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Comparison of safety and immunogenicity in the elderly after receiving either Comirnaty or Spikevax monovalent XBB1.5 COVID-19 vaccine

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SUMMARY

Background: The emergence of SARS-CoV-2 variants necessitates ongoing evaluation of vaccine performance. This study evaluates and compares the safety and immunogenicity of the Comirnaty and Spikevax monovalent XBB.1.5 COVID-19 vaccines in an elderly population.

Methods: Altogether, 129 elderly individuals were recruited between 2 January and 3 February 2024, and received a booster dose of either Comirnaty (n=59) or Spikevax (n=70) monovalent XBB.1.5 COVID-19 vaccine. Blood samples were collected at before and one month after vaccination. Immunogenicity was assessed by measuring the percentage of $IFN\gamma^+CD4^+$ and $IFN\gamma^+CD8^+$ T cells, and neutralizing antibody titers (NT50) using a surrogate virus neutralization test (sVNT). Adverse reactions were recorded and analyzed.

Findings: Both vaccines significantly increased the percentage of $IFN\gamma^+CD8^+$ T cells against XBB.1.5 and wild-type (WT) SARS-CoV-2 at one-month post-vaccination. Spikevax induced a significantly higher percentages of $IFN\gamma^+CD8^+$ and $CD4^+$ T cells against XBB.1.5 than Comirnaty ($p < 0.001$). The proportion of participants showing a positive T cell response to XBB1.5 after vaccination was higher in the Spikevax group (64.3% CD8, 71.4% CD4) than in the Comirnaty group (42.4% CD8, 57.6% CD4). Spikevax also elicited higher NT50 levels against XBB1.5, JN.1 and the latest variant KP.2 than Comirnaty (XBB1.5: $p < 0.01$; KP.2: $p < 0.05$). Fever was more common in the Spikevax group (fever: p=0.006). However, all side effects were short-term and resolved on their own.

Interpretation: Both vaccines induce neutralizing antibody to XBB1.5, JN.1 and KP.2. Specifically, Spikevax induces higher cellular and humoral immune responses than Comirnaty in the elderly, but it is also associated with a higher incidence of fever. These findings can guide public health strategies for vaccinating the elderly population.

Introduction

The evolution of SARS-CoV-2 from the wild-type (WT) strain to the currently circulating JN.1 variant has necessitated continuous updates and adaptations in vaccine development.[1–3] The first generation of COVID-19 vaccines was based on the monovalent WT antigen.[4,5] A number of vaccines have been developed by applying the same WT antigen but through various delivery techniques.[6]

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Despite initial success, these vaccines have faced challenges due to the continuous viral mutations, which enable SARS-CoV-2 to escape antibody responses triggered by the antigen, even after several booster doses. [2,7–9]

To address this, modified vaccines have been developed using updated antigens. The bivalent WT/BA.4–5 vaccines represented a significant advancement, incorporating antigens from both the original WT and the BA.4–5 variants.[10] Recently, the latest generation of monovalent vaccines, using the spike protein of the XBB.1.5 variant as the antigen, has been introduced.[11] Pfizer (Comirnaty) and Moderna (Spikevax) have developed such vaccines, which have become available since September 2023. These two vaccines utilize the same XBB.1.5 antigen but are delivered using different lipid nanoparticle (LNP) formulations. Several reports showed that this XBB.1.5 monovalent vaccine could trigger protective level of antibody against its subvariants and others such as JN.1.[12–14]

However, while preventing infection in the general population has become less of a public health priority due to widespread prevalence of the virus and ability to escape herd immunity, protecting the elderly remains crucial as they face a higher risk of severe disease progression and mortality upon infection with new SARS-CoV-2 variants. In addition to antibody responses, T cell responses play a critical role in the immune defense against SARS-CoV-2.[15] T cells contribute to the control and clearance of the virus through various mechanisms, including the direct killing of infected cells by cytotoxic T lymphocytes (CTLs) and the support of antibody production by helper T cells.[16,17] T cell-mediated immunity is particularly important for long-term protection and reducing disease severity, as T cells can recognize and respond to viral epitopes that may be less susceptible to mutations.[18]

Despite the availability of the new XBB.1.5 vaccines, there has been no comparative study on their performance in terms of safety and immunogenicity, particularly the T-cell response triggered in the elderly population. This information is essential for governments to make informed decisions regarding vaccine selection and distribution. In Hong Kong, both vaccines are provided free of charge to the elderly.[19] This study aims to compare the safety and immunogenicity of the Comirnaty and Spikevax monovalent XBB.1.5 COVID-19 vaccines in an elderly cohort. By evaluating antibody and T-cell responses post-vaccination, we aim to provide critical insights into the performance of these vaccines. This study will ultimately guide public health strategies to protect the most vulnerable members of our society.

Methods

Cohort study design and participants

A total of 129 adults aged 60–91 years were recruited from the Chinese University of Hong Kong Medical Centre or Prince of Wales Hospital in Hong Kong SAR, China, between 2 January and 3 February 2024. Individuals who were immunocompromised, following the guidelines from the Centre for Health Protection, HKSAR Department of Health (www.chp.gov.hk/files/pdf/faqs_on_immunocompromised_persons.pdf, accessed 1 October 2024), who (1) had been on active immunosuppressive malignancy treatment over the past 12 months; (2) were recipients of solid organ or stem cell transplant and on immunosuppressive treatment; (3) had severe primary immunodeficiency or on chronic dialysis; (4) had advanced and untreated HIV; (5) had been on active immunosuppressive drugs, or in the past 6 months had received immunosuppressive chemo- or radiotherapy were excluded. Ten milliliters of heparinized blood was collected from each donor within one day before vaccination and at one month after receiving one dose of either Comirnaty (Pfizer) or Spikevax (Moderna) monovalent XBB.1.5 COVID-19 Vaccine.

