COVID-19 IMMUNITY TASK FORCE

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

CITF/CanCOVID Research Results & Implications Series

How long does immunity to COVID-19 last?

Waning immunity, boosters, and dosing intervals

Questions & Answers

February 4, 2022

At the CITF/CanCOVID Research Results & Implications seminar on waning immunity, boosters, and dosing intervals, the over 600 participants flooded our experts with important questions, many of which went unanswered because we ran out of time.

Fortunately, we kept track of those questions and have listed them here, along with answers directly from our experts.

QUESTIONS ANSWERED BY

Andrew Costa, MD

Associate Professor and Schlegel Chair in Clinical Epidemiology & Aging, McMaster University

1. At what point do we worry about blunting?

I assume by 'blunting' you're referring to waning immunity over time. We've observed that the quantity and quality of antibodies wanes at approximately 90-120 days, post 2nd dose and post 3rd dose, for both long-term care (LTC) and retirement home (RH) residents. It should be noted that there is individual variation in the rate at which antibody quantity and quality wanes, but at approximately 90 -120 days, we have found a consistent drop. The 'worry' associated with this finding depends on the evolving threat of variants and the spread. For example, in the current Omicron wave, we can assume that previous doses provide LTC and RH residents with some (or even good) protection from severe disease. Still, the threat of catastrophic disruption in care due to out of control spread of infection (even if 'milder') has meant that a 4th dose has been recommended to offer LTC and RH residents the best possible outcome.

2. Do your findings in LTC homes apply even to the few young people in those residences? It is primarily age (and comorbidity) that drive your findings, do you think?

Largely yes, they do apply. We don't find that age is a strong driver of vaccine response because often younger persons in LTC are frail despite their younger age. We are looking for variables that influence response, but have not found accurate 'smoking guns' to date. We're bringing in more detailed data to look at that question in greater detail.

3. Are conclusions the same for those in long-term facilities and community dwellers?

The general trend that vaccine-mediated immunity wanes over time is consistent, but we can't confirm if vaccine effectiveness is equivalent, overall, in long-term care facilities compared to the general public.

4. Did you study the duration of the different doses of different vaccines?

Consistent with previous work, the most significant contributor to immune protection (beyond changes in variants) is the time since vaccination. The vaccine manufacturer dosing schedules and additional dose recommendations were consistent across mRNA vaccines used in Ontario. Also, the dosages used for each mRNA vaccine have been consistent in our study homes. There is more limited variation in the timing between doses in congregate settings since access to vaccines occurred in a more consistent and organized fashion. These factors limit our ability to examine the role of timing and dosage.

5. Your data would suggest a 4th dose at three months. Is this the right interval? Is this strategy going to be applied to recommending 5th and 6th doses as well? Does this 4th dose strategy extend beyond the LTC /retirement home populations?

Three months is the observable time of decline, and so it suggests it's the right interval for the Omicron wave. More on that here (scroll down to recommendation document download): **https://www.publichealthontario.ca/en/about/our-organization/external-advisory-committees/oiac**

The 4th dose and interval recommendations do not necessarily apply to future doses or other populations. For LTC/RH, that question continues to be monitored. Other studies are monitoring other populations.

6. Would you recommend a 4th dose of Moderna for a person who has previously not had Moderna so as to induce a better immune response?

Any available mRNA dose is expected to offer substantial additional protection. If supply allows for choice, then Moderna is generally recommended in Ontario based on available immune marker data. Since we can't accurately quantify the real clinical benefits of an additional Moderna vs. Pfizer dose, waiting for a Moderna dose is definitely not recommended. **https://www.publichealthontario.ca/en/about/our-organization/external-advisory-committees/oiac**

7. 4th doses are just as important for community-dwelling older adults - those "aging in place" - who rely on informal/family and formal caregivers. Yet we prevent these older adults from getting 4th doses on the same schedule as older adults in LTC homes. How can we convince governments to offer 4th doses to community-dwelling seniors, as well, after three months?

If we could more accurately identify community-dwelling older adults who match a similar profile of LTC and RH residents such that we could study them and generate evidence to inform a recommendation, then I think a 4th dose could be recommended.

