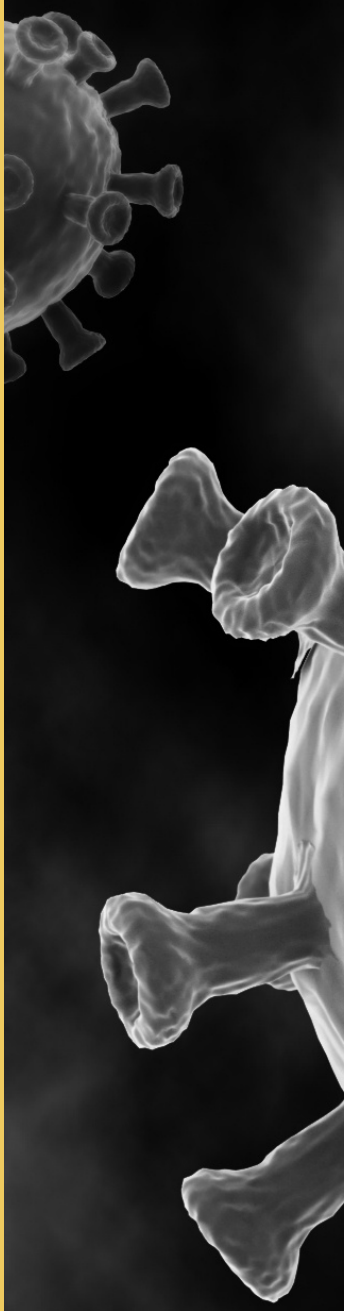
The Canadian **DONATION** and **TRANSPLANTATION** Research Program

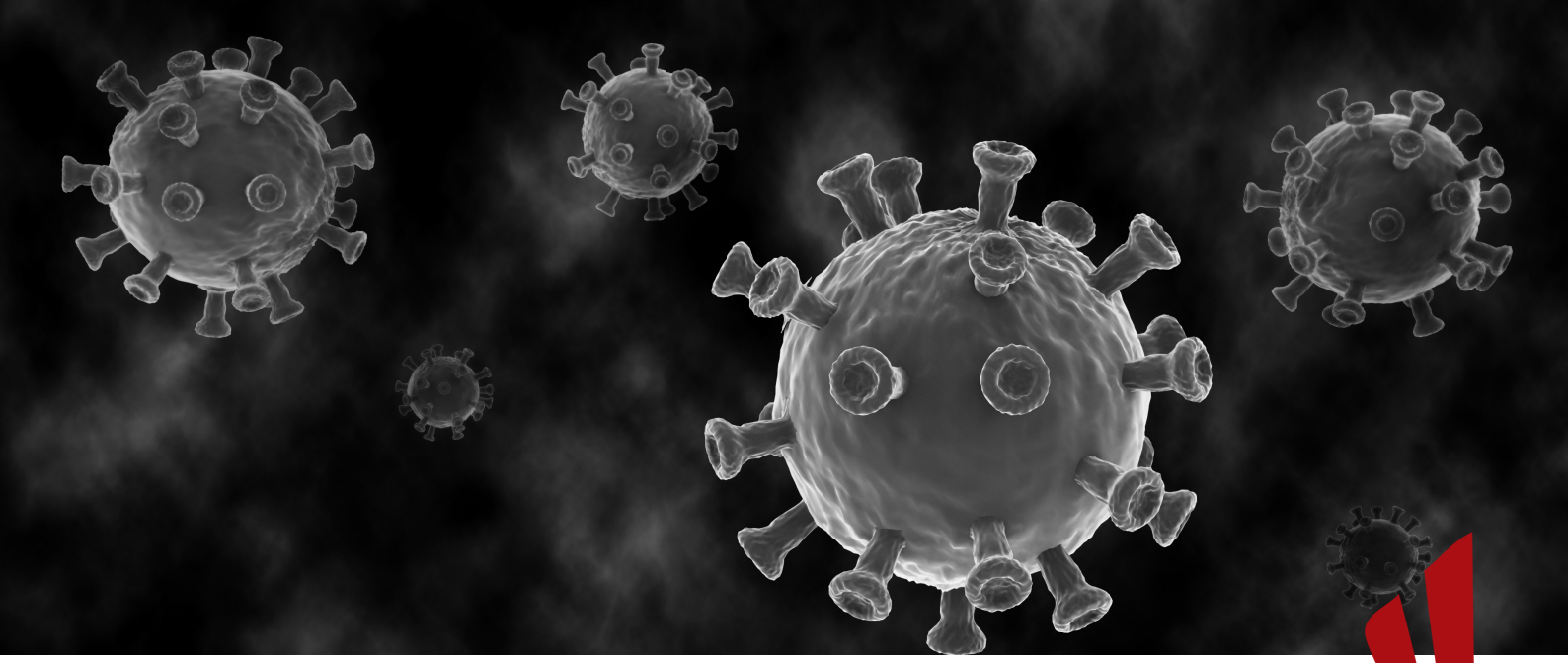
Programme de recherche en **DON** et **TRANSPLANTATION** du Canada

