National Transplant Consensus Guidance on COVID-19 Vaccine

Introduction

The following document provides expert consensus guidance that can be used by provincial organ donation organizations and regional transplant and donation programs to guide the management of COVID-19 vaccination in transplant recipients.

It is understood that each organization, program, and jurisdiction will develop their own policies. Since the situation is evolving, regular teleconferences will be held with national experts to discuss and update this consensus guidance. These discussions, and the consensus itself, will continue to be informed by recommendations from the Canadian Society for Transplantation, Canadian Blood Services' advisory committees, Health Canada, Public Health Agency of Canada, WHO, provincial agencies, and international partners (including UK and Spain).

This document was last updated on November 1, 2021 and will continue to be updated as new evidence and information becomes available.

What do we know about COVID-19 and transplant recipients?

COVID-19 is a disease caused by the SARS-CoV-2 virus that is predominantly a respiratory virus but can cause multi-system disease. Several organ transplant recipients have contracted COVID-19 and symptoms have ranged from mild disease to the need for ICU care and death. COVID-19 appears to have a greater severity in transplant recipients but the role of immunosuppression is unclear. Many transplant patients are older and have comorbid conditions such as chronic kidney disease, diabetes, and heart/lung disease that increases the risk of severe COVID-19 disease. Lung transplant patients also seem to be at particularly high risk of severe disease.

What is the status of COVID-19 vaccines in Canada?

There are several formulations of the COVID-19 vaccine that have been approved or are in various stages of development.

<u>mRNA Vaccines:</u>

Two mRNA vaccines (Pfizer/BioNTech and Moderna) have been authorized by Health Canada for use. Both vaccines are composed of mRNA in a lipid nanoparticle and have specific storage conditions. Approximately 70,000 persons have participated in placebo-controlled phase 3 trials with these vaccines. The Pfizer vaccine has an efficacy of 95% in immunocompetent persons and is for use in persons 12 years of age and older. The Moderna vaccine has a 94.1% efficacy and is used in persons 18 years of age and older. Both vaccines are given as a two dose series.

Adenovirus Vector Vaccines:

Two vaccines (University of Oxford/AstraZeneca and Johnson & Johnson) have been authorized for use by Health Canada. Both vaccines are adenovirus vector vaccines that can be stored at 2 to 8 °C, similar to standard vaccines. The Oxford/AZ vaccine uses a chimpanzee adenovirus vector to encode spike protein and has 62 to 90% efficacy in a phase 3 trial. It is given as a 2-dose series, 4 to 12 weeks apart. Due to a lack of data in older populations, the National Advisory Committee on Immunization has recommended this vaccine for persons less than or equal to 65 years of age. The J&J vaccine uses the Ad26 vector to encode spike protein and has 66% overall efficacy with its one dose preparation although has 86% efficacy in preventing severe disease. It is given as a single dose.

Vaccines may have reduced efficacy for circulating variants and therefore efforts are being made to study booster doses of vaccine that could be effective against SARS-CoV-2 variants.

What are the side effects of COVID-19 vaccine?

Local and systemic side effects can occur after any of the four vaccines. These include tenderness, swelling, and redness at the injection site. Relatively common systemic symptoms include fever, myalgias, and headache. In the Pfizer vaccine trial, systemic symptoms were more common in younger age groups and after the second vaccine dose. Similarly, in the Moderna vaccine trial, there were more systemic events after the second dose. Adenovirus vector vaccines appear to have a similar side effect profile to mRNA vaccines.

For the Oxford/AZ vaccine, several cases of thrombosis and thrombocytopenia have been reported worldwide during post-licensure use. The mechanism of action appears to be similar to spontaneous heparin-induced thrombocytopenia (called Vaccine-Induced Immune Thrombotic Thrombocytopenia or VITT). The estimate in Canada as of April 28, 2021 is 1 in 100,000. There have been few reported cases of VITT with the J&J vaccine.

For the mRNA vaccines, a small number of cases of myocarditis and/or pericarditis following immunization have been reported in Canada and internationally. The estimate according to CDC is 12.6 per million doses.These have been more frequently reported in males, younger adults under 30 years of age, and after a second dose of vaccine. The majority of these cases have been mild.

Systemic symptoms from vaccination are similar to COVID-19 disease so patients receiving vaccine should be counseled on the possibility of these symptoms occurring in the first few days after each dose.

What data are available about the COVID-19 vaccine in transplant recipients?

