Durability of ChAdOx1 nCoV-19 (AZD1222) vaccine and hybrid humoral immunity against variants including Omicron BA.1 and BA.4 six months after vaccination: a randomised, phase 1b/2a trial.

Shabir A. Madhi,[1,2] Gaurav Kwatra,[1,2] Simone I Richardson, [3,4] Anthonet L Koen,[1] Vicky Baillie,[1] Clare L. Cutland,[2] Lee Fairlie,[5] Sherman D Padayachee,[6] Keertan Dheda,[7] Shaun L Barnabas,[8] Qasim Ebrahim Bhorat,[9] Carmen Briner,[1,10] Khatija Ahmed,[6,11] Parvinder K Aley,[12] Sutika Bhikha,[1] A.E. Bhorat,[9] Aliasgar Esmail,[7] Elizea Horne,[5] Haajira Kaldine[3,4], Christian K. Mukendi [1] , Vimbai Sharon Madzorera[3,4], Nelia P. Manamela,[3,4] Mduduzi Masilela,[6] S. Tandile Hermanus,[3,4] Thopisang Motlou,[3,4] Nonkululeko Mzindle[3,4], Suzette Oelofse,[7] Faeezah Patel,[5] Sarah Rhead,[12] Lindie Rossouw,[5] Carol Taoushanis,[1,2] Samuel van Eck,[5] Teresa Lambe,[12,13] Sarah Gilbert,[15,16] Andrew J. Pollard,[12,16], Penny L. Moore,[3,4] Alane Izu.[1,2]

Affiliations

1. South African Medical Research Council Vaccines and Infectious Diseases Analytics Research Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa.
2. African Leadership in Vaccinology Expertise, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa.
3. National Institute for Communicable Diseases of the National Health Laboratory Services, Johannesburg, South Africa
4. South African Medical Research Council Antibody Immunity Research Unit, School of Pathology, University of the Witwatersrand, Johannesburg, South Africa
5. Wits Reproductive Health and HIV Institute, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
6. Setshaba Research Centre, Tshwane, South Africa
7. Centre for Lung Infection and Immunity, Division of Pulmonology, Department of Medicine and UCT Lung Institute, University of Cape Town, South Africa

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=4173050

8. Family Centre for Research with Ubuntu, Department of Paediatrics, Stellenbosch University, Cape Town, South Africa
9. Soweto Clinical Trials Centre, Soweto, South Africa
10. Perinatal HIV Research Unit, Faculty of Health Science, University of the Witwatersrand, Johannesburg, South Africa
11. Faculty of Health Sciences, Department of Medical Microbiology, University of Pretoria, Pretoria, South Africa
12. Oxford Vaccine Group, Department of Paediatrics, University of Oxford, UK
13. Chinese Academy of Medical Science, Oxford Institute, University of Oxford, Oxford, UK
14. Jenner Institute, Nuffield Department of Medicine, University of Oxford, UK
15. Nuffield Department of Medicine, University of Oxford, ORCRB, Oxford, UK
16. NIHR Oxford Biomedical Research Centre, Oxford, UK

Word Count: Abstract: 346 Text 4213

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=4173050

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=4173050

Research in Context

Evidence before this study

Covid-19 vaccination using a single dose of AZD1222, AD26.CoVs.S, BNT162.b2 and mRNA-1273 vaccines following infection with SARS-CoV-2 results in significantly increased antibody titers. Antibodies induced by infection or vaccines are correlated with prevention of infection as well as the attenuation of clinical severity of SARS-CoV-2 infection, through virus neutralization and Fc effector functions. The AZD1222 vaccine is widely used across Africa, much of which has an extremely high level of prior infection as indicated by sero-surveys. However, the durability, breath and capacity to mediate Fc effector functions of antibodies that result from AZD1222 vaccination following infection is unknown.

Added value of this study

We expand previous observations to show that anti spike protein IgG, anti receptor binding domain (RBD) IgG, neutralizing antibodies (NAb) and antibody dependent cellular cytotoxicity (ADCC) mediating antibodies are significantly enhanced in titer and breadth after a single dose of AZD1222 following infection compared with vaccination alone. Enhanced titers result in increased ability to neutralize variants of concerns (VOCs) including the highly immune-evasive Omicron BA.1 and BA.4 sub-lineages, which now dominate global infections, as well as SARS-CoV-1. Furthermore, antibodies remain elevated 180 days post-vaccination in previously infected individuals compared with participants who only had vaccine-induced immunity, including against many VOCs. Our data also show limited boosting of anti-S IgG, anti-RBD IgG, NAb or ADCC following a second dose of AZD1222 within four weeks of the first dose in previously infected individuals, unlike in those with no evidence of infection prior to vaccination. As antibody titers are the best current biomarker of vaccine efficacy against symptomatic Covid-19, understanding the durability and breadth of these heightened antibody responses directly informs the long-term vaccine effectiveness in areas with a high force of SARS-CoV-2 infection where vaccine coverage is still limited.

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=4173050

Implications of all the available evidence

These data show that a single dose of the AZD1222 following SARS-CoV-2 infection results in binding and neutralizing titers that persist for more than 6 months post-vaccination. Furthermore, the ability of these boosted antibodies to neutralize VOCs including BA.1 and BA.4 was enhanced, with implications for the ability of hybrid-immunity elicited antibodies to protect against future VOCs. The limited boost conferred by a second dose of AZD1222 in previously infected individuals brings into question the immediate utility of a second dose 4 weeks later in populations with a high prior force of infection. Serosurveys in South Africa and elsewhere in Africa indicate 90% of the population have been infected with SARS-CoV-2 since the start of the pandemic. Consequently, our data indicate that even a single dose of AZD1222 at the general population level in Africa where Covid-19 vaccine rollout is lagging, may be a valuable, cost-effective intervention to significantly enhanced the magnitude and quality of antibody responses to SARS-CoV-2.

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=4173050

Abstract

Background: Covid-19 vaccine rollout is lagging in Africa, where there has been a high force of SARS-CoV-2 infection. We evaluated the effect of SARS-CoV-2 infection prior to vaccination with the ChAdOx-nCoV19 (AZD1222) vaccine on antibody responses through to 180 days (D180).

Methods: We undertook a post-hoc immunogenicity analysis after two doses of AZD1222 in a randomised, placebo-controlled phase Ib/2a study undertaken in South Africa. Recipients were stratified by serological assessment of SARS-CoV-2 infection prior to 1st dose into baseline seropositive or baseline seronegative groups. Binding immunoglobulin G (IgG) to spike (anti-S) and receptor binding domain (anti-RBD) were measured prior to first dose (D0), 2nd dose (D28), and at D42 and D180. Neutralizing antibody (NAb) against SARS-CoV-2 variants D614G, Beta, Delta, Gamma, A.VOI.V2, Omicron BA1 and BA.4 variants and SARS-CoV-1, were measured by pseudovirus assay (D28, D42 and D180). Antibody dependent cellular cytoxicity against D614G and Delta was measured at D28 and D42.

Findings

Anti-S (and anti-RBD) IgG geometric mean concentrations (GMCs) were higher throughout in the baseline seropositive than seronegative group, persisting to D180 (GMCs: 517.8 vs 82.1 BAU/ml). Similarly, the percentage who had anti-S IgG ≥264BAU/ml (i.e. putative 80% risk reduction threshold [PRRT] against wild type (WT)/Alpha symptomatic Covid-19) was 76.6% vs 13.8% at D180. Also D614G NAb geometric mean titres (GMT) were higher in the baseline seropositive than seronegative group, as was the percentage with titres ≥185 (80% PRRT against WT/Alpha Covid-19) even at D180 (92.0% vs 18.2%). Similar findings were observed for Beta, A.VOI.V2 and Gamma at D28, D42 and D180. NAb GMTS against BA.1 and BA.4 were higher in the baseline seropositive than seronegative group at D28 (499 vs. 14; and 436 vs. 25.0) and D42 (535 vs. 16; and 429 vs. 25.0), as was the percentage with NAb titres ≥185 for BA.1 and BA.4 at D28 (84.0% and 87.5% vs. 0%) and D42 (84.0% and 87.5% vs. 0%).

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=4173050

Interpretation

A single dose of AZD1222 in the general African population, where Covid-19 vaccine coverage is low and SARS-CoV-2 seropositivity is 90%, could enhance the magnitude and quality of antibody responses to SARS-CoV-2.

