Immunogenicity of SARS-CoV-2 vaccines BBV152 (COVAXIN®) and ChAdOx1 nCoV-19 (COVISHIELD™) in seronegative and seropositive individuals in India: a multicentre, nonrandomised observational study

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Summary

Background There are limited global data on head-to-head comparisons of vaccine platforms assessing both humoral and cellular immune responses, stratified by pre-vaccination serostatus. The COVID-19 vaccination drive for the Indian population in the age group 18–45 years began in April 2021 when seropositivity rates in the general population were rising due to the delta wave of COVID-19 pandemic during April–May 2021.

Methods Between June 30, 2021, and Jan 28, 2022, we enrolled 691 participants in the age group 18–45 years across four clinical sites in India. In this non-randomised and laboratory blinded study, participants received either two doses of Covaxin® (4 weeks apart) or two doses of Covishield™ (12 weeks apart) as per the national vaccination policy. The primary outcome was the seroconversion rate and the geometric mean titre (GMT) of antibodies against the SARS-CoV-2 spike and nucleocapsid proteins post two doses. The secondary outcome was the frequency of cellular immune responses pre- and post-vaccination.

Findings When compared to pre-vaccination baseline, both vaccines elicited statistically significant seroconversion and binding antibody levels in both seronegative and seropositive individuals. In the per-protocol cohort, Covishield™ elicited higher antibody responses than Covaxin® as measured by seroconversion rate (98.3% vs

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74.4%, p < 0.0001 in seronegative individuals; 91.7% vs 66.9%, p < 0.0001 in seropositive individuals) as well as by anti-spike antibody levels against the ancestral strain (GMT 1272.1 vs 75.4 binding antibody units/ml [BAU/ml], p < 0.0001 in seronegative individuals; 2089.07 vs 585.7 BAU/ml, p < 0.0001 in seropositive individuals). As participants at all clinical sites were not recruited at the same time, site-specific immunogenicity was impacted by the timing of vaccination relative to the delta and omicron waves. Surrogate neutralising antibody responses against variants-of-concern including delta and omicron was higher in Covishield™ recipients than in Covaxin® recipients; and in seropositive than in seronegative individuals after both vaccination and asymptomatic infection (omicron variant). T cell responses are reported from only one of the four site cohorts where the vaccination schedule preceded the omicron wave. In seronegative individuals, Covishield™ elicited both CD4+ and CD8+ spike-specific cytokine-producing T cells whereas Covaxin® elicited mainly CD4+ spike-specific T cells. Neither vaccine showed significant post-vaccination expansion of spike-specific T cells in seropositive individuals.

Interpretation Covishield™ elicited immune responses of higher magnitude and breadth than Covaxin® in both seronegative individuals and seropositive individuals, across cohorts representing the pre-vaccination immune history of most of the vaccinated Indian population.

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Keywords: Vaccine response; COVID; Seropositive; Covaxin; Covishield; Immune response; Antibodies; T cells

Introduction

As of Dec 14, 2021, inactivated, vectored and mRNA vaccines comprised 43%, 28% and 26% respectively of the total 10.6 billion doses of COVID-19 vaccines administered in the world.[1] Despite this large share of the vaccination landscape, there are few studies that make comprehensive head-to-head comparisons of both humoral and cellular immune response elicited by these vaccine platforms.[2–5] As of Sep 1, 2022, India carried out the world's largest COVID-19 vaccination drive across 3006 vaccine centres covering all its state and union territories and has administered 1.7 billion doses of Covishield™ (ChAdOx-1 nCoV-19, manufactured by Serum Institute of India) and 0.35 billion doses of Covaxin® (inactivated vaccine adjuvanted with a TLR7/8 agonist, manufactured by Bharat Biotech).[6] These two vaccines administered in India, together represent 15% of the total COVID-19 vaccine doses administered in the world. However, there is a paucity of data comparing the immunogenicity of the two vaccines.

Prior studies comparing Covishield™ and Covaxin® were limited to addressing only antibody responses and in the health care worker population who were immunized prior to the delta wave of the COVID-19 pandemic[7–11] (See Supplementary Table S1). However, there is limited data on cellular immune responses elicited by these vaccines and no direct head-to-head comparisons or stratification by pre-vaccination serostatus.[11]

Vaccination following exposure to the delta or omicron variants of SARS-CoV-2 is likely to affect the quality, quantity, and duration of immune responses. For determining future COVID-19 vaccination policy when pan-coronavirus or sarbecovirus vaccines become available, it becomes important to consider pre-vaccination immune history of most of the vaccinated Indian population. Comparison of vaccine platforms stratified by serostatus will also inform vaccine development against future pandemics, which are likely due to climate change, ecosystem destabilisation and lowering of herd immunity (latter attributed to vaccine hesitancy against both established and newer vaccine regimes). We therefore compared the immune responses elicited by the two main SARS-CoV-2 vaccines utilised in India, stratified by serostatus.

Methods

Study design and participants

This study was done in healthy adults aged 18–45 years at four recruitment sites and laboratory sites: recruitment; Bangalore Baptist Hospital (BBH), King Edward Memorial Hospital Research Center (KEMHRC), Symbiosis University Hospital and Research Center (SUHRC), and St. John's Medical College (SJMC) and laboratory; National Centre for Biological Sciences (NCBS), Institute for Stem Cell Science and Regenerative Medicine (InStem), National Chemical Laboratory (NCL), Indian Institute of Science Education and Research Pune (IISER-Pune), St. John's Research Institute (SJRI).

Research in context

Evidence before this study

We identified 8 primary studies that compared the immunogenicity of the COVID-19 vaccines Covaxin and Covishield, after two doses. Two of these studies were from the same cohort, reporting different timepoints and were considered as one. Five studies were conducted in healthy adults and included in this analysis. Four of these five studies administered Covishield doses at 28 days apart, unlike the 84-day interval used for the general population. In an observational cross-sectional pan-India study comparing humoral responses against spike protein in SARS-CoV-2 naïve healthcare workers, seroconversion, and antibody titres after two vaccine doses were higher in participants vaccinated with Covishield (97.8% and 114 arbitrary units/ml [AU/ml]) than in those vaccinated with Covaxin (79.3% and 45.3 AU/ml). In participants with prior history of SARS-CoV-2 infection, antibody titres were 302.9 AU/ml and 256.3 AU/ml after vaccination with Covishield and Covaxin, respectively. In another observational study in healthcare workers recovered from SARS-CoV-2 infection, Covishield elicited statistically significant higher levels of anti-spike antibodies than Covaxin. In a third observational study in seronegative healthcare workers, Covishield elicited statistically significantly higher antibody levels than Covaxin after both the first and second dose of vaccine and these differences persisted at week 24. All participants in above studies were vaccinated prior to the delta wave and cellular responses were not measured. A fourth longitudinal observation study also demonstrated higher responses in participants vaccinated with Covishield than Covaxin in both seronegative (100% vs 62.5% seroconversion rate) and seropositive participants (1740 vs 469 median neutralisation titre). Limitations in sample size did not allow direct comparison of cellular responses elicited by Covishield and Covaxin. The fifth study compared Covaxin with Covishield administered either at 28-day or 84-day intervals, but results were confounded by a 68% infection rate between the vaccine doses.

Added value of this study

Our study provides a comprehensive and longitudinal perspective, tracking the trajectory of antibody responses elicited by Covaxin and Covishield in seronegative and seropositive participants across four different sites during the different waves of SARS-CoV-2 infection. Here we compare both humoral responses and cellular responses elicited by two doses of Covaxin and Covishield using the vaccination schedule used for the general population (administered 28 days and 84 days apart, respectively) in both seronegative and seropositive participants. Covishield elicits higher antibody responses against the ancestral strain as well as variants-of-concern such as delta and omicron. Covishield also elicited stronger CD4 and CD8 T cell responses in the earliest cohort used to track T cell responses, whereas Covaxin induced only CD4 T cell responses against spike protein in seronegative participants. Neither vaccine significantly enhanced T cell responses in seropositive participants.

Implications of all the available evidence

The results of our study support the available evidence on the superiority of Covishield in eliciting higher levels of antibodies against the ancestral spike protein, compared to Covaxin. It adds further evidence to the efficacy of Covishield by demonstrating increased levels of antibodies against variants-of-concern including delta and omicron and increased T cell responses.

SARS-CoV-2 vaccine-naïve participants were screened for serostatus and recruited at BBH, KEMHRC, SUHRC and SJRI using a combination of anti-spike and/or anti-nucleocapsid antibodies, either qualitative or quantitative, manufactured by either Roche Diagnostics, Abbott Laboratories or Liaison DiaSorin at each clinical site. Recruitment was done using a combination of unbiased as well serostatus-confirmed inclusion. Baseline samples were re-tested and classified for their serostatus using DiaSorin TrimericS and MSD platforms at Christian Medical College (CMC), Vellore. Sample size calculations were not performed, and recruitment numbers were based on the capacity at each site. All the participants were enrolled after obtaining informed written consent. Participants with a history of medical illness or prior severe COVID-19 that required ventilation or administration of biologics such as convalescent plasma or monoclonal antibodies were excluded. Vaccine-naïve participants were administered two doses of either Covaxin® at 4-week interval or Covishield™ at 12-week interval per the prevailing government norms. Allocation of participants to vaccine arms was non-randomised and per participant-choice. Participants in the Covaxin® arm were sampled at Day 0 (prior to first dose of vaccine), Day 28 (prior to second dose of vaccine), Day 42, Day 84, month 6 and month 9. Participants in the Covishield™ arm were sampled at Day 0 (prior to the vaccine dose), Day 28, Day 84 (prior to the second dose), Day 98, month 6 and month 9. Participants were followed bi-monthly for symptoms of COVID-like illness. The qualifying symptoms of COVID-like illness included fever (≥38 °C) or cough or sore throat or shortness of breath or anosmia/ageusia or malaise or fatigue or vomiting or diarrhoea. The trial was approved by the Institutional Ethics Committee (BBH/IRB/2021/33, NCBS/IEC-27/01, inStem/IEC-23/02, IISERP-IHEC/Admin/2021/018, SIU/IEC/298, KEMHRC/RVM/EC/1225, NCL-IHEC/SEP2021/001,

SJRI-298/2021) at each site and registered at the Clinical Trial Registry of India (CTRI) website (CTRI/2021/09/036258).

Procedures

Binding antibodies against the trimeric spike protein in all study participants were measured using the LIAISON SARS-CoV-2 TrimericS IgG assay on the DiaSorin platform per the manufacturer's instructions. The assay measures between antibody levels 4.81 and 2080 binding antibody units/ml (BAU/ml). Samples with titres greater than 2080 BAU/ml were auto-diluted 1:20 per the manufacturer instructions, providing an extended measuring interval until 41600 BAU/ml. The assay cut-off of 33.8 BAU/ml was used to determine seropositivity. In samples with titre <33.8 BAU/ml, seroconversion was defined as an increase in titre to >33.8 BAU/ml following vaccination. In samples with titre >33.8 BAU/ml, seroconversion was defined as at least 2-fold increase in titre following vaccination. For values less than 33.8 BAU/ml, the assay is not sensitive to distinguish between seronegative and participants with lower antibody levels.

Binding antibodies against trimeric spike protein of SARS CoV-2, nucleocapsid, receptor binding domain (RBD) and N-terminal domain (NTD) were measured using the MSD V-Plex SARS-CoV-2 Panel 1 (IgG) kit. Angiotensin converting enzyme 2 (ACE2) inhibition activity was measured using the MSD V-Plex SARS-CoV-2 Panel 13 (ACE2) and Panel 25 (ACE2) kits at a 1:50 dilution per the manufacturer's instructions.

Neutralising antibodies were measured in a microneutralisation assay. Vero E6 cells were seeded at 10,000 cells per well in a 96-well tissue culture plate. After 24 h, heat inactivated plasma samples were diluted in DMEM supplemented with 2% FBS in a 2-fold dilution series. The diluted plasma (75 µL) was mixed with 75 µL of SARS-CoV-2 Italian INMI1 strain (NR-52284, BEI resources; MOI = 0.01). This mixture was incubated for 1 h in a humidified 37 °C incubator supplemented with 5% CO_2. The plasma-virus mixture was then added to the cell monolayer and incubated for 1 h in the incubator. The plasma-virus mixture was removed from the cell monolayer, and the cells were replenished with fresh media supplemented with 2% FBS and incubated for 48 h. Duplicate wells containing cells only and cells with virus diluent were included as controls. A previously titred plasma sample was used as positive control in all the assays. After 48 h of incubation. Microscopic images are recorded using an inverted optical microscope and Q-capture pro-7.0 software. Neutralisation titre was defined as the highest dilution of plasma at which there was complete rescue of virus-induced cytopathic effects on the cell monolayer. Representative images are shown in Supplementary Fig. S3a. Microneutralisation assay was performed with institutional biosafety clearances (TFR:NCBS:37IBSC2021/RP, inStem/G-141(3)-20/CJ, inStem/G-141(3)-20/AK and NCBS:37IBSC2021/VS1).

