



**COVID-19
IMMUNITY
TASK FORCE**

**GROUPE DE TRAVAIL
SUR L'IMMUNITÉ
FACE À LA COVID-19**

Summary report # 11

**People at higher risk due to other health
conditions & COVID-19**

Background

People with health conditions that affect their immune system have been more vulnerable to severe outcomes from COVID-19 than the general population. Moreover, the primary two doses of mRNA vaccines have tended to be less robust and long-lasting in immunocompromised people.

For our 11th *Research Results and Implications Seminar*, we brought together CITF-funded researchers studying the effects of COVID-19 on people who suffer from health conditions and/or take medications that leave their immune systems compromised, including **solid organ transplant recipients and people with immune-mediated inflammatory diseases, inflammatory bowel disease, chronic kidney disease, and HIV**.

Among the questions they addressed:

- What are the risks that people with immune problems face from SARS-CoV-2 infection?
- Are vaccines safe and effective for these individuals?
- How do medications that impair the immune system affect COVID-19 and vaccine effectiveness?
- What added precautions should these people take?

Researchers and CITF-funded studies included

Focus	Presenters, lead researcher(s) and affiliation	Study population	Location of study
HIV	Dr. Ann N. Burchell University of Toronto; Unity Health Toronto & Dr. Cecilia T. Costiniuk McGill University; McGill University Health Centre On behalf of research led by Dr. Aslam Anis	30,000 PLWH	Ontario & British Columbia
Immune-Mediated Inflammatory Disease	Dr. Vinod Chandran University Health Network; University of Toronto	150 adults	Toronto
Inflammatory Bowel Disease	Dr. Gilaad Kaplan University of Calgary On behalf of the Safety immunogenicity of Covid-19 vaccines in systemic immune mediated inflammatory Diseases (SUCCEED) study led by Dr. Sasha Bernatsky		
Solid organ transplant recipients	Dr. Deepali Kumar University of Toronto; University Health Network		
Chronic Kidney Disease	Dr. Sara Wing St. Michael's Hospital, Toronto On behalf of research led by Drs. Matthew Oliver and Michelle Hladunewich	8,457 adult patients on dialysis	Ontario

At a glance: key findings from CITF-funded research

The findings in this summary are, in some instances, unpublished, and have not yet been peer-reviewed. Details about these findings are found below.

Key findings:

- **COVID-19 vaccines have proven to be safe** for people at higher risk of severe COVID-19 due to their pre-existing health conditions.
- **Vaccines have worked well at generating immune responses** and warding off severe disease and death in various high-risk populations.
- **Keeping up to date with the recommended vaccine booster schedule** (i.e., a dose roughly three months after the previous dose or an infection) is important to sustain adequate levels of protection.
- **Two doses of vaccine provide insufficient protection for immunocompromised people.** Thus, in most cases, three doses are necessary to elicit an adequate immune response against COVID-19 and ought to be considered the primary regimen.

More in depth

Scope of the problem faced by immunocompromised people

Immunocompromised people are at greater risk of severe illness and death from COVID-19 compared to the general population:

- 40,000 people in Canada received a solid organ transplant (1). Based on international research, people who received a solid organ transplant have experienced a 4% higher rate of hospitalization from COVID-19 than otherwise healthy people in the United States (2).
- Over 7 million Canadians live with immune-mediated inflammatory diseases (IMID) - which include people with rheumatoid arthritis, ankylosis spondylitis, psoriasis and psoriatic arthritis, and inflammatory bowel disease (IBD). Based on data from the UK (3), people with IMID have experienced:
 - 8.27 deaths per 1000 person-years from COVID-19, compared to 4.88 among the general population; and
 - 14.31 COVID-19 related hospitalizations per 1000 person-years, compared to 8.77 among the general population.
- Between 1.3 and 2.9 million Canadians have a chronic kidney disease (CKD) (4), a population that suffers a:
 - 63% higher risk of hospitalization from SARS-CoV-2 infection than people without CKD, based on a review of international research (5).
 - 44.6% mortality rate from COVID-19 compared to a 4.7% mortality rate among CKD patients without COVID-19 over the same time span, based on an Italian study conducted during the pre-Omicron era (6).
- More than 62,000 Canadians live with HIV (7). According to a review of international research, people living with HIV have endured a 24% higher risk of becoming infected with SARS-CoV-2 and a 78% higher risk of death when compared to people without HIV (8).

