UNIVERSITÉ DE GENÈVE
FACULTY OF MEDICINE

# Rationale for the administration of booster doses – an immunological perspective

**Prof. Arnaud Didierlaurent**

**Centre de Vaccinologie, Genève**

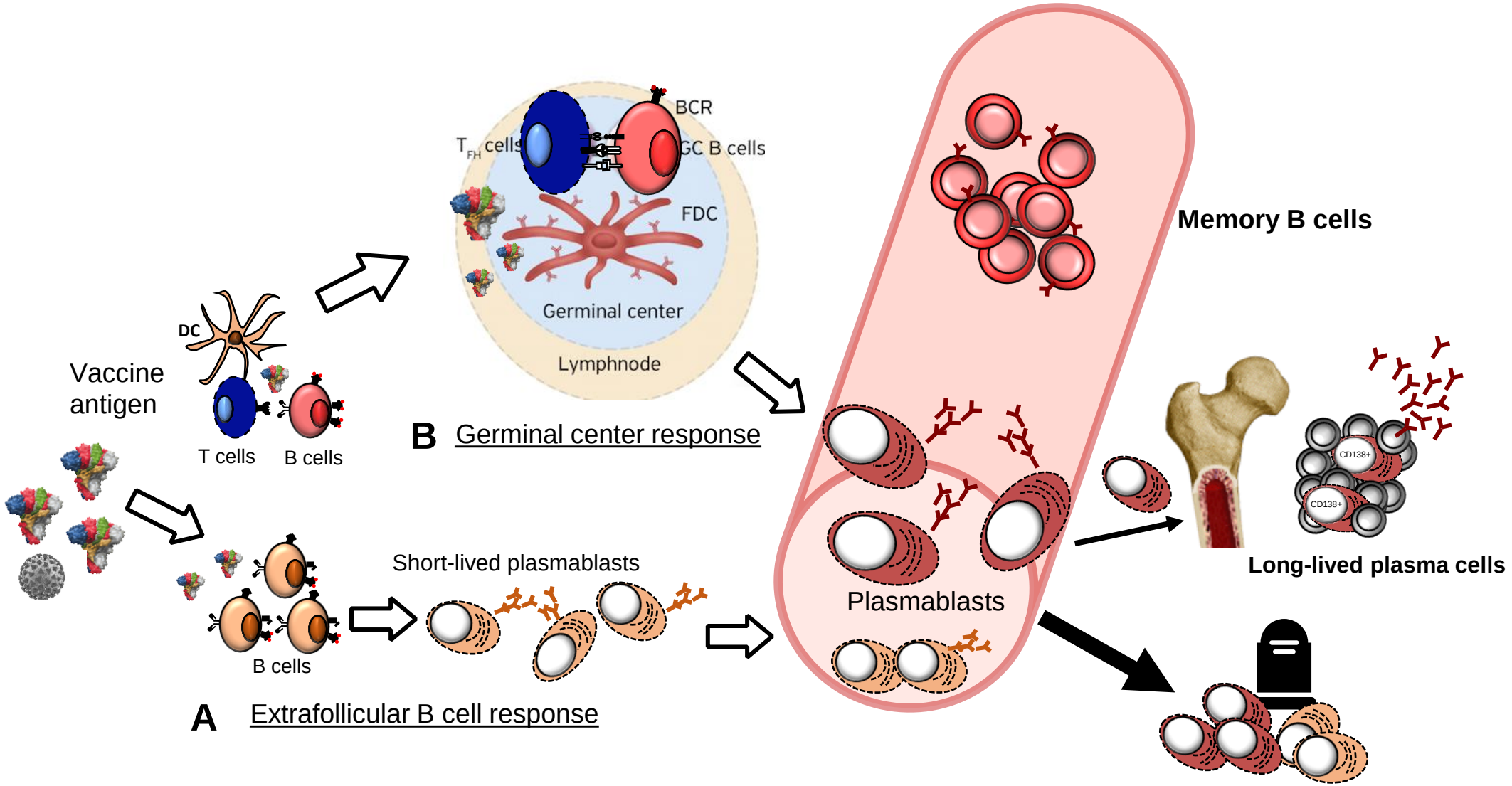
GNN Webinar, May 2nd 2022

# Key points

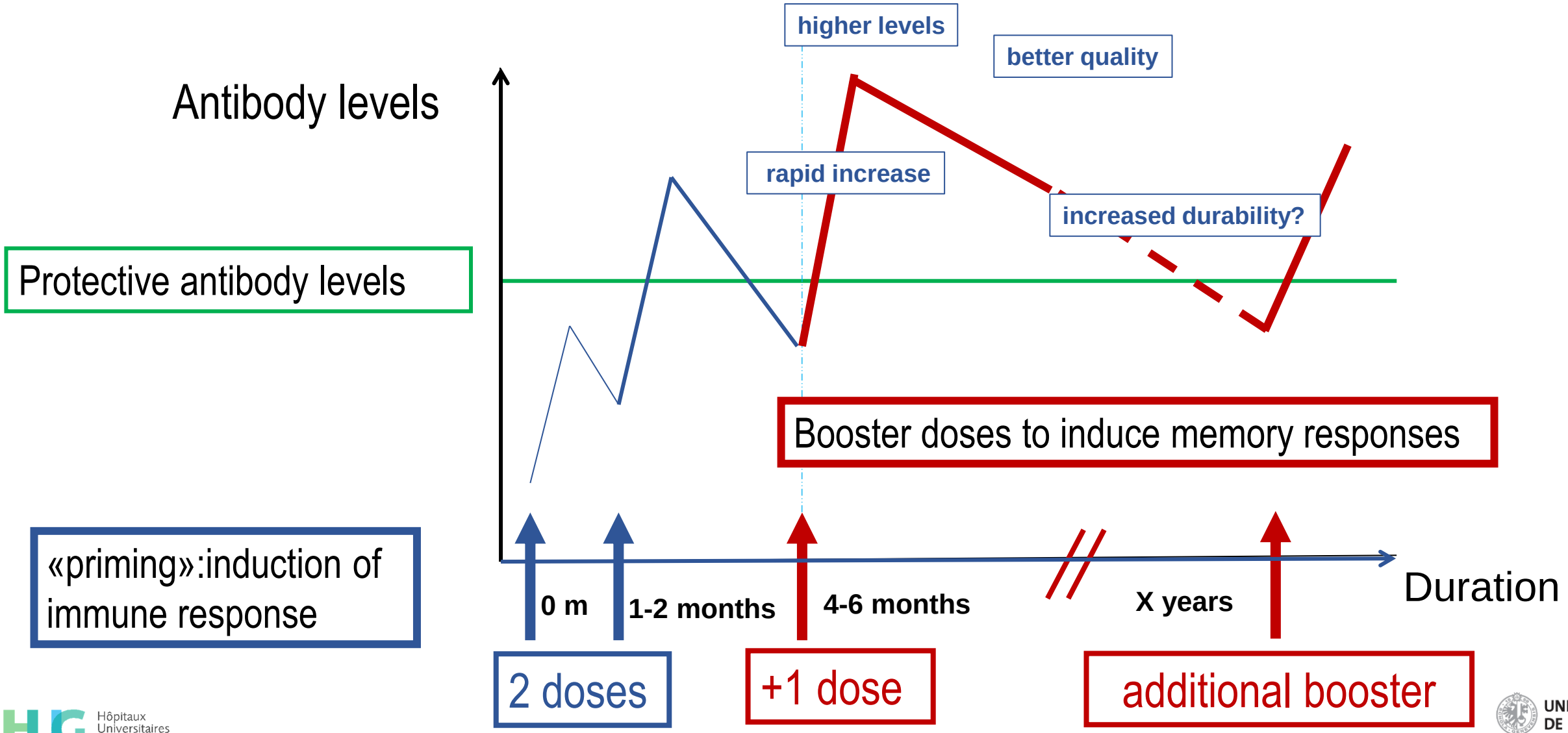
- Principles of booster vaccines
- Key factors determining memory responses: timing, dose, vaccine type..
- « Immune fatigue »- the plateau effect!
- Immuncompromised patients and need for boosters

