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- Information on the MDAR report: https://sciscore.com/reports/MDAR-Report.php
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How to cite the SciScore reports for this article:

Asamoah-Boaheng M, Grunau B, Haig S, Karim ME, Kirkham T, *et al*. SciScore reports for: 11-month SARS-CoV-2 immunogenicity decay, and associated factors, among mRNA vaccinees: Implications for Booster Vaccination. *Access Microbiology*. 2023. https://doi.org/10.1099/acmi.0.000678.v2.1

ITHENTICATE® REPORT

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Document Identifier: **2213_650bfebb355d48.43890075**

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
Consent: Participants provided electronic consent upon enrolment.
Inclusion and Exclusion Criteria
Study participants:For this investigation, we included participants who provided two blood samples after receiving only two mRNA vaccines of the same type (either two doses of BNT162b2, or two doses of mRNA-1273 vaccines).
Attrition
not detected.
Sex as a biological variable
The various factors included in the model were: participant age (years, continuous variable), female sex at birth (vs. male); “racialized” (including those who self-described their ethnicity or race as South Asian, Chinese, Black, Filipina, Latin American, Arab, Southeast Asian, West Asian, Korean, or Japanese) (vs. whites)”; “BMI: 18.5 to <25kg/m2 (vs. others)”, “BMI ≥ 25kg/m2 (vs others)”; “BNT162b2 vaccine (vs. mRNA-1273)”; “short vaccine dosing interval (binary variable, “short” defined as a vaccine dosing interval less than the median value); and past medical history (including covariates: hypertension, diabetes, asthma, liver diseases, and cancer).
Subject Demographics
Weight: The various factors included in the model were: participant age (years, continuous variable), female sex at birth (vs. male); “racialized” (including those who self-described their ethnicity or race as South Asian, Chinese, Black, Filipina, Latin American, Arab, Southeast Asian, West Asian, Korean, or Japanese) (vs. whites)”; “BMI: 18.5 to <25kg/m2 (vs. others)”, “BMI ≥ 25kg/m2 (vs others)”; “BNT162b2 vaccine (vs. mRNA-1273)”; “short vaccine dosing interval (binary variable, “short” defined as a vaccine dosing interval less than the median value); and past medical history (including covariates: hypertension, diabetes, asthma, liver diseases, and cancer).
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
Antibodies			
Serological Testing:We tested all samples with: (1) Elecsys Anti-SARS-CoV-2 (nucleocapsid) [Roche Diagnostics International Ltd, Rotkreuz, Switzerland] assay20,21 to confirm eligibility; (2) the quantitative Roche Elecsys Anti-SARS-CoV-2 (S) (Roche Diagnostics International Ltd, Rotkreuz, Switzerland) assay for measuring spike total antibody concentrations; and (3) the Meso Scale Discovery (MSD) V-PLEX COVID-19 Coronavirus Panel 2 IgG assay for measuring IgG to spike and receptor-binding domain (RBD) antigens.	Anti-SARS-CoV-2 (nucleocapsid)		
	Anti-SARS-CoV-2		
	receptor-binding domain (RBD) antigens.		
Study outcomes:The primary outcome was total anti-spike antibody concentrations (measured with the Elecsys assay), and the secondary outcomes were IgG concentrations to spike and RBD antigens (measured with the VPLEX assay).	anti-spike		
Antibody concentrations (including: total anti-spike, anti-spike IgG and anti-RBD IgG antibody concentrations) were presented as geometric mean (GM) with corresponding geometric standard deviations (GSD).	anti-spike, anti-spike IgG		
	anti-RBD IgG		

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	Yes, 6 antibodies detected, 0 RRID provided : Anti-SARS-CoV-2 (nucleocapsid) : Anti-SARS-CoV-2 : receptor-binding domain (RBD) antigens. : anti-spike : anti-spike, anti-spike IgG : anti-RBD IgG 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.	Not detected.	
Provide statement confirming informed consent obtained from study participants.	Participants provided electronic consent upon enrolment.	
Report on age and sex for all study participants.	**Age:**Not detected. **Sex:**The various factors included in the model were: participant age (years, continuous variable), female sex at birth (vs. male); “racialized” (including those who self-described their ethnicity or race as South Asian, Chinese, Black, Filipina, Latin American, Arab, Southeast Asian, West Asian, Korean, or Japanese) (vs. whites)”; “BMI: 18.5	

Human research participants	Yes (indicate where provided: page no/section/legend)	n/a
	to <25kg/m2 (vs. others)", "BMI **Sex:≥Sex:** 25kg/m2 (vs others)"; "BNT162b2 vaccine (vs. mRNA-1273)"; "short vaccine dosing interval (binary variable, "short" defined as a vaccine dosing interval less than the median value); and past medical history (including covariates: hypertension, diabetes, asthma, liver diseases, and cancer).	

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	Study participants:For this investigation, we included participants who provided two blood samples after receiving only two mRNA vaccines of the same type (either two doses of BNT162b2, or two doses of mRNA-1273 vaccines).	

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.	Not detected.	
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.	Not detected.	

