COVID-19 IMMUNITY TASK FORCE | GROUPE DE TRAVAIL SUR L'IMMUNITÉ FACE À LA COVID-19

CanCOVID

Seminar Series | Research Results & Implications

How long does immunity to COVID-19 last?

Waning immunity, boosters, and dosing intervals

January 24, 2022 | 12:30 p.m. to 2:00 p.m. EST

Moderator

Nazeem Muhajarine, PhD

Professor, Community Health and Epidemiology, University of Saskatchewan

Lead, Public Health, Health Systems and Social Policy Pillar, Coronavirus Variants Rapid Response Network (CoVaRR-Net)

Director, Saskatchewan Population Health and Evaluation Research Unit, Theme Lead Advisor, CanCOVID

Speakers

- **Dr. Timothy Evans**, Introduction
- **Dr. Jeffrey Kwong,** Effectiveness of COVID-19 vaccines over time in Ontario
- **Dr. Dawn Bowdish** & **Dr. Andrew Costa,** COVID-19 vaccinations & infections in long-term care
- **Dr. Victor Ferreira** (on behalf of Dr. Deepali Kumar), Prospective evaluation of COVID-19 vaccines in transplant recipients & dosing intervals and their impact on the quality of immune response in healthcare workers
- **Dr. Timothy Evans,** Synthesis and policy implications

Timothy Evans

MD, PhD, COVID-19 Immunity Task Force
Executive Director

COVID-19 Immunity Task Force mandate

Established by the Government of Canada in April 2020

Mandate:

Catalyze, support, fund, and harmonize knowledge on SARS-CoV-2 immunity for federal, provincial, and territorial decision-makers to inform their efforts to protect Canadians and minimize the impact of the COVID-19 pandemic.

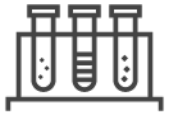
CITF: Priority areas of research

SEROPREVALENCE STUDIES

Assess the extent of SARS-CoV-2 infection across Canada

IMMUNE SCIENCE

Understand the nature of immunity arising from infection



IMMUNE TESTING

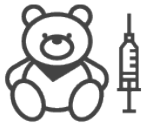
Develop improved antibody testing methods

VACCINE SURVEILLANCE

Help monitor the effectiveness and safety of vaccines

BOOSTERS

Understand if and when different populations need booster shots



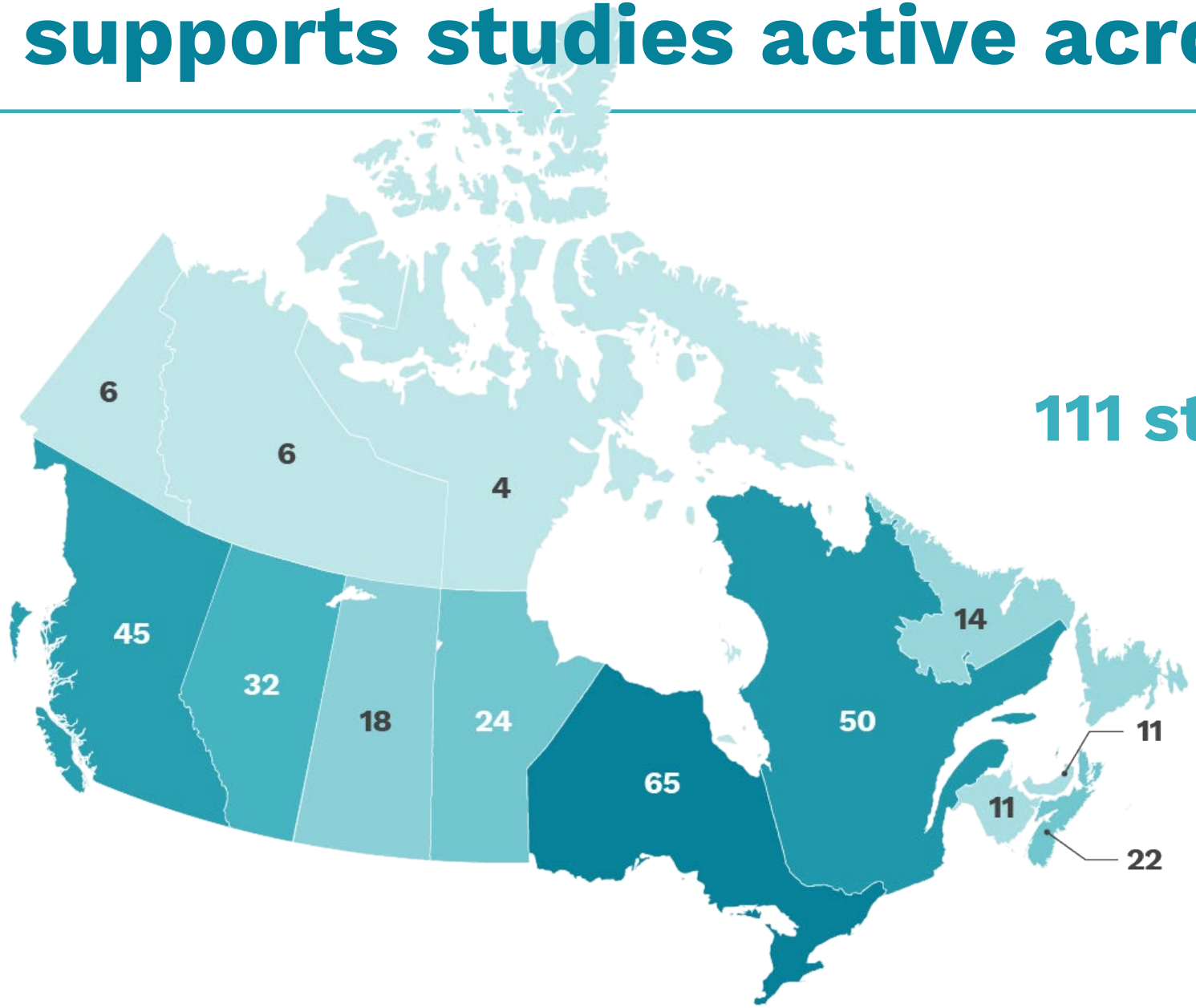
PEDIATRIC VACCINATION

Research safety, effectiveness and immunogenicity of vaccines in children under 21

IMMUNITY MODELLING

Model trends in overall immunity across Canada

CITF supports studies active across Canada

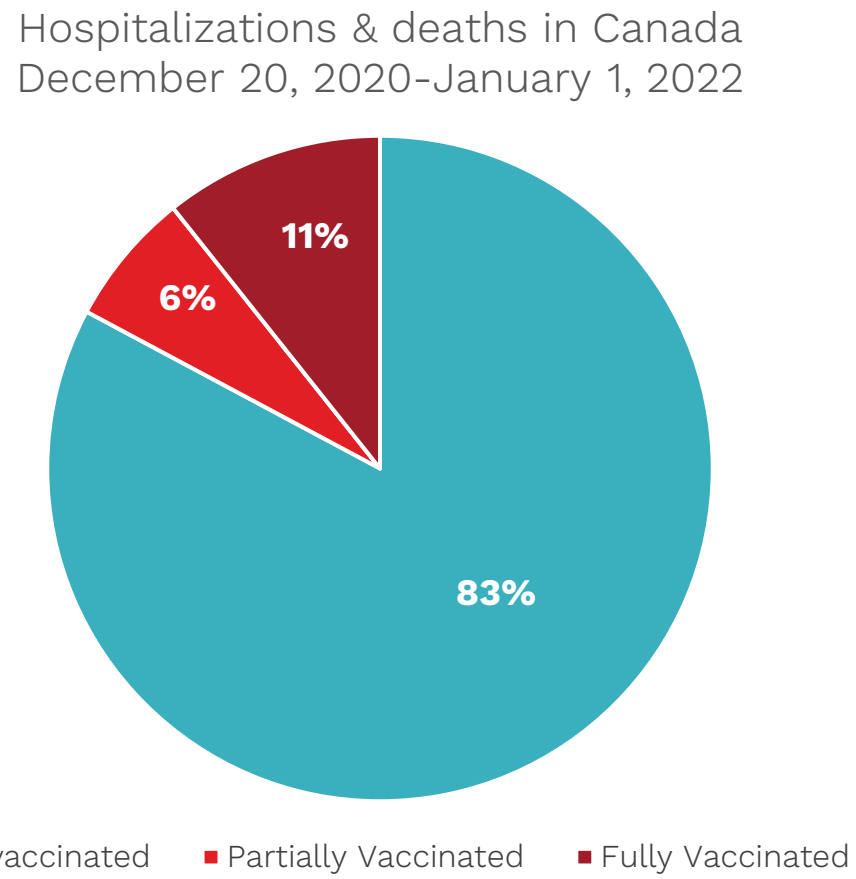


111 studies

Vaccines: a critical resource to protect Canadians from COVID-19

- Low levels of infection-acquired immunity in Canada through to November 2021
- Once available in December 2020, vaccines became a critical vehicle for accelerating the immune protection of Canadians
- Vaccines have delivered as promised, preventing thousands of hospitalizations and deaths and decreasing infection/transmission
- Vaccine roll-out across Canada – both the scale and the longer dosing intervals – have also contributed positively to population immune protection

Vaccines: highly successful at protecting Canadians from severe outcomes



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

However, antibody wane is real

- Vaccine surveillance has identified some concerning trends:
  - Wane in antibodies, especially in older age groups and immunocompromised
  - New Omicron variant associated with high levels of breakthrough infections and transmission despite full vaccination
- This presentation focuses on the evidence on wane in antibodies from CITF supported studies

Results are being shared in real-time

- The results in this presentation are a mix of published and unpublished material
- Some results have gone through peer-review, others not
- When we discuss Omicron, you can be sure results have not gone through peer-review, as we've only been dealing with the variant for a bit over a month

Effectiveness of COVID-19 vaccines over time in Ontario

Ontario

Jeff Kwong

MD, MSc, CCFP, FRCPC
Senior Scientist, ICES
Scientist, Public Health Ontario
Professor, University of Toronto

Disclaimer

I have no conflicts of interest to declare related to this study.

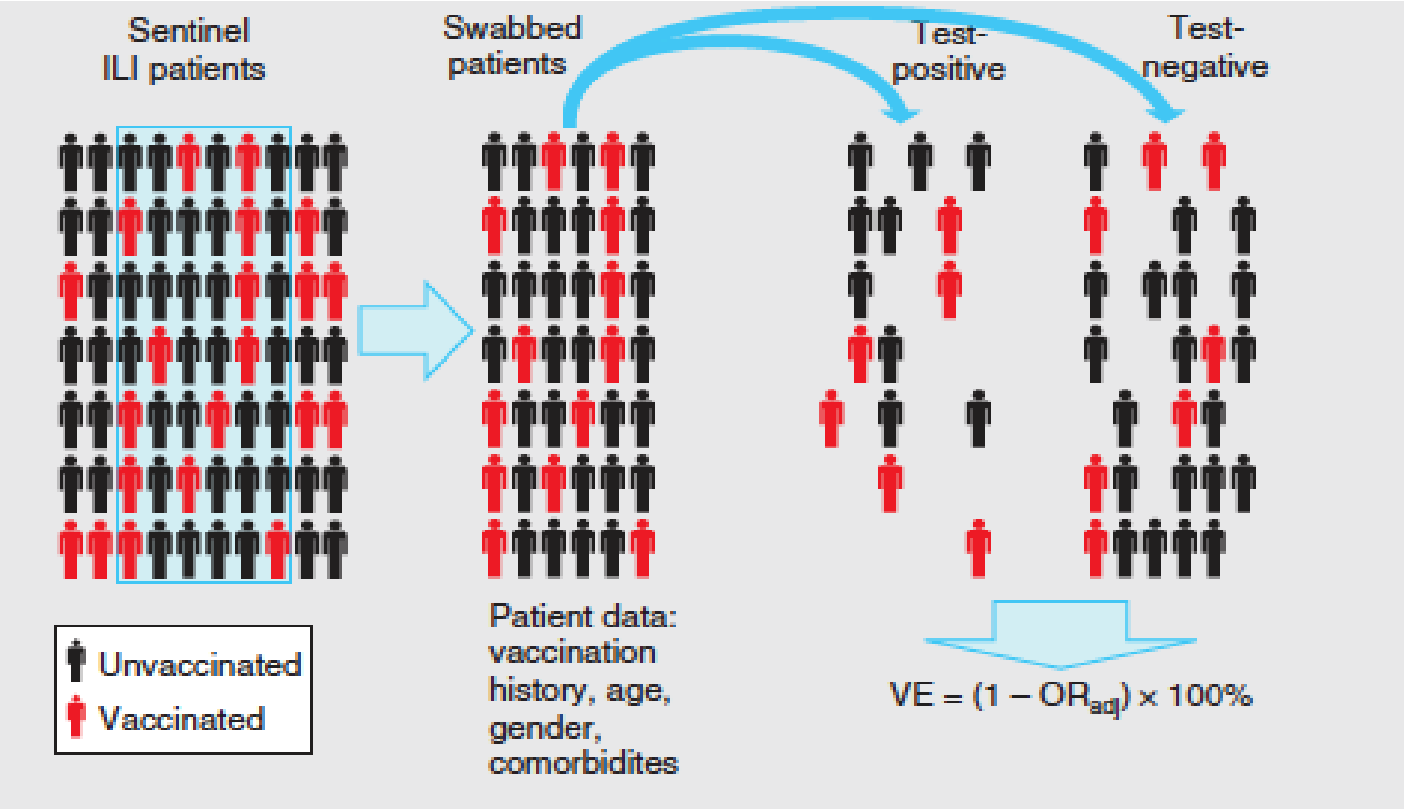
Background

- Numerous studies have found that vaccine effectiveness (VE) declines over time
- Some studies have found lower VE against Delta than against Alpha
- Some studies have found higher VE with longer interval between doses
- Evaluating waning of VE in Canada is challenging due to simultaneous changes in circulating SARS-CoV-2 lineages and vaccination program policies (i.e., dosing interval changes due to vaccine supply constraints)

Objective

To estimate **vaccine effectiveness** against multiple outcomes over time, while accounting for changes in circulating SARS-CoV-2 lineages and dosing intervals.

Test-negative design



$$\text{OR} = \frac{\text{odds of vaccination in TP}}{\text{odds of vaccination in TN}}$$

$$\text{VE} = (1 - \text{OR}) \times 100\%$$

Sullivan SG, et al. Potential of the test-negative design for measuring influenza vaccine effectiveness: a systematic review. *Expert Review of Vaccines* 2015;13(12):1571-91.

Methods

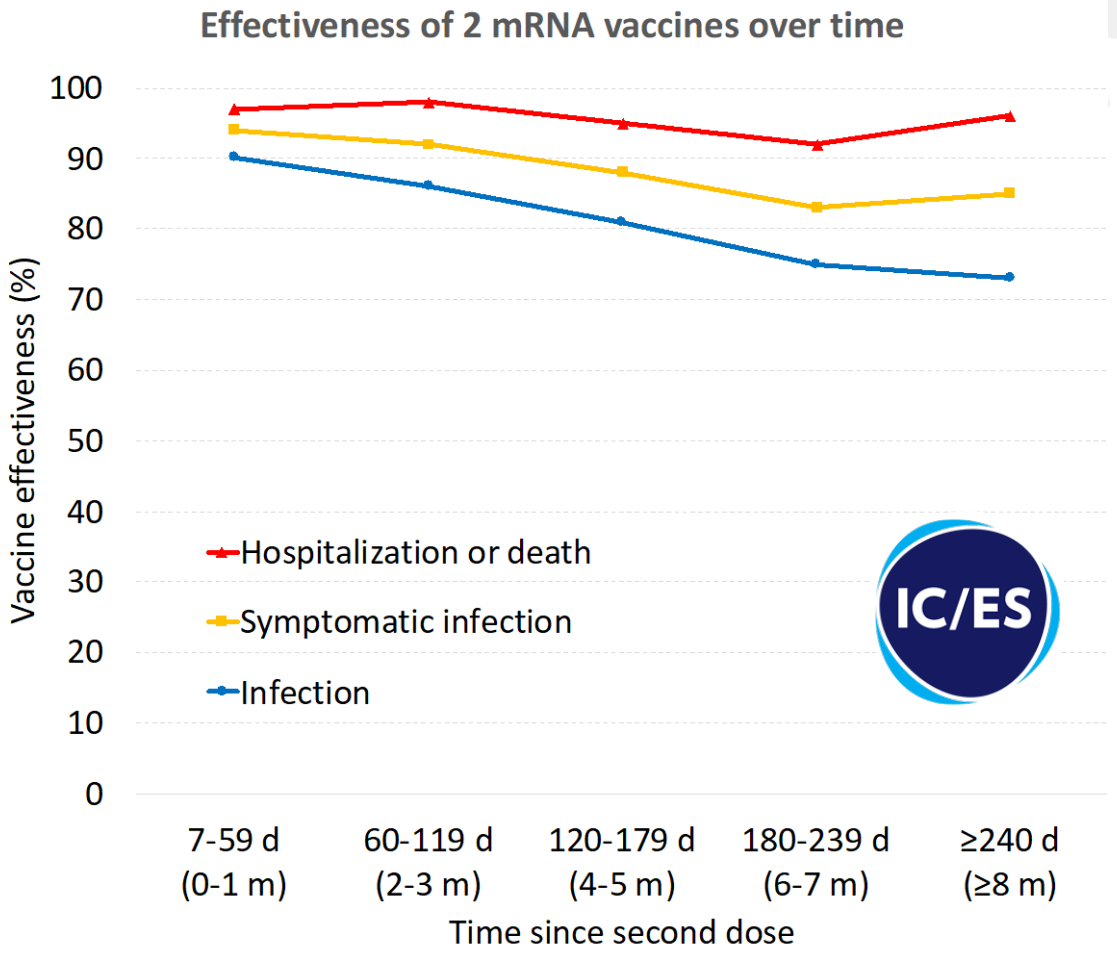
- Study population
  - Aged ≥16 years, community-dwelling
  - Tested for SARS-CoV-2 during 3 periods:
    - Mixed Wuhan strain and Alpha period (11 Jan to 4 Apr)
    - Alpha period (5 Apr to 27 Jun): ~77% Alpha
    - Delta period (28 Jun to 1 Nov): ~97% Delta
- Outcomes
  - Infection (irrespective of symptoms or severity)
  - Symptomatic infection
  - Severe outcomes (hospitalization or death)

