Appendix 1 (as supplied by the authors)

"**Efficacy and safety of convalescent plasma for severe COVID-19 based on evidence in other severe respiratory viral infections: Systematic review and meta-analysis**"

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Appendix to: Devasenapathy N, Ye Z, Loeb M, et al. Efficacy and safety of convalescent plasma for severe COVID-19 based on evidence in other severe respiratory viral infections: a systematic review and meta-analysis. *CMAJ* 2020. doi: 10.1503/cmaj.200642.

Protocol for systematic review on use of convalescent plasma in SARS-CoV-2, SARS-CoV, MERS-CoV, influenza and Ebola virus infection

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak first in Wuhan and then spreading across China into more than 20 countries, represents a profound threat to world health. Based on data released by the Chinese government on February 13, the number of diagnosed patients in China was 59907, 8204 of whom experienced critical illness and 1368 of whom died – a toll considerably greater than that exacted by the severe acute respiratory syndrome coronavirus (SARS-CoV).

Of the several treatment options proposed (1), convalescent plasma has shown promising results in severe acute respiratory infections (2). Further, there is some evidence on mortality benefit in Ebola virus infections (3). The safety and effectiveness of use of convalescent plasma could help clinicians caring for SARS-CoV patients, and systematic summaries of the available evidence are needed to inform the discussion.

Therefore, we will conduct a systematic review to summarize the relevant evidence. Because we anticipate a paucity of direct evidence addressing the use of convalescent plasma in SARS-CoV-2, we will also summarize available evidence in addressing efficacy of convalescent plasma in the treatment of SARS-COV-1 and middle-east respiratory syndrome coronavirus (MERS-CoV) and influenza virus (H1N1, H7N9, H5N1 any other influenza causing severe respiratory illness). Safety of convalescent plasma given to those infected with Corona, Ebola and influenza virus, will be systematically summarized.

Methods

PICO question

1. The use of convalescent plasma in patients infected with COVID-19

Population: Patients infected with severe COVID-19

Intervention: Intravenous convalescent or hyper immune plasma

Comparisons: Management without use of convalescent plasma

Key Outcomes:

Mortality, extent of recovery, length of ICU stay, length of hospital stay, days of mechanical ventilation, viral load

Adverse outcomes: Intravascular volume overload related complications and transfusion-related acute lung injury, allergy or anaphylaxis, and any other patient-important safety outcomes that study reports include.

Because we anticipate a paucity of direct evidence addressing our question, we will also look for both benefit and safety evidence from a number of other patient populations:

- patients infected with SARS-CoV 1 requiring hospitalization

- patients infected with MERS-CoV requiring hospitalization

- patients with influenza virus respiratory infection requiring hospitalization

Apart from the above viruses, we will also look for evidence regarding safety of convalescent plasma in patients infected with Ebola virus requiring hospitalization.

Search strategy

We will develop our literature search in collaboration with a research information specialist. The search will include Medline, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and a PubMed search for studies not yet indexed or not found in Medline. We will review reference lists of all included studies and relevant systematic reviews for additional references. Trials registration websites and conference proceedings will not be searched because of urgency considerations in this rapid review.

We will search medRxiv previews and Chinese databases [NKI, WanFang, CQVIP and Sinomed]. We will also identify systematic reviews and look use eligible studies from those reviews

The search will be designed to obtain original eligible studies on the use of convalescent plasma in patients infected with SARS-CoV 1, MERS, Ebola, influenza and SARS-CoV-2. This search strategy will contain two parts: Convalescent plasma and diseases (SARS-CoV 1, MERS-CoV, Ebola, influenza, SARS-CoV-2)).

Search terms

Virus family	**Viruses**	**Treatment (synonyms or related terms)**
Corona virus category	SARS-CoV MERS SARS-CoV-2/COVID 19	convalescent plasma (CP) , convalescent blood product (CBP) Hyper immune plasma
Orthomyxoviridae	Influenza (H1N1) Influenza (H7N9)	
Filoviridae	Ebola virus*	

** only non-respiratory virus included for safety outcome only*

Eligibility criteria

For SARS-CoV, MERS-CoV, Ebola, influenza, SARS-CoV-2 we will include randomised controlled trials (RCTs) and observational studies that compared the use of convalescent plasma to treatment without convalescent plasma and reported on at least one of our outcomes of interest. We will exclude case series in which all patients, or no patients, received convalescent plasma.

Study selection

Pairs of reviewers will independently screen titles and abstracts, and review the full texts of potential eligible studies to determine the final eligible studies. Disagreements will be resolved by discussion or by referring to a third reviewer.

