

Passive immunotherapy - focus on convalescent plasma and hyperimmune immunoglobulin

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Summary of talk

- Passive Immunotherapy
 - What is it?
 - Is there any evidence it works against SARS-CoV-2?
 - What is the evidence in the omicron era?

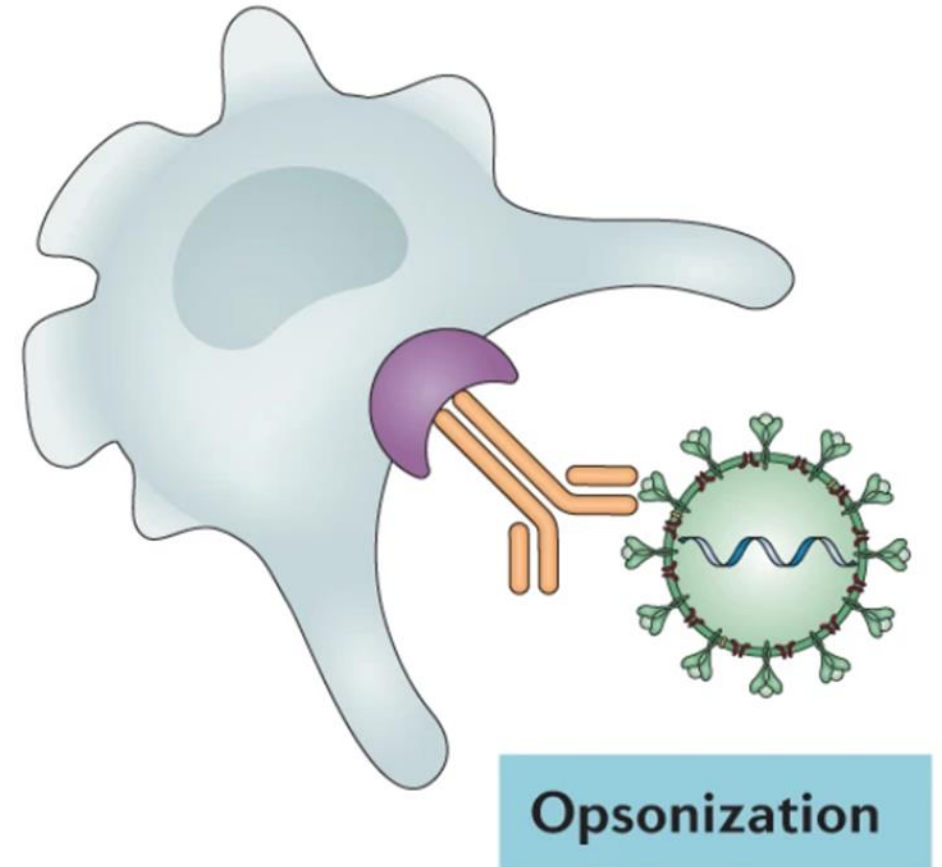
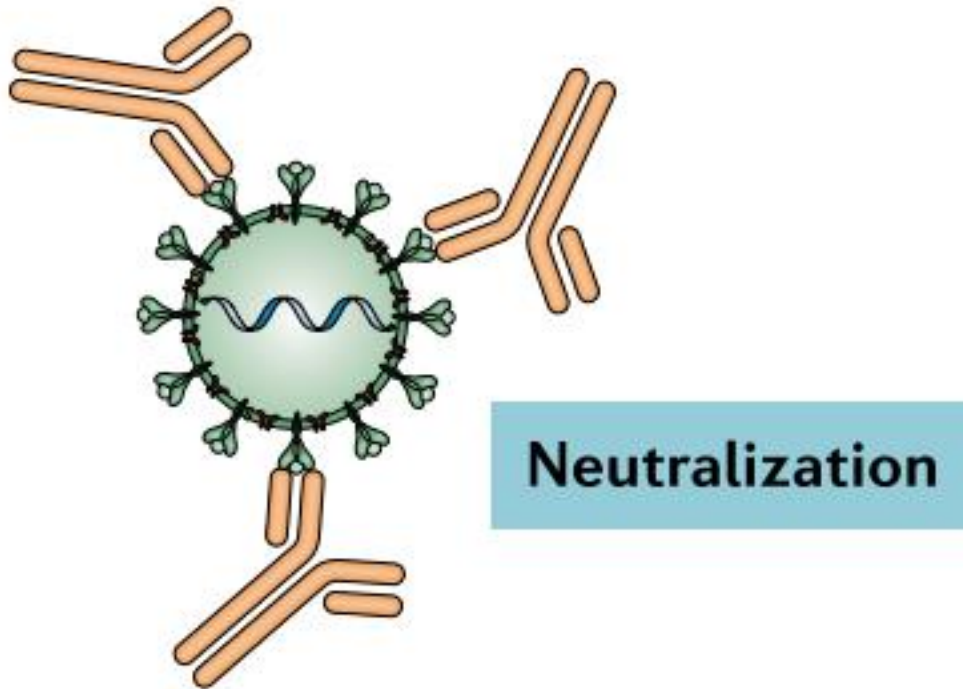




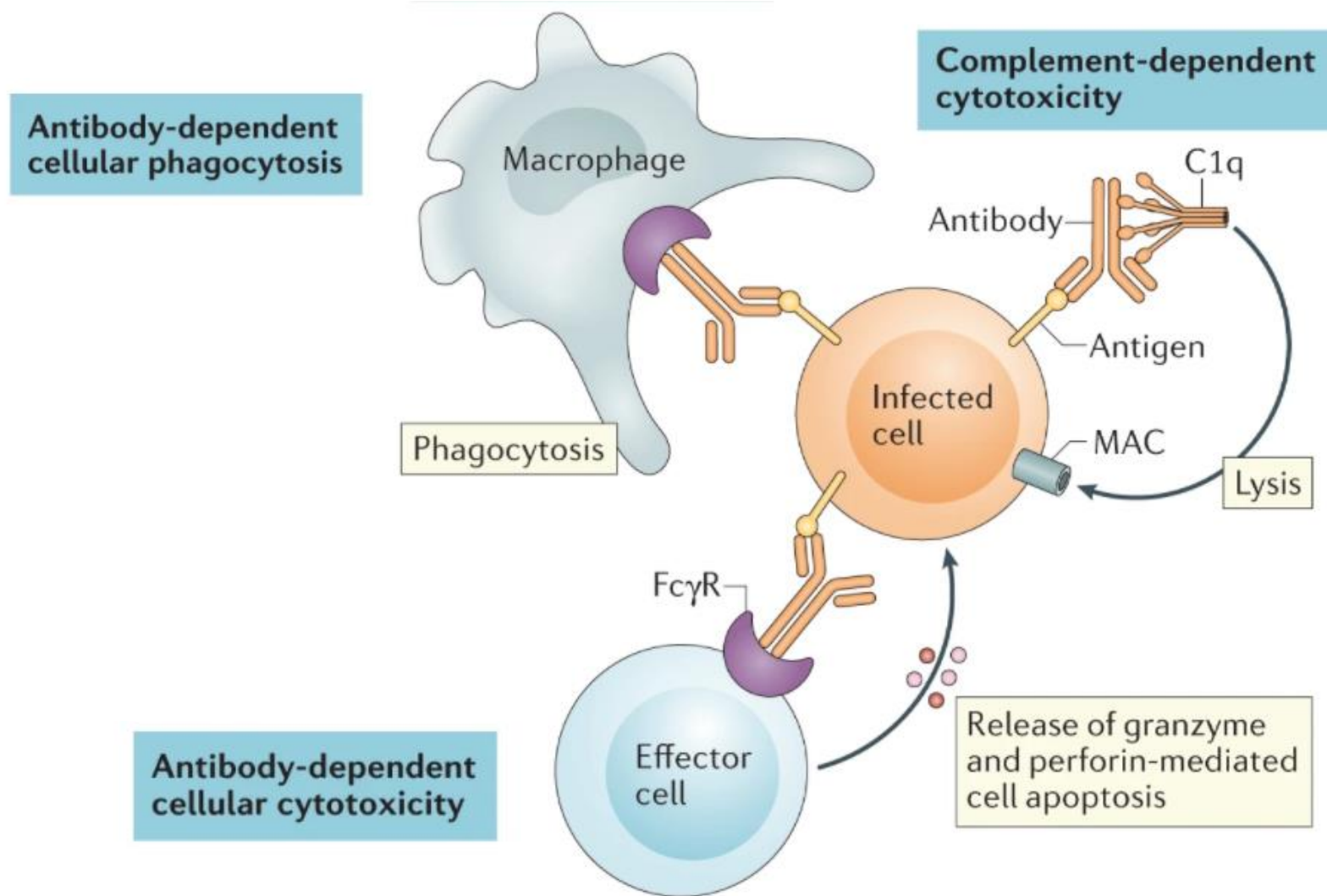
Passive Immune Therapies

	Convalescent plasma	Hyperimmune globulin	Monoclonal antibodies
Speed of production (after pandemic onset)	Fast (weeks)	Moderate (Months)	Slow (Months to years)
Adapts to viral variants	Yes	Yes	No
Amount of antibody	Variable	Fixed - total Ab	Fixed - neutralizing Ab
Route of administration	IV	IV, IM, SC	IV, IM, SC
Derived from blood	Yes	Yes	No
Cost	£	££	££££
Availability	Any country that produces plasma products	Simple manufacturing process	Limited – complex manufacturing process