T cell responses were measured from frozen peripheral blood mononuclear cells previously isolated from heparinised blood as per standard protocols. Briefly, PBMCs were thawed, washed and resuspended in a 50 ml polypropylene tube and rested for 4 h in a 37 °C/5% CO_2 incubator. 1.5 million cells/well were stimulated with 1 µg/ml of SARS-CoV-2 Prot S Complete, or a mix of Prot N and Prot M at 1 µg/ml each in a 37 °C/5% CO_2 incubator. Cells left unstimulated or stimulated with PHA-P served as negative and positive controls respectively for every sample. Co-stimulatory antibodies (1 µg/ml each of anti-CD28 and anti-CD49d) were included in all test conditions. After 2 h, Brefeldin A was added to all wells for a final concentration of 5 µg/ml. Cells were incubated for an additional 16 h. At the end of the stimulation period, cells were washed and stained with a viability dye (Live/dead fixable dye) for 10 min at room temperature, followed by incubation with a cocktail of surface stain antibodies (anti-CD14 BV650, anti-CD16 BV650, anti-CD20 BV650, anti-CD4 Alexa700 and anti-CD8 BV605) for 20 min at 4 °C. After washing, cells were fixed, permeabilised and stained with a cocktail of intracellular stain antibodies (anti-CD3 Cy7APC, anti-IFNγ BV421, anti-IL2 PE and anti-TNF BV785) for 20 min at 4 °C. After additional washes, cells were fixed again and acquired on flow cytometer BD LSRFortessa within 24 h. Data were analysed using FlowJo 10.8.1. A control sample (treated similarly as the test samples) was included in every run of the assay. Paired samples from the same participant were tested within the same run. Cytokine gates for flow cytometry were set using the unstimulated controls and maintained for a given run. A representative gating strategy is shown in Supplementary Fig. S4a. Antigen-specific frequencies were calculated by subtraction of background responses from the unstimulated control of each sample. Assay limit of detection was set to 0.002% based on inclusion criteria of acquiring minimum 50,000 live CD4+ T cells in each sample. Responses less than 0.002% were set to 0.002%.

Statistical analysis

For antibody analyses, within-group comparisons across timepoints were tested using two-way ANOVA with Tukey's correction. Between-group comparisons after each vaccine dose were tested using two-way ANOVA with Sidak's correction. Differences between pre-vaccination and post-vaccination T cell responses were

compared using Kruskal–Wallis test with Dunn's correction. All statistical analyses were performed with GraphPad Prism 9.4.1. A p value less than 0.05 was considered as statistically significant.

Role of the funding source

The funders had no role in writing of the manuscript or the decision to submit for publication. No payments have been received from any pharmaceutical agency for writing this article. Authors were not precluded from accessing the data and accept responsibility to submit for publication.

Results

Study population

Between June 30, 2021 and Jan 28, 2022, we enrolled 691 participants in the age group 18–45 years across four sites in urban and rural Bengaluru and Pune, India. The four clinical sites recruited participants in a staggered fashion and coincide with the different waves of vaccination in India following the delta wave when vaccines became widely available (Fig. 1). As per the prevailing government norms, participants received either two doses of Covaxin® (at 28 days apart) or two doses of Covishield™ (at 3 months apart). The omicron wave in early 2022 overlapped with the second dose of vaccine at two clinical sites and with both doses at one clinical site. A total of 16 vaccine-unrelated serious adverse events were observed. Participants were sampled at six timepoints for antibody analyses and at four timepoints for cellular analyses. The vaccine groups were subdivided as seronegative or seropositive at baseline, based on the binding antibody titres against the trimeric spike protein (using a globally comparable and standardised test, the Diasorin TrimericS IgG). The clinical sites used a combination of unbiased enrollment and pre-screening for anti-spike and/or anti-nucleocapsid antibodies to achieve enough participants within each serostatus. The 506 participants who received the second dose of vaccine on day 28–30 for Covaxin® or day 84–91 for Covishield™, completed all visits until 2 weeks post the second dose of vaccine and did not have symptomatic real-time PCR (rtPCR)-confirmed SARS-CoV-2 infection at least until 2 weeks post the second dose of vaccine, formed the per-protocol population (Table 1). The four study groups, classified based on baseline serostatus and vaccine received, were similar for age and gender across the full cohort ($p = 0.7534$ and 0.8931 respectively) as well as within each cohort (Table 1). The numbers of participants with prior SARS-CoV-2 infections (RTPCR confirmed) were small in each cohort (24 in BBH, 7 in KEMHRC, 0 in SUHRC and 7 in SJRI) and did not vary statistically significantly between the study groups within each cohort ($p > 0.05$, Table 1).

Seroconversion rates following vaccination in the per-protocol population

Following vaccination, each dose of vaccine led to a statistically significant increase in the magnitude of anti-spike antibodies over baseline in both seronegative individuals and seropositive individuals (Fig. 2a, Supplementary Table S2), as measured using the DiaSorin TrimericS assay platform.[12] At all the timepoints tested, geometric mean titres (GMTs) in the Covishield™ arm were higher than in the Covaxin® arm. We therefore compared seroconversion rates between the Covaxin® and Covishield™ arms, within each baseline serostatus group. Seroconversion was defined as change in titre from <33.8 BAU/ml (manufacturer-specified assay cut off for seropositivity) to >33.8 BAU/ml or an increase in titre by at least 2-fold if pre-vaccine titre was already >33.8 BAU/ml.

In the baseline seronegative population, seroconversion rates in the Covaxin® arm following the first and second doses of vaccine were 36.6% and 74.4%, respectively ($p < 0.0001$) (Fig. 2b, Table 2, Supplementary Table S2 and Supplementary Fig. S1). Of 36.6% participants who responded to the first dose of Covaxin®, only 14.6% responded additionally to the second dose. Also, 37.8% participants did not show significant immune responses after the first dose and seroconversion occurred only after the second dose. Furthermore, 25.6% participants classified as non-responders appeared to show detectable antibody responses after the second dose but did not cross the seropositivity cut-off of the assay. In the seronegative Covishield™ arm, seropositivity rates were 93.2%, and 98.3% following the first and second doses respectively ($p < 0.0001$). The differences in seroconversion rates between the two vaccines in seronegative individuals were significant in the overall cohort both after the first and second dose ($p < 0.0001$) and in two of the four clinical sites after the second dose (Supplementary Table S2; see also Fig. 4).

In the baseline seropositive group, Covaxin® administration led to an increase in antibody titre by at least 2-fold over baseline in 51.8% and 66.9% participants, following the first dose and second dose respectively ($p < 0.0001$, Table 2, Supplementary Table S2). Among the 51.8% first-dose responders, only 11.5% participants also additionally responded to the second dose of vaccine while the other 40.3% participants did not show a further increase in titres after the second dose of vaccine. Also, 10.8% participants responded only to the second dose of vaccine and 37.4% participants did not respond to either dose (Fig. 2b and Supplementary Fig. S1a). In the Covishield™ group, antibody titres increased at least 2-fold over baseline in 95.2%, and 91.7% participants after the first and second doses respectively ($p < 0.0001$, Supplementary Table S2). Furthermore, 10.1% participants responded to both vaccine doses, 85.1% participants responded only to the

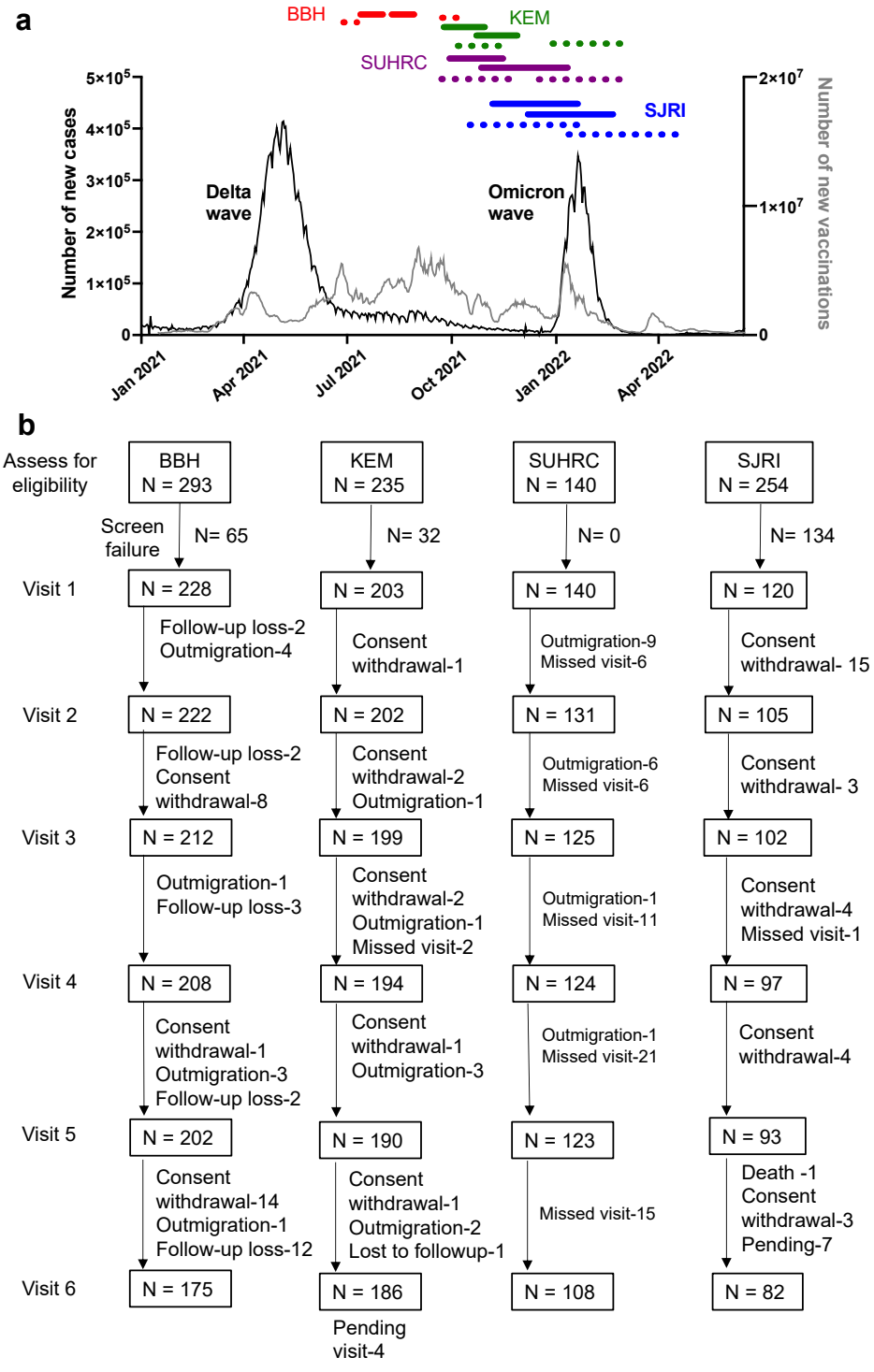

Fig. 1: **Participant recruitment and vaccination schedule in the context of delta and omicron waves and vaccination status in the country**. (a) Recruitment schedules across the sites. Horizontal coloured lines show the time span during which the first and second doses of vaccine were administered in each site. Solid lines represent the first and second dose of Covaxin® and dotted lines represent the first and second dose of Covishield™. (b) Participant recruitment and follow-up in each of the cohorts. BBH: Bangalore Baptist Hospital, KEM: King Edward Memorial Hospital Research Center, SUHRC: Symbiosis University Hospital and Research Center, SJRI: St. John's Research Institute.

	Seronegative		Seropositive		p-value
	Covaxin	Covishield	Covaxin	Covishield	
N					
Overall	82	117	139	168	
BBHHRC	25	50	43	56	
KEM	37	28	55	56	
SUHRC	9	18	28	30	
SJRI	11	21	13	26	
Age, years					
Overall	30	30	30	30	0.7534
BBH	33 (24.0–37.5)	35 (26.0–38.0)	33 (25.0–41.0)	31 (27.0–37.5)	0.7716
KEMHRC	30 (23.0–36.5)	27 (23.0–33.0)	29 (25.0–34.0)	29 (24.0–35.0)	0.6167
SUHRC	30 (25.0–35.0)	26 (21.8–33.0)	28 (24.0–35.8)	29 (23.8–36.3)	0.4139
SJRI	28 (19.0–31.0)	30 (22.5–34.0)	30 (18.5–36.5)	26 (19.8–35.3)	0.6385
Sex					
Men	45 (54.9%)	61 (52.1%)	70 (50.4%)	84 (50.0%)	
Women	37 (45.1%)	56 (47.9%)	69 (49.6%)	84 (50.0%)	0.8931
Prior Covid Infection					
Overall					
BBH	0 (0%)	0 (0%)	13 (30.2%)	11 (19.6%)	0.2451[a]
KEMHRC	1 (2.7%)	0 (0%)	6 (10.9%)	1 (1.8%)	0.0606[a]
SUHRC	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
SJRI	0 (0%)	0 (0%)	3 (23.1%)	4 (15.4%)	0.6664[a]

Data are median with interquartile range or n (%). Differences in age and gender were compared using one-way ANOVA and chi-squared test respectively. [a]Differences in numbers of participants with prior Covid infection were compared between the seropositive Covaxin® and Covishield™ groups using Fisher's exact test. BBH: Bangalore Baptist Hospital, KEM: King Edward Memorial Hospital Research Center, SUHRC: Symbiosis University Hospital and Research Center, SJRI: St. John's Research Institute. Related to Fig. 1.