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-23-00126.pdf

By Michael Asamoah-Boaheng

WORD COUNT	7686	TIME SUBMITTED	21-SEP-2023 09:27AM
		PAPER ID	102907120

Access Microbiology

11-month SARS-CoV-2 immunogenicity decay, and associated factors, among mRNA vaccinees: Implications for Booster Vaccination

--Manuscript Draft--

Reviewer 1 Comments to Author:
11-month SARS-CoV-2 immunogenicity decay, and associated factors, among mRNA 2 vaccinees: Implications for Booster Vaccination

Title needs work. I don't think its the "immunogenicity" which decays over that period; i think this is the incorrect terminology. Needs to be a bit snappier as well.

Response: **We thank the reviewer for their thoughtful comments. We have revised the title as suggested. See revised document attached.**

Need to make sure that the raw data is made available as they discuss calculation of decay rates based on this.

Response: **Thank you. The CORSIP data used can be publicly accessed via this link: https://portal.citf.mcgill.ca/.**

Otherwise this is a very high quality paper which i considered insightful and which I enjoyed reading.

Response: **Thank you.**

The only thing I think needs to be considered, is that there is a lack of discussion around "protective" levels of antibodies in this context, what is known and what is considered protective, and then how appropriate these arbitrary cut-offs are, given many people will retain significant protection in the absence of detectable antibody response to many viruses, how much is this a consideration in this case, it should at least be considered in the discussion.

Response: **We thank the reviewers for this comment. We have added a discussion on the protective levels of antibodies based on our results. Please see revised manuscript.**

I have minor suggestions asside from changes to the title

Response: Thank you.

Line 36: Define CORSIP

Response: Thank you for your comment. We have defined CORSIP in full as suggested. Please see revised manuscript attached.

Line 193: The vaccine is immunogenic, the participants are immunised. Should read "Long term protection afforded by immunisation of serially-tested middle-aged vaccinees with two doses of mRNA vaccine was investigated"

Response: Thank you for this. We have revised this statement as suggested.

Reviewer Comments to Author: REVIEWERS REPORT
11-month SARS-CoV-2 immunogenicity decay, and associated factors, among mRNA vaccinees: Implications for Booster Vaccination

General comment
In the paper '11-month SARS-CoV-2 immunogenicity decay, and associated factors, among mRNA vaccinees: Implications for Booster Vaccination', Asamoah-Boateng et al, described the decay profile of binding antibody responses from participants that have received two doses of mRNA vaccines (BNT162b2 and mRNA-1273). They showed that the binding antibody responses peaked at about 21 days post-vaccination and plateaus at about ten months with a half-life of 94 days. They also showed that several factors, such as older age, vaccine type and timing of booster dosage, were associated with the decay rate of antibody immune responses. The background knowledge is explicit, the methodology is rigorous, and the findings are clear. However, the article will benefit from minor revisions on the points noted below.

Response: We thank the reviewer for this thoughtful comment.

The word immunogenicity in the title is broad; however, the study focuses on binding antibody responses. The author may need to include in the limitation why they didn't measure T cell response which is also covered under immunogenicity. They may change immunogenicity to binding antibody decay, which is what they did.

Response: We thank the reviewer for this comment. We have revised the title of this study as suggested and also added the limitation of not measuring T-cell response in our study. See revised manuscript attached.

Secondly, the methodology will be clearer if the authors indicate the timing of the blood sampling. Were both first and second blood samples collected at the same time for each participant? It was until Lines 130-132 that they talked about grouping the participants into quartiles that I inferred the samples were not collected at the same time. If the samples were not collected simultaneously, it might be better to delete the word serially in the discussion because the sample collection wasn't serial.

Response: We thank the reviewer for this comment. The first and the second blood samples were collected at different times. From Table 1, the median dates of the first and second blood sample collection were "April 16, 2021" and "July 17, 2021" respectively. We had already indicated the differences in timing of blood sampling in the manuscript. Please see page 7 under the results section.

Moreso, in the discussion, reference 26 Line 206 did not agree with the result of this work because the immunity declined within one month, while in this study, the immunity peaked at 21 days, almost one month. The author needs to clarify and provide a reason for the results' differences.

Response: We thank the reviewer for their valuable comment. We have removed this reference from the discussion section for clarity.

Also, the reference for the study cited in lines 207-210 needed to be provided.

Reference: **Thank you for your comment. We have added the reference to the statement on line 207-210.**

Finally, for other minor comments, figure 2 is unclear whether the time point shown is for the first or second blood collection or both and similarly in Figure S1.

Response: **Thank you. All blood collections were done after the second vaccine dose. Hence the time shown is for both first and second blood collections (i.e the interval between the second vaccine dose and all blood collections). We have written a footnote under each figure to clarify this.**

Line 82, the 19 in COVID-19, is missing. The age range for the participants needs to be provided. Line 158 should read a mean age 'of' not 'was'.

Response: Thank you for this comment. We have addressed the comments above. Please see revised manuscript attached.

11-month SARS-CoV-2 binding antibody decay, and associated factors, among mRNA vaccinees: Implications for Booster Vaccination

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Abstract

Background: We examined the 11-month longitudinal antibody decay among 2-dose mRNA vaccinees, and identified factors associated with faster decay.

Methods: The study included samples from the COVID-19 Occupational Risk, Seroprevalence and Immunity among Paramedics (CORSIP) longitudinal observational study of paramedics in Canada. Participants were included if they had received two mRNA vaccines without prior SARS-CoV-2 infection and provided two blood samples post-vaccination. The outcomes of interest were quantitative SARS-CoV-2 antibody concentrations. We employed spaghetti and scatter plots (with kernel-weighted local polynomial smoothing curve) to describe the trend of the antibody decay over 11-months post vaccine and fit a mixed effect exponential decay model to examine the loss of immunogenicity and factors associated with antibody waning over time.