Method of action

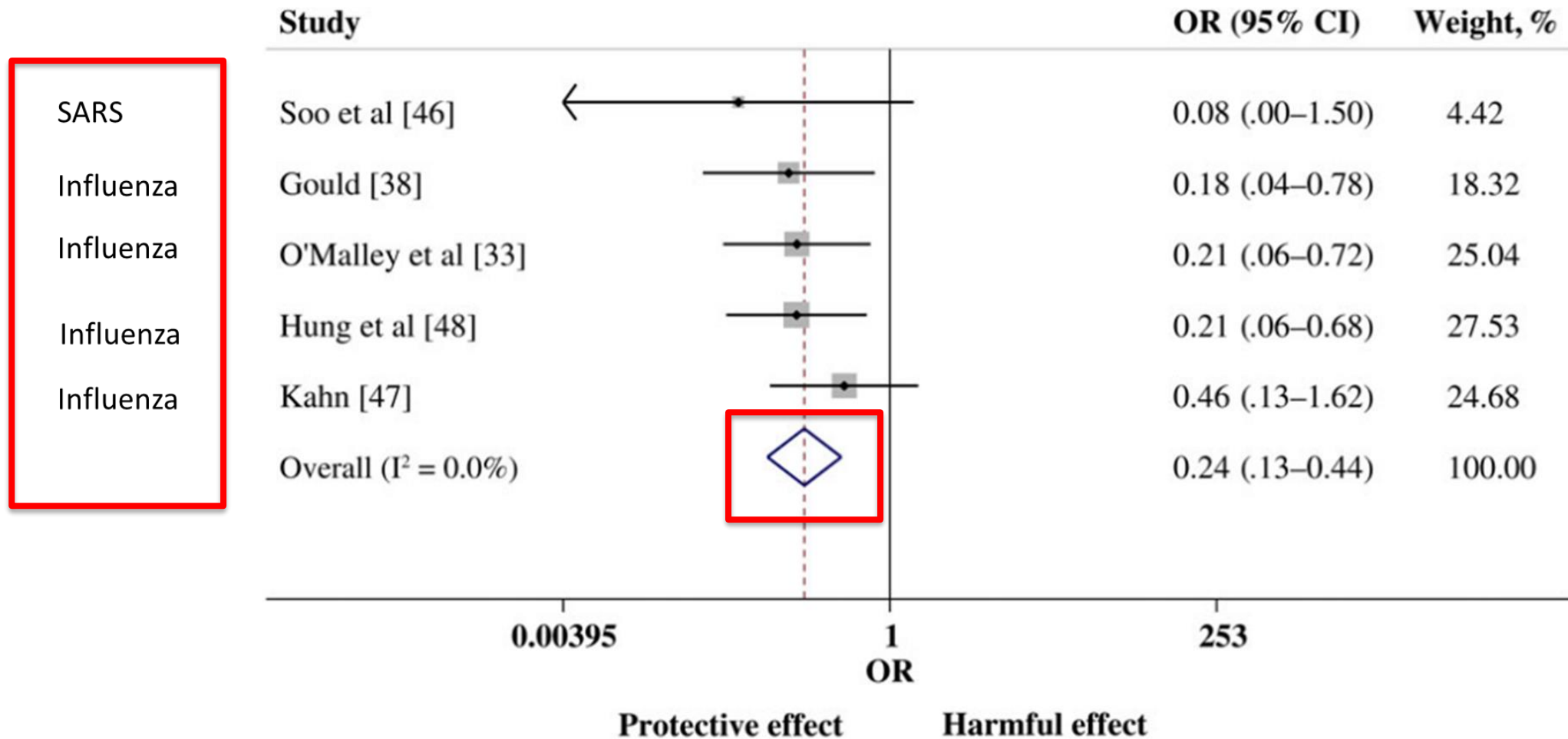


Method of action





All-cause mortality – previous pandemics



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

- 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**

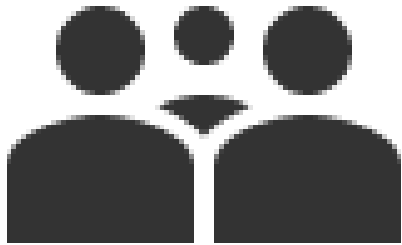




Convalescent plasma programme



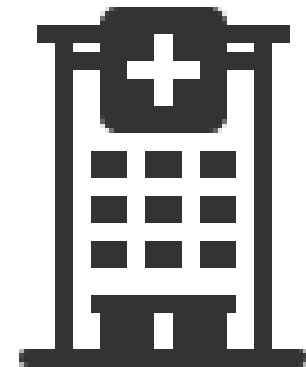
Blood and Transplant



Over 250,000 people
offered to donate plasma

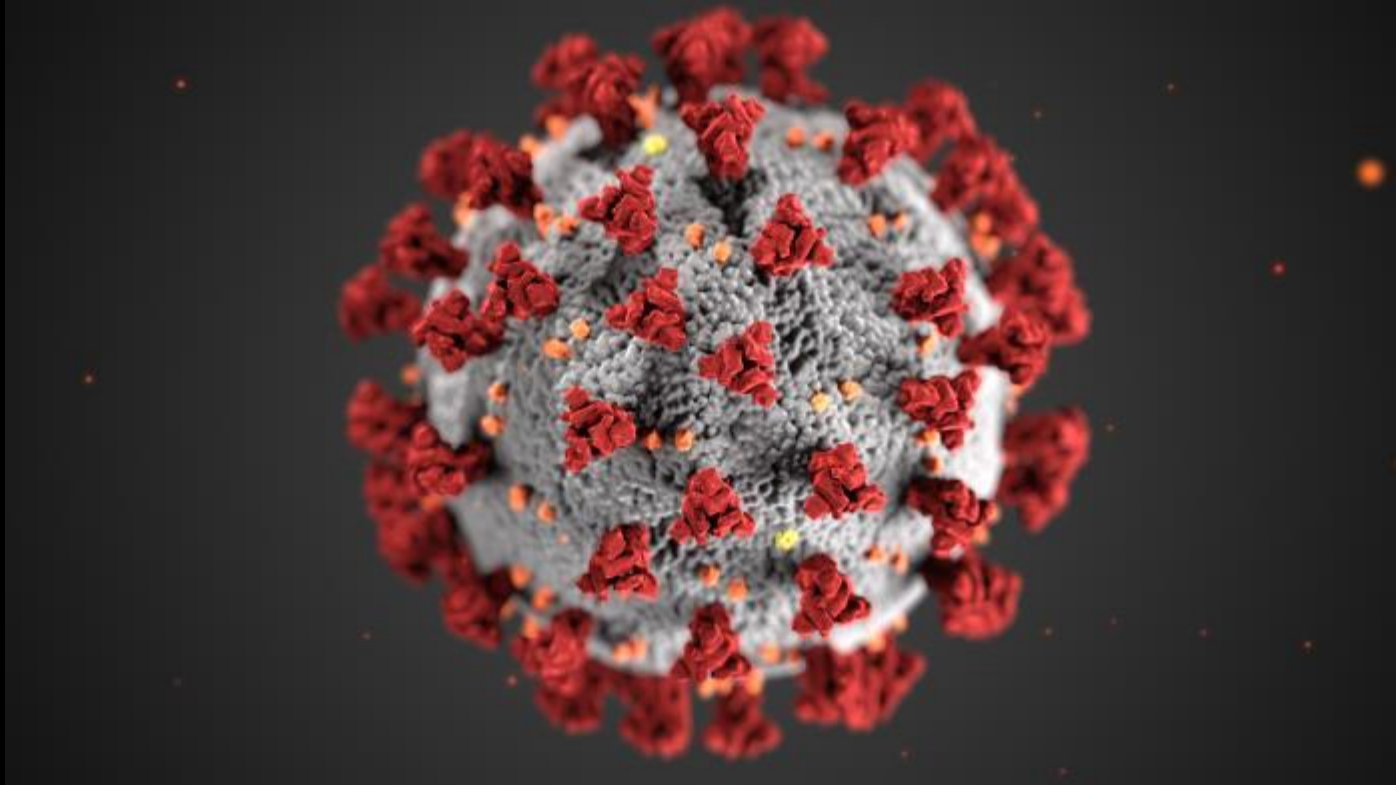


Over 1,000 new colleagues
recruited and trained



233 hospitals took
part in the trials

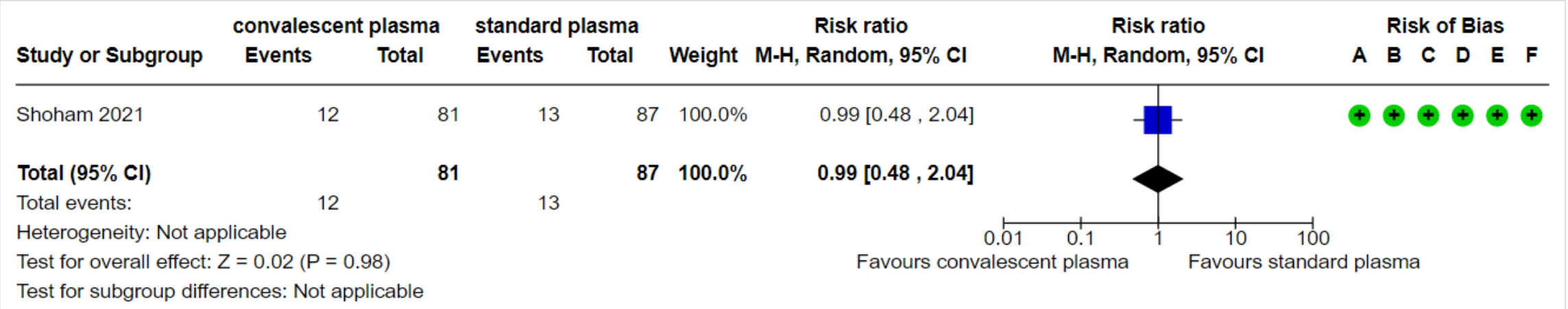
Does passive immune therapy work against SARS-CoV-2?



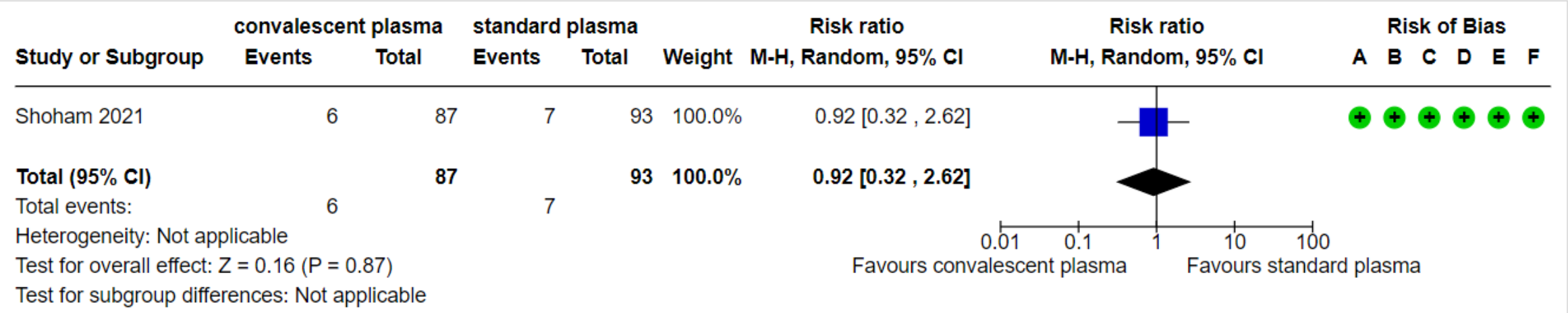
Tixagevimab and cilgavimab – prophylaxis – PROVENT

Outcome	Absolute Effect		Relative effect (95% CI)	No. of participants (RCTs)	GRADE
	Placebo or standard care	Tixagevimab and cilgavimab (95% CI)			
Infection with SARS-CoV-2 within 6 months	27 per 1000	12 per 1000 (8 to 19)	0.45 (0.29 to 0.71)	4685 (1 RCT)	MODERATE
