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Assessing immunogenicity of COVID-19 vaccines in Long Term Care Facility Staff and Residents

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Long term care (LTC) homes in Canada have been disproportionately affected by the COVID-19 pandemic. To date, more than 80% of Canadian deaths due to COVID-19 occurred in LTC home residents.[1-3] Several studies have shown that SARS-CoV-2-infected LTC staff are one of the major drivers of COVD-19 outbreaks in LTC homes and subsequent resident deaths.[1,3-6] Therefore, prevention of infection is of utmost importance in LTC. Widespread uptake of a vaccine that is safe and effective, by both staff and residents of LTC homes, could dramatically reduce the risk of outbreaks of serious illness.

The first two licensed COVID-19 vaccines are a result of collaborations between Pfizer and BioNTech, and ModernaTx, Inc. and the National Institute of Allergy and Infectious Diseases (NIAID), respectively. Phase 3 clinical trials assessing the safety, efficacy, and immunogenicity of these mRNA vaccines, BNT162b2 (2 doses, 30 μg each, 3 weeks between first and second dose) and mRNA-1273 (2 doses, 100 μg each, 1 month between first and second dose), have demonstrated short term vaccine efficacies of 95% and 94.5%, and acceptable safety profiles.[7-9] The FDA issued EUA on December 11, 2020 for the Pfizer-BioNTech BNT162b2 vaccine in preventing COVID-19 in individuals 16 or older.[10] Health Canada approved the Pfizer-BioNTech vaccine on December 11th, and approved the Moderna vaccine on December 22nd, 2020. In Canada, the first COVID-19 vaccine was administered to a LTC home resident in Quebec City on December 14, 2020.[11] The FDA approved the Moderna-sponsored mRNA-1273 vaccine in preventing COVID-19 in ≥18 year old individuals on December 17.[9,12]

On-going evaluation of the immunogenicity of COVID-19 vaccines in different sub-populations and over time is important, as this will provide information on the predicted effectiveness of vaccines in different sub-populations, the interchangeability of vaccines, and the duration of protection.[13] Our current understanding of the human immune response to SARS-CoV-2 does not enable us to determine the degree of protection COVID-19 vaccines confer upon individuals against asymptomatic infection and transmission.[14] This is especially important in the context of transmission from asymptomatic LTC home staff to residents. Although both BNT162b2 and mRNA-1273 vaccines were highly effective in preventing symptomatic and/or severe COVID-19, the currently available data do not permit conclusions about the effect of these vaccines on rates of asymptomatic infections and SARS-CoV-2 transmission.[7-9] A meta-analysis conducted by Cevik *et al.*[15] showed that asymptomatic individuals clear the virus from their bodies faster than symptomatic individuals, but this does not necessarily translate into less SARS-CoV-2 transmission.

The immunogenicity of both BNT162b2 and mRNA-1273 vaccines has been assessed in phase 1 trials.[14,16-17] Both vaccines elicited robust titres of neutralizing antibodies, and polarized cellular responses robustly towards a CD4+ TH1 subtype response.[8,16-17] Widge *et al.*[14] reported that

humoral responses have so far been studied up to 119 days after the first dose of the Moderna-sponsored mRNA-1273 vaccine in 34 participants, and these responses have been sustainable. The cellular immune response to mRNA-1273 has been studied in 20 participants up to 43 days after they were given the first dose of mRNA-1273, and a robust TH1-biased response has so far been detected.[17] Humoral response to BNT162b2 has been studied up to day 35 after the first vaccine dose, and is sustainable.[16] Durability of these responses are currently being studied in larger phase 2/3 studies by the companies.

One critically important gap regarding the currently available immunogenicity and efficacy data for both vaccines is that individuals from LTC homes have not been included in any randomized to the vaccines, and the oldest participant in both phase 1 trials was 82 years old.[16] This makes it difficult to extrapolate the immunogenicity data to LTC residents due to the fact that according to the Government of Ontario[18] and a study conducted by Huyer *et al.*,[19] the median age of LTC homes residents in Ontario is approximately 86 years.

This study therefore aims to longitudinally evaluate the immunogenicity of Moderna and Pfizer-BioNTech-sponsored COVID-19 vaccines in Ontario long term care home staff and residents, and to assess whether positive tests and symptomatic and asymptomatic disease occur more or less commonly in vaccinated staff of long term care homes.

