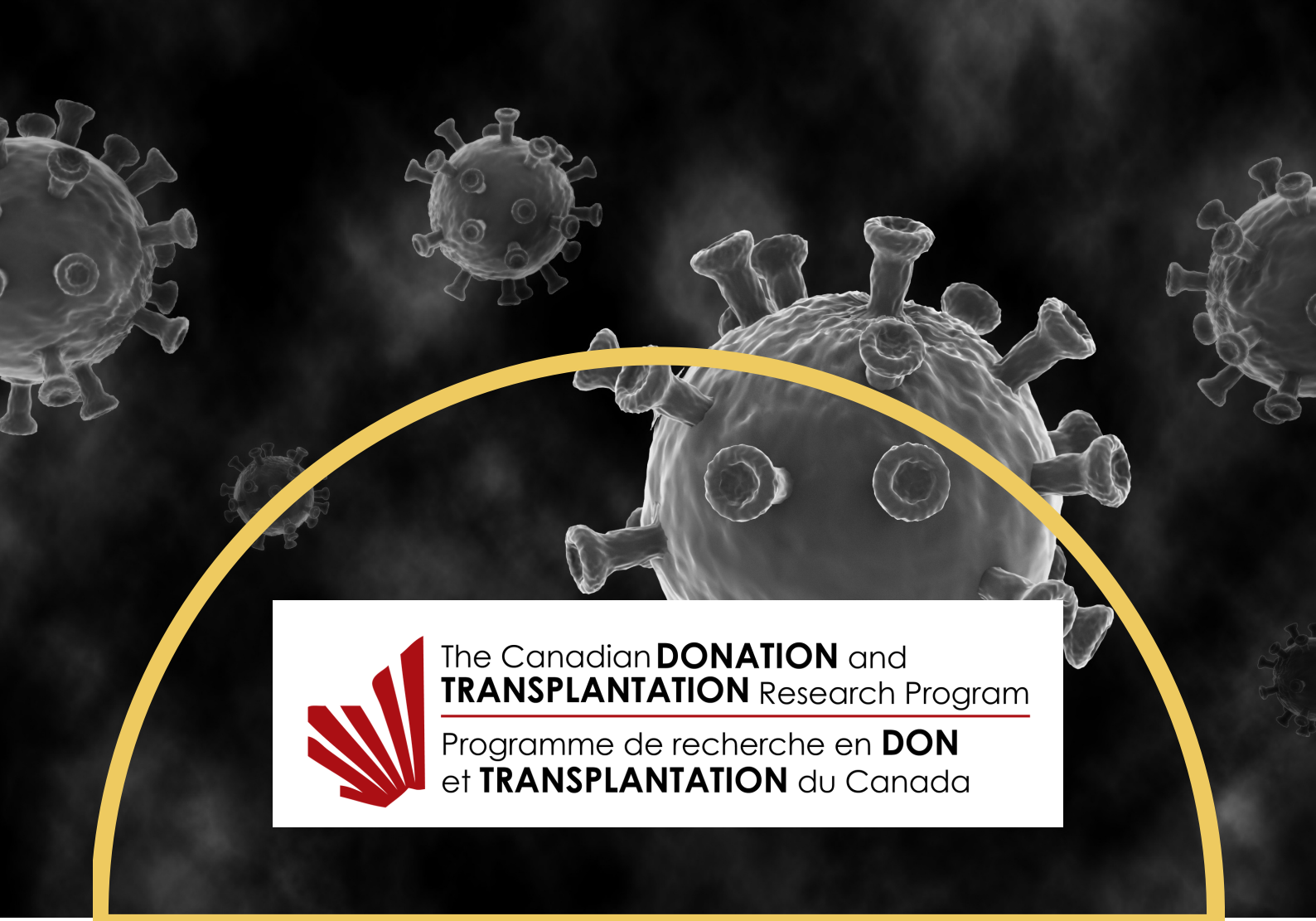


The Canadian **DONATION** and **TRANSPLANTATION** Research Program

Programme de recherche en **DON** et **TRANSPLANTATION** du Canada

COVID-19 VACCINATION IN TRANSPLANT PATIENTS

EXPERT PANEL MEETING REPORT

JANUARY 6, 2021

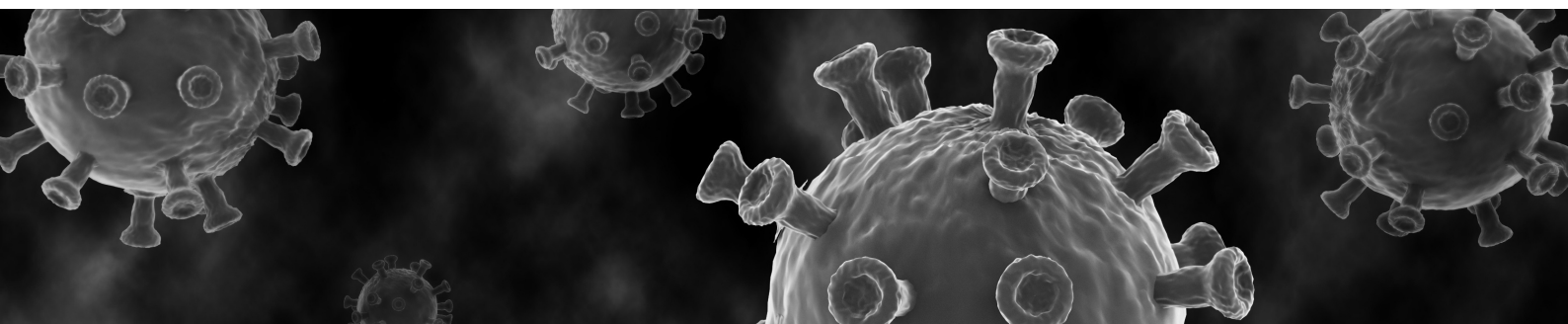
INTRODUCTION

Expert Panel meeting report | January 6, 2021

Canada is one of the first countries in the world to roll out its COVID-19 vaccination program. The opportunity is to use our Canadian collaborative network of stakeholders to develop a coordinated knowledge generation roadmap to fill outstanding knowledge gaps around vaccination in transplant patients.

The Canadian Donation and Transplantation Research Program (CDTRP) is developing a National Strategy to fill the knowledge gaps around COVID-19 vaccination in transplant recipients in Canada. This national effort should bring together major stakeholders in transplantation (CDTRP, CST, CTTC, CBS, TTS ID, ODTC collaborative and others), PHAC, FRQS, and CIHR III, public health experts, immunization policymakers and Canadian Immunization Research Network (CIRN) members of provincial immunization expert advisory committees. CDTRP will hold a National Strategy workshop January 29, 2021 with all stakeholders. The Workshop discussions and agenda will be based on the outstanding knowledge gaps identified by a panel of experts.

To achieve this ambitious plan and to guide this initiative, on January 6, 2021, CDTRP convened experts in the fields of solid organ and stem cell transplantation, transplant infectious diseases, immunization, public health and patient partners to identify knowledge gaps around vaccination for COVID-19 in transplant patients.



