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Yap J, Kayda I, Asamoah-Boaheng M, Haig S, Kirkham T, *et al*. SciScore reports for: The relationship between the number of COVID-19 vaccines and infection with Omicron ACE2 inhibition at 18-months post initial vaccination in an adult cohort of Canadian paramedics. *Access Microbiology*. 2023. https://doi.org/10.1099/acmi.0.000725.v2.1

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Document Identifier: **2338_655350e5f0d742.01226591**

SciScore Report

Below you will find your SciScore report containing three tables. Your score is calculated based on adherence to scientific rigor criteria (Table 1) and identification of key biological resources (Table 2). Table 3 contains statistical tests and oligonucleotides but is not scored. If SciScore makes any mistakes, please contact us to help us learn and improve.

Table 1: Rigor Adherence Table

Ethics
IRB: The CORSIP study began enrolling participants in January 2021, after receiving research ethics board approvals from the University of British Columbia (H20-03620) and the University of Toronto (40435).
Consent: Participants provided electronic consent upon enrolment and completed questionnaires regarding health and sociodemographic information, COVID-19 vaccination history and status, and history of SARS-CoV-2 infections confirmed by positive polymerase chain reaction (PCR) test and/or rapid antigen test (RAT) results.
Inclusion and Exclusion Criteria
Participant and Sample SelectionAmong CORSIP participants enrolled between January 2021 and November 2022, we included participants who had received two or three doses of any Health Canada approved mRNA COVID-19 vaccine (BNT162b2 and mRNA-1273).
Attrition
not detected.
Sex as a biological variable
not detected.
Subject Demographics
Age: not detected.
Weight: not detected.
Randomization
not detected.
Blinding
not detected.
Power Analysis
not detected.

Replication
not required.

Table 2: Key Resources Table

Your Sentences	REAGENT or RESOURCE	SOURCE	IDENTIFIER
Software and Algorithms			
Statistical AnalysesAnalyses were performed using GraphPad Prism Version 9.5.0 (GraphPad Software, San Diego, CA).	GraphPad		Suggestion: (GraphPad Prism, RRID:SCR_002798)(link)

Other Entities Detected

Your Sentences	Recognized Entity
Statistical Tests	
The median percent inhibition between two groups was compared using a non-parametric Mann-Whitney U test.	Mann-Whitney U test

SciScore is an automated tool that is designed to assist expert reviewers by finding and presenting formulaic information scattered throughout a paper in a standard, easy to digest format. ***SciScore is not a substitute for expert review.*** SciScore also checks for the presence and correctness of several unique identifiers, including RRIDs (research resource identifiers) in the manuscript, detects sentences that appear to be missing RRIDs, and can even suggest RRIDs under certain circumstances. **All RRID suggestions should be verified;** only the author can know whether the suggestions are correct.

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Materials Design Analysis Reporting (MDAR) Checklist for Authors

The MDAR framework establishes a minimum set of requirements in transparent reporting applicable to studies in the life sciences (see Statement of Task: doi:10.31222/osf.oio/9sm4x.). The MDAR checklist is a tool for authors, editors and others seeking to adopt the MDAR framework for transparent reporting in manuscripts and other outputs. Please refer to the MDAR Elaboration Document for additional context for the MDAR framework.

Materials

Antibodies	Yes (indicate where provided: page no/section/legend)	n/a
For commercial reagents, provide supplier name, catalogue number and RRID, if available	No antibodes detected. Please add identifiers for all resources where possible	

Cell Materials	Yes (indicate where provided: page no/section/legend)	n/a
Cell lines: Provide species information, strain. Provide accession number in repository OR supplier name, catalog number, clone number, OR RRID	No cell lines detected Please add identifiers for all resources where possible	
Primary cultures: Provide species, strain, sex of origin, genetic modification status.	Not currently checked by SciScore	

Experimental Animals	Yes (indicate where provided: page no/section/legend)	n/a
Laboratory animals: Provide species, strain, sex, age, genetic modification status. Provide accession number in repository OR supplier name, catalog number, clone number, OR RRID	No organisms detected Please add identifiers for all resources where possible	
Animal observed in or captured from the field: Provide species, sex and age where possible	Not currently checked by SciScore	
Model organisms: Provide Accession number in repository (where relevant) OR RRID	See laboratory animals section for information.	

Plants and microbes	Yes (indicate where provided: page no/section/legend)	n/a
Plants: provide species and strain, unique accession number if available, and source (including location for collected wild specimens)	Not currently checked by SciScore	
Microbes: provide species and strain, unique accession number if available, and source	Not currently checked by SciScore	

Human research participants	Yes (indicate where provided: page no/section/legend)	n/a
Identify authority granting ethics approval (IRB or equivalent committee(s), provide reference number for approval.	The CORSIP study began enrolling participants in January 2021, after receiving research ethics board approvals from the University of British Columbia (H20-03620) and the University of Toronto (40435).	
Provide statement confirming informed consent obtained from study participants.	Participants provided electronic consent upon enrolment and completed questionnaires regarding health and sociodemographic information, COVID-19 vaccination history and status, and history of SARS-CoV-2 infections confirmed by positive polymerase chain reaction (PCR) test and/or rapid antigen test (RAT) results.	
Report on age and sex for all study participants.	**Age:**not detected. **Sex:**not detected.	

Design

Study protocol	Yes (indicate where provided: page no/section/legend)	n/a
For clinical trials, provide the trial registration number OR cite DOI in manuscript.	Not detected.	

Laboratory protocol	Yes (indicate where provided: page no/section/legend)	n/a
Provide DOI or other citation details if detailed step-by-step protocols are available.	Not detected.	

Experimental study design (statistics details)	Yes (indicate where provided: page no/section/legend)	n/a
State whether and how the following have been done, or if they were not carried out		
Sample size determination	not detected.	
Randomization	not detected.	
Blinding	not detected.	
inclusion/exclusion criteria	Participant and Sample SelectionAmong CORSIP participants enrolled between January 2021 and November 2022, we included participants who had received two or three doses of any Health Canada approved mRNA COVID-19 vaccine (BNT162b2 and mRNA-1273).	

