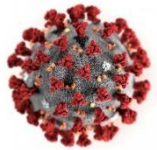


Virologist view of the pandemic

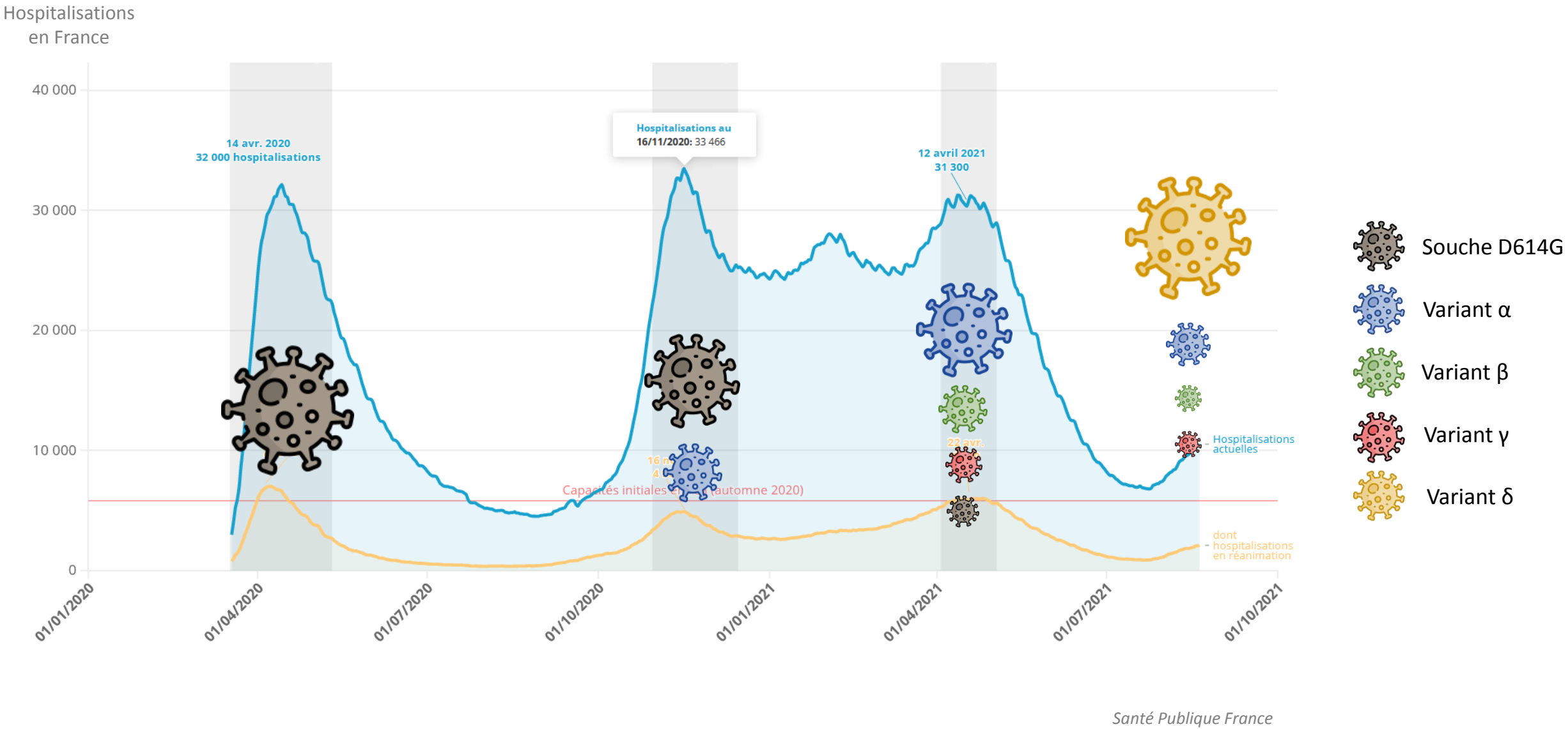
Pr. Samira FAFI-KREMER

INSTITUT DE VIROLOGIE

INSERM UMR S_1109, UNIVERSITÉ DE STRASBOURG,

CHU DE STRASBOURG

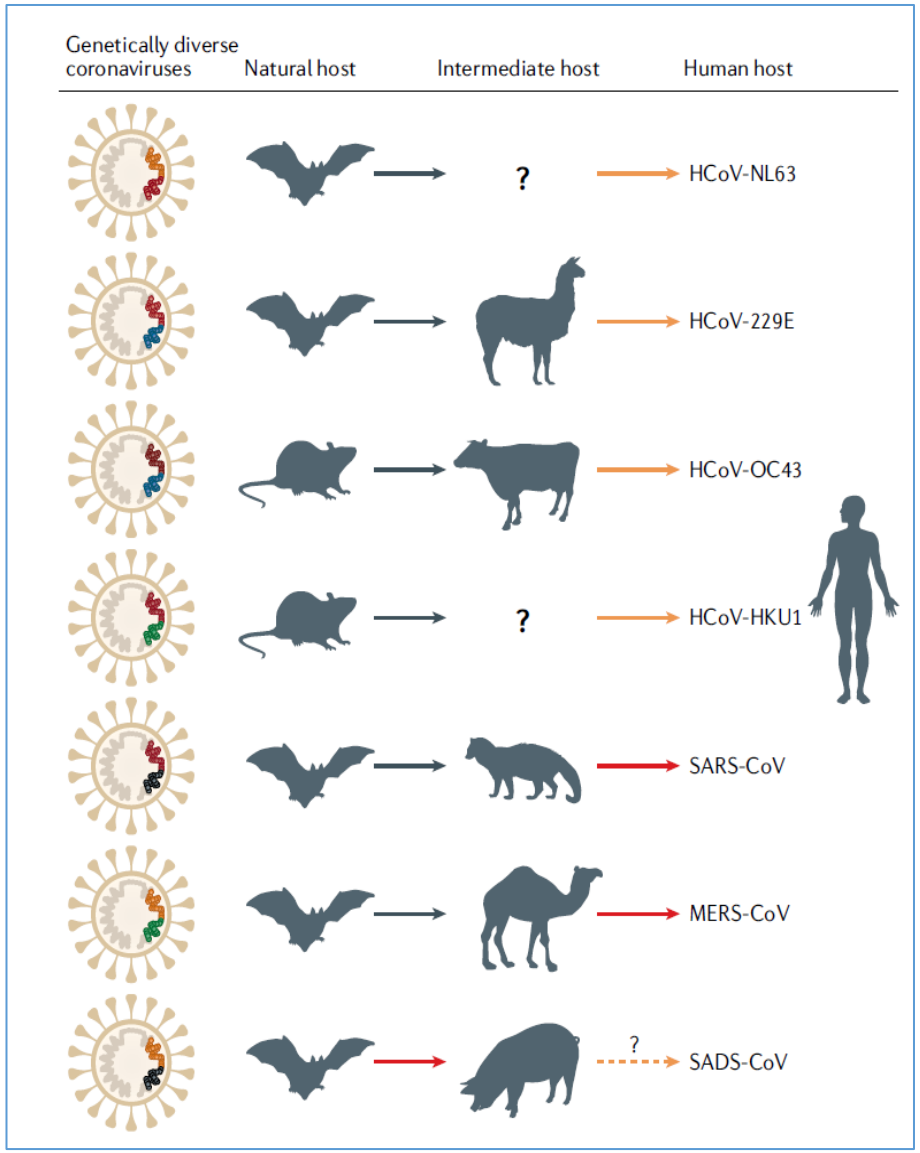
COVID-19 pandemic

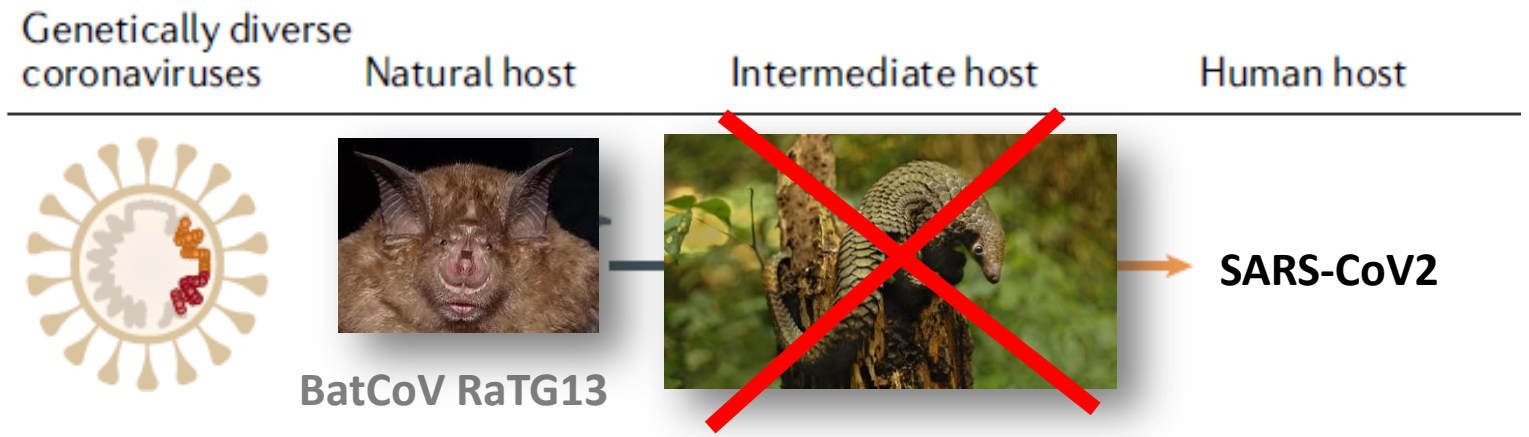


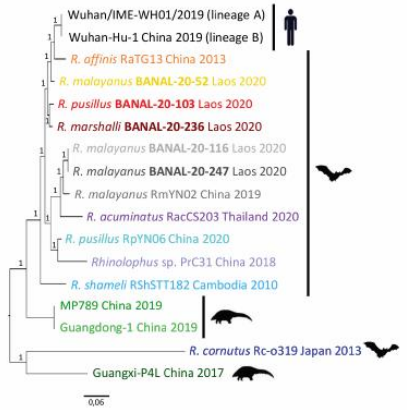
Santé Publique France

nature

A pneumonia outbreak associated with a new coronavirus of probable bat origin







Presence of new bat sarbecoviruses that seem to have the same potential for infecting humans as early strains of SARS-CoV-2.

BIOLOGICAL SCIENCES - ARTICLE

Coronaviruses with a SARS-CoV-2-like receptor-binding domain allowing ACE2-mediated entry into human cells isolated from bats of Indochinese peninsula

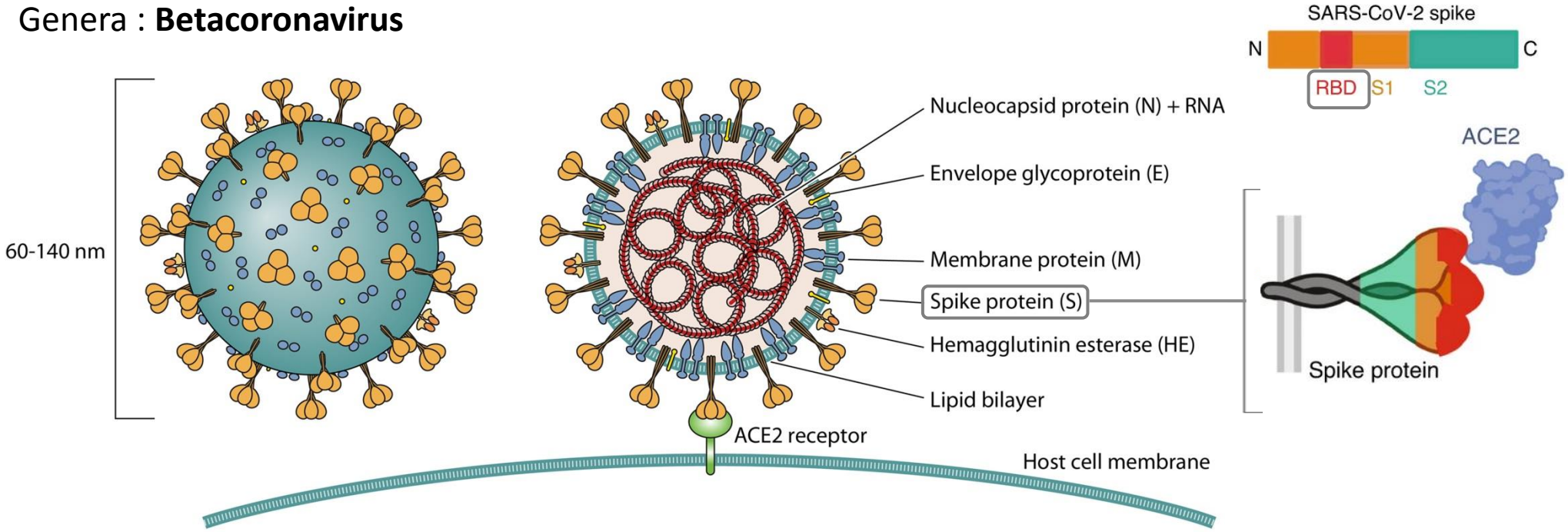
Temmam et al Preprint 2021 (Institut Pasteur)

