26es JNI 2025 TOURS
et la région Centre - Val de Loire VINCI
Journées Nationales d'infectiologie
du mercredi 11 juin 2025 au vendredi 13 juin 2025
Journée Nationale de Formation des Paramédicaux en Infectiologie
Jeudi 12 juin 2025

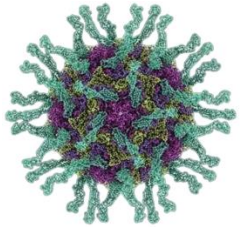
Déclaration de liens d'intérêt avec les industriels de santé en rapport avec le thème de la présentation (loi du 04/03/2002) :

L'orateur ne souhaite pas répondre ☐

- Intervenant : **Guy GOROCHOV**
- Titre : **Passé et futur des vaccins non injectables**

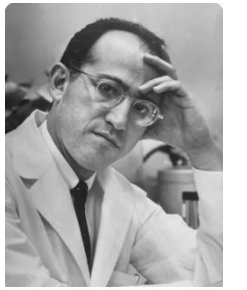
• Consultant ou membre d'un conseil scientifique : Xanadu (USA)	☑ OUI	☐ NON
• Conférencier ou auteur/rédacteur rémunéré d'articles ou documents	☐ OUI	☑ NON
• Prise en charge de frais de voyage, d'hébergement ou d'inscription à des congrès ou autres manifestations	☐ OUI	☑ NON
• Investigateur principal d'une recherche ou d'une étude clinique	☑ OUI	☐ NON

Successful oral polio vaccine induce IgA



Positive-stranded RNA enterovirus (*Picornaviridae)*
Infects via Ig-like receptor CD155
Three main serotypes : PV-1, PV-2 and PV-3

- Infection via the fecal–oral route, inItial replication in gastrointestinal tract
- Paralytic poliomyelitis (- 1% infections) only after systemic penetartion and central nervous system replication
- → selective motor neuron destruction



Jonas Salk
1914 1955 1995

- **Inactivated** ("dead") injected vaccine (**IPV**)
- Induces **IgG and IgM** that prevent translocation
- IPV prevents most complications **but unable to prevent the initial intestinal infection**

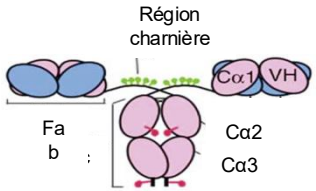
Albert Sabín
1906 1954 1961 1962 1993

- **Oral attenuated** polio vaccine (**OPV**)
  - OPV against PV-1 licenced
    - OPV against PV-2 and PV-3 licenced

- Generates **IgA** in tonsils and gastrointestinal track **blocking intestinal virus replication**

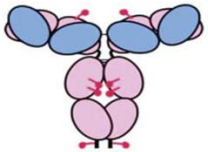
Structure des IgA

IgA1

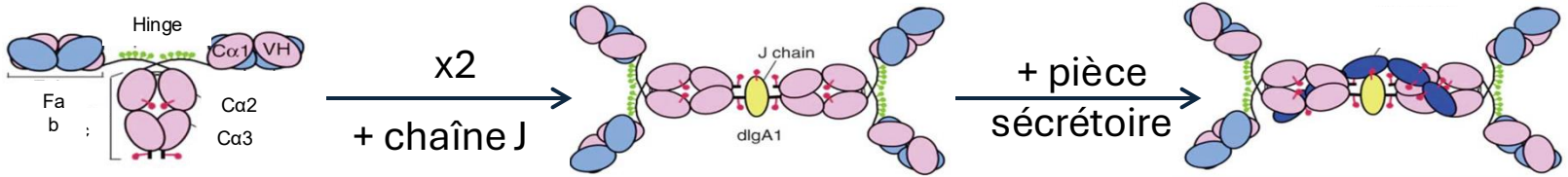


Majoritaire dans le sérum

IgA2



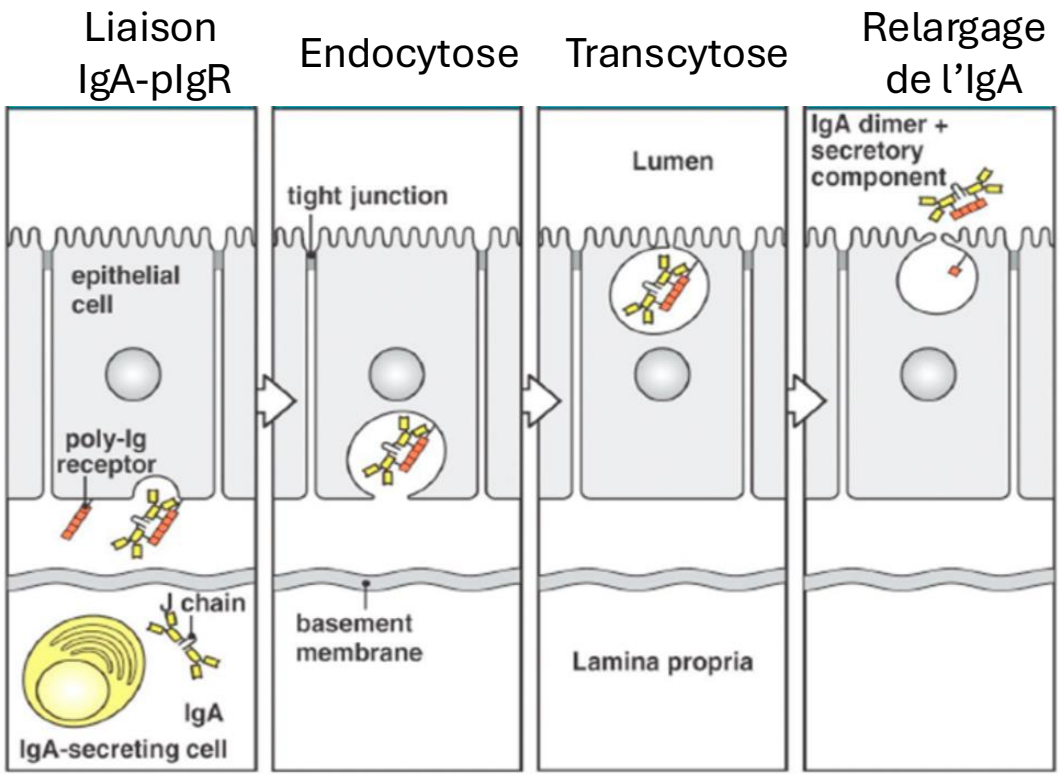
+++ au niveau des muqueuses



IgA sécrétoire

Hapfelmeier et al. Science 2010 ; Woof et al. Mucosal Immunol. 2011

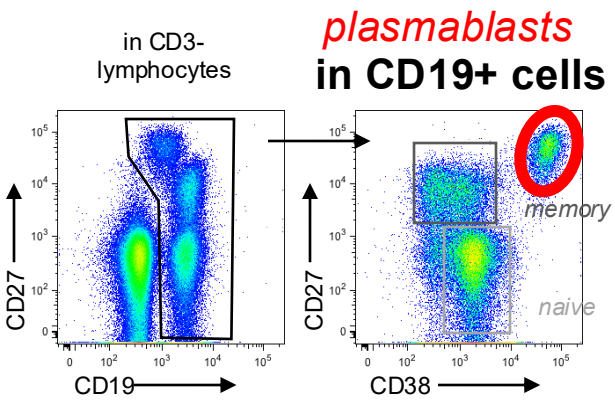
Transport des IgA au niveau des muqueuses