8. I'd like to know more about vaccine dosage in the seniors' study. Were the results from seniors who received a full dose of Moderna for their booster or the 50% dose? Do you believe the dose size matters?

In our study, the Moderna doses were all 100mcg, not the 50mcg dose commonly used in younger groups for the 3rd dose. We *think* dose matters (but not sure how much), but we haven't been able to compare different doses of the same vaccine since only one dose was used in our study homes (and we presume largely across Ontario).

9. Are there vaccine efficiency data per age group or/and comorbidities? Since the virus mainly causes severe outcomes for the elderly and people with comorbidities, and since there is some data presenting an important risk for myocarditis in young males vaccinated with Pfizer, shouldn't we have more personalized/fine-tuned recommendations for vaccination?

You identify an important opportunity and challenge that we're currently trying to address by examining factors that strongly influence acquired immunity. If we can identify those factors, there is hope that we can make more specific recommendations.

10. Do you think that future boosters should be adapted for newer variants (since all vaccines currently target the original strain)? Or do you think that could compromise immunity if future variants emerge from ancestral lineages (as was the case with Omicron)?

Variant specific vaccines are currently in trial phase, and of course we hope they will offer greater protection from circulating variants.

11. Do you have any published work on the comparison of different intervals between doses in LTC homes?

Not in LTC, since there is little variation. There is more variation in retirement homes since access was different (generally). We hope to have enough samples soon to examine this.

12. Is it a realistic strategy to go booster-to-booster to solve the COVID-19 pandemic? What are the potential long-term effects of receiving multiple boosters?

In the absence of a proven alternative and with strong evidence supporting the effectiveness of vaccines, 'boosters' are part of the strategy to contain COVID-19 effectively. The need for boosters in any population is a matter of ongoing study, and many external panels review all available evidence to make recommendations.

13. What would be the best interval to manage waning antibodies as we are going for a recurrent boost in the future?

Repeated from above: In the absence of a proven alternative and with strong evidence supporting the effectiveness of vaccines, 'boosters' are part of the strategy to contain COVID-19 effectively. The need for boosters in any population is a matter of ongoing study, and many external panels review all available evidence to make recommendations.

14. How much of the increased effectiveness after a 3rd dose is related to it being the accumulation of vaccine, and how much of it is due to the fact it is just the most recent dose?

Both are factors in our data, and the relative importance is emerging. The answer likely depends on the clinical outcomes (e.g., infection vs. severe infection) and is complicated by variant.

15. Can you please comment on the clinical importance of the differences in immune responses between the Pfizer and Moderna vaccines? The differences seem very small, and without a defined immunological correlate of protection, these differences may be meaningless.

The weight of overall evidence across studies supports Moderna in this population; however, you are correct that the clinical importance may be small. This is why the recommendation is to receive any available dose, with Moderna being preferred.

QUESTIONS ANSWERED BY

Victor H. Ferreira, PhD

Scientific Associate, Ajmera Transplant Centre, Department of Medicine, University Health Network

16. Were there any factors associated with different responses to the vaccine in the immunocompromised population in your study, like age, sex, race, and other health comorbidities?

Yes, several factors have been identified in the transplant setting that may influence the outcome of vaccination, including the type of immune-suppressing drugs used or the degree to which you are immunosuppressed. The immunosuppressive drugs used in the transplant setting have been shown to impair vaccine responses in several studies. Being on a regimen called "triple immunosuppression," where you receive three different classes of immunosuppressive medications - a calcineurin inhibitor, an antimetabolite, and a corticosteroid (e.g., prednisone) - is often associated with the poorest vaccine responses. Of note, the antimetabolites, in particular mycophenolate/mycophenolic acid, may exert the greatest impact on vaccine responses. In some studies, liver transplant recipients tend to respond best, with lung recipients generating the lowest responses. This, too, is likely a reflection of immune suppression because liver recipients generally receive less immunosuppression compared to lung recipients. The time from transplant is another factor that can influence vaccine responses. The closer one is to transplantation, the more immune-suppressed one is. This is due to the combination of induction immunosuppression used at the time of transplant and the maintenance immunosuppression used to prevent rejection after transplantation. It is recommended to wait at least one month after transplantation to begin or resume vaccine schedules as immune responses are generally lowest in the weeks following transplantation. Age has also been identified as a potential factor, with older transplant patients generating lower responses than younger cohorts in some studies. Other factors have been identified, but evidence of their role is less clear.

