Omicron BA.1-specific T-cell responses in adults vaccinated with CoronaVac or BNT162b2 in Hong Kong: an observational cohort study

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Summary

Background The primary aim of using vaccines in public health responses to SARS-CoV-2 variants of concern is to reduce incidence of severe disease, for which T-cell responses are essential. There is a paucity of data on vaccine-induced T-cell immunity to omicron (B.1.1.529). We aimed to compare SARS-CoV-2 omicron BA.1-specific T-cell responses in adults vaccinated with CoronaVac or BNT162b2.

Methods For this observational cohort, we recruited adults (aged ≥18 years) from three vaccination centres in Hong Kong. We included participants from four cohorts (cohort 1: participants who received two doses of either BNT162b2 or CoronaVac, cohort 2: participants who received two doses and a booster, cohort 3: participants who received two doses and a booster and had a breakthrough omicron infection, and cohort 4: participants who had a previous non-omicron infection and subsequently received one dose of vaccine). People with confirmed history of COVID-19 at recruitment were excluded from cohort 1 and cohort 2. We collected blood samples before vaccination (for cohort 1 and 2), 1-month following vaccination (for all cohorts), and during convalescence for cohort 3 and 4) and determined the proportion of IFNγ$^+$CD4$^+$ and IFNγ$^+$CD8$^+$ T cells in peripheral blood against SARS-CoV-2 using flow cytometry with peptide pools of SARS-CoV-2 wild type or omicron BA.1. The primary outcome was proportion of CD4$^+$ and CD8$^+$ T cells against SARS-CoV-2 1 month after exposure (ie, vaccination or breakthrough infection).

Findings Overall, between May 21, 2020, and Aug 31, 2021, we recruited 659 participants (231 [35%] men and 428 [65%] women). Of these participants, 428 were included in cohort 1 (214 [50%] received BNT162b2 and 214 [50%] received CoronaVac); 127 in cohort 2 (48 [38%] received all BNT162b2, 40 [31%] received all CoronaVac, and 39 [31%] received two CoronaVac and a booster with BNT162b2); 58 in cohort 3, and 46 in cohort 4 (16 [35%] received CoronaVac and 30 [65%] received BNT162b2). Vaccine-induced T-cell responses to the wild-type and omicron BA.1 variants were generally similar in adults receiving two doses of either CoronaVac (CD4$^+$ cells p=0·33; CD8$^+$ cells p=0·70) or BNT162b2 (CD4$^+$ cells p=0·28; CD8$^+$ cells p=1·0). Using a peptide pool of all structural proteins for stimulation, BNT162b2 induced a higher median frequency of omicron-specific CD4$^+$ T cells in adults younger than 60 years (CD4$^+$ cells 0·012% *vs* 0·010%, p=0·031; CD8$^+$ cells 0·003% *vs* 0·000%, p=0·055) and omicron-specific CD8$^+$ T cells in people aged 60 years or older (CD4$^+$ cells 0·015% *vs* 0·006%, p=0·0070; CD8$^+$ cells 0·007% *vs* 0·000%, p=0·035). A booster dose of either BNT162b2 or CoronaVac after two doses of CoronaVac boosted waning T-cell responses, but T-cell responses did not exceed those at 1 month after the second dose (CoronaVac CD4$^+$ p=0·41, CD8$^+$ p=0·79; BNT162b2 CD4$^+$ p=0·70 CD8$^+$ p=0·80).

Interpretation The evidence that mRNA and inactivated vaccines based on the ancestral SARS-CoV-2 virus elicited T-cell responses to SARS-CoV-2 omicron variants might explain the high observed vaccine effectiveness against severe COVID-19 shown by both types of vaccine, despite great differences in neutralising antibody responses. The use of either vaccine can be considered if the primary aim is to reduce severity and death caused by the new omicron subvariants; however, BNT162b2 is preferable for adults older than 60 years.

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Introduction

Pango lineage B.1.1.529 of SARS-CoV-2, designated omicron, is a variant of concern that was first detected in South Africa in November, 2021, and has spread worldwide.[1] Although the disease severity is generally milder than the preceding delta variant (B.1.617.2), omicron is more transmissible and has caused substantial morbidity and mortality in unvaccinated older people (ie, ≥65 years).[2] To date, the inactivated whole-virion SARS-CoV-2 vaccine CoronaVac (Sinovac) and lipid

Research in context

Evidence before this study

CoronaVac and BNT162b2 are currently the two most widely used COVID-19 vaccines globally. Although there are increasing data on antibody responses elicited by these vaccines against omicron-linage viruses, data are scarce on vaccine-induced T-cell immunity to omicron. We searched PubMed for articles published between Jan 1, 2020, and May 20, 2022, in English with the search terms "Omicron" AND "T cell" AND "CoronaVac" AND "BNT162b2" and manually screened all retrieved articles. We did not find any studies that compared the omicron-reactive T-cell responses between adults receiving CoronaVac or BNT162b2 vaccines or that compared the omicron-reactive T-cell responses from adults who had received CoronaVac followed by homologous or heterologous booster doses of either BNT162b2 or CoronaVac.

Added value of this study

To our knowledge, we conducted the first head-to-head comparative study on T-cell immune responses to the omicron SARS-CoV-2 variant elicited by CoronaVac and BNT162b2 vaccines. Although it is known that two doses of either CoronaVac or BNT162b2 fail to induce antibodies against omicron, our results showed that two doses of either vaccine elicited large omicron-specific $CD4^+$ and $CD8^+$ responses compared with the response in people before vaccination. However, two doses of BNT162b2 induced higher omicron-specific $CD4^+$ and $CD8^+$ T-cell responses in adults aged 60 years or older than did CoronaVac. A third dose of either BNT162b2 or CoronaVac boosted waning T-cell responses compared with responses before the third dose, but response levels did not exceed those seen 1 month after the second dose. Memory phenotypes were identified in both $CD4^+$ and $CD8^+$ T cells after two doses of CoronaVac or BNT162b2 vaccine, suggesting that both of them can provide a long-term protection.

Implications of all the available evidence

Our findings have implications for policies for the global control of COVID-19 control. Both CoronaVac and BNT162b2 provide T-cell responses to omicron, which might partly explain the good field vaccine efficacy of CoronaVac vaccine against severe omicron subvariant disease despite poor neutralising antibody responses.

nanoparticle encapsulated mRNA vaccine BNT162b2 (Pfizer–BioNTech) are the two most widely used COVID-19 vaccines worldwide.[3] Both vaccines have been used since February, 2021 in Hong Kong, where at least 91·2% of people have received two doses and 74·6% of people have received three doses of either vaccine. Mutations in the spike protein of the omicron variants result in a substantial loss of COVID-19 vaccine-elicited neutralising antibody titres.[4] Studies have shown that two doses of CoronaVac or BNT162b2 did not elicit protective concentrations of neutralising antibodies against omicron subvariants BA.1 or BA.2.[4–7] Three doses of BNT162b2 or a booster dose of BNT162b2 given to those who had received two doses of CoronaVac elicited adequate concentrations of omicron-specific neutralising antibodies, whereas three doses of CoronaVac did not.[7] These findings might have implications for populations who have been vaccinated with CoronaVac and similar inactivated whole-virion vaccines.[4–7] However, head-to-head comparisons on the T-cell responses elicited by the two vaccines have not been reported so far.

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Since omicron variants became dominant in the human population, reducing disease severity, hospitalisation, and death through vaccination is the primary aim for public health. Observational cohort studies showed that using BNT162b2 as a booster dose provided optimal vaccine effectiveness against severe outcomes that are caused by omicron.[8,9] The vaccine effectiveness of inactivated whole-virion vaccines (eg, CoronaVac) against the severe outcomes of omicron infection was unclear when this variant first emerged, and many countries that mainly used inactivated whole-virion vaccines have switched to a heterologous booster vaccine.[10] However, a subsequent observational study in Hong Kong reported that two or three doses of CoronaVac or two doses of BNT162b2 offered high vaccine efficacy against severe or fatal disease in young (ie, <60 years) and older (ie, ≥60 years) adults during an omicron BA.2 outbreak, which was first detected in Hong Kong in January, 2022 and peaked in early March, 2022.[11] This observation is inconsistent with the relatively poor omicron neutralising antibody responses that are elicited by CoronaVac, and data for the comparative T-cell responses are needed to explain the mechanisms of the observed vaccine protection induced by CoronaVac.[5]

T-cell responses correlate with reduced viral load or disease severity in humans and non-human primates.[12,13] The conserved regions of structural protein in CoronaVac might provide cross-reactive T-cell responses against omicron. In this study, we aimed to provide a head-to-head comparison of $CD4^+$ and $CD8^+$ T-cell responses in adults with vaccination strategies using CoronaVac and BNT162b2.