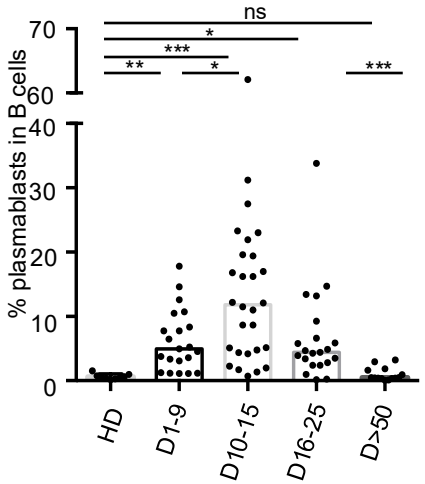


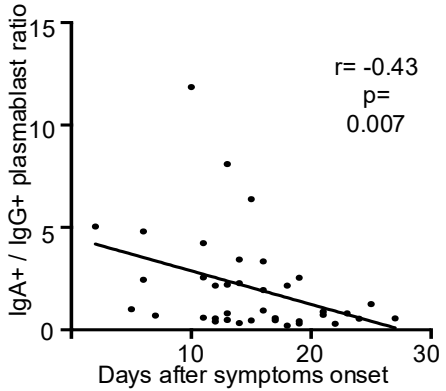
pIgR
Récepteur aux Ig polymériques

Hapfelmeier et al. Science 2010 ; Woof et al. Mucosal Immunol. 2011

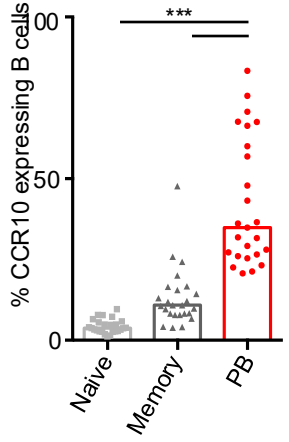
IgA+ plasmablasts peak around D10 post-symptoms







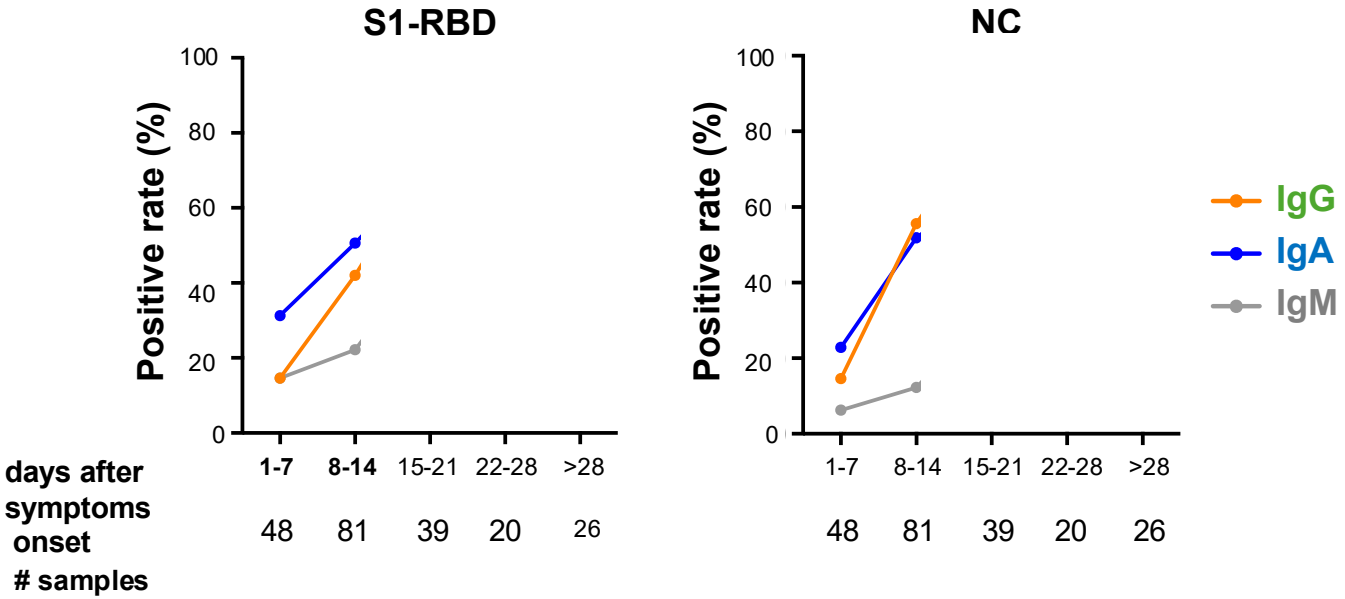
CCR10 + B cells



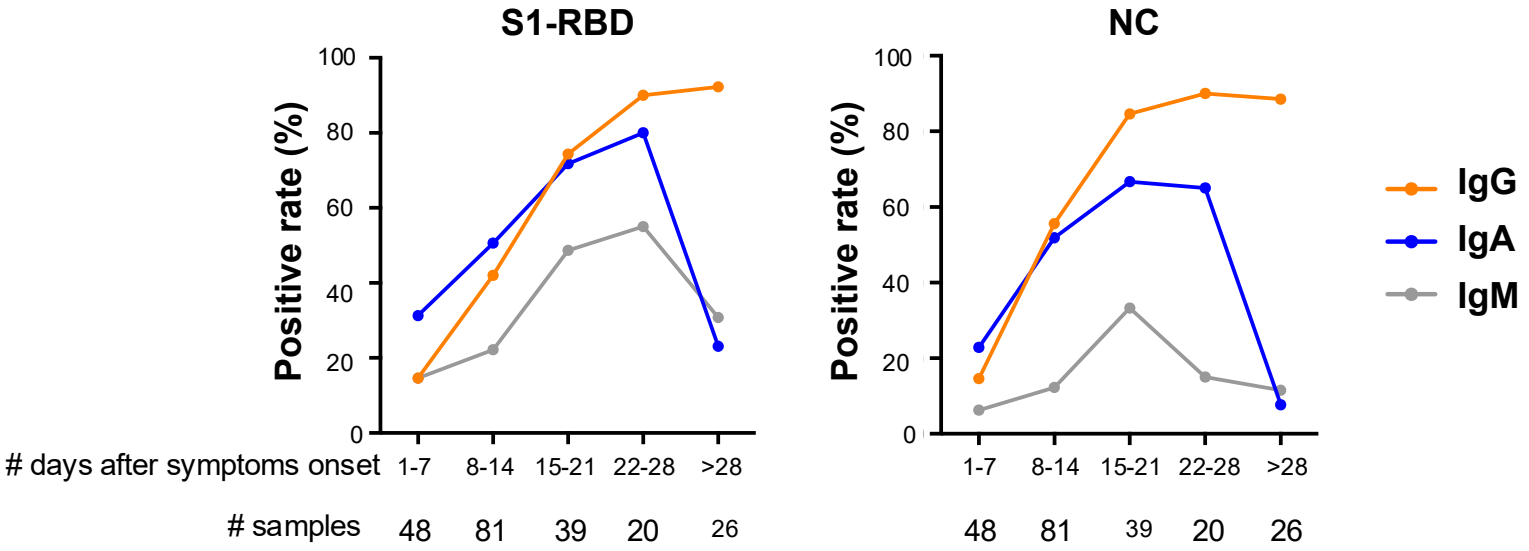
Homing pulmonaire

Sterlin… Gorochov et al. Sci Transl Med. Dec 2020

Early anti-Sars2 IgA response in blood (also in lung)