17. Given the percentage of SOTR having positive antibodies after the 3rd dose, especially against Omicron, should the 6-month interval for their booster dose be reconsidered?

I think it would be reasonable to provide a booster anytime after three months from the 3rd dose. This is, of course, assuming that the 4th dose will provide additional protection - that work needs to be done.

QUESTIONS ANSWERED BY

Jeff Kwong, MD, MSC, CCFP, FRCPC

Senior Scientist, ICES, Scientist, Public Health Ontario, and Professor, Department of Family & Community Medicine and Dalla Lana School of Public Health, University of Toronto

18. What is the recommendation with respect to boosters for a person who has become infected with COVID-19? If they are eligible for their next dose, should they get it right away or should they wait a month after infection before receiving their next dose of vaccine, including their booster?

Current guidance varies. The US CDC has advised waiting 30 days after an infection before getting vaccinated. Toronto Public Health and some other public health units in Ontario have recommended getting vaccinated once no longer self-isolating or symptomatic. Hopefully, more evidence will emerge so that guidance will be more consistent.

19. In cases of hospitalization and death, was there a clear distinction between those WITH COVID vs. BECAUSE of COVID, thereby providing clear causal data?

The data source for severe outcomes was the Public Health Case and Contact Management (CCM) system, and public health staff is instructed to only include events that are attributable to COVID infection, so all severe outcomes are considered to be BECAUSE of COVID.

20. Is it fair to say that VE is higher when we have an interval of 56 days between the first and second dose? Can we use this information when considering 4th boosters?

Our analyses suggest that VE against infection differs by less than 5% when comparing individuals with longer (8+ weeks) vs. shorter (<5 weeks) dosing intervals.

21. What does negative vaccine effectiveness mean (reference slide 23 in Dr. Kwong's presentation)?

Negative VE means that vaccination is associated with an increased risk of infection. Our updated analyses show that it was likely a result of several biases related to using infection as the outcome during the period when Omicron emerged, which coincided with reduced access to testing.

22. Time elapsed post-2nd dose appears to be the strongest predictor for vaccine effectiveness. However, we do know whether people who waited longer to receive a second dose (or were only later eligible to receive it) differ in terms of socio-demographics and possibly other factors to those who received it earlier? How do you control for confounding factors that are linked to both vaccination time and health outcomes?

Through our multivariable logistic regression models, we controlled for several demographic and socio-economic factors in our analyses, including age, sex, geographic region, and four area-level measures (from Census data, measured at the level of Dissemination Area): household income, persons per dwelling, proportion of non-health essential workers, and proportion self-reporting as a visible minority. However, since we estimate VE at different time intervals following the second dose, it may be difficult to completely control for differences in the vaccinated populations at different points in time. This may require further investigation.

23. Dr. Kwong, very interesting findings. Regarding where you show a VE of 37% after three doses against Omicron infection: does this suggest whether a 4th dose makes sense, or if there should be a retooling of the current vaccine to make it Omicron-specific?

Our updated analyses that examined VE against symptomatic infection found VE to be 61% after a third dose. It's difficult to say whether the general population will need a fourth dose. Data from other jurisdictions (e.g., UK) suggest waning of VE that starts shortly after a third dose, but another variant may emerge by the time Omicron-specific vaccines are available.

24. For the samples that were screened using SGTF, do you have a way of going back and evaluating whether these are BA.2 sub-lineages of Omicron, which lack the deletion and therefore would not be detected by S-gene drop out? It would be interesting to see if any of these samples are actually sub-lineages of Omicron and, if so, how they behaved in terms of symptoms and vaccine response.

