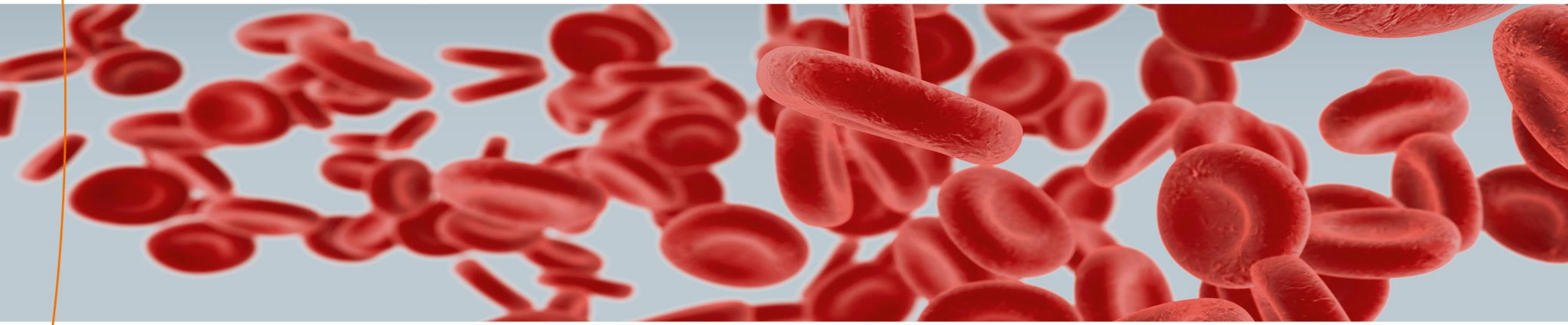
Gebruik van convalescent plasma: effectief voor nu en voor toekomstige pandemieen?



Cynthia So-Osman, MD, PhD, M Sc Epid

Sanquin Bloedbank en Erasmus MC

Sanquin
Blood Bank

Format disclosure-slide voor sprekers op nascholingsbijeenkomsten

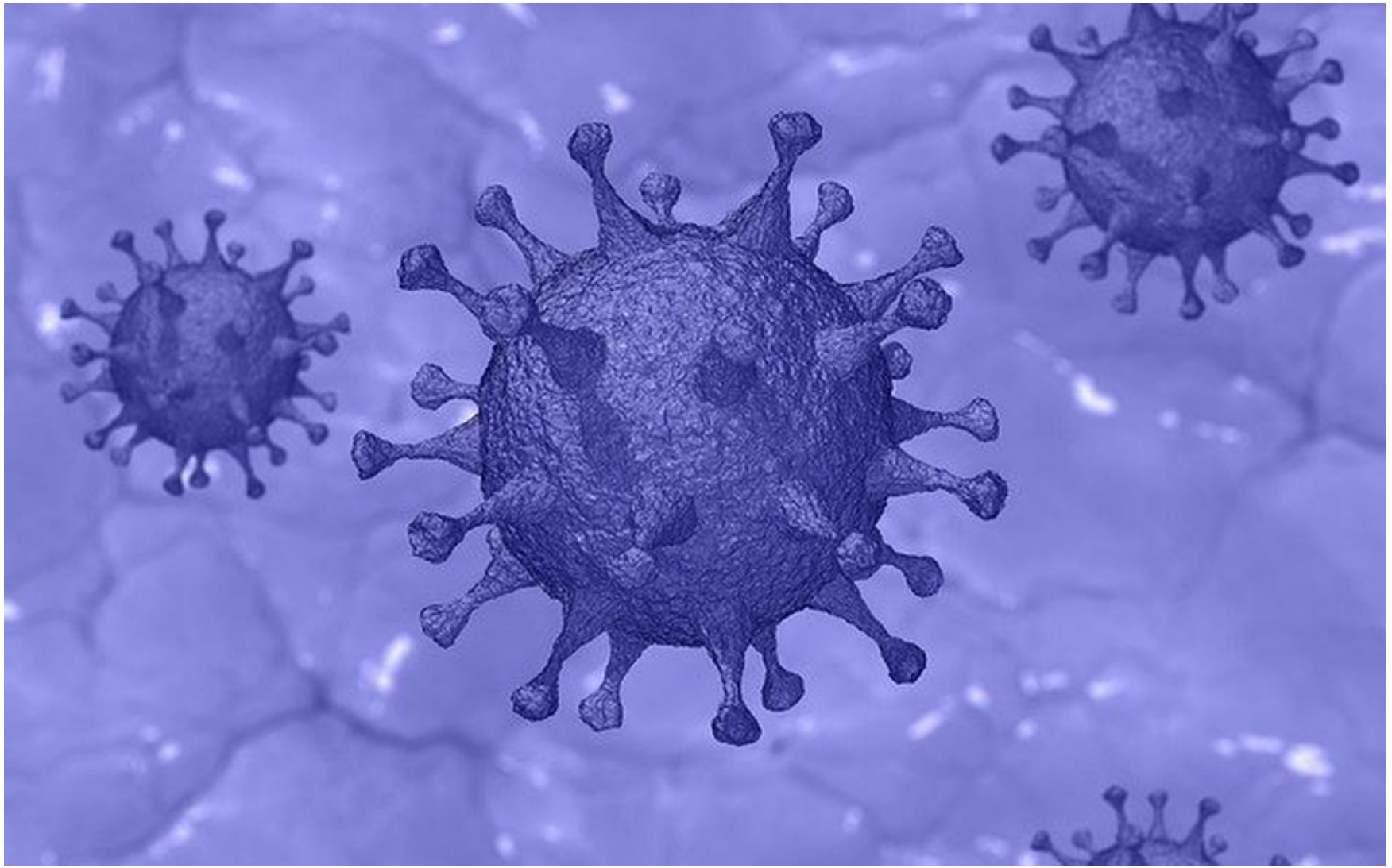
Disclosure belangen spreker	
Geen (potentiële) belangenverstrengeling	Ik heb geen potentiele belangenverstrengeling
Voor bijeenkomst mogelijk relevante relaties[1]	**Bedrijfsnamen**
• Sponsoring of onderzoeksgeld[2] • Honorarium of andere (financiële) vergoeding[3] • Aandeelhouder[4] • Andere relatie, namelijk …[5]	• • • •

Inhoud

- Overzicht wetenschappelijk bewijs van de werking en veiligheid van convalescentenplasma en hyperimmune Immunoglobulines
- Focus op specifieke patiënten subgroepen
- Wat zit er nog in de pijplijn ?
- Conclusies (effectief voor toekomstige pandemieen?)

Sanquin
Blood Bank

De COVID-19 pandemie



Convalescent plasma

- SARS-CoV1 (2003)
- Influenza A H1N1 (2009)
- MERS (2012)
- COVID-19 (CCP) (2020)

Types of antibody therapy

	CCP	Hyperimmune Serum (Polyclonal IgG)	Monoclonal Antibodies
Speed of access	Weeks (as soon as convalescents appear)	>1 year	>1 year
Safety issues	Safe (pathogen inactivation, possible plasma protein allergies)	Safe (solvent/detergent, but ABO-incompatible)	Extremely safe (recombinant technology)
Potency	Very high (high PRNT titer; includes neutralizing IgA and IgM, and factors other than antibodies)	High (no IgA; less IgG_3)	High (nanomolar IC_{50}) Very high for Ab cocktails
Cost	€	€€	€€€
Logistics	+2–+8°C (if fresh) or <−25°C (if frozen); i.v.	+2–+8°C; s.c./i.v.	+2–+8°C; s.c./i.v.
Scalability	Not easily scalable	Easily scalable	Very easily scalable

PRNT, plaque reduction neutralization test.

What is the evidence telling us?

Guidance documents from:

- WHO
- FDA
- ISBT
- AABB
- ……

Together with loads of papers (published or unpublished)

medRxiv

THE PREPRINT SERVER FOR HEALTH SCIENCES

FDA NEWS RELEASE

FDA Issues Emergency Use Authorization for Convalescent Plasma as Potential Promising COVID–19 Treatment, Another Achievement in Administration's Fight Against Pandemic

For Immediate Release: August 23, 2020

VoxSanguinis
The International Journal of Transfusion Medicine
ISBT International Society of Blood Transfusion
Vox Sanguinis (2020)

ORIGINAL PAPER

DOI: 10.1111/vox.12970

Guidance for the procurement of COVID-19 convalescent plasma: differences between high- and low-middle-income countries

Evan M. Bloch,[1,†] Ruchika Goel,[1,2,†] Silvano Wendel,[3] Thierry Burnouf,[4,5] Arwa Z. Al-Riyami,[6] Ai Leen Ang,[7] Vincenzo DeAngelis,[8] Larry J. Dumont,[9,10,11] Kevin Land,[12,13] Cheuk-kwong Lee,[14,15] Adaeze Oreh,[16] Gopal Patidar,[17] Steven L. Spitalnik,[18] Marion Vermeulen,[19] Salwa Hindawi,[20] Karin Van den Berg,[19] Pierre Tiberghien,[21] Hans Vrielink,[22] Pampee Young,[23] Dana Devine[24,25,†] & Cynthia So – Osman[22,26,†]

