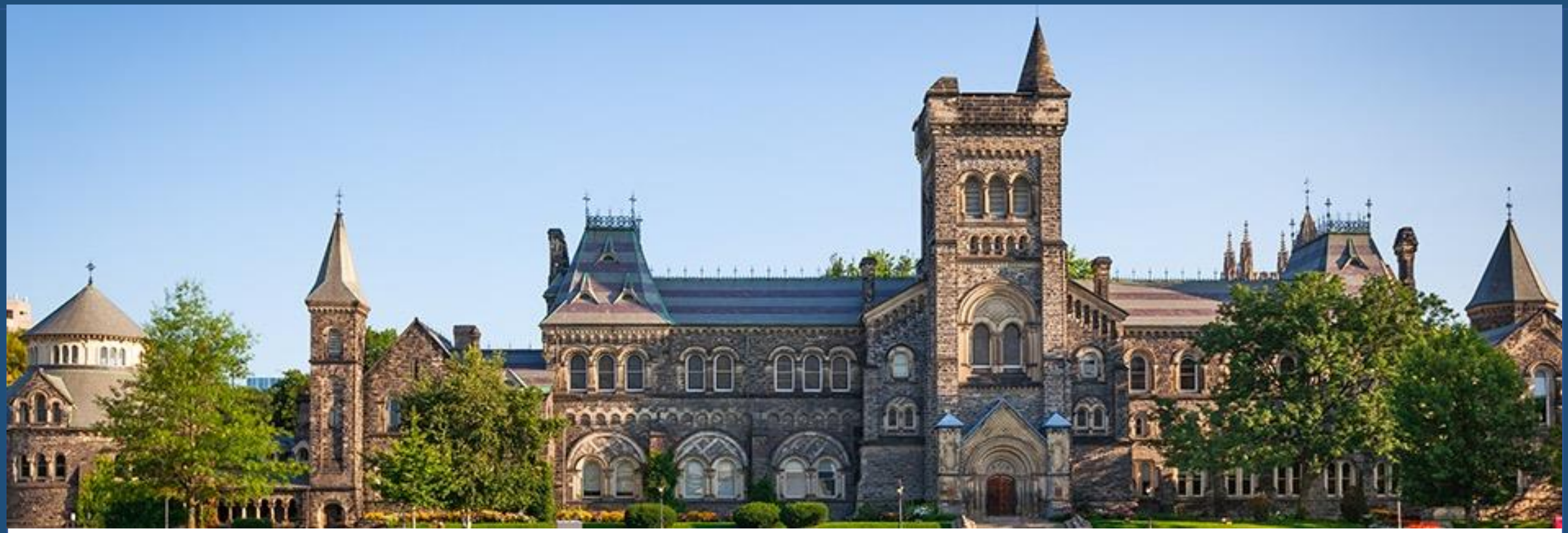


Omicron breakthrough infection induces superior mucosal and humoral immunity to SARS-CoV-2 variants than booster vaccination

Gommerman and Decaluwe labs

CITF meeting session 3.1; 9th March, 2023

@Jengommerman

UNIVERSITY OF TORONTO

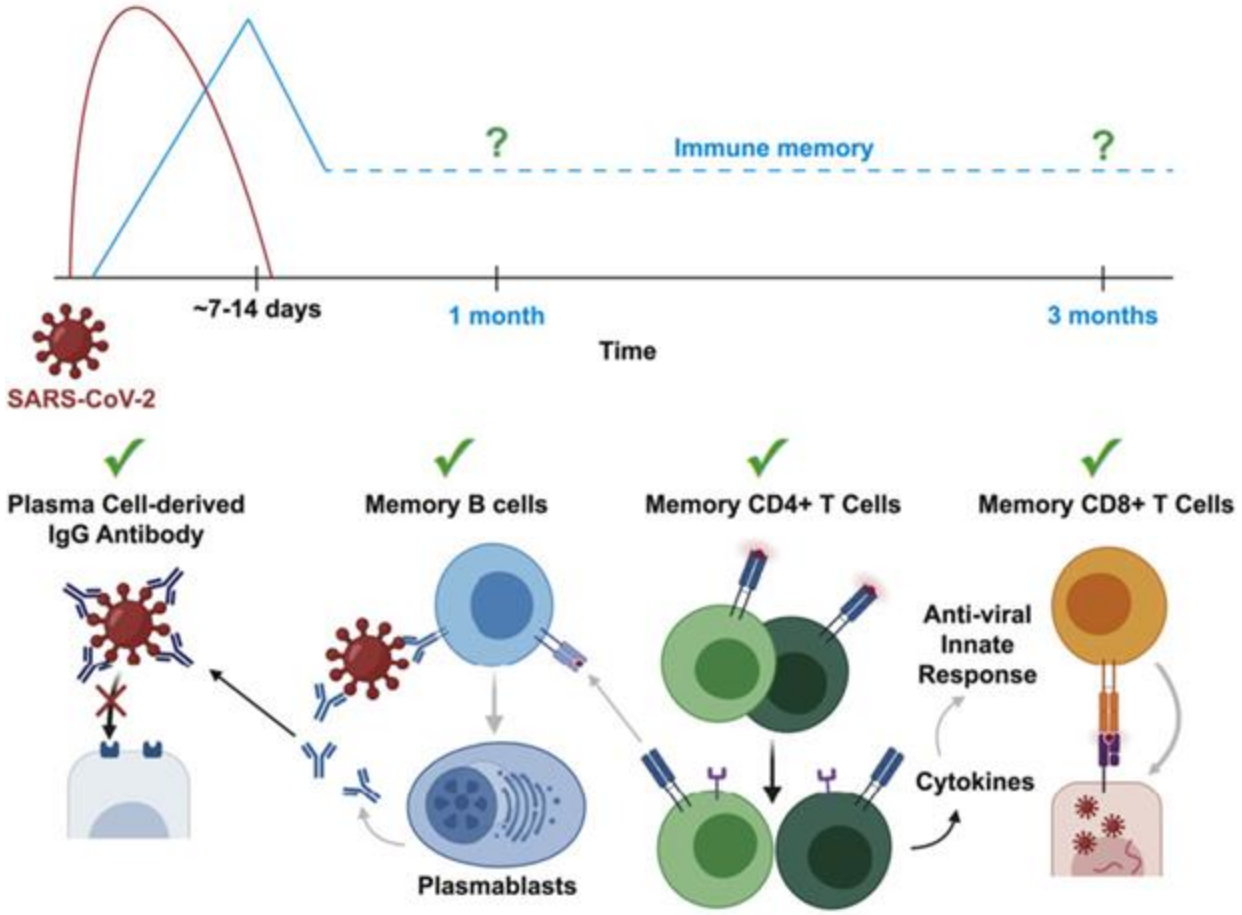
Université de Montréal

CoVaRR-Net

Immunity to SARS-CoV-2

Infection with SARS-CoV-2 results in:

- Memory B and T cells in the blood
- Plasma cells in the bone marrow
- Mucosal immune response?



Rodda et al, Cell 2021

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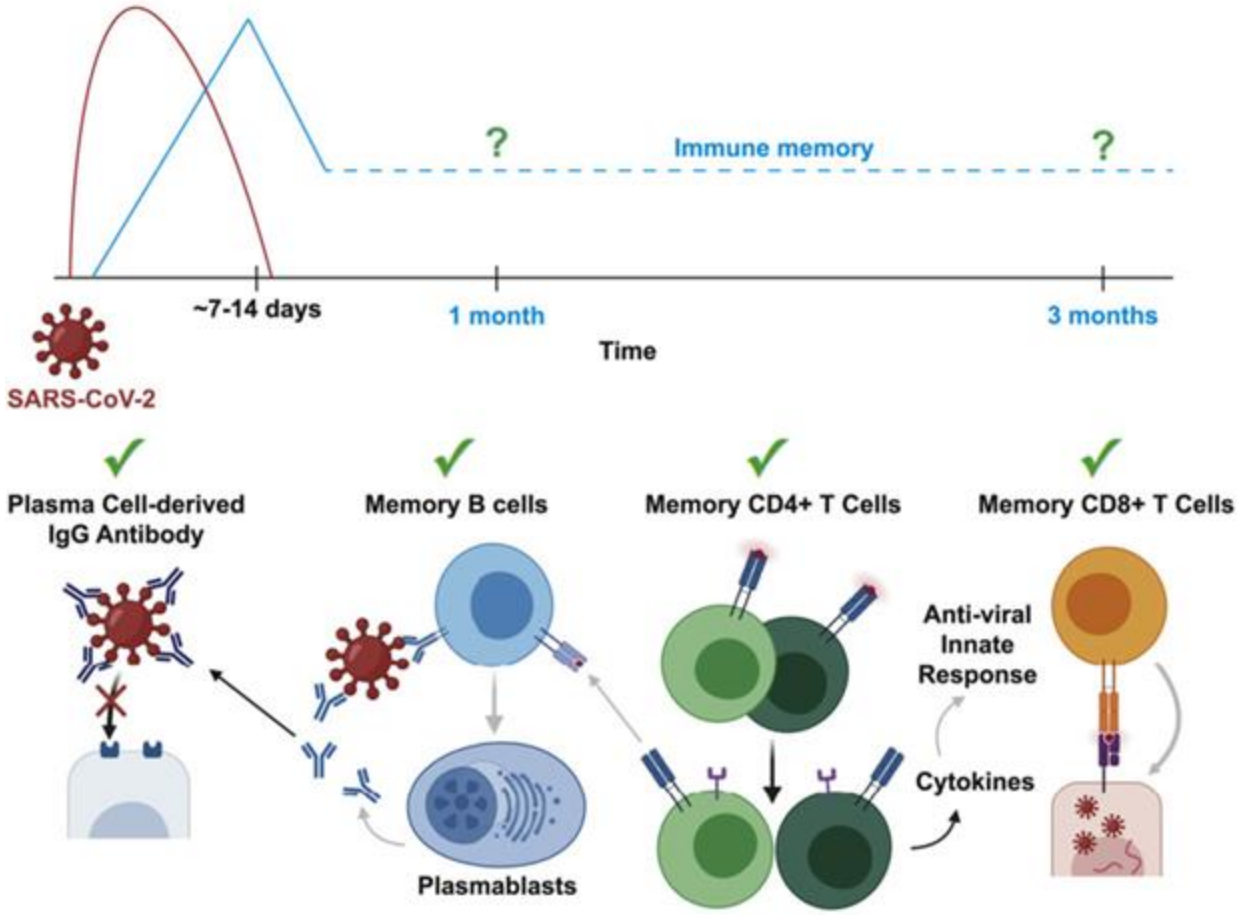
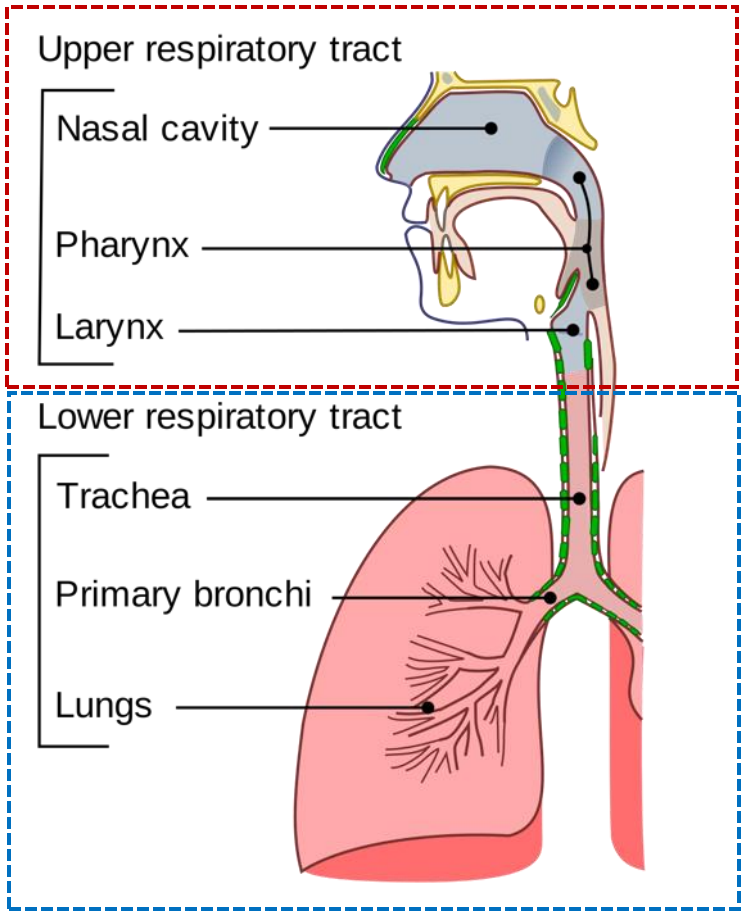


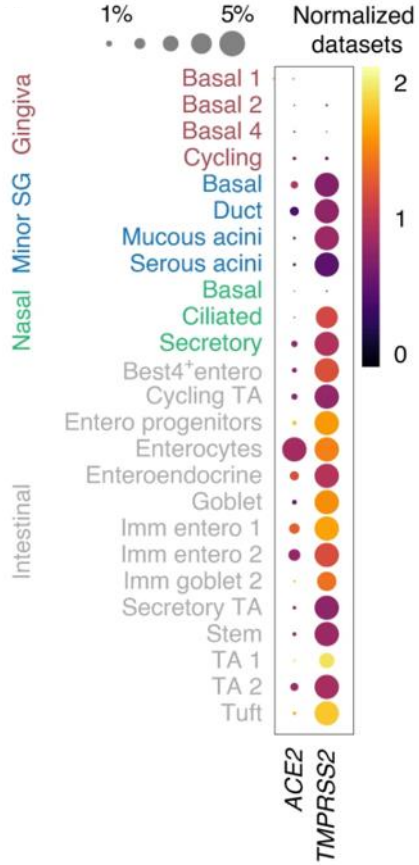
Rodda et al, Cell 2021

Where does SARS-CoV-2 infection occur?

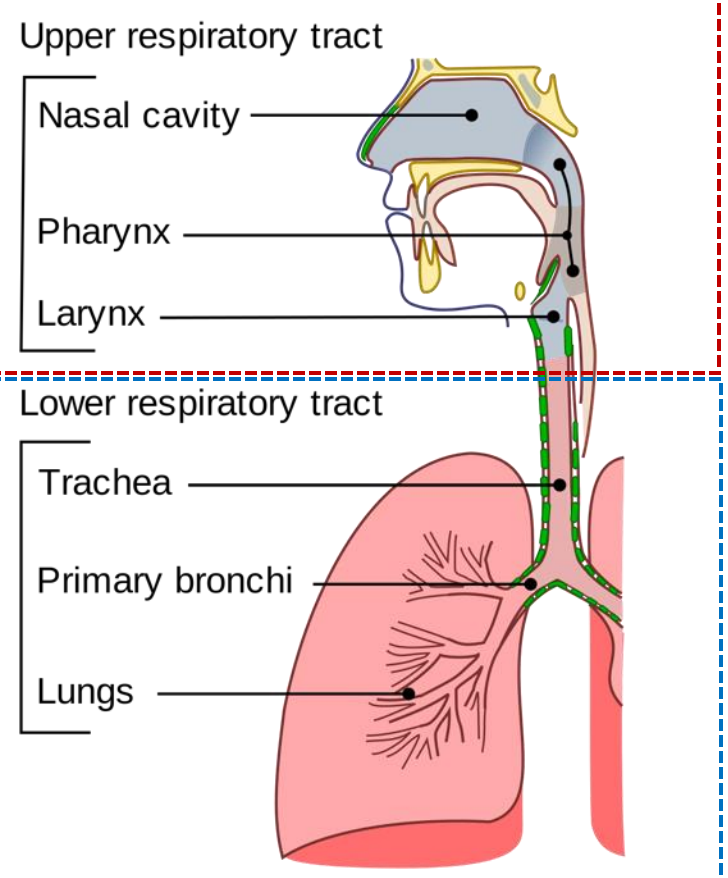
- SARS-CoV-2 initially infects the *upper respiratory tract* (Tay *et al*., 2020)



- Cellular targets (*coexpress ACE-2 and TMPRSS*):
  - Airway epithelial cells, alveolar epithelial cells, vascular endothelial cells
  - Salivary gland duct epithelial cells (Liu *et al*., 2011)
  - Minor salivary gland epithelia (Huang *et al*., 2021)



Today's Talk:



- SARS-CoV-2 initially infects the upper respiratory tract

Question: What does the salivary Ab response look like?

