Tonia Tauh, MD, FRCPC, Michelle Mozel, MSc, Paula Meyler, MD, FRCPC, Susan M. Lee, MAS, MD, FRCPC

What is the evidence for extending the SARS-CoV-2 (COVID-19) vaccine dosing schedule?

With off-label COVID-19 vaccine dosing being widely used as a way to increase the number of people receiving their first dose, and hearing physicians' concerns about the safety of such a practice, a research group at Royal Columbian Hospital in British Columbia undertook an analysis of the data, published and unpublished, and conclude that a longer gap between doses is likely warranted given the circumstances.

ABSTRACT: Vaccine rollout for SARS-CoV-2 (COVID-19) in British Columbia is underway with two approved mRNA vaccines (Pfizer-BioNTech and Moderna). Traditionally, an inactivated or attenuated pathogen may have been used as a vaccine, whereas mRNA and DNA vaccines provide genetic material that instruct the body's cells to produce a viral spike protein antigen. Presently, both mRNA vaccines are approved for use as a two-dose schedule given either 21 days or 28 days apart. However, there is a relative scarcity of vaccine compared to the population of British Columbia. BC's public health officials have proposed a delay between the primary vaccination and booster to 35 days from the recommended 21 and 28 days. Based on unpublished data available to the National Advisory Committee on Immunization through Health Canada for both the Pfizer-BioNTech and Moderna vaccines, there was no difference in vaccine efficacy between the people who got their second dose at day 19 and the people who got it at day 42. Various jurisdictions around the world are permitting a prolonged second dosing interval. Despite the paucity of clinical trial data, it is likely that increasing the interval between the first and second doses of COVID-19 mRNA vaccines by Pfizer-BioNTech and Moderna is safe, both in the intervening period between doses and for long-term efficacy. Extending the vaccine schedule is likely warranted in order to allow the widest population to receive the first dose.

Drs Tauh, Meyler, and Lee are staff anesthesiologists at Royal Columbian Hospital. Ms Michelle Mozel is a clinical research coordinator in the Department of Anesthesia at Royal Columbian Hospital. Drs Tauh and Meyler are clinical instructors and Dr Lee is an assistant clinical professor in the Department of Anesthesiology, Pharmacology, and Therapeutics at the University of British Columbia.

This article has been peer reviewed.

A successful vaccination strategy against SARS-CoV-2 (COVID-19) may be a cornerstone in the resolution of the current pandemic. If it is to be effective, an efficient vaccination rollout is important as the epidemic puts extreme pressure on health services. A rapid vaccine rollout has many roadblocks, from some people's initial hesitancy to receive a novel vaccine to supply chain distribution challenges. If we are to contain and control the outbreak, we must establish from data that the vaccines are not only safe but also effective and widely available. With the current limitations on vaccine supply, our society must balance vaccinating as many people as possible in short order with the strict timing recommendations for the vaccines as they were designed and studied. As such, a question has arisen by patients and providers alike: to what degree can we alter the recommended dosing regimen without impacting effectiveness?

What are mRNA and DNA vaccines?

Traditionally, an inactivated or attenuated pathogen may have been used as a vaccine. In contrast, novel mRNA (Moderna and Pfizer-BioNTech) and DNA (Oxford-AstraZeneca) vaccines provide genetic material that instruct the body's cells to produce a viral spike protein antigen. This antigen, which cannot cause disease, will go on to elicit an immune response. As the cells produce the antigen, antibodies will neutralize the whole virus. Further, later infection may activate memory T cells to generate an early antibody response to attenuate infection.[1] While the COVID-19 mRNA vaccines are new, mRNA vaccines have been in development for many years. However, since the Moderna and Pfizer-BioNTech vaccines are the first mRNA vaccines to be widely used, little is known about their side effects, long-term efficacy, or the effect of off-label dosing schedules.

What dosing schedules for COVID-19 vaccines are approved based on clinical trial data?

