EMA Workshop

Primary efficacy endpoints for antivirals and monoclonal antibodies
intended to treat COVID-19 and influenza.
05-06 June 2025

Peter Horby
Pandemic Sciences Institute, University of Oxford

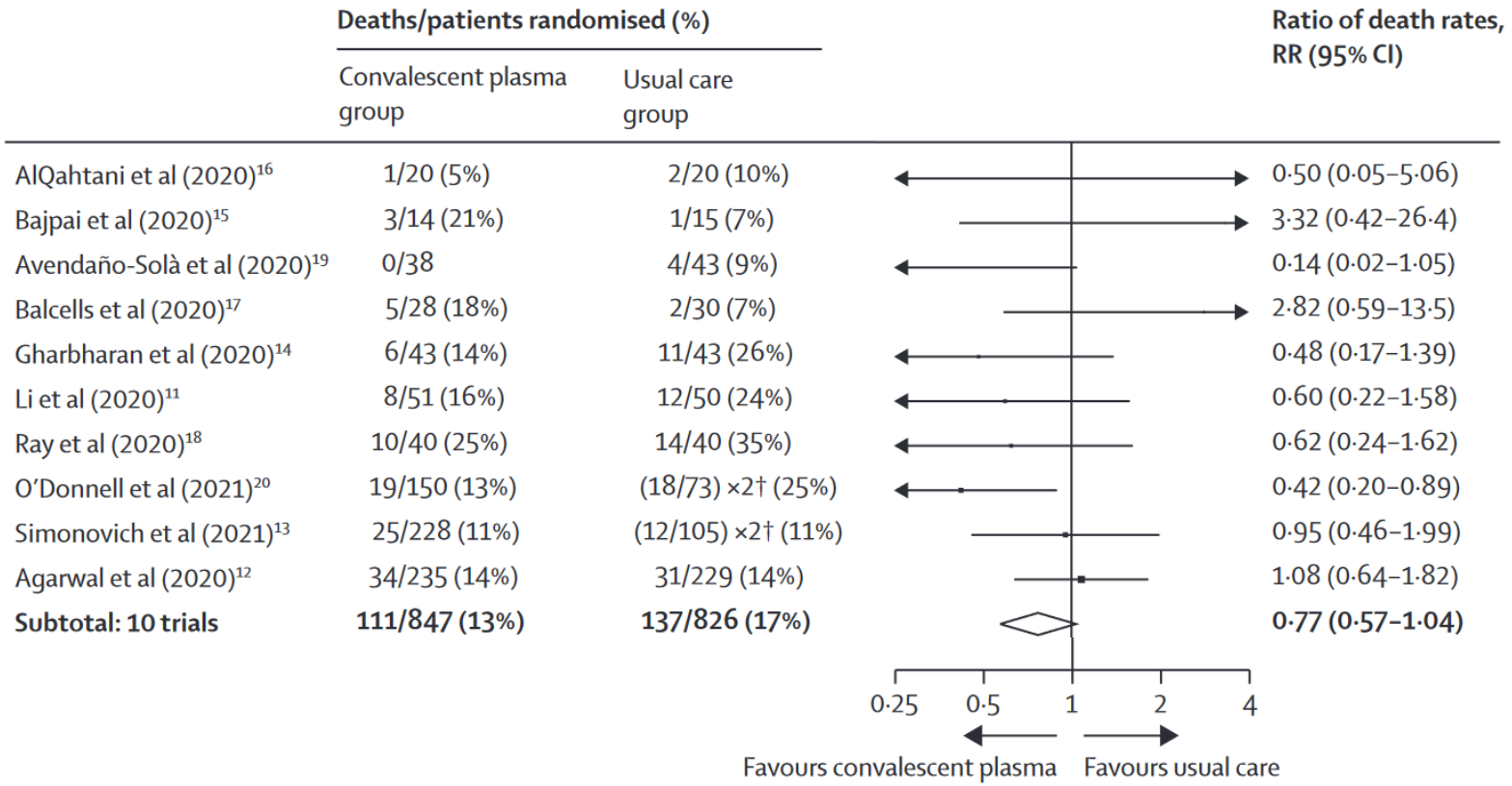
Challenges in evidence generation for COVID-19 mAbs

Challenges in evidence generation for mAbs

1. Sample size
2. Choice of primary analysis population
3. Dose
4. Resistance

1. Sample size? Convalescent plasma

- By March 2021, ten trials had included 1,700 inpatients
- One encouraging trial