Ethics statement

This study was approved by the Joint Chinese University of Hong Kong-New Territories East Cluster (Ref no: 2020.229) Clinical Research Ethics Committee.

Plasma and PBMC isolation

The blood samples were centrifuged at 3000 xg for 10 min at room temperature for plasma collection. Peripheral Blood Mononuclear Cells (PBMC) were isolated using Ficoll-Paque Plus medium (Cytiva) according to the manufacturer's protocol. The cells were then resuspended in the fetal bovine serum (FBS) containing 10% of dimethyl sulfoxide (DMSO). The plasma and PBMC were stored at −80 °C and liquid nitrogen respectively until use.

T-cell response by flow cytometry

Chemically synthesized peptide libraries used for T-cell stimulation were obtained from GL Biochem (Shanghai, China). Peptide pools used for the wild type strain was based on the amino acid sequence of the SARS-CoV-2/human/CHN/IQTC01/2020 (GenBank: MT123290.1). For XBB1.5 peptides, defining mutations were decided with reference from https://covariants.org/variants. Each peptide was synthesized as a 20-mer with ten overlapping amino acid residues. Peptide pools covering the entire spike (S) proteins were used. To test the T cell response, 10^5 to 10^6 cryopreserved PBMCs were recovered overnight. Cells were aliquoted into three equal portions into 96-well round bottom plates before being treated with 300 nM overlapping peptide pool or 0.5% DMSO in RPMI-1640 medium as negative control in a stimulation mix at 37 °C with 5% CO2 for 16–24 h. A further treatment with 1% of GolgiPlus and GolgiStop protein transport inhibitors (BD Biosciences) was carried out at 37 °C, 5% CO2 for 4–6 h. Staining was performed as described using Zombie NIR-APC/Cy7, anti-human CD3-PE/Dazzle 594, CD4-BV605, CD8-AlexaFluor700, CCR7-PerCP/Cy5.5, CD45RA-APC, CD19-BV510, NCAM1-BV510, CD14-BV510 and IFNγ-FITC antibodies (BioLegend, San Diego, CA, USA).[18] The experiment was further positively controlled by the inclusion of a cell activation cocktail from BD Biosciences. Fluorescence signals from stained cells were detected and quantified using an AttuneNxT flow cytometer (ThermoFisher Scientific). A representative gating strategy is now included as Supplementary Figure 1. Data were analyzed using FlowJo v.10. Only samples with 80% or higher cell viability were analyzed. Each data was subtracted with the respective DMSO background prior to further data analysis. Limit-of-detection of the machine was set at 0.001% after background subtraction.

16-plex surrogate virus neutralization test

A 16-plex RBD panel of biotinylated proteins was prepared. The RBDs included in this study are as follows: SARS-CoV-2 (Wuhan-hu-1, Alpha, Beta, Delta, DeltaPlus, Lambda, Gamma, BA.1, BA.2, BA.5, EG.5, XBB, XBB1.5, XBB1.16, JN.1) and SARS-CoV-1. Proteins were produced in-house in HEK293T cells. RBD proteins were enzymatically biotinylated and coated on MagPlex-Avidin microspheres (Luminex) at 5 μg RBD protein per 1 million beads for use in the sVNT assay. RBD-coated beads (25 μl, 600 per antigen) were pre-incubated with 25 μl heat inactivated serum at 1:100, for 15 min at 37 °C with agitation (200 rpm), followed by addition of 50 μl of PE-conjugated human ACE2 (2 mg/ml; GenScript) and incubated for an additional 15 min at 37 °C with agitation. After two washes with 1% BSA in 1 M NaCl PBS, the final readings were acquired using the MAGPIX system (Luminex, array reader v2.6.1, microplate platform v2.1.15, Bio-Plex manager software v6.2.0.175) following manufacturer's instruction. To assess surrogate virus neutralization, the

mean fluorescence intensity (Mean FI) of each RBD bead region was used to calculate: % inhibition = 100*(Mean FI of 30 negative pre-pandemic samples -individual FI)/Mean FI of 30 negative prepandemic samples. Percentage inhibition > =20% is typically considered as positive for SARS-CoV-2 neutralizing antibody, while percentage inhibition < 20 was considered as negative.

Surrogate virus neutralization test (sVNT)

SARS-CoV-2 surrogate virus neutralization test kits were obtained from GenScript, Inc., NJ, USA, and the tests were carried out according to the manufacturer's instructions. The test sera (10 μl) and positive and negative controls were serial diluted from 1:10 or 1:100000 and mixed with an equal volume of horseradish peroxidase (HRP) conjugated to XBB1.5, KP.2 or wild-type strain of SARS-CoV-2 spike receptor binding domain (RBD) (6 ng) and incubated for 30 min at 37 °C. A 100 μl volume of each mixture was added to each well on the microtiter plate coated with ACE-2 receptor. The plate was sealed and incubated at room temperature for 15 min at 37 °C. Plates were then washed with wash solution and tapped dry, and 100 μl of 3,3′,5,5′-tetramethylbenzidine (TMB) solution was added to each well and incubated in the dark at room temperature for 15 min. The reaction was stopped by addition of 50 μl of Stop Solution to each well and the absorbance read at 450 nm in an ELISA microplate reader. The assay validity was based on values representing optical density at 450 nm (OD450) for positive and negative results falling within the range of recommended values. On the basis of the assumption that the positive and negative controls gave the recommended OD450 values, percent inhibition of each serum was calculated as follows: percent inhibition (1 - sample OD value/negative-control OD value) x 100. Percent inhibition values of 20% or more are regarded as positive results.

