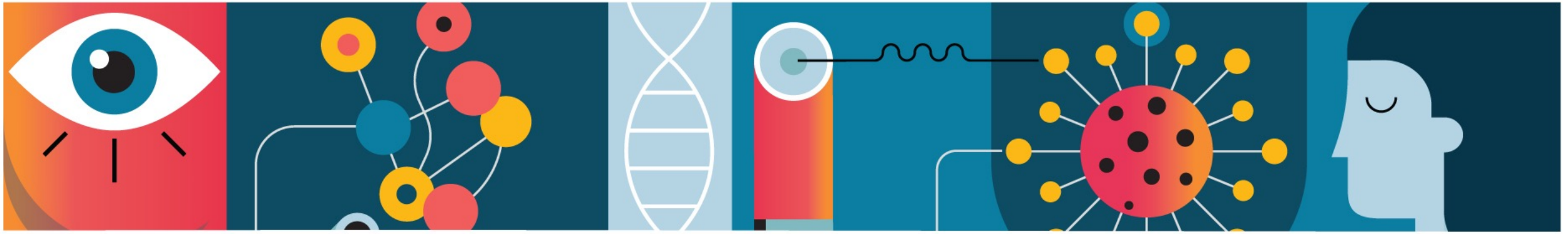
Eurosurveillance 25 1996-2021



COVID 19 vaccine: The role of immunology supporting the design and adaptation of vaccination strategies

Pr Lelièvre Jean-Daniel *(Henri Mondor Hospital -Vaccine Research Institute - France)*

ecdc EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

Declaration of Interest (last 4 years)

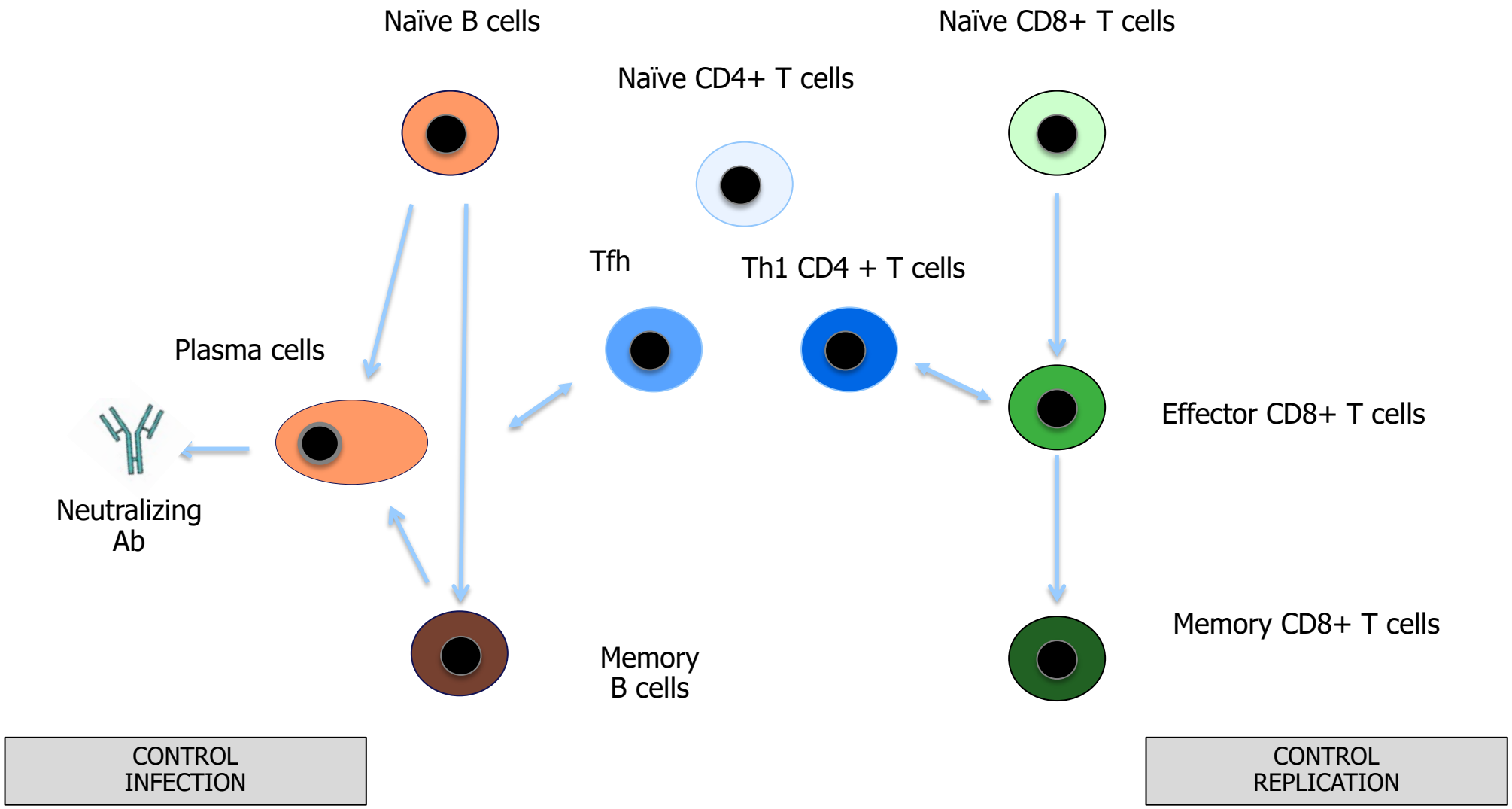
Financial interests with pharmaceutical companies

