COVID-19 IMMUNITY TASK FORCE

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

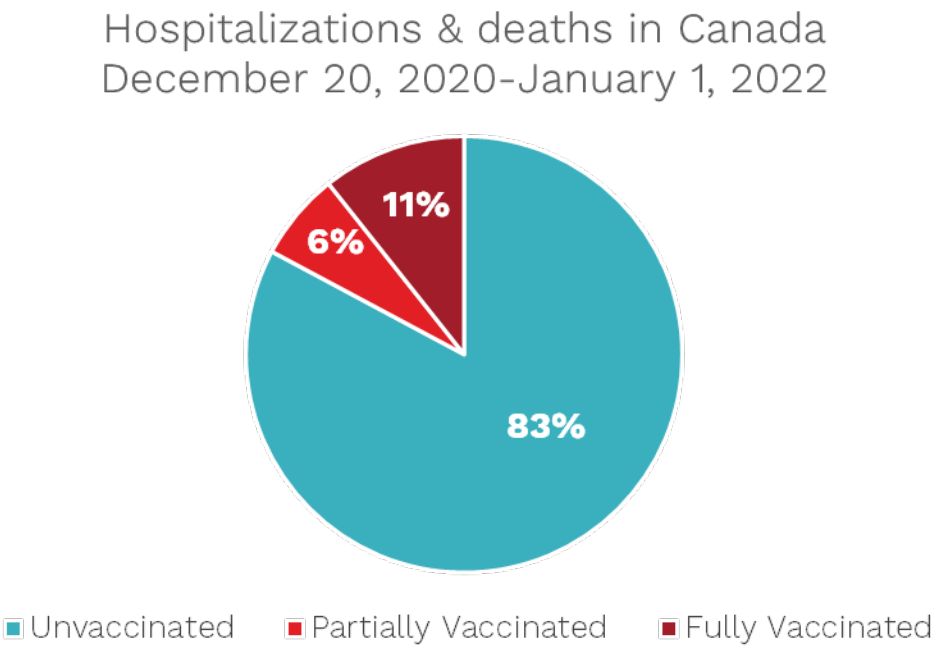
Summary report #4

How long does immunity to COVID-19 last?

Waning immunity, boosters, and dosing intervals

Background

Vaccines have been serving their purpose: they continue to be excellent at protecting people from severe disease and death.



Source: Public Health Agency of Canada, https://health-infobase.canada.ca/covid-19/epidemiological-summary-covid-19-cases.html

That said, data show that infection- and vaccine-induced immunity to COVID-19 wanes over time. This is especially a concern for certain at-risk groups such as older people and the immunocomprised. Further, the new variant, Omicron, is associated with high levels of breakthrough infections and transmission, despite full vaccination.

With all this in mind, federal, provincial, and territorial health officials across Canada have followed the science in advocating third dose (booster) mRNA vaccines within three to six months after completing an initial two-dose regimen, with timing depending on various factors such as age and comorbidities. Research, including the **COVID-19 Immunity Task Force (CITF)**-funded studies in this summary, is exploring the duration of immunity and correlates of protection, the effectiveness of boosters, and the interval between doses that optimize protection. The results of these studies are guiding policy-makers in their decisions about vaccination strategies and informing public health guidelines in the on-going effort to ensure the safety of all Canadians.

At a glance: key findings from CITF-funded research

The findings in this summary are preliminary and, for the most part, unpublished and have not yet been peer-reviewed. All findings detailed below come from the studies listed on page 4.

Vaccine effectiveness (VE) against severe outcomes of COVID-19 has remained very high, even with the Omicron variant, although protection against infection tends to decline with time

- A third vaccine dose provides significant protection against severe disease or death from Omicron.
- In the general public:
    - VE against symptomatic infection from Delta was good eight months after a second dose.
    - Any lost VE was reinstated seven days after a booster.
    - Protection against symptomatic infection from Omicron was lower than against previous variants after two doses and was modest after a booster.
    - However, a booster was found to give excellent protection against hospitalization and death whether due to Delta or Omicron.