Sample definition and in-laboratory replication	Yes (indicate where provided: page no/section/legend)	n/a
State number of times the experiment was replicated in laboratory	Not detected.	
Define whether data describe technical or biological replicates	Not detected.	

Ethics	Yes (indicate where provided: page no/section/legend)	n/a
Studies involving human participants: State details of authority granting ethics approval (IRB or equivalent committee(s), provide reference number for approval.	The CORSIP study began enrolling participants in January 2021, after receiving research ethics board approvals from the University of British Columbia (H20-03620) and the University of Toronto (40435).	
Studies involving experimental animals: State details of authority granting ethics approval (IRB or equivalent committee(s), provide reference number for approval.	Not detected.	
Studies involving specimen and field samples: State if relevant permits obtained, provide details of authority approving study; if none were required, explain why.	Not detected.	

Dual Use Research of Concern (DURC)	Yes (indicate where provided: page no/section/legend)	n/a
If study is subject to dual use research of concern, state the authority granting approval and reference number for the regulatory approval	Not currently checked by SciScore	

Analysis

Attrition	Yes (indicate where provided: page no/section/legend)	n/a
State if sample or data point from the analysis is excluded, and whether the criteria for exclusion were determined and specified in advance.	not detected.	

Statistics	Yes (indicate where provided: page no/section/legend)	n/a
Describe statistical tests used and justify choice of tests.	The median percent inhibition between two groups was compared using a non-parametric Mann-Whitney U test.	

Data availability	Yes (indicate where provided: page no/section/legend)	n/a
State whether newly created datasets are available, including protocols for access or restriction on access.	Not detected.	
If data are publicly available, provide accession number in repository or DOI or URL.	Not detected.	
If publicly available data are reused, provide accession number in repository or DOI or URL, where possible.	Not detected.	

Code availability	Yes (indicate where provided: page no/section/legend)	n/a
For all newly generated code and software essential for replicating the main findings of the study:		
State whether the code or software is available.	Not detected.	
If code is publicly available, provide accession number in repository, or DOI or URL.	Not detected.	

Analysis

Adherence to community standards	Yes (indicate where provided: page no/section/legend)	n/a
MDAR framework recommends adoption of discipline-specific guidelines, established and endorsed through community initiatives. Journals have their own policy about requiring specific guidelines and recommendations to complement MDAR.		
State if relevant guidelines (eg., ICMJE, MIBBI, ARRIVE) have been followed, and whether a checklist (eg., CONSORT, PRISMA, ARRIVE) is provided with the manuscript.	Not currently checked by SciScore	

ACMI-D-23-00192.pdf

By Brian Grunau

WORD COUNT	7299	TIME SUBMITTED	14-NOV-2023 10:49AM
		PAPER ID	104234591

Access Microbiology

The relationship between the number of COVID-19 vaccines and infection with Omicron ACE2 inhibition at 18-months post initial vaccination in an adult cohort of Canadian paramedics

--Manuscript Draft--

Reviewers' comments and responses to custom questions:

Please rate the manuscript for methodological rigour
Reviewer 1: Poor

Please rate the quality of the presentation and structure of the manuscript
Reviewer 1: Poor

To what extent are the conclusions supported by the data?
Reviewer 1: Partially support

Do you have any concerns of possible image manipulation, plagiarism or any other unethical practices?
Reviewer 1: No:

If this manuscript involves human and/or animal work, have the subjects been treated in an ethical manner and the authors complied with the appropriate guidelines?
Reviewer 1: Yes:

Reviewer 1 Comments to Author: This article focused on ACE2 percent inhibition against omicron BA4/5 and wilt-type Wuhan Hu-1 after two or three Wuhan Hu-1 platform mRNA vaccinations. The authors found that additional vaccines did not improve ACE2 inhibition to BA4/5, but post-infection. However, it is not clear where the novelty of this study lies, as many previous studies have demonstrated that multiple doses of vaccines corresponding to the origin strain do not increase neutralizing antibody activity against the Omicron strain. The sample size was not large, and the omicron strain was only BA4.5, so there was little information on other mutant strains (at least alpha, delta, BA1, or BA2 should be considered). The study population is also limited to paramedics (probably healthy young people). Furthermore, I think that there is a lack of data regarding judgments based solely on ACE2 percent inhibition rate as a surrogate marker, rather than on neutralizing antibodies or clinical efficacy. Data is lacking if the primary outcome is the ACE2 percent inhibition rate (for example, no vaccine, one dose, four doses, or subjects of various ages and backgrounds).

I think that significant revisions are necessary for publication in a professional journal.

Thank you for your comments. Although other studies have demonstrated that increasing the number of original mRNA vaccine doses does not improve neutralizing antibody levels against earlier strains of Omicron, our study's novelty comes from the fact that we assessed neutralizing antibody activity against a more recent (and therefore more divergent) Omicron strain (BA4/5) and that we are looking at a unique and important the study population of working age healthcare workers who are a specific priority group for COVID-19 vaccination campaigns. Further, our findings help contribute to and corroborate prior studies.

Our study design relied on self-reported data which has its own limitations discussed in the manuscript (Line 256-262). Unfortunately, we did not have the resources or was it our objective to study other mutant strains of SARS-CoV-2. We focused on BA.4/5 as it was the predominant variant at the time of this study's conception. It was not feasible to include other groups of interest such as no vaccine, one dose, or four doses due to the lack of data for our primary outcome of 18 months post-initial Wuhan Hu-1 platform mRNA vaccines. During our study timeframe, most Canadian paramedics followed public health recommendations of vaccine dosing intervals: 2 doses of the original mRNA vaccine in the first half of 2021, 1 booster dose of the original mRNA vaccine end of 2021 or early 2022, and lastly bivalent boosters in the Fall or Winter of 2022. Thus, it would be unreasonable to include individuals who received a fourth dose due to the interval between their blood collection and a more potent effect on immune response, especially for individuals who received a bivalent vaccine.