Table 1: **Demographic characteristics of the per-protocol population.**

first dose and 4.8% did not respond to either dose. The differences in seroconversion rates between the two vaccines after the first and second doses were statistically significant in the overall cohort ($p < 0.0001$). In both vaccine arms, non-responsiveness to vaccination was associated with higher pre-vaccination antibody titres (Supplementary Fig. S1b).

Though trends in vaccine-wise and serostatus-wise immunogenicity outcomes remained the same within each of the four cohorts, the magnitude of differences between study arms were impacted by the recruitment period of the cohorts (Fig. 1a). Notably, the two cohorts with significant differences in seroconversion rates between the vaccines had sampled participants in the Covaxin® arm prior to the omicron wave, while the other two cohorts with higher seroconversion rates for Covaxin® had dosed and/or sampled the Covaxin® arm during the omicron wave. The trends in differences in cohort-wise immunogenicity between the two vaccines in seropositive individuals was similar to that of the seronegative individuals. Cohorts that were vaccinated and sampled soon after the delta wave had lower seroconversion rates for Covaxin® than for Covishield™. Cohorts that were vaccinated and sampled overlapping the omicron wave displayed comparable immunogenicity between the two vaccines (Supplementary Table S2; Supplementary Fig. S2).

Magnitude of anti-spike antibodies following vaccination in the per-protocol population

The GMT in the seronegative Covaxin® group increased from 8.4 BAU/ml at baseline to 19.2 BAU/ml and 75.4 BAU/ml following the first dose and second doses, respectively (Fig. 2c, Table 2 and Supplementary Table S2). In the seronegative Covishield™ group, titres increased from 7.9 BAU/ml to 354.3 BAU/ml and 1272.1 BAU/ml following the first and second doses, respectively ($p < 0.0001$ after both doses). The GMTs in the Covishield™ arm were higher than in the Covaxin® arm at both time points and the difference was statistically significant ($p < 0.0001$).

The GMT in the seropositive Covaxin® group increased from 175.4 BAU/ml to 398.2 BAU/ml and 585.7 BAU/ml following the first dose and second doses of vaccine respectively ($p = 0.0037$ and <0.0001, Fig. 2c). In the seropositive Covishield™ arm, GMT increased from 158.21 BAU/ml to 3569.69 BAU/ml and 2089.07 BAU/ml following the first dose and second doses of vaccine respectively ($p < 0.0001$). Despite waning of antibody titres between weeks 4 and 12, a second dose of

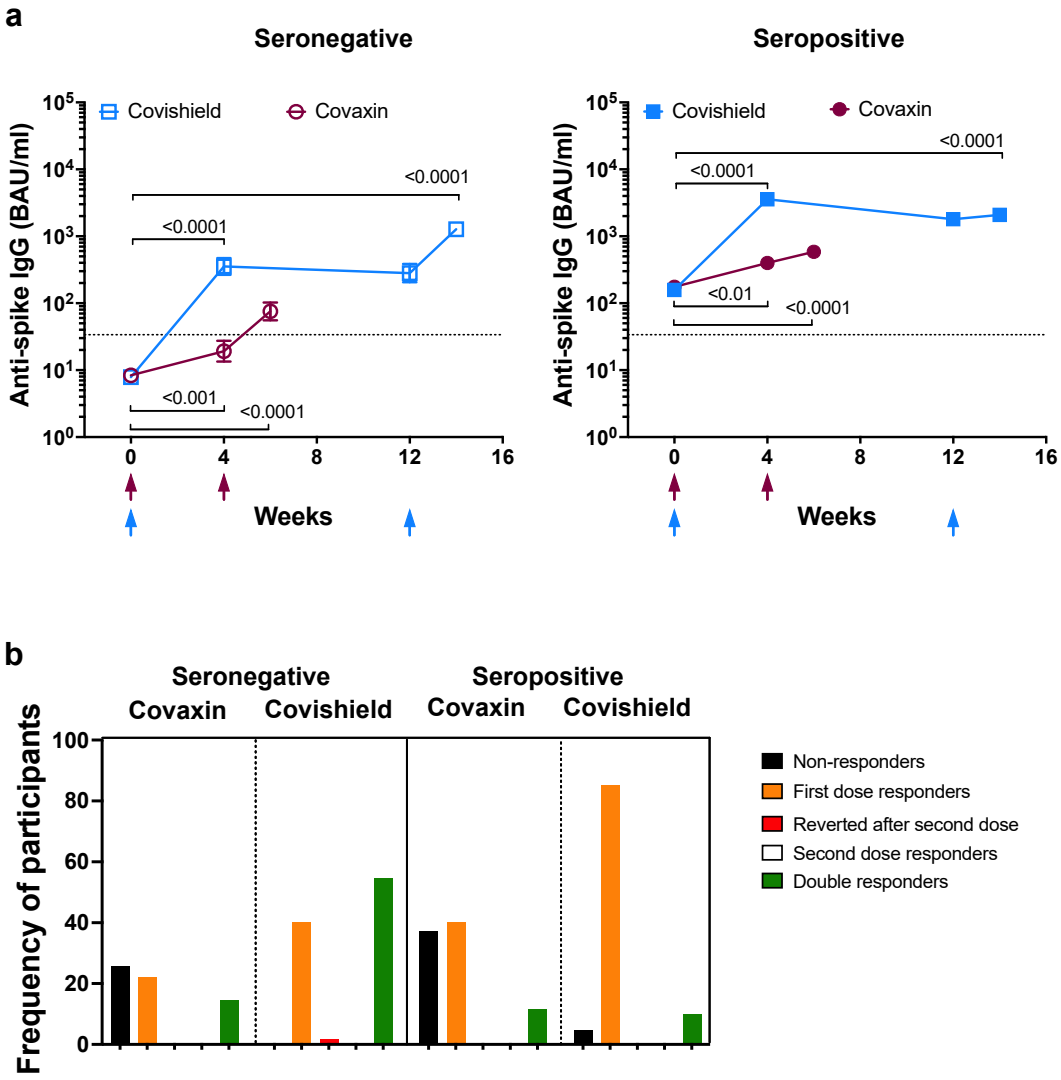

Fig. 2: **Antibody responses following vaccination in the per-protocol population from all cohorts**. Antibody responses against ancestral spike protein were measured on the Diasorin TrimericS platform in the per-protocol population across the full cohort. Participants were classified as either seronegative (n = 82 for Covaxin®, open red circles; 117 for Covishield™, open blue squares) or seropositive (n = 139 for Covaxin®, filled red circles; 168 for Covishield™, filled blue squares) at baseline using the assay cut-off of 33.8 BAU/ml (horizontal dotted line). (a) Data are shown as geometric mean ± 95% CI. Within-group comparisons to the baseline were assessed using a two-way ANOVA with Tukey's correction for multiple comparisons. (b) Bar graphs show seroconversion rates. Seroconversion was defined as change from <33.8 to >33.8 for those with titres <33.8 BAU/ml prior to the vaccine dose. For those with titres >33.8 BAU/ml, seroconversion was defined as increase in titre by at least 2-fold following the vaccine administration. (c) Between group comparisons after each vaccine dose were made using two-ANOVA with Sidak's correction. (d) Neutralizing responses were measured as inhibition of cytopathic effects by Italian strain INMI1 on VeroE6 cells in a microneutralization assay (see Supplementary Fig. S3a). Participants were classified as either seronegative or seropositive using a cut-off of 33.8 BAU/ml for ancestral spike binding on the TrimericS platform. Samples from baseline and 2-weeks post the second dose of vaccine were tested. The corresponding antibody trajectories for the matched samples are shown in Supplementary Fig. S3c and d. Statistical comparisons were made using two-way ANOVA with Sidak's correction. For all statistical analyses, p-values >0.05 are denoted as ns (not statistically significant).

Covishield™ at week 12 did not restore the antibody levels seen after the first dose of vaccine. After each dose, the difference in titres between the vaccines was found to be statistically significant dose ($p < 0.0001$).

Considering the pre-vaccination titres in the seropositive group as a reference for convalescent titres, GMT after first and second dose of Covishield™ in seronegative individuals were 2.1-fold and 7.6-fold

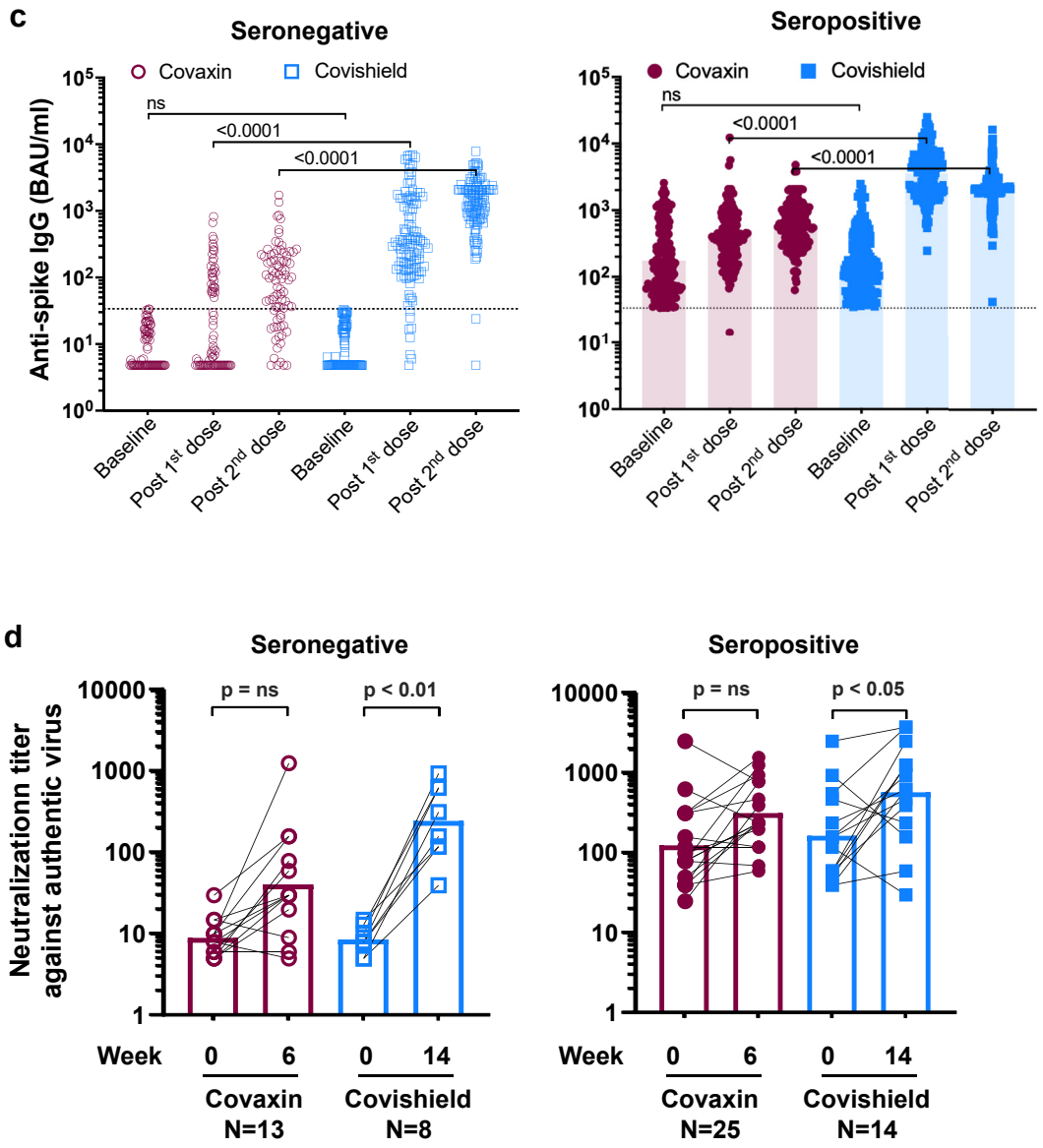

Fig. 2: (continued).

higher respectively, whereas two doses of Covaxin® in seronegative individuals remained 2.2-fold lower than that of the convalescents.

Magnitude of anti-spike antibodies within each cohort

In the seronegative Covaxin® arm, there was a trend towards increasing post-vaccine antibody titres in the cohorts that started recruitment later and overlapped with the omicron wave. However, the inter-cohort differences in the GMTs were not statistically significant, likely due to insufficient sample size in some of the cohorts (Supplementary Fig. S2).

