Clinical Infectious Diseases

BRIEF REPORT

A Higher Antibody Response Is Generated With a 6- to 7-Week (vs Standard) Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Vaccine Dosing Interval

Brian Grunau,[1,2,3] Michael Asamoah-Boaheng,[2,4] Pascal M. Lavoie,[5] Mohammad Ehsanul Karim,[1,6] Tracy L.Kirkham ,[7,8] Paul A. Demers,[6,7,8] Vilte Barakauskas,[9] Ana Citlali Marquez,[9,10] Agatha N. Jassem,[9,10] Sheila F. O'Brien,[11] Steven J. Drews,[11,12] Scott Haig,[3] Sheldon Cheskes,[13] and David M. Goldfarb[9]

[1]Centre for Health Evaluation & Outcome Sciences, University of British Columbia, Canada; [2]Department of Emergency Medicine, University of British Columbia, Canada; [3]British Columbia Emergency Health Services, British Columbia, Canada; [4]Faculty of Medicine, Clinical Epidemiology, Memorial University of Newfoundland, Canada; [5]Department of Pediatrics, University of British Columbia, Canada; [6]School of Population and Public Health, University of British Columbia, Canada; [7]Dalla Lana School of Public Health, University of Toronto, Toronto, Canada; [8]Ontario Occupational Cancer Research Centre, Ontario, Canada; [9]Department of Pathology and Laboratory Medicine, University of British Columbia, Canada; [10]Public Health Laboratory, British Columbia Centre for Disease Control, British Columbia, Canada; [11]Canadian, Blood ServicesCanada; [12]Laboratory Medicine and Pathology, University of Alberta, Alberta, Canada; and [13]Li Ka Shing Knowledge Institute and Division of Emergency Medicine, Department of Family and Community Medicine, University of Toronto, Ontario, Canada

The optimal dosing interval for severe acute respiratory syndrome coronavirus 2 vaccines remains controversial. In this prospective study, we compared serology results of paramedics vaccinated with mRNA vaccines at the recommended short (17–28 days) vs long (42–49 days) interval. We found that a long dosing interval resulted in higher spike, receptor binding domain, and spike N terminal domain antibody concentrations.

Keywords. SARS-CoV-2; COVID-19; vaccine; antibodies; spike.

Clinical trial investigations have demonstrated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines to be highly efficacious in preventing symptomatic disease. However, results are limited to a single vaccine administration schedule, typically 3 or 4 weeks between vaccine doses [1, 2]. This may not be the optimal schedule at the individual level to achieve robust and long-lasting immunity or at the population level to achieve the fastest and overall community-level protection. One study reported that ChAdOx1 (AstraZeneca) vaccine efficacy improved with longer vaccine dosing intervals (up to approximately 3 months) [3]. We investigated the differences in immune response according to vaccine dosing intervals of <4 weeks vs 6–7 weeks among paramedics who received mRNA vaccines.

METHODS

Study Design

Samples were from the COVID-19 (coronavirus disease 2019) Occupational Risks, Seroprevalence and Immunity among Paramedics in Canada (CORSIP) study participants. CORSIP is an observational cohort (commenced in January 2021) study of adult paramedics in Canada, approved by the University of British Columbia and University of Toronto research ethics boards, with the goal of investigating occupational risks and seroprevalence of SARS-CoV-2 immune measures among paramedics. CORSIP participants provided blood samples upon enrollment (that were used for this analysis), sociodemographic questionnaire data, and the dates and results of all SARS-CoV-2 polymerase chain reaction (PCR) tests and vaccinations.

Participants

We included samples from CORSIP participants who had received 2 doses of the BNT162b2 (Pfizer) and/or mRNA-1273 (Moderna) vaccines. We excluded participants with evidence of a preceding SARS-CoV-2 infection (a positive PCR test or reactive Roche nucleocapsid Elecsys Anti-SARS-CoV-2 assay [4]), given the known differential impact on antibody responses post-vaccination [5].