VoxSanguinis
The International Journal of Transfusion Medicine
ISBT International Society of Blood Transfusion
Vox Sanguinis (2020)

ORIGINAL PAPER

DOI: 10.1111/vox.12973

Clinical use of Convalescent Plasma in the COVID-19 pandemic: a transfusion-focussed gap analysis with recommendations for future research priorities

Arwa Z. Al-Riyami,[1] Richard Schäfer,[2] Karin van den Berg,[3,4] Evan M. Bloch,[5] Lise J. Estcourt,[6] Ruchika Goel,[7,8] Salwa Hindawi,[9] Cassandra D. Josephson,[10,11] Kevin Land,[12,13] Zoe K. McQuilten,[14,15] Steven L. Spitalnik,[16] Erica M. Wood,[14,15] Dana V. Devine[17,18] & Cynthia So-Osman[19,20]

VoxSanguinis
The International Journal of Transfusion Medicine
ISBT International Society of Blood Transfusion
Vox Sanguinis (2021)

ORIGINAL PAPER

DOI: 10.1111/vox.13067

Understanding the role of therapeutic plasma exchange in COVID-19: preliminary guidance and practices

Gopal K. Patidar,[1] Kevin J. Land,[2,3] Hans
Steven L. Spitalnik,[9] Yashaswi Dhiman,[1]

VoxSanguinis
The International Journal of Transfusion Medicine
ISBT International Society of Blood Transfusion
Vox Sanguinis (2021)

ORIGINAL PAPER

DOI: 10.1111/vox.13096

Lessons learned in the collection of convalescent plasma during the COVID-19 pandemic

Silvano Wendel,[1] Kevin Land,[2,3] Da

VoxSanguinis
The International Journal of Transfusion Medicine
ISBT International Society of Blood Transfusion
Vox Sanguinis (2021)

INTERNATIONAL FORUM

DOI: 10.1111/vox.13114

International Forum on the Collection and Use of COVID-19 Convalescent Plasma: Responses

Arwa Z. Al-Riyami, Thierry Burnouf, Mark Yazer, Darrell Triulzi, Levent Tufan Kumaş, Levent Sağdur, Nil Banu Pelit, Renée Bazin, Salwa I. Hindawi, Maha A. Badawi, Gopal K. Patidar, Hem Chandra Pandey, Rahul Chaurasia, Roberta Maria Fachini, Patrícia Scuracchio, Silvano Wendel, Ai Leen Ang, Kiat Hoe Ong, Pampee Young, Jarkko Ihalainen, Antti Vierikko, Yan Qiu, Ru Yang, Hua Xu, Naomi Rahimi-Levene, Eilat Shinar, Marina Izak, Carlos Alberto Gonzalez, David Martin Ferrari, Paula Verónica Cini, Robby Nur Aditya, Ratti Ram Sharma, Suchet Sachdev, Rekha Hans, Divjot Singh Lamba, Lise Sofie H. Nissen-Meyer, Dana V. Devine, Cheuk Kwong Lee, Jennifer Nga-Sze Leung, Ivan Fan Ngai Hung, Pierre Tiberghien, Pierre Gallian, Pascal Morel, Khuloud Al Maamari, Zaid Al-Hinai, Hans Vrielink, Cynthia So-Osman, Vincenzo De Angelis, Pierluigi Berti, Angelo Ostuni, Giuseppe Marano, Michel Toungouz Nevessignsky, Magdy El Ekiaby, James Daly, Veronica Hoad, Sinyoung Kim, Karin van den Berg, Marion Vermeulen, Tanya Nadia Glatt, Richard Schäfer, Rita Reik, Richard Gammon, Melissa Lopez, Lise Estcourt, Sheila MacLennan, David Roberts, Vernon Louw & Nancy Dunbar

VoxSanguinis
The International Journal of Transfusion Medicine
ISBT International Society of Blood Transfusion
Vox Sanguinis (2021)

REVIEW

DOI: 10.1111/vox.13076

ABO blood group and COVID-19: a review on behalf of the ISBT COVID-19 working group

Ruchika Goel,[1,2,†] Evan M. Bloch,[1,†] France Pirenne,[3] Arwa Z. Al-Riyami,[4] Elizabeth Crowe,[1] Laetitia Dau,[1] Kevin Land,[5,6] Mary Townsend,[5] Thachil Jecko,[7] Naomi Rahimi-Levene,[8] Gopal Patidar,[9] Cassandra D. Josephson,[10] Satyam Arora,[11] Marion Vermeulen,[12] Hans Vrielink,[13] Celina Montemayor,[14] Adaeze Oreh,[15] Salwa Hindawi,[16] Karin van den Berg,[17,18] Katherine Serrano,[19,20] Cynthia So – Osman,[21,22] Erica Wood,[23] Dana V. Devine,[19,20,†] Steven L. Spitalnik[24,†] & the ISBT COVID-19 Working Group

Vox Sanguinis:

WILEY

Top Cited Article 2020-2021

Congratulations to:

Arwa Z. Al-Riyami

whose paper has been recognized as a **top cited** paper in:

VOX SANGUINIS

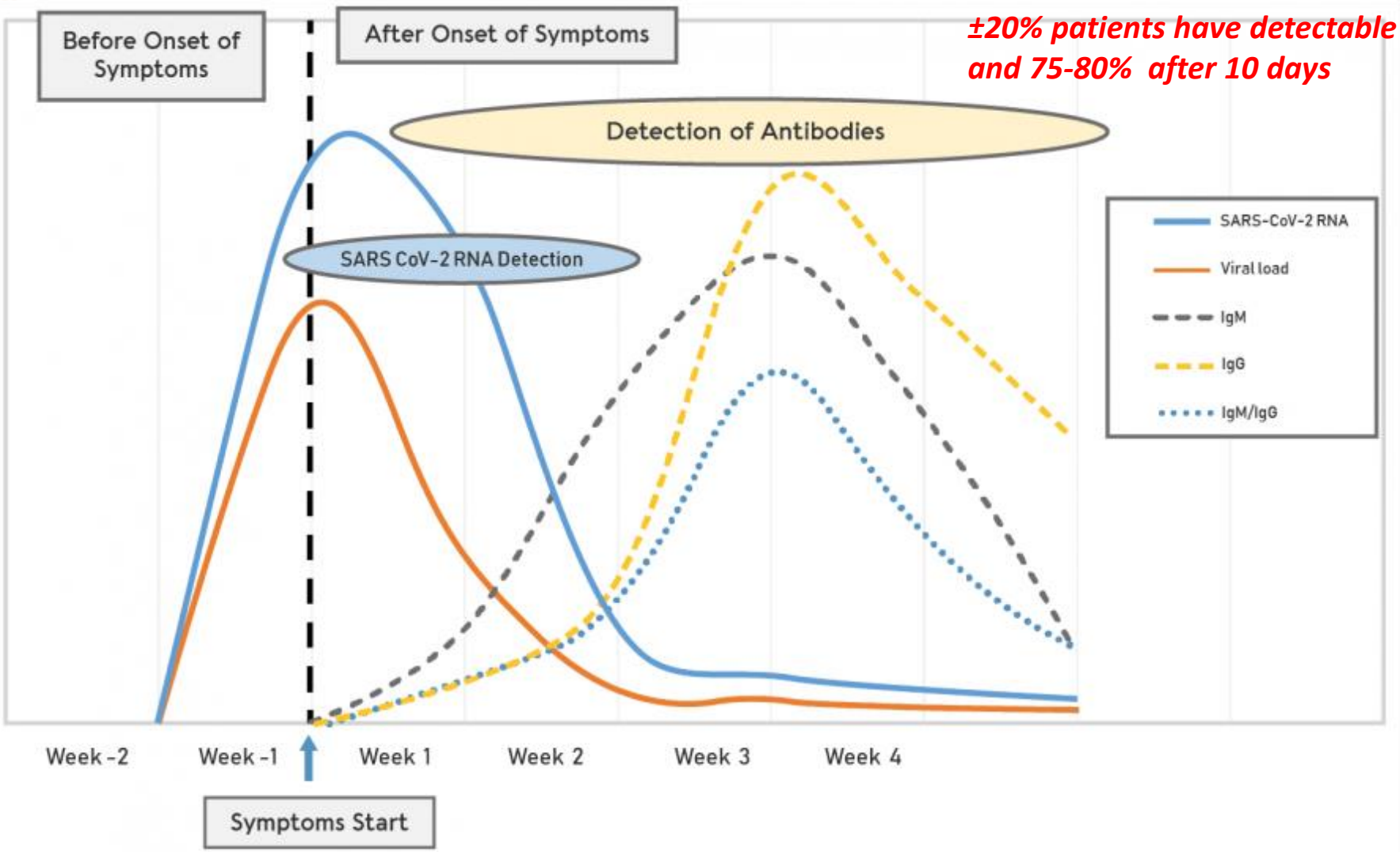
ABO blood group and COVID-19: a review on behalf of the ISBT COVID-19 working group

