COMMENTARY

COVID-19 vaccination: why extend the interval between doses?

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On March 3, 2021, faced with ongoing morbidity and mortality from coronavirus disease 2019 (COVID-19) and insufficient supplies of authorized, available vaccines against COVID-19 in Canada, the National Advisory Committee on Immunization (NACI) issued a strong recommendation to allow for an extended interval between vaccine doses in order to maximize the number of people protected as quickly as possible. NACI's recommendation was released in the form of a rapid response due to the urgency of the situation and was based on a review of the evidence, principles of immunology, historical experience with vaccines, modelling studies, and consideration of ethics, equity, feasibility and acceptability. Since then, we have seen many questions and concerns raised. This article aims to provide further explanation behind the rationale and prepare healthcare providers with information they need, as they support their patients in the vaccination roll-out.

KEY WORDS: COVID-19; vaccination; interval; public health

Le 3 mars 2021, devant la morbidité et la mortalité continues causées par la maladie à coronavirus 2019 (COVID-19) et l'offre insuffisante de vaccins autorisés et disponibles contre la COVID-19 au Canada, le Comité consultatif national de l'immunisation a publié une forte recommandation préconisant un intervalle prolongé entre les doses des vaccins, afin d'optimiser le nombre de personnes protégées le plus rapidement possible. La recommandation du comité, qui a pris la forme d'une réponse rapide en raison de l'urgence de la situation, repose sur l'examen des données probantes, les principes immunologiques, l'expérience des vaccins, les études de modélisation et les principes d'éthique, d'équité, de faisabilité et d'acceptabilité. De nombreuses questions et inquiétudes ont été soulevées depuis. Le présent article vise à mieux expliquer les motifs de cette recommandation et à fournir aux dispensateurs de soins l'information dont ils ont besoin pour soutenir leurs patients pendant le déploiement de la vaccination.

MOTS-CLÉS : COVID-19; intervalle; santé publique; vaccination

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On March 3, 2021, faced with ongoing morbidity and mortality from coronavirus disease 2019 (COVID-19) and insufficient supplies of authorized, available vaccines against COVID-19 in Canada, the National Advisory Committee on Immunization (NACI) issued a strong recommendation to allow for an extended interval between vaccine doses in order to maximize the number of people protected as quickly as possible (1). NACI's recommendation was released in the form of a rapid response (1) due to the urgency of the situation and was based on a review of the evidence, principles of immunology, historical experience with vaccines, modelling studies, and consideration of ethics, equity, feasibility and acceptability. Since then, we have seen many questions and concerns raised. We want to provide further explanation

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behind the rationale and prepare healthcare providers with information they need, as they support their patients in the vaccination roll-out.

No jurisdiction has an infinite supply of vaccines or the ability to deliver them to a population instantaneously. Countries such as the United Kingdom that have developed and can produce their own vaccines had higher per capita first-quarter supplies of vaccines than Canada. Yet, the UK's Joint Committee on Vaccination and Immunisation reviewed the literature and recommended that priority be given to first doses "above offering others their second dose" (2). This included the recommendation to administer the second dose of the Pfizer-BioNTech up to 12 weeks after the first dose (3) – importantly offering both a precedent and an early source of real-world evidence to inform the vaccine roll-out in other jurisdictions. NACI reasoning was based on recommendations and data from other jurisdictions.