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=4173050

Background

The effectiveness of vaccine or infection induced adaptive immunity against severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infection, which causes coronavirus disease (Covid-19), differs by variants of concern (VOC). The magnitude of increase in anti-spike protein (anti-S) binding immunoglobulin G (IgG) and neutralizing antibody (NAb) induced by COVID-19 vaccines were directly correlated with vaccine efficacy against symptomatic Covid-19 due to the wild type (WT) or Alpha VOC in phase III efficacy trials[1]. Furthermore, similar thresholds of anti-S IgG and NAb against WT SARS-CoV-2 have been proposed as surrogate for risk reduction for the non-replicating chimpanzee adenovirus vector SARS-CoV-2 vaccine (ChAdOx1 nCoV19 or AZD1222), messenger ribonucleic acid - 1273 (mRNA-1273) and non-replicating adenovirus 26 vector (Ad26CoV2.S) Covid-19 vaccine against symptomatic Covid-19 by WT or Alpha VOC[2,3]. Antibodies induced by infection or vaccines could also attenuate the clinical course of SARS-CoV-2 infection through Fc effector functions, including antibody dependent cellular cytotoxicity (ADCC)[4].

Infection with SARS-CoV-2 prior to Covid-19 vaccination is associated with robust anti-S IgG and NAb against WT virus after a single dose of AZD1222, AD26.CoVs.S and mRNA (i.e. BNT162.b2 and mRNA-1273) vaccines[5-8]. A second dose of AZD1222 or mRNA vaccines within 3-8 weeks after the initial dose in individuals previously infected by SARS-CoV-2, results in only modest further increase of anti-S IgG and NAb titres. In contrast, a second dose of AZD1222 and more markedly so for mRNA vaccines in individuals who were SARS-CoV-2 naive at time of vaccination, induces a multi-fold increase in anti-S IgG and NAb titres.[9,10] The anti-S IgG and NAb titres following a single dose of AZD1222 or mRNA in individuals vaccinated after SARS-CoV-2 infection are greater or equal to compared with antibody responses following two doses of the homologous vaccine in SARS-CoV-2 naïve individuals[11-13]. Similar findings were observed in people living with HIV (PLWH) in an earlier analysis of the AZD1222 (COV005 trial) study undertaken in South Africa[14]. Covid-19 vaccine and infection induced protection against severe Covid-19 is seemingly mainly

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=4173050

mediated by T-cell induced immunity, which is less affected by mutations in VOCs which have evolved to date. Nevertheless, heightened magnitude of NAb induced by Covid-19 vaccine following SARS-CoV-2 infection (i.e. hybrid immunity) compared with Covid-19 vaccine or SARS-CoV-2 infection only induced immunity, could better mitigate protection against non-severe Covid-19 even due to VOC with NAb evasive mutations[15].

The main focus of this analysis was to evaluate the effect of SARS-CoV-2 infection prior to first dose of the AZD1222 vaccine on the post-vaccine antibody kinetics through to Day 180 (D180). We report on the antibody kinetics of anti-S IgG, anti-receptor binding domain (anti-RBD) IgG, NAb against WT, multiple VOCs (including Omicron BA.1, BA.4) and SARS-CoV-1, and Fc effector function to WT and Delta VOC.

Methods

We analysed samples collected in a randomized, placebo controlled Phase Ib/IIa trial which evaluated the safety, immunogenicity and efficacy of AZD1222. Details of the multi-centre study undertaken in South Africa have been described, including interim analysis of vaccine efficacy and immunogenicity through to 14 days following the first two doses of AZD1222 in PLWH and HIV-negative individuals[14,16]. Participants were enrolled into the study between June 24, 2020 and November 9, 2020. The study protocol, detail of the inclusion and exclusion criteria and randomization is available at www.nejm.org/doi/suppl/10.1056/NEJMoa2102214/suppl_file/ nejmoa2102214_protocol.pdf. Healthy adults aged 18 to 65 years who were eligible for study participation were randomly assigned (1:1) via a computer-generated system with full allocation concealment, to receive two intramuscular injections of either AZD1222 or saline placebo (0·9% sodium chloride; placebo group), given 28 days apart[14,16]. Enrolment of the initial cohort of 70 HIV-uninfected individuals included in the phase Ib study occurred between June 24, 2020, and July 29, 2020; and the rest enrolled through to November 09, 2020.

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=4173050

There was a higher than anticipated percentage of HIV-uninfected participants (322/1683; 19%) without a documented history of Covid-19 but who tested positive for anti-nucleocapsid (anti-N) IgG at time of randomization (forthwith referred to as baseline seropositive group). Consequently, we performed a post hoc analysis of durability of antibody responses comparing AZD1222 recipients with and without SARS-CoV-2 infection prior to receipt of the first dose of study injection. Sampling time points for measuring antibody responses included the day of first study injection (Day 0; D0), at time of 2nd dose of study injection (Day 28; D28), fourteen days after the 2nd dose (Day 42; D42) and six months post study entry (D180).

The immunogenicity (anti-RBD and anti-S IgG and NAb against Asp614Gly WT [D614G] and Beta variant only) of AZD1222 in PLWH through to D42, including stratified by pre-vaccination SARS-CoV-2 infection status, and immunogenicity through to D42 in a smaller subset HIV-uninfected individuals who were SARS-CoV-2 naive (26 placebo and 27 AZD1222 recipients) enrolled in the phase Ib has been previously published[14]. For this report, we expanded testing of immune responses in the HIV-uninfected cohort to an additional 243 HIV-uninfected participants enrolled into phase II of the study, who were randomly selected after stratification by baseline anti-N IgG sero-status. We aimed to include approximately 75 AZD122 recipients who were baseline anti-N IgG seropositive and 75 who were anti-N seronegative at enrolment. Participants with any inter-current SARS-CoV-2 infection between enrolment and D180, whether diagnosed by nucleic acid amplification test or anti-N IgG sero-conversion by D180, were excluded from the final analysis; Figure 1. This was a descriptive, hypothesis generating study and did not include any sample size calculation.

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=4173050

Immunological assay methods

Binding antibodies were measured by singleplex bead-based immunoassays on the Luminex platform to quantify serum IgG binding to full length spike and RBD; and reported in binding antibody units per millilitre (BAU/ml) as described[14]. The anti-RBD and anti-S (full length spike) assay was calibrated against a research reagent for anti-SARS-CoV-2 antibody (code 20/130 supplied by National Institute for Biological Standards and Control, Herts, UK). Anti-N IgG was measured as previously described[16].

Neutralizing antibody responses were evaluated in a random subset of samples using a pseudovirus neutralizing antibody assay (PSVN) against D614G and the following SARS-CoV-2 variants: A.VOI.V2, Beta, Delta, Gamma, Omicron BA.1, Omicron BA.4; as well as SARS-CoV-1. Pseudovirus neutralization assays were performed as described[17], on a random selection of samples using the SARS-CoV-2 Wuhan-1 spike gene sequence mutated to match D614G (ancestral), Beta, A.VOI.V2, Gamma, Omicron BA.1 and BA.4 as detailed in the supplementary material. Titers were calculated as the reciprocal plasma dilution (ID_{50}) causing 50% reduction of infection. Another post-hoc study objective was evaluation of ADCC through to D180 in a random subset of 30 samples, as described in the supplementary text[18].

Statistical methods

Geometric mean concentrations (GMC) and 95% confidence intervals (95% CI) were calculated for anti-S IgG, anti-RBD IgG and ADCC IgG against D614G and Delta VOC, which were evaluated at D0, D28 (day of 2nd dose of study injection), D42 and D180. Pseudovirus neutralizing antibody geometric mean titres (GMT) and 95% CI were evaluated at D28, D42 and D180. Titres below the lower limit of quantification (LLQ) were given the value of half of the LLQ. We calculated 95% CIs for GMCs or GMTs by back transforming the 95% CI for log antibody concentrations or titres.