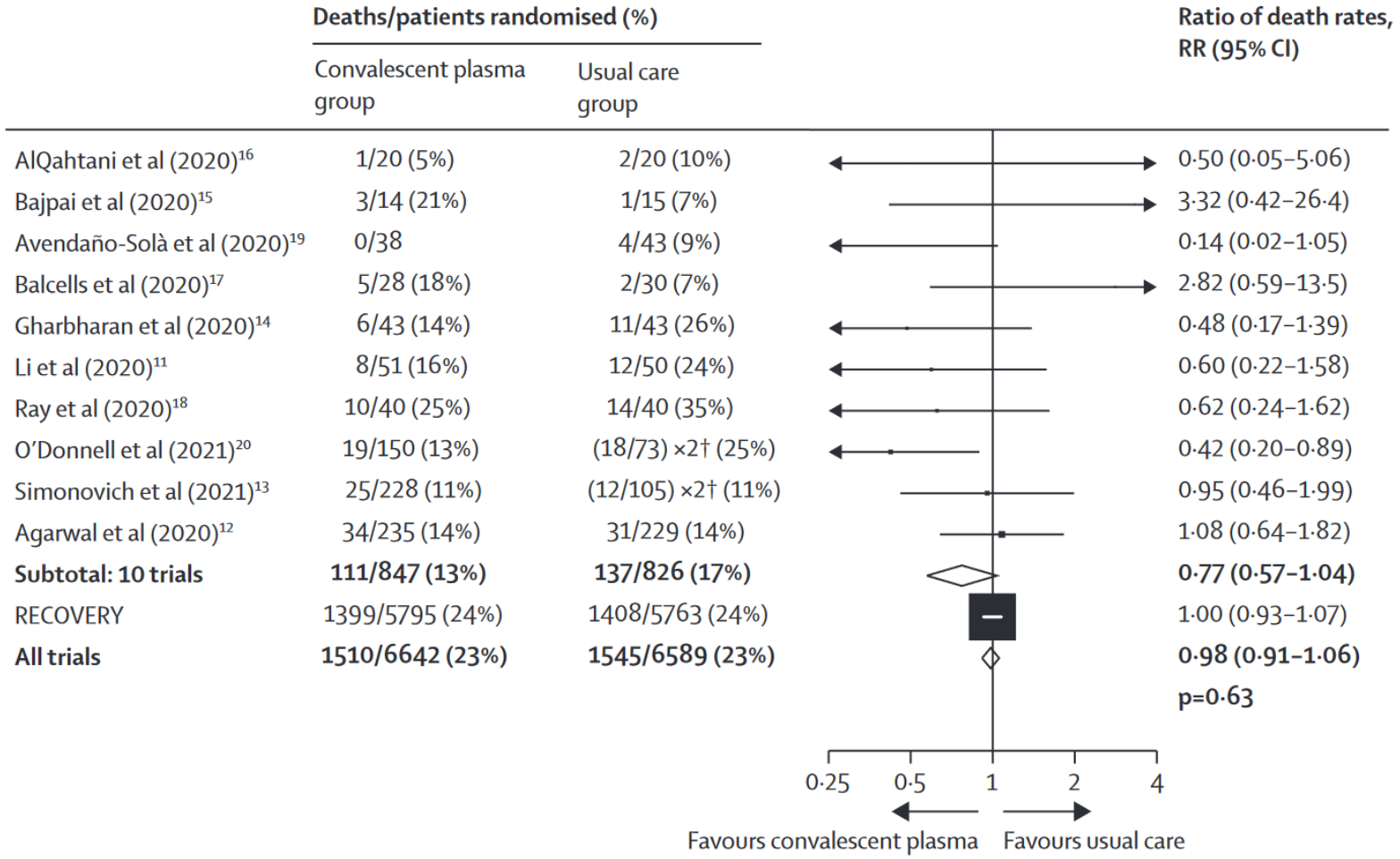


	Deaths/patients randomised (%)		Ratio of death rates, RR (95% CI)
	Convalescent plasma group	Usual care group	
AlQahtani et al (2020)[16]	1/20 (5%)	2/20 (10%)	0·50 (0·05–5·06)
Bajpai et al (2020)[15]	3/14 (21%)	1/15 (7%)	3·32 (0·42–26·4)
Avendaño-Solà et al (2020)[19]	0/38	4/43 (9%)	0·14 (0·02–1·05)
Balcells et al (2020)[17]	5/28 (18%)	2/30 (7%)	2·82 (0·59–13·5)
Gharbharan et al (2020)[14]	6/43 (14%)	11/43 (26%)	0·48 (0·17–1·39)
Li et al (2020)[11]	8/51 (16%)	12/50 (24%)	0·60 (0·22–1·58)
Ray et al (2020)[18]	10/40 (25%)	14/40 (35%)	0·62 (0·24–1·62)
O'Donnell et al (2021)[20]	19/150 (13%)	(18/73) ×2† (25%)	0·42 (0·20–0·89)
Simonovich et al (2021)[13]	25/228 (11%)	(12/105) ×2† (11%)	0·95 (0·46–1·99)
Agarwal et al (2020)[12]	34/235 (14%)	31/229 (14%)	1·08 (0·64–1·82)
Subtotal: 10 trials	**111/847 (13%)**	**137/826 (17%)**	**0·77 (0·57–1·04)**

Taken together, trials were consistent with **no effect** of CP, or a **40% reduction in mortality**

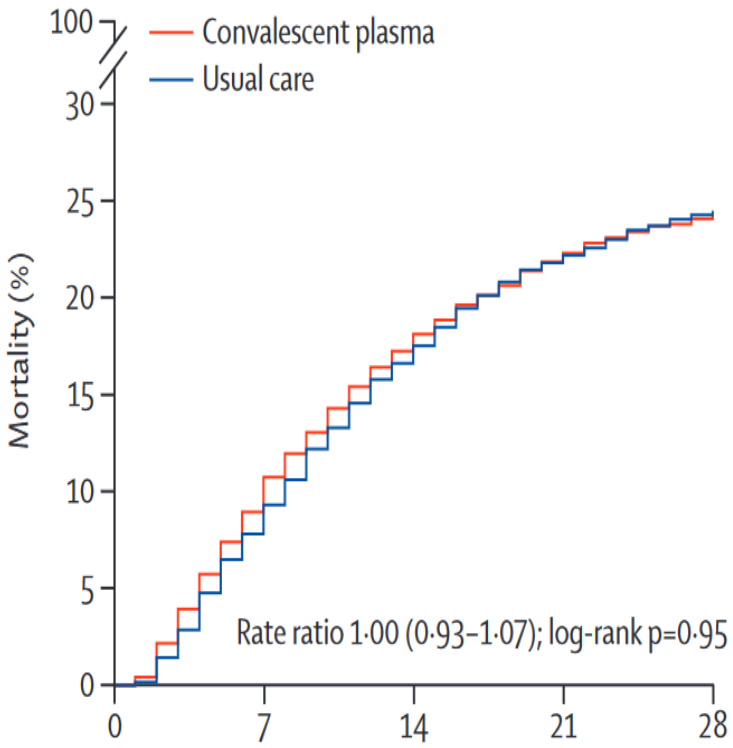
1. Sample size? Convalescent plasma – x7