Although transplant recipients were not enrolled in phase 3 studies of COVID-19 vaccines, multiple recent studies have assessed the safety and the response of mRNA-

based vaccines in solid organ transplant (SOT) recipients. These studies did not show any unexpected short term local and systemic side effects of vaccine. However, overall, the studies have shown a lower antibody response to vaccine among SOT recipients when compared to the general population. Emerging studies have shown a detectable SARS-CoV-2 specific T-cells response in some patients, despite a lack of antibody response; therefore, SOT recipients might derive clinical benefit from the vaccine despite an absent antibody response. Studies to assess vaccine effectiveness, particularly for protection against severe COVID-19 as a clinical end-point in SOT, are still limited. Some case series have reported breakthrough infections, hospitalizations, and death, despite full vaccination. However, these are uncontrolled reports and other studies have shown a reduction in severe disease following full vaccination.

Can transplant patients receive the COVID-19 vaccine?

Although further data are needed, the opinion of experts is that transplant patients may receive any of the authorized COVID-19 vaccines. Experts believe that based on the mechanism of action of mRNA vaccines, there is no reason to suspect that adverse events will be any different than in the general population. Similarly, the adenovirus used in vector vaccines is non-replicative and therefore, such vaccines can be given to transplant recipients. Therefore, transplant recipients can receive any of the currently authorized vaccines available to them, assuming age requirements are met.

In summary, based on expert opinion, the potential benefits of vaccine likely outweigh the theoretical risks. All vaccines lead to a vaccine-specific immune response and the generation of alloimmunity or rejection following vaccination is unlikely based on the mechanisms of the vaccines, and the broad experience with other vaccines in the transplant population.

Should transplant patients receive a 3rd dose of vaccine?

A recently published randomized controlled trial, and other observational studies in SOT recipients, have shown that a third dose of mRNA vaccine increased both SARS-CoV-2-specific humoral and cellular responses, with an acceptable safety profile. Despite three doses of vaccine, some SOT recipients will continue to have poor immune responses and potentially remain unprotected. Therefore, it is critical that household contacts and healthcare workers be fully vaccinated. Moreover, transplant recipients should continue to follow infection control measures.

Although more data assessing long-term vaccine effectiveness and its impact on rates of rejection are required, the data that is currently available suggest that SOT recpients benefit from a 3rd dose of COVID-19 vaccine.

The best timing for third dose vaccine is unclear at this time but can be considered at 2 months after the second dose. There is no need to do serology testing before or after a third dose of vaccine. This is because: a) there is no threshold currently that predicts protection; b) even after two doses, the vast majority of transplant recipients are below the antibody level achieved by healthy controls; c) T-cell responses may increase after a third dose despite a low antibody response.

Can transplant patients receive a different type of vaccine for their second and third dose?

Persons who received Oxford/AZ vaccine may receive either Oxford/AZ vaccine or an mRNA vaccine for their second dose. However, where possible, the third dose should be an mRNA vaccine and preferably the same vaccine used for the first and/or second doses. The mRNA vaccines' immune response appears to be better than for the adenoviral vector vaccines in transplant recipients. Having said this, mRNA vaccines are generally interchangeable.

For optimum vaccine efficacy, it is recommended that:

- It is recommended that vaccines be administered in the pre-transplant setting, with the final dose at least 1 to 2 weeks prior to transplant whenever possible.
- In post-transplant patients, wait at least 1 month after transplant to provide the vaccine, regardless of induction therapy.
- Ideally, the full 2-dose series (Pfizer, Moderna, Oxford/AZ) should be given at the recommended interval. If the patient undergoes transplantation between the first and second doses, provide the second dose at > 1 month after transplant. Additional doses are not recommended.
- Prolonging dosing interval beyond that studied in phase 3 trials is not recommended for transplant recipients since immunogenicity may be lower and wane more quickly.
- In patients undergoing active treatment for acute rejection, vaccination can be deferred for a 1-month period.
- Avoid giving vaccine for at least 3 months after rituximab for improved efficacy.
- If a patient has had COVID-19 before, it is prudent to wait until symptom resolution and the individual is no longer considered infectious, prior to giving COVID-19 vaccine.
- COVID-19 vaccines and other vaccines can be given on the same day, as well as co-administered within 14 days.
- Vaccine should not be given to patients that have had an anaphylactic reaction to a known component of the vaccine (i.e., polyethylene glycol in mRNA vaccines).
- Antibody testing is not recommended after vaccination. The levels of protective antibody and association with vaccine effectiveness are not known.
- Since efficacy is expected to be lower than the general population, it is strongly recommended that patients continue to practice infection control measures. In addition, household contacts of the transplant recipient should also be vaccinated when possible.

What about pediatric transplant patients?

On May 5, 2021, Health Canada authorized the Pfizer-BioNTech COVID-19 vaccine for use in children 12 to 15 years of age. Approval for younger children (age 5-11) is expected imminently. The opinion of experts is that SOT children 12 to 15 years of age

may receive the Pfizer vaccine. Data are lacking for children under 12 years of age including those with transplants; but once approved, we expect similar recommendations to apply to younger pediatric transplant recipients.

