

Ministry of Health

Vaccine Clinical Advisory Group (VCAG) Recommendations on Exceptions to Extended Dose Intervals for COVID-19 vaccines

March 26, 2021 (Updated May 25th, 2021)

Context

The National Advisory Committee on Immunization (NACI) released updated guidance on COVID-19 vaccines, recommending that the interval between the first and second dose be extended up to 4 months, which has been adopted in Ontario with a limited number of exceptions. This recommendation is based on the importance of maximizing vaccination within the context of limited vaccine supply and significant community transmission. To make this decision NACI considered:

- Review of recent scientific studies of efficacy and effectiveness of COVID-19 vaccines
- Real world effectiveness demonstrating a sustained high level of protection after the first dose of the COVID-19 vaccine
- Immunological principles and vaccine science
- Modelling data from the Public Health Agency of Canada that examined different strategies to prevent the greatest numbers of symptomatic disease, hospitalizations and deaths
- The ethics, equity, feasibility, and acceptability (EEFA) Framework
- Vaccine supply projections

The Vaccine Clinical Advisory Group brings together clinical and public health physician experts to provide recommendations for Ontario's COVID-19 vaccine program. It provides expert advice for special populations and the considerations needed with respect to COVID-19 vaccination.

The Vaccine Clinical Advisory Group (VCAG) strongly supports the evidence-informed public health approach of delaying the administration of the second doses to maximize the number of individuals receiving a first dose of vaccine at this time of constrained vaccine supply.

The VCAG identified specific populations for which there continues to be limited available data on vaccine efficacy and effectiveness, who are at increased risk of severe outcomes from COVID-19 and who may have a suboptimal immune response to vaccines on the basis of their underlying condition. The VCAG discuss recommendations for these populations, recognizing that the evidence is constantly developing and that recommendations will continually be re-examined as new data emerge.

The VCAG analysis carefully considers the constrained vaccine supply and the impact of shortened dose intervals on the availability of first doses for other at-risk populations with rates of high morbidity and mortality (e.g., the elderly).

Decision making on exceptions to the extended dose interval is informed by:

- The VCAG's support for an evidence-informed public health approach of reaching the maximum number of individuals with the projected vaccine supply over the next several weeks and months.
- The VCAG's commitment to considering clinical evidence of immune response and immunological principles, balanced by real-world evidence on vaccine effectiveness. When available, the latter will be carefully considered due to the fact that the immune correlates of protection are not yet established for COVID-19.

With respect to vaccine supply, the VCAG reviews Ontario's projected vaccine supply to understand the vaccine supply constraints faced by Ontario.

Consideration is given to geographic spread of infection to impacted populations, as recommendations herein can impact vaccine supply for first doses. Emphasis is made on the temporality of the situation whereby recommendations will continually be re-assessed to ensure they reflect emerging science and vaccine supply improvements. For example, if a change in vaccine supply allows for quicker access to first doses for all eligible Ontarians, second doses for all Ontarians could be administered prior to the current extended second dose interval of up to 4 months.

Special Populations

1. Pregnancy

The immune response to vaccination in pregnant individuals is not expected to be significantly different when compared to the general population. Even though pregnancy is an immunologically altered state, response to vaccines is adequate (Government of Canada, 2021). Clinical trials of pertussis, tetanus toxoid, and inactivated polio vaccine administered during pregnancy have demonstrated normal adult immunologic responses (Government of Canada, 2021). As vaccination rollout continues, the population risk will decrease for all. Currently, there is limited data available on any benefit to the fetus to be able to draw definitive conclusions.

Recommended Dose Interval: At this time, in the context of constrained vaccine supply, the extended dose interval is believed to be appropriate for pregnant individuals in the authorized age group.

2. Immunocompromising conditions and immunosuppressive therapies

Individuals with immunocompromising medical conditions and those on immunosuppressive therapies were largely excluded from the clinical trials for the COVID-19 vaccines, limiting our knowledge of the efficacy of COVID-19 vaccines. Given the heterogeneity within this group, the immune response to the vaccine could be highly variable.