EXTENDING THE DOSING INTERVAL TO SAVE LIVES

In early March 2021, Canada's vaccine supply was still ramping up as were immunization programs, at the same time as jurisdictions were confronted with ongoing sustained community transmission and the emergence of SARS-CoV-2 variants of concern (VOC), in particular the B.1.1.7. thought to be more infectious than the original virus. In this context, NACI urgently reviewed available vaccine effectiveness data and was able to support its dosing interval recommendations considering these new emergent data. First, data from the provinces of Quebec and British Columbia revealed that the mRNA vaccines effectiveness in Canadian long-term care facility residents and healthcare workers was above 80%. There was no evidence of decreasing effectiveness of the first vaccine dose during the studied period, with data available up to 8 weeks in Quebec and British Columbia. Vaccine effectiveness was between 70 and 80% in the United Kingdom (Pfizer-BioNTech) (4,5) with no evidence of decline over the weeks that were studied by Public Health England. These data are being updated regularly as vaccine effectiveness surveillance is ongoing and NACI will be apprised of the results. Second, mathematical modelling data developed by the Public Health Agency of Canada (PHAC) compared the impact of different vaccination strategies. This data model (currently being prepared for publication as at the time of writing) incorporated vaccine efficacy estimates from the trials, vaccine effectiveness estimates from real-world evidence

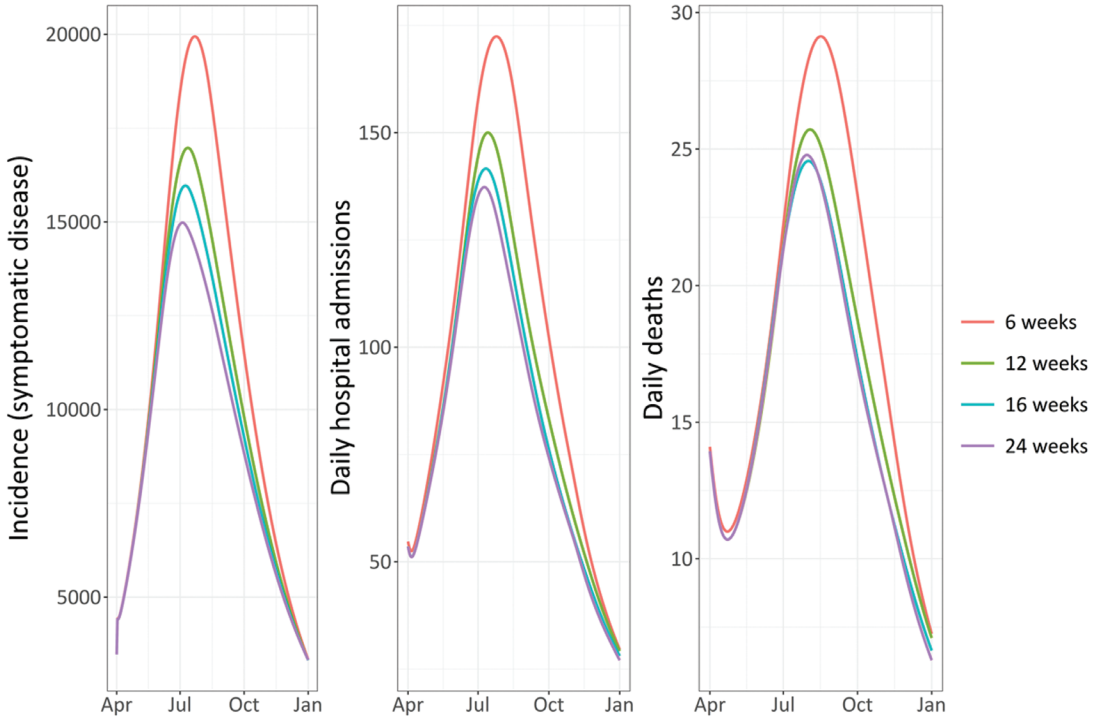

Figure 1: Daily incidence of symptomatic COVID-19, hospitalizations, and deaths from the model assuming a 3rd wave (R_{eff} = 1.2) beginning in April 2021. Figure shows dose 1 effectiveness against symptomatic COVID-19 of 85% and effectiveness against infection of 42.5% (i.e. 50% of VE disease). Deaths do not include those occurring in long-term care facilities, which were not included in the model (23)

and a waning protection parameter (4% per week, which is higher than has been observed to date in real-world studies). The model showed that longer intervals (up to 6 months), even assuming waning protection, saved more lives and prevented more hospitalizations, with evidence of benefits at the population level (Figure 1). Although a six-month interval would have greater population-level benefits according to mathematical modelling, a six-month interval was unnecessary because, based on data presented to the committee by the PHAC, vaccine supply projections in the second quarter were such that after four months 80% of Canadians over the age of 16 would have had access to a first dose of vaccine.

