Randomized immunogenicity and safety study of heterologous versus homologous COVID-19 booster vaccination in previous recipients of two doses of CoronaVac COVID-19 vaccine

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Abstract

The inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac, Sinovac) is one of the most widely used COVID-19 vaccines and is administered in a two-dose schedule. A third dose of the homologous or a different vaccine may boost waning immunity and provide improved protection particularly against emerging new coronavirus variants.

Methods

We conducted a phase 4 randomised single-blind two-centre safety and immunogenicity study of a third heterologous booster dose of either the recombinant adenoviral-vectored ChAdOx1 nCoV-19 vaccine (AZD1222, AstraZeneca), an mRNA vaccine (BNT162b2, Pfizer/BioNTech), or a recombinant adenoviral vectored vaccine (AD26.COV2-S, Janssen), compared with a third homologous booster dose of CoronaVac in Brazilian adults who had received two doses of CoronaVac 6 months previously.

The primary outcome was non-inferiority of anti-spike IgG antibodies 28 days after the booster dose in the heterologous boost groups compared with homologous regimen. Secondary outcomes included neutralising antibody titres at day 28, local and systemic reactogenicity profiles, adverse events and serious adverse events.

Results

Between 16 August 2021 and 1 September 2021, 1240 participants were randomised in São Paulo and Salvador, of whom 1239 were vaccinated. 1205 returned for their Day 28 visit and were eligible for inclusion in the primary analysis. Antibody levels were low prior to administration of a booster dose with 20.4 % (CI) of adults aged 18-60 years and 8.9% (CI) of older adults (aged more than 60 years) having detectable neutralising antibodies.

At Day 28 after the booster vaccine all groups had a substantial rise in IgG antibody levels. The geometric fold-rise from baseline to day 28 was 90 (95%CI 77, 104) for ChAdOx1 nCoV-19, 12 (95%CI 11, 14) for CoronaVac, 77 (95%CI 67, 88) for AD26.COV2-S, and 152 (95%CI 134, 173) for BNT162b2.

All heterologous regimes had anti-spike IgG responses at Day 28 that were superior to homologous booster responses. Geometric mean ratios (heterologous vs homologous) were 7.0 (95%CI 6.1, 8.1) for ChAdOx1 nCoV-19, 6.7 (95% CI 5.8, 7.7) for AD26.COV2-S vaccine, and 13.4 (95% CI 11.6, 15.3) for BNT162b2.

All heterologous boost regimens induced high levels of pseudovirus neutralising antibodies with 100% seropositivity in all groups except for the homologous boost in older adults which achieved 66.7% seropositivity. Geometric mean ratios (heterologous vs homologous) were 10.6 (95%CI 7.2, 15.6) for ChAdOx1 nCoV-19, 8.7 (95% CI 5.9, 12.9) for AD26.COV2-S vaccine, and 21.5 (95% CI 14.5, 31.9) for BNT162b2.

Conclusion

Antibody responses were low at 6 months after prior immunisation with two doses of CoronaVac, However, all four vaccines administered as a third dose induced a significant increase in binding and neutralising antibody, which may improve protection against infection.

Funding

The study was funded by the Ministry of Health, Brazil, and sponsored by Instituto D'Or de Pesquisa e Ensino (IDOR). The investigators acknowledge, in-kind support from AstraZeneca for the serological assays presented in this manuscript.

Study registration: Registro Brasileiro de Ensaios Clínicos (RBR – 9nn3scw)

Research in Context

Evidence before this study

By December 2021 8.6 billion doses of COVID-19 vaccines had been deployed worldwide to reduce severe disease and death caused by the SARS-CoV-2. The most widely used vaccines are mRNA, viral vector and inactivated vaccines, with widespread 2 dose priming undertaken in LMICs with the inactivated vaccines from Sinovac and Sinopharm. As a result of waning immunity after 2 doses of COVID-19 vaccines and some evidence of reduced effectiveness, many countries are now considering offering 3rd or booster doses. We searched PubMed for studies in 2021 on booster doses of vaccines for individuals who had received 2 priming doses of the inactivated vaccine, CoronaVac. We found that heterologous boosting of CoronaVac with recombinant adenovirus type-5 COVID-19 vaccine produced greater neutralising antibody titres than homologous boosting in a randomised trial in China[1]. Similar findings are included in a preprint from Thailand comparing heterologous boosting with ChAdOx1 nCoV-19, BNT162b2 or BBIBP-CorV (Sinopharm, Beijing, China), 3-4 months after CoronaVac.

Added Value of this study

We report a comprehensive analysis of the immunogenicity and safety of homologous and heterologous boosting of the inactivated vaccine CoronaVac. We show that there are low levels of antibody present at 6 months after 2 doses of CoronaVac and largely undetectable neutralising antibodies. A 3rd dose of CoronaVac boosts these responses but stronger boosts are achieved with 2 different viral vector vaccines tested and the highest antibody levels are observed after an mRNA boost.

Implications of the available evidence

Heterologous boosting of the inactivated vaccine, CoronaVac, results in more robust immune responses than homologous boosting and may enhance protection.

Background

The inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac, Sinovac Life Sciences, China and Instituto Butantan, Brazil) has been widely used in large-scale vaccination programmes in many countries.

In phase 3 randomised controlled clinical trials two-doses of CoronaVac showed varying efficacy against symptomatic COVID-19 disease, with efficacy estimates of 83.5%, 50.7%, and 65.9% in Turkey[2], Brazil[3], and Chile[4]. Efficacy against COVID-19 hospitalisation was higher with 83·7% (95%CI 58·0-93.7) efficacy in Brazil[3] and 87.5% (95% CI, 86.7 to 88.2) in Chile.[4] In real-world use, a test-negative case control study in Brazil showed 46.8% (38.7% to 53.8%) effectiveness against symptomatic infection and 55.5% (46.5% to 62.9%) effectiveness against hospital admission during spread of the Gamma variant.[5]

Waning of immune responses have been observed following immunisation with COVID-19 vaccines with reduced protection against infection and some loss of protection against hospitalisation and death, particularly among older adults. A third dose of CoronaVac (homologous boost) has been shown to be immunogenic.[6,7] However, boosting with a heterologous vaccine may provide greater immunity and protection against variants of concern. Heterologous boosting of CoronaVac with recombinant adenovirus type-5 COVID-19 vaccine produced greater neutralising antibody titres than homologous boosting in a randomised trial in China[1]. Similar findings have been observed in Thailand in a preprint comparing heterologous boosting with ChAdOx1 nCoV-19, BNT162b2 or BBIBP-CorV (Sinopharm, Beijing, China), 3-4 months after CoronaVac[8]. In mouse models heterologous boost of CoronaVac with one of 3 different vaccines performed better than homologous boosting.[9,10]

In this study we compared the safety and immunogenicity of a third heterologous booster dose of one of three different vaccines, with a homologous boost in adults in Brazil who previously received two doses of CoronaVac.