Results: This analysis included 652 blood samples from 326 adult paramedics. Total anti-spike antibody levels peaked on the 21st day (antibody level 9,042U/mL) after the second mRNA vaccine dose. Total anti-spike antibody levels declined thereafter, with a half-life of 94 [95% CI: 70, 143] days, with levels plateauing at 295 days (antibody level 1021 U/mL). Older age, vaccine dosing interval <35 days, and the BNT162b2 vaccine (compared to mRNA-1273 vaccine) were associated with faster antibody decay.

Conclusion: Antibody levels declined after the initial mRNA series with a half-life of 94 days, plateauing at 295 days. These findings may inform the timing of booster vaccine doses and identifying individuals with faster antibody decay.

Keywords: SARS-CoV-2; Immunogenicity decay; Risk factors; antibody levels, mRNA COVID-19 vaccines.

Introduction

Data from observational studies and randomized controlled trials have demonstrated the effectiveness of COVID-19 vaccines against symptomatic illness, COVD-19-related hospitalizations, complications, and death[1–3,4]. However, the long-term duration of vaccine-induced immunity is unclear. Previous studies document waning of SARS-CoV-2 antibody levels after both vaccination and infection,[5] with anti-spike levels decreasing substantially as early as three months after the second BNT162b2 dose[6]. Humoral responses have been shown to be significantly decreased six months after the receipt of the second dose of BNT162b2 vaccine, especially among older adults (≥ 65 years) and those with compromised immune systems[6–11]. However, data on the long-term (>6 month) immunogenicity post-SARS-CoV-2 vaccination remain scarce.[6,7,10,11].

Given evidence of waning SARS-CoV-2 humoral immune responses after vaccination, booster vaccinations have been implemented in many jurisdictions; however, the optimal timing for boosters remains unclear. There is growing evidence that SARS-CoV-2 antibody levels provide a measure of COVID-19 risk[12–14] and COVID-19 severity,[15–17] a relationship that has been shown to be present even within the Omicron era[18]. Thus, antibody levels may inform decisions regarding the optimal timing of a booster vaccination. Further, given that immunity has been shown to differ based on individual characteristics, it is possible that the optimal booster schedule may vary within different patient groups. Currently there is limited data showing the long-term durability of, and factors associated with, antibody levels post-vaccination. We sought to investigate antibody waning 11 months after two mRNA vaccine doses among adult COVID-19 naïve paramedics in Canada, and factors associated with these outcomes.

Methods

Study setting, design, and ethics

Our study included samples of paramedics from the Occupational Risks, Seroprevalence, and Immunity among Paramedics in Canada (CORSIP) study[19]. CORSIP is a longitudinal observational study investigating the seroprevalence of SARS-CoV-2 antibodies among adult (≥ 19 years) Canadian paramedics. Participants provided blood samples and data from structured questionnaires on vaccination and COVID-19 history, past medical history, demographic and workplace characteristics.

Study participants

For this investigation, we included participants who provided two blood samples (at different times) after receiving only two mRNA vaccines of the same type (either two doses of BNT162b2, or two doses of mRNA-1273 vaccines). We excluded participants who had evidence of prior SARS-CoV-2 infection at any time prior to the second blood collection, based on reported positive nucleic acid amplification viral testing or a reactive blood sample on the Elecsys Nucleocapsid Anti-SARS-CoV-2 [Roche, IND, USA] assay.[20] The CORSIP data used for this study can be publicly assessed through the website of Canada COVID-19 Immunity Task Force (CITF) website via the link: https://portal.citf.mcgill.ca/.

Serological Testing

We tested all samples with: (1) Elecsys Anti-SARS-CoV-2 (nucleocapsid) [Roche Diagnostics International Ltd, Rotkreuz, Switzerland] assay[20,21] to confirm eligibility; (2) the quantitative

Roche Elecsys Anti-SARS-CoV-2 (S) (Roche Diagnostics International Ltd, Rotkreuz, Switzerland) assay for measuring spike total antibody concentrations; and (3) the Meso Scale Discovery (MSD) V-PLEX COVID-19 Coronavirus Panel 2 IgG assay for measuring IgG to spike and receptor-binding domain (RBD) antigens.

Study outcomes

The primary outcome was total anti-spike antibody concentrations (measured with the Elecsys assay), and the secondary outcomes were IgG concentrations to spike and RBD antigens (measured with the VPLEX assay).

Statistical analysis

We described continuous variables with mean and standard deviation (SD) for near normally distributed variables without any influential outliers, or median (with interquartile range [IQR]) for skewed or non-normally distributed variables. Categorical variables were described with counts and percentages. Antibody concentrations (including: total anti-spike, anti-spike IgG and anti-RBD IgG antibody concentrations) were presented as geometric mean (GM) with corresponding geometric standard deviations (GSD). We described the longitudinal changes in SARS-COV-2 antibodies 11 months after the second mRNA vaccine dose with scatter (with Kernel-weighted local polynomial smoothing curve)[22,23] and spaghetti plots. Using the Kernel-weighted local polynomial smoothing approach with Epanechnikov kernel function[22], we generated the smoothing values and their corresponding smoothing grids and estimated the peak antibody concentration based on the maximum kernel-weighted values. The smoothing grid (days after the second vaccine) that corresponded to the maximum kernel-weighted smoothing value was considered as the day of the peak antibody level. We used the double exponential

decay (DED) model[24] to determine the time at which the antibody level stopped declining (the "plateau level") [See supplementary material].