# Key immune parameters controlling memory response to vaccines

# Vaccine responses- Induction of B-cell memory

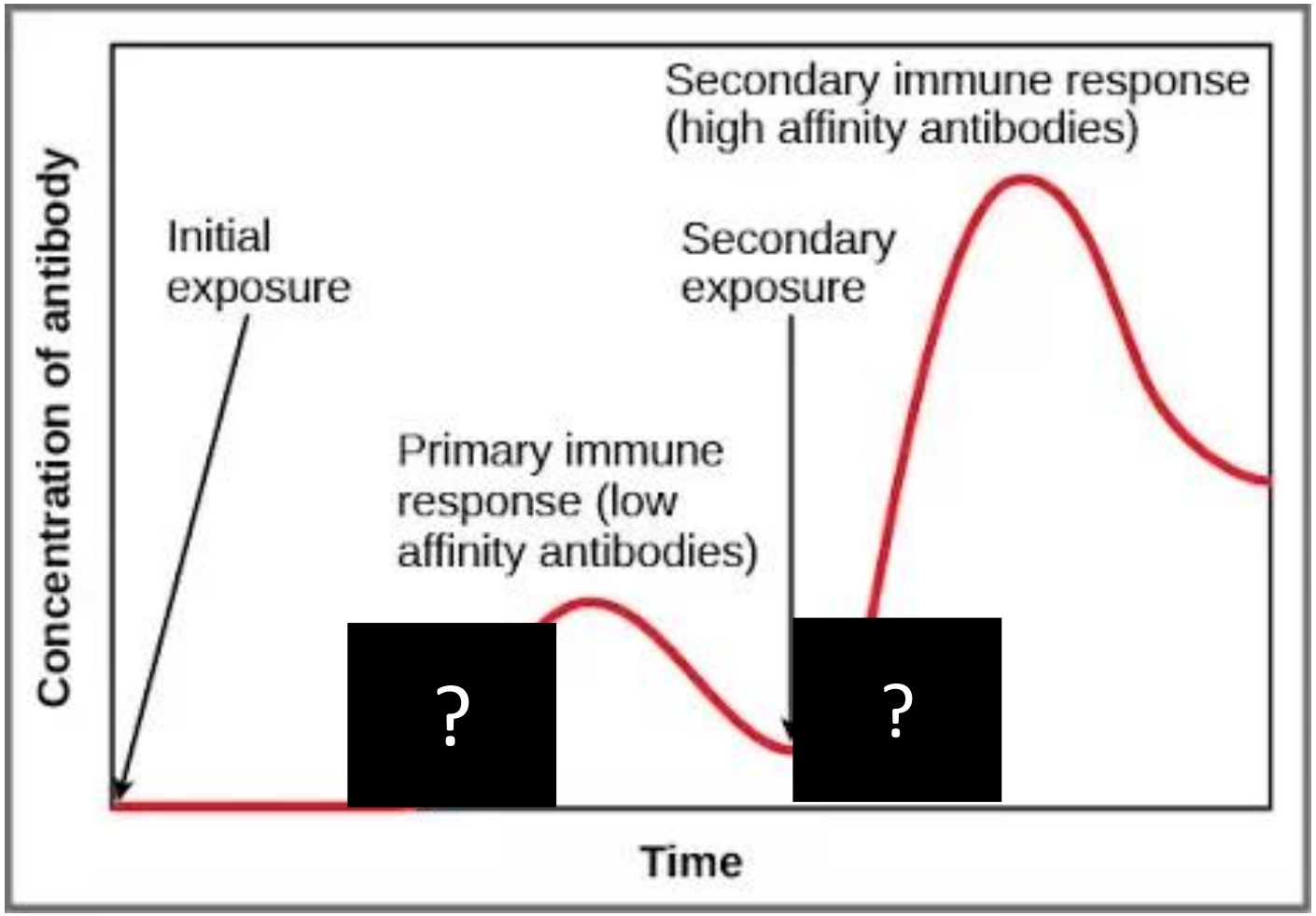


# What to expect from classical vaccine boosters

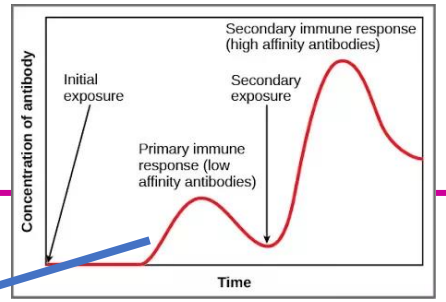


# Prime/boost response- a complex interplay of T and B cell response



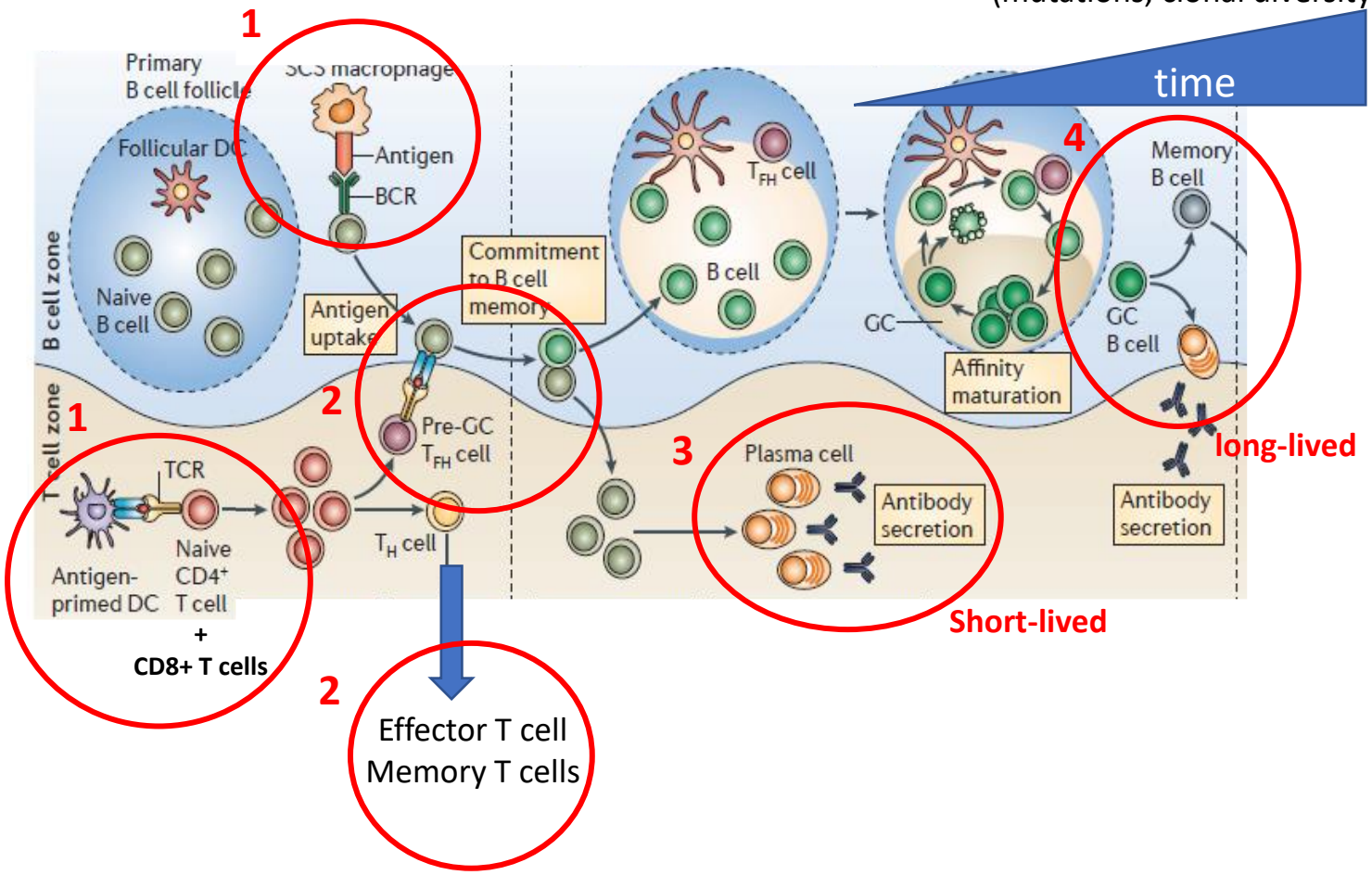


# Prime/boost response- a complex interplay of T and B cell response




**priming**

**Affinity maturation**
(mutations, clonal diversity)



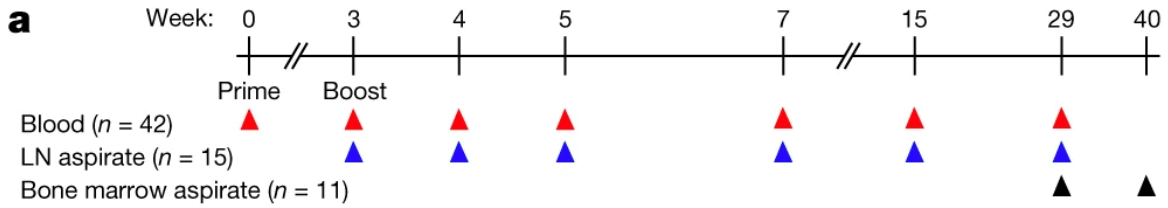

**Memory B cells undergo affinity maturation during several months (survival of the fittest)**

**↑affinity for Ag of their surface IgG**

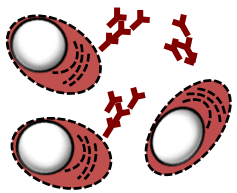
McHeyzer-Williams, Nature Reviews 2012

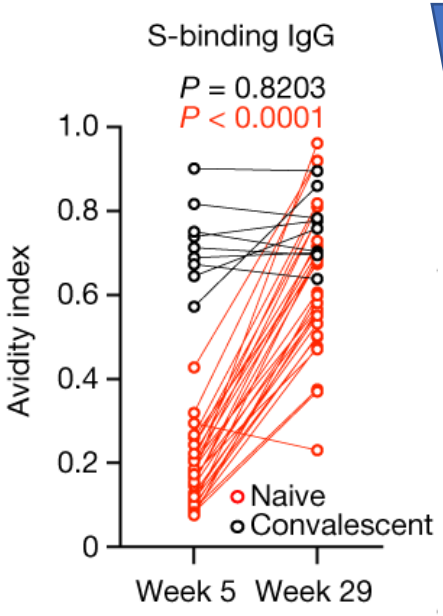
# Persistence of affinity maturation 6 months following 2 doses of mRNA COVID-19 vaccination





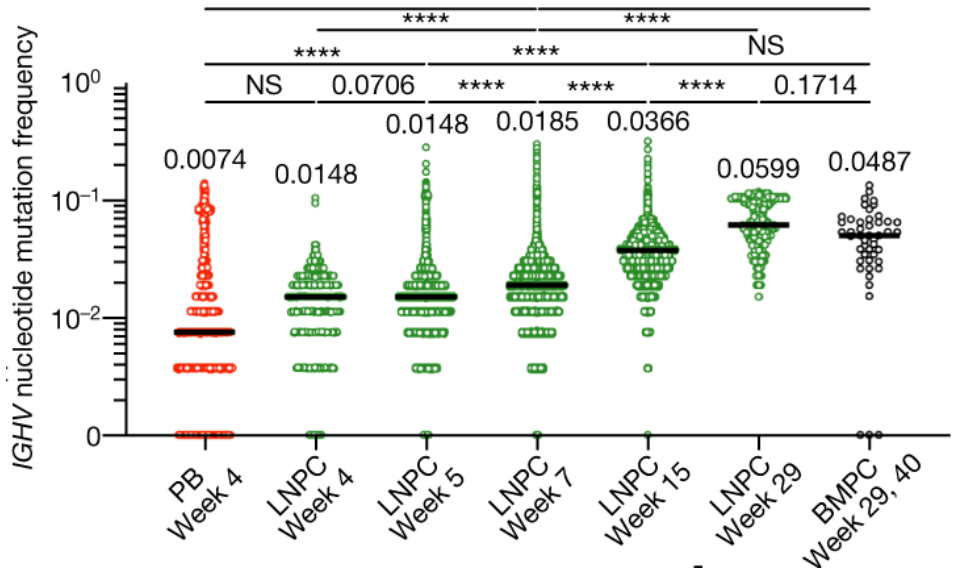

## Antibody avidity





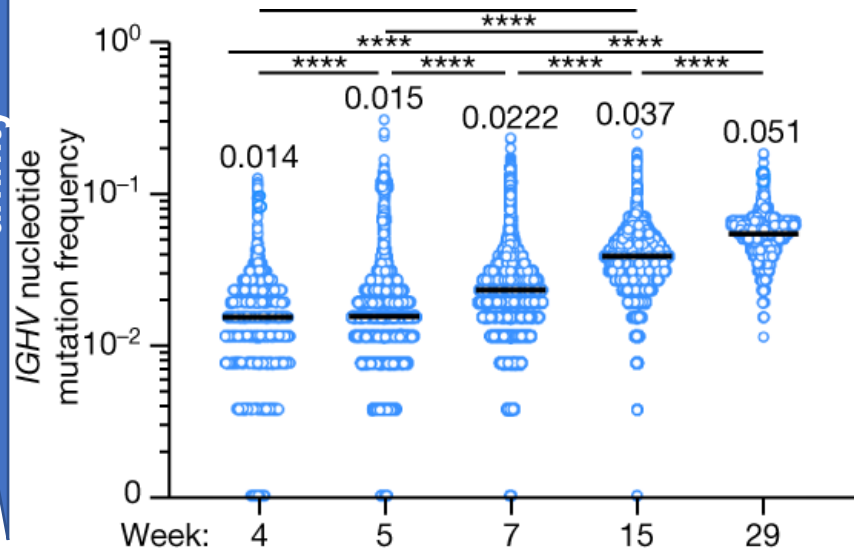

affinity

## Somatic hypermutations of S-specific plasmablasts and plasma cells




affinity

## Somatic hypermutations of S-specific GC B cells

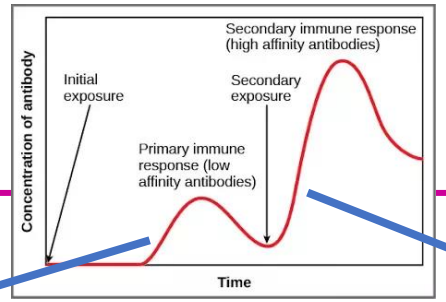





Kim W Nature 2022, https://doi.org/10.1038/s41586-022-04527-1

UNIVERSITÉ DE GENÈVE
FACULTY OF MEDICINE

# Prime/boost response- a complex interplay of T and B cell response

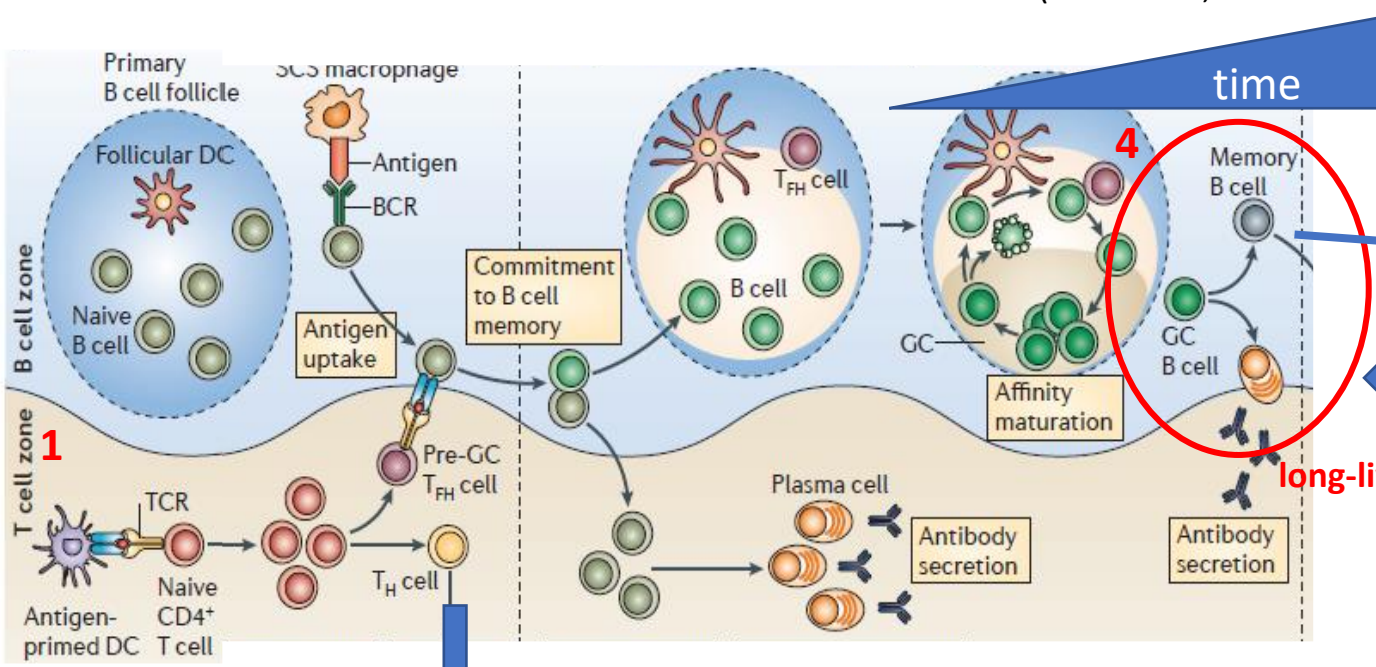



**priming**

**boosting**

**Affinity maturation**
(mutations, clonal diversity)

**Further maturation**

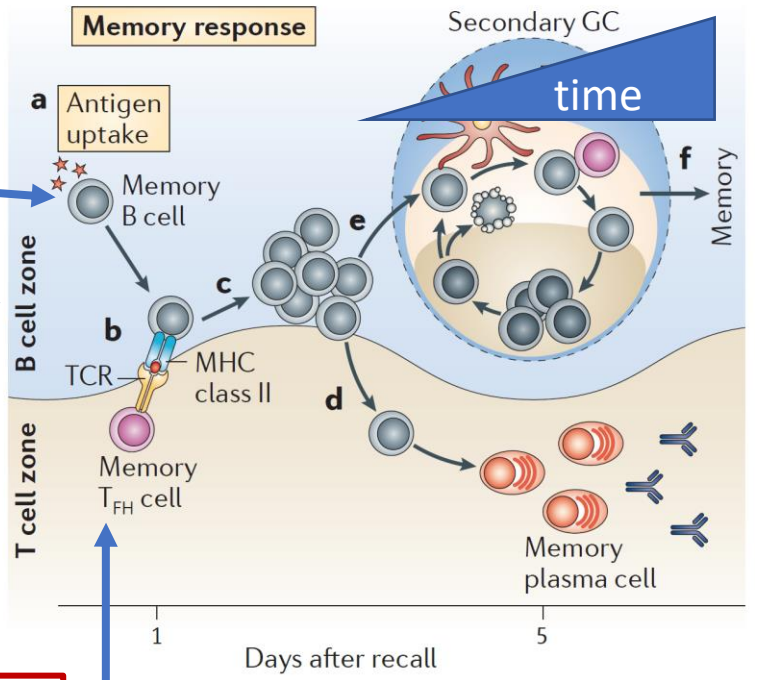



2

Effector T cell
Memory T cells

**long-lived**

Week/months




**Long interval (≥4 months) btwn 2 doses:**
**-> affinity maturation of memory B cells – enhanced capacity to respond to antigen**

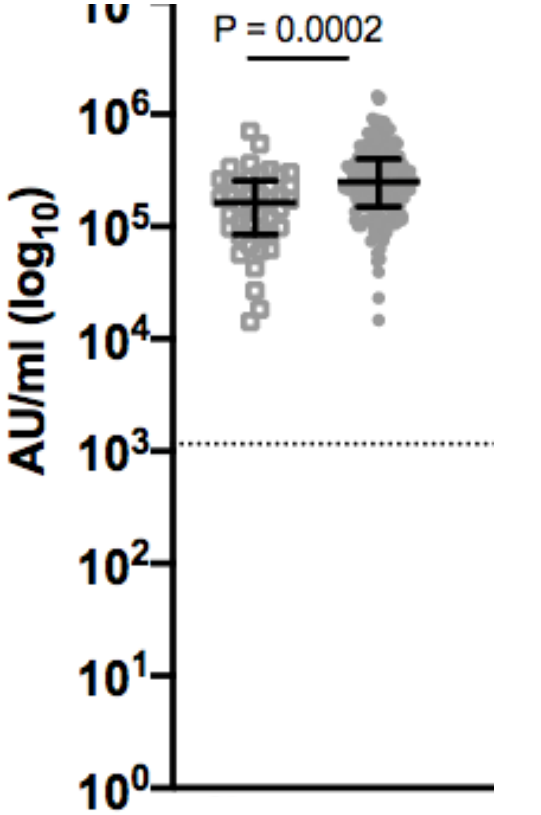
**Ab with higher affinity and broader repertoire**