Clinical use of Convalescent Plasma in the COVID-19 pandemic: a transfusion-focussed gap analysis with recommendations for future research priorities

Efficacy of CCP

The CONCOVID study

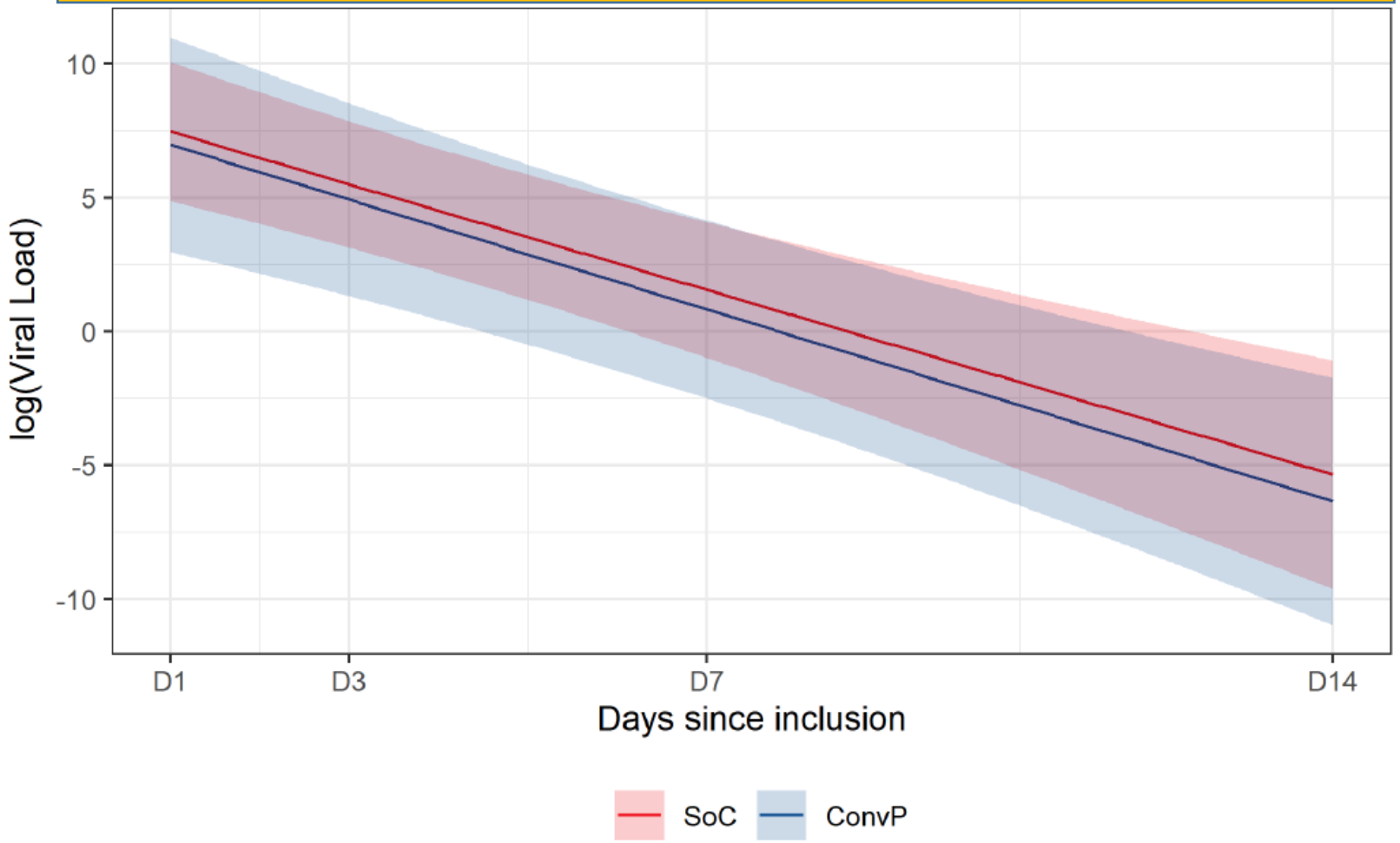
±20% patients have detectable ab after 7 days and 75-80% after 10 days



Mean of 10 days of COVID-19 symptoms (IQR 6 – 15)
& 2 days in hospital (IQR 1 – 3 days)

The CONCOVID study

No difference in viral clearance



Effective when high titred and early

- FDA Letter Of Authorization (Feb 2021)

Therefore, this EUA authorizes only the use of high titer COVID-19 convalescent plasma, for the treatment of hospitalized patients with COVID-19, early in the course of disease. The use of low titer COVID-19 convalescent plasma is not authorized under this EUA.

Cochrane living systematic reviews

- **Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a rapid review.** Valk SJ, Piechotta V, Chai KL, Doree C, Monsef I, Wood EM, Lamikanra A, Kimber C, McQuilten Z, So-Osman C, Estcourt LJ, Skoetz N. **Cochrane Database Syst Rev.** 2020 **May** 14;5(5):CD013600. doi: 10.1002/14651858.
- **Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review.** Piechotta V, Chai KL, Valk SJ, Doree C, Monsef I, Wood EM, Lamikanra A, Kimber C, McQuilten Z, So-Osman C, Estcourt LJ, Skoetz N. **Cochrane Database Syst Rev**. 2020 **Jul** 10;7(7):CD013600. doi: 10.1002/14651858.
- **Convalescent plasma and hyperimmune immunoglobulin to prevent infection with SARS-CoV-2.** Sarah J Valk, Vanessa Piechotta, Catherine Kimber, Khai Li Chai, Nicole Skoetz et al. **Cochrane database of Syst Rev.** 2021 **Jan**. CD013802 doi: 10.1002/14651858.
- **Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review.** Piechotta V, Iannizzi C, Chai KL, Valk SJ, Kimber C, Dorando E, Monsef I, Wood EM, Lamikanra AA, Roberts DJ, McQuilten Z, So-Osman C, Estcourt LJ, Skoetz N.Piechotta V, et al. **Cochrane Database Syst Rev**. 2021 **May** 20;5(5):CD013600. doi: 10.1002/14651858.CD013600.pub4 *(updated)*

Cochrane Library

Cochrane Database of Systematic Reviews

Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review (Review)

Piechotta V, Iannizzi C, Chai KL, Valk SJ, Kimber C, Dorando E, Monsef I, Wood EM, Lamikanra AA, Roberts DJ, McQuilten Z, So-Osman C, Estcourt LJ, Skoetz N

Cochrane Database of Systematic Reviews 2021, Issue 5. Art. No.: CD013600.
DOI: 10.1002/14651858.CD013600.pub4.

We found 13 studies with 48,509 participants that investigated convalescent plasma. All but one of the studies included participants with moderate to severe COVID-19. We did not find any studies that investigated hyperimmune immunoglobulin. Studies mainly took place in hospitals, in countries all over the world.

Key messages

- We are very confident that convalescent plasma has no benefits for the treatment of people with moderate to severe COVID-19.
- We are uncertain about the effects of convalescent plasma for treating people with mild COVID-19 or who have no symptoms.
- We found about 130 ongoing, unpublished and recently published studies. We will update our review with evidence from these studies as soon as possible. New evidence may answer our remaining questions.

FDA update dec 2021

On December 28, 2021, having concluded that revising this EUA is appropriate to protect the public health or safety under Section 564(g)(2)(C) of the Act (21 U.S.C. § 360bbb-3(g)(2)(C)), FDA is again reissuing the March 9, 2021 letter of authorization in its entirety with revisions to: limit the authorization to the use of COVID-19 convalescent plasma with high titers of anti-SARS-CoV-2 antibodies for the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment; revise acceptable tests and increase

Geen uniformiteit in titers…..

Appendix A: Table of Tests Acceptable for Use in the Manufacture of COVID-19 Convalescent Plasma with High Titers of Anti-SARS-CoV-2 Antibodies

Tests Acceptable for Use in the Manufacture of COVID-19 Convalescent Plasma with High Titers of Anti-SARS-CoV-2 Antibodies			
Manufacturer (listed alphabetically)	**Assay**	**Previous Qualifying Result**	**Revised Qualifying Result**
Abbott	AdviseDx SARSCoV-2 IgG II (ARCHITECT and Alinity i)	≥ 840 AU/mL	≥ 1280 AU/mL
Diasorin	LIAISON SARS-CoV-2 TrimericS IgG	≥ 52 AU/mL	≥ 87 AU/mL
GenScript	cPass SARS-CoV-2 Neutralization Antibody Detection Kit	Inhibition ≥ 68%	Inhibition ≥ 80%
Kantaro	COVID-SeroKlir, Kantaro Semi-Quantitative SARS-CoV-2 IgG Antibody Kit	Spike ELISA > 47 AU/mL	Spike ELISA > 69 AU/mL
Ortho	VITROS Anti-SARS-CoV-2 IgG Quantitative Reagent Pack	N/A	>200 BAU/mL
Roche	Elecsys Anti-SARS-CoV-2 S	≥ 132 U/mL	> 210 U/mL

Clinical Practice Guidelines from the Association for the Advancement of Blood and Biotherapies (AABB): COVID-19 Convalescent Plasma

Recommendation 1 (Outpatient): AABB suggests CCP transfusion in addition to the usual standard of care for outpatients with COVID-19 who are at high-risk of disease progression (weak recommendation, moderate certainty evidence).