IgA decrease in blood after one month of evolution



Gorochov et al JAMA NO 2024

Question:

Can mRNA vaccines, which are intramuscularly administered, induce on their own mucosal immunity?

Importance:

Still considerable controversy regarding this issue

Réponse mucosale dans les essais vaccinaux Covicompare

Gorochov G, Ropers J, **Launay O**, Dorgham K, da Mata-Jardin O, Said Lebbah, Durier C, Radenne A, Desaint C, Vieillard LV, Rekacewicz C, Lachatre M, Parfait B, Batteux F, Hupé P, Ninove L, Lefebvre M, Conrad A, Dussol B, Maakaroun-Vermesse Z, Melica G, Nicolas JF, Verdon R, Kiladjian J, Loubet P, Schmidt-Mutter C, Dualé C, Ansart S, Botelho-Nevers E, Lelièvre JD, de Lamballerie X, Kieny MP, Tartour E, Paul S.

AP-HP. Sorbonne Université

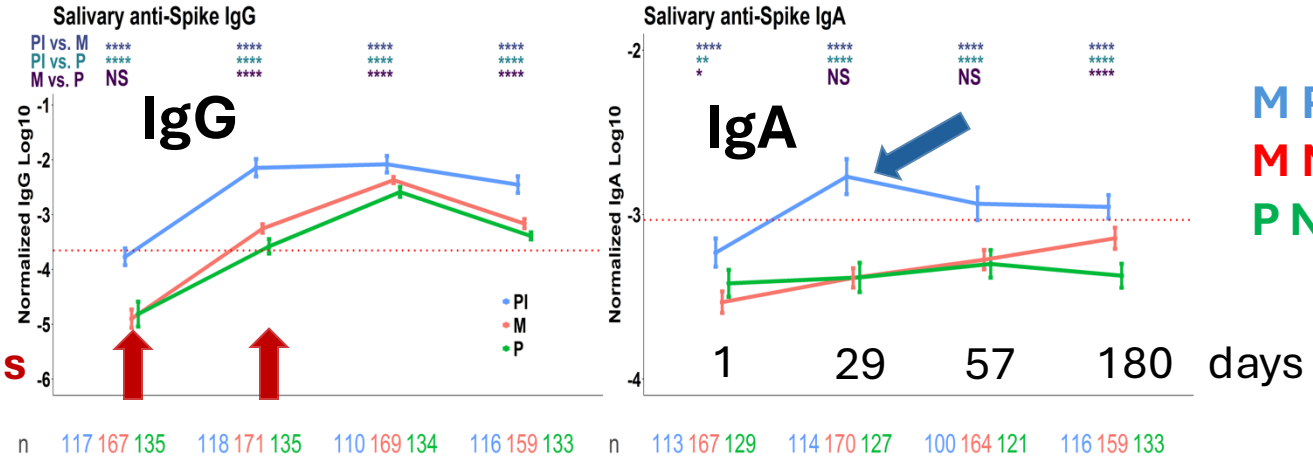
ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

anrs MALADIES INFECTIEUSES ÉMERGENTES Inserm

F-CRIN Network i-reivac Innovative clinical research network in vaccinology

mRNA-induced significant mucosal response only after previous SARS-CoV-2 infection