We agree that ACE inhibition is not as clinically relevant as clinical outcomes, and have acknowledged this in the limitations section. However, we believe ACE2 percent inhibition was an appropriate surrogate marker for immunity as has been shown to be highly correlated with live viral neutralization titres, and has been also previously used in many other studies as a

correlate of immunity (references listed below and discussed on Lines 255-256). ACE2 inhibition testing allows for analysis of larger samples, in comparison to labour-intensive live viral neutralization titres. Further, our findings help contribute to and corroborate prior studies.

Tan CW, Chia WN, Qin X, Liu P, Chen MIC, Tiu C, Hu Z, Chen VCW, Young BE, Sia WR, Tan YJ, Foo R, Yi Y, Lye DC, Anderson DE, Wang LF. A SARS-CoV-2 surrogate virus neutralization test based on antibody-mediated blockage of ACE2-spike protein-protein interaction. *Nat Biotechnol*. 2020;38(9):1073-1078. doi:10.1038/S41587-020-0631-Z.

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Khoury DS, Cromer D, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, Subbarao K, Kent SJ, Triccas JA, Davenport MP. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med 2021 277*. 2021;27(7):1205-1211. doi:10.1038/s41591-021-01377-8.

Grunau B, Prusinkiewicz M, Asamoah-Boaheng M, et al. Correlation of SARS-COV-2 viral neutralizing antibody titers with anti-spike antibodies and ACE-2 inhibition among vaccinated individuals. *Microbiology Spectrum*. 2022;10(5). doi:10.1128/spectrum.01315-22

Dolscheid-Pommerich R, Bartok E, Renn M, Kümmerer BM, Schulte B, Schmithausen RM, Stoffel-Wagner B, Streeck H, Saschenbrecker S, Steinhagen K, Hartmann G. 2022. Correlation between a quantitative anti-SARS-CoV-2 IgG ELISA and neutralization activity. *J Med Virol* 94:388–392. doi: 10.1002/jmv.27287

Tea F, Ospina Stella A, Aggarwal A, Ross Darley D, Pilli D, Vitale D, Merheb V, Lee FXZ, Cunningham P, Walker GJ, Fichter C, Brown DA, Rawlinson WD, Isaacs SR, Mathivanan V, Hoffmann M, Pöhlman S, Mazigi O, Christ D, Dwyer DE, Rockett RJ, Sintchenko V, Hoad VC, Irving DO, Dore GJ, Gosbell IB, Kelleher AD, Matthews GV, Brilot F, Turville SG. 2021. SARS-CoV-2 neutralizing antibodies: longevity, breadth, and evasion by emerging viral variants. *PLoS Med* 18:e1003656. doi: 10.1371/journal.pmed.1003656

Please rate the manuscript for methodological rigour
Reviewer 2: Good

Please rate the quality of the presentation and structure of the manuscript
Reviewer 2: Satisfactory

To what extent are the conclusions supported by the data?
Reviewer 2: Partially support

Do you have any concerns of possible image manipulation, plagiarism or any other unethical practices?
Reviewer 2: No:

If this manuscript involves human and/or animal work, have the subjects been treated in an ethical manner and the authors complied with the appropriate guidelines?
Reviewer 2: Yes:

Reviewer 2 Comments to Author:

1. Methodological rigour, reproducibility and availability of underlying data
Did the authors adjust the neutralizing Ab titer considering comorbidities and previous infection while comparing two or three doses of vaccination?
were the neutralizing Abs potency assessed by cVNT test? if yes, provide the result, if not it should be discussed as a limitation of the study.

Thank you for the comment. No adjustments were made to the ACE2 percent inhibition based on comorbidities or previous infection as the goal of our study was to compare the immune strength of groups with varying vaccine doses and the presence or absence of a previous infection. However, we added that we lacked data on participant co-morbidities and have described this in our limitations section. We also acknowledged in our limitation section the lack of conventional viral neutralizing tests.

2. Presentation of results
The results must be presented in a better order and clear to the readers especially those related to Fig.3.

Thank you for the feedback. We made modifications to Figure 3 for clarity in the terminology for prior SARS-CoV-2 infection updated in the plot legend and x-axis of the boxplots. The Figure 3 and 4 legends have also been modified to ensure clarity regarding the "+" and "-" scheme of the table along the x-axis. If needed, we are happy to make any additional changes to the figures' presentation with more specific feedback.

3. How the style and organization of the paper communicates and represents key findings
This is satisfying.

4. Literature analysis or discussion
Can be improved if the authors consider other cVNT and neutralizing Abs response from different platforms including protein vaccines in the same 180 days follow-up (find at https://doi.org/10.1038/s41598-023-35147-y).

Thank you for this comment. We agree that using cVNTs may increase the confidence in our results. However, in this study we chose to use ACE2 inhibition as our outcome. cVNT testing is labour intensive and thus typically limited to a smaller number of samples. In our study we used ACE2 inhibition as it allowed us to test a much larger number of samples.

Regarding protein vaccines, there was a limited number of participants who received protein-based vaccines. Canadian vaccination was primarily limited to mRNA vaccines from Pfizer or Moderna.

5. Any other relevant comments

Manuscript with tracked changes (private)

The relationship between the number of COVID-19 vaccines and infection with Omicron ACE2 inhibition at 18-months post initial vaccination in an adult cohort of Canadian paramedics

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*These co-first authors contributed equally to this work.