Recommendation 2 (Inpatient): AABB recommends against CCP transfusion for unselected hospitalized individuals with moderate or severe disease (strong recommendation, high certainty evidence). This recommendation does not apply to immunosuppressed patients or those who lack antibodies against SARS-CoV-2.

Recommendation 3 (Inpatient): AABB suggests CCP transfusion in addition to the usual standard of care for hospitalized patients with COVID-19 who do not have SARS-CoV-2 antibodies detected at admission (weak recommendation, low certainty evidence).

Recommendation 4 (Inpatient): AABB suggests CCP transfusion in addition to the usual standard of care for hospitalized patients with COVID-19 and pre-existing immunosuppression (weak recommendation, low certainty evidence).

Recommendation 5 (Prophylaxis): AABB suggests against prophylactic CCP transfusion for uninfected individuals with close contact exposure to a person with COVID-19 (weak recommendation, low certainty evidence).

Good clinical practice statement: CCP is most effective when transfused with high neutralizing titers to infected patients early after symptom onset.

New data since the last Cochrane update May 2021

(17 March 2021 - 03 March 2022)

1) Outpatients, 3 RCTs with 1,963 participants:

- 1 new RCT (CCP vs. Placebo/standard of care alone)
- 2 new RCTs (CCP vs. Standard plasma)

2) Inpatients, 23 RCTs with 18,442 participants:

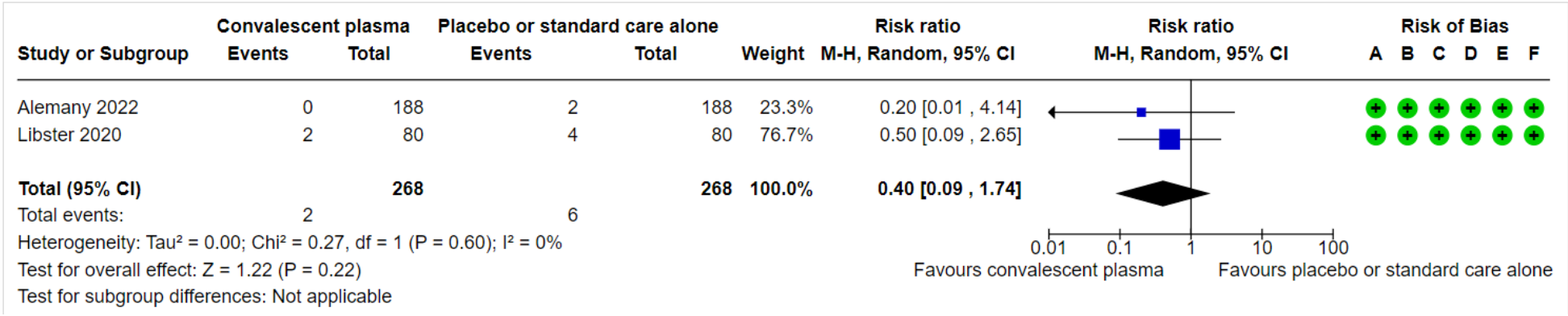
- 5 new full journal publication → former preprints
- 14 new RCTs (CCP vs. Placebo/standard of care alone)
- 3 new RCTs (CCP vs. Standard plasma)
- 1 new RCT (CCP vs. Human immunoglobulin)

3) Important subgroup results for inpatients:

- 6 RCTs with 12,592 participants for **SARS-CoV-2 antibody serostatus at baseline** (antibody-negative vs. antibody positive)
- 2 RCTs with 2,124 participants for **Immune status** (immunodeficiency vs. no immunodeficiency)

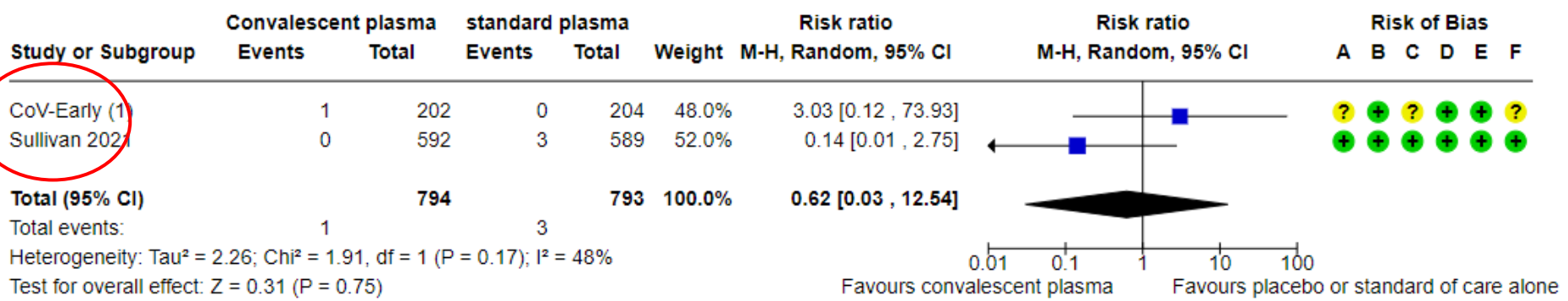
4) New review on post-exposure prophylaxis: **1 RCT with 168 participants** (CCP vs. standard plasma)

a) Outpatient, CP vs. placebo/SOC; mortality at day 28



	Outpatient, CP vs. SoC/placebo
Outcome	Mortality by day 28
GRADE	⊕⊕◯◯ Low[1, 2]
Notes	1 downgraded two levels for very serious imprecision, low number of participants/events and wide confidence interval

b) Outpatient, CP vs. standard plasma; mortality at day 28

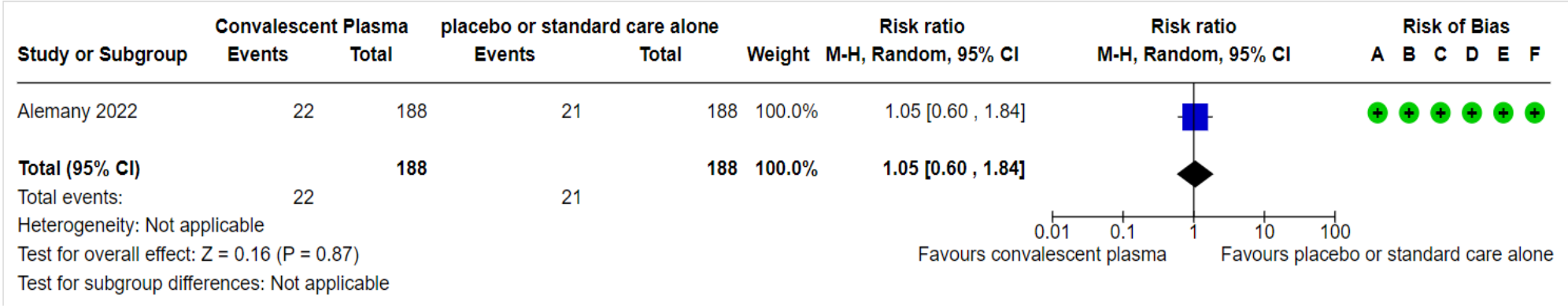


Footnotes

(1) Study is not published yet, data obtained from pooled analyses of published study

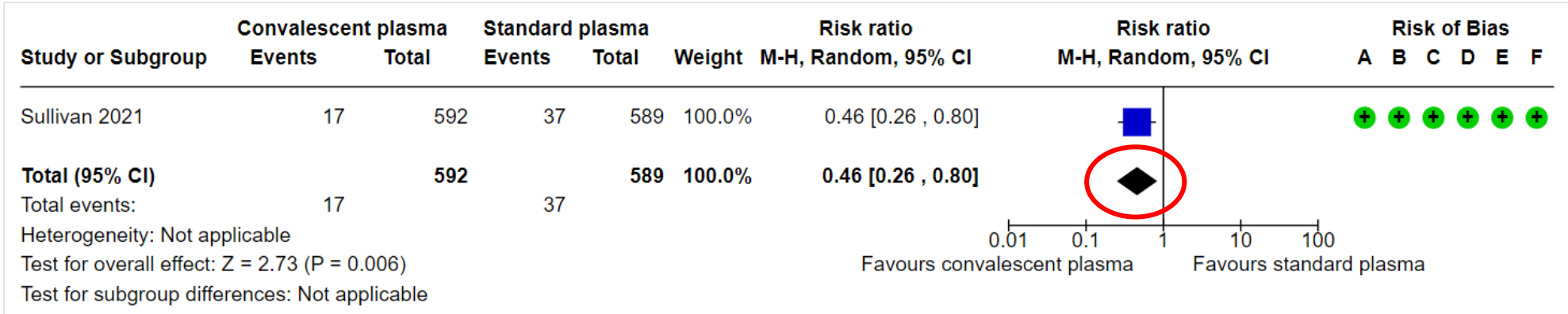
	Outpatient, CP vs. standard plasma
Outcome	Mortality by day 28
GRADE	⊕◯◯◯ Very low[1, 2]
Notes	1 downgraded two levels for very serious imprecision, low number of participants/events and wide confidence interval 2 downgraded one level for serious inconsistency, effects in opposite directions

a) Outpatient, CP vs. placebo/SOC, admission to hospital/death within 28 days



	Outpatient, CP vs. SoC/placebo
Outcome	Hospitalisation/ Mortality by day 28
GRADE	⊕⊕◯◯ Low[1, 2]
Notes	1 downgraded two levels for very serious imprecision, low number of participants/events and wide confidence interval

b) Outpatient, CP vs. standard plasma, admission to hospital/death within 28 days