Presently, both mRNA vaccines (Moderna and Pfizer-BioNTech) are approved for use as a two-dose schedule given either 21 days (Pfizer-BioNTech)[2,3] or 28 days (Moderna)[4] apart. Upon administration of the first dose of the Pfizer-BioNTech vaccine, partial immunity is acquired against severe COVID-19 symptoms, typically by 7 days, with 52.4% efficacy between 7 to 14 days and 89% between days 15 to 21 after dose 1. Protection continues to climb to 92.6% for the Pfizer-BioNTech vaccine after the second dose.[2] Of note, single-dose efficacy was not a primary outcome of the trial, but rather extrapolated by subgroup analysis and thus based on fewer data.[2,3] The Moderna vaccine showed 50.8% efficacy of the first dose on days 1 to 14 and 92.1% efficacy at 14 or more days after the first dose (80.2% overall after dose 1).[4,5] No clinical trials have been able to judge how long immunogenicity lasts following one dose, but we do know that efficacy after the first dose increases with time until the second dose is administered.

The Oxford-AstraZeneca vaccine, which is a DNA vaccine via an adenovirus vector, is still under review and is not approved for use in Canada. The first and second doses were scheduled 28 days apart in the Phase 2/3 clinical trial. A single-dose regimen was also included in the study, although it showed lower neutralizing antibody titres than the two-dose regimen.[6,7]

What data exist on deviations from approved dosing schedules?

Unpublished data from Pfizer-BioNTech and Moderna and published Oxford-AstraZeneca dosing interval trials demonstrate patient level data on longer dosing intervals. Based on unpublished data available to the National Advisory Committee on Immunization through Health Canada for both the Pfizer-BioNTech and Moderna vaccines, there was no difference in vaccine efficacy between the people who got their second dose at day 19 and the people who got it at day 42.[8,9] Importantly, there was no decrease in protection between the first dose and the second dose.

Trials of the Oxford-Astra-Zeneca vaccine did include different spacing between doses and found that a longer gap (2 to 3 months) led to a greater immune response.

Similarly, the trials of the Oxford-AstraZeneca vaccine did include different spacing between doses and found that a longer gap (2 to 3 months) led to a greater immune response, but the overall participant numbers were small.[6,7] In the UK study, 59% (1407 of 2377) of the participants who had two standard doses received the second dose between 9 and 12 weeks after the first. In the Brazilian study, only 18.6% (384 of 2063) received a second dose between 9 and 12 weeks after the first. The combined trial results found that vaccine efficacy at 14 days post–dose 2 was higher in the group with more than 6 weeks between doses than in the group with less than 6 weeks between doses (65.4% vs. 53.4%).[6,7]

What do governing bodies around the world recommend?

The unpublished data from Pfizer-BioNTech and Moderna and published data from Oxford-AstraZeneca on dosing intervals gave several consensus groups reason to advocate for a prolonged dosing interval up to 42 days (6 weeks). The British Society of Immunology stated that, "Most immunologists would agree that delaying a second 'booster' dose of a protein antigen vaccine (such as the two approved COVID-19 vaccines [Pfizer-BioNTech and Oxford-AstraZeneca]) by 8 weeks would be unlikely to have a negative effect on the overall immune response post-boost. We also would not expect any specific safety issues to arise for the individual due to delaying the second dose, other than an increased potential risk of disease during the extended period due to lowered protection."[10]

In an attempt to extend the initial phases of vaccination to a larger proportion of people, the Joint Committee on Vaccines and Immunization, along with the UK Chief Medical Officers have approved a prolonged second dosing interval up to 12 weeks for the Pfizer-BioNTech and Oxford-AstraZeneca vaccines.[11,12] The WHO has suggested that "…extending dose 2 up to 42 days may not be unreasonable."[13] The US CDC has stated that there is no maximum interval between first and second doses for either vaccine.[14]

The **Table** summarizes current recommendations from various regulating bodies. The US FDA and Pfizer-BioNTech have both maintained that the clinically tested dosing schedule should be followed.[2,15] The Government of Canada advocates for maintaining the recommended dosing schedule; however, it states, "If, due to logistical constraints, jurisdictions cannot complete the two-dose COVID-19 vaccine series as close as possible to the authorized or alternative schedules outlined in Table 2, they may refer to Appendix C for a summary of considerations and options on ethics, equity, feasibility and acceptability summarized in NACI's Core Ethical Dimensions Filter of the EEFA Framework and the accompanying ethics analysis."[16] BC Provincial Health Officer Dr Bonnie Henry has announced extending the second dosing of both vaccines (Pfizer-BioNTech and Moderna) to 35 days.[17]

TABLE. Dosing interval recommendations for mRNA COVID-19 vaccines from a variety of international and Canadian jurisdictions.