Development of clinical COVID-19 symptoms within 6 months	18 per 1000	Pre-vaccine era		5172 (1 RCT)	HIGH
All-cause mortality within 6 months	4 per 1000	2 per 1000	0.54 (0.00 to 1.07)	5197 (1 RCT)	LOW
Admission to hospital within 6 months	Small number immunocompromised N = 173		(3 to 35)	(0.00 to 0.59) (1 RCT)	LOW
Serious adverse events	33 per 1000	37 per 1000 (28 to 51)	1.12 (0.83 to 1.52)	5197 (1 RCT)	LOW

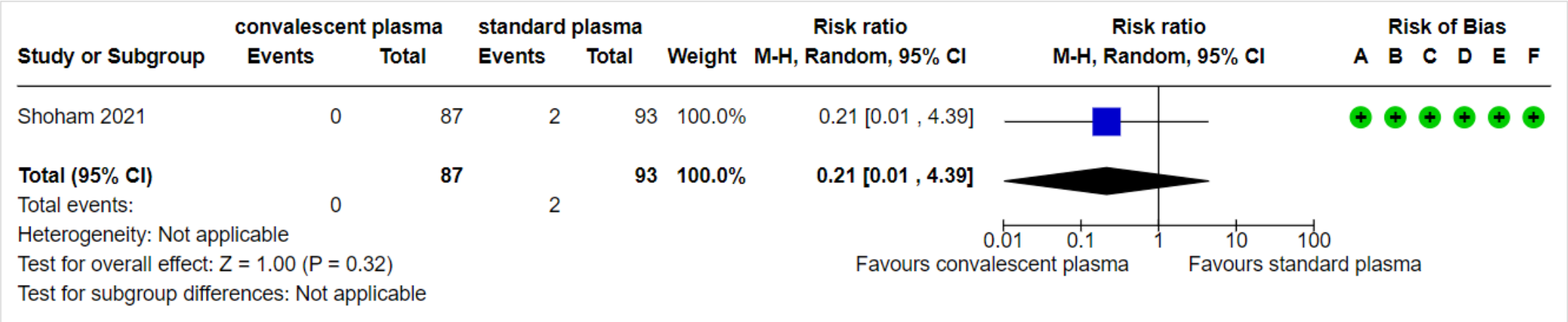
Prophylactic, CCP vs. Standard plasma, infection with SARS-CoV-2 within 30 days



Prophylactic, CCP vs. Standard plasma, development of symptoms within 30 days



Prophylactic, CP vs. Standard plasma, admission to hospital within 30 days due to COVID-19



What we know about passive immune therapy preventing SARS-CoV-2 in pre-vaccine era



Decreases risk of symptomatic SARS-CoV-2 and probably decreases risk of infection



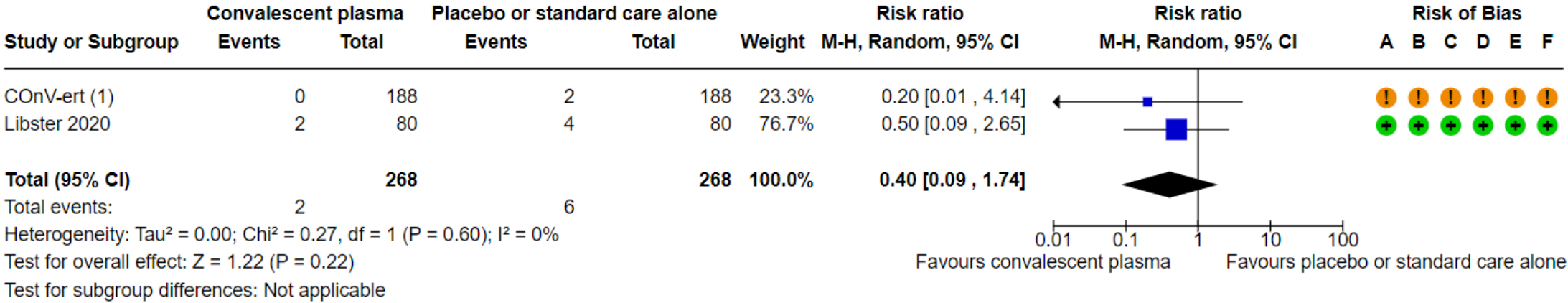
May decrease risk of hospital admission

May or may not reduce risk of death (not enough data)