	Outpatient, CP vs. Standard plasma
Outcome	Hospitalisation/ Mortality by day 28
GRADE	⊕⊕⊕◯ Moderate[1]
Notes	1 downgraded one level for serious imprecision, low number of events

CoV-Early study

Early Convalescent Plasma Therapy for high-risk patients with COVID-19 in primary care

PROTOCOL

Version	:	**3.0**
Date	:	**5 November 2020**
Principal investigator EMC	:	**Bart Rijnders and Casper Rokx**
Principal investigator LUMC	:	**Jaap Jan Zwaginga**
Sponsor	:	**Erasmus MC**
Funder	:	**ZONMW**
Clinical research organization	:	**HOVON Data Center**
ID	:	**NL74972.078.20**
Clinicaltrials.gov	:	**NCT04589949**

Age 70 or older OR Age 50-69 + one of the following risk factors

- Obesity with BMI 35 or higher
- Born as a male person
- Cardiac or pulmonary disease (e.g. atrial fibrillation, CAD, heart failure, COPD, asthma)
- History of neurological disease (e.g. stroke or any other chronic debilitating neurological disease)
- Diabetes for which medical therapy is needed
- Chronic kidney disease with GFR <60 ml/min
- Reumatic disease (e.g. reumatoid arthritis, Systemic lupus erythematosus, psoriatric artritis)
- Immunodeficiency (e.g. organ or allogeneic transplantation, systemic immunosuppressive drugs)
- Cancer not in complete remission for >1 year (excluding baso -or spinocellular skin cancers)
- Untreated HIV and CD4 T-cells <200/microliter
- Chronic liver disease (liver cirrhosis child pugh A/B/C or other disease leading to liver dysfunction)
- (CRP > 30 or SARS-CoV-2 RT-PCR Ct value <25)

Age 18-50

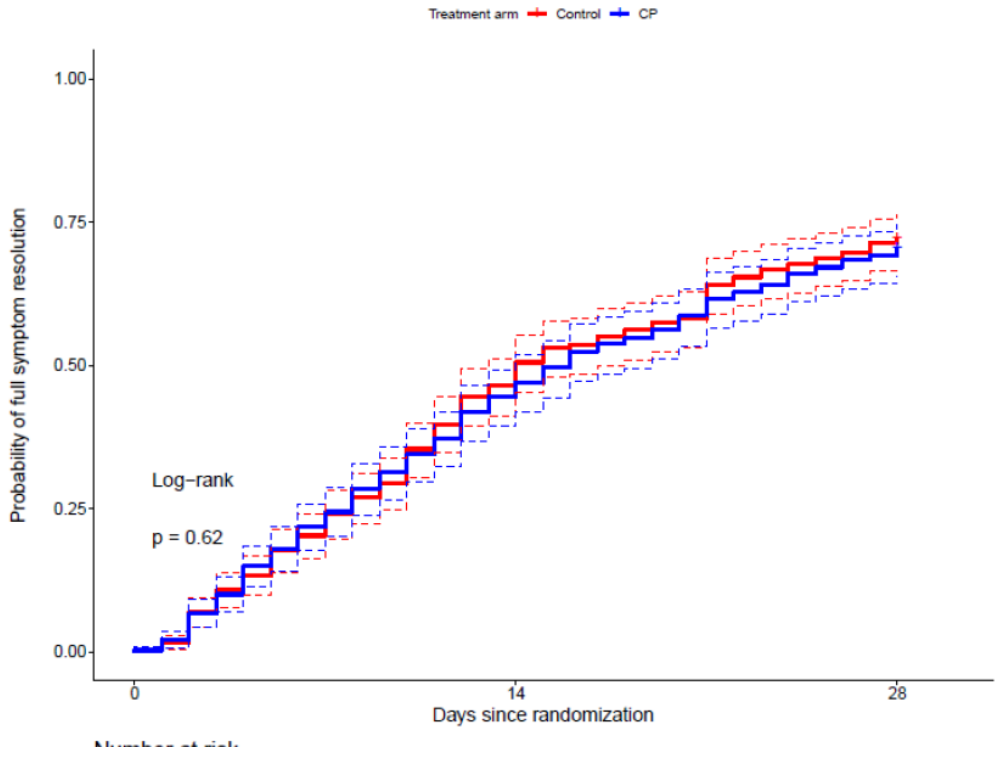
- Severely immunocompromised (inherited deficiency OR HD oral corticosteroids, transplantation)

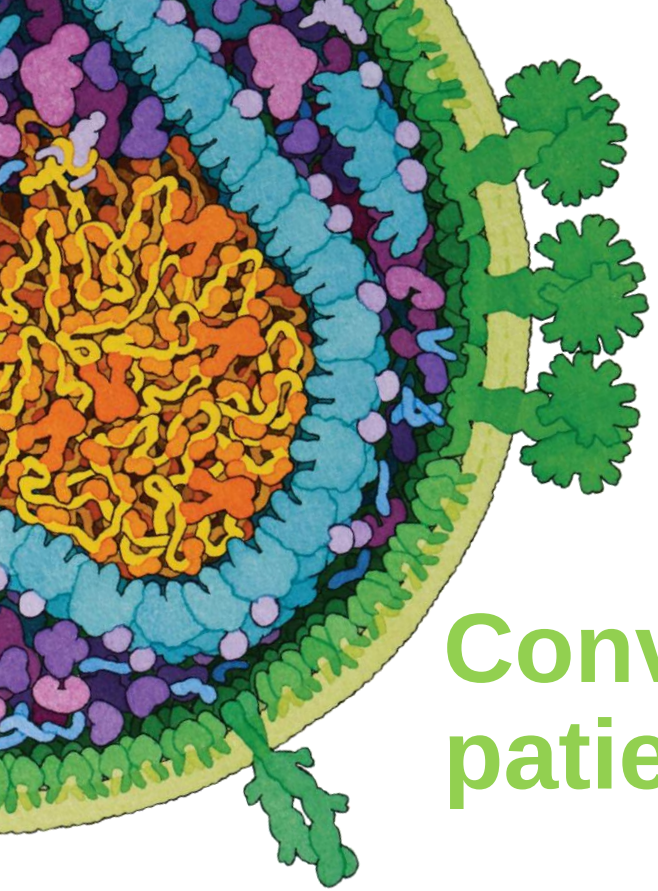
Title: Convalescent plasma for outpatients with early COVID-19

Subtitle: A pooled analysis of two randomized clinical trials

Pere Millat-Martinez, Arvind Gharbharan, …., Francis Swaneveld, Ellen van der Schoot, ……Jaap Jan Zwaginga, Bart Rijnders, for the ConV-ert, CoV-Early and COMPILEhome study groups

medRxiv 2021.11.30.21266810; doi: https://doi.org/10.1101/2021.11.30.21266810





SCIENCE SPOTLIGHT™

Convalescent plasma in B-cel depleted patients and active COVID-19

Arvind Gharbharan, MD, MSc, Carlijn C.E. Jordans, MD, MSc, Adam A. Anas, MD, PhD, Susanne Bogers, MsC, Corine H. Geurts van Kessel, MD, PhD, Casper Rokx, MD, PhD, Bart J.A. Rijnders, MD, PhD

Disclosure:

Nothing to disclose

Erasmus University Medical Centre
Department of Internal Medicine, Section of Infectious Diseases
Rotterdam, the Netherlands

CROI 2021

Patients and results:

- 23 patients: median 50 years and 26 days of illness

  Lymphoma (10), auto-immune (8), CLL (2), B-ALL (1), MS (1)
  Rituximab (19), Blinatumomab (1), Obinutuzumab (1), XLA (1), Ocrelizumab (1)
  outpatients (6), hospitalized (11), on ICU (6)

- Outcome:

  In 20/23 patients quick recovery (1-2 days)
  PCR ➡ negative in all 20 cases

blood® 12 NOVEMBER 2020 | VOLUME 136, NUMBER 20

Brief Report

CLINICAL TRIALS AND OBSERVATIONS

Convalescent plasma therapy for B-cell–depleted patients with protracted COVID-19