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Keywords: SARS-CoV-2; Omicron; spike; COVID-19; vaccination

Data Summary:

All supporting data can be found at: https://www.covid19immunitytaskforce.ca/citf-databank/#accessing

Abstract

The coronavirus disease 2019 (COVID-19) pandemic, caused by the SARS-CoV-2 virus, has rapidly evolved since late 2019, due to highly transmissible Omicron variants. While most Canadian paramedics have received COVID-19 vaccination, the optimal ongoing vaccination strategy is unclear. We investigated neutralizing antibody (NtAb) response against wild-type (WT) Wuhan Hu-1 and Omicron BA.4/5 lineages based on the number of doses and past SARS-CoV-2 infection, at 18 months post initial vaccination (with a Wuhan Hu-1 platform mRNA vaccine [BNT162b2 or mRNA-1273]). Demographic information, previous COVID-19 vaccination, infection history, and blood samples were collected from paramedics 18 months post initial mRNA COVID-19 vaccine dose. Outcome measures were ACE2 percent inhibition against Omicron BA.4/5 and WT antigens. We compared outcomes based on number of vaccine doses (two vs. three) and previous SARS-CoV-2 infection status, using the Mann-Whitney U test. Of 657 participants, the median age was 40 years (IQR 33-50) and 251 (42%) were females. Overall, median percent inhibition to BA.4/5 and WT was 71.61% (IQR 39.44-92.82) and 98.60% (IQR 83.07-99.73), respectively. Those with a past SARS-CoV-2 infection had a higher median percent inhibition to BA.4/5 and WT, when compared to uninfected individuals overall and when stratified by two or three vaccine doses. When comparing two vs. three WT vaccine doses among SARS-CoV-2 negative participants, we did not detect a difference in BA.4/5 percent inhibition, but there was a difference in WT percent inhibition. Among those with previous SARS-CoV-2 infection(s), when comparing two vs. three WT vaccine doses, there was no observed difference between groups. These findings demonstrate that additional Wuhan Hu-1 platform mRNA vaccines did not improve NtAb response to BA.4/5, but prior SARS-CoV-2 infection enhances NtAb response.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing the coronavirus disease 2019 (COVID-19) pandemic, has resulted in millions of deaths worldwide [1]. The development and widespread distribution of mRNA COVID-19 vaccines, such as BNT162b2 and mRNA-1273, have minimized severe COVID-19 illness and death [2]. Previous studies have found robust immunological responses to wild-type and Delta lineages of SARS-CoV-2 at 6-months post initial vaccination, particularly with two doses of mRNA-1273 [3]. However, continued evolution of the SARS-CoV-2 virus has introduced several novel variants since the initial doses of mRNA vaccine were administered. Thus, long-term follow-up of immunogenicity is warranted. The highly contagious BA.1 (Omicron) variant of concern was first detected in Canada in November 2021. Due to its increased transmissibility, Omicron led to a surge of new SARS-CoV-2 infections and became the predominant circulating lineage by 2022 [4]. Various subvariants of Omicron, including BA.4/5, subsequently emerged and continue to impact public health globally [5]. In response, several booster vaccination campaigns have been launched and offered additional doses of the original, wild-type (WT) Wuhan Hu-1 platform mRNA vaccines. However, it is unclear if additional wild-type mRNA vaccines have incremental benefit during the Omicron era.

As new SARS-CoV-2 lineages arise, there is less clarity regarding the long-term effectiveness and immunogenicity of the original mRNA vaccines against novel Omicron lineages. In addition, with a large magnitude of the population having been previously infected with SARS-CoV-2, particularly Omicron, it would also be beneficial to understand immunogenicity elicited by previous infection and whether booster wild-type vaccine doses confer additional protection. Such knowledge will also have implications for future waves of infection, during which the available vaccines do not match the circulating strains. For the above reasons, we sought to investigate the humoral immunogenicity against the WT and Omicron BA.4/5 strains at 18 months post-initial mRNA vaccine, comparing groups based on past SARS-CoV-2 infection and the number of WT-directed mRNA vaccine doses.

Materials and Methods

Study Design and Setting

Samples for this analysis were selected from participants in the "COVID-19 Occupational Risks, Seroprevalence, and Immunity among Paramedics in Canada (CORSIP)" study, who were working paramedics in the Canadian provinces of British Columbia, Alberta, Saskatchewan, Manitoba, or Ontario. The CORSIP study began enrolling participants in January 2021, after receiving research ethics board approvals from the University of British Columbia (H20-03620) and the University of Toronto (40435). Participants provided electronic consent upon enrolment and completed questionnaires regarding health and sociodemographic information, COVID-19 vaccination history and status, and history of SARS-CoV-2 infection confirmed by positive polymerase chain reaction (PCR) test and/or rapid antigen test (RAT) results. Participants were asked to provide blood samples and survey data at 6-month intervals, including at an 18-month timepoint, following their first dose of a COVID-19 mRNA vaccine (if vaccinated).

Participant and Sample Selection

Among CORSIP participants enrolled between January 2021 and November 2022, we included participants who had received two or three doses of any Health Canada approved mRNA COVID-19 vaccine (BNT162b2 and mRNA-1273). We focused on these vaccines, given that the vast majority of CORSIP participants were recipients. Participants were included if they had provided a blood sample at 18 months +/- 2 weeks from the date of their first vaccine dose. We excluded participants: 1) who received a bivalent vaccine (bivalent vaccines had just been released at the 18-month timepoint and very few of our participants had received them); 2) who only received one vaccine dose; 3) who received four vaccine doses; 4) who received non-mRNA vaccines 5) who had incomplete vaccine and/or infection history (e.g vaccine or infection date or type of vaccine missing); 6) who had a self-reported previous SARS-CoV-2 infection or COVID-19 vaccination within 60 days prior to this blood collection timepoint (given the expected immunological response in this initial phase post-antigen exposure).

Laboratory Testing

All samples were tested with the V-PLEX SARS-CoV-2 Panel 28 ACE2 Kit (Meso Scale Discovery, MD, USA) to measure the percent inhibition of ACE2 for both the wild-type Wuhan Hu-1 and BA.4/5 spike antigen. This assay platform has previously been shown to perform as a reliable surrogate for live virus neutralization [6,7]. All blood serum samples were tested according to the manufacturer's instructions. All samples were also tested with the Roche Elecsys Anti-SARS-CoV-2 Nucleocapsid (N) protein assay (Roche Diagnostics Corp., Indianapolis, IN, USA) assay to immunologically identify samples from participants with previous SARS-CoV-2 infection.