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=4173050

We analysed the proportion of individuals with an anti-S, anti-RBD IgG concentration and PSVN NAb titre predictive of 80% risk reduction of symptomatic Covid-19 (referred to as putative risk reduction threshold [PRRT]) due to WT and mainly Alpha VOC using the approach described by Feng et al for the AZD1222 vaccine, adapted for VOCs[19]. The proposed thresholds predictive of 80% risk reduction against WT or Alpha VOC (referred to as WT/Alpha) symptomatic Covid-19 were: anti-S IgG of 264 BAU/ml, anti-RBD IgG of 506 BAU/ml and PSVN NAb titre of 185. The variant-specific NAb threshold associated risk reduction of symptomatic Covid-19 has not been established for variants emerging since Alpha VOC. Nevertheless, we used the same PSVN NAb threshold proposed for 80% risk reduction of symptomatic Covid-19 due to WT/Alpha, as a putative threshold for 80% risk reduction of symptomatic Covid-19 for other SARS-CoV-2 variants. We used a normal approximation method to calculate 95% CIs for proportions.

This is a descriptive study and no considerations were taken into account for multiple testing.

Ethical considerations

The study was approved by the South African Health and Pharmaceutical Products Regulatory Authority (SAHPRA) and the Human Ethics Research Committees of the various sites. Signed informed consent was obtained from all study participants. The COV005 study is registered with ClinicalTrials.gov, NCT04444674, and the Pan African Clinical Trials Registry, ACTR202006922165132.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. AstraZeneca reviewed the data from the trial and the final manuscript before submission, but the academic authors retained editorial control

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=4173050

Findings

For this study, we expanded testing of immune responses in the HIV-uninfected cohort to those enrolled in phase II and included 313 participants (128 placebo and 185 AZD1222 recipients). We do not report further on the kinetics of antibody in the placebo group in this manuscript. After exclusions, 149 AZD1222 participants remained eligible in the final analysis, 99 of whom were anti-N sero-positive prior to the first dose of AZD1222 and 58 of whom were baseline sero-negative and remained free of SARS-CoV-2 infection through to D180; Figure 1. The median age of participants was 30 years and 52.7% were male. The median time following the 2nd dose of AZD1222 at which immunogenicity was evaluated (i.e. D42) was 14 days; and persistence of antibody was measured through to a median of 148 days following (i.e. D180) 2nd dose of AZD1222. The demographics were similar between AZD1222 recipients who were baseline anti-N IgG sero-positive and sero-negative; Supplementary Table S1.

Anti-RBD and anti-S IgG kinetics in AZD1222 vaccine recipients stratified by baseline anti-N IgG sero-status.

As expected, anti-S IgG GMCs at D0 was higher among the baseline seropositive (183.2BAU/ml) compared with the sero-negative group (1.1 BAU/ml). Nevertheless, only 42.5% of the seropositive group had antibody concentrations above putative risk reduction threshold (PRRT) for symptomatic WT/Alpha Covid-19. The anti-S IgG GMCs remained higher in the baseline seropositive compared with seronegative group at D28, D42 and D180; Figure 2a and Supplementary Table S2.

Between D0 and D28, the fold increase in anti-S IgG GMC was lower in the baseline seropositive (11.0) compared with the seronegative group (112.9). Nevertheless, GMCs remained higher in the seropositive group for anti-S IgG (2040.5 vs. 136.4 BAU/ml). The percentage of individuals with anti-S IgG above the PRRT against WT/Alpha at D28

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=4173050

remained higher in the baseline seropositive (92.1%) compared with seronegative group (25.5%).

Between D28 and D42, there was no significant increase in anti-S IgG GMC in the baseline seropositive group, but a 4.1 fold increase in the seronegative group. Nevertheless, the D42 anti-S IgG GMCs remained higher in the baseline seropositive group (2194.9 vs. 538.4 BAU/ml). Furthermore, even the D28 (post 1st dose) anti-S IgG GMC in the baseline seropositive group (2040.5 BAU/ml) was higher than the D42 peak GMCs in the seronegative group (538.4 BAU/ml). The percentage of individuals with anti-S IgG above the PRRT against WT/Alpha Covid-19 at D42 remained higher in the baseline seropositive (96.6%) than seronegative group (74.1%).

Between D42 and D180, there was less of a decline in anti-S GMC in the baseline seropositive (73.5%) compared with seronegative group (84.7%); and anti-S IgG GMC remained higher in the seropositive group (517.8 vs 82.1 BAU/ml). Furthermore, the percentage of individuals with anti-S IgG above PRRT against WT/Alpha Covid-19 remained higher in the baseline seropositive (76.6%) compared with seronegative group (13.8%) at D180. The D180 anti-S IgG GMCs in the seropositive group (517.8 BAU/ml) was similar to the D42 peak GMCs in the seronegative group (538.4 BAU/ml); as was the percentage of people with IgG concentrations above the PRRT against WT/Alpha Covid-19 (76.6% vs. 74.1%, respectively); Figure 2 a-b and Supplementary Table S2.

The dynamics of anti-RBD IgG and differences between the baseline seropositive and seronegative groups were similar to that observed for anti-S IgG. Generally, the percentage of individuals with IgG greater than the PRRT against WT/Alpha symptomatic Covid-19 was lower for anti-RBD IgG than anti-S IgG; Figure 2 a-b and Supplementary Table S2.

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=4173050

Antibody dependent cellular cytotoxicity in AZD1222 vaccine recipients stratified by baseline anti-N IgG sero-status.

The ADCC IgG GMT was higher in the baseline seropositive compared with the seronegative group at D0 against D614G (499 vs. 46 relative light units (RLU) and Delta variant (382 vs. 38 RLU). There was a greater fold increase in ADCC IgG GMT in the baseline seronegative compared with seropositive group by D28 against D614G (9.6 vs 1.6 fold increase) and Delta variant (9.0 vs 1.7 fold). Nevertheless, the ADCC IgG GMT remained higher in the baseline seropositive compared with seronegative group for D614G (807.8 vs. 440.2) and Delta (636.6 vs. 297.2) at D28.

Between D28 and D42, there was no further increase in ADCC IgG GMT in the seropositive group, compared with 2.3 and 2.7 fold increase against D614G and Delta variant, respectively, in the seronegative group. Consequently, there was no difference in ADCC IgG GMT against D614G or Delta between the baseline seropositive compared with seronegative group at D42. Also, the ADCC IgG GMT at D180 did not differ by baseline sero-status for either D614G or Delta; Figure 3 and Supplementary Table S3. The geometric mean of the ADCC IgG D614G to Delta ratio was similar between the baseline seropositive and seronegative vaccine recipients at each time point and ranged between 1.1 to 1.5; Suppl Table S3.

Pseudovirus neutralizing (PSVN) antibodies to multiple variants stratified by baseline anti-N IgG sero-status in AZD1222 recipients

PSVN GMTs against D614G were higher at D28, D42 and D180 in the baseline seropositive compared with the seronegative group. Also, a higher percentage of the baseline seropositive (92.0%) than seronegative group (27.3%) had NAb above PRRT against WT/Alpha symptomatic Covid-19 at D28. The GMTs against D614G increased 5.6 fold between D28 (81) and D42 (451) in the seronegative group, whilst there was only 1.3 fold increase (1496 to 1933) in the seropositive group. Nevertheless, GMTs was 4.3 fold higher

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=4173050

in the baseline seropositive compared with seronegative group at D42; although the percentage with titres above PRRT against D614G was now similar between the groups (100% vs 84.6%, respectively). The NAb titres against D614G decreased by 69.5% and 82.6% in the baseline seropositive and seronegative groups, respectively, between D42 and D180; and GMT remained higher in the seropositive group (590 vs. 78). By D180, the baseline seropositive group were again more likely (92.0%) to have NAb above the PRRT against D614G than the seronegative group (18.2%); Figure 4a-b and Suppl Table S4.

The NAb GMTs against D614G was 1.5 to 12.8 fold higher than against Beta VOC at the different time points. At D28, 76.0% of the baseline seropositive compared with none of the seronegative group had NAb above the PRRT against Beta symptomatic Covid-19. There was only a modest fold increase in NAb against Beta between D28 and D42 in the baseline seropositive (1.5) and seronegative (2.2) groups. The D180 NAb GMT against Beta in the seropositive group (178) was 5.1 fold higher than the peak at D42 in the seronegative group (35). The percentage of individuals with NAb titres greater that PRRT against Beta symptomatic Covid-19 was consistently higher in the baseline seropositive than seronegative group at D28 (76.0% vs. 0%), D42 (76.0% vs 0%) and D180 (52.0% vs. 18.2%); Figure 4a-b and Suppl Table S4.