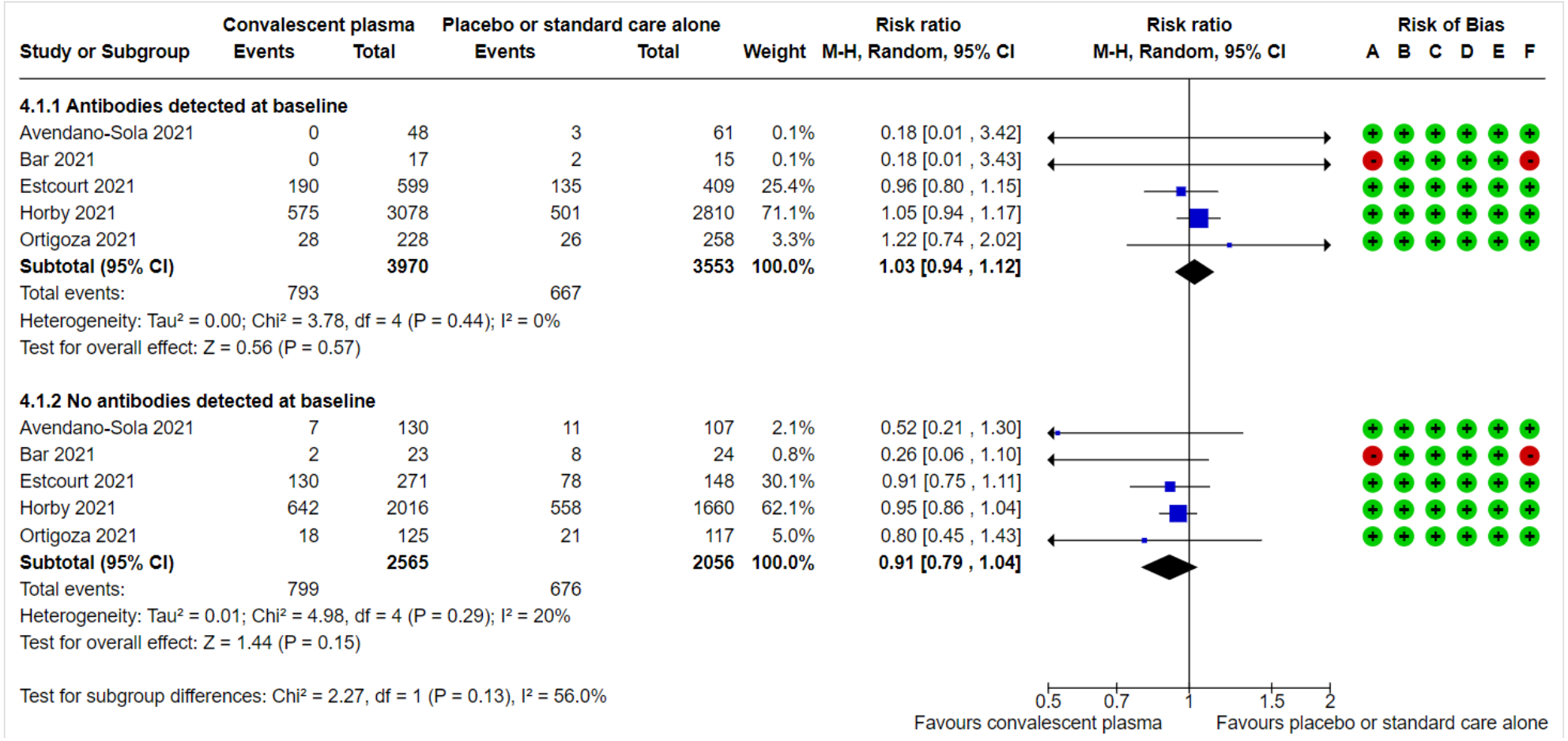
Thomas Hueso,[1,2] Cécile Pouderoux,[3] Hélène Péré,[4,5] Anne-Lise Beaumont,[6] Laure-Anne Raillon,[3] Florence Ader,[3,7] Lucienne Chatenoud,[8,9] Déborah Eshagh,[10] Tali-Anne Szwebel,[10] Martin Martinot,[11] Fabrice Camou,[12] Etienne Crickx,[13] Marc Michel,[13] Matthieu Mahevas,[13] David Boutboul,[14,15] Elie Azoulay,[16] Adrien Joseph,[16] Olivier Hermine,[17,18] Claire Rouzaud,[19] Stanislas Faguer,[20] Philippe Petua,[21] Fanny Pommeret,[22] Sébastien Clerc,[23] Benjamin Planquette,[23] Fatiha Merabet,[24] Jonathan London,[25] Valérie Zeller,[25] David Ghez,[1] David Veyer,[6,26] Amani Ouedrani,[8,9] Pierre Gallian,[27,28] Jérôme Pacanowski,[6] Arsène Mékinian,[29] Marc Garnier,[30] France Pirenne,[28,31] Pierre Tiberghien,[28,32] and Karine Lacombe[6,33]

specific SARS-CoV-2 antibody response. We report a series of 17 consecutive patients with profound B-cell lymphopenia and prolonged COVID-19 symptoms, negative immunoglobulin G (IgG)-IgM SARS-CoV-2 serology, and positive RNAemia measured by digital polymerase chain reaction who were treated with 4 units of COVID-19 convalescent plasma. Within 48 hours of transfusion, all but 1 patient experienced an improvement of clinical symptoms. The inflammatory syndrome abated within a week. Only 1 patient who needed

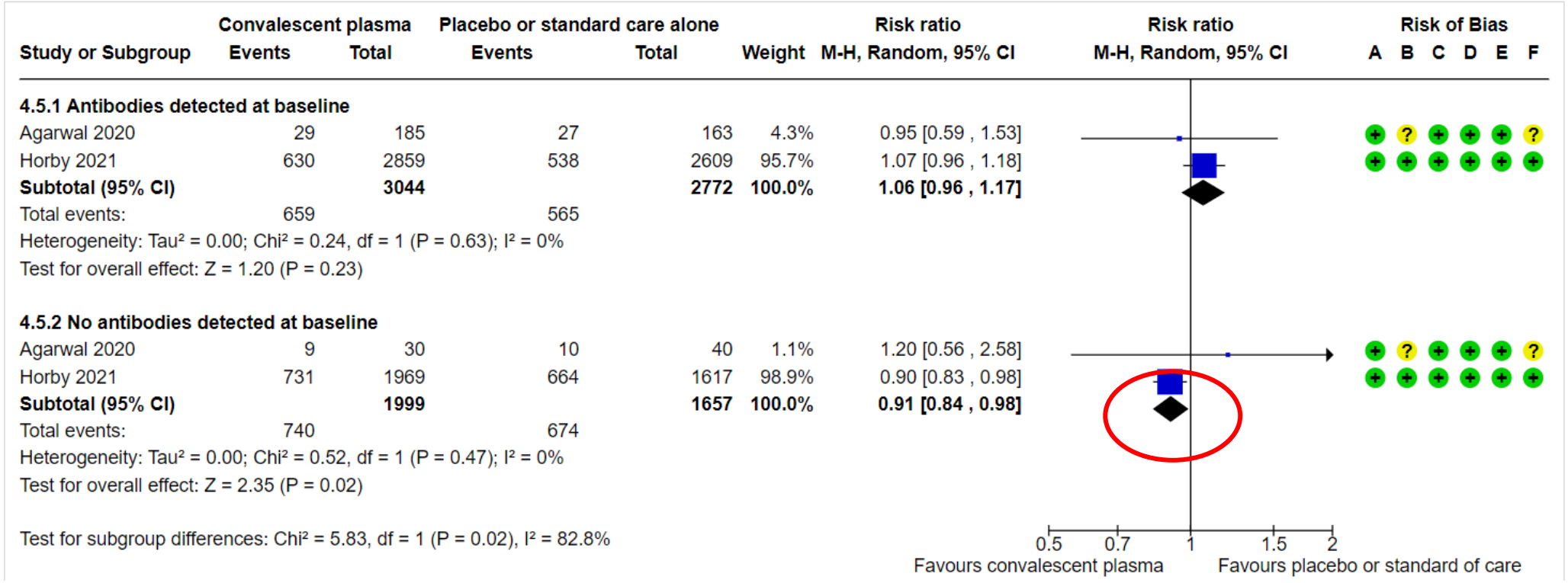
Cochrane review subgroups – in hospital

- Antibodies detected at baseline (positive vs. negative)
  - All-cause mortality at up to day 28
  - Need for invasive mechanical ventilation or death at up to day 28

Inpatient, antibodies Y/N, mortality at day 28



Inpatient, antibodies Y/N need for IMV or death by day 28



Safety of CCP

Mayo Clinic Proceedings
COVID-19 Convalescent Plasma in 20,000 Patients

Safety Update: COVID-19 Convalescent Plasma in 20,000 Hospitalized Patients

Michael J. Joyner[1#*], MD, Katelyn A. Bruno[2#], PhD, Stephen A. Klassen[1#], PhD, Katie L.

Conclusion: These updated data provide robust evidence that transfusion of convalescent plasma is safe in hospitalized patients with COVID-19, and support the notion that earlier administration of plasma within the clinical course of COVID-19 is more likely to reduce mortality.