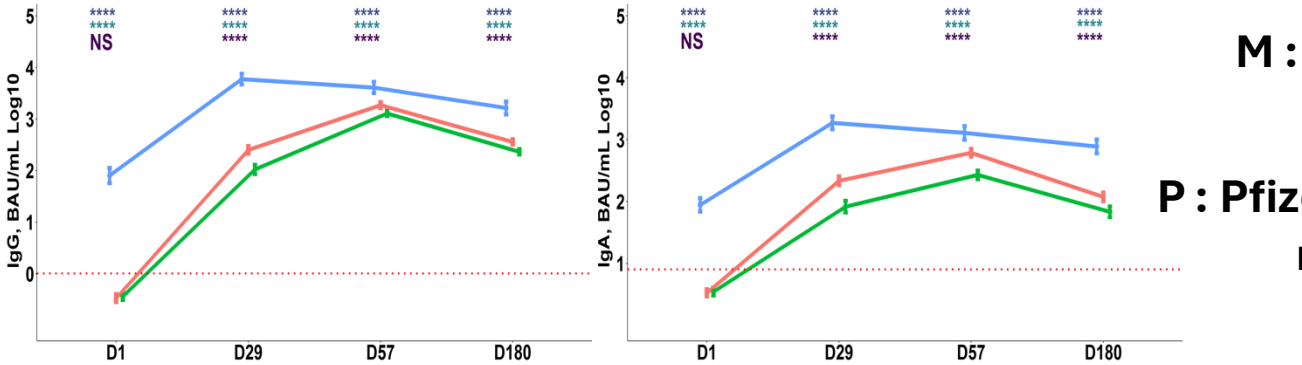
SALIVA



2 injections

M PRE-INF.
M NAIVE
P NAIVE

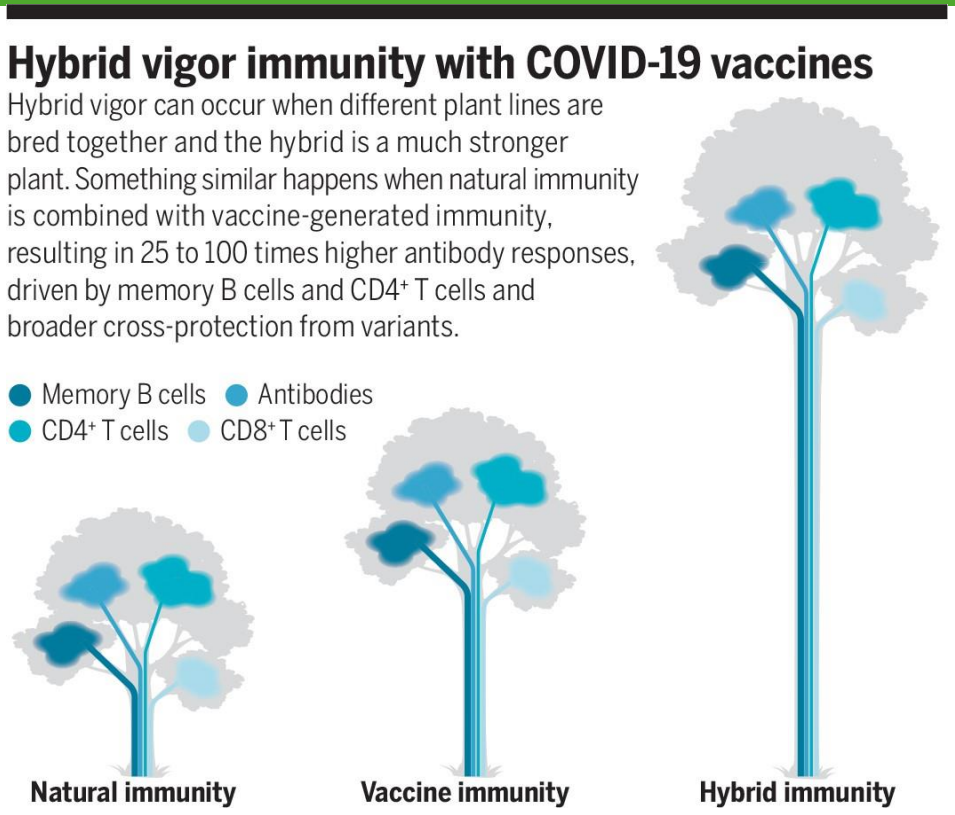
SERUM



M : Moderna
n=180

P : Pfizer-BioNTech
n=267

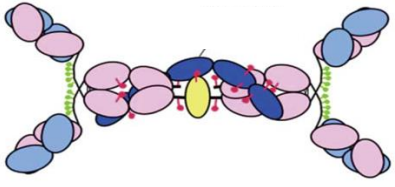
Hybrid immunity: a new concept



Shane Crotty, Science 2021

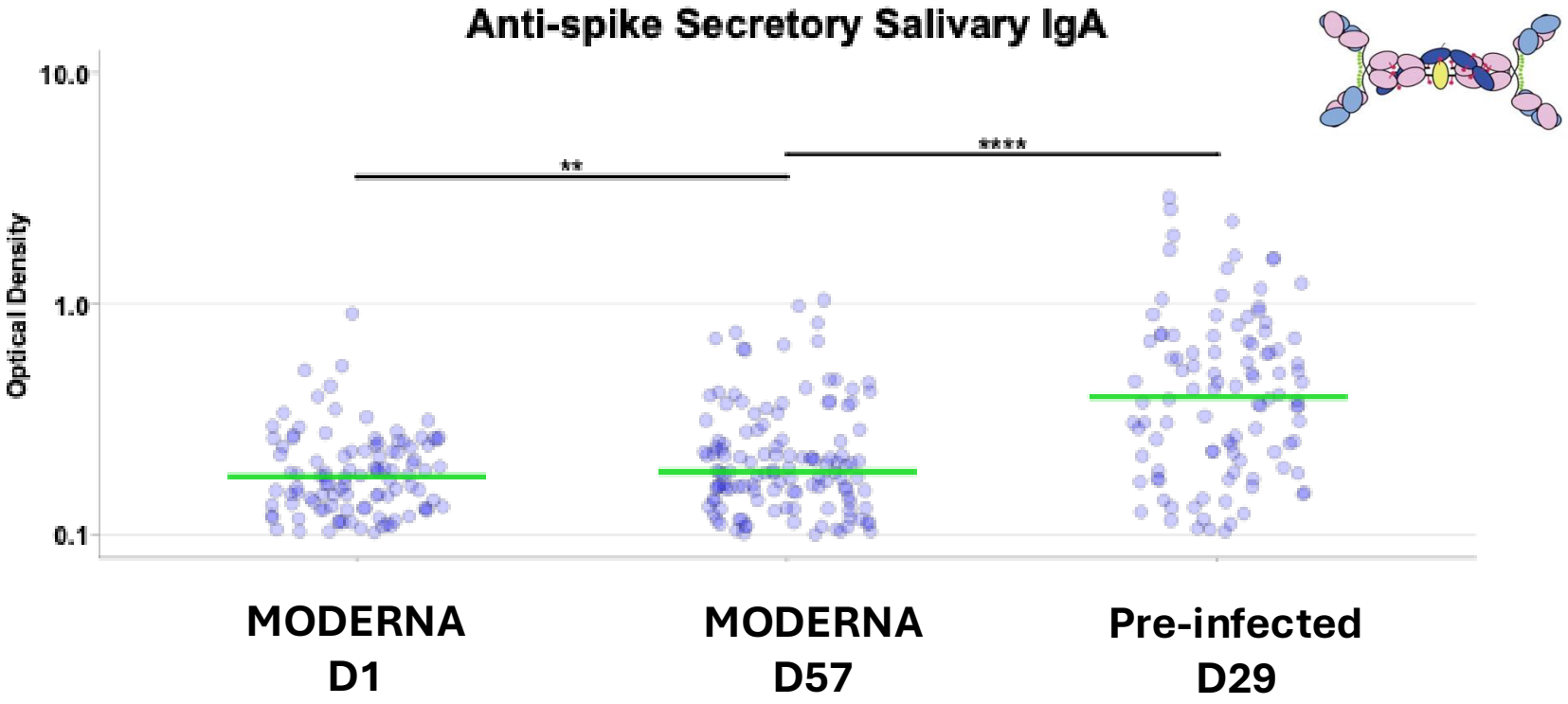
Question:

Pas du tout d'IgA sécrétoires induites par la vaccination ARN?

