Convalescent Plasma for the treatment of COVID-19: not the results

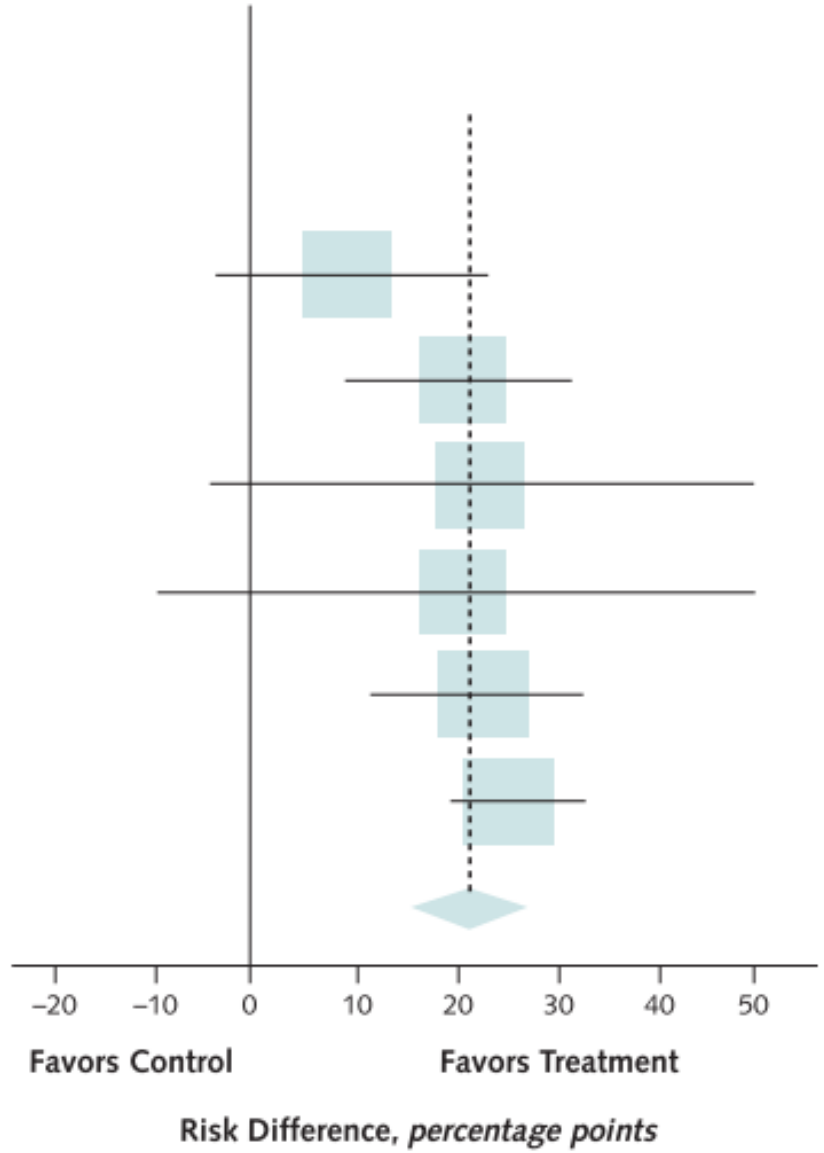
Dr Lise Estcourt
Director Clinical Trials Units, NHSBT

Summary of talk

- What is convalescent plasma
- What is the evidence from previous infectious diseases
- What is the current evidence
- What next

What is convalescent plasma?

Study (Reference)	Mortality Rate, *n/n (%)*		Risk Difference (95% CI), *percentage points*
	Treatment Group	Control Group	
Stoll (17)	25/56 (45)	201/379 (53)	8 (–6 to 22)
O'Malley and Hartman (18)*	3/46 (7)	28/111 (25)	19 (8 to 29)
Ross and Hund (19, 20)	6/28 (21)	9/21 (43)	21 (–5 to 47)
Kahn (21)	12/25 (48)	12/18 (67)	19 (–11 to 48)
Gould (22)	2/30 (7)	82/290 (28)	22 (11 to 32)
McGuire and Redden (23, 24)*	6/151 (4)	120/400 (30)	26 (21 to 31)
Overall	54/336 (16)	452/1219 (37)	21 (15 to 27)



Luke et al. Ann Intern Med. 2006;145:599-609.