In the seronegative Covishield™ arm, there were minor but statistically significant differences in the baseline titres, suggesting that some of the participants who were classified as seronegative by the TrimericS platform may have been previously exposed and antibody levels may have waned off at the time of recruitment. Nevertheless, all cohorts reached similar titres after the first dose. Statistically significant differences again arose at week 12 due to differential antibody

	Seronegative		p-value	Seropositive		p-value
	Covaxin	Covishield		Covaxin	Covishield	
Seroconversion rate						
4 weeks after first dose						
Overall	36.6%	93.2%	<0.0001	51.8%	95.2%	<0.0001
BBH	20.0%	92.0%	<0.0001	37.2%	92.9%	<0.0001
KEMHRC	35.1%	96.4%	<0.0001	50.9%	100.0%	<0.0001
SUHRC	22.2%	100.0%	<0.0001	67.9%	100.0%	0.0006
SJRI	90.9%	85.7%	>0.9999	69.2%	84.6%	0.4023
2 weeks after second dose						
Overall	74.4%	98.3%	<0.0001	66.9%	91.7%	<0.0001
BBH	52.0%	96.0%	<0.0001	60.5%	87.5%	0.0039
KEMHRC	75.7%	100.0%	0.0077	63.6%	94.6%	<0.0001
SUHRC	100.0%	100.0%	>0.9999	78.6%	100.0%	0.0093
SJRI	100.0%	100.0%	>0.9999	76.9%	84.6%	0.6664
GMT						
Baseline						
Overall	8.4 (7.2–9.7)	7.9 (6.9–8.9)	0.9885	175.4 (144.8–212.5)	158.2 (135.8–184.3)	0.4040
BBH	7.2 (5.7–9.1)	5.7 (5.0–6.5)	0.3810	230.7 (164.5–323.5)	233.4 (177.5–307.0)	0.9979
KEMHRC	8.7 (6.8–11.0)	7.9 (5.9–10.7)	0.9987	197.3 (142.9–272.6)	110.9 (89.3–137.7)	0.0022
SUHRC	8.4 (4.4–16.0)	14.6 (10.6–20.1)	0.5450	89.1 (64.0–124.0)	133.0 (96.8–182.7)	0.9649
SJRI	10.5 (6.8–16.3)	9.9 (7.0–13.9)	0.9994	185.6 (91.5–376.7)	179.8 (110.7–292.0)	0.9996
4 weeks after first dose						
Overall	19.2 (13.4–27.4)	354.3 (265.7–472.5)	<0.0001	398.2 (338.6–468.3)	3569.7 (3148.7–4046.9)	<0.0001
BBH	11.1 (6.5–19.1)	224.4 (148.3–339.5)	0.0014	368.6 (288.3–471.3)	3719.1 (2903.6–4763.8)	<0.0001
KEMHRC	17.8 (10.2–31.0)	415.4 (237.0–727.9)	0.0138	439.3 (334.3–577.3)	4479.9 (3765.8–5329.2)	<0.0001
SUHRC	12.7 (4.5–36.1)	917.5 (453.4–1856.8)	0.0061	232.5 (181.1–298.6)	2641.1 (2066.2–3376.0)	<0.0001
SJRI	119.5 (57.4–248.7)	376.4 (166.3–851.7)	0.0590	1081.8 (563.1–2078.1)	2836.7 (1915.8–4200.2)	0.2516
2 weeks after second dose						
Overall	75.4 (55.6–102.3)	1272.1 (1061.4–1524.7)	<0.0001	585.7 (511.3–670.9)	2089.07 (2313.8–1886.2)	<0.0001
BBH	33.6 (19.0–59.4)	1085.6 (762.4–1545.8)	<0.0001	586.5 (476.5–722.0)	2128.4 (1714.1–2642.8)	<0.0001
KEMHRC	80.3 (51.6–125.1)	1369.1 (1028.7–1822.3)	<0.0001	602.9 (478.9–758.9)	2051.0 (1742.3–2414.4)	<0.0001
SUHRC	144.5 (94.2–221.7)	1517.6 (1001.5–2299.5)	0.0002	389.8 (295.0–515.1)	2136.2 (1716.3–2658.8)	<0.0001
SJRI	224.2 (110.8–453.5)	1446.4 (1068.9–1957.2)	<0.0001	1240.0 (798.8–1924.9)	2035.0 (1602.7–2583.9)	0.2838
Neutralization: GMT						
Baseline						
BBH	8.8 (6.4–12.2)	8.4 (6.0–11.7)	>0.9999	123 (66.7–226.8)	161.8 (76.3–342.9)	0.8967
2 weeks after second dose						
BBH	40.1 (16.1–100.0)	241.6 (97.4–599.2)	0.0802	310.6 (187.9–513.2)	563.2 (243.6–1302)	0.0146

Data are either percentages or geometric mean (GMT) and 95% confidence intervals. Comparisons of seroconversion rates were made using Fisher's exact test. Differences in GMTs in the overall cohort across time between the two vaccines were assessed by two-way ANOVA with Sidak's correction for multiple comparisons. BBH: Bangalore Baptist Hospital, KEM: King Edward Memorial Hospital Research Center, SUHRC: Symbiosis University Hospital and Research Center, SJRI: St. John's Research Institute. Related to Fig. 2.

Table 2: **Vaccine-elicited antibody responses in the per-protocol population.**

kinetics across cohorts. At week 12, the BBH cohort that was sampled prior to the omicron wave had the lowest titre at 90.5 BAU/ml, KEMHRC and SUHRC cohorts that received the second dose and were sampled during the omicron wave were intermediate at 366.5 and 611.2 BAU/ml and the SJRI cohort that was positively impacted by the Omicron wave during and between the first and second doses had the highest titre at 1522.1 BAU/ml. The SJRI cohort with first dose vaccination during the omicron wave showed increase in antibody titres between weeks 4 and 12, whereas the other three cohorts showed stable or declining titres. These differences in week 12 were nullified at week 14 due to the second dose of vaccine, with all cohorts reaching similar antibody titres irrespective of their exposure to infection and/or vaccination.

In the seropositive Covaxin® group, between-cohort differences in titres were in the 2.4–2.6 fold range, some of which were significant. In the seropositive Covishield™ group, the baseline titres showed

statistically significant variation across cohorts but normalised after the first dose of vaccination. The differences among the cohorts in exposure to the omicron wave was not manifested in the antibody responses in the seropositive Covishield™ group.

We also measured neutralising antibodies using the authentic SARS-CoV-2 virus at baseline and at two weeks post second dose of vaccine. We compared baseline neutralising antibody titres in a subset of participants from one BBH cohort and their matched anti-spike binding antibody titres and ACE2 inhibition in the two vaccine arms. The neutralisation titres measured in the assay correlated significantly ($p < 0.0001$) with the TrimericS anti-spike IgG and with anti-spike IgG and ACE2 inhibition against wild-type and delta strains measured using the MSD platform (Supplementary Fig. S3b). Covishield™ elicited significant levels of neutralising antibodies in both seronegative individuals (GMT 8.4 to 241.6; $p = 0.0085$) and seropositive individuals (GMT 161.8 to 563.2; $p = 0.0263$). However, Covaxin® failed to elicit statistically significant increases in GMT in the Covaxin® group, although the GMT increased from 8.8 to 40.1 in seronegative individuals and 123.0 to 310.6 in seropositive individuals (Fig. 2d). The spike-binding antibody titers (TrimericS) and anti-spike and anti-nucleocapsid IgG levels (MSD) at baseline and post vaccination in matched seronegative and seropositive individuals from each vaccine arm has been shown in Supplementary Fig. S3b and c.

T cell responses following vaccination

Across all vaccine platforms against SARS-CoV-2, spike-specific antibodies wane considerably over a six-month period, and it has been proposed that adaptive immune memory, especially T cells, might be sufficient to ward off symptomatic infection and severe disease. We therefore measured the frequency of spike-specific CD4 and CD8 T cell responses at baseline and at 2 weeks post second vaccine dose in a subset of participants from the earliest recruited cohort (BBH). Supplementary Fig. S4 shows representative gating strategy for viable responding CD4 and CD8 cells, intracellular cytokine staining in the presence and absence of specific peptides and antibody trajectories for samples included in the intracellular cytokine staining (ICS) assay. In concordance with the spike antibody-based (TrimericS) classification of participants into seronegative and seropositive individuals at baseline, the frequencies of cytokine-positive CD4 T cells against the ancestral spike peptide pool in the baseline seropositive group were significantly higher ($p < 0.01$) compared to the seronegative group (Supplementary Fig. S5). However, neither total CD4 nor CD8 T cell responses against a pool of nucleocapsid and matrix peptides nor the frequencies of cytokine-positive CD8 T cells against the spike protein were statistically significant between seronegative and seropositive individuals at baseline (Supplementary Fig. S5a). The frequency of spike-specific IFNγ, IL2 and TNF-producing CD4 T cells were significantly enhanced in baseline seropositive compared to seronegative individuals. Notably, the frequency of spike-specific and nucleocapsid-specific IL2-producing CD4 T cells positively correlated (with the magnitude of their respective -binding antibodies at baseline (Supplementary Fig. S5b and c)).

In seronegative individuals, both Covaxin® and Covishield™ led to an increase in median spike-specific cytokine-positive CD4 T cells following vaccination (0.002%–0.01% and 0.005%–0.07% respectively, Fig. 3a), though the fold change was statistically significant only in the Covishield™ arm ($p = 0.0022$). Given the lower seroconversion rate in the seronegative Covaxin® arm, we split this group further based on both TrimericS and MSD data as antibody-responders vs non-responders (Supplementary Fig. S6). As expected, significant spike-specific CD4 T cells were observed in the Covaxin® antibody responder group (0.002%–0.024%, $p < 0.05$) (Supplementary Fig. S6a and b). The spike-specific CD8 T cell responses were only detected in the Covishield™ arm (0.002%–0.035%, $p < 0.05$) but not in the Covaxin® arm (Fig. 3a). When analysed for individual cytokines, Covishield™ elicited significant IFNγ, IL2 and TNF responses in CD4 T cells, whereas Covaxin® elicited IL2 and TNF responses, however these did not reach statistical significance. Despite elicitation of nucleocapsid antibodies by Covaxin®, we did not detect a significant expansion of the CD4 T cells against the N + M peptide pool (Supplementary Fig. S6c).

In seropositive individuals, we did not detect a statistically significant increase in the frequency of spike-specific cytokine-positive CD4 or CD8 T cells with either vaccine (Fig. 3b). In both vaccine arms, there was a trend for group medians of cytokine-producing T cells in antibody non-responders to decrease following vaccination and in responders to either marginally increase or remain stable (Supplementary Figs. S7a and b). However, when the cytokines were analysed individually, there appeared to be a trend for spike-specific CD8 T cell responses to increase after vaccination in the seropositive Covishield™ arm (Supplementary Fig. S7c).

Impact of the omicron wave on binding antibody responses

Due to exposure of the Indian population to the omicron wave, durability of vaccine-elicited responses in the study participants could not be assessed as asymptomatic infection may have affected the quantity and quality of immune responses. However, in the earliest cohort (BBH), data from participants free of symptoms (based on follow-up for clinical signs), but presumably infected asymptomatically (based on rise in nucleocapsid titers) available from baseline until 6 months post first-dose of vaccine. Despite low peak antibody responses at week 6,

