Global Vaccine and Immunization Research Forum 2023
Grand Hyatt, Incheon, Republic of Korea
28 – 30 March 2023

# Mucosal Immunity

## *What's special about it and can vaccines induce it?*

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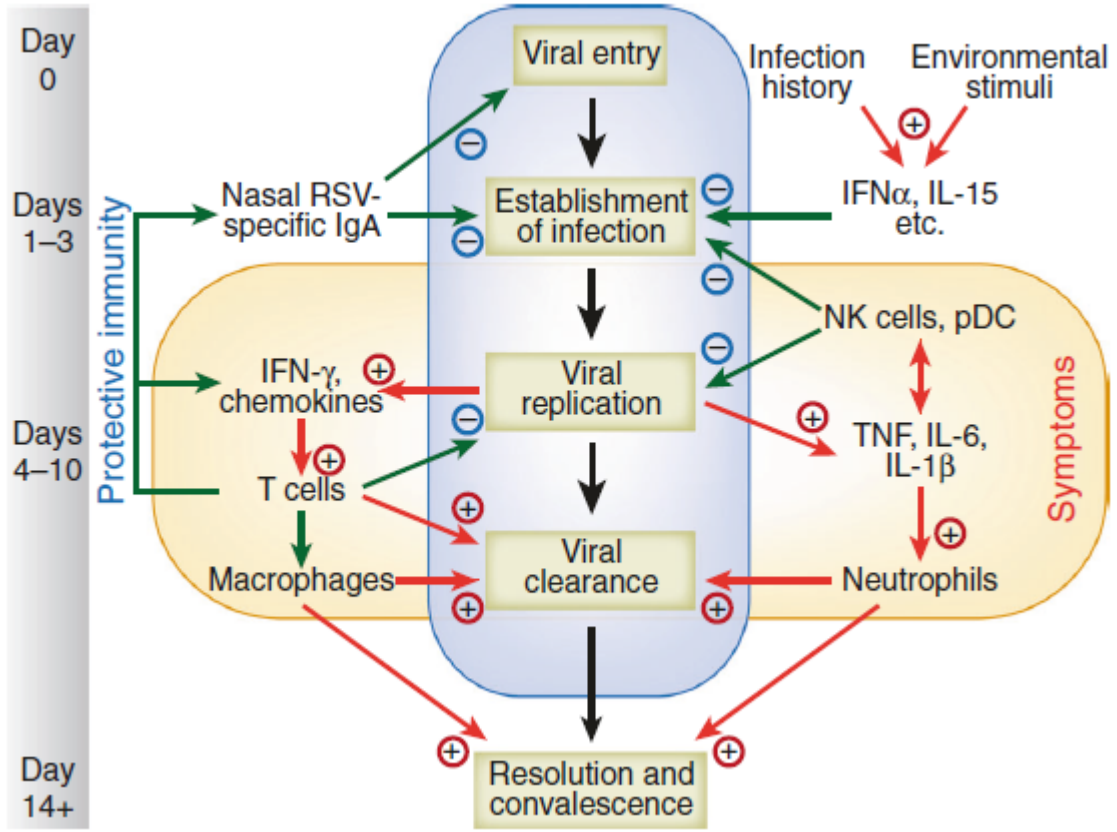
Mucosal Immunology
OFFICIAL JOURNAL OF THE SOCIETY FOR MUCOSAL IMMUNOLOGY, PUBLISHED BY SPRINGER NATURE

**(2020)** 13:566–573

## Seasonal and pandemic influenza: 100 years of progress

Jake Dunning, Ryan S. Thwaites, Peter J.M. Openshaw

- **About 75% of all lymphocytes are mucosal**
- Viral entry into the respiratory epithelium is blocked by specific mucosal antibody, mucus and antimicrobial proteins.
- Inflammatory mediators produced locally, influenced by genetic factors, environment and local exposure history
- Innate immune responses by airway cells, macrophages, and NK cells impede viral replication
- T-cell responses are involved in viral clearance




https://doi.org/10.1038/s41385-020-0287-5

https://www.sciencedirect.com/science/article/pii/S1933021922003233?via%3Dihub

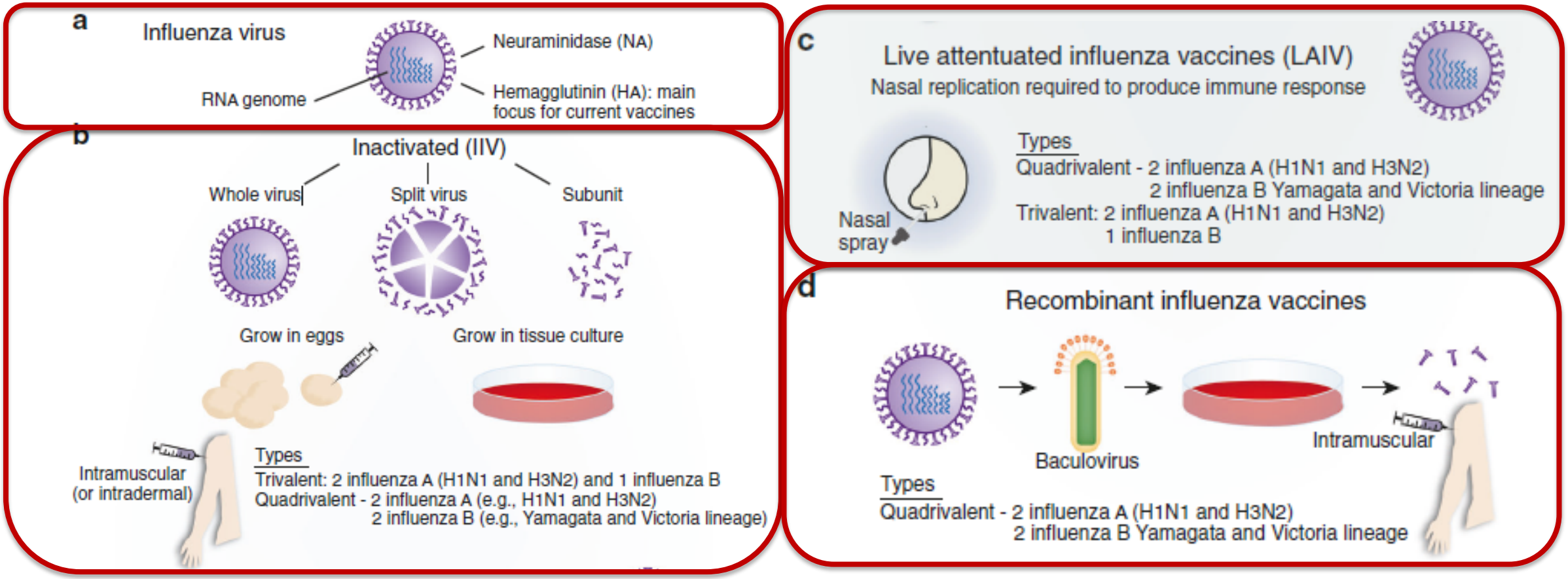
REVIEW ARTICLE

# Seasonal and pandemic influenza: 100 years of progress, still much to learn

MucosalImmunology

https://doi.org/10.1038/s41385-020-0287-5

Jake Dunning[1], Ryan S. Thwaites[2] and Peter J. M. Openshaw[2]




Mucosal Immunology (2020) 13:566–573

# A spatially resolved atlas of the human lung characterizes a gland-associated immune niche

Elo Madissoon, Amanda J. Oliver, … et al Kerstin B. Meyer

*Nature Genetics* **55**:66–77 (2023)