To further demonstrate differences in antibody levels after vaccination, we categorized samples into quartiles based on the number of days they were collected after the second vaccine dose, and plotted box-and-whisker plots to diagram antibody levels.

We modeled the persistence of antibody levels over time using a mixed effect exponential decay (ED) model. The mean structure of the exponential decay model with random intercept and slope is given by:

$$log_{10}(Ab_{i,j}) = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i}).T_{i,j} + \varepsilon_{i,j}$$

β_0 and β_1 are the fixed effects intercept and decay rate respectively, while b_{0i} and b_{1i} are the subject-specific (random effects) intercept and decay rates respectively. $\varepsilon_{i,j}$ represents the random error term for participant 'i' at time (day) "j" which is assumed to be normally distributed; $log_{10}(Ab_{i,j})$ is the mean log antibody titer at time $T_{i,j}$ post vaccination[9,25]. To determine the waning of antibody levels over time, we used the mixed effects ED model to estimate the half-life (the time the peak antibody level was reduced by 50%)[9] . Thus, the half-life ($t_{1/2}$) was estimated as[25]:

$$t_{1/2} = \frac{log_{10}(0.5)}{\beta_1}$$

Further, we fit a mixed effect ED model to investigate the factors associated with antibody decay over the 11-month study observation period. The mixed effect ED model with random intercept

was used to account for the repeated measurements of antibody concentrations for each participant at the two different time points. This model has been used in other studies that investigated antibody waning among vaccinated individuals over time[9,25].The various factors included in the model were: participant age (years, continuous variable), female sex at birth (vs. male); "racialized" (including those who self-described their ethnicity or race as South Asian, Chinese, Black, Filipina, Latin American, Arab, Southeast Asian, West Asian, Korean, or Japanese) (vs. whites)"; "BMI: 18.5 to <25kg/m^2 (vs. others)", "BMI $\geq$25kg/m^2 (vs others)"; "BNT162b2 vaccine (vs. mRNA-1273)"; "short vaccine dosing interval (binary variable, "short" defined as a vaccine dosing interval less than the median value); and past medical history (including covariates: hypertension, diabetes, asthma, liver diseases, and cancer).

Results

The study included 652 samples from 326 paramedics, with a mean age of 42 (SD=11) years, where 46% were female. The majority of the study participants (82%) were vaccinated with two doses of BNT162b2 vaccine while the remaining 18% received two doses of mRNA-1273.

Table 1 shows patient characteristics, intervals between vaccines and blood collection dates, and outcome measures. The first and second blood collection occurred at a median of 59 (IQR 29, 94) and 156 (IQR 145, 176) days after the second vaccine dose, respectively. The GM (GSD) of the total anti-spike antibody concentration at the first and second blood collection was 2940 (3.5) U/mL and 1455 (2.4) U/mL, respectively; for anti-spike IgG was 102,051(3.1) AU/mL and 30,956 (2.0) AU/mL, and for anti-spike RBD was 66,986 (3.8) AU/mL and 17,406 (2.3) AU/mL, respectively.

Figures 1 (spaghetti plots) and 2 (scatter plots, with smooth curve), and Supplementary Figure S1 (box plots), describe the longitudinal changes in antibody concentrations during the 11 months after the second vaccine. The peak values for total anti-spike (9,042 U/mL), anti-spike IgG (323,980 AU/mL), and anti-RBD IgG (249,051 AU/mL) antibody concentrations were all recorded on the 21st day after the second vaccine dose (Figure 2 and supplementary Table S1). On the 288th day after vaccination, total anti-spike antibody levels stopped declining, plateauing at 1021 U/mL (Figure 2 and supplementary Table S1) which was 11% of the peak value. Anti-spike IgG and Anti-RBD IgG levels plateaued at 321 days (5.3% of the peak value) and 308 days (4.8% of the peak value) days post-vaccination, respectively (see supplementary Tables S1-S4).

The half-lives of the total antibody, anti-spike IgG, and anti-spike RBD concentrations were 94 (95% CI: 70-143) days, 68 (95% CI: 56-89) days, and 61 (95% CI: 49-79) days respectively (Table 2). The mixed-effects ED model identified several independent factors associated with a faster 11-month rate of post-vaccine anti-spike total antibody decay (Table 3), including: older age, a vaccine dosing interval < 35 days, and BNT162b2 (vs. mRNA-1273) vaccine type. Results examining outcomes of anti-spike and anti-RBD IgG antibody concentrations were largely consistent, except: (1) shorter vaccine dosing interval which was not significantly associated with anti-spike and anti-RBD IgG antibody decay over time; and, (2) BMI was not associated with total anti-spike antibody decay, however was associated with anti-spike and anti-RBD IgG antibody decay.