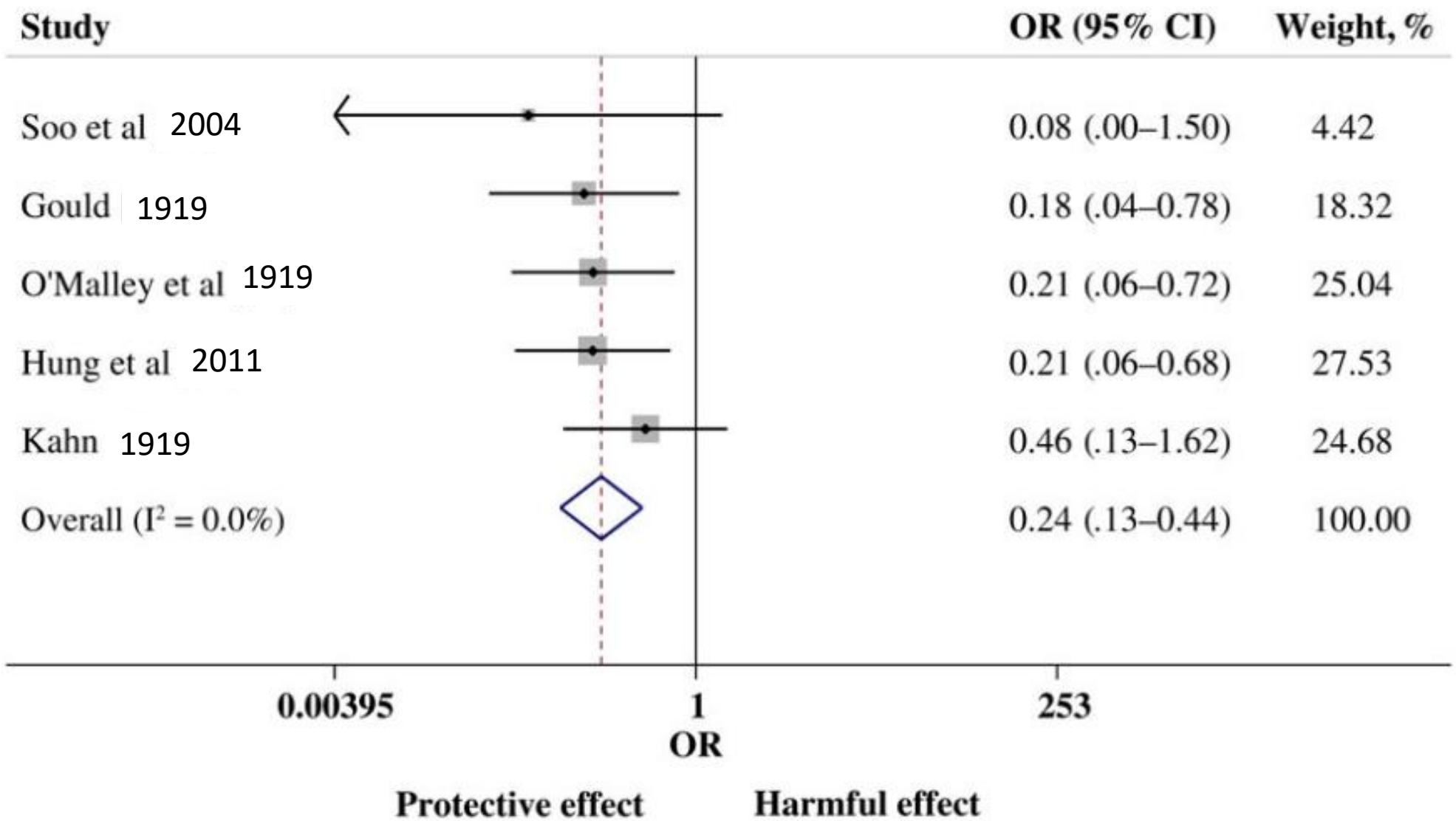
SARS

Influenza

Influenza

Influenza

Influenza



Mair-Jenkins et al. The Journal of Infectious Diseases 2015;211:80–90.

ORIGINAL ARTICLE

Evaluation of Convalescent Plasma for Ebola Virus Disease in Guinea

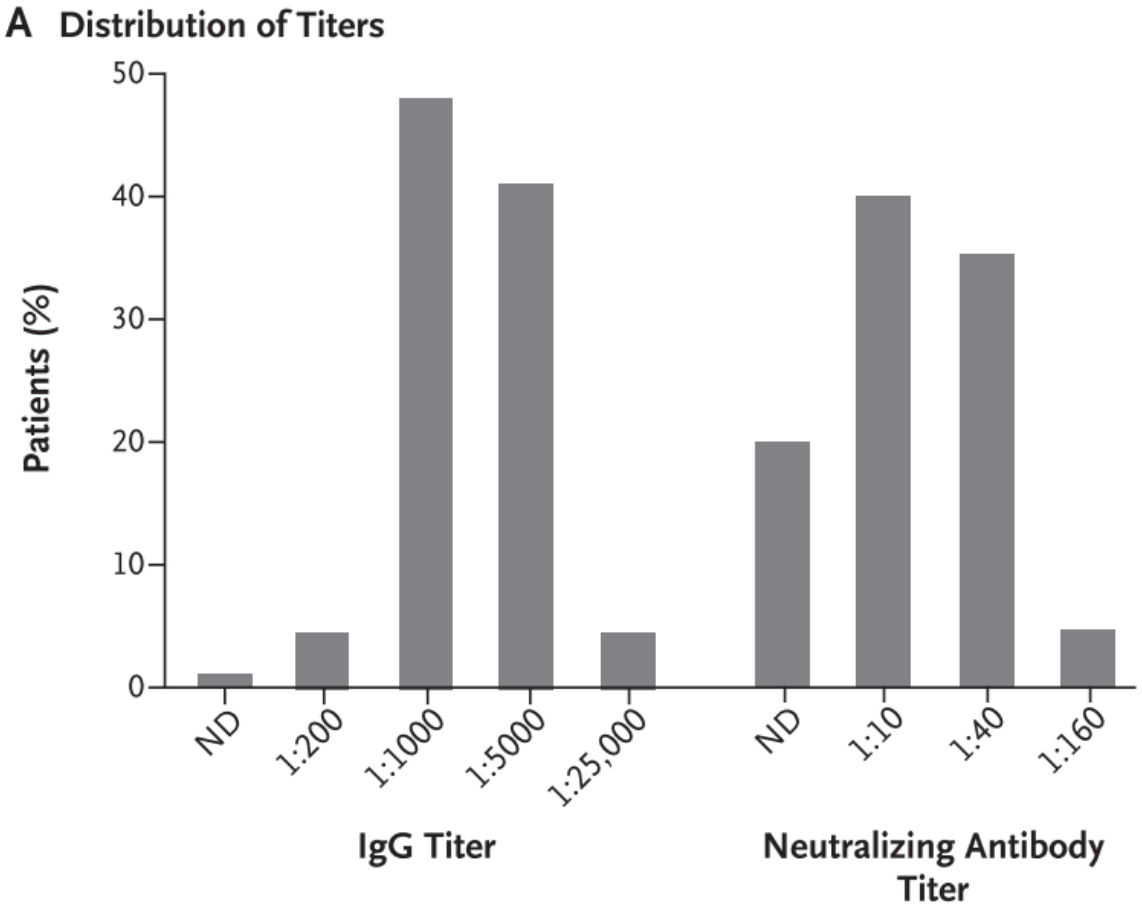
J. van Griensven, T. Edwards, X. de Lamballerie, M.G. Semple, P. Gallian, S. Baize, P.W. Horby, H. Raoul, N. Magassouba, A. Antierens, C. Lomas, O. Faye, A.A. Sall, K. Fransen, J. Buyze, R. Ravinetto, P. Tiberghien, Y. Claeys, M. De Crop, L. Lynen, E.I. Bah, P.G. Smith, A. Delamou, A. De Weggheleire, and N. Haba, for the Ebola-Tx Consortium*

