National Advisory Committee on Immunization (NACI) rapid response: Additional dose of COVID-19 vaccine in immunocompromised individuals following 1- or 2- dose primary series

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On this page

- Preamble
- Background
- Methods
- Summary of evidence
  - Burden of illness in Canada
  - Summary of evidence on 2-dose COVID-19 vaccine series in immunocompromised individuals
  - Summary of evidence on an additional dose of COVID-19 vaccine following a 2-dose series
  - Additional information and considerations
- Recommendations
- Research priorities
- References
- Abbreviations
- Acknowledgments

Preamble

The National Advisory Committee on Immunization (NACI) is an External Advisory Body that provides the Public Health Agency of Canada (PHAC) with independent, ongoing and timely medical, scientific, and public health advice in response to questions from PHAC relating to immunization.

In addition to burden of disease and vaccine characteristics, PHAC has expanded the mandate of NACI to include the systematic consideration of programmatic factors in developing evidence-based recommendations to facilitate timely decision-making for publicly funded vaccine programs at provincial and territorial levels.

The additional factors to be systematically considered by NACI include: economics, ethics, equity, feasibility, and acceptability. Not all NACI Statements will require in-depth analyses of all programmatic factors. While systematic consideration of programmatic factors will be conducted using evidence-

informed tools to identify distinct issues that could impact decision-making for recommendation development, only distinct issues identified as being specific to the vaccine or vaccine-preventable disease will be included.

This statement contains NACI's independent advice and recommendations, which are based upon the best current available scientific knowledge. This document is being disseminated for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph. Recommendations for use and other information set out herein may differ from that set out in the product monographs of the Canadian manufacturers of the vaccines. Manufacturer(s) have sought approval of the vaccines and provided evidence as to its safety and efficacy only when it is used in accordance with the product monographs. NACI members and liaison members conduct themselves within the context of PHAC's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

Background

Immunocompromised individuals, including those receiving immunosuppressive therapy, are a very heterogeneous population some of whom may respond differently to vaccines and thus require unique considerations regarding immunization. To date, people with moderately to severely compromised immune systems have been observed to generally have lower antibody responses and lower vaccine effectiveness from Coronavirus disease 2019 (COVID-19) vaccines than immunocompetent individuals, although this varies depending on the underlying condition or immunosuppressive agents. Individuals with various conditions associated with immunocompromise were excluded from the manufacturer-conducted randomized controlled COVID-19 vaccine efficacy trials and it is uncertain what vaccination strategy will most optimally protect these individuals from illness and severe outcomes due to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection.

There is currently a resurgence of COVID-19 cases in some regions of Canada fuelled by the highly transmissible Delta variant that was declared a global variant of concern by the World Health Organization in May 2021. The Delta variant has been observed to increase the risk of infections due to its higher transmissibility. Breakthrough infections (infection in fully vaccinated people) have occurred with the Delta variant. This may be due to some degree of evasion of vaccine-induced immunity or waning of vaccine-induced immunity over time, or poor immune response to initial vaccine doses (as might occur amongst those who are moderately or severely immunocompromised). Delta has also been shown to be more virulent compared to previous strains resulting in a higher percentage of cases requiring hospital care, most notably in unvaccinated individuals, but also to some extent in vaccinated individuals when compared to the Alpha variant [1]. In order to reduce the risk of breakthrough infections among vulnerable groups several countries including Israel, the United States, France, Germany, the United Kingdom, Denmark and Norway have implemented, or are planning to implement, the administration of third doses of COVID-19 vaccine in some immunocompromised populations.

NACI previously preferentially recommended that a complete COVID-19 vaccine series (defined as a 2-dose series) with an mRNA COVID-19 vaccine should be offered to individuals in the authorized age group who are immunocompromised due to disease or treatment. Recent studies have demonstrated that some people who do not respond after two doses, particularly those who are moderately to

severely immunocompromised, develop antibodies after a third dose of an mRNA vaccine; and that there are increases in antibody titres following a third dose for some of those who do respond to an initial primary series. There is increasing evidence that antibody titres are related to vaccine effectiveness, (including against viral variants) and may relate to the duration of protection and protection against severe disease. However, a correlate of protection has not yet been defined.