Methods

Study design and participants

We conducted an observational cohort study of participants recruited from three vaccination centres in Hong Kong: the Chinese University of Hong Kong Medical Centre, Prince of Wales Hospital, and Kowloon Bay Vaccination Center.[14] Eligible participants were adults (aged ≥18 years) who had received a COVID-19 vaccine schedule and were grouped into four cohorts (cohort 1: participants who received two doses of either BNT162b2 or CoronaVac, cohort 2: participants who

received two doses and a booster, cohort 3: participants who received two doses and a booster and had a breakthrough omicron infection, and cohort 4: participants who had a previous non-omicron infection and subsequently received one vaccine dose). Participants in cohort 4 were recruited exclusively from the Prince of Wales Hospital. We excluded people with a confirmed history of COVID-19 at the day of sampling from cohorts 1 and 2.

We recruited cohort 1 between March 10 and August 31, 2021, as part of a previous study.[14] As part of the previous study, we had previous serological confirmation that participants in this cohort did not have previous COVID-19 infection.[14] Cohort 1 received two doses of either BNT162b2 or CoronaVac vaccine during the study, according to the manufacturer's recommendation.

We recruited cohort 2 between March 10 and Aug 31, 2021. To form this cohort, we invited a subset of participants who had received two doses of CoronaVac in our previous observational study[14] to be randomly assigned to receive a booster dose of either CoronaVac or BNT162b2,[15] and peripheral blood mononuclear cells (PBMCs) from these participants were included in this study. We also included in cohort 2 additional participants who had received three doses of BNT162b2 who were recruited as part of this present study.

We recruited cohort 3 between March 10 and June 28, 2021. To be included in cohort 3, participants had to have received a full vaccination schedule (ie, two doses and a booster) and report a breakthrough infection during the fifth wave (ie, starting on Dec 31, 2021) of the omicron outbreak in Hong Kong.

We recruited cohort 4 between May 21, 2020, and March 30, 2021. Participants in this cohort had COVID-19 during this time period (ie, not during omicron) and received their first vaccine dose between May 26–Oct 18, 2021. We collected blood samples from these participants at 6 or 12 months during their convalescence as well as 1 month after they received the vaccines.

This study was approved by the Joint Chinese University of Hong Kong-New Territories East Cluster (reference number 2020.229) and Hong Kong West Cluster HKU/HA HKW (reference number UW 20–169) Clinical Research Ethics Committee. All participants provided written informed consent.

Outcomes

The primary outcome was proportion of $CD4^+$ and $CD8^+$ T cells against SARS-CoV-2 (using flow cytometry) 1 month after exposure (ie, vaccination or breakthrough infection). Secondary outcomes were neutralising antibody titres (using surrogate virus neutralisation tests [sVNT]) of plasma against wild type SARS-CoV-2 or omicron BA.1 and the proportion of omicron-reactive T cells stratified by age (<60 *vs* ≥60 years) and vaccine type (CoronaVac *vs* BNT162b2).

Procedures

For cohorts 1 and 2, we collected 10 mL of heparinised peripheral blood from each participant before vaccination and 1 month after receiving the second vaccine dose and 1 month after receiving the third (booster) vaccine dose.[14,15] For cohort 3, a blood sample was collected approximately 1 month after the breakthrough infection. For cohort 4, peripheral blood samples were collected during convalescence from non-omicron infection, 6–12 months after symptom onset, and an additional blood sample was collected 1 month after they had received one dose of vaccine. Blood samples were centrifuged at 3000×g for 10 min at room temperature for plasma collection. PBMCs were isolated using Ficoll-Paque Plus medium (Cytiva, Amersham, UK) according to the manufacturer's protocol. The cells were then resuspended in fetal bovine serum containing 10% of dimethyl sulfoxide (DMSO). The plasma was stored at –80°C and PMBCs were cryopreserved in liquid nitrogen until use.

The sVNT was performed according to the manufacturer's recommendations (GenScript, Piscataway, NJ, USA) using SARS-CoV-2 spike receptor-binding domain of the wild-type or omicron BA.1 virus. Inhibition of 30% or more was regarded as positive in accordance with the manufacturer's recommendation.

Peptide pools for the wild-type strain were based on the amino acid sequence of SARS-CoV-2/human/CHN/IQTC01/2020 (GenBank accession number MT123290.1). Defining mutations of omicron BA.1 were obtained from the CoVariants website.[16] Complete overlapping 20mer spike, nucleocapsid, membrane, and envelope (S/M/N/E) peptides (20mer peptide overlapping by ten amino acids) from wild-type and omicron BA.1 were synthesised by GL Biochem (Shanghai, China; appendix p 10).

See Online for appendix

Cryopreserved PBMCs were thawed, allowed to recover overnight, and stimulated with an overlapping peptide pool representing the SARS-CoV-2 proteins (300 nM) or DMSO (0·5% in Roswell Park Memorial Institute 1640 medium, Life Technologies, Carlsbad, CA, USA) as control for 24 h at 37°C. GolgiPlug (BD Biosciences, San Jose, CA, USA) containing brefeldin A (1% in phosphate-buffered saline PBS) and GolgiStop (BD Biosciences, San Jose, CA, USA) containing monensin were added to the stimulation mix. Cells were stained with Zombie NIR (Biolegend, San Diego, CA, USA), anti-human CD3, CD4, CD8, CCR7, CD45RA, CD19, NCAM (NCAM1), CD14, IFNγ, IL-4, TNF, and IL-2 antibodies (Biolegend, San Diego, CA, USA) according to our previous study[14] before data acquisition from the samples. Stained cells were quantified using flow cytometry (AttuneNxT, Thermo Fisher Scientific, Waltham, MA, USA) and analysed by FlowJo version 10. Representative fluorescence-activated cell sorting plots and gating strategy are shown in the appendix (p 2). Data from samples were

included in subsequent analyses if cell viability was above 80%.

The demographic information of each participant was collected through a questionnaire on their visit to the vaccination centre. Data for gender were collected through the questionnaire and options were male or female.

Statistical analysis

Continuous variables (ie, sVNT, T-cell data, and memory T-cell data) were reported as median and IQR, and categorical data were presented as proportions. To establish whether there was an imbalance in participants' demographic characteristics between the two types of vaccines used for the initial doses, we used Wilcoxon rank-sum test for continuous variables and Fisher's exact test for the categorical variables. Data for sVNT, T-cell phenotype, and memory phenotype were compared by Wilcoxon rank-sum test within each cohort. The comparisons of T cells and memory cells were further adjusted for potential confounders, such as age and gender, by multiple linear regression. For the comparisons of immunity parameters (ie, sVNT, T-cell data, and memory T-cell data) between two groups, we used the Wilcoxon rank sum (Mann Whitney U) test for unpaired data and Wilcoxon matched-pairs signed rank test for paired data. For the comparisons of immunity parameters between more than two groups, we used Kruskal-Wallis