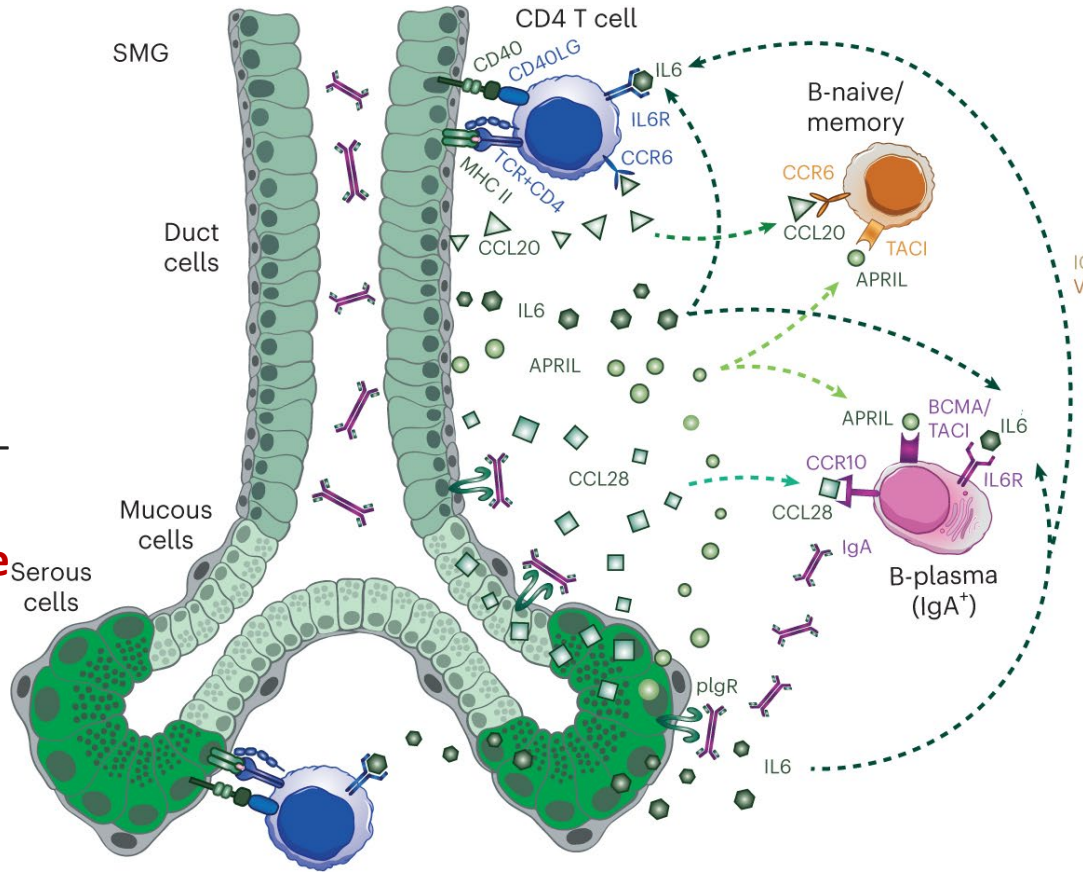
nature genetics

Profiled 5 proximal-to-distal locations of healthy human lungs using multi-omic single cell/nuclei and spatial transcriptomics (lungcellatlas.org)

**Identified 80 cell types/states** from >190,000 cells including *11 new cell types*

**Discovered new anatomical compartment**: epithelial, vascular, stromal and nerve bundle micro-environment with novel peribronchial fibroblasts, providing a **survival niche for IgA plasma cells in the airway submucosal glands (SMG).**

**This 'gland-associated immune niche'** promoting longevity and antibody secretion locally through expression of CCL28, APRIL and IL-6.




See comment: https://www.nature.com/articles/s41588-022-01244-3

https://www.nature.com/articles/s41588-022-01243-4.pdf

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Journal of Visualized Experiments

Click Here to Watch this Article on JoVE

# Absorption of Nasal and Bronchial Fluids: Precision Sampling of the Human Respiratory Mucosa and Laboratory Processing of Samples

Ryan S Thwaites et al

The methods of nasal absorption using synthetic absorptive matrices (SAM) to absorb the mucosal lining fluid of the human respiratory tract.

- Non-invasive technique
- Absorbs fluid from the inferior turbinate
- Causes minimal discomfort.
- Yields reproducible results
- Allows frequently repeat sampling

Download video file.(106M, mp4)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5908664/

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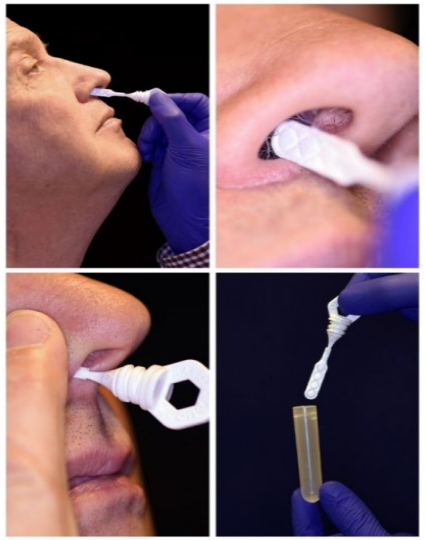
# LAIV Challenge

- Use LAIV as a human challenge agent in young adults to study:
  - Viral shedding
  - Effect of pre-existing immunity: humoral and cellular
  - The innate response to LAIV: association with generation of immunity
  - **The (mucosal) humoral immune response to LAIV**

**Dr Ryan Thwaites**



# **Study design:** n=40 healthy 18-30 y.o.

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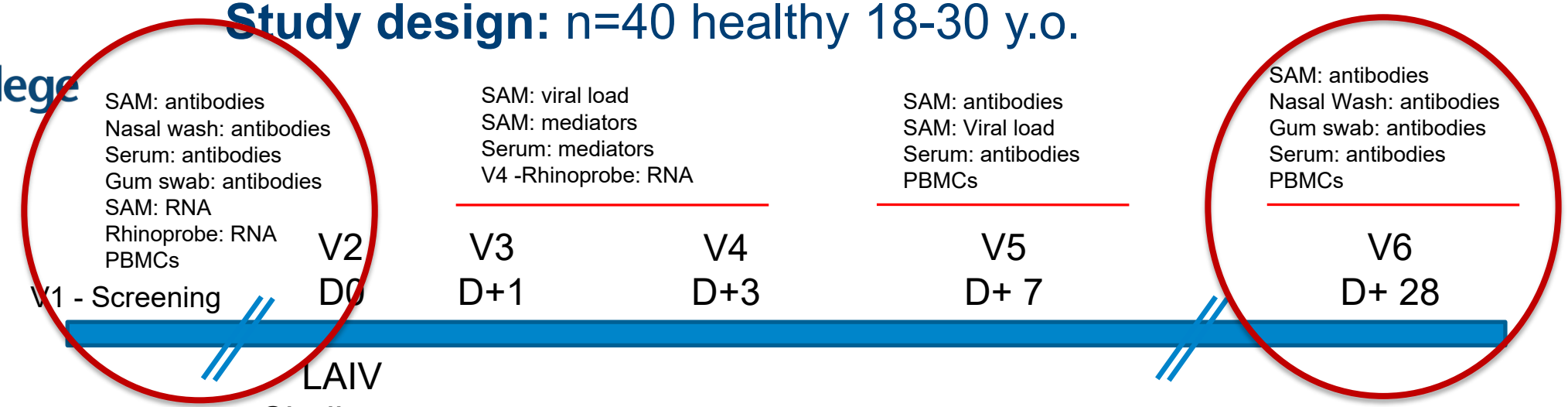


**Dr Ryan Thwaites**

No screening criteria (“all-comers” approach)