McHeyzer-Williams, Nature Reviews 2012

# Increasing the interval between mRNA COVID-19 vaccine dose 1 and 2 increases quantity and quality of antibody responses

UNIVERSITÉ DE GENÈVE
FACULTY OF MEDICINE

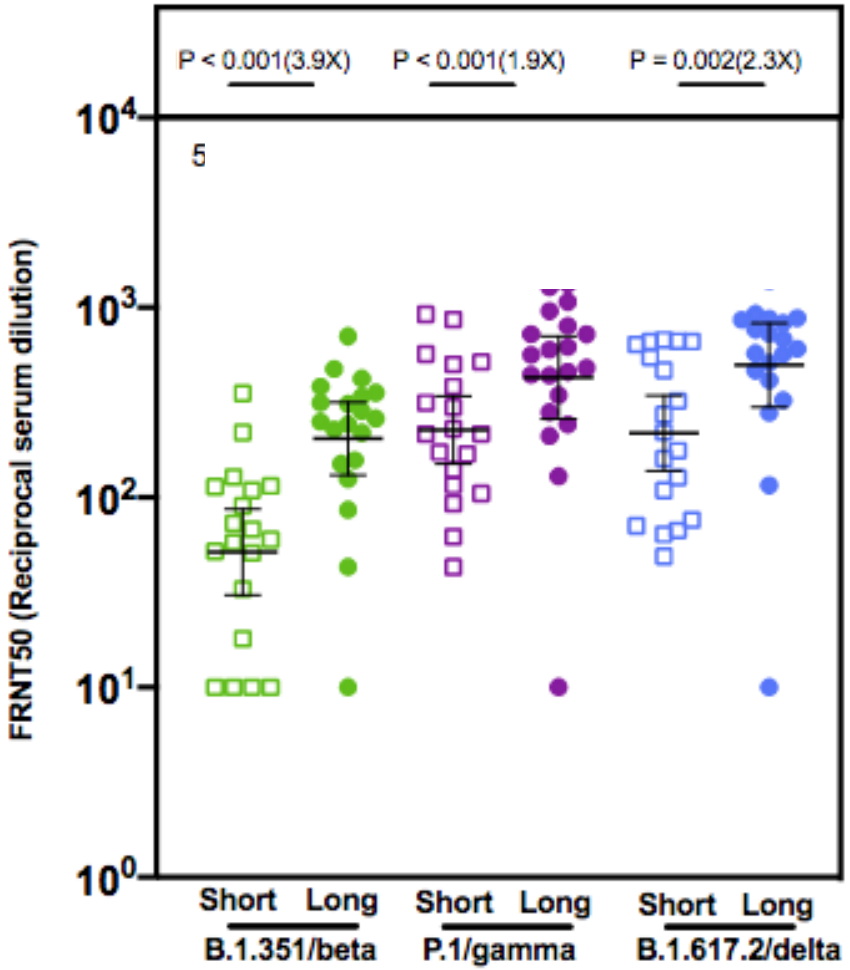
## Anti-spike antibody titers 1 month after the 2nd dose




naive individuals,
vaccination with BNT162b2
n= 57 short interval
n=277 long interval

**Intervals between doses**

## Neutralizing antibody titers 1 month after the 2nd dose




Hôpitaux Universitaires Genève

Payne RP Cell 2021, https://doi.org/10.1016/j.cell.2021.10.011

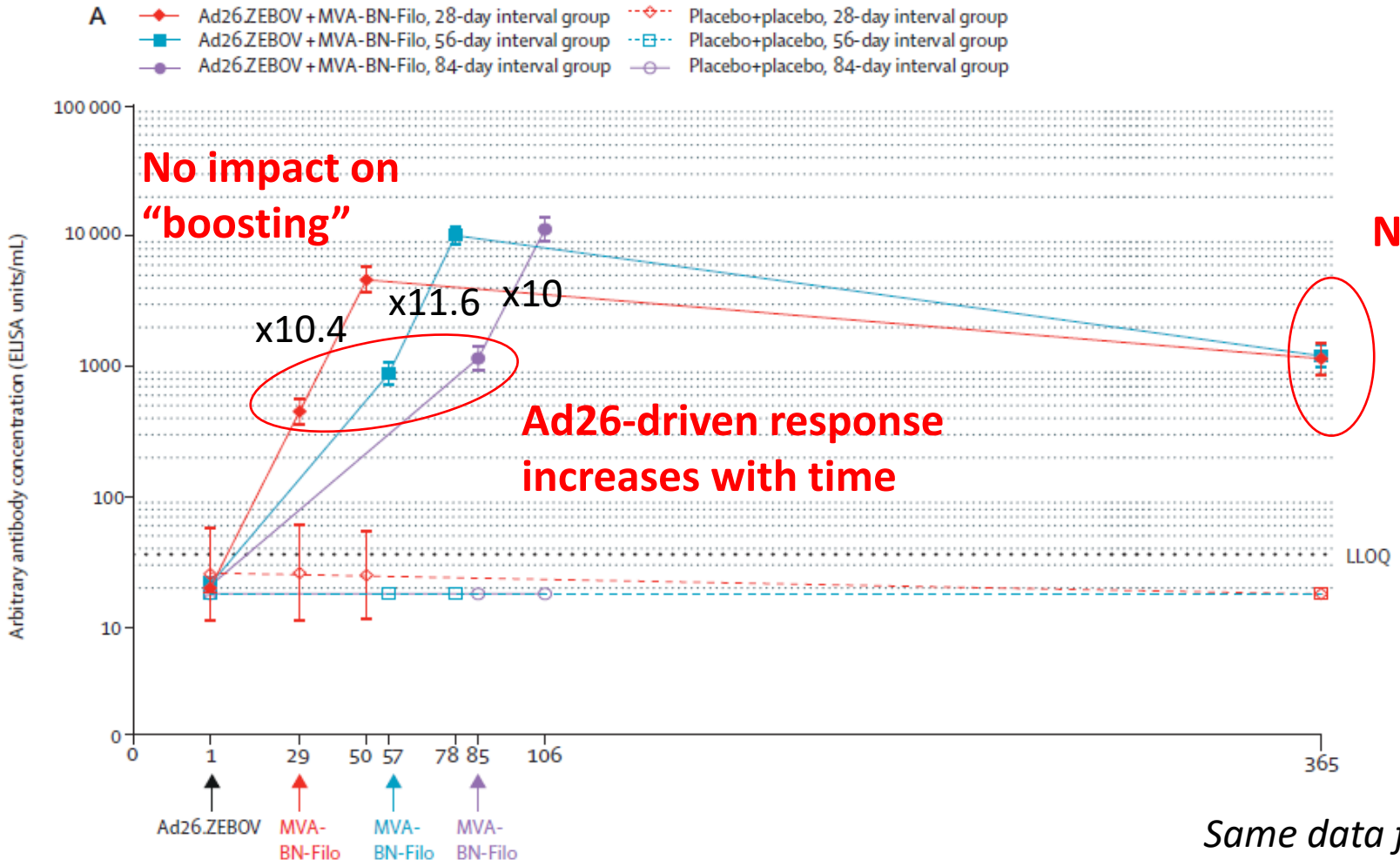
UNIVERSITÉ DE GENÈVE
FACULTY OF MEDICINE

# Does the interval between 1st and 2nd dose matter? Yes, but may only be short term

UNIVERSITÉ DE GENÈVE
FACULTY OF MEDICINE

Phase II – Ad26/MVA

**Compare 28 days, 56 days and 84 days intervals**



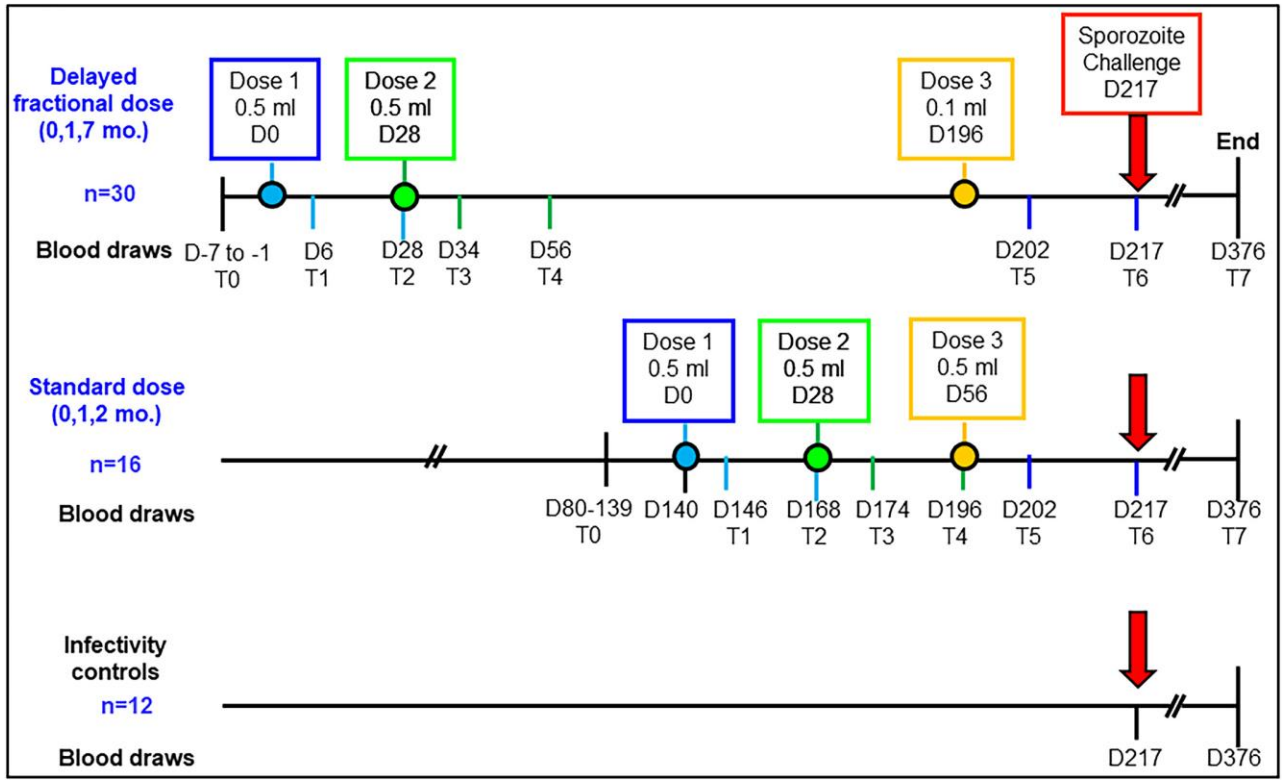

**No long term change**

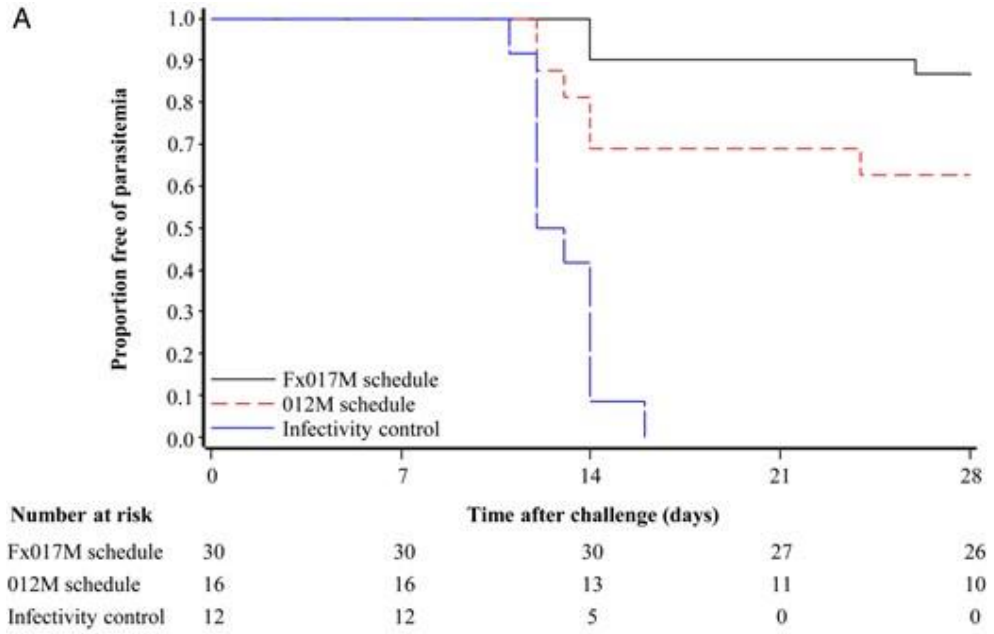
*Same data for neutralizing Ab*
*No difference for T cell response*