Methods

- Exposure
  - Time since second dose (for any combination of 2 mRNA COVID-19 vaccines)
  - Interval between doses
- Covariates
  - Age, sex, geographic region
  - Biweekly period of test (calendar time)
  - Number of SARS-CoV-2 tests prior to start of vaccination program (proxy for HCWs)
  - Influenza vaccination (proxy for health behaviours)
  - Comorbidities
  - Area-level measures: income, essential workers, household size, visible minorities

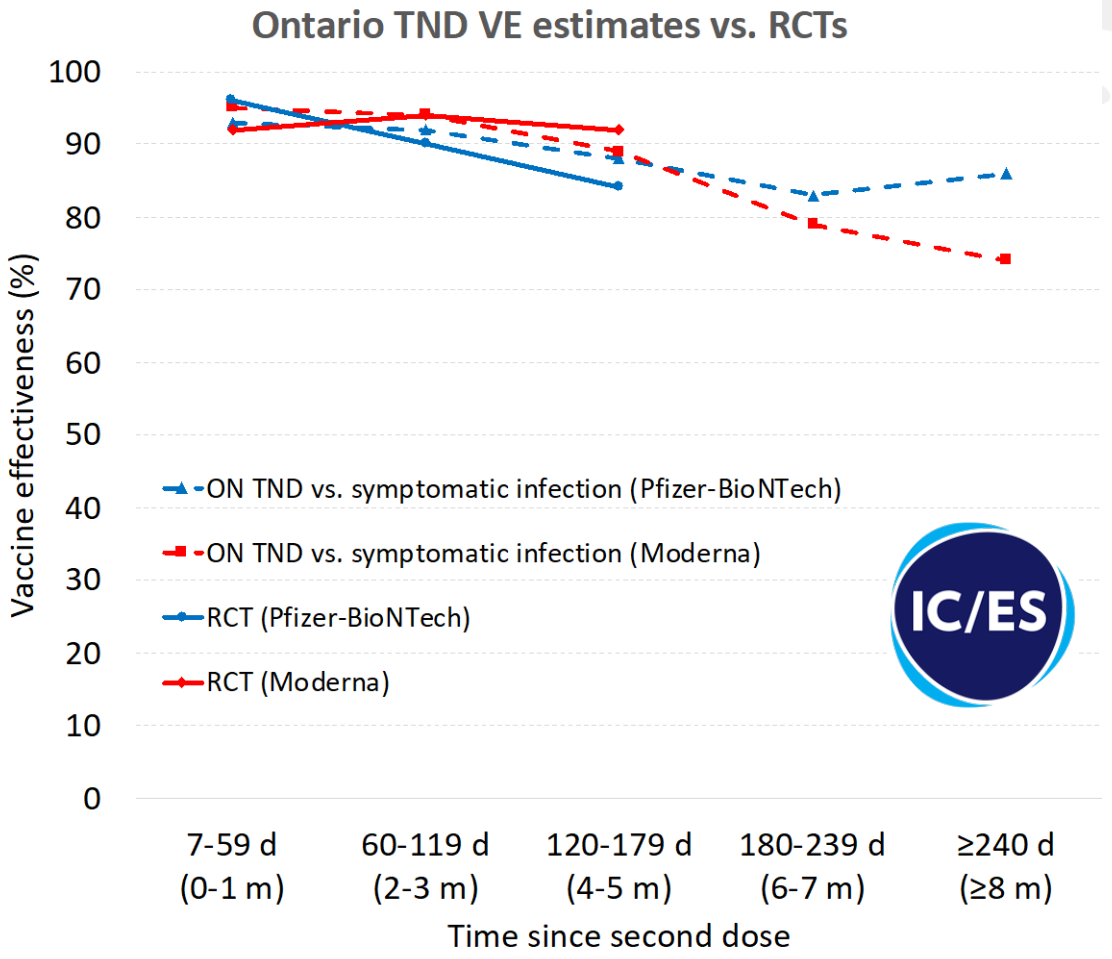
Waning of VE against any SARS-CoV-2 lineage varies by outcome

- VE is consistently higher against severe outcomes than against symptomatic infection and infection
  - VE against severe outcomes remained above 90%
  - VE against infection declined from 90% to 73% by ≥8 months



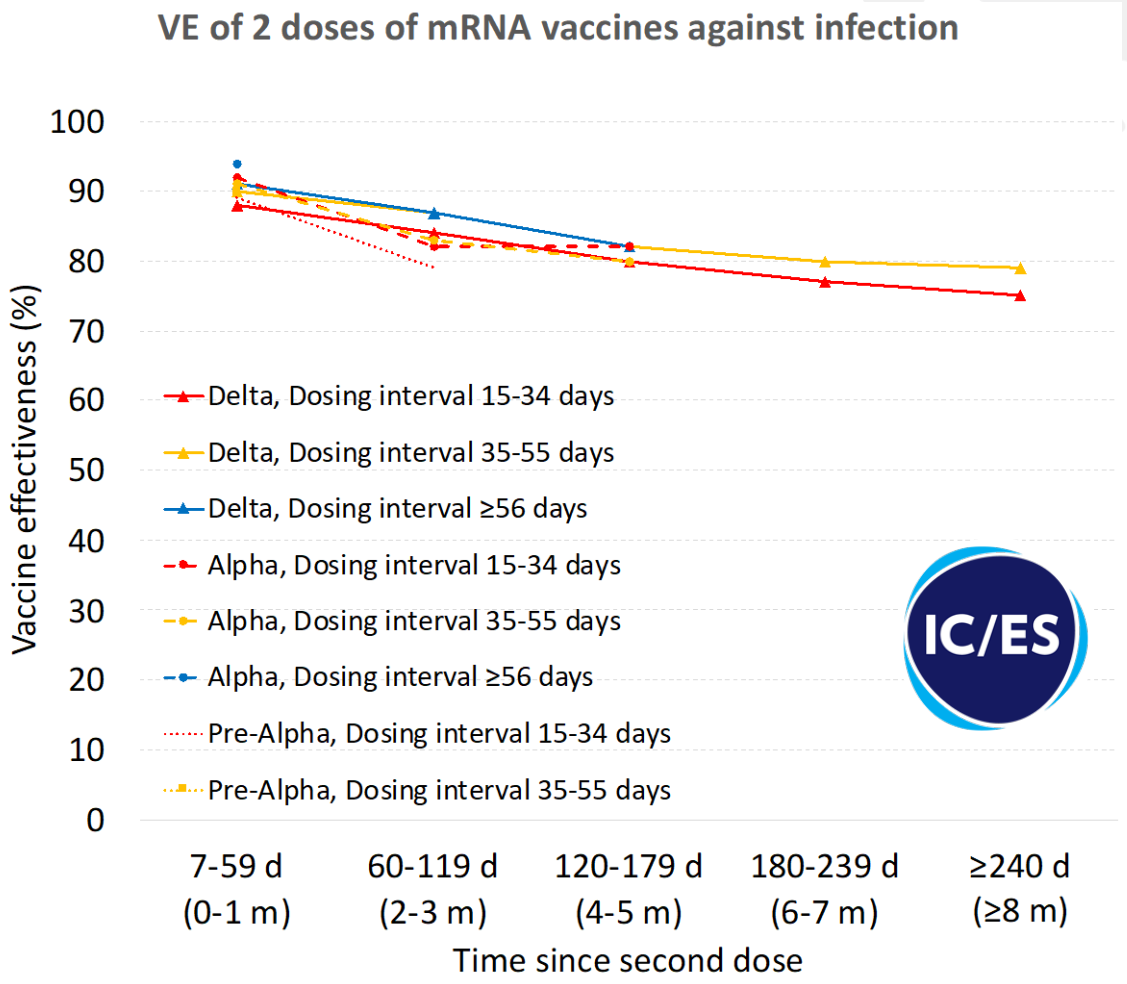
Test-negative design estimates align with randomized controlled trials

- Ontario test-negative design VE estimates for symptomatic infection are similar to randomized controlled trials 4-5 months after second dose (differences <5%)
- Differences in VE between Pfizer and Moderna vaccines at ≥8 months may relate to differences in vaccine recipients



Time since second dose impacts VE most

- VE against infection wanes steadily over time regardless of SARS-CoV-2 lineage and dosing interval
- Time since second dose has greater impact on VE than SARS-CoV-2 lineage or dosing interval

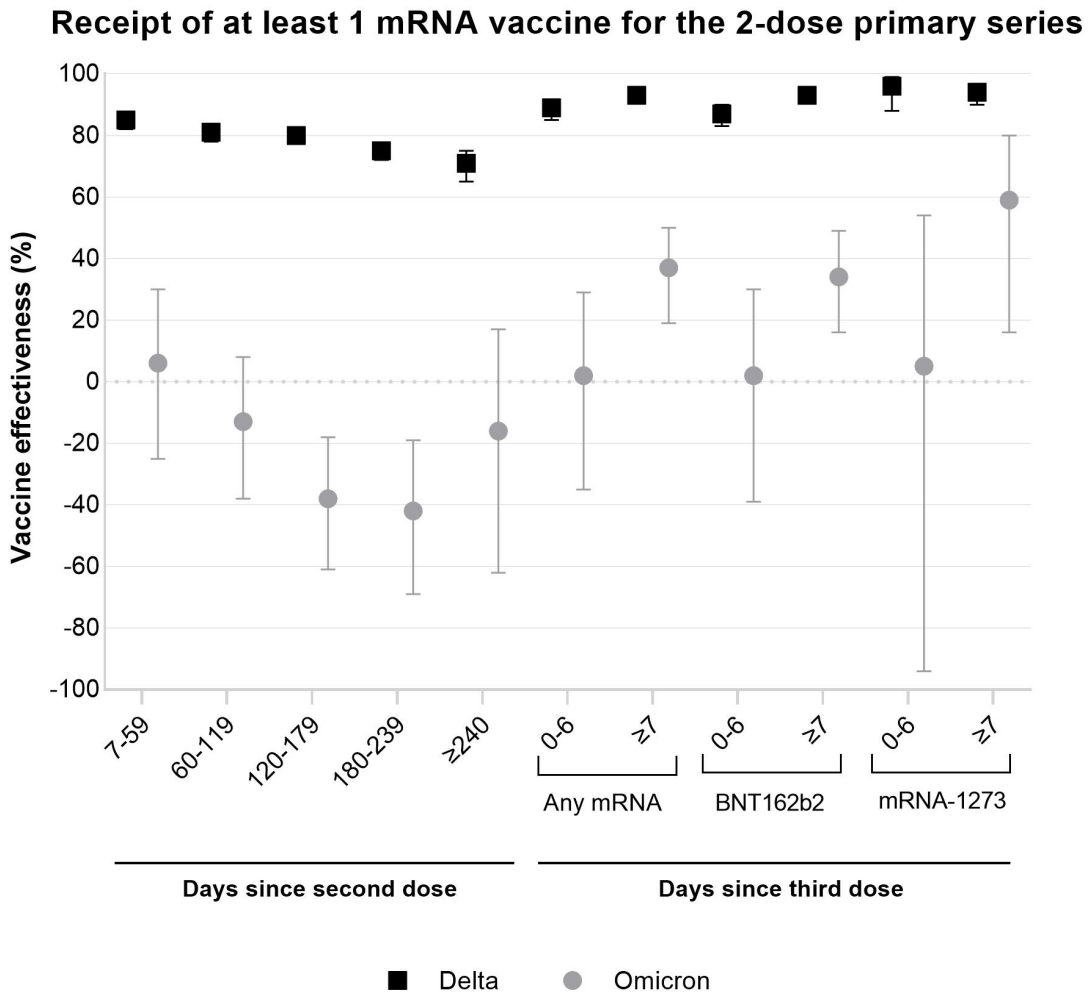


VE against Omicron

- Preliminary analysis: pre-print posted on medRxiv on 1 Jan 2022
- Study population
  - Aged ≥18 years, community-dwelling
  - Tested for SARS-CoV-2 between November 22 and December 19, 2021 (first 4 weeks after identification of Omicron in Ontario)
- Outcome
  - Infection (irrespective of symptoms or severity)
  - Classified cases as Omicron or Delta based on whole genome sequencing or presence of S-gene target failure or by date of test

Preliminary analysis: VE against infection caused by Omicron vs. Delta

- VE against **infection** caused by **Delta:**
  - 71% by ≥8 months after second dose
  - 93% after third dose
- VE against **infection** caused by **Omicron:**
  - Far lower than against Delta after second dose
  - 37% after third dose

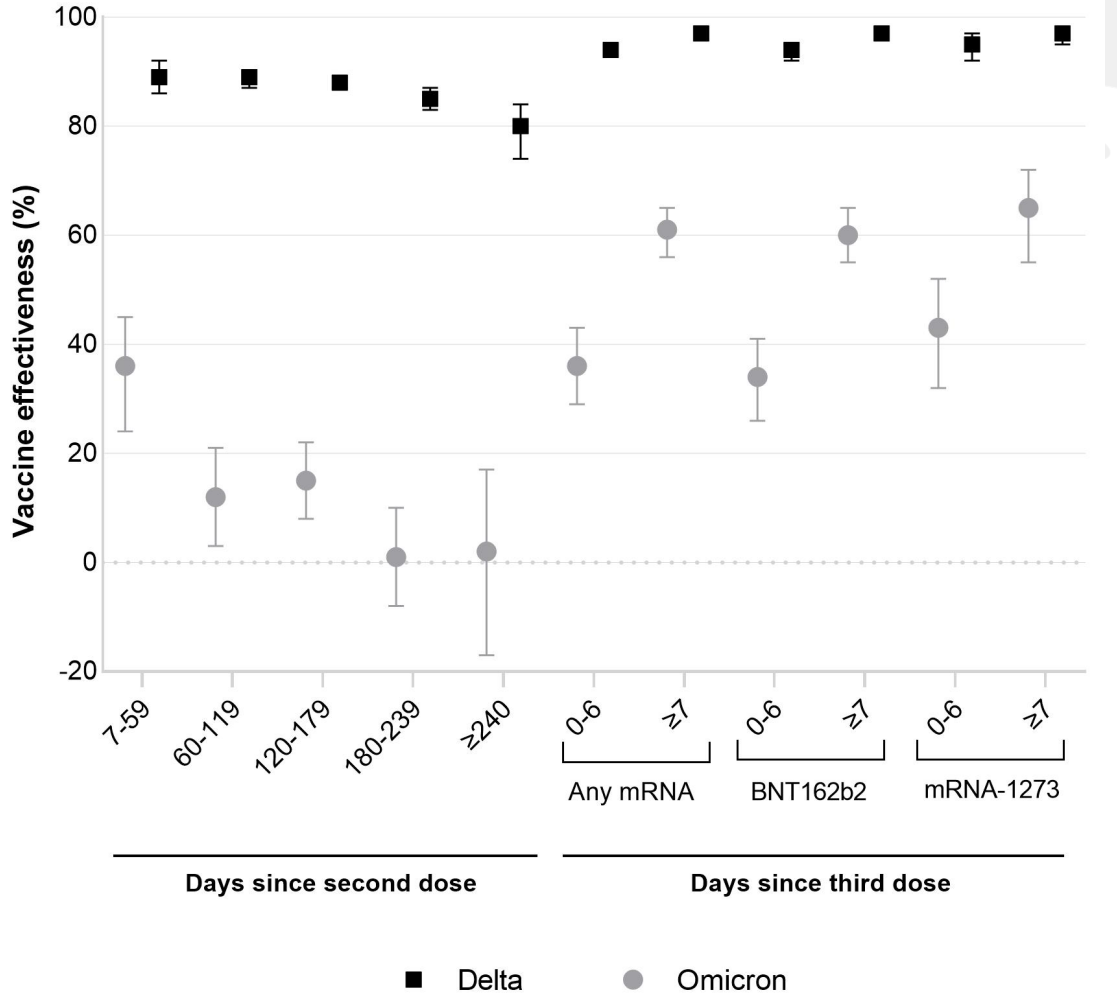


Updated data: VE against Omicron

- Updated analysis to be posted on medRxiv soon
- Study population
  - Aged ≥18 years, community-dwelling
  - Tested for SARS-CoV-2 from December 6-26, 2021 (Weeks 3, 4, and 5 after first identification of Omicron in Ontario; period of universal testing for SGTF)
- Outcomes
  - Symptomatic infection
  - Severe outcomes (hospitalization or death)
  - Classified cases as Omicron or Delta based only on sequencing or SGTF