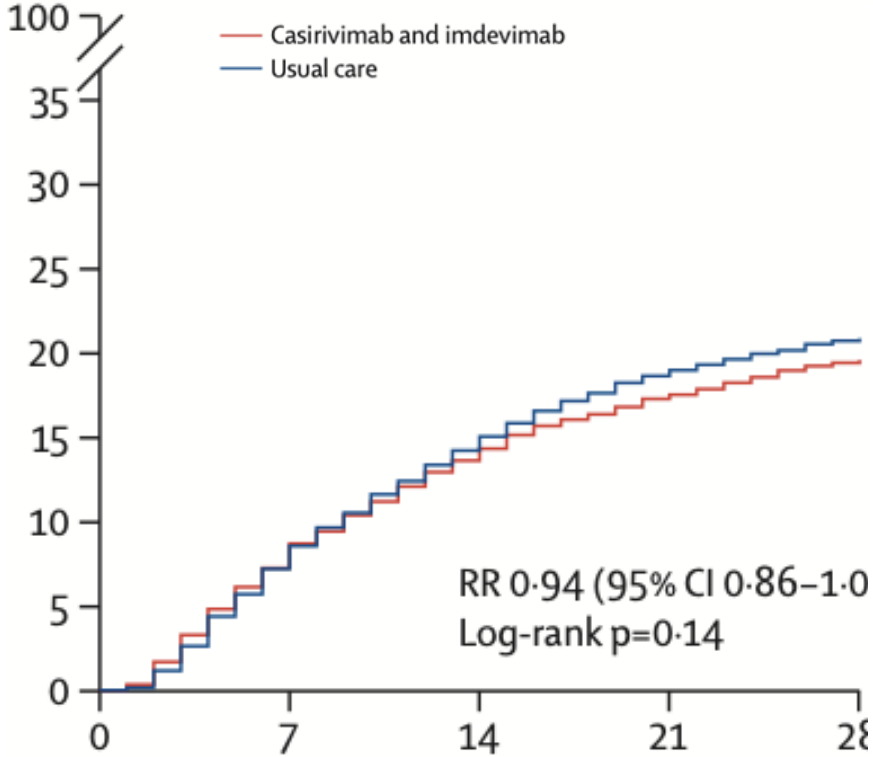
- 1673 vs 11558 patients

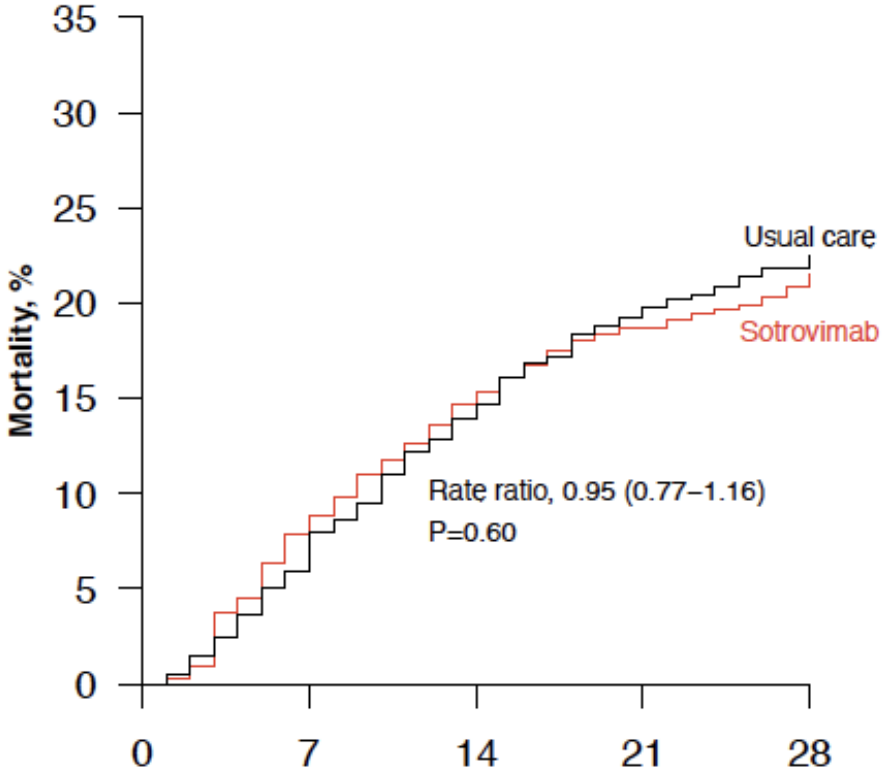


	Deaths/patients randomised (%)		Ratio of death rates, RR (95% CI)
	Convalescent plasma group	Usual care group	
AlQahtani et al (2020)[16]	1/20 (5%)	2/20 (10%)	0·50 (0·05–5·06)
Bajpai et al (2020)[15]	3/14 (21%)	1/15 (7%)	3·32 (0·42–26·4)
Avendaño-Solà et al (2020)[19]	0/38	4/43 (9%)	0·14 (0·02–1·05)
Balcells et al (2020)[17]	5/28 (18%)	2/30 (7%)	2·82 (0·59–13·5)
Gharbharan et al (2020)[14]	6/43 (14%)	11/43 (26%)	0·48 (0·17–1·39)
Li et al (2020)[11]	8/51 (16%)	12/50 (24%)	0·60 (0·22–1·58)
Ray et al (2020)[18]	10/40 (25%)	14/40 (35%)	0·62 (0·24–1·62)
O'Donnell et al (2021)[20]	19/150 (13%)	(18/73) ×2† (25%)	0·42 (0·20–0·89)
Simonovich et al (2021)[13]	25/228 (11%)	(12/105) ×2† (11%)	0·95 (0·46–1·99)
Agarwal et al (2020)[12]	34/235 (14%)	31/229 (14%)	1·08 (0·64–1·82)
Subtotal: 10 trials	**111/847 (13%)**	**137/826 (17%)**	**0·77 (0·57–1·04)**
RECOVERY	1399/5795 (24%)	1408/5763 (24%)	1·00 (0·93–1·07)
All trials	**1510/6642 (23%)**	**1545/6589 (23%)**	**0·98 (0·91–1·06)**
			p=0·63