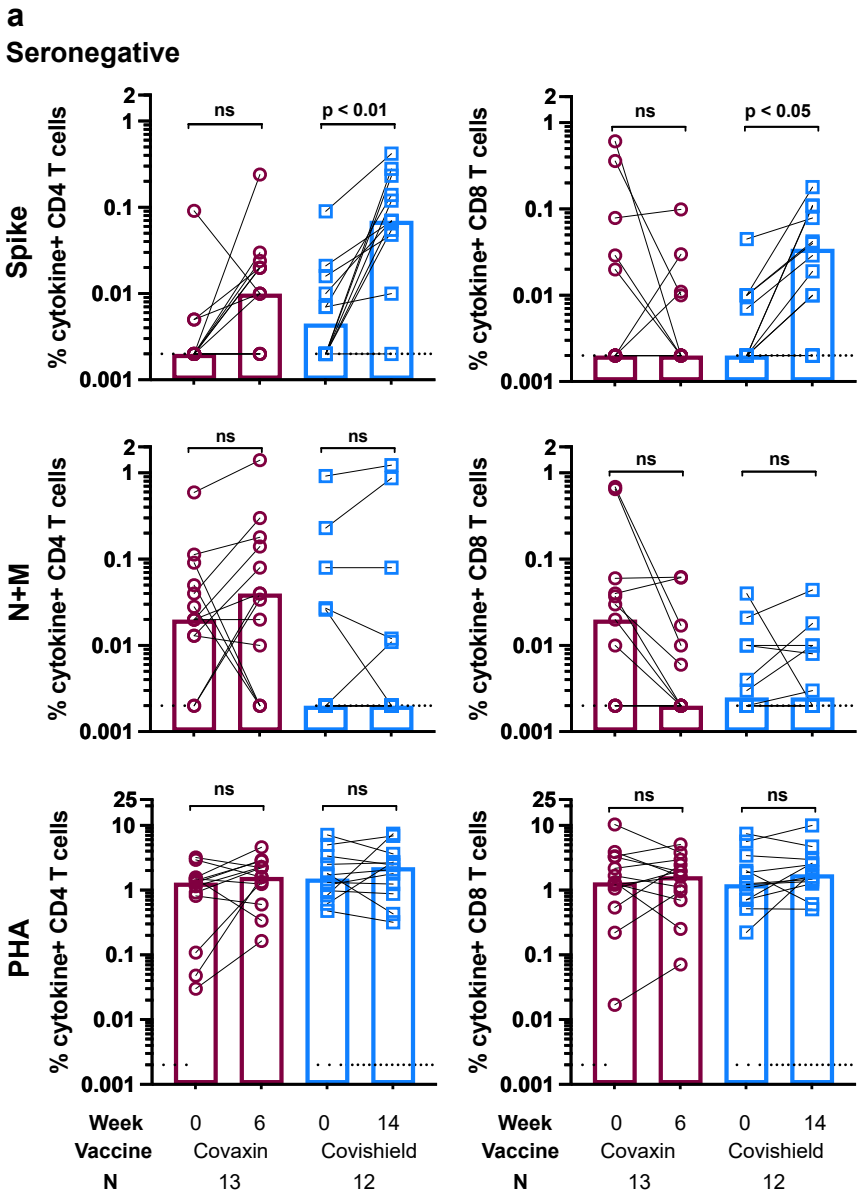

Fig. 3: **Vaccine-induced T cell responses**. Frequency of spike-specific CD4 or CD8 T cells expressing at least one cytokine amongst IFNγ, IL2 and TNF in response to stimulation with either spike peptide pool, mixture of nucleocapsid and matrix peptide pools or PHA, following vaccination in (a) Seronegative Covaxin® (red) or Covishield™ (blue) (b) Seropositive Covaxin® (red) or Covishield™ (blue). Frequencies are shown after background subtraction from the unstimulated control. Differences between pre- and post-vaccination responses were compared using Kruskal–Wallis test with Dunn's correction. p-values >0.05 are denoted as ns (not statistically significant).

the seronegative Covaxin® group showed stable antibody responses until week 12 and week 25, hovering around the seropositivity cut-off at 33.8 BAU/ml (Table 3 and Fig. 4a). Similar trends were observed when samples were tested on the MSD platform with a higher dynamic range. Notably, week 25 was sampled during the omicron wave in January 2022 and participants may have been variably sampled either prior to or after asymptomatic omicron infection. In support of this, the individual spike and nucleocapsid antibody trajectories between weeks 12 and 40 suggest that almost all participants in the seronegative Covaxin® group might have asymptomatic SARS-CoV-2 infections during this period. Though Covaxin® administration led to increase in both spike and nucleocapsid antibodies at weeks 4 and 6, the increase in titre at week 40 was much

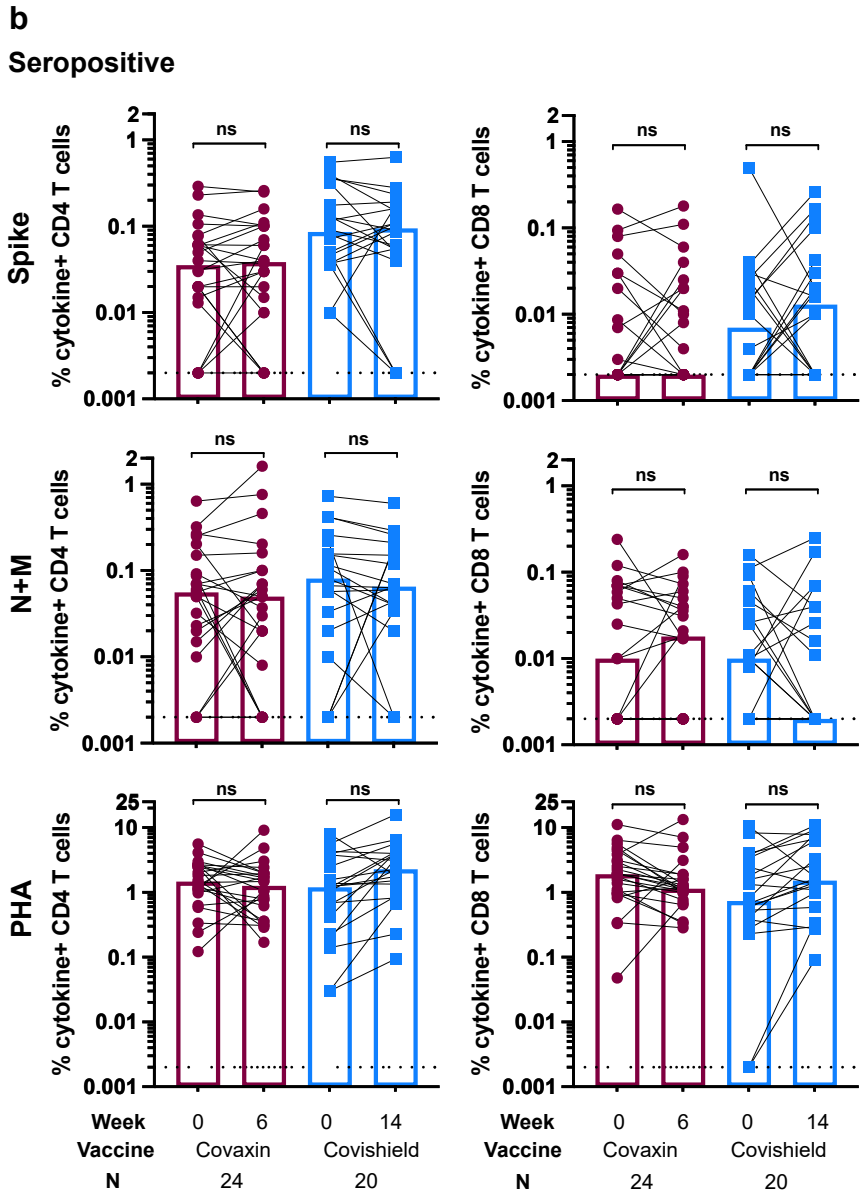

Fig. 3: (continued).

higher. This suggests that both spike and nucleocapsid antibodies were sub-optimally induced by the Covaxin® formulation. The seronegative Covishield™ group was predominantly sampled during December 2021, several days before the omicron wave was recorded in India, and therefore it is not clear if the 4.1-fold decline in antibody titres between the peak antibody response at week 14 and week 25 is truly reflective of antibody waning. Like the Covaxin® arm, titres increased 3.8-fold between week 25 and week 40 in the seronegative Covishield™ arm.

Sampling in the seropositive groups of the BBH cohort followed the same vaccine-wise trend as in the seronegative group (Fig. 4b). Between weeks 6, and 25, titres declined by 2.4-fold in the seropositive Covaxin® group (Table 3). In comparison to the 4.1-fold decline in the seronegative Covishield™ arm, the seropositive Covishield™ arm only showed a 2.1-fold decline in antibody levels between weeks 14 and 25. At week 40, most participants in the seropositive Covishield™ arm had increased nucleocapsid antibodies, with a >10-fold increase in GMT, suggesting a possibility of

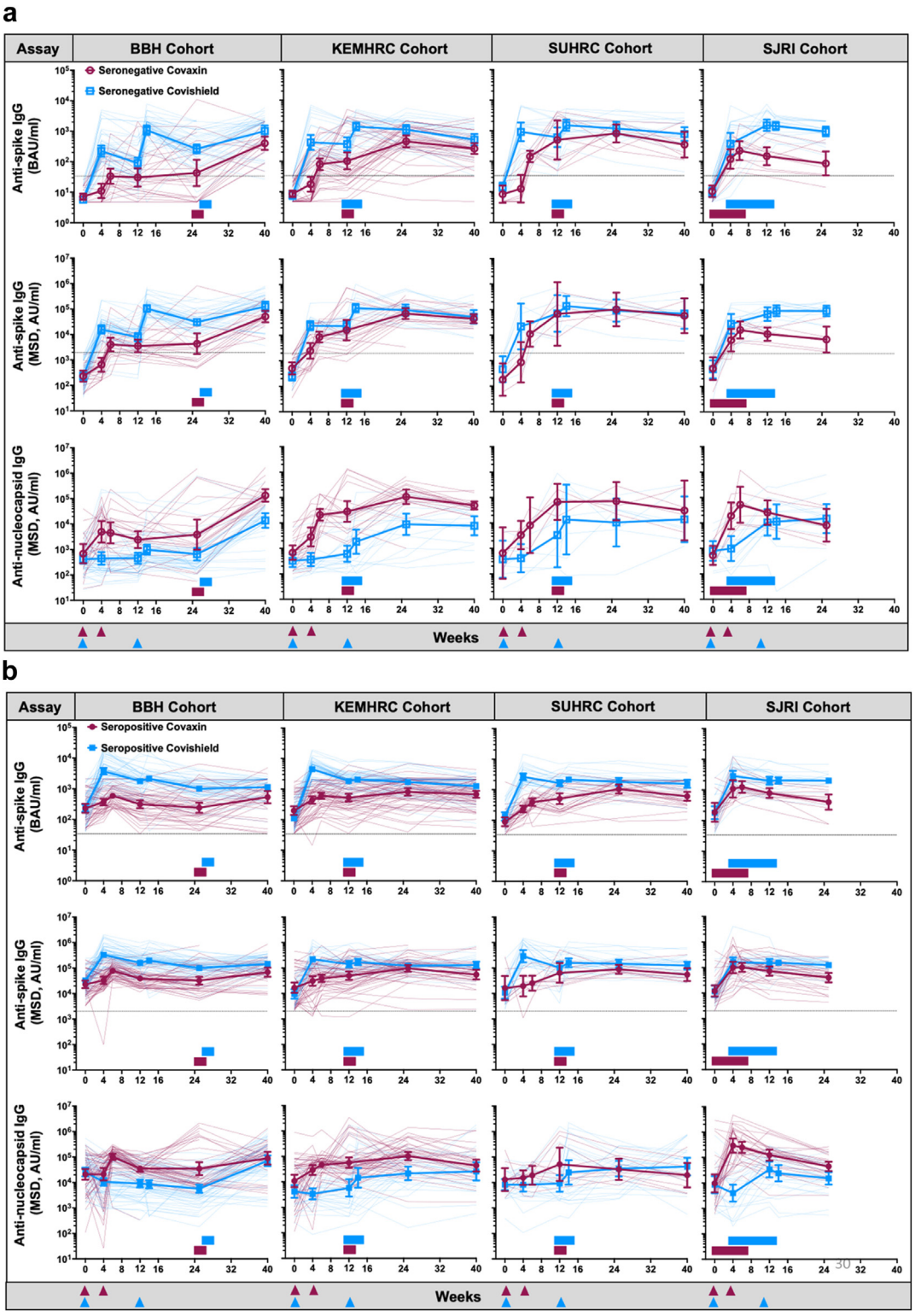

Fig. 4: **Durability and breadth of antibody responses following vaccination and exposure to the omicron wave**. Durability of antibody responses against spike protein (both Diasorin TrimericS and MSD platforms) and nucleocapsid protein (MSD) are shown for each cohort as geometric mean ± 95% CI for (a) seronegative and (b) seropositive individuals. Inhibition of ACE2 binding to the indicated spike proteins is shown as medians with interquartile range for (c) seronegative and (d) seropositive individuals. Trajectories for individual participants are shown as thin background lines. Horizontal bars (red–Covaxin®, blue–Covishield™) within each graph show timepoints in which sampling was performed during the Omicron wave.