Statistics

Categorical demographic data were shown as proportions. T-cell response and antibody levels were reported as medians (interquartile ranges). Categorical values were analyzed by Chi-square test or Fisher's exact test. Continuous values were analyzed by one-way ANOVA. Comparisons were determined by multiple comparisons with Bonferroni adjustment correcting for covariates (age, gender, COVID-19 infection history, days since last dose and number of previous SARS-CoV-2 vaccine doses). The significance of the results, both before and after adjustment, for each figure is presented in Supplementary Table 1. P values less than 0.05 were regarded as significant.

Results

More participants reported fever after received Spikevax than those who received Comirnaty monovalent XBB.1.5 vaccine

We recruited a total of 129 individuals who were aged 60–91 and were planning to receive one dose of either the Spikevax or Comirnaty monovalent XBB.1.5 vaccine between 2 January and 3 February 2024. Of these, 70 participants received the Spikevax vaccine and 59 received the Comirnaty vaccine as a booster. The mean (± SD) age of the two groups was 71.0 ± 5.1 years (Spikevax) and 70.6 ± 5.5 years (Comirnaty). There was no significant difference in age and gender between the two groups (age: p=0.653; gender: p=0.076). Other demographic details, such as comorbidities and vaccine history, including COVID-19 and others, were also compared (Table 1, Supplementary Table 2). Samples from all individuals collected from each time point were tested by ELISA against the ORF8 to determine their COVID-19 infection status (Table 1, Supplementary Figure 2). Local and systemic adverse reactions were assessed and compared between the two groups (Table 2). More participants in the Comirnaty group reported no adverse events at the injection site (p=0.053) or systemic reactions (p < 0.001) than those receiving Spikevax. Particularly, more participants in the Spikevax group reported fever (p=0.006) compared to the Comirnaty group. However, all these side effects were short-term and resolved on their own.

Table 1
Demographic Characteristics of the Participants.

	Spikevax (n=70)	Comirnaty (n=59)	P-value
Age, years [Mean ± SD, Median]	71.0 ± 5.1, 70.5	70.6 ± 5.5, 69.0	0.653
Gender			0.076
Female	35 (50.0%)	20 (33.9%)	
Male	35 (50.0%)	39 (66.1%)	
Smoking	2 (2.9%)	4 (6.8%)	0.407
Alcohol Consumption	29 (42.0%)	21 (35.6%)	0.587
Regular exercise	45 (65.2%)	43 (72.9%)	0.345
Comorbidities			
Cardiovascular diseases	9 (12.9%)	8 (13.6%)	0.999
Diabetes mellitus	6 (8.6%)	10 (17.0%)	0.185
Chronic respiratory disease	1 (1.4%)	2 (3.4%)	0.592
Vaccine History			
Influenza	8 (11.4%)	3 (5.1%)	0.226
Hepatitis A/B	9 (12.9%)	14 (24.7%)	0.165
Mumps	1 (1.4%)	0 (0.0%)	0.999
Pneumococcal conjugate vaccine	29 (41.4%)	24 (40.7%)	0.999
Rabies	1 (1.4%)	1 (1.7%)	0.999
Typhoid	2 (2.9%)	2 (3.4%)	0.999
Days from the last dose [Mean ± SD, Median]	474.4 ± 167.8, 412.5	427.9 ± 142.7, 382.0	0.079
COVID-19 infected history	39 (55.7%)	33 (55.9%)	0.999
Number of COVID-19 vaccine doses received before this study [Median, IQR]	4, 3–5	4, 4–5	0.315

Continuous variables were compared between the two study groups using t-test. Categorical variables were compared between the two study groups using Chi-square test. If the assumption of the Chi-square test was violated, exact test was used instead. SD: Standard deviation. IQR: Interquartile range

Table 2
Adverse events of the Participants.

	Spikevax (n=70)	Comirnaty (n=59)	P-value
Local reactions			
Pain	34 (48.6%)	25 (42.4%)	0.595
Erythema	2 (2.9%)	0 (0.0%)	0.500
Pruritus	7 (10.0%)	2 (3.4%)	0.179
Swelling	11 (15.7%)	6 (10.2%)	0.438
None of the above	15 (21.4%)	22 (37.3%)	0.053
Systemic reactions			
Fever	11 (15.7%)	1 (1.7%)	0.006
Fatigue	18 (25.7%)	7 (11.9%)	0.072
Diarrhea	0 (0.0%)	0 (0.0%)	-
Muscle pain	9 (12.9%)	5 (8.5%)	0.572
Nausea	0 (0.0%)	0 (0.0%)	-
Headache	7 (10.0%)	2 (3.4%)	0.179
Cough	2 (2.9%)	0 (0.0%)	0.500
Anorexia	3 (4.3%)	0 (0.0%)	0.250
Hypoesthesia	1 (1.4%)	0 (0.0%)	0.999
Dizziness	2 (2.9%)	2 (3.4%)	0.999
Abdominal distention	0 (0.0%)	0 (0.0%)	-
Peripheral edema	1 (1.4%)	0 (0.0%)	0.999
Abdominal pain	0 (0.0%)	0 (0.0%)	-
Vomiting	0 (0.0%)	0 (0.0%)	-
Drowsiness	6 (8.6%)	2 (3.4%)	0.288
Joint pain	4 (5.7%)	3 (5.1%)	0.999
Rash	2 (2.9%)	0 (0.0%)	0.500
Palpitation	0 (0.0%)	1 (1.7%)	0.457
None of the above	36 (51.4%)	47 (79.7%)	< 0.001

Categorical variables were compared between the two study groups using Chi-square test. If the assumption of the Chi-square test was violated, exact test was used instead.