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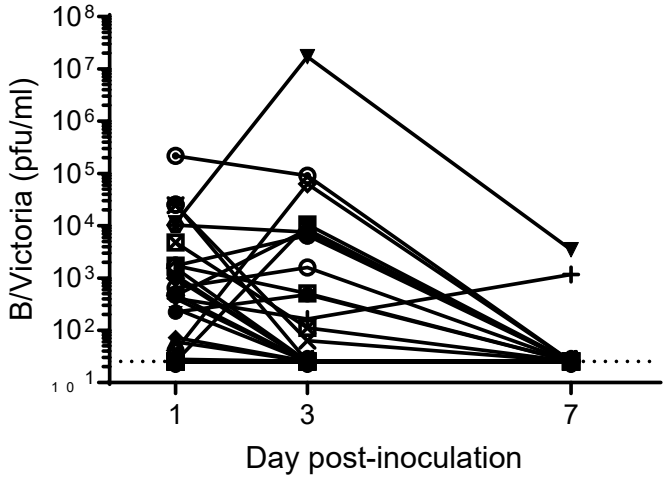
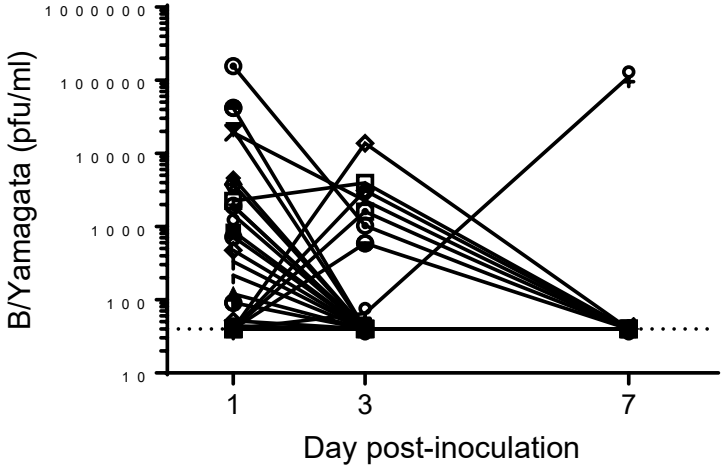
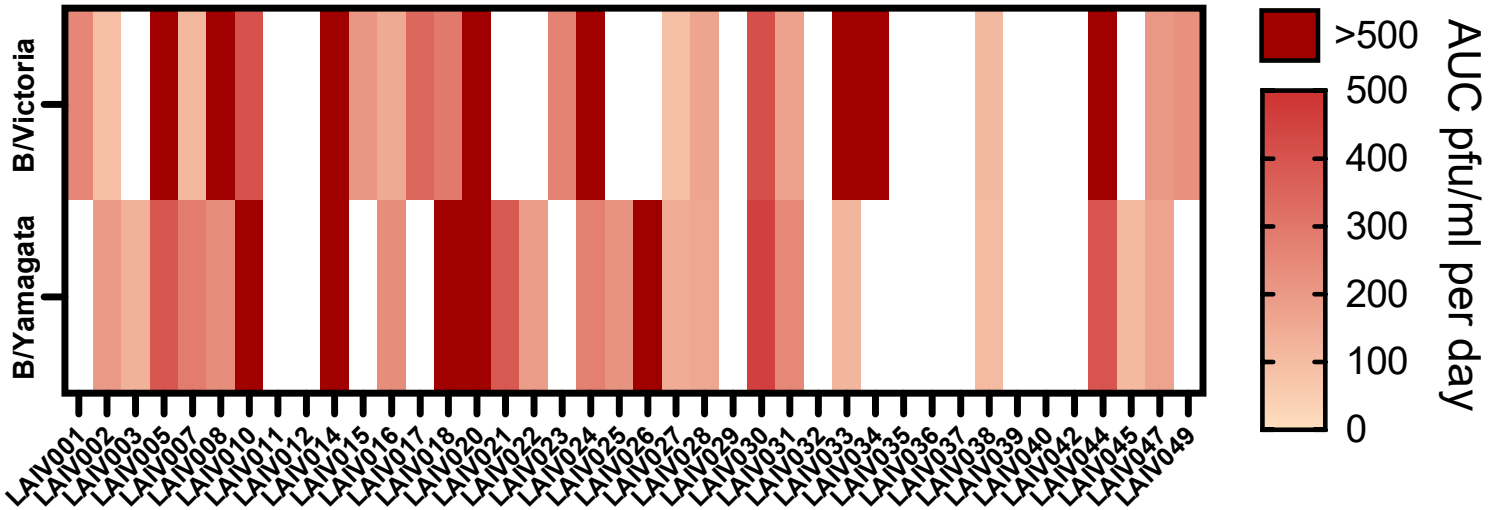
# Viral shedding




- Shedding not observed for A viruses (but there is an antibody response…)
- Quantity of B virus shedding unrelated to the scale/nature of antibody response

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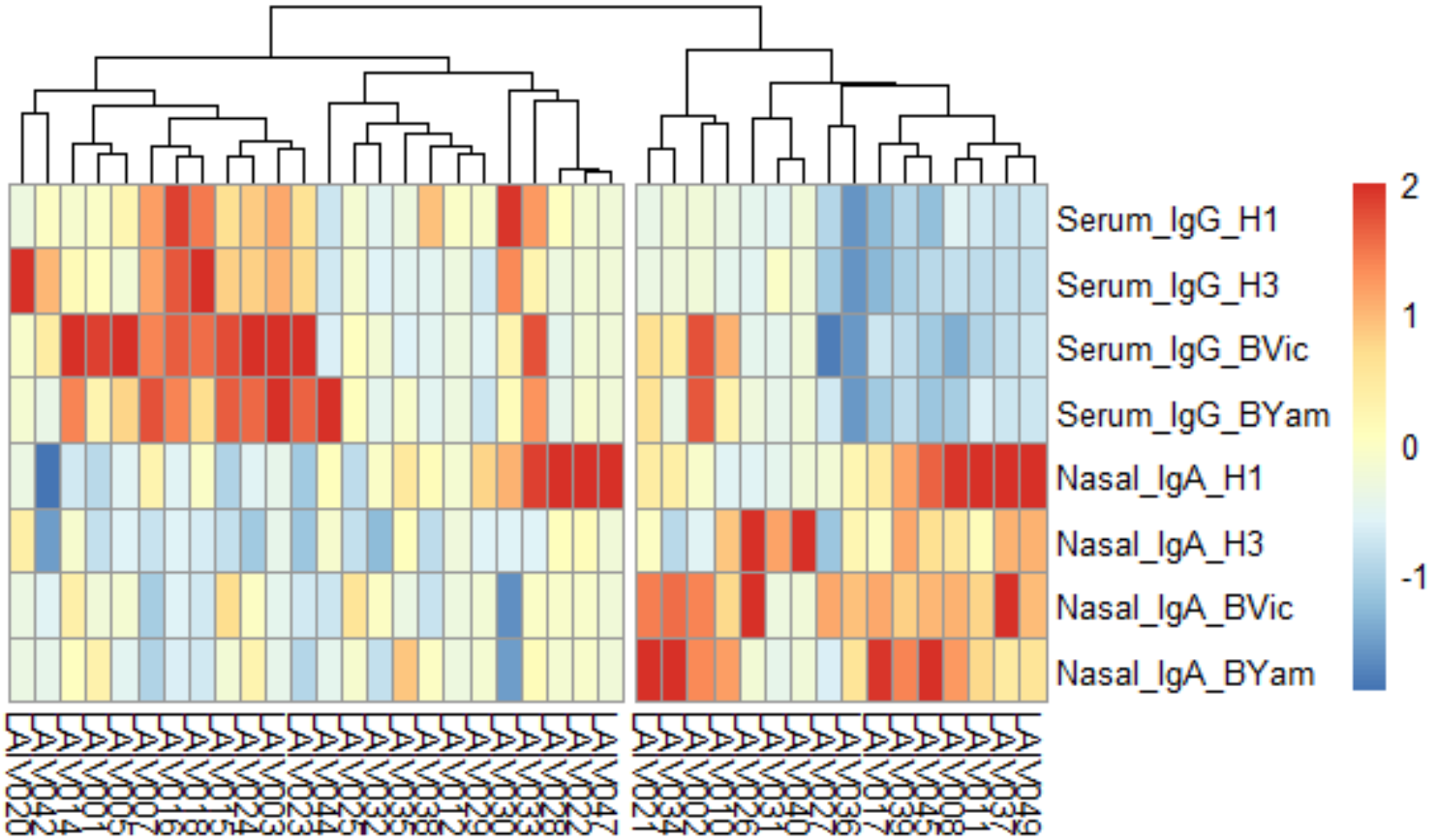
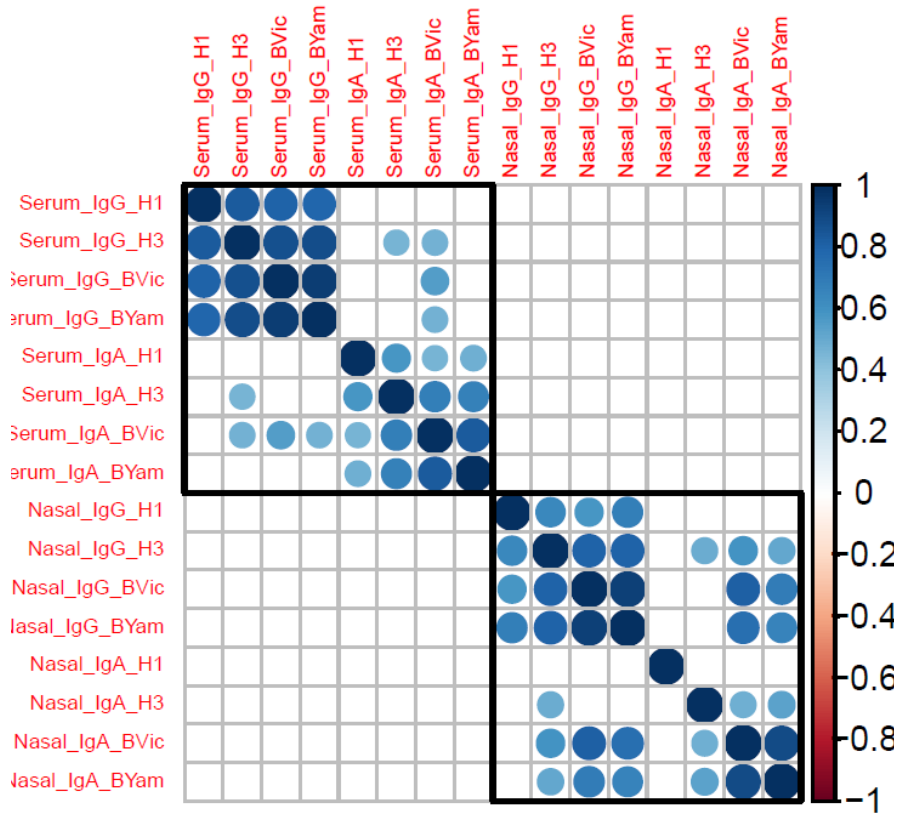
# Antibody response: Compartmentalisation