The incidence of all serious adverse events was low; these included transfusion reactions (*n*=89; <1%), thromboembolic or thrombotic events (*n*=87; <1%), and cardiac events (*n*=680, ~3%). Notably, the vast majority of the thromboembolic or thrombotic events (*n*=55) and cardiac events (*n*=562) were judged to be unrelated to the plasma transfusion *per se*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Convalescent Plasma Antibody Levels and the Risk of Death from Covid-19

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CONCLUSIONS

Among patients hospitalized with Covid-19 who were not receiving mechanical ventilation, transfusion of plasma with higher anti–SARS-CoV-2 IgG antibody levels was associated with a lower risk of death than transfusion of plasma with lower antibody levels. (Funded by the Department of Health and Human Services and others; ClinicalTrials.gov number, NCT04338360.)

nature medicine

ARTICLES

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OPEN

Convalescent plasma for hospitalized patients with COVID-19: an open-label, randomized controlled trial

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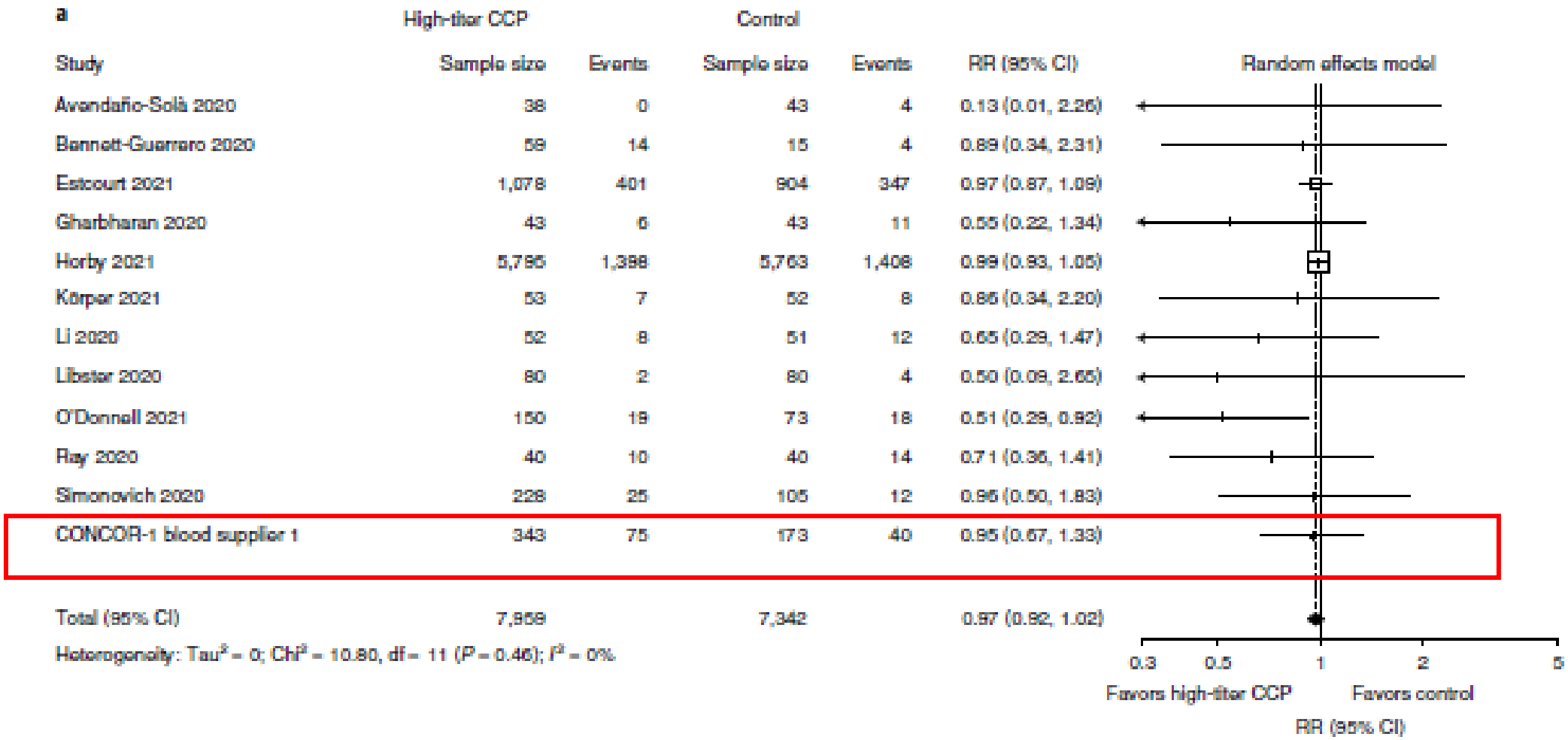
The efficacy of convalescent plasma for coronavirus disease 2019 (COVID-19) is unclear. Although most randomized controlled trials have shown negative results, uncontrolled studies have suggested that the antibody content could influence patient outcomes. We conducted an open-label, randomized controlled trial of convalescent plasma for adults with COVID-19 receiving oxygen within 12 d of respiratory symptom onset (NCT04348656). Patients were allocated 2:1 to 500 ml of convalescent plasma or standard of care. The composite primary outcome was intubation or death by 30 d. Exploratory analyses of the effect of convalescent plasma antibodies on the primary outcome was assessed by logistic regression. The trial was terminated at 78% of planned enrollment after meeting stopping criteria for futility. In total, 940 patients were randomized, and 921 patients were included in the intention-to-treat analysis. Intubation or death occurred in 199/614 (32.4%) patients in the convalescent plasma arm and 86/307 (28.0%) patients in the standard of care arm—relative risk (RR) = 1.16 (95% confidence interval (CI) 0.94–1.43, $P = 0.18$). Patients in the convalescent plasma arm had more serious adverse events (33.4% versus 26.4%; RR = 1.27, 95% CI 1.02–1.57, $P = 0.034$). The antibody content significantly modulated the therapeutic effect of convalescent plasma. In multivariate analysis, each standardized log increase in neutralization or antibody-dependent cellular cytotoxicity independently reduced the potential harmful effect of plasma (odds ratio (OR) = 0.74, 95% CI 0.57–0.95 and OR = 0.66, 95% CI 0.50–0.87, respectively), whereas IgG against the full transmembrane spike protein increased it (OR = 1.53, 95% CI 1.14–2.05). Convalescent plasma did not reduce the risk of intubation or death at 30 d in hospitalized patients with COVID-19. Transfusion of convalescent plasma with unfavorable antibody profiles could be associated with worse clinical outcomes compared to standard care.

Studies that used high titre plasma



a

Study	High-titer CCP Sample size	High-titer CCP Events	Control Sample size	Control Events	RR (95% CI)
Avendaño-Solà 2020	38	0	43	4	0.13 (0.01, 2.26)
Bennett-Guerrero 2020	59	14	15	4	0.89 (0.34, 2.31)
Estcourt 2021	1,078	401	904	347	0.97 (0.87, 1.09)
Gharbharan 2020	43	6	43	11	0.55 (0.22, 1.34)
Horby 2021	5,795	1,398	5,763	1,408	0.99 (0.93, 1.05)
Körper 2021	53	7	52	8	0.86 (0.34, 2.20)
Li 2020	52	8	51	12	0.65 (0.29, 1.47)
Libster 2020	80	2	80	4	0.50 (0.09, 2.65)
O'Donnell 2021	150	19	73	18	0.51 (0.29, 0.92)
Ray 2020	40	10	40	14	0.71 (0.36, 1.41)
Simonovich 2020	228	25	105	12	0.96 (0.50, 1.83)
CONCOR-1 blood supplier 1	343	75	173	40	0.95 (0.67, 1.33)
Total (95% CI)	7,959		7,342		0.97 (0.92, 1.02)

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 10.80$, df = 11 ($P = 0.46$); $I^2 = 0\%$

Random effects model

0.3 0.5 1 2 5

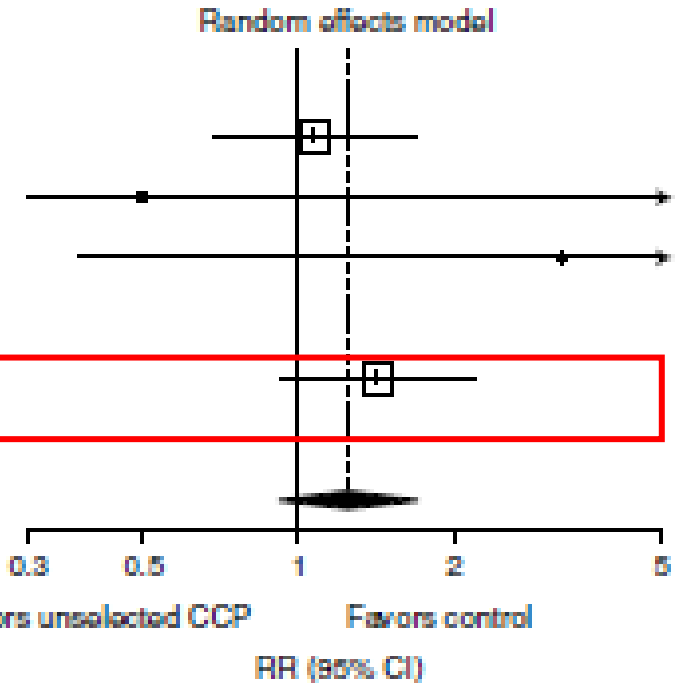
Favors high-titer CCP Favors control

RR (95% CI)