COVID-19 VACCINATION IN TRANSPLANT RECIPIENTS

NATIONAL STRATEGY WORKSHOP REPORT

January 29, 2021





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PREAMBLE

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, immunization and COVID-19 research networks, public health experts, immunization policymakers, and members of provincial immunization expert advisory committees. CDTRP hosted a **National Strategy Workshop on January 29, 2021 with all stakeholders.**

The backbone for the workshop agenda was based on an expert panel meeting held January 6, 2021, convening experts in the field 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. The goal of the National Strategy Workshop was to seek the input of the Canadian stakeholder community about priority topics for study and how to move the priority research ideas forward to implementation in an aligned and coordinated way.

41 representatives from **31 stakeholder organizations** registered for the Workshop, representing diverse sectors and perspectives, including the not-for-profit sector, government, academic, health care, public health, and patients/families (see page 4 for the full list of participating organizations).

The Workshop began with a presentation of the initiative by Dr. Marie-Josée Hébert and Dr. Mélanie Dieudé. Participants then divided into smaller breakout rooms, first discussing the questions: “How should we prioritize the studies identified on a knowledge generation roadmap? Are there key ideas missing?" After consolidation of the breakout discussions with the help of the rapporteurs, the whole group produced a consensus ordering of the priority topics for discussion. The examination of the first two of these priorities in detail formed the agenda for two subsequent cycles of breakout and consolidation discussions. The workshop concluded with an assembled consensus knowledge generation roadmap and a summary of the key points for planning and implementation of the two priority sets of studies.

> **How should we prioritize the studies identified on a knowledge generation roadmap? Are there key ideas missing?**

LIST OF CONTRIBUTING STAKEHOLDERS

- American Society of Nephrology
- BC Centre for Disease Control
- BC Vaccine Evaluation Center
- Canadian Blood Services (CBS)
- Canadian Cardiovascular Society (CCS)
- Canadian Immunization Research Network (CIRN)
- Canadian Institute for Health Information (CIHI)
- Canadian Liver Foundation (CLF)
- Canadian National Vaccine Safety Network (CANVAS)
- Canadian Society for Transplantation (CST)
- Canadian Transplant Association (CTA)
- Can-SOLVE CKD
- Canadian Donation and Transplantation Research Program (CDTRP)
- Cell Therapy Transplant Canada (CTTC)
- Centre d'excellence sur le partenariat avec les patients et le public (CEPPP)
- Canadian Institutes of Health Research (CIHR) - The Institute of Infection and Immunity (III)
- COVID-19 Immunity Task Force (CITF)
- First Nations and Métis Organ Donation and Transplantation Network
- Fonds de recherche du Québec – Santé
- Health Canada
- Heart and Stroke Foundation of Canada
- Héma-Québec
- Institute for Clinical Evaluative Sciences (ICES)
- Institut national de santé publique du Québec
- Institut universitaire de cardiologie et de pneumologie de Québec
- Kidney Foundation of Canada (KFOC)
- Leukemia & Lymphoma Society of Canada
- Public Health Ontario
- Réseau Québécois COVID
- The Hospital for Sick Children
- The Transplantation Society (TTS)
- Transplant Research Foundation of BC (TRFBC)
- Trillium Gift of Life Network (TGLN)

BACKGROUND: COVID-19 VACCINATION IN 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. 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 not recommended for SOT, 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 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).