Methods

We conducted a phase 4 randomised single-blind two-centre safety and immunogenicity study (RHH-001) of a third heterologous booster dose of either the recombinant adenoviral vectored ChAdOx1 nCoV-19 vaccine (AZD1222, AstraZeneca), mRNA vaccine (BNT162b2, Pfizer/BioNTech), or recombinant adenoviral vectored vaccine (AD26.COV2-S, Janssen), compared with a third homologous boost with inactivated whole virion COVID-19 vaccine CoronaVac (Sinovac/Butantan).

Male and female participants who had received their second doses of CoronaVac 182 days (+/- 30 days) prior to enrolment, and had given informed consent, were randomised to receive

one of four different booster vaccines in a 5:5:5:6 ratio. The computer randomisation was conducted using RedCAP version 11.1.14, stratified by site and day of randomisation, with block size of 42. The randomisation ratio was chosen to minimise vaccine wastage as the vaccines were supplied in 5, 6 or 10 dose vials, therefore 42 participants could be enrolled and vaccinated in a block with no wastage. Participants were blind to the vaccine they had received until the second visit, 28 days after vaccination. Blood samples for immunogenicity were taken prior to vaccination and at day 28 post-vaccination.

Participant exclusion criteria included history of laboratory confirmed COVID-19 or serious vaccine-related adverse reactions, known bleeding disorders, neurological disorders or history of Guillain-Barré syndrome, subjects on immunosuppressive medications, receipt of other investigational products, other vaccines, monoclonals, IVIG or other blood products.

Outcomes

The primary outcome was anti-spike IgG antibodies 28 days after the booster dose. Secondary outcomes included pseudovirus neutralising antibody titres at day 28, local and systemic reactogenicity profiles, adverse events and serious adverse events.

Vaccines

1. CoronaVac (CV) is an inactivated COVID-19 vaccine developed by Sinovac in partnership with Instituto Butantan. Each 0.5-mL dose contains 600 SU of inactivated SARS-CoV-2 virus.
2. ChAdOx1 nCoV-19 is a recombinant chimpanzee adenovirus which encodes full length spike SARS-CoV-2 glycoprotein, each 0.5-mL dose contains 5 x 10^{10} viral particles, developed by Oxford University in collaboration with AstraZeneca and produced in partnership with FioCruz.
3. BNT162b2 is a mRNA vaccine incorporated into lipid nanoparticles, each 0.3 mL contains 30 μg of SARS-CoV-2 Spike (S) protein messenger RNA, developed by BioNTech in collaboration with Pfizer.
4. Ad26.COV2-S is a recombinant adenovirus type 26 which encodes SARS-CoV-2 spike glycoprotein used as a single dose of 0.5 mL containing 5 x 10^{10} viral particles, develop by Johnson and Johnson.

Laboratory Assays

A validated multiplexed immunoassay (3-plex ECL based assay on the MSD platform, PPD Vaccines, Richmond, VA, USA) was used to measure anti-spike, receptor binding domain (RBD), and nucleocapsid responses. Antibody neutralisation on a random subset of 200 participants was measured with a lentivirus-based pseudovirus particle expressing the D614 SARS-CoV-2 spike protein (Monogram Biosciences, South San Francisco, CA, USA).

Statistical methods

Antibody data were log-transformed prior to analysis. Geometric mean ratios comparing heterologous with homologous regimens, were calculated by taking the anti-log of the mean difference between groups. Confidence intervals for the geometric mean ratio with lower bounds greater than 0.67 were considered evidence of non-inferiority. Superiority comparisons were conducted where non-inferiority was shown. To test the difference between response in younger and older adults, a linear model was fitted to log-transformed antibody values, adjusting for baseline antibody levels and vaccine group. The interaction term for vaccine group by age group was also tested but was not significant and was not included in the final model.

The primary analysis population included subjects who were randomized, received at least one dose of the study vaccines/comparators and provided post-vaccination immunogenicity data. Missing data were not imputed.

Sample size calculations

The study used a non-inferiority design with the main hypothesis being that the anti-spike IgG induced by heterologous vaccine schedules is non-inferior to antibody induced by the homologous vaccine schedule, using a non-inferiority marge for the geometric mean ratio (heterologous vs homologous) of 0.67.

$$H_0: GMC_{heterologous} / GMC_{homologous} \leq 0.67$$

$$H_1: GMC_{heterologous} / GMC_{homologous} > 0.67$$

Assuming a standard deviation of 0.4 for anti-spike IgG 28 days after the booster dose, 90% power and alpha of 0.0167 due to three comparisons of heterologous versus homologous schedules, the study required 124 evaluable subjects per age group and study arm. Allowing for 20% loss to follow up or incomplete data and the required randomisation ratio, 1240 were planned for enrolment.

Role of the funding source

The study was funded by the Ministry of Health, Brazil and sponsored by Instituto D'Or de Pesquisa e Ensino (IDOR). Ethical approval was given by National Ethical Review Committee, Comissão Nacional de Ética em Pesquisa (CONEP). The investigators acknowledge, in-kind support from AstraZeneca for the serological assays presented in this manuscript. The funders had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Study registration: Registro Brasileiro de Ensaios Clínicos (RBR – 9nn3scw)

Results

Between 16 August 2021 and 1 September 2021, 1240 participants were randomised in two age groups (18 to 60 years and 61 years or older) across two sites in Sao Paulo, and Salvador, of whom 1239 were vaccinated. One participant was vaccinated with a vaccine to which they had not been randomised. (Figure 1). 1205 (97%) returned for their Day 28 visit and were eligible for inclusion in the primary analysis.

Participants included in the primary analysis ranged in age from 21 to 98 years (median 60 years). The median time since receipt of the second dose of CoronaVac was 180 days (range: 152, 210). 729/1205 (60.5%) of participants were female and 814/1205 (68%) were white. The most common pre-existing comorbidity was hypertension, present in 365/1205 (30%) of participants. Baseline characteristics were balanced across the four vaccine arms of the trial (Table 1).

Safety and reactogenicity

The most common solicited local vaccine reaction in the first seven days was injection site pain, experienced by 76% of those receiving BNT162b2, 63% for ChAdOx1 nCoV-19, 60% for Ad26.COV2-S and 39% for CoronaVac. Headaches were common for ChAdOx1 nCoV-19 and Ad26.COV2-S recipients (49% and 46%) respectively, compared with 20% and 30% for CV and BNT162b2 respectively. Myalgia was also commonly reported, in 43%, 10%, 40%, and 23% of ChAdOx1 nCoV-19, CV, Ad26.COV2-S, and BNT162b2 respectively. Fever and chills were common for ChAdOx1 nCoV-19 (15% and 33%), and Ad26.COV2-S (12% and 26%), but not for recipients of CoronaVac (1% and 7%) or BNT162b2 (2% and 9%). (Figure 2).