- COVID-19 vaccines are injected via the parenteral route

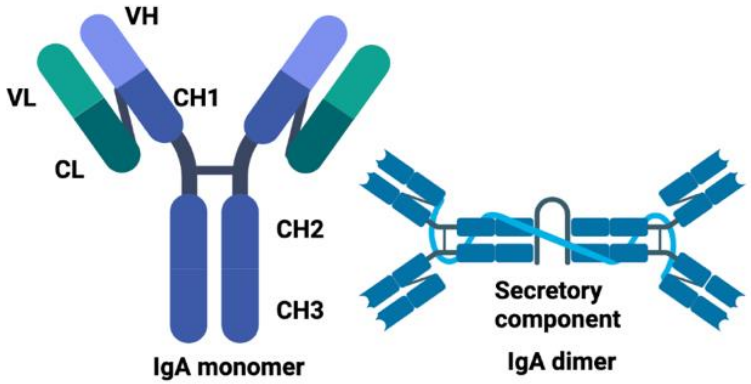
Question: Do they elicit any immunity in the URT?

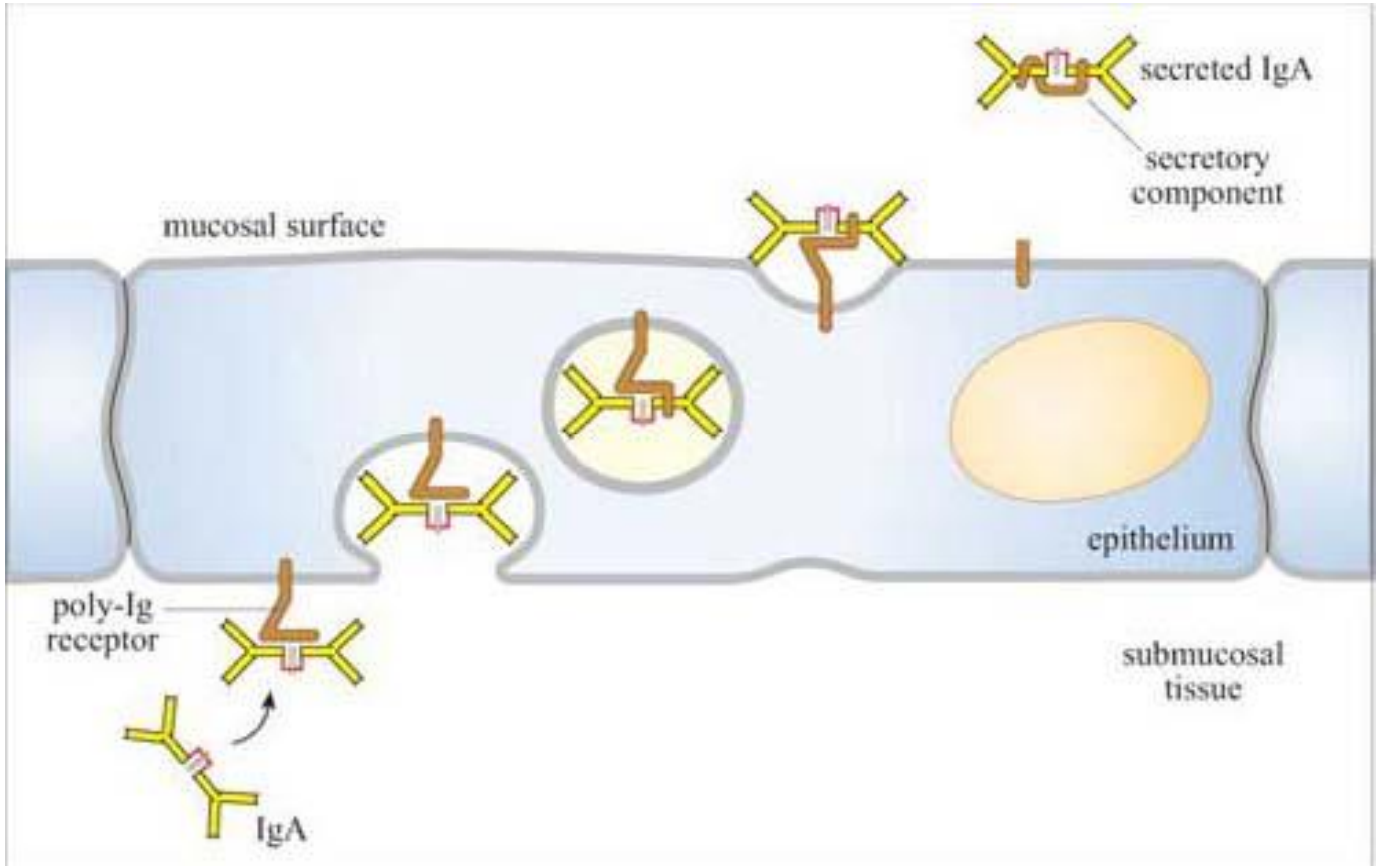
- Many people have had systemic vaccination AND infection

Question: How does this impact systemic and mucosal immunity?

Antibody production at mucosal surfaces

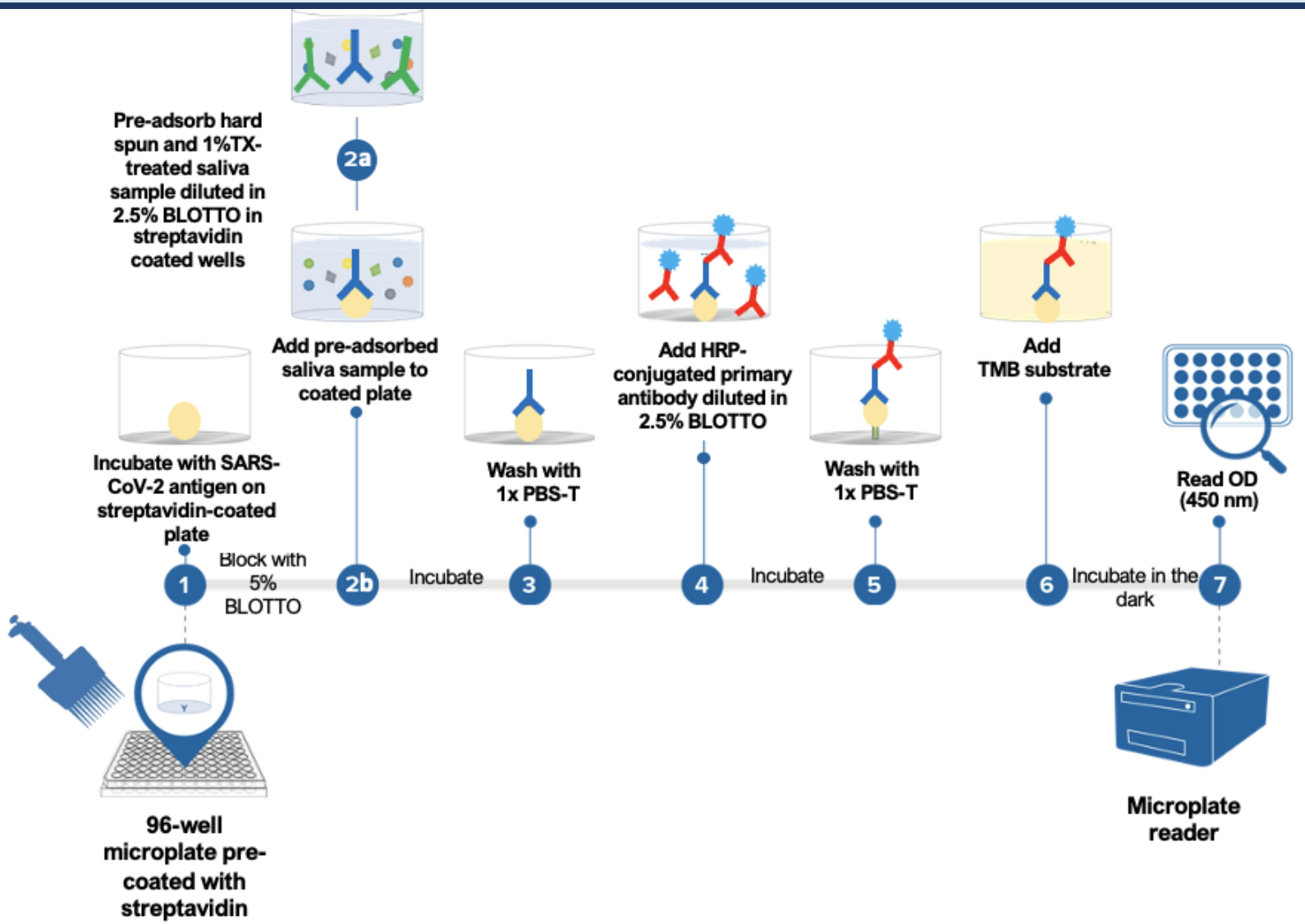
- At steady state, IgA is directed at the commensal microbiota
- Mucosal viral infections (enteric, airway) also provoke IgA
- IgA have potent neutralizing activity: Potential for sterilizing immunity





Sterlin et al, Science 2021

Measuring mucosal Ab to SARS-CoV-2



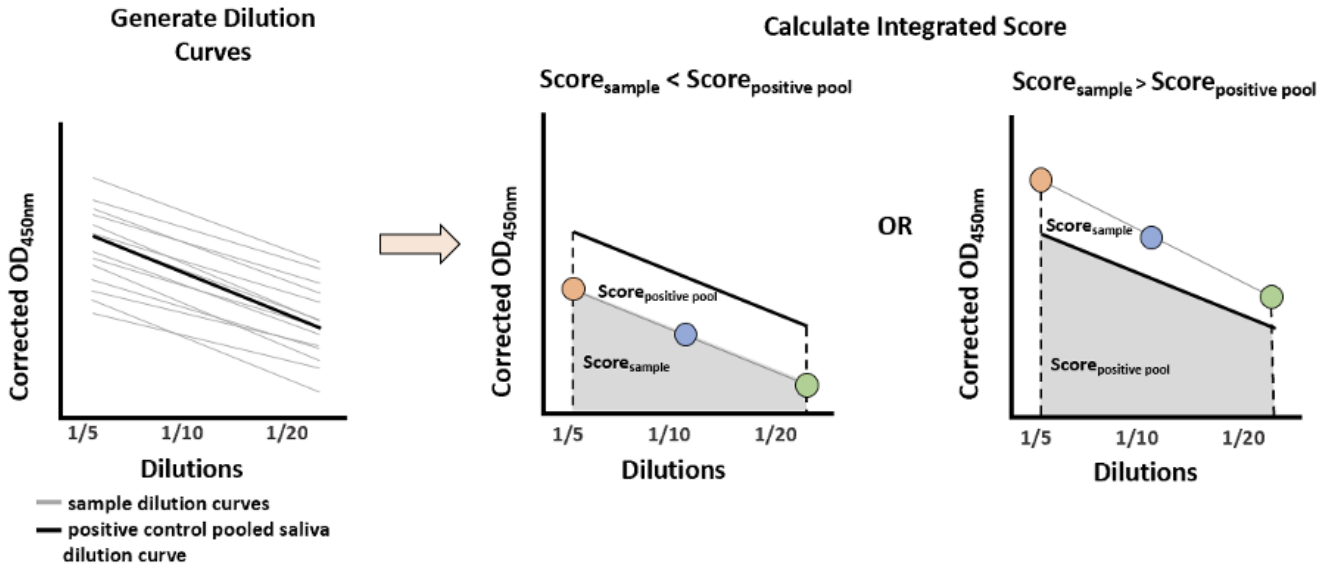
Measuring mucosal Ab to SARS-CoV-2

Plate each saliva sample into 4 wells:

1. No antigen and saliva at 1/5 dilution
2. With antigen and saliva at 1/5 dilution
3. With antigen and saliva at 1/5 dilution
4. With antigen and saliva at 1/5 dilution

Subtract background

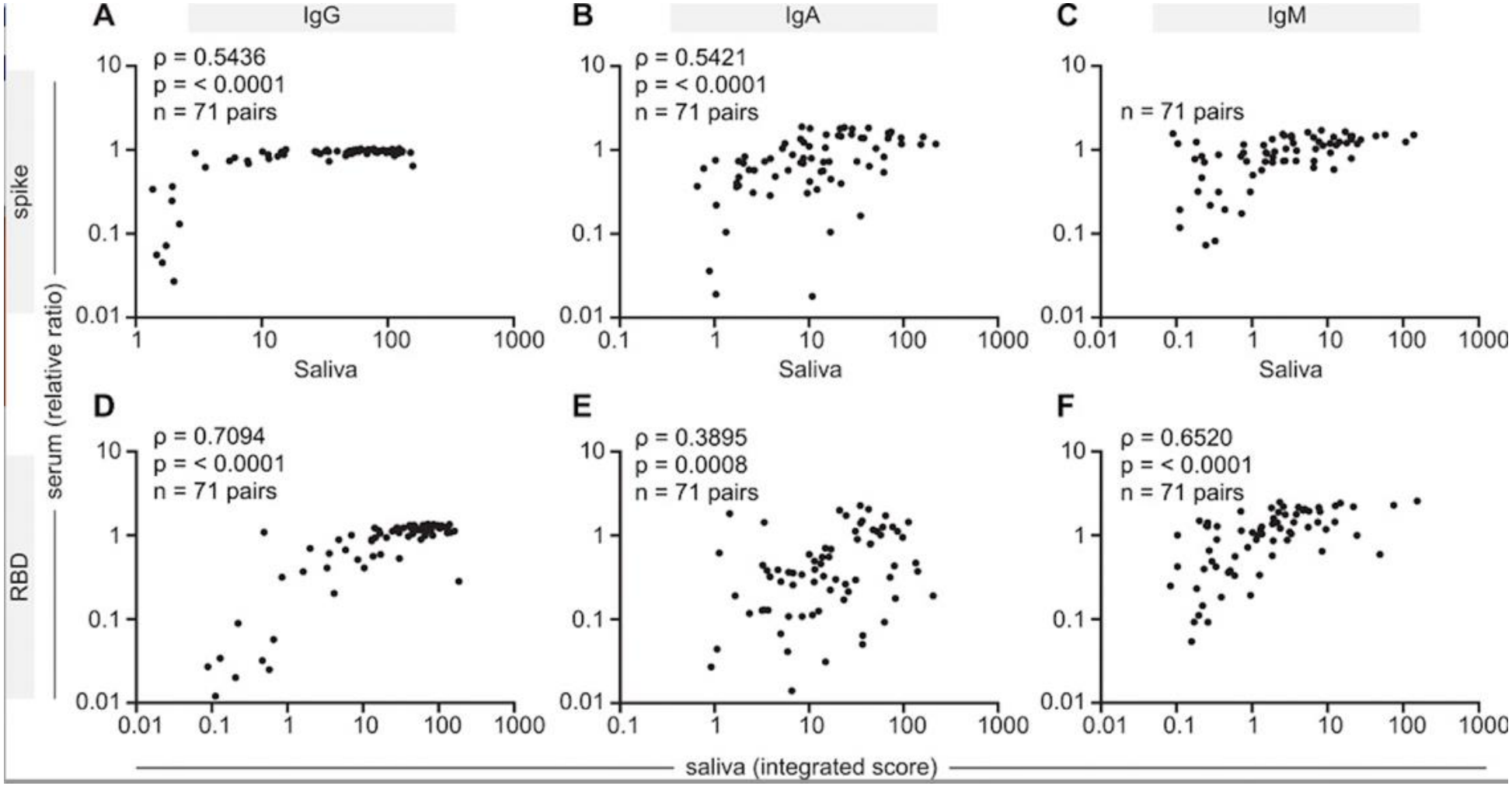
1/5 value
1/10 value
1/20 value



For each sample:

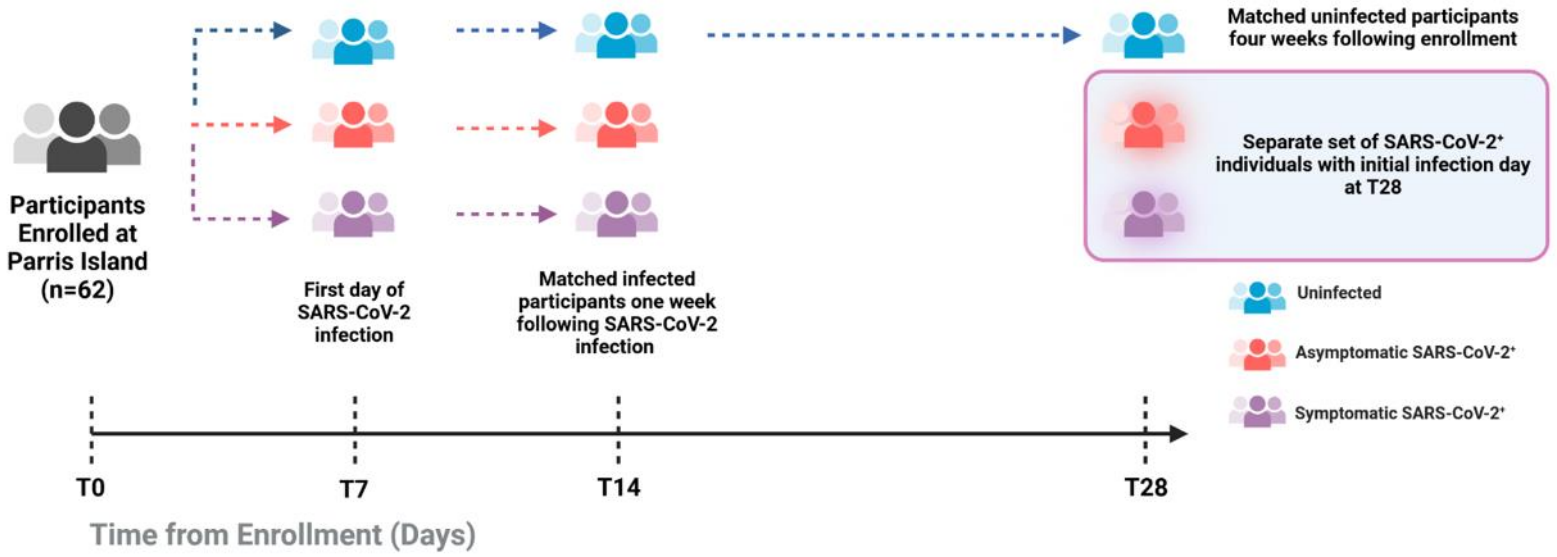
$$\text{Integrated Score} = \left(\frac{\text{Score}_{\text{sample}}}{\text{Score}_{\text{positive pool}}} \right) \times 100\%$$

Salivary versus serum Ab response to SARS-CoV-2: First 120 days



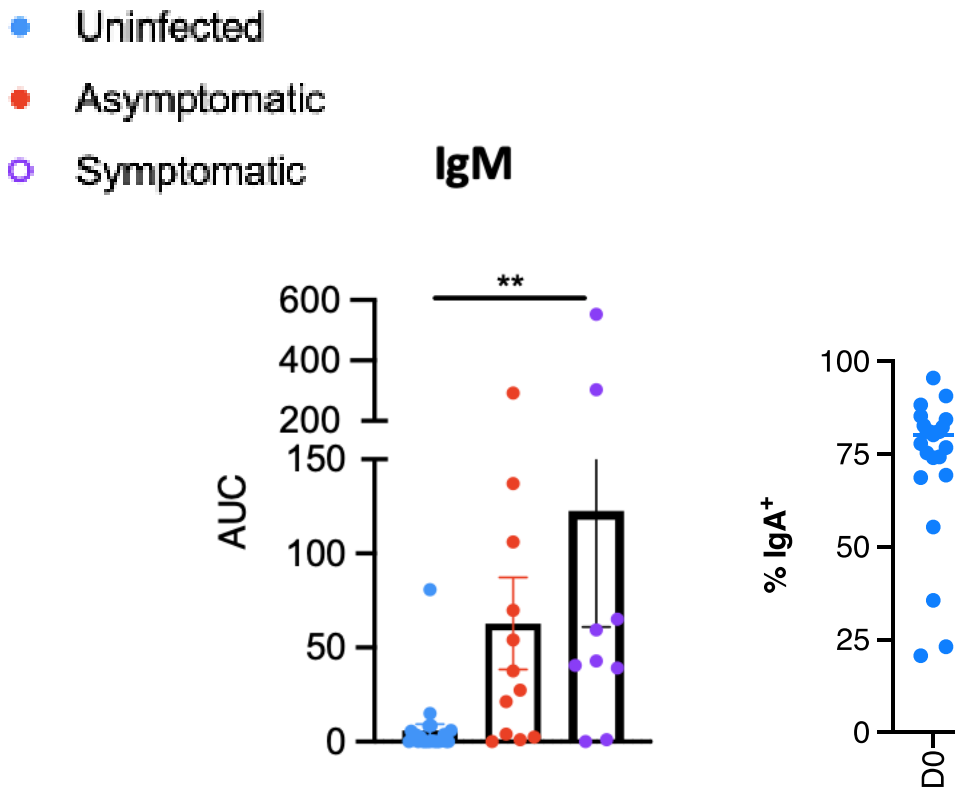
Isho et al, Science Immunology 2020

What about immediately following exposure?

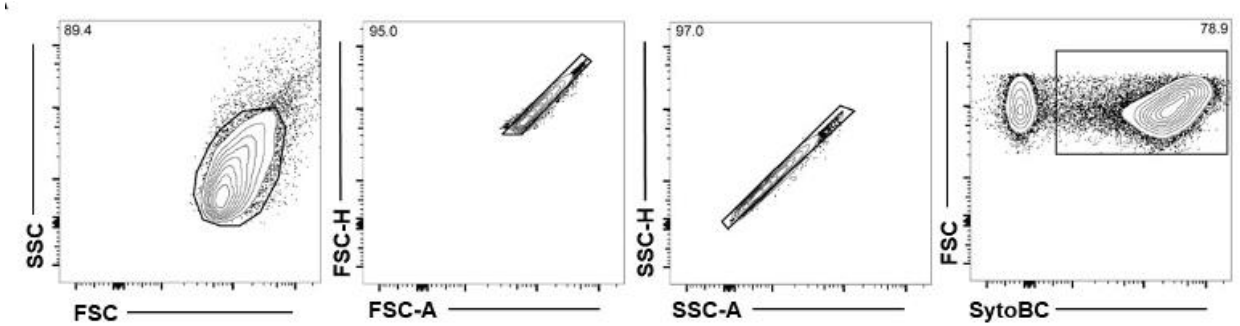


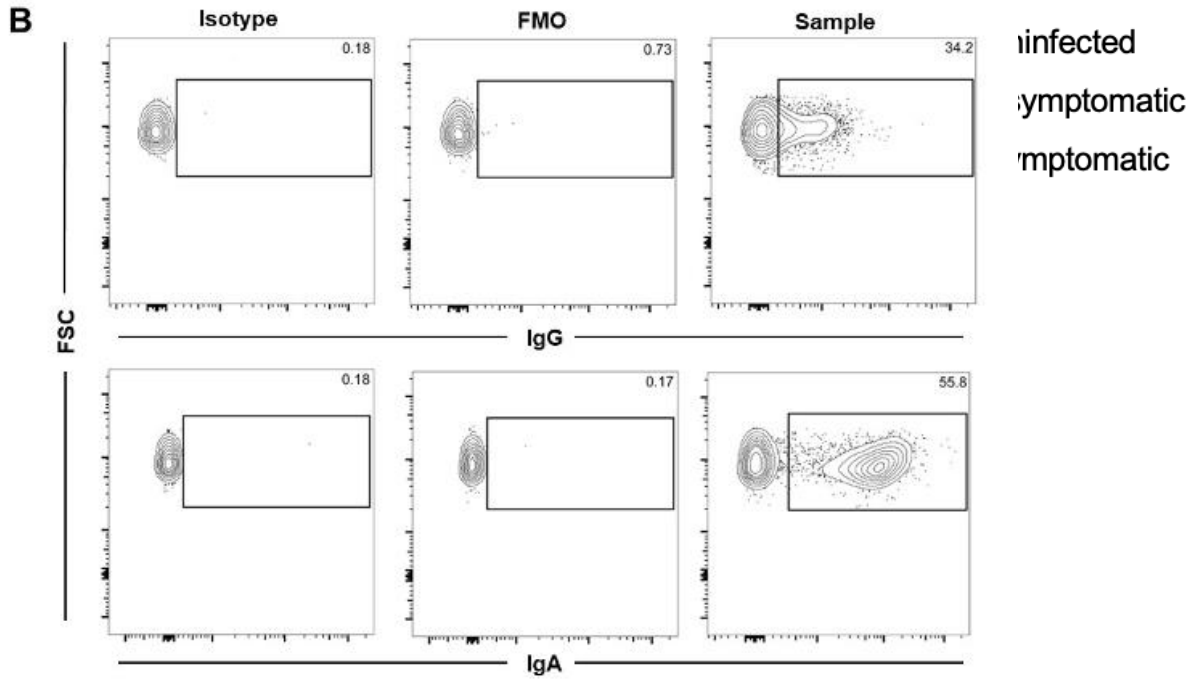
Andrew Letizia et al, *NEJM* 2020

What about immediately following exposure?



Switched IgA/IgG response not detected at this timepoint





Summary I

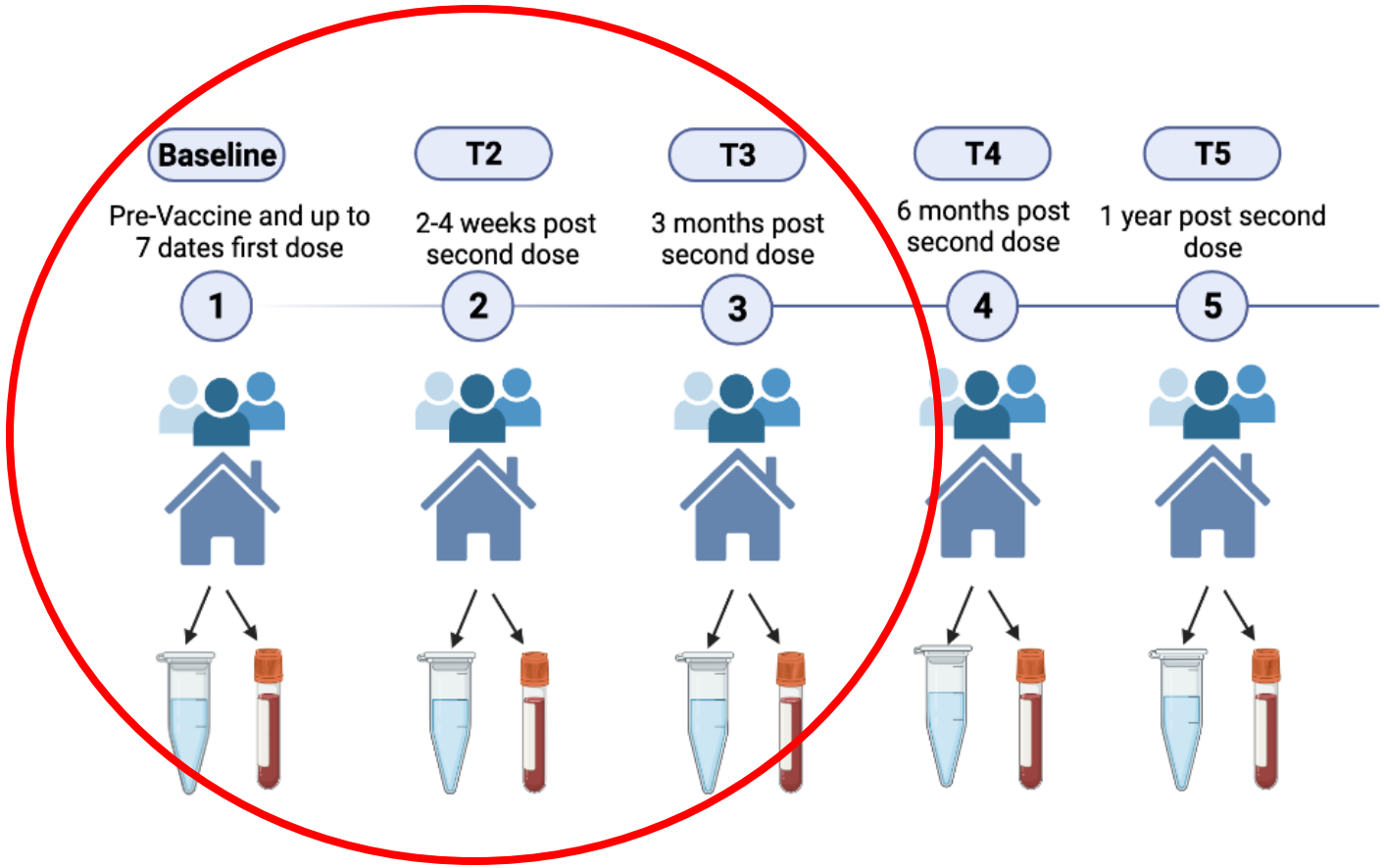
- We can detect a local antibody response in the saliva of SARS-CoV-2 infected people that correlates with they systemic antibody response.
- Early in infection, alterations in the anti-commensal IgA response are observed

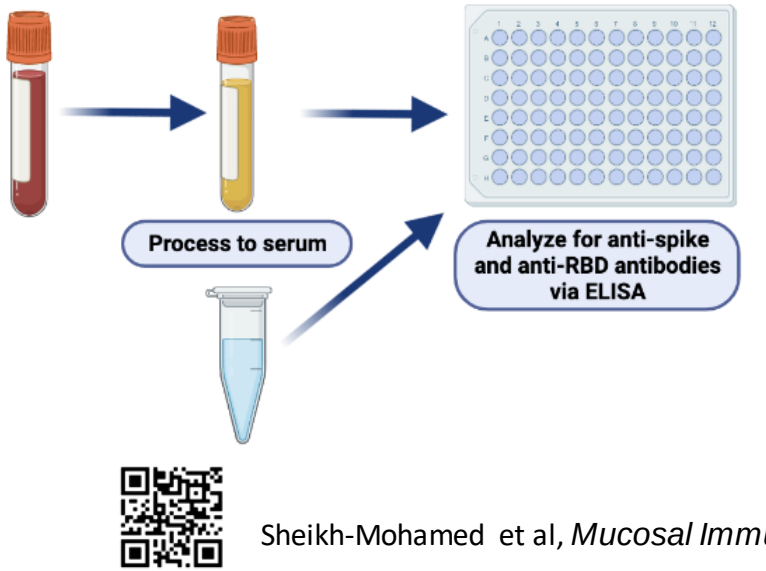
Question: Do COVID-19 vaccines elicit any immunity in the saliva?