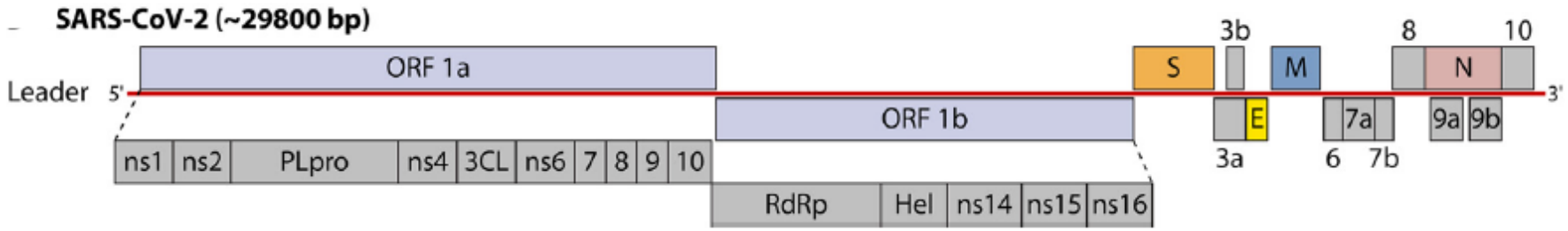
SARS-CoV-2

Enveloped virus

Family : **Coronaviridae**

Genera : **Betacoronavirus**



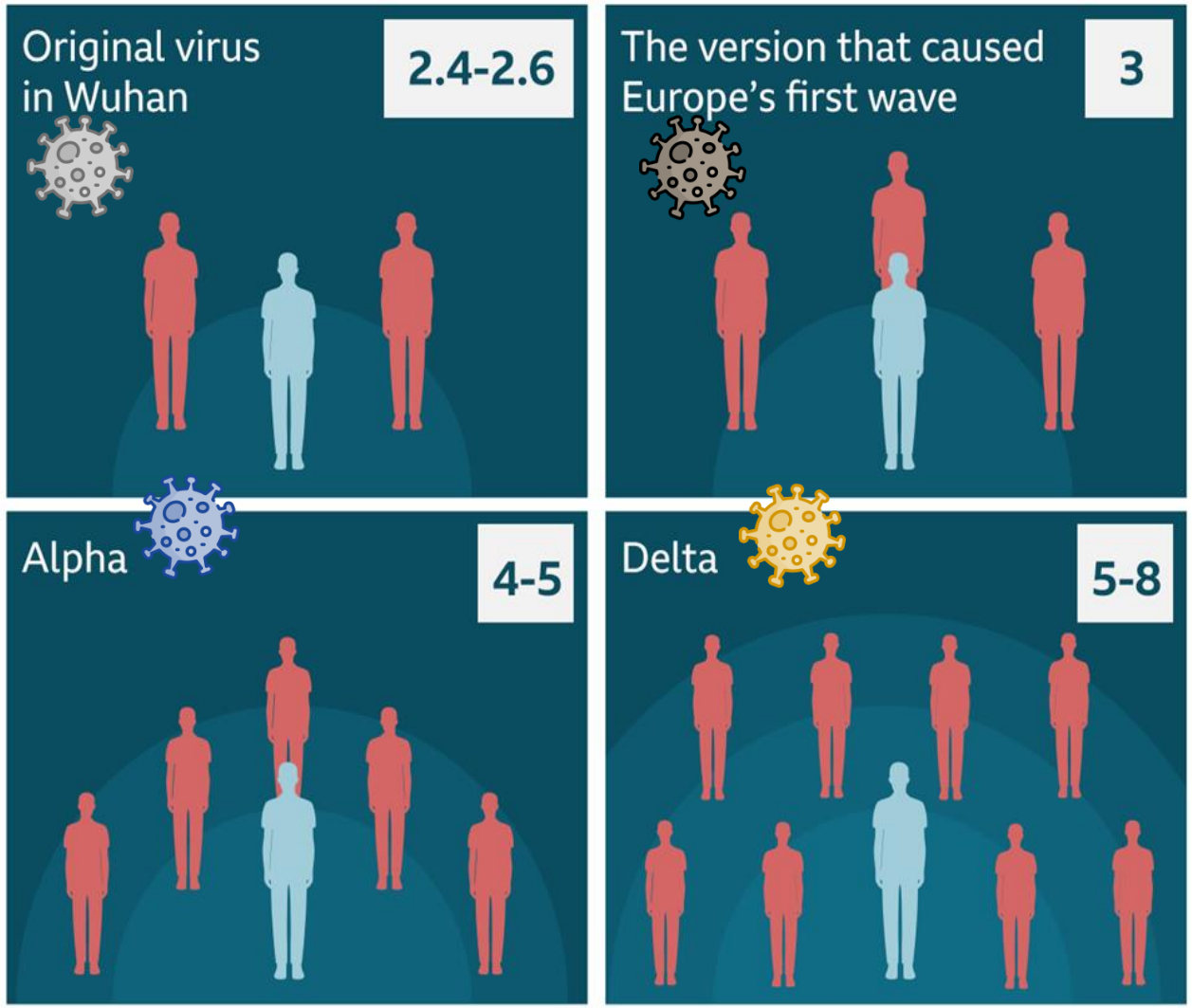


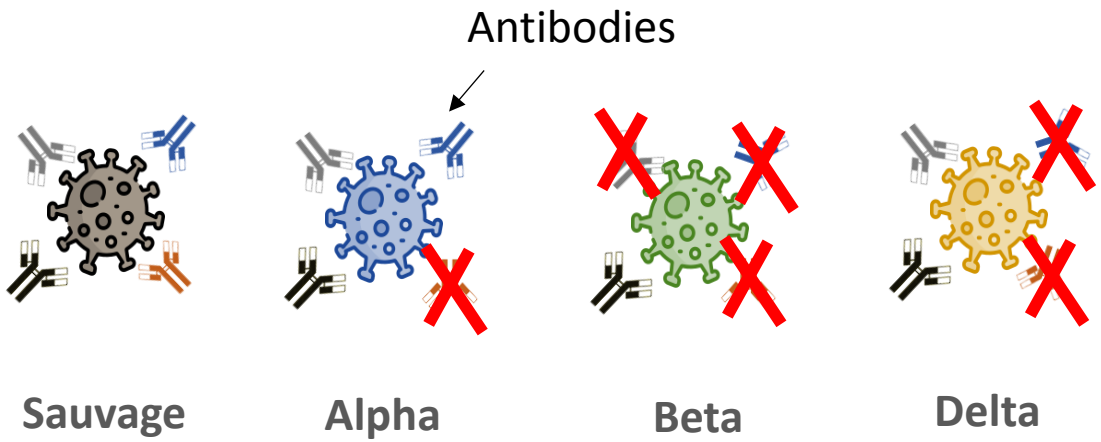
Key role in viral entry

Main target of immune response

SH Safiabadi Tali et al, Clin Microbiol Rev. 2021; Hua J et al., Nature 2020

Emergence of SARS-CoV-2 variants





- Long term spread of SARS-CoV-2

➢ Emergence of variants

➢ Improved replication capacity

➢ Increased immunological escape

Beta >> delta > alpha

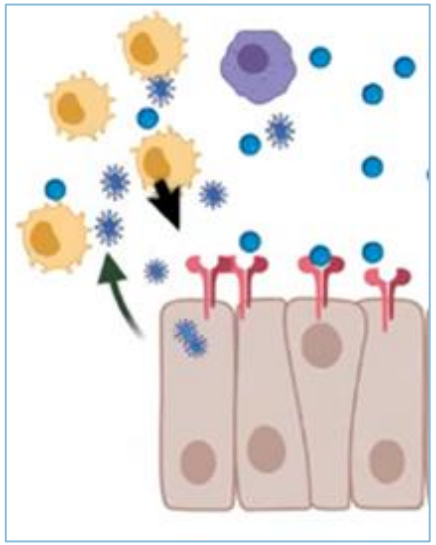
Imperial College, Lancet

Key questions

- Comment évolue la réponse immunitaire après l’infection?
- Comment évolue la réponse immunitaire après le vaccin?

Innate and adaptive immune response

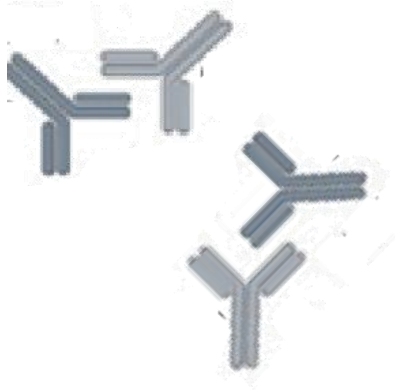
Innate response



Adaptive response

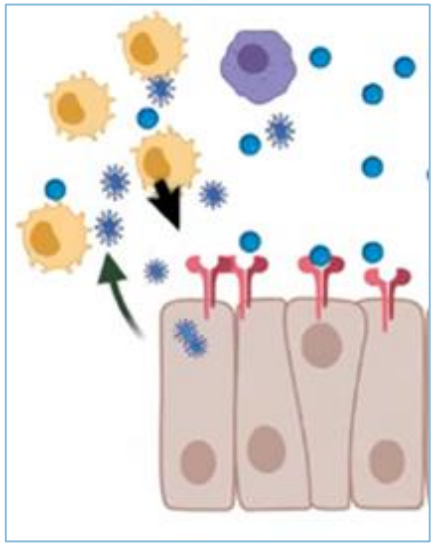
T cell response

Humoral response (antibodies)



Innate and adaptive immune response

Innate response



Hours

0 6 12

Infection

Adaptive response

T cell response

CD4

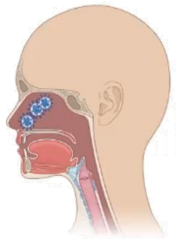
CD8

Humoral response (antibodies)