LIST OF CONTRIBUTING EXPERTS AND THEIR AFFILIATIONS

Name	Primary hospital or university affiliation	Expertise
Allen, Upton	Sickkids, University of Toronto	Transplant Infectious Diseases
Bédard, Sylvain	CRCHUM, Université de Montréal	Patient partner expert
Burton, Catherine	University of Alberta	Pediatric Transplant Infectious Disease
Chaudhury, Prosanto	McGill University Health Center	Abdominal transplant surgeon
Clarke, Brian	Libin Cardiovascular Institute, University of Calgary	Heart Transplantation
Coldwell, Kristi	TRFBC	Patient partner expert
Delisle, Jean-Sébastien	HMR, Université de Montréal	Hematopoietic cell transplantation and immunology
Dieudé, Mélanie	CRCHUM, Université de Montréal	Immunology
Gill, John	St-Paul's Hospital, University of British Columbia	Kidney Transplantation
Hébert, Marie-Josée	CRCHUM, Université de Montréal	Kidney Transplantation
Humar, Atul	University Health Network	Transplant Infectious Diseases
Kumar, Deepali	University Health Network	Transplant Infectious Diseases
Kwong, Jeffrey	ICES and University of Toronto	Vaccine epidemiology
Mah, Allison	Vancouver General Hospital, University of British Columbia	Transplant Infectious Diseases
McNeil, Shelly	Dalhousie University	Adult Infectious Diseases and vaccinology
Poirier, Charles	CRCHUM, Université de Montréal	Lung Transplantation
Sadarangani, Manish	Vaccine Evaluation Center, BC Children's Hospital Research Institute	Vaccinology
Schiff, Jeffrey	University of Toronto	Kidney and Pancreas Transplantation
Simard, Marc-André	Université de Montréal	Bibliometry
Tait, Caroline	University of Saskatchewan	Indigenous Health
Top, Karina	Dalhousie University	Immunization
West, Lori	Alberta Transplant Institute, University of Alberta	Heart transplantation