Question: Is a mucosal (IgA) response associated with protection against breakthrough (BT) infections?

Characterizing salivary Ab in COVID-19 vaccinated subjects

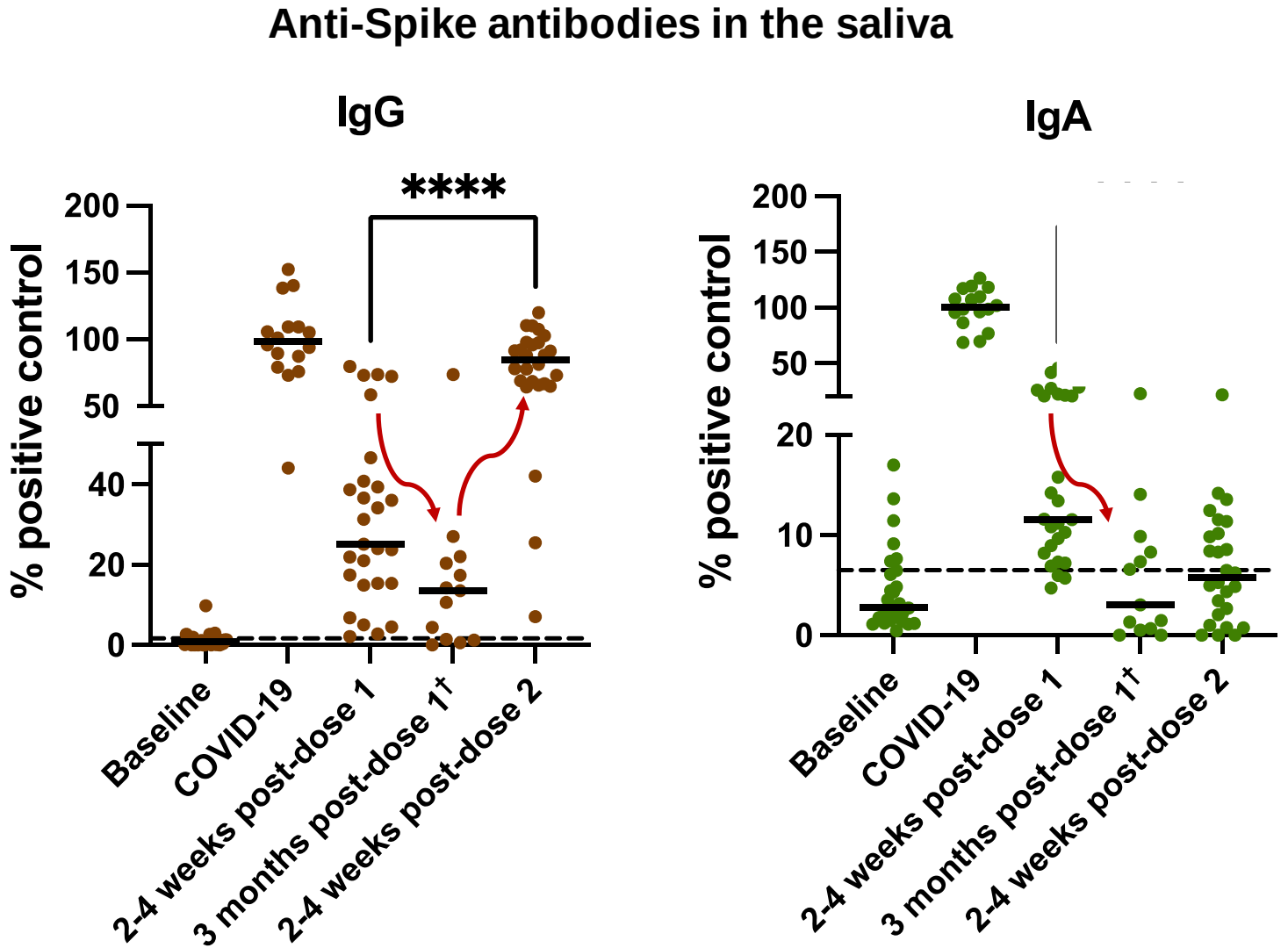
- Are anti-SARS-CoV-2 antibodies detectable in the saliva post mRNA COVID-19 vaccination?
- **Cohort :** UofT staff and students





Sheikh-Mohamed et al, *Mucosal Immunology* 2022

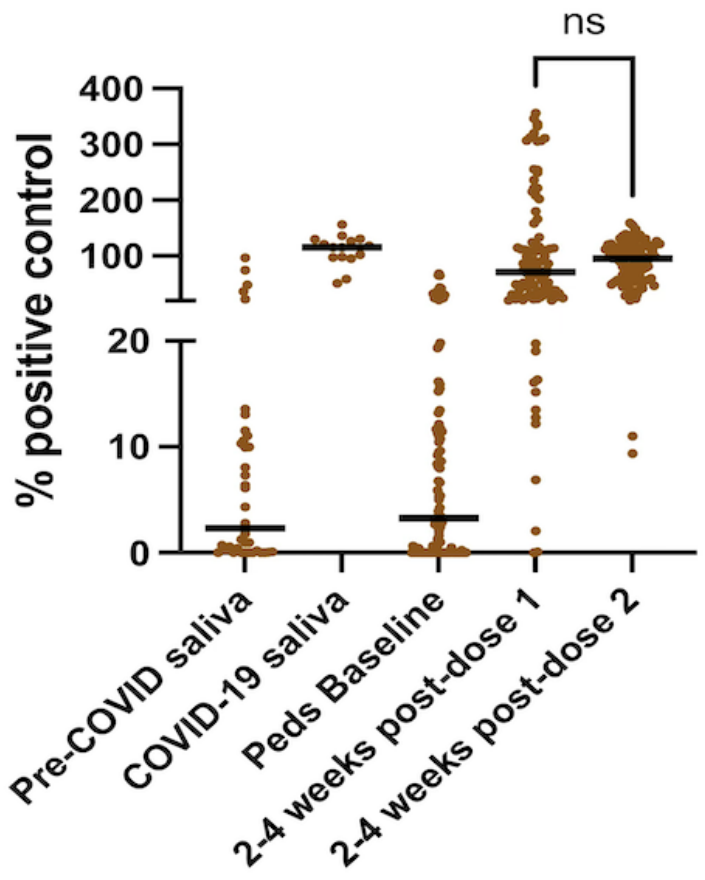
mRNA vaccines induces transient SIgA response that declines in most people

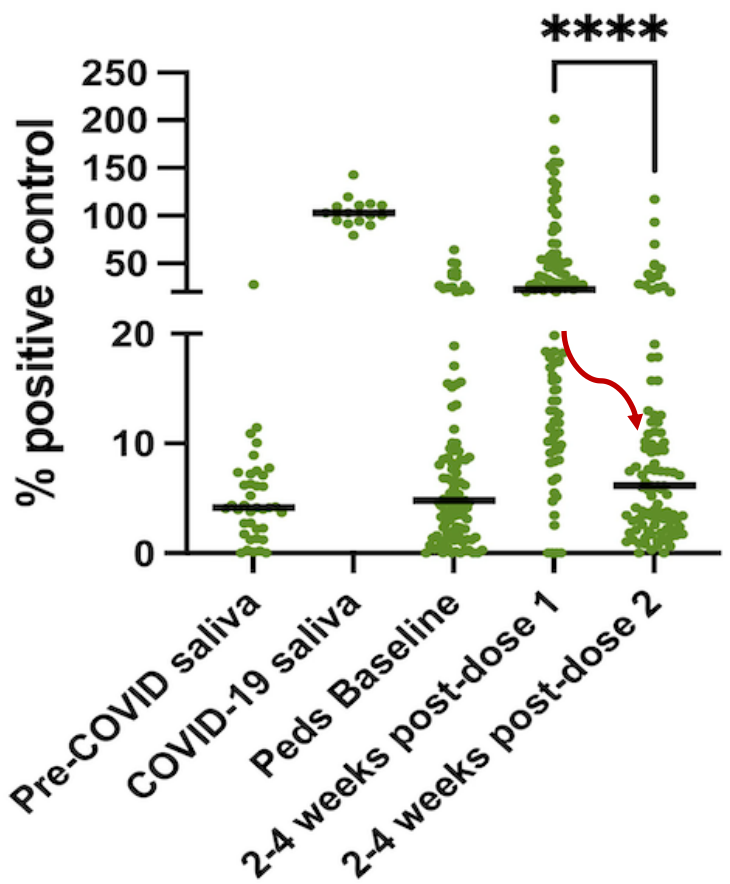


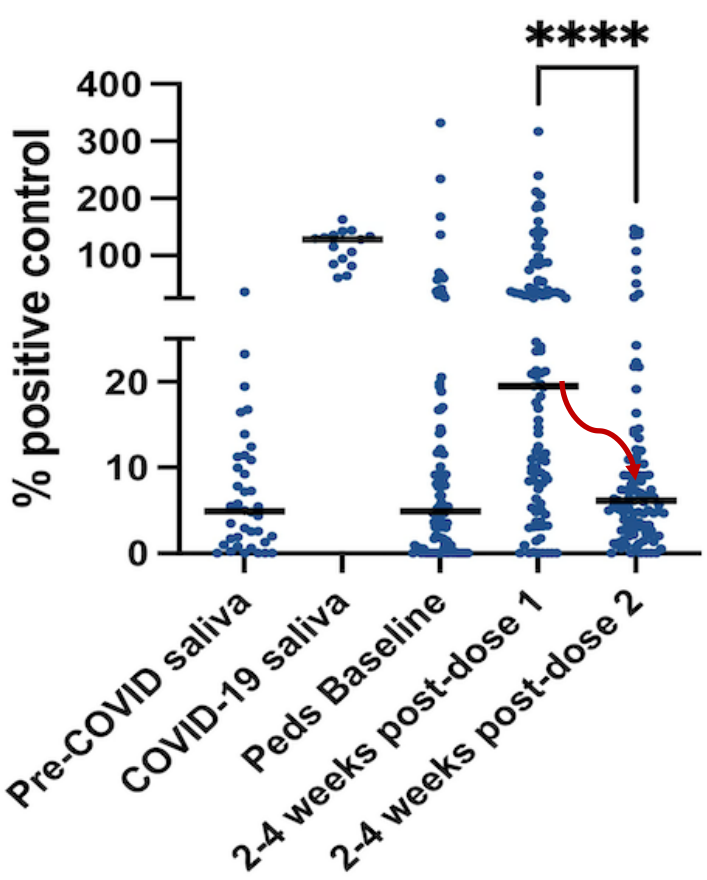
Sheikh-Mohamed et al, *Mucosal Immunology* 2022

Friedman pair-wise multiple comparison test & Mann Whitney

What does this response look like in a pediatric cohort?

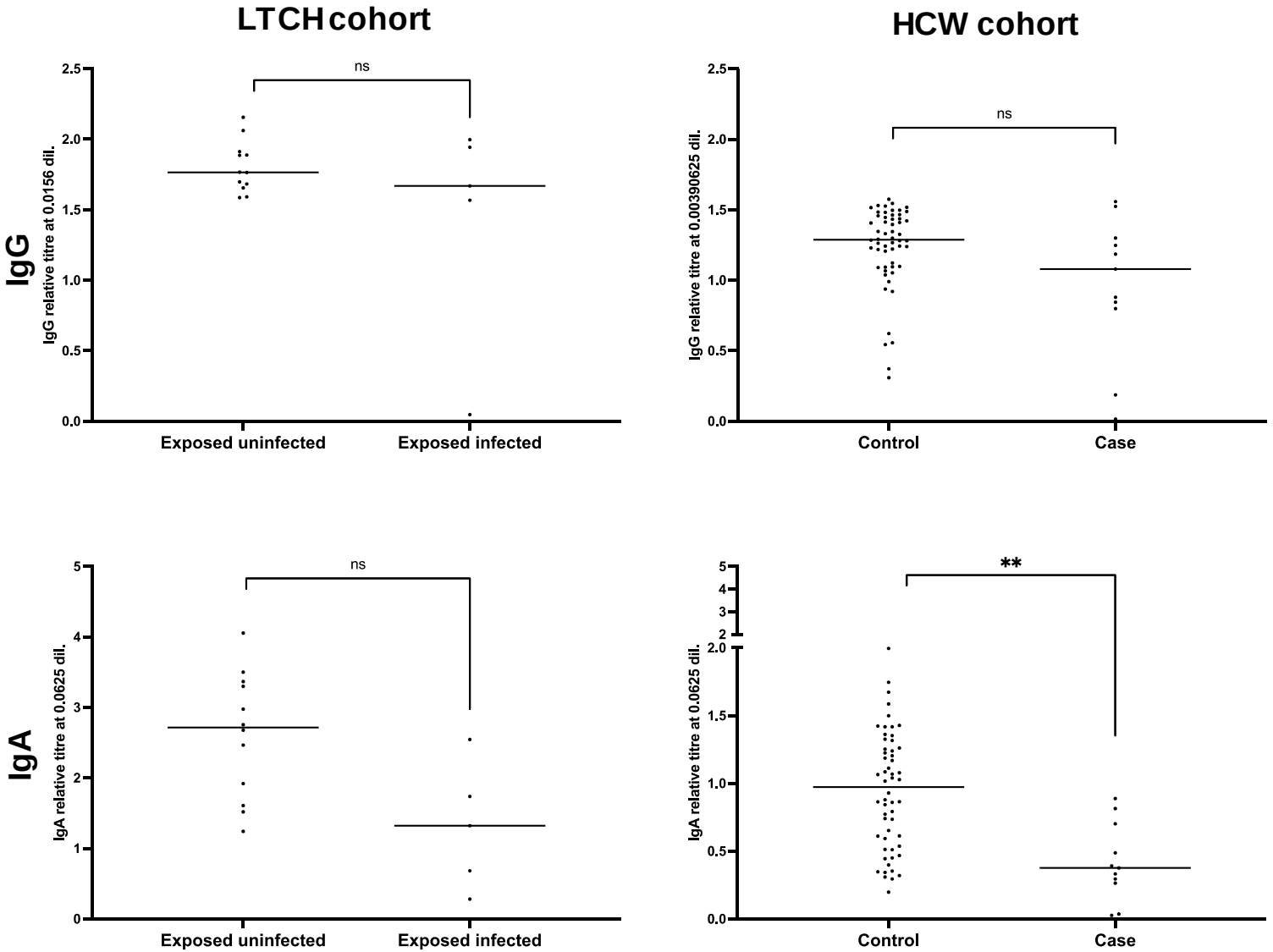






Stats test used: Friedman pair-wise multiple comparison test

Are low IgA levels post vaccination associated with breakthrough infection?