2. Population? All participants







Convalescent plasma
N=1158

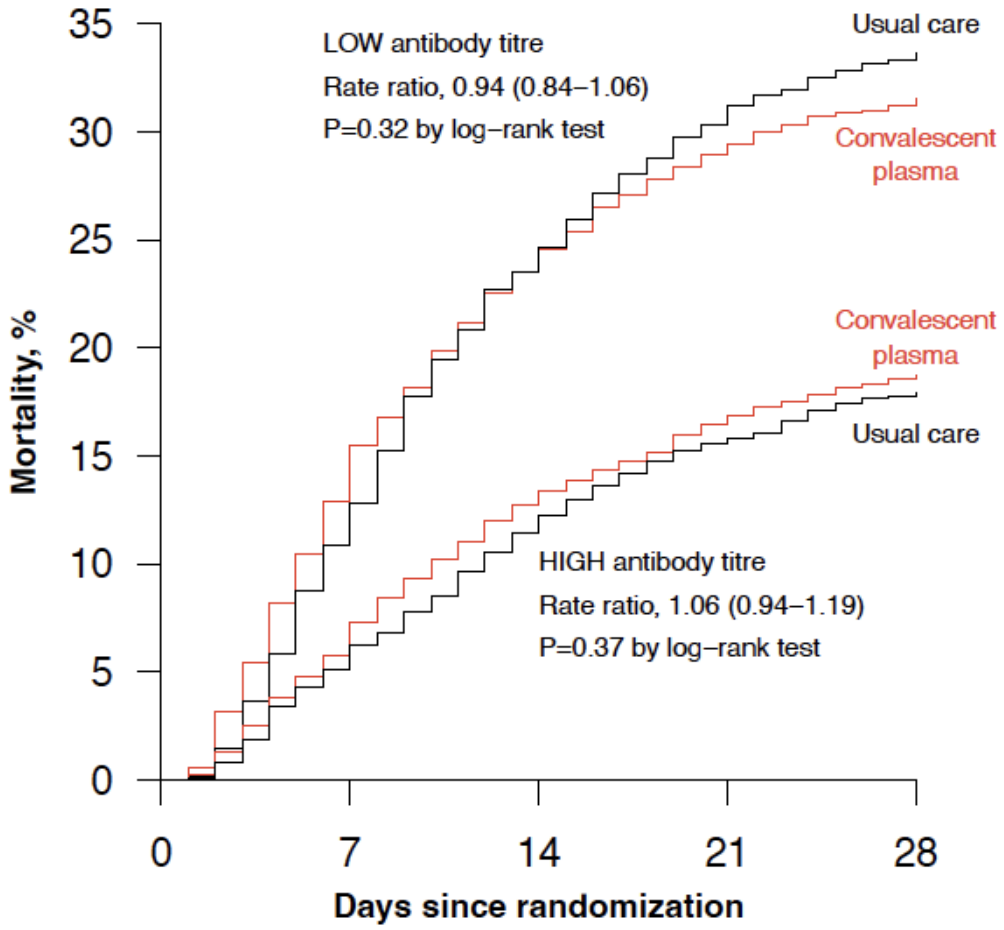
REGEN-CoV2
N=9785

Sotrovimab
N=1723

Convalescent plasma

- Mortality much higher in patients with low anti-SARS-CoV-2 antibody titre (Spike IgG) vs high titre*
- *Possible* small benefit in patients who were anti-SARS-COV-2 antibody negative at the time of entry