Whole genome sequence surveillance in Ontario has revealed very little BA.2 circulating in Ontario (approximately 0.1% of sequenced specimens as of early January).

25. Really nice presentation. Has IC/ES made vaccine and variant information widely available to the researcher community?

There are multiple ways to access ICES data. I suggest you visit our website (**www.ices.on.ca**; see Data and Analytic Services for one option to access ICES data holdings), or you can connect with an ICES Scientist to discuss.

26. Does co-morbidity affect VE?

Other studies I have seen suggest that immunocompromised individuals and those with a greater number of chronic medical conditions experience lower VE.

27. Was there any correlation between those who had the flu shot and positivity for SARS-COV-2?

In separate analyses (not yet published), we found influenza vaccination to be associated with reduced COVID outcomes. We also found the same for periodic health exams (what used to be called “annual physical exams”). We believe this is evidence of residual confounding from differences in health behaviours rather than actual protection receiving influenza vaccines (or periodic health exams).

28. What is the optimal threshold of vaccine effective against the Delta, Omicron, and other variants?

I’m not sure that there is an optimal threshold of vaccine effectiveness. Ideally it would be 100%.

29. On estimating vaccine effectiveness, does your team have any data on how history of natural infection impacts VE estimates? Could VE estimates be downwardly biased if a portion of the unvaccinated population has some degree of immunity from natural infection?

I forgot to mention that we adjusted for previous confirmed SARS-CoV-2 infection in our Omicron/Delta analysis. The problem is for people who have previously unconfirmed SARS-CoV-2 infection, and if this is differential by vaccination status. I would have to give more thought to whether this would more likely bias VE estimates upward vs. downward. Are vaccinated individuals less likely to have the previous infection because they are more careful, or more likely to have an infection because they have more exposure? If vaccination decreases symptoms, vaccinated individuals might be less likely to go for testing, but vaccinated individuals may be more likely to get tested. It’s very tricky!

30. Thinking about vaccine effectiveness and waning immunity over time, what data do you have about re-infections and intervals between first and subsequent infections? For those who have had breakthrough infections, at what point is one likely to revert to a negative result after swabbing IF a valid, reliable test is used? How can one identify if they have a second infection or if they continue to have a lingering primary infection?

We controlled for previous laboratory-confirmed infections, fully acknowledging that we cannot identify infections that were not confirmed by laboratory testing. I am currently involved in work with other colleagues looking at the risk of infection following a previous

infection. It's difficult to say when a person will revert to a negative result after an infection; we know that some individuals will test positive on PCR long after an infection (but are not considered contagious). Distinguishing a new infection from a previous infection is ideally based on the identification of a different variant on the second infection, but sometimes that information is not available. Some studies have used a period of 90 days to indicate a new infection, although there have been cases of individuals who have positive PCR tests for prolonged periods after their initial infection.

31. There is emerging evidence that natural immunity against COVID-19 is superior to vaccination. Before suggesting having a 4th dose, shouldn't we wait to assess the new immunity levels acquired in the population due to infection with the Omicron variant?

I think the challenge with infection-induced immunity is that it may be more variable than vaccine-induced immunity. I agree that assessing immunity levels in the population due to Omicron infection would be worthwhile before deciding on widespread fourth doses. However, I'm not sure we have identified an optimal immune correlate of protection.

32. When you say reduced COVID outcomes, do you mean fewer infections/ symptoms/severe disease? That is very interesting about physical exams. I wonder what the connection is?

Our not-yet-published work looking at influenza vaccines (and periodic health exams) and COVID-19 outcomes suggest that both exposures are associated with reduced infections, hospitalizations, and even death. To me, this is most likely residual confounding - people who receive influenza vaccines and see their doctors for periodic health exams likely engage in other health behaviours that reduce their risk of infection and severe outcomes (e.g., wearing masks, washing hands, following guidance on physical distancing, etc.).

33. Could you comment on boosters in teenagers?

NACI released guidance on the use of boosters among adolescents aged 12-17 on January 28. They are only recommending boosters for a selected high-risk population at this time.