There were five serious adverse events recorded. Three serious adverse events were considered possibly related to the vaccine received: In the BNT162b2 group an 83-year old woman experienced pulmonary embolism and deep vein thrombosis 2 days after vaccination; In the AD26.COV2-S group a 52-year-old woman experienced a subconjunctival haemorrhage 2 days after boosting and a 71-year old male experienced a pulmonary embolism. Unrelated serious adverse events included one case of bullous erysipelas in the ChAdOx1 nCoV-19 arm, and one case of coronary arterial disease requiring stent insertion in the AD26.COV2-S arm. All participants recovered and were discharged home.

There were no COVID-19 cases identified during the study.

Immunogenicity

At baseline there were no significant differences in anti-spike IgG across the four randomised groups (p=0.26). At Day 28 after the booster vaccine all groups had a substantial rise in antibody levels. The geometric fold-rise (GMFR) from baseline to day 28 was 90 (95%CI 77, 104) for ChAdOx1 nCoV-19, 12 (95%CI 11, 14) for CoronaVac, 77 (95%CI 67, 88) for AD26.COV2-S, and 152 (95%CI 134, 173) for BNT162b2. (Figure 3, Table 2).

All heterologous regimes had anti-spike IgG at Day 28 that were superior to those induced by the homologous boost. Geometric mean ratios (GMR) (heterologous vs homologous) were 7.0 (95%CI 6.1, 8.1) for ChAdOx1 nCoV-19, 6.7 (95% CI 5.8, 7.7) for AD26.COV2-S vaccine, and 13.4 (95% CI 11.6, 15.3) for BNT162b2 (Table 3, Figure 3). Similar responses were seen with anti-RBD IgG (Table S2) but not with anti-nucleocapsid IgG (Table S1). Responses in older adults were 19% lower than in younger adults at day 28, across all vaccines when tested in a linear model adjusted for vaccine group and baseline antibody levels (GMR 60+years vs 18-60 years: 0.81, 95%CI 0.73, 0.89, adjusted for vaccine group and baseline anti-spike IgG). In the older age group the GMFR was 91.5 (95% CI 72.6, 115.2) for ChadOx1 nCoV-19, 12.5 (95% CI 10.3, 15.2) for Coronavac, 78.8 (65.1, 95.2) for AD26.COV2-S, and 165.4 (95% CI 138.1, 198.1) for BNT162b2.

Pseudovirus neutralisation titres were available on a random subset of participants. 6 months after the second dose of CoronaVac and prior to the booster, 28/194 (14.4%) of the population had detectable neutralising antibodies. This was lower in older adults (9/101, 8.9%) than in adults aged 18 – 60 years (19/93, 20.4%), p=0.022. All participants in the three

heterologous booster groups had neutralisation titres that were above the lower limit of detection 28 days after vaccination compared with 38/46 (82.6%) responders in the homologous Coronavac arm. All heterologous regimens were superior to the homologous boost regimen, with GMRs of 10.6 (95%CI 7.2, 15.6) for ChAdOx1 nCoV-19, 8.7 (95% CI 5.9, 12.9) for Ad26.COV2-S, and 21.5 (95%CI 14.5, 31.9) for BNT162b2 (Figure 4, Table 3 & Table S4).

Discussion

In this study, we have shown that a third dose booster of the four vaccines tested, provides a substantial increase in immune responses after two doses of CoronaVac, when administered 6 months after the second dose.

Both homologous and heterologous COVID-19 booster vaccinations given 6 months after two doses of CoronaVac were safe and strongly enhanced the humoral immune responses. The magnitude of the immune boost was greater with the adenoviral vectored vaccines and mRNA vaccine than with the homologous regimen. In older adults the difference in neutralising antibody titers was 8 – 22 fold higher for a heterologous boost than for a homologous boost with Coronavac. In a preprint by Pan and colleagues, a third dose of CoronaVac given 6 months after the second dose resulted in an approximately 20-fold increase in neutralising antibody titres from a low baseline, higher than the 7-fold increase seen here for pseudo-neutralising titres, or 12-fold rise seen for anti-spike IgG[7]. Differences in study population and laboratory assays may account for this discrepancy in absolute booster response, but substantial booster responses were observed in both studies.

Correlates of protection analysis of trial data from the UK phase 3 ChAdOx1 nCoV-19 vaccine efficacy trial showed that a median anti-spike IgG level of 139306 AU/ml, and a pseudovirus neutralising antibody titre of 982 IC_{50} (140 IU/mL using the WHO international standard 20/136) was associated with 90% VE.[11] Using the same assays, geometric mean antibody levels for the adenoviral-vectored vaccines in this study were 2.4-fold higher than the 90% VE correlate, and the mRNA vaccine had a geometric mean 4.8-times higher than the 90% correlate, suggesting that antibody levels in these groups would be associated with very high protection against symptomatic infection with variants circulating prior to February 2021. After the booster, the CoronaVac group had a geometric mean titre which corresponded to the 80% VE correlate using the values from Feng et al.[11]

Immune responses are not always higher with heterologous boosting, highlighting the importance of generating primary data as shown here. Homologous boosting with a second or third dose of BNT162b2 produced higher antibody responses than a heterologous boost with an adenoviral-vectored vaccine (ChAdOx1 nCoV-19 or Ad26.COV2-S), or an adjuvanted protein vaccine (NVX-CoV2373,Novavax), or a heterologous mRNA vaccine (CVnCov, CureVac)[12,13]

The WHO has not recommended widespread use of booster doses of COVID-19 vaccines due to continuing inequity in distribution of first doses of vaccines to many parts of the world[14]. However, third doses are recommended for the immunocompromised and boosters are advised where there is evidence of waning effectiveness against severe disease or due to new VoCs. No recommendations have been made regarding whether homologous or heterologous boosting should be preferred. Our study shows that either of the four vaccines tested will produce a strong immune boost as a third dose after two doses of CoronaVac but heterologous boosting produces a substantially better response in this study. This may be especially relevant for the older adult population. It is not yet clear how long immunity will persist after a third dose and follow up at 6 months in this study will provide a comparison of antibody waning across the four vaccines tested.