Available evidence on the response to COVID-19 immunization for these populations was carefully considered to inform recommendations on dose intervals that could be made regarding certain sub-populations. The benefit of this approach allowed the VCAG to make recommendations for vulnerable groups that are at high risk of mortality and suboptimal response to immunization based on current evidence. The limitations of this approach were also acknowledged. The VCAG is committed to an ongoing review of evidence and immunological principles to inform recommendations for other sub-groups for which theoretical risks of poor immune response to COVID-19 immunization exist. Furthermore, the VCAG acknowledges that alternate strategies of protection should be considered where the risk of severe disease and mortality is high and immune response to COVID-19

immunization is sub-optimal; the VCAG is committed to examining these in the weeks ahead.

a. Transplant

Individuals who have received hematopoietic stem cell transplants are known to experience a prolonged period of immune suppression following transplantation, while solid organ transplant recipients undergo a significant degree of immune suppression persisting indefinitely [Government of Canada, 2021]. Evidence is emerging specific to transplant patients that indicate a poor immune response to COVID-19 immunization with mRNA vaccines, particularly impacted by the type of immunotherapy being administered and the timing of the therapy in relation to vaccine administration (Boyarsky et al., 2021, Benotmane et al., 2021). Mortality rates from COVID-19 continue to be high (Canadian Blood Services, 2021) for this relatively small population (approximately 12,000 individuals in Ontario). These patients also tend to have higher viral loads, which increases concerns about their risk of transmission to others (Aydillo et al., 2020). The emerging clinical research available, in the absence of vaccine clinical trial data or real-world effectiveness studies, indicate that the first dose of a COVID-19 vaccine series yields poor immune response (Boyarsky et al., 2021; Ilies et al., 2021).

Recommended Dose Interval: Transplant recipients in the authorized age group (including solid organ transplants and hematopoietic stem cell transplants) should receive the COVID-19 vaccine at the dose interval, as indicated in the product monographs for COVID-19 vaccines. Continuous monitoring of emerging research and real-world effectiveness studies is warranted and ongoing consideration of alternate methods of increasing protection for this group (e.g., ring vaccination) will be assessed by the VCAG moving forwards.

b. Stable, active treatment for malignant hematologic disorders and non-hematologic malignant solid tumor

Malignant hematologic disorders and non-hematologic malignant solid tumors are known to create unique challenges in immunization due to the therapeutic use of immunosuppressive therapy during active treatment (Government of Canada, 2021). Evidence is still emerging specific to COVID-19 immunization in these populations. The timing of immunization is of the utmost importance for this population and should be carefully considered by the individual in consultation with their treating

health care provider. In Ontario, this population includes approximately 30,000 individuals in whom hematological malignancy was diagnosed within the last year and approximately 50,000 patients receiving chemotherapy treatment for a non-hematological malignancy in 2019/20. The emerging clinical research available, in the absence of clinical trial data or real-world effectiveness studies, indicate that the immune response of the first dose of a COVID-19 vaccine series is low in hematological and solid tumor patients compared to healthy controls, but can be significantly boosted by a second dose at 3 weeks. The evidence is preliminary and cannot predict whether this may be due to a cancer diagnosis, immunosuppressive treatment or other confounding comorbidities (Monin-Aldama et al., 2021).

Recommended Dose Interval: Individuals in the authorized age group, with malignant hematologic disorders or non-hematologic malignant solid tumors that are receiving stable, active treatment (chemotherapy, targeted therapies, immunotherapy), excluding individuals receiving solely hormonal therapy and/or radiation therapy, should receive the COVID-19 vaccine at the dose interval as indicated in the product monographs. In keeping with current practice, ideally, vaccination should occur at a time when they are most likely to mount immune responses. Continuous monitoring of emerging research and real-world effectiveness studies is warranted, and ongoing consideration of alternate methods of increasing protection for this group (e.g., ring vaccination) will be assessed by the VCAG going forwards.