Serological Testing

We tested all samples using the Roche nucleocapsid Elecsys Anti-SARS-CoV-2 assay (to confirm eligibility); the Ortho-Clinical Diagnostics VITROS Anti-SARS-CoV-2 Total Antibody assay, which targets the spike protein; the Meso scale discovery (MSD) V-PLEX COVID-19 Coronavirus Panel 2 immunoglobulin G (IgG) assay, which measures IgG to the SARS-CoV-2 spike, receptor binding domain (RBD), spike N terminal domain (NTD), and nucleocapsid (N) antigens; and the quantitative Roche spike Elecsys Anti-SARS-CoV-2 S assay (validated range of 0.4–2500 U/mL [6]; samples with the maximum value were analyzed with this result). See the Supplementary Methods for further details.

Statistical Analyses

We classified samples according to the following a priori determined vaccine dosing intervals: the recommended "short interval" (17–28 days; the Centre for Disease Control recommends 21- and 28-day vaccine dosing intervals for the BNT162b2 and mRNA-1273 vaccines, respectively, but state that the second vaccine dose may be given up to 4 days early [7]) and the "long

Received 13 August 2021; editorial decision 28 October 2021; published online 30 November 2021.
Correspondence: Brian Grunau, BC Resuscitation Research Collaborative, 1190 Hornby St., 4th Floor, Vancouver, B.C. V6Z 2K5, Canada (Brian.Grunau2@vch.ca).

Clinical Infectious Diseases® 2021;XX(XX):1–4

https://doi.org/10.1093/cid/ciab938

interval" (42–49 days). We compared group characteristics using parametric and nonparametric tests, as appropriate. We created scatterplots for the Roche spike, MSD spike, and RBD results, with cubic spline curves [8]. The distribution of values from all antibody assays were visualized using box plots stratified by the second vaccine-to-blood sampling interval. We compared antibody concentrations (spike, RBD, NTD, and N) between groups by fitting 4 multiple linear regression models (1 for each antibody) to demonstrate the association between the antibody concentration and the dosing interval group, adjusting for the second vaccine-to-blood sampling interval. For each fit, we assessed differences between groups using the test for regression coefficient (*t* test) for the difference between the mean antibody level [9]. For these models, we excluded participants with blood sampling ≤14 days after their second dose, given the rapid antibody concentration rise that is observed in this immediate post-second dose vaccine period [10]. We repeated the above methods for the following 3 secondary analyses: include an interaction term between vaccine type and dosing interval group in the model (to determine if the relationship between vaccine interval and antibody concentration varied by vaccine type); include ethnicity and education level adjustment covariates in the model; and within subgroups defined by vaccine type.

RESULTS

We included 186 participants in the analysis, of whom 131 (70.4%) were vaccinated with the BNT162b2 vaccine, 55 (29.6%) with the mRNA-1273 vaccine, and 1 (0.54%) with both. The median age was 38 years (interquartile range [IQR], 33–45), and 15% were racialized. Blood sampling followed the second vaccine dose by a median of 56 days (IQR, 29–76).

Participant characteristics, classified by vaccine dosing interval group, are listed in Supplementary Table 1. The age of participants, the date of the first vaccine dose, and the proportion with comorbidities were similar. There were significant between-group differences for education level, vaccine type, and vaccine-to-blood sampling intervals. The Ortho Anti-SARS-CoV-2 Total Antibody was reactive for all samples within both groups.

Figure 1 and Supplementary Figures 1–5 show antibody concentrations as a function of second vaccine-to-sampling intervals. Regression models demonstrated significantly higher antibody concentrations in individuals who experienced longer vaccine intervals when evaluating the MSD (t = 2.211, $P = .028$) and Roche (t = 7.703, $P < .0001$) spike, as well as MSD RBD (t = 4.044, $P < .0001$) and NTD (t = 3.684, P < .0001) antibody concentrations. We did not detect between-group differences for MSD N antibody concentrations (t = 1.772, $P = .078$).

Within our secondary analysis, the interaction term between vaccine type and dosing interval was insignificant for all antibody models (Supplementary Table 2). The model that incorporated education level and ethnicity demonstrated results consistent with the primary analysis (Supplementary Table 3). When antibody concentrations stratified by vaccine type were examined separately, long vaccine intervals demonstrated higher Roche spike antibody concentrations for the BNT162b2 and mRNA-1273 vaccines (Supplementary Table 4).

DISCUSSION

Optimal vaccine dosing intervals are of critical importance at the population and individual levels, particularly in the context of global vaccine supply challenges. We found that compared to the recommended (≤4 week) dosing interval, a 6- to 7-week interval for mRNA vaccines resulted in higher spike-related antibody concentrations. Increased development of germinal center B cells associated with vaccine dosing intervals may explain this observation [11]. These data may help inform COVID-19 vaccination strategies, especially in settings where vaccine supplies remain constrained.