Little overlap between plasma IgG and nasal IgA responses – often one or the other

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Dr Ryan Thwaites

# Summary of LAIV Ab findings

- Response in plasma HAI only in those with low baseline titres
- Antibody response more frequent in nasal samples than plasma
- **Antibody responses in nasal and plasma are independent**

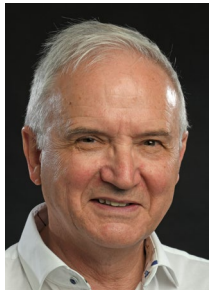
# ISARIC preparedness platform

*Kenny Baillie*

- Developed in the wake of the flu pandemic
- Uses WHO-approved clinical data tool from MOSAIC
- Sleeping platform, launched 2011
- Pre-agreements in place with >200 UK hospitals

*Calum Semple*

ISARIC 4C
Coronavirus
Clinical
Characterisation
Consortium



*Peter Openshaw*

*Kenny Baillie*

*Calum Semple*

**307 997**
Number of patients (all tiers)

**305 127**
Number of patients (Tier 0)

**847**
Number of patients (Tier 1)

**2 023**
Number of patients (Tier 2)

**Hospitalized COVID-19 patients recruited**

**Tier 0**
- Demographic data
- Outcome
- Comorbidities

**Tier 1**
Single sample set:
- Plasma/serum
- Nasal swabs
- Urine + Stool

**Tier 2**
- Serial biological sample sets

https://argoshare.is.ed.ac.uk/isaric4c_recruitment/render_site.html

Updated 6th June 2022

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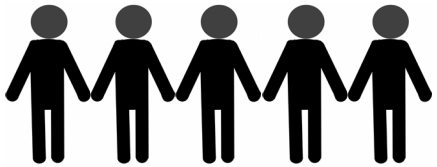
MRC Medical Research Council | UKCIC UK Coronavirus Immunology Consortium | PHOSP-COVID Improving long-term health outcomes | ISARIC 4C

# 446 participants



226 patients ISARIC and PHOSP
127 patients PHOSP (convalescent only)
93 patients from ISARIC only (acute only)

**6 to 9 month visit:**
Median: 16th March 2021
(September 2020 to August 2021)

**>12 month visit:**
Median: 11th July 2021
(March 2021 to March 2022)

Dr Felicity Liew

Recruitment to ISARIC4C

Visit 1

Visit 2

Visit 3


0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Months

Recruitment to PHOSP-COVID

Participants vaccinated

February 2020 to March 2021

Prior to emergence of Omicron variant (November 2021)

Median date of vaccination:
20th February 2021
(December 2020 to March 2022)

**356 Nasosorption samples**

**569 Plasma samples**

Clinical data: vaccination, persistent symptoms

Image take from: Thwaites, R. S. *et al.*,. J. Vis. Exp. (2018).