Discussion

We investigated the long-term anti-spike antibody concentrations afforded by immunization of serially-tested middle-aged vaccinees with two doses of mRNA vaccine over 11 months after receiving the second vaccine who had no evidence of prior SARS-CoV-2 infection. Antibody concentrations reached maximum levels on day 21 after the second dose, subsequently declined with a half-life of 94 days, and then plateaued at a level of 1021U/mL after approximately 10 months. Previous studies have looked at long term antibody concentrations subsequent to other beta coronavirus infections and have found some variability with for example one study of more mild MERS-CoV infections demonstrated relatively rapid antibody seroreversion[26], while another pre-print study of antibody responses in health care workers with SARS-CoV-1 infections found persistence of detectable antibody responses beyond 12 years in most those tested[27]. For SARS-CoV-2 infections there is also some variability in the reports but it appears that detectable antibody responses are maintained for up to three years[28]. Our study provides additional insights into the longer-term dynamics of SARS-CoV-2 anti-spike antibody concentration following a two dose mRNA vaccine series. Serum IgG levels following other vaccinations often will stay at a relatively stable plateau level for many years (e.g. following measles and rubella vaccination) but this duration is less clear for SARS-CoV-2 vaccination. This study demonstrates that detectable antibodies are present and have generally reached a plateau in most previously healthy individuals at 10 months post two dose vaccination series. It remains unclear if subsequent induction of long-lived plasma cells through either re-exposure to antigen via infection or vaccination will result in a new higher steady state for anti-spike antibody levels. It is also unclear what protection, particularly against severe disease is provided during this period of plateaued antibody levels. Further longitudinal clinical studies would be needed to better understand this dynamic and may allow for antibody measurement as means for

215 determining if booster vaccine doses are needed. We found older age, a vaccine dosing interval
216 <35 days, and the BNT162b2 (vs. mRNA-1273) vaccine to be associated with a faster rate of
217 post-vaccination total anti-spike antibody decay. These data may assist decision makers with the
218 timing of booster vaccination doses. Modification of vaccination schedules may be warranted for
219 those shown to have faster antibody decay, including older individuals, those with a shorter
220 vaccine dosing interval, and those who received the BNT162b2 vaccine. It may also be
221 warranted to prioritize mRNA-1273 dosing for groups that are at greater risk for rapid antibody
222 decay.

223 Previous studies have investigated post-vaccine antibody decay up to six months after the second
224 vaccine dose, and as well as the factors associated with antibody decline. In a study that
225 investigated the safety and immunogenicity of two mRNA-based COVID-19 vaccines, the
226 immune response after receiving two doses of BNT162b2 was lower in the older individuals (65-
227 85 years) than the younger age group (18 to 55 years)[29]. Pérez-Alós et al[8] modelled the waning
228 of immunity after SARS-CoV-2 vaccination for up to 230 days after the first dose and found
229 decay of antibody levels over time. Additionally, their study found a decrease in antibody levels
230 among older individuals (more than 60 years) independent of previous infection. These findings
231 are consistent with our study which demonstrates faster antibody decay among older individuals
232 after receiving two mRNA vaccine doses. This data, in combination with previous evidence
233 shows that older individuals are more likely to have severe COVID-19[30,31], and thus, supports
234 consideration of earlier booster vaccination strategies (which have been incorporated into some
235 clinical recommendations [32–34]).

236 Our results showed that patients vaccinated with BNT162b2, vs. mRNA-1273, demonstrated a
237 faster post-vaccine antibody decay, which may have implications for booster dose timing.

Previous studies have shown a similar differences between these vaccines, including mRNA-1273 demonstrating higher humoral immunogenicity,[35] and a lower risk of breakthrough infections and COVID-19 related hospitalizations[36]. We also found extended mRNA vaccine dosing intervals '≥ 35 days' to be associated with a slower rate of antibody decay, which is congruent with previous investigations demonstrating improved immunogenicity and vaccine effectiveness with longer, compared to standard, vaccine dosing intervals[37–39,40].

The optimal timing of booster vaccination remains unclear, with some advocating for annual COVID-19 vaccines[41]. Given the existing evidence demonstrating that SARS-CoV-2 antibody levels are associated with COVID-19 risk[12–14] and disease COVID-19 severity,[15–17] antibody models may play a role in informing booster vaccination strategies. Our 11-month data indicates that antibody levels peak within 1 month, and then decline up to approximately 10 months. It is therefore unclear if an annual booster campaign will provide adequate protection and this will at least partially depend on whether SARS-CoV-2 will become primarily associated with seasonal infections.

Limitations

This observation study has several limitations. There may be additional confounding variables affecting immunogenicity decay that we did not account for. Our study participants included middle-aged paramedics in Canada; results may differ in other patient populations. Antibody levels have been shown to be associated with COVID-19 clinical outcomes, however, remain surrogate markers of immunity, and thus actual clinical outcomes may differ. Also, our study did not measure and investigate other markers of immune response such as T-cell responses.

Conclusion

Anti-spike SARS-CoV-2 antibody levels peaked within 21 days after the second mRNA vaccine, and subsequently declined, plateauing at approximately 10 months after the second dose. Older age, shorter vaccine dosing interval (< 35 days), and the BNT162b2 vaccine were associated with a faster rate of post-vaccination antibody decay. These findings may inform booster frequency, including patient-specific schedules.

Conflict of interest

The authors declare no conflict of interest.

Funding:

This study was supported by funding from Government of Canada, through the COVID-19 Immunity Task Force. M.A-B is supported by the Michael Smith Health Research BC/Center for Health Evaluation & Outcome Sciences Research Trainee award. M.E.K. is supported in part by a Scholar Award from the Michael Smith Foundation for Health Research, partnered with Centre for Health Evaluation and Outcome Sciences. B.G. is supported by the Michael Smith Foundation for Health Research.