Pollack, Launay, NEJM, 2020

# Effect of dose and timing

RTS'S Malaria Vaccine
Human challenge model
Phase II



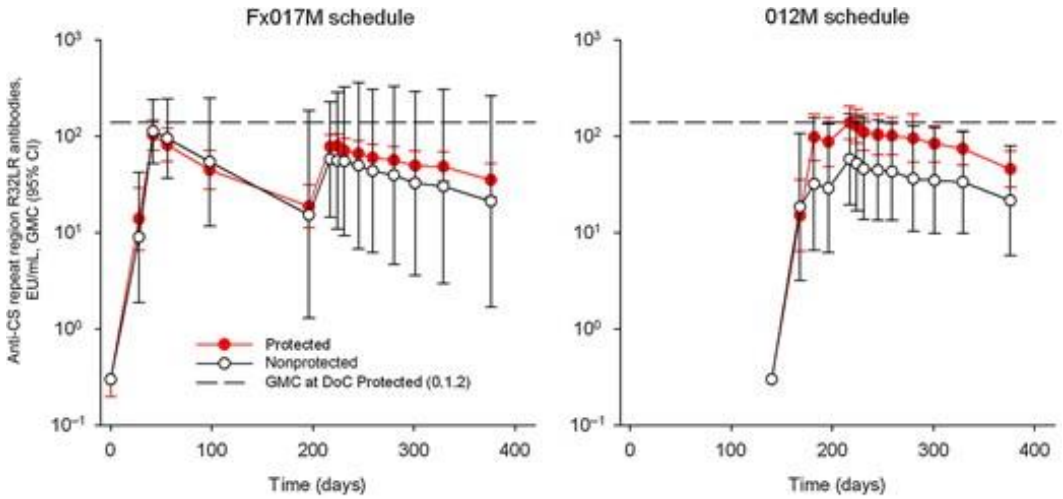



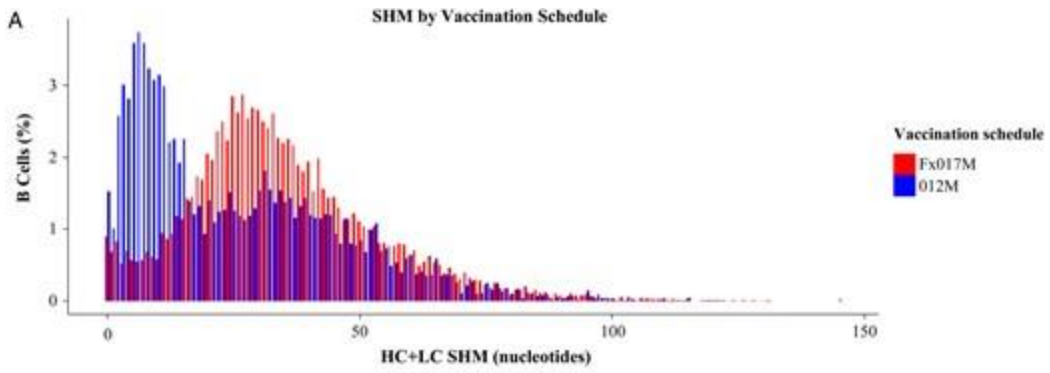

| Number at risk | | | | | |
|---|---|---|---|---|---|
| Fx017M schedule | 30 | 30 | 30 | 27 | 26 |
| 012M schedule | 16 | 16 | 13 | 11 | 10 |
| Infectivity control | 12 | 12 | 5 | 0 | 0 |

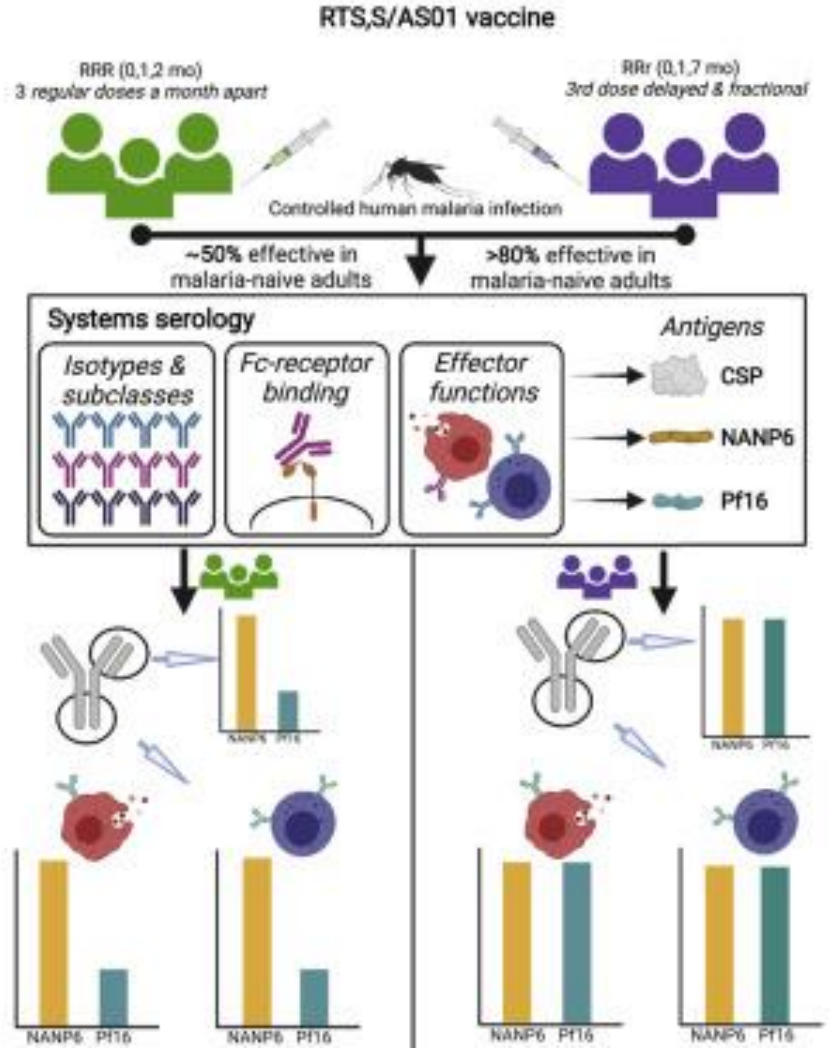
Regules et al. J Infect Dis.. 2016 Sep 1;214(5):762-71; Pallikkuth et al., Elife; 2020 Apr 29;9:e51889;

# Effect of dose and timing on boosting

## Impact on quality rather than quantity !



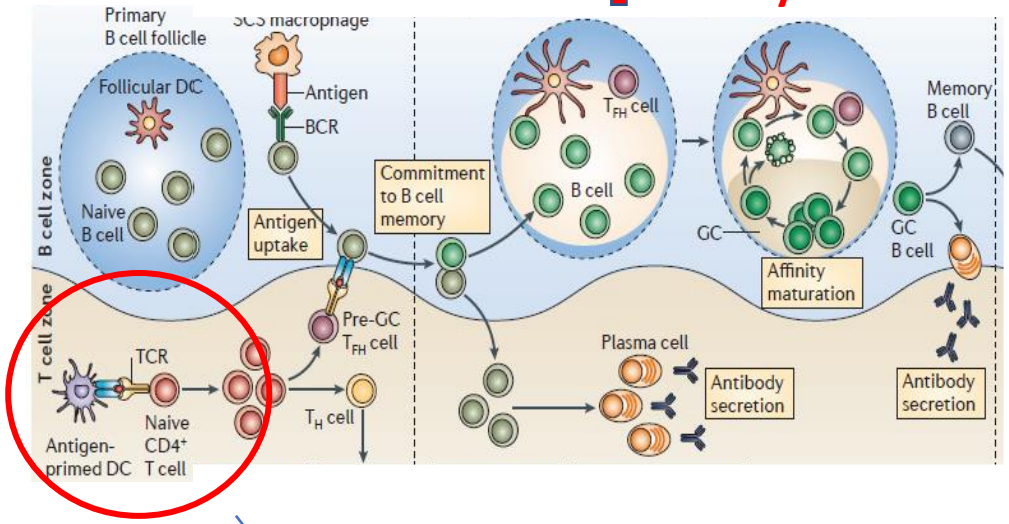

Regules et al. J Infect Dis.. 2016 Sep 1;214(5):762-71; Das, Med, Volume 2, Issue 11, 12 November 2021

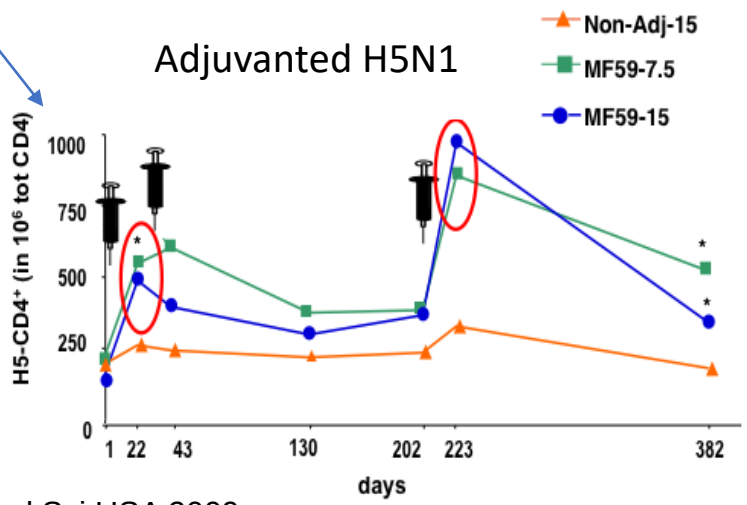
# Influence of the type of vaccine for priming
# Learnings from adjuvanted Flu vaccines

UNIVERSITÉ DE GENÈVE
FACULTY OF MEDICINE

## 1st dose

**Affinity maturation**



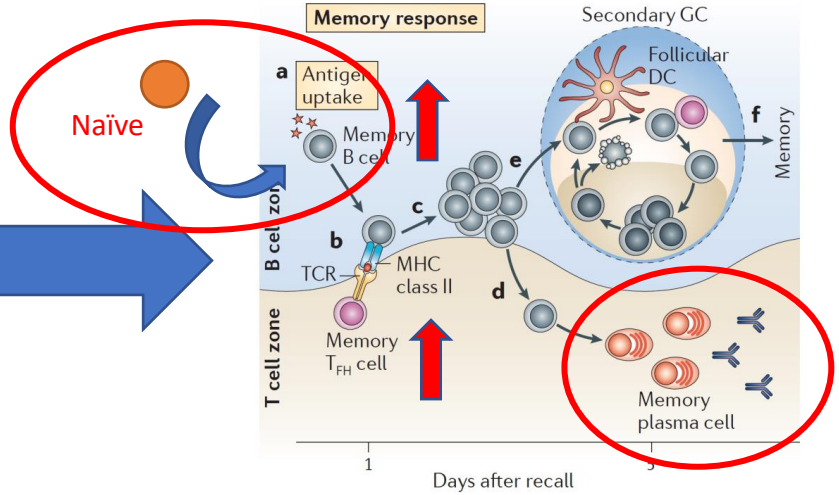




**Increased T cell Response**

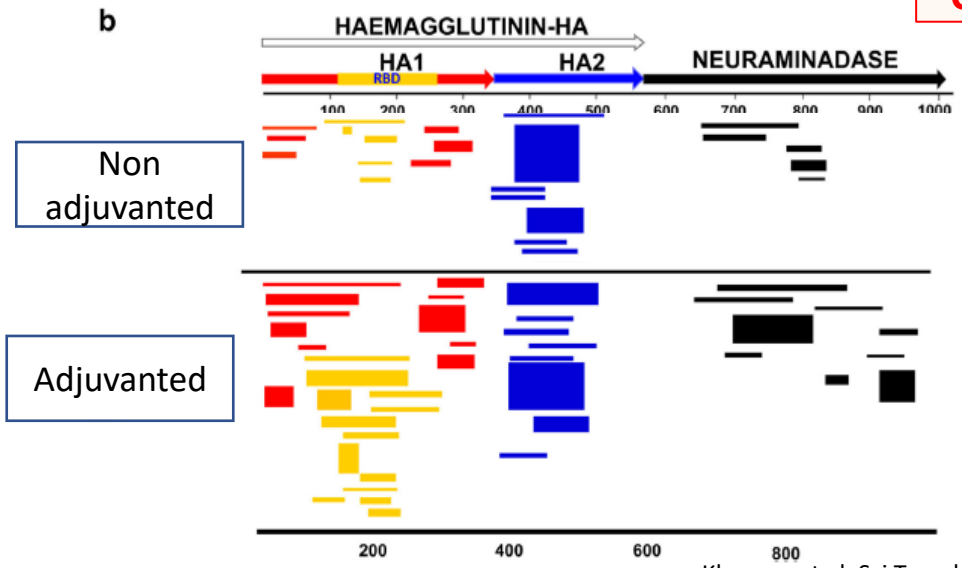
Galli et al, Proc Natl Acad Sci USA 2009