Organization	In favor of extending dosing interval	In favor of maintaining dosing as recommended by manufacturer
Pfizer-BioNTech[2]		"The safety and efficacy of the vaccine has not been evaluated on different dosing schedules as the majority of trial participants received the second dose within the window specified in the study design . . . There is no data to demonstrate that protection after the first dose is sustained after 21 days."
British Society of Immunology[10]	"…delaying a second 'booster' dose of a protein antigen vaccine (such as the two approved COVID-19 vaccines [Pfizer-BioNTech and AZN]) by 8 weeks would be unlikely to have a negative effect on the overall immune response post-boost."	
US FDA[15]		"The second dose should be administered as close to the recommended interval as possible," i.e., 21 days and 28 days respectively.
WHO[13]	"…the interval between doses may be extended up to 42 days (6 weeks), on the basis of currently available clinical trial data."	
European Medicines Agency[9]	"…the maximum interval of 42 days between the first and the second dose of the Pfizer-BioNtech vaccine should be respected to obtain full protection."	
US CDC[14]	"There is no maximum interval between the first and second doses for either vaccine. Therefore, if the second dose is administered >3 weeks after the first Pfizer-BioNTech vaccine dose or >1 month after the first Moderna vaccine dose, there is no need to restart the series."	
Government of Canada[16]		Pfizer-BioNTech minimum interval—19 days, authorized interval—21 days, alternate interval—28 days Moderna minimum interval—21 days, authorized interval—28 days, alternate interval—none
Government of Quebec[18]	"Les experts ont devoilé que la deuxième dose du vaccin soit administrée entre 42 et 90 jours après la première dose" *Experts have recommended that the second dose of the vaccine be administered between 42-90 days after the first dose.*	
Government of Ontario[19]	Extend doses up to 42 days for some recipients of Pfizer-BioNtech. • Long-term care residents, high-risk retirement home residents and their essential caregivers, and concurrently vaccinated staff: second dose of Pfizer-BioNtech vaccine in 21 to 27 days. · All other recipients of the Pfizer-BioNtech vaccine: second dose 21 - 42 days · Moderna vaccine: 28 days	
Government of Alberta[20]	Second doses of COVID-19 vaccine will be offered within 42 days of the first dose	
Government of British Columbia[17]	Extend second dose to 35 days. "A 35-day interval aligns with the operational reality that vaccine supplies will be back-end loaded with more vaccine scheduled to arrive in February and March 2021 than in December 2020 and January 2021 so everyone vaccinated will receive their second dose as scheduled in the coming weeks."	

Summary and recommendation

Upon learning that off-label vaccine dosing was being proposed in British Columbia, and hearing that physicians were concerned about the safety of such a practice, our research group at Royal Columbian Hospital in British Columbia undertook our own analysis of the data, published and unpublished. While new data may arise in the future that will challenge these conclusions, based on our analysis of currently available data, we support British Columbia's decision to extend the dosing interval of Pfizer-BioNTech and Moderna vaccines from 21/28 days to 35 days for the following reasons:

- There are inadequate vaccine supplies to maintain the maximum rate of primary vaccinations while adhering to strict approved dosing schedules for those who have already received the first dose.
- Partial immunity is granted after the first vaccine dose, as demonstrated in clinical trials.

- Immunity does not appear to wane for the duration studied (up to 42 days).
- There is no obvious biological basis to believe that the long-term efficacy of the booster dose will be negatively affected by a short delay in receiving it.

In an ideal world, there would be ample vaccine and adequate logistical machinery to mass vaccinate the entire population using approved, clinical-trial tested dosing intervals. Unfortunately, jurisdictions around the globe are facing shortages that require us to face the inequities of vaccine distribution, balance the ethical principles of beneficence, non-maleficence, and justice. While there are no large clinical trial published data to guide prolonged delays of the second dose, there are data to suggest that delaying the second dose likely preserves the long-term boost in immunity without an unacceptable decrease in immunity in the intervening period between doses. Therefore, delaying the second dose, which allows for wider primary vaccination (and therefore a faster route to immunizing the most vulnerable members of our population), seems a reasonable option in situations of vaccine shortage, such as what we are currently facing in BC, throughout Canada, and around the world. ■

Delaying the second dose, which allows for wider primary vaccination (and therefore faster route to immunizing the most vulnerable members of our population), seems a reasonable option in situations of vaccine shortage.

Competing interests

None declared.