Non-randomised study – 84 participants
compared to 418 historical control

2x 200 to 250mls convalescent plasma

Risk of death 31% CCP vs. 38% control group
(risk difference, −7%; 95% CI, −18 to 4)
(adjusted for age and CT value −3 %; 95% CI, −13 to 8)

Antibody levels not assessed prior to transfusion



Why were major convalescent plasma programmes not part of pandemic planning?

Department of Health & Social Care

Policy paper

UK pandemic preparedness

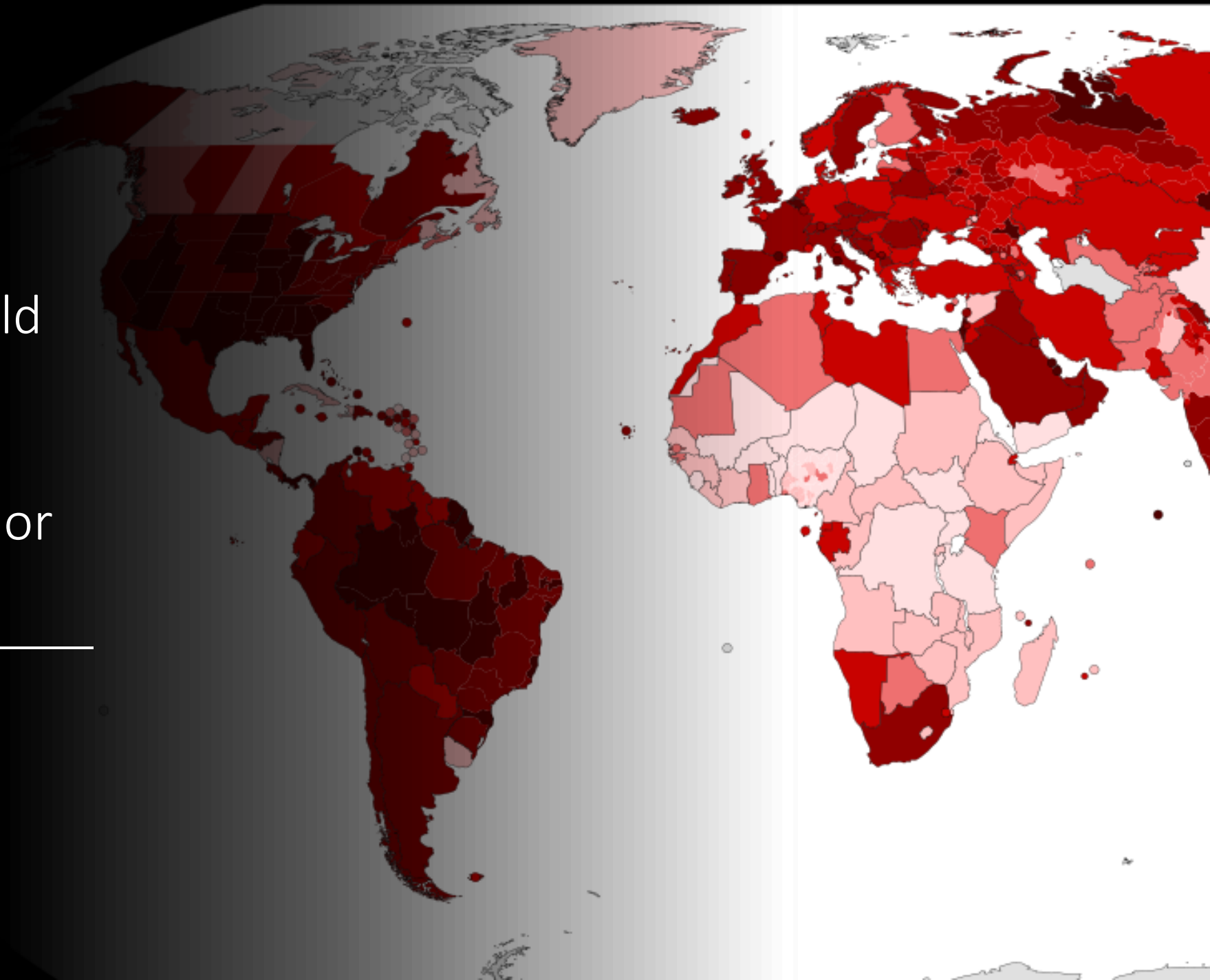
- Evidence not based on high quality evidence
- Observed lower mortality could reflect selection bias or publication bias
- Questions of potential harm remained open - antibody dependent enhancement
- **Without good evidence for effectiveness and safety, health services did not prioritise investment in co-ordinated collection, testing, manufacture and issue of CP**