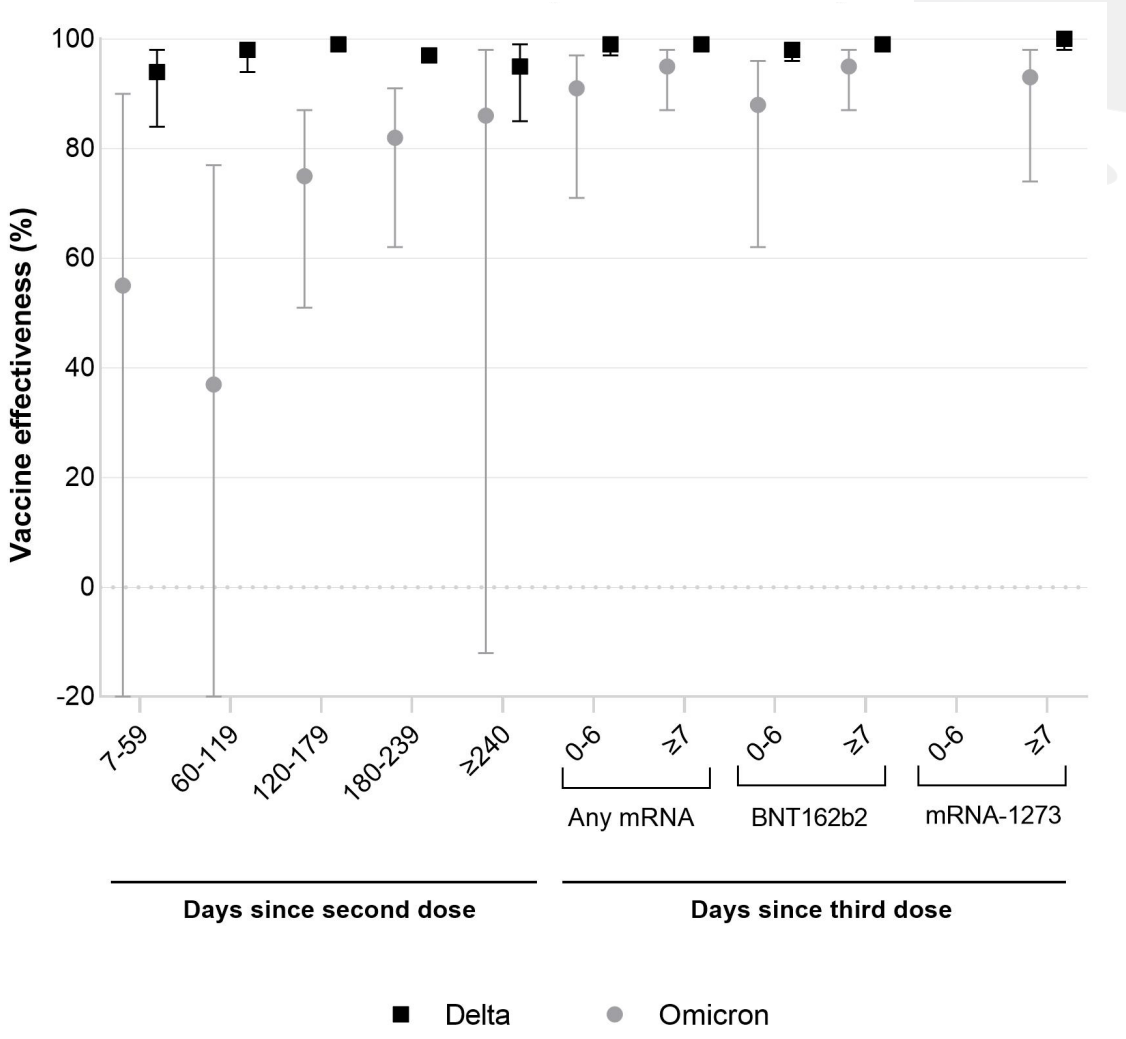
VE against symptomatic infection caused by Omicron vs. Delta

- VE against **symptomatic infection** caused by **Delta:**
  - Declined to 80% by ≥8 months after second dose
  - Recovered to 97% after third dose
- VE against **symptomatic infection** caused by **Omicron:**
  - Far lower than against Delta after second dose
  - Was 61% after third dose

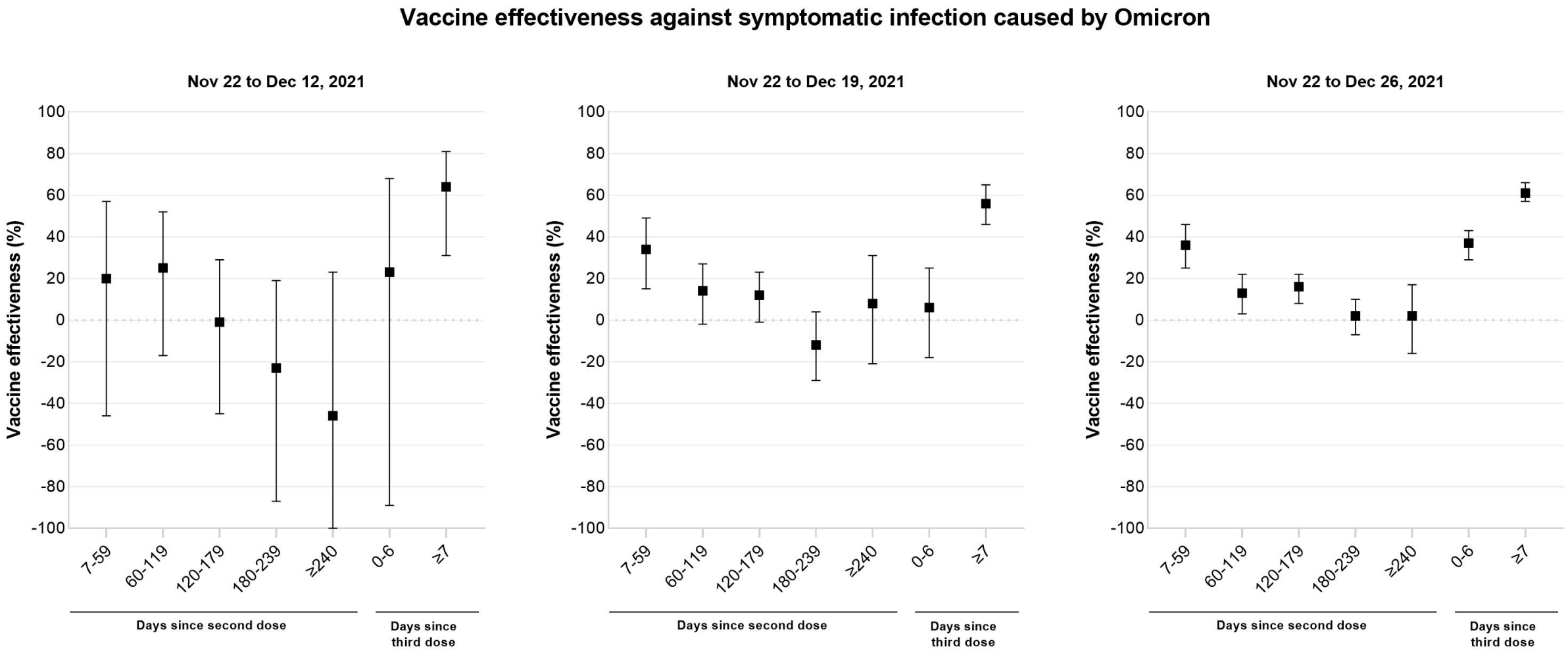


VE against **severe outcomes** caused by Omicron vs. Delta

- VE against **severe outcomes** caused by **Delta**:
  - Still very high at 95% by ≥8 months after second dose
  - 99% after third dose
- VE against **severe outcomes** caused by **Omicron:**
  - ~82-86% after second dose
  - 95% after third dose



Evolution of VE against symptomatic infection over time



Learnings/challenges

- Choice of outcome measure: VE against infection is more susceptible to downward bias than symptomatic infection and severe outcomes
  - Indication(s) for testing
- Study period: Estimating VE in initial weeks following Omicron circulation is susceptible to downward bias
  - Differential exposure to Omicron in vaccinated and unvaccinated populations
- Classifying Omicron vs. Delta: Using dates to define Omicron is susceptible to upward bias in VE estimates
  - Misclassification of unvaccinated Delta cases as Omicron
- Access to PCR testing and availability of WGS & SGTF varied over time

Conclusions

- VE wanes steadily over time following the second dose, more so against infection and symptomatic infection than against severe outcomes
- Time since second dose receipt (up to ≥8 months) is a more important determinant of VE than SARS-CoV-2 lineage (pre-Omicron) or dosing interval
- For symptomatic infection, VE against Omicron is lower than against Delta, whether after 2 or 3 doses, but for severe outcomes VE against Omicron is comparable to Delta after the third dose
- Estimating VE against Omicron is challenging

Provincial Collaborative Network Study Team

Ontario

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Cindy Fong
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Kevin Brown
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Funded by

COVID-19 IMMUNITY TASK FORCE
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CIRN
CANADIAN IMMUNIZATION RESEARCH NETWORK

CIHR IRSC

Public Health Agency of Canada
Agence de la santé publique du Canada

COVID-19 vaccinations & infections in long-term care

Ontario

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Andrew Costa

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

McMaster University

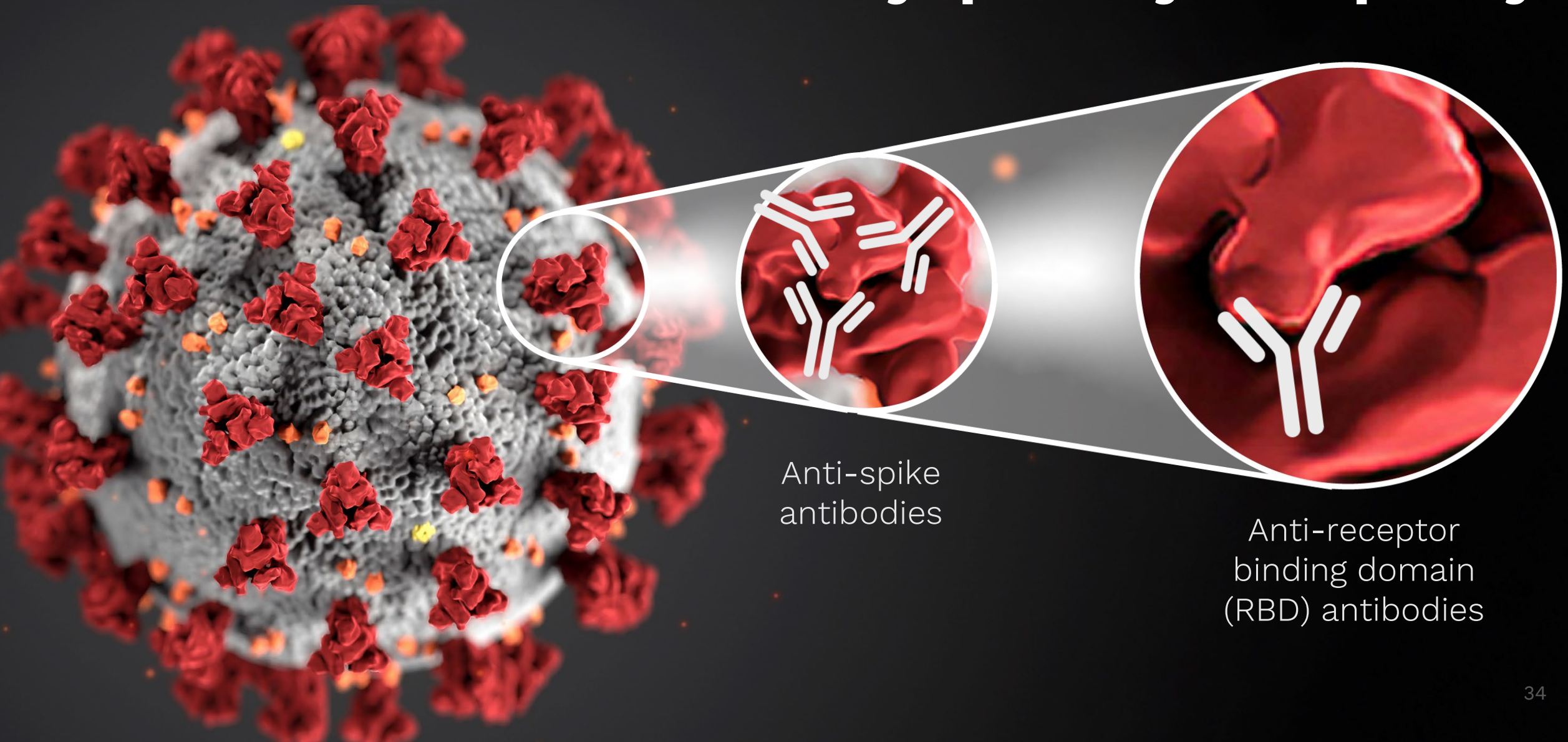
Schlegel Villages

St. Joseph's Health System Elder Care

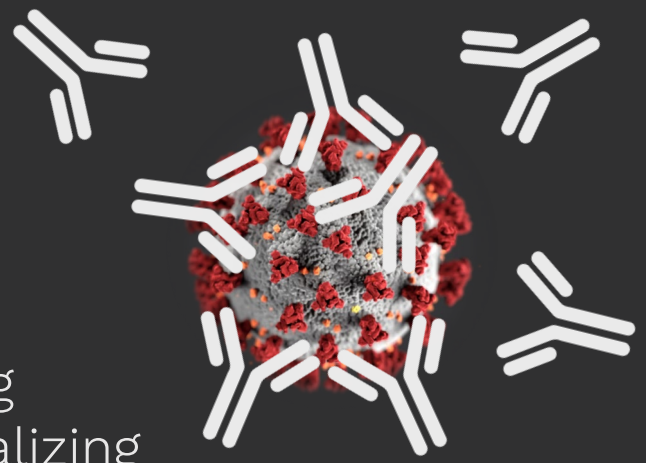
Disclaimer

We do not have any conflicts of interest specific to this study.