Author contribution

Conceptualization: M.A-B, B.G, D.G, M.E.K, T.K, P.M.L, S.S, S.J.D, S.F.O, V.B, A.C.M, A.J, D.G. *Data curation*: M.A-B, B.G, D.G, T.K. *Formal analysis*: M.A-B, B.G, D.G, M.E.K, T.K, P.M.L, S.S, S.J.D, S.F.O, V.B, A.C.M, A.J, D.G. *Funding acquisition*: B.G, D.G, T.K, M.A-B. *Investigation*: M.A-B, B.G, D.G, M.E.K, T.K, P.M.L, S.S, S.J.D, S.F.O, V.B, A.C.M, A.J, D.G.

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Ethical approval

The study was approved by the University of British Columbia (Reference number: H20-03620), and University of Toronto (Reference number: 40435) research ethics boards. Participants provided electronic consent upon enrolment.

Data summary statement

The CORSIP data used for this study can be publicly assessed through the website of Canada COVID-19 Immunity Task Force (CITF) website via the link: https://portal.citf.mcgill.ca/.

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FIGURE LEGENDS

Figure 1: Spaghetti plots of longitudinal changes in antibody concentrations 11 months after 2 mRNA vaccine doses

**Days after second vaccine dose (derived from the timing between second vaccine dose and all blood collections)

Figure 2: Scatter plots (*with kernel-weighted local polynomial smoothing curve*) of longitudinal changes in antibody concentrations 11 months after 2 mRNA vaccine dose.

*Vertical lines indicate the time the peak antibody level was recorded, and the time at which the antibody levels plateaued; **horizontal lines indicate the peak antibody level and the value the antibody levels plateaued respectively.

**Days after second vaccine dose (derived from the timing between second vaccine dose and all blood collections)

Table 1: Participants characteristics

Variables	N (%) or Mean (SD) or Median (IQR)
Baseline characteristics	**N = 326 (*at baseline*)**
Age, years, mean (SD)	42 (11)
Female Sex (at birth), n (%)	151 (46)
Racialized	25 (7.7)
Body Mass Index (BMI), mean (SD)	27 (5.0)
Obesity (≥ 30 Kg/m^2), n (%)	88 (27)
Tobacco use, n (%)	13 (4.0)
Medical History, n (%)	
Hypertension	30 (9.2)
Diabetes	5.0 (1.5)
Asthma	55 (17)
Chronic Lung Disease	3.0 (0.9)
Heart diseases	1.0 (0.3)
Kidney diseases	1.0 (0.3)
Liver disease	5.0 (1.5)
Cancer	7.0 (2.1)
Vaccine type, n (%)	
Pfizer (BNT162b2)	268 (82)
Moderna (mRNA-1273)	60 (18)
Vaccine doses, n (%)	
1st & 2nd doses (BNT162b2)	266 (82)
1st & 2nd doses (mRNA-1273)	60 (18)
Vaccine dosing Interval (days), Median (IQR)	35 (28, 42)
Time related variables	
BC 1 date, median (IQR)	2021/04/16 (2021/03/11, 2021/06/02)
BC 2 date, median (IQR)	2021/07/17 (2021/07/09, 2021/08/25)
BC_1-to-BC_2 interval (days), Median (IQR)	100 (76, 132)
V_2-to-BC_1 interval (days), Median (IQR)	59 (29, 94)
V_2-to-BC_2 interval (days), Median (IQR)	156 (145, 176)
Outcome variables (at follow-up)	
Quantitative Antibody Concentrations, GM (GSD)	
Blood Collection 1	
Anti-Spike total antibody concentration	2940 (3.5)
Anti-Spike IgG concentration	102051(3.1)
Anti-RBD IgG concentration	66986 (3.8)
Blood Collection 2	
Anti-Spike total antibody concentration	1455 (2.4)
Anti-Spike IgG concentration	30956 (2)
Anti-RBD IgG concentration	17406 (2.3)

SD: Standard deviation; gMean: geometric mean; gSD: geometric standard deviation; IQR: Interquartile range; BC1, first blood collection date; BC2, second blood collection date; V_2 : Second vaccine dose date; Vaccine dosing interval, the number of days between V1 and V2; *Racialized*: means other non-white races including Asian ethnic groups, blacks, and others.

Table 2: Estimated half-life

Models	Random Intercept (95% CI)	Adjusted decay rates, β (95% CI) (Days after vaccine 2)	Half-life (95% CI)
Model 1	2.54e-14 (0.00)	-0.0032 (-0.0043, -0.0021)	94 (70, 143)
Model 2	0.17 (0.15, 0.20)	-0.0044 (-0.0054, 0.0034)	68 (56, 89)
Model 3	0.25 (0.21, 0.29)	-0.0049 (-0.0062, -0.0038)	61 (49, 79)

All models adjusted for age, vaccine type (BNT162b2 vs mRNA-1273), Sex at birth (Female vs Male), race (Racialized vs white), tobacco use, vaccine dosing interval, BMI:18.5-25Kg/m^2; "BMI: <18.5 Kg/m^2"; underweight, and medical history (hypertension, diabetes, asthma, and Cancer)

Outcome variable for model 1 is Total Anti-spike Antibody Concentration;

Outcome variable for model 2 is Anti-Spike IgG Antibody Concentration;

Outcome variable for model 3 is Anti-RBD IgG Antibody Concentration

Table 3: Mixed effect modelling of changes in antibody concentrations 11 months after second dose