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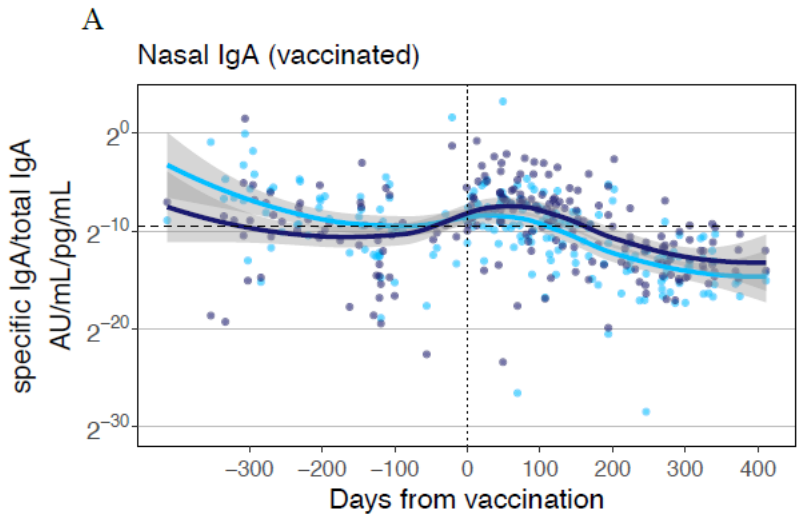
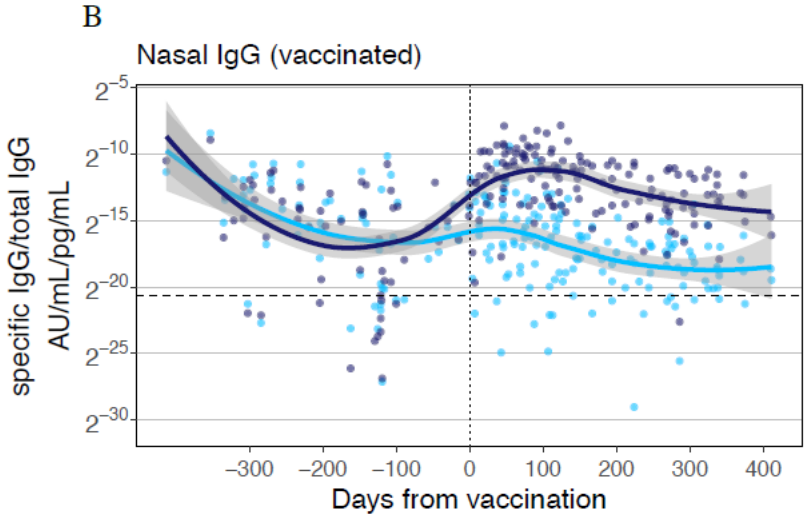
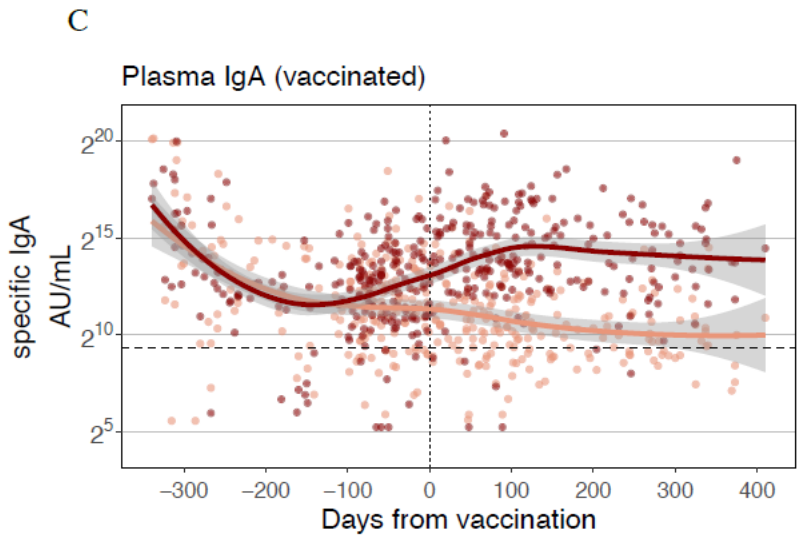
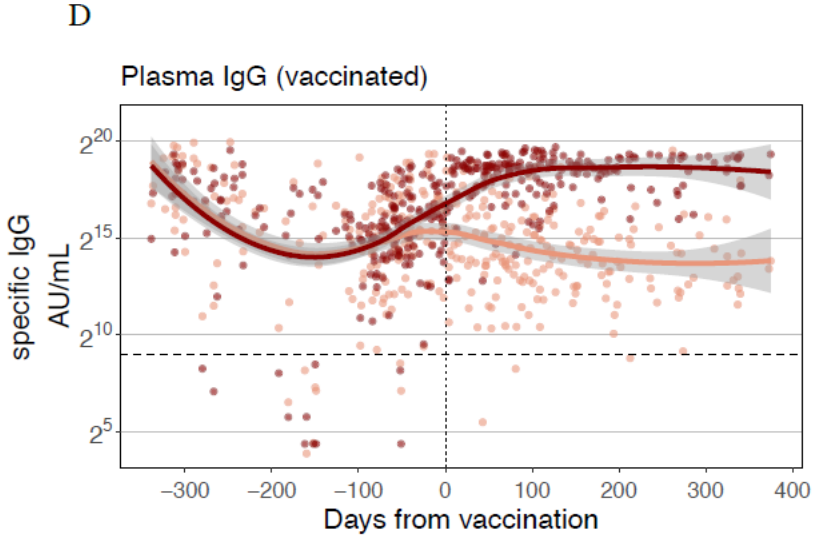
# Nasal IgA is not affected by vaccination, nasal IgG mirrors plasma