Antibody quantity and quality

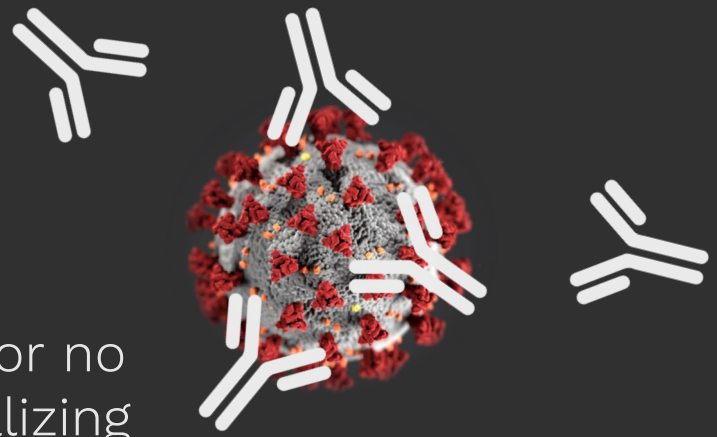


Antibody quantity and quality

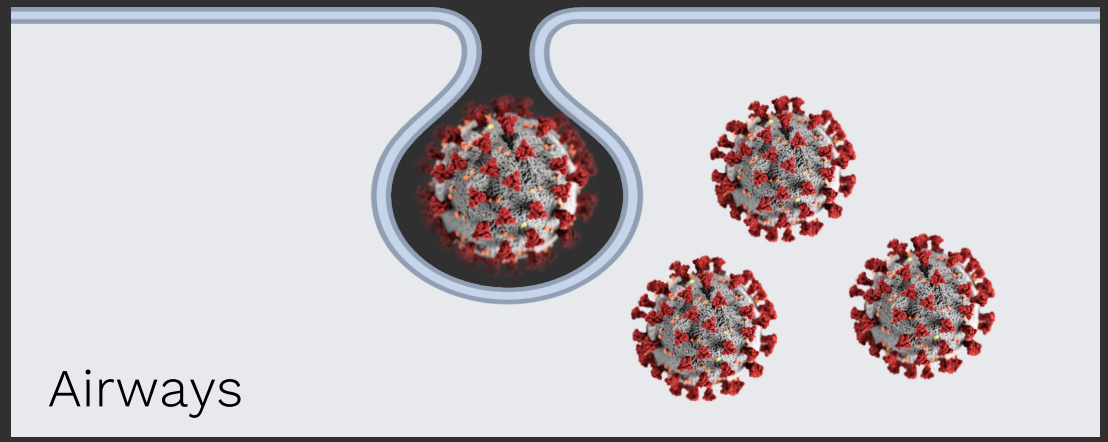


Strong neutralizing antibodies

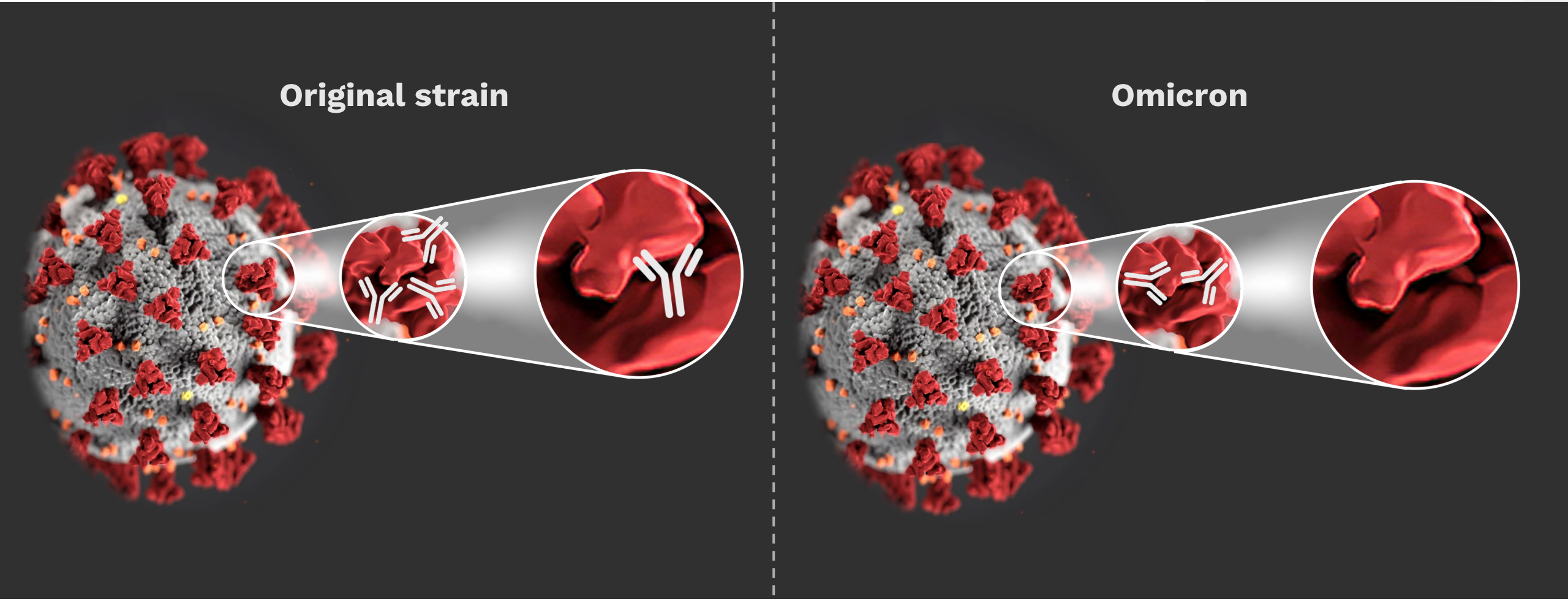
Airways



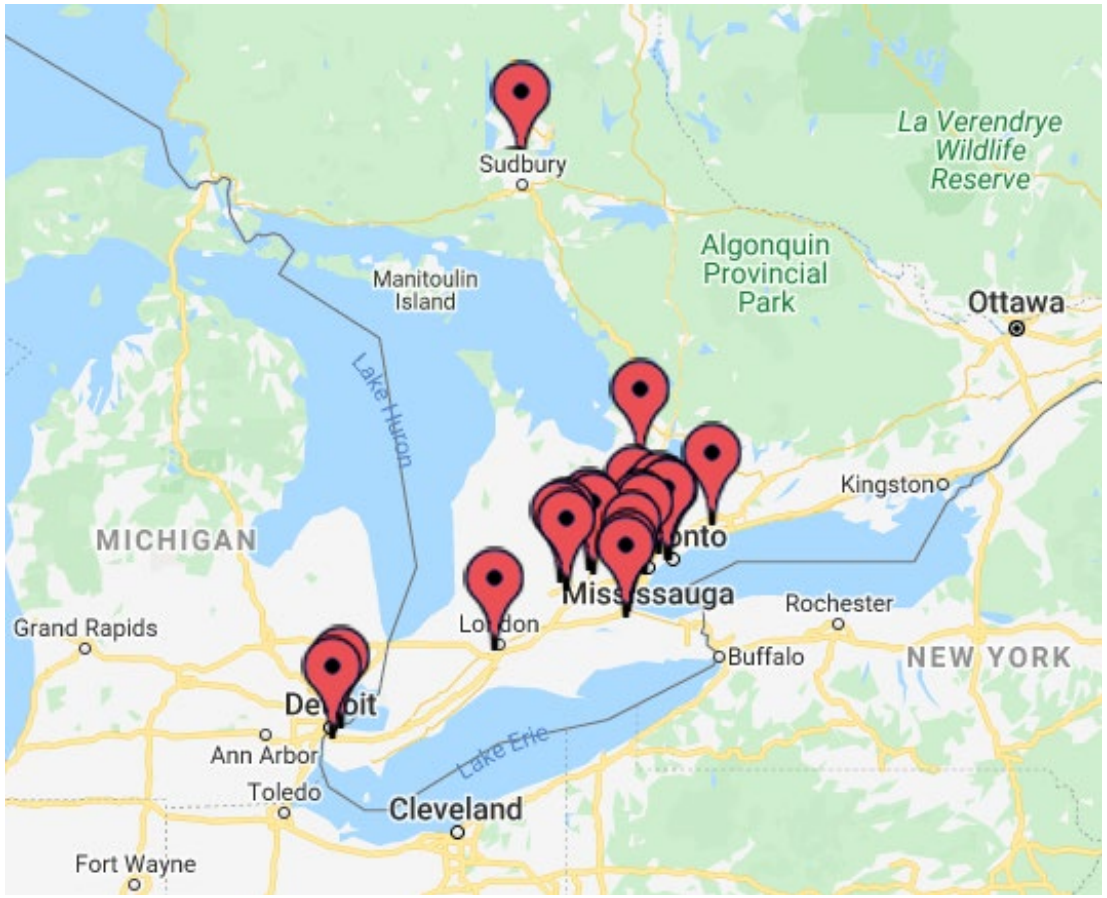
Weak or no neutralizing antibodies



With Omicron we may need quantity over quality



Retirement and long-term homes (Science = Partnership)



SCHLEGEL VILLAGES

AMICA SENIOR LIFESTYLES

St. Joseph's HEALTH SYSTEM ELDER CARE

ST. JOSEPH'S Lifecare Centre BRANTFORD

St. Joseph's Villa Dundas

St. Joseph's HEALTH CENTRE GUELPH
Serving with Compassion, Care and Courage

Caring... beyond the moment
Au-delà des soins présents
St. Gabriel's Villa Of Sudbury
Villa St-Gabriel de Sudbury

Shalom Village
Honouring our Fathers and our Mothers

Finlandia Village
sudburyn suomalainen lepokotiyhdistys
sudbury finnish rest home society incorporated

COVID in LTC Study @CovidInItc · Aug 24, 2021

“I wanted to do this research initiative because I like the prospect of helping people and contributing to science in a positive way.” Today we are spotlighting Margaret, a resident at the Village of Erin Meadows! Thank you Margaret for your participation! #StopCOVIDinLTC

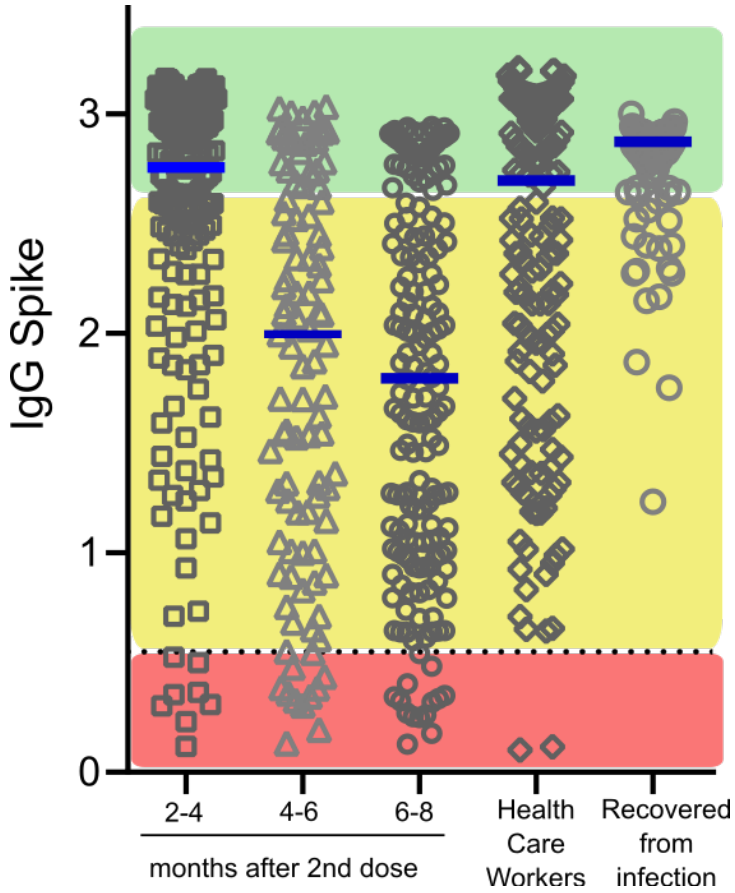
Schlegel Villages @SchlegelVillage · Jul 21, 2021

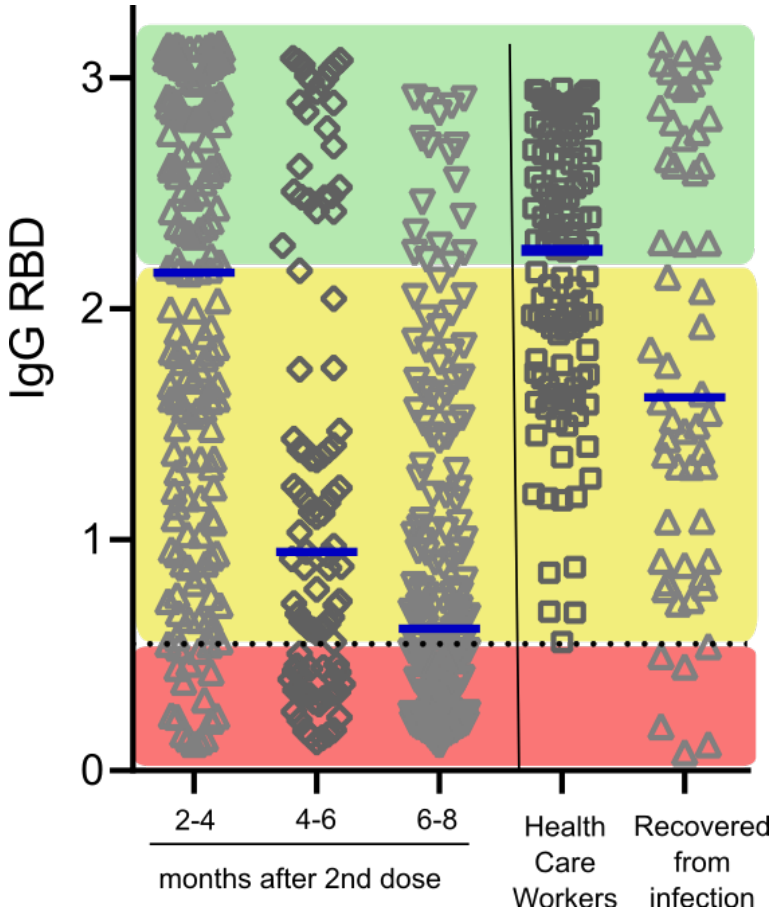
"We should share whatever information we can to help them come up with answers," says Chris Nelson, which is why she and her parents are part of the important #Covid19 Immunity Study (@CovidInItc) led by @McMasterU.

schlegelvillages.com/news/combined-...

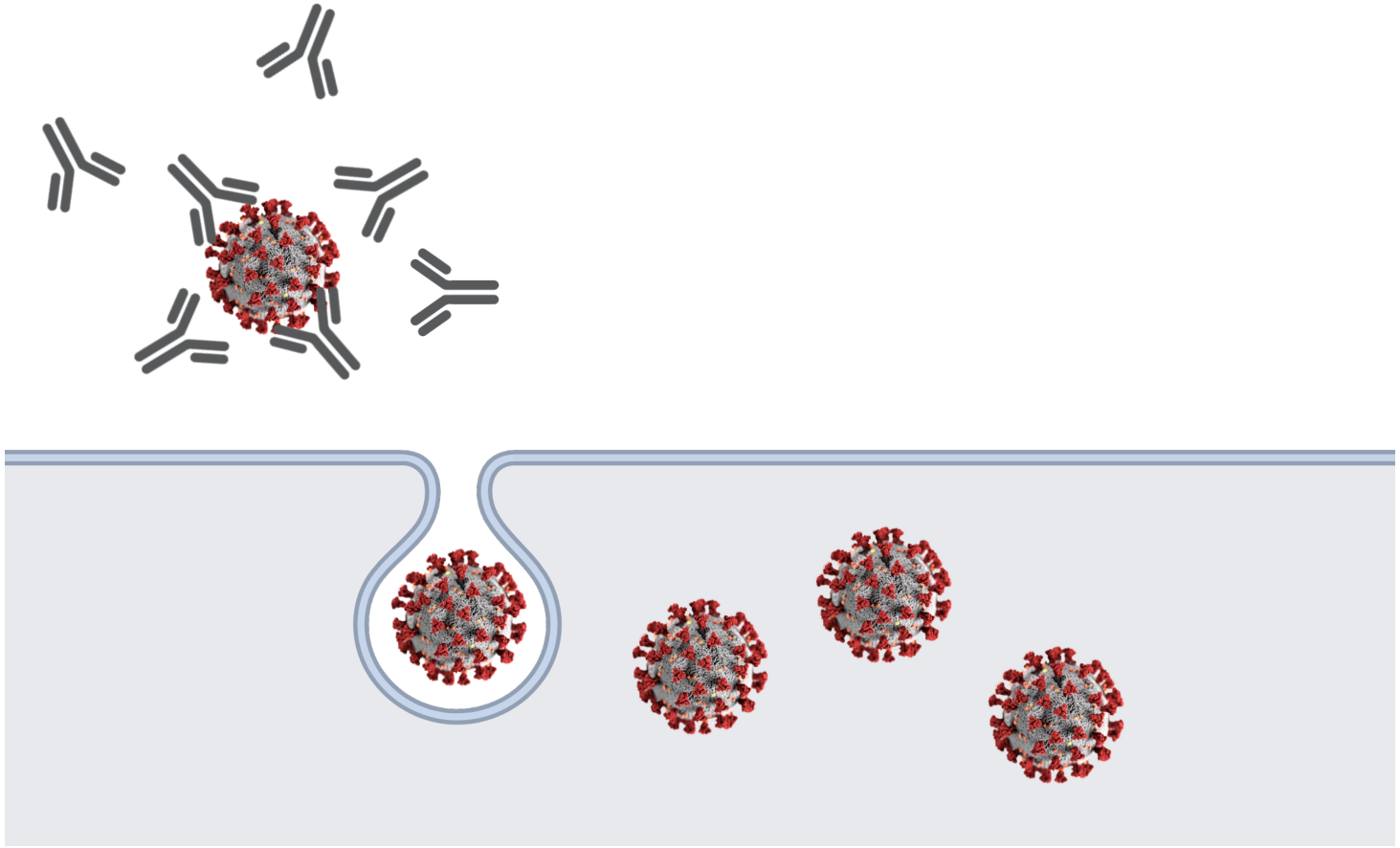
@MsMacrophage @Andrew_P_Costa

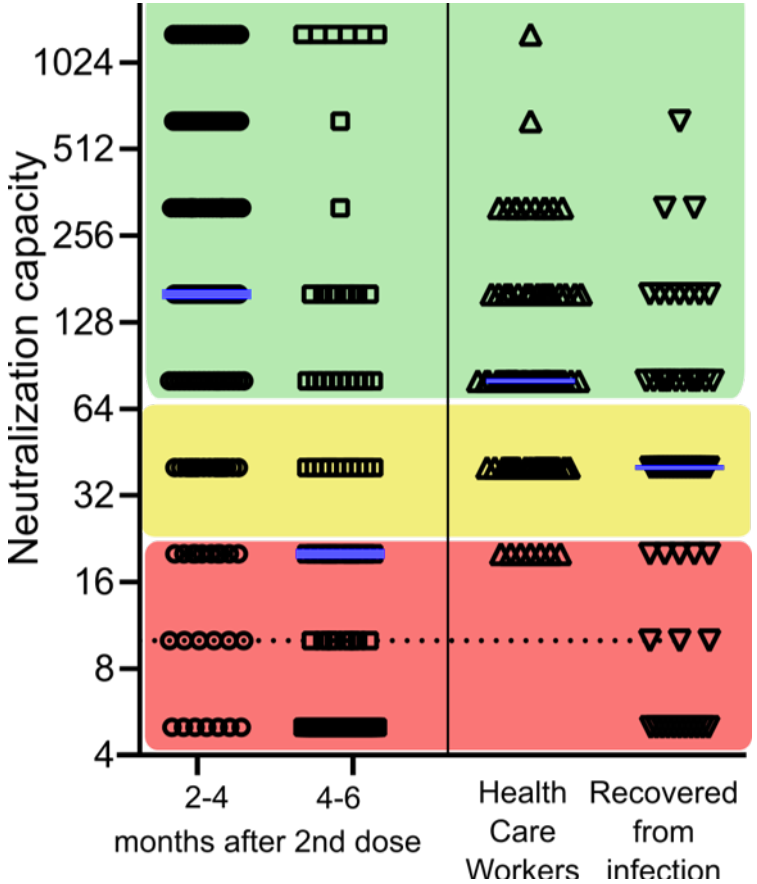
Antibodies declined over time in LTC residents (after 2nd dose)