The "up to 4 months" interval was recommended with the full expectation that it would be dynamic, with the interval changing based on evidence, including the possibility that domestic or international surveillance might suggest that the interval should be shortened to avoid breakthrough infections in either the general population or specific sub-populations, such as immunocompromised individuals. NACI continues to monitor this evolving evidence. It is important to remember that vaccines do not act like drugs, where we must maintain an effective dose across regular intervals. Vaccines exploit the principle of immune memory. The immune response will be refined with every exposure to the same antigen, even after variable intervals, where a longer time between doses can give the system more time to perfect a response.

NACI'S ROLE IN A PUBLIC HEALTH EMERGENCY

NACI is an independent volunteer external expert advisory body to the Public Health Agency of Canada that makes recommendations for the use of authorized vaccines in Canada in the context of public programs and population health. The provinces and territories determine policies within their jurisdictions and adapt the recommendations to their local situation and epidemiology. The committee makes recommendations that are evidence-informed but will make expert-opinion recommendations when necessary and be transparent when recommendations are expert opinion, rather than evidence-based. In this case, the urgency of the situation required an expert opinion built on solid evidentiary foundations. NACI triangulated multiple sources of strong direct (6) and indirect evidence in support of an extended interval for vaccines against COVID-19.

From a regulatory perspective, despite limited follow-up times, Health Canada authorized COVID-19 vaccines based on primary analyses per protocol of ongoing Phase 3 clinical trials under the Interim Order respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19 (7). Delaying decisions or waiting for longer follow-up to be completed would have been contrary to the objectives of Canada's pandemic response, that is, to minimize serious illness and overall deaths while minimizing societal disruption (3). Aiming to avoid similar potential consequences, the same objectives guided NACI as it provided advice to Canada's governments during this public health emergency.

A case in point: When NACI recommended the use of the mRNA vaccines in December 2020, there were no data on the long-term immunity following a complete two-dose schedule, as clinical trial data were analyzed approximately two months after receipt of the second dose (8,9). Yet, NACI and other immunization advisory and regulatory committees around the world agreed that using COVID-19 vaccines to curtail the pandemic was the first priority and should be accompanied by careful monitoring of vaccine safety and effectiveness. We are now learning from those preliminary real-word studies.

NACI also recommended, based on severity of illness, to prioritize elderly Canadians, starting with those residing in long-term care facilities, given how devastating COVID-19 has been for these individuals (10). At the time, there were some data from randomized clinical trials (8,9) on the safety, immunogenicity, and efficacy of COVID-19 vaccines in individuals 65 years and older, but the eldest group represented a very small proportion of enrolled participants and there were sparse data on residents from long-term care facilities. Based on results in seniors with underlying medical conditions, the burden of illness in long-term care facility residents, and an analysis of ethics and equity, NACI opted to start with that population (11), despite the limited direct evidence available, knowing that provinces and territories have strong vaccine effectiveness and safety surveillance systems in place that could allow for modifications of recommendations, if required. This decision has already saved many Canadian lives, and we have seen the overwhelming outbreaks dwindle among our most vulnerable in long-term care settings (12).

OTHER CONSIDERATIONS: PUBLIC HEALTH VALUES AND CIRCUMSTANCES

It is widely understood that most clinical decisions are evidence-informed, with practitioners weighing evidence, the context or circumstances, and the patient's values or preferences. Accordingly, guideline panels are encouraged to make concrete recommendations in the context of sparse evidence to support clinicians and patients who do not have the same resources or expertise (13), using pre-defined frameworks that take into account a range of relevant considerations. NACI has explicit processes to systematically assess a spectrum of considerations (14,15). Much like clinicians when the literature does not give us the perfect answer for our patient's situation, National Immunization Technical Advisory Groups (16)

must make decisions with the distinction that our "patient" is the population rather than the individual.