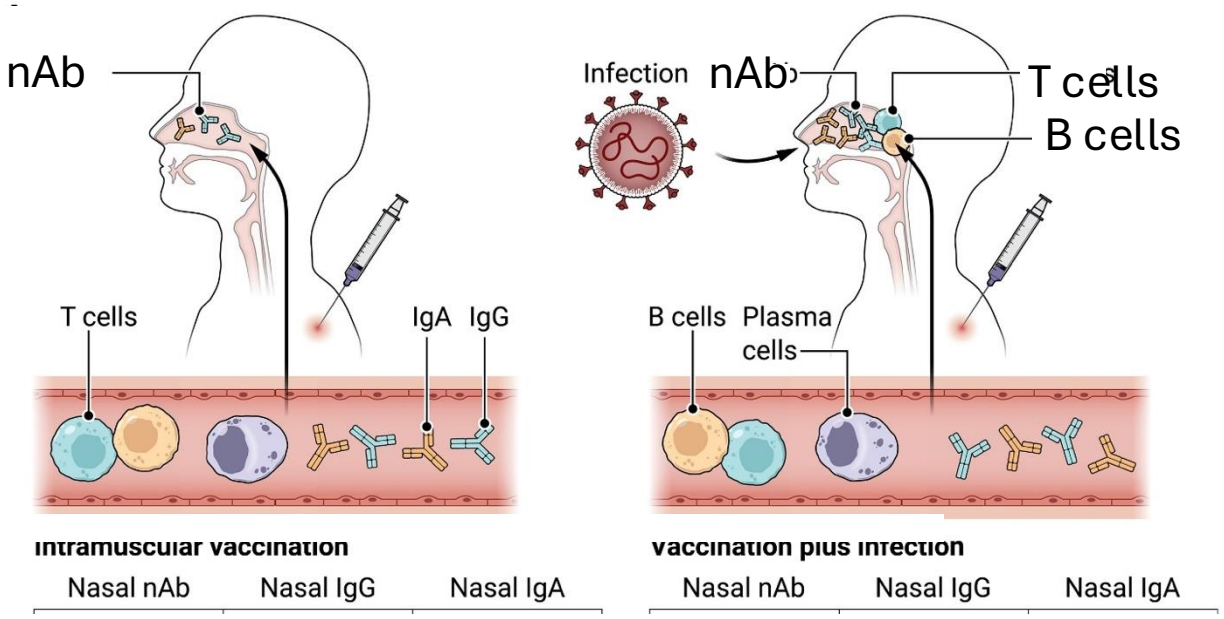


?

Discrète augmentation des IgA sécrétoires 1 mois après la deuxième injection du vaccin Moderna

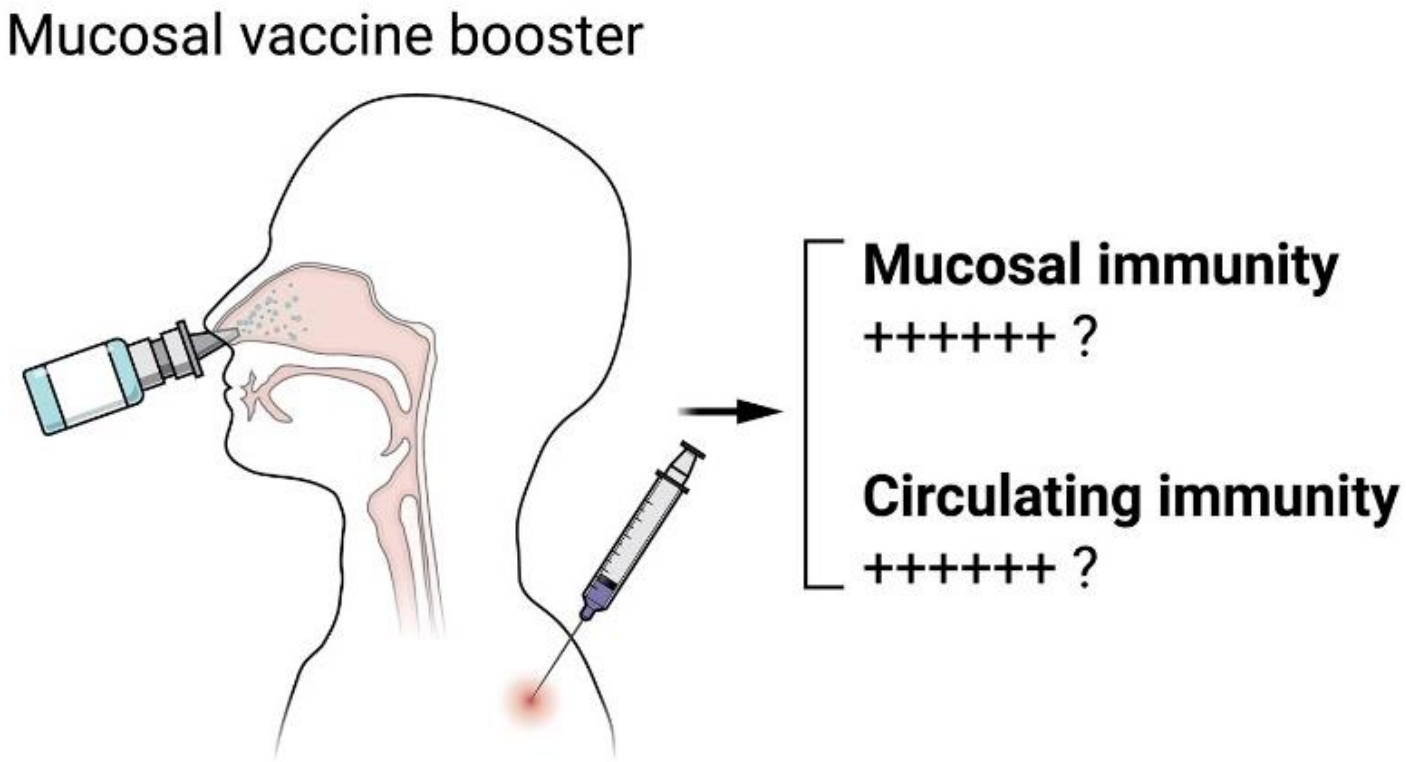


Current IM vaccines: suboptimal nasal immunity



Tang S. et al. STM 2024

Future: IM RNA + mucosal RNA vaccine



Tang S. et al. STM 2024

Mucosal vaccine platforms

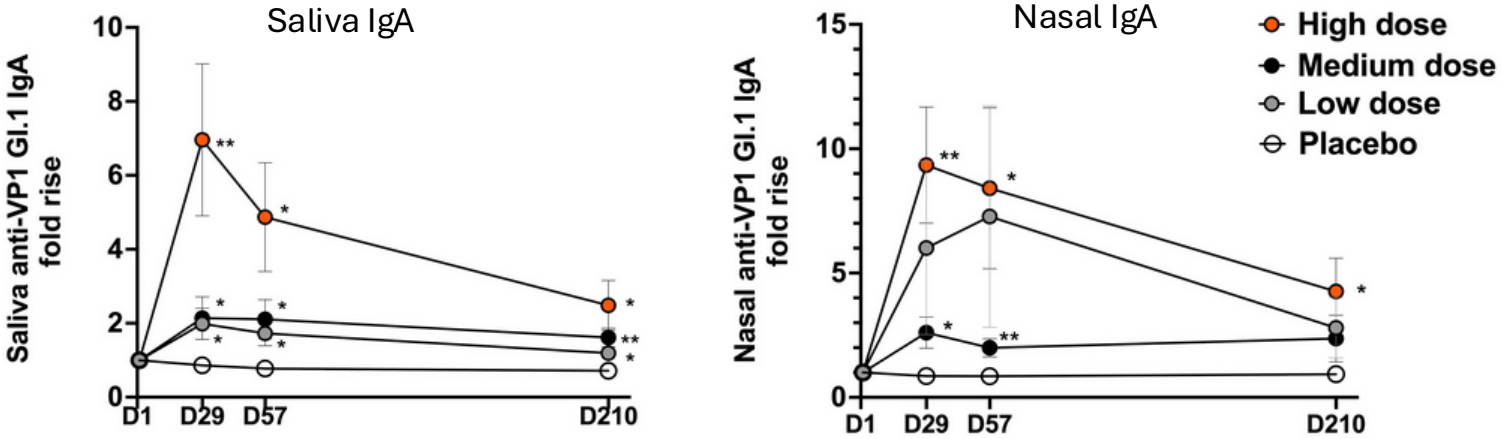
Vaccine Platform	Benefit	Limitations
Subunit/nanoparticle	• Safe and well tolerated • Response enhanced by adjuvant	• Requires adjuvant • Adjuvant-specific adverse events • Slow to upscale
Viral vector vaccines (replicating or nonreplicating)	• Strong cell-mediated response • Experience with licensed vaccines	• Complex manufacturing • Baseline vector immunity • Vector-specific adverse events • Restrictions (replicating) (immunocompromised, pregnancy)
Genetic material (eg, mRNA, DNA)	**• Strong immune response • Efficiency and adaptability**	**• Degradation • Ultrafreezing storage (mRNA) • Risk insertion (DNA)**