The greater degree of reactogenicity seen with heterologous boosting in our study reflects similar findings from other randomised controlled trials such as the Com-COV study which compared homologous and heterologous boosting with ChAdOx1 nCoV-19 and BNT162b2 and found greater reactogenicity with heterologous schedules[15]. Similarly, the COV-BOOST study of third doses of 7 different vaccines, showed greater reactogenicity in some heterologous schedules: mRNA-1273 after two doses of ChAdOx1 nCoV-19 or two doses of BNT162b2; and ChAdOx1 nCoV-19 or Ad26.COV2-S after two doses of BNT162b2.[13]

This study was conducted only in Brazil and so it is not known if these findings will translate to other populations, though two geographically distinct sites were used in an ethnically diverse population. Whilst not all available vaccines could be tested, a range of platforms were assessed, including inactivated vaccines, viral vectors and mRNA, representing the products most widely available in populations where inactivated vaccines have been deployed.

In conclusion, this study shows that use of all four vaccines as a third booster dose is safe and provides a strong immune response, which is more robust when a heterologous vaccine is used.

Acknowledgements

Role of the funding source

The study was funded by the Ministry of Health, Brazil and sponsored by Instituto D'Or de Pesquisa e Ensino (IDOR). Ethical approval was given by National Ethical Review Committee, Comissão Nacional de Ética em Pesquisa (CONEP). The investigators acknowledge, in-kind support from AstraZeneca for the serological assays presented in this manuscript. TL received support from The Chinese Academy of Medical Sciences (CAMS) Innovation Fund for Medical Science (CIFMS), China (2018-I2M-2-002).

The funders had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

The views expressed in this publication are those of the authors and not necessarily those of the NIHR or the UK Department of Health and Social Care.

Declaration of Interests

AJP is chair of the UK Department of Health and Social Care's Joint Committee on Vaccination and Immunisation, but does not participate in policy advice on coronavirus vaccines, and is a member of the WHO Strategic Advisory Group of Experts (SAGE). AJP is an NIHR Senior Investigator. TL is named as an inventor on a patent application covering ChAdOx1 nCoV-19. Oxford University has entered into a partnership with AstraZeneca for further development of ChAdOx1 nCoV-19. All other authors declare no competing interests.

Author contributions

Conceptualisation (SACC, AJP), supervision (PA, LW, AVAM, SACC, AJP, TL, MV), data curation (ARS, MB, SNFdG, MMN, MIdMP, IG, NS, MMF, RNdAM, ISQO, BSFS, MF), laboratory work (TL, SB), statistical analysis (MV, LC), funding acquisition (SACC), writing – original draft (MV), and writing – review & editing (SACC, RC, AJP, TL). All authors critically reviewed and approved the final version. All authors confirm they had full access to all the data in the study and accept responsibility to submit for publication

Tables and Figures

Table 1 Baseline characteristics (Primary analysis population)

Characteristic	Detail	Overall	ChAdOx1 nCoV-19	CoronaVac	Ad26.COV2-S	BNT162b2
	N vaccinated	1205	296	281	295	333
Sex	Male	476 (39.5%)	117 (39.5%)	116 (41.3%)	114 (38.6%)	129 (38.7%)
	Female	729 (60.5%)	179 (60.5%)	165 (58.7%)	181 (61.4%)	204 (61.3%)
Age	18-60 years	616 (51.1%)	150 (50.7%)	148 (52.7%)	153 (51.9%)	165 (49.5%)
	Over 60 years	589 (48.9%)	146 (49.3%)	133 (47.3%)	142 (48.1%)	168 (50.5%)
	Mean	55.8	56.4	56.1	55.2	55.4
	Standard Deviation	17.8	18.5	17.6	16.8	18.3
	Median	60	60	58	59	61
	Minimum	21	21	21	22	21
	Maximum	98	96	95	98	95
Race	White	814 (67.6%)	200 (67.6%)	181 (64.4%)	203 (68.8%)	230 (69.1%)
	Black	57 (4.7%)	13 (4.4%)	13 (4.6%)	14 (4.7%)	17 (5.1%)
	Mixed	275 (22.8%)	70 (23.6%)	72 (25.6%)	65 (22%)	68 (20.4%)
	Yellow	57 (4.7%)	12 (4.1%)	15 (5.3%)	13 (4.4%)	17 (5.1%)
	Not informed	2 (0.2%)	1 (0.3%)	0 (0%)	0 (0%)	1 (0.3%)
Medical History	Type 2 Diabetes Mellitus	127 (10.5%)	39 (13.2%)	33 (11.7%)	34 (11.5%)	21 (6.3%)

Characteristic	Detail	Overall	ChAdOx1 nCoV-19	CoronaVac	Ad26.COV2-S	BNT162b2
	Heart Failure	9 (0.7%)	2 (0.7%)	3 (1.1%)	3 (1%)	1 (0.3%)
	CPOD	9 (0.7%)	2 (0.7%)	4 (1.4%)	1 (0.3%)	2 (0.6%)
	Hypertension	365 (30.3%)	99 (33.4%)	91 (32.4%)	84 (28.5%)	91 (27.3%)
	Cancer	126 (10.5%)	38 (12.8%)	28 (10%)	27 (9.2%)	33 (9.9%)
	Immunosuppressed	3 (0.2%)	0 (0%)	0 (0%)	1 (0.3%)	2 (0.6%)
	Chronic Kidney Disease	7 (0.6%)	3 (1%)	3 (1.1%)	0 (0%)	1 (0.3%)
	Coronary Artery Disease	61 (5.1%)	17 (5.7%)	19 (6.8%)	7 (2.4%)	18 (5.4%)
	Cardiomyopathy	7 (0.6%)	1 (0.3%)	1 (0.4%)	2 (0.7%)	3 (0.9%)
	Sickle Cell Anaemia	1 (0.1%)	0 (0%)	0 (0%)	0 (0%)	1 (0.3%)
	Obesity	80 (6.6%)	20 (6.8%)	15 (5.3%)	24 (8.1%)	21 (6.3%)
	HIV	2 (0.2%)	0 (0%)	0 (0%)	0 (0%)	2 (0.6%)
Time since second vaccine (days)	Mean	178.4	178.9	177.4	178.7	178.6
	Standard Deviation	9.9	9.7	10.3	9.6	10.1
	Median	180	180	179	180	180
	Minimum	152	152	152	152	152
	Maximum	210	206	199	210	208