Sotrovimab – outpatient – COMET-ICE

Outcome	Absolute Effect		Relative effect (95% CI)	No. of participants (RCTs)	GRADE
	Placebo or standard care	Sotrovimab (95% CI)			
All-cause mortality (D30)	3 per 1000	1 per 1000 (0 to 28)	0.33 (0.01 to 8.18)	583 (1 RCT)	LOW
Clinical progression (oxygen requirement)	65 per 1000	7 per 1000 (1 to 29)	0.11 (0.02 to 0.45)	583 (1 RCT)	LOW
Clinical progression (IMV or death)	10 per 1000	1 per 1000 (0 to 28)	0.14 (0.01 to 2.76)	583 (1 RCT)	LOW
Admission to hospital or death (D30)	72 per 1000	10 per 1000 (3 to 35)	0.14 (0.04 to 0.48)	583 (1 RCT)	LOW
Serious adverse events	59 per 1000	16 per 1000 (7 to 37)	0.27 (0.12 to 0.63)	868 (1 RCT)	LOW

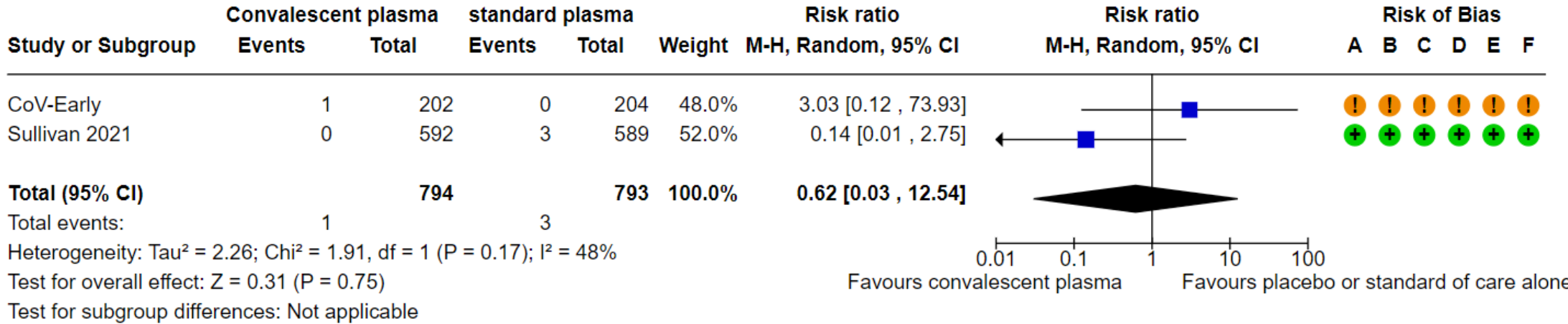
CCP vs. placebo/SOC; mortality at day 28



Footnotes

(1) Study not published yet, data was provided by study investigators on request

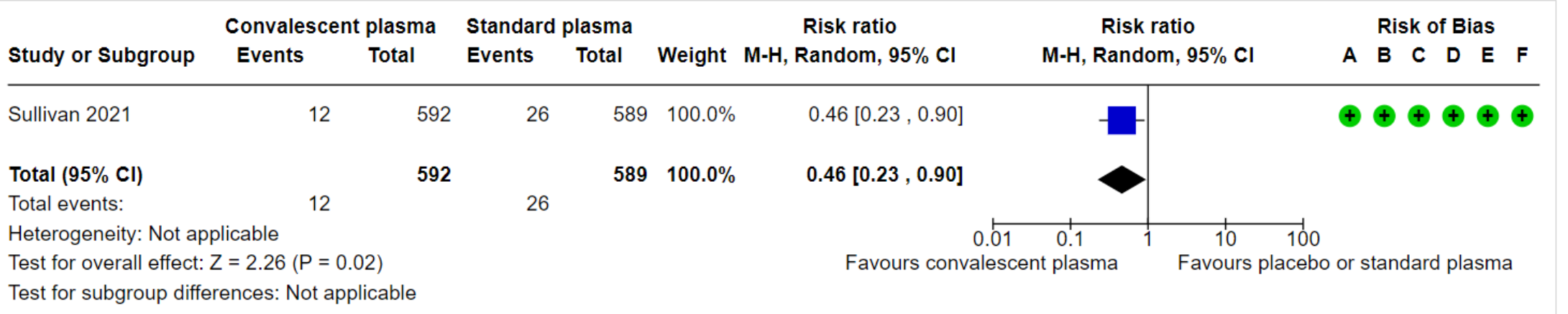
CCP vs. standard plasma; mortality at day 28



CCP vs. placebo/SOC, Need for hospitalisation with at least need of oxygen by mask or nasal prongs or death (WH0 >= 5)



CCP vs. standard plasma, Need for hospitalisation with at least need of oxygen by mask or nasal prongs or death (WH0 >= 5)



What we know about passive immune therapy treating SARS-CoV-2 infections in outpatients



May or may not reduce mortality (not enough data)

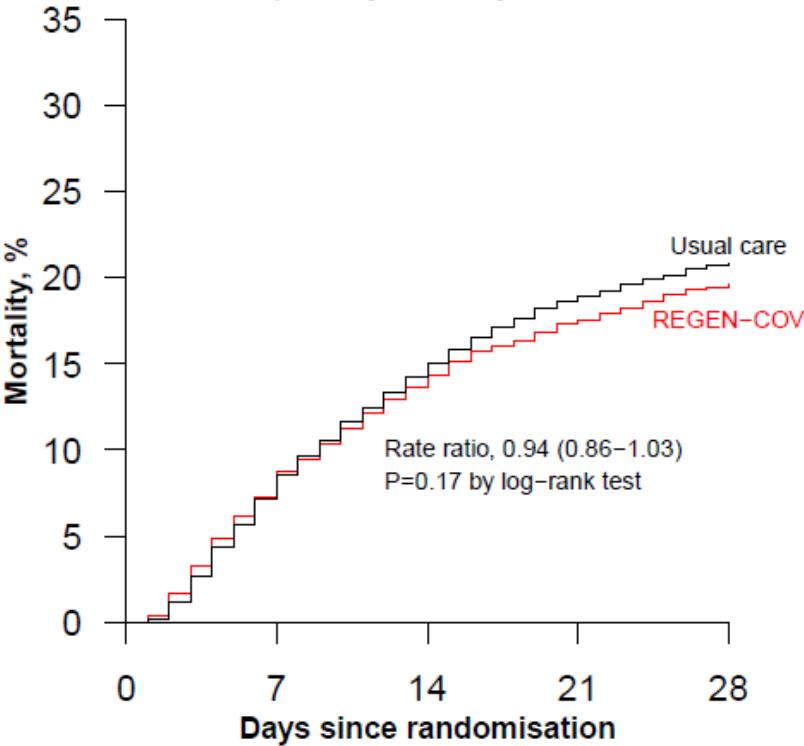


May reduce risk of hospital admission and need for oxygen therapy

Casirivimab/imdevimab – inpatient - RECOVERY

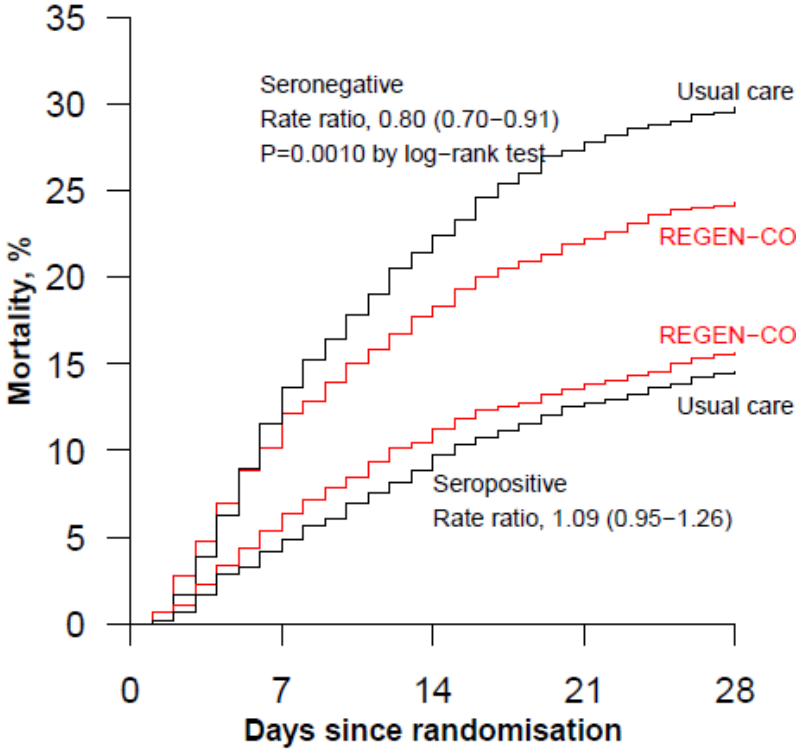
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b) All participants