	Cohort 1: participants who received two doses (n=428)*		Cohort 2: participants who received two doses and a booster (n=127)†			Cohort 3: participants who received two doses and a booster and had a breakthrough omicron infection (n=58)	Cohort 4: participants who had a previous non-omicron infection and then received one dose of BNT162b2 or CoronaVac (n=46)‡
	BNT162b2 (n=214)	CoronaVac (n=214)	2 BNT62b2 +1 BNT162b2 (n=48)	2 CoronaVac +1 BNT162b2 (n=39)§	2 CoronaVac +1 CoronaVac (n=40)		
Recruitment date period	March 10–Aug 31, 2021	March 10–Aug 31, 2021	March 10–Aug 31, 2021	March 10–Aug 31, 2021	March 10–Aug 31, 2021	March 10–June 28, 2021	May 21, 2020–March 30, 2021
Median age, years (IQR)	46 (35–57)	52 (45–58)	50 (42–59)	52 (46–57)	50 (46–57)	50 (44–58)	57 (47–64)
Gender							
Female	133 (62%)	154 (72%)	24 (50%)	25 (64%)	28 (70%)	42 (72%)	22 (48%)
Male	81 (38%)	60 (28%)	24 (50%)	14 (36%)	12 (30%)	16 (28%)	24 (52%)
Lifestyle habits							
Smoker	9 (4%)	14 (7%)	1 (2%)	3 (8%)	3 (8%)	2 (3%)	1 (2%)
Alcohol consumption	95 (44%)	83 (39%)	20 (42%)	13 (33%)	18 (45%)	24 (41%)	18 (39%)
Regular exercise	103 (48%)	110 (51%)	30 (63%)	21 (54%)	23 (58%)	28 (48%)	23 (50%)
Comorbidities							
Cardiovascular diseases	19 (9%)	5 (2%)	3 (6%)	0	3 (8%)	4 (7%)	5 (11%)
Diabetes	12 (6%)	12 (6%)	4 (8%)	2 (5%)	2 (5%)	5 (9%)	5 (11%)
Chronic respiratory disease	5 (2%)	4 (2%)	1 (2%)	2 (5%)	2 (5%)	2 (3%)	1 (2%)
Vaccine history							
Influenza	131 (61%)	123 (58%)	35 (73%)	27 (69%)	29 (73%)	38 (66%)	16 (35%)
Received every year	75 (35%)	58 (27%)	19 (40%)	12 (31%)	16 (40%)	20 (35%)	4 (9%)
Received once within 2 years	42 (20%)	55 (26%)	14 (29%)	15 (39%)	12 (30%)	17 (29%)	8 (17%)
Received once but not within previous 2 years	14 (7%)	10 (5%)	2 (4%)	0	1 (3%)	1 (2%)	4 (9%)
Never received	83 (39%)	91 (43%)	13 (27%)	12 (31%)	11 (28%)	20 (35%)	23 (50%)
Hepatitis A/B	115 (54%)	64 (30%)	25 (52%)	14 (36%)	12 (30%)	16 (28%)	9 (20%)
Mumps	41 (19%)	14 (7%)	14 (29%)	4 (10%)	1 (3%)	5 (9%)	1 (2%)
Pneumococcal conjugate vaccine	20 (9%)	4 (2%)	4 (8%)	1 (3%)	1 (3%)	2 (3%)	4 (9%)
Rabies	11 (5%)	8 (4%)	4 (8%)	3 (8%)	1 (3%)	2 (3%)	0
Typhoid	12 (6%)	6 (3%)	4 (8%)	1 (3%)	1 (3%)	1 (2%)	1 (2%)
Haemorrhagic fever	3 (1%)	0	2 (4%)	0	0	1 (2%)	0
COVID-19 history in household	2 (1%)	1 (1%)	0	0	0	0	23 (50%)
Convalescent from SARS-CoV infection	1 (1%)	1 (1%)	1 (2%)	0	0	0	0

Data are n (%), unless otherwise stated. *Recruited as part of a previous study.[14] †Recruited as part of a previous study.[15] ‡Seven participants in cohort 4 did not complete the questionnaire. §One participant excluded due to insufficient peripheral blood mononuclear cells for analysis.

Table 1: **Baseline characteristics**

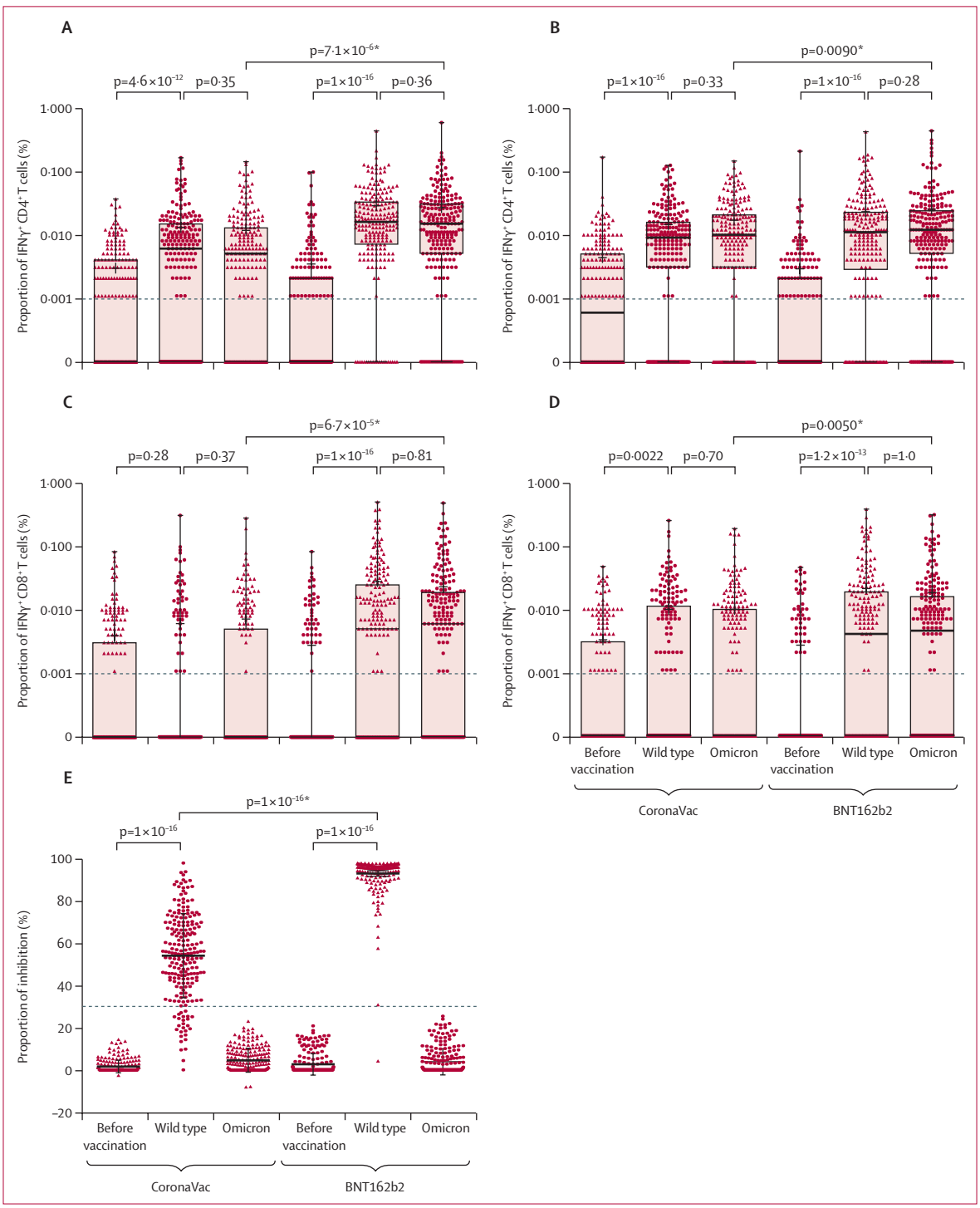


Figure 1: **T-cell and antibody responses against SARS-CoV-2 in adults who received two doses of CoronaVac or BNT162b2 vaccines (cohort 1)**
Peripheral blood mononuclear cells collected 1 month after two doses of CoronaVac (n=214) or BNT162b2 (n=214) vaccines were stimulated with pooled spike or structural (ie, S/M/N/E) peptide pools. The proportions of $CD4^+$ T cells that are $IFN\gamma^+$ stimulated by spike peptide pools (A) and S/M/N/E peptide pools (B) and the proportions of $IFN\gamma^+CD8^+$ T cells stimulated by spike peptide pools (C) and S/M/N/E peptide pools (D) against wild-type or omicron BA.1 virus were measured by flow cytometry. The limit of detection following background (dimethyl sulfoxide) subtraction was 0·001, as indicated by the horizontal dashed lines. (E) The percentage of inhibition detected by the surrogate neutralisation test in the plasma of the two vaccine groups using the receptor-binding domain of the wild-type and omicron BA.1 virus. The positive threshold of the surrogate neutralisation test was 30%, as indicated by the horizontal dashed line. Whiskers indicate the minimum and maximum of the data. The upper and lower limits of the box indicate the IQR around the median. The cross represents the mean. Data within the same vaccine group were compared by the Friedman multicomparisons test followed by post-hoc pairwise Wilcoxon rank sum test paired with Benjamini-Hochberg correction. Wilcoxon rank-sum test was used to test between different subgroups. S/M/N/E=spike, membrane, nucleocapsid, and envelope proteins. *p value was generated by multiple linear regression model adjusting by age and gender.