Data extraction

Pairs of reviewers will extract data. Disagreements will be resolved by discussion or, if necessary, by a third reviewer.

Risk of bias assessment

Two reviewers will independently assess the risk of bias for each randomized controlled trial using a modified Cochrane Collaboration tool that includes sequence generation, allocation sequence concealment, blinding, and missing outcome data. Each criterion will be judged as definitely or probably low risk of bias, or probably or definitely high risk of bias.(4) Two reviewers will independently assess the risk of bias for each observational study using a modified version of the Newcastle-Ottawa Scale.(5)

Data synthesis or analysis

If the evidence permits, we will conduct meta-analysis for each of SARS-CoV-1, MERS-CoV and SARS-CoV-2 for efficacy outcomes. Since SARS-CoV-1, MERS-CoV and SARS-CoV-2 are all coronaviruses, we will consider conduct a meta-analysis that combines data from each of the three conditions.

For safety outcomes we will conduct meta-analysis that combines data from each of the three conditions SARS-CoV-1, MERS, Ebola, influenza, SARS-CoV-2

Subgroup Analysis

For each systematic review we will examine to see if the effect differs in those with mild, moderate or severe disease with the a priori hypothesis that larger effects with steroids will be see in those with more severe disease. Categorization may depend on what is specified in the study reports.

Quality of evidence

We will use the GRADE approach to assess the quality of evidence. Randomised controlled trials start as high quality and observational studies start as low quality.

Evidence Summary

We will summarize the evidence both narratively and in GRADE evidence profiles.

Group team

We have an interdisciplinary team for conducting this systematic review

Name	Role
Niveditha	Systematic reviewer
Zhikang Ye	Systematic reviewer
Borna	Systematic reviewer
Yingqi	Systematic reviewer
Fang Fang	Systematic reviewer
Gordon Guyatt	Methodologist

Timeline

We will finish this systematic review before March 21st

Study selection	March 4 to 10
Data extraction and risk of bias	March 11 to 15
Statistical analysis and GRADE assessment	March 16 to 17
Interpreting results and writing manuscript	March 18 to April 21

Funding

There is no funding for this systematic review.

References

1. Zhang L, Liu Y. Potential Interventions for Novel Coronavirus in China: A Systematic Review. J Med Virol. 2020.
2. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, Cleary P, Khaw FM, Lim WS, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. J Infect Dis. 2015;211(1):80-90.
3. Lee JS, Adhikari NKJ, Kwon HY, Teo K, Siemieniuk R, Lamontagne F, et al. Anti-Ebola therapy for patients with Ebola virus disease: a systematic review. BMC Infect Dis. 2019;19(1):376.
4. Guyatt GH, Busse JW. Modification of Cochrane Tool to assess risk of bias in randomized trials.
5. Guyatt, GH, Busse J, Methods Commentary: Risk of Bias in Cohort Studies. https://www.evidencepartners.com/resources/methodological-resources/risk-of-bias-in-cohort-studies/.

Section 2
Search Strategy and search results

Summary of search and strategy convalescent plasma

March 26th 2020

MEDLINE 459
EMBASE 586
Central 26
PubMed 94
MedRxiv (77)
Chinese databases (103)

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Search Strategy:
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1 hemorrhagic fever, ebola/ or marburg virus disease/ (5545)
2 (EVD and ebola).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1025)
3 ebola virus disease.mp. (2026)
4 Ebola hemorrhagic fever.mp. (244)
5 (ebola adj5 (case* or patient* or treatment* or outcome* or fatality or mortality)).mp. (1341)
6 exp Coronavirus/ (11168)
7 exp Coronavirus Infections/ (9433)
8 (coronavir* or coronovir* or SARS or MERS or MERS-COV or SARS-COV or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019-nCOV or COVID-19).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (22997)
9 exp Influenza, Human/ (48134)
10 exp influenzavirus a/ or influenza a virus/ or exp influenzavirus b/ (44034)
11 (influenza or flu).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (114454)
12 or/1-11 (143683)
13 (convales* and (plasma or serum or serotherap)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (3548)
14 (convales* and (blood and product*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (366)
15 Hyper-immun*.mp. (461)
16 (convales* and immunoglobulin*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1501)
17 (convales* and hyperimmun*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (133)
18 or/13-17 (4866)
19 12 and 18 (459)