Our data demonstrated differences in all spike-related antibody binding concentrations. We used 2 assays to test the spike antibody concentration; despite differences in the curves, both were qualitatively consistent. We did not detect a difference in the relationship between vaccine dosing intervals and antibody concentrations based on vaccine type. For the regression model, we elected to censure samples collected in the first 2 weeks post-second dose vaccination given prior antibody dynamics studies that showed this universally as a period of rapid antibody increase [10]. However, our data curves suggest that in both groups, antibody concentrations increased for approximately 3 weeks post-second vaccination dose and then declined.

Only 1 peer-reviewed study has reported differences in vaccine dosing intervals, an analysis using data from 3 ChAdOx1 (AstraZeneca) vaccine clinical trials that concluded that vaccine efficacy (based on symptomatic PCR-confirmed disease) increased from 55% to 81% when the dosing interval was increased from <6 weeks to 12 weeks [3]. While there is currently no peer-reviewed mRNA vaccine data for comparison, other data have been reported. A recent study of the BNT162b2 vaccine in participants aged ≥80 years reported that an 11- to 12-week vaccine dosing interval, comparison with 3 weeks, resulted in higher anti-spike antibodies (measured 2 weeks after the second dose) [12]. Another investigation of participants aged 50–89 years found higher antibody concentrations among those with 65- to 84-day (vs 19- to 29-day) dosing intervals [13]. Our study extends this finding to a younger population and also examines a different dosing interval, demonstrating consistent results. Several studies performed across various populations have shown a correlation between both binding antibody and/or neutralizing antibody concentrations and vaccine efficacy [14]. We observed persistence of high antibody levels in the longer interval group, and this suggests that a delayed second