The additional or third dose being considered for moderately to severely immunocompromised persons should be distinguished from that of a booster dose. The intent of a booster dose is to restore protection that may have waned over time in individuals who responded adequately to an initial 1- or 2-dose primary vaccine series. Additional doses beyond the standard primary vaccine series, such as discussed in this statement, provide an opportunity for individuals who may not have achieved an adequate level of protection from the standard primary vaccine series to develop a better immune response.

Guidance objective

The objective of this guidance document is to provide advice on the use of an additional dose of a COVID-19 vaccine following receipt of a standard 1- or 2-dose primary series in moderately to severely immunocompromised individuals in Canada.

Methods

NACI has reviewed direct and indirect evidence available up to August 11, 2021 on efficacy/effectiveness, safety and immunogenicity of the standard 1- or 2- dose primary series, and the safety and immunogenicity of an additional dose of COVID-19 vaccine following a standard primary series in individuals who are immunocompromised due to disease or treatment. As of August 11, 2021 no data on the efficacy/effectiveness of an additional dose after a primary series of COVID-19 vaccine was available. There were thus only immunogenicity and safety data. NACI also reviewed a summary report from the PHAC Public Health Ethics Consultative Group (PHECG) on ethical considerations related to the provision of third doses of COVID-19 vaccines prepared on August 12, 2021.

Following a comprehensive review of available evidence, NACI approved the recommendations outlined below on September 1, 2021.

Details of NACI's evidence-informed recommendation development process can be found elsewhere [2] [3].

Defining immunocompromised individuals

To operationalize guidance for this population, NACI has reviewed a number of sources to identify which immunocompromised populations would likely benefit most from an additional dose of COVID-19 vaccine at this time. These sources have included evidence available in published and grey literature, the Canadian Immunization Guide chapter on Immunization of Immunocompromised Persons, and eligibility criteria for additional doses of COVID-19 vaccine in immunocompromised people currently being used by other jurisdictions. In addition, the clinical expertise of the committee informed the definition of immunocompromised individuals for the recommendations outlined in this statement.

Summary of evidence

Burden of illness in Canada

Immunocompromised individuals, including those receiving immunosuppressive therapy, are at increased risk for prolonged infection and serious complications from SARS-CoV-2 infection. Canadian surveillance data collected since December 2020 indicates that the proportion of COVID-19 cases that are hospitalized or admitted into intensive care unit (ICU), without adjusting for age, is 4-5 times higher than for the general population amongst individuals 12 years of age and older who are reporting either immunodeficiency or malignancy than amongst the general population [4]. This was also observed when data was limited to Delta-specific cases reported since March, 2021 [5].

Summary of evidence on 2-dose COVID-19 vaccine series in immunocompromised individuals

Effectiveness of a 2-dose COVID-19 vaccine series in immunocompromised individuals

Although the evidence is limited, observational studies show a reduction in vaccine effectiveness against SARS-CoV-2 infection and COVID-19 disease in immunocompromised adults when compared to the general population (based on use of the vaccines as per the manufacturers' schedules). A pooled analysis of three large population-based cohort studies [6] [7] [8] estimated vaccine effectiveness against any SARS-CoV-2 infection after the second dose in immunocompromised persons to be 79% (95% confidence interval (CI): 69 - 91%), compared to vaccine effectiveness after the second dose in the general population of 90% (95% CI: 86 - 95%) [9]. Another pooled analysis of two large case-control studies [10] [11] also against infection estimated vaccine effectiveness to be 88% (95% CI: 83 - 93%) in immunocompromised persons and 91% (95% CI: 84 - 98%) in the general population [9]. The criteria for being considered immunocompromised was not defined in these studies, and these analyses do not provide sufficient data to determine vaccine effectiveness for specific immunocompromising conditions or treatments.