Figure 1 CONSORT diagram

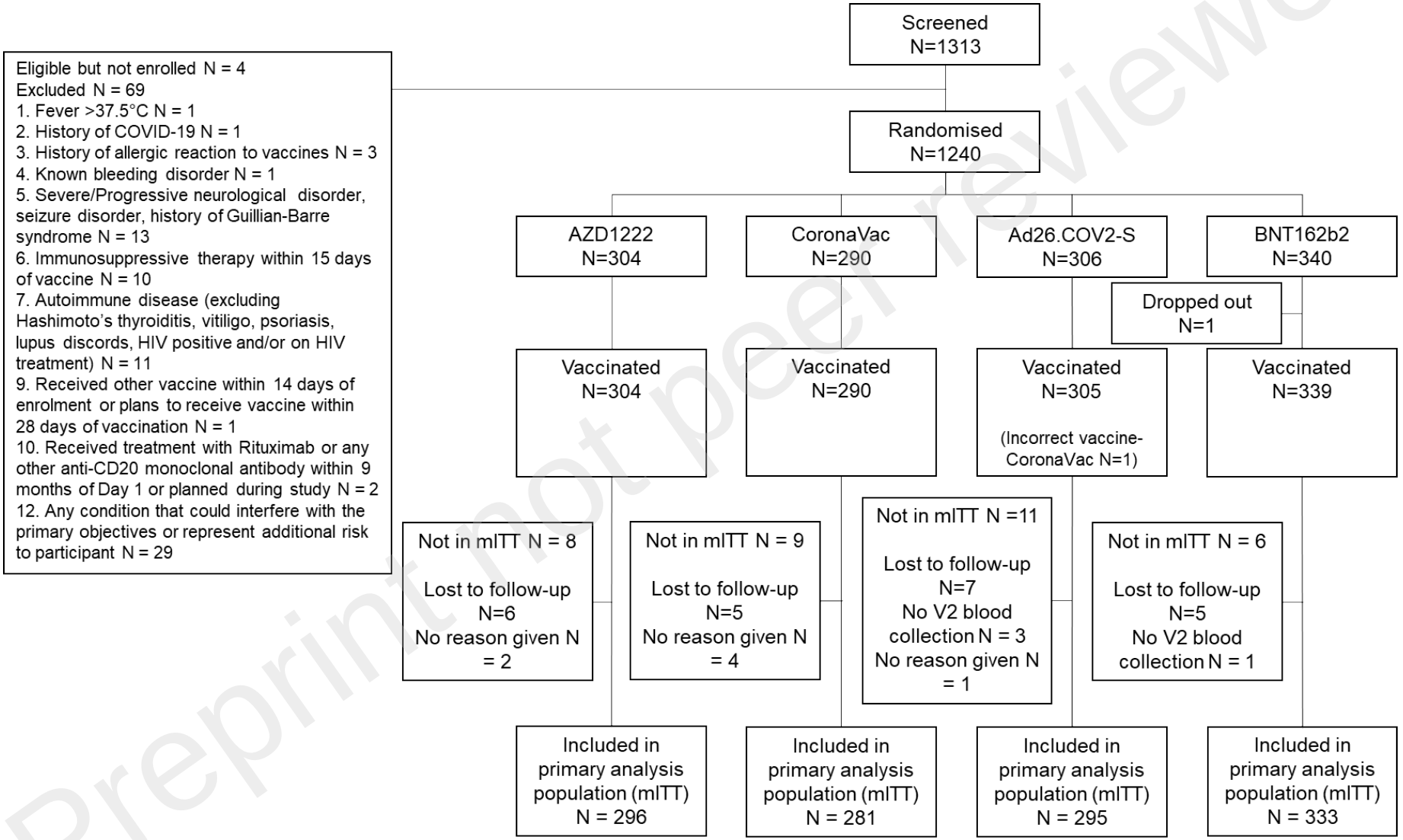
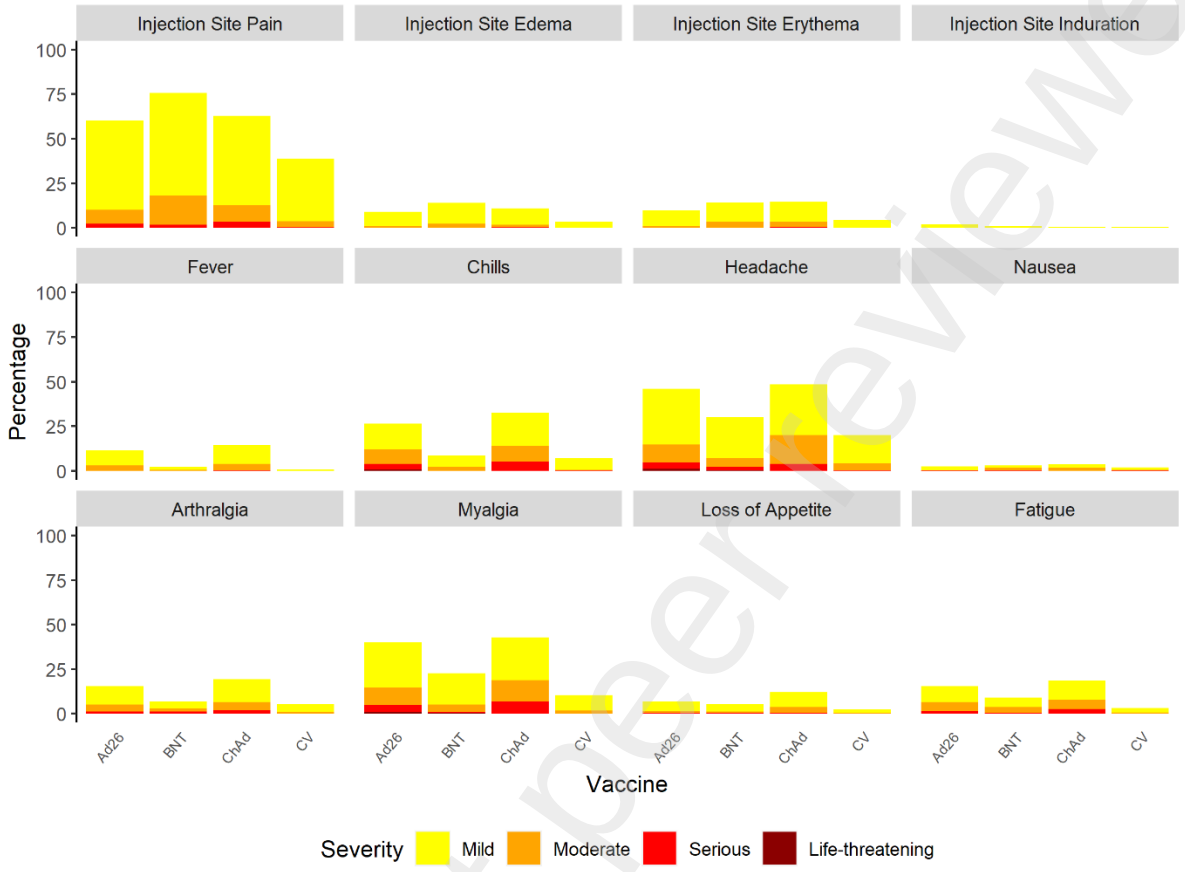
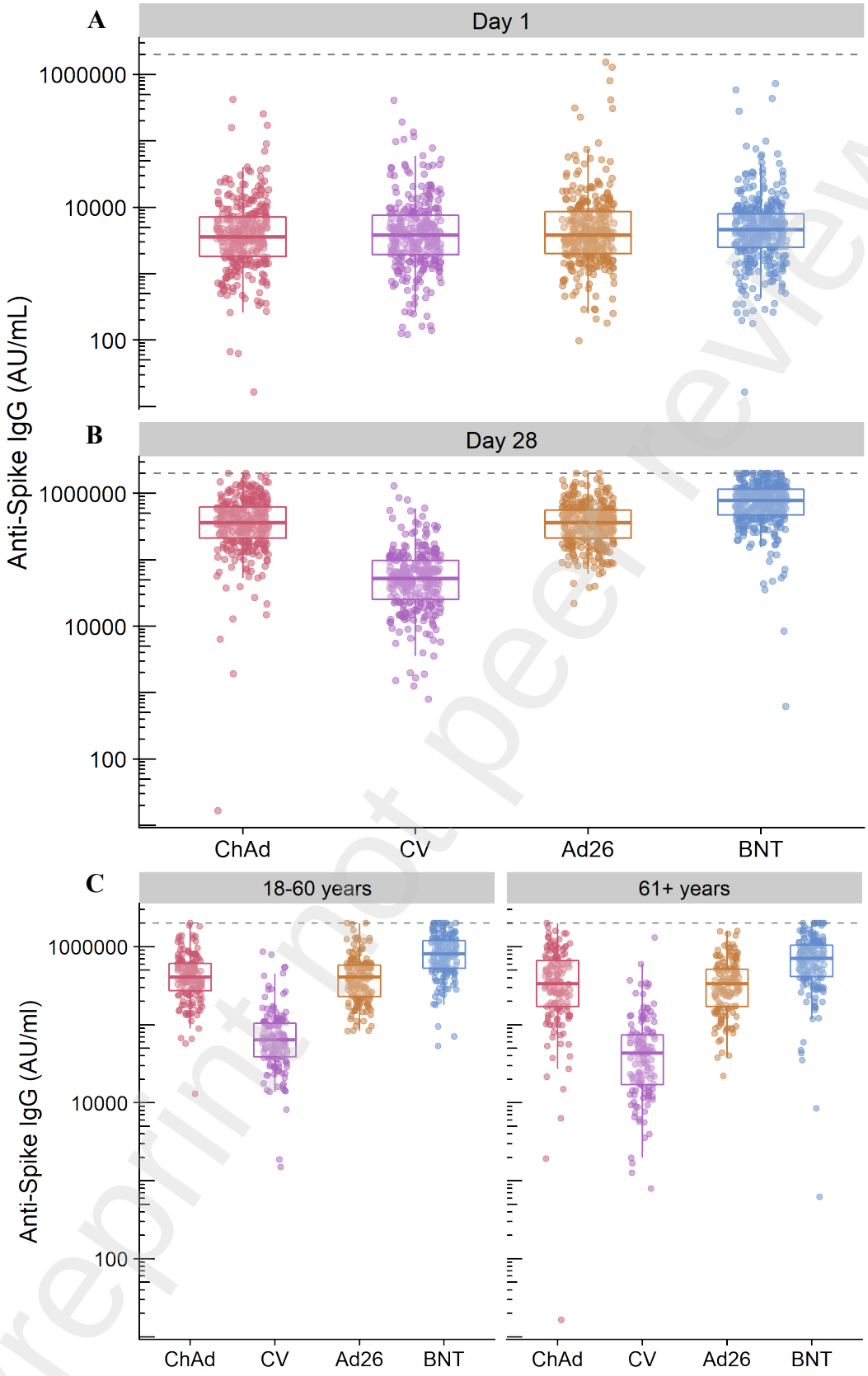