- *With individual benefit:* Gilead® : participation in national board, preparation of course and article, clinical investigator end 2019
- *Without individual benefit:* Jansen® investigator of Ebola vaccine trial in the framework of the European project IMI2 - EBOVAC2 end 2018

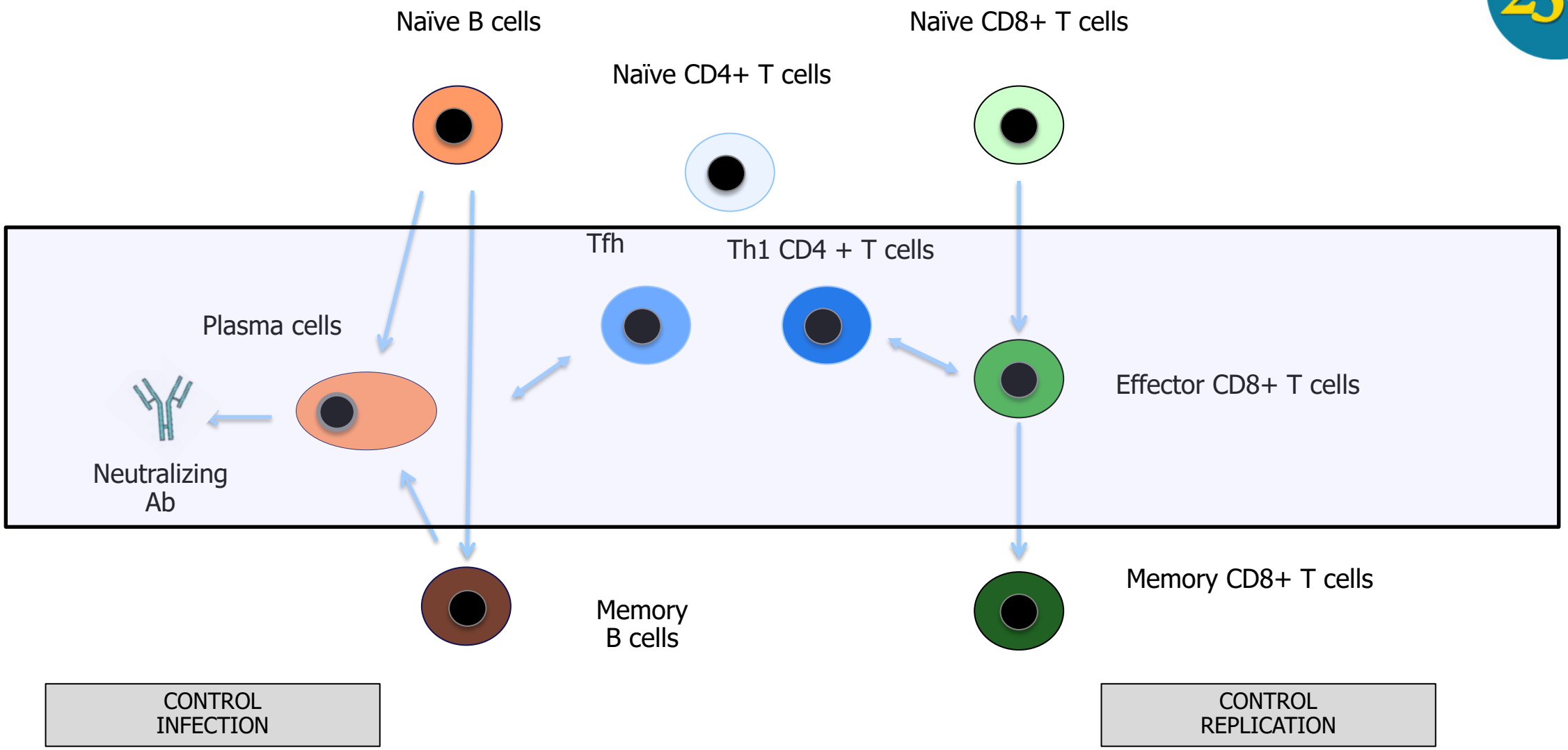
Non-financial interests related to vaccination