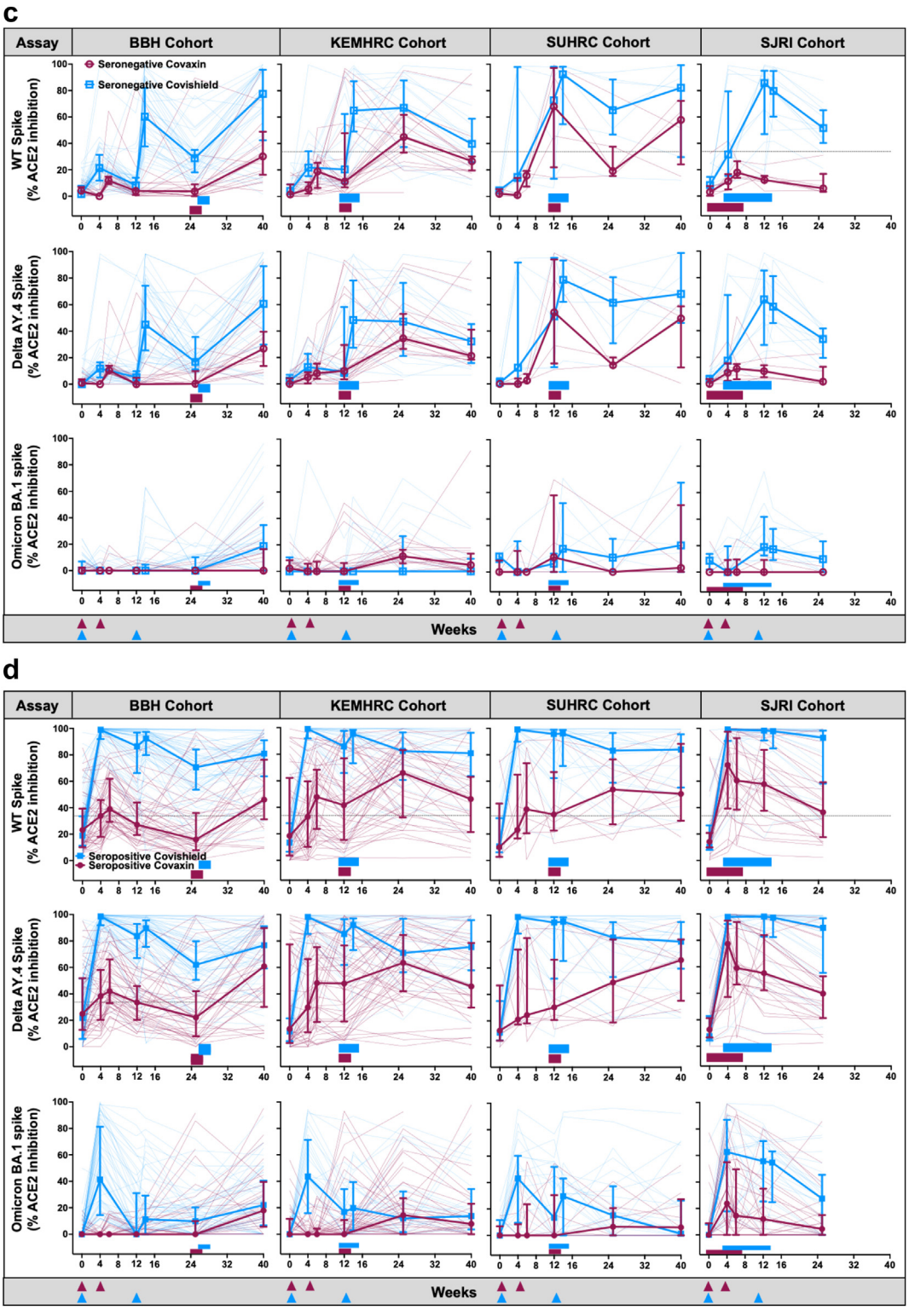

Fig. 4: (continued).

Weeks	BBH				KEMHRC				SUHRC				SJRI			
	Covaxin		Covishield		Covaxin		Covishield		Covaxin		Covishield		Covaxin		Covishield	
	N	GMT	N	GMT	N	GMT	N	GMT	N	GMT	N	GMT	N	GMT	N	GMT
Seronegative																
TrimericS: Anti-spike IgG, BAU/ml																
0	25	7.2	50	5.7	37	8.6	28	7.9	9	8.4	18	14.6	11	10.5	21	9.9
4	25	11.1	50	224.4	37	17.8	28	415.4	9	12.7	18	917.5	11	119.5	21	376.4
6	25	33.6			37	80.3			9	144.5			11	224.2		
12	24	30.6	50	90.5	37	102.8	28	366.5	9	499.9	18	611.2	11	148.3	21	1522.1
14			50	1085.6			28	1369.1			18	1517.5			21	1446.4
25	23	43.1	49	264.4	37	450.4	28	1081.7	9	820	17	1185.5	9	85.8	19	946.2
40	19	403.5	41	1019.4	36	259.6	28	511.5	8	350.5	18	779.8				
MSD: Anti-spike IgG, BAU/ml																
0	20	231.8	46	229.5	20	504.3	19	244.2	4	179.9	7	457.3	7	505.4	12	470.9
4	20	645.7	46	15719.1	20	2474.5	19	23987.6	4	859.8	7	21749.1	7	6537.0	12	28771.6
6	20	4008.4			20	8590.5			4	11,003			7	16571.9	12	69260.7
12	20	3539.6	46	7733.7	20	16089.4	19	23247.0	4	67486.9	7	70438.9			12	93220.5
14			46	103864.0			19	117621.5			7	136459.4	7	11335.9		
25	20	4327.1	43	30627.3	20	71654.4	19	98669.5	4	100948.6	7	91441.2	6	6962.5	12	92135.9
40	17	50642.8	37	125199.4	15	45162.1	15	53587.8	4	57184.7	7	69839.1				
MSD: Anti-nucleocapsid IgG, BAU/ml																
0	20	685.9	46	409.1	20	683.6	19	328.4	4	654.8	7	373.9	7	533.4	12	799.1
4	20	4962.1	46	445.4	20	2827.7	19	363.7	4	3359.6	7	412.5	7	19084.7	12	991.0
6	20	4498.2			20	20822.6			4	8126.7			7	52294.1	12	
12	20	2432.2	46	458.2	20	28188.7	19	616.7	4	67414.5	7	3327.9		25723.8	12	10571.3
14			46	980.9			19	1835.3			7	13597.8	7			11352.9
25	20	3853.5	43	654.2	20	106659.6	19	8861.8	4	71633.5	7	10466.8	6	8124.3	12	14898.9
40	17	133915.3	37	13869.8	15	48948.6	15	7749.9	4	31068.8	7	13949.2				
Seropositives																
TrimericS: Anti-spike IgG, BAU/ml																
0	43	230.7	56	233.4	55	197.3	56	110.9	28	89.1	30	133	13	185.6	26	179.8
4	43	368.6	56	3719.1	55	439.3	56	4479.8	28	232.5	30	2641.1	13	1081.8	26	2836.7
6	43	586.5			55	602.8			28	389.8			13	1240.0		
12	43	311.7	56	1777.6	55	527.1	56	1837.5	26	506.9	30	1634.7	13	789.9	26	1988.5
14			56	2128.3			56	2051.0			30	2136.2			26	2035.0
25	40	239.6	56	1000.6	55	806.6	55	1687.1	22	1052.3	26	1796.2	12	399.8	26	1997.0
40	31	531.1	52	1125	52	673.4	53	1246.4	25	606.8	25	1556.9				
MSD: Anti-spike IgG, BAU/ml																
0	48	22886.6	61	32425.5	47	16785.1	30	9617.3	9	16330.5	24	10,669	29	12073.5	24	11858.0
4	48	33108.8	61	329560.1	47	30914.7	30	218476.6	9	19505.9	24	290565.7	29	99866.4	24	165810.6
6	48	78109.3			47	39105.5			9	25394.2			29	101417.9		
12	47	38879.2	61	159959.9	47	49912.8	29	140845.1	9	63,985	24	102187.4	29	72678.7	24	146550.6
14			61	196292.6			30	170945.6			24	159328.1			24	153350.7
25	43	32265.5	61	99022.4	47	96214.8	29	121662.4	8	88284.3	23	147,542	26	40078.7	24	124253.2
40	29	68808.4	55	144008.2	30	55083.3	24	130229.7	9	55013.1	24	123932.2				
MSD: Anti-nucleocapsid IgG, BAU/ml																
0	48	20813.4	61	25779.4	47	10870.6	30	4186.4	9	12966.5	24	8235.3	29	9686.8	24	8556.6
4	48	21120.7	61	10550.5	47	29146.9	30	3377.0	9	15377.3	24	8152.2	29	294581.9	24	3990.0
6	48	102266.4			47	46651.2			9	19122.9			29	251790.9		
12	47	35307.8	61	9176.0	47	56722.4	29	5786.9	9	51697.3	24	9124.7	29	124433.6	24	33996.8
14			61	8495.0			30	14478.5			24	24892.6			24	24141.3
25	43	34701.8	61	5681.1	47	101982.0	29	21519.7	8	32809.3	23	34,990	26	44857.3	24	15181.7
40	29	90117.5	55	71163.5	30	43713.9	24	25698.9	9	19404.7	24	41913.8				

Data are shown as N and geometric mean titers. BBH: Bangalore Baptist Hospital, KEM: King Edward Memorial Hospital Research Center, SUHRC: Symbiosis University Hospital and Research Center, SJRI: St. John's Research Institute. Related to Fig. 4a and b.

Table 3: **Antibody titers in all cohorts across all study timepoints.**

asymptomatic omicron infection. However, a corresponding increase in the spike antibody titres was not observed. It is likely that spike antibodies may have waned faster than nucleocapsid antibodies between weeks 25 and 40 or that omicron-specific spike antibodies elicited during the wave were not detected using the spike protein against the WT strain.

In the KEMHRC cohort, the omicron wave hit between weeks 11 and 15. Parallelly, the anti-nucleocapsid titres increased between weeks 12, 14 and 25. At the post-omicron sampling point at week 25, spike antibody levels were similar in Covaxin® and Covishield™ arms in both the serogroups. Between weeks 25 and week 40, the decline in spike antibody titres were low and additional sampling will be needed to address comparison between vaccines.

In the SUHRC cohort, the omicron wave occurred between weeks 11 and 15. As KEMHRC cohort was exposed to omicron wave around similar time frames, the preliminary results suggest the trends in anti-spike responses to be similar for SUHRC and KEMHRC cohorts. In the SJRI cohort, the omicron wave hit during the primary vaccination period and manifested as higher post-vaccination anti-spike as well as anti-nucleocapsid antibody titres than other cohorts in the Covaxin® arm. In both seronegative individuals and seropositive individuals, antibody decline by week 25 appeared to be faster in the Covaxin® arm than in the Covishield™ arm. However, a direct comparison of the vaccine-specific antibody decay rates could not be made due to the differences in the time between vaccination, sampling, and infection.

Breadth of antibody responses against SARS-CoV-2 variants of concern (VoCs)

We next used the ACE2 inhibition assay on the MSD platform to measure surrogate neutralisation against the major SARS-CoV-2 lineages and sub-lineages at all timepoints.

In seronegative individuals, vaccination with Covishield™ consistently elicited higher ACE2 inhibition activity than Covaxin® against wild-type (WT) and delta variant spike proteins in both the BBH and KEMHRC cohorts (Fig. 4c; Table 4). Neither vaccine elicited omicron-specific antibodies. The omicron wave was associated with increased activity against WT, delta, and BA.1 in the BBH cohort at weeks 25–40, though vaccine-specific differences cannot be assessed due to differences in the timing of exposure and sampling. The omicron wave elicited higher responses against WT and delta than against BA.1. Similar trends were observed in the KEMHRC cohort that was exposed to the omicron variant at a much earlier time post-vaccination than the BBH cohort. Interestingly, in the SJRI cohort, where participants were co-exposed to WT strain by vaccination and the omicron strain through infection, stronger responses were elicited against WT than against omicron variant. Unlike the sparse sampling in the BBH and KEMHRC cohorts, the SJRI cohort was sampled very closely during the omicron wave, but still did not detect strong omicron responses. This suggests that the omicron spike protein in asymptomatic infection may not be as immunogenic as WT, though this needs to be confirmed by measurement of mucosal immune responses.

In seropositive individuals, Covishield™ vaccination elicited strong and near-saturation levels of antibodies against both WT and delta variant spike proteins in all three cohorts (Fig. 4d; Table 4). Interestingly, a single dose of Covishield™ elicited relatively strong omicron-specific responses in seropositive individuals. However, a second dose of Covishield™ did not increase responses and the median activity remained lower than after the first dose. Vaccination with Covaxin® increased activity against WT and delta variant but not against omicron variant. At week 4, omicron-specific responses were higher in the infection plus vaccination SJRI cohort than in the breakthrough-infection cohorts of BBH and KEMHRC. Correspondingly, omicron-specific responses waned slower in the SJRI cohort than in the BBH and KEMHRC cohorts.

Overall, the breadth and potency of responses against SARS-CoV-2 VoCs was higher with Covishield™ than with Covaxin®, and in seropositive individuals than in seronegative individuals.