Figure 2 Local and systemic solicited adverse reactions in the first 7 days after vaccination (safety population)



Ad26: Ad.26.COV2-S; BNT: BNT162b2; ChAd: ChAdOx1 nCoV-19; CV: CoronaVac

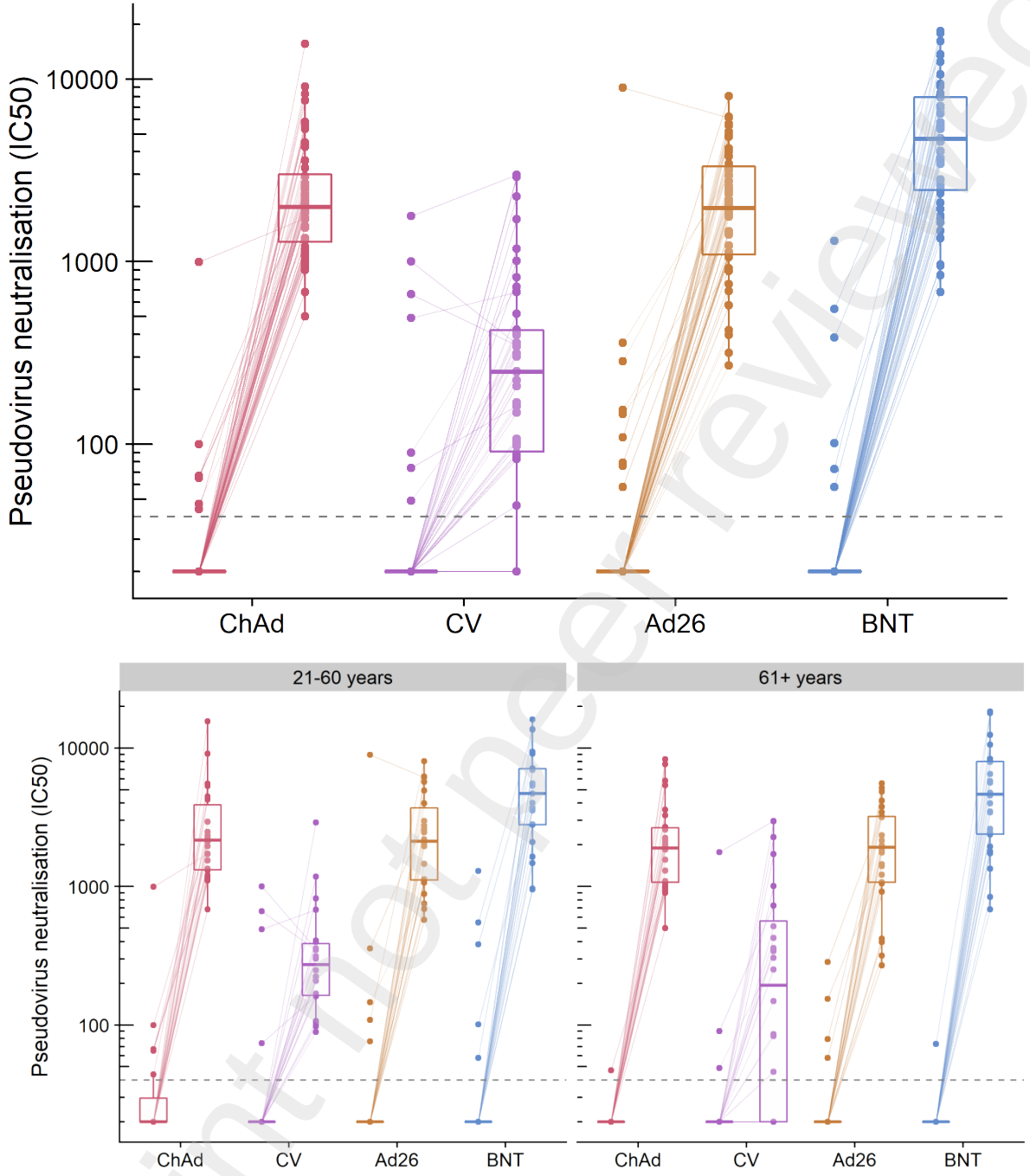
Figure 3 Anti-spike IgG by multiplex immunoassay by study day and age