Days

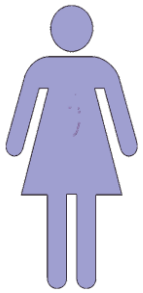
1 3 6

Mild COVID-19 = effective innate immune response

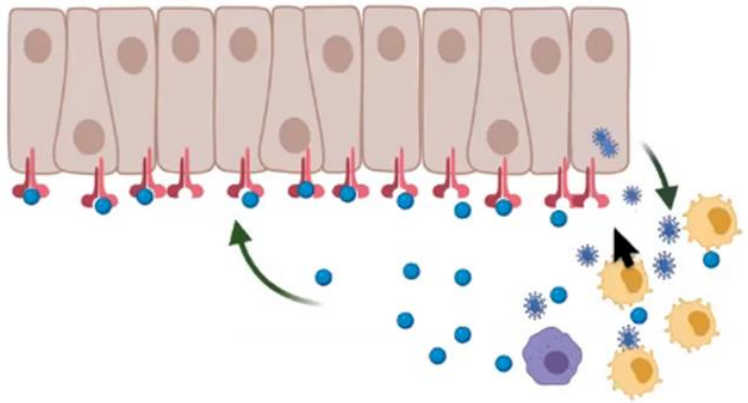


Small viral inoculum

Young people and women

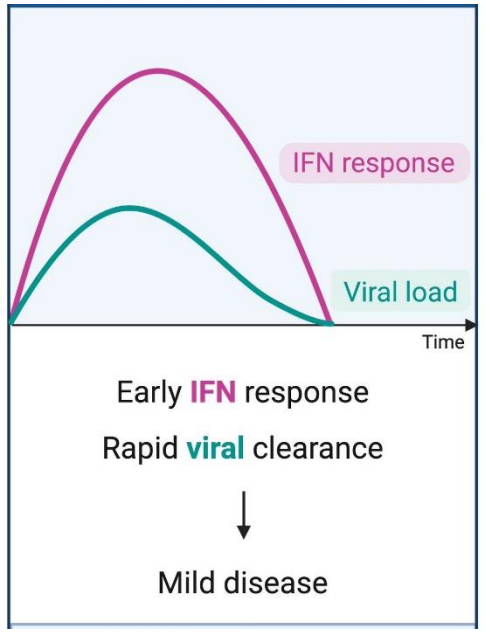


Antiviral state protects neighboring cells

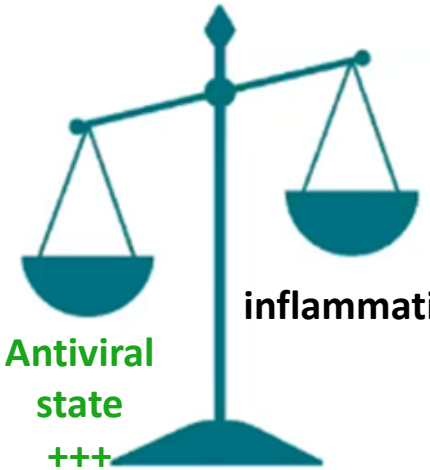


Viral RNA triggers plasmacytoid dendritic cells (pDc) to secrete Type I IFN

Early stimulation of type 1 IFN



Innate immune response

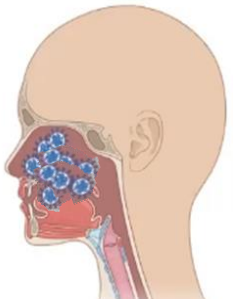


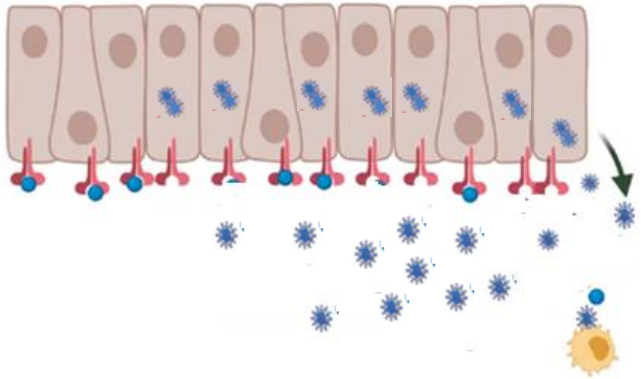
Rapid viral clearance

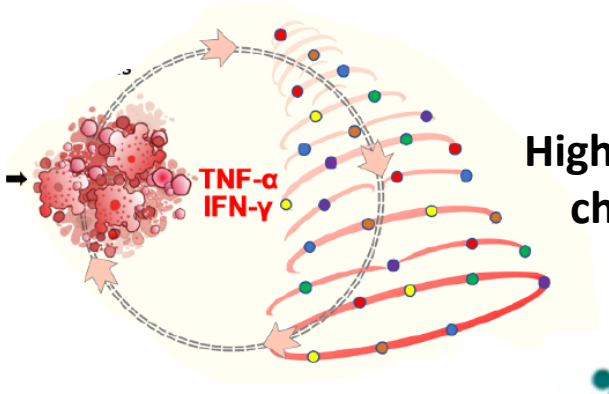
Asymptomatic or mild disease

Iwasaki , Nature 2020; Zhang et al Science 2020, Shiv Pllai, Lecture 2020

Severe COVID: unbalance between antiviral state and inflammation

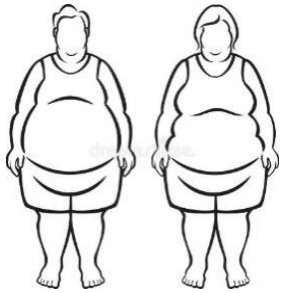




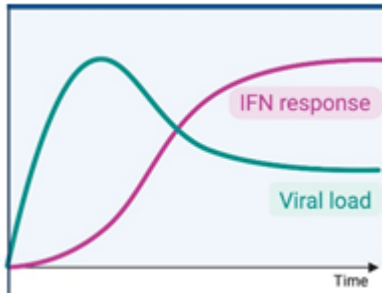


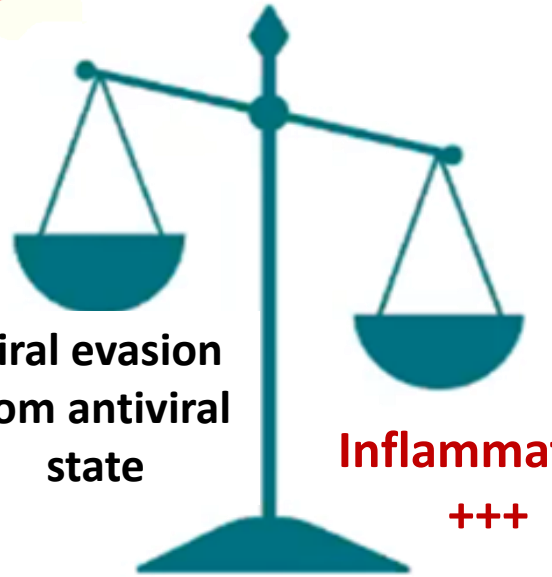
High production of inflamatory chemokines and cytokines

High viral inoculum



Production retardée ou absente de l'IFN type 1

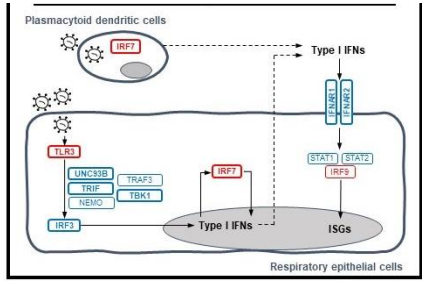




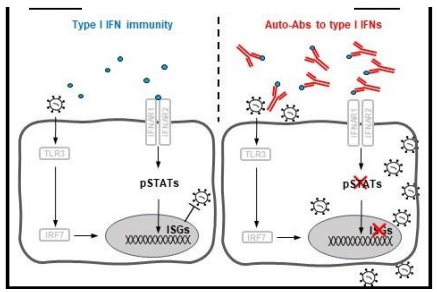
Viral evasion from antiviral state

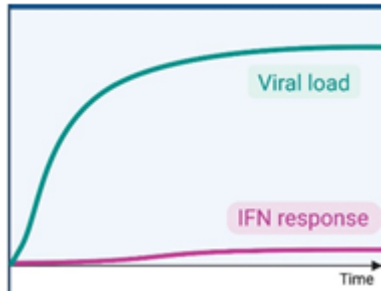
Inflammation +++

Mutations génétiques



Auto-anticorps

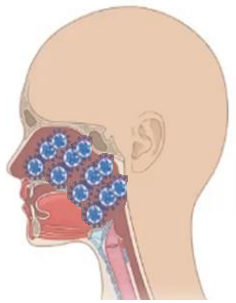




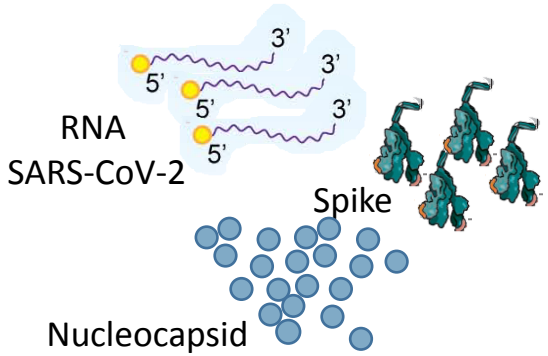
hyper-inflammation= Severe COVID

Iwasaki , Nature 2020; Zhang et al Science 2020, Shiv Pllai, Lecture 2020

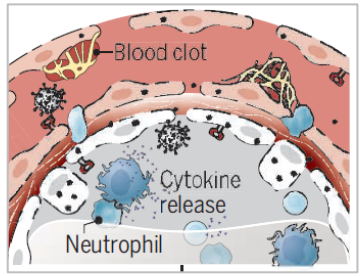
Severe COVID: unbalance between antiviral state and inflammation



High viral inoculum and comorbidities



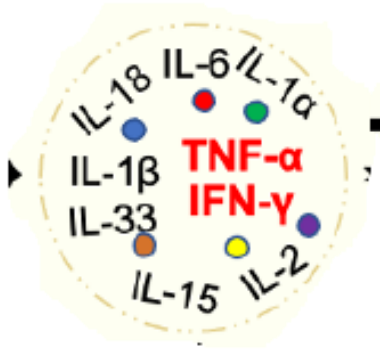
PAMPs

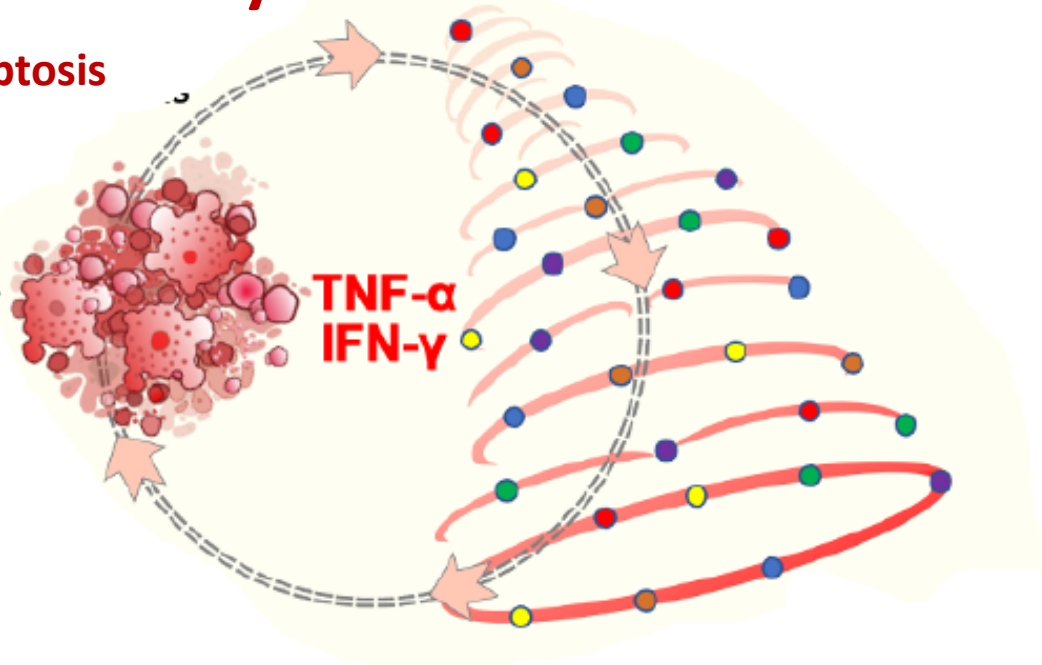


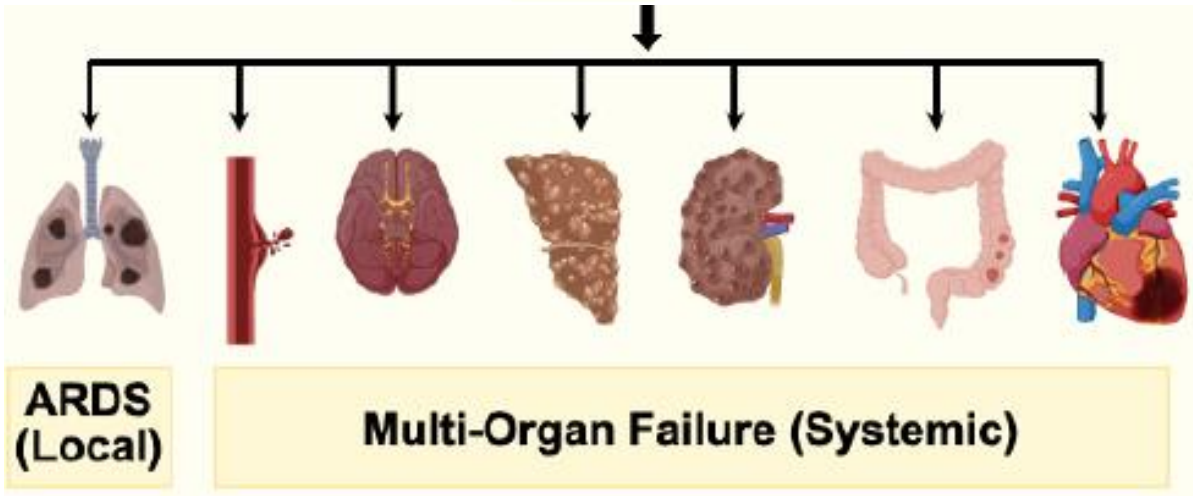
Cellular debris (DAMPs)

Cytokine storm

PANoptosis







Cytokine Shock Syndromes Markers

Ferritin	↑	B cells	↓	RBC	↑
LDH	↑	T cells	↓	HCT	↑
ALT	↑	Platelets	↓	Hb	↑
AST	↑	PCT	↓		
BUN	↑				