- Member of the Technical Commission of vaccinations of the HAS (French NITAG)
- Member of the WHO IVIR-AC
- Vaccine expert at the French High Council for Public Health
- Vaccine expert ANSM (French national drug safety agency)
- Head of clinical research at the VRI (Vaccine Research Institute – French labex – Academic)
- Member of the Covireivac INSERM network
- WP leader of the European project EHVA (HIV vaccine)
- WP leader of the European VACELERATE project (COVID vaccine)
- WP leader of the EU-JAV European project (vaccine coverage)

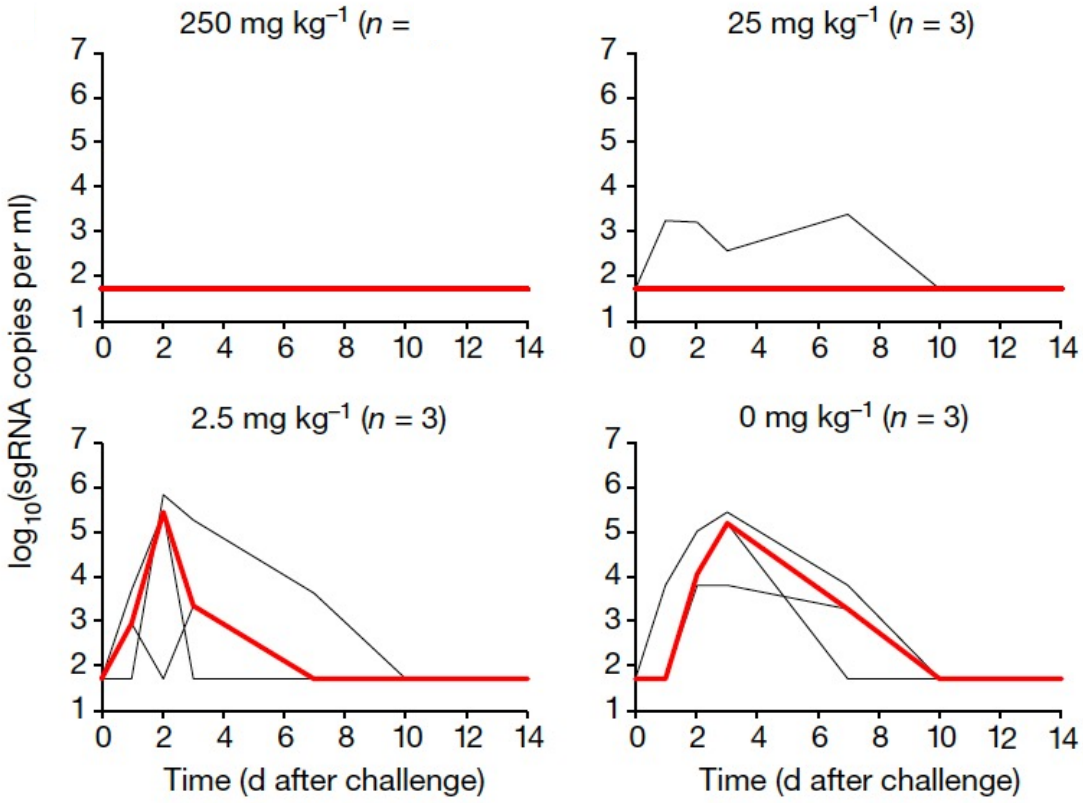
Immune responses that control infection

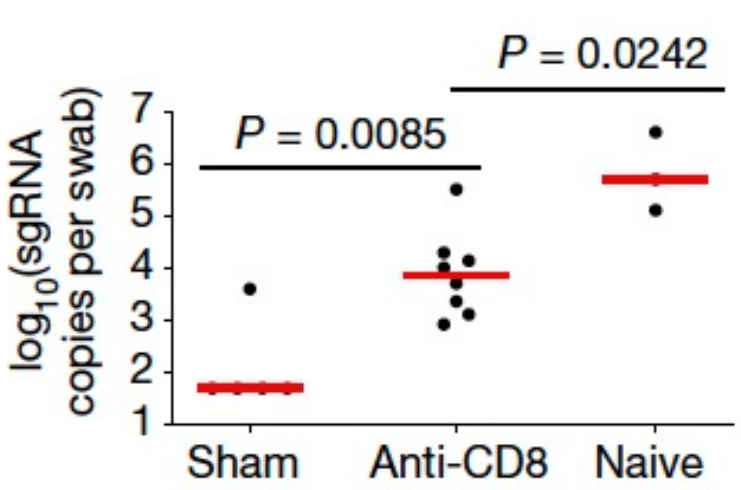


Immune responses that control infection



Correlates of protection in Non Human Primates





McMahan K et al , *Nature* , **2020,** doi : 10.1038/s41586-020-03041-6