Discussion

In a longitudinal study that includes pre-vaccination baselines, we compared the immune responses elicited by the two main SARS-CoV-2 vaccines utilised in India. The comparison was designed to explore vaccination-induced immune responses in both seronegative and seropositive participants. In general, the data show that Covishield™ elicited immune responses of higher magnitude than Covaxin®. This is supported by four lines of evidence as described below. First, in seronegative participants, the adenovirus vectored vaccine, Covishield™, elicited near-complete seroconversion rates between 98.3 and 100%. Seroconversion for Covaxin® was more variable, reaching >90% only in cohorts that were vaccinated and therefore had samples collected closer to the omicron wave (the SUHRC and SJRI cohorts). Seroconversion for Covaxin® in the pre-omicron cohorts (52.0% and 75.7% for BBH and KEMHRC cohorts, respectively) was much lower than rates reported from the phase 2 trial.[13] This difference may be due to the method of testing for antibodies. Our study measured seroconversion using a binding antibody assay based on stabilized spike trimer protein (DiaSorin TrimericS). This assay is reported to be selective for neutralizing rather than non-neutralizing antibodies whereas the phase 2 trial utilized in-house assays which have not been validated. Similar to

Weeks	BBH				KEMHRC				SUHRC				SJRI			
	Covaxin		Covishield		Covaxin		Covishield		Covaxin		Covishield		Covaxin		Covishield	
	N	Median	N	Median	N	Median	N	Median	N	Median	N	Median	N	Median	N	Median
Seronegative																
WT Spike, % inhibition																
0	20	4.2	46	1.6	20	1.5	19	4.1	4	2	7	4.6	7	3.1	12	8.5
4	20	0.0	46	21.4	20	5.6	19	21.8	4	1	7	14.7	7	11.2	12	31.6
6	20	12.0			20	18.9			4	15.7			7	17.9		
12	20	4.0	46	8.4	20	11.2	19	20.5	4	67.9	7	72.7	7	12.2	12	85.7
14			46	60.2			19	65.0			7	92.4			12	79.7
25	20	3.7	43	28.8	20	44.9	19	67.0	3	19.3	7	65.3	6	5.9	12	51.6
40	17	30.2	37	77.5	15	26.7	15	39.7	4	57.9	7	82.2				
Delta AY.4 Spike, % inhibition																
0	20	1.0	46	0.0	20	0.0	19	2.5	4	0	7	0.9	7	0.0	12	3.4
4	20	0.0	46	11.9	20	5.1	19	12.8	4	0	7	12.3	7	8.4	12	17.5
6	20	10.4			20	8.1			4	2.6			7	11.4		
12	20	0.0	46	5.3	20	9.9	19	9.3	4	54.1	7	51.1	7	9.6	12	63.6
14			46	45.0			19	48.3			7	78.7			12	58.2
25	20	0.4	43	16.8	20	34.4	19	47.2	3	14.1	7	61.4	6	1.7	12	33.8
40	17	26.9	37	60.6	15	21.3	15	32.1	4	49.5	7	68				
Omicron BA.1 Spike, % inhibition																
0	20	0.0	46	0.0	20	2.3	19	0.0	4	0	7	11.7	7	0.0	12	8.6
4	20	0.0	46	0.0	20	0.0	19	0.0	4	0	7	0	7	0.0	12	0.0
6	20	0.0			20	0.0			4	0			7	0.0		
12	20	0.0	46	0.0	20	0.0	19	0.0	4	11.1	7	6.3	7	0.0	12	19.0
14			46	0.0			19	0.0			7	17.6			12	17.3
25	20	0.0	43	0.0	20	11.5	19	0.0	3	0	7	10.8	6	0.0	12	9.7
40	17	0.0	37	18.5	15	4.8	15	0.0	4	3.1	7	20.1				
Seropositives																
WT Spike, % inhibition																
0	48	23.2	61	19.0	47	18.5	29	13.4	9	10	24	10.7	29	14.3	24	10.4
4	48	33.8	61	99.0	47	32.9	29	99.1	9	23.2	24	99.1	29	72.3	24	99.1
6	48	39.0			47	47.8			9	38.7			29	60.5		
12	47	27.3	61	86.4	47	41.6	29	85.9	9	34.8	24	95.7	29	57.8	24	98.2
14			61	92.4			29	95.4			24	96.1			24	97.9
25	43	16.0	61	70.6	47	66.0	29	82.5	8	53.7	24	83.1	26	36.5	24	92.9
40	29	46.1	55	80.9	30	46.2	24	80.8	9	50.4	24	84				
Delta AY.4 Spike, % inhibition																
0	48	24.9	61	21.7	47	13.6	29	11.6	9	12.7	24	11.1	29	12.6	24	7.5
4	48	38.3	61	98.6	47	29.8	29	98.2	9	21.1	24	98.6	29	77.4	24	97.8
6	48	42.0			47	48.2			9	24.4			29	59.1		
12	47	33.5	61	83.6	47	47.8	29	85.3	9	30.3	24	94.4	29	55.2	24	98.0
14			61	89.6			29	92.0			24	95.1			24	97.3
25	43	22.1	61	62.0	47	63.5	29	70.9	8	49.1	24	83.1	26	39.8	24	89.5
40	29	60.8	55	76.8	30	45.6	24	75.4	9	66	24	80				
Omicron BA.1 Spike, % inhibition																
0	48	0.0	61	0.0	47	0.0	29	0.0	9	0	24	0	29	0.0	24	0.0
4	48	0.0	61	41.4	47	0.0	29	43.7	9	0	24	43.1	29	23.7	24	62.7
6	48	0.0			47	0.0			9	0			29	14.6		
12	47	0.0	61	0.0	47	0.0	29	17.0	9	0	24	13.4	29	11.9	24	55.7
14			61	11.4			29	19.8			24	29.7			24	54.7
25	43	0.0	61	9.8	47	14.5	29	11.9	8	6.6	24	15.2	26	4.5	24	27.4
40	29	17.9	55	22.1	30	7.8	24	13.8	9	6.1	24	1.4				

Data are shown as N and median. BBH: Bangalore Baptist Hospital, KEM: King Edward Memorial Hospital Research Center, SUHRC: Symbiosis University Hospital and Research Center, SJRI: St. John's Research Institute. Related to Fig. 4c and d.

Table 4: **Inhibition of ACE2 binding to SARS-CoV-2 WT, Delta AY.4 and Omicron BA.1 spike in all cohorts across all study timepoints.**

seronegative individuals, seroconversion in seropositive individuals was higher in Covishield™ than in Covaxin® recipients. A significant proportion of seropositive Covaxin® recipients (37.4%) did not respond to vaccination.

Second, in addition to greater rates of seroconversion, Covishield™ also elicited higher antibody titres (GMT) than Covaxin® in both seronegative individuals and seropositive individuals. These trends were observed in three cohorts (BBH, KEMHRC and SUHRC) that had completed vaccination prior to the omicron wave. The fourth cohort (SJRI), in which the vaccination overlapped with the omicron wave, showed comparable post-vaccination antibody titres in the Covishield™ and Covaxin® recipients.[14] However, antibody titres in this fourth cohort with delayed recruitment confirmed that the waning of the immune response was slower in Covishield™ recipients.[14] Importantly, we also confirmed these findings using an independent assay platform, the MSD platform which has a higher dynamic range.

Third, in parallel to the antibody responses in the earliest cohort (BBH), Covishield™ elicited a higher frequency of both CD4 and CD8 T cells while Covaxin® elicited mainly CD4 T cell responses. The frequencies and quality of cytokine-expressing T cells that we report in the seronegative Covishield™ arm are broadly consistent with prior studies, though the dosing interval in those studies was only 4 weeks.[15,16] The poor CD8 responses from Covaxin® is not unexpected given that TLR7/8 agonists need to be physically linked to the antigen to induce CD8 T cell responses in mice,[17] which is not the case with Covaxin®. In humans, however, in vivo antigen synthesis using either live viruses, non-replicating virus vectors or mRNA/DNA vaccines and classical MHC-I-presentation of antigen remain the only ways to elicit robust anti-viral CD8 T cells. Nevertheless, vaccine-elicited CD8 T cell responses in the blood have not yet been demonstrated as a correlates of protection (CoP) against severe COVID-19 in humans, and therefore the significance of spike-specific CD8 T cell responses is not clear. In seropositive participants, the vectored vaccine enhanced antibody responses in more participants and these were greater in magnitude than the inactivated vaccine, without a strong expansion of pre-existing spike-specific CD4 T cells in the blood. In both vaccine groups, lack of immunogenicity in a subset of seropositive individuals was associated with higher pre-vaccination antibody titres. Of note, the T-cell responses to the two vaccines in the SJRI cohort which comprised mostly of COVID-19 exposed individuals, differed in magnitude when they were segregated based on their baseline nucleocapsid titres.[14] This is consistent with studies on mRNA vaccines in seropositive subjects where a single dose induced a rapid increase in antibody titers.[18,19] The negative role of high levels of circulating antibodies on vaccine immunogenicity and/or efficacy has also been observed with other vaccines.[20–22] The high levels of anti-SARS-CoV-2-spike seropositivity in the population suggests that the development of spike-based pan-coronavirus vaccines and their deployment through public health campaigns must consider the immune history of the population.

Fourth, in a subset of participants, we tested neutralising responses using an authentic WT virus assay, and surrogate neutralising responses using an ACE-2 inhibition assay against several SARS-CoV-2 variants. In every SARS-CoV-2 variant tested, Covishield™ elicited higher responses than Covaxin®.

The superiority of vectored vaccines over inactivated vaccines for antibody responses against SARS-CoV-2 has been demonstrated by other studies.[7–11] Further, inactivated viral vaccines have historically been of lower immunogenicity, requiring 4 doses in the primary series for the inactivated polio vaccine and the rabies vaccine. The inactivated hepatitis A vaccine is given as two doses, but the doses are spaced six months apart. In contrast, the primary immunisation series of all inactivated COVID-19 vaccines have been only two doses spaced 2–4 weeks apart. However, as a sole exception, the inactivated vaccine VLA-2001 (Valneva's inactivated COVID-19 vaccine manufactured using the Vero cell platform) demonstrated non-inferiority for seroconversion rate and superiority for neutralizing titres against ChAdOx1-S[23] (developed by Oxford-AstraZeneca and manufactured by AstraZeneca; same as Covishield™ tested in this study).

Notwithstanding the lower magnitude of spike antibodies reported in this study, Covaxin® has demonstrated comparable or only moderately lower efficacy against SARS-CoV-2 variant waves from ancestral to delta variant,[24,25] suggesting that non-neutralising spike-binding antibodies and antibodies against non-spike virion proteins could be contributors to the correlates of protection (CoP). All available vectored and mRNA-based COVID-19 vaccines are based on the spike protein and therefore published CoP studies from the high-income countries have only been able to address the role of antibodies against the spike protein.[26–29] Emerging pre-clinical data suggest a potential role for vaccine-elicited nucleocapsid responses in controlling virus replication in the lung.[30] The nucleocapsid protein could be an attractive target owing to limited sequence evolution compared to spike protein. But the shorter durability of circulating antibodies against nucleocapsid protein compared to spike protein following infection, necessitates the study of the comparative durability of vaccine-elicited nucleocapsid versus spike antibodies. Here, we show that Covaxin® elicits nucleocapsid antibodies but those antibody levels seem to be sub-optimal; considering that antibody levels increase further upon breakthrough omicron infection. It is likely that nucleocapsid antibodies and potential Fc-dependent antibody effector functions elicited by Covaxin® lower the

threshold of anti-spike neutralising antibodies required for protection. In a study which considered neutralising titres to predict protective efficacy, early phase clinical trial data from Covaxin® was included. Modelling in this study suggests that Covaxin® might be as good, if not better, than Covishield™ in efficacy.[31] However, our data seems to suggest otherwise. The lack of planned (or publicly accessible) CoP analyses for Covaxin® are a missed opportunity for a more coordinated global vaccine development response.

As has been shown by others in seronegative individuals, two doses of vaccine did not elicit omicron-specific responses.[32–35] Interestingly, in seropositive individuals, only a single dose of Covishield™ elicited measurable omicron-specific responses assayed using inhibition of ACE2 binding. Most other studies that demonstrated the need for three or four exposures to spike before elicitation of omicron-specific neutralising responses were unable to study the effect of second exposure due to cohort sampling limitations. It remains possible that prior exposure to delta rather than ancestral strain may have led to better omicron responses in the seropositive cohort in this study. Curiously, a second dose of Covishield™ did not elicit the same level of anti-omicron activity as the first dose and needs further investigation.

The results and of our study are strengthened by the size of the cohort, sampling at multiple sites, longitudinal follow-up for clinical signs of COVID infection, measurement of humoral responses to the ancestral and other SARS-CoV-2 variants and T cell responses induced by the vaccines with interpretation of results within the larger context of infection waves in the country. The cohort that we have studied here is unique in being first exposed to the delta variant through infection followed by exposure to the ancestral strain through vaccination. On the other hand, previous studies were predominantly based on ancestral strain-based vaccination or infection followed by breakthrough infection with variants. The exposure to delta variant prior to the ancestral strain may have pre-disposed the immune system to have broader responses and can be addressed further by measuring variant-specific T cell responses.

Our study has few limitations. In this study, we have not specifically measured the levels of non-neutralising antibodies or non-neutralising functions that may be important for vaccine efficacy, and the durability of the vaccine-elicited immune responses could not be assessed due to the omicron wave. Asymptomatic omicron infection referred to in this study is solely based on antibody titres measured several weeks apart and does not have a concomitant RT-PCR test. The sparce sampling during the omicron wave in most of the participants also limits direct quantitative comparisons of the vaccines during the omicron wave. While it appears that Covaxin® vaccination was associated with poor omicron responses during breakthrough asymptomatic infection and was likely due to prior imprinting from non-neutralising antibodies or narrow WT-specific neutralising antibodies, further studies will be needed to assess this phenomenon. Also, our study population is limited to pre-vaccination serostatus and not to confirmed prior infection or exposure. It therefore remains possible that while most seronegative participants may have remained unexposed between the beginning of the pandemic and the time of study recruitment, a subset of seronegative individuals may have been exposed previously but seroreverted at the time of recruitment due to decline in circulating antibody titres. In the absence of a CoP for Covaxin®, the immunogenicity results cannot be extrapolated to infer vaccine efficacy.