The NAb kinetics against A.VOPI.V2, Gamma and SARS-CoV-1 between the seropositive and seronegative group, as well as percentage at each time point above the putative risk reduction threshold, were similar to that observed for Beta VOC; Fig 4 a-b; Supplementary Table 4.

The NAb GMTs against D614G was 2.1 to 7.4 fold higher than against Delta at the different time points. Against Delta variant, there was no significant increase in NAb GMTs after the 2nd dose of AZD1222 (between D28 and D42) in the baseline seropositive or seronegative group, however, GMT remained higher in the seropositive group (451 vs 38) at D42. The D180 NAb GMT titre against Delta in the seropositive group was similar to the D42 peak NAb GMT in the seronegative group. The percentage of individuals with NAb above the

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=4173050

PRRT against Delta symptomatic Covid-19 was consistently higher in the baseline seropositive than seronegative group at D28 (92.0% vs. 18.2%), and D42 (92.0% vs 9.1%), whilst being similar at D180 (32.0% vs. 27.3%); Figure 4a-b and Suppl Table S4.

The NAb GMTs against D614G was 3.0 to 27.4 fold higher than against Omicron BA.1. At D28, the NAb GMTs against BA.1 was higher in the seropositive (499) than seronegative group (14). There was no increase in NAb against BA.1 in either the baseline anti-N IgG seropositive or seronegative group following the 2nd dose of AZD1222, and NAb GMTs remained higher in the seropositive group at D42 (535 vs 16). The percentage of individuals with NAb above the PRRT against BA.1 symptomatic Covid-19 was 84% at D28 and D42 in the seropositive group, and 0% in the seronegative group. There was a 96% reduction in BA.1 NAb GMT between D42 and D180 in the seropositive group, with only 4.0% of them still having titres above the PRRT at D180; Figure 4a-b and Suppl Table S4.

Kinetics of NAbs against Omicron BA.4 mirrored Omicron BA.1. NAb GMTs against BA.4 were higher in the seropositive group compared with the seronegative group at all time points. For seropositive group, NAb GMTs decreased over time, while Nab GMTs ranged from 13 to 16 between D28 and D180 in the seronegative group. The percentage of individuals with NAb above the PRRT against BA.4 symptomatic Covid-19 was 87.5% at D28 and D42 in the seropositive group, and 0% in the seronegative group. At D180, no participants had a titre above the putative threshold and there was a 90.4% decrease in the NAb GMT from D42 in the baseline sero-positive group.

Except for poor correlation of anti-S IgG and NAb against BA.1 at D180, the correlation between anti-S IgG and NAb against D614G was modest (Spearman's correlation: 0.57 to 0.59 at D28 and D42). The correlation was modest to good for other variants (0.54 to 0.93); Supplementary Fig S1 and Supplementary Table S5.

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=4173050

Interpretation

The findings of our study demonstrate that SARS-CoV-2 infections, prior to vaccination primed the immune system for a more robust humoral immune response to the AZD1222 primary series compared with individuals who were SARS-CoV-2 naïve when vaccinated. Similar observations were reported by other studies on AZD1222 vaccine as an effective booster for after initial priming with SARS-CoV-2 infection[20].

Furthermore, a second dose of AZD1222 within four weeks of the first dose in individuals who were baseline sero-positive, did not result in further increase in anti-S IgG, anti-RBD IgG, NAb or ADCC. In contrast there were substantial increases in antibody levels following the second dose of AZD1222 in individuals who were sero-negative at baseline. Similar observations were reported by other after the primary series for AZD1222 for anti-S and NAb to WT,[21] as well as for mRNA and Ad26.CoV2.v2[5,22]. However, we expand the observations to include the implications of hybrid-induced immunity compared with AZD1222-only induced immunity on kinetics of anti-S, anti-RBD and ADCC through to D180. Furthermore, we analysed the impact of hybrid immunity induced neutralizing antibody activity to several SARS-CoV-2 variants, including Omicron BA.1 and BA.4, which now dominate global infections.

The baseline anti-N IgG seropositive compared with seronegative AZD1222 recipients maintained higher concentrations of anti-S and anti-RBD IgG through to D180. Also, a greater percentage of vaccine recipients with hybrid immunity had NAb above the PRRT against symptomatic Covid-19 due to D614G, Beta, A.VOI.V2 and Gamma through to D180. Although a higher percentage of baseline seropositive compared with seronegative group also had NAb titres above the PRRT against symptomatic Covid-19 due to Delta (92.0% vs. 9.1%), BA.1 (84% vs. 0%) and BA.4 (87.5% vs 0%) at D42, this was no longer evident by D180. The antibody-evasiveness of Omicron BA.1 and BA.4 has been well described for convalescent sera and Covid-19 vaccines[23-26].

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=4173050

The higher potential vaccine effectiveness even against variants demonstrating relative resistance to NAb activity imputed from our analysis, is corroborated from real world vaccine effectiveness in which hybrid immunity with mRNA vaccines had higher vaccine effectiveness against BA.1 and BA.2 infection (52-57%) compared with only two doses of mRNA vaccine induced immunity (0%)[27]. The higher hybrid immunity induced vaccine effectiveness could be attributable to the greater magnitude of binding and NAb induced after only a single dose of vaccine compared with even the peak antibody responses at D42 in the baseline sero-negative group. Also, the repertoire of immune responses following vaccination after past infection compared with in a SARS-CoV-2 naïve individual may vary in terms of antibody targets and degree of affinity maturation and through a broader repertoire of $CD4^+$ and $CD8^+$ immune responses[28]. Antibody mediated Fc effector function evaluated here, albeit in a small subset, demonstrated that infection alone (at D0), as well as vaccine-only induced immunity elicited cross-reactive ADCC against D614G and Delta; with the ADCC IgG demonstrating less waning through to D180 compared with binding IgG and NAb levels. This is consistent with previous reports of antibodies retaining the ability to mediate Fc effector function against VOCs[18].

We previously reported from the same study the lack of vaccine efficacy against mild-moderate symptomatic COVID-19 due to the Beta variant (VE: 10%; 95%CI: -79 to 55%) in individuals who were anti-N IgG seronegative at enrolment. The lack of AZD1222 vaccine effectiveness against Beta is consistent with our observation that none of the baseline seronegative group had NAb above the PRRT against Beta variant symptomatic Covid-19 at D42. In contrast, among the baseline seropositive group, the percentage with NAb above the putative protective threshold was 71.7% at D28 and remained high through to D180 (51.9%). This illustrates the need for exercising caution in extrapolating from studies done early on in the pandemic when a lower percentage of the populations were infected by SARS-COV-2 compared to the present when the population is broadly SARS-CoV-2 experienced[29].

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=4173050

Notably, most individuals with hybrid immunity (92% at D28 and D42) had NAb against Delta had NAb titres above the PRRT compared with only 9% of those with vaccine-only induced immunity (9%). The final analysis of study recorded vaccine efficacy of 77.1% (95% CI: 30.4, 94.4) against the Delta variant, with the cases having accrued 9-10 months after the 2nd dose of AZD1222, independent of baseline anti-N IgG serostatus; and vaccine efficacy against wild type virus was 91% (95%CI: 35%-100%)[30]. We have not completed anti-N IgG at all the time points as a proxy for SARS-CoV-2 infections over and above the cases documented by nucleic acid amplification test positivity. Nevertheless, a sero-survey prior to the Delta variant wave in several South African provinces showed SARS-CoV-2 sero-positivity rates of 32-63% by January 2021[31]. This could have contributed to high level of protection against Delta, which dominated in South Africa between May 2021 to early November 2021 despite the low NAb activity induced by vaccine alone.

We had un-blinded the study and offered dosing of the placebo group and a third dose to the vaccinated group prior to the onset of the Omicron dominant wave. Consequently, we cannot extrapolate whether the high percentage of individuals with hybrid immunity who had NAb above the PRRT against BA.1 at D42 (84%), translated into vaccine effectiveness against mild-moderate COVID-19 due to Omicron BA1. Notably, 70% of COVID-19 unvaccinated adults in Gauteng Province (South Africa), where most sites involved in this study were based, were sero-positive prior to the Omicron dominant wave in South Africa[16].