Solid organ transplant recipients

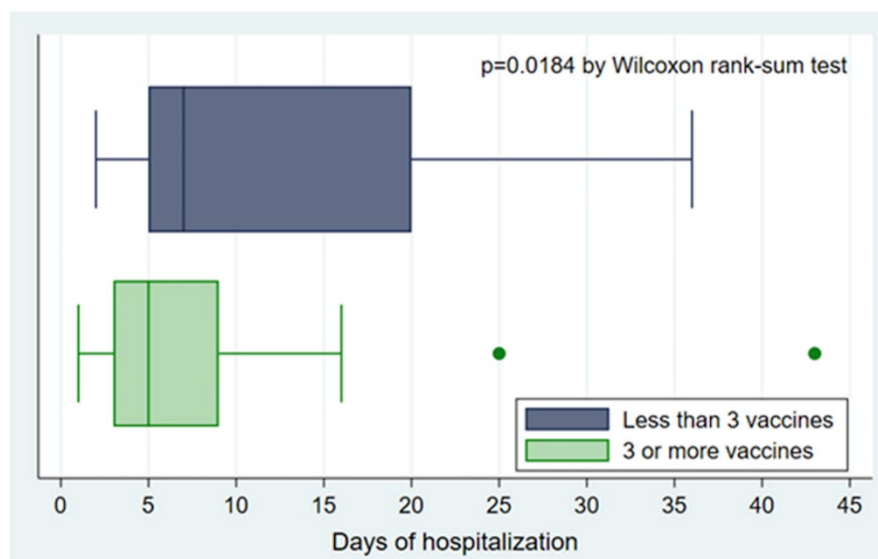
Following an organ transplant, people face a lifetime of immunosuppressant medications in order to avoid organ rejection. Often, they need more doses or higher doses of vaccines, including, but not limited to, COVID-19 vaccines, to achieve sufficient immune responses. Many patients who received a solid organ transplant did not mount an adequate immune response against SARS-CoV-2 from two doses of vaccine.

Based on a randomized control trial, Dr. Deepali Kumar showed evidence that a **third mRNA vaccine dose was necessary to increase the levels of antibody and T-cell responses in recipients of solid organ transplants**. T-cells are important because, besides actively participating in the destruction of a virus during an infection, they also participate in stimulating the memory of the immune system (i.e., its capacity to recognize a previously encountered virus).

Antibody levels decay over time, and so does their neutralization capacity – particularly against Omicron – within one to three months after the third dose was administered. Three months after a third dose, there were greater reductions in neutralization activity against Omicron BA.1 than against the ancestral (wild type) virus – up to 200-fold greater.

However, a third dose was protective against severe disease, as evidenced by the finding that **those who received a third dose were 60% less likely to be hospitalized with COVID-19 than those with fewer doses.** The decrease in the average length of hospital stay is another clinical sign that the third dose is protective.

Vaccination status (less than three vaccines and three or more vaccines)



Solera et al, *Clin Infect Dis*, 2022

Data from a pan-Canadian cohort of more than 500 people with solid organ transplants showed that a fourth vaccine dose was very effective at further increasing antibody levels.

In a comparison of people with solid organ transplants, lung transplant recipients fared the worst after each of four doses of vaccine, while liver recipients had the highest anti-receptor binding domain (RBD) responses to vaccines, followed by kidney and heart transplant recipients. It is believed that lung transplant recipients do not do as well because they are the most immunosuppressed of people with solid organ transplants.

While cautioning about the risk of infection, **the data show that hybrid immunity (a combination of SARS-CoV-2 infection and COVID-19 vaccination) offers higher immunity than vaccination alone, as well as cross-protection between variants.** Of 75 transplant patients who were infected with BA.1 after two or three doses of vaccine, 90% developed BA.1 neutralizing antibodies, while 69% developed cross-protection against the BA.5 variant of Omicron.