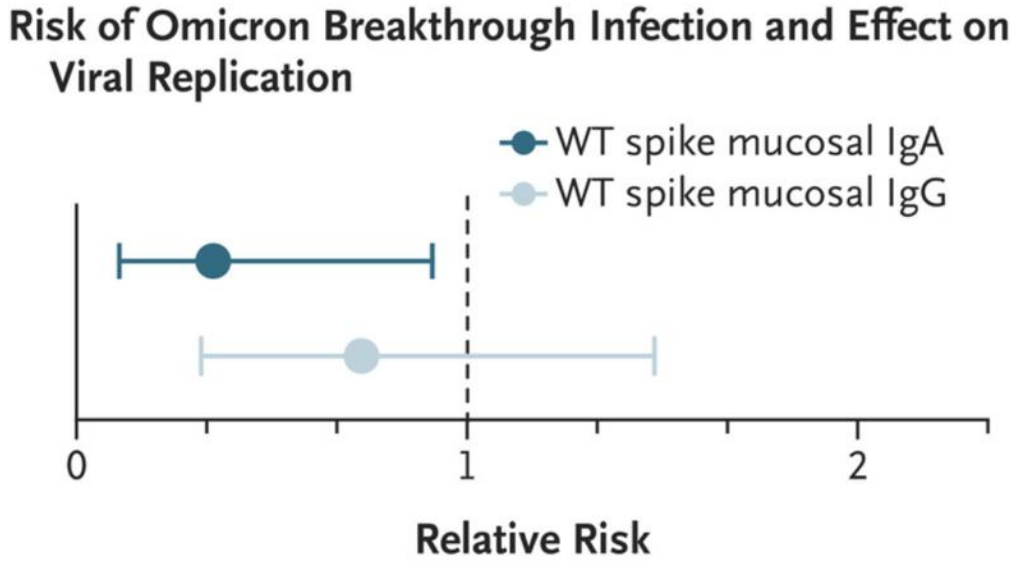


LTCH Residents	Sheba Healthcare Workers
Older	Younger
Vaccinated with Moderna's mRNA1273	Vaccinated with Pfizer's BNT162b2
Gamma variant	Alpha variant
Toronto	Sheba

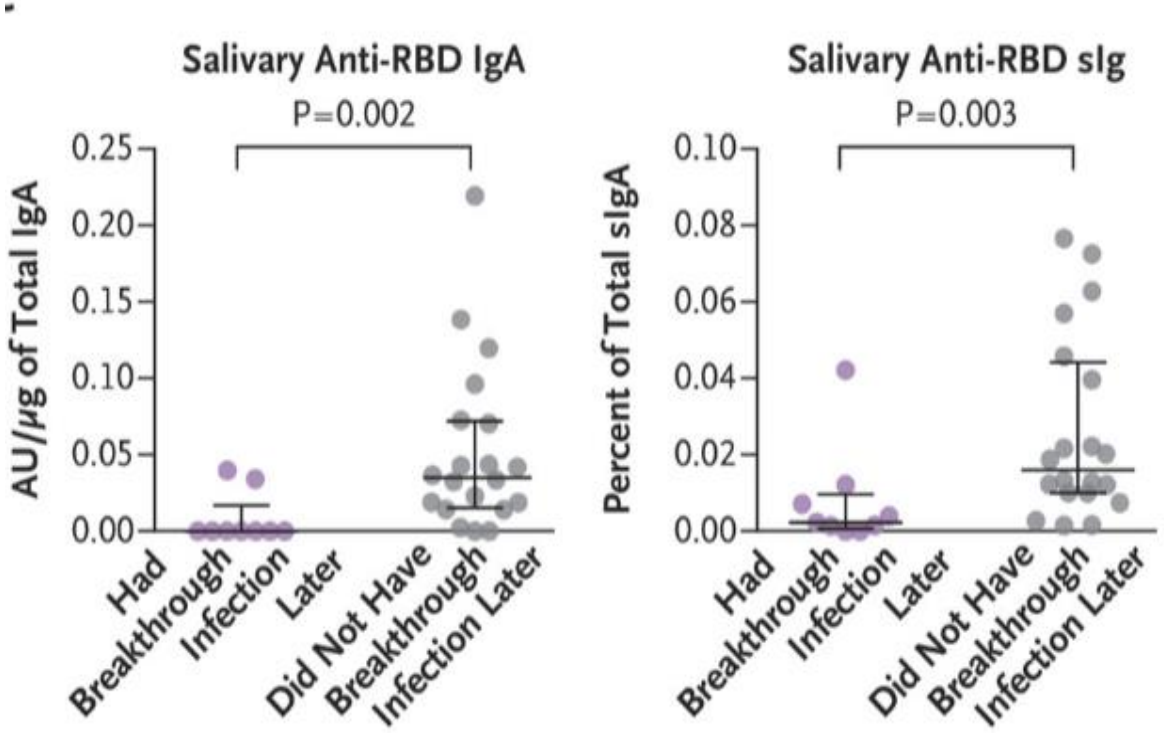
Sheikh-Mohamed et al, *Mucosal Immunology* 2022

Stats test used: Kruskal-Wallis with multiple comparison correction

Are low IgA levels post vaccination associated with breakthrough infection?



Havervall et al, NEJM 2022



Zuo et al, NEJM 2022

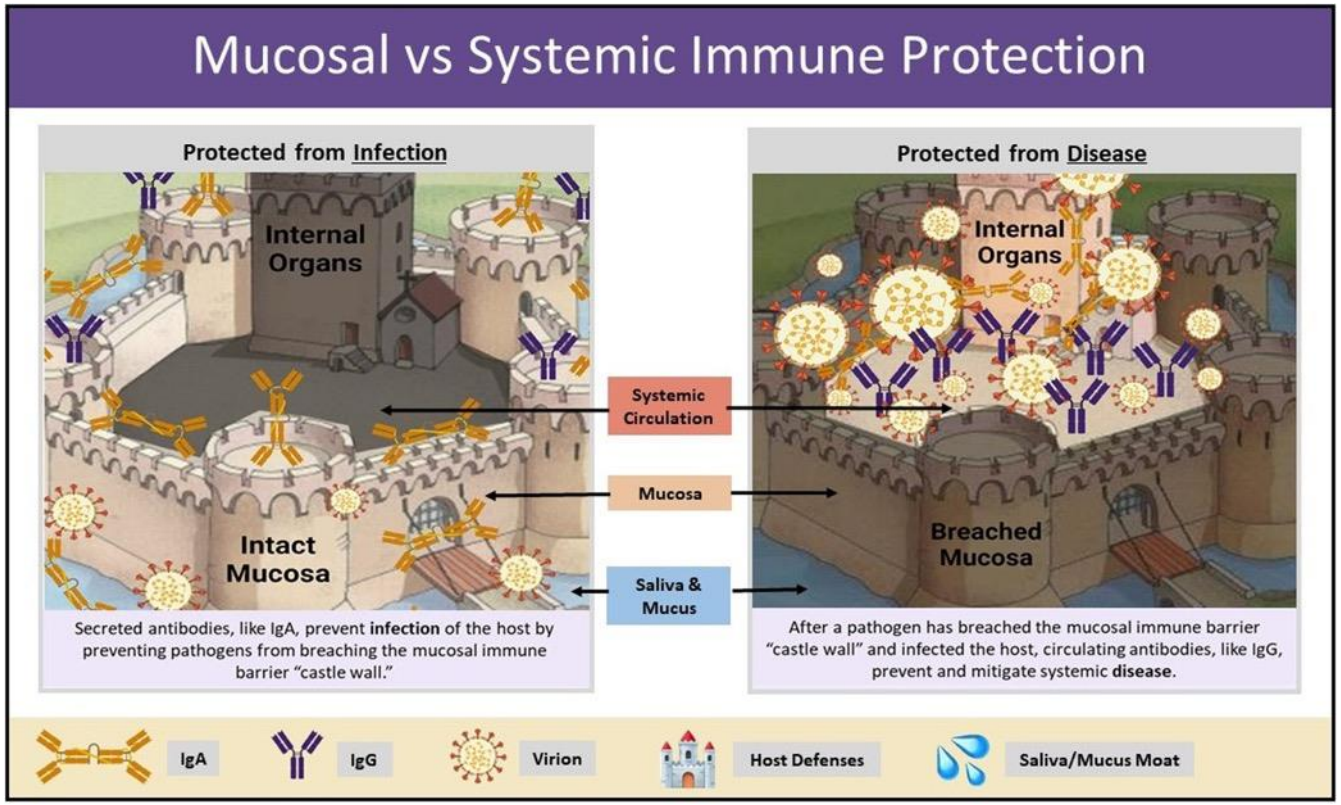
Summary II

- A weak, transient and variable SIgA response is induced after 1 dose of mRNA
- People with BT infections have lower levels of serum and mucosal anti-Spike IgA

Question: How does a combination of systemic (vaccine) **and** mucosal exposure (infection) impact systemic and mucosal immunity?

Why do we care about mucosal immunity post-vaccination?

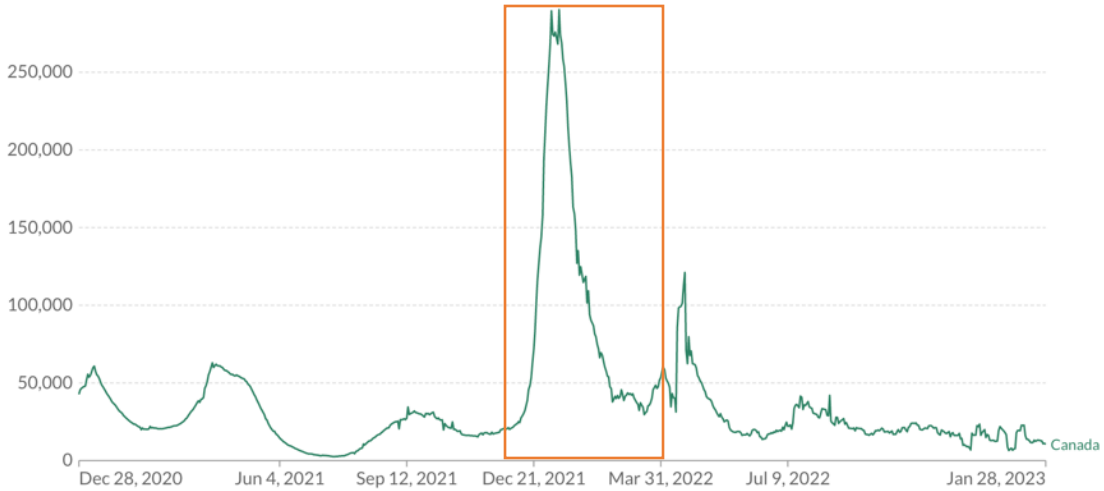
- COVID-19 vaccines did a great job at preventing severe disease and death
- Person-to-person transmission is still a problem
- Increasingly transmissible variants (Omicron)
- Vaccination strategies that capitalize on the castle walls have the potential to induce sterilizing immunity



Sheikh-Mohamed*, Sanders* et al, Immunological Reviews, 2022

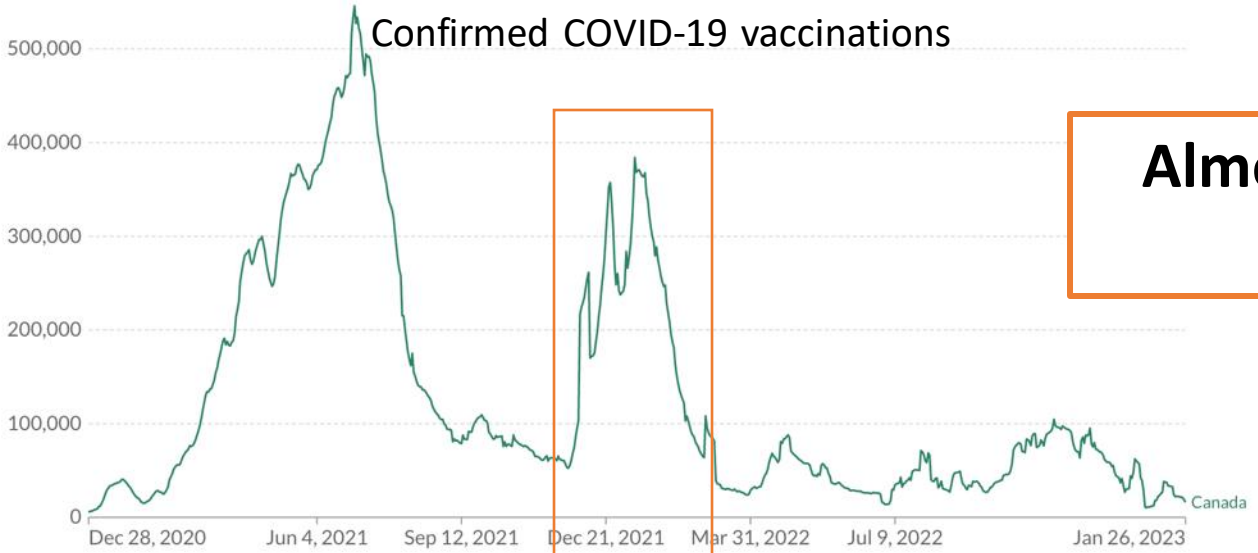
Infection vs vaccination dynamics in Canada

Confirmed COVID-19 cases



Confirmed COVID-19 deaths

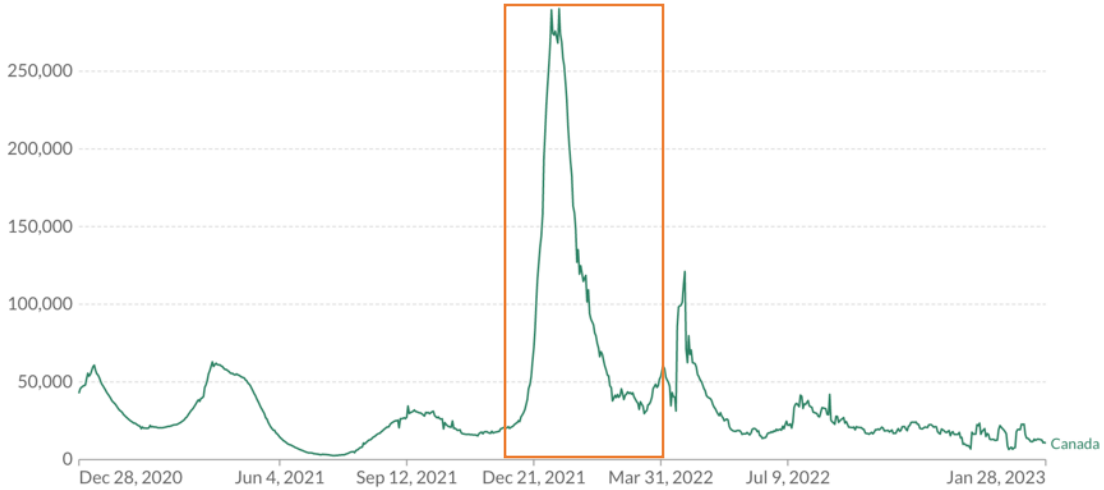
Confirmed COVID-19 vaccinations



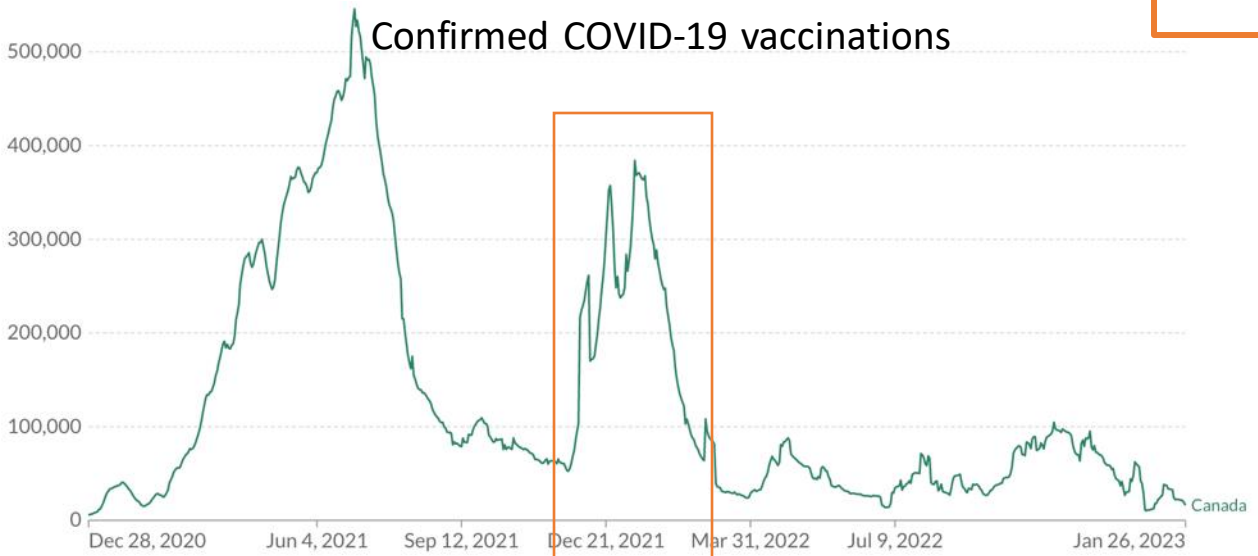
Almost 100% of infections in March 2022 were Omicron infections