Limitations of our study include that we focussed only on vaccine and infection induced binding humoral responses, which are important contributors to protecting against SARS-CoV-2 infection and mild-moderate COVID[1,4]. We did not evaluate $CD4^+$ and $CD8^+$ T lymphocyte responses, which likely attenuate the clinical severity of COVID-19. Notably, $CD4^+$ and $CD8^+$ T-cell responses induced by vaccines and past infection are preserved, even against the highly mutated Omicron BA.1 variant harbouring more than 30 S-protein mutations [32]. Another limitation was using the PSVN threshold associated with 80% risk reduction of WT/Alpha symptomatic Covid-19, as a putative threshold for risk reduction due

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=4173050

to the other analysed variants, for which individual thresholds for risk reduction are yet to be derived. Also, our study is limited to the baseline sero-positive group having been infected with the WT virus and it's unclear whether primary infection with other variants would yield similar observations as we have shown.

Overall, these data indicate that vaccine effectiveness against symptomatic COVID-19 is likely to differ at an individual and population level depending on prior SARS-CoV-2 infection. Also, the limited boost in antibody responses following a 2nd dose of a vaccine suggest limited value at the population level (excluding immunocompromised individuals) of a second dose of vaccine 4 weeks later in settings where there has been a high force of past SARS-CoV-2 infections. It is, however, possible that a longer interval between the first two doses could confer benefit in individuals with past SARS-CoV-2 infection. This is pertinent in many low income African countries where Covid-19 vaccine rollout is still lagging, but 79% of the population had been infected with SARS-CoV-2 by mid-November 2021 prior to the circulation of the highly transmissible Omicron variant[33].

Declaration of interests

Oxford University has entered into a partnership with AstraZeneca for further development of ChAdOx1 nCoV-19 (AZD1222). SCG is cofounder of Vaccitech, a collaborator in the early development of this vaccine candidate, and is named as an inventor on a patent covering use of ChAdOx1-vectored vaccines (PCT/GB2012/000467) and a patent application covering this SARS-CoV-2 vaccine (GB2003670.3). TL is named as an inventor on a patent application covering ChAdOx1 nCoV-19 and was a consultant to Vaccitech. All other authors declare no competing interests.

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=4173050

Author contributions

SAM conceived the trial and is the national principal investigator. SAM, GK, CLC, VB, SCG, AJP, PLM and AI wrote the protocol and designed the trial. SAM, ALK, AI, CLC, VB, CT, PLM and GK designed the trial and oversaw the conduct of the trial, database design and development, site selection and training, data collection, data cleaning, and interpretation of results. AI did the statistical analysis. ALK, LF, SDP, KD, SLB, QEB, EL and CB are trial site principal investigators and enrolled participants, collected data, and prepared the manuscript. KA, PKA, SB, AE, EH, AJ, LR, FP, CT, AT and SVK oversaw the implementation of the trial at sites or collected data, or both. SIR, HK, SM, NPM, TH, TM, NM, CM, PLM generated and analysed the data. SAM, GK, SG, PLM and AI prepared the manuscript. SAM and AI accessed and verified the data. All authors had full access to all of the data in the study and had final responsibility for the decision to submit to publication.

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=4173050

References

1. Khoury DS, Cromer D, Reynaldi A, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med* 2021; **27**(7): 1205-11.
2. Gilbert PB, Montefiori DC, McDermott AB, et al. Immune correlates analysis of the mRNA-1273 COVID-19 vaccine efficacy clinical trial. *Science* 2022; **375**(6576): 43-50.
3. Fong Y, McDermott AB, Benkeser D, et al. Immune Correlates Analysis of a Single Ad26.COV2.S Dose in the ENSEMBLE COVID-19 Vaccine Efficacy Clinical Trial. *medRxiv* 2022.
4. Zohar T, Loos C, Fischinger S, et al. Compromised Humoral Functional Evolution Tracks with SARS-CoV-2 Mortality. *Cell* 2020; **183**(6): 1508-19 e12.
5. Keeton R, Richardson SI, Moyo-Gwete T, et al. Prior infection with SARS-CoV-2 boosts and broadens Ad26.COV2.S immunogenicity in a variant-dependent manner. *Cell Host Microbe* 2021; **29**(11): 1611-9 e5.
6. Bates TA, McBride SK, Leier HC, et al. Vaccination before or after SARS-CoV-2 infection leads to robust humoral response and antibodies that effectively neutralize variants. *Sci Immunol* 2022; **7**(68): eabn8014.
7. Zhong D, Xiao S, Debes AK, et al. Durability of Antibody Levels After Vaccination With mRNA SARS-CoV-2 Vaccine in Individuals With or Without Prior Infection. *JAMA* 2021; **326**(24): 2524-6.
8. Saadat S, Rikhtegaran Tehrani Z, Logue J, et al. Binding and Neutralization Antibody Titers After a Single Vaccine Dose in Health Care Workers Previously Infected With SARS-CoV-2. *JAMA* 2021; **325**(14): 1467-9.
9. Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med* 2021; **384**(5): 403-16.
10. Voysey M, Costa Clemens SA, Madhi SA, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. *Lancet* 2021; **397**(10277): 881-91.
11. Ebinger JE, Fert-Bober J, Printsev I, et al. Prior COVID-19 Infection and Antibody Response to Single Versus Double Dose mRNA SARS-CoV-2 Vaccination. *medRxiv* 2021.
12. Ali H, Alahmad B, Al-Shammari AA, et al. Previous COVID-19 Infection and Antibody Levels After Vaccination. *Frontiers in Public Health* 2021; **9**.
13. Bradley T, Grundberg E, Selvarangan R, et al. Antibody Responses after a Single Dose of SARS-CoV-2 mRNA Vaccine. *New England Journal of Medicine* 2021; **384**(20): 1959-61.
14. Madhi SA, Koen AL, Izu A, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 in people living with and without HIV in South Africa: an interim analysis of a randomised, double-blind, placebo-controlled, phase 1B/2A trial. *Lancet HIV* 2021; **8**(9): e568-e80.
15. Rossler A, Riepler L, Bante D, von Laer D, Kimpel J. SARS-CoV-2 Omicron Variant Neutralization in Serum from Vaccinated and Convalescent Persons. *N Engl J Med* 2022; **386**(7): 698-700.
16. Madhi SA, Baillie V, Cutland CL, et al. Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant. *N Engl J Med* 2021; **384**(20): 1885-98.
17. Wibmer CK, Ayres F, Hermanus T, et al. SARS-CoV-2 501Y.V2 escapes neutralization by South African COVID-19 donor plasma. *Nat Med* 2021; **27**(4): 622-5.
18. Richardson SI, Manamela NP, Motsoeneng BM, et al. SARS-CoV-2 Beta and Delta variants trigger Fc effector function with increased cross-reactivity. *Cell Rep Med* 2022; **3**(2): 100510.
19. Feng S, Phillips DJ, White T, et al. Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection. *Nat Med* 2021; **27**(11): 2032-40.