34. If 3rd dose boosters improve protection against variants but also decline over time, what is the plan? Do we wait until each new VOC to start boosting, or do you plan for pre-emptive boosters in preparation for the next variant?

I think there are just too many uncertainties to say anything definitive in response to your questions. Yes, it appears that VE against infection wanes after a third dose, but if protection against severe outcomes is maintained, then we likely won't need to rush to provide fourth doses to the majority of the population. We don't know if/when new variants will emerge or how they will behave (i.e., how immune-evasive, transmissible, or virulent they will be), so it's difficult to plan for them. In an ideal world, we would have "universal"

SARS-CoV-2 vaccines that would be effective regardless of spike protein mutations, potentially eliminating the need for reformulated boosters, but if and when they will be available is unknown.

35. If a 3rd dose was given only one month after the 2nd dose, and six months have elapsed, should the person get another dose?

I believe in this situation, the third dose that was received only one month after the second dose would not be counted, and the individual would be eligible for another dose, but it would be best to check with local public health officials.

36. Was there any research conducted comparing VE against symptomatic infection vs. reinfection with COVID (i.e., getting COVID twice)?

We did not look at this in the work I presented, but this work is underway in Ontario, and I believe it has been done in other countries.

37. Any updates on vaccination and pregnant women? There still exists a dichotomy between those who believe it is safe and those who do not. Any further statistics than the minimal sets out at the moment?

Pregnant people are recommended to receive COVID vaccines. They are at high risk of complications from COVID infection, and safety data to date suggest no harm to the parent or the fetus/infant.

Note from CITF Secretariat: our funded researchers presented results on this topic at our last CITF/CanCOVID seminar. ***View the presentation, the PPT or read the summary here.***

38. We saw data on very at-risk populations, but I'm curious about healthy, low-risk populations. How does VE measure for populations below 40, for example?

Our study included both high-risk and low-risk groups - ~55-60% of the subjects in our analyses had no chronic health conditions, and about half were <40 years - so our VE estimates represent a mixture of both groups.

39. Dr. Kwong's slide seems to show that VE against severe outcomes increased a little after 6-7 months. Is that a meaningful increase that indicates maturation of the immune response?

I think that a slight increase in VE observed 8+ months after the second dose relates to the types of individuals who were vaccinated early in Ontario's vaccination program (mainly healthcare workers and retirement home residents). They might be better protected than the general population for various reasons (e.g., good access to personal protective

equipment, greater adherence to public health guidance, etc.). Another factor is that the sample size is small, so the estimates are less stable.

40. Do we have any preliminary data suggesting whether the 5-17-year-old age group will require the third booster?

No data on this to my knowledge at this time.... we'll probably have data in the 12-17-year-old age group before the 5-11-year-olds given the rollout of vaccinations

Note that VE results in QC are markedly different when all tests are included in the analysis or when stratification is made by reason of testing (much better VE estimates even with two vaccine doses).

Thank for you for sharing that, Philippe. It would be great to see the results from Quebec and other provinces.

41. Given the imprecision of the VE estimates against severe outcomes with Omicron, do you think the 3rd dose significantly increases VE against severe outcomes, or are there just too few cases after a 2nd dose to be able to conclude if there is a difference?

It's hard to say for sure, but I think 2-dose VE against severe outcomes caused by Omicron is somewhat lower than against Delta. If you go to the Ontario Science Table dashboard, there is a figure that shows how vaccine effectiveness against infection, hospitalization, and ICU admission change over time. The decrease in VE against hospitalization observed in December is consistent with lowered VE with the emergence of Omicron in Ontario.

42. What was the interval between the 2nd and 3rd doses for the VE estimates?

The interval between second and third doses varied considerably. It could have been as short as 84 days (roughly three months), but for most subjects included in the analysis, it was more than 168 days (approximately six months).

43. For those who contracted Omicron prior to receiving their third dose, what is the risk for re-infection, and is a booster vaccination still needed?

Boosters are still recommended for those who have already been infected by Omicron for optimal protection from re-infection.

44. Does monoclonal antibody treatment work with Omicron?

Some do. Sotrovimab, from GSK/Vir does.