Figure S1: Mortality at 28 days, According to Recipient Antibody Titre

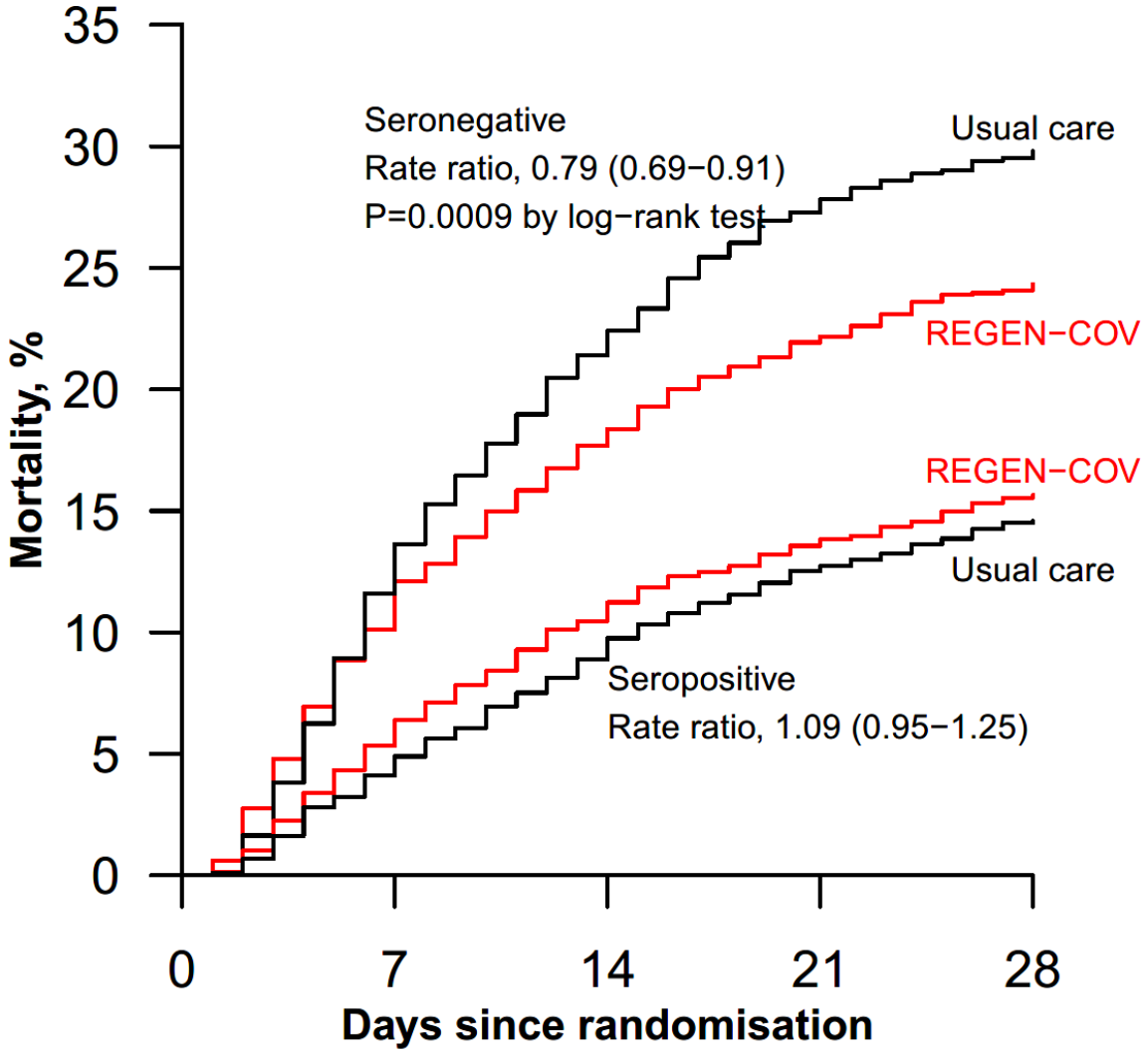


* <8 x10^6 units; ≥8 x10^6 units. *Lancet Infect Dis* 2020; **20:** 1390–400.