In summary, we show that a vectored vaccine elicits stronger and broader anti-spike responses than an inactivated vaccine. We also show that omicron-specific antibody responses from asymptomatic infection wane faster than WT-specific and delta-specific antibody responses. Non-responsiveness to vaccination in seropositive subjects is associated with higher baseline antibody titres. The role of the duration between the delta wave and vaccination in driving both antibody and cellular immune responses is under investigation.

It remains to be seen how the withdrawal of the zero-COVID policy will affect the largely uninfected Chinese population which was either vaccinated with the original ancestral strain based inactivated virus vaccine (Sinovac or Sinopharm) a year or more ago or remained unvaccinated, given that the currently circulating omicron variants have diverged significantly from the ancestral viruses used for making these vaccines. Public health programmes which are making plans now for expanding booster dose coverage will benefit from the use of heterologous boosters rather than repeating the homologous primary dose. This has been demonstrated by studies that examined homologous and heterologous boosting with Covaxin® and Covishield™,[36] Coronavac followed by BBIBP-CorV, AZD1222 or BNT162b2[37] and AZD1222 followed by AZD1222, NVX-CoV2373, VLA2001, BNT162b2, mRNA-1273, Ad26.CoV2.S or CVnCoV.[5] These findings have policy implications for booster vaccine. Furthermore, the findings suggest that public health vaccination campaigns should be followed-up with extensive immunological analyses of the general population using validated assays. These findings also indicate that the development and deployment of booster doses and pan-coronavirus vaccines for populations with high levels of exposure and vaccine coverage should consider the prevailing magnitude and quality of immune responses in the population. Further, CoP analyses must be mandatory and planned for vaccines administered through the national health programme.

Contributors

Conceptualisation and study design: MA, SB, GD, BR, DA, CE, JJ, AK, MD, AB, PR, LSS, AV, VB, GK, SM; **Data curation:** MA, SB; **Formal analysis:** MA; **Funding acquisition:** LSS, GK, SM; **Investigation:** SB, PN, VS, AP, SI; **Project administration:** GD, AP, PS, RG, BR, DA, PS, MA, SS, UD, CB, MJ, SC, AG, CJ, AJ, NR, GD, VR, CE, AK, MD, AB, PR, SM; **Resources:** RFJ, PN, VS, AP, VM, JB, KP, AT, GM, RG, BR, SR, DA, SS, AS, PP, RS, SG, AU, PA, AN, ST, MB, RY, MV, SS, UD, CB, MJ, LRI, AG, CJ, AK, VS, AJ, NR, SR, VA, GD, VR, CE, AK, MD, AB; **Supervision:** MA, CJ, CE, AK, AC, AR, MD, AB, PR, LSS, AV, VB, GK, SM; **Visualisation:** MA, SM; **Writing-Original draft:** MA, SM; **Writing-Review and Editing:** All authors.

Data sharing statement

All data in this manuscript is derived from clinical samples, and is maintained securely in de-identified form as authorized by institutional human ethical committee approvals obtained for this observational study. These data will be made available upon request to the corresponding authors with the submission of appropriate statutory authorization for their use.

Declaration of interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lansea.2024.100361.

References

1 Mallapaty S, Callaway E, Kozlov M, Ledford H, Pickrell J, van Noorden R. How COVID vaccines shaped 2021 in eight powerful charts. *Nature*. 2021;600:580–583.
2 Zhang Z, Mateus J, Coelho CH, et al. Humoral and cellular immune memory to four COVID-19 vaccines. *Cell*. 2022;185:2434–2451.e17.
3 Sablerolles RSG, Goorhuis A, GeurtsvanKessel CH, et al. Heterologous Ad26.COV2.S prime and mRNA-based boost COVID-19 vaccination regimens: the SWITCH trial protocol. *Front Immunol*. 2021;12:3922.
4 Agrati C, Capone S, Castilletti C, et al. Strong immunogenicity of heterologous prime-boost immunizations with the experimental vaccine GRAd-COV2 and BNT162b2 or ChAdOx1-nCOV19. *NPJ Vaccines*. 2021;6:1–4.
5 Munro APS, Janani L, Cornelius V, et al. Articles Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial. *Lancet*. 2021;398. https://doi.org/10.1016/S0140-6736(21)02717-3.
6 India. COVID-19 vaccines administered by vaccine type 2022 | Statista. https://www.statista.com/statistics/1248301/india-covid-19-vaccines-administered-by-vaccine-type/. Accessed December 12, 2022.
7 Singh AK, Phatak SR, Singh R, et al. Antibody response after first and second-dose of ChAdOx1-nCOV (CovishieldTM®) and BBV-152 (CovaxinTM®) among health care workers in India: the final results of cross-sectional coronavirus vaccine-induced antibody titre (COVAT) study. *Vaccine*. 2021;39:6492–6509.
8 Parai D, Choudhary HR, Dash GC, et al. Single-dose of BBV-152 and AZD1222 increases antibodies against spike glycoprotein among healthcare workers recovered from SARS-CoV-2 infection. *Travel Med Infect Dis*. 2021;44. https://doi.org/10.1016/J.TMAID.2021.102170.
9 Choudhary HR, Parai D, Chandra Dash G, et al. Persistence of antibodies against spike glycoprotein of SARS-CoV-2 in healthcare workers post double dose of BBV-152 and AZD1222 vaccines. *Front Med*. 2021;8. https://doi.org/10.3389/FMED.2021.778129.
10 Zare H, Rezapour H, Fereidouni A, et al. Analysis and comparison of anti-RBD neutralizing antibodies from AZD-1222, Sputnik V, Sinopharm and Covaxin vaccines and its relationship with gender among health care workers. *Immun Ageing*. 2022;19. https://doi.org/10.1186/S12979-022-00303-X.
11 Arankalle V, Kulkarni-Munje A, Kulkarni R, et al. Immunogenicity of two COVID-19 vaccines used in India: an observational cohort study in health care workers from a tertiary care hospital. *Front Immunol*. 2022;13. https://doi.org/10.3389/FIMMU.2022.928501.
12 Mahmoud SA, Ganesan S, Naik S, et al. Serological assays for assessing postvaccination SARS-CoV-2 antibody response. *Microbiol Spectr*. 2021;9. https://doi.org/10.1128/spectrum.00733-21.
13 Ella R, Reddy S, Jogdand H, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: interim results from a double-blind, randomised, multicentre, phase 2 trial, and 3-month follow-up of a double-blind, randomised phase 1 trial. *Lancet Infect Dis*. 2021;21:950–961.
14 Rakshit S, Babji S, Parthiban C, et al. Polyfunctional CD4 T-cells correlating with neutralising antibody is a hallmark of COVISHIELDTM and COVAXIN® induced immunity in COVID-19 exposed Indians. *NPJ Vaccines*. 2023;8:134.
15 Swanson PA, Padilla M, Hoyland W, et al. AZD1222/ChAdOx1 nCoV-19 vaccination induces a polyfunctional spike protein-specific TH1 response with a diverse TCR repertoire. *Sci Transl Med*. 2021;13. https://doi.org/10.1126/SCITRANSLMED.ABJ7211.
16 Rakshit S, Adiga V, Ahmed A, et al. Evidence for the heterologous benefits of prior BCG vaccination on COVISHIELDTM vaccine-induced immune responses in SARS-CoV-2 seronegative young Indian adults. *Front Immunol*. 2022;13. https://doi.org/10.3389/FIMMU.2022.985938.
17 Kastenmüller K, Wille-Reece U, Lindsay RWB, et al. Protective T cell immunity in mice following protein-TLR7/8 agonist-conjugate immunization requires aggregation, type I IFN, and multiple DC subsets. *J Clin Invest*. 2011;121:1782–1796.
18 Krammer F, Srivastava K, Alshammary H, et al. Antibody responses in seropositive persons after a single dose of SARS-CoV-2 mRNA vaccine. *N Engl J Med*. 2021;384:1372–1374.
19 Moncunill G, Aguilar R, Ribes M, et al. Determinants of early antibody responses to COVID-19 mRNA vaccines in a cohort of exposed and naïve healthcare workers. *eBioMedicine*. 2022;75. https://doi.org/10.1016/J.EBIOM.2021.103805.
20 Ubillos I, Ayestaran A, Nhabomba AJ, et al. Baseline exposure, antibody subclass, and hepatitis B response differentially affect malaria protective immunity following RTS,S/AS01E vaccination in African children. *BMC Med*. 2018;16. https://doi.org/10.1186/S12916-018-1186-4.
21 McNamara HA, Idris AH, Sutton HJ, et al. Antibody feedback limits the expansion of B cell responses to malaria vaccination but drives diversification of the humoral response. *Cell Host Microbe*. 2020;28:572–585.e7.
22 Wild K, Smits M, Killmer S, et al. Pre-existing immunity and vaccine history determine hemagglutinin-specific CD4 T cell and IgG response following seasonal influenza vaccination. *Nat Commun*. 2021;12. https://doi.org/10.1038/S41467-021-27064-3.
23 Lazarus R, Querton B, Corbic Ramljak I, et al. Immunogenicity and safety of an inactivated whole-virus COVID-19 vaccine (VLA2001) compared with the adenoviral vector vaccine ChAdOx1-S in adults in the UK (COV-COMPARE): interim analysis of a randomised,

controlled, phase 3, immunobridging trial. *Lancet Infect Dis*. 2022;22. https://doi.org/10.1016/S1473-3099(22)00502-3.
24 Ella R, Reddy S, Blackwelder W, et al. Efficacy, safety, and lot-to-lot immunogenicity of an inactivated SARS-CoV-2 vaccine (BBV152): interim results of a randomised, double-blind, controlled, phase 3 trial. *Lancet*. 2021;398:2173–2184.
25 Ahmed TI, Rishi S, Irshad S, Aggarwal J, Happa K, Mansoor S. Inactivated vaccine Covaxin/BBV152: a systematic review. *Front Immunol*. 2022;13. https://doi.org/10.3389/FIMMU.2022.863162.
26 Gilbert PB, Montefiori DC, McDermott AB, et al. Immune correlates analysis of the mRNA-1273 COVID-19 vaccine efficacy clinical trial. *Science*. 2022;375:43–50.
27 Fong Y, McDermott AB, Benkeser D, et al. Immune correlates analysis of the ENSEMBLE single Ad26.COV2.S dose vaccine efficacy clinical trial. *Nat Microbiol*. 2022;7. https://doi.org/10.1038/S41564-022-01262-1.
28 Feng S, Phillips DJ, White T, et al. Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection. *Nat Med*. 2021;27:2032–2040.
29 Fong Y, Huang Y, Benkeser D, et al. Immune correlates analysis of the PREVENT-19 COVID-19 vaccine efficacy clinical trial. *medRxiv*. 2022. https://doi.org/10.1101/2022.06.22.22276362.
30 Hajnik RL, Plante JA, Liang Y, et al. Dual spike and nucleocapsid mRNA vaccination confer protection against SARS-CoV-2 Omicron and Delta variants in preclinical models. *Sci Transl Med*. 2022;14. https://doi.org/10.1126/SCITRANSLMED.ABQ1945.
31 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;27:1205–1211.
32 Carreño JM, Alshammary H, Tcheou J, et al. Activity of convalescent and vaccine serum against SARS-CoV-2 Omicron. *Nature*. 2022;602:682–688.
33 Cele S, Jackson L, Khoury DS, et al. Omicron extensively but incompletely escapes Pfizer BNT162b2 neutralization. *Nature*. 2022;602:654–656.
34 Garcia-Beltran WF, Denis KJ, Hoelzemer A, et al. mRNA-based COVID-19 vaccine boosters induce neutralizing immunity against SARS-CoV-2 Omicron variant. *Cell*. 2022;185:457–466.e4.
35 Muecksch F, Wang Z, Cho A, et al. Increased memory B cell potency and breadth after a SARS-CoV-2 mRNA boost. *Nature*. 2022;607:128–134.
36 Rose W, Raju R, Babji S, et al. Immunogenicity and safety of homologous and heterologous booster vaccination of ChAdOx1 nCoV-19 (COVISHIELD TM) and BBV152 (COVAXIN®): a non-inferiority phase 4, participant and observer-blinded, randomised study. *Lancet Reg Health Southeast Asia*. 2023;12:100141.
37 Kanokudom S, Assawakosri S, Suntronwong N, et al. Safety and immunogenicity of the third booster dose with inactivated, viral vector, and mRNA COVID-19 vaccines in fully immunized healthy adults with inactivated vaccine. *Vaccines (Basel)*. 2022;10. https://doi.org/10.3390/VACCINES10010086.