Infection vs vaccination dynamics in Canada

Confirmed COVID-19 cases

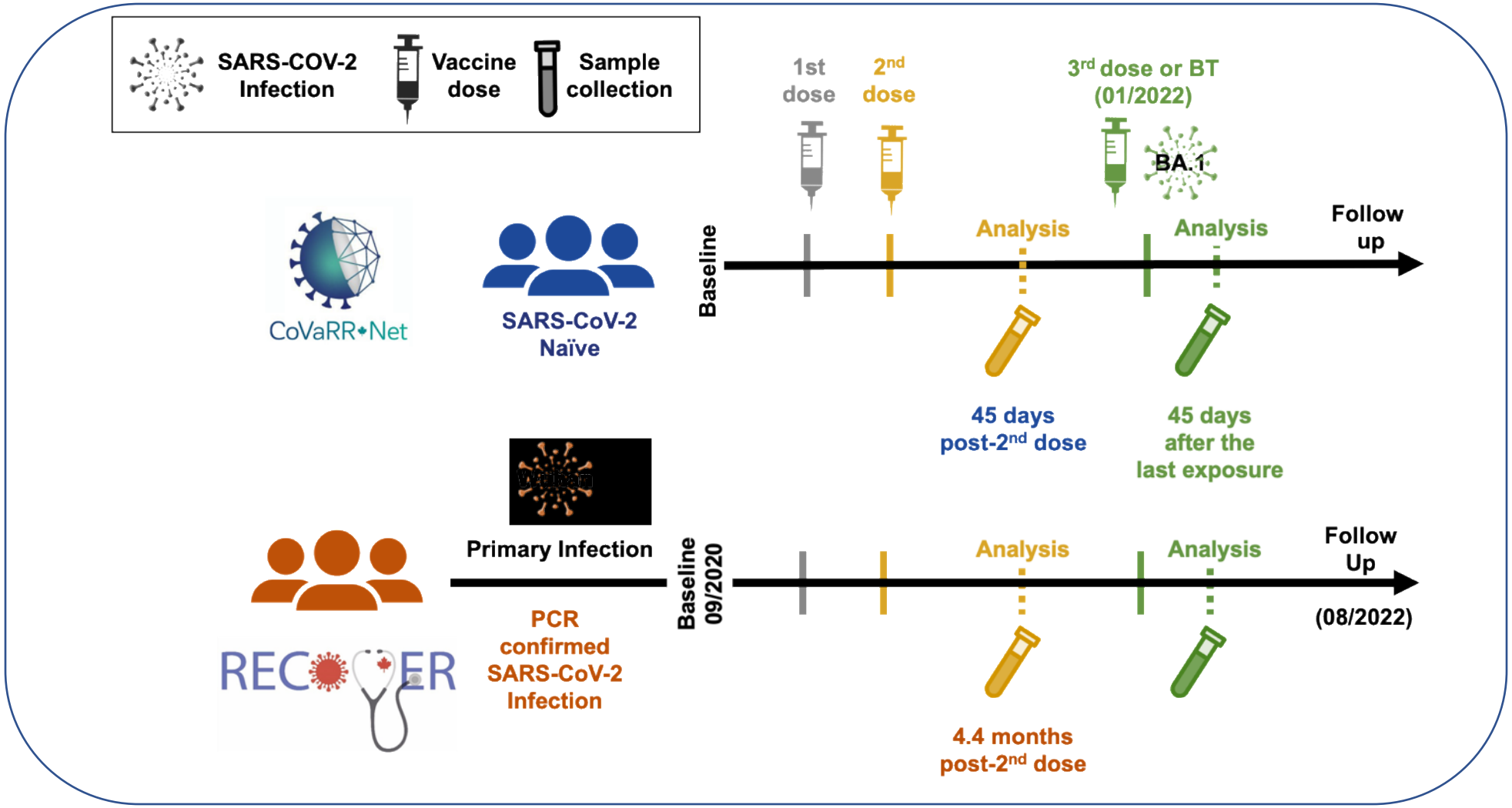


Confirmed COVID-19 vaccinations

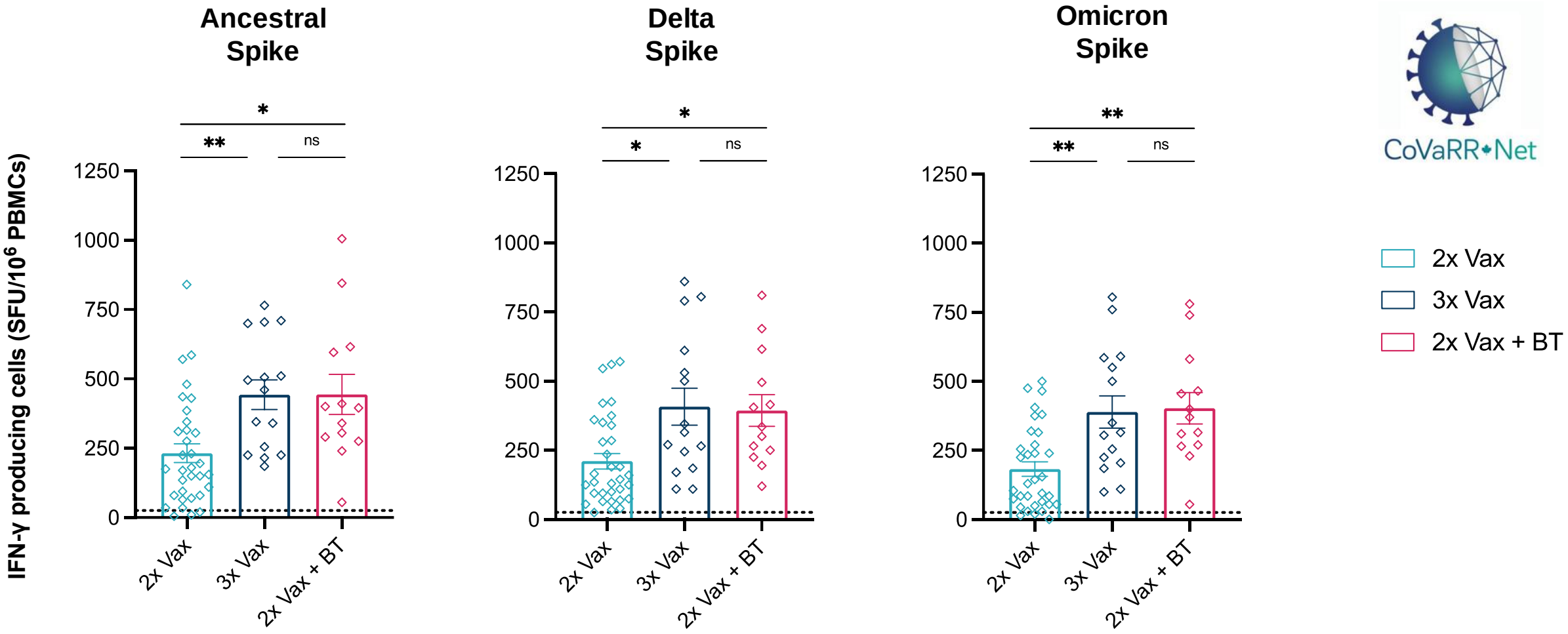


Almost 100% of infections in Q1 2022 were Omicron infections

Is a BT infection equivalent to a 3rd dose of mRNA?