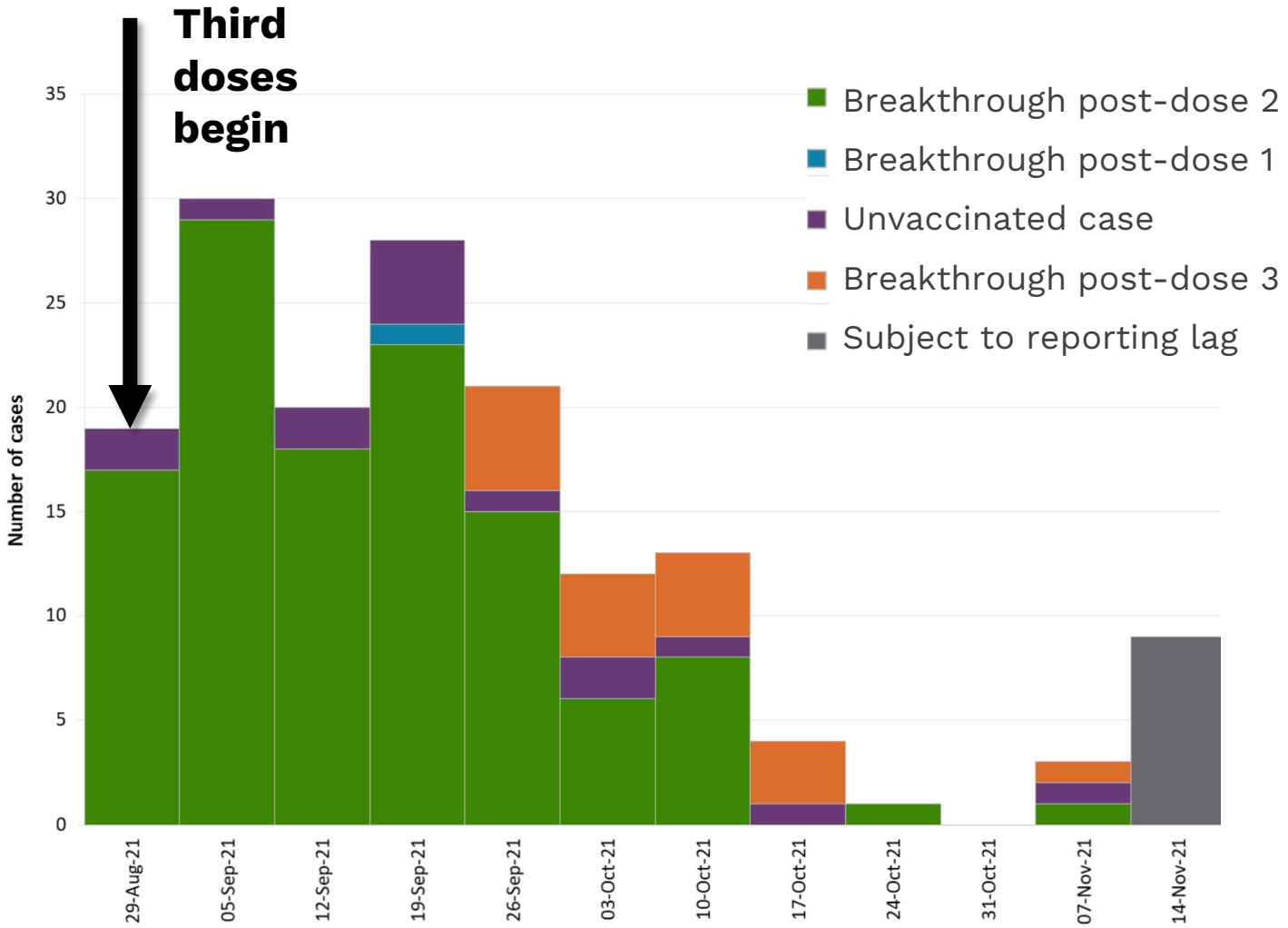
Neutralizing antibodies declined substantially over time in LTC residents (after 2nd dose)





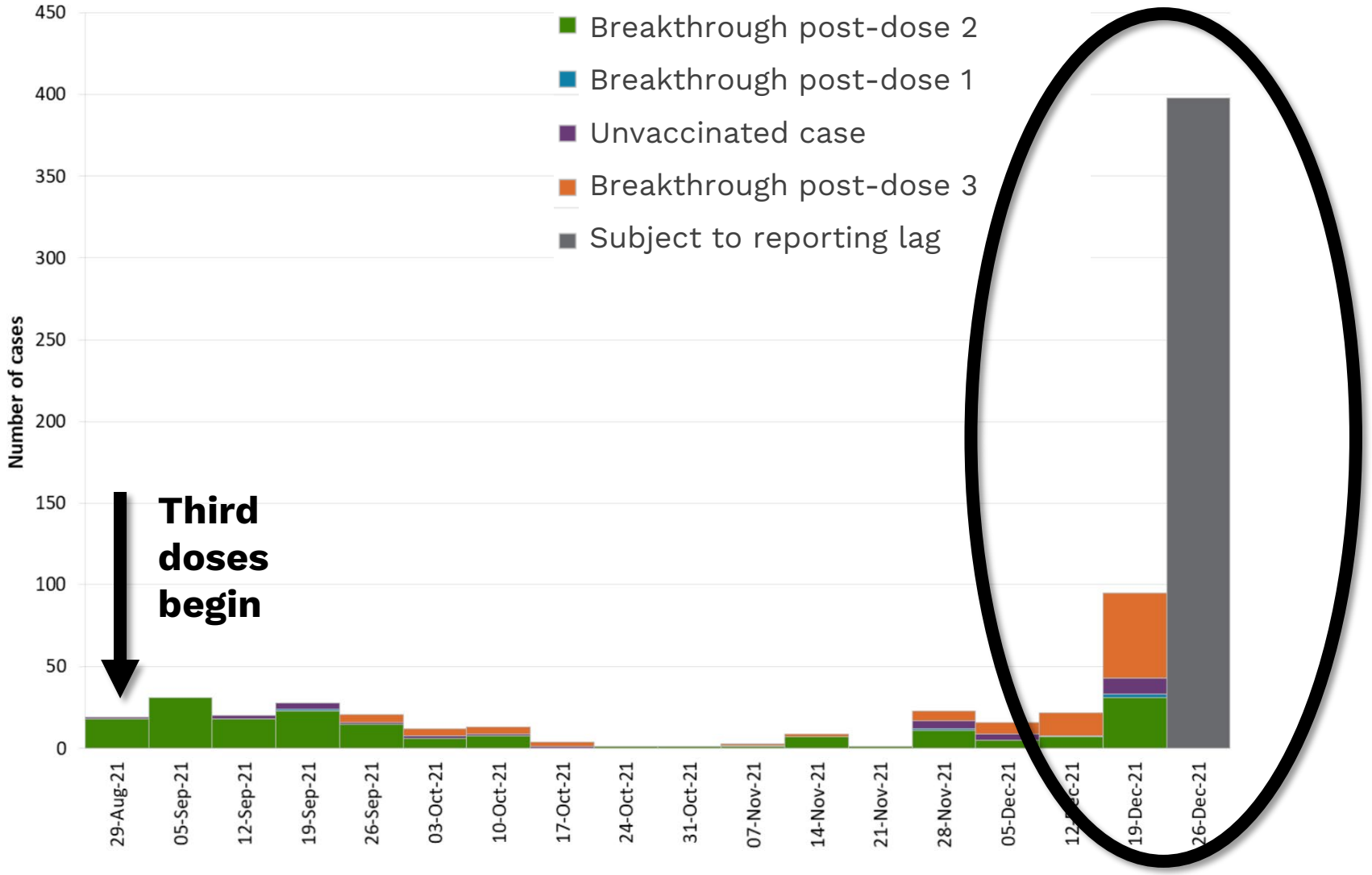
Third dose came just in time for long-term care

Figure 1: Number of COVID-19 long-term care home resident cases by vaccination status and reported week: Ontario, August 29, 2021 to November 20, 2021



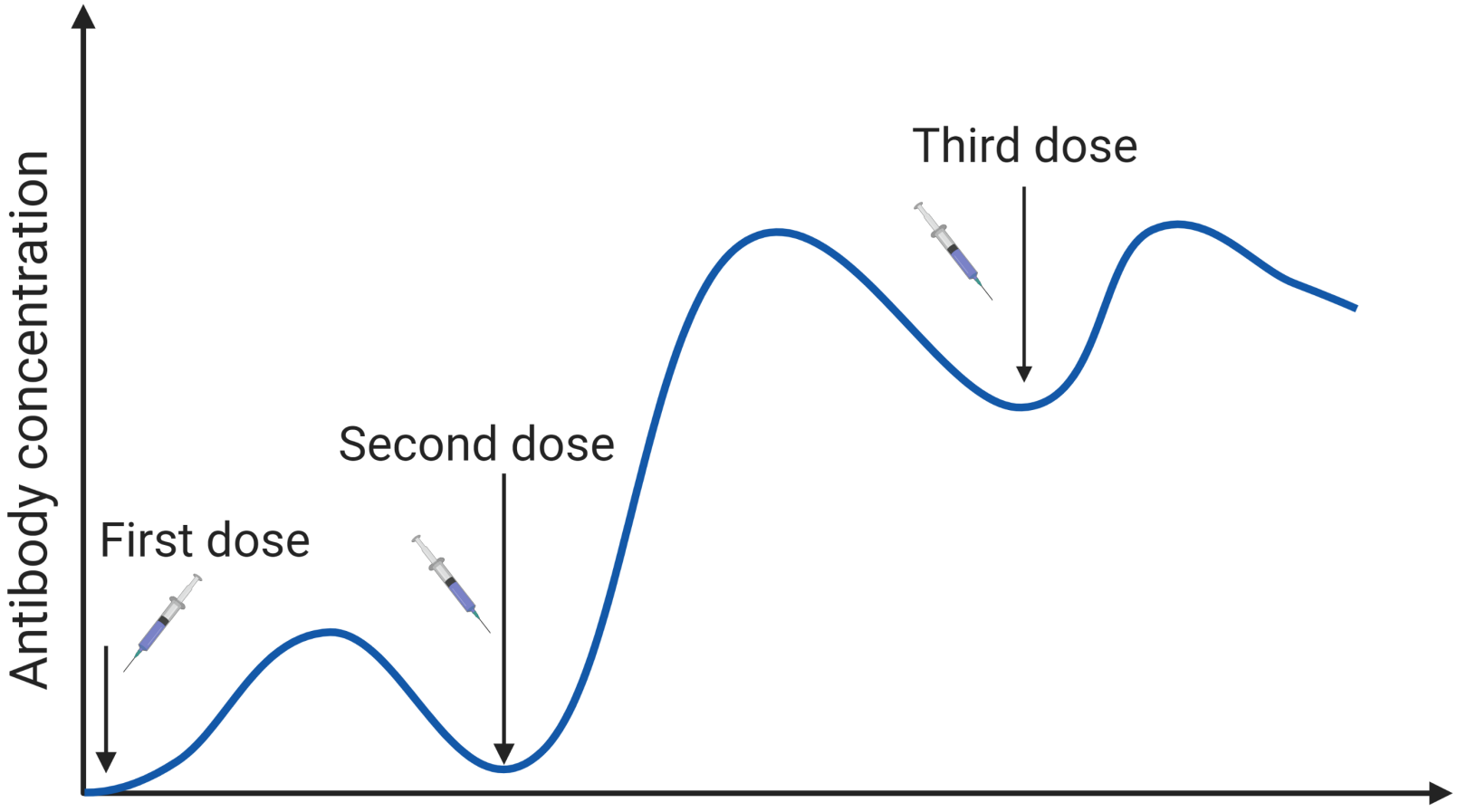
Source: Public Health Ontario data

...But then came Omicron



Source: Public Health Ontario data

Will a third dose help in older and frail adults?



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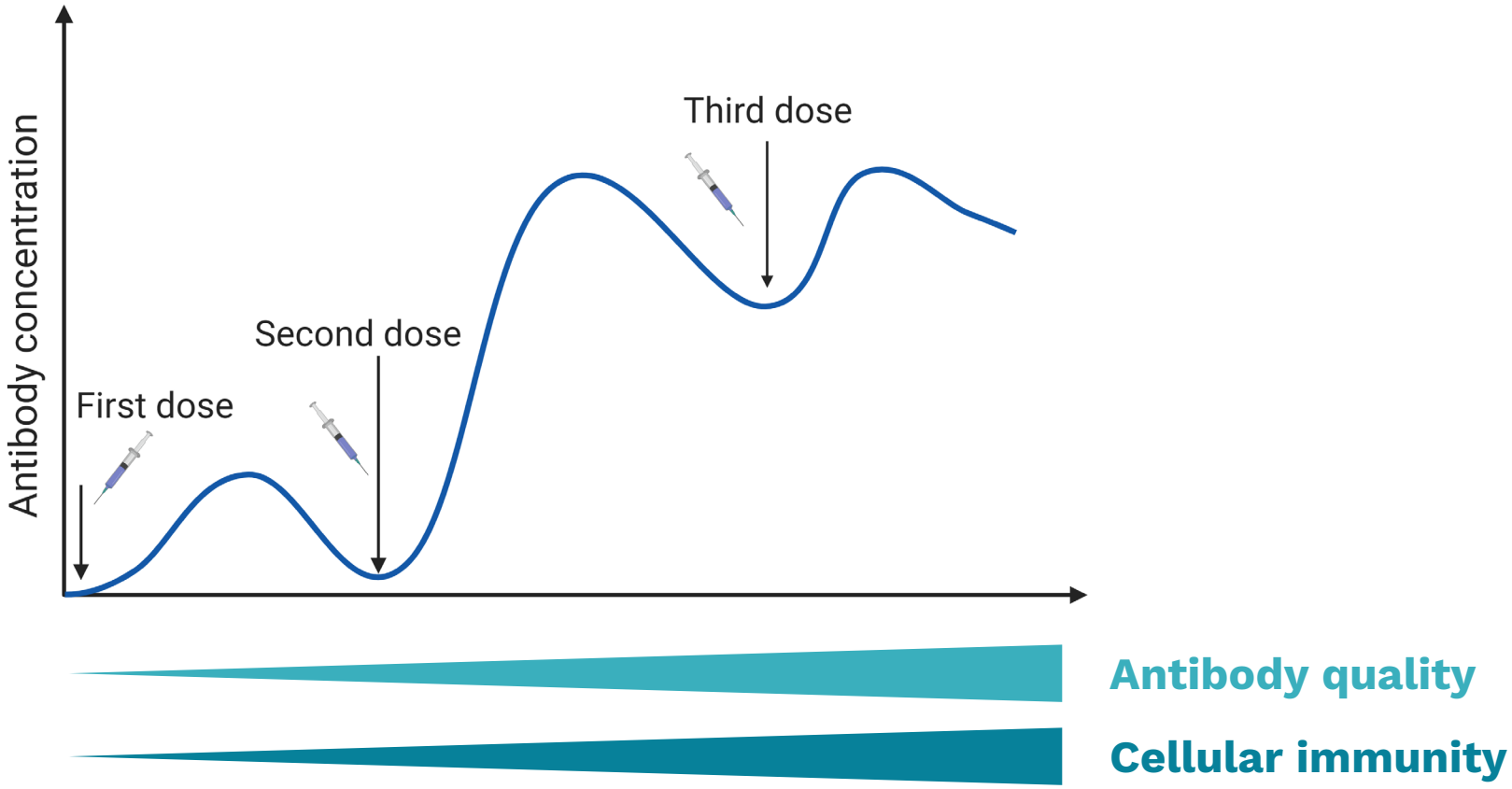
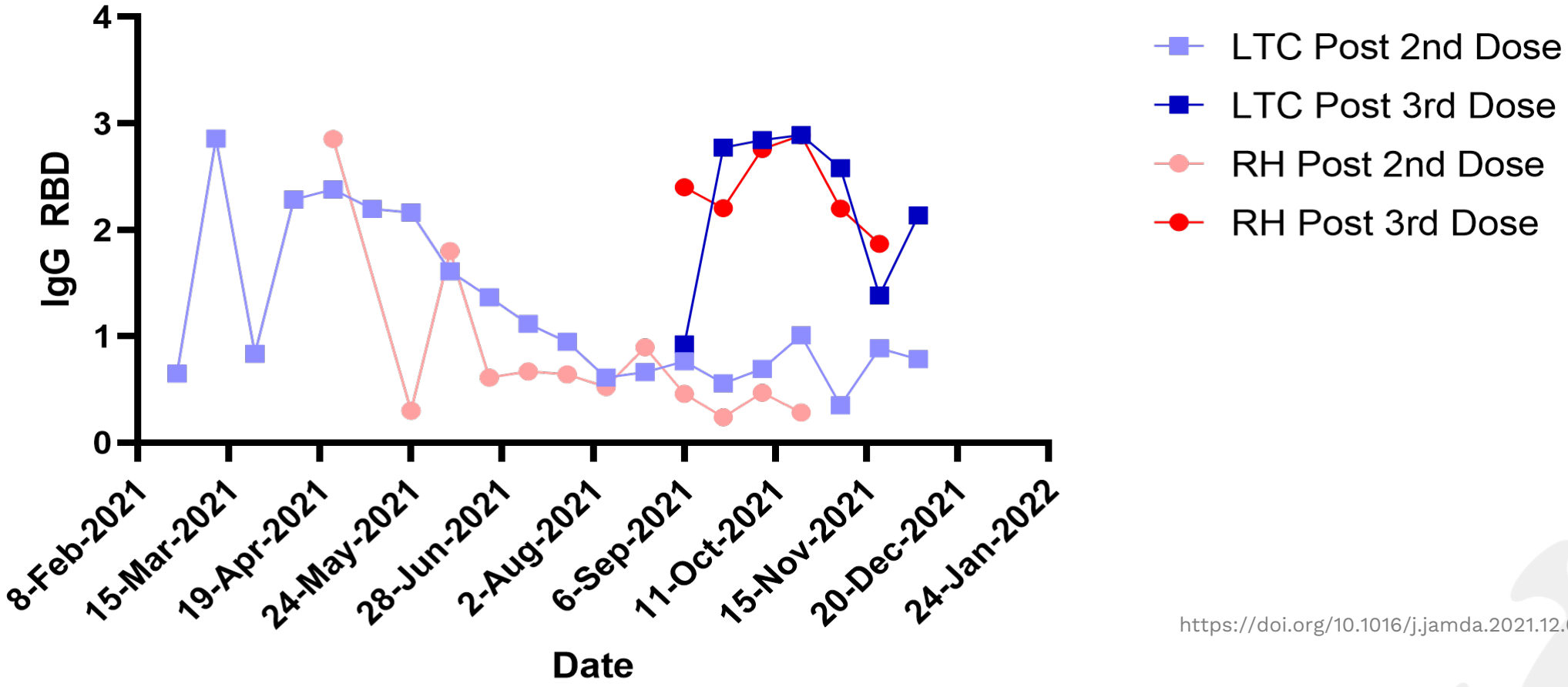
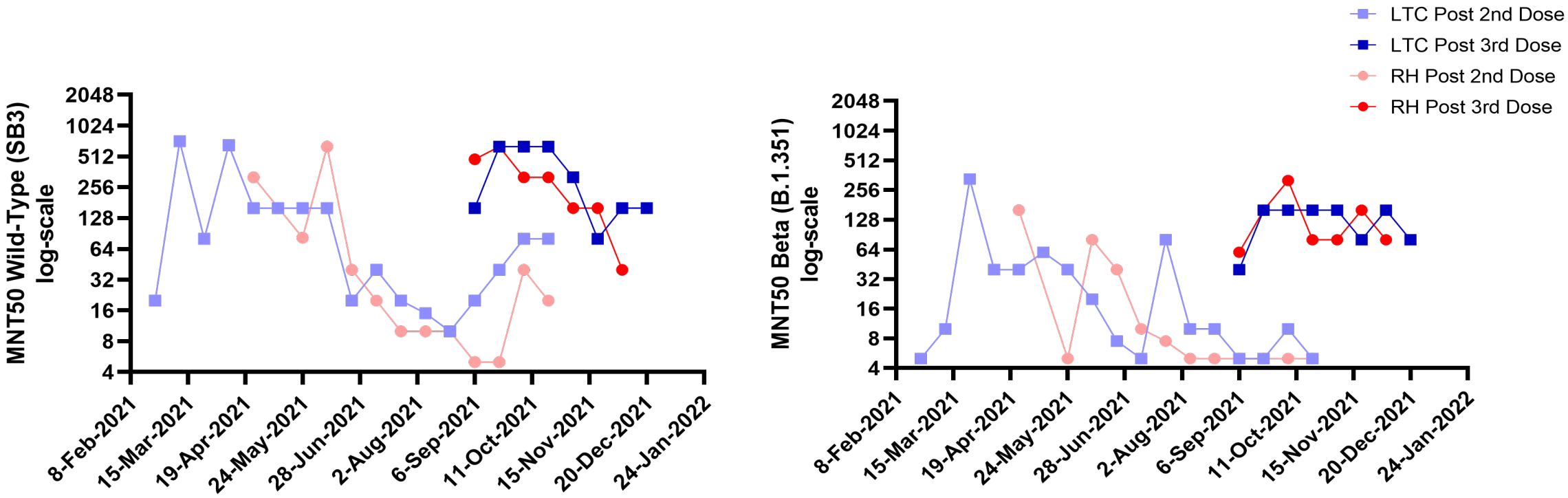