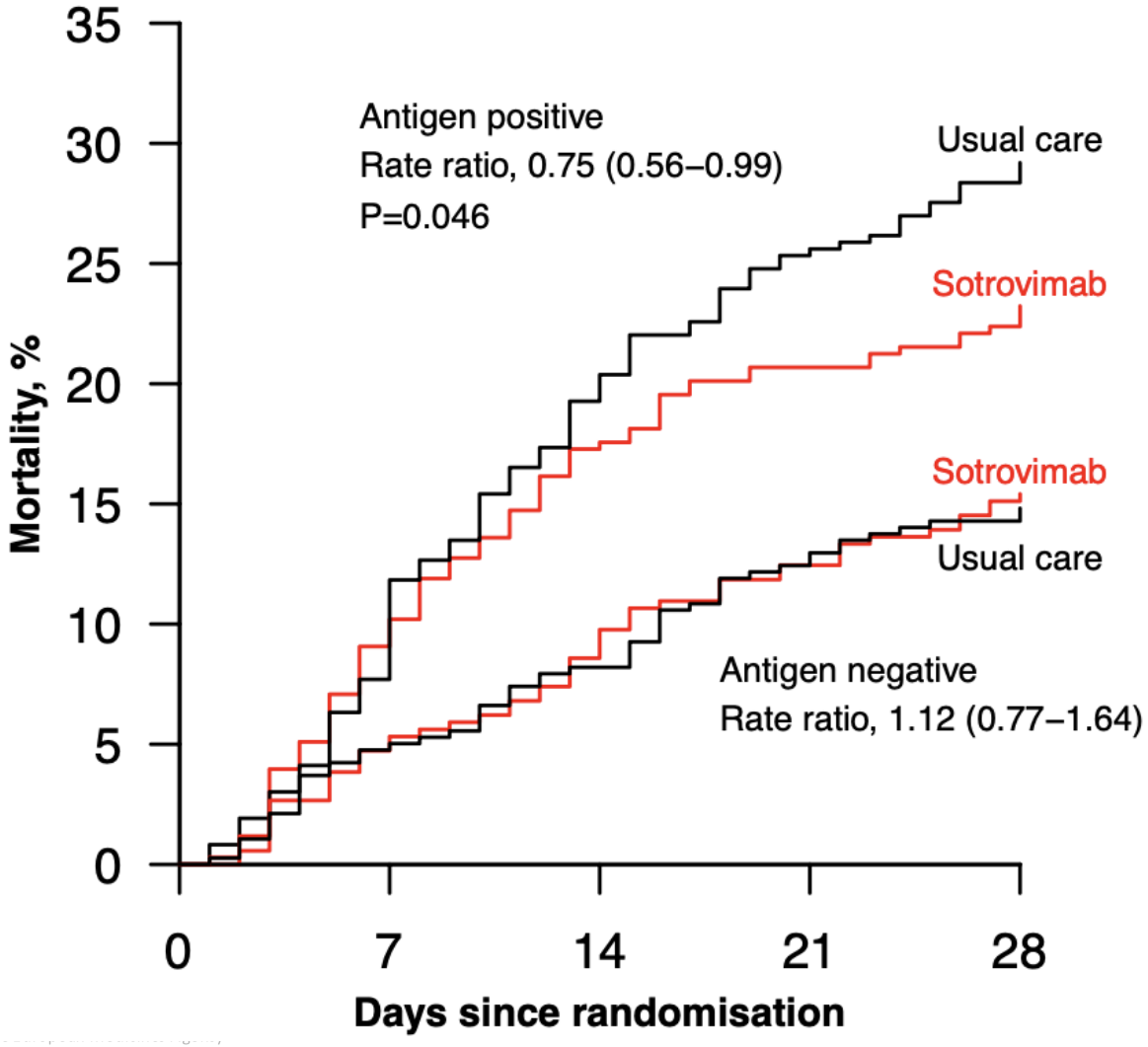
mAbs

Mortality much higher in sero –ve / antigen +ve patients **AND** therapeutic effect only observed in this population

Casirivimab + imdevimab



Sotrovimab



Selection of biomarker critical

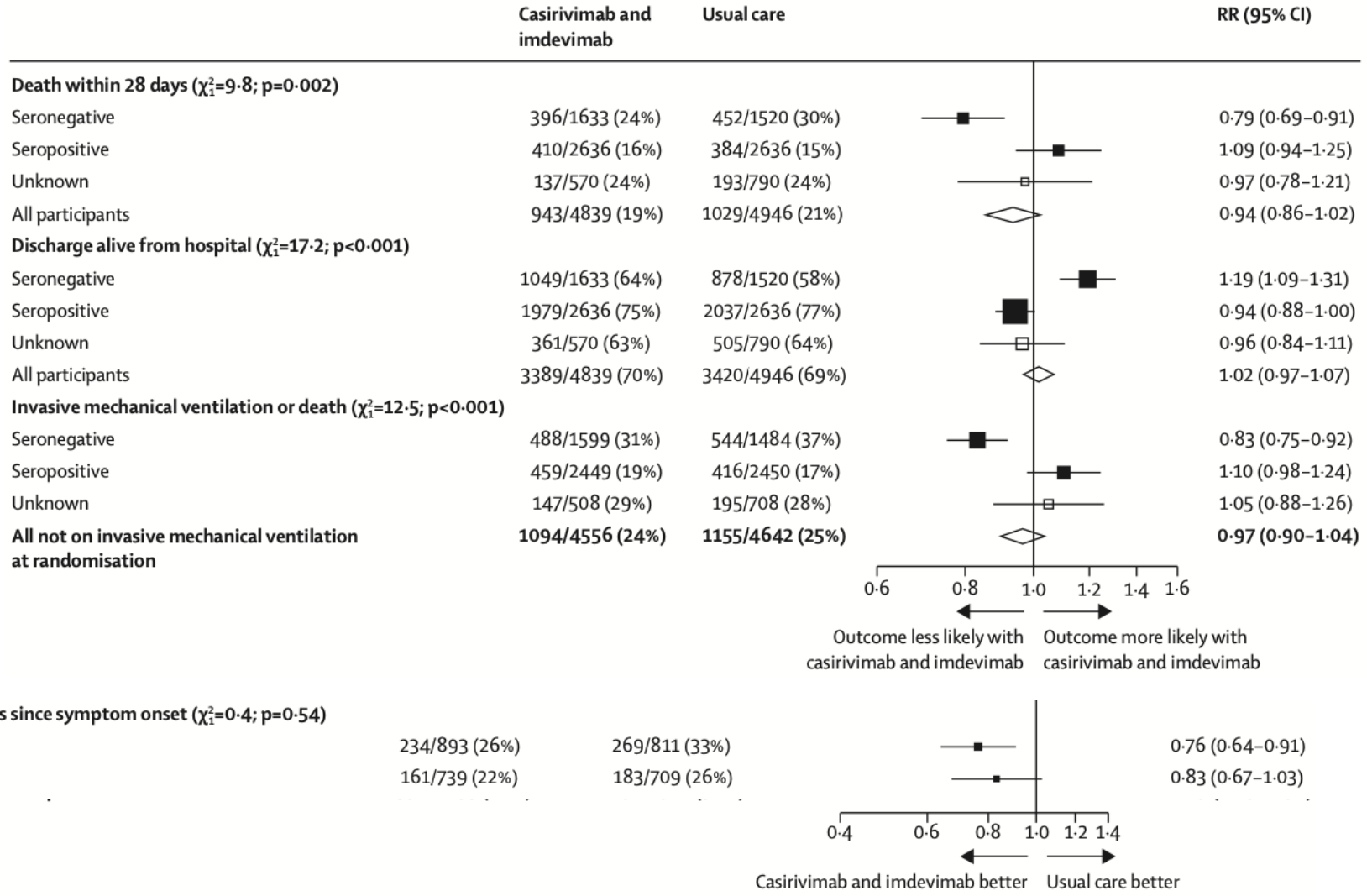
Sotrovimab: September 2023

- Only 19% participants anti-S negative (vaccination +/- prior infection)
- 70% anti-N negative but anti-N seronegativity no longer associated with increased mortality (20% seropositive vs 21% seronegative). In contrast with RECOVERY participants recruited in 2020/21 (14% seropositive vs 30% seronegative). Suggests anti-N serostatus is no longer a good marker of immune response to the acute infection.
- Viral nucleocapsid antigenemia – indicates acute infection and associated with outcome and treatment response ACTIV-3/TICO

Lancet Respir Med 2022; 10: 972–84.
Ann Intern Med. 2022 Feb;175(2):234-243

Time since onset vs. biomarker (Ab or Ag)