Adapted from Karki et al, Cell 2020

Innate and adaptive immune response

Innate response

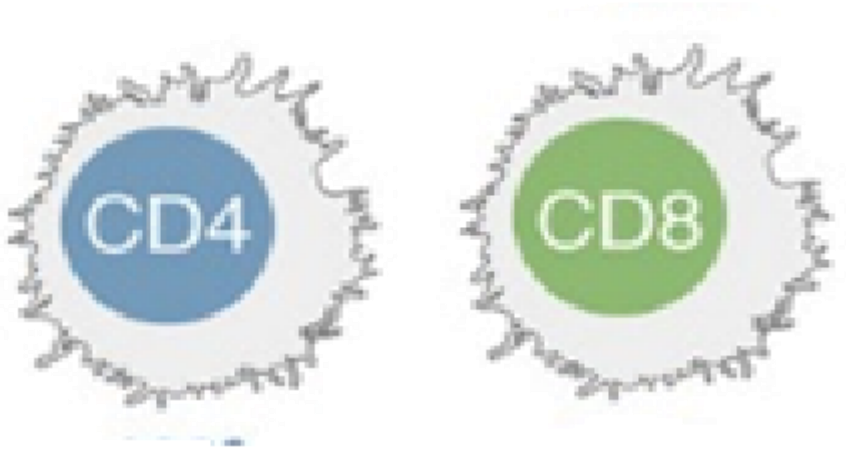
Hours

0 6 12

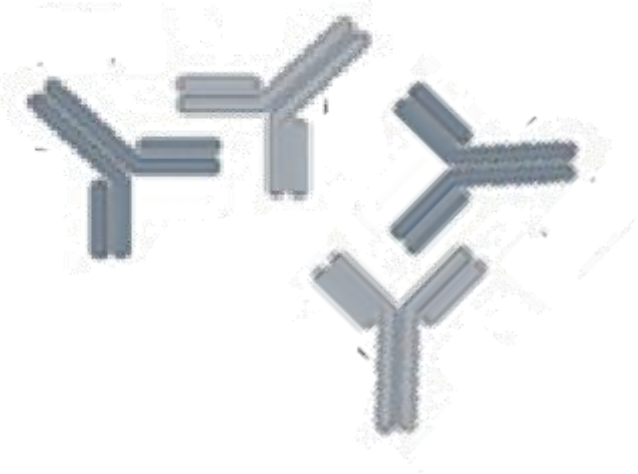
Infection

Adaptive response

T cell response



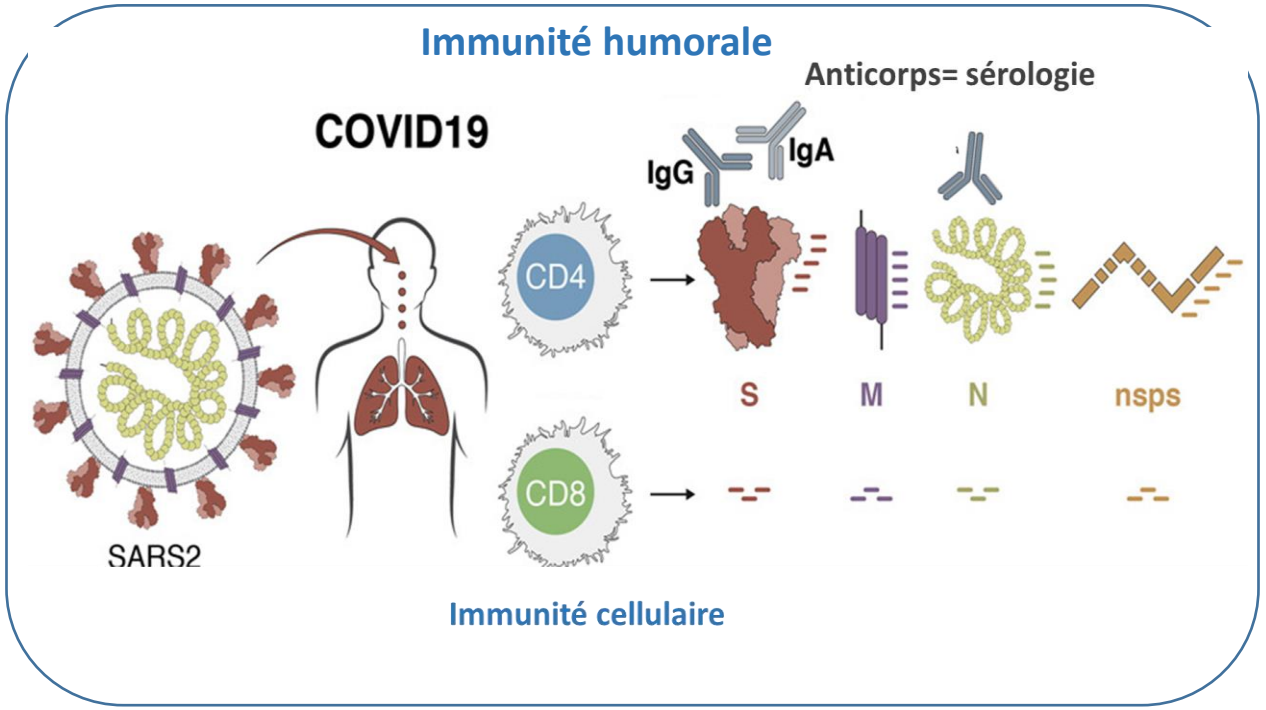
Humoral response (antibodies)

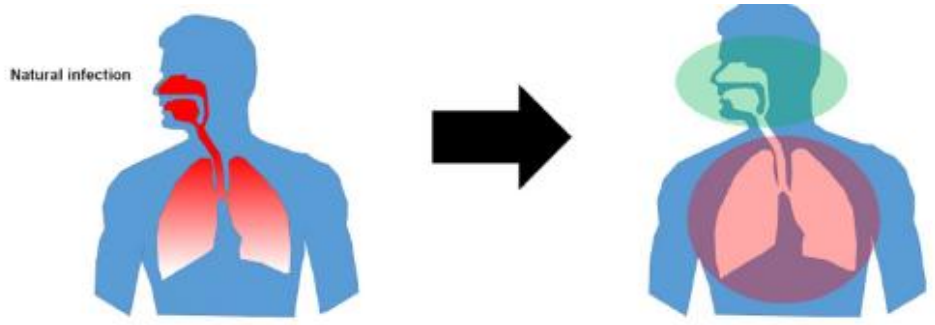


Days

1 3 6

Immune response after SARS-CoV-2 infection





Adapté de Grifoni et al, Cell 2020; Krammer F, Nature 2020

Antibody response to SARS-COV-2: SeroCoVHUS study

Prospective, longitudinal, monocentric study:
1,496 workers recruited in Strasbourg University Hospital (SHU), France

March 2020: 1st wave start

Inclusions
6th April – 7th May 2020

June – August 2020

September– December 2020

February – May 2021

M1 **M3-6** **M7-9** **M11-13**

SARS-CoV-2 serology

Demographic, clinical, and biological data

Antibody response to SARS-COV-2: SeroCoVHUS study

1,496 workers in SUH
screened by SARS-CoV-2 serology
between 6th April and 7th May (M1)

1,309 with at least
one follow-up timepoint
(M3-6 and/or M7-9 and/or M11/13)

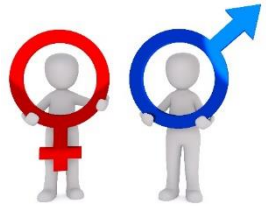
COVID-19 history
at inclusion (M1)

Negative (COVID-19-)
n=916

Convalescent (COVID-19+)
n=393

(345 RT-PCR+)

- 10 (2.5%) asymptomatic
- **367 (93.4%) mild disease**
- 16 (4.1%) moderate disease
- No severe disease



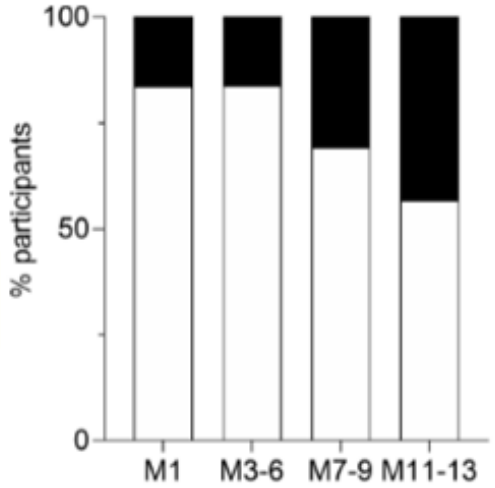
3.5 F / 1 H

Median BMI: 23.7
(IQR: 21.3 – 27.0)

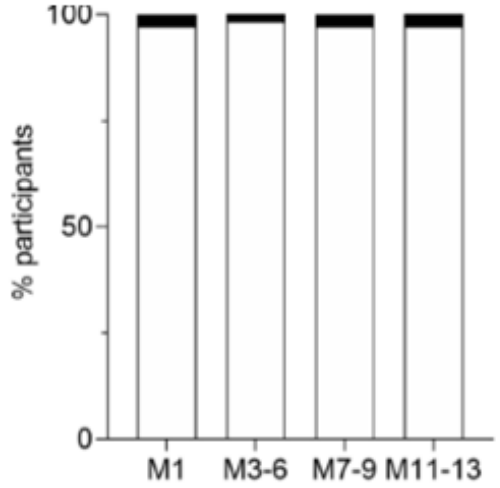
Serology after COVID-19

COVID-19+ cohort (n = 393)