test for unpaired data and Friedman test for paired data followed by post-hoc analysis with Dunn's test for unpaired data and pairwise Wilcoxon rank sum test for paired data for multiple comparisons. Statistical analyses were performed with Graph Pad Prism 8.0 and R version 4.2.1. p values less than 0·05 were considered as significant. Patients with missing data were excluded from analysis.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Overall, 659 participants across the four cohort were included in this study (428 [65%] in cohort 1, 127 [19%] in cohort 2, 58 [9%] in cohort 3, and 46 [7%] in cohort 4), characteristics of each cohort are shown in table 1. The study design and the key results are summarised in the appendix (p 3). Cohort 1 visits occurred between March 10 and Aug 31, 2021 for the first visit before vaccination and between May 9 and Oct 31, 2021 for the second visit 1 month after second dose. Cohort 2 visits occurred between March 10 and Aug 31, 2021 for the first visit before vaccination; May 9 and Oct 31, 2021 for the second visit 1 month after second

	Aged <60 years				Aged ≥60 years		
	CoronaVac (n=174)	BNT162b2 (n=174)	Non-adjusted p value	Adjusted p value*	CoronaVac (n=40)	BNT162b2 (n=40)	Non-adjusted p value
Age, years	50 (44–55)	42 (32–54)	$3{\cdot}68\times10^{-6}$	..	63 (61–71)	63 (62–65)	0·57
Gender	..	..	0·018	..	..	..	..
Female	134 (77%)	113 (65%)	..	..	20 (50%)	20 (50%)	1·0
Male	40 (23%)	61 (35%)	..	..	20 (50%)	20 (50%)	..
Proportion of total CD4⁺ and CD8⁺ cells before vaccination (wild-type pool), %							
Spike							
IFNγ⁺CD4⁺	0·000% (0·000–0·004)	0·000% (0·000–0·002)	0·034	0·57	0·000% (0·000–0·003)	0·000% (0·000–0·002)	0·95
IFNγ⁺CD8⁺	0·000% (0·000–0·003)	0·000% (0·000–0·000)	0·038	0·31	0·000% (0·000–0·000)	0·000% (0·000–0·000)	0·75
S/M/N/E							
IFNγ⁺CD4⁺	0·001% (0·000–0·005)	0·000% (0·000–0·002)	$4{\cdot}93\times10^{-5}$	0·63	0·000% (0·000–0·005)	0·000% (0·000–0·002)	0·47
IFNγ⁺CD8⁺	0·000% (0·000–0·003)	0·000% (0·000–0·000)	0·0050	0·36	0·000% (0·000–0·000)	0·000% (0·000–0·001)	0·86
Proportion of total CD4⁺ and CD8⁺ cells after second dose (wild-type pool), %							
Spike							
IFNγ⁺CD4⁺	0·006% (0·000–0·016)	0·015% (0·007–0·033)	$2{\cdot}79\times10^{-9}$	$1{\cdot}27\times10^{-4}$	0·005% (0·000–0·012)	0·020% (0·008–0·044)	$8{\cdot}24\times10^{-6}$
IFNγ⁺CD8⁺	0·000% (0·000–0·000)	0·005% (0·000–0·023)	$2{\cdot}63\times10^{-12}$	$1{\cdot}87\times10^{-4}$	0·000% (0·000–0·000)	0·007% (0·000–0·037)	0·0010
S/M/N/E							
IFNγ⁺CD4⁺	0·010% (0·003–0·016)	0·010% (0·003–0·022)	0·38	0·041	0·007% (0·000–0·012)	0·013% (0·002–0·035)	0·019
IFNγ⁺CD8⁺	0·000% (0·000–0·012)	0·003% (0·000–0·016)	0·078	0·056	0·000% (0·000–0·008)	0·006% (0·000–0·060)	0·0090
Proportion of total CD4⁺ and CD8⁺ cells after second dose (omicron pool), %							
Spike							
IFNγ⁺CD4⁺	0·005% (0·000–0·013)	0·013% (0·005–0·031)	$3{\cdot}07\times10^{-9}$	$3{\cdot}58\times10^{-5}$	0·004% (0·000–0·013)	0·019% (0·006–0·032)	$1{\cdot}44\times10^{-5}$
IFNγ⁺CD8⁺	0·000% (0·000–0·005)	0·006% (0·000–0·018)	$6{\cdot}56\times10^{-8}$	0·0030	0·000% (0·000–0·002)	0·007% (0·000–0·030)	0·0010
S/M/N/E							
IFNγ⁺CD4⁺	0·010% (0·003–0·023)	0·012% (0·004–0·024)	0·57	0·031	0·006% (0·000–0·014)	0·015% (0·006–0·026)	0·0070
IFNγ⁺CD8⁺	0·000% (0·000–0·010)	0·003% (0·000–0·015)	0·090	0·055	0·000% (0·000–0·012)	0·007% (0·000–0·026)	0·035

Data are median (IQR) or n (%). *The p values were compared using Wilcoxon rank-sum test and then adjusted by age and gender using multiple linear regression.

Table 2: **Statistical comparison of T-cell responses from vaccinees who received two doses of COVID-19 vaccine (cohort 1)**

dose; Aug 18 and Sept 16, 2021 for the third visit before booster dose; and Sept 18, 2021 and April 4, 2022 for the fourth visit 1 month after booster dose. Cohort 3 visits occurred between Sept 18, 2021, and April 17, 2022 for the first visit 1 month after booster dose and between March 25 and July 22, 2022 for the second visit 1 month after convalescence. Cohort 4 visits occurred between Dec 30, 2020 and Aug 19, 2021 for the first visit 6 or 12 months after convalescence and between June 23 and Nov 24, 2021 for the second visit 1 month after vaccination.

For cohort 1, we randomly selected the samples from 428 adults who received two doses of CoronaVac (n=214) or BNT162b2 (n=214) between March 10 and Aug 31, 2021; this recruitment occurred as part of out previous study, which involved 726 participants.[14]

We collected plasma and PBMC samples from all participants, both before first dose of vaccination and 1 month after the second dose of either the CoronaVac (n=214) or BNT162b2 (n=214) vaccine, from which T-cell responses were determined (figure 1, appendix pp 16–17). Our previous experiment showed that T-cell responses were not significantly induced in the BNT162b2 group using only the non-spike structural peptides (ie, membrane, nucleocapsid, and envelope), as expected, and thus this stimulation approach was not adopted in this comparison study (appendix p 4).