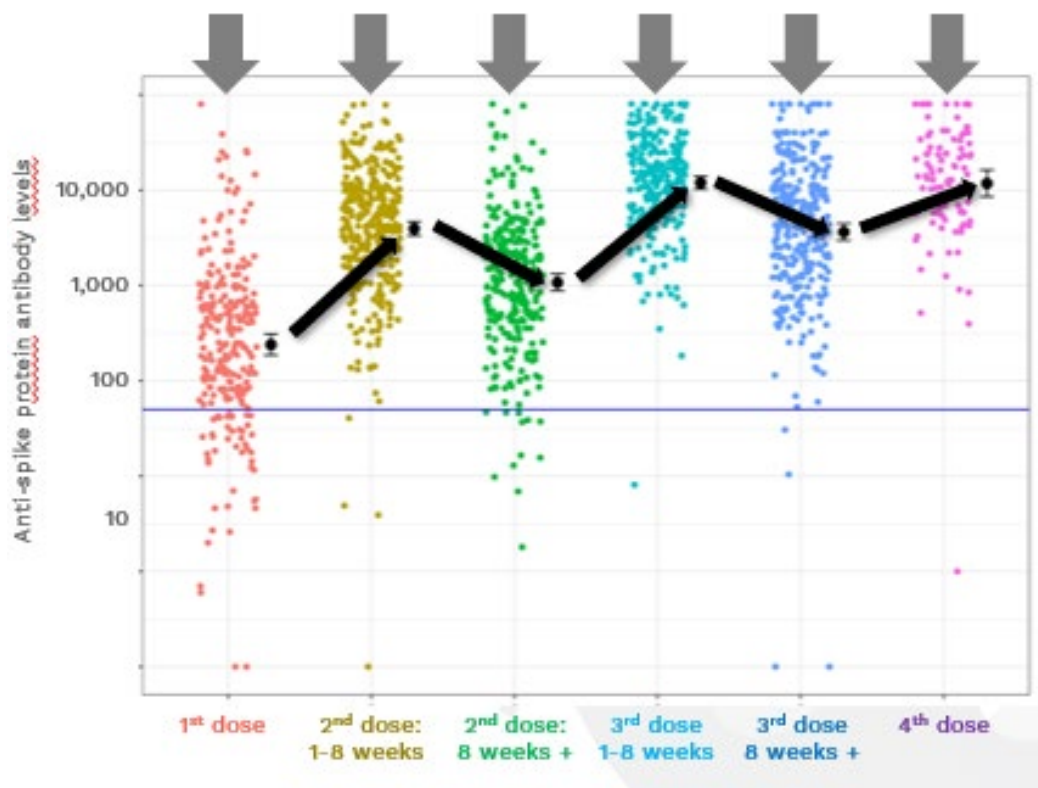
Immune-mediated inflammatory Diseases (IMID)

Dr. Vinod Chandran's IMPACT (*IMmune resPonse After COVID-19 vaccination during maintenance Therapy in IMID*) study found that:

- Antibody responses against the spike (S) protein and its receptor binding domain (RBD) increased following a second dose of COVID-19 vaccine when compared to the first dose, but started declining by three months post-second dose.
- Lower levels of antibodies and lower neutralization capacity against all SARS-CoV-2 strains (ancestral, Delta, and Omicron) were observed in individuals on anti-tumor necrosis inhibitor therapy (anti-TNF) therapy.
- T-cell responses similarly declined, and more so than in “healthy” controls (individuals recruited in the study for comparison purposes who don't have any IMID).
- Two doses of Moderna vaccine produced higher levels of anti-S and anti-RBD antibodies than two doses of Pfizer, but age and sex did not significantly affect antibody responses.
- A third dose of mRNA vaccine induced strong T cell-mediated and antibody-mediated immunity in people with IMID, restoring the antibody and cellular responses that had waned three months after the second dose.
- The third dose also induced similar cellular immunity to the Omicron B.1.1.529 variant as to the ancestral virus in people with IMID.

Antibody response in people with inflammatory bowel disease (IBD)

Dr. Gilaad Kaplan showed that antibodies increased, decayed, and then robustly recovered between the first and fourth dose of mRNA vaccine.