Immunogenicity of a 2-dose mRNA COVID-19 vaccine series in immunocompromised individuals

The impact of immunocompromise on seroconversion after vaccination varies according to specific conditions and/or immunosuppressive therapy. Not all immunocompromised populations have been studied in detail. Some studies have shown that immunogenicity is substantially decreased in some immunocompromised adults when compared to healthy vaccine recipients [9]. This notably included individuals with malignancy (solid and hematological) [12] [13] [14] [15] [16] [17] [18] [19] [20] [21] [22] [23] [24] [25] [26] [27] [28] [29] [30] [31] [32] [33] [34] [35] [36] [37] [38] [39] [40] [41] [42] [43] [44] [45] [46] [47] [48] [49] [50] [51] [52] [53] [54] [55], multiple sclerosis when treated with immunosuppressive therapy [56] [57] [58], solid organ transplant recipients [10] [15] [41] [50] [59] [60] [61] [62] [63] [64] [65] [66] [67] [68] [69] [70] [71] [72] [73] [74] [75] [76] [77] [78] [79] [80] [81] [82] [83] [84] [85] [86] [87] [88] [89] [90] [91] [92] [93] [94] [95] [96] [97] [98] [99], and those with primary immune deficiency [50] [100] [101] [102].

The clinical significance of this difference in seroconversion and its impact on vaccine effectiveness is not known.

Safety of a 2-dose COVID-19 vaccine series in immunocompromised individuals

The safety profile of mRNA vaccines in real-world observational studies in this population has been comparable to what has been observed in the general population, with no unexpected or serious safety signals to date, including no worsening of an immunocompromising condition that has been attributed to the vaccine.

Summary of evidence on an additional dose of COVID-19 vaccine following a 2-dose series

Efficacy/effectiveness of an additional COVID-19 vaccine dose following a 2-dose primary series in immunocompromised individuals

There are currently no data on the efficacy/effectiveness of an additional dose of a COVID-19 vaccine following a 1- or 2-dose primary series in individuals with immunocompromising conditions.

Immunogenicity of an additional dose of COVID-19 vaccines following a 2-dose primary series in immunocompromised individuals

Emerging evidence indicates that humoral immune responses increase after a third dose of mRNA COVID-19 vaccine is administered to adults with immunocompromising conditions, although the degree of increase varies between studies and according to the type of immunocompromising condition or treatment. From 10 studies [103] [104] [105] [106] [107] [108] [109] [110] [111] [112] evaluating 2,075 patients, including one randomized-controlled trial [112], the overall pooled increase in the proportion of immunosuppressed individuals who seroconverted after an additional dose was 13% (95%CI: 5% - 22%) [9]. These studies assessed seroconversion in solid organ transplant recipients, and individuals with hematologic malignancies, and individuals receiving hemodialysis. The greatest increase in proportion of those who seroconverted after the third dose was in solid organ transplant recipients. In the majority of studies, all three doses were mRNA vaccines. Some individuals received the AstraZeneca [113] or Janssen COVID-19 vaccine [105] [106] [107] [108] as their third dose, however data specific to these vaccines as additional dose is not available. In some studies, although the increase in proportion of those who seroconverted was small, median antibody titers increased after the third dose compared to after the second dose. There was a significant amount of heterogeneity between studies due to differences in the populations that were studied. Given the limited size of the studies available to date and the lack of a defined immunological correlate of protection, there are limitations to interpreting the significance of these results.

Safety of an additional dose following a 2-dose primary series in immunocompromised individuals

In ten studies in adults, (five in solid organ transplant patients [105] [107] [110] [111] [114], three in patients on dialysis [104] [106] [108], one in patients with non-hematologic cancer [115] and one in patients with hematologic cancer [109]), the reactogenicity of a third dose of COVID-19 vaccine was similar to that of prior doses. In nearly all studies, the third dose was an mRNA vaccine, with the exception of one study where Janssen was also used for some study participations as an additional dose following a 2-dose mRNA COVID-19 vaccine primary series [105]. However, there are no data specific to the Janssen COVID-19 vaccine when used as an additional dose in this population. No worsening of underlying disease was reported after immunization, however a few cases of graft versus host disease or organ rejection were reported. Without unvaccinated controls however, it is not possible at this time to determine if receipt of a third COVID-19 vaccine dose could potentially be associated with an increased risk of rejection in this population. No serious adverse events were deemed to be associated with the vaccine.