EMBASE

Database: Embase <1974 to 2020 March 05>
Search Strategy:
---
1 exp coronavirinae/ (10717)
2 exp Coronavirus infection/ (10970)
3 (coronavir* or coronovir* or SARS or MERS or MERS-COV or SARS-COV or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019-nCOV or COVID-19).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (28173)
4 or/1-3 (32399)
5 Ebola hemorrhagic fever/ (5589)
6 filovirus infection/ or marburg hemorrhagic fever/ (505)
7 (EVD and ebola).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (1247)
8 ebola virus disease.mp. (2334)
9 hemorrhagic fever, ebola.mp. (1040)
10 (ebola adj5 (case* or patient* or treatment* or outcome*)).mp. (1595)
11 or/5-10 (7546)
12 exp influenza A/ or exp influenza/ or exp influenza B/ (83541)
13 (influenza or flu).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (159856)
14 or/1-13 (193747)
15 (convales* and (plasma or serum or serotherap or hyperimmun* or immunoglobulin*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (7498)
16 (convales* and (blood and product*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (785)
17 15 or 16 (7876)
18 14 and 17 (586)

Cochrane
Search Name: COVID
Date Run: 07/03/2020 03:51:52
Comment:

ID Search Hits
#1 MeSH descriptor: [Coronavirus] explode all trees 11
#2 MeSH descriptor: [Coronavirus Infections] explode all trees 12
#3 ((coronavir* or coronovir* or SARS or MERS or "MERS-COV" or "SARS-COV" or "SARS-COV-2" or COV or NCOV or "2019nCOV" or "2019-nCOV" or "COVID-19")):ti,ab,kw (Word variations have been searched) 1247
#4 #1 or #2 or #3 1247
#5 MeSH descriptor: [Ebolavirus] explode all trees 25
#6 MeSH descriptor: [Hemorrhagic Fever, Ebola] explode all trees 32
#7 EVD and ebola 36
#8 ebola virus disease 106
#9 Ebola hemorrhagic fever 145
#10 (ebola NEAR/5 (case* or patient* or treatment* or outcome* or fatality or mortality)) 73
#11 #5 or #6 or #7 or #8 or #9 or #10 193
#12 MeSH descriptor: [Influenza, Human] explode all trees 2595
#13 MeSH descriptor: [Influenza A virus] explode all trees 836

#14 MeSH descriptor: [Influenza B virus] explode all trees 270
#15 influenza or flu 9757
#16 convales* and (plasma or serum or serothaerp* or hyperimmun* or immunoglob*) 329
#17 convales* and (blood and product*)58
#18 #16 or #17 356
#19 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 11097
#20 #18 and #19 in Trials 26

PubMed 94
Search (((virus or viral))) AND ((((convales* and (plasma OR serum OR serotherapy OR hyperimmun* OR immunoglobulin*)))) AND (((publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb] OR pubstatusaheadofprint)))) Sort by: PublicationDate 94

April 19, 2020

MEDLINE
Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Search Strategy:

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1 hemorrhagic fever, ebola/ or marburg virus disease/ (5602)
2 (EVD and ebola).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1046)
3 ebola virus disease.mp. (2071)
4 Ebola hemorrhagic fever.mp. (245)
5 (ebola adj5 (case* or patient* or treatment* or outcome* or fatality or mortality)).mp. (1365)
6 exp Coronavirus/ (12243)
7 exp Coronavirus Infections/ (10626)
8 (coronavir* or coronovir* or SARS or MERS or MERS-COV or SARS-COV or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019-nCOV or COVID-19).mp. (28455)
9 exp Influenza, Human/ (48463)
10 exp influenzavirus a/ or influenza a virus/ or exp influenzavirus b/ (44279)
11 (influenza or flu).mp. (115685)
12 or/1-11 (150230)
13 (convales* and (plasma or serum or serotherap)).mp. (3584)
14 (convales* and (blood and product*)).mp. (367)
15 Hyper-immun*.mp. (464)
16 (convales* and immunoglobulin*).mp. (1510)
17 (convales* and hyperimmun*).mp. (133)
18 or/13-17 (4910)
19 12 and 18 (487)
20 limit 19 to ed=20200301-20200419 (9)

EMBASE (Ovid SP)

Database: Embase <1974 to 2020 April 17>

Search Strategy:

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1 exp coronavirinae/ (12615)
2 exp Coronavirus infection/ (11918)
3 (coronavir* or coronovir* or SARS or MERS or MERS-COV or SARS-COV or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019-nCOV or COVID-19).mp. (31767)
4 or/1-3 (36029)
5 Ebola hemorrhagic fever/ (5674)
6 filovirus infection/ or marburg hemorrhagic fever/ (508)
7 (EVD and ebola).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (1253)
8 ebola virus disease.mp. (2350)
9 hemorrhagic fever, ebola.mp. (1040)
10 (ebola adj5 (case* or patient* or treatment* or outcome*)).mp. (1606)
11 or/5-10 (7635)
12 exp influenza A/ or exp influenza/ or exp influenza B/ (84216)
13 (influenza or flu).mp. (161021)
14 or/1-13 (198417)
15 (convales* and (plasma or serum or serotherap or hyperimmun* or immunoglobulin*)).mp. (7546)
16 (convales* and (blood and product*)).mp. (793)
17 15 or 16 (7927)
18 14 and 17 (604)
19 limit 18 to em=202008-202052 (20)