CONTEXT

COVID-19 is a disease caused by the SARS-CoV-2 virus that is predominantly a respiratory virus but can cause multi-system disease. Whether COVID-19 is more severe due to immunosuppression is unclear. However, many transplant patients also have other comorbidities (e.g., advanced age, chronic kidney disease, diabetes, and heart/lung disease) that put them at increased risk of severe COVID-19 disease. Lung transplant patients also seem to be at particularly high risk of severe disease.

VACCINATION IN TRANSPLANT RECIPIENTS

In general, many different types of vaccines (inactivated vaccine, protein subunit recombinant, particle vaccines or virus-like vaccines) are considered safe for transplant recipients. Live attenuated vaccines are generally not recommended for SOT [1], but may be used with restrictions in HSCT recipients. Replicating viral vector vaccines are not recommended for either population. RNA vaccines (BioNTech/Pfizer, Moderna) and non-replicating viral vector vaccines (AstraZeneca, Gamaleya) are considered low-risk but have never been tested in transplant populations. No COVID-19 vaccine has been tested in transplant patients.

COVID-19 VACCINES

Several COVID-19 vaccines are in development around the world. To date, two vaccines based on mRNA lipid nanoparticle platforms have been approved by Health Canada.

- The Pfizer COVID-19 vaccine was authorized in Canada on December 9, 2020, given in 2 doses, for 16yrs+. It requires ultra-cold storage and reports 95% efficacy.
- The Moderna COVID-19 vaccine was authorized in Canada on December 23, 2020, given in 2 doses, for 18yrs+. It reports 94% efficacy (but only 86% in people 65 years and older).

For both vaccines, side effects include local, tenderness, swelling, fever, fatigue, headache, chills, and muscle aches. In both Pfizer and Moderna vaccine trials, systemic symptoms were more common in younger age groups and after the second dose.

[1] With the exception of live varicella vaccine, now recommended in pediatric SOT recipients meeting specific conditions – per the International Pediatric Transplant Association guidelines

CURRENT TRANSPLANT-SPECIFIC GUIDELINES

Given the absence of data in transplant patients, transplant-specific guidelines are currently based on expert opinion and suggest that the benefits of vaccination likely outweigh the risks.

INTERNATIONAL GUIDELINES

Transplant societies (AST, ISHLT, BST) generally recommend COVID-19 vaccines for pre- and post-transplant patients, as soon as they are eligible (even if they have had a previous SARS-CoV-2 infection), but patients should be advised that safety/efficacy data is unavailable and that they should report adverse events. Most societies recommend close monitoring of vaccinated transplant recipients to acquire data on safety and efficacy of the vaccines.

The Transplantation Society Infectious Disease group (TTS ID) also released international guidelines on January 5, 2021. They state that transplant recipients may be vaccinated with any of the COVID-19 vaccines (except live-attenuated vaccines (LAV) and replicating viral vector (VVr) vaccines), as soon as they are approved and available. They also recommend that all transplant recipients should receive the vaccine, irrespective of past SARS-CoV-2 infection or positive SARS CoV-2 antibodies, as case reports of reinfection in immunocompromised patients suggest that protection after a first infection is not fully protective and may wane over time. TTS ID guidelines suggest that:

- For SOT, the ideal timing of vaccination is uncertain in the post-transplantation setting. Vaccination should be delayed at least one month from transplant surgery. A risk-benefit assessment should weigh the community transmission risks against the likelihood of adverse events.
- For HSCT, in regions with accelerated transmission rates, COVID-19 vaccination may start at the 3rd month of HSCT. In regions where the risk of community acquisition of COVID-19 is lower, it is reasonable to wait until the sixth month after HSCT when better vaccine response is expected.