Limitations of these studies include small sample sizes, short follow up periods and heterogeneous populations/vaccine schedules. Due to the small size of these studies and limited follow-up times, the impact of additional doses on rare adverse events in these populations are unknown.

The risk of myocarditis and/or pericarditis following receipt of an mRNA COVID-19 vaccine is currently reported more commonly after second doses compared to first doses. The risk of myocarditis and/or pericarditis associated with an additional dose of an mRNA vaccine, including when given to immunocompromised individuals, is unknown at this time. NACI is continuing to monitor the evidence and will update recommendations as information becomes available.

For further information, please refer to NACI's Recommendations on the use of COVID-19 vaccines.

Additional information and considerations

Timing of the additional dose

There is currently limited data to determine the optimal interval between the initial 1- or 2-dose series or with an additional dose. Dosing intervals between the second and third doses varied across studies, ranging from 28 days to 127 days, with the majority of studies having assessed an interval of 2 to 3 months between doses [104] [105] [106] [107] [108] [110] [111] [112]. A longer interval between the second and third doses, such as that used in most of the studies, is likely to result in better immune response. However, delaying the third dose increases the period of time during which the immunocompromised individual may be sub-optimally protected and could leave the immunocompromised individual susceptible to SARS-CoV-2 infection while waiting to be vaccinated with the additional dose.

In general, NACI recommends that immunocompromised individuals be immunized at the time when when maximum immune response can be anticipated:

- Immunize prior to any planned immunosuppression such that optimal immunogenicity is achieved, if possible.
- Delay immunization if the immunodeficiency is transient (if this can be done safely because exposure is unlikely in the individual's setting and circumstance).
- Stop or reduce immunosuppression to permit better vaccine response, if appropriate. For more details on the timing of vaccination in relation to immunosuppressive therapy, please consult the chapter on Immunization of immunocompromised persons in the Canadian Immunization Guide.

Vaccine product considerations

Studies assessing additional doses in immunocompromised individuals have primarily used mRNA vaccines, for both the initial primary series and additional dose. There are very limited data on the Janssen vaccine, and no data on the AstraZeneca COVID-19 vaccine as an additional dose in this population at this time. No safety concerns have been identified with additional doses following a homologous and heterologous 1- or 2-dose primary series in the evidence available to date.

In a meta-analysis of 22 studies [15] [16] [17] [27] [42] [46] [53] [58] [75] [87] [97] [116] [117] [118] [119] [120] [121] [122] [123] [124] [125] [126] assessing seroconversion after the initial 2-dose series in immunocompromised and dialysis populations, Pfizer-BioNTech had slightly lower pooled rates of seroconversion than Moderna with relative risk of 0.94

(95% CI = 0.91 to 0.97) with moderate heterogeneity between studies (I2 = 65%, $\chi 2 = 59.6$, $p<0.0001$) [9]. A proportion of this heterogeneity was due to the Pfizer-BioNTech vaccine lower pooled rate of seroconversion in solid organ transplant patients in particular.

Ethics and Equity Considerations

Evidence has shown that some immunocompromised individuals have a reduced immune response to the use of the COVID-19 vaccines as per the manufacturers' schedules. Although some reduction in vaccine effectiveness has been identified when compared to the general population, the extent of the loss is unclear due to the limited evidence in this population and heterogeneous nature of immunocompromising conditions and treatments. Vaccination strategies aimed at protecting these vulnerable populations have also varied across studies and jurisdictions Although waiting for vaccine effectiveness data for this population would increase the certainty of this recommendation, an assessment of the benefits and harms given the available evidence on immunogenicity and safety supports offering an additional dose in order to optimize direct protection from vaccine if possible, despite the limited evidence. The additional dose provides an opportunity to attain protective immunity against COVID-19 and thus contribute to equity since a three-dose schedule may be required for an effective primary vaccine series in this population. It will be necessary to ensure a robust informed consent process that clearly communicates both what is known and unknown about the risks and benefits of receiving a third dose (including the off-label status of NACI's recommendation).