## 2nd dose

**Affinity maturation**




**Broader repertoire**
**Higher affinity**
**Cross-neutralizing**



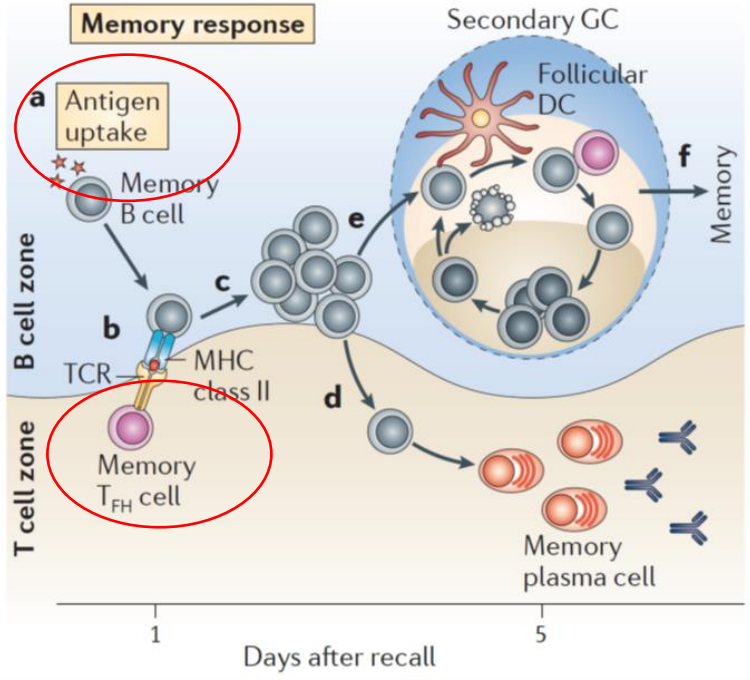

Khurana et al. Sci Transl Med. 2011; Npj Vaccine, 2018

# Key points

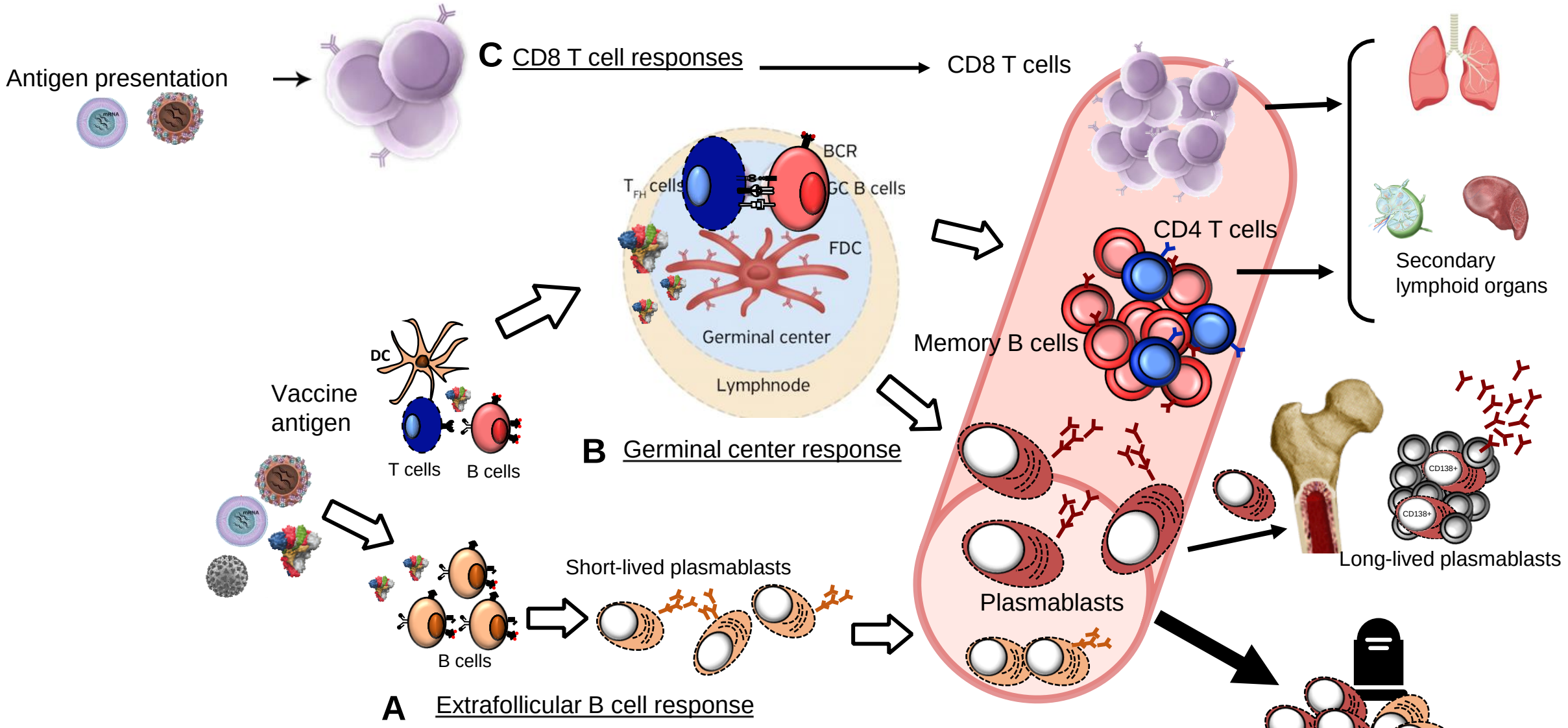
- Priming is key! (needs good memory TFh and B cells, affinity maturation)

- Key factors:

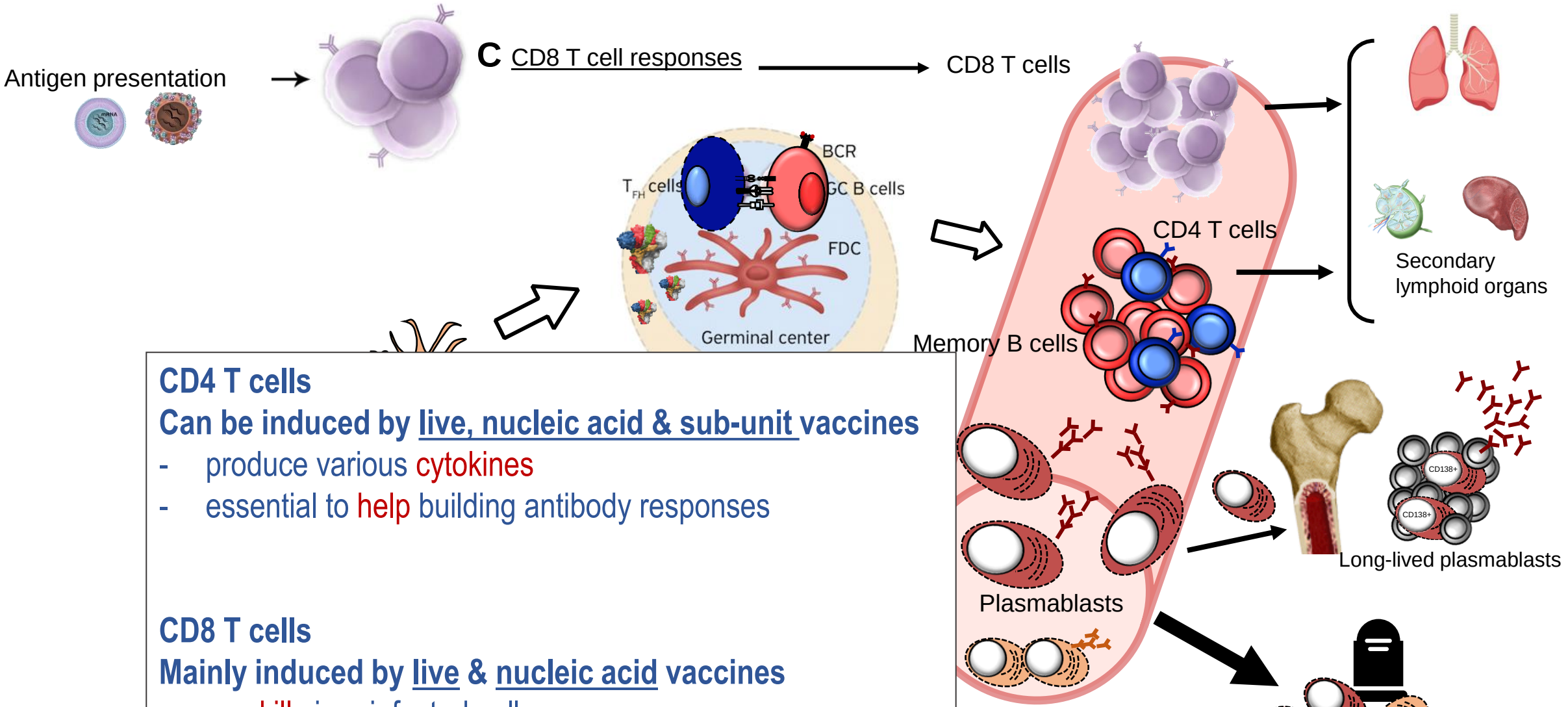
  - Timing between doses- usually the longer the interval, the better!
  - Nature of the vaccine (ex: adjuvants) -> impact on quality of immune response (innate, Tfh, B cell activation)
  - Homology of sequence/conformation used for boosters -> heterologous prime/boost



# Vaccine responses- Induction of T-cell memory



# Vaccine responses- Induction of T-cell memory




**CD4 T cells**

**Can be induced by live, nucleic acid & sub-unit vaccines**

- produce various cytokines
- essential to help building antibody responses

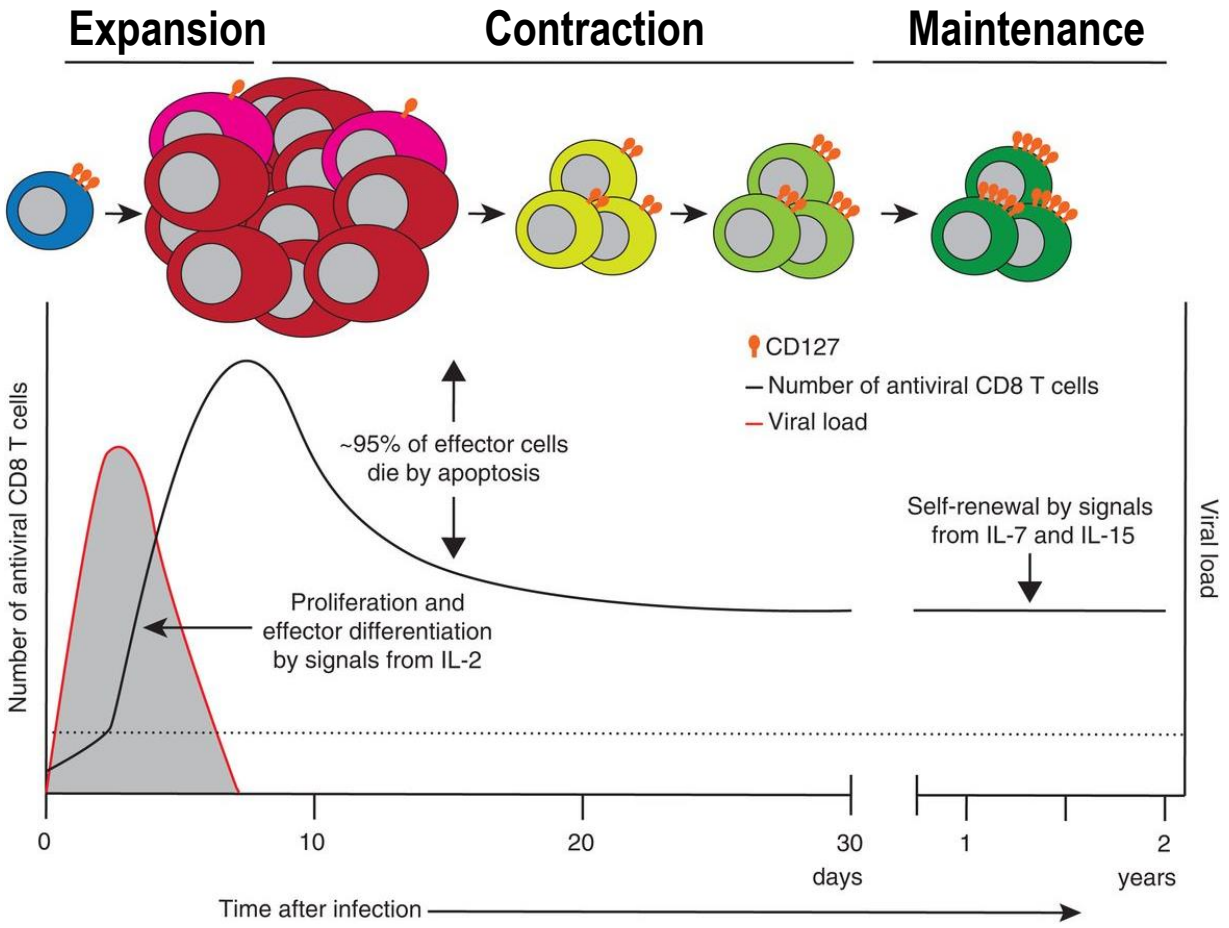
**CD8 T cells**

**Mainly induced by live & nucleic acid vaccines**

- can kill virus-infected cells
- contribute to termination of infection (IFNγ +++)

# T-cell differentiation into effector or memory T cells

Number of antigen-specific T cells




95% of (terminal) effector cells die during contraction phase

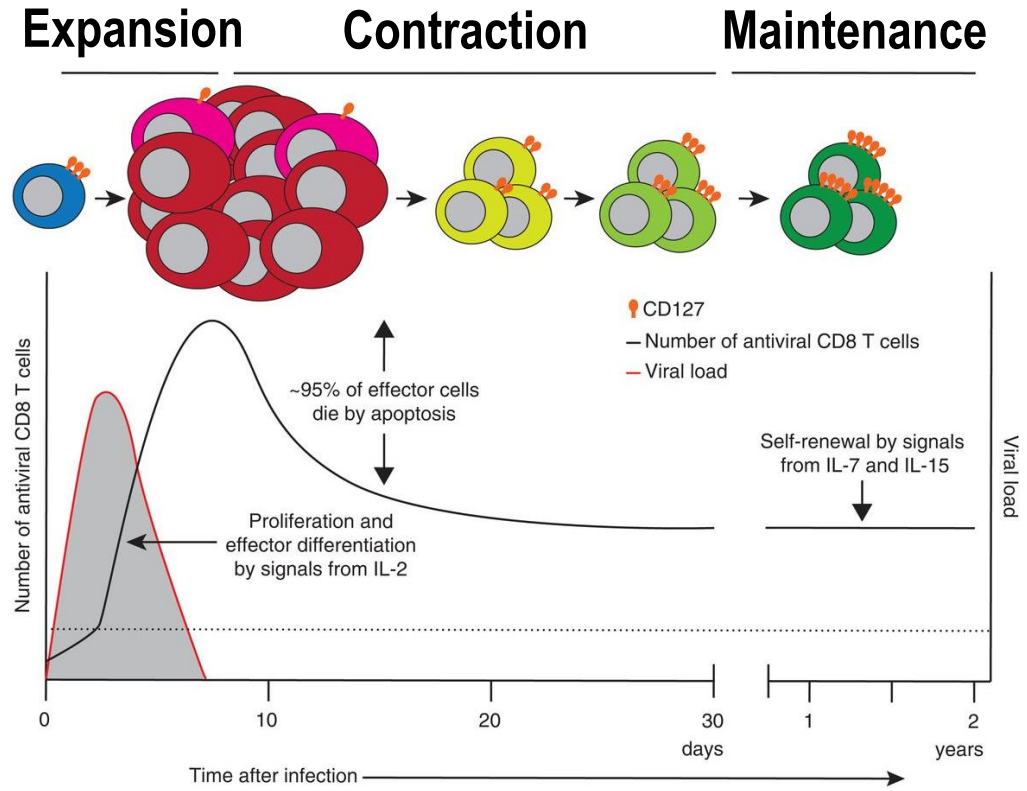
**Memory T cells:**

- **Effector memory T cells**
  - express effector molecules
  - rapid action in case of (re)infection
  - circulating and in tissues
- **Central memory T cells**
  - resting
  - reservoir in lymphoid tissues