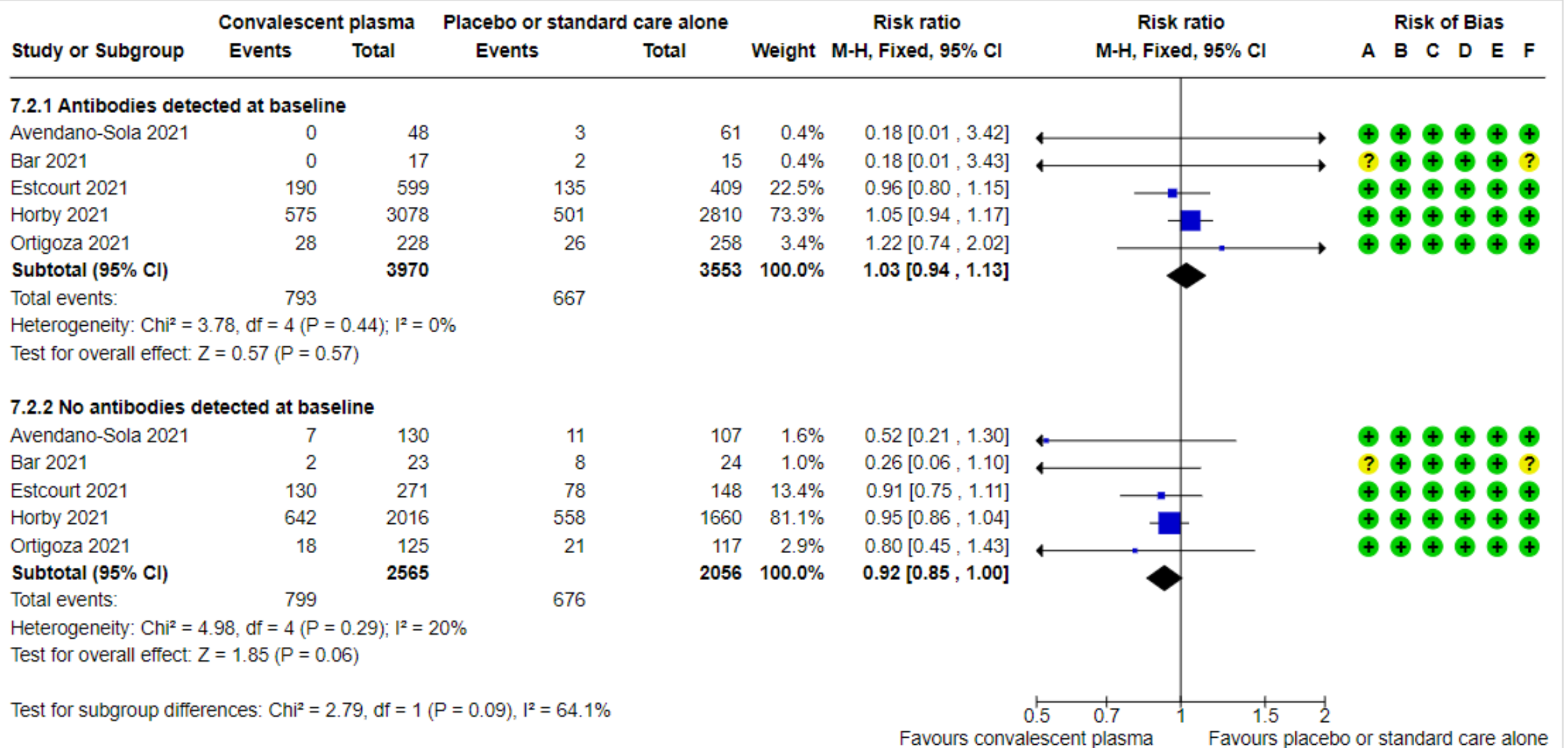
No. at risk					
REGEN-COV	4839	4388	4112	3952	3848
Usual Care	4946	4504	4182	3980	3888

a) Seronegative vs seropositive

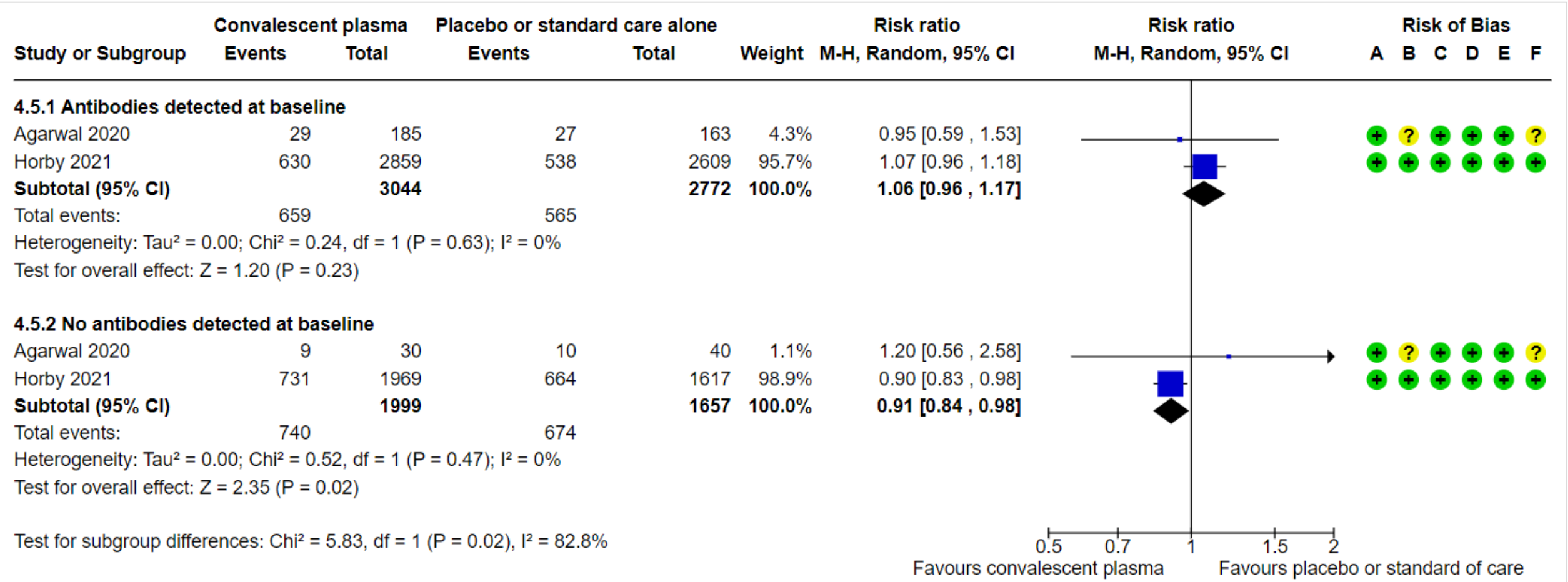


No. at risk, Seronegative					
REGEN-COV	1633	1429	1325	1260	1224
Usual Care	1520	1308	1173	1088	1059
No. at risk, Seropositive					
REGEN-COV	2636	2452	2322	2252	2201
Usual Care	2636	2503	2375	2292	2243