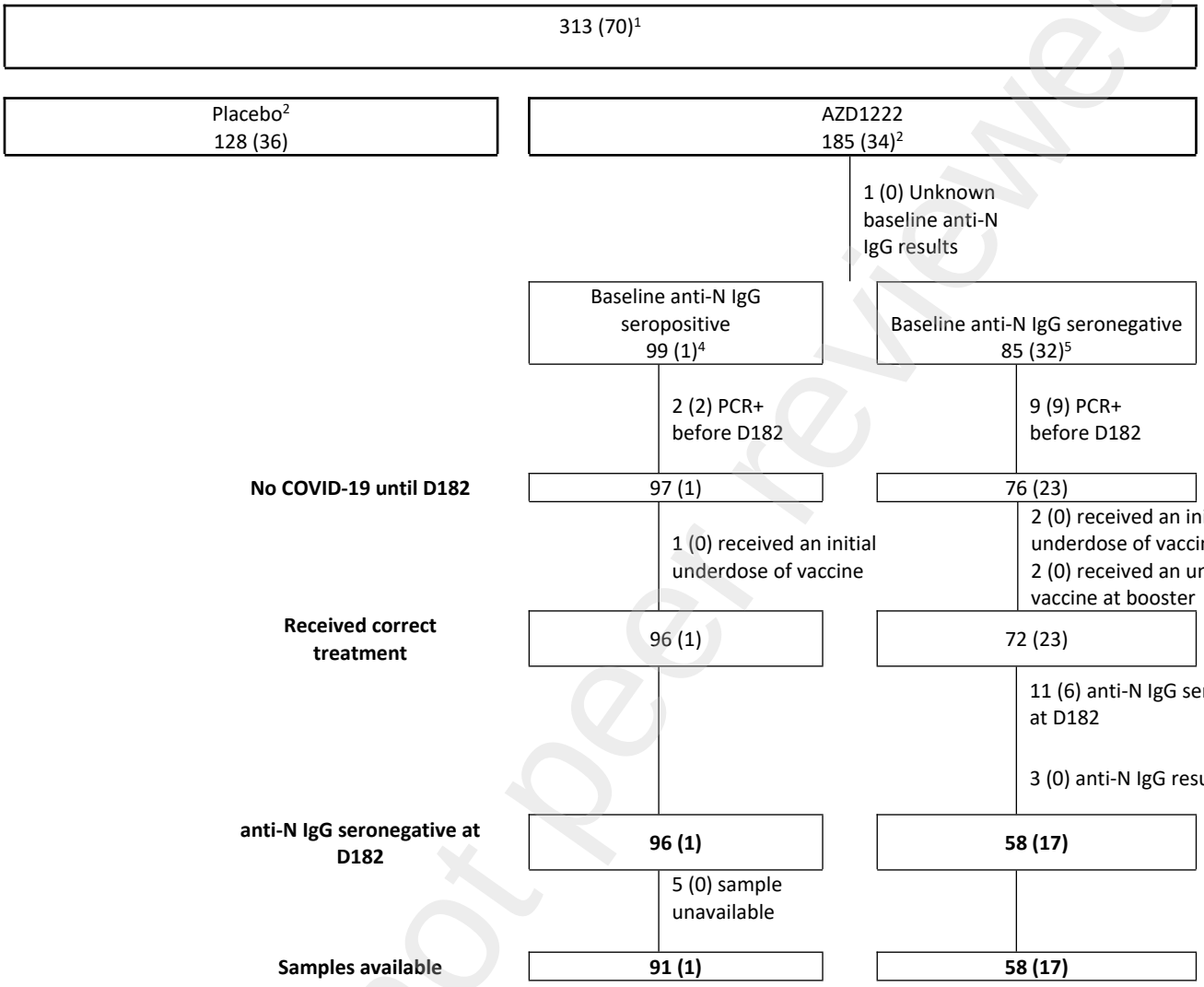
This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=4173050

20. Chibwana MG, Moyo-Gwete T, Kwatra G, et al. AstraZeneca COVID-19 vaccine induces robust broadly cross-reactive antibody responses in Malawian adults previously infected with SARS-CoV-2. *BMC Medicine* 2022; **20**(1): 128.
21. Gelanew T, Mulu A, Abebe M, et al. A single dose ChAdOx1 nCoV-19 vaccine elicits high antibody responses in individuals with prior SARS-CoV-2 infection comparable to that of double dose vaccinated SARS-CoV-2 infection naïve individuals. *Research square* 2022: rs.3.rs-1250175.
22. Angyal A, Longet S, Moore SC, et al. T-cell and antibody responses to first BNT162b2 vaccine dose in previously infected and SARS-CoV-2-naive UK health-care workers: a multicentre prospective cohort study. *Lancet Microbe* 2022; **3**(1): e21-e31.
23. Liu L, Iketani S, Guo Y, et al. Striking antibody evasion manifested by the Omicron variant of SARS-CoV-2. *Nature* 2022; **602**(7898): 676-81.
24. Tuekprakhon A, Huo J, Nutalai R, et al. Antibody escape of SARS-CoV-2 Omicron BA.4 and BA.5 from vaccine and BA.1 serum. *Cell* 2022.
25. Cao Y, Yisimayi A, Jian F, et al. BA.2.12.1, BA.4 and BA.5 escape antibodies elicited by Omicron infection. *Nature* 2022.
26. Wang Q, Guo Y, Iketani S, et al. SARS-CoV-2 Omicron BA.2.12.1, BA.4, and BA.5 subvariants evolved to extend antibody evasion. *bioRxiv* 2022: 2022.05.26.493517.
27. Altarawneh HN, Chemaitelly H, Ayoub HH, et al. Effects of Previous Infection and Vaccination on Symptomatic Omicron Infections. *N Engl J Med* 2022.
28. Muecksch F, Weisblum Y, Barnes CO, et al. Affinity maturation of SARS-CoV-2 neutralizing antibodies confers potency, breadth, and resilience to viral escape mutations. *Immunity* 2021; **54**(8): 1853-68 e7.
29. Viana R, Moyo S, Amoako DG, et al. Rapid epidemic expansion of the SARS-CoV-2 Omicron variant in southern Africa. *Nature* 2022; **603**(7902): 679-86.
30. Koen AL, Izu A, Baillie V, et al. Efficacy of the AZD1222 (ChAdOx1 nCoV-19) COVID-19 Vaccine Against SARS-CoV-2 Variants of Concern. *medRxiv* 2022: 2022.07.18.22277743.
31. Sykes W, Mhlanga L. Prevalence of anti-SARS-CoV-2 antibodies among blood donors in Northern Cape, KwaZulu-Natal, Eastern Cape, and Free State provinces of South Africa in January 2021. 2021.
32. Keeton R, Tincho MB, Ngomti A, et al. T cell responses to SARS-CoV-2 spike cross-recognize Omicron. *Nature* 2022; **603**(7901): 488-92.
33. Madhi SA, Kwatra G, Myers JE, et al. Population Immunity and Covid-19 Severity with Omicron Variant in South Africa. *N Engl J Med* 2022; **386**(14): 1314-26.

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=4173050

Figure 1: Consort diagram for individuals selected for investigation on effect of prior SARS-CoV-2 infection on antibody kinetics following AZD1222 through to Day 180.



[1]Neutralisation assays were done on all Phase 1b participants and an additional random sample of Phase II vaccinated baseline anti-N IgG seropositive participants. In total 41 vaccinated participants (17 from Phase 1b) and 9 placebo participants (all Phase 1b) had neutralisation assays done.

[2]The antibody kinetics of the placebo group is not reported further in this manuscript.

[3]Number of participants enrolled in the Phase 1b study are shown in parenthesis

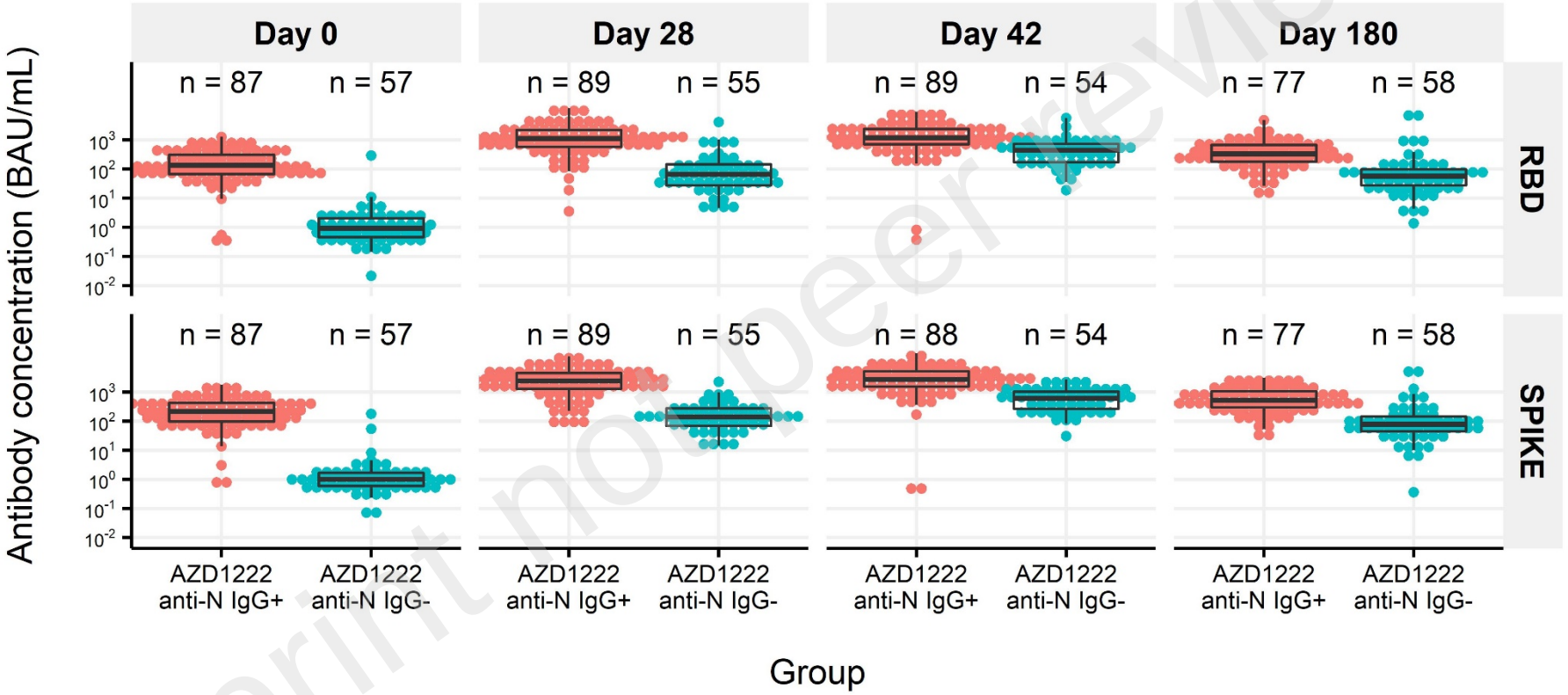
[4]There were 25 vaccinated participants who were anti-N IgG seropositive at baseline that had a neutralisation results (only 1 from Phase 1b). All 25 participants with baseline anti-N IgG seropositive results were included in the analysis of the neutralisation data.