Variables	Model 1: Total Anti-Spike Antibody β (95% CI)	Model 2: Anti-Spike IgG β (95% CI)	Model 3: Anti-RBD IgG β (95% CI)
Fixed effects			
Days after the second dose	-0.0032 (-0.0043, -0.0021)*	-0.0044 (-0.0054, 0.0034)*	-0.0049 (-0.0061, -0.0038)*
Female sex (vrs Male sex)	-0.0046 (-0.11, 0.11)	-0.033 (-0.13, 0.064)	0.0024 (-0.12, 0.12)
Age (years)	-0.0060 (-0.011, -0.00058)*	-0.0079 (-0.013, -0.0031)*	-0.0070 (-0.013, -0.0012)*
Racialized (vrs white)	-0.0097 (-0.18, 0.16)	0.085 (-0.057, 0.23)	0.073 (-0.099, 0.24)
(BMI: 18.5 to <25 kg/m^2) vs (others)	-0.20 (-0.49, 0.093)	0.21 (0.0054, 0.41)*	0.23 (-0.015, 0.48)
(BMI ≥25kg/m^2) vs Others	-0.0073 (-0.29, 0.28)	0.37 (0.15, 0.58)*	0.38 (0.13, 0.64)*
Tobacco use	-0.16 (-0.42, 0.11)	-0.12 (-0.32, 0.085)	-0.12 (-0.37, 0.12)
Vaccine type (BNT162b2 vrs mRNA-1273)	-0.30 (-0.44, -0.17)*	-0.15 (-0.27, -0.031)*	-0.21 (-0.36, -0.066)*
Shorter Dose 1-to-Dose 2 interval (<35 days)	-0.29 (-0.40, -0.18)*	0.022 (-0.076, 0.12)	-0.075 (-0.19, 0.044)
Medical History			
Hypertension	-0.18 (-0.38, 0.0088)	-0.0062 (-0.16, 0.15)	-0.038 (-0.22, 0.15)
Diabetes	-0.047 (-0.47, 0.38)	-0.078 (-0.46, 0.30)	-0.066(-0.52, 0.39)
Asthma	0.077 (-0.061, 0.21)	0.10 (-0.019, 0.23)	0.13 (-0.021., 0.27)
Liver disease	-0.082 (-0.51, 0.34)	0.013 (-0.36, 0.39)	-0.00088 (-0.46, 0.45)
Cancer	-0.14 (-0.50, 0.22)	0.033 (-0.28, 0.35)	-0.012 (-0.40, 0.37)
Random component			
Intercept/constant (95% CI)	2.54e-14 (0)	0.17 (0.15, 0.20)	0.25 (0.21, 0.29)

β (95% CI): Effects estimate (95% Confidence interval); **β** values estimates were shown to 2 significant figures; p values were shown to 3 decimal places, se: standard error; BMI: Body Mass Index (Kg/m^2).

*** = P<0.05**

SUPPLEMENTARY MATERIALS

Supplementary Methods

The Double exponential decay (DED) model is expressed mathematically as:

$$\boldsymbol{Ab_{levels} = Plateau + SpanFast * \exp(-KFast * T) + SpanSlow * \exp(-KSlow * T)}$$

Where, $\boldsymbol{SpanFast = (Y_0 - plateau) * PercentFast * 0.01}$

$$\boldsymbol{SpanSlow = (Y_0 - Plateau) * (100 - PercentFast) * 0.01}$$

$\boldsymbol{Y_0}$ is antibody levels ($\mathbf{Ab}_{levels}$) when the time "**T**" is zero. The ***Plateau*** is the antibody level at the infinite times; ***KFast*** and ***KSlow*** are the two rate constants expressed as the inverse of the time "**T**" in the x-axis; ***TauFast*** and ***TauSlow*** are the two-time constants and they are estimated as the inverse of the rate constants (i.e. **1/KFast** and **1/Kslow**).

Half-life (fast) and ***Half-life (slow)*** are the time units of the Time "**T**" and are computed as (**ln2/K**); and ***PercentFast*** is the fraction of the **span** (defined as the distance between $\boldsymbol{Y_0}$ and ***Plateau*** point)[24].