Objectives:

Primary

1. To compare antibody titers to the spike trimer, its receptor binding domain (RBD) and nucleocapsid proteins after vaccination in residents as compared to staff of long term care facilities.

Exploratory

2. To compare antibody titers after infection with COVID19 to those after vaccination in residents of LTC homes
3. To assess the decline in antibody titers over time in residents and staff of LTC homes
4. To assess the extent to which antibody titers are boosted by vaccination in persons who have previously been infected with SARS-CoV-2
5. To assess humoral, cellular, and mucosal immunity prevalence to SARS-CoV-2 in subsets of LTCH staff (infected, pre/post receipt of the vaccine)

Methods

Inclusion criteria: LTCH staff, residents and caregivers in LTCHs in southern Ontario (for sample shipping feasibility purposes), who intend to get a COVID-19 vaccine (or who have received the vaccine within the previous 14 days) will be eligible to participate. *Note that only staff will be recruited into studies which include T cell immunity testing.*

Exclusion criteria: Within these subgroups, those who do not intend to take a COVID-19 vaccine will not be eligible to participate.

Data collection

When recruiting through LTCHs, study staff will approach LTCH staff, caregivers and residents/SDMs at eligible LTCHs or notify staff via staff organizations (e.g., the Ontario PSW Association whose members work directly at LTCH) to invite them to participate in the study. .

When recruiting through partner organizations for staff, these organizations will post or email information about the study, and eligible staff will self-identify and contact the study to discuss participation.

When recruiting through LTCHs, study staff will approach the administrators and/or directors of care of long term care homes in the greater Toronto area. If they agree, they will notify their residents, substitute decision makers (SDM) and staff to ask if the study can contact them to talk to them about participation. If these individuals do not opt-out of being contacted, they will be able to be approached. Residents/SDMs will be notified by email or by telephone, depending on how the home usually contacts them, and will be offered the opportunity to opt out of the program.

For staff, these administrators may support with informing them of the study by sending out study information (see Staff Study Poster and information sheet) and setting up informational webinars. Through these recruitment avenues, staff will have the opportunity to opt out of receiving further communication about the study by letting the administrator or the study know that they do not wish to be contacted. The administrator will then share with us the contact information of all LTCH staff who did not opt-out of further communication. Study staff will reach out to these staff via phone to invite them to participate in the study (see LTC immunogenicity Consent Script staff).

Staff will be also be given information sheets about the study when they present for their weekly NP swab testing, and asked to contact the study if they are interested in participating.

Sample size for residents:
We will continue to recruit residents until we have 100 residents who have not previously been infected with COVID-19 and 50 residents who have had previous documented infections. In total, 150 residents will participate in this study.

Sample size for staff:
We will enroll up to 250 staff for this study. Specifically, we will recruit 150 staff for saliva and venous blood samples. Staff who wish to participate but do not agree to the saliva and venous blood sampling will be invited to provide fingerstick blood spots to a maximum of 100 participants.

Consent for the study will be obtained over the telephone, with the consent form then emailed or mailed to participants, with the email documenting which elements of the study they have agreed to. A script for consent will be followed to ensure that all elements are covered, and a checklist completed for each consent to document date and time, and elements of the study which have been agreed to. For LTCH staff, once participants have provided consent, the study

personnel will record the participants' vaccine and COVID-19 status information and responses to a baseline demographic and medical questionnaire using the questionnaire.. Research staff will also write down participants' responses on the data collection form as they share the information.

At the time of consent, we will ask staff to provide their preferred method of contact (e.g., email, phone [calls or texting]) and will primarily use that method for further contacts Individuals who don't know when they will receive their vaccine at the time of recruitment will submit baseline bloodwork at enrolment, and be asked to contact the study when their vaccination is scheduled. Staff participants who have not contacted study with a scheduled vaccination date will be contacted weekly to check if vaccination has been scheduled or administered.

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Participants who participate in the collection of multiple venous blood and saliva samples will receive a $50 reimbursement for time and travel expenses associated with each blood draw. .