CANADIAN RECOMMENDATIONS

Health Canada has not contraindicated the vaccine for immunocompromised people although it has stated that there are no data on efficacy and adverse events in this population. **The National Advisory Committee on Immunization (NACI)** now recommends that a complete COVID-19 vaccine series may be offered to individuals who are immunosuppressed due to disease or treatment in the authorized age group in this population, if a risk assessment deems that the benefits outweigh the potential risks for the individual, and if informed consent includes discussion about the absence of evidence on the use of COVID-19 vaccine in this population.

Based on expert opinion and in line with international guidelines, the **Canadian Society for Transplantation has concluded** that the potential benefits of vaccine outweigh any theoretical risks or concerns about immunogenicity and safety. The CST recommends that vaccine may be given to the pre- and post-transplant patient population when it is available to them and that transplant patients should be made aware of the lack of safety and efficacy data and report adverse events. Similarly, **Cell Therapy and Transplant Canada (CTTC)** recognizes the lack of efficacy and safety data but aligns with American and European guidelines for hematopoietic cell transplant recipients. The CTTC recommends vaccination for patients (for some cases as early as three months post-transplant) and the vaccination of patients' primary caregivers.

DISCUSSION SUMMARY

What are the key new or unanswered questions, and outstanding knowledge gaps to fill?

COVID-19 VACCINE EFFECTIVENESS IN TRANSPLANT POPULATIONS

The current COVID-19 vaccines were not administered to transplant or other immunosuppressed individuals in the phase 3 trials.

Question: **How should we assess effectiveness?**

- Effectiveness at preventing SARS-CoV-2 infection or disease-related outcomes in clinical trials/epi studies
- Clinical/epidemiological evaluation with a disease endpoint? Which ones?

Question: **How should we define immunogenicity?**

- Surrogate marker of effectiveness?
- No known correlates of protection yet but responses in transplant patients can be compared to healthy controls, and do not need large sample sizes
  - Non-neutralizing antibodies
  - Neutralizing antibodies
  - T cell-mediated responses
  - Durability of response

Key questions to be addressed in vaccinated transplant recipients:

- Immunogenicity (neutralizing antibody production and T-cell responses) to the vaccine
- Case fatality rates
- How immune responses to vaccine correlate to clinical outcomes

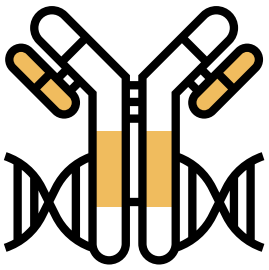
Important considerations:

- Ability to link vaccination history, laboratory diagnosis of COVID-19 and clinical history (e.g., pre/post transplant, immunosuppression, etc.)
- Studies should consider:
  - Pediatrics
  - Indigenous populations as they suffer disproportionate consequences from COVID-19 due to a range of factors including poor housing conditions, limited access to health care, and prevalence of co-morbidities

- Important to consider other racialized communities as well
- Remote and rural populations are usually left out of the major centre studies and should be taken into consideration in these studies.

- **Patients perspective and concerns:**
  - Follow-up boosters and duration of protection: are these different for immunosuppressed patients?
  - Need closer follow-up after vaccination to monitor impact

IMMUNOGENICITY



As a large sample size is required for the assessment of vaccine effectiveness there was a consensus that a focus on immunogenicity could be a shorter-term goal, as it does not require a large sample size. However, at this time there is no established correlate of protection for COVID-19, so immunogenicity studies may be difficult to interpret with regards to protection, and should include antibody and T cell studies.