References

1. Pardi N, Hogan M, Porter F, et al. mRNA vaccines—A new era in vaccinology. Nat Rev Drug Discov 2018;17:261-279.
2. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2020;383:2603-2615.
3. US Food and Drug Administration. Vaccines and related biological products advisory committee briefing document. Accessed 11 January 2021. www.fda.gov/media/144246/download.
4. Baden LR, Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med 2021;384:403-416.
5. Public Health England. COVID-19: The green book, chapter 14a. Coronavirus (COVID-19) vaccination information for public health professionals. Accessed 19 January 2021. www.gov.uk/government/publications/covid-19-the-green-book-chapter-14a.
6. Voysey M, Clemens SA, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: An interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet 2021;397:99-111.
7. Knoll M, Wonodi C. Comment: Oxford–AstraZeneca COVID-19 vaccine efficacy. Lancet 2021:397:72-74.
8. BC Centre for Disease Control. Public health statement on deferral of second dose COVID-19 vaccine in BC, 27 January 2021. Accessed 27 January 2021. www.bccdc.ca/Health-Info-Site/Documents/COVID-19_vaccine/Public_health_statement_deferred_second_dose.pdf.
9. Reuters. EU says interval between Pfizer vaccine doses should be respected. 4 January 2021. Accessed 11 January 2021. www.reuters.com/article/us-health-coronavirus-ema-pfizer-idUSKBN2991Z3.
10. British Society for Immunology. British Society for Immunology statement on COVID-19 vaccine dosing schedules. 4 January 2021. Accessed 11 January 2021. www.immunology.org/policy-and-public-affairs/briefings-and-position-statements/COVID-19-vaccine-dosing-schedules.
11. UK Joint Committee on Vaccination and Immunisation. Advice on priority groups for COVID-19 vaccination 30 December 2020. Accessed 19 January 2021. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/950113/jcvi-advice-on-priority-groups-for-covid-19-vaccination-30-dec-2020-revised.pdf.
12. Joint Committee on Vaccination and Immunisation (UK). Optimising the COVID-19 vaccination programme for maximum short-term impact. Short statement from the Joint Committee on Vaccination and Immunisation (JCVI). 31 December 2020. Accessed 11 January 2021. https://app.box.com/s/uwwn2dv4o2d0ena726gf4403f3p2acnu.
13. World Health Organization. World Health Organization Interim recommendations for use of the Pfizer-BioNTech COVID-19 vaccine, BNT162b2, under emergency use listing. Interim guidance. 8 January 2021. Accessed 11 January 2021. www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-BNT162b2-2021.1.
14. US Centers for Disease Control. Interim clinical considerations for use of mRNA COVID 19 vaccines currently authorized in the United States. 6 January 2021. Accessed 11 January 2021. www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html.
15. US Food and Drug Administration. Vaccines and Related Biological Products Advisory Committee meeting December 17, 2020 FDA briefing document; Moderna COVID-19 vaccine. Accessed 11 January 2021. www.fda.gov/media/144434/download.
16. Government of Canada. Recommendations on the use of COVID-19 vaccines. Updated 12 January 2021. Accessed 14 January 2021. www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/recommendations-use-covid-19-vaccines.html#b4.
17. Henry B. Letter from Dr Bonnie Henry to Doctors of BC et al. regarding two dose COVID-19 vaccination series. 13 January 2021. Accessed 19 January 2021. https://mcusercontent.com/ba1eed881833c3cf6cb9907be/files/8f7dca26-9261-47ce-a6f7-2dc7c911a07e/PHO_Letter_DOBC_re_Two_Dose_Series_Jan_12_2021_FINAL.pdf.
18. Government of Quebec. Pandémie de la COVID-19—Le Québec prend les moyens pour vacciner le plus de personnes vulnérables le plus rapidement possible. 13 January 2021. Accessed 19 January 2021. www.msss.gouv.qc.ca/ministere/salle-de-presse/communique-2571.
19. Government of Ontario. Ontario achieves key milestone with vaccinations in long-term care [news release]. 19 January 2021. Accessed 19 January 2021. https://news.ontario.ca/en/release/60011/ontario-achieves-key-milestone-with-vaccinations-in-long-term-care.
20. Government of Alberta. COVID-19 vaccine distribution overview. Accessed 19 January 2021. www.alberta.ca/covid19-vaccine.aspx.