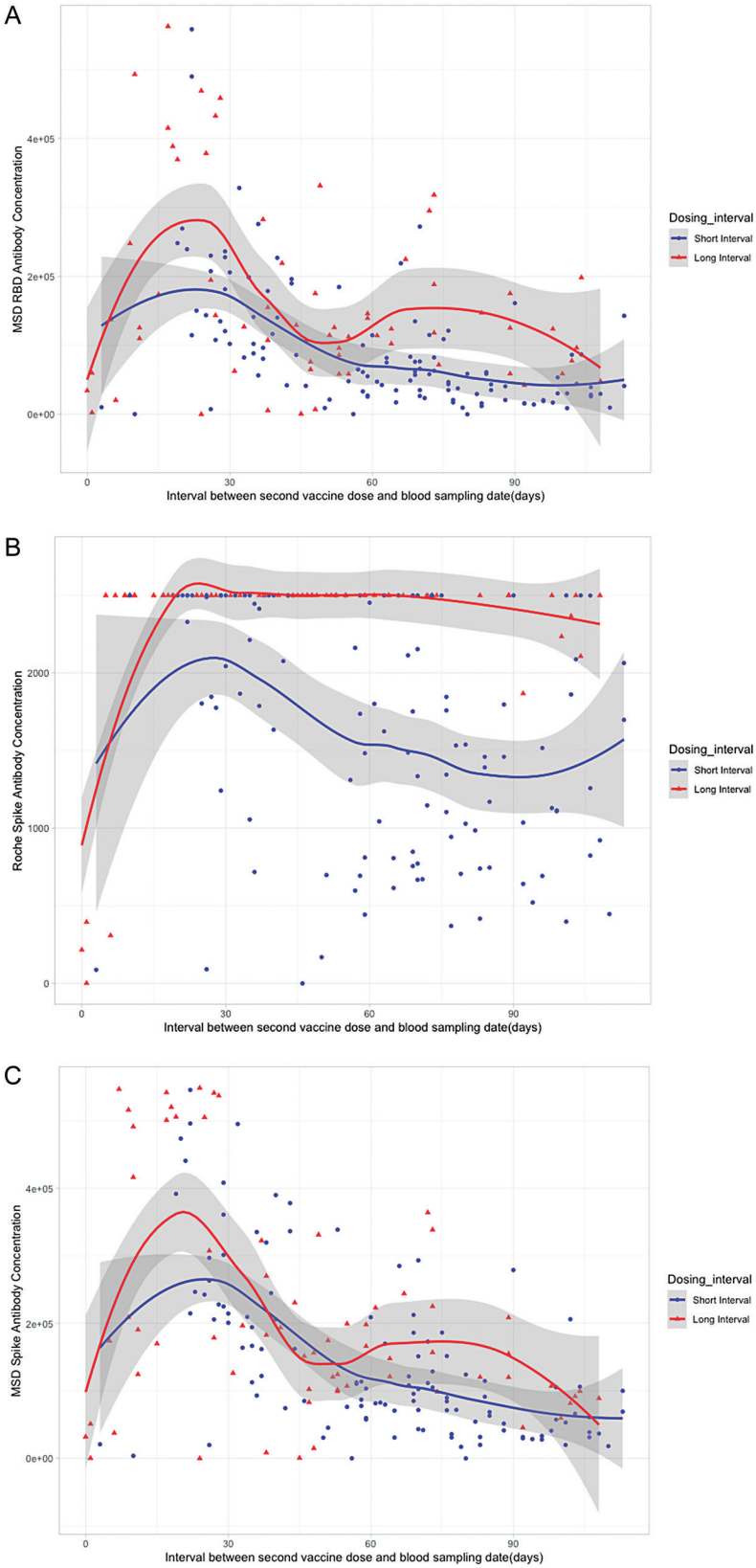

Figure 1. Scatterplot of MSD spike (*A,* Au/mL), Roche spike (*B,* U/mL), and MSD RBD (*C,* Au/mL) antibody concentrations, with cubic spline curves (and 95% confidence intervals). For the Roche spike assay, the maximum value of 2500 U/L occurred in 35 (30%) samples of the short interval group and 60 (88%) samples of the long interval group. Abbreviations: MSD, Meso scale discovery; RBD, receptor binding domain.

dose strategy may allow for deferral of third vaccine doses (that are already being provided in some jurisdictions [15]).

In addition to individual-level benefits, delayed dosing strategies may improve protection at the community level. Two epidemiological simulation studies have estimated that delayed vaccination schedules result in reduced cumulative mortality [16, 17]. Although evidence was lacking at the time, some countries elected to implement delayed dosing strategies early in the vaccination rollout [18], a decision that now appears to have been reasonable.

Our study has some limitations. We may have misclassified some cases when we excluded samples due to prior COVID-19. Our study was observational, and confounders such as ethnicity, vaccine type, and education cannot be excluded. We accounted for second vaccine-to-blood sampling interval variability in our regression analysis; however, there may be residual bias. Future studies may choose to standardize vaccine-to-blood collection intervals. The Roche spike assay had a maximum value of 2500 U/mL, which may have decreased our ability to detect a difference. Our study included paramedics in Canada, primarily of White ethnicity, whose immunity may be systematically different from the general population, populations in other regions, or other ethnic groups. While antibody levels are correlative of protection, we did not examine vaccine efficacy in a real-life setting. Our data were limited to blood samples obtained up to 113 days after the second vaccine dose, and we cannot comment on longer-term immune responses.

CONCLUSIONS

A SARS-CoV-2 vaccine dosing interval of 6–7 weeks compared with a standard dosing interval (<4 weeks) resulted in higher anti-spike antibodies detected in the blood of vaccinated individuals. These data may inform ongoing international COVID-19 vaccination efforts.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. We acknowledge the contributions of all participating paramedics: Tara Martin, David O'Neill, Heba Qazilbash, Dong Vo, Yann-Charles Lafontant, Sadaf Sediqi, Sandra Jenneson, Robert Schlamp, Justin Yap, Veronica Chow, the BC Children's Hospital Biobank, Hamid Razzaghian, Jennie Helmer, Richard Armour, Ian Drennan, Jim Christenson, Jocelyn Srigley, Jennifer Bolster, Nechelle Wall, Brian Twaites, Valerie Conrod, and Chelsie Osmond; all partnering paramedic services; the Canadian Association of Paramedics; and local partnering paramedic unions.

Financial support. This study was supported by funding from the government of Canada, through the COVID-19 (coronavirus disease 2019) Immunity Task Force. M. E. K. is supported in part by a Scholar Award from the Michael Smith Foundation for Health Research, partnered with the Centre for Health Evaluation and Outcome Sciences. B. G. is supported by the Michael Smith Foundation for Health Research.