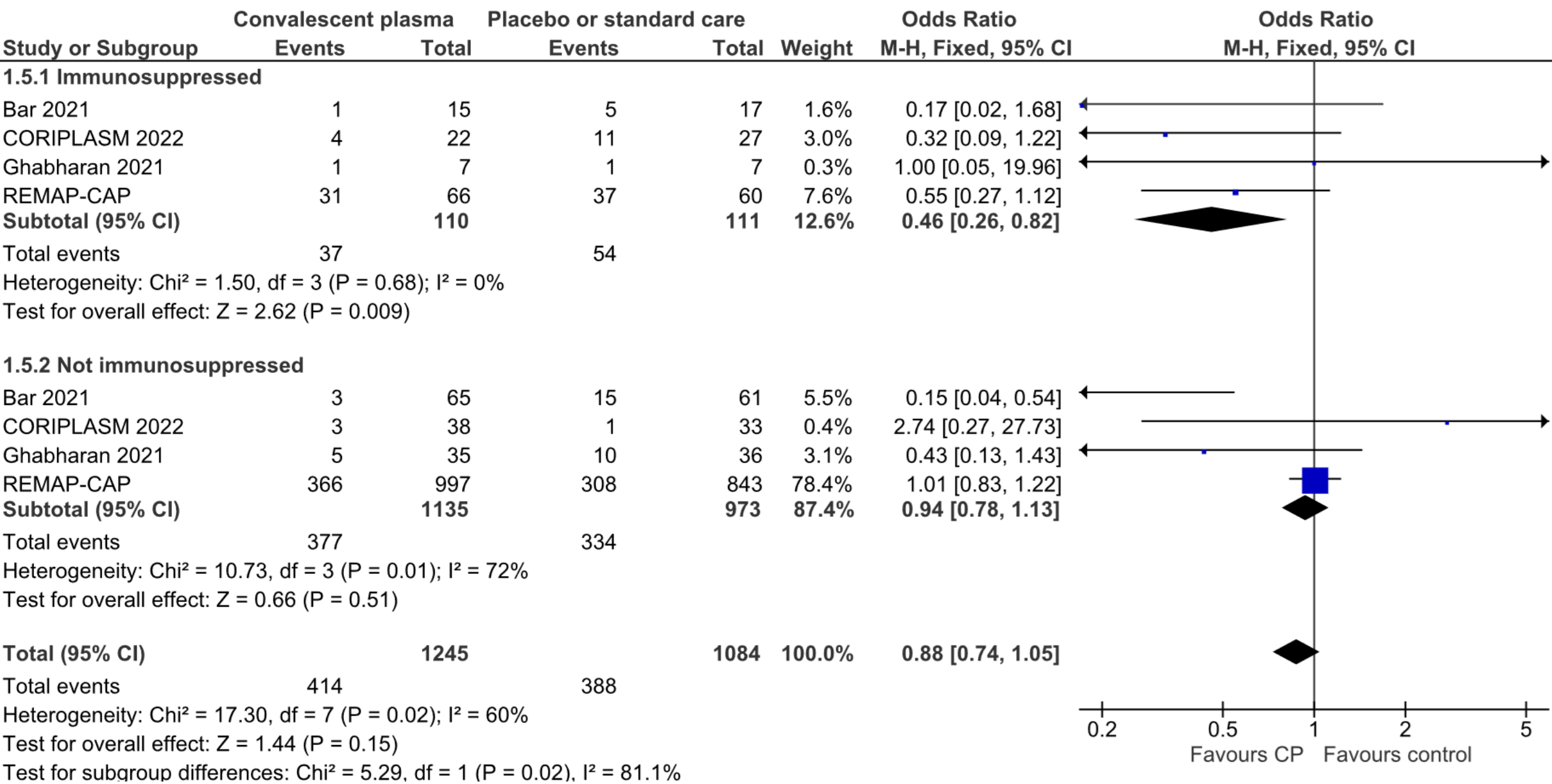
CCP vs. SoC/placebo subgroup antibodies, mortality at day 28



CCP vs. SoC/placebo subgroup antibodies, need for IMV or death by day 28



CCP vs. SoC/placebo subgroup immunosuppression, mortality at day 28



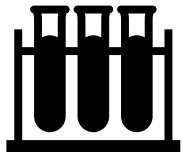
What we know about passive immune therapy treating SARS-CoV-2 infections in inpatients in pre-omicron era