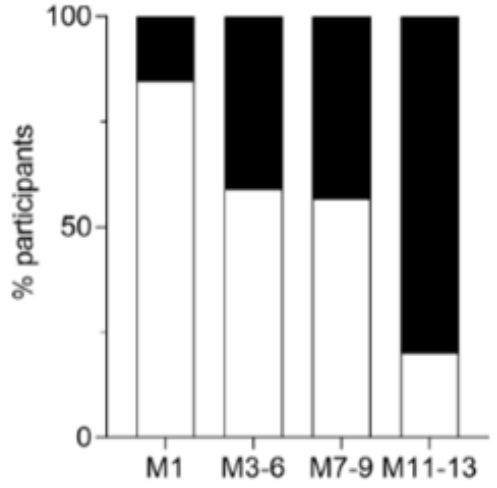
Lateral flow assay
anti-RBD IgG



CMIA
anti-RBD IgG



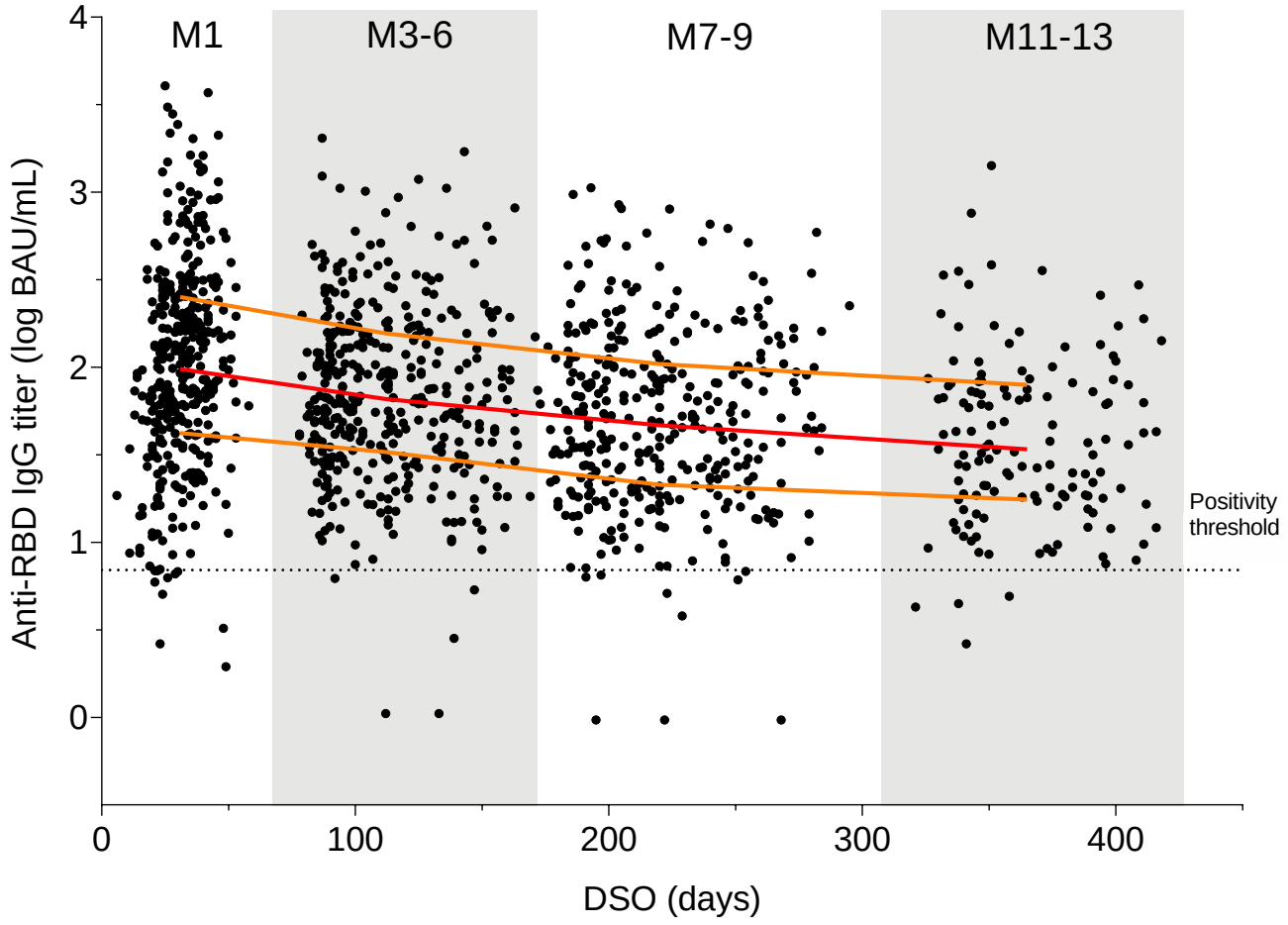
ELISA
anti-N IgG



Seropositivity rate strongly depends on the serological assay used

Gallais F. et al, EbioMedicine, 2021

Antibody persistence after COVID-19



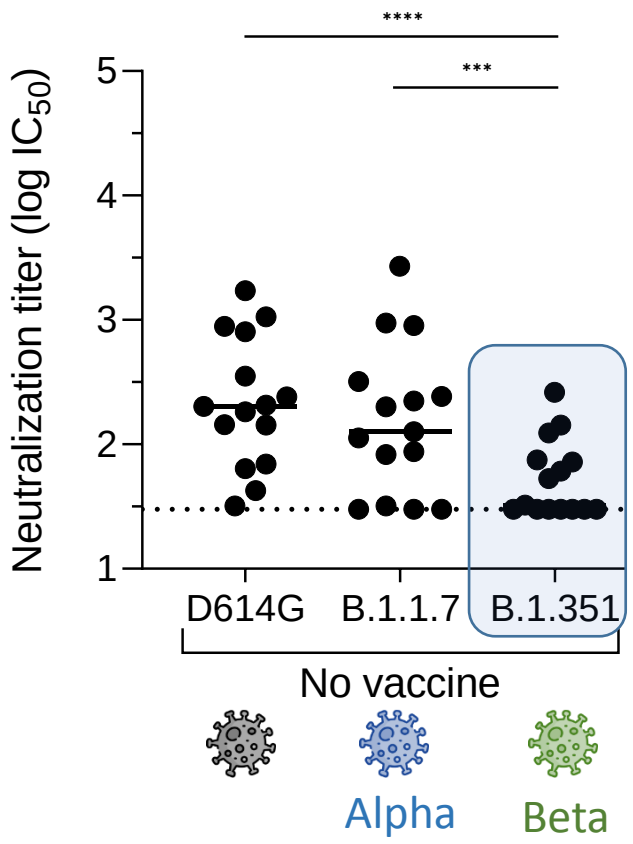
Evolution of anti-RBD IgG

- **Decrease up to 6 months**
- **Stabilization one year after infection**
  - Median: 35 BAU/mL
  - $t_{1/2}$: 725 days

Anti-SARS-CoV-2 antibodies persist more than one year after infection

Gallais F. et al, EbioMedicine, 2021

SARS-CoV-2 neutralizing antibody titers



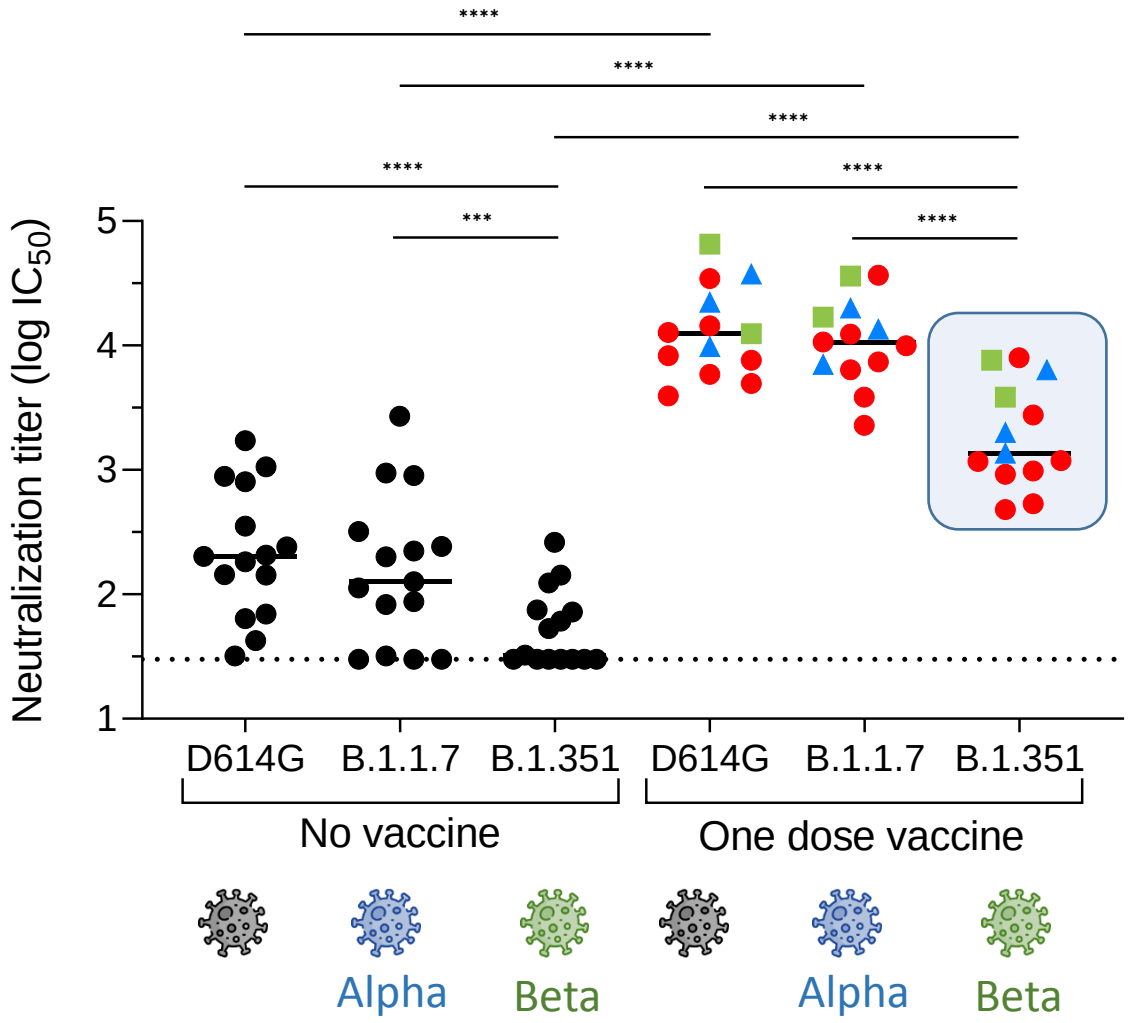
15 COVID-19+ unvaccinated participants

The β variant is poorly sensitive

to seric antibodies one year after infection

Gallais F. et al, EbioMedicine, 2021

SARS-CoV-2 neutralizing antibody titers



13 COVID-19+ vaccinated participants

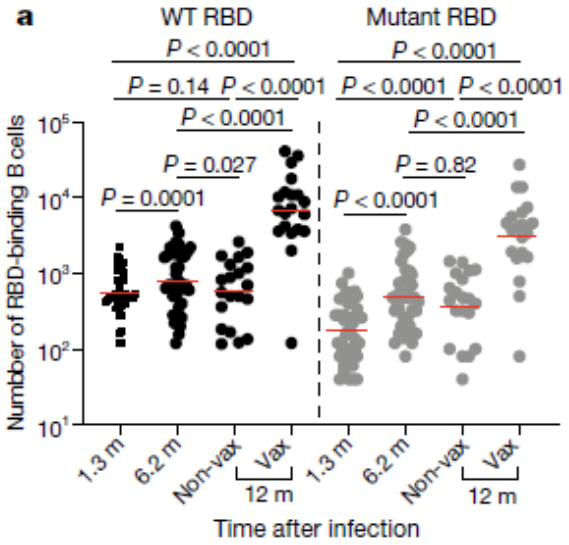
- Astrazeneca
- Moderna
- Pfizer-BioNTech

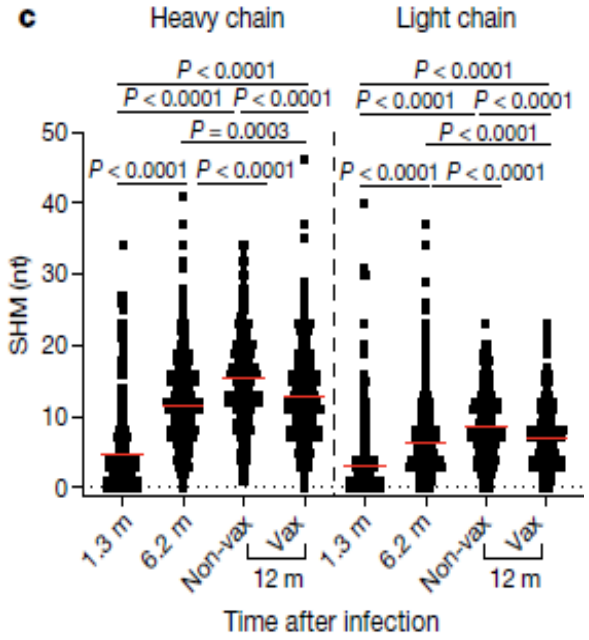
Strong neutralization of β variant after vaccination

Gallais F. et al, EbioMedicine, 2021

Expansion of SARS-CoV-2 specific memory B cells

N=63 COVID-19 convalescents followed-up during 12 months





- Persistence of RBD antigen binding memory B cells up to 12 months post-infection
- Increase of the number after vaccination

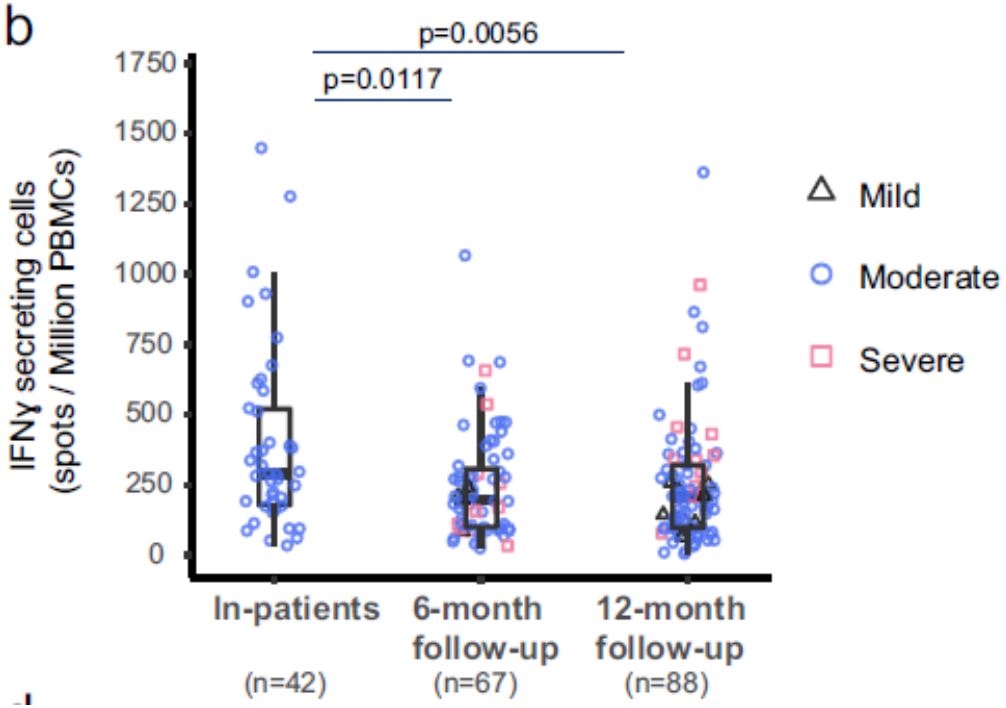
- Somatic hypermutation (SHM) of antibody genes continued between 6 and 12 months post-infection