- Samples could be available from various sites in Canada to complete immunogenicity studies on a relatively short timeline.
- Immunogenicity might act as a surrogate marker to answer some of the concerns of public health specialists. From a public health perspective, they want to determine that if transplant patients receive the vaccine, that it will be effective and therefore it will be an appropriate utilization of a scarce resource (i.e. COVID-19 vaccine).
- Such studies would need to determine which and how many samples to collect to test both humoral and cell-mediated responses.
- There may be subtle differences in immunogenicity and immune activation between the two mRNA vaccines so it will be important to capture which one people receive. Provinces are capturing specific product (e.g., lot #, date of administration).
  - Should include distinct transplant populations, given variability in immunosuppression

AVOIDING DUPLICATION: FAVORING ALIGNMENT

It was noted that several studies in the US are looking at antibody responses to COVID-19 vaccines and are using mechanical 'leeching' to collect blood from patients at home (multicentre effort led by Robin Avery and Dorry Segev: https://transplantvaccine.org/). Important to note that these studies do not currently assess T cell responses.

In addition, a collaboration with The COVID-19 Immunity Task Force (CITF) to avoid duplication would allow comparison between immunogenicity studies in different populations.

IDENTIFYING VACCINE RECIPIENTS AND DATA COORDINATION

Studies depend on identification of vaccine recipients. In particular, an effectiveness endpoint requires a large sample size. Provincial immunization registries exist in all provinces and territories and will need to be linked to the transplant databases. Although all provinces are capturing who is being vaccinated, provincial databases might not capture all the data needed in the context of transplantation. BC for example is capturing vaccine data in a provincial registry. BC Centre for Disease Control is undertaking analyses involving data linkage and overall vaccine effectiveness assessment – there may be potential to link to the transplant database.

- The possibility of linking different databases relevant to transplant patients should be considered in the future. For example, this would include initiating discussions with CORR and CIHI.
- The CIRN Provincial Collaborative Network is funded to evaluate effectiveness using administrative databases in several provinces (BC, Alberta, Manitoba, Ontario, Quebec) including in immunocompromised and transplant populations.
    - The CIRN Serious Outcomes Surveillance Network conducts active surveillance for COVID-19 in a Network of Canadian hospitals in order to evaluate COVID-19 vaccine safety and effectiveness, but sample size will be limited for the assessment of effectiveness in transplant recipients.
- Some transplant recipients are already getting the vaccine in Canada (i.e., health care workers, patients residing in long term care facilities.
- Could these individuals provide valuable preliminary data before mass vaccination on recipients begins?

CAREGIVER VACCINATION

An outstanding issue is the consideration of prioritizing household contacts of transplant recipients.

- There is currently no data on the impact of COVID-19 vaccines in reducing virus transmission, whether in the general population or transplant population.
- CTTC is recommending vaccination in transplant patients and also their caregivers.
- It is known that vaccination provides individual protection (prevents symptomatic disease) in the general population. It is unknown if the vaccine prevents infection itself, or transmission. There are ongoing clinical trials to look at this.
- Understanding if vaccination prevents transmission from caregivers and other family members is key, particularly in pediatrics due to higher rates of asymptomatic infection. Issues around prevention of virus transmission may be particularly important in immunocompromised patients who, if infected, may remain infectious for a prolonged virus for period of time. It is important from a public health perspective to capture this data.

AGE DIFFERENCES

Younger age is associated with fewer and lower risk of COVID-19 complications in the general population. Pediatric trials are currently underway. At present, the National Advisory Committee on Immunization states that the Pfizer-BioNTech vaccine may be offered to adolescents aged 12-16 years if benefit is felt to outweigh potential risks. There are no data on the safety or efficacy of COVID-19 vaccines no in pediatric transplant populations. To study these patients may require access to different databases (schools, day cares). Adults will have more rapid access to vaccination, so adult studies are likely to be more feasible initially to assess vaccine immunogenicity and efficacy.

COVID-19 VACCINE SAFETY IN TRANSPLANT POPULATIONS

Measuring safety in the general population and transplant patients is not the same. There is a theoretical risk of immune activation with vaccination in general. In transplant patients, viral infections can trigger a rejection episode or graft-vs-host disease (GVHD), although this is rare. mRNA vaccines have not been used in transplant patients. There are no safety data in the transplant population.

mRNA COVID-19 vaccines (Pfizer and Moderna) trigger a strong innate, humoral and cellular Th1-skewed immune response and may also induce a strong Type 1 interferon response.