3rd dose restored declining antibodies… but subsequent decline similar to post 2nd dose trend



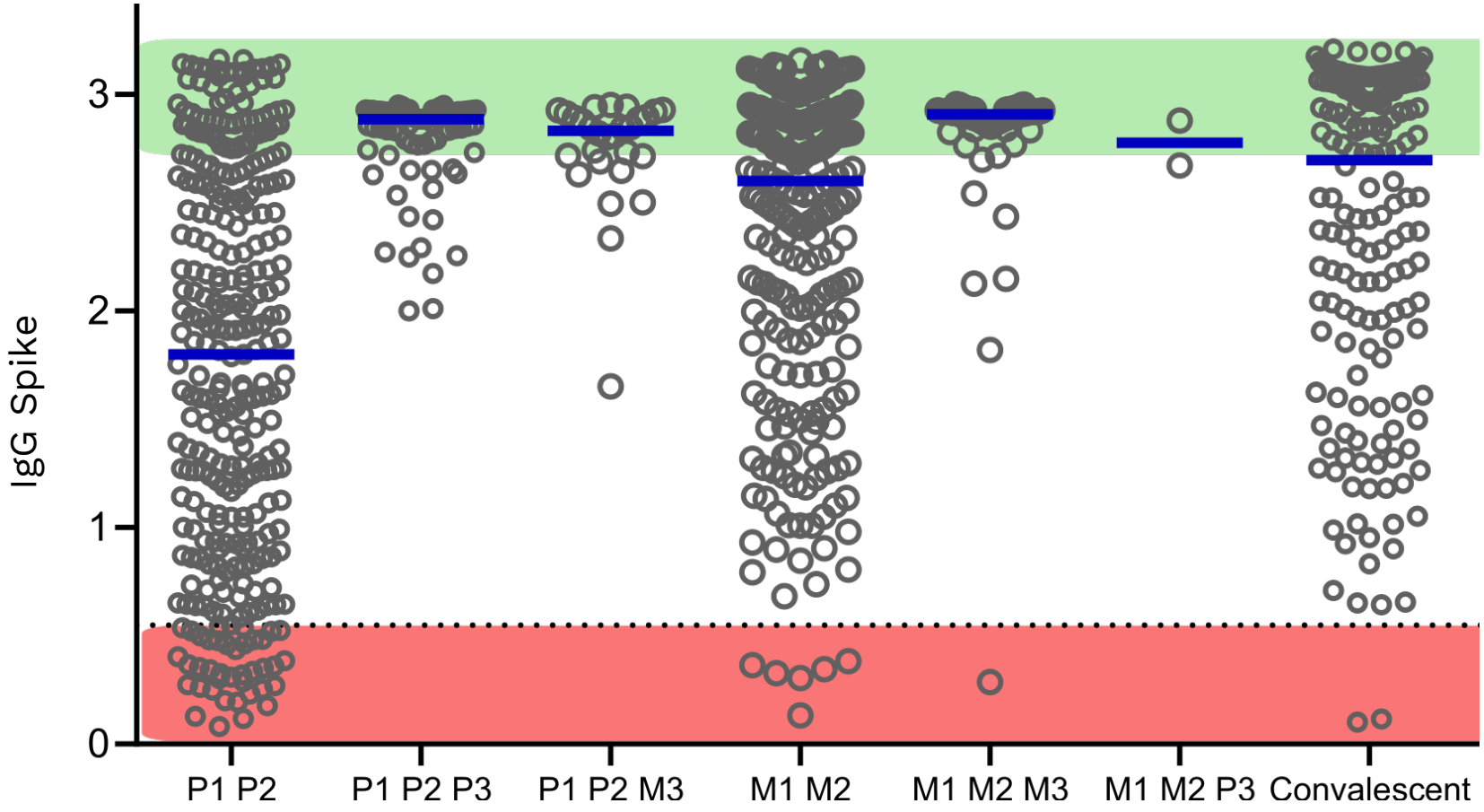
https://doi.org/10.1016/j.jamda.2021.12.035

3rd dose restored neutralizing antibodies… but decline from peak still apparent



https://doi.org/10.1016/j.jamda.2021.12.035

Three doses better than two doses & Moderna (100 mcg) provides more robust response



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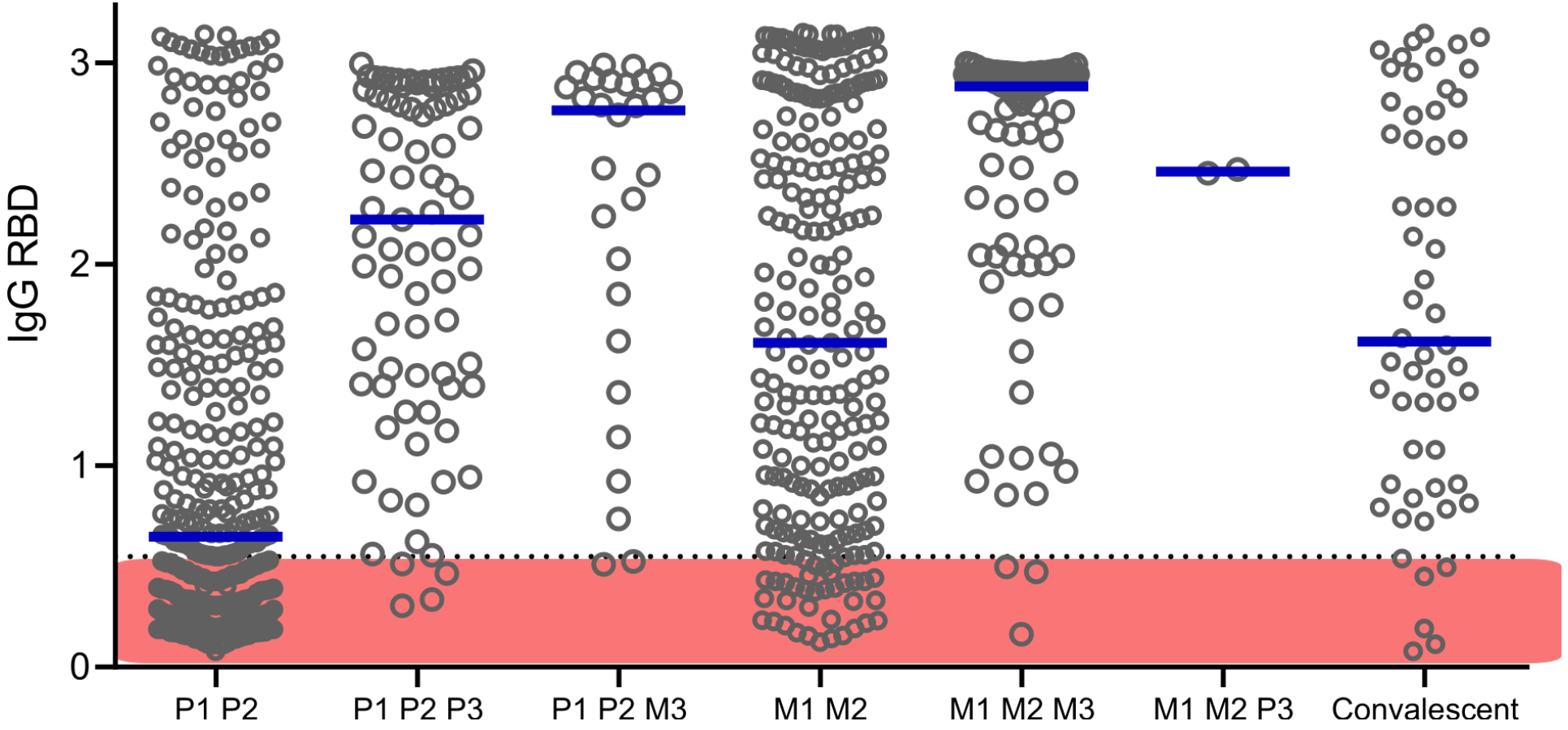
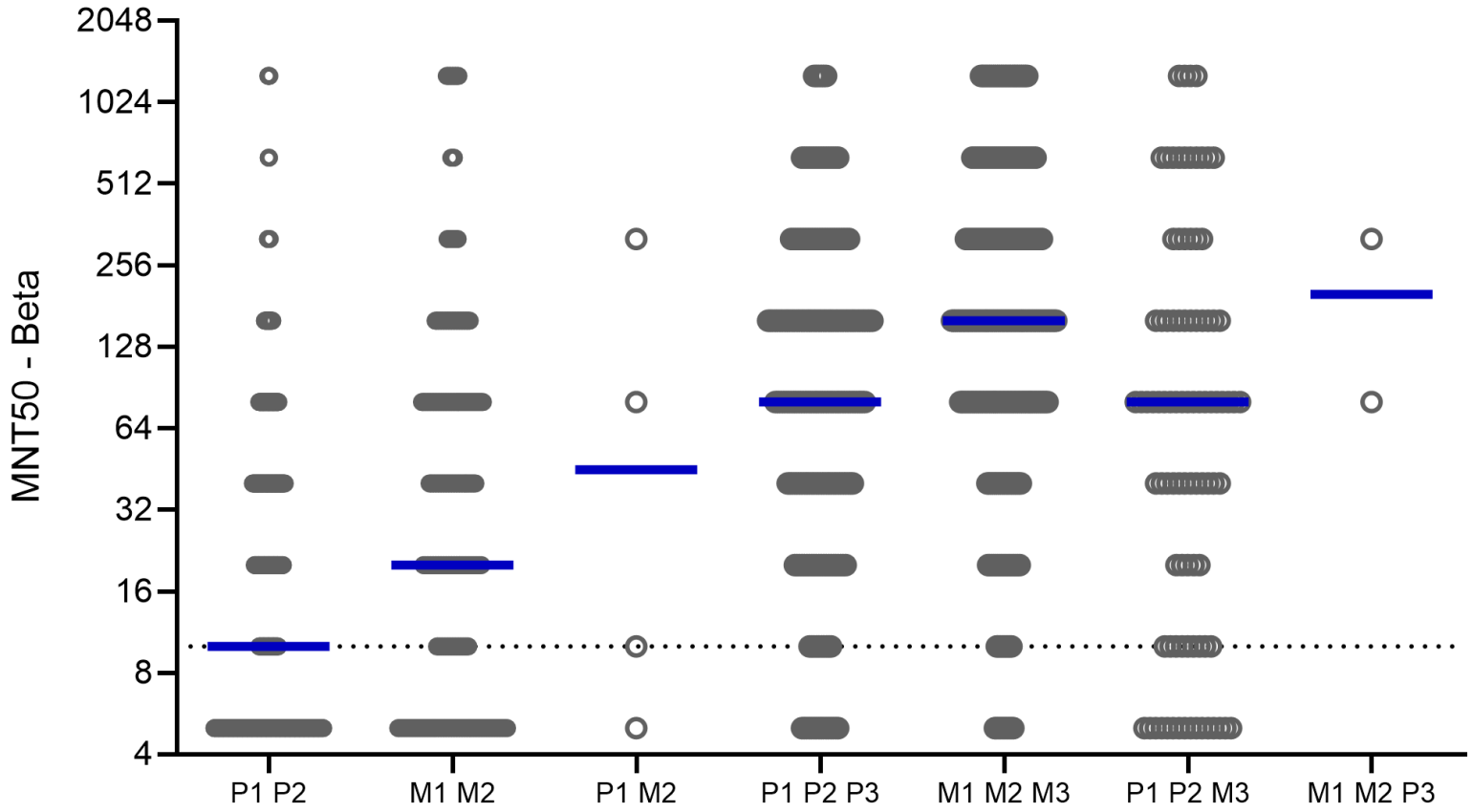


Three doses better than two doses & Moderna (100 mcg) provides more robust response



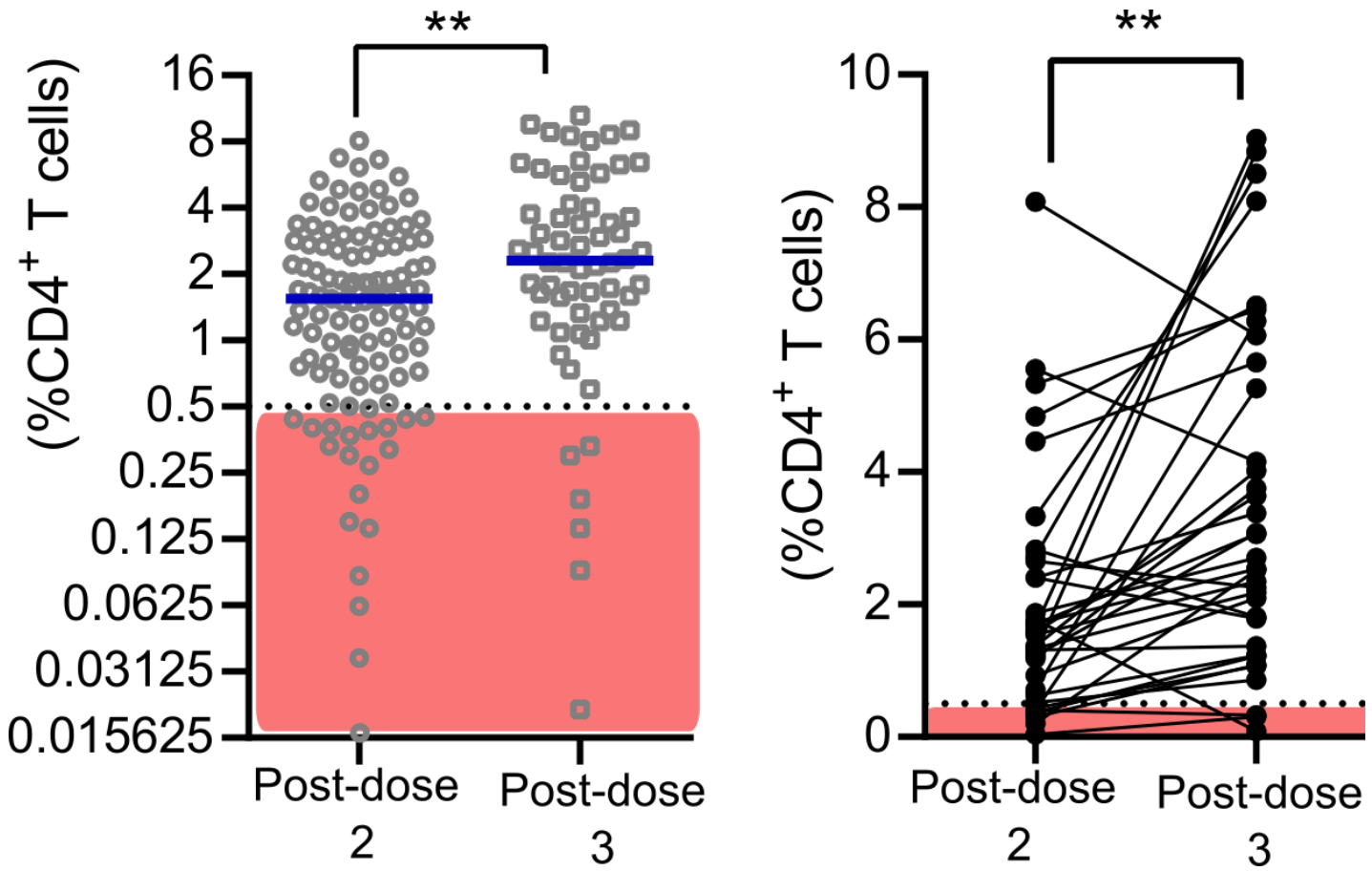
Antibody responses

- Susceptibility to infection
- Transmission

Cellular responses

- Severe infection, hospitalization & death

Cellular immunity continues to improve with more doses



Those who got 3 doses of Moderna had **more spike-specific memory CD4+ T cells** than those who had 3 doses of Pfizer.