c. Dialysis

Patients requiring hemodialysis or peritoneal dialysis (approximately 12,500 people in Ontario) are at high risk of severe illness with an infection of COVID-19. The same population has been documented as having a suboptimal immune response from the initial dose of a 2 dose vaccine series; however, there is an improved response after the second dose (Goupil et al., 2021; Grupper et al 2021 and Schrezenmier et al 2021). Studies are limited but consistent in their findings that after the second dose at the recommended product monograph interval, there is evidence of an improved immune response that will reduce the risk of negative health outcomes from a COVID-19 infection (Grupper et al 2021; Schrezenmier et al 2021 and Simon et al., 2021). While the literature reviewed focused primarily on the hemodialysis population, a similarly suboptimal immune response after the first dose of vaccine, with an improved immune response after the second dose at the product

monograph of a 2 dose vaccine series, is expected in the peritoneal dialysis population.

Recommended Dose Interval: Individuals undergoing hemodialysis or peritoneal dialysis in the authorized age group are recommended to receive the COVID-19 vaccine at the dose interval indicated in the product monographs.

d. Individuals on Immunosuppressive Therapy

Individuals with autoimmune/inflammatory disease who were immunosuppressed due to either disease or treatment were either excluded from, or included in small numbers, the Phase III trials of currently available COVID-19 vaccines. Data with respect to the impact of COVID-19 vaccine efficacy in those with immunosuppression due to disease or medications, is thereby limited but with new studies/data, current information will develop. Some data does exist for the impact of immunosuppressive medications on other vaccines, and this, too, is being considered in the context of limited COVID-19 vaccine-specific information (Eisenberg et al., 2013; Furer et al 2020) .

The recommendation, below, has been formed on the basis of a) evidence for impact of these immunosuppressive medications on COVID-19-related outcomes (Strangfeld et al., 2021) b) evidence of impact of these medications on vaccine efficacy or immunogenicity (Baker et al., 2020; Eisenberg et al., 2013) and c) the potential risk/harm associated with deferring treatment with these immunosuppressives in order to maximize vaccine efficacy.

Recommendations about other immunosuppressive therapies for autoimmune/inflammatory disease may follow as new evidence emerges and/or as vaccine supply permits.

Recommended Dose Interval:

Individuals in the authorized age group who are taking an **anti-CD20 agent** (e.g., rituximab, ocrelizumab, ofatumumab) may receive the second dose of COVID-19 vaccine (of a 2-dose series) in accordance with the interval specified on the vaccine product monograph.

The timing of the vaccine should be decided with the treating provider in order to optimize the immune response from the vaccine series and minimize delays in management of their underlying condition.

Please note: Patients receiving Rituximab and other anti-CD20 monoclonal antibodies may have a reduced immune response to vaccines in general that can extend up to 6 months following treatment completion (Houot et al 2020).

3. Age

The VCAG recognizes increasing age as the predominant driver of mortality and morbidity in COVID-19 infections and the need to include older age within the recommendations. There are approximately 800,000 Ontarians over the age of 80. There is emerging evidence that suggests there is a poor immune response, as measured by neutralizing antibodies to first dose COVID-19 vaccine, in the over 80 population (Collier et al., 2021; Mueller et al., 2021). However, real-world effectiveness data for COVID-19 immunization in elderly adults (including frail patients with extensive co-morbid disease) demonstrate a significant reduction in symptomatic SARS-CoV-2 positive cases following the first dose of vaccine with even greater protection against severe disease (Lopez Bernal et al., 2021; Hyams et al., 2021; BC Centre for Disease Control, 2021; INSPQ, 2021).

The VCAG also considered that reserving second doses of COVID-19 vaccine for certain age-based sub-groups would reduce vaccine availability for other priority age-based sub-groups experiencing increased morbidity and mortality risks from SARS-CoV-2 infections.

Recommended Dose Interval: While age is a significant driver of mortality and morbidity in the COVID-19 pandemic, available real world evidence indicates that the first dose of a COVID-19 vaccine series provides substantial protection against the risk of severe disease, hospitalization and death in the elderly population. At this time, in the context of constrained vaccine supply, the extended dose interval is believed to be appropriate for older individuals. This recommendation continues to be re-evaluated as evidence emerges, including emerging data on vaccine effectiveness in Ontario, and COVID-19 vaccine supply forecasts are updated.

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