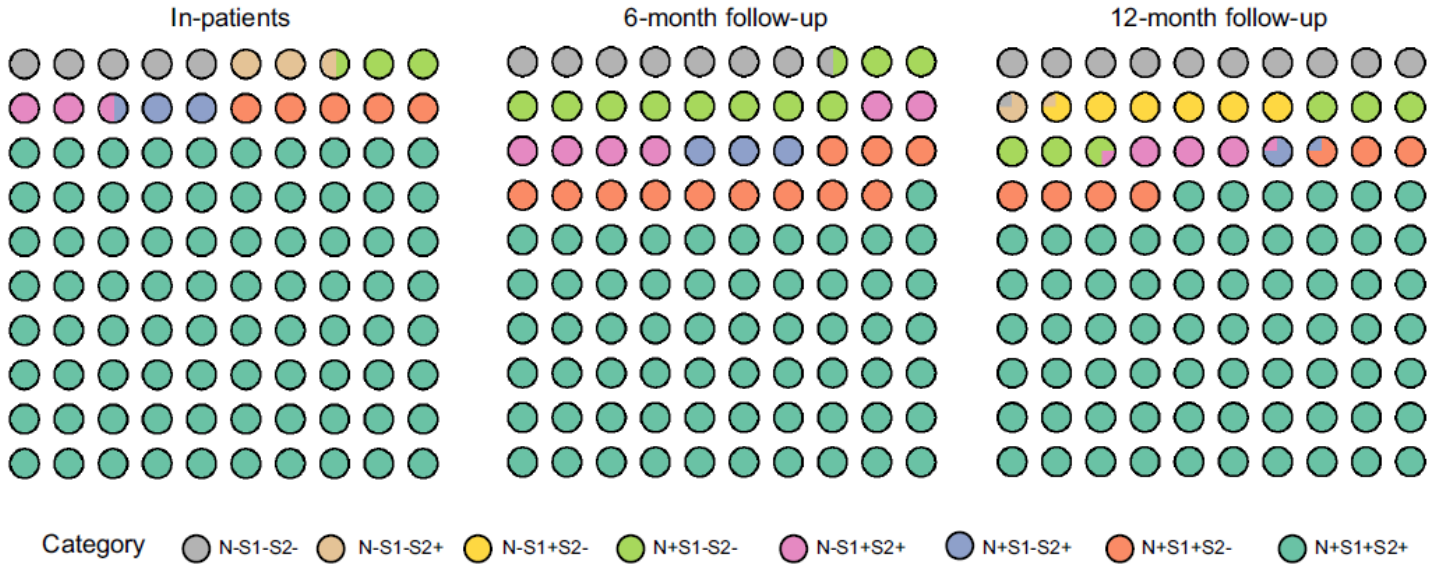
Long-term persistence of germinal centers after infection

Wang Z et al Nature 2021

SARS-CoV-2 specific T cell response

- N=204 COVID-19 (Guangzhou, China)
  - severe (14%), moderate (79%), mild (6%)





After COVID-19, SARS-CoV-2 specific T cell response lasts up to 12 months

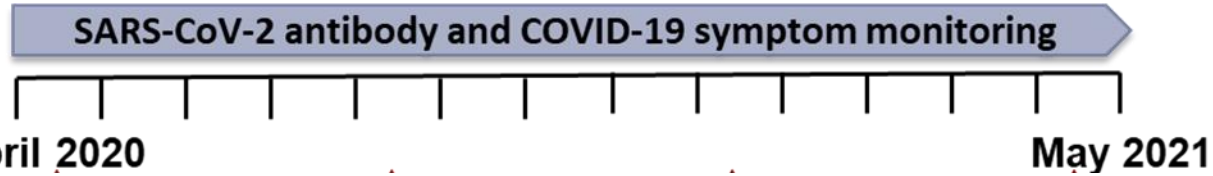
Feng C. et al, Nat Comm, 2021

Risk of new SARS-CoV-2 infection

COVID-19 positive
N=393

Reinfection

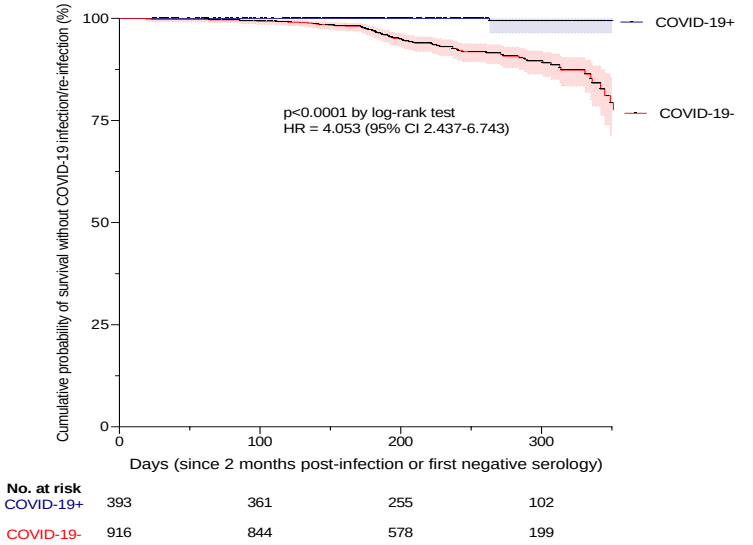
N=1

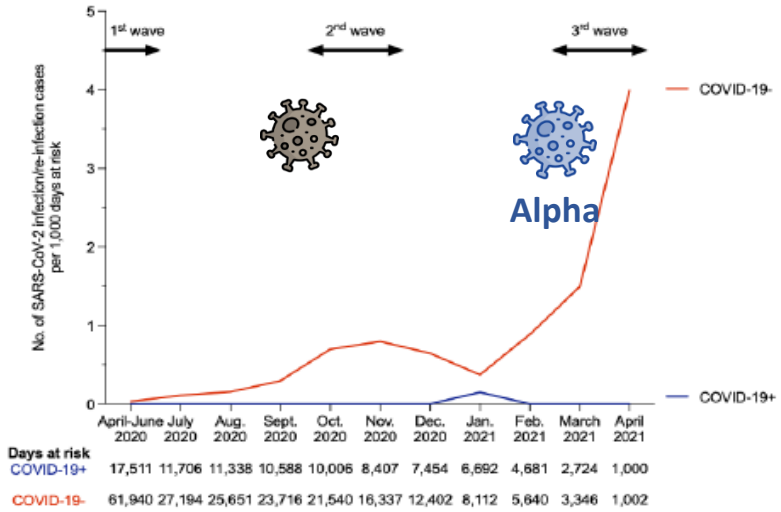


COVID-19 negative
N=916

New infections

N=69

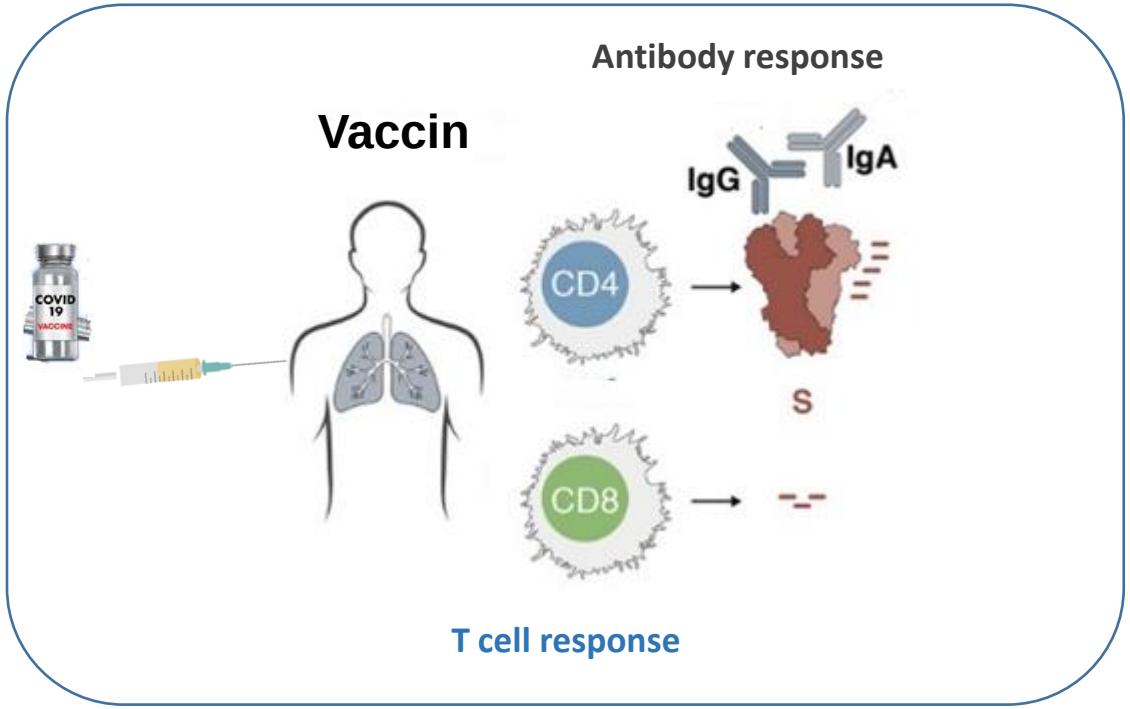


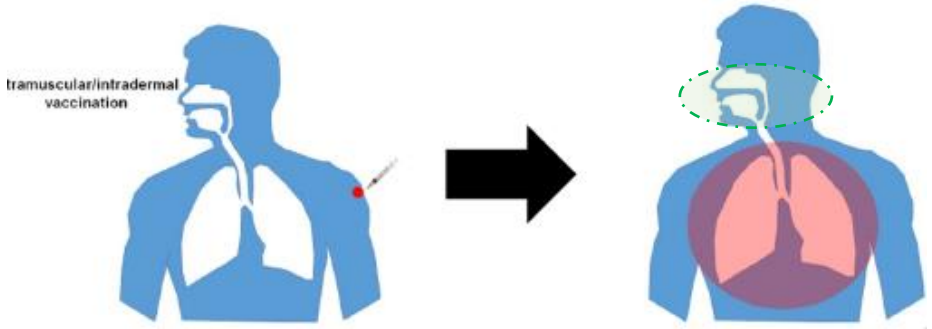


COVID-19+ : Relative reduction of new infection incidence of 96.7% during the first year

Gallais F. et al, EbioMedicine, 2021

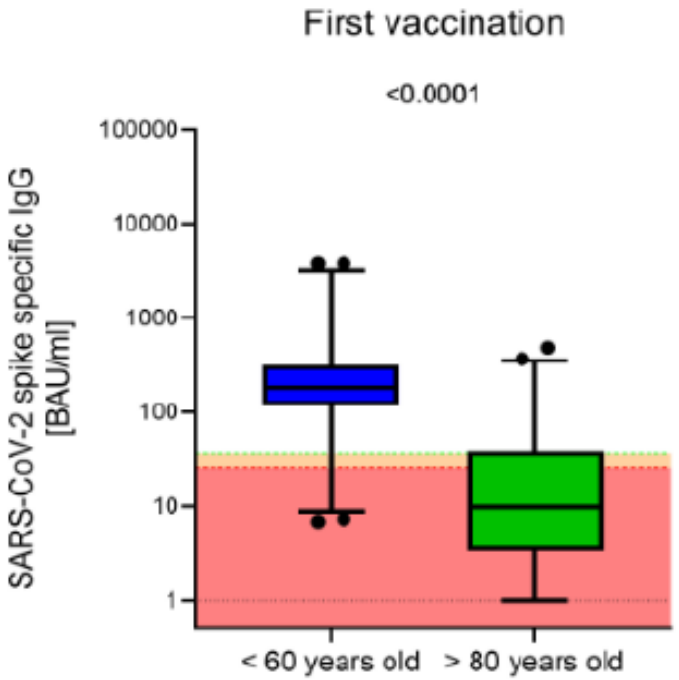
Immune response after COVID-19 vaccine

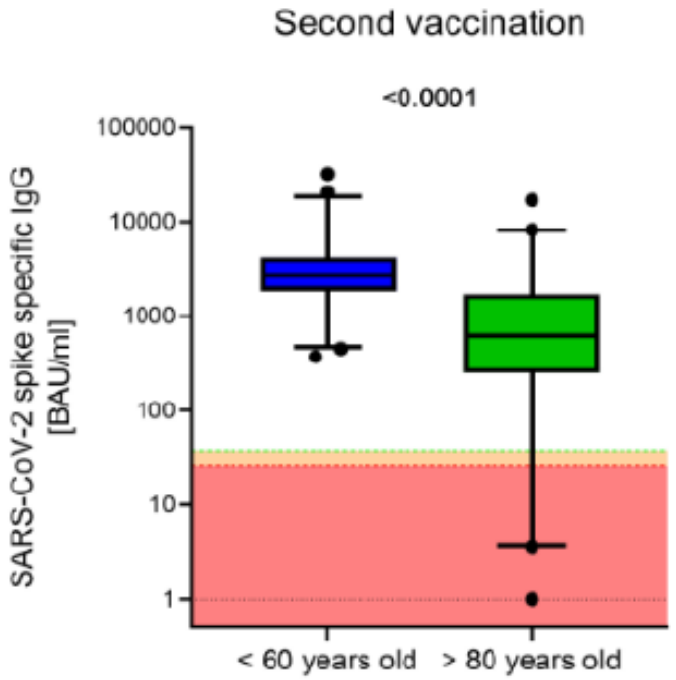


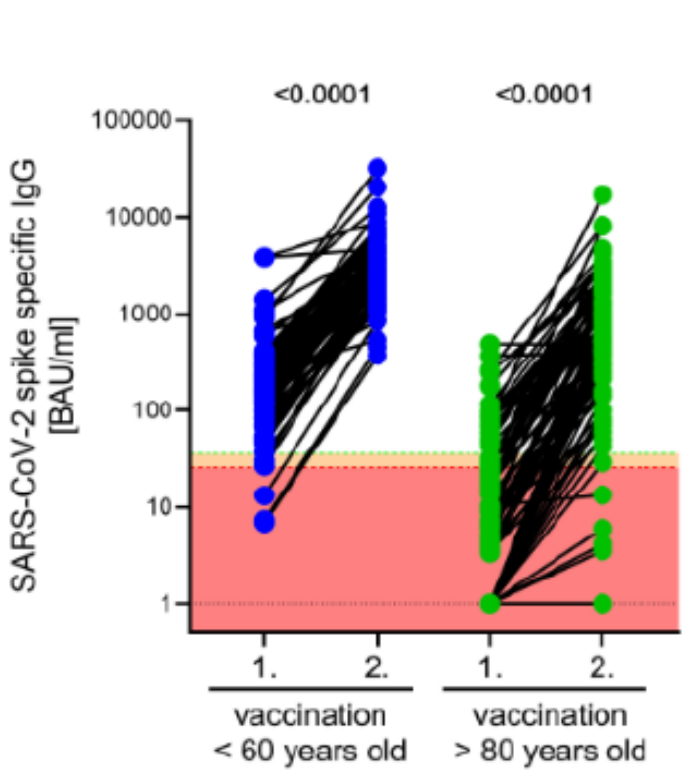


Adapté de Grifoni et al, Cell 2020; Krammer F, Nature 2020

Vaccine response_ according to age







Vaccine response:

