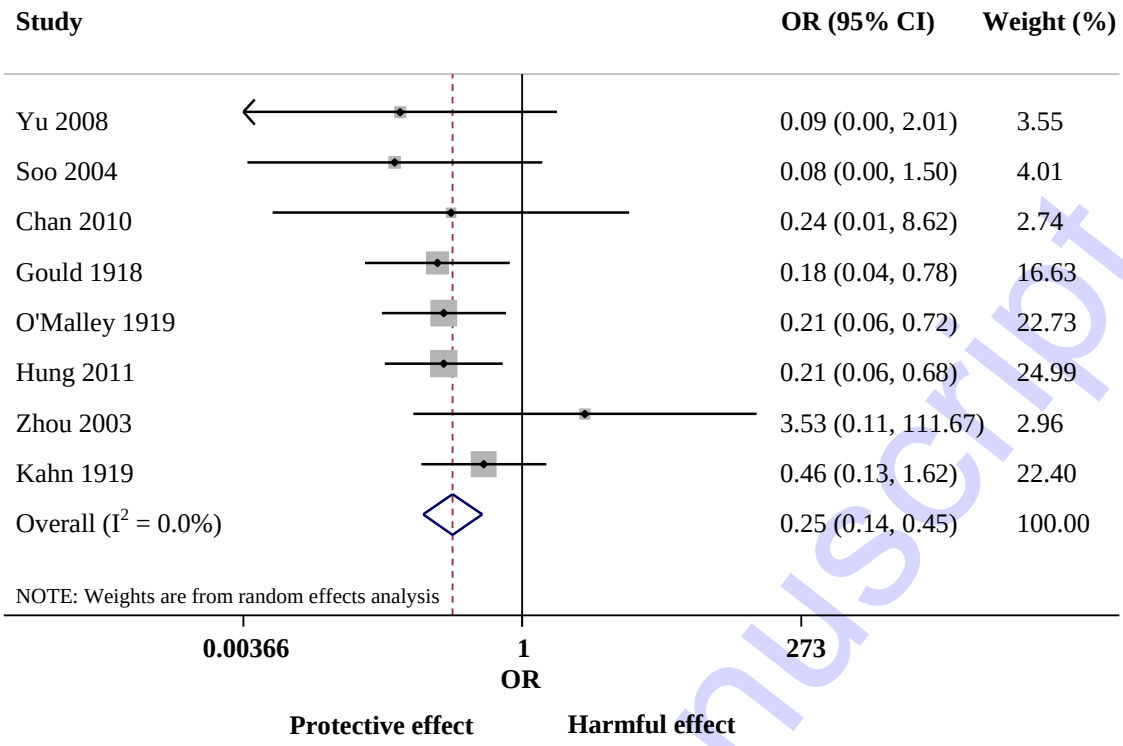
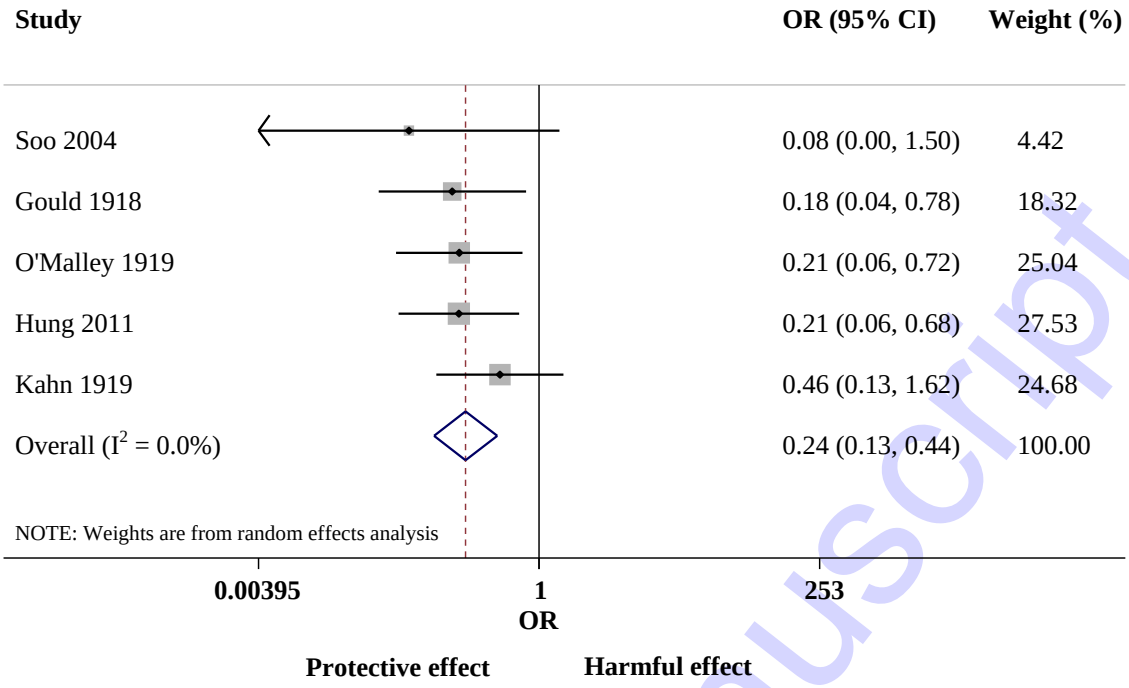






OR = odds ratio; CI = confidence interval



OR = odds ratio; CI = confidence interval

Table 1. Risk of bias assessment in the eligible systematic reviews using US Agency for Healthcare Research and Quality tool