What are the national and international recommendations?

The CDC Advisory Committee on Immunization Practices (ACIP;U.S.) and the Joint Committee on Vaccination and Immunisation (JCVI; U.K.) has prioritized the immunocompromised population for vaccination. The AST (American Society of Transplantation) and ISHLT (International Society for Heart and Lung Transplantation) have also recommended COVID-19 vaccine for transplant patients.

Several countries, including France, Israel, and the U.S., have now approved third doses for transplant recipients.

The National Advisory Committee on Immunization in Canada states that complete three dose vaccine series with an mRNA COVID-19 vaccine should be offered to individuals in authorized age groups, including those who are immunosuppressed. Efficacy may be lower in the immunosuppressed state so immunocompromised patients should continue to practice infection control measures against COVID-19 until further notice.

Vaccination of health care providers

As the efficacy of vaccines is lower in SOT, and SARS-COV-2 continues to circulate and evolve, we support mandatory vaccination for health care providers (physicians, surgeons and allied health professionals) involved in the care of solid organ transplant candidates and recipients with at least two doses of COVID-19 vaccine; to minimize the risk of infection to themselves, and decrease the risk of transmission to their patients.

What is the rationale for mandating COVID-19 vaccines pre-transplant?

We strongly support transplant program requirements for transplant candidates to receive COVID-19 vaccine prior to transplantation.The rationale is as follows:

1. Solid organ transplant (SOT) candidates and recipients are at increased risk of severe COVID-19 disease and death compared to the general population.
2. COVID-19 vaccines are immunogenic in patients with end stage renal disease on dialysis and patients with liver cirrhosis and can reduce COVID-19 infections while on the transplant waitlist.
3. COVID-19 vaccines are much less immunogenic when given in the post-transplant period.
4. SOT candidates and recipients have greater healthcare interactions and can spread SARS-CoV-2, when infected, to other inpatients or outpatients who are immunosuppressed or have chronic illnesses.
5. The Canadian Society of Transplantation, the American Society of Transplantation and the International Society for Heart and Lung Transplantation

have recommended vaccination pre-transplant.

6. Transplantation involves scarce resources and organs are offered to those in which appropriate care of the organ is possible post-transplant.
7. Transplant candidates are assigned many responsibilities and requirements in the pre-transplant setting in order to be eligible for listing. Adherence to medical measures is an important factor when programs determine listing.
8. In general, if safety requirements cannot be met pre- and post-transplant, then alternative therapies for organ failure may be preferable (eg, dialysis, ventricular assist devices, medical management).
9. Exemptions may be considered for medical indications (eg. Allergy to COVID-19 vaccine), or urgent need (eg, fulminant hepatic failure).
10. There may be additional considerations in pediatric populations as less data are available, but the vaccine is still strongly recommended in approved pediatric age groups.

Recommendations regarding the implementation of a pre-transplant vaccination mandate

1. Any policy that makes the COVID-19 vaccine mandatory should be transparent and be announced with enough time for transplant candidates and healthcare staff to adhere to the mandate.
2. Candidates should have time to obtain their vaccines before the policy is implemented, as is done for healthcare professionals.
3. The healthcare system has a duty to maximize efforts at education and reassurance of vaccine hesistant candidates.
4. Transplant programs should endeavour to address any uncertainties, concerns, or misperceptions candidates may have through evidence-based patient education.
5. The vaccine policy should be reassessed on a regular basis.

Summary

Given that: (a) COVID-19 can cause serious illness in a transplant recipient, (b) transplant recipients often have comorbidities, (c) the mechanism of action of vaccine is specific, and (d) transplantation is not a contraindication to COVID-19 vaccine according to Health Canada, we recommend that vaccine should be given to the pre- and post-transplant patient population. Based on expert opinion, we recommend that the potential benefits of vaccine outweigh any theoretical risks or concerns about graft dysfunction. Due to the severity of COVID-19 in this population, we also recommend that transplant patients remain a priority for vaccination. Based on available data, we recommend a third dose of mRNA vaccine to SOT recipients. Transplant patients should be made aware that they may not have adequate protection from vaccine alone and advised to continue infection control measures. In addition, household contacts of the transplant recipient should be vaccinated.

Disclaimer

The guidance provided is not meant to replace clinical judgement. The field is also rapidly evolving and as such the guidance will likely change over time. Any clinical decisions should be made in consideration of the latest available information.

Endorsement

These guidelines were written by the Canadian Society of Transplantation's Transplant Infectious Diseases Group, reviewed by the CST Ethics Committee and endorsed by the Canadian Society of Transplantation.

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