Available SARS-CoV-2 mucosal vaccines

Vaccine	Manufacturer	Platform	Administration	Country of Origin
Convidecia Air Ad5-nCoV	CanSino Biologics	Adenovirus (Ad-5) vector	Nebulizer/aerosolized spray	China
iNCOVACC, BBV154	Bharat Biotech	Chimpanzee adenovirus vector (Ad36)	Intranasal disposable dropper	India
Razi Cov Pars	Razi Vaccine and Serum Research Institute	Recombinant protein subunit + plant oil in water adjuvant system (RAS-01)	Intranasal spray	Iran
Gam-COVID-Vac	Russian Health Ministry	Adenovirus vector recombinant (Ad26 and Ad5 vectors)	Intranasal spray	Russia
Pneucolin dNS1-RBD	Beijing Wantai Biological Pharmacy Enterprise	Live-attenuated influenza virus vector-based	Intranasal spray	China

Babu TM, The Journal of Infectious Diseases 2025

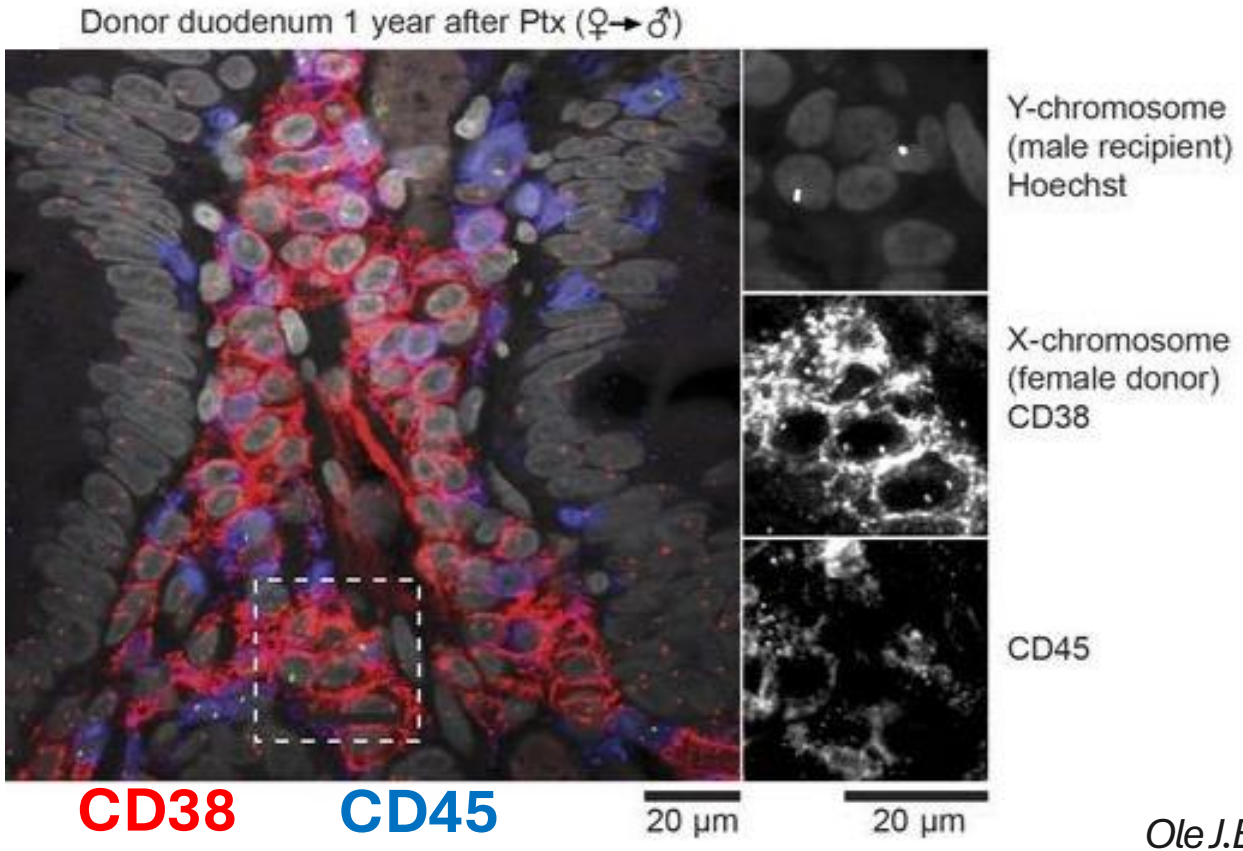
Oral norovirus-encoding adenoviral vector induce saliva and mucosal IgA



Delivery of norovirus major capsid protein VP1 to the small intestine

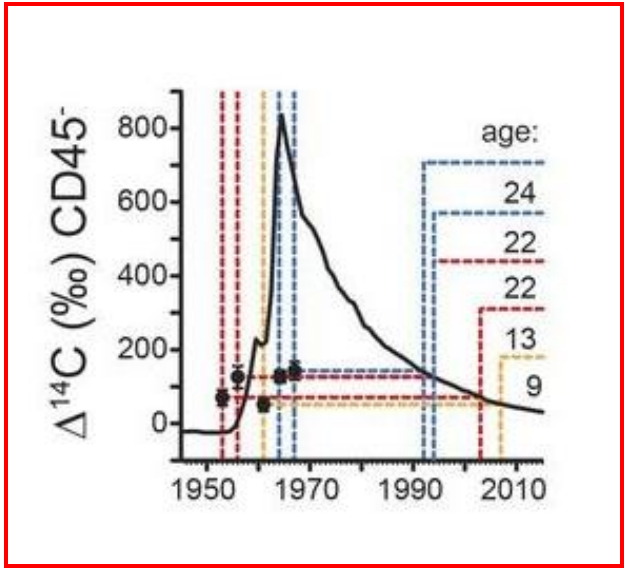
Flitter B. et al. Sci immunology, 2025

Plasma cells persist for decades in grafted (sex-mismatched) human intestine



Ole J.B. Landsverk et al. JEM

Median age of mucosal plasmocytes is 22 years



Birth date of humans cells calculated using atmospheric carbon-14 decrease after the atomic Test Ban Treaty in 1963