NHS
Blood and Transplant

Convalescent plasma in COVID-19

100 ongoing convalescent plasma RCTs around the world

15 RCTs around the world recruiting 500 or more participants



Study	Country	Number of participants	Severity of illness	Days from symptom onset	Intervention	Control
Agarwal	India	464	WHO 5	8	CP	Standard care
Siminovich	Argentina	333	WHO 4 to 5	8	CP	Saline
Libster	Argentina	160	WHO 2 to 3	<3	CP	Saline
Li	China	103	WHO ≥ 5	27 to 30	CP	Standard care
Rasheed	Iraq	49	WHO ≥ 6	21 to 28	CP	Standard care
Hamdy-Salman	Egypt	30	WHO ≥ 5	30	CP	Saline
Gharbaran	Netherlands	86	WHO ≥ 4	9 to 11	CP	Standard care
Avendano Sola	Spain	81	WHO 4 to 5	8	CP	Standard care
Ray	India	80	WHO 5 to 6	NR	CP	Standard care
Balcells	Chile	58	WHO 4 to 6	5 to 6	CP	Delayed CP
Al-Qhatani	Bahrain	40	WHO 5 to 7	NR	CP	Standard care
Baipai	India	29	WHO 5 to 7	NR	CP	Plasma

NHS
Blood and Transplant

Outpatients

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults

R. Libster, G. Pérez Marc, D. Wappner, S. Coviello, A. Bianchi, V. Braem, I. Esteban, M.T. Caballero, C. Wood, M. Berrueta, A. Rondan, G. Lescano, P. Cruz, Y. Ritou, V. Fernández Viña, D. Álvarez Paggi, S. Esperante, A. Ferreti, G. Ofman, Á. Ciganda, R. Rodriguez, J. Lantos, R. Valentini, N. Itcovici, A. Hintze, M.L. Oyarvide, C. Etchegaray, A. Neira, I. Name, J. Alfonso, R. López Castelo, G. Caruso, S. Rapelius, F. Alvez, F. Etchenique, F. Dimase, D. Alvarez, S.S. Aranda, C. Sánchez Yanotti, J. De Luca, S. Jares Baglivo, S. Laudanno, F. Nowogrodzki, R. Larrea, M. Silveyra, G. Leberzstein, A. Debonis, J. Molinos, M. González, E. Perez, N. Kreplak, S. Pastor Argüello, L. Gibbons, F. Althabe, E. Bergel, and F.P. Polack, for the Fundación INFANT–COVID-19 Group*

160 participants hospitalised with COVID-19
Argentina
Multicentre - blinded
Elderly outpatients within 72 hours symptom onset
(≥ 75 yrs or 65 to 74 with comorbidities)
CP given as 250mls
Ab titre >1:1000 IgG S

Primary outcome: severe respiratory disease defined as a respiratory rate ≥30 and/or an O2 sat<93% in room air up to 25 days

Stopped early - decreased numbers of cases

16% (13/80) receiving plasma vs. 31% receiving placebo developed severe respiratory disease [RR(95%CI)= 0.52(0.29,0.94); p=0.026)]
RRR=48%

2 receiving plasma vs. 4 receiving placebo died (NS).

NHS
Blood and Transplant

Inpatients

RESEARCH

Check for updates

FAST TRACK

Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial)

Anup Agarwal,[1] Aparna Mukherjee,[1] Gunjan Kumar,[1] Pranab Chatterjee,[1] Tarun Bhatnagar,[2] Pankaj Malhotra,[3] on behalf of the PLACID Trial Collaborators

Participants hospitalised with moderate COVID-19
India
Multicentre – open label
464 adults
Adults (Median age 52)
PaO2/FiO2 ratio 200 to 300mm Hg or RR > 24 or O2 ≤ 93%
Excluded: patients with PaO2/FiO2 <200 mm Hg or shock

CP given as two 200ml units 24 hours apart
Median Ab titre not measured prospectively
Only 70% of participants received at least 1 unit of CCP with detectable neutralising Abs (1:20)

Only 28% of participants received at least 1 unit of CCP with neutralising Abs ≥ 1:80.