Recommendations

1. **For those who have not yet been immunized, NACI recommends that moderately to severely immunocompromised [*] individuals in the authorized age groups should be immunized with a primary series of three doses of an authorized mRNA vaccine. (Strong NACI Recommendation)**
2. **For those moderately to severely immunocompromised [*] individuals in the authorized age groups who have previously received a 1- or 2-dose complete primary COVID-19 vaccine series (with a homologous or heterologous schedule using mRNA or viral vector vaccines), NACI recommends that an additional dose of an authorized mRNA COVID-19 vaccine should be offered. (Strong NACI Recommendation)**
    - **2a. An additional dose of a viral vector vaccine should only be considered when other authorized COVID-19 vaccines are contraindicated or inaccessible. Informed consent for an additional dose of viral vector vaccine should include discussion about the lack of evidence on the use of an additional dose of viral vector COVID-19 vaccine in this population. (Discretionary NACI Recommendation)**

For guidance on the timing of vaccination for transplant recipients and those requiring immunosuppressive therapies, for a more fulsome list of conditions leading to primary immunodeficiency, and for further information on immunosuppressive therapies, refer to Immunization of Immunocompromised Persons in the Canadian Immunization Guide (CIG), Part 3 - Vaccination of Specific Populations.

Additional considerations, summary of evidence and rationale

- Current evidence suggests a reduction in vaccine effectiveness against SARS-CoV-2 infection and/or COVID-19 disease in immunocompromised individuals when compared to the general population. Emerging data also show that immunogenicity is decreased in some immunocompromised populations when compared to healthy vaccine recipients.
- Evidence in some immunocompromised populations indicates that humoral immune responses increase after an additional dose of COVID-19 vaccine is administered to these individuals and that this is associated with a modest increase in overall proportion of individuals who seroconvert.
- In small studies, the reactogenicity of an additional dose of COVID-19 vaccine was similar to that of prior doses.
- Studies assessing additional doses in immunocompromised individuals have primarily used mRNA vaccines, for both the initial primary series and additional dose. Moderna COVID-19 vaccine may produce a greater immune response in this population. Investigations are ongoing.
- The **minimal interval between the 1- or 2- dose primary series and the additional dose should be 28 days**. As shown with immunogenicity data, an interval longer than the minimum 28 days between doses is likely to result in a better immune response. However, if a longer interval is being considered, then risk factors for exposure (including local epidemiology and circulation of variants of concern) and risk of severe disease should also be taken into account. Some immunocompromised individuals may still be susceptible after the 1 or 2-dose primary series, so their period of susceptibility until receipt of the additional dose will also increase if the interval between doses is increased.
- In general, NACI recommends immunization of immunocompromised individuals at a time when the immune response can be maximized. However, delaying COVID-19 vaccinations to maximize the response (including delaying offering an additional dose) needs to be weighed against the increased period of susceptibility and risk of infection and subsequent serious complications.
- The efficacy/effectiveness of an additional dose of COVID-19 vaccine following a 1- or 2- dose primary series in immunocompromised individuals is currently unknown. A diminished immune response to the additional dose may also occur. Therefore, **immunocompromised individuals should continue to follow recommended public health measures for prevention and control of SARS-CoV-2 infection and transmission**. It is also important that household members, healthcare workers providing care, and other close contacts of the immunocompromised be vaccinated to provide indirect protection for these individuals.
- The availability of data on the immunogenicity and safety of additional doses for specific immunocompromising conditions varies, with no data on the vaccine efficacy/effectiveness for any immunocompromising conditions or treatments. A range of factors can impact the relative degree of immunodeficiency and response to COVID-19 vaccines in immunocompromised individuals. Informed consent should include discussion about the limited evidence for the use of an additional dose of any of the authorized COVID-19 vaccines, including if the vaccine being offered is not authorized for the use of additional doses at this time.
- Although there are no data in immunocompromised adolescents specifically, the patterns of immune responses observed in immunocompromised adults compared to the general population can be extrapolated to this age group.
- Informed consent for additional doses of COVID-19 vaccine should include a discussion of the potential for increased risk of myocarditis and pericarditis following receipt of mRNA COVID-19 vaccine, which is currently reported more commonly after second doses compared to first doses.