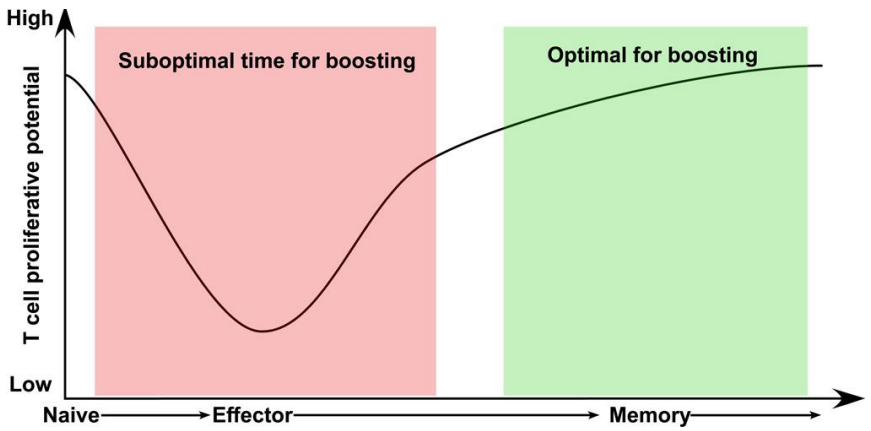
Hashimoto M, Cold Spring Har Persp Biol 2017

# When is the best timing to boost T cell responses?

Number of antigen-specific T cells




T cell proliferative potential

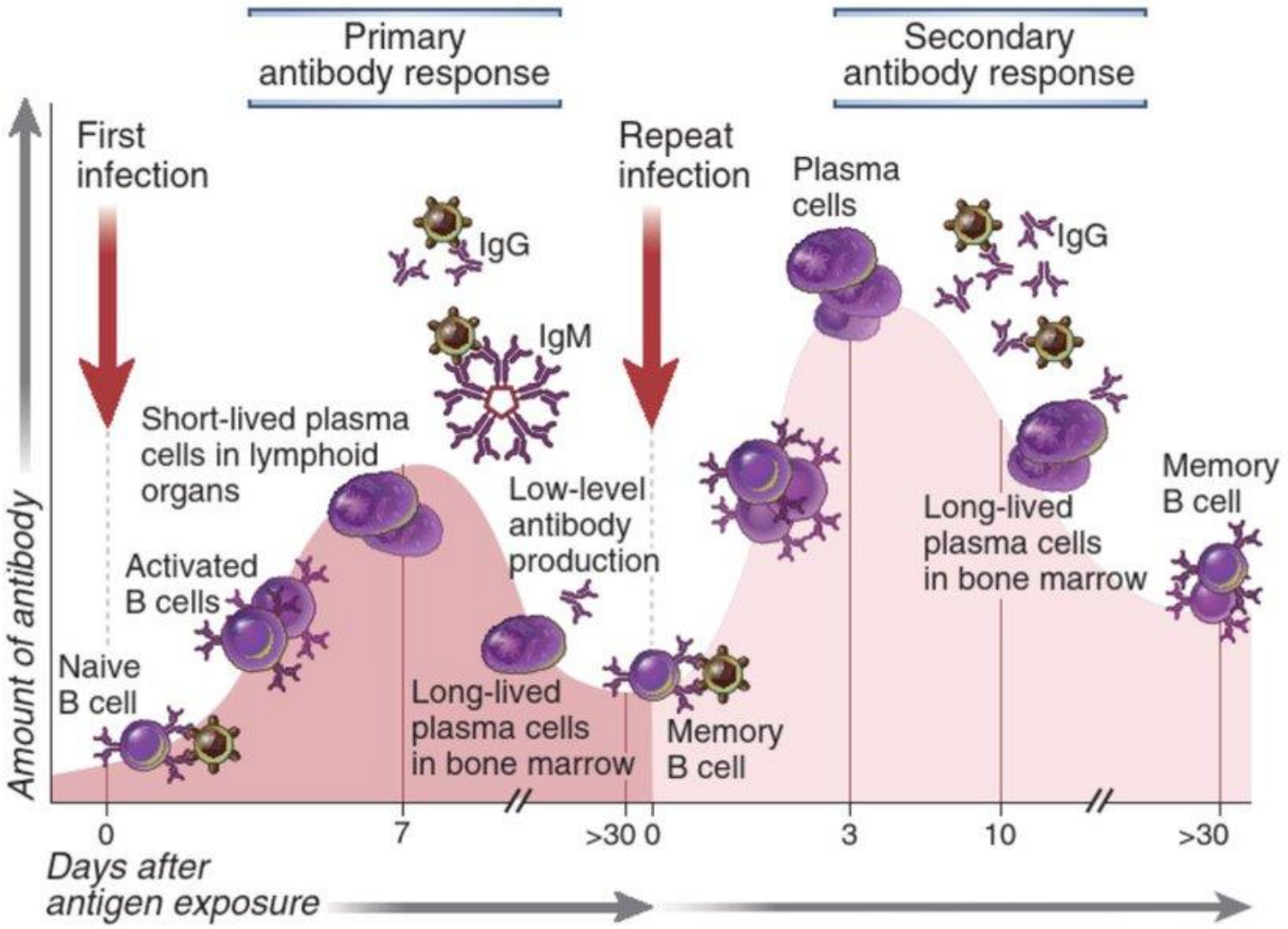



**T cell responses are lower when booster is given too early**

Hashimoto M, Cold Spring Har Persp Biol 2017, Sallusto F, Immunity 2010

# What we measure and what we don't….

# Measure of antibody versus memory response…

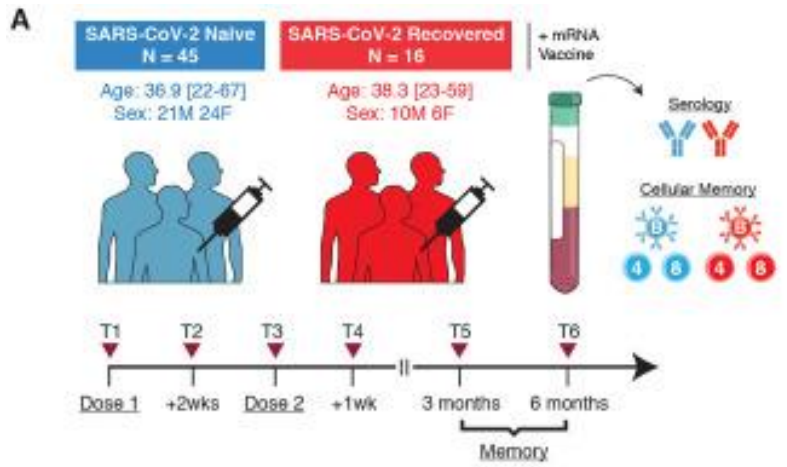


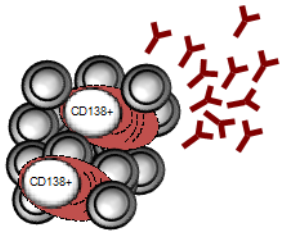

1. Antibodies are produced by different B cells (short-lived vs long-lived) depending on timing post vaccination

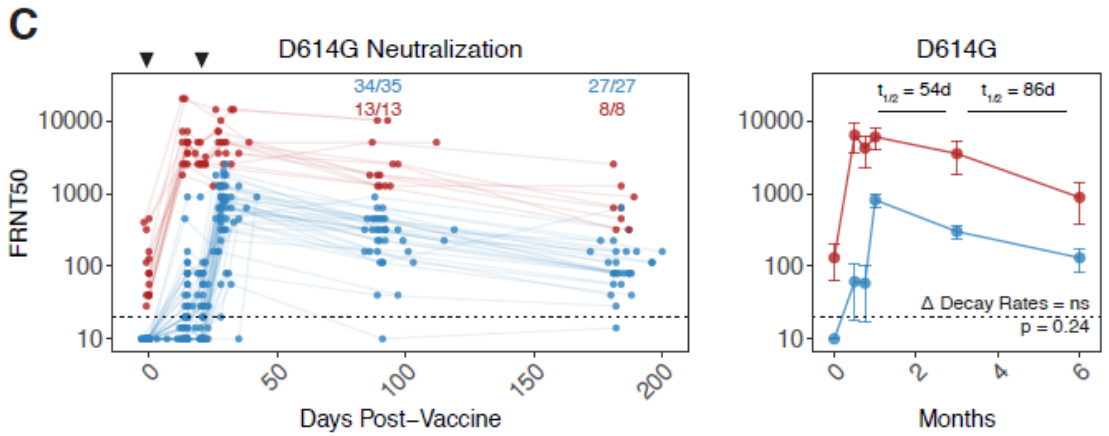
2. **Low antibody level does not mean absence of memory responses!!**

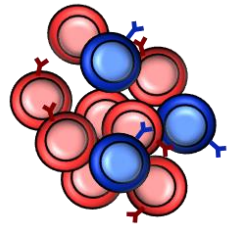
Abbas, Lichtman, Pillai. Cellular and molecular Immunology, 2017

# Evidence of reduced antibody level but INCREASED memory

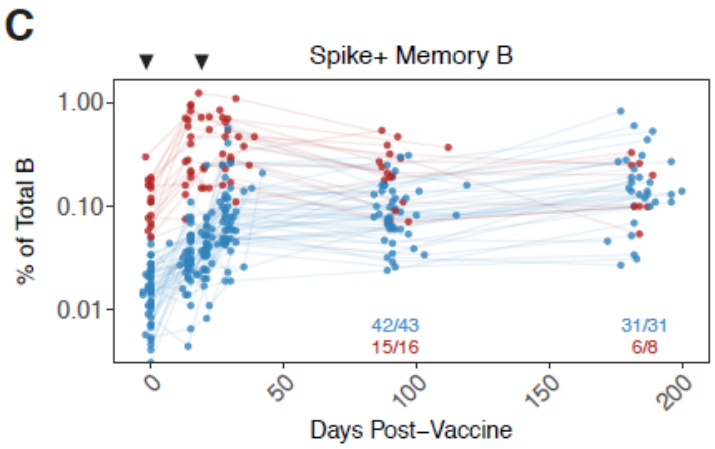


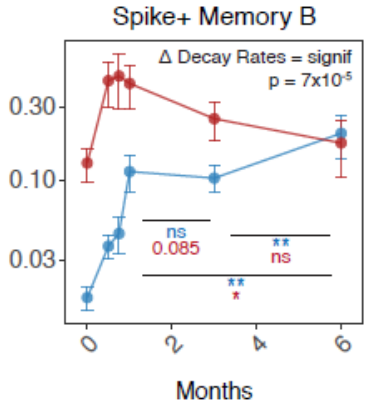



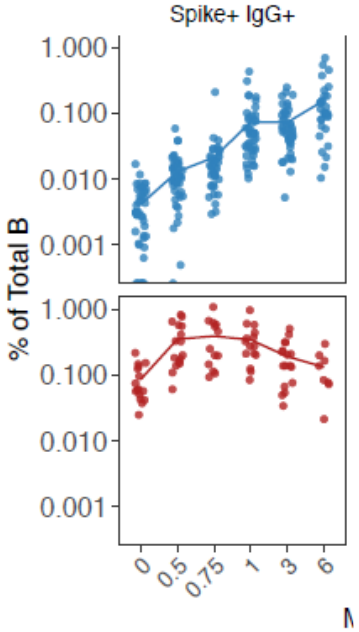



Memory B cells



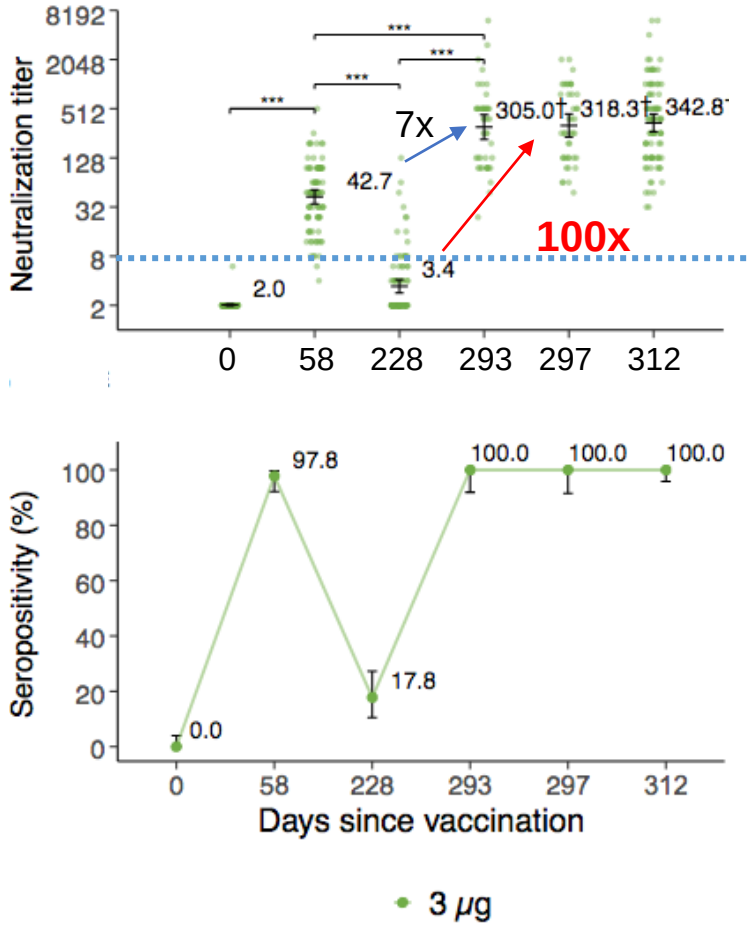

Goel RR,. bioRxiv. 2021 Aug 23:2021.08.23.457229. doi: 10.1101/2021.08.23.457229

# Example of inactivated vaccine booster

phase I/II, vaccine: Sinovac;  N=90, 3µg (dosage approuvée), booster 8 months post 2nd dose