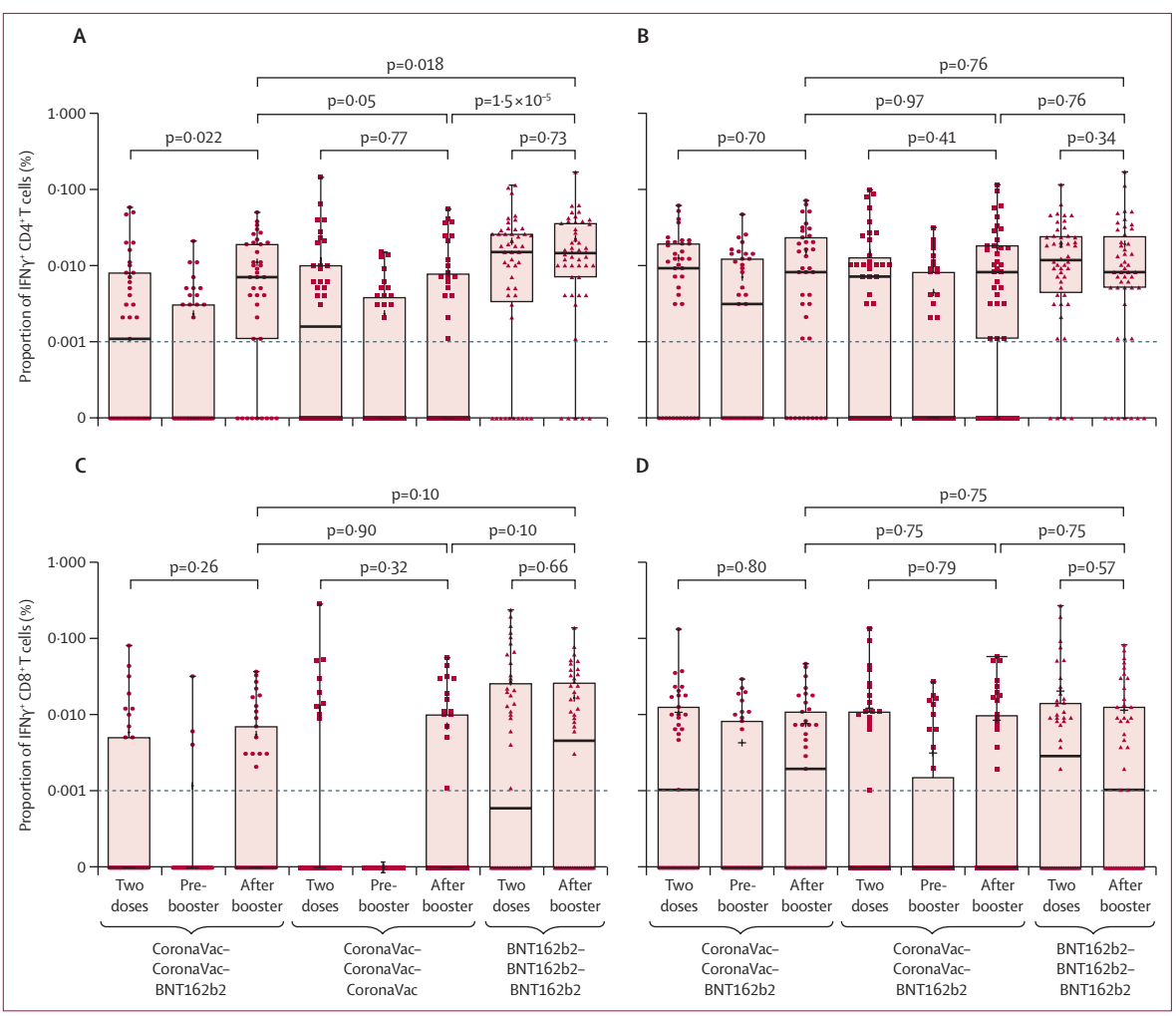


Figure 2: **T-cell responses against omicron BA.1 variant of SARS-CoV-2 in adults who received a booster dose of either CoronaVac or BNT162b2 (cohort 2)**
Peripheral blood mononuclear cells from 1 month after receiving the second vaccine dose and immediately before (excluding participants who received three doses of BNT162b2, due to availability of data) and 1 month after receiving a booster dose of either CoronaVac or BNT162b2 vaccine were stimulated with pooled spike or structural (S/M/N/E) peptides of omicron BA.1. n=39 for the CoronaVac–CoronaVac–BNT162b2 group, n=40 for the CoronaVac–CoronaVac–CoronaVac group, and n=48 for the BNT162b2–BNT162b2–BNT162b2 group. The proportions of IFNγ$^+$CD4$^+$ T cells stimulated with spike peptides (A) and S/M/N/E peptides (B) and the proportions of IFNγ$^+$CD8$^+$ T cells stimulated with spike peptides (C) and S/M/N/E peptides (D) were measured by flow cytometry. Whiskers indicate the minimum and maximum of the data. The upper and lower limits of the box indicate the IQR around the median. The cross represents the mean. The limit of detection following background (dimethyl sulfoxide) subtraction was 0·001, as indicated by the horizontal dashed lines. Data were compared by Friedman multicomparisons test followed by post-hoc pairwise Wilcoxon rank sum test paired with Benjamini-Hochberg correction (within each vaccine group at different timepoints) or Wilcoxon rank-sum test (between different vaccine strategies). S/M/N/E=spike, membrane, nucleocapsid, and envelope proteins.

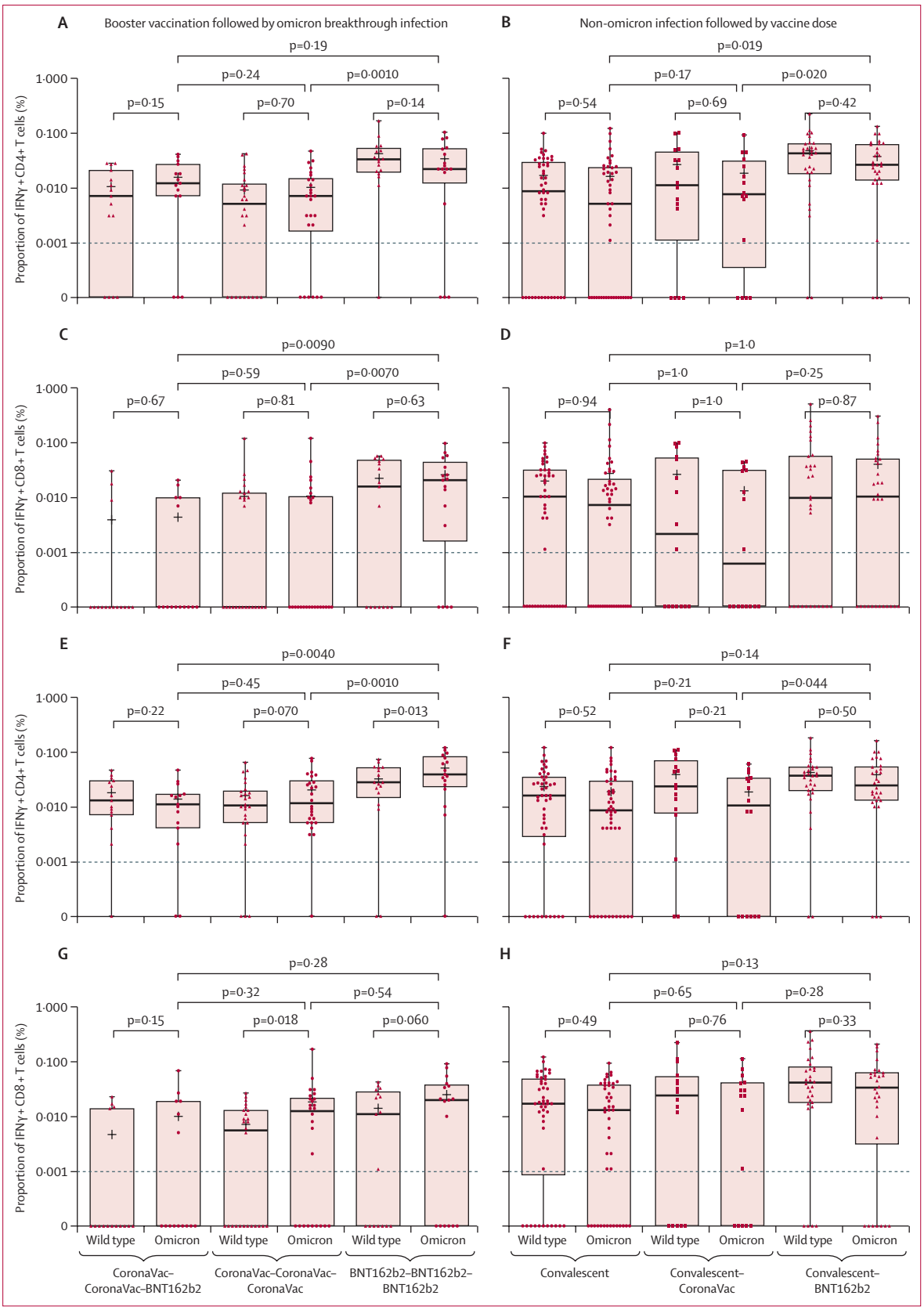
We detected higher proportions of $CD4^+$ and $CD8^+$ T-cell responders (ie, people with a T-cell response higher than 0·0001%) to the spike pool in the BNT162b2 group than in the CoronaVac group (appendix p 17). Additionally, although there were more $CD8^+$ T-cell responders in the BNT162b2 group than in the CoronaVac group, no significant difference was identified in $CD4^+$ T-cell responders between the two vaccine groups when the S/M/N/E pool was used for stimulation. There was a significant increase of wild-type spike-specific $IFN\gamma^+CD4^+$ T cells ($p=4·6\times10^{-12}$), but not of $IFN\gamma^+CD8^+$ ($p=0·42$) T cells, in people who received two doses of CoronaVac compared with their corresponding samples taken before vaccination (figure 1A, C). However, when the wild-type S/M/N/E peptide pool was used, both $IFN\gamma^+CD4^+$ and $IFN\gamma^+CD8^+$ T cells were significantly increased (figure 1B, D). In the BNT162b2 group, both $IFN\gamma^+CD4^+$ and $IFN\gamma^+CD8^+$ T cells were significantly increased in response to stimulation with either wild-type spike or S/M/N/E peptide pools (figure 1A–D). There was no significant difference between the T-cell responses against wild-type and omicron virus in each of the two vaccine groups using any stimulation condition (figure 1). Moreover, we identified that the BNT162b2 group had significantly higher numbers of $IFN\gamma^+CD4^+$ and $IFN\gamma^+CD8^+$ T cells to both wild-type and omicron than the CoronaVac group after adjusting for age and gender using a multiple linear regression model (appendix p 17). There was no significant change in the results if other covariates were enrolled into the regression model (ie, cardiovascular disease, vaccination history [influenza, mumps, hepatitis A, hepatitis B, and pneumococcal conjugate vaccines], and SARS-CoV infection history). None of the samples from the two-dose vaccine groups were positive to the omicron BA.1 receptor-binding domain by sVNT (figure 1E).