Third dose (booster) vaccines are indicated for all adults

- Because immunity wanes over time, evidence supports a booster to the original two-dose vaccine regimen.

Delayed dosing interval improved immune response

- Among a cohort of healthcare workers, anti-RBD antibodies after two doses of Pfizer/Comirnaty vaccine were approximately 3.2 times higher in the group that received a second dose 8-16 weeks after the first, compared with those who had their second dose 3-6 weeks after the first.
- Neutralization of Alpha, Delta, and Beta variants was 2 times higher in the delayed group.

Residents of long-term care (LTC) homes and the immunocompromised are among those particularly affected by waning antibodies

- Among long-term care (LTC) residents, anti-spike and anti-RBD antibodies declined 4-8 months after a second vaccine dose. The neutralization ability of these antibodies declined within 4-6 months. Boosters restored neutralization in this population, but the pattern of decline post-third dose is similar to the waning trend already observed.
- Severely immunocompromised solid organ transplant recipients (SOTRs) have an 82 times higher risk of breakthrough infection and 485 times higher risk of hospitalization/death after two doses of vaccine than does the general population. Following a booster dose of Moderna/Spikevax they had improvements in all parameters of immunity against Alpha, Beta, and Delta variants. Further analyses are ongoing to study the protection parameters of immunity against Omicron.

CITF-supported research studies included

Focus	Lead researcher(s) and affiliation	Research population	Location of study
Effectiveness of COVID-19 vaccines over time in Ontario	**Dr. Jeff Kwong** IC/ES, Public Health Ontario & University of Toronto	General population	Ontario
COVID-19 vaccinations & infections in long-term care	**Dr. Dawn Bowdish** **Dr. Andrew Costa** McMaster University	Residents of retirement and long-term care homes	Ontario
Prospective Evaluation of COVID-19 Vaccine in Transplant Recipients (PREVenT) COVID & Does the interval between first and second doses impact the quality of immune response in healthcare workers?	**Dr. Victor Ferreira** on behalf of Dr. Deepali Kumar University Health Network	Solid organ transplant recipients (SOTR)	Canada

More in depth: latest results

Two primary factors have affected the consensus on how to optimize vaccine effectiveness, and, thus, the ongoing protection of the population, against the worst effects of COVID-19:

1. The **rate** at which antibodies to SARS-CoV-2 infection wanes.
2. The **continued mutation of the virus** has challenged the antibody response triggered by vaccines to recognize and respond to infection.

The CITF has compiled the preliminary results from three of its funded studies here.

The Omicron variant has been a game-changer

Omicron's extremely high transmissibility has resulted in a massive surge in the numbers of persons infected. Even though Omicron results in less severe disease than the Delta and other earlier variants, the hospital system has, nonetheless, been overwhelmed owing to the sheer number of cases and the higher risk of hospitalization and death among the vulnerable and unvaccinated. The high rate of breakthrough infections among the vaccinated has led to booster or third doses that have been evaluated through research conducted by Dr. Jeff Kwong at the University of Toronto.

- A third vaccine dose provides significant protection against Omicron:
  - 95% protection from severe disease.
  - 61% protection from symptomatic infection.

Vaccines have provided durable protection against severe illness

According to the latest data (covering December 6-26, 2021), Dr. Jeff Kwong's study of the general public (the sample being those 18 years and older in Ontario) found:

- VE against **severe outcomes** caused by Delta:
  - 95% by eight months after second dose.
  - 99% after third dose.
- VE against **severe outcomes caused by Omicron**:
  - ~82-86% after second dose.
  - Was 95% after third dose.
- VE against **symptomatic infection** caused by Delta:
  - Was 80% eight months after a second dose.
  - Recovered to 93% at seven days after a booster.
- VE against **symptomatic infection** caused by Omicron:
  - Was far lower than against Delta after a second dose.
  - Was 61% seven days after a booster.

The immune-compromised, including solid organ transplant recipients (SOTR), face particular challenges from COVID-19

An estimated 3% of Canadians may be immunocompromised due to disease (e.g., diabetes, multiple sclerosis), illness (e.g., cancer, HIV), or age. Studies of people with immune systems that make them more susceptible to infection are crucial.