Supplementary Figures

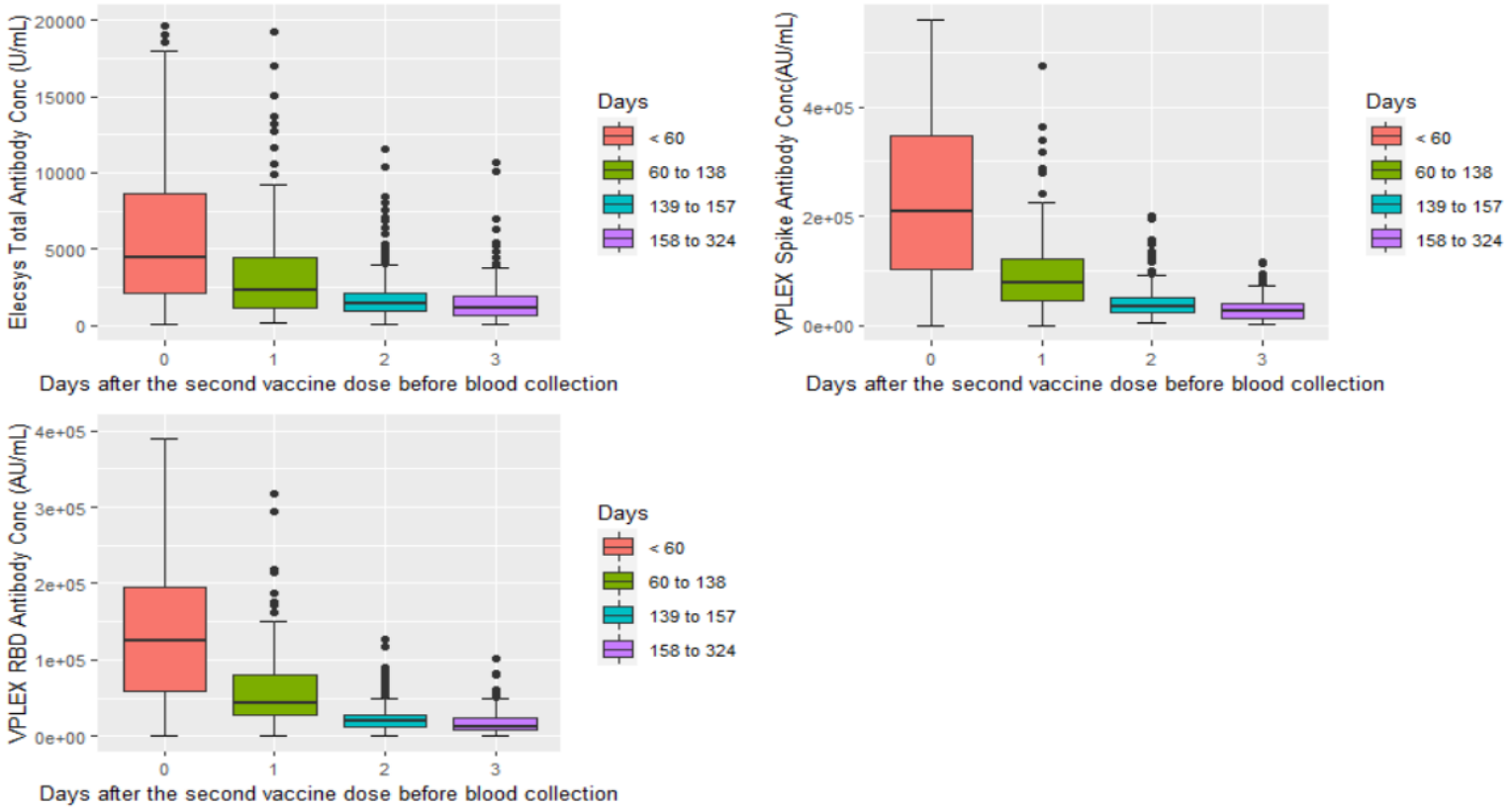

Figure S1: Box and whisker plot of antibody concentration decay by days after second vaccine (categorized into four quartiles). Days (time) was calculated as the time interval between the date of the second dose and the date of first and second blood collections.

Supplementary Tables

Table S1: Estimated peak antibody concentrations.

Antibody concentration	Peak antibody value	Day (P)	Plateau value	Day (L)
Total Anti-Spike Antibody concentration	9,042	21	1021	288
Anti-Spike IgG Concentration	323,980	21	17287	321
Anti-RBD IgG Concentration	249,051	21	11909	308

Day (P): the day the peak antibody levels were recorded; *Day (L)*: the day/time the lowest antibody level was recorded. Lowest IgG value defined as the value equal to when the antibody levels declined to less than 5% of the peak antibody value.

Table S2: Table showing results from the DED for Total antibody concentration (U/mL)

Two phase decay	
Best-fit values	
Y0	9741
Plateau	**1021**
PercentFast	77.73
KFast	0.01835
KSlow	0.007189
Half Life (Slow)	96.42
Half Life (Fast)	37.78
Tau (slow)	139.1
Tau (fast)	54.51
Rate constant ratio	2.552
Goodness of Fit	
Robust Sum of Squares	32.63
RSDR	320.0
Constraints	
PercentFast	0 < PercentFast < 100
KFast	KFast > 1*KSlow
KSlow	KSlow > 0

Table S3: Table showing results from the DED model for anti-spike IgG (AU/mL)

Two phase decay	Hit constraint
Best-fit values	
Y0	311950
Plateau	**17287**
PercentFast	~ 25.43
KFast	~ 0.01488
KSlow	0.01488
Half Life (Slow)	46.58
Half Life (Fast)	~ 46.58
Tau (slow)	67.21
Tau (fast)	~ 67.21
Rate constant ratio	~ 1.000
Goodness of Fit	
Robust Sum of Squares	40.60
RSDR	6108
Constraints	
PercentFast	0 < PercentFast < 100
KFast	KFast > 1*KSlow
KSlow	KSlow > 0

Table S4: Table showing results from the DED model for anti-RBD IgG (AU/mL)

Two phase decay	
Best-fit values	
Y0	244272
Plateau	**11909**
PercentFast	86.06
KFast	0.01716
KSlow	0.01716
Half Life (Slow)	40.40
Half Life (Fast)	40.40
Tau (slow)	58.29
Tau (fast)	58.29
Rate constant ratio	1.000
Goodness of Fit	
Robust Sum of Squares	37.81
RSDR	5875
Constraints	
PercentFast	0 < PercentFast < 100
KFast	KFast > 1*KSlow
KSlow	KSlow > 0

Figure 1

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Figure 2

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