Variable Definitions

A past SARS-CoV-2 infection was defined as: 1) self-reported positive result on a rapid antigen test (RAT) or polymerase chain reaction (PCR) test; or, 2) a reactive Roche Elecsys Anti-SARS-CoV-2 N assay. We classified previous SARS-CoV-2 infections as Omicron vs. pre-Omicron, which was determined based on the date of the participant's last self-reported positive PCR or RAT test result: a positive test result on January 1, 2022 or later were defined as having an Omicron infection, whereas those with positive results on November 26, 2021 or earlier were considered infected with a pre-Omicron lineage. The majority of COVID-19 cases in Canada beyond this date were Omicron[4]. We considered those with positive results between November 27, 2021 to December 31, 2021 to have an unspecified infection (and thus excluded from Omicron vs pre-Omicron comparisons) to account for a combination of pre-Omicron and Omicron lineages circulating during this period. For cases that were classified as having a previous SARS-CoV-2 infection based on a reactive Elecsys test, to control for the possibility of a pre-Omicron antibody being detected during the Omicron time period, SARS-CoV-2 infections identified by Roche Nucleocapsid assay had to have a reactive test during the Omicron period and a previous non-reactive test(s) to be considered an Omicron infection (otherwise these were excluded from Omicron vs pre-Omicron comparisons).

Outcome Measures

The primary and secondary outcomes were ACE2 percent inhibition to the BA.4/5 and WT antigens, respectively. Due to being the predominant circulating lineages at the time of blood collection[4], BA.4/5 lineages were specifically selected for analysis.

Statistical Analyses

Analyses were performed using GraphPad Prism Version 9.5.0 (GraphPad Software, San Diego, CA). Participant characteristics and outcomes were reported as counts (with percentages) for categorical variables, and median (with interquartile range [IQR]) for continuous variables. Outcome measures were reported as median with interquartile range (IQR). The median percent inhibition between two groups was compared using a non-parametric Mann-Whitney U test. A *P* value of less than 0.05 was considered statistically significant.

We performed several comparisons. First, we compared groups based on whether the participant had received two vs. three vaccines, to investigate the potential impact of repeated dosing with an ancestral strain vaccine on humoral response to an antigenically divergent, more contemporary variant (BA.4/5). Second, we divided participants into four groups, based on the number of vaccines and past SARS-CoV-2 infection history (2 doses and no previous SARS-CoV-2 infections ["2 doses uninfected"], 3 doses and no previous SARS-CoV-2 infections, 2 doses and previous SARS-CoV-2 infection(s) ["2 doses infected"], and 3 doses and previous SARS-CoV-2 infection(s)) and compared each group to all others. In the third comparison, we further divided the subgroups with previous SARS-CoV-2 infection(s) into those who had a pre-Omicron vs. Omicron vs. unspecified infection, to investigate whether a prior Omicron infection elicited greater NtAb response.

Results

This study included a total of 657 participants out of 3956 enrolled as of November 2022, 251 (42%) of whom were female (Figure 1). The median participant age was 40 years (IQR 33-50 years); 18-month blood samples were collected between June 2022 and November 2022. Participants had a median of 248 days (IQR 224-276 days) between their last vaccination date and their blood collection, and half of the participants were vaccinated exclusively with BNT162b2. Additional participant characteristics are summarized in Table 1.

In the first comparison of two vs. three vaccines (Figure 2), we observed no significant difference in percent inhibition to BA.4/5 with two vaccine doses (n = 136; 74.67%, IQR 40.24-93.82) vs. three vaccine doses (n = 521; 69.30%, IQR 39.34-92.60). Similar findings are observed in Figure 2B when comparing two doses (n = 136; 98.75%, IQR 83.48-99.75) with three doses (n = 521; 98.54%, IQR 83.06-99.73) ACE2 percent inhibition to WT.

Figure 3 shows the results of the second comparison where participants are divided into four subgroups based on the number of vaccines and SARS-CoV-2 infection history. For percent inhibition against BA.4/5, the median percent inhibition was: (1) 35.4% (IQR 25-44) for two doses uninfected (n=42); (2) 86.0% (IQR 67-97) for two doses infected (n=94); (3) 40.7% (IQR 29-56) for three doses uninfected (n=244); and, (4) 89.5% (IQR 77-97) for three doses infected (n=277). Within all four subgroups, those with a previous, unspecified SARS-CoV-2 infection(s) had a greater percent inhibition against both BA.4/5 and WT, when compared to uninfected participants. When examining BA.4/5, we did not detect a difference between those with two vs. three vaccines, when comparing amongst the infected or uninfected cases. When examining WT ACE2 inhibition, we observed a difference between those with

two vs. three vaccine doses in uninfected participants, but not when examining previously infected participants.

Figure 4 shows results of the third comparison based on the type of preceding SARS-CoV-2 infection strain. We observed significantly greater ($P < 0.001$) percent inhibition to BA.4/5 when comparing individuals with three doses and Omicron infection (n = 210; median 92.65, IQR [80-97]) with three doses and pre-Omicron infection (n = 23; 75.83, IQR [45-91]) (Figure 4A). We also observed a significantly greater percent inhibition ($P < 0.05$) in individuals with three doses and prior Omicron infection compared to those with two doses and prior Omicron infection. In contrast, percent inhibition to WT was consistently high across all groups and showed no significant differences with varying infection type or increasing number of vaccine doses (Figure 4B).

Discussion

We examined NtAb response against the Omicron and wild-type strains from a prospective cohort of 657 Canadian paramedics. We observed that those with prior SARS-CoV-2 infection(s), compared to uninfected individuals, demonstrated greater ACE2 percent inhibition against WT and BA.4/5 lineages. Interestingly, our data indicate that additional WT-directed vaccines did not lead to either enhanced nor reduced humoral immunogenicity against more recent Omicron variants, regardless of whether they had been previously infected or not. These data suggest that providing additional WT-directed vaccine doses after two doses did not provide additional benefit in the current time period, which may have implications for future decisions regarding additional dosing strategies when available vaccines do not match the current circulating strains.