A field vaccine effectiveness study in Hong Kong showed that two doses of BNT162b2 provided better vaccine effectiveness against severe or fatal COVID-19 in older adults (ie, aged ≥60 years) than did CoronaVac.[11] However, the difference in the young adult group (ie, aged <60 years) was marginal. Therefore, we further performed a stratified analysis to determine the frequency of omicron-reactive $IFN\gamma^+$ T cells in people who received two doses of vaccine on the basis of age (ie, aged <60 years or ≥60 years) and vaccine type (ie, CoronaVac or BNT162b2; table 2; appendix p 5). When comparing the results between the younger and older adults who received the same vaccine, there were no significant differences in the number of omicron-reactive $IFN\gamma^+CD4^+$ and $IFN\gamma^+CD8^+$ T cells in response to the spike or S/M/N/E peptide pool, except for in younger adults who received CoronaVac, who showed a higher number of $CD4^+IFN\gamma^+$ T cells using S/M/N/E peptide pool for stimulation, which was borderline significant ($p=0·0498$; appendix p 17). When comparing the results between the two vaccine groups using spike or S/M/N/E peptide pools, both younger (after adjustment for age and gender) and older adults in the BNT162b2 group showed significantly higher numbers of $IFN\gamma^+CD4^+$ T cells to omicron than did those who received CoronaVac (table 2). However, the numbers of $IFN\gamma^+CD4^+$ T cells to omicron using S/M/N/E were not significantly different between those who received BNT162b2 and CoronaVac in the younger age group before the data were adjusted for age and gender. No adjustment was applied for the older group since there was no significant difference between age and gender in the two groups. BNT162b2 vaccine also elicited significantly higher numbers of omicron-reactive spike-specific $IFN\gamma^+CD8^+$ T cells than did CoronaVac, in both younger and older adult groups (table 2). When using the S/M/N/E pool for stimulation, there was a significantly higher number of omicron-reactive $IFN\gamma^+CD8^+$ T cells in the older but not in the younger adult group who received BNT162b2 compared with the corresponding age groups of those who had received CoronaVac. All stratified subgroups showed similar numbers of $IFN\gamma^+CD4^+$ or $IFN\gamma^+CD8^+$ T cells in response to stimulation with wild-type and omicron virus (appendix p 5). The results from the sVNT assay in the age-stratified groups are shown in the appendix (p 6).

Some participants in our two-dose cohort received a booster (ie, cohort 2) and continued to be followed up for 24 months after they received the booster (table 1). The intervals between the second and third doses were 95·3 days for CoronaVac followed by BNT162b2, 99·4 days for three doses of CoronaVac, and 238·1 days for three doses of BNT162b2. We compared the omicron-reactive $IFN\gamma^+CD4^+$ and $IFN\gamma^+CD8^+$ T cells among those

Figure 3: **T-cell responses from vaccinated adults after omicron breakthrough infection (cohort 3) or adults after convalescence from non-omicron infection who received one dose (cohort 4)**

Peripheral blood mononuclear cells were collected 1 month after people who had previously been vaccinated with a booster strategy had omicron breakthrough infection (n=58) or 1 month after people who had recovered from non-omicron SARS-CoV-2 infection received one dose of CoronaVac or BNT162b2 (n=46). Cells were stimulated with pooled spike or structural (S/M/N/E) peptides of either wild-type or omicron BA.1 virus. The proportions of $IFN\gamma^+CD4^+$ T cells stimulated with spike peptides in people with omicron breakthrough infection after booster vaccination (A) and people who received a vaccine after recovery from non-omicron infection (B), proportions of $IFN\gamma^+CD8^+$ T cells stimulated with spike peptides in people with omicron breakthrough infection after booster vaccination (C) and people who received a vaccine after recovery from non-omicron infection (D), proportions of $IFN\gamma^+CD4^+$ T cells stimulated with S/M/N/E peptides in people with omicron breakthrough infection after booster vaccination (E) and people who received a vaccine after recovery from non-omicron infection (F), and proportions of $IFN\gamma^+CD8^+$ T cells stimulated with S/M/N/E peptides in people with omicron breakthrough infection after booster vaccination (G) and people who received a vaccine after recovery from non-omicron infection (H) were measured by flow cytometry. Whiskers indicate the minimum and maximum of the data. The upper and lower limits of the box indicate the IQR around the median. The cross represents the mean. The limit of detection following background (dimethyl sulfoxide) subtraction was 0·001, as indicated by the horizontal dashed line. Data for wild-type and omicron virus were compared by Wilcoxon matched-pairs signed rank test. Wilcoxon rank-sum test was used to test between different subgroups. S/M/N/E=spike, membrane, nucleocapsid, and envelope proteins.


A
Booster vaccination followed by omicron breakthrough infection
B
Non-omicron infection followed by vaccine dose
C
D
E
F
G
H
Proportion of IFNγ+CD4+ T cells (%)
Proportion of IFNγ+CD8+ T cells (%)
1·000
0·100
0·010
0·001
0
p=0·19
p=0·24
p=0·0010
p=0·15
p=0·70
p=0·14
p=0·019
p=0·17
p=0·020
p=0·54
p=0·69
p=0·42
p=0·0090
p=0·59
p=0·0070
p=0·67
p=0·81
p=0·63
p=1·0
p=1·0
p=0·25
p=0·94
p=1·0
p=0·87
p=0·0040
p=0·45
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p=0·50
p=0·28
p=0·32
p=0·54
p=0·15
p=0·018
p=0·060
p=0·13
p=0·65
p=0·28
p=0·49
p=0·76
p=0·33
Wild type
Omicron
CoronaVac–CoronaVac-BNT162b2
CoronaVac–CoronaVac–CoronaVac
BNT162b2–BNT162b2–BNT162b2
Convalescent
Convalescent–CoronaVac
Convalescent–BNT162b2