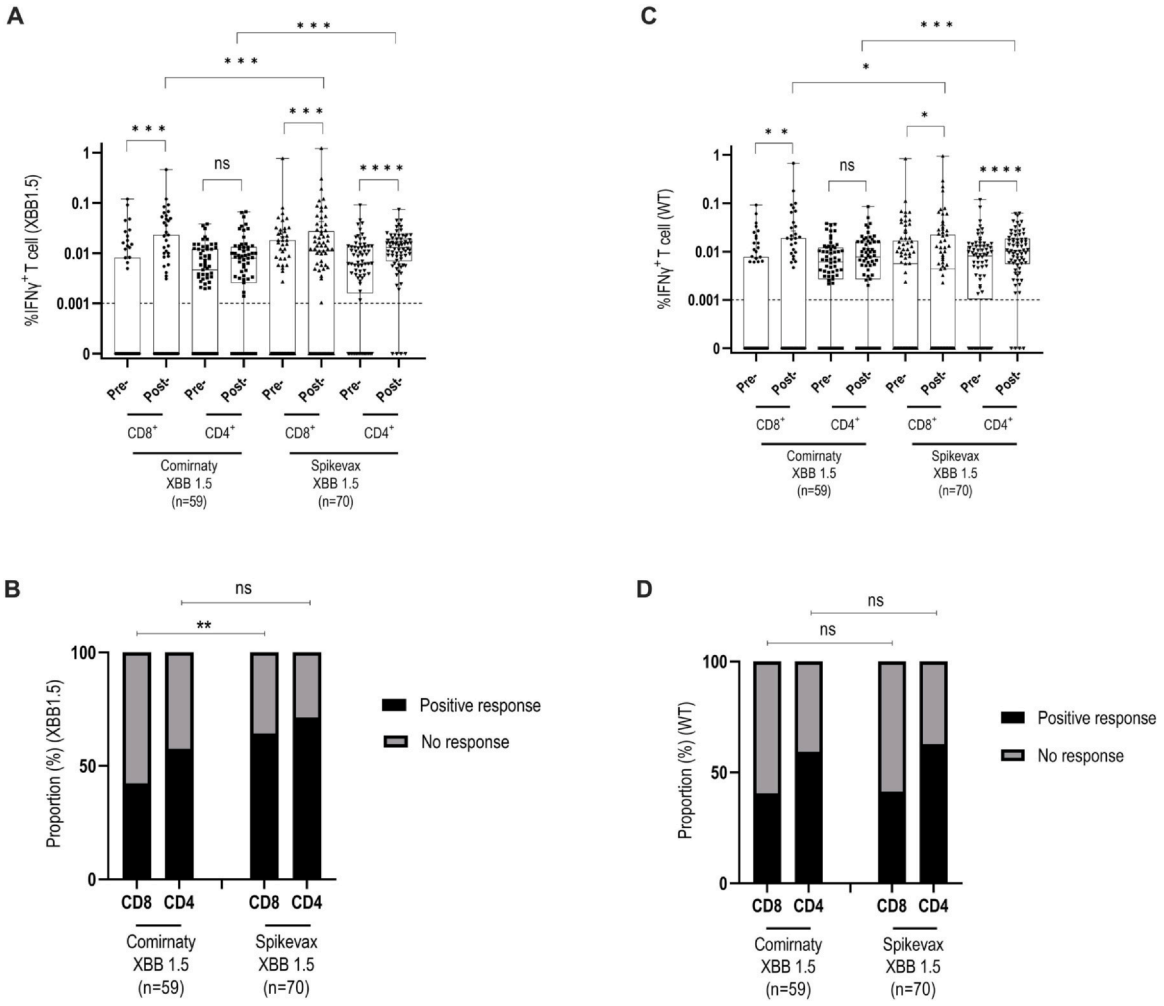

Fig. 1. T cell response against SARS-CoV-2 in elderly individuals who received either the Comirnaty or Spikevax monovalent XBB 1.5 COVID-19 vaccine. PBMCs from elderly individuals who received a booster dose of either Comirnaty (n=59) or Spikevax (n=70) monovalent XBB 1.5 COVID-19 vaccine were stimulated with pooled spike peptides. The percentage of IFNγ$^+$CD8$^+$ and IFNγ$^+$CD4$^+$ T cells against XBB 1.5 (A) or WT (C) was measured by flow cytometry. The dotted line represents the limit of detection following background (DMSO) subtraction. (B and D) The proportion of participants that showed responsiveness to the vaccine. A positive response to the vaccination from a donor is defined as the percentage of reactive T cells at one month after vaccination being higher than the corresponding result before vaccination from the same donor. In A and C, data are presented as box and whiskers, with the error bars representing the minimum and maximum values. Data within the same vaccine group were compared using the pairwise Wilcoxon rank sum test. The Mann-Whitney U test was used to compare different subgroups. NS represents $p > 0.05$ and is defined as statistically non-significant. P values were generated by a multiple linear regression model adjusted for age, gender, and other covariates (see methods). *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$, ****: $p < 0.0001$.