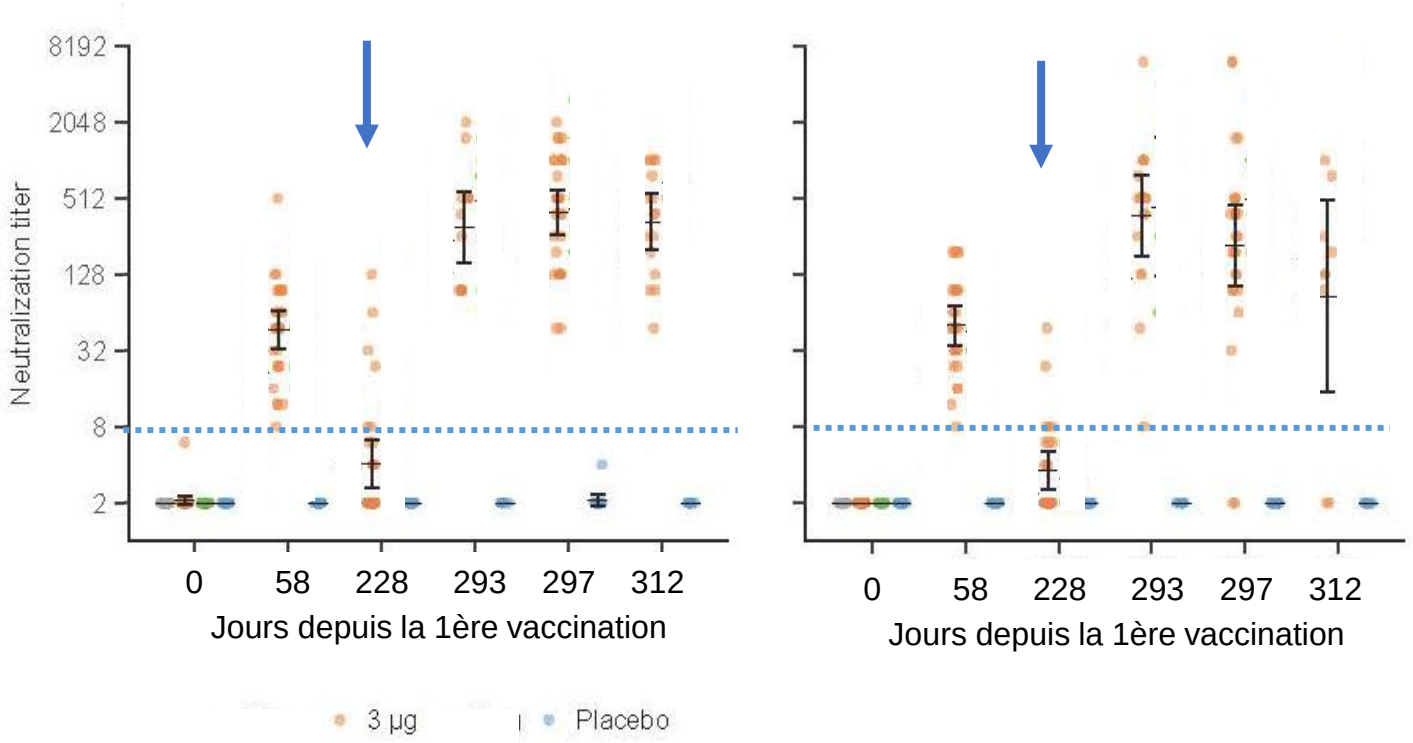
Taux de neutralization

Seropositivité (%)

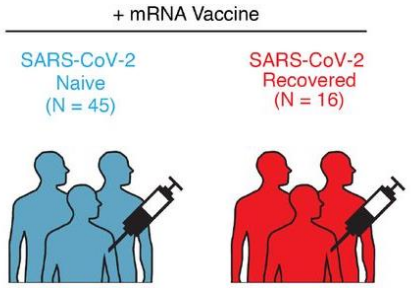



**65-69 ans (n=29)**

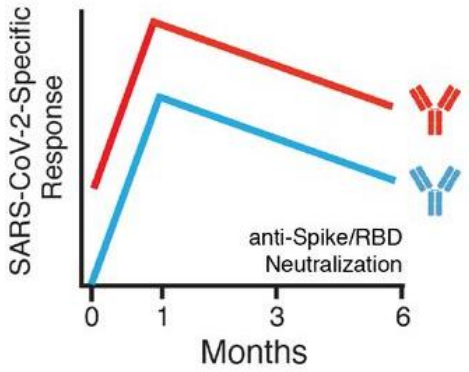
**≥ 70 ans (n=26)**



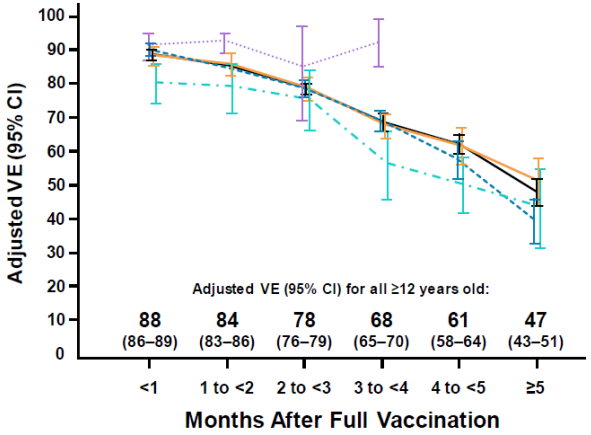
# Parallels between a decrease in immunogenicity and effectiveness (pre-omicron)




Antibodies




SARS-CoV-2 Infection

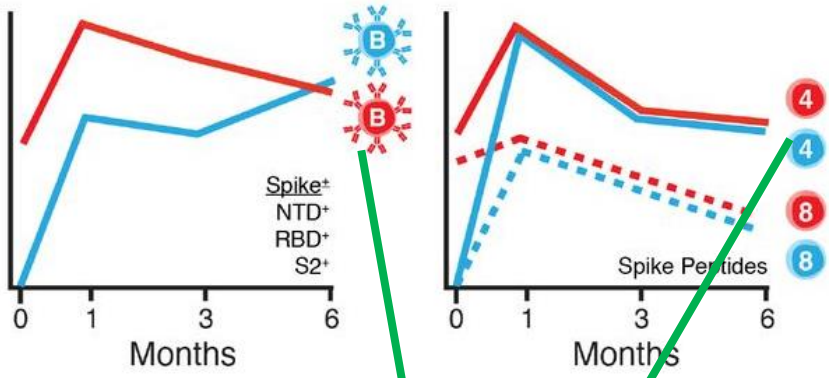



?

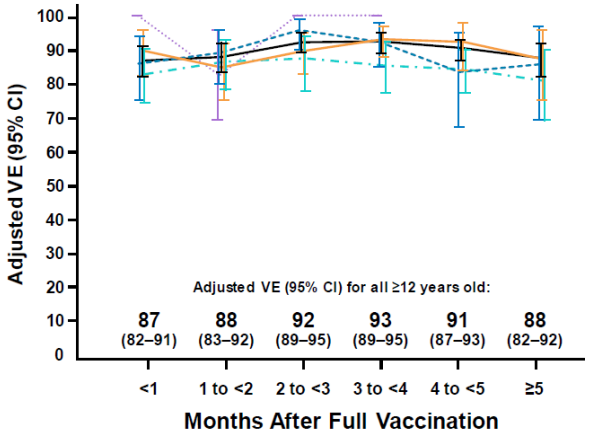
correlate of protection

Memory B Cells

Memory T Cells



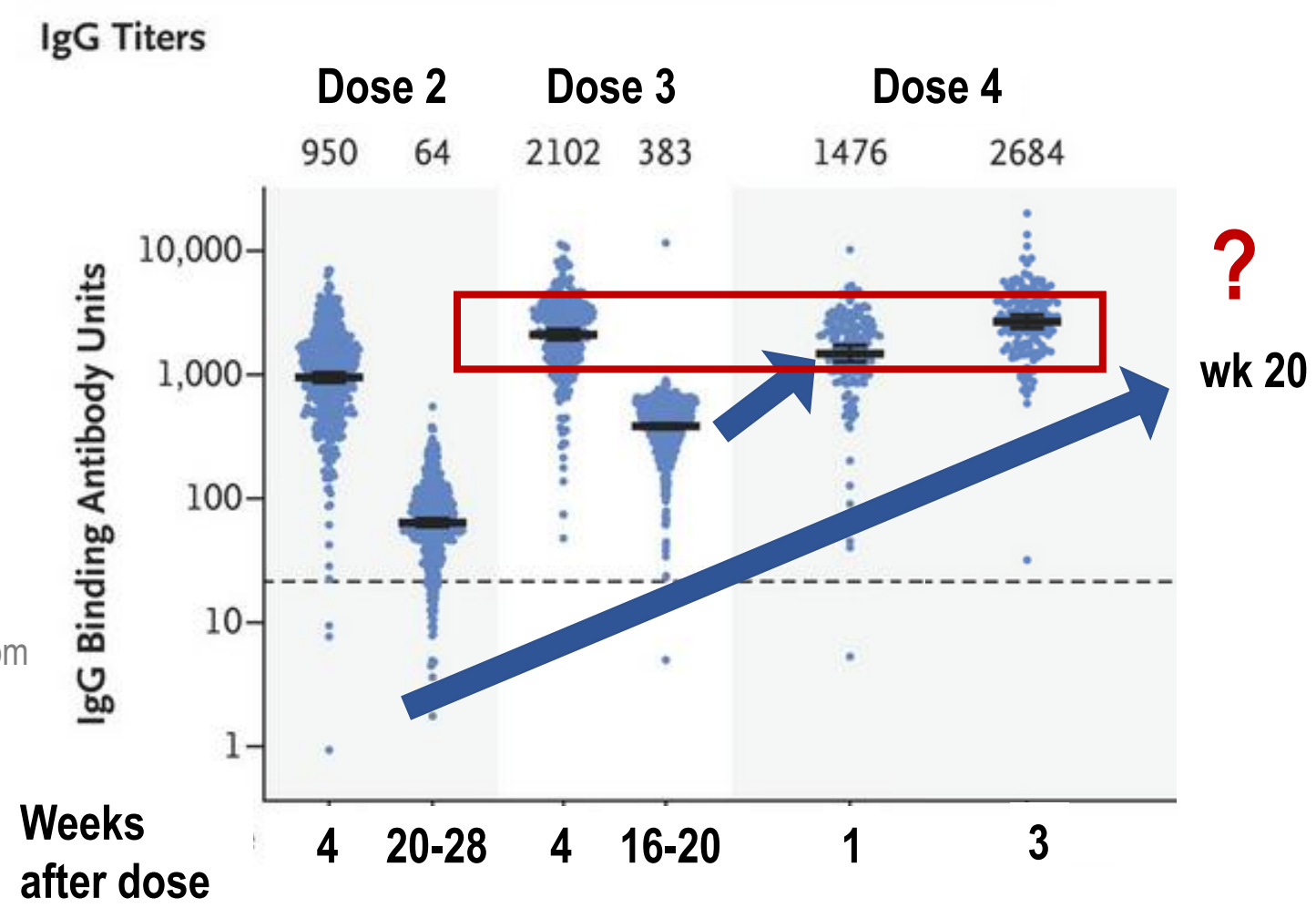

COVID-19-Related Hospitalization




Six-month effectiveness of BNT162b2 mRNA COVID-19 vaccine in a large US integrated health system: a retrospective cohort study. Tartof SY 2021

# Does the response reach a plateau after subsequent boosting
# What is the mechanism?

# Do antibody levels reach higher levels with each subsequent boost?




n=154 individuals from SHEBA HCW cohort BNT162b2

Rapid increase in antibody titers 1wk after dose 4

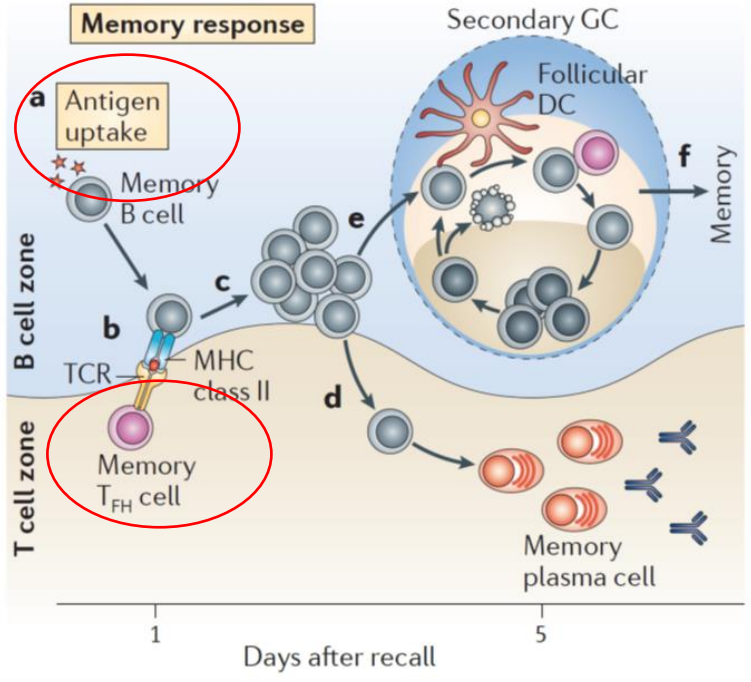
No difference in the peak response between dose 3 and 4 -> **plateau**

***Same for neutra***

Kinetics of antibody decay after dose 4 ? similar to after dose 3?