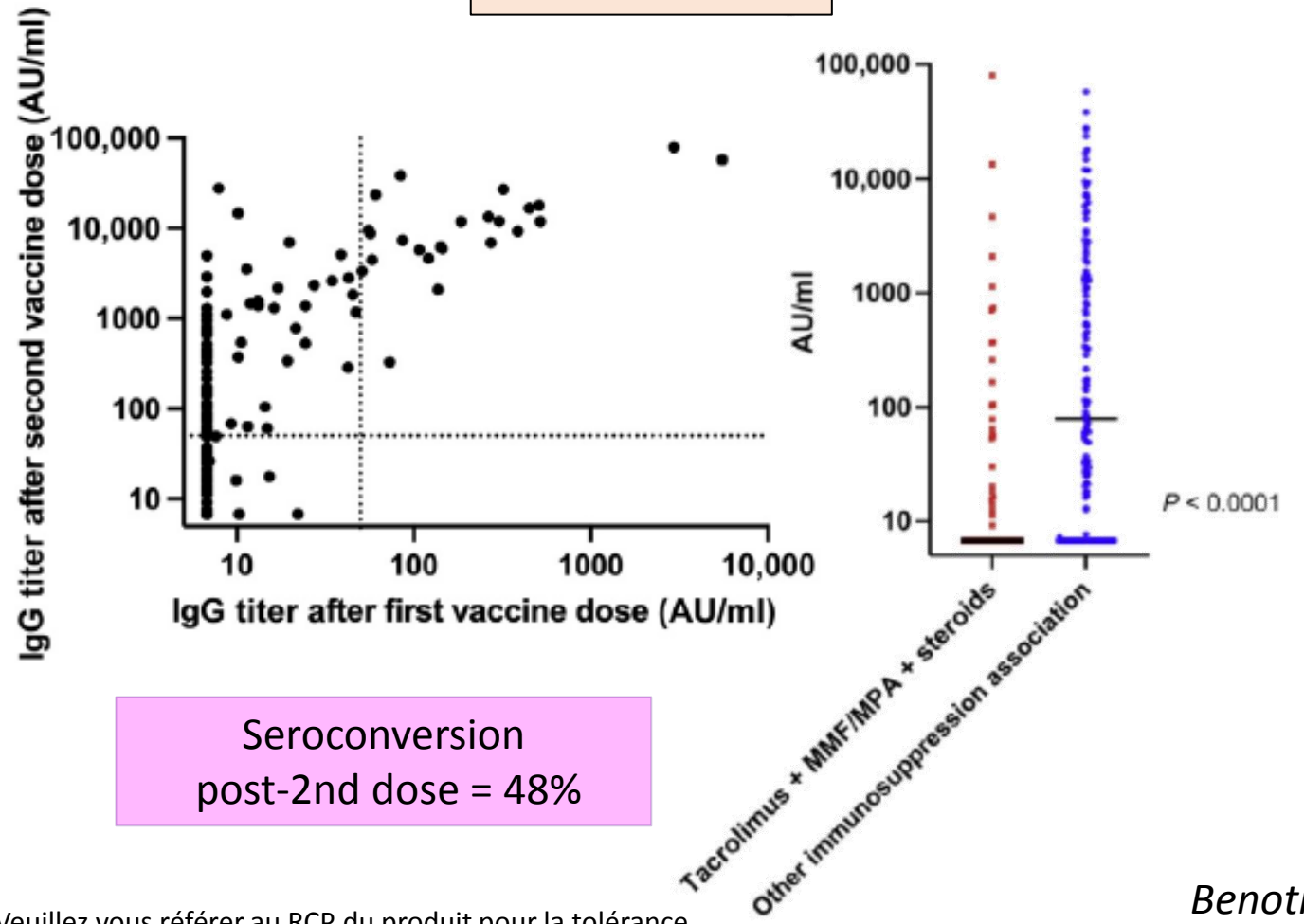
- Individuals <60 ans: 98%
- Individuals > 80 ans : 69%

Muller et al, Medrxiv 2021

Vaccine response and immunosuppression

A cohort of kidney transplant recipients (Strasbourg University Hospital) (n= 204)

2 doses Moderna



Seroconversion
post-2nd dose = 48%

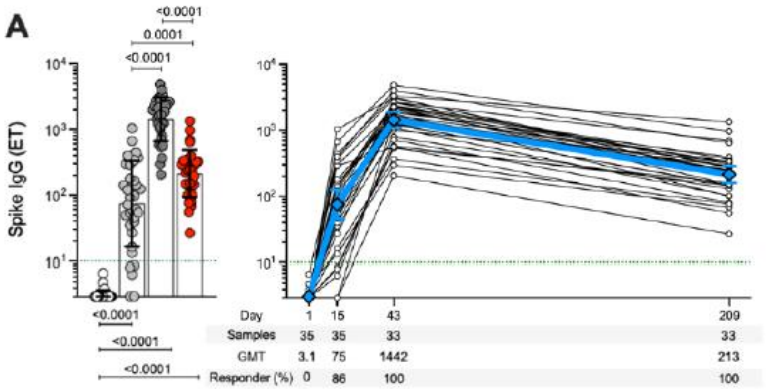
Benotmane et al, Kidney International, 2021 and JAMA 2021

Veuillez vous référer au RCP du produit pour la tolérance

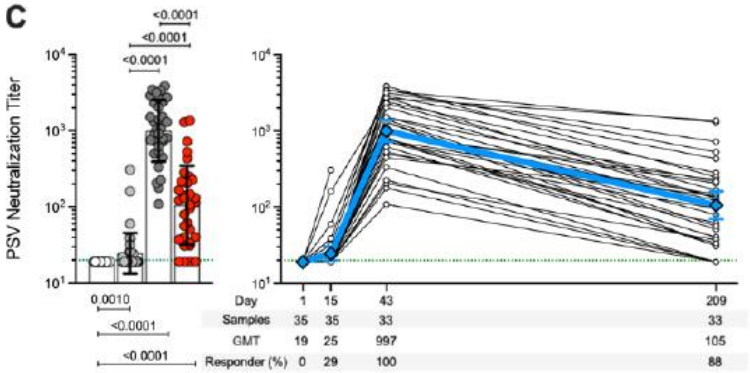
Humoral response after Low-dose mRNA-1273 COVID-19 vaccine

- Open-label, age de-escalation phase 1 trial (mRNA-1273 vaccine 25-µg), follow-up 209 days

Anti-Spike antibodies



Neutraliz antibodies

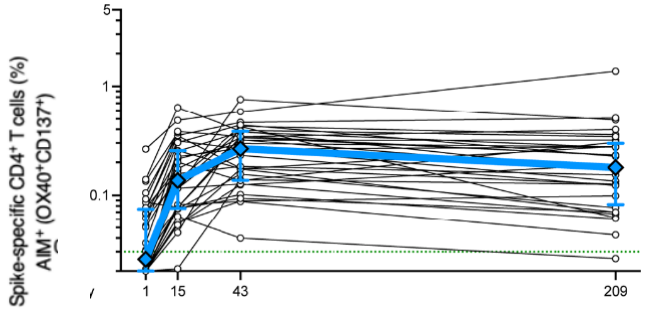


- Anti-spike and -RBD IgG maintained for at least 7 months after the first vaccination, for 100% (33/33) of subjects
- SARS-CoV-2 PSV neutralizing titers were detected:
  - in 29% (10/35) of subjects after one vaccination,
  - 100% after two vaccinations (33/33)
  - 88% (29/33) maintained detectable neutralizing antibodies for at least 6 months after the second vaccination

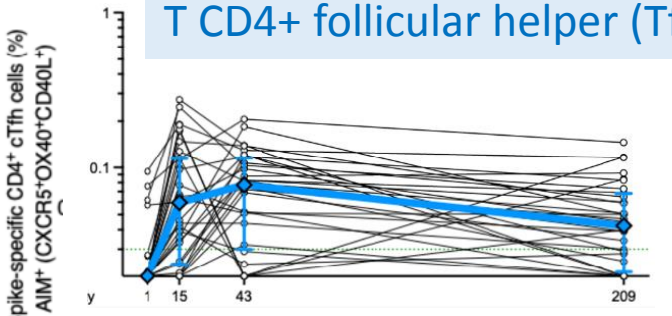
Mateus J. et al, Science, 2021

Low-dose mRNA-1273 COVID-19 vaccine generates durable and robust memory T cell response

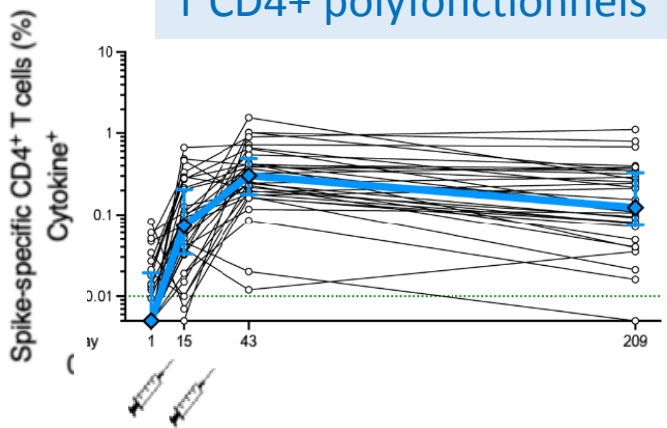
Memory T CD4+ cells



T CD4+ follicular helper (Tfh)



T CD4+ polyfonctionnels

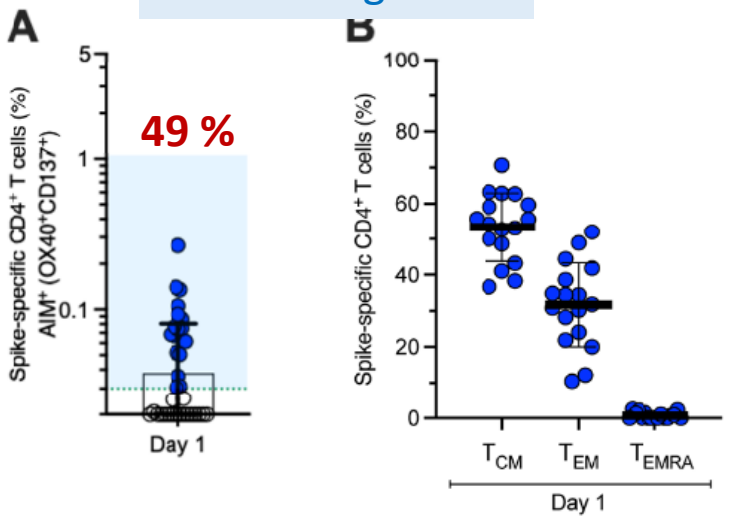


- The Spike–specific CD4+ T cell response rate increased to 100% (32/32) after the second vaccination and was maintained for at least 6 more months.
- Spike-specific memory CD4+ T cell frequencies at 7 months were similar to those observed for COVID-19 cases
- Spike-specific cTFH cells were detectable in 94% of subjects
- were still detected in 63% of vaccinees 6 months after the second vaccination
- Spike-specific CD4+ T cells exhibited multifunctionality comparable to that of CMV-specific cells