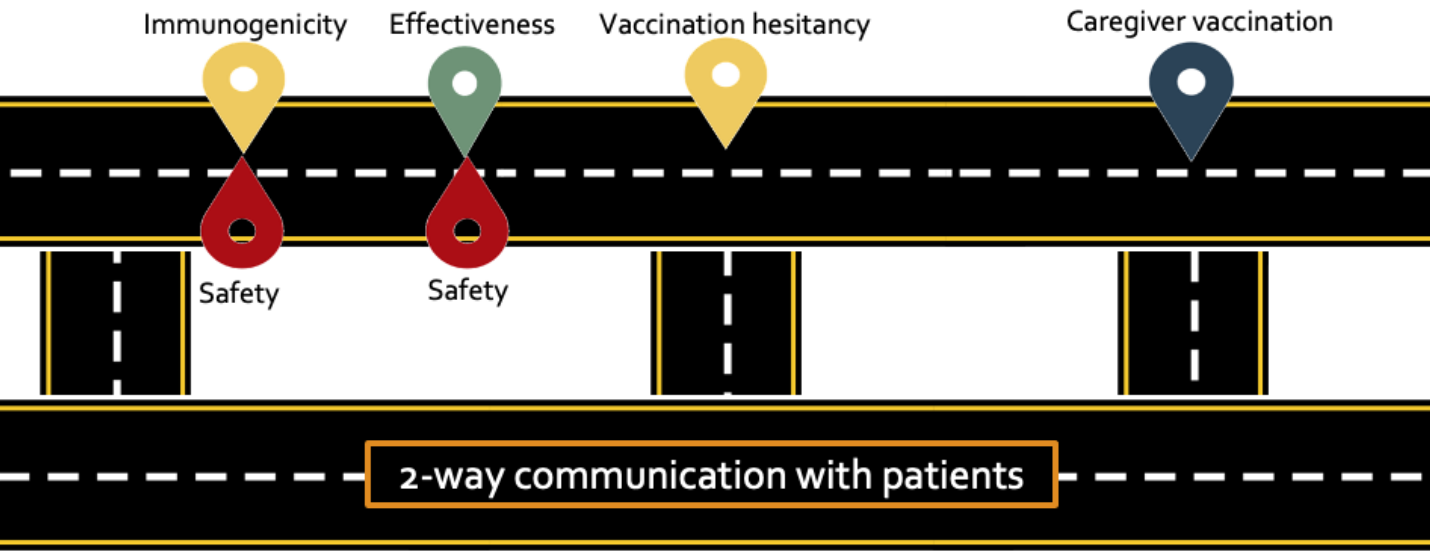
For both vaccines, side effects include local, tenderness, swelling, fever, fatigue, headache, chills, and muscle ache. In both Pfizer and Moderna vaccine trials, systemic symptoms were more common in younger age groups and after the second dose.

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. There are currently no data on COVID-19 safety, efficacy and effectiveness in the transplant population. Transplant-specific societies generally recommended COVID-19 vaccine to be given to pre- and post-transplant patients when available. These guidelines are based on expert opinion. They underline that transplant patients should be made aware of the lack of safety and efficacy data and encouraged to report any adverse events. Most societies recommend tight monitoring of vaccinated transplant recipients to acquire important data on safety and efficacy of the vaccines.

WORKSHOP OUTCOME: A KNOWLEDGE GENERATION ROADMAP

Discussion Question: How should we prioritize the studies identified on a knowledge generation roadmap? Are there key ideas missing?



COMMUNICATION AND SAFETY SHOULD BE INTEGRATED INTO PRIORITY STUDIES

COMMUNICATION

In considering the prioritization of the identified research topics, there was strong consensus that two-way communication with patients should be incorporated through an integrated and ongoing strategy. Transplant recipients are used to taking risk/benefit data into account in decision-making, but require clear information. There should be an awareness that mistrust can arise from changing information. Tailored strategies are needed for different communities, particularly Indigenous communities, where trust in the health care system may be lacking.Why these studies need to be done must be communicated to patients, which is likely to improve research enrolment and uptake. It should be considered whether data analysis can be completed in phases, to continually inform patients. Linking to patient or patient advisory organizations may speed communication efforts.