Spikevax induced higher T cell response to the XBB.1.5 spike antigen than Comirnaty

Blood samples from each donor were collected before (within one day before vaccination) and one month after receiving the booster. We determined the percentage of IFNγ$^+$CD4$^+$ or IFNγ$^+$CD8$^+$ T cells upon treating the PBMCs with either WT or XBB.1.5 spike peptide pools. Our results show that Spikevax significantly increased both CD4$^+$ and CD8$^+$ T cell responses to the WT and XBB.1.5 spike peptides when comparing pre- and post-vaccination (Fig. 1A and C). However, while Comirnaty showed an increase in CD8$^+$ T cell response to the spike of both viruses, no significant upregulation of CD4$^+$ T cell response was found. The percentage of IFNγ$^+$CD4$^+$ T cells responding to XBB.1.5 in participants who had received Spikevax was significantly higher than those who had received Comirnaty post-vaccination ($p < 0.001$). Considering the proportion of participants who showed a positive T cell response to XBB.1.5 after vaccination (an increase in IFNγ$^+$CD4$^+$ or CD8$^+$ T cells comparing pre- and post-vaccination), 64.3% (CD8) and 71.4% (CD4) of the Spikevax group showed positive T cell response, compared to 42.4% (CD8) and 57.6% (CD4) in the Comirnaty group (Fig. 1B). A significantly higher percentage of CD8 responders to XBB.1.5 was found in the Spikevax group than the Comirnaty group ($p < 0.01$). No significant difference was found in the percentages of CD4 responders to XBB.1.5 or CD4/8 responders to WT between the two groups (Fig. 1B and D).

We also compared the memory phenotype of WT- and XBB- reactive T cells. All groups showed predominantly effector memory phenotype while in the Spikevax group, vaccination led to a significant shift of XBB-reactive CD8$^+$ TEM to TEMRA T cell phenotype (Supplementary Figure 3).

Spikevax triggered higher neutralizing antibody titer to the latest circulating variants than Comirnaty

The neutralization titer 50 (NT50) to either XBB.1.5, KP.2 or WT in the plasma samples was serial diluted and determined by a surrogate neutralization test (sVNT) using the receptor-binding domains of the respective strains. Both vaccines significantly induced the NT50 to XBB.1.5, KP.2 and WT when comparing pre- and post-vaccination levels ($p < 0.0001$ for all pre- versus post-vaccination comparisons) (Fig. 2A-C, Supplementary Figure 4A). However, the levels of NT50 to all tested viruses were significantly higher in the Spikevax