Overall, an increased number of WT mRNA vaccine doses was not associated with an increased percent inhibition against BA.4/5, except in those individuals with two doses and a prior Omicron era infection. These findings differ from prior studies that examined antibody neutralization against wild type[8] and original Omicron (B.1.1.529) variants [9] with two doses showing reduced NtAb response. However, these studies only assessed responses after relatively short periods post second doses (up to 7 months). Several studies have shown greater NtAb responses among vaccinated individuals with a prior infection compared to those without [10,11]. However, two studies have found no difference due to prior BA.1 infection between two vaccination and three vaccination groups [12,13]. Carazo et al found no significant difference in reducing the risk of infection to BA.2 from a prior BA.1 infection across two vaccine doses vs three vaccine doses [12], and Zheng et al found no difference in 50% neutralization titer (NT50) in prior BA.1 infected individuals with either two or three vaccine doses [13]. When compared to our findings, the observed differences could be attributed to methodological differences such as the intervals between sample testing and prior infection(s), different SARS-CoV-2 variants, COVID-19 vaccine types and outcome measures selected, and study design used. Further, the statistically significant improvement in percent inhibition in those with prior Omicron infection and a third dose observed in our data could also be due to differences in subgroup sample sizes and characteristics such as vaccine type (e.g BNT162b2 and mRNA-1273), vaccination intervals, and the possibility of multiple prior infections, which were not able to be estimated based on our study's cohort. Although statistically significant, the median percent inhibition was relatively high across both groups and may not be clinically significant in the context of hospitalization rate, infection burden, and/or disease severity. The finding that additional Wuhan Hu-1 platform mRNA vaccines did not improve immunogenicity may have policy implications, given that use

of these vaccines may have little further utility, when given alone or in combination with vaccines directed at other strains.

A potential concern with repeated vaccine doses using antigen from an ancestral strain is the phenomenon of "original antigenic sin", where repeated exposure to one antigen may result in the immune response being preferentially directed towards the primary antigen even when infected with a new variant/strain. This has been described with influenza and other RNA viruses [14,15]. Interestingly, our data shows that additional vaccine doses against the wild-type SARS-CoV-2 strain did not appear to diminish the median percent inhibition against BA.4/5. This could be due to the mRNA vaccines eliciting some cross-neutralization against variants of concern (VoC), such as Omicron and its sublineages [16]. However, these vaccinated individuals may still potentially be susceptible to VoCs, given the observed differences in median percent inhibition to BA.4/5 and WT, regardless of the number of vaccine doses or prior SARS-CoV-2 infection. Thus, our findings contribute to the current literature in supporting vaccine guidelines that emphasize the importance of bivalent vaccines designed to target Omicron variants, rather than providing boosters against the original strain [17,18]. As new SARS-CoV-2 lineages emerge and new vaccines are designed, our findings also provide some insight into biological patterns of immune response related to prior infection and vaccination dose.

This study has limitations. Firstly, we used percent ACE2 inhibition for the outcome measure, which is a surrogate marker for immunity. Although not as clinically relevant as clinical outcomes, ACE2 inhibition has been shown to correlate with live virus neutralization (the gold standard for antibody efficacy and predictive of clinical immune response[19-21]), and has been used extensively as a marker for immunity in other studies[3,6,7,22,23]. We utilized self-reported data regarding participant characteristics, which are prone to recall bias, inaccuracies, and incompleteness. The Roche Elecsys Anti-SARS-CoV-2 N assay used to classify some self-reported SARS-CoV-2 negative participants as SARS-CoV-2 positive is reported to have a 90% sensitivity[24]. Further, these positive participants were missing the date of their prior infection. Additionally, we were unable to determine if participants had multiple prior infections or completely estimate the time interval from infection to blood draw due to the study design and unreliability of self-reported data. No post hoc correction was applied in our statistical analysis. Due to the observational nature of this study, comparisons were made between potentially uneven groups that may differ in measured and/or unmeasured characteristics. For example, one such confounder would be the lack of participant data on potential therapies or medications taken that could alter the immune response such as corticosteroids or chemotherapy. Lastly, the lack of data on participant comorbidities could impact immune response strength[25].

Conclusion

Those with previous SARS-CoV-2 infection demonstrated higher ACE2 percent inhibition against WT and BA.4/5 antigens, compared to those without a prior infection. Three vs. two Wuhan Hu-1 platform vaccines doses improved percent inhibition to WT, but not BA.4/5 antigens.

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Author contributions

Conceptualization: BG, DG. Data curation: JY, IK. Funding Acquisition: BG, DG. Investigation: JY, IK. Methodology: BG, DG, JY, IK, MA-B. Project administration: BG, DG. Supervision: BG, DG. Writing – original draft: JY, IK. Writing – review & editing: BG, DG, JY, IK, MA-B, SH, SC, TK, PD.