Data Collection

Dried blood spots
Residents, staff and caregivers who agree will have dried blood spots obtained by either study at the LTC home or by LTC home staff (at the discretion of the LTC home) on four occasions:

1. from 14 days before to 14 days after they receive their first dose of a vaccine against COVID-19 (every effort will be made to obtain bloodwork prior to vaccine program roll out, but it may not be possible to do so)
2. immediately before receiving their second dose of vaccine
3. 14 days after receiving their second dose of vaccine
4. 4 months after receiving their second dose of vaccine

The following information will also be collected for residents and staff: age, sex, underlying illness, medications being taken at baseline, prior COVID infection, and date and severity of that infection. At each follow up to arrange specimen collection, participants will be asked if they had a documented infection since their last sample was taken. Residents and staff will also be asked if they would be willing to provide 10mls of blood at 2 weeks after the second dose of vaccine, and for permission to be contacted about future studies. This serum specimen will be collected at the home for residents, and either at the LTCH or at the most convenient Lifelabs location for staff/caregivers. For participants who agree to have serum drawn, the dried blood spot to be collected at 2 weeks post vaccine will not be necessary.

Clinical and demographic information will be obtained from staff/caregivers by interview, and instructions and supplies for obtaining dried blood spots will be couriered to their home or workplace.

At the end of the study, a final call will be made to confirm whether or not the participant was diagnosed with COVID during the study.

Staff who agree to larger volume blood samples and saliva samples
As outlined above, we will study COVID-19 immunity at baseline (up to 7 days post vaccine), 2-4 weeks after the 2nd dose of vaccine, 6 months and 12 months post-2nd dose. If we are unable to identify a sufficient number of participants who have not yet received their first dose of vaccine, we will include staff who are willing to provide blood 2-4 weeks after the 2nd dose and 6 months after the 2nd dose.

Research staff/facilitators will reach out to participants to ask them to complete the saliva samples, and blood samples (through in-person, phone or Zoom). See Saliva and Blood Sample Recruitment Script for In-Person, Phone or Zoom).

Participants will be asked to email/text or telephone the study office when their second dose of vaccine is scheduled, and when their blood work has been done. At each point of contact they will be asked also to report whether they have been tested for COVID and what the test result was. Participants will be advised that if they choose to use email to communicate with study staff, it is not considered a secure form of communication and should not be used to convey sensitive information. The study personnel will write down participants' responses on the data collection form as they share the information.

We recognize that infections may occur which will result in vaccination or bloodwork being deferred because a participant is required to be in isolation at a relevant time point. Participants will be told that these delays will not hinder participation in the study.

The following tests will be done:

- **At baseline (up to 7 days post-vaccine):**
    - Blood draw of 2 ACD (yellow top, 10ml) tubes and one serum (gold or tiger top 5 ml). Total = 25 ml.
    - Saliva (one salivette tube).
- **14-28days post COVID vaccine 2nd vaccine dose:**
    - Blood draw of one serum (gold or tiger top 5 ml), OR blood draw of 2 ACD (10ml) tubes and one serum tube (5ml) for those who were enrolled more than 7 days after their first dose of vaccine
    - Saliva (salivette tube);
- **6 months post 2nd dose vaccine dose:**
    - Blood draw of one serum (gold or tiger top 5 ml),
    - Saliva (salivette tube)
- **12 months from baseline:**
    - Blood draw of 2 ACD (yellow top, 10ml) tubes and one serum (gold or tiger top 5 ml). Total = 25 ml. Thus, total volume of blood to be drawn during the study is 60 ml,
    - Saliva (salivette tube)

Additional Detail on Saliva Samples via Salivettes:

Saliva samples will be collected via salivettes at baseline and approximately 14 days post 2nd dose, 6 months, and 12 months post-vaccine. Salivettes will contain a cotton swab that participants are instructed to hold the swab in their mouth and chew for 2 minutes (in order to enhance saliva production) and then transfer the swab into a tube.

Salivette kits will be sent and/or delivered to LTCHs for completion by the consenting participants. LTCH staff will be able to pick up their kit on-site. Each Salivette kit will be accompanied by a label that will need to be filled out by participants Research staff members/facilitators will work with the LTCH staff and their household members to teach them how to self-collect. Strategies to provide these instructions may include, but are not limited to, hard-copy and/or virtual instruction sheets (see Salivette Instructions) and one-to-one calls or zoom meetings.

Participants will complete the Salivette collection onsite where they will be stored in a refrigerator prior to pick up by study staff. Study staff or a courier service will then transport salivettes to Dr. Gommerman's lab for storage and analysis. The results will not be communicated back to the participants as not enough is yet known about saliva antibody testing to provide informative results.