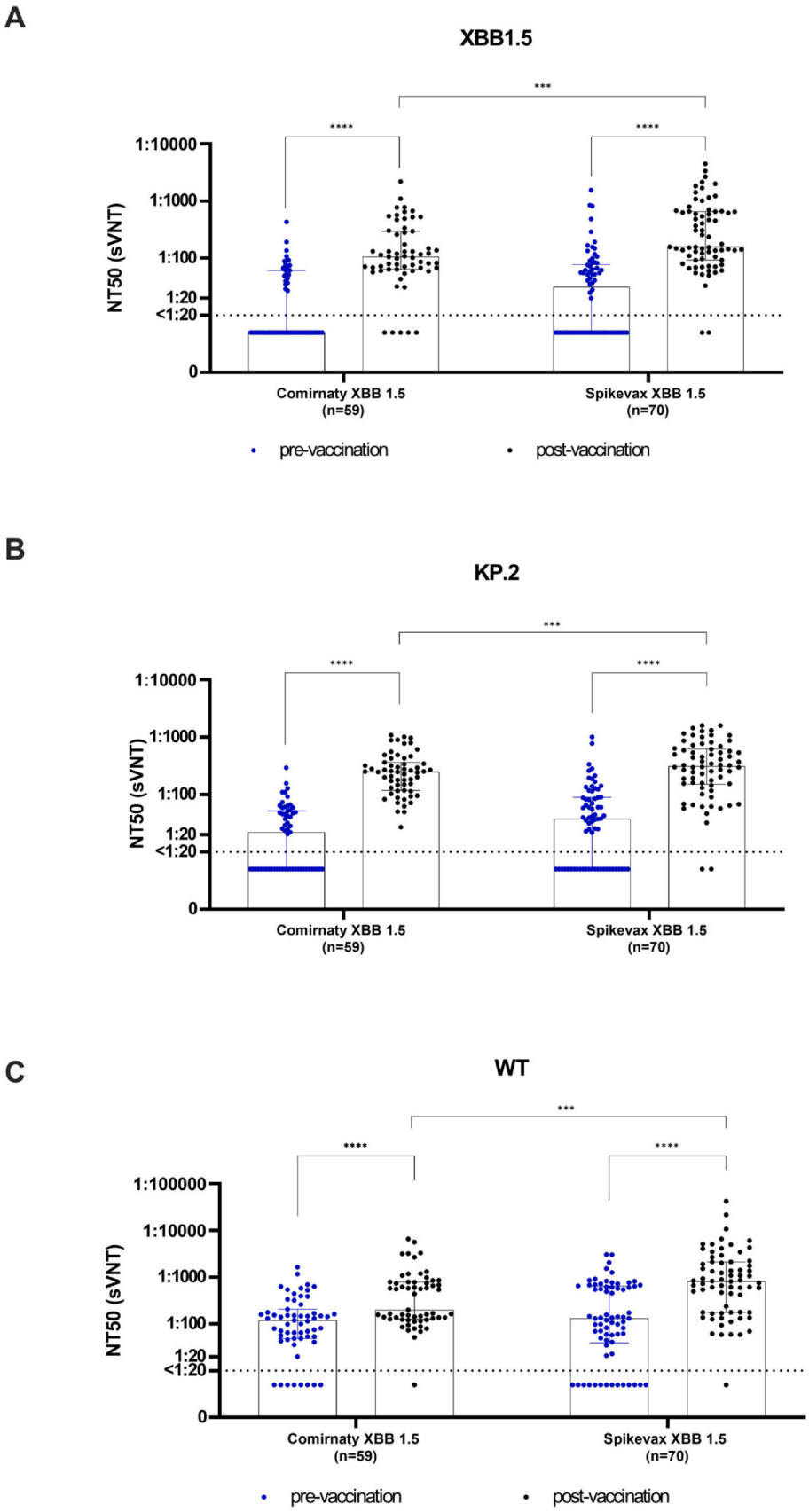

Fig. 2. Neutralization titer 50 of the plasma against SARS-CoV-2 in elderly individuals who received either the Comirnaty or Spikevax monovalent XBB 1.5 COVID-19 vaccine. Plasma collected from before and one month after receiving a booster dose of either Comirnaty (n=59) or Spikevax (n=70) monovalent XBB 1.5 COVID-19 vaccine was serially diluted and tested with a surrogate neutralization test (sVNT) using the receptor-binding domain of either XBB1.5 or WT. The neutralization titer 50 (NT50) of each sample was calculated using Prism 8.0. Data within the same vaccine group were compared using the pairwise Wilcoxon rank sum test. The Mann-Whitney U test was used to compare different subgroups. NS represents $p > 0.05$ and is defined as statistically non-significant. P values were generated by a multiple linear regression model adjusted for age, gender, and other covariates (see methods). ***: $p < 0.001$, ****: $p < 0.0001$.

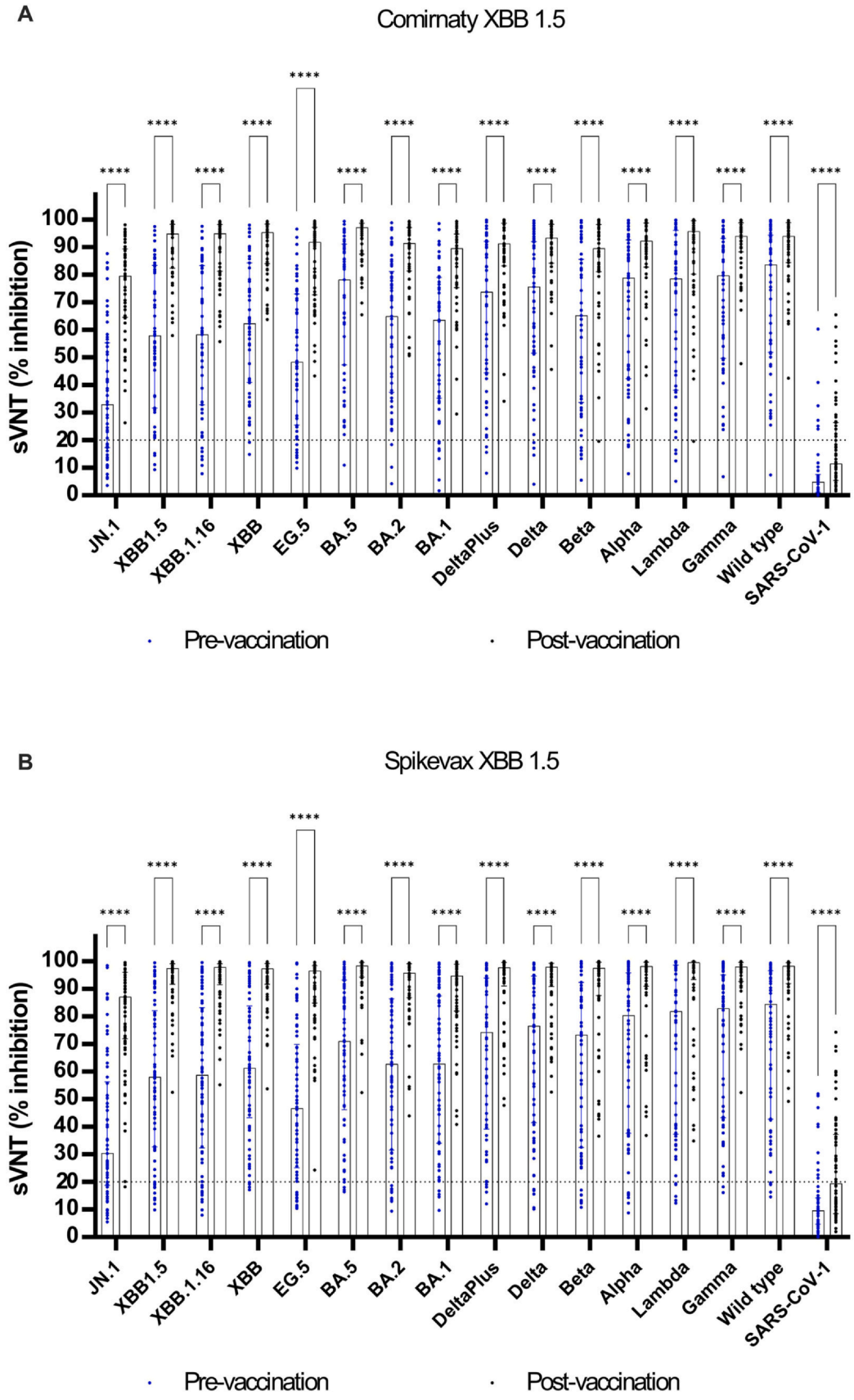

Fig. 3. Both Comirnaty and Spikevax monovalent XBB 1.5 COVID-19 vaccines induce neutralizing antibodies against different SARS-CoV-2 variants. Plasma collected from elderly individuals before and one month after receiving a booster dose of either Comirnaty (n=59) or Spikevax (n=70) monovalent XBB 1.5 COVID-19 vaccine was diluted 1:100 and tested using a 16-plex surrogate virus neutralization test (sVNT) with the receptor-binding domain (RBD) of various SARS-CoV-2 variants (JN.1, XBB1.5, XBB1.16, XBB, EG.5, BA.2, BA.1, DeltaPlus, Delta, Beta, Alpha, Lambda, Gamma, WT) and SARS-CoV-1. The dashed line at 20% indicates the detection limit of the sVNT. Bars represent the mean values, and error bars represent the standard deviation. Data within the same vaccine group were compared using the pairwise Wilcoxon rank sum test. NS represents $p > 0.05$ and is defined as statistically non-significant. ****: $p < 0.0001$.