[5]There were 16 Phase 1b vaccinated participants who were anti-N IgG seronegative at baseline that had neutralisation results. Of these, two had PCR+ result before D182 and three had an anti-N IgG seropositive response at D182. A total of 11 vaccinated participants with baseline anti-N IgG seronegative results were included in the analysis of the neutralisation data.

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=4173050

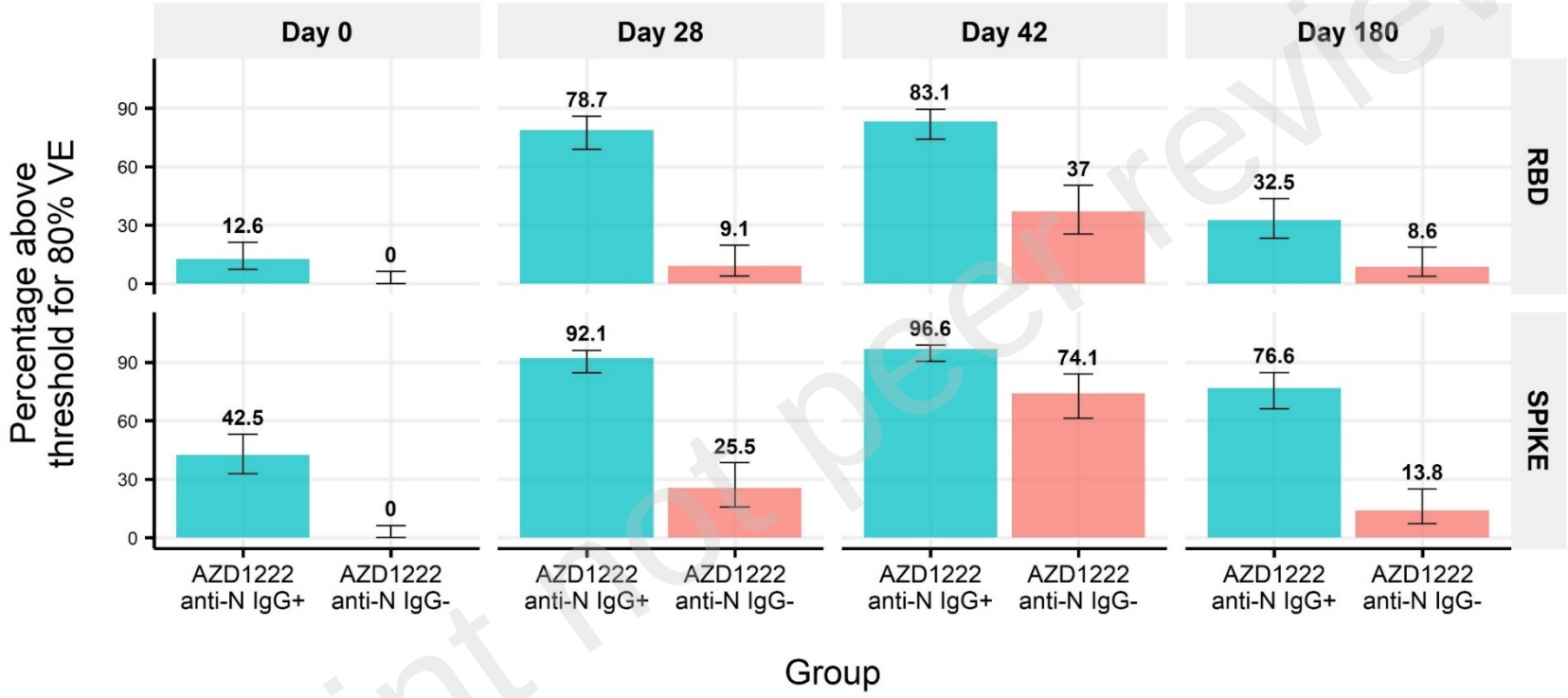
Figure 2a: Antibody kinetics in HIV-negative group comparing AZD1222 vaccinated individuals who were anti-Nucleocapsid IgG seropositive or seronegative at time of first dose of vaccine.



Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=4173050

Figure 2b: Percentage of participants with anti- receptor binding domain IgG and anti-Spike IgG concentrations above the threshold for 80% risk reduction against wild type or Alpha variant of concern,[1] comparing AZD1222 vaccinated individuals who were anti-Nucleocapsid IgG seropositive (anti-N IgG+) or seronegative (anti-N IgG-) at time of first dose of vaccine.