** Differences in those with previous infection not shown*

Summary

- Improved humoral and cellular immunity post 3rd mRNA vaccine dose in nursing home and retirement homes residents
  - Moderna most recommended
- Data support equivalent polices for nursing homes and frail older adults in other congregate settings
- 4th vaccine dose expected to maintain best possible humoral and cellular immunity for Omicron threat

Our team

Immunology Team

Dr. Jessica Breznik (Cellular Immunity), Dr. Ali Zhang (Neutralization antibodies), Dr. Angela Huygh (antibody analysis), Megan Hagerman (quality assurance), Lucas Bilaver, Braeden Cowborough (technicians)

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Convalescent data courtesy of **Dr. Ishac Nazy** & team and the CONCOR-1 trial

Healthcare worker dosing schedule data courtesy of **Drs. MyLinh Duong & Darryl Leong** and the TIMING study

**unpublished & confidential*

Partners

McMaster University

Schlegel Villages

St. Joseph's Health System Elder Care

AMICA Senior Lifestyles

Shalom Village — Honouring our Fathers and our Mothers

Health Sciences North Research Institute
Institut de recherches d'Horizon Santé-Nord

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COVID-19 Immunity Task Force
Groupe de travail sur l'immunité face à la COVID-19

Prospective Evaluation of COVID-19 Vaccine in Transplant Recipients (PREVenT) COVID

All of Canada

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Disclaimer

I do not have any conflicts of interest specific to this study.

What does it mean to be “immune-compromised”?

- About 3% of Canadians may be immune-compromised
- One or more components of the immune system are weakened
- Increased risk for infection and cancer
- What can cause compromised immunity?
  - Congenital disease (primary immunodeficiency)
  - Illness: HIV/AIDS, some cancers (e.g. hematological cancers)
  - Certain immunosuppressive medications or therapies such as those used for chronic inflammatory disorders, some cancers, and **organ transplantation** (solid organ vs stem cell)

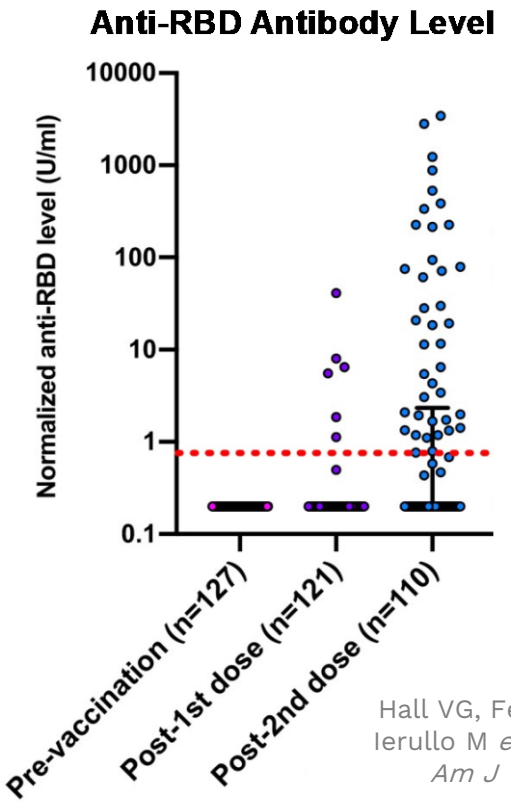
Solid organ transplant recipients (SOTR) are immune compromised and at high risk for severe COVID-19

- SOTR are often on lifelong immunosuppressive medications that cause moderate to severe impairment of antibody and cellular immunity
- More likely to have severe infections, including COVID-19
- Experience suboptimal responses to some vaccines
- Severely immunocompromised people, like SOTR, were excluded from all major vaccine trials → how do COVID vaccines work in this vulnerable group?
  - This can inform other groups that receive medical immunosuppression

SOTR mount suboptimal immune responses to two doses of mRNA vaccine

- We assessed immune responses in SOTR receiving two doses of Moderna[1]:
  - 34.5% (38/110) of SOTR were positive for anti-RBD antibodies
  - 26.9% had virus neutralizing antibodies
  - 47.9% had a positive (polyfunctional) CD4+ T-cell response
  - Response estimates for the general public with 2 doses: >90%

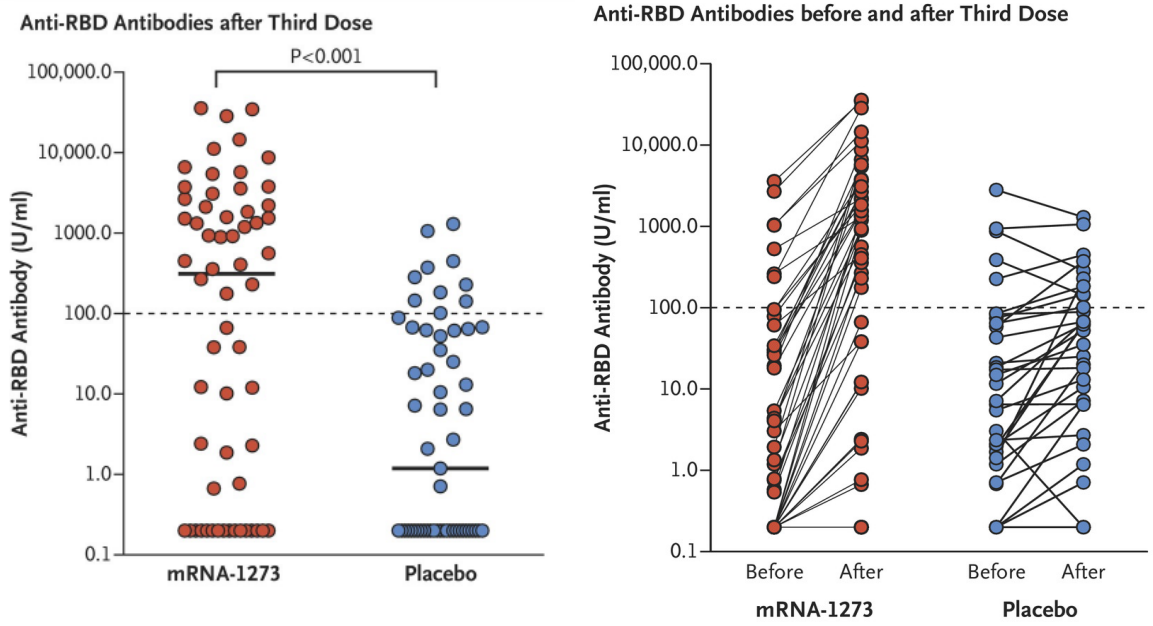
Compared to the vaccinated general public, SOTR with two doses had **82x higher risk** of breakthrough infection, **485x higher risk** of hospitalization/death[2]



Hall VG, Ferreira VH, Ierullo M *et al.*, 2021; *Am J Transplant*

Vaccine responses improve with three doses of mRNA vaccine in SOTR

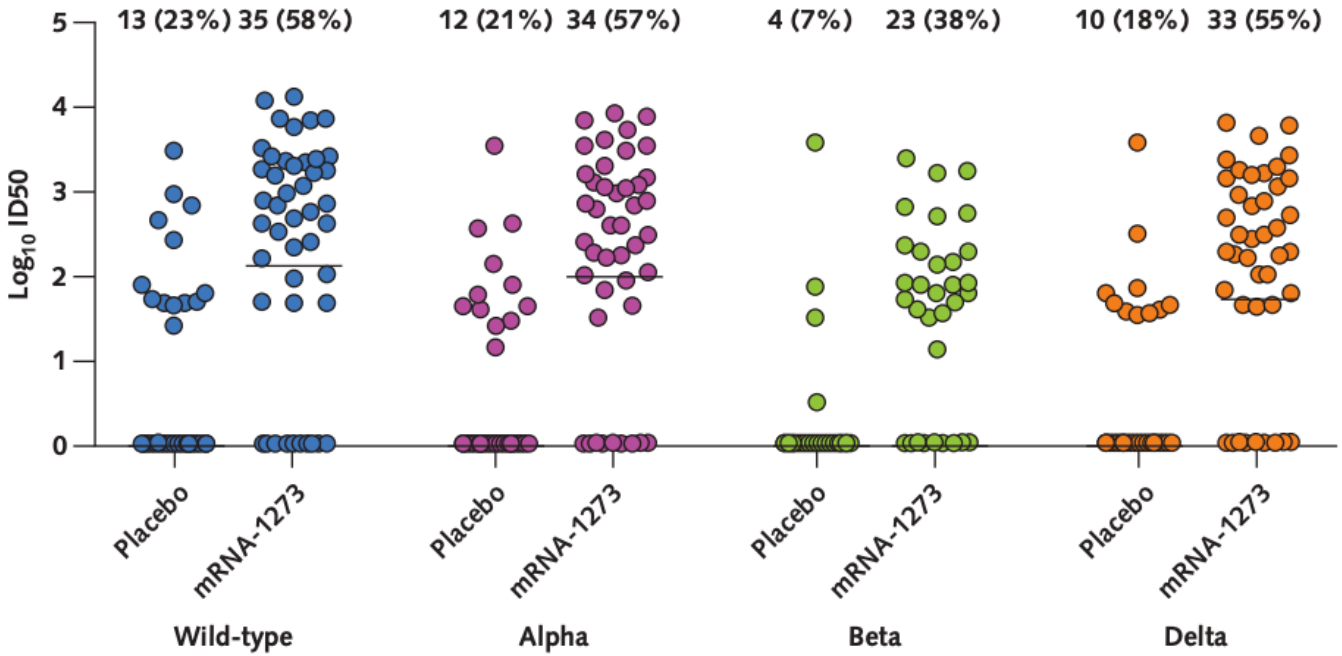
- We performed a double blind, randomized control trial to evaluate the safety and immunogenicity of a 3rd dose of Moderna in SOTR
- Improvement in all parameters measured, including:
  - 55% (31/60) were positive for anti-RBD antibodies vs 18% (10/57) in placebo group
  - Spike-specific polyfunctional CD4+ T-cell frequency increased 6X



Hall VG, Ferreira VH, Ku T *et al.*, 2021; *N Eng J Med*

Three doses of mRNA vaccine significantly increased neutralizing antibodies against variants of concern

Three doses **significantly increased** neutralizing antibodies including vs. Alpha, Beta, Delta[4]



Kumar D, Ferreira VH, Hall VG *et al.* 2021, *Ann Intern Med*

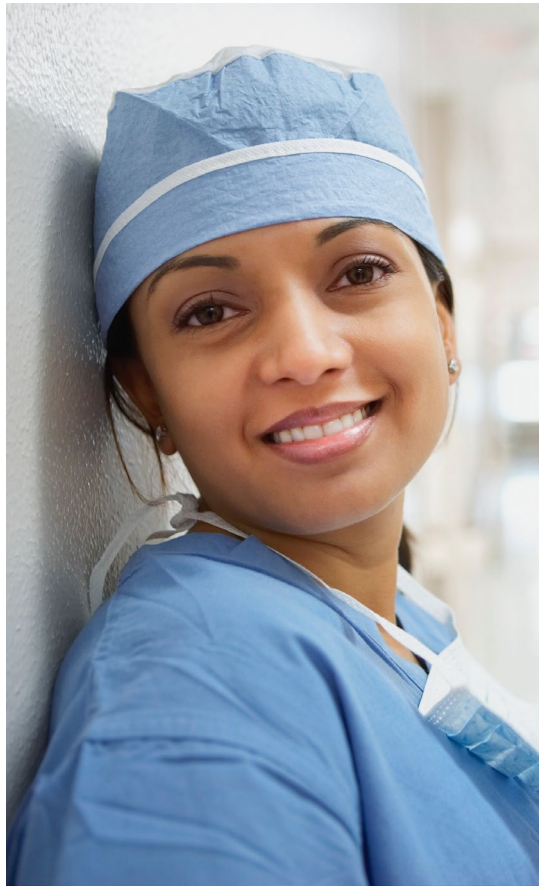
Summary and Next Steps

- Three doses complete the primary series of vaccination for SOTR, but these responses are still lower compared to the general public with 2-3 doses
- Preliminary observation: under 20% of SOTR were positive for neutralizing antibodies targeting Omicron after three doses

- Therefore, additional vaccine strategies may be needed:
  - 4th doses
  - Preventive monoclonal antibodies
  - Different vaccine platforms
- National collaborative research study: *Prospective Evaluation of COVID-19 Vaccine in Transplant Recipients: A National Strategy* - **PREVenT COVID** (Project Lead: Dr. Deepali Kumar, MD (UHN))
  - Pediatric, adult solid organ and hematopoietic stem cell transplant recipients

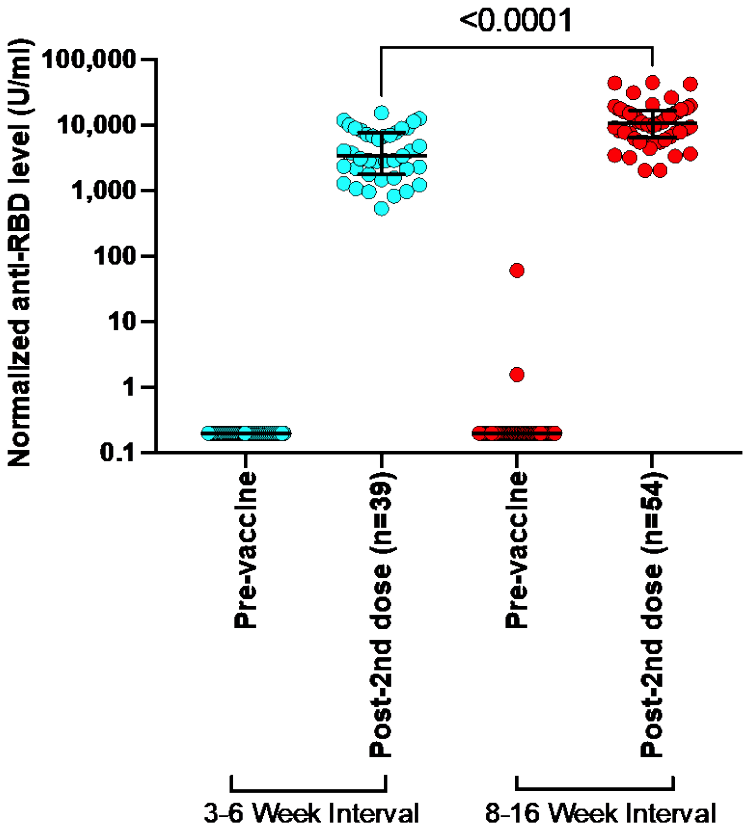
Immunogenicity of standard vs delayed interval dosing in healthcare workers

- The manufacturer recommended interval between 1st and 2nd doses of mRNA vaccines is 3-4 weeks
- Canada announced 4-month delay between doses in March 2021
- We compared immune responses in healthcare workers (HCW) receiving the Pfizer vaccine:
  - Standard (3-6 week) vs. delayed (8-16 week) interval between doses
  - Accepted for publication in *Nature Immunology*[5]



Delayed Pfizer vaccination enhanced antibody immunity and induced robust T-cell responses in HCW