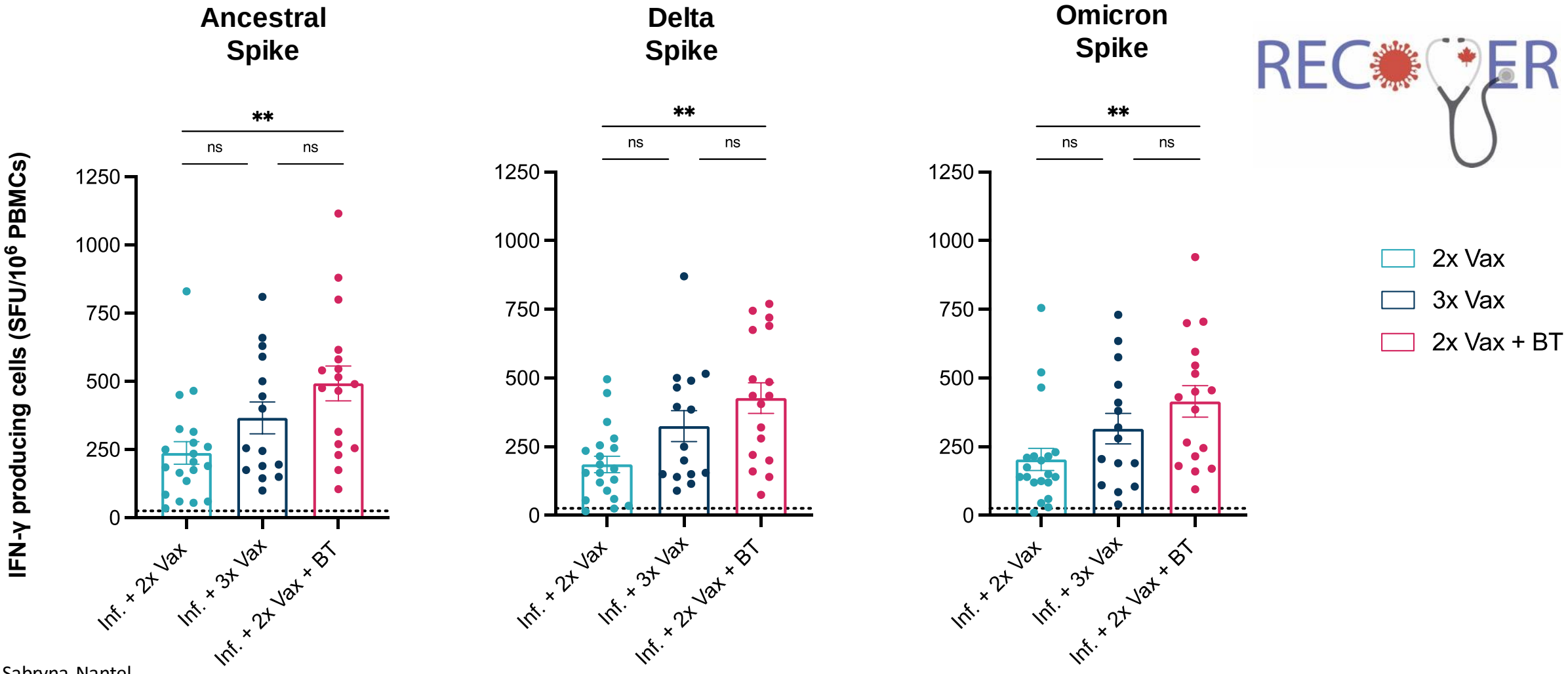


Impact of BT on T cell-derived IFNγ



Data from Sabryna Nantel
Sabryna Nantel, Salma Sheikh-Mohamed, In Preparation

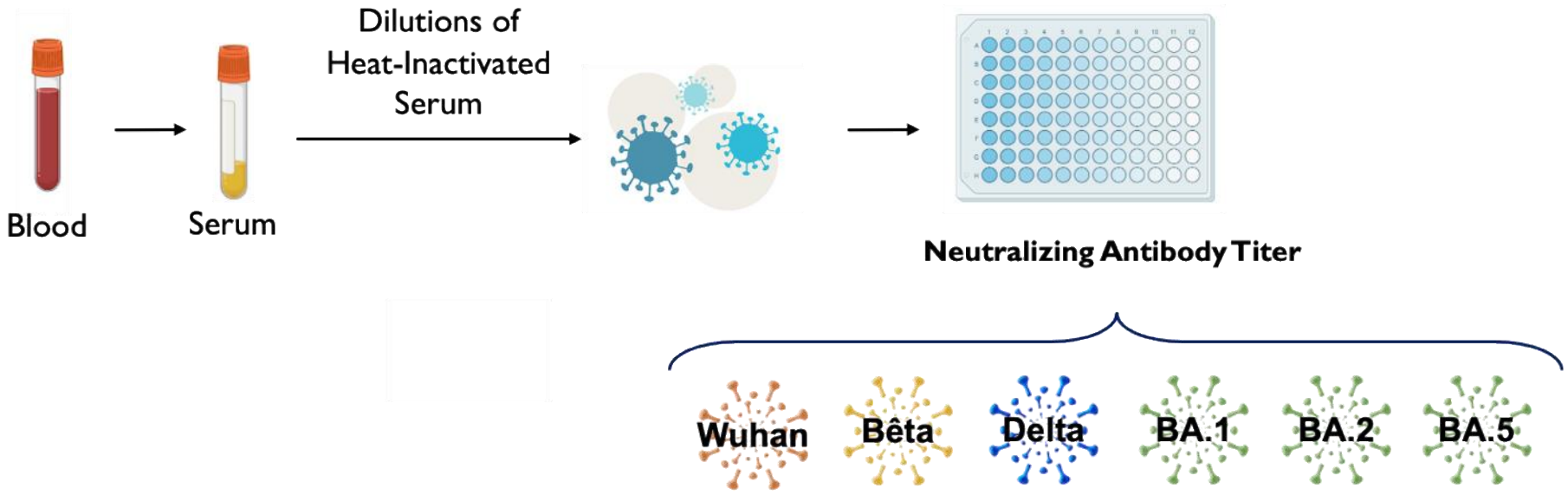
Impact of BT on T cell-derived IFNγ



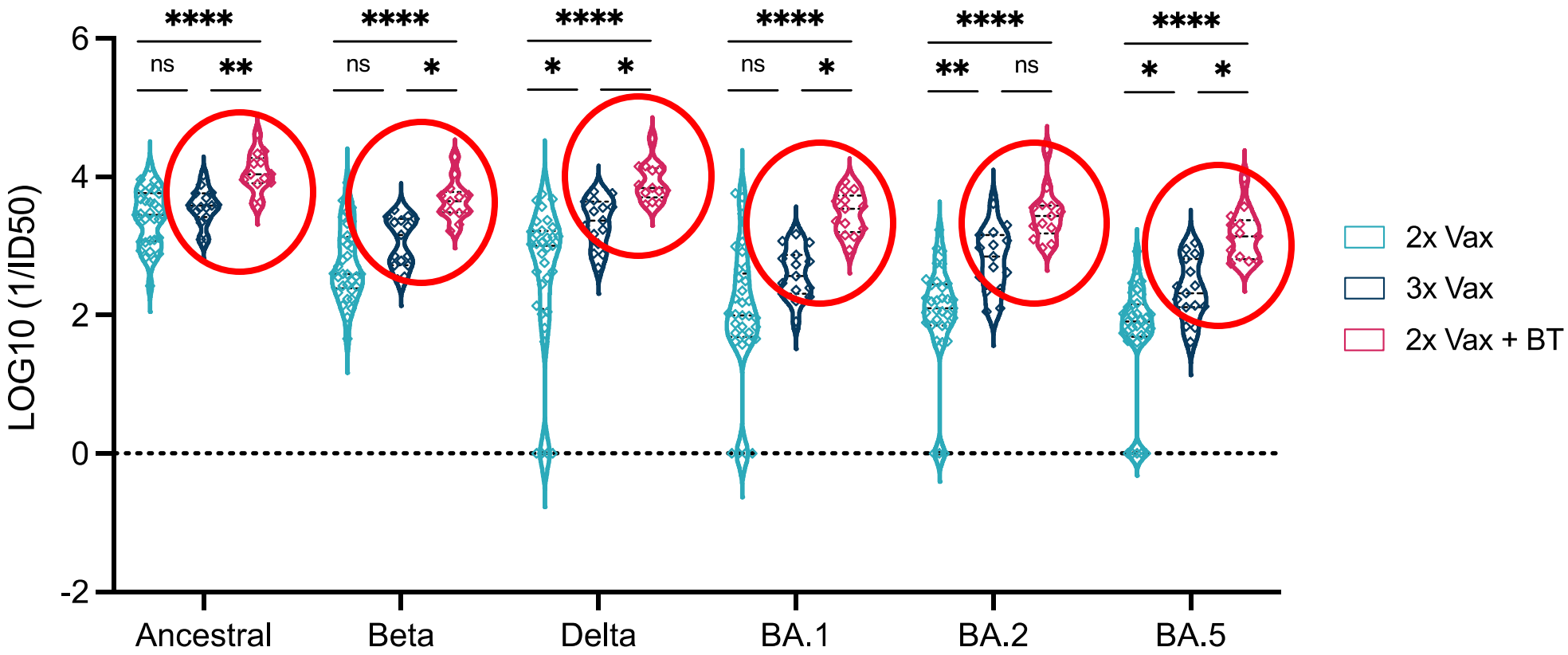
Data from Sabryna Nantel

Sabryna Nantel, Salma Sheikh-Mohamed, In Preparation

Impact of BT on systemic humoral immunity



Impact of Omicron BT on nAb

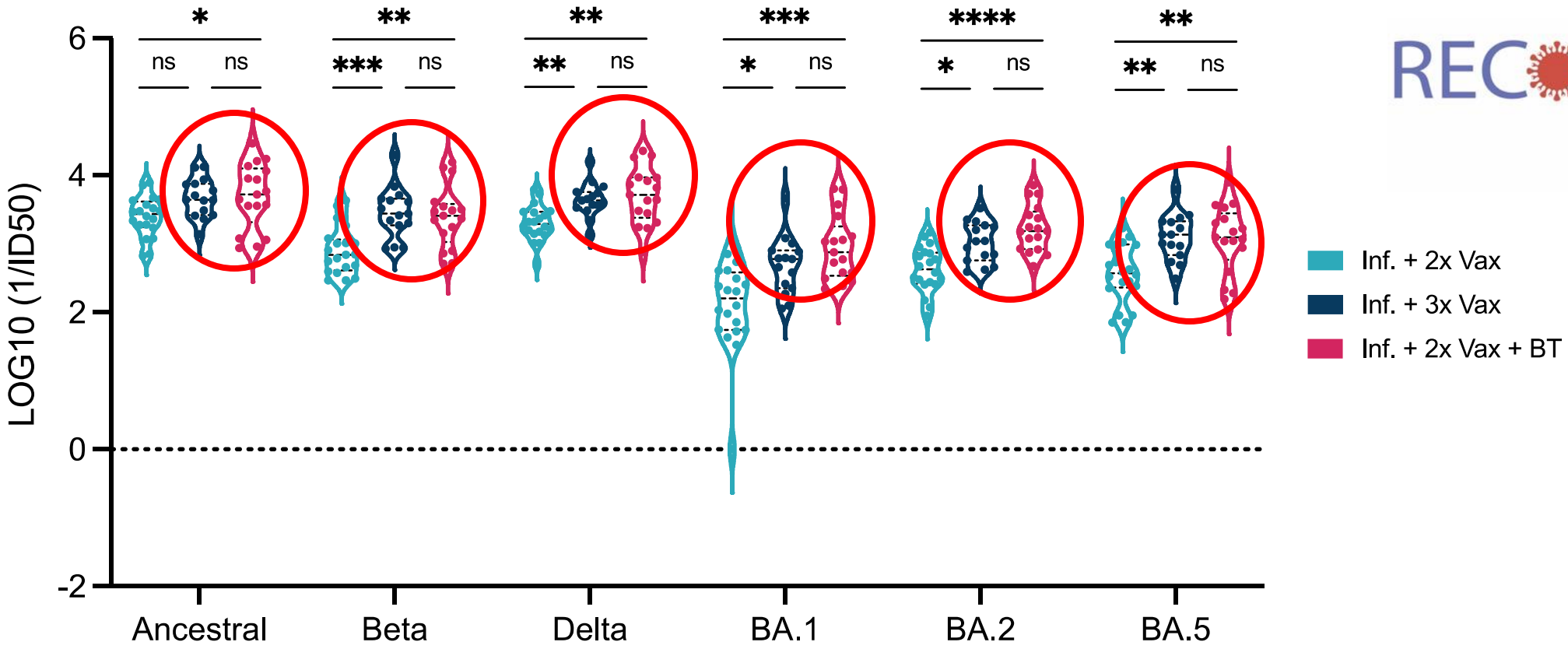


CoVaRR-Net

Data from Dr. Anne-Claude Gingras
Sabryna Nantel, Salma Sheikh-Mohamed, In Preparation

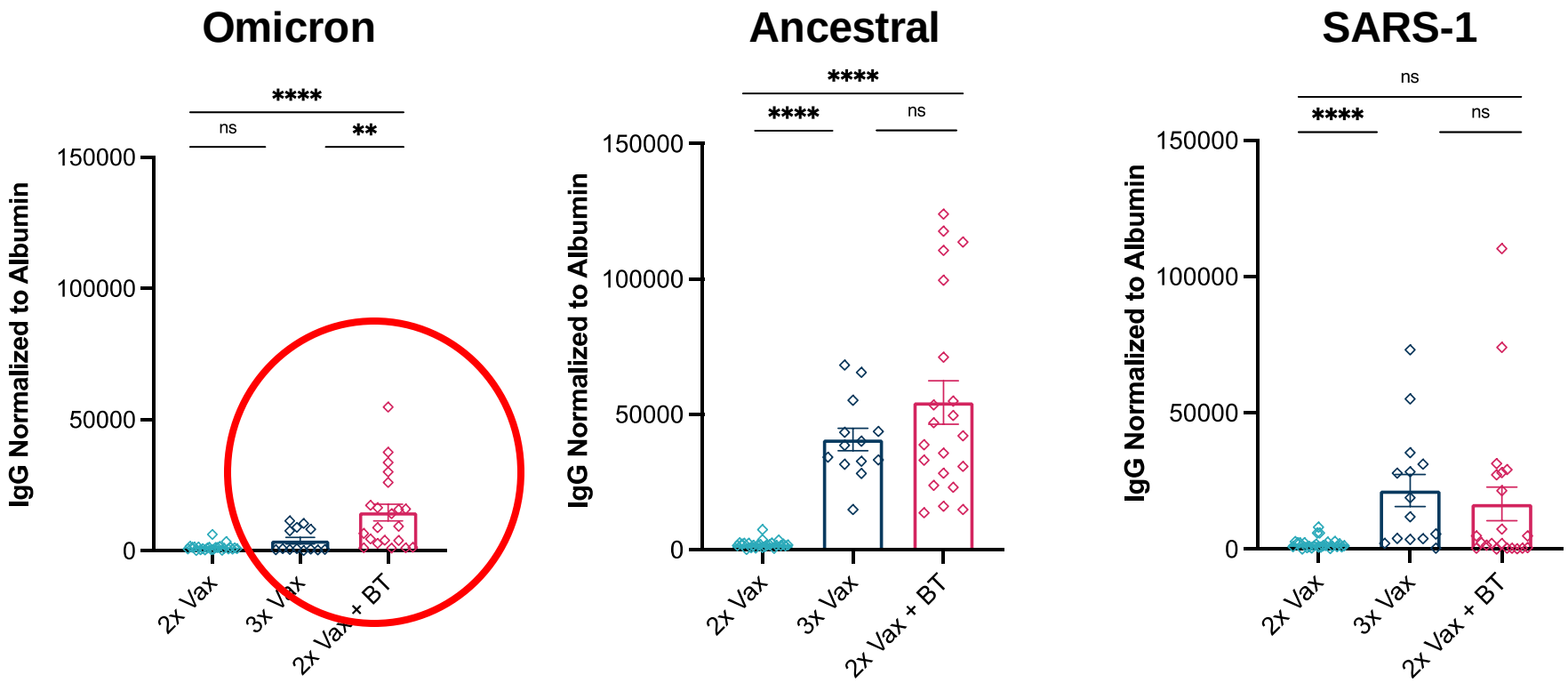
Similar results with PRNT assay (Heidi Bloom, NML)

Impact of Omicron BT on nAb



Impact of Omicron BT on anti-SPIKE salivary Ab

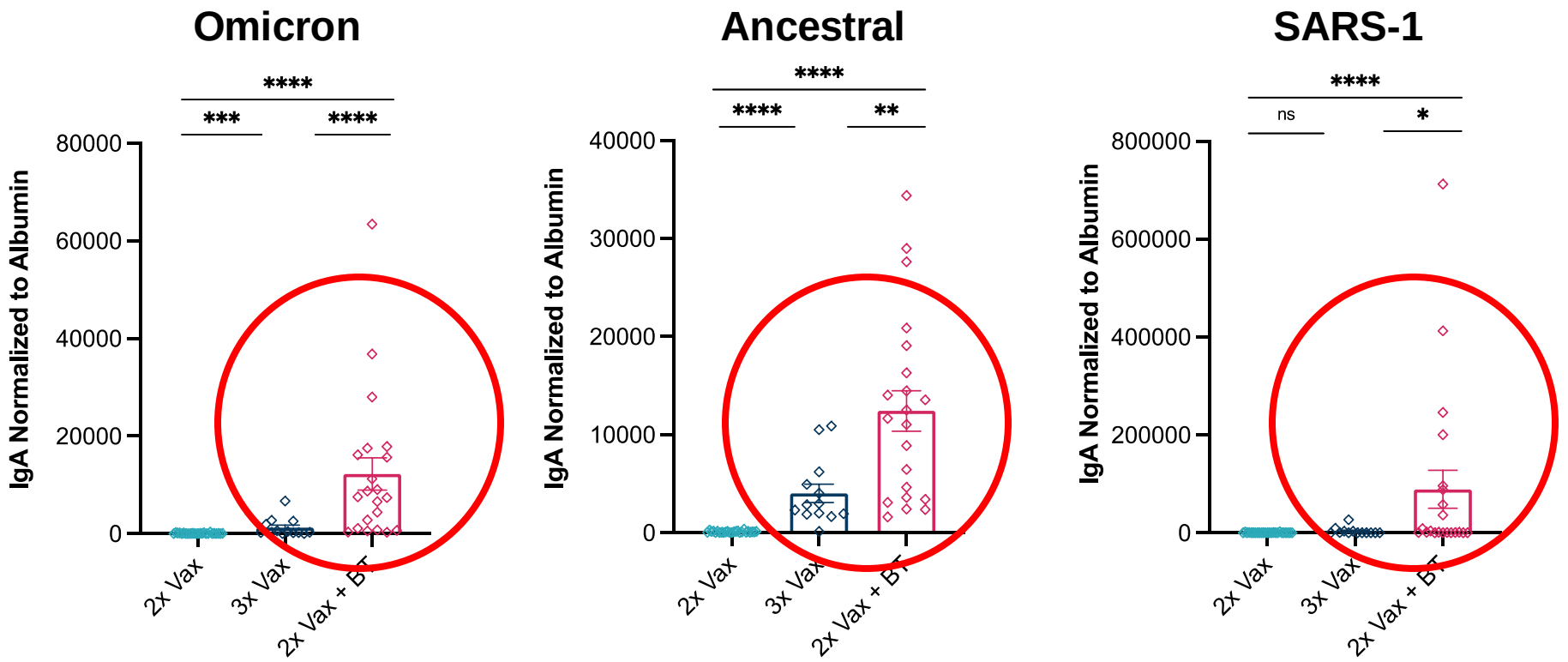
IgG



Data from Salma Sheikh-Mohamed
Sabryna Nantel, Ssalma Sheikh-Mohamed, In Preparation

Impact of Omicron BT on anti-SPIKE salivary Ab

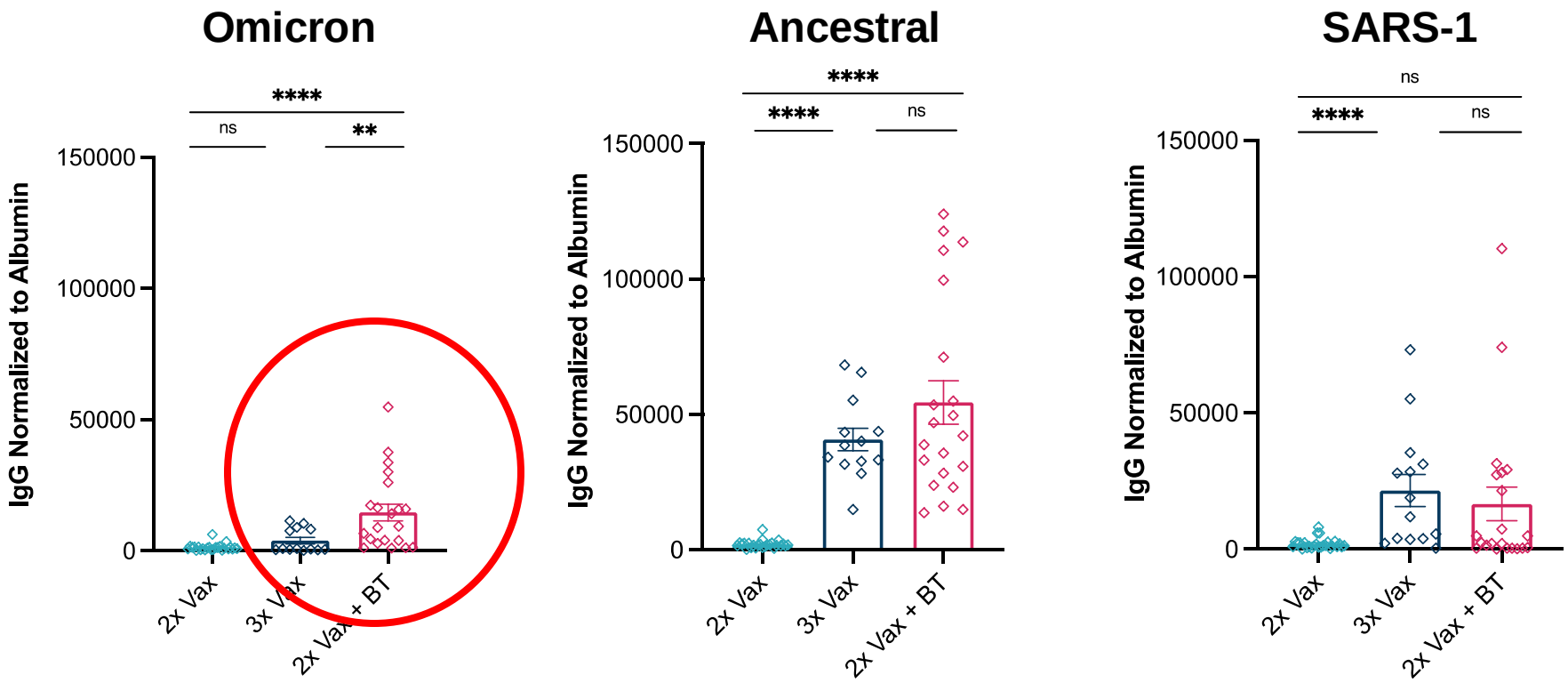
IgA



Data from Salma Sheikh-Mohamed
Sabryna Nantel, Ssalma Sheikh-Mohamed, In Preparation