The risk of myocarditis and/or pericarditis associated with a third dose of an mRNA vaccine, including when given to immunocompromised individuals, is unknown at this time Recipients of mRNA vaccine should be advised to seek medical attention if they develop symptoms including chest pain, shortness of breath, or palpitations. As a precautionary measure, the additional dose of mRNA COVID-19 vaccine should be deferred in individuals who have experienced myocarditis or pericarditis following any preceding dose of mRNA COVID-19 vaccine until more information is available. NACI will continue to monitor the evidence and update recommendations as needed.

- Individuals who are unable to receive an mRNA vaccine may be offered a viral vector vaccine, however the risk of Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT), Capillary Leak Syndrome (CLS), and Guillain-Barré syndrome (GBS) following viral vector COVID-19 vaccines should be discussed as part of the informed consent process.
- Serological testing is not recommended before or after COVID-19 vaccination. An immunological correlate of protection has yet to be defined and serological tests may not reflect the full array of immune responses generated after vaccination (e.g. cellular immune responses). The clinical significance of commercially available serological test results is unknown and should not be used to predict vaccine failure on an individual basis.
- NACI will be continuing to monitor the safety and effectiveness of COVID-19 vaccines, in individuals who are immunocompromised, including following an additional dose, and additional immunocompromised populations, and will update recommendation as needed.
- Guidance on the use of additional and/or booster doses of a COVID-19 vaccine for other specific populations (e.g. long-term care residents) including optimal timing is being considered by NACI. NACI will continue to monitor the evidence regarding the need for and effectiveness of booster doses for these specific populations and the general population and update guidance as required.

Refer to Recommendations on the Use of COVID-19 vaccines for further information on COVID-19 vaccines.

Research priorities

What is the optimal product, vaccine doses, interval between doses, and number of doses for immunocompromised individuals to ensure protection against SARS-CoV-2?

What is the efficacy/effectiveness of additional doses in immunocompromised individuals including:

- Against symptomatic infection
- Against severe disease, transmissibility, and death.

If adequate protection in immunocompromised individuals can be achieved with an additional dose, then what is the duration of this protection in immunocompromised individuals and will a booster dose/series be required?

What are the adaptive and innate immunity thresholds for protection in immunocompromised individuals?

What is the risk of myocarditis/pericarditis following an additional dose of an mRNA vaccine, including in immunocompromised individuals?

Further immunological evidence is needed in the following areas to inform efficacy/effectiveness predictions:

- How do immune responses change over time; what is the durability of immune responses against SARS-COV-2 over the long-term? What is the impact of vaccine dose, vaccine product or interval on durability?
- Which immune responses are most important for protection from infection (adaptive or innate immunity), severe disease or transmissibility? What is the role of humoral vs. cellular immunity in preventing immune escape of viral variants?
- Are immunoglobulin (Ig)A/IgG/IgM antibodies protective against SARS-CoV-2 and what is the correlate of protection?

Additional research priorities are listed in NACI's statement on Recommendations for the use of COVID-19 vaccines.

References

* Moderately to severely immunosuppressed includes individuals with the following conditions:

- Active treatment for solid tumour or hematologic malignancies
- Receipt of solid-organ transplant and taking immunosuppressive therapy
- Receipt of chimeric antigen receptor (CAR)-T-cell therapy or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy)
- Moderate to severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome)
- Stage 3 or advanced untreated HIV infection and those with acquired immunodeficiency syndrome
- Active treatment with the following categories of immunosuppressive therapies: anti-B cell therapies (monoclonal antibodies targeting CD19, CD20 and CD22), high-dose systemic corticosteroids (refer to the CIG for suggested definition of high dose steroids), alkylating agents, antimetabolites, or tumor-necrosis factor (TNF) inhibitors and other biologic agents that are significantly immunosuppressive.

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Abbreviations

Abbreviation Term

CI

Confidence interval

COVID-19

Coronavirus disease 2019

NACI
National Advisory Committee on Immunization

mRNA
messenger ribonucleic acid

PHAC
Public Health Agency of Canada

SARS-CoV-2
Severe Acute Respiratory Syndrome Coronavirus 2

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