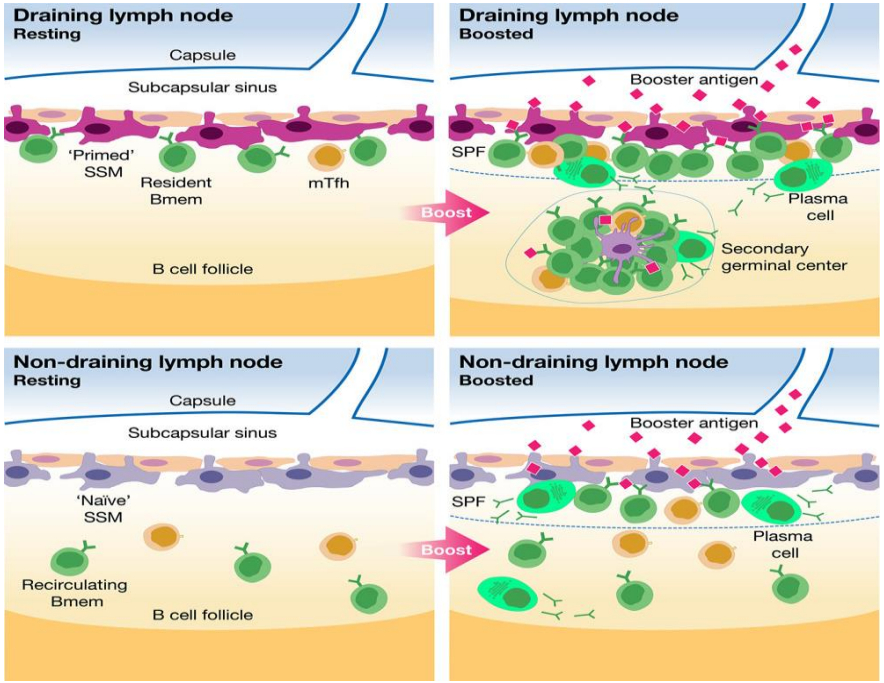
Ole J.B. Landsverk et al. JEM 2017

Bergmann, Science 2009

Conclusions

- SARS-CoV-2-specific IgA levels clearly rise up above detection threshold only in pre-infected individuals (**hybrid immunity**)
- mRNA vaccination *per se* cannot induce a strong mucosal antibody response
- **mucosal specific IgA** detected in **naïve individuals** are mainly of blood-, and to a lesser extent of mucosal-origin
- Further studies are needed in order to determine the level of mucosal IgA preventing **vaccine breakthrough**

COVID vaccine works FASTER with both doses in same arm (peak 5-7 d n=30)

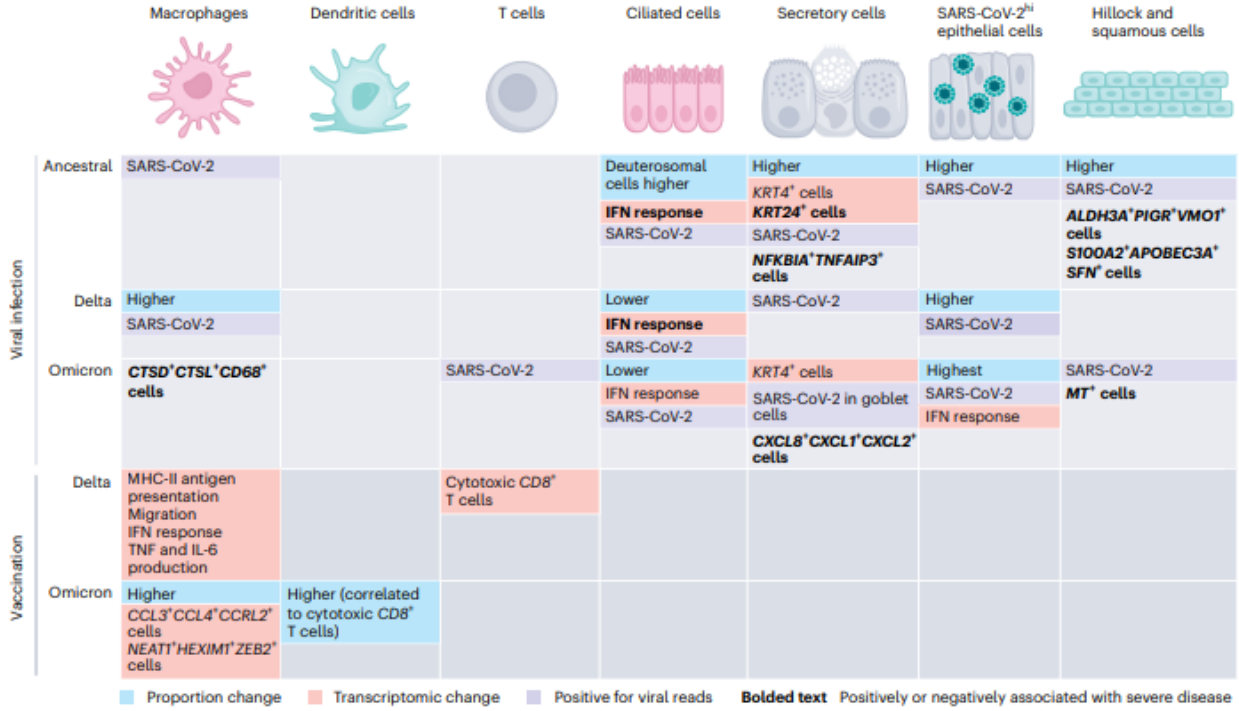


GREATER response at **3 weeks** after 2nd dose of Pfizer COVID-19 vaccine **in opposing arms.** JCI 2024 (n=950)
More newly activated naive B cells?

Antigen drains to the skin-dLN via the afferent lymphatics into the subcapsular sinus (SCS). Bmem and mTfh cells localize to the outer B cell follicle, where they scan CD169^{+} subcapsular sinus macrophages (SSMs).
The subcapsular region may provide a niche for Bmems and Tfh cells (adhesion molecules, chemokines, cytokines, and survival factors).
Subcapsular proliferative foci (SPF)

Dhenni. R. et al. Cell, 2025
Fazli. S. et al. J. Clin. Invest.,2024

Also NON-IMMUNE mucosal responses



Debbie van Baarle et al. Nature immunology, 2025

Mucosal immunity works but serologic mucosal correlates of protection are lacking

- Mucosal infection is inducing resident memory T cells
- **Vaccination + breakthrough infections → more durable nasal neutralizing antibodies**
- **More reinfections in convalescents lacking mucosal neutralizing antibodies**

Declercq J. *et al.* *Sci. Transl. Med. 2024*

Puhach O. *et al.* *EBioMedicine. 2023*

Lasrado N. *et al.* *Sci. Transl. Med. 2024*

Planas D. *et al.* *Med 3. 2022*

Gorochov G. *et al.* *JAMA Netw Open. 2024*

Tang J. *et al.* *Sci. Immunol. 2022*

Goldberg Y. *et al.* *N. Engl. J. Med. 2022*

RNA IM vaccines: protective mucosal immunity?