The antibody response is important for protection, but CD8 T cells are also involved, especially when the antibody level drops in the blood

Immune responses that control reinfection

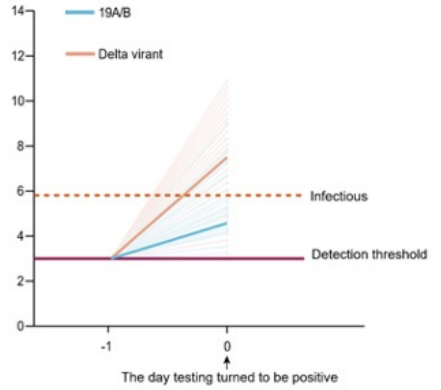
What is key are the responses that will control the infection or reinfection.

It depends on the kinetics of infection and the variability of the virus

Strain : identical or closed Viral replication kinetic : fast	Strain : identical or closed Viral replication kinetic : slow	Strain : different
High levels of neutralizing antibodies CD8+ T cell EM	Memory B cells CD8+ T cell CM	Memory B cells Less impact of mutations for CD8 T response

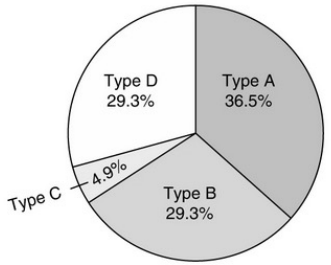
Understanding the evolution of memory populations and the kinetics of viral replication are key elements in determining the relevance of a booster dose