No benefit seen for unselected adult population requiring hospital or ICU care

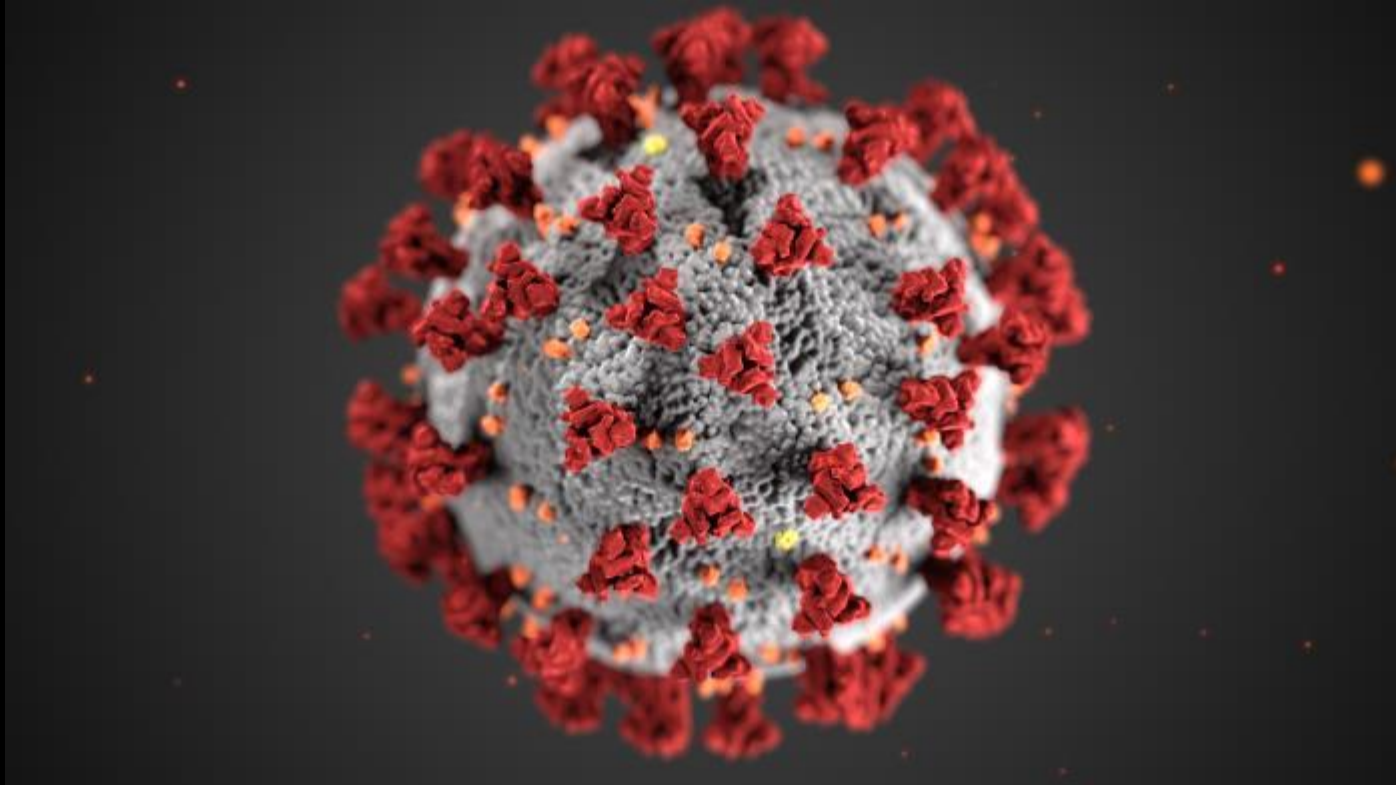


May be a benefit in immunocompromised patients



Benefit in antibody negative patients

In the era of Omicron and vaccination



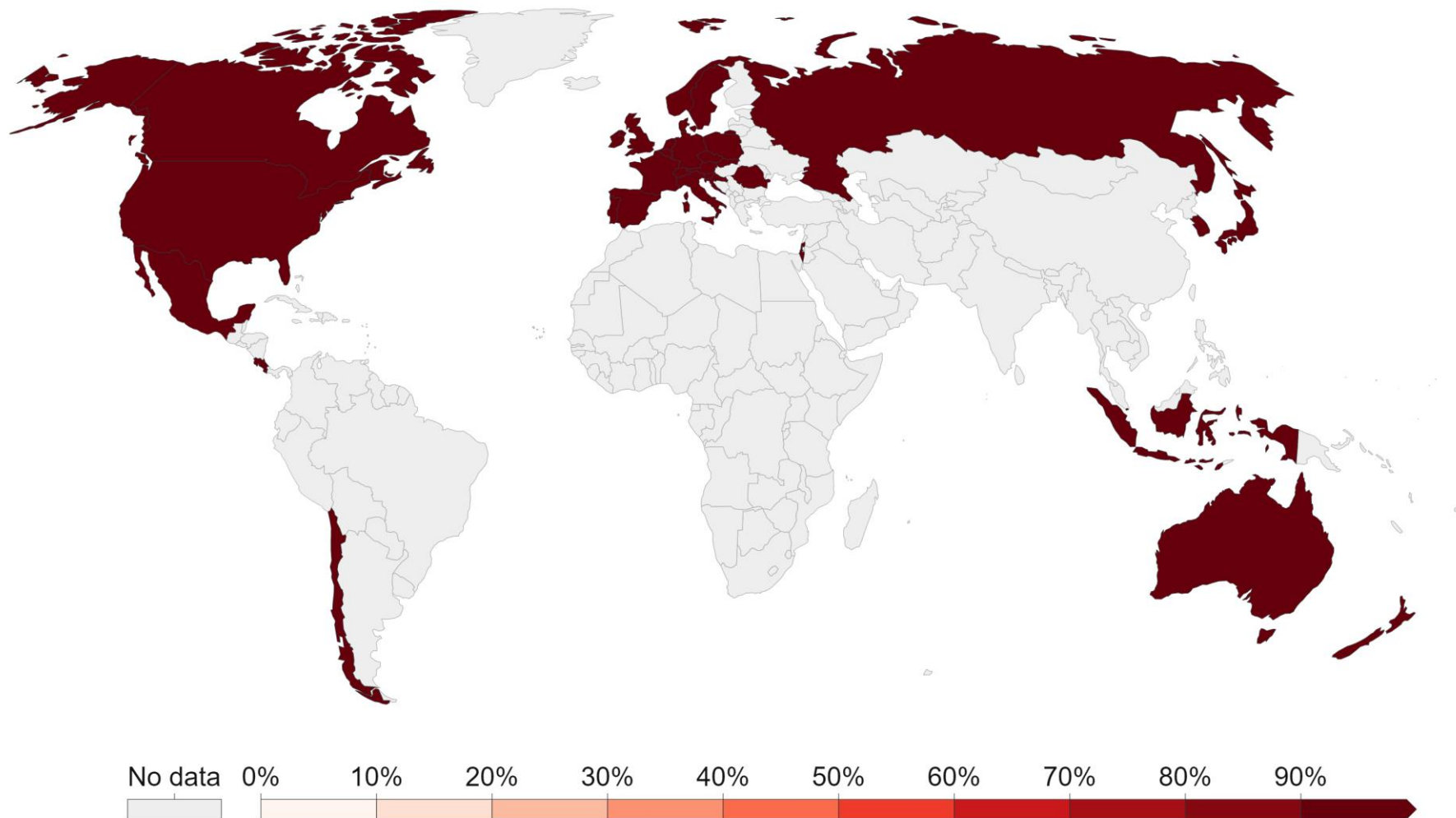
Immunosuppressed population	Estimated number in England November 2020
Receiving immunosuppressive therapy e.g. rituximab	114,000
Blood cancers	188,000
Other solid cancers receiving chemotherapy	56,000
Lung cancer receiving radical radiotherapy	3,000
Long-term steroids	1,367
Stem cell transplants (within 6 months)	2,000
Stem cell transplants + immunosuppression	681
Solid organ transplants	56,000
Total	Approx 500,000

Monoclonal Immune Therapies with licenses/EUA

Monoclonal Ab (mAb)	Site of action	Evidence of resistance (VoC) ≥ 10 fold reduction in neutralization
Bamlanivimab	RBD on spike protein	Yes – beta, gamma, delta, omicron (BA.1, BA.2, BA.2.12.1, BA.4, BA.5, BA.2.75)
Bamlanivimab plus etesevimab	overlapping epitopes on RBD on spike protein	Yes – beta, gamma, omicron (BA.1, BA.2, BA.2.12.1, BA.4, BA.5, BA.2.75)
Casirivimab plus imdevimab	non-overlapping epitopes on RBD on spike protein	Yes – omicron (BA.1, BA.2, BA.2.12.1, BA.4, BA.5, BA.2.75)
Tixagevimab plus cilgavimab (long-acting)	non-overlapping epitopes on RBD on spike protein	Yes – omicron (BA.1, BA.4, BA.5, BA.2.75)
Sotrovimab	RBD of the spike protein conserved between SARS-CoV and SARS-CoV-2	Yes – omicron (BA.2, BA.2.12.1, BA.4, BA.5, BA.2.75)
Regdanvimab	RBD on spike protein	Yes – beta, gamma, delta, omicron (BA.2, BA.2.12.1, BA.4, BA.5, BA.2.75)
Bebtelovimab (outpatients only)	RBD on spike protein	No
Adintrevimab	RBD on spike protein	Yes – omicron (BA.1, BA.2, BA2.121.1, BA.4, BA.5, BA.2.75)

Share of SARS-CoV-2 sequences that are the omicron variant, Sep 12, 2022

Share of omicron variant in all analyzed sequences in the preceding two weeks.



Source: GISAID, via CoVariants.org – Last updated 19 September 2022

OurWorldInData.org/coronavirus • CC BY

Note: This share may not reflect the complete breakdown of cases, since only a fraction of all cases are sequenced. Recently-discovered or actively-monitored variants may be overrepresented, as suspected cases of these variants are likely to be sequenced preferentially or faster than other cases.



Visual summary of recommendation

Last updated

16 Sep 2022

Population

This recommendation applies only to people with these characteristics:



Interventions

Disease severity

Non-severe

Absence of signs of severe or critical disease

Severe

Oxygen saturation <90% on room air

Signs of pneumonia

Signs of severe respiratory distress 

Critical

Requires life sustaining treatment

Acute respiratory distress syndrome

Sepsis

Septic shock



Visual summary of recommendation

Last updated

16 Sep 2022

Population

This recommendation applies only to people with these characteristics:

Disease severity

Non-severe

Severe

Critical

Recommendation 1

Supportive care

Strong 

Weak 

or

Casirivimab and imdevimab

Weak 

Strong 



Patients with covid-19



We recommend against treatment with casirivimab-imdevimab





Visual summary of recommendation

Last updated

16 Sep 2022

Population

This recommendation applies only to people with these characteristics:

Disease severity

Non-severe

Severe

Critical

Recommendation 1

Supportive care

Strong 

Weak 

or

Sotrovimab

Weak 

Strong 



Patients with covid-19



We recommend against treatment with sotrovimab

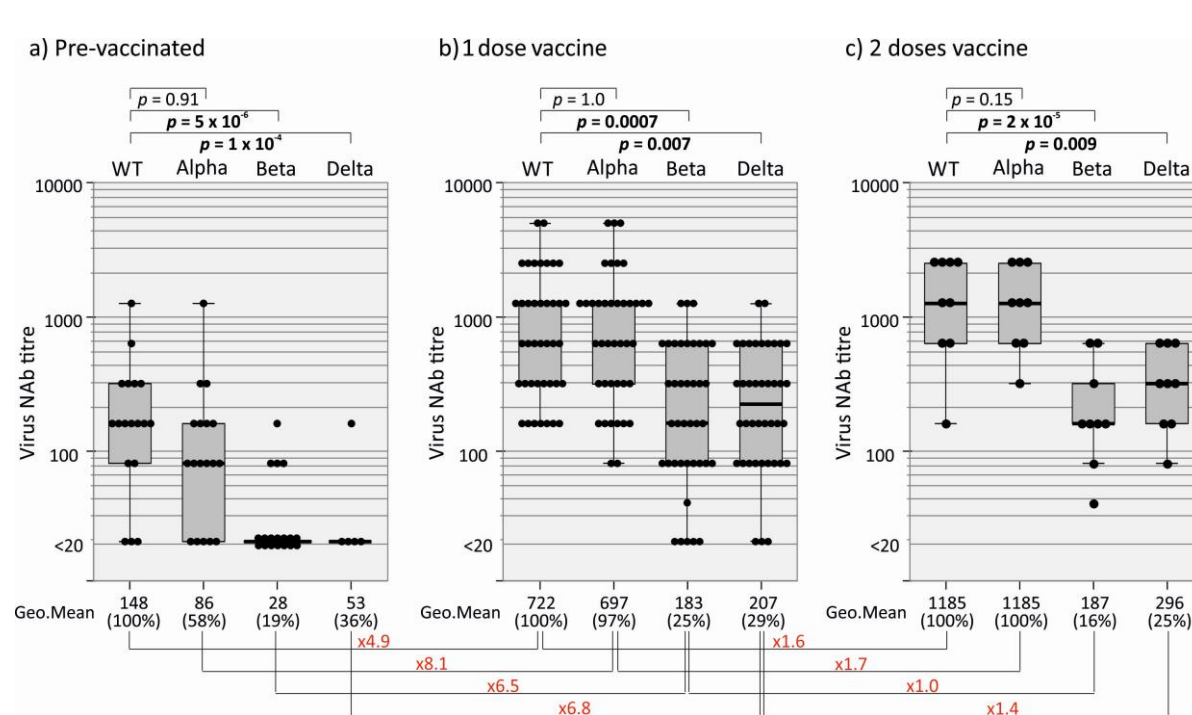


Vaccinated
convalescent
plasma

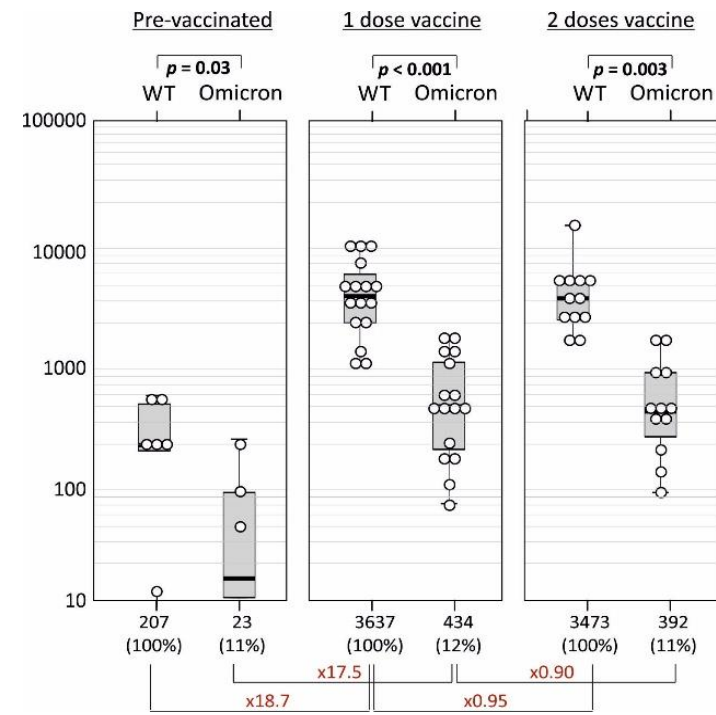


Omicron update on convalescent plasma from infected and vaccinated donors

- A random sample of our convalescent plasma donors, originally infected with wild-type or alpha variant, were tested for neutralising antibodies against alpha, beta, delta and omicron variants after receiving AstraZeneca or Pfizer vaccine (n=134)
- The results showed that vaccinated convalescent donors had developed high-titres of neutralising antibodies also against omicron variant, not circulating at the time of sampling



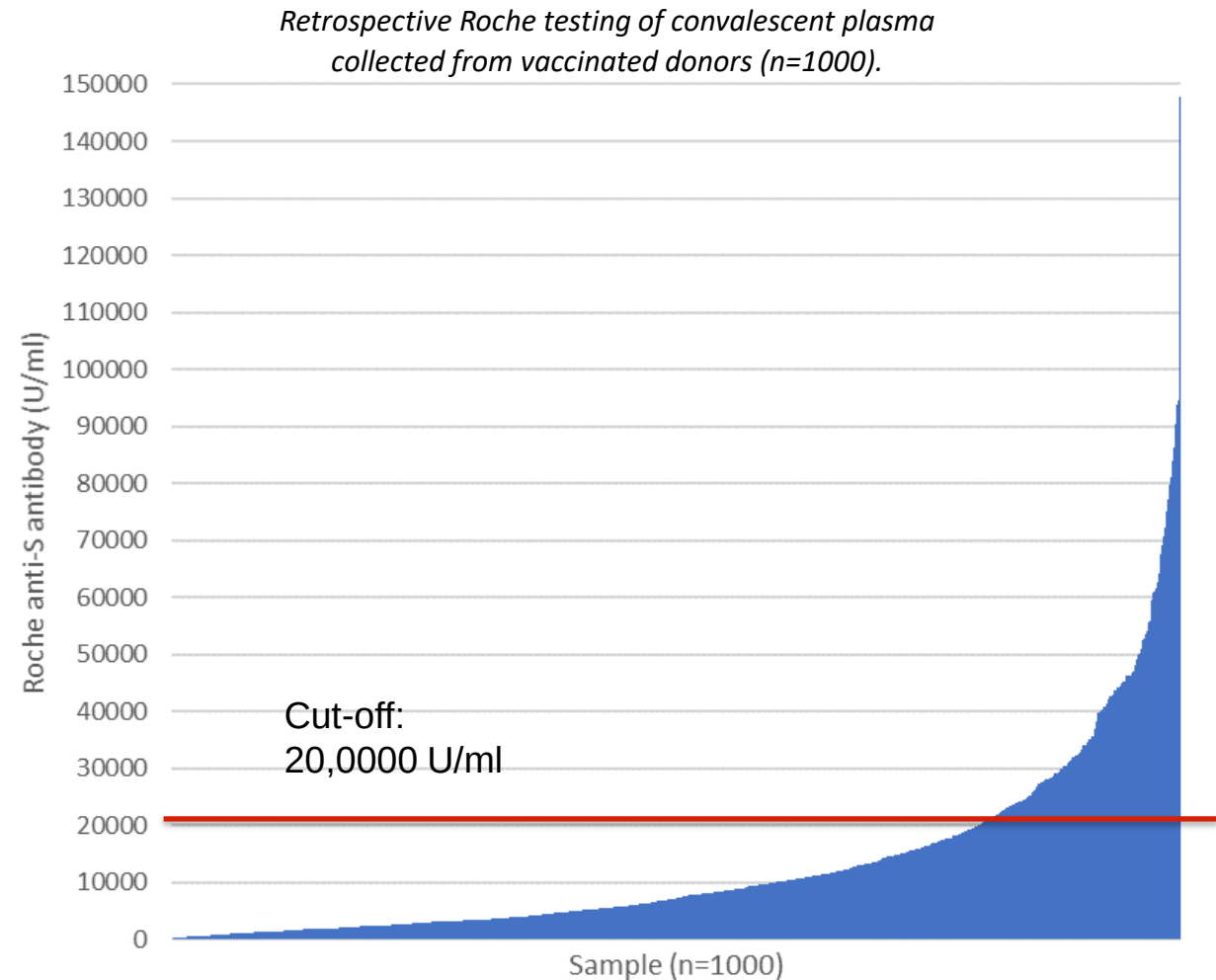
Live virus microneutralisation assay, titres scored visually based on 90% inhibition.



Live virus focus reduction microneutralisation assay, titres calculated based on 50% of inhibition.

Omicron update on convalescent plasma from infected and vaccinated donors

- Previously used EUROimmun IgG s/co over 6.0 as threshold for high titre plasma in UK. Neutralising antibodies against WT variant at least 1:100
- 1000 convalescent plasma donations were selected for retrospective testing
 - Selection of high-titre donations (EUROimmun IgG s/co over 10.0)
 - All donors known to have received at least one dose of vaccine prior to plasma collection in February-March 2021 (vaccination data from NHS Digital)
 - 200 donations contained high levels of antibodies based on Roche Elecsys anti-S assay (titre over 20,000 U/ml) and these also showed good levels of neutralising antibodies against Omicron variant (median 1:1068)





Hypothesis

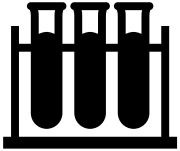
Treatment with high-titre ABO-compatible convalescent plasma from donors who have already been vaccinated reduces the risk of hospitalisation (defined as at least one overnight inpatient hospital stay with progressive COVID-19 symptoms) or death within 28 days in people with mild COVID-19 symptoms aged 70 years or over, or who are under 70 years with multiple comorbidities or immunosuppression.



Hypothesis

Treatment with high-titre ABO-compatible convalescent plasma from donors who have already been vaccinated improves survival to hospital discharge with reduced use of ICU-level organ support in hospitalised patients with immunosuppression.

What we know about passive immune therapy in omicron era



Most monoclonal therapies with a license or EUA do not neutralise omicron variants



Polyclonal therapy – vaccinated convalescent plasma does neutralise omicron – selected plasma – high antibody threshold. Plasma can neutralize variants not detected at time of collection



Need more evidence from ongoing trials REMAP-CAP (inpatients) and COVIC-19 (outpatients)



THANK YOU



Can you help someone else recover to
COVID-19: be the difference