Additional Detail on Blood Samples

By setting up appointments with eligible and consenting staff members, a study RC/phlebotomist will meet participants on-site at their LTCH to obtain blood samples at baseline (i.e., pre-vaccine) and 14 days, 6 months, and 12 months post-2nd vaccine dose. Alternatively, participants can choose to visit a Life Labs site (will be provided with a requisition) to collect their blood sample. Life Labs will then ship the blood samples to the labs outlined below.

To increase engagement, we will use the TDM to create and deliver up to three reminders about completing the salivettes and blood draws to participants who consented to participating in the study and providing samples.See Saliva and Blood Sample Reminder Scripts for Phone/Zoom, and Email.

Data management/sharing/security

- Any personal health information collected as part of this study, will be kept confidential and will not be shared with anyone outside the study except as required by law. Identifying information collected will be kept separate from study files and will be destroyed once the data collection and analysis are finished. Any information or laboratory samples collected for the study will be identified with a unique study number only.No names or identifying information, with the exception of participant's professional role, will be shared or used in any publication or presentations that result from this research.
- One of the study funders, the COVID-19 Immunology Task Force (CITF), has a data sharing protocol for all funded projects. We will transfer relevant anonymized study data to the CITF as a part of these standard data sharing requirements. External

researchers will be able to submit a request to the CITF to receive access to all CITF data through their data access committee. The CITF will employ a rigorous checklist to ensure that these external requests follow all necessary ethical and privacy protocols.

- The data provided to the CITF will be stored on the CITF Database. The data on the CITF Database will be held under the custodianship of McGill University or one of its collaborators and be shared via the cloud, both nationally and internationally. Data in the CITF Database can be used by researchers across Canada and in other countries following Data Access Committee (DAC) approval. These transfers will also be made in compliance with Canadian law and research ethics.
- A DAC will be responsible for reviewing applications for access to the data and for approving applications that respect the privacy and access policies of the CITF. The DAC will require that researchers confirm that their intended research activities have received necessary ethics approvals. The data may also be shared with other COVID-19 research databases that follow similar protections and procedures as the CITF Database.
- Addiitonal information is available via this presentation CITF: https://www.covid19immunitytaskforce.ca/wp-content/uploads/2020/12/RDM-Webinar-for-CITF-Studies_20201127.pdf

Antibody measurement

Dried blood spots (DBS) and serum will be analyzed for antibodies (IgG) against the spike trimer, its receptor binding domain (RBD) and nucleocapsid proteins in the laboratory of Dr. Anne-Claude Gingras at Sinai Health System. The measurement uses an Enzyme Linked Immunosorbent Assay (ELISA), developed in-house, and optimized for sensitivity and specificity parameters [Isho et al., Sci Immunol, 2020]. Adaptation to a dried blood spot regimen was performed in collaboration with the National Microbiology Laboratory (NML) who distributed paired plasma and contrived DBS for assay optimization. Correlations in the spike, RBD and nucleocapsid assays between plasma/DBS was > 0.95 [Note that the spike-IgG assay has already been used to support a large study; Jha et al., Action to Beat Coronavirus, manuscript submitted]. All antigens are provided by the National Research Council of Canada (NRC) alongside positive reference (humanized VHH72 anti-RBD) and secondary detection reagent (anti-human IgG, HRP-fusion), and have been validated on large cohorts of positives from TIBDN and pre-COVID sera (Colwill et al., in prep).

Essentially, DBS will be collected on Whatman 903 cards using a blade lancet (such as the blue top BD Microtainer contact-activated lancet) for fingerprick puncture. No identifying information will be listed on the cards, but a barcode will be affixed. Collection of ≥2 filled spots on the card will be requested (though 1 spot may be sufficient for one pass at the assays). Cards will be air dried (according to the manufacturer's instructions), and placed in individual sealable bags, along with a dessicant pouch, and transported to the lab. Transport will be at room temperature. Upon reception in the lab, the cards will be placed at 4°C for short-term storage, or frozen (at lower than -20°C) for long term storage. Cards will be brought to room temperature before the packages are open, and a portion of the spot (6 mm) will be extracted

manually or with a semi-automated hole puncher directly into a 96-well plate. Antibodies will be eluted from the punches by the addition of PBS-Tween with 1% Triton-X100 , and incubation at room temperature with shaking for ≥ 4 hours. The ELISAs will be performed, either in automated (chemiluminescence) or manual (colorimetric) mode, using protocols first described in Isho et al., Sci Immunol, 2020.[20] Results will be reported as ratios to positive controls added to each plate, after QC is performed on each batch. Results will be returned to the Principal Investigator electronically for the de-identified samples.