# “immune fatigue” upon repeated boosting?

- T (or B) cell exhaustion is usually seen in chronic infection/ antigen exposure
- It mainly leads to the anergy of memory T cells
- Plateau effect is likely due to a “space constraints” in the long-lived plasma cells in bone marrow and T cell memory pool

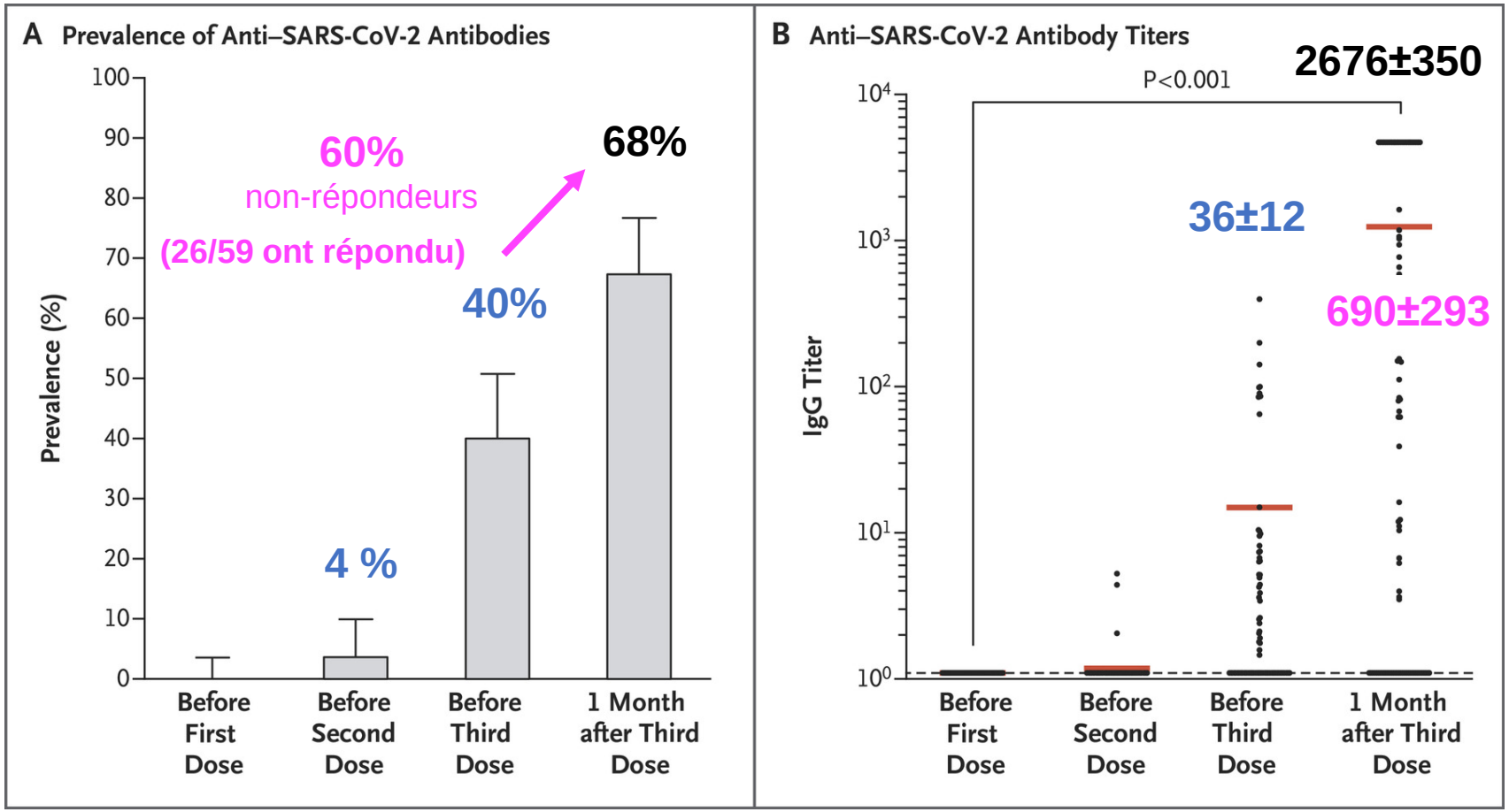


# Beneficial impact of booster for IC patients

# The humoral response is boosted following a 3rd vaccine dose in transplant patients

Retrospective study (France)
(BioNTech/Pfizer)
n= 101 transplanted
- 78 renal
- 12 hepatic
- 8 pulmonary
- 3 pancreas

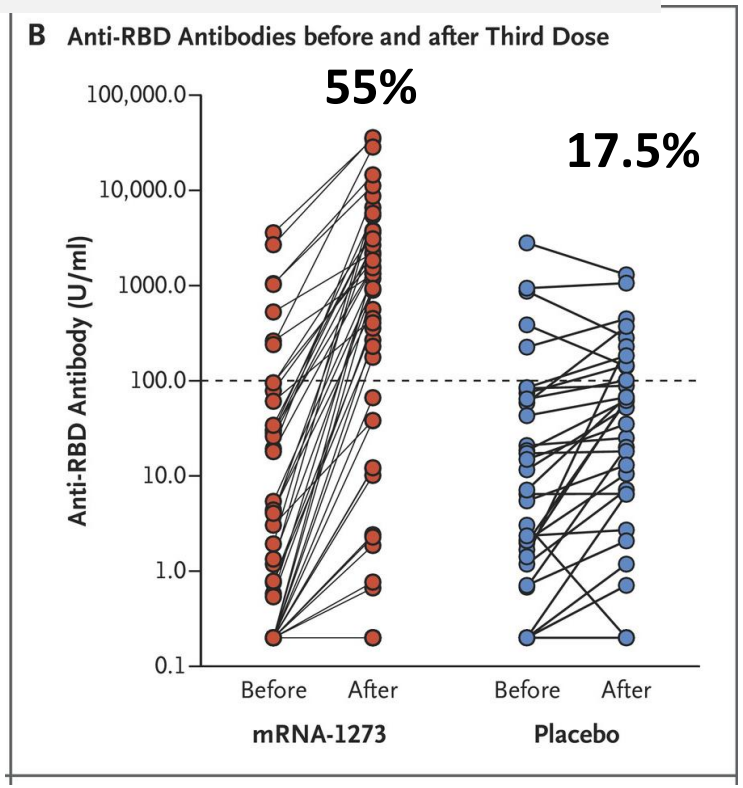
2 doses at 4 weeks
then 3rd dose after 61+/- 1 day

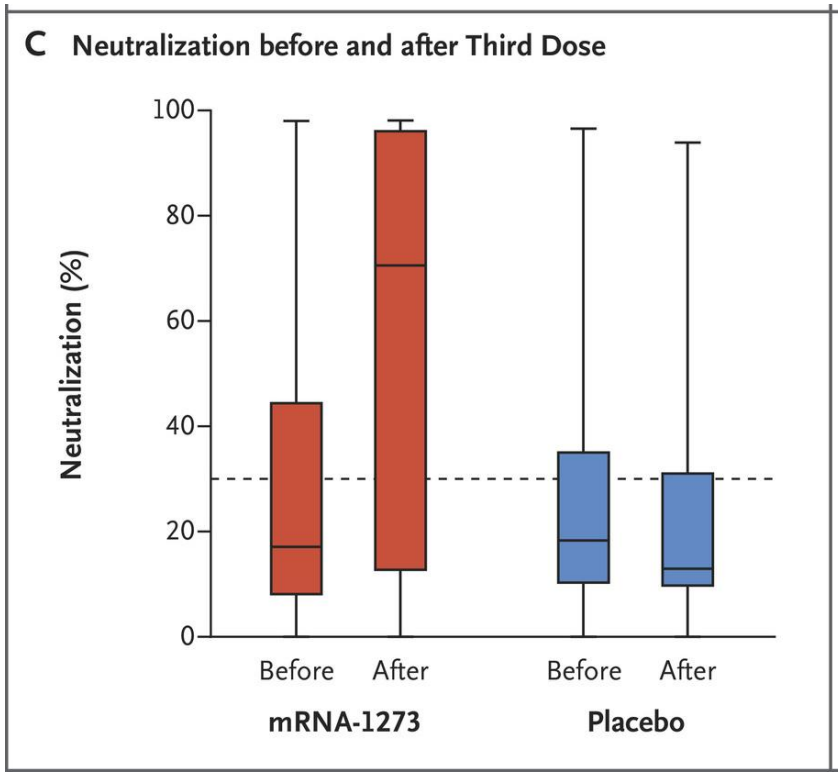


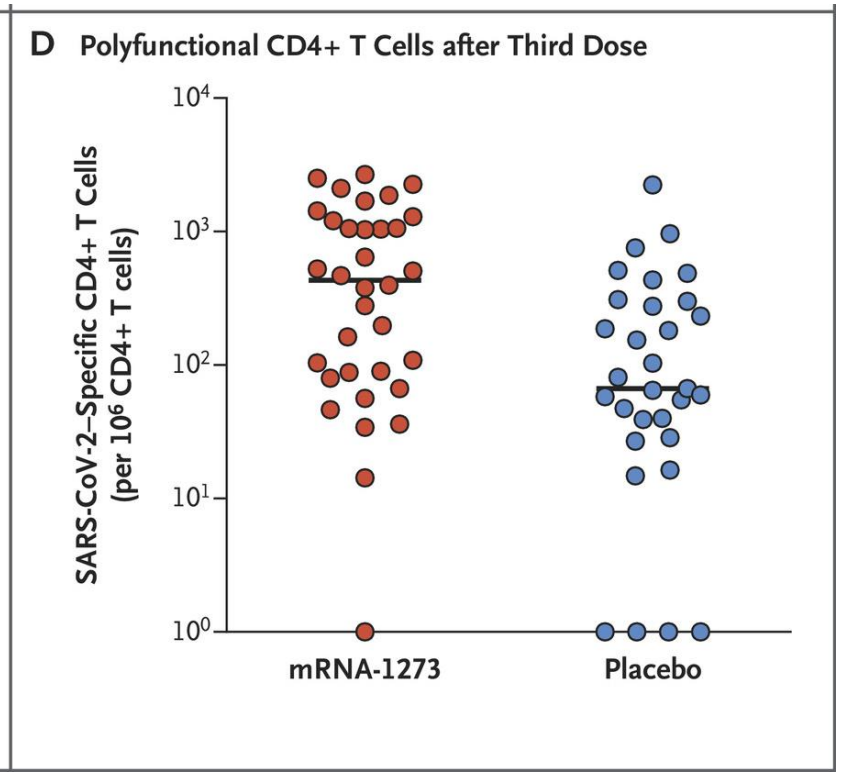

Nassim Kamar et al, August 12, 2021, N Engl J Med 2021; 385:661-662

# A 3rd vaccine dose induces a humoral and cellular T CD4+ response in the transplanted population

Randomized study
n= 60 Moderna, n=57 placebo

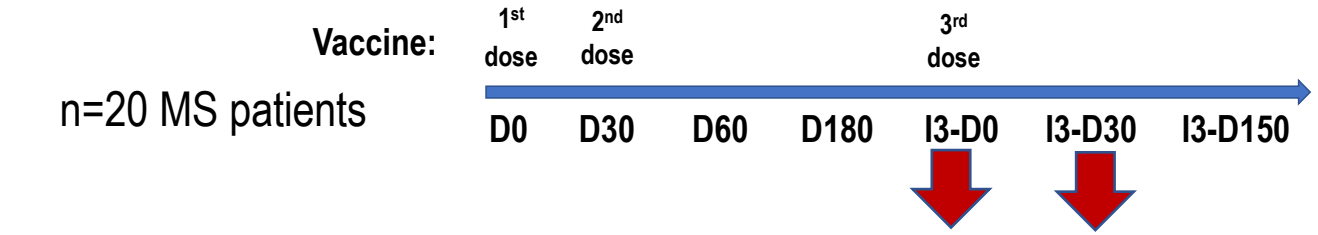


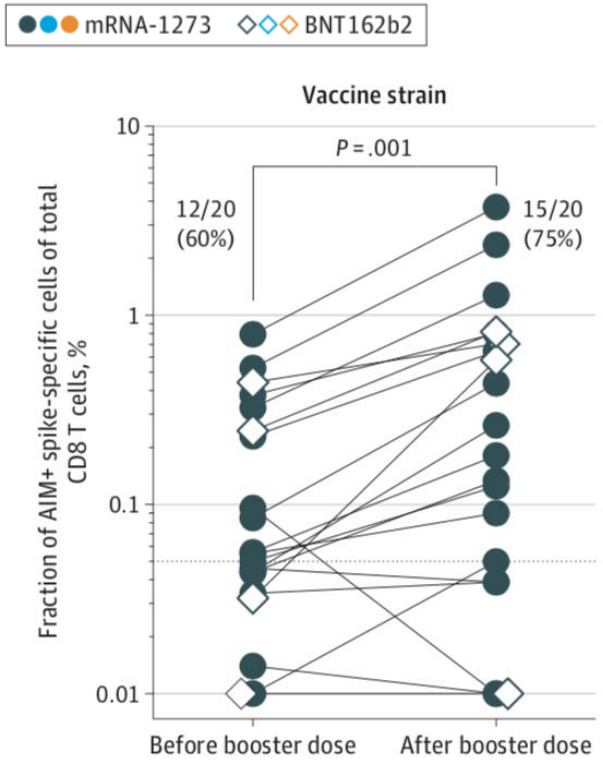



# A third dose boosts CD8 T cells cross-recognizing the variants Delta and Omicron

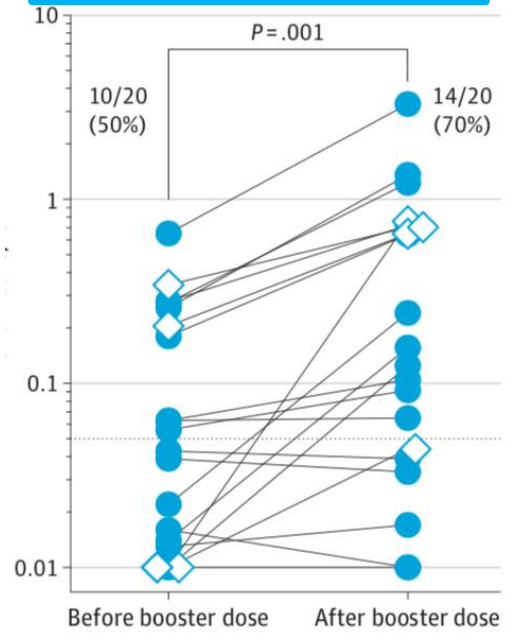
n=20 MS patients



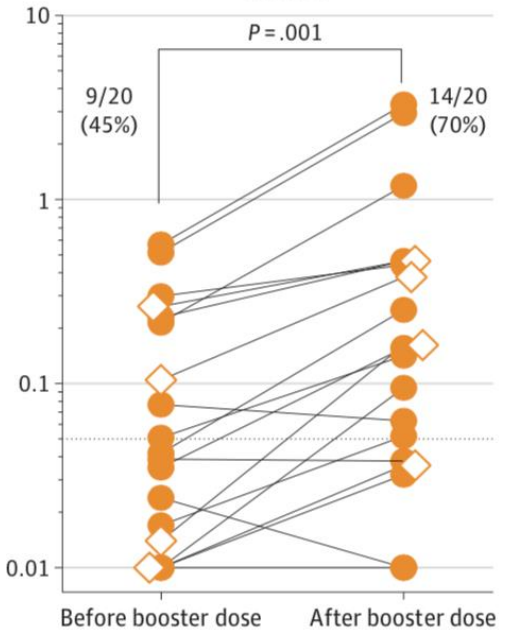

## Delta

89.3% of vaccine-strain




## Omicron

71.1 % of vaccine-strain




Wilcoxon signed rank test , including all individuals

Madelon N, Heikillä N et al, JAMA Neurol 2022

# (Some) open questions

- When is the best timing to re-boost vulnerable patients?
- Will the next emerging variant escape vaccine-induced memory response?
- Impact of heterologous vaccination and infections on long term memory response and protection against severe diseases…

# Thank you