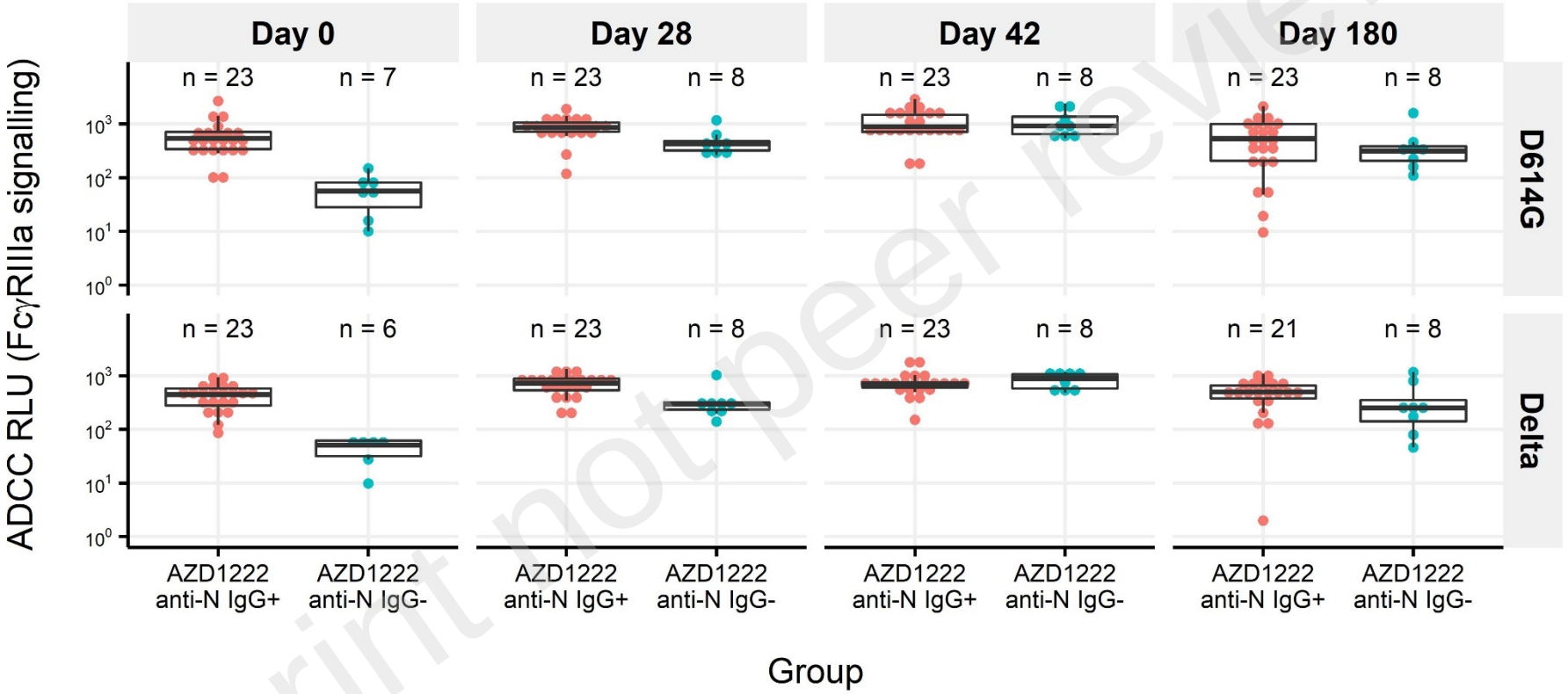


[1]The putative binding immunoglobulin G (IgG) threshold associated with 80% risk reduction of wild type or Alpha variant of concern symptomatic Covid-19 was as determined by Feng et al; and was 264 binding arbitrary units per millilitre (BAU/ml) for anti-spike IgG and 506 for anti- receptor binding domain IgG.

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=4173050

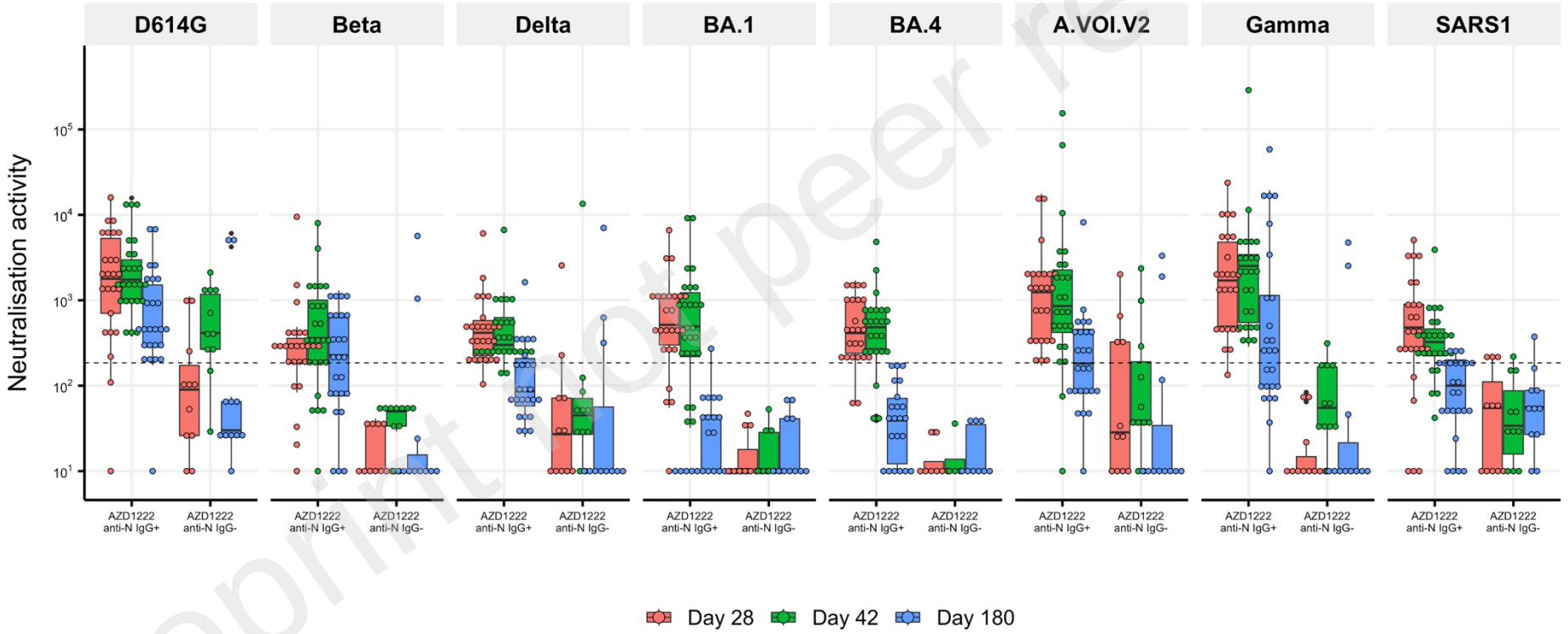
Figure3: Antibody dependent cellular cytotoxicity (ADCC) relative light unit (RLU) FcγRIIIa signalling in HIV-uninfected AZD1222 vaccinated individuals who were anti-Nucleocapsid IgG seropositive (anti-N IgG+) or seronegative (anti-N IgG-) at time of the first vaccine.



Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=4173050

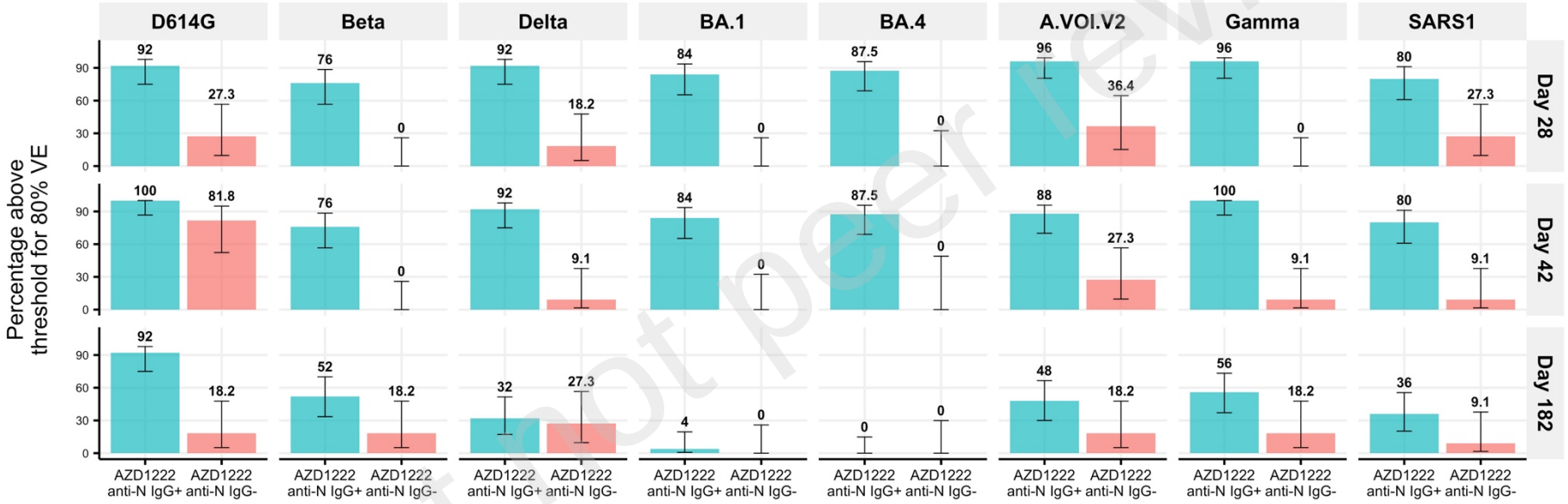
Figure 4a: Pseudovirus neutralization antibody activity to multiple variants in HIV negative individuals at one month after 1st AZD1222 dose (D28), 14 days (D42) and 142 days (D180) the second dose of AZD1222, stratified by baseline anti-Nucleocapsid IgG seropositive (anti-N IgG+) or seronegative (anti-N IgG-) at time of 1st vaccine dose.



Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=4173050

Figure 4b: Examining the percentage of participants with ID50 concentrations above the putative threshold for 80% risk reduction of symptomatic Covid-19 in AZD1222 vaccinated individuals who were anti-Nucleocapsid IgG seropositive (anti-N IgG+) or seronegative (anti-N IgG-) at time of first dose of vaccine.



[1]The putative pseudovirus neutralization assay (PSVN) antibody titre of 185 was associated with 80% risk reduction of wild type or Alpha variant of concern symptomatic Covid-19 was as determined by Feng et al. We presumed that the same threshold may apply for PSVN for the other variants, and SARS-CoV-1.

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=4173050