Samples will also be tested using the in vitro surrogate neutralization enzyme immunosorbent assay (snELISA) which assesses if the antibodies can block the spike RBD from binding to its receptor ACE2. This plate-based assay provides evidence that the generated antibodies have potential to neutralize the virus in vivo. We have shown that the snELISA assay correlates well with the more complex plaque-reduction neutralization assay that requires live virus.(14) All of these assays have been developed by Anne-Claude Gingras under REB study #20-0078-E.

Expected results: Upon natural infection by SARS-CoV-2, levels of IgG against spike, its RBD and the nucleocapsid reach a maximum at ~21-28 days, following which they decrease but remain for at least 3 months above the threshold for detection in our assays.[20] Based on data from clinical trials, vaccine-induced levels of spike and its RBD can persist for at least a similar time frame. Both the Moderna and Pfizer vaccines are spike-based (as are all vaccines secured by the Canadian government) so reactivity to nucleocapsid should only be from natural infection.

Using the additional blood samples, Dr. Ostrowski's laboratory at Unity Health will perform T-cell ELISPOT assays to determine the effect of cross reactivity in seronegative individuals and influence on SARS-COV-2 infection and vaccine immune responsiveness.

Data Analysis

Antibody Analysis/Sample size

The primary analysis will ask whether there is a detectable difference in antibody titers to the spike protein of SARS-CoV-2 in previously uninfected residents as compared to staff 14 days after receiving their second dose of vaccine. Based on the mean and standard deviation of convalescent serum for TIBDN participants with COVID (mean spike protein 0.91, SD 0.209), a sample size of 84 previously uninfected residents and 42 previously uninfected staff will be required to detect a decrease in the mean titre from 0.91 to 0.80 (a 10% decline in titers post-vaccination). We anticipate that antibody measurement post-second dose of vaccine will be missing for 10-15% of residents (due to withdrawal, hospital admission at the time, or death), and that a small percentage of residents may have been infected but undiagnosed (and have antibodies present at baseline). In addition, we do not know what proportion of staff who agree to participate will have been infected, and we wish as part of an exploratory analysis to compare antibody levels in staff who have and have not been infected; this will enroll 100 previously uninfected residents and 100 staff overall for this end-point. The 50 additional residents who have been infected will provide a comparison of antibody level post-vaccination in residents who have and have not previously been infected.

For T cell and salivary immunity studies, we will aim to enroll 150 staff; we anticipate that approximately 20% will have previously been infected. Although too few data are available for a formal sample size calculation, these numbers are anticipated to permit us to identify how T cell responses to vaccine differ in previously infected and uninfected participants, and to assess changes in T cell response over time.

Other endpoints will be exploratory and will ask:

1. How antibody titers after infection with COVID19 compare to those after vaccination in residents of LTC homes: for this analysis, we will compare titers adjusted for time since infection (titers increase to approximately day 21, then decrease marginally to day 90). We will also validate that measuring antibody levels to spike and nucleoprotein will distinguish effectively between vaccination and infection (spike will be present after vaccination and infection; nucleoprotein only after infection);
2. What the decline in antibody titers over time is in residents and staff of LTC homes
3. Whether vaccination boosts antibody titers after infection with SARS-CoV-2, and what the pattern of decline in these antibody titers is compared to the decline in titers after vaccination.
4. What is the humoral, cellular, and mucosal immunity prevalence to SARS-CoV-2 in subsets of LTCH staff (infected, pre/post receipt of the vaccine)

Saliva Samples

Dr. Gommerman will conduct ELISA for detecting SARS-CoV-2 antigen specific IgA and IgG in saliva samples using her established methods [20]. We will assess the association between antibody response and antibody levels in saliva and serum.

Expected results: Upon natural infection by SARS-CoV-2, levels of IgM/IgA in the saliva appear within 7-15 days and then fall below the limit of detection by 90 days post-infection. In contrast, IgG antibodies to SARS-CoV-2 will remain relatively stable throughout a 90 day test period. However, in response to vaccination, it is unclear whether we will detect any of these antibodies in the saliva. This is critical to determine – absence of antibodies in the saliva would indicate that SARS-CoV-2 transmission may not be prevented by vaccination. If antibodies are detected in the saliva, comparing the level of these antibodies with those observed in response to natural infection will be informative.

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