In this case, modelling showed that a six-month interval would effectively allow first doses for the entire adult population and give us the most health gains at a population level, even under assumptions of waning protection. This is hardly surprising given the reality that arresting disease transmission by wide vaccine coverage cuts the risks to all demographic groups. As well, using prior knowledge of vaccinology, it is also likely that two-dose vaccine series will produce a better boosting response when a longer interval between doses is used (17). Furthermore, the decision for COVID-19 vaccine trials with mRNA platforms to have short intervals may not be based on immunological principles. It is equally probable that trials were designed with a brief interval between doses so as to ensure the highest possible efficacy in the shortest time, thereby allowing for trials to be completed as quickly as possible. The COVID-19 vaccine from AstraZeneca was shown to be more efficacious with a 12-week or longer interval between doses when compared to a 4–8-week interval (3). Moreover, experience with human papillomavirus (HPV) vaccine series in adolescents is illuminating in this regard (18). The HPV authorized vaccine series in adolescents was originally three doses at zero, two, and six months. We learned over time that only two doses were needed rather than three to achieve the same effectiveness and that the interval between the first and final dose should be six rather than two months (18).

Canada is not currently in a situation where the B.1.351 (VOC that originated in South Africa) is widespread. B.1.1.7 is emerging as the dominant strain, as was the case when the United Kingdom embarked on its successful first-doses-fast campaign. If B.1.351 were to become widespread and evidence were to emerge that a first dose was ineffective, NACI would revisit the recommendation of extended interval between doses. Moreover, the presumption that a partially protective vaccine (i.e., one that does not prevent symptomatic infection, but does protect against severe disease) would not reduce transmission is far from certain (19). Indeed, any partially protective vaccine would almost certainly lower viral titres and there are clinical data demonstrating that high viral loads are directly correlated with risk of transmission (20).

Some have claimed that partial protection would foster the development of new variants. This is speculative. Lowering viral titres reduces the rate of viral evolution, and the relative contribution of lower viral titres versus the evolutionary pressure to "escape" immunity is not well understood. Even if true, there is still an ethical imperative to protect as many people from severe disease as possible and as fast as possible, given that viral evolution will continue regardless of the presence of vaccines. In the fields of influenza and other viral vaccine preventable diseases, in which these types of studies have been most rigorously performed (21), it is unclear to what extent vaccine-mediated immunity contributes to antigenic drift and the emergence of novel variants at the population level (22). Indeed, we have already witnessed the emergence of antigenically distinct variants (i.e., VOC that originated in South Africa and Brazil) independent of any vaccine-mediated pressure.

CONCLUSION

We know this recommendation has led to controversy. In a pandemic, there are no simple solutions. Timely decisions need to be made with imperfect data and in good faith, without undue political or commercial influences. This approach aims to minimize death and disease at a population level. Health Canada authorizes vaccines based on evidence of safety, efficacy, immunogenicity, and quality standards. NACI's recommendations are informed by evidence on burden of illness, vaccine characteristics (including safety, efficacy, immunogenicity), as well as ethics, equity, feasibility, and acceptability of recommendations (15).

Furthermore, flexibility and transparency are essential. Growth in vaccine supplies may indeed enable shortening of intervals, and provinces and territories set policy based on the advice to reflect local conditions. Above all, there must be ongoing surveillance of both Canadian and international experience and research with a view to changing course as evidence evolves. This, to us, is the only responsible way to act. We now call upon you, trusted healthcare providers, to work with your colleagues and patients to help explain this decision and why it will protect us all. The conversations may not be easy, but they are absolutely necessary.

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