Impact of Omicron BT on anti-RBD salivary Ab

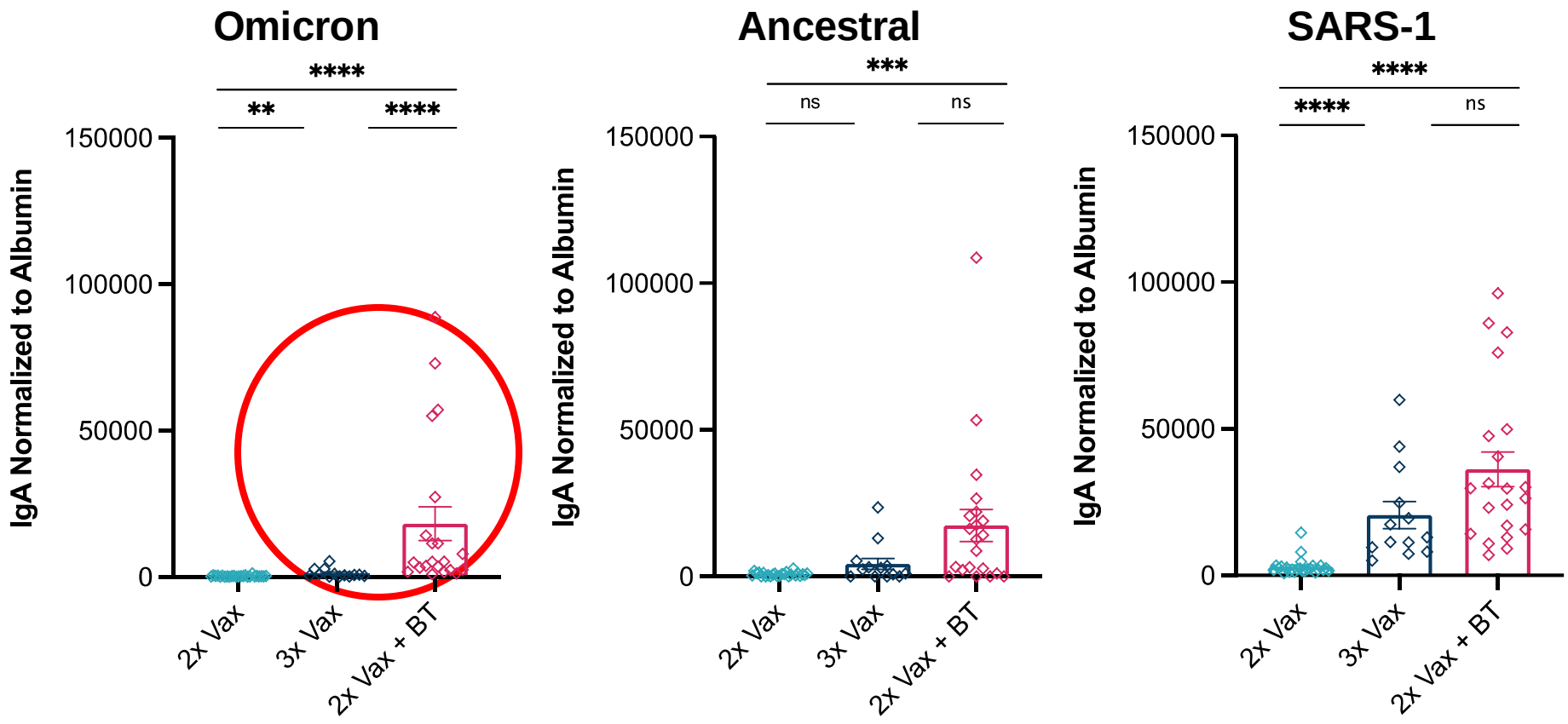
IgG



Data from Salma Sheikh-Mohamed
Sabryna Nantel, Ssalma Sheikh-Mohamed, In Preparation

Impact of Omicron BT on anti-RBD salivary Ab

IgA



Data from Salma Sheikh-Mohamed
Sabryna Nantel, Ssalma Sheikh-Mohamed, In Preparation

Impact of Omicron BT on salivary Ab

	OMICRON	ANCESTRAL	SARS-1
Anti-Spike IgG	↑		
Anti-Spike IgA	↑	↑	↑
Anti-RBD IgG	↑		
Anti-RBD IgA	↑		

Data from Salma Sheikh-Mohamed
Sabryna Nantel, Ssalma Sheikh-Mohamed, In Preparation

Summary III

- Omicron BT increases serum nAb to VOC
- Omicron BT increases IgG/IgA salivary Ab to Omicron
- Omicron BT increases anti-Spike IgA to Wuhan SARS-CoV-2 and SARS-1

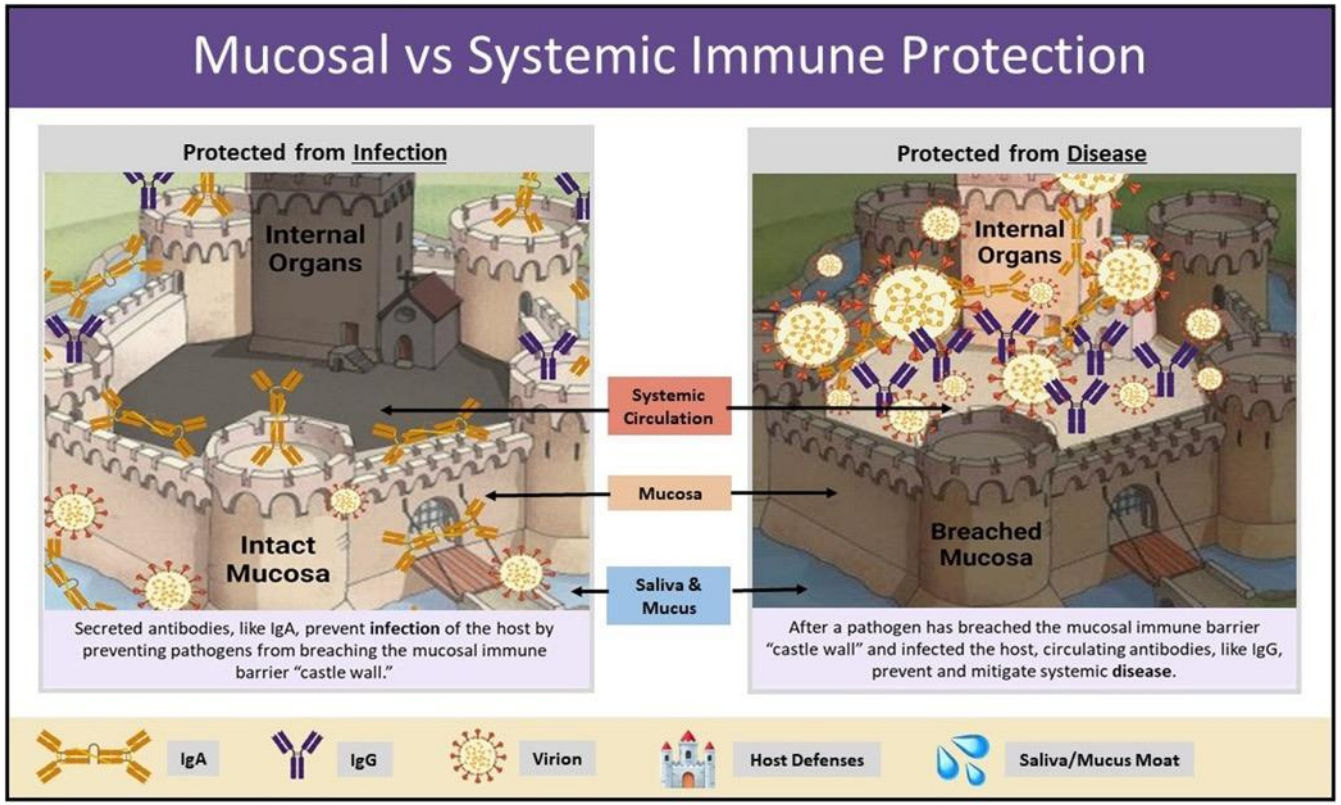
Question: Will a combination of i.m. and i.n. vaccination promote sterilizing immunity and if so, what is the "magic combination?"

Question: Should we care?

YES!!

Why do we care about mucosal immunity post-vaccination?

- COVID-19 vaccines did a great job at preventing severe disease and death
- Person-to-person transmission is still a problem
- Increasingly transmissible variants (Omicron)
- Vaccination strategies that capitalize on the castle walls have the potential to induce sterilizing immunity



Sheikh-Mohamed*, Sanders* et al, Immunological Reviews, 2022

Next steps in COVID-19 vaccination

Developer (location)	Vaccine type	Delivery method	Status
Bharat Biotech (Hyderabad, India)	Viral vector; non-replicating	Intranasal (drops)	Company says two phase III studies completed, unpublished. Data submitted to regulators in India.
CanSino Biologics (Tianjin, China)	Viral vector; non-replicating (Aerosolized version of approved intramuscular vaccine)	Inhaled through nose and mouth	Approved by Chinese regulators.
Beijing Wantai Biological Pharmacy (Beijing)	Live attenuated	Intranasal (spray)	Phase III study under way in 40,000 people.
Razi Vaccine and Serum Research Institute (Karaj, Iran)	Protein subunit	Intranasal (spray)	Received emergency authorization in Iran in October 2021; in phase III trial (status unknown).
Codagenix (Farmingdale, New York) and Serum Institute of India (Pune)	Live attenuated	Intranasal (drops)	Phase II/III efficacy study in 20,000 people under way at undisclosed locations in Africa; part of the World Health Organization's Solidarity Trial Vaccines.
Icahn School of Medicine at Mount Sinai (New York City) and Laboratorio Avi-Mex (Mexico City, Mexico)	Viral vector; non-replicating	Intranasal (drops or spray)	Phase II study under way in 396 people in Mexico City.
AstraZeneca (Cambridge, UK) and University of Oxford (Oxford, UK)	Viral vector; non-replicating (adenovirus)	Intranasal (spray)	Phase I study completed (both as first dose and as booster).
Meissa Vaccines (Redwood City, California)	Live recombinant	Intranasal (drops or spray)	Phase I study under way (both as first dose and as booster).
CyanVac (Athens, Georgia)	Viral vector; live, replicating	Intranasal (spray)	Phase I study under way.
Center for Genetic Engineering and Biotechnology (Havana, Cuba)	Protein subunit	Intranasal (spray)	Phase II study in up to 5,000 participants in Cuba.

Waltz et al, Nature 2022

Lessons Learned

1) Consider innovative ways to combine different cohorts and collaborate to answer certain questions

2) Importance of networks to collaborate with key experts and answer critical research questions (RECOVER, CoVaRR-Net, …)

3) Share samples and protocols to be positioned for clinical trial readouts (ongoing international working groups)

Thank you!

GommerLab
Salma Sheikh-Mohamed
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Dr. Zhijie Li (UofT)
Dr. Andrew Letizia (US Navy)
Dr. Heidi Wood (NML)
Dr. Marc-André Langlois
Dr. Ciro Piccirillo (McGill)
Dr. Mark Brockman (SFU)
Dr. Laurie Seifried (UofT)

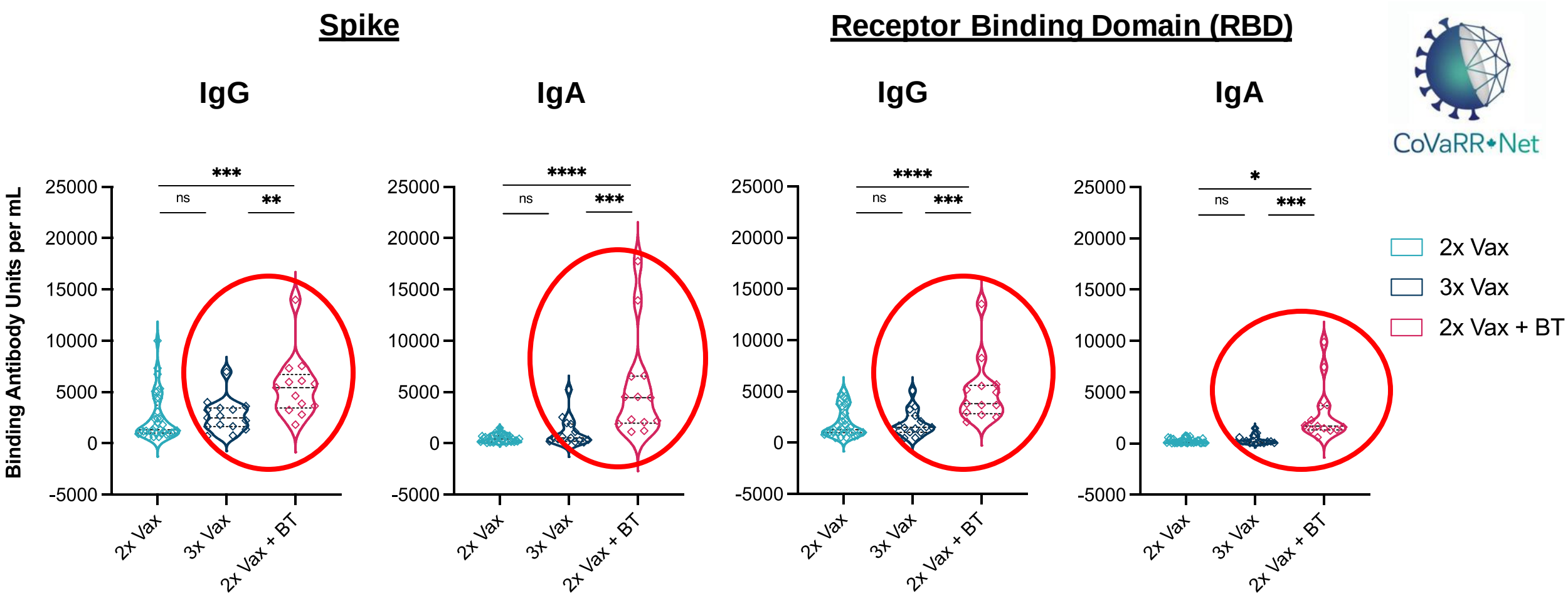
And all of our study participants!!






COVID-19 IMMUNITY TASK FORCE
GROUPE DE TRAVAIL SUR L'IMMUNITÉ FACE À LA COVID-19
Mount Sinai Hospital
CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada
CoVaRR-Net
RECOVER

Impact of Omicron BT on binding Ab



Data from Dr. Anne-Claude Gingras
Sabryna Nantel, Salma Sheikh-Mohamed, In Preparation