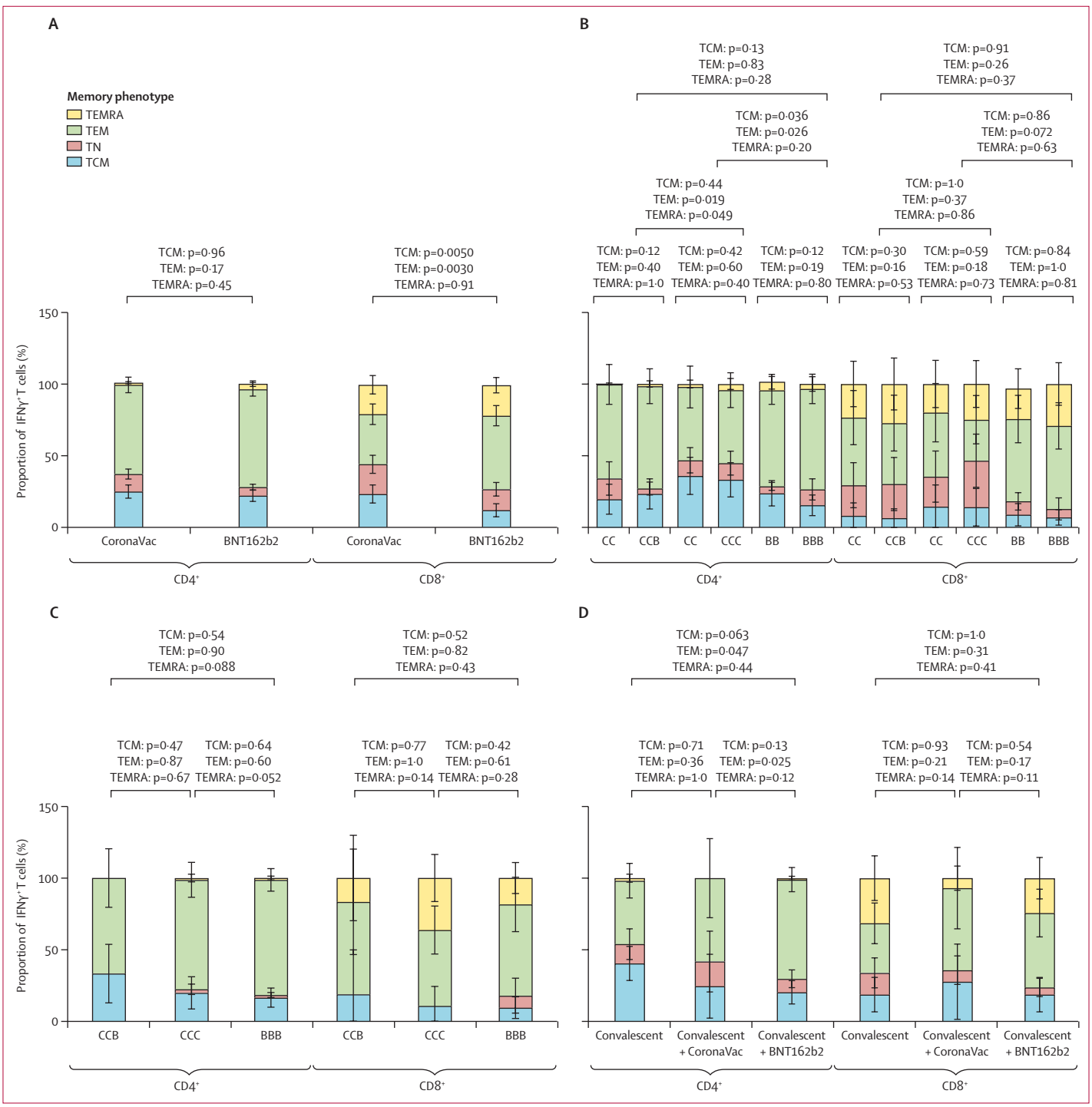

***Figure 4*: Memory phenotypes of the omicron-specific T cells from adults who received CoronaVac or BNT162b2 vaccine under different stimulation conditions**

The phenotype of IFNγ$^+$CD4$^+$ and IFNγ$^+$CD8$^+$ TEMs (CCR7$^-$CD45RA$^-$), TCMs (CCR7$^+$CD45RA$^-$), TEMRAs (CCR7$^-$CD45RA$^+$), or TNs (CCR7$^+$CD45RA$^+$) responding to the omicron spike, membrane, nucleocapsid, and envelope peptide pool were determined from the peripheral blood mononuclear cells of participants after different vaccine combinations. Phenotypes characterised 1 month after two doses (A) or three doses of vaccine (B). (C) Phenotypes characterised 1 month after breakthrough omicron infection after previous booster vaccination. (D) Phenotypes characterised 1 month after the participants who had recovered from a non-omicron infection (n=46) received one dose of CoronaVac or BNT162b2. Bars represent the mean values and error bars represent 95% CI. Comparisons between vaccine groups were performed using the Wilcoxon rank-sum test. BB=BNT162b2–BNT162b2. BBB=BNT162b2–BNT162b2–BNT162b2. CC=CoronaVac–CoronaVac. CCB=CoronaVac–CoronaVac–BNT162b2. CCC=CoronaVac–CoronaVac–CoronaVac. TCM=central memory T cell. TEM=effector memory T cell. TEMRA=terminally differentiated effector memory T cell. TN=naive T cell.

with a booster dose of either BNT162b2 (n=39) or CoronaVac (n=40) who previously received two doses of CoronaVac and among those who received two doses and a booster of BNT162b2 (n=48). There was no significant difference in age and gender among the three boosted groups (appendix p 18). The percentage of inhibition in the sVNT to the receptor-binding domains of wild-type and omicron from the plasma of the three cohorts were consistent with our previous report (appendix p 6).[5,15] We observed waning of the SARS-CoV-2 S/M/N/E-reactive IFNγ$^+$CD4$^+$ and IFNγ$^+$CD8$^+$ T-cell numbers in people with two doses of CoronaVac immediately before the third dose. The third dose of either CoronaVac or BNT162b2 boosted these T cells (figure 2; appendix p 7). In comparison with the number of T cells observed 1 month after the second dose, we identified that all booster strategies elicited similar numbers of omicron-reactive IFNγ$^+$CD4$^+$ and IFNγ$^+$CD8$^+$ T cells in response to the S/M/N/E pool (figure 2). Homologous booster of BNT162b2 led to a significantly higher number of omicron spike-reactive IFNγ$^+$CD4$^+$ T cells than the two booster groups that received two doses of CoronaVac as the primary vaccination (figure 2). No significant difference was identified in the IFNγ$^+$CD8$^+$ T cells between the three booster groups.

Among people who had omicron BA.2 breakthrough infection after they had received two doses and a booster vaccine (ie, cohort 3; appendix p 19), we observed that the breakthrough infection did not induce significantly more IFNγ$^+$CD4$^+$ and IFNγ$^+$CD8$^+$ T cells to omicron than to the wild-type virus, with the exception of S/M/N/E-reactive CD4$^+$ responses in people who had received three doses of BNT162b2 and S/M/N/E-reactive CD8$^+$ responses in people who had received three doses of CoronaVac (figure 3A, C, E, G). Moreover, three doses of BNT162b2 resulted in a higher number of IFNγ$^+$CD4$^+$ T cells, but not IFNγ$^+$CD8$^+$ T cells, in response to omicron S/M/N/E peptide pool stimulation groups than did the other two vaccine booster groups, in which the participants received CoronaVac for their first two doses (figure 3E, G).

We also investigated whether patients who had recovered from SARS-CoV-2 before the omicron outbreak (ie, cohort 4) might have cross-reactive T-cell responses to omicron and whether a single dose of either CoronaVac or BNT162b2 might affect T-cell responses. 16 participants received CoronaVac and 30 participants received BNT162b2 (appendix p 20). Samples were taken 6–12 months after infection and before vaccination for comparison. There was no significant difference in the frequency of IFNγ$^+$CD4$^+$ and IFNγ$^+$CD8$^+$ T cells between wild-type and omicron peptide pools before or after their vaccination (figure 3B, D, F, H). When comparing the two vaccine groups, the convalescent patients who received one dose of BNT162b2 had a higher proportion of omicron-reactive IFNγ$^+$CD4$^+$ T cells than did the CoronaVac group with both the spike and the S/M/N/E peptide pools (figure 3B, F).