Test for evidence of heterogeneity of treatment effect



	Casirivimab and imdevimab	Usual care	RR (95% CI)
Death within 28 days (χ^2_1=9·8; p=0·002)			
Seronegative	396/1633 (24%)	452/1520 (30%)	0·79 (0·69–0·91)
Seropositive	410/2636 (16%)	384/2636 (15%)	1·09 (0·94–1·25)
Unknown	137/570 (24%)	193/790 (24%)	0·97 (0·78–1·21)
All participants	943/4839 (19%)	1029/4946 (21%)	0·94 (0·86–1·02)
Discharge alive from hospital (χ^2_1=17·2; p<0·001)			
Seronegative	1049/1633 (64%)	878/1520 (58%)	1·19 (1·09–1·31)
Seropositive	1979/2636 (75%)	2037/2636 (77%)	0·94 (0·88–1·00)
Unknown	361/570 (63%)	505/790 (64%)	0·96 (0·84–1·11)
All participants	3389/4839 (70%)	3420/4946 (69%)	1·02 (0·97–1·07)
Invasive mechanical ventilation or death (χ^2_1=12·5; p<0·001)			
Seronegative	488/1599 (31%)	544/1484 (37%)	0·83 (0·75–0·92)
Seropositive	459/2449 (19%)	416/2450 (17%)	1·10 (0·98–1·24)
Unknown	147/508 (29%)	195/708 (28%)	1·05 (0·88–1·26)
All not on invasive mechanical ventilation at randomisation	**1094/4556 (24%)**	**1155/4642 (25%)**	**0·97 (0·90–1·04)**

0·6 0·8 1·0 1·2 1·4 1·6

Outcome less likely with casirivimab and imdevimab

Outcome more likely with casirivimab and imdevimab

Days since symptom onset (χ^2_1=0·4; p=0·54)			
≤7	234/893 (26%)	269/811 (33%)	0·76 (0·64–0·91)
>7	161/739 (22%)	183/709 (26%)	0·83 (0·67–1·03)

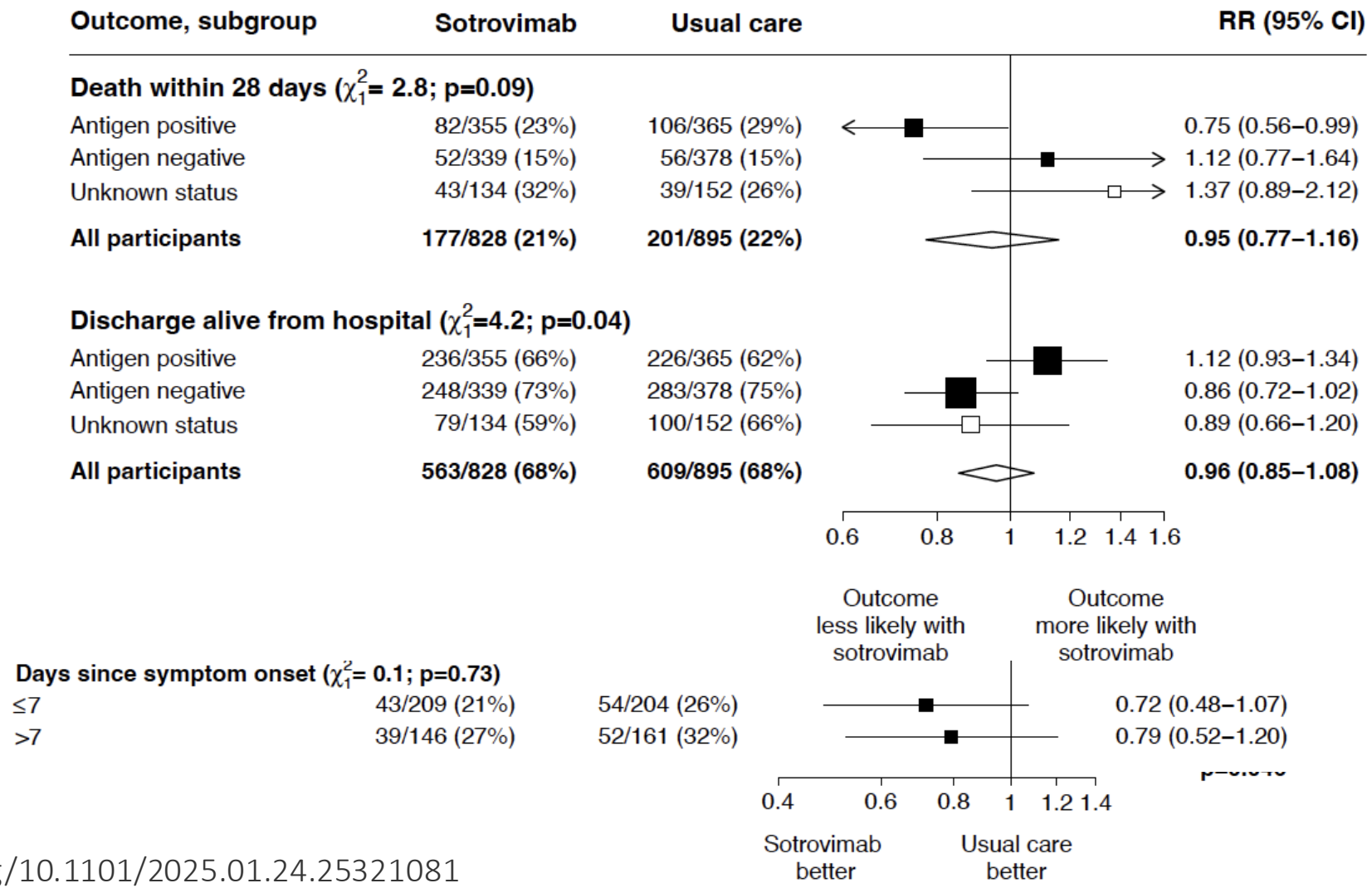
0·4 0·6 0·8 1·0 1·2 1·4

Casirivimab and imdevimab better

Usual care better

Time since onset vs. biomarker (Ab or Ag)