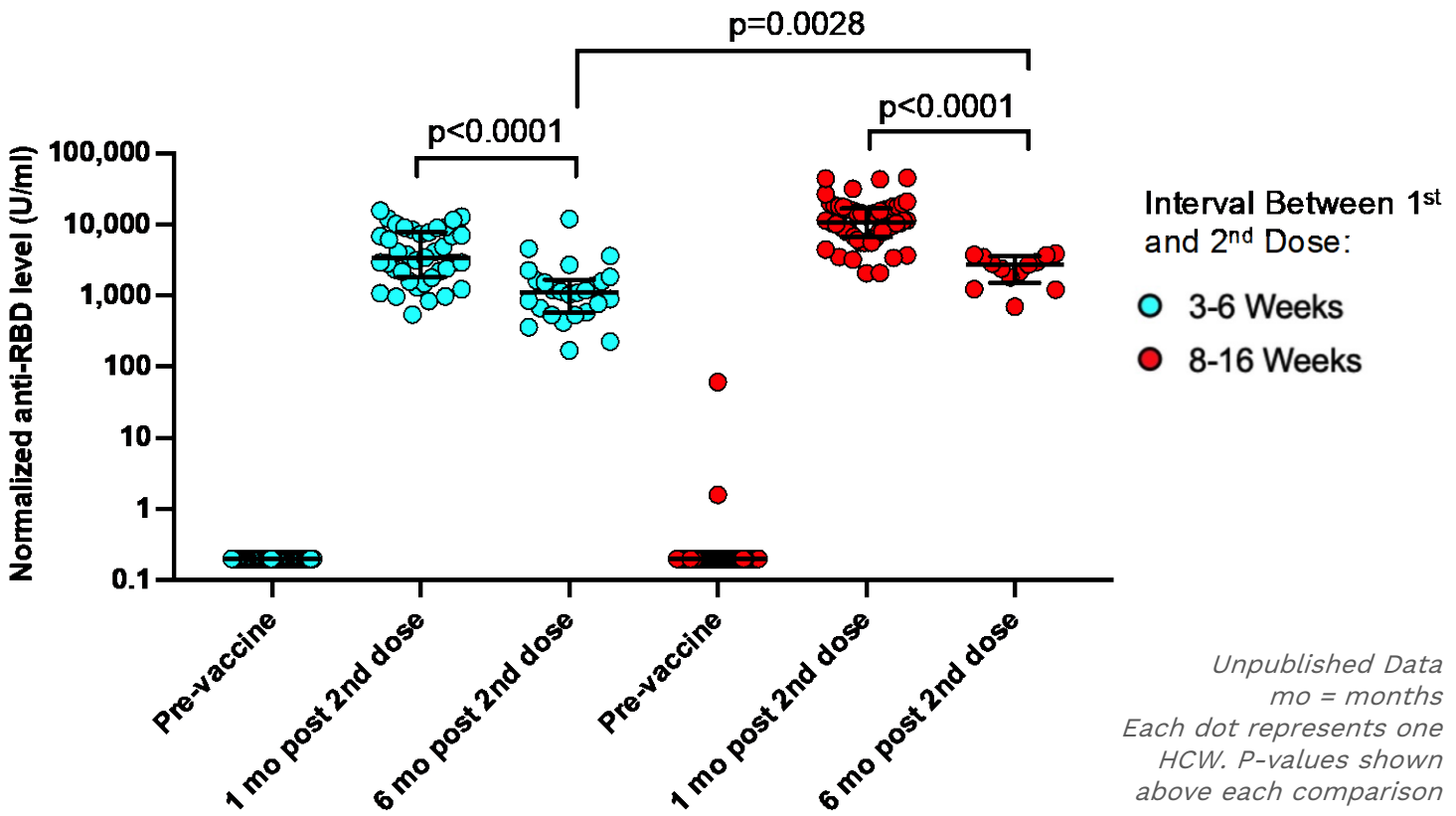
- Most HCW were positive for anti-RBD antibodies
  - Antibody levels were approximately 3.2x higher in the delayed-interval group
- Most HCW were positive for neutralizing antibodies, including those targeting VOCs
  - Alpha, Beta and Delta
- T-cell responses were mostly similar regardless of dosing interval, but some evidence of lower CD4 T-cell detection in the delayed group



Hall VG, Ferreira VH, Wood H *et al* 2022, *Nat Immunol*

Durability of anti-RBD antibody response with standard vs delayed interval dosing in HCW

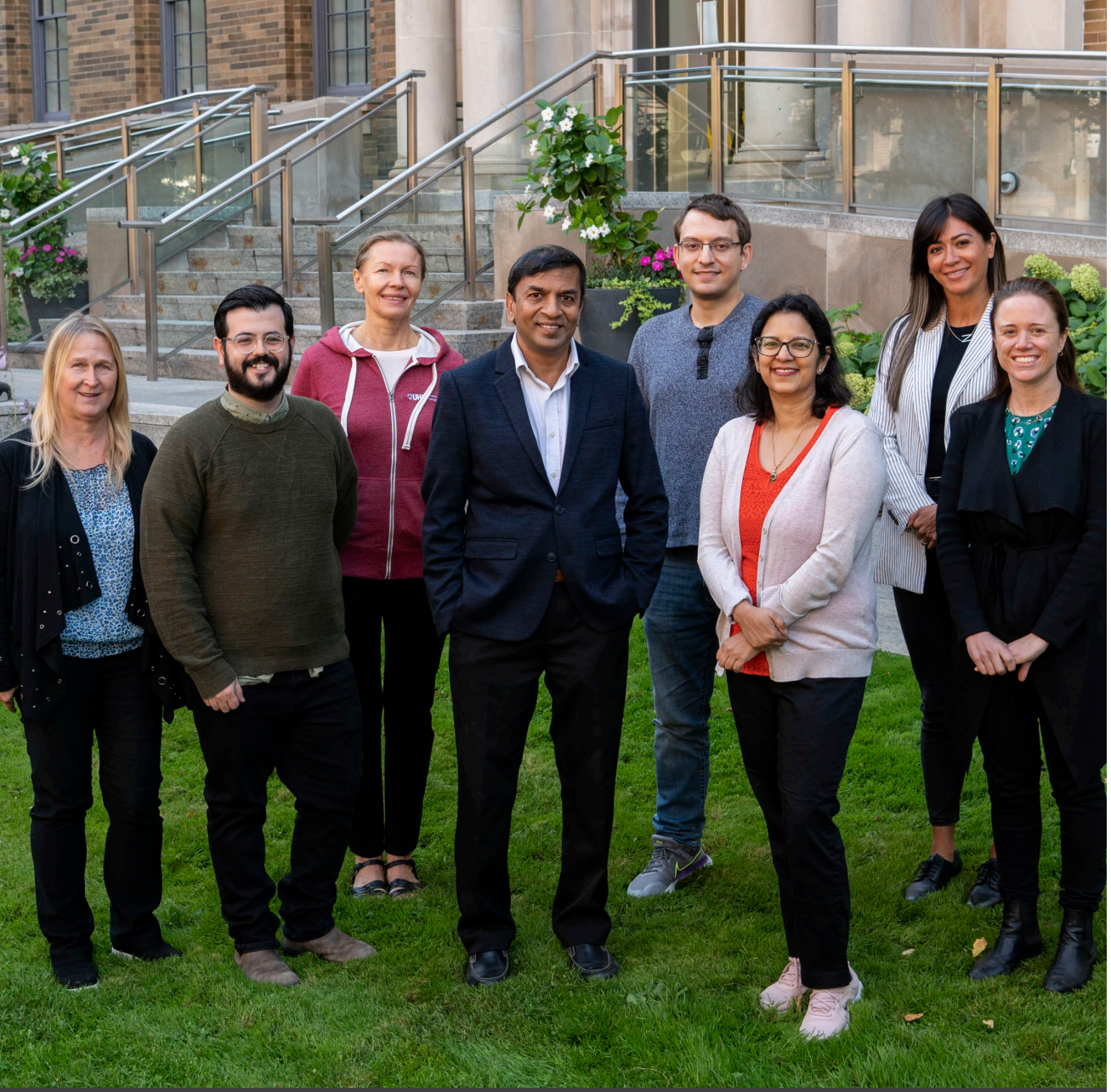
- We measured antibody levels at 1 and 6 months post vaccination in HCW
- Antibody levels declined between 1 and 6 months
- Anti-RBD antibody positivity was unchanged
- Anti-RBD antibody levels in delayed group still higher at 6 months



Unpublished Data
mo = months
Each dot represents one HCW. P-values shown above each comparison

Summary and next steps

- Delayed dosing strategies for Pfizer in healthcare workers resulted in **higher antibody responses**, including neutralizing antibodies, and robust T cell responses
- At 6-months post-second dose:
  - Antibody levels do decline, but antibody positivity is unchanged
  - Antibody levels in delayed group greater at 6 months post second dose
- Next steps: Omicron testing, long term-durability, role of boosters



Left to right: B Majchrzak-Kita, V Ferreira, I Bahinskaya, A Humar, M Ierullo, D Kumar, N Pinzon, V Hall

Study Team

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Laval: Dr. Sacha De Serres
SickKids: Dr. Upton Allen

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UHN Ajmera Transplant Centre

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1. Hall VG, Ferreira VH, Ierullo M et al. (2021). Humoral and cellular immune response and safety of two-dose SARS-CoV-2 mRNA-1273 vaccine in solid organ transplant recipients. *Am J Transplant,* 21(12):3980-9.

2. Qin C, Moore LW, Anjan S et al. (2021). Risk of Breakthrough SARS-CoV-2 Infections in Adult Transplant Recipients. *Transplantation*, 105(11), e265-6.

3. Hall VG, Ferreira VH, Ku T et al. (2021). Randomized Trial of a Third Dose of mRNA-1273 Vaccine in Transplant Recipients. *N Engl J Med,* 385:1244-6.

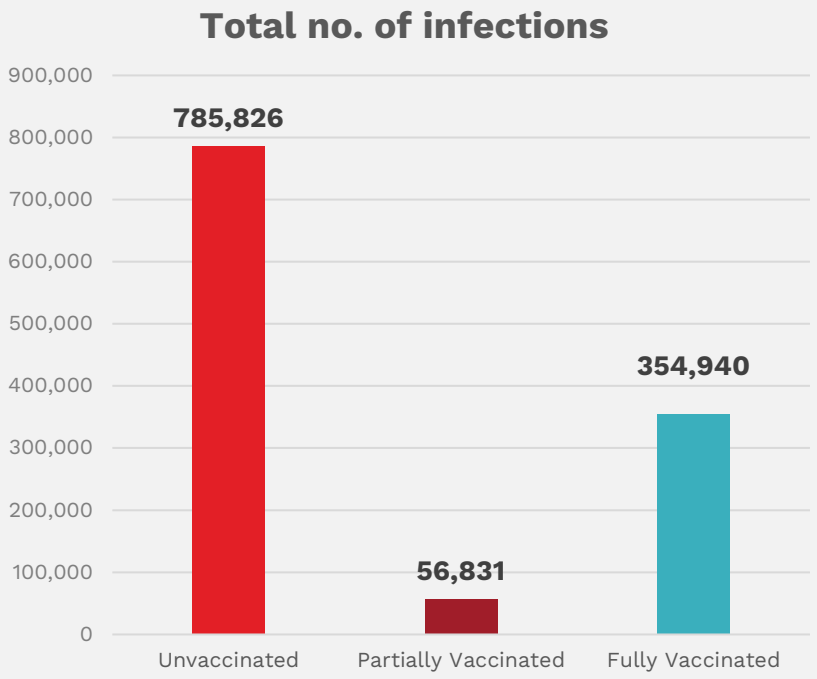
4. Kumar D, Ferreira VH, Hall VG et al. (2021). Neutralization of SARS-CoV-2 Variants in Transplant Recipients After Two and Three Doses of mRNA-1273 Vaccine: Secondary Analysis of a Randomized Trial. *Ann Intern Med,* doi: 10.7326/M21-3480

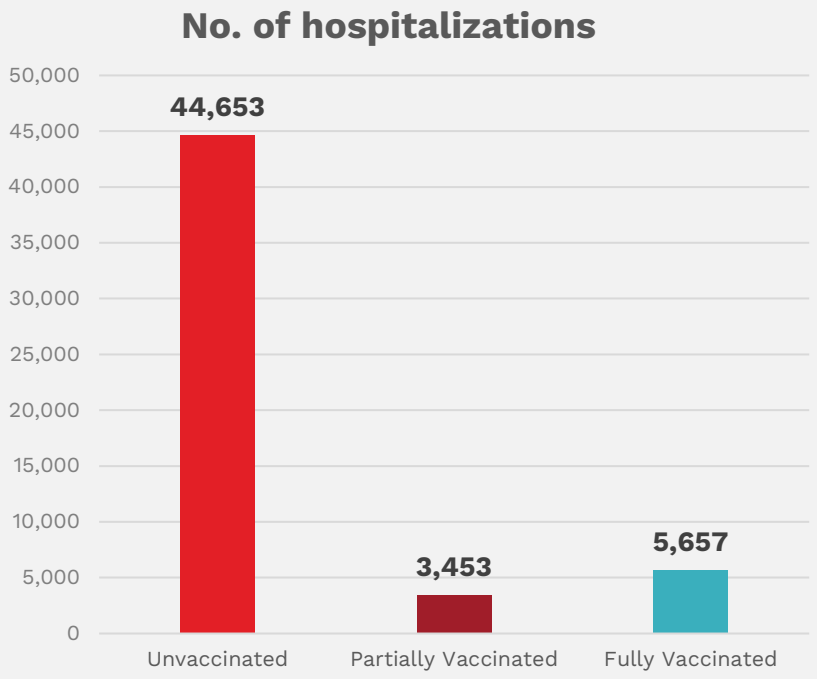
5. Hall VG, Ferreira VH, Wood H et al. (2022). Delayed interval BNT162b2 mRNA COVID-19 vaccination enhances humoral immunity and induces robust T-cell responses. *Nat Imm*. Accepted.

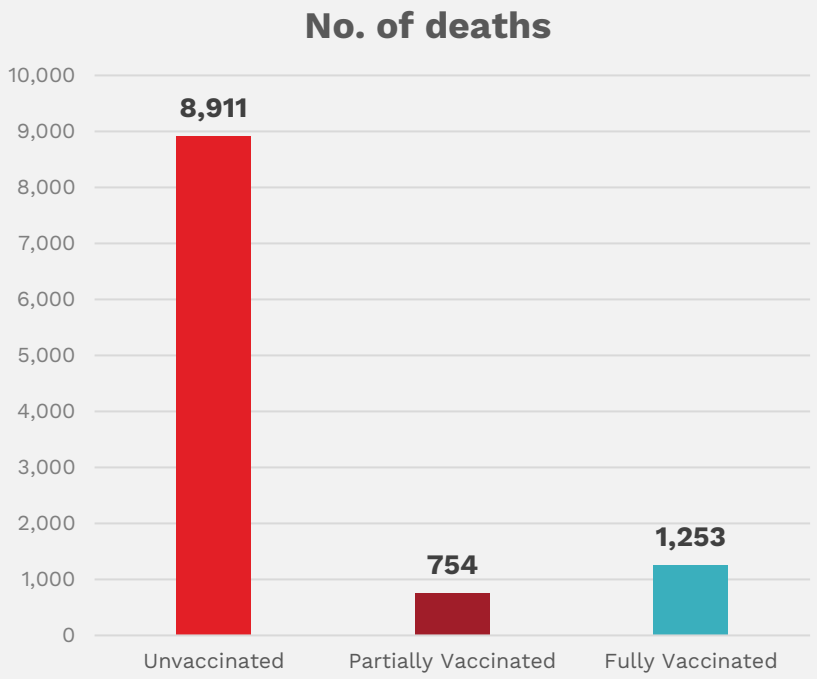
Timothy Evans

MD, PhD, COVID-19 Immunity Task Force
Executive Director

COVID-19 vaccines have been lifesavers







The unvaccinated have a **66% greater chance** of getting infected

The unvaccinated have an **83% greater chance** of getting very sick

The unvaccinated have a **82% greater chance** of dying

Number of confirmed COVID-19 cases reported to PHAC by vaccination status December 20, 2020-January 01, 2022
Source: https://health-infobase.canada.ca/covid-19/epidemiological-summary-covid-19-cases.html

Key findings: vaccines have prevented infection and transmission – more so prior to Omicron

- 8 months post-dose 2 (not including Omicron) (Kwong):
  - VE against severe disease remained **above 95%**
  - VE against infection **declined to 71%**
- Within 7 days of 3rd dose, VE against infection **recovered to 93%** (Kwong)
- 3rd dose vs. Omicron (Kwong):
  - 95% protection from **severe disease**
  - 61% protection from **symptomatic infection**

3rd dose/boosters have helped to improve immune protection, especially for those at risk

- 3rd dose/booster improved all parameters of immunity amongst SOTR against the Alpha, Beta, and Delta variants (Kumar/Ferreira)
- Booster doses provided better neutralization against SARS-CoV-2 variants in LTC residents (Bowdish/Costa)
- Boosters are required for all adults several months past dose 2 as a decline in VE is observed 2 months after dose 2, and continues over the subsequent 6 months (Kwong)

Factors to consider

- **Dose Interval:** Protection from infection risk is higher in HCWs who had a longer dose interval compared to HCWs who had a shorter interval (Kumar/Ferreira)
- **Time since 2nd dose** determines risk of infection more than SARS-CoV-2 lineage or initial dosing interval (Kwong)
- **Vaccine type matters:** Antibody quality & quantity was higher/longer and memory CD4+ T cells were higher among LTC residents who received Moderna vs. Pfizer (Costa/Bowdish)

Research to support policy

- Current Canadian policy promoting universal vaccination remains fully supported by research
- Booster doses for all adults beginning with those at greatest risk is also supported by the latest research
- Omicron wave reinforces universal vaccination and boosters but given high rates of infection and transmission must be accompanied by public health measures to decrease risk of infection/transmission.

Gaps in our knowledge

- Further research required to find out:
  - Whether and when boosters should be recommended for children and teens
  - Whether, when, and for whom additional or regular boosting will be required once SARS-CoV-2 becomes endemic
- CITF has studies in the field looking at these questions
- Policymakers will continue to be updated as data emerges

You'll find our summary of this seminar at

covid19immunitytaskforce.ca

Questions?

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