Primary outcome: composite of progression to severe disease (PaO2/FiO2 ratio <100 mm Hg) any time within 28 days of enrolment or all cause mortality at 28 days

Trial comparing convalescent plasma versus standard care

No difference seen in primary or secondary outcomes

Underpowered

Levels of antibody in CCP very low or undetectable

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia

V.A. Simonovich, L.D. Burgos Pratx, P. Scibona, M.V. Beruto, M.G. Vallone, C. Vázquez, N. Savoy, D.H. Giunta, L.G. Pérez, M..L. Sánchez, A.V. Gamarnik, D.S. Ojeda, D.M. Santoro, P.J. Camino, S. Antelo, K. Rainero, G.P. Vidiella, E.A. Miyazaki, W. Cornistein, O.A. Trabadelo, F.M. Ross, M. Spotti, G. Funtowicz, W.E. Scordo, M.H. Losso, I. Ferniot, P.E. Pardo, E. Rodriguez, P. Rucci, J. Pasquali, N.A. Fuentes, M. Esperatti, G.A. Speroni, E.C. Nannini, A. Matteaccio, H.G. Michelangelo, D. Follmann, H.C. Lane, and W.H. Belloso, for the PlasmAr Study Group*

Participants hospitalised with severe COVID-19
Argentina
Multicentre – blinded
333 adults (228 CP:105 placebo)
Adults (Median age 62)
PaO2/FiO2 ratio < 300mm Hg or O2 < 93% or SOFA score ≥ 2 points above baseline
Excluded: MV or organ failure

CP given as single donor or plasma pool (median 500mls)
Ab titre > 1:1000 Ig G (median 1:3200)

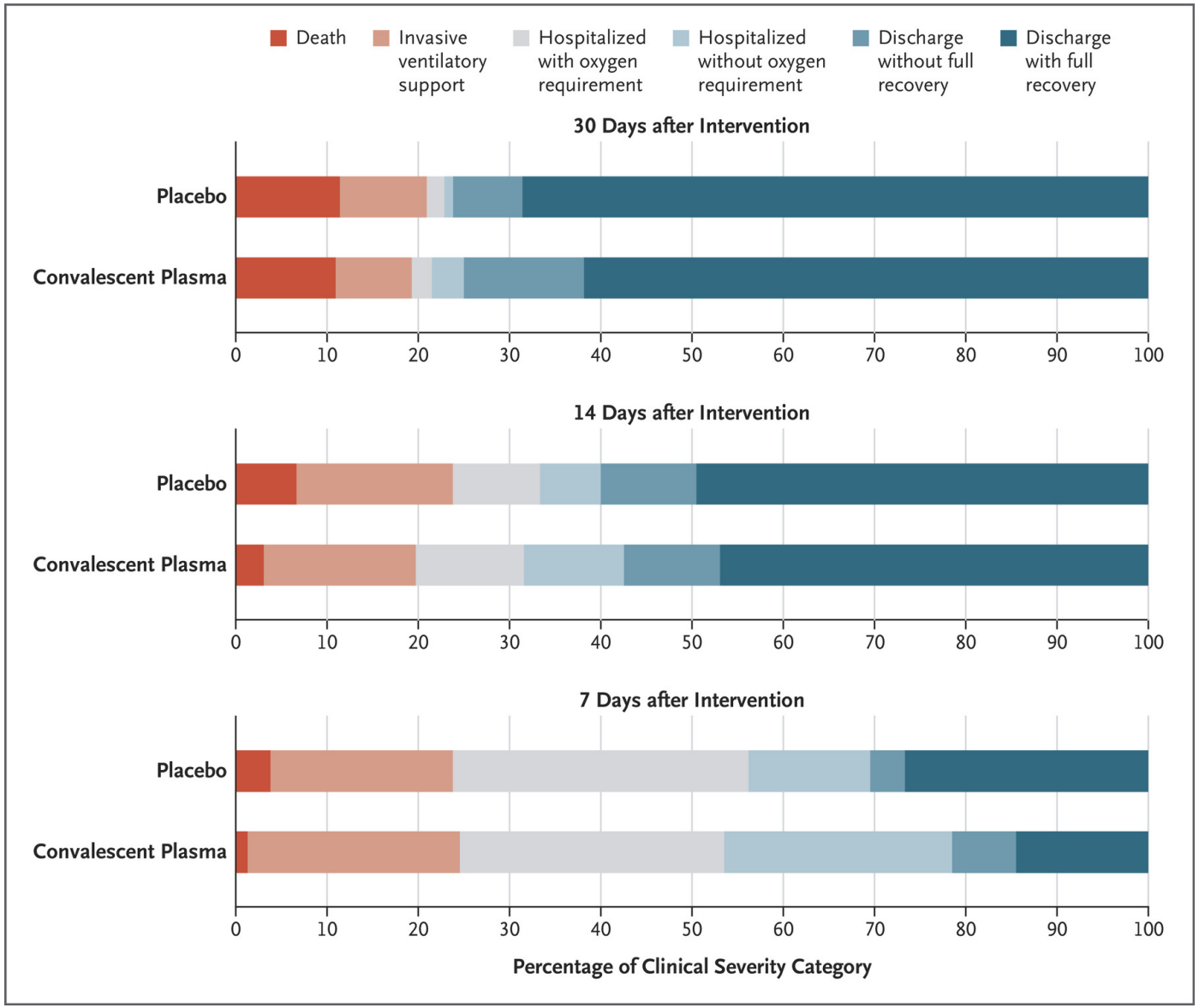
Median neutralising antibody titre 1:300, IQR 136-511