Memory phenotypes of T cells indicate long-term protection after vaccination. We identified the phenotype of the IFNγ$^+$CD4$^+$ and IFNγ$^+$CD8$^+$ T cells responding to the spike or structural peptide pool in people who were vaccinated with different vaccines (figure 4; appendix pp 8–9). Memory IFNγ$^+$CD4$^+$ and IFNγ$^+$CD8$^+$ T cells were further classified as central memory, effector memory, and effector memory T cells re-expressing CD45RA by use of the surface markers CCR7 and CD45RA (appendix p 2). We identified that effector memory T cells were the major phenotype among the IFNγ$^+$CD4$^+$ and IFNγ$^+$CD8$^+$ T cells after participants received two or three doses of vaccine, one dose of vaccination subsequent to convalescence from infection, and had breakthrough infection after vaccination. IFNγ$^+$CD8$^+$ effector memory T cells re-expressing CD45RA were present in all vaccine conditions. When comparing the results of two doses of vaccination, participants who received CoronaVac had a lower proportion of IFNγ$^+$CD8$^+$ effector memory T cells but a higher proportion of IFNγ$^+$CD8$^+$ central memory T cells than participants who received BNT162b2. No significant difference was observed between the two vaccines in the omicron-specific IFNγ$^+$CD4$^+$ memory phenotype (figure 4A). Booster doses of either vaccine did not significantly change the memory phenotype of omicron-specific CD4$^+$ and CD8$^+$ T cells compared with two doses of vaccine (figure 4B). The memory phenotype of T cells in participants who received various booster strategies was not significantly different after omicron breakthrough infection (figure 4C). We made the same observation in participants who received one dose of vaccine after convalescence from non-omicron SARS-CoV-2 infection; however, people who received CoronaVac had lower proportion of IFNγ$^+$CD4$^+$ effector memory T cells than the BNT162b2 group (figure 4D).

Discussion

In this study, we provided data for the T-cell responses to wild-type and omicron BA.1 virus peptides in head-to-head comparisons of people who had received CoronaVac or BNT162b2 COVID-19 vaccines in Hong Kong. Most of the samples from our cohort were collected before the large omicron BA.2 outbreak in 2022, a time when the overall infection rate in Hong Kong was low, with overall population-based seroprevalence of approximately 1% (unpublished). Thus, our study population reflected the immune responses elicited by vaccines with minimal confounding by unsuspected natural infection, except in the known non-omicron SARS-CoV-2 infection and omicron breakthrough infection groups.

We tested the T-cell responses from the two vaccine groups using spike peptides (an antigen presented by both vaccines) and a peptide pool derived from all structural proteins (S/M/N/E). Our results showed that peptides from non-spike structural protein (N/M/E) did not significantly stimulate the T cells in our BNT162b2

group but did so in the CoronaVac group (appendix p 4), suggesting that CoronaVac can stimulate T-cell responses against the non-spike structural protein of SARS-CoV-2. Thus, comparison by use of S/M/N/E peptide pools represents the overall T-cell responses expected from CoronaVac, and we can also compare the total T-cell responses between the two vaccine groups. Importantly, although cytotoxic $CD8^+$ T cells often react with nucleoprotein, it has been reported that they can also target residues 269–277 on the spike epitope, which might explain a T-cell protective role of the mRNA vaccine.[17,18] Overall, our results show that, although two doses of BNT162b2 induced greater antibody and spike-specific T-cell responses than the CoronaVac vaccine, CoronaVac significantly induced T-cell response to S/M/N/E (figure 1), perhaps offsetting its somewhat lower magnitude of humoral response. Although participants who received two doses of BNT162b2 showed higher $CD4^+$ T-cell response to spike or S/M/N/E than those who received CoronaVac at all ages, CoronaVac and BNT162b2 induced similar levels of $CD8^+$ T-cell response to S/M/N/E in the younger age group (ie, aged <60 years).

Since SARS-CoV-2 is currently highly prevalent in the human population worldwide, reducing disease severity, hospitalisation, and death through vaccination is the primary aim of public health. Although T cells might not functionally prevent infection, they are known to reduce virus replication by eliminating virus-infected cells and thus control disease progression.[19] Several studies have shown the protective role of T cells during SARS-CoV-2 infection.[12,13,20,21] For instance, the presence of $CD8^+$ T cells was essential for reducing the viral load in experimental rechallenge of vaccinated macaques.[13,20] People with cancer and B-cell deficiencies had a milder severity of COVID-19 if they had a large specific $CD8^+$ T-cell response.[21] Although antibody waning is often observed after vaccination, the vaccine effectiveness against admission to intensive care units or severe disease was maintained for more than 5 months at around 71% in people who had received two doses of BNT162b2 in South Africa.[8] Similar results were reported from a study of vaccine effectiveness during an omicron BA.2 outbreak in Hong Kong.[11] In contrast to the apparently poor serum neutralising antibody titres against the omicron variants elicited by two doses of BNT162b2 and CoronaVac or three doses of CoronaVac, field vaccine effectiveness against severe disease and death was 88·2% (95% CI 84·4–91·1) following two doses of BNT162b2, 74·1% (67·8–79·2) following two doses of CoronaVac, and 98·1% (97·1–98·8) following three doses of either vaccine.[11] Our results have shown that two or three doses of CoronaVac or BNT162b2 can induce similar $CD4^+$ and $CD8^+$ T-cell responses against the omicron variant, which might explain the unexpectedly high vaccine effectiveness of CoronaVac against severe disease and death observed in the field.

In contrast to the markedly improved neutralising antibody responses observed with heterologous vaccination (ie, BNT162b2 booster after two doses of CoronaVac) compared with homologous booster of CoronaVac, heterologous booster led to only a slight increase in spike-specific CD4 T-cell responses to omicron. Our findings showed that a booster dose of either vaccine strategy (ie, heterologous booster of BNT162b2 after two doses of CoronaVac or homologous booster of CoronaVac) restored waning SARS-CoV-2-reactive T-cell responses observed with time after the second dose of both vaccines (figure 2). Notably, memory T cells for omicron BA.1 were found in all vaccine strategies investigated in our study. These memory T cells migrate into tissue and reactivate during a new SARS-CoV-2 infection.[22,23] Thus, these T-cell responses might continue to be effective and protective against severe disease from variants, such as omicron, for a long period of time. Our data suggest that two doses of either BNT162b2 or CoronaVac can activate T-cell responses to SARS-CoV-2 and its variants, and should be administered across the population, especially in people at high risk of severe complications, such as older people. Booster doses provide a boost for waning T-cell immunity, even with CoronaVac, even though this vaccine does not elicit adequate concentrations of omicron-specific neutralising antibody.

There were some limitations in our study. First, peripheral blood T cells represent only 2·0–2·5% of the total T-cell population in the body.[24] Thus, detection of T-cell responses from the peripheral blood might not fully reflect the spectrum of T-cell immunity in the vaccinees. Since most participants in our cohort showed induction of antibodies against the wild-type virus, it is possible that SARS-CoV-2-specific T cells were elicited after vaccination but might not be acquired during sampling of peripheral blood. Additionally, in our study, blood was mostly collected 1 month after the vaccine dose, but T-cell responses from some vaccinees might peak at 7–21 days. Second, the participants in our booster cohort were mainly younger adults (ie, aged <60 years). Although we observed that CoronaVac induced weaker T-cell responses than did BNT162b2 in older adults (ie, aged ≥60 years) who received two doses of vaccine, whether a CoronaVac booster dose might have a similar effect on T-cell responses as BNT162b2 booster dose in older adults needs further investigation. Third, we used flow cytometry to quantitively measure the T-cell responses to the viral proteins of SARS-CoV-2 and to determine the T-cell phenotypes. Although this intracellular staining approach can identify the phenotype in each T cell, it is less sensitive than the ELIspot method to measure IFNγ secreted by the T cells. The small number of PBMCs that we collected from the participants prevented us from adopting ELIspot as an additional assay in this investigation. Finally, the relationship between the HLA subsets and the T-cell responses was not determined in our study.

In summary, we have shown that two doses of either CoronaVac or BNT162b2 vaccines elicit T-cell responses that are cross-reactive to omicron BA.1 but that BNT162b2 elicits better T-cell responses in older adults than does CoronaVac. A booster vaccine dose of either vaccine restores waning T-cell responses after the second vaccine dose. T-cell responses appear to better associate with observed outcomes from field studies of the vaccine effectiveness of CoronaVac vaccine against severe disease and death than do neutralising antibody responses.

Contributors

CKPM, MP, and DSH designed the study. CKPM, KY, H-LL, KCLi, KKPC, SSN, FWK, and DSH coordinated and carried out cohort recruitment. CKPM, CC, YS, KCLa, and KML performed the T-cell and antibody analyses. CKPM, CC, SZ, MP, and DSH analysed the data. CKPM, T-OC, and SZ carried out all statistical analyses. CKPM, MP, and DSH drafted the manuscript. All authors critically reviewed and commented on the manuscript. CKPM and MP accessed and verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Deidentified data relating to the study are available on reasonable request to the corresponding authors.

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