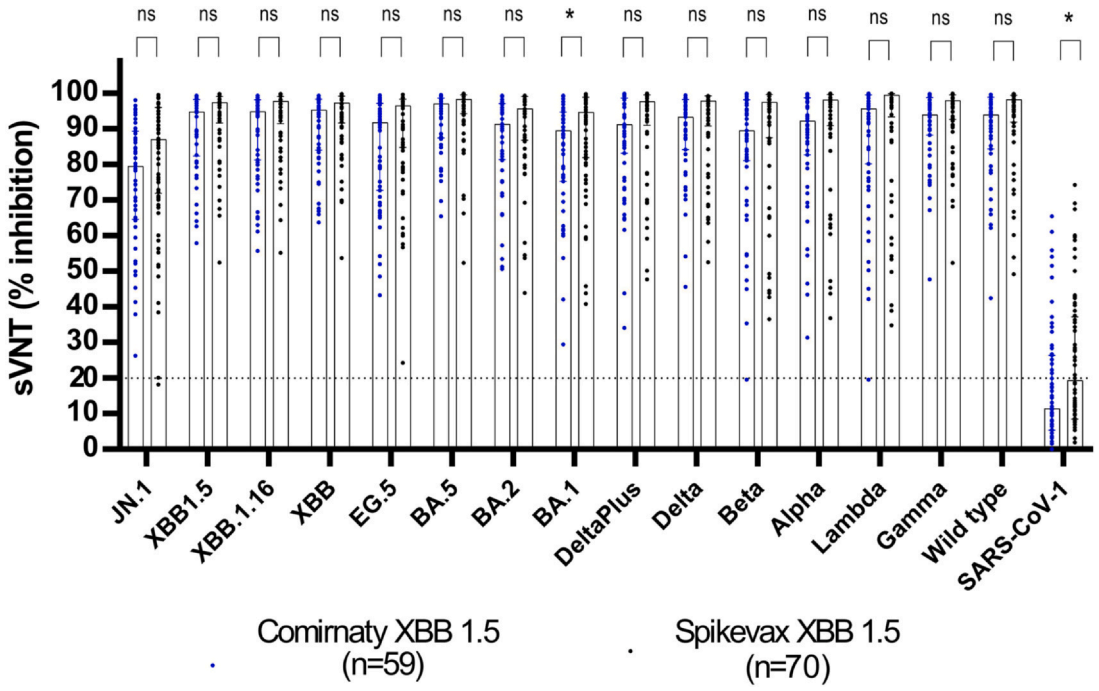

Fig. 4. Comparing neutralizing titers of plasma against different SARS-CoV-2 variants in elderly individuals who received either the Comirnaty or Spikevax monovalent XBB 1.5 COVID-19 vaccine. The percentage of inhibition from 1:100 diluted plasma collected from elderly individuals one month after receiving a booster dose of either Comirnaty (n=59) or Spikevax (n=75) monovalent XBB 1.5 COVID-19 vaccine was compared using a 16-plex surrogate virus neutralization test (sVNT) with the receptor-binding domain (RBD) of various SARS-CoV-2 variants (JN.1, XBB1.5, XBB1.16, XBB, EG.5, BA.2, BA.1, DeltaPlus, Delta, Beta, Alpha, Lambda, Gamma, WT) and SARS-CoV-1. The dashed line at 20% indicates the detection limit of the sVNT. Bars represent the mean values, and error bars represent the standard deviation. The Mann-Whitney U test was used to compare data between different subgroups. NS represents $p > 0.05$ and is defined as statistically non-significant. P values were generated by a multiple linear regression model adjusted for age, gender, and other covariates (see methods). *: $p < 0.05$.

group than those who had received Comirnaty (XBB.1.5: $p < 0.001$; KP.2: $p < 0.001$; WT: $p < 0.001$). Using the 16-plex bead-based sVNT, we compared the levels of neutralizing antibody titers against different SARS-CoV-2 strains, including JN.1, XBB, XBB.1.16, XBB.1.5, EG.5, BA.5, BA.2, BA.1, DeltaPlus, Delta, Beta, Alpha, Lambda, Gamma, the ancestral WT strain, and SARS-CoV-1. At 1:100 dilution, both vaccines showed significant induction of neutralizing titers to all tested strains when comparing pre- and post-vaccination levels ($p < 0.0001$ for all comparisons) (Fig. 3A and B). Both vaccines showed comparable levels of inhibition to different variants post-vaccination, except for slightly higher inhibition to BA.1 and SARS-CoV-1 in the Spikevax group ($p < 0.05$ for both comparisons) (Fig. 4).