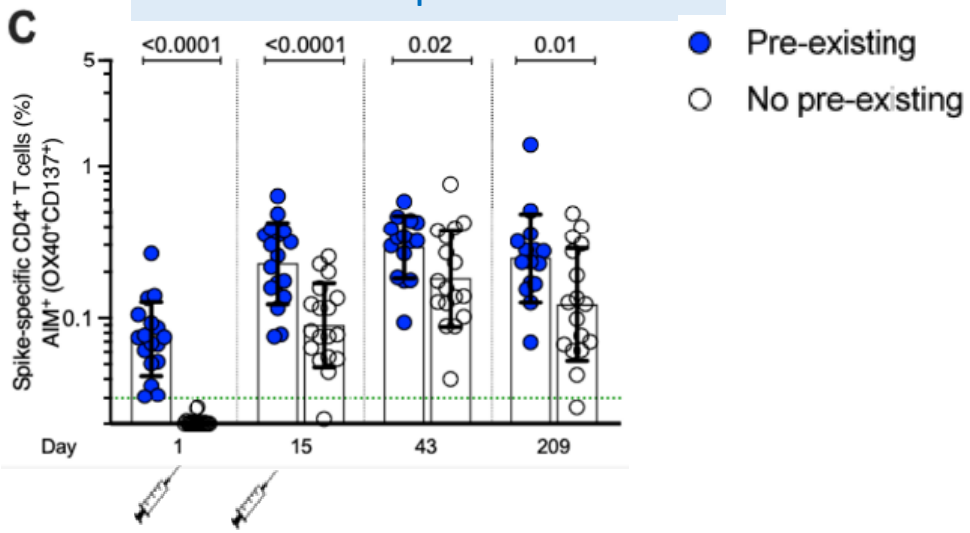
Mateus J. et al, Science, 2021

… and enhanced by cross-reactive cells

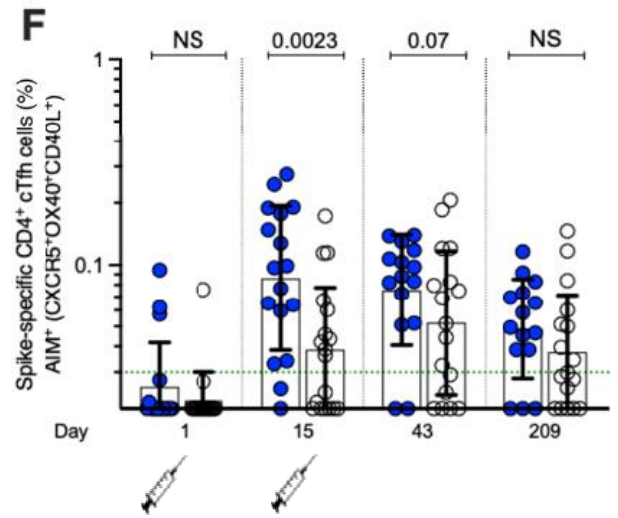
Pre-existing T CD4



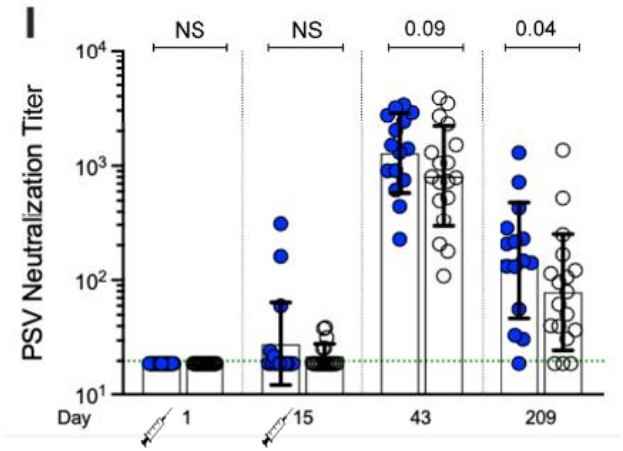
SARS-COV-2 specific T CD4+



T CD4+ (Tfh)



Neutralizing antibodies

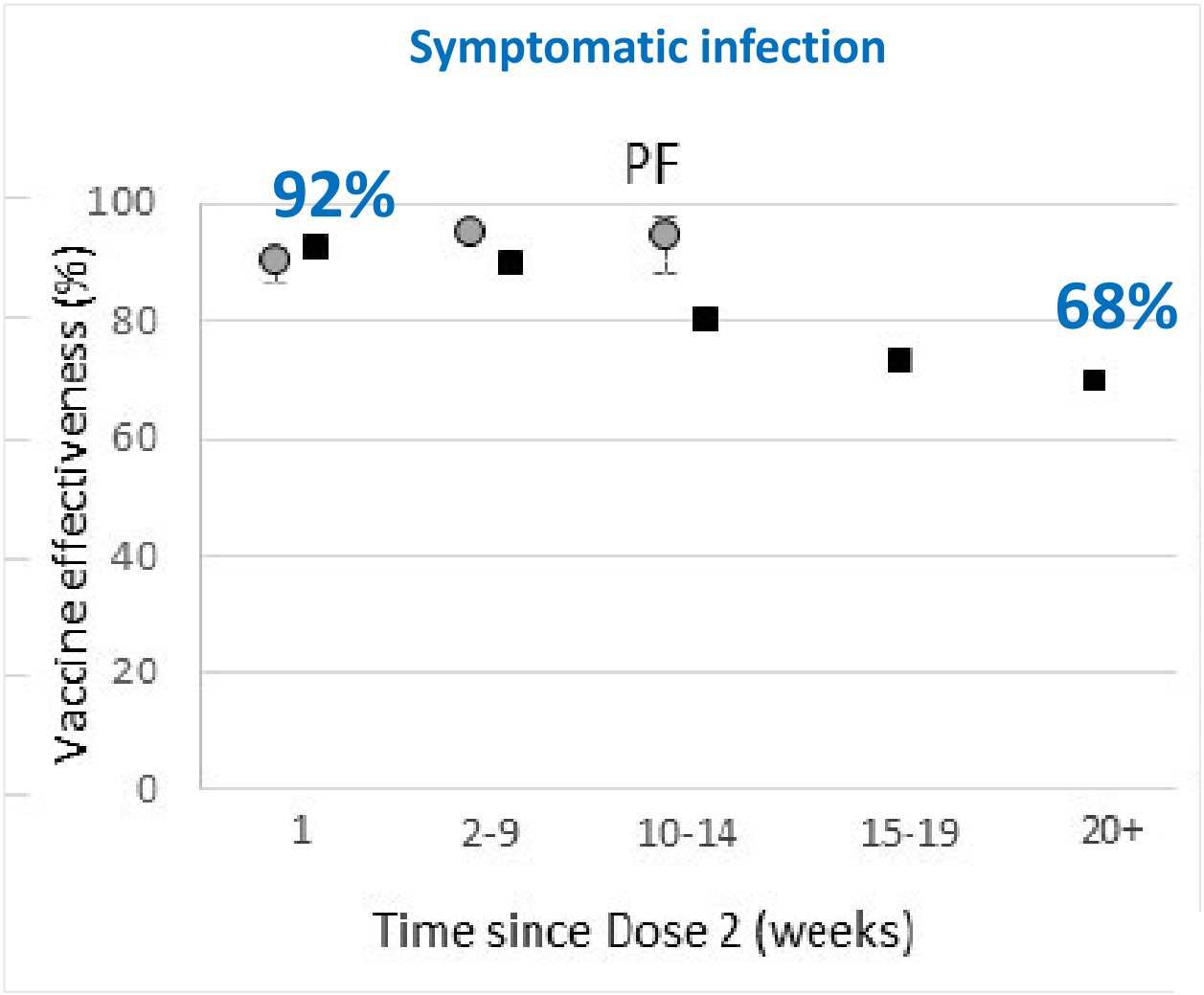


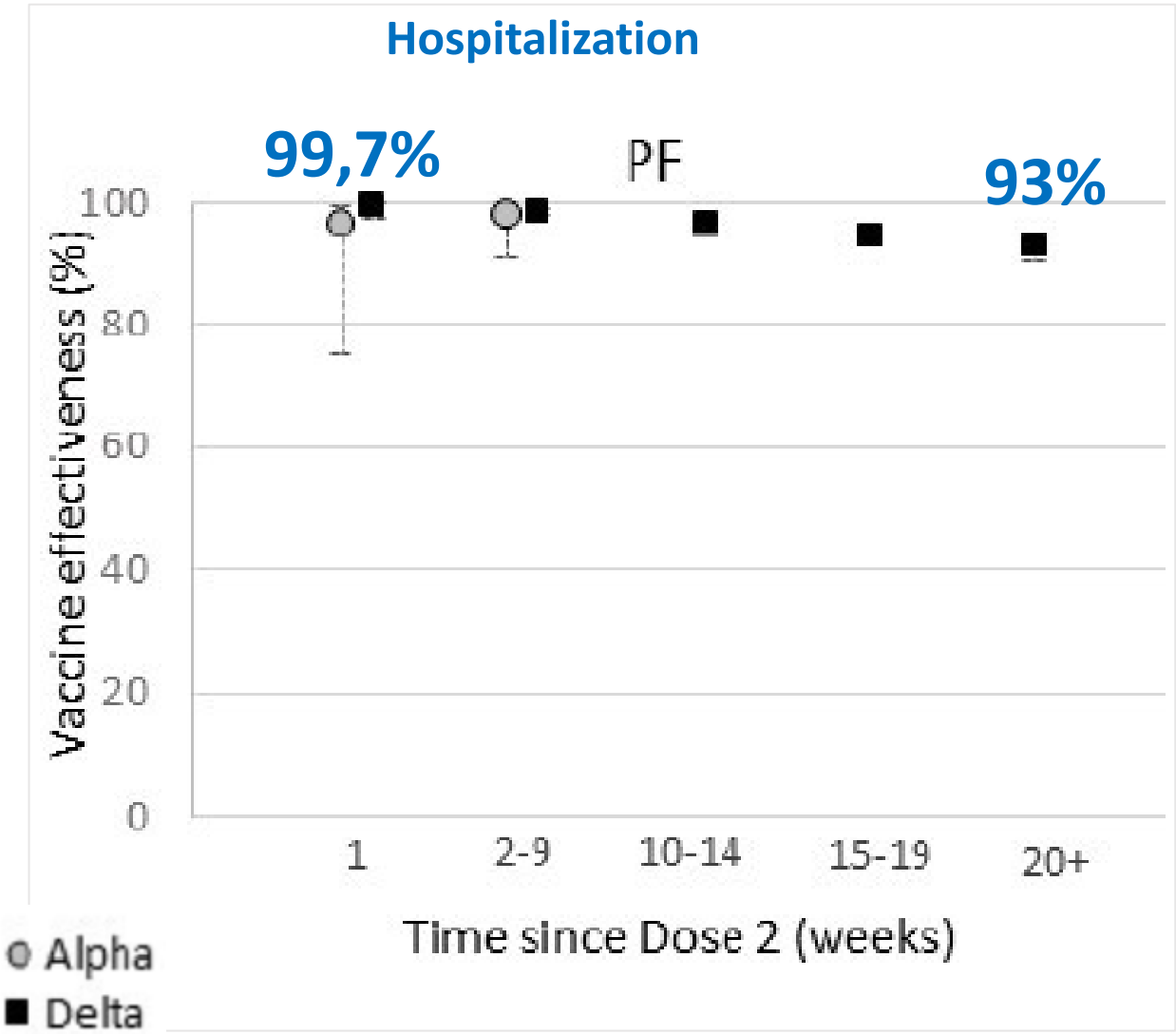
- Subjects with pre-existing cross-reactive CD4+ T cell memory had increased CD4+ T cell and antibody responses to the vaccine.

- Cross-reactive memory TFH cells may both accelerate B cell priming and antibody responses to a new antigen, and also increase robustness of long-term humoral immunity.

Mateus J. et al, Science, 2021

Vaccine efficacy_PHE (n ≈3,7 millions)

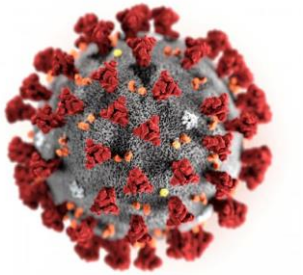




Andrews N. et al, PHE 2021; Ramsay M. ESCV, 2021

Key questions

- Comment évolue la réponse immunitaire après l'infection?
  - Réponse B et T robuste qui dure jusqu'à 13 mois
  - Une seule dose de vaccin suffit pour acquerir une protection contre tous les variants
- Comment évolue la réponse immunitaire après le vaccin?
  - La réponse au vaccin est influencé par l'âge et l'immunosuppression
  - Réponse B et T robuste qui dure jusqu'à 7 mois
  - La cinétique des anti-S est similaire à celle après infection



Merci pour votre attention