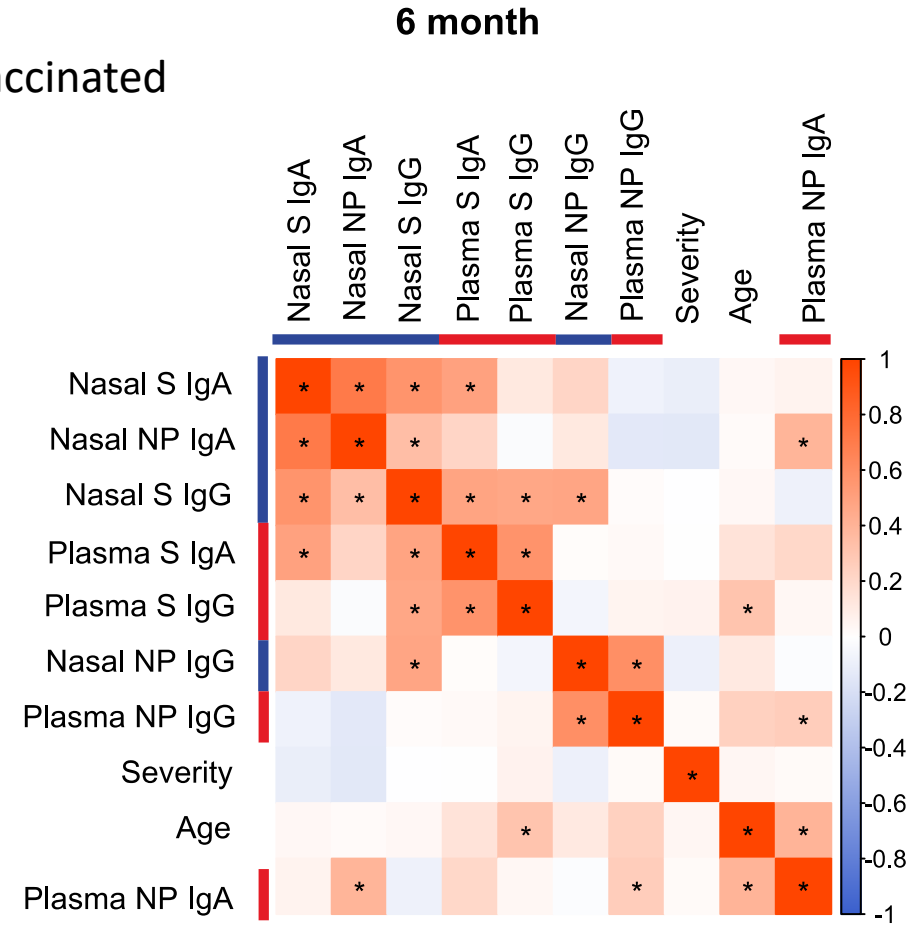




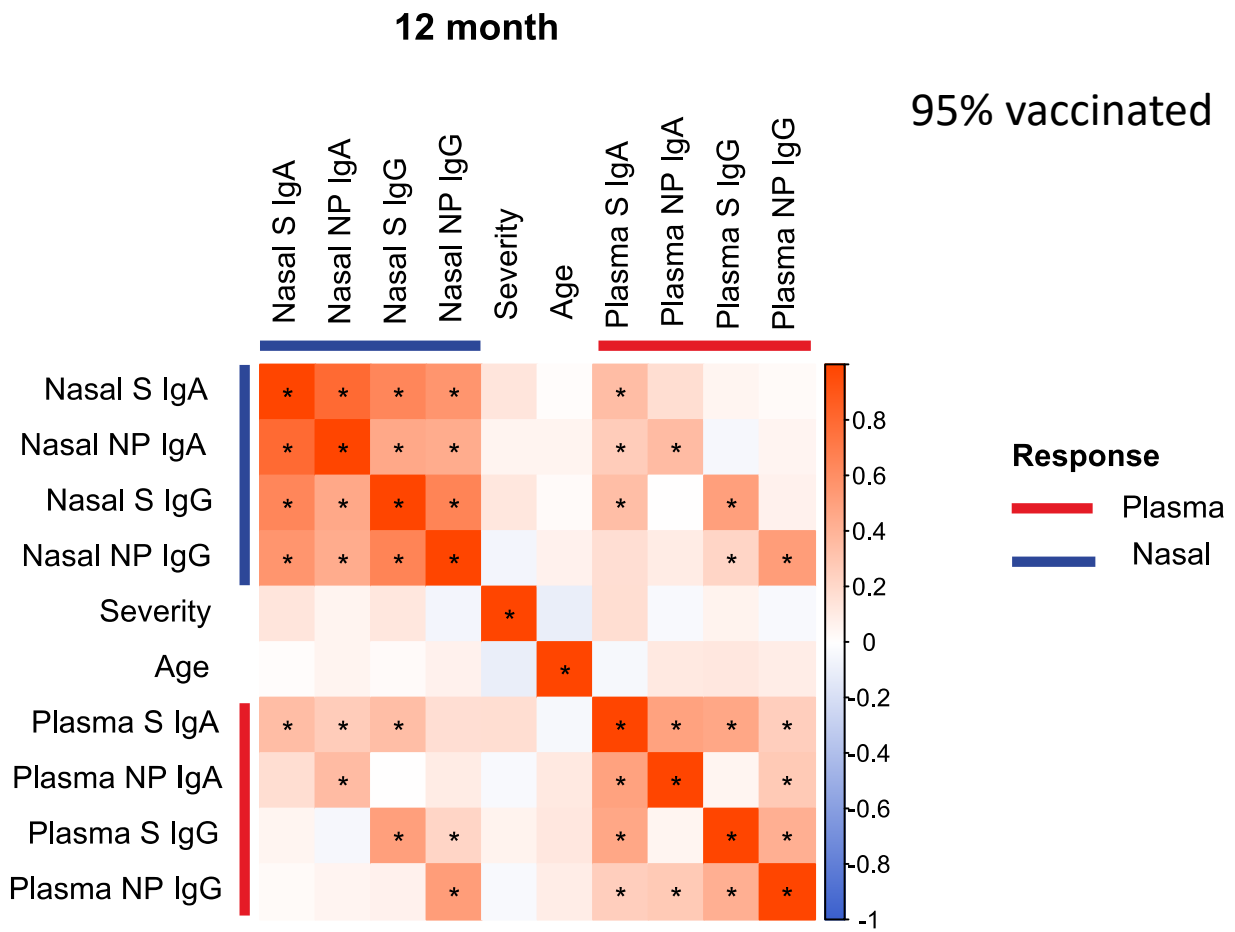




# The nasal IgA response is compartmentalized after vaccination

93% vaccinated




95% vaccinated



CellPress

Immunity

# Upper airway and brain protection by plasma cells: A local affair

Rebecca Cornelis[1] and Ziv Shulman[1,*]
[1]Department of Systems Immunology, Weizmann Institute of Science, Rehovot 7610001, Israel
*Correspondence: ziv.shulman@weizmann.ac.il
https://doi.org/10.1016/j.immuni.2022.10.012

VOLUME 55, ISSUE 11, P1972-1974, NOVEMBER 08, 2022

A mucosal barrier protects the brain from viral invasion through the olfactory mucosa

This barrier restricts the passage of circulating antibodies into the mucosa

Specialised plasma cells are present in a mucosal niche; these prevent viral infection of the airways and the brain through local antibody production.

https://doi.org/10.1016/j.immuni.2022.10.012

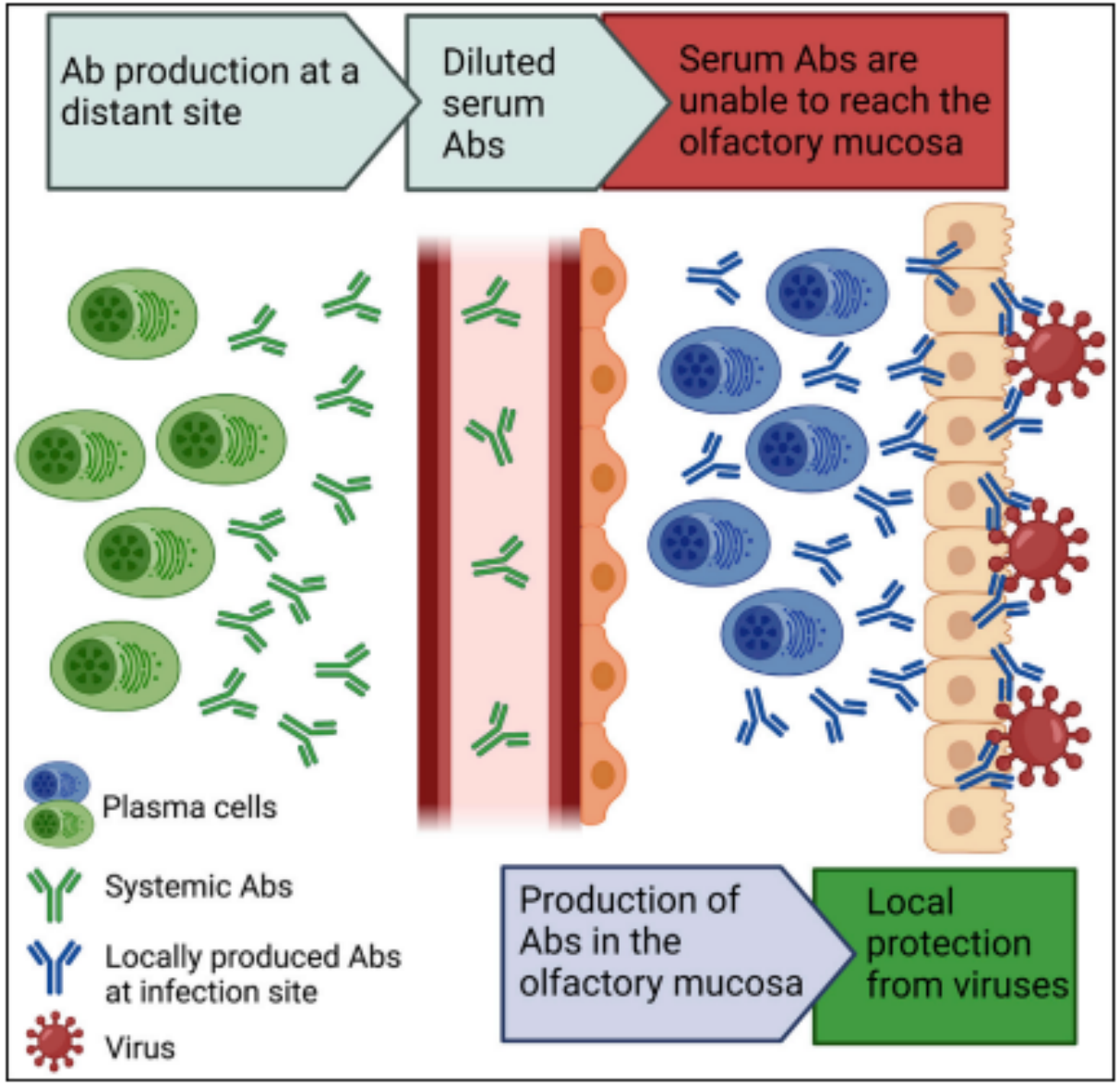



Figure 1. Plasma cells are recruited to olfactory mucosa and secrete protective antibodies that provide local protection from respiratory viral infections

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HIC-Vac

www.hic-vac.org

wellcome

**£3m, 5 year Medical Research Council/Wellcome-funded network to:**

*Support, develop and advocate the use of human infection challenge, to…*

- improve understanding of infections, and the diseases they cause
- enhance the development of new/better vaccines/treatments for infections of global importance

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MRC Medical Research Council

GCRF

BBSRC bioscience for the future

University of Oxford

LMIC, low-to-middle-income countries. HIC-Vac homepage. Available from: www.hic-vac.org. Accessed November 2022.