Primary outcome: clinical status 30 days after intervention
1- death
2- invasive ventilatory support
3- hospitalized with supplemental oxygen requirements
4- hospitalized without supplemental oxygen requirements
5- discharged without full return of baseline physical function
6- discharged with full return of baseline physical function

Trial comparing convalescent plasma versus placebo

Overall mortality was 10.96% in the convalescent plasma group and 11.43% in the placebo group, for a risk difference of −0.46 percentage points (95% CI, −7.8 to 6.8)

Only 80% power to detect proportional OR 1.8


Death
Invasive ventilatory support
Hospitalized with oxygen requirement
Hospitalized without oxygen requirement
Discharge without full recovery
Discharge with full recovery
30 Days after Intervention
Placebo
Convalescent Plasma
0 10 20 30 40 50 60 70 80 90 100
14 Days after Intervention
Placebo
Convalescent Plasma
0 10 20 30 40 50 60 70 80 90 100
7 Days after Intervention
Placebo
Convalescent Plasma
0 10 20 30 40 50 60 70 80 90 100
Percentage of Clinical Severity Category

Le Infezioni in Medicina, n. 3, 357-366, 2020

ORIGINAL ARTICLES

The therapeutic potential of convalescent plasma therapy on treating critically-ill COVID-19 patients residing in respiratory care units in hospitals in Baghdad, Iraq

Anwar M. Rasheed[1], Dhurgham F. Fatak[1], Hashim A. Hashim[2], Mohammed F. Maulood[3], Khulood K. Kabah[1], Yaqoob A. Almusawi[4], Ahmed S. Abdulamir[5]

Participants hospitalised with life-threatening COVID-19
Iraq
Multicentre
49 adults

CP given as one 400ml transfusion over 2 hours

Median Ab titre not measured prospectively
Donors were moderately or strongly positive on SARS-CoV-2 ELISA

Trial comparing convalescent plasma versus standard care

Suggested decreased mortality 1/21 versus 8/28

Suggested decreased duration of severe disease by 4 days

Underpowered

Duration of infection prior to enrolment 14 to 16 days

RECOVERY

Randomised Evaluation of COVID-19 Therapy

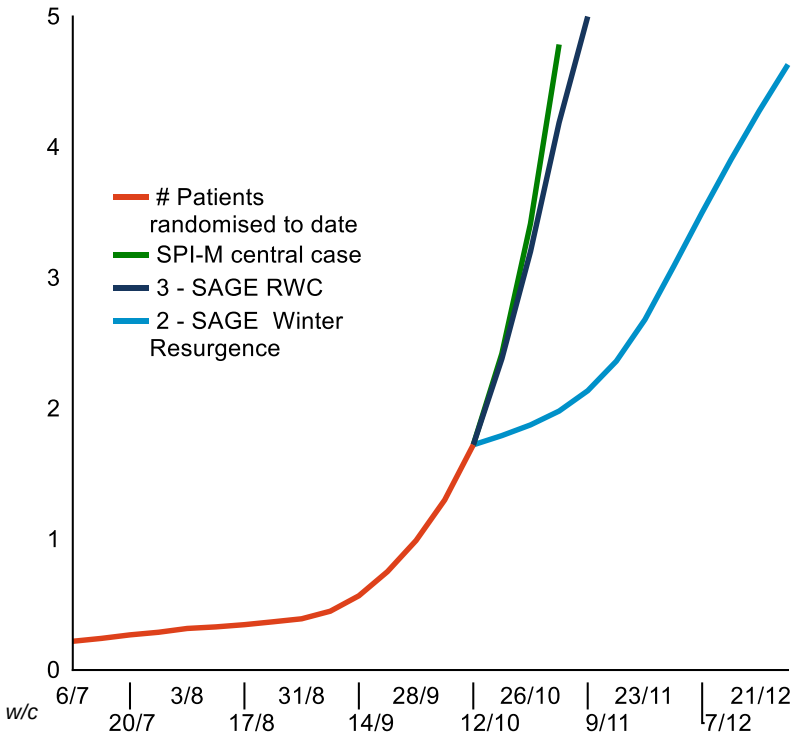
Convalescent plasma UK trial

- Hospitalised patients – children and adults
- CP versus standard care (+/- other randomised treatments)
- 2 units of CP given on study days 1 & 2
- Powered to see 20% reduction in overall 28-day mortality