Because of their long-term dependence on immunosuppressants, solid organ transplant recipients (SOTRs) have a suboptimal response to anti-COVID-19 vaccines. Compared to the vaccinated U.S. general public, SOTRs with two doses had an 82 times higher risk of breakthrough infection, and a 485 times higher risk of hospitalization/death.

- A double blind, randomized control trial to evaluate the safety and immunogenicity of a third dose of Moderna/Spikevax in SOTRs, led by Dr. Deepali Kumar of the University Health Network, showed improvements in all parameters of immunity against Alpha, Beta, and Delta variants. This confirmed the findings of other studies supporting the benefit and safety of three doses among SOTRs.

Long-term care (LTC) residents are in particular need of boosters

In a study of residents of LTC homes led by Drs. Dawn Bowdish and Andrew Costa from McMaster University, it was determined that:

- Both antibodies and neutralizing antibodies declined significantly in LTC residents within 4-6 months after receiving their second dose.
- The third dose came just in time for LTC residents, as Canada saw an increase in the number of breakthrough cases in the fall of 2021. A timely third dose reduced breakthrough infections considerably.
- The arrival of Omicron has, however, meant an increase in the number of breakthrough cases despite a third dose of vaccine.
- The antibody concentration in LTC residents increased significantly right after a third dose, but started to decline again, much like what was seen after the second dose, suggesting further doses may be required.

Time since second dose and the interval between doses impacts VE

- Time since a second dose has a greater impact on VE than the SARS-CoV-2 lineage or the dosing interval between the two doses, according to research done by Dr. Jeff Kwong at the University of Toronto.
- Dr. Kwong found that VE began declining two months after the second dose and continued steadily over the following six months, underscoring the imperative for third dose boosters.
- That said, several studies have found that a longer dosing interval between the first two doses has proven to increase several factors related to immunity. Among the results compiled here, Dr. Deepali Kumar's team found that in a cohort of healthcare workers who received a second dose of Pfizer/Comirnaty 8-16 weeks after the first dose had 3.2 times higher levels of anti-RBD antibodies than the group who received their second dose 3-6 weeks after the first.
    - The decline was more pronounced among those who received their second shot at the shorter interval.

Vaccine type is relevant

In their LTC study, Drs. Dawn Bowdish and Andrew Costa found that:

- Antibody *quality & quantity* were higher and lasted longer among LTC residents who received the Moderna/Spikevax mRNA vaccine than those who received the Pfizer/Comirnaty vaccine;
- More memory CD4+ T cells were made among those vaccinated with Moderna/Spikevax.
- The third dose of Moderna elicited a stronger antibody response than did Pfizer in long-term care residents.

Policy implications

The scientific evidence of waning antibody levels clearly supports the need for adults to receive third dose boosters in order to provide adequate and longer lasting protection against COVID-19. This imperative has been amplified by the Omicron variant, which swept across Canada in November 2021 and continues to be the variant driving up case counts and hospitalizations. Its ability to evade immune responses means that, with so many more people becoming infected, reducing the spread of disease through public health initiatives (e.g., masking, physical distancing, avoiding large gatherings) and full vaccination remains critical. Though breakthrough infections are more common with Omicron due to the numerous variations in its genetic code for the Spike protein, booster shots have proven effective in limiting serious illness and mortality.

Canada's National Advisory Committee on Immunization (NACI) recommends mRNA boosters for adults aged 18 and older in order to combat waning antibodies. Scientists continue to study whether boosters should be recommended for children and teens and whether, eventually, additional or regular boosting will be required once the pandemic recedes and SARS-CoV-2 becomes endemic. For example, research shows that a three dose vaccine regimen produces a lower antibody response among SOTRs and LTC residents compared with the general public. This opens the possibility of pursuing a different vaccine strategy for at-risk populations, whether it be a fourth dose, administration of preventive monoclonal antibodies, developoment of different vaccine platforms or moving to early treatment of infection with anti-virals. Going forward, vaccination strategies are likely to continue to be tailored to specific populations.