Repeated COVID-19 mRNA-based vaccination contributes to SARS-CoV-2 neutralizing antibody responses in the mucosa

Jozefien Declercq, Sarah Gerlo, Sharon Van Nevel, Natalie De Ruyck, Gabriele Holtappels, Liesbeth Delesie, Els Tobback, Inés Lammens, Nikita Gerebtsov, Koen Sedeyn, Xavier Saelens, Bart N Lambrecht, Philippe Gevaert, Linos Vandekerckhove, Stijn Vanhee

2024, *Science Translational Medicine*

SARS-CoV-2 mRNA vaccination induces an intranasal mucosal response characterized by neutralizing antibodies

Kevin T. Cao, Catalina Cobos-Uribe, Noelle Knight, Rithika Jonnalagadda, Carole Robinette, Ilona Jaspers, Meghan E. Rebuli

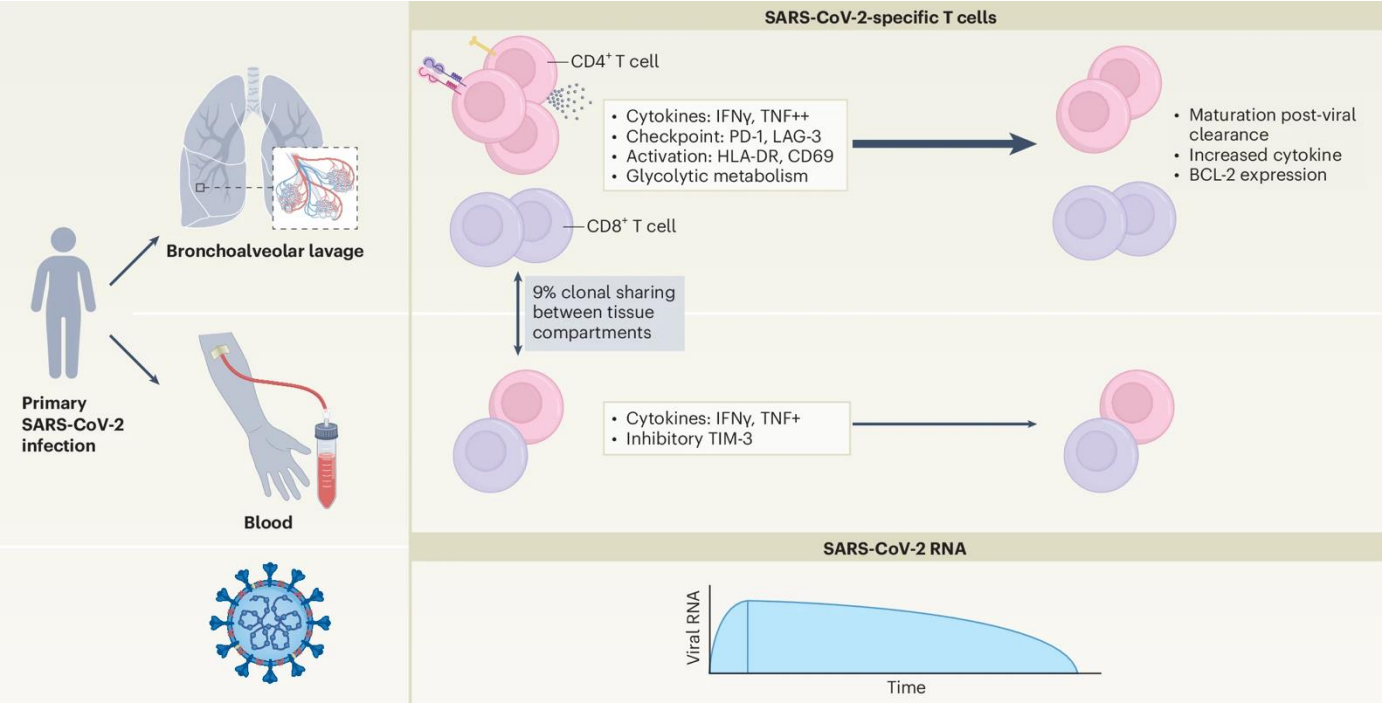
2023, *Journal of Allergy and Clinical Immunology Global*

Intramuscular mRNA BNT162b2 vaccine against SARS-CoV-2 induces neutralizing salivary IgA

Miri Stolovich-Rain, Sujata Kumari, Ahuva Friedman, Saveliy Kirillov, Yakov Socol, Maria Billan, Ritesh Ranjan Pal, Kathakali Das, Peretz Golding, Esther Oiknine-Djian, Salim Sirhan, Michal Bejerano Sagie, Einav Cohen-Kfir, Naama Gold, Jamal Fahoum, Manoj Kumar, Maya Elgrably-Weiss, Bing Zhou, Miriam Ravins, Yair E. Gatt, Saurabh Bhattacharya, Orly Zelig, Reuven Wiener, Dana G. Wolf, Hila Elinav, Jacob Strahilevitz, Dan Padawer, Leah Baraz, Alexander Rouvinski

2023, *Frontiers in Immunology*

Local T cells are important

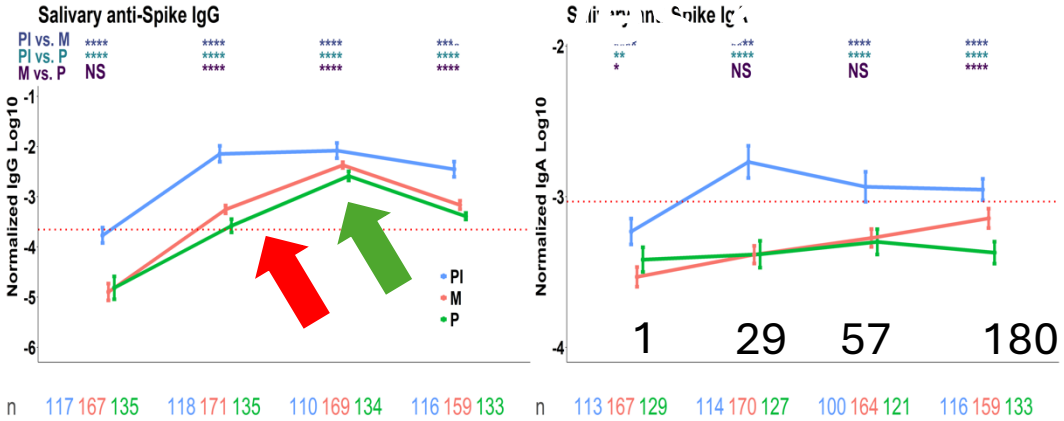


The differences between tissue (top) or systemic (middle) immune responses are shown. Virus-specific T cells from the lower respiratory tract display increased levels of cytokine production, activation and clonal expansion. The production of checkpoint proteins is associated with high levels of activation. Strong responses correlate with viral clearance, and mucosal T cells then mature to an activated tissue-resident memory phenotype. Viral clearance (bottom) is represented as a graph showing lower viral RNA over time.

Moss P. Nature Immunol, 2025

A systemic origin for saliva IgG IN COVID-

SALIVA



M PRE-INF.
M NAIVE
P NAIVE

days

SERUM