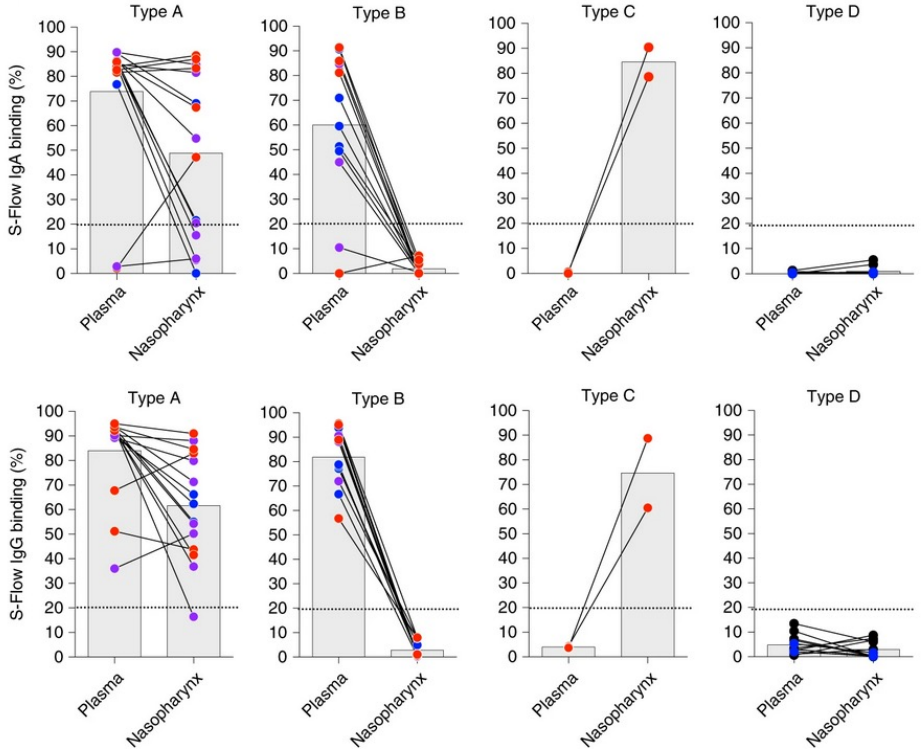
In the context of COVID19 infection, due to the appearance of VOCs and their rapid replication kinetics, long-term protection requires optimal maturation and mobilization of memory populations, particularly B cells



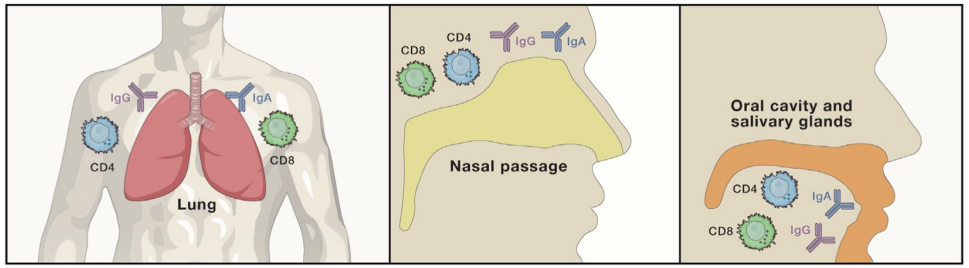
Li B et al ,medRxiv, **2021**,
doi : 10.1101/2021.07.07.21260122

Mucosal response is also important





Smith N et al, *Nat Immunol,* **2021** doi: 10.1038/s41590-021-01028-7



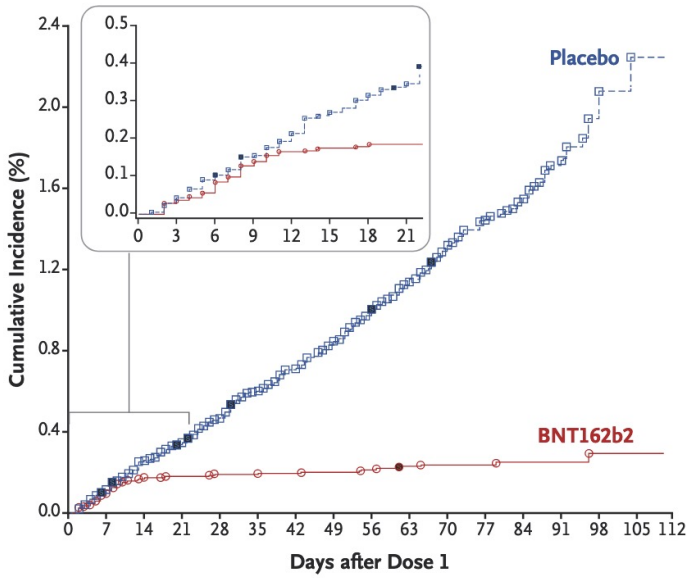
Sette A & Crotty S, *Cell,* **2020** doi: 10.1016/j.cell.2021.01.007

The mucosal response has been much less studied than the systemic response. The presence of antibodies in mucosa may result from passive diffusion from the blood

The mucosal response is variable from one individual to another, correlated or not with the systemic response or the severity of symptoms and depending on the local microbiome (Smith N et al, *Nat Immunol,* **2021**, doi: 10.1038/s41590-021-01028-7)

When it is present it seems to persist for several months (Fröberg J et al, *Nat Comm,* ***2021***, doi: 10.1038/s41467-021-25949-x)