Ad26: Ad.26.COV2-S; BNT: BNT162b2; ChAd: ChAdOx1 nCoV-19; CV: CoronaVac. A: Day 0; B: Day 28, C: Day 28 responses by age group

See Table 2 for summary statistics and comparisons. Dotted line shows upper limit of the assay.

Figure 4 Pseudovirus neutralisation titres before and 28 days post vaccination



% seropositive:	D1: 26.9% D28: 100%	D1: 18.2% D28: 100%	D1: 18.2% D28: 100%	D1: 17.4% D28: 100%	D1: 3.8% D28: 100%	D1: 12.5% D28: 66.7%	D1: 16% D28: 100%	D1: 3.8% D28: 100%

Ad26: Ad.26.COV2-S; BNT: BNT162b2; ChAd: ChAdOx1 nCoV-19; CV: CoronaVac.
See Table 3 and S3 for summary statistics. Line connect values from the same participant. Dotted line shows lower limit of the assay. Values below the limit were substituted with a titre of 20. Participants with antibody titres above the lower limit are considered seropositive.

Table 2 Anti-spike IgG by multiplex immunoassay (Primary analysis population)

Age	Day		ChAdOx1 nCoV-19	CoronaVac	Ad26.COV2-S	BNT162b2
All		N	296	281	295	333
	Day 1	Geometric Mean	3744.7	3898.9	4378.8	4432.9
		95% Confidence Interval	3251.5, 4312.7	3350.9, 4536.6	3760.2, 5099.2	3880.4, 5064
	Day 28	Geometric Mean	335212.8	48404.9	336851.1	674267.3
		95% Confidence Interval	295598.3, 380136.3	42491.3, 55141.6	308341.6, 367996.7	615632.7, 738486.5
	Day 28/Day 1	N	296	281	294	333
		GMFR	89.5	12.4	76.8	152.1
		95% Confidence Interval	77.2, 103.8	10.8, 14.2	66.6, 88.4	133.5, 173.3
Age Groups						
18-60		N	150	148	153	165
	Day 1	Geometric Mean	4495.3	5057.4	5060.8	5479.1
		95% Confidence Interval	3798, 5320.6	4220.6, 6060.2	4117.1, 6220.8	4499.9, 6671.3
	Day 28	Geometric Mean	394095.7	62503	380571.5	765117.7
		95% Confidence Interval	349737.8, 444079.7	53810, 72600.4	340997.8, 424737.9	692029.4, 845925.2

Age	Day		ChAdOx1 nCoV-19	CoronaVac	Ad26.COV2-S	BNT162b2
	Day 28/Day 1	N	150	148	152	165
		GMFR	87.7	12.4	75	139.6
		95% Confidence Interval	72.6, 105.9	10.2, 15	60.7, 92.5	115.6, 168.7
Over 60		N	146	133	142	168
	Day 1	Geometric Mean	3103.9	2918.9	3750.3	3600.1
		95% Confidence Interval	2476, 3891	2291.8, 3717.6	2995.3, 4695.7	3019.7, 4292
	Day 28	Geometric Mean	283866.4	36421.5	295348.1	595547.3
		95% Confidence Interval	227360.8, 354415.1	29498.8, 44968.8	257097.8, 339289.3	512753.7, 691709.5
	Day 28/Day 1	N	146	133	142	168
		GMFR	91.5	12.5	78.8	165.4
		95% Confidence Interval	72.6, 115.2	10.3, 15.2	65.1, 95.2	138.1, 198.1

Table 3 Comparisons of Heterologous v Homologous regimens

Age		ChAdOx1 nCoV-19	CoronaVac	Ad26.COV2-S	BNT162b2
Anti-spike IgG by multiplex immunoassay					
All	N	296	281	294	333
	GMR (Heterologous v Homologous)	7.0	ref	6.7	13.4
	95% Confidence Interval	6.1, 8.1	ref	5.8, 7.7	11.6, 15.3
18-60 years	N	150	148	152	165
	GMR (Het v Hom)	6.4	ref	6.1	12.1
	95% Confidence Interval	5.5, 7.6	ref	5.1, 7.2	10.3, 14.2
Over 60 years	N	146	133	142	168
	GMR (Het v Hom)	7.6	ref	7.3	15
	95% Confidence Interval	6.1, 9.5	ref	5.8, 9.2	12, 18.6
Pseudovirus neutralising antibody titres					
All	N	52	46	47	49
	GMR (Het v Hom)	10.6	ref	8.7	21.5
	95% Confidence Interval	7.2, 15.6	ref	5.9, 12.9	14.5, 31.9

18-60 years	N	26	22	22	23
	GMR (Het v Hom)	8.2	ref	7.2	15.6
	95% Confidence Interval	5.2, 12.9	ref	4.5, 11.4	9.8, 24.7
Over 60 years	N	26	24	25	26
	GMR (Het v Hom)	14.2	ref	10.5	30.7
	95% Confidence Interval	7.6, 26.5	ref	5.6, 19.5	16.5, 57.1