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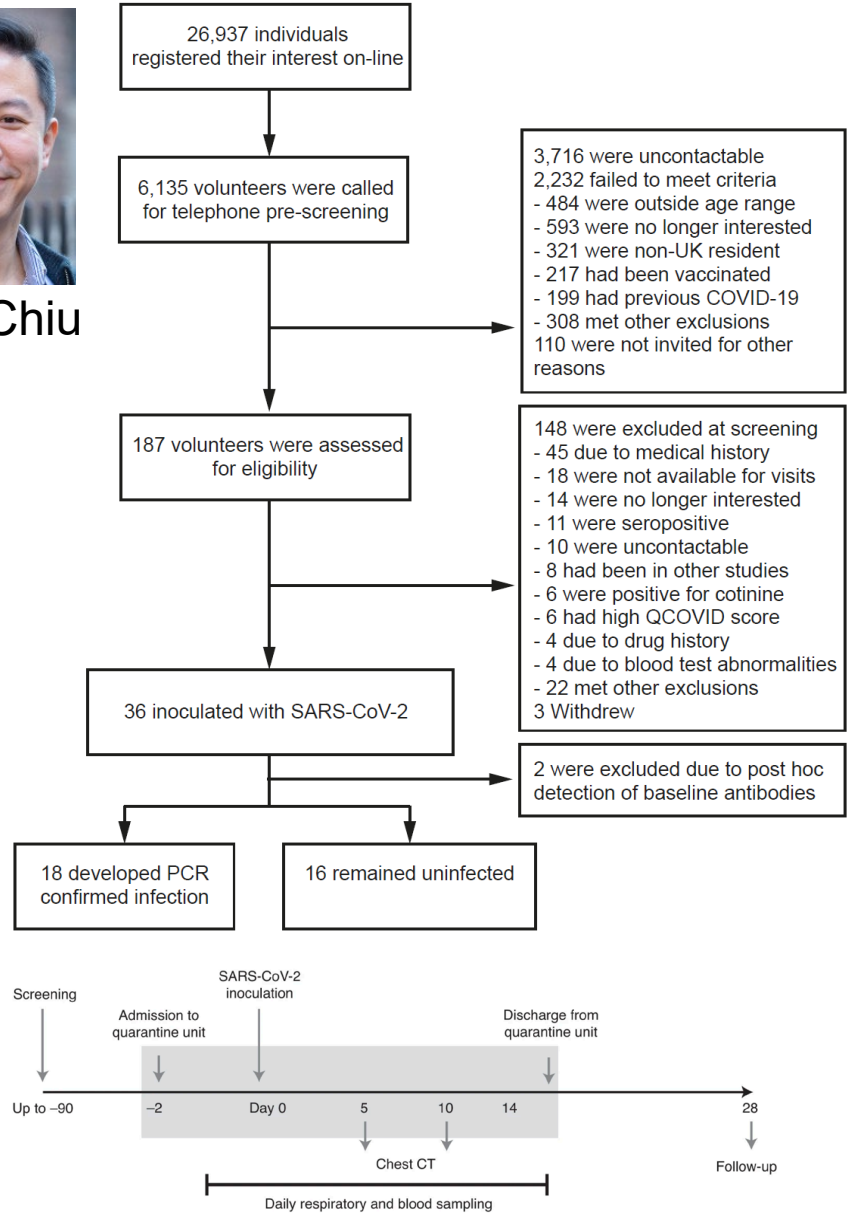
# First SARS-CoV-2 challenge study

Chris Chiu

## *Clinical design and recruitment*

- Extensive public support & interest: ~27,000 on-line registrations
- Before vaccines were available
- Screening+++: healthy, seronegative, willing & able




*Nature Medicine* **28:**1031–1041 **(2022)**

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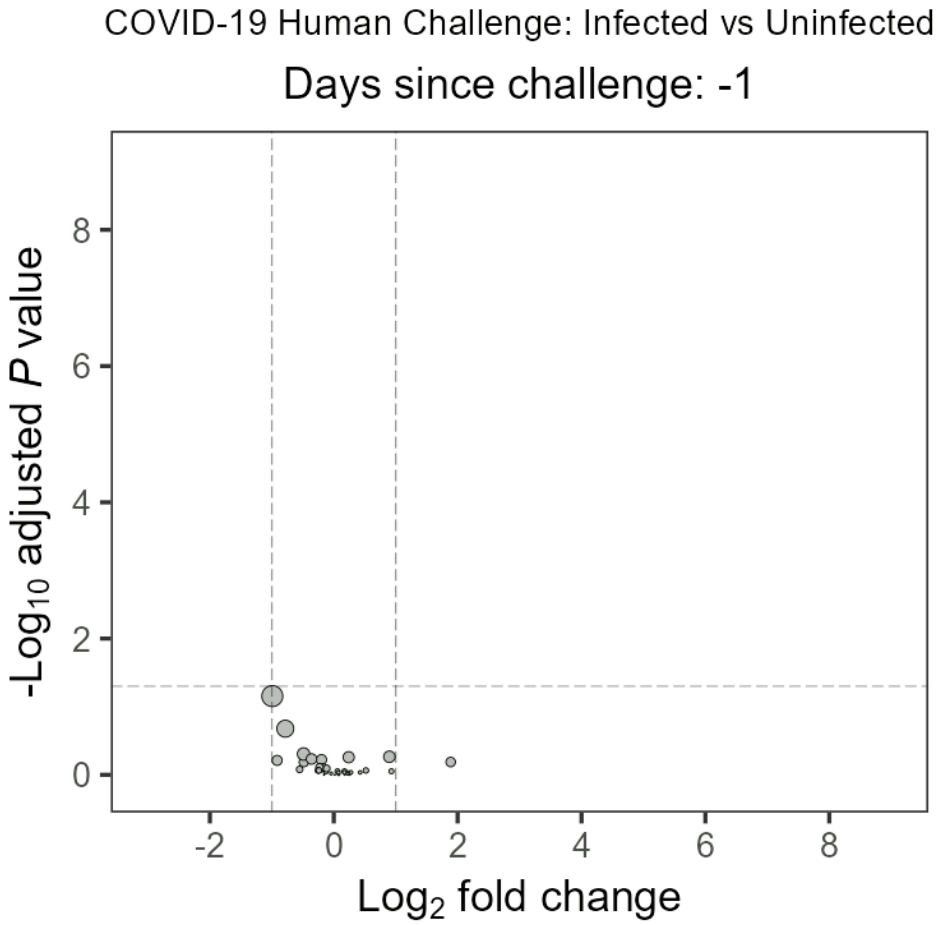
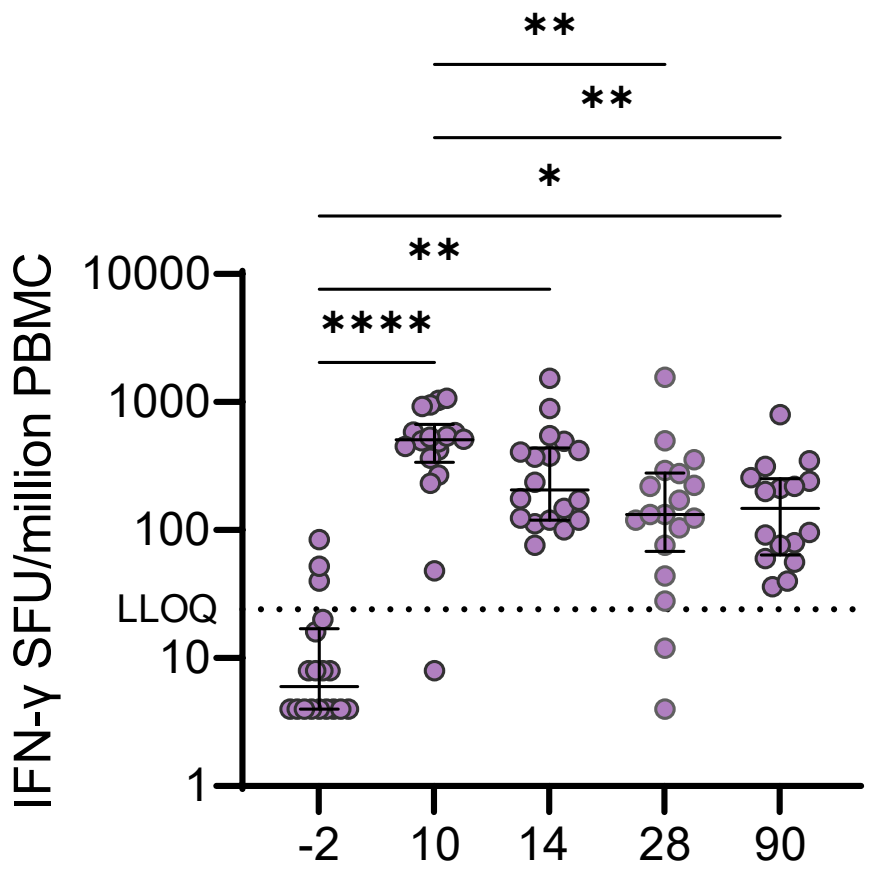
Ryan Thwaites, Matt Siggins, Helen Wagstaffe, Chris Chiu *et al*