Figure 3: Primary and secondary outcomes, overall and by baseline antigen status



doi: https://doi.org/10.1101/2025.01.24.25321081

Specification of primary analysis critical

Convalescent plasma

- All randomised participants (whole population)

REGEN-CoV2

- *'the primary outcome will first be assessed among participants who are known to be seronegative at randomisation. If the null hypothesis is rejected in the seronegative group at 2-tailed p=0.05, then the primary outcome will be assessed among the whole population.'*

Sotrovimab

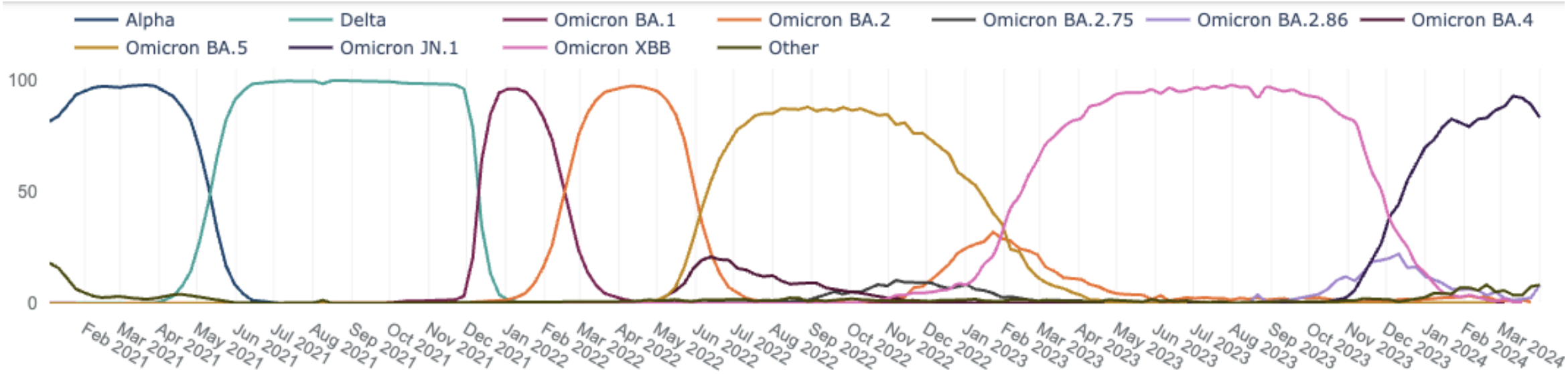
- *'primary outcome will first be assessed among participants who are known to have high antigen at randomisation. If the null hypothesis is rejected in the high antigen group at 2-tailed p=0.05, then the primary outcome will be assessed among the whole population'*

3. Dose of antibody

	Dose	mg IgG
Convalescent plasma	2 units high titre CVP	100-800mg?*
REGEN-CoV2	8g	8000 mg
Sotrovimab	1g	1000 mg

*PLoS One. 2024 Nov 1;19(11):e0311777.

4. Resistance – Relative? Overcome by dose?



<u>Omicron and lineages</u>

REGEN-CoV2

Significant resistance

Sotrovimab

Omicron BA.1 ~5 fold reduction

BA.2, BA.4, BA.5 and XBB ~20 fold (but IC50 still well below MIC in plasma)

BA.2.86 & JN.1 highly resistant

Viral load

	Sotrovimab (n=355)	Usual care (n=365)	RR (95% CI) or mean difference	p-value
Primary outcome				
28-day mortality	82 (23%)	106 (29%)	0.75 (0.56-0.99)	0.046
Secondary outcomes				
Median (IQR) time to being discharged alive, days	13 (7 to >28)	16 (7 to >28)		
Discharged from hospital within 28 days	236 (66%)	226 (62%)	1.12 (0.93-1.34)	
Receipt of invasive mechanical ventilation or death*	82/340 (24%)	102/354 (29%)	0.82 (0.64-1.03)	
Invasive mechanical ventilation	14/340 (4%)	11/354 (3%)	1.71 (0.81-3.61)	
Death	74/340 (22%)	100/354 (28%)	0.74 (0.58-0.95)	
Subsidiary clinical outcomes				
Use of ventilation†	41/269 (15%)	41/267 (15%)	0.97 (0.66-1.44)	
Non-invasive ventilation	40/269 (15%)	41/267 (15%)	0.95 (0.64-1.41)	
Invasive mechanical ventilation	6/269 (2%)	3/267 (1%)	1.82 (0.47-7.11)	
Successful cessation of invasive mechanical ventilation ‡	5/15 (33%)	3/11 (27%)	1.07 (0.25-4.65)	
Use of haemodialysis or haemofiltration §	12/347 (3%)	6/356 (2%)	1.97 (0.77-5.06)	
Virological outcomes				
Baseline-adjusted viral load (log copies/ml) on day 3	4.89 (0.10)	4.94 (0.10)	-0.05 (-0.32, 0.23)	
Baseline-adjusted viral load (log copies/ml) on day 5	4.26 (0.11)	4.35 (0.10)	-0.09 (-0.38, 0.20)	

Summary of some challenges

1. Sufficiently large trial
2. Choice of target population
   - Enrichment for higher event rate
   - Enrichment for probability of treatment effect
   - Selection of biomarker
   - Specification of primary analysis
3. Antibody dose
4. Resistance