Trial Completion: Anticipated and Actual

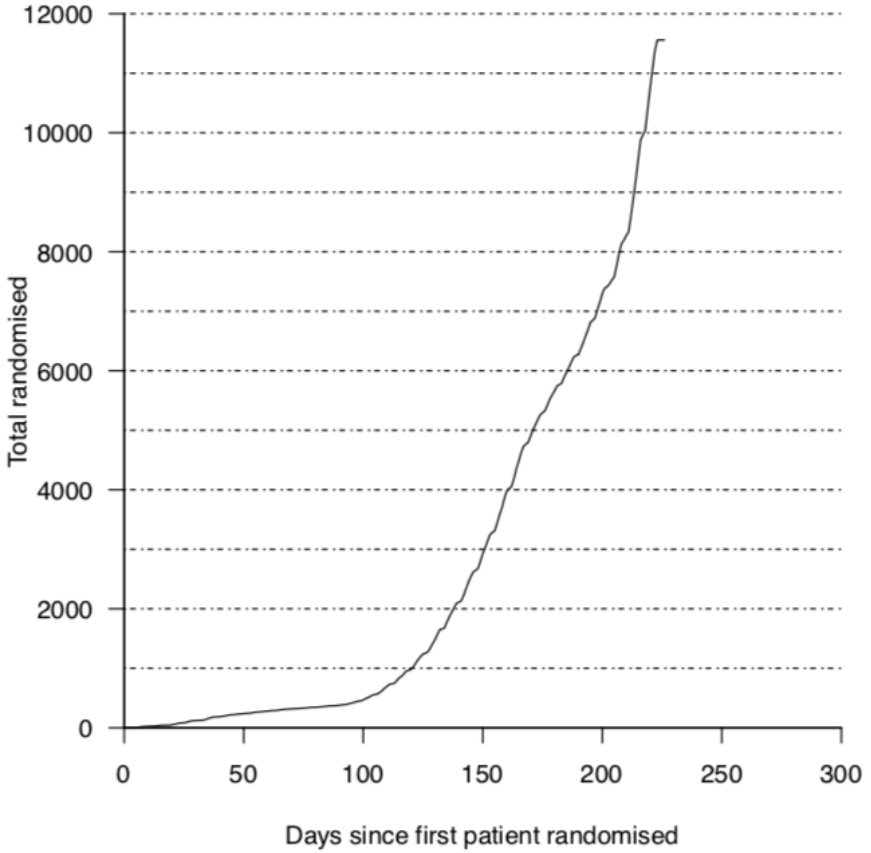
Anticipated trials progress

Patients included in RECOVERY Trial (K)



Epidemic curve: closest to SAGE RWC

Recruitment to CONVALESCENT PLASMA vs its control



Close of RECOVERY trial

- Enhanced power to look at anti-SARS-CoV antibody negative group
- Study closed to recruitment for mechanically ventilated on Jan 7th
- Study closed on Jan 15th
  - total approx. 12000 recruited
- Preliminary analysis
  - 1873 reported deaths among 10,406 randomised patients
  - no significant difference in the primary endpoint of 28-day mortality
  - 18% CP vs. 18% usual care alone; risk ratio 1.04 [95%CI 0.95-1.14]; p=0.34
- No signal for harm

Patient characteristic in RECOVERY trial

- DMC had results of anti-SARS-CoV antibody test for their analyses
- 40% of patients were antibody negative
- Patient characteristics
  - Median time since symptom onset was 9 days
    - 6% of patients not requiring oxygen
    - 86% of patients on supplementary oxygen
    - 8% of patients mechanically ventilated
- Spectrum of disease is moderate to severe
    - a small minority (n=600) not requiring oxygen at time of enrolment

Analysis of RECOVERY trial

- All cause 28 day mortality
  - Time to discharge if alive
  - Use of mechanical ventilation

- Pre-specified sub-group analysis (approx. terciles)
  - Age, sex, ethnicity
  - Pre-existing antibody
  - No oxygen or oxygen or ventilation
  - <7 and >7 days since onset of symptoms

- Additional non-randomised comparison of antibody levels in donor plasma
  - EUROIMMUNE, Roche anti-S ELISA and Live virus nAbs (Deb Hung, BROAD)

Antibody titres of initial sample of donors

- In first 400 donors EUROIMMUNE S/CO > 6
  - Mean nAb 1:399 with median nAb ~ 1:250 but may have changed during trial

- In the trials

  - 25% received two units with EUROIMMUNE 6-7.99
  - 50% received one units with EUROIMMUNE 6-7.99 and one unit 8-12
  - 25% received two units with EUROIMMUNE 8-12

  - Measurement of individual unit nAbs will allow antibody dose to be determined

  - Mutation mismatch between donor and recipient cannot be determined
    - Effective titre may be reduced to variable extent ~ three fold

Convalescent plasma UK trial

- Adults admitted to ITU within last 48 hours
- Confirmed COVID
- CP versus standard care (+/- other randomised treatments)
- CP on study day 1 and day 2
- Intensive blood and respiratory sampling for a subgroup (approx. 200 participants)

Close of REMAP-CAP trial

- Recruitment to severe patients closed on Jan 11th by DSMC
- 2000 recruited
- For severe patients
  - 921 patients with 28 day-follow up
  - Low probability of < 2.2% that CP decreased the number of days requiring intensive care support or death by 20% or more
- Recruitment for moderate patients closed on Jan 18th after RECOVERY closed

Analysis for REMAP-CAP trial

- Organ support free days
- 28 day mortality
- Progression to mechanical ventilation or ECMO
- Time to discharge from ICU and from hospital
- SAEs