SAFETY

There was consensus that safety considerations should be integrated into the priority studies, and not considered as a separate issue. It was noted that the CANVAS network could assist in streamlining/capturing adverse events (real-time monitoring of safety data, to be set up). Data should be gathered on how participants react to the vaccine (frequency of local and systemic symptoms), and how to detect rare adverse events (rejection, disease flare). Safety endpoints include autoantibodies, donor-specific antibodies assessed with immunogenicity markers, pre/post comparison (leverage biobanks).

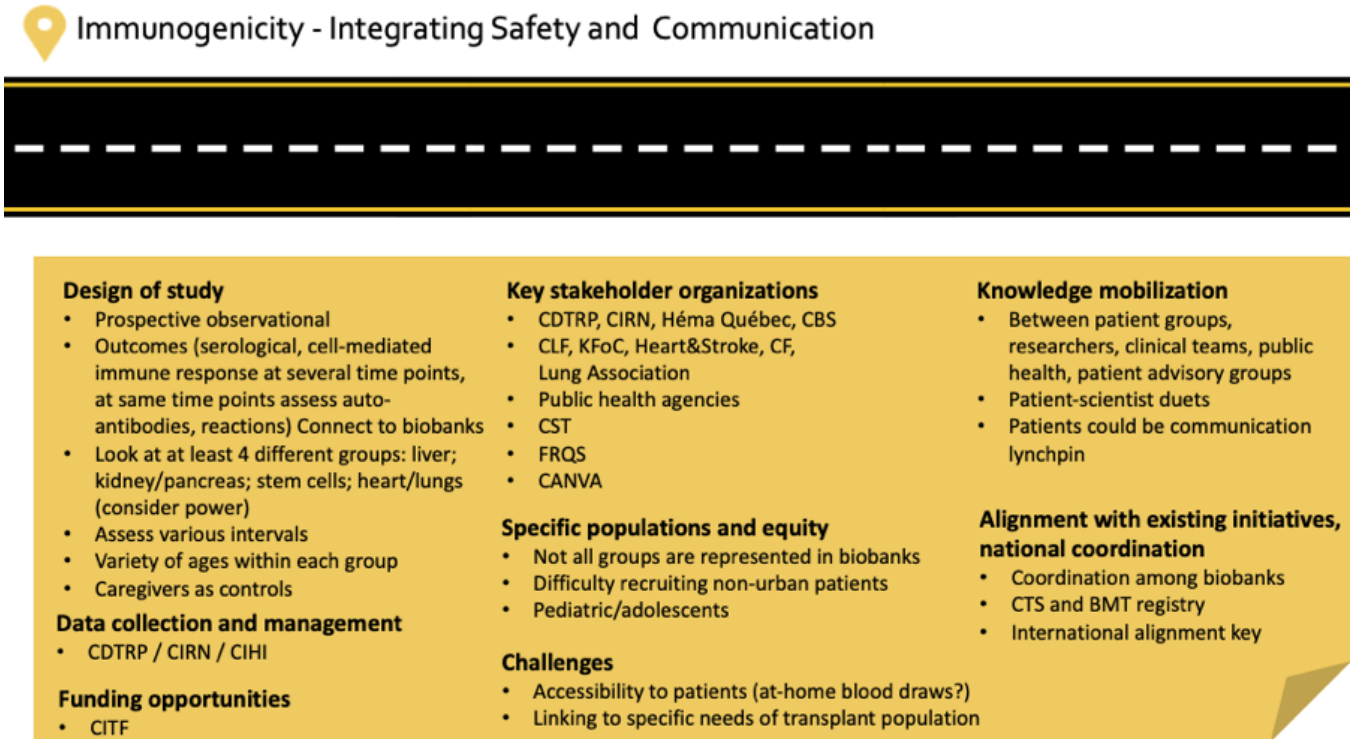
Principal safety outcomes to consider as a part of study designs: Rejection, Graft vs Host Disease (GvHD) and Reactivation /activation of auto-immune disorders.

- **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 they were immunized or not. 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.