Cochrane Library

Search Name: COVID
Date Run: 19/04/2020 15:28:50
Comment:

ID	Search	Hits
#1	MeSH descriptor: [Coronavirus] explode all trees	11
#2	MeSH descriptor: [Coronavirus Infections] explode all trees	38
#3	((coronavir* or coronovir* or SARS or MERS or "MERS-COV" or "SARS-COV" or "SARS-COV-2" or COV or NCOV or "2019nCOV" or "2019-nCOV" or "COVID-19")):ti,ab,kw (Word variations have been searched)	1286
#4	#1 or #2 or #3	1286
#5	MeSH descriptor: [Ebolavirus] explode all trees	27
#6	MeSH descriptor: [Hemorrhagic Fever, Ebola] explode all trees	36
#7	EVD and ebola	36
#8	ebola virus disease	105
#9	Ebola hemorrhagic fever	144
#10	(ebola NEAR/5 (case* or patient* or treatment* or outcome* or fatality or mortality))	72
#11	#5 or #6 or #7 or #8 or #9 or #10	193
#12	MeSH descriptor: [Influenza, Human] explode all trees	2606
#13	MeSH descriptor: [Influenza A virus] explode all trees	839
#14	MeSH descriptor: [Influenza B virus] explode all trees	272
#15	influenza or flu	9763
#16	convales* and (plasma or serum or serotherap* or hyperimmun* or immunoglob*)	324
#17	convales* and (blood and product*)	58
#18	#16 or #17	351

#19	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	11139
#20	#18 and #19 in Trials	25
#21	#20 with Cochrane Library publication date Between Feb 2020 and Apr 2020	0

PubMed

Recent queries in pubmed

Search	Query	Items found	Time
#10	Search ((((((virus or viral))) AND ((((convales* and (plasma OR serum OR serotherapy OR hyperimmun* OR immunoglobulin*)))) AND (((publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb] OR pubstatusaheadofprint))))))) AND ((((("2020/03/01"[Date - Publication] : "3000"[Date - Publication])) OR ("2020/03/01"[Date - Entrez] : "3000"[Date - Entrez])) OR ("2020/03/01"[Date - Create] : "3000"[Date - Create]))	24	9:41:09
#9	Search ((("2020/03/01"[Date - Publication] : "3000"[Date - Publication])) OR ("2020/03/01"[Date - Entrez] : "3000"[Date - Entrez])) OR ("2020/03/01"[Date - Create] : "3000"[Date - Create])	292215	9:40:18
#8	Search ("2020/03/01"[Date - Publication] : "3000"[Date - Publication])	251529	9:39:14
#7	Search ("2020/03/01"[Date - Entrez] : "3000"[Date - Entrez])	180237	9:39:01
#6	Search ("2020/03/01"[Date - Create] : "3000"[Date - Create])	189884	9:38:37
#1	Search ((((virus or viral))) AND ((((convales* and (plasma OR serum OR serotherapy OR hyperimmun* OR immunoglobulin*)))) AND (((publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb] OR pubstatusaheadofprint)))))	108	9:35:24

Section 3: Summary of search results by date and database

Search sources	**March 6, 2020**	**Between 6th March 6 and April 19**	**Between April 19 and April 26th**	**Summary**
International Health care databases (Medline, Embase, Pubmd for (non-indexed studies) and Cochrane Central	Medline (459) Embase (586) Pubmed (94) CENTRAL (26)	Medline (9) Embase (20) Pubmed (24) Central (0)	Pubmed (9)	**Total=1227** Duplicate removed with end note=305 Duplicates with Covidence=107 **Total screened removal of duplicates= 815** **Full text =79**
Non peer reviewed sources (international)	medRxiv (77) upto March11, 2020	Not done	medrXiv (170) upto April 26 2020	**Total 170** **FT=4**
Chinese databases CNKI WanFang CQVIP Sinomed Chinaxiv	Not done	CNKI (103) WanFang (0) CQVIP (0) Sinomed (0) 24 March, 2020 and updated on 19th April	Chinaxiv (11) upto April 25	**Total=114** **FT=0**
Total screened				**815+170+114=1099**

*** From cross references full text=6**

Total searched=1151
Total screened=1099
Total FT=89
Total extracted=6