- Models for sub-group analysis of organ support free days
  - Age, sex, site, time during pandemic, convalescent plasma and control interventions, corticosteroid and immune modulation interventions
  - Baseline clinical status – mechanical ventilation
  - Presence of virus by RT-PCR at enrolment
  - Presence of anti-SARSCoV-2-antibodies at enrolment (28% antibody neg)
  - Antibody levels in donor plasma
    - EUROIMMUNE, Roche anti-S ELISA and live virus nAbs

- Individual patient analysis will combine data from both trial

Antibody based therapy for COVID-19

NHS Blood and Transplant

- Evidence of **substantial effect of convalescent plasma in Argentinian RCT with 160 patients (Libster et al NEJM 2021)**
  - **vulnerable patients (> 75 or 65-74 with co-morbidities) only 3d of symptoms**
  - given one unit of high-titre plasma (28% of donors accepted)
  - **respiratory disease in 13/80 (16%) with CP and 25/80 (30%) in controls**
  - RR 0.52 (85% CI 0.29-0.94)
  - Substantial dose effect
    - Higher than median dose RR 0.29
    - Lower than median dose RR 0.75

- **US data observational study of CP (Joyner et al NEJM 2021)**
  - 30-day mortality in 115/515 (22.3%) in those receiving one unit of high titre, 549/2002 (27.2%) of medium titre 166/561 (29.6%) low titre CP

  - Mortality in high vs low titre RR 0.62 not ventilated, RR1.02 ventilated

Antibody based therapy for COVID-19

NHS Blood and Transplant

- Preliminary results from two large randomised trials do not show overall benefit for moderately or severely ill patients
- No evidence for effects in mechanically ventilated patients
- Analyses of sub-groups may show an effect and one may speculate that effects are now only likely to be seen in those
  - Treated early within 7 days of symptoms appearing
  - and/or treated with higher viral nAb titres
- Final results early March

A third CP trial: COVIC-19

- Planning for a third trial for pre-hospital immunocompromised and vulnerable patients testing positive for COVID-19
    - Over 70s
    - Or adults
        - Chemotherapy
        - Haem-onc patients, HSCT and solid organ transplant patients
        - Other immunosuppressive therapy or conditions
- Intervention – high titre convalescent plasma as out-patient or in the community
- Outcome – hospital admission with moderate or severe COVID-19
- Significant need and significant numbers may remain after vaccination
- International recruitment

Summary and next steps

- **Still no solid RCT evidence to drive policy**
  - No efficacy seen in REMAP CAP and RECOVERY and final analysis now underway
  - Significant sub-groups of early disease and high-titre remain to be analysed
- **Planning for a third trial for pre-hospital immunocompromised or vulnerable patients testing positive for COVID-19**
- **Challenges of escape variants and treatment of severely immunocompromised patients**
- **Continued need for collection of high-titre plasma**
  - To support trials
  - To provide plasma if the planned trial or other trials change policy
  - Hospitalised, male and older COVID patients more likely to have high antibody tite
- **Development of hyperimmune immunoglobulin**

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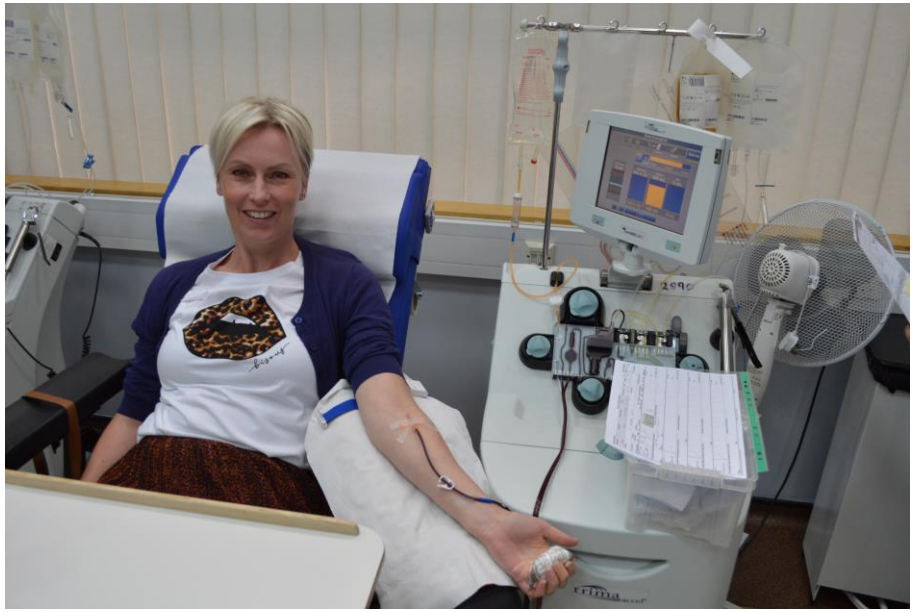

https://www.nhsbt.nhs.uk/how-you-can-help/convalescent-plasma-clinical-trial/

Especially welcome if hospitalised OR men OR >35 yo
Very interested in taking NHS staff with good level of anti-COVID antibodies
Call 0300 123 23 23 and mention you are NHS colleagues