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Supplementary Tables

Table S1 Anti-N IgG by multiplex immunoassay in primary analysis population

Age	Day		ChAdOx1 nCoV-19	CoronaVac	Ad26.COV2-S	BNT162b2
All		N	296	281	295	333
	Day 1	Geometric Mean	498.4	505.6	536.7	583.7
		95% Confidence Interval	410.8, 604.7	408, 626.5	440.6, 653.7	478.8, 711.6
	Day 28	Geometric Mean	469.1	10619.7	522.6	567.1
		95% Confidence Interval	385.9, 570.2	8524, 13230.8	423.9, 644.3	464.5, 692.3
	Day 28/Day 1	N	296	281	294	333
		GMFR	0.9	21	1	1
		95% Confidence Interval	0.9, 1	17.4, 25.3	0.9, 1	0.9, 1
18-60		N	150	148	153	165
	Day 1	Geometric Mean	759.9	892.9	740.6	1027
		95% Confidence Interval	585.6, 986.2	682.1, 1168.9	577.1, 950.5	774.6, 1361.6
	Day 28	Geometric Mean	718.8	21465.8	681.7	979.5
		95% Confidence Interval	547.2, 944.2	17364.5, 26535.8	528, 880.2	740.1, 1296.2
	Day 28/Day 1	N	150	148	152	165

Age	Day		ChAdOx1 nCoV-19	CoronaVac	Ad26.COV2-S	BNT162b2
		GMFR	0.9	24	0.9	1
		95% Confidence Interval	0.9, 1	18.5, 31.2	0.8, 1	0.9, 1
Over 60		N	146	133	142	168
	Day 1	Geometric Mean	323.1	268.5	380.2	335.1
		95% Confidence Interval	246.2, 424	197.1, 365.8	281.1, 514.2	259.9, 432.2
	Day 28	Geometric Mean	302.5	4853	392.5	331.6
		95% Confidence Interval	232.3, 394	3391.6, 6944.1	281.2, 547.7	255.1, 431
	Day 28/Day 1	N	146	133	142	168
		GMFR	0.9	18.1	1	1
		95% Confidence Interval	0.9, 1	13.8, 23.7	0.9, 1.2	0.9, 1.1

Table S2 Anti-RBD IgG by multiplex immunoassay in primary analysis population

Age	Day		ChAdOx1 nCoV-19	CoronaVac	Ad26.COV2-S	BNT162b2
All		N	296	281	295	333
	Day 1	Geometric Mean	3957.3	3897.7	4558.7	4780.1
		95% Confidence Interval	3408.7, 4594.2	3296, 4609.3	3868.5, 5372.1	4147.4, 5509.3
	Day 28	Geometric Mean	447510.2	59445.8	430521.6	827704.7
		95% Confidence Interval	394652, 507448.2	51861.4, 68139.4	390411.9, 474752.2	754136.9, 908449.3
	Day 28/Day 1	N	296	281	294	333
		GMFR	113.1	15.3	94.2	173.2
		95% Confidence Interval	96.4 132.6	13.2 17.6	80.8 109.9	150.5 199.3
18-60		N	150	148	153	165
	Day 1	Geometric Mean	5044.8	5426.6	5506.9	6002.4
		95% Confidence Interval	4225.2, 6023.4	4478.1, 6576	4451.2, 6813.1	4877.4, 7386.9
	Day 28	Geometric Mean	539116.9	80848.8	499357.2	937168.4
		95% Confidence Interval	481381.6, 603776.8	70004, 93373.6	448598.4, 555859.3	850063.4, 1033198.8
	Day 28/Day 1	N	150	148	152	165
		GMFR	106.9	14.9	90.4	156.1
		95% Confidence Interval	87.6 130.4	12.2 18.2	72.6 112.5	127.7 190.8

Age	Day		ChAdOx1 nCoV-19	CoronaVac	Ad26.COV2-S	BNT162b2
Over 60		N	146	133	142	168
	Day 1	Geometric Mean	3083.6	2697	3723.9	3822.2
		95% Confidence Interval	2433.1, 3908.1	2055.5, 3538.8	2898.4, 4784.6	3160.7, 4622.2
	Day 28	Geometric Mean	369578.9	42218.9	366934.6	732649.9
		95% Confidence Interval	295375.6, 462423.2	33612.9, 53028.2	311263.8, 432562.3	626469.6, 856826.7
	Day 28/Day 1	N	146	133	142	168
		GMFR	119.9	15.7	98.5	191.7
		95% Confidence Interval	93.2 154.2	12.7 19.3	79.1 122.7	157.3 233.5

Table S3 Pseudovirus neutralising antibody titres

Age	Day		ChAdOx1 nCoV-19	CoronaVac	Ad26.COV2-S	BNT162b2
All		N	52	46	47	49
	Day 1	Geometric Mean	25.2	30.1	30.5	24.7
		95% Confidence Interval	20.9, 30.2	21.7, 41.8	21.9, 42.4	20.2, 30.1
	Day 28	Geometric Mean	2136.9	211.1	1843.6	4325.8
		95% Confidence Interval	1753.9, 2603.6	136.8, 325.6	1445.7, 2351	3403.6, 5498
	Day 28/Day 1	N	52	46	47	49
		GMFR	84.9	7.0	60.5	175.5
		95% Confidence Interval	64.1, 112.5	4.4, 11.1	42.5, 86.1	135.2, 227.8
18-60		N	26	22	22	23
	Day 1	Geometric Mean	30.6	34.4	35.6	29.5
		95% Confidence Interval	21.5, 43.8	19.7, 60	18.6, 68.1	19.5, 44.6
	Day 28	Geometric Mean	2327.6	288.2	2071.5	4396.9
		95% Confidence Interval	1740.4, 3113	197.3, 420.9	1460.6, 2937.9	3106.2, 6224
	Day 28/Day 1	N	26	22	22	23
		GMFR	76	8.4	58.2	149
		95% Confidence Interval	46.4, 124.4	4.5, 15.6	31.2, 108.7	97.3, 228.1

Age	Day		ChAdOx1 nCoV-19	CoronaVac	Ad26.COV2-S	BNT162b2
Over 60		N	26	24	25	26
	Day 1	Geometric Mean	20.7	26.6	26.6	21
		95% Confidence Interval	19.3, 22.1	17.8, 40	19.8, 35.7	19, 23.3
	Day 28	Geometric Mean	1961.9	158.7	1663.9	4263.9
		95% Confidence Interval	1477.2, 2605.6	73.4, 342.7	1164.6, 2377.2	2992, 6076.6
	Day 28/Day 1	N	26	24	25	26
		GMFR	94.9	6	62.5	202.8
		95% Confidence Interval	70, 128.8	2.9, 12.2	41, 95.3	145.3, 283.2