IMMUNOGENICITY

There was consensus that immunogenicity studies represent a top research priority, whereas a surveillance study of effectiveness should be planned on the long-term. A summary of points captured in the consolidation discussion with the whole group is on the next page.



Study design:

- Immunogenicity studies would not require large numbers of patients, so design might be easier (50-100 participants per vaccine per transplant type).

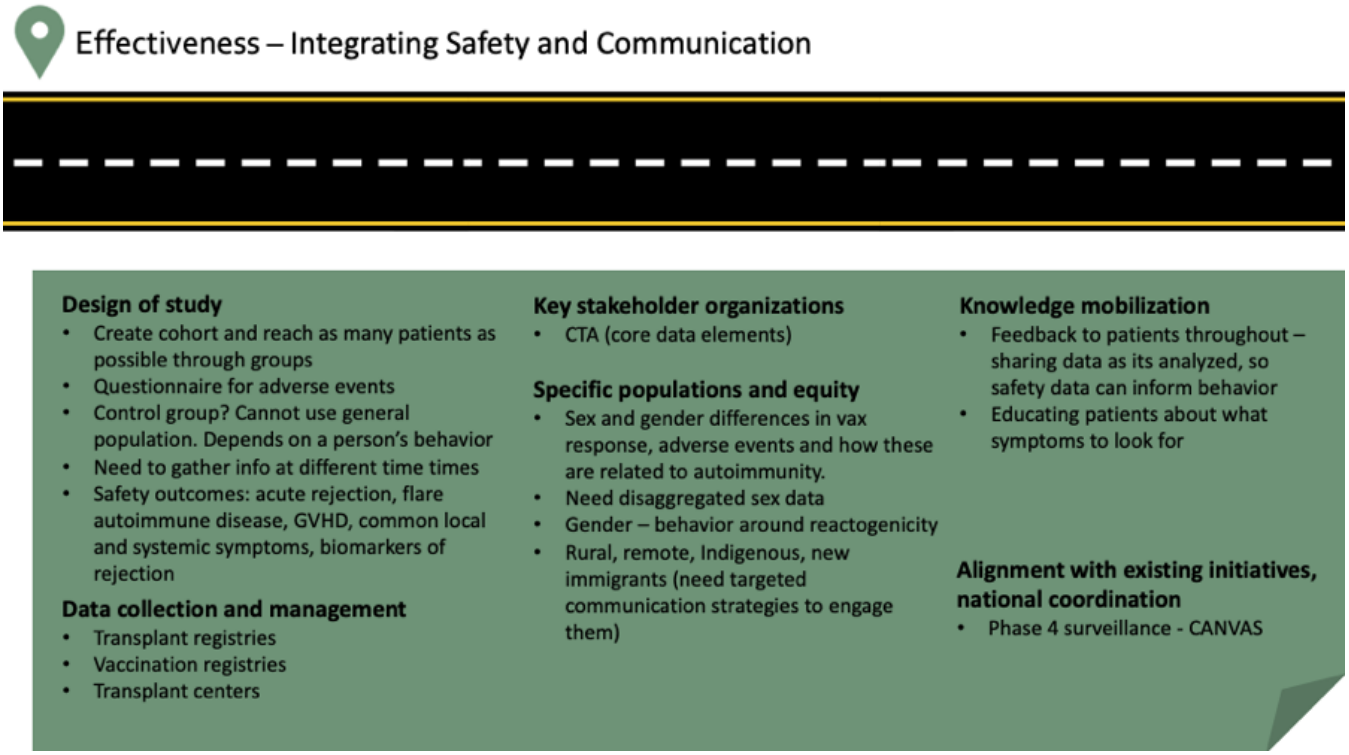
- Adults are at increased risk of COVID-19 complications; the view was shared that starting studies in the adult population would make sense and could inform both the adult and pediatric population. It could make sense to start with older patients, while including younger participants would inform also as to whether immunosuppression vs age makes a difference. Studies in general pediatric population underway; it would be preferable to get these results before studies in the pediatric transplant population.

- Studies should be designed with accessibility in mind: patient participation will be lower if there are requirements for blood draws, medical visits, etc.
  - Case report form for transplant centres (?)
  - Are patients the lynchpin for the collection of data?
  - Empowering patients to know to with whom and how to communicate
  - Are there connections to make to contact tracing?