Discussion

In this study, we compared the safety and immunogenicity of the two most updated Moderna (Spikevax) and Pfizer-BioNTech (Comirnaty) monovalent XBB.1.5 mRNA COVID-19 vaccines, with similar mechanisms of action but different in their specific formulations and content. Both vaccines use messenger RNA (mRNA) to encode the same spike protein of the new variant, which prompts the immune system to generate a protective response. However, the Moderna vaccine contains a higher dose of mRNA, with 50 micrograms for their booster doses, compared to Pfizer's 30 micrograms per dose. Additionally, the lipid nanoparticle (LNP) formulations, which are used to encapsulate and deliver the mRNA, vary between the two vaccines. These LNPs not only play a crucial role in the stability and delivery efficiency of the mRNA, but potentially influence the immune response and side effect profile.[20–22] Importantly, Moderna's SM-102 was found to deliver mRNA more efficiently and induce higher antibody production in mice than Pfizer's ALC-0315.[23] This is in line with our observation that Spikevax induced moderately higher neutralizing antibody titers against WT, XBB.1.5 and KP.2 strains than Comirnaty (Fig. 2). Despite so, data has shown that both vaccines have high efficacy in preventing COVID-19, particularly severe disease, across diverse populations.[24–27] Neutralizing antibody titers were comparably high for both vaccines against different SARS-CoV-2 strains tested too (Figs. 3–4).

All our participants were over 60 years old and still at risk of developing severe disease and death after receiving a booster over time.[28] The similar demographic background of the two groups provides us with a head-to-head comparison of the performance of the vaccines in the elderly. Based on the self-reported questionnaire, there were more participants in the Spikevax group who had experienced fever after receiving the XBB.1.5 booster. Higher frequencies of side effects were also reported in the previous version of Moderna vaccine.[27,29] It may be due to either the higher dosage of mRNA or the choice of LNP used in Spikevax.

Previous studies have highlighted the immunogenicity of the Spikevax XBB vaccine for its capability to induce cross-neutralizing antibodies in adults and in young children, despite occurrence of mild local and systemic adverse effects.[30] In adults, more prevalent non-severe adverse effects have been reported in Spikevax than Comirnaty WT vaccine recipients, while an association was observed between incidence of adverse effect and post-3 dose vaccination antibody titers.[31] Our work expanded upon these studies to evaluate the XBB vaccines in a comparative manner using laboratory approaches and had similar findings in a cohort with mainly elderly people. While more work remains to be done on other age groups, events of side effects may lead to vaccine hesitancy among the elderly, and the difference between the two vaccine types should be taken into account when formulating mRNA vaccines for children.

Both the Comirnaty and Spikevax XBB.1.5 COVID-19 vaccines significantly increased the percentages of $IFN\gamma^+$ $CD8^+$ T cells to

XBB.1.5 at one-month post-vaccination in the elderly participants. However, Spikevax elicited a significant increase in the XBB.1.5 reactive-IFNγ^+ CD4$^+$ T cells, whereas Comirnaty did not show a significant change in CD4$^+$ T cell response. Moreover, the proportion of positive responders was higher in the CD8$^+$ T cell population in Spikevax when compared to Comirnaty. These differences suggest that Spikevax not only enhances the cytotoxic T-cell response but also supports a stronger helper T-cell response, which is crucial for coordinating the overall immune response and providing long-term immunity. Importantly, we found an induction of neutralizing antibody against the new FLiRT variants KP.2 after received either one of the two XBB vaccines. Although Spikevax induced higher level of antibodies against the KP.2 as measured by the neutralization titer 50 in sVNT, both vaccines showed comparable levels of neutralization to the other variants such as JN.1 when we measured their neutralizing titer at 1:100 dilution. Taken together, these findings highlight the superior capacity of Spikevax to activate T cell- and humoral-mediated immunity in the elderly, which is critical for reducing disease severity and improving clinical outcomes in this vulnerable population.

A limitation of the study is that sVNT was mainly used instead of plaque reduction neutralization assay (PRNT) which is considered as a gold standard to evaluate the level of neutralizing antibody. However, it has been demonstrated that the results from sVNT are highly comparable to the PRNT while BSL3 facility is not required.[32] Besides, it has been shown that both T cell and B cell responses upon SARS-CoV-2 vaccination may vary among different ethnic groups. While our study only included East Asians in the cohort, further studies are necessary to confirm safety and immunogenicity of the XBB vaccines in other ethnic groups. [33] Finally, although the experience of SARS-CoV-2 infection was determined using our ORF8 ELISA, the timing of their infection and its potential influence on the outcome of the XBB vaccine remains uncertain. However, we have compared the antibody levels to WT, XBB1.5 and KP.2 between those with positive and negative responses to ORF8 (Supplementary Figure 4B). There is no significant difference between the two groups in each vaccine cohort (Spikevax or Comirnaty) suggesting that the previous infection does not influence the immunogenicity of monovalent XBB1.5 COVID-19 vaccine. Nevertheless, the majority of our cohort showed no infection during the study period, as only one participant exhibited a dramatic increase in ORF8 ELISA results, indicating the experience of SARS-CoV-2 infection (Supplementary Figure 2).

Due to the expected evolution of the virus further from JN.1, the WHO has advised the use of a monovalent JN.1 lineage as the antigen in future formulations of COVID-19 vaccines. While more research is needed on the protection efficiency of JN.1 antigen to antigenic variants, vaccination programmes should continue to apply any of the WHO emergency-use listed or prequalified COVID-19 vaccines and vaccination should not be delayed in anticipation of access to vaccines with an updated composition.[1] In conclusion, our results have shown that the Spikevax XBB.1.5 monovalent COVID-19 vaccine induces higher cellular and humoral immune response than the Comirnaty vaccine. However, vaccinees of Spikevax may experience more short-term side effects after immunization.

Author contributions

C.K.P.M and D.S.H conceived the research idea and designed the study. K.Y., K.C.L. and K.K.P.C coordinated and carried out cohort recruitment. Y.S.T., K.C.C. and C.K.P.M. analyzed the data. Y.S.T., C.W.T., C.C. and Y.S. performed the experiments. Y.S.T., C.K.P.M. and D.S.H. wrote the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2024.106374.

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