Domain	Luke *et al*. (2006): Mortality & Serious adverse events	Ortiz *et al*. (2013): Mortality	Stockman *et al*. (2006): Serious adverse events
Study question	Low risk of bias	Moderate risk of bias	Low risk of bias
Search strategy	Low risk of bias	Moderate risk of bias	Moderate risk of bias
Inclusion and exclusion criteria	Moderate risk of bias	Low risk of bias	Low risk of bias
Interventions	Moderate risk of bias	Moderate risk of bias	Low risk of bias
Outcomes	Low risk of bias	Moderate risk of bias	Low risk of bias
Data extraction	Moderate risk of bias	Moderate risk of bias	Moderate risk of bias
Study quality and validity	Low risk of bias	Low risk of bias	Moderate risk of bias
Data synthesis and analysis	Low risk of bias	Low risk of bias	Low risk of bias
Results	Low risk of bias	Moderate risk of bias	Low risk of bias
Discussion	Low risk of bias	Low risk of bias	Moderate risk of bias
Funding or sponsorship	Low risk of bias	Low risk of bias	Low risk of bias

Table 2. Risk of bias assessment in the eligible prospective cohort study using The Cochrane Collaboration tool

Domain	Hung *et al.* (2011): mortality	Hung *et al.* (2011): viral load
Sequence generation	High risk of bias	High risk of bias
Allocation concealment	High risk of bias	High risk of bias
Blinding of participants, personnel and outcome assessors	High risk of bias	Unclear risk of bias
Incomplete outcome data	Low risk of bias	High risk of bias
Selective outcome reporting	Low risk of bias	Low risk of bias

Table 3. Summary of narrative synthesis

Viral aetiology	**Mortality** Intervention: 699, Control: 568, Unknown: 60*	**Length of hospital stay** Intervention: 92, Control: 16*	**Critical care support** Intervention: 92, Control: 16*	**Antibody levels** Intervention: 4, Control: 0*	**Viral load** Intervention: 7, Control: 0, Unknown: 44*	**Adverse events** Not reported at patient level
SARS-CoV	Absolute reduction in the risk of mortality varied from 7% (95% CI -2·39 to 18·68) to 23% (95% CI 5·59 to 42·02) in two studies at medium to high risk of bias. Subgroup analyses suggest early treatment beneficial. Four non-comparative studies found CFR varied from 0% (0/1) to 12.5% (10/80).	Likelihood of discharge by day 22 was 54% greater (95% CI 24·8% to 84·6%) after treatment (77% vs 23%) in one study. A non-comparative study reported 47% of treated patients discharged by day 22, both at moderate to high risk of bias. Results suggest early treatment beneficial.	No data reported in identified studies	No comparative data reported. Increased antibody levels up to day 5 after treatment in one study of health care workers at high risk of bias.	No comparative data reported. Decrease in viral load reported after treatment in one non-comparative study at high risk of bias.	No adverse events or complications reported after treatment.
Influenza A(H1N1)pdm09	Relative reduction in odds of mortality of 80% (adjusted odds ratio 0·20; 95% CI 0·06 to 0·69) in one prospective study was at moderate risk of bias. Subgroup analyses suggest early treatment beneficial. One comparative study showed no significant benefit. Two non-comparative studies found CFR varied from 0% (0/1) to 25% (0/4).	Mean duration of stay shorter after treatment (36·6 days compared to 60 days, p = 0·23) in one study at moderate risk of bias.	Reductions in ICU length of stay (reduction in mean duration 3·34 days), mechanical ventilation (4 days) and ECMO (10·3 days) reported by one study at moderate risk of bias.	No data reported in identified studies	Significantly lower viral load after treatment at days 3, 5, and 7 post ICU admission in subgroup analysis of one prospective study at moderate to high risk of bias. One non comparative study found reduction in viral load after treatment.	No adverse events or complications reported after treatment.
Avian influenza A(H5N1)	Non-significant benefits following intervention in one study with comparator data. Three case reports reported no deaths.	No comparative data reported. Length of hospital stay was 94 days in a case report at high risk of bias.	No comparative data reported. Report of treatment allowing discontinuation of mechanical ventilation in a case report at high risk of bias.	Specific antibodies detected between day 7 and day 16 post treatment in a case report at high risk of bias.	No comparative data reported. Three studies reported reductions in viral load after treatment.	No adverse events or complications reported after treatment.
Spanish influenza A(H1N1) **	Pooled absolute reduction in CFR 21% (95% CI 15% to 27%) reported by a meta-analysis at low risk of bias. This pooled six studies, including two studies using convalescent blood. Subgroup analyses suggest early treatment beneficial. Absolute reduction in the risk of mortality ranged from 18·66% (95% CI 10.62 to 47.95) to 21·60% (95% CI 11.28 to 31.93) in three studies at high risk of bias. Ten non-comparative studies found CFR varied from 0% (0/2) to 50% (7/14).	No data reported in identified studies.	No data reported in identified studies.	No data reported in identified studies.	No data reported in identified studies.	Three studies reported chills, increased, temperature and sweats after infusion.

95% CI = 95% confidence interval; ICU = intensive care unit; SARS-CoV = severe acute respiratory syndrome coronavirus; CFR = case fatality rate; ECMO = extracorporeal membrane oxygenation; * = number of patients in each group; ** = all studies report use of convalescent plasma except in 11 studies where convalescent serum was used to treat Spanish influenza A(H1N1) and one meta-analysis of six studies, two of which reported use of convalescent blood to treat Spanish influenza A(H1N1); additional data pertaining to individual studies is available within the supplementary information (including comparator data where presented)