Potential conflicts of interest. S. D. has acted as a content expert on respiratory viruses for Johnson & Johnson (Janssen); received grant funding outside of the submitted work from the Canadian Institutes of Health Research, Alberta Innovates, and University of Alberta Hospital Foundation; received consulting fees from Roche; received support from Johnson and Johnson (Janssen) in publishing a paper; and received severe acute respiratory syndrome coronavirus 2 serology test kits from Abbott. All remaining authors: No reported conflicts of interest. The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Polack FP, Thomas SJ, Kitchin N, et al; C4591001 Clinical Trial Group. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med **2020**; 383:2603–15.
2. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med **2021**; 384:403–16.
3. Voysey M, Costa Clemens SA, Madhi SA, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. Lancet **2021**; 397:881–91.
4. Ainsworth M, Andersson M, Auckland K, et al. Performance characteristics of five immunoassays for SARS-CoV-2: a head-to-head benchmark comparison. Lancet Infect Dis **2020**; 20:1390–400.
5. Ebinger JE, Fert-Bober J, Printsev I, et al. Antibody responses to the BNT162b2 mRNA vaccine in individuals previously infected with SARS-CoV-2. Nat Med **2021**; 27:981–4.
6. Cobas. Elecsys anti-SARS-CoV-2 S V 1.0. Published **2021**. Available at: https://www.rochecanada.com/content/dam/rochexx/roche-ca/products/docs/package_inserts/Anti-SARS-CoV-2-S-09289267190-EN-Can.pdf. Accessed 10 August 2021.
7. Centers for Disease Control and Prevention. COVID-19 vaccines. Published **2021**. Available at: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html. Accessed 11 August 2021.
8. Gauthier J, Wu QV, Gooley TA. Cubic splines to model relationships between continuous variables and outcomes: a guide for clinicians. Bone Marrow Transplant **2020**; 55:675–80.
9. Montgomery D, Peack E, Vining G. Introduction to linear regression analysis. New Jersey, USA: John Wiley & Sons, Inc., **2012**.
10. Wheeler SE, Shurin GV, Yost M, et al. Differential antibody response to mRNA COVID-19 vaccines in healthy subjects. Martinez MA, ed. Microbiol Spectr **2021**. doi:10.1128/Spectrum.00341-21.
11. Pettini E, Pastore G, Fiorino F, Medaglini D, Ciabattini A. Short or long interval between priming and boosting: does it impact on the vaccine immunogenicity? Vaccines **2021**; 9:289.
12. Parry H, Bruton R, Stephens C, et al. Extended interval BNT162b2 vaccination enhances peak antibody generation in older people. medRxiv doi:10.1101/2021.05.15.21257017.
13. Amirthalingam G, Bernal J, Andrews N, et al. Higher serological responses and increased vaccine effectiveness demonstrate the value of extended vaccine schedules in combatting COVID-19 in England. medRxiv doi:10.1101/2021.07.26.21261140.
14. Earle KA, Ambrosino DM, Fiore-Gartland A, et al. Evidence for antibody as a protective correlate for COVID-19 vaccines. Vaccine **2021**; 39:4423–8.
15. Heller J. Israel to offer Pfizer booster shot against COVID-19 to the over-60s. Reuters. Available at: https://www.reuters.com/world/middle-east/israel-offer-third-shot-pfizer-vaccine-people-over-60-israeli-news-reports-2021-07-29/. Accessed 3 August 2021.
16. Romero-Brufau S, Chopra A, Ryu AJ, et al. Public health impact of delaying second dose of BNT162b2 or mRNA-1273 covid-19 vaccine: simulation agent based modeling study. BMJ **2021**:n1087. doi:10.1136/bmj.n1087.
17. Moghadas SM, Vilches TN, Zhang K, et al. Evaluation of COVID-19 vaccination strategies with a delayed second dose. Read AF, ed. PLoS Biol **2021**; 19:e3001211.
18. Balch B. Canada took a risk delaying second COVID-19 vaccine doses. Now, its vaccination campaign is one of the best in the world. Available at: https://www.aamc.org/news-insights/canada-took-risk-delaying-second-covid-19-vaccine-doses-now-its-vaccination-campaign-one-best-world. Accessed 2 August 2021.