- Points for consideration for study design, for a prospective observational study. Include four types of transplant, considering statistical power:
  - Liver
  - Kidney and pancreas
  - Heart and lungs
  - Stem cells

- Participants should be of various ages to assess the impact of age; co-morbidities, time since transplant, different vaccines
- Different intervals between doses should be tested. Should take advantage of differences between schedules and products used across jurisdictions
- What immunization protocol (21-28 days vs longer) works best, what should be the interval, how should we modify the immunization protocol.
- Patients should have blood specimens taken before and after immunization. Important to look at response in transplant patients after vaccination at multiple time points.
- Duration of the immune response after vaccination. Measure antibody responses and T-cell responses - many samples will need to be collected in order to miss a minimum of time points. Assays - Serological (antibodies) commercial vs research and T-cell (flow cytometry. Neutralization assays. Make sure to be in phase with other groups internationally (non-transplant).
- Logistics required for sample handling/processing.
- Administration of vaccines and sample collection need to be coordinated, but do not need to be done at the same place.
- BMT and SOT are very different (level of immunosuppression, immune reconstitution)
- Work with CITF to find lab(s) doing standardized assays
- Coordinate with US/UK studies - US only doing serology
- Coordinate with other immunosuppressed groups receiving similar drugs
- Biobanking residual specimens for follow up studies
- Ensure representativeness of patients enrolled in biobanks

EFFECTIVENESS



Study design:

- Need to implement a communication channel with the patients to favor patient engagement, empowerment and their participation in the cohort study
- Negative control studies to consider: the control group must be carefully considered, as the general population cannot be used.
- Longitudinal cohort study using linked administrative data in multiple provinces, with the collaboration of transplant registries/networks. Assess COVID-19 status before and after and assess variant genotype
- New variants / multi-disciplinary aspect - Genomics
- Assessments after each dose
- Online surveys - resources - electronic surveillance
- Observational study - for safety, transplant-specific outcomes
- Self-controlled case series analysis - incidence of rejection/GVHD post-vaccination versus other periods

- Alignment with national phase IV surveillance studies

- Outcomes: acute rejection, flare autoimmune disease, GVHD, common local and systemic symptoms (severity/duration)
  - Patient reporting of adverse events → link to transplant team
    - Almost any symptom can be sign of rejection (organ-specific), biomarkers of rejection/flare
  - Opportunistic manifestations of immune dysregulation - EBV (peds)/CMV/HSV/VZV reactivation, BK? (not reliably captured in registries)

- Knowledge mobilization
  - Educate patients on what to look for and who to contact if new symptoms appear
  - Empower patients to educate each other and be champions for the study

- Specific populations and equity considerations
  - Sex/gender differences in vaccine responses/reactogenicity and in transplant/autoimmunity
  - Rural, remote, new immigrants, Indigenous, racialized groups, intersectionality race/ethnicity and risk
  - Communication strategies targeted to different groups' needs

NEXT STEPS

As vaccination programs are already rolling out across Canada, the first studies in the consensus national knowledge generation roadmap should be rapidly executed. This should happen in parallel to the implementation of a strong communication strategy with all stakeholders (especially patients and families) for timely and impactful knowledge exchange and mobilization.

Concerning the top priority studies discussed at the workshop (Immunogenicity; Effectiveness), the next step is seeking funding opportunities. For example, on February 4, 2021, the Canadian Vaccine Surveillance Reference Group (VSRG), in partnership with the COVID-19 Immunity Task Force (CITF), and with the support of the Public Health Agency of Canada (PHAC), launched a call for proposals to assess the safety and effectiveness of current and future SARS-CoV-2 vaccines deployed in Canada. To develop a proposal based on the consensus discussions, we will create a smaller, agile writing group, while involving and consulting stakeholders consistent with their mandates and interests expressed during the workshop, formalizing partnerships where appropriate.

Other immediate next steps are to constitute working groups to develop the identified priorities that we did not have time to cover during the workshop (e.g., vaccination hesitancy). Across all initiatives, international feedback should be sought to ensure alignment and limit duplication with international initiatives.