Dr. Kaplan also established that younger people with IBD had a stronger immune response to vaccination than did older individuals. For example, after the third dose of a SARS-CoV-2 vaccine, each decade of increased age was associated with a 12% decrease in anti-spike (S) antibody levels. These findings suggest that **older patients with IBD would benefit the most from a fourth dose of COVID-19 vaccine.**

Antibody levels were lower in people with IBD taking an immunosuppressive medication, such as anti-TNF monotherapy (e.g. infliximab, adalimumab), combination therapies, and corticosteroids (e.g. prednisone). Corticosteroid use at the time of vaccine administration was associated with the lowest antibody response across all medication classes. However, **antibody levels recovered following a third dose of vaccine in patients taking these treatments, except for those on oral corticosteroids.** Therefore, these patients may particularly benefit from a fourth dose.

As well, Dr. Kaplan found that **vaccines were as safe for those with IBD as for the general population** and were not associated with flare-ups of their condition.

People on dialysis

While two doses of vaccine were effective in reducing COVID-19 among people on dialysis when the Alpha and Delta variants were predominant, the third dose had an even higher impact during the Omicron wave (December 1, 2021 – February 28, 2022), according to data presented Dr. Sara Wing. **Three doses reduced SARS-CoV-2 infection by 42% and severe COVID-19 illness by 60% compared with two doses of mRNA vaccine.**

Hybrid immunity offered the most robust protection, as the lowest risk of infection and severe illness was observed in patients with a prior infection and three doses of vaccine. For this group, vaccine effectiveness was estimated to be 83%, when compared to those with two doses and no prior infection. There was no statistically significant difference in vaccine effectiveness between Moderna and Pfizer vaccines.

People living with HIV (PLWH)

It is important to study the effects of COVID-19 on people living with HIV (PLWH) because they have exhibited increased risk of severe outcomes due to a variety of intersecting vulnerabilities. Furthermore, **PLWH display poor immunogenicity to common vaccines**, such as influenza, pneumococcal, meningococcal and Hepatitis A and B vaccines, so it is important to understand how this population responds to COVID-19 vaccines.

Insofar as whether COVID-19 vaccines effectively prevent infection with SARS-CoV-2 and COVID-19 disease among PLWH, Drs. Burchell and Costiniuk, and their team, found:

- Vaccine effectiveness (VE) of two doses of vaccine against SARS-CoV-2 infection was broadly similar among PLWH compared to the general population, prior to the emergence of Omicron variants. Similarly, two doses offered substantial protection against symptomatic and severe COVID-19 illness.
- VE decreased more rapidly following the second dose in PLWH than in people without HIV.
- VE is expected to be lower against Omicron variants, and in individuals with AIDS-defining illness, low CD4, unsuppressed viral load, or other immunocompromising conditions.

With respect to the immune response of PLWH to COVID-19 vaccines:

- The third dose of COVID-19 vaccine elicited a stronger immune response than the second dose, as shown by the higher levels of anti-RBD and anti-S antibodies.
- PLWH mounted similar antibody responses to HIV-negative individuals following both the second and third COVID-19 vaccine doses.
- After the third dose, antibodies were detected both in PLWH with well-controlled HIV on anti-retroviral therapy (ART) and in PLWH with less stable HIV. Neither older age, low CD4 count, nor having comorbidities was associated with reduced antibody responses.
- Neither the type of COVID-19 vaccine received (mRNA-based or not) nor the length of the interval between the first two doses significantly affected antibody responses post-third dose.
- When compared to HIV-negative individuals, fewer PLWH had detectable antibodies against SARS-CoV-2 after their second dose, but the difference resolved after the third dose, which indicates that timely boosters are required.
- Additional information will help continue to inform COVID-19 vaccination guidelines for PLWH:
 - Durability of antibody response.
 - Neutralization capacity.
 - Contribution of cell-mediated immunity.

Policy implications

- **Three doses of mRNA vaccine ought to be considered a primary series for immunocompromised populations**, as two doses are inadequate for protection against severe COVID-19 disease. **Boosters are important** because immunity wanes over time.
- **Those who come in regular contact with immunocompromised people – caregivers, family, friends – need to be vaccinated.**
- Notwithstanding the robust immune response induced by hybrid immunity, **vaccination is the most important defense against COVID-19.**
- **New bivalent vaccines may offer greater protection.** However, since there is no clear evidence favouring one of the available bivalents over any other, people are encouraged to get whichever vaccine is being offered when they are due for a booster dose.
- People with other health conditions – like those discussed here – **are more at risk of severe COVID-19 and therefore should continue to be cautious:** wear masks, practice physical distancing, avoid crowded settings, and get regular boosters.

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