# Local mediator response, systemic T cells



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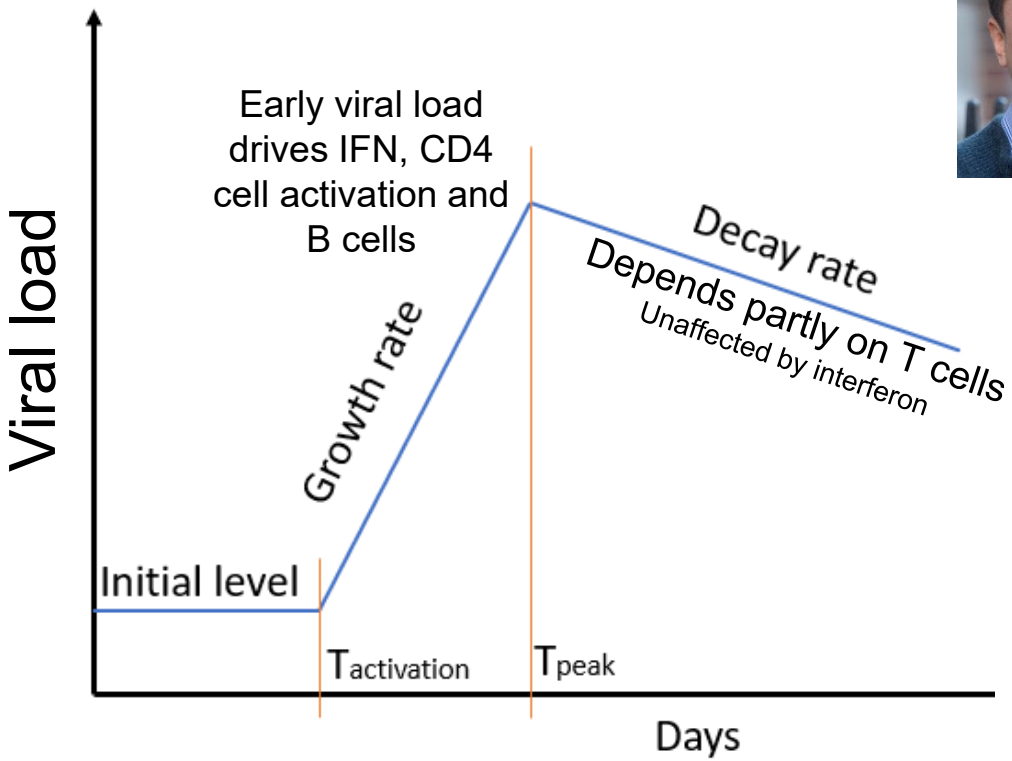
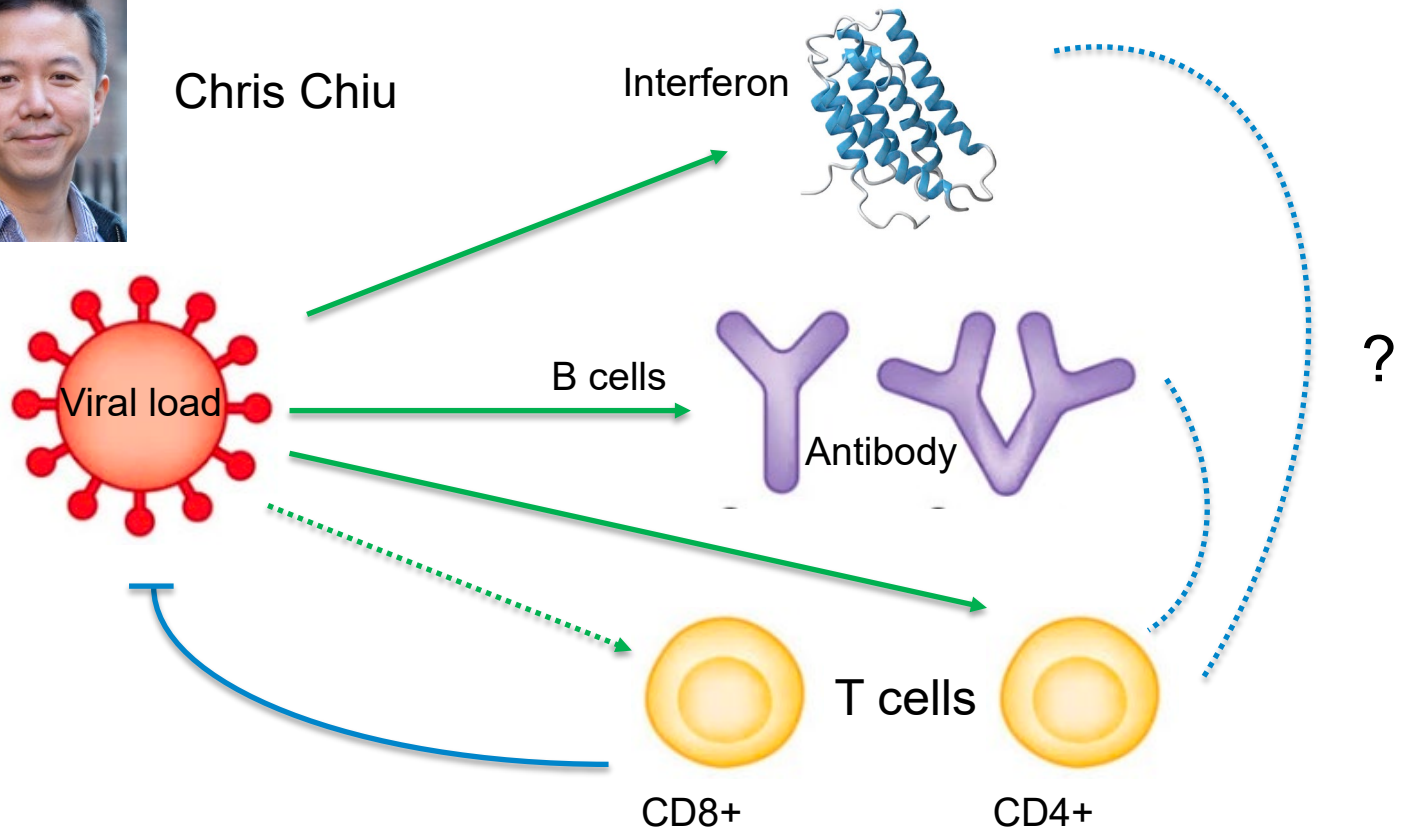
# Summary of events in primary SARS-CoV-2 infection

Chris Chiu



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# Conclusions

**Systemic immunity is great at preventing systemic illness**

- It is well induced by intramuscular vaccines
- Can be long-lived

**Mucosal immunity is necessary for local protection**

- Controlled separately from systemic immunity
- Induced by mucosal vaccines and by local infection
- Typically lasts only a few months (unless boosted)

***How can mucosal responses be induced to control transmission?***