Conflicts of Interest

None

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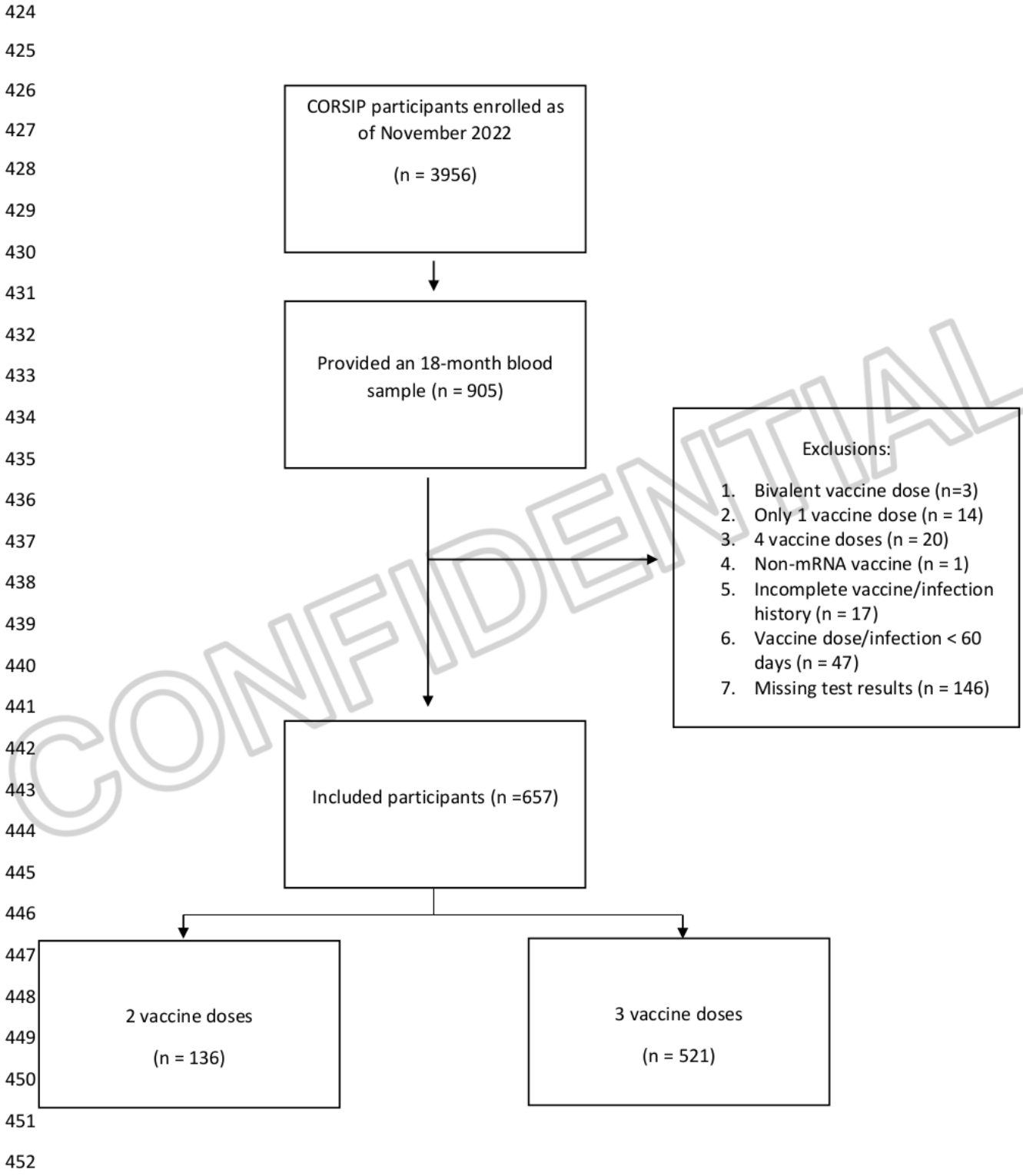

Figure 1. Participant selection flow diagram

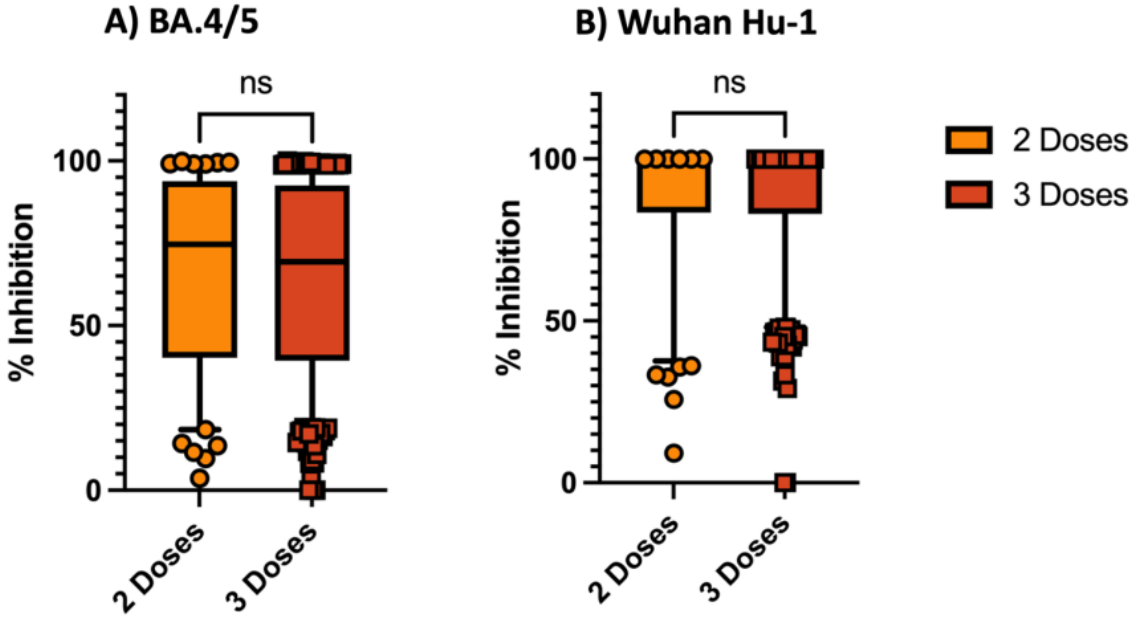

Figure 2. ACE2 percent inhibition to (A) BA.4/5 and (B) Wuhan Hu-1 by vaccine dose
ns, not significant; box plot shows median and interquartile range (IQR); whiskers, 5-95th percentile; 2 doses, n = 136; 3 doses, n = 521.

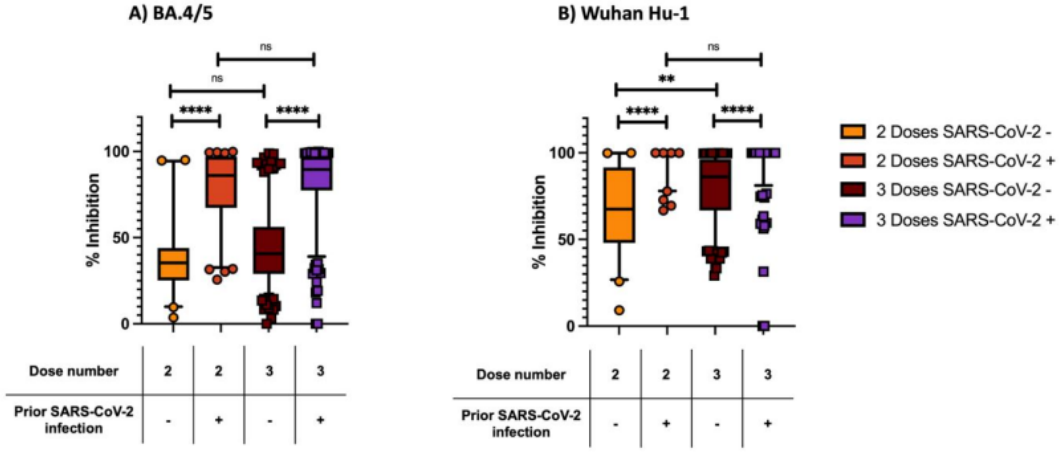

Figure 3. ACE2 percent inhibition to (A) BA.4/5 and (B) Wuhan Hu-1 by vaccine dose and prior SARS-CoV-2 infection status