- **Reactivation of auto-immune disorders** that were the precursor to transplantation is also important to consider. A portion of recipients receive transplants due in part to their autoimmune disease leading to organ failure. This concern is two-fold for this unique subset:
  a. to avoid reactivation that could lead to adverse effects on the graft
  b. inducing a flare of their underlying condition that will have adverse impacts on quality of life. There may be unique considerations for these patients.

- **GvHD:** It would not be easy and would require a lot of effort in individual centres to monitor increased or worsening GVHD in relation to the timing of vaccination. Since these vaccines are new, this is a major knowledge gap. One would need to consider whether the vaccine is causing the GvHD. This would require a huge number (thousands) of patients to answer, and data collection would be retrospective.

- **Rejection:** It is critical to understand the risk of rejection in solid organ transplant recipients.
  - To look at the risk of rejection post-vaccination, there are certain case-only methods that assess risk of specific adverse events in relation to the vaccine versus a remote interval (i.e., pre-vaccination) which can be studied using administrative data (cases of acute rejection and vaccination status).
  - It is possible to do this with a few hundred or a dozen cases. It may also be more feasible to study of surrogate outcomes before rejection (Donor Specific Antibodies (DSA), T and B-cell responses, TRA at baseline and after 1st and 2nd dose), and surrogate outcomes of graft function (e.g. for kidney: creatinine, proteinuria, albumin).

- **Case-controlled retrospective study approach.** For immune events, one could consider a simple case-controlled retrospective study approach.
  - For example, a year from now, one could study all rejection events to identify if transplant recipients were immunized or not prior to rejection. This would require prospectively determining what to capture in a case report form (CRF) or in databases.
  - It is expected that additional data besides patient death/graft loss would be needed. CRF would need to be developed through CIHI and could be piggy-backed onto the CORR database for example.
  - There would need to be a national consensus between all pertinent players to determine what outcomes to look at and be able to compare.
  - Key organizations for consensus building would include the CST organ working groups for SOT, and CTTC for HSCT.

- **Vaccine associated enhanced disease:**
  - A priority adverse event with COVID vaccines.
  - Discussions on how to monitor this (e.g., in admin data, through public health surveillance system) are ongoing.
  - It is important to evaluate if vaccination leads to worse symptoms if a person subsequently gets infected, particularly in immunocompromised individuals.

VACCINE HESITANCY, COMMUNICATION, AND EDUCATION

Vaccine hesitancy could be a major barrier to the roll-out effort. It would be important to determine factors contributing to hesitancy in those expressing unwillingness to receive the vaccine.

- Some of these hesitations may be influenced by psychosocial variables that accompany vaccine discussion and decisions in transplant recipients and their caregivers.
- Robust, pertinent, clear and consensus information is needed to empower recipients to get the vaccine – trusted sources need to use social media to share real information.
- It is important to determine how to provide good information via social media and be purposeful in addressing this from a knowledge perspective to the public to promote vaccination.
- It could be helpful to study this in different locations.
- Indigenous perspectives:
  - there is a great fear of losing Elders, so some communities are looking forward to getting the vaccine.
  - there is also some distrust and a lack of information to make a clear choice about vaccination
  - these considerations might vary in different communities
  - it is important to determine how people are getting their information and why they decide to get the vaccine or not

There are already focus groups of COVID-19 patients that exist – it would be possible to add questions about these issues to current surveys. There are some groups looking at vaccine hesitancy already, including behavioural scientists. We should determine areas of synergy with these groups.

- **From the patient perspective:**
  - National data should be reported, studied and shared. This is vital.
  - It is also helpful if communications are standardized, regardless of what province recipients receive the vaccine in.
  - There should be clarity on who is going to be responsible for consolidating this information, making inferences on the data and putting forth future practice recommendations.
  - We will need to ensure a coordinated and cohesive message and education campaign for recipients and caregivers around vaccination geared specifically at them.
  - Many people think a vaccine will be a solution to the current situation. The general understanding of vaccines is primarily to avoid live vaccines: people do not grasp the immunologic limitations.