Mixed titre studies

Study	Unselected CCP Sample size	Events	Control Sample size	Events	RR (95% CI)
Agarwal 2020	235	34	229	31	1.07 (0.68, 1.68)
AlQahtani 2020	20	1	20	2	0.50 (0.05, 5.08)
Bajpai 2020	14	3	15	1	3.21 (0.38, 27.40)
Hamdy Salman 2020	15	0	15	0	
CONCOR-1 blood supplier 2/3/4	271	66	134	23	1.42 (0.93, 2.17)
Total (95% CI)	555		413		1.25 (0.92; 1.69)

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 2.15$, df = 3 ($P = 0.54$); $I^2 = 0\%$



Resultaten veiligheid en rol antilichaamprofiel

(CI) 0.94-1.43, $P = 0.18$). Patients in the convalescent plasma arm had more serious adverse events (33.4% versus 26.4%; RR = 1.27, 95% CI 1.02-1.57, $P = 0.034$). The antibody content significantly modulated the therapeutic effect of convalescent

Effect-modifying role of antibodies in convalescent plasma. The distributions of antibodies in convalescent plasma units varied by blood supplier (Fig. 4, Supplementary Table 9 and Extended Data Fig. 7); therefore, antibody analyses controlled for supplier to address possible confounding. Transfusion of convalescent plasma

4 ab profielen getest in multivariabel model

- Anti--RBD eigenschap
- Neutralisatie eigenschap

  26% reductie primaire uitkomst

  (OR 0,74; 95% CI 0,57-0,95)

- Anti-S IgG

  53% toename primaire uitkomst
  (OR 1,53; 95% CI 1,14-2,05)

- ADCC eigenschap

  34% reductie primaire uitkomst

  (OR 0,66; 95% CI 0,50-0,87)

Safety…….

- Low titre products harmful?
- Anti-S IgG harmful (unfavorable antibody profile)?

- Ab profiel zou van invloed kunnen zijn op effectiviteit convalescent plasma (kwalitatief), naast titer (kwantitatief)

Conclusies CONCOR-1 studie

- CCP does not reduce risk for intubation of death by 30 d in hospitalized pts with COVID-19
- Transfusion of CCP with unfavorable ab profiles could be associated with worse clinical outcome compared to standard care
- Low titre convalescent plasma products may be harmful

- Controle-groepen zijn van groot belang voor interpretatie van uitkomsten

Cochrane Library

Cochrane Database of Systematic Reviews

Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review (Review)

Piechotta V, Iannizzi C, Chai KL, Valk SJ, Kimber C, Dorando E, Monsef I, Wood EM, Lamikanra AA, Roberts DJ, McQuilten Z, So-Osman C, Estcourt LJ, Skoetz N

- We are uncertain whether convalescent plasma increases or reduces the risk of:
- grade 3 and 4 adverse events (RR 0.90, 95% CI 0.58 to 1.41; 4 RCTs, 905 participants; low-certainty evidence)
- serious adverse events (RR 1.24, 95% CI 0.81 to 1.90; 2 RCTs, 414 participants; low-certainty evidence).

Voorlopige conclusies CCP

- CCP not effective in hospitalized patients/late in disease (>7 days after onset)
- CCP may be effective early (< 7 days) in disease
- CCP may be effective in immunocompromised patients without abs
- CCP product is more effective when high titred
- CCP seems to be safe, but beware low titres plasma or unfavorable antibody profile!

Convalescent Plasma for Covid-19 — Making Sense of the Inconsistencies

Lise Estcourt, M.B., B.Chir., and Jeannie Callum, M.D.

NEJM May 5, 2022

Two ongoing trials may provide additional clarity regarding the use of convalescent plasma in patients with Covid-19. The COVIC-19 trial (Early High-Titre Convalescent Plasma in Clinically Vulnerable Individuals with Mild COVID-19; ClinicalTrials.gov number, NCT05271929) plans to enroll 680 outpatients in two target groups (participants who are ≥70 years of age or who are <70 years of age with coexisting conditions, and participants with immunocompromise). In the immunoglobulin domain of the REMAP-CAP trial (NCT02735707), the investigators plan to enroll hospitalized patients with immunocompromise.

Hyperimmune Immunoglobulin (H-Ig) use for COVID-19 patients

Citation: Clin Transl Sci (2020) 13, 835–837; doi:10.1111/cts.12816

COMMENTARY

Active Therapy with Passive Immunotherapy May Be Effective in the Fight against COVID-19

Christopher J. Morabito[1]* and Bagirath Gangadharan[2]

H-IG HAS THE POTENTIAL TO BE A SUSTAINABLE IMMUNOTHERAPY

SARS-CoV-2 hyperimmune globulin for severely immunocompromised patients with COVID-19: a randomised, controlled, double-blind, phase 3 trial

- Sammy Huygens, Quincy Hofsink, Inger S Nijhof, Abraham Goorhuis, Arnon P Kater, Peter AW te Boekhorst, Francis Swaneveld, Věra MJ Novotný, Susanne Bogers, Matthijs RA Welkers, Grigorios Papageorgiou, Bart J Rijnders, Jarom Heijmans

- medRxiv 2022.04.04.22273314; doi: https://doi.org/10.1101/2022.04.04.22273314

Table 2. Primary and secondary outcomes[1]

	COVIG group (n = 10)	IVIG group (n = 8)	RR (95% CI)	Fisher's exact test (*p*)
Severe course of COVID-19	2 (20)	7 (88)	*0·23 (0.06 – 0.81)*	*0.015*
Severe course of COVID-19 in seronegative patients	1/8 (13)	7/8 (88)	*0·14 (0.02 – 0.91)*	
Mortality at 28 days	0 (0)	3 (38)		
Median duration of hospitalization[2]	9 (4 to 15)	9 (4 to 17)		
Indication for adjunctive ventilator support	2 (20)	5 (63)		
Admission to an intensive care unit due to respiratory insufficiency	1 (10)	3 (38)		
Lack of clinical improvement at day 7 or any day thereafter	0 (0)	3 (38)		
Readmission for COVID-19	0 (0)	2 (25)		

Cochrane hIG living systematic review May 2022

- **Key messages**
- Hyperimmune immunoglobulin is evaluated for treatment of coronavirus disease 2019 (COVID-19).
- We identified **five published studies** for people with moderate-to-severe disease (n=957)
- We do not have enough evidence to know whether hyperimmune immunoglobulin affects death from any cause or cause serious harms.
- Hyperimmune immunoglobulin may have little to no impact on clinical worsening up to day 28.
- There are no data for people with COVID-19 with no symptoms (asymptomatic) or people with mild COVID-19.
- We found **ten ongoing studies**. We will update this review when their results become available.

Sanquin Blood Bank

Monoclonal antibodies for COVID-19

- Treatment with REGEN-COV in Dutch guidelines for:
- Hospitalized immunocompromised pts with neg ab screen, oxygen dependent
- Based on thin evidence, namely RECOVERY/REMAPCAP lit

- **Not for Omicron variant!**

- Sotrovimab for Delta, but also not for Omicron variant:

High incidence of sotrovimab resistance and viral persistence after treatment of immunocompromised patients infected with the SARS-CoV-2 Omicron variant

Sammy Huygens, Bas Oude Munnink, Arvind Gharbharan, Marion Koopmans, Bart Rijnders

medRxiv 2022.04.06.22273503; doi: https://doi.org/10.1101/2022.04.06.22273503

Recent: PROVENT study

Intramuscular AZD7442 (Tixagevimab–Cilgavimab) for Prevention of Covid-19

M.J. Levin, A. Ustianowski, S. De Wit, O. Launay, M. Avila, A. Templeton, Y. Yuan, S. Seegobin, A. Ellery, D.J. Levinson, P. Ambery, R.H. Arends, R. Beavon, K. Dey, P. Garbes, E.J. Kelly, G.C.K.W. Koh, K.A. Near, K.W. Padilla, K. Psachoulia, A. Sharbaugh, K. Streicher, M.N. Pangalos, and M.T. Esser, for the PROVENT Study Group*

- For pts who have moderate-to-severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments that make it likely that they will not mount an adequate immune response to COVID-19 vaccination; or
- For pts for whom vaccination is not recommended due to a history of severe adverse reaction to a COVID-19 vaccine or COVID-19 vaccine component.

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DOI: 10.1056/NEJMoa2116620

Is er plaats voor convalescent plasma in toekomstige pandemieen?

- **Mogelijk wel!**

- VROEG beschikbaar
- Relatief snel en gemakkelijk verkrijgbaar
- Wanneer geen vaccinaties beschikbaar
- Wanneer geen antistoffen aanwezig
- polyclonaal

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Nicole Skoetz

Lise Estcourt

Jaap Jan Zwaginga

Cochrane Haematology

Trusted evidence.
Informed decisions.
Better health.