P < 0.0001, ****; P < 0.0021, ** ; ns, not significant; box plot shows median and interquartile range (IQR); whiskers, 5-95th percentile; -, no prior SARS-CoV-2 infection; +, prior SARS-CoV-2 infection; 2 doses no prior infection, n = 42; 2 doses with prior infection, n = 94; 3 doses no prior infection, n = 244; 3 doses with prior infection, n = 277. Comparisons were performed between two groups at a time.

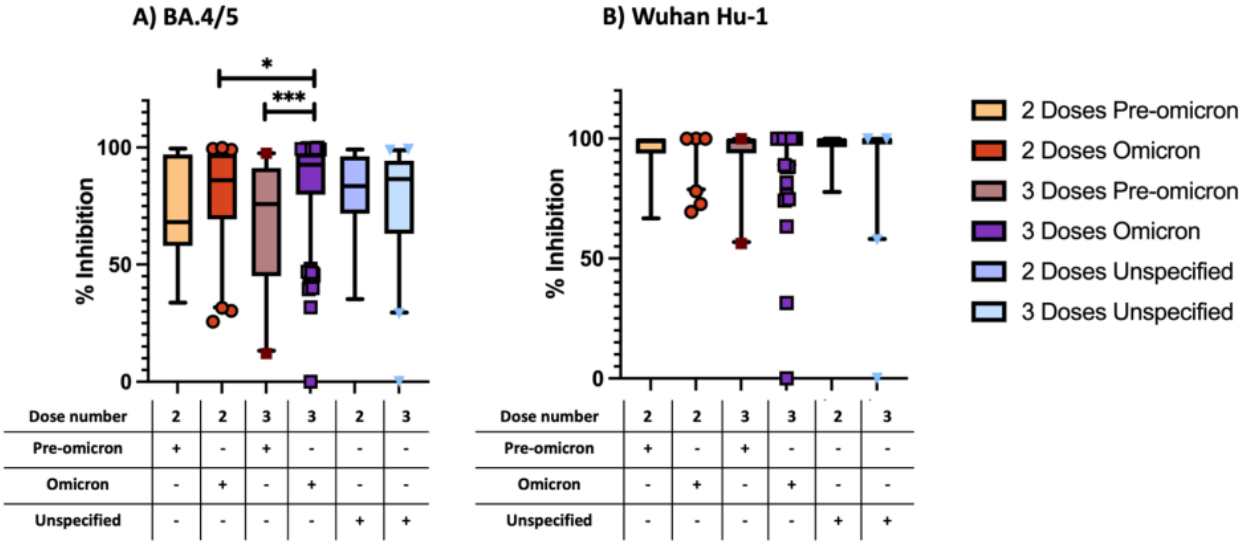

Figure 4. ACE2 percent inhibition to (A) BA.4/5 and (B) Wuhan Hu-1 by vaccine dose and pre-Omicron, Omicron, or unspecified SARS-CoV-2 infection status

$P < 0.001$, ***; $P < 0.05$, *; ns, not significant; box plot shows median and interquartile range (IQR); whiskers, 5-95th percentile; +, indicates a prior SARS-CoV-2 infection type; -, indicates the absence of a prior SARS-CoV-2 infection type; 2 doses prior pre-omicron infection, n = 7; 2 doses prior omicron infection, n = 71; 2 doses prior unspecified infection, n = 16; 3 doses prior pre-omicron infection, n = 23; 3 doses prior omicron infection, n = 210; 3 doses prior unspecified infection, n = 44. Comparisons were performed between two groups at a time.

Characteristics	2 vaccines (n = 136)	3 vaccines (n = 521)
Age (median, IQR)	38 (31-50)	40 (34-50)
Sex		
Female	43 (39)	208 (40)
Male	67 (61)	285 (55)
Missing	26 (19)	28 (5.4)
Last vaccine-to-BC interval (days)	485 (431-507)	241 (217-255)
2nd vaccine to BC (days)	485 (431-507)	501 (447-510)
COVID+ history	94 (69)	277 (53)
Omicron COVID	71 (52)	210 (40)
Pre-omicron COVID	7 (5.1)	23 (4.4)
Unspecified COVID	16 (12)	44 (8.4)
COVID-to-BC interval (days)	160 (116-197)	145 (95-202)
Missing	29 (21)*	96 (18)*
ACE2 % Inhibition		
BA.4/BA.5	75 (40-94)	69 (39-93)
Wuhan Hu-1	99 (83-100)	99 (83-100)
Vaccine 1		
mRNA-1273	33 (24)	157 (30)
BNT162b2	103 (76)	364 (70)
Vaccine 2		
mRNA-1273	101 (74)	154 (30)
BNT162b2	35 (26)	367 (70)
Vaccine 3		
mRNA-1273	-	256 (49)
BNT162b2	-	265 (51)

Table 1. Participant characteristics at 18-month blood collection from first original mRNA vaccine date
SD, standard deviation; COVID+, prior SARS-CoV-2 infection; COVID-, uninfected individual; Omicron COVID, SARS-CoV-2 infection reported on January 1, 2022 or later; Pre-omicron COVID, SARS-CoV-2 infection reported on November 26 or prior; unspecified infection reported between Nov 27, 2021 to December 31, 2021 or prior SARS-CoV-2 infection determined by reactive N-Roche assay with no prior unreactive N-Roche result; BC, blood collection; *, participants determined to be positive through N-Roche assay where date of COVID-19 is unknown.

Figure 1

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