COVID 19 vaccine - First phase 3 trial results



	BNT162b2 Vaccine	Placebo
Symptomatic Covid-19	8	162
	N=18198	N=18325
Severe Covid-19	1	9
	N=21669	N=21686

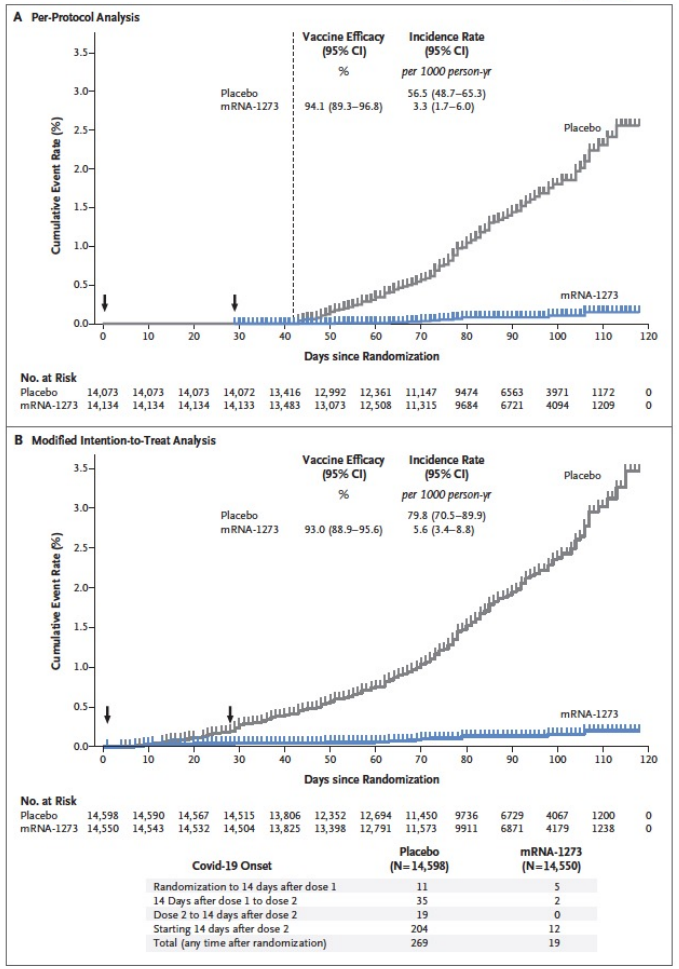
Vaccine efficacy of 95% (95% credible interval, 90.3–97.6%)

Polack FP et al, *NEJM,* **2020**
doi : 10.1056/NEJMoa2034577

	Total number of cases	ChAdOx1 nCoV-19		Control		Vaccine efficacy (CI*)
		n/N (%)	Incidence rate per 1000 person-years (person-days of follow-up)	n/N (%)	Incidence rate per 1000 person-years (person-days of follow-up)	
All LD/SD and SD/SD recipients	131	30/5807 (0·5%)	44·1 (248 299)	101/5829 (1·7%)	149·2 (247 228)	70·4% (54·8 to 80·6)†
COV002 (UK)	86	18/3744 (0·5%)	38·6 (170 369)	68/3804 (1·8%)	145·7 (170 448)	73·5% (55·5 to 84·2)
LD/SD recipients	33	3/1367 (0·2%)	14·9 (73 313)	30/1374 (2·2%)	150·2 (72 949)	90·0% (67·4 to 97·0)‡§
SD/SD recipients	53	15/2377 (0·6%)	56·4 (97 056)	38/2430 (1·6%)	142·4 (97 499)	60·3% (28·0 to 78·2)
COV003 (Brazil; all SD/SD)	45	12/2063 (0·6%)	56·2 (77 930)	33/2025 (1·6%)	157·0 (76 780)	64·2% (30·7 to 81·5)‡
All SD/SD recipients	98	27/4440 (0·6%)	56·4 (174 986)	71/4455 (1·6%)	148·8 (174 279)	62·1% (41·0 to 75·7)
Other non-primary symptomatic COVID-19 disease¶	18	7/5807 (0·1%)	10·3 (248 299)	11/5829 (0·2%)	16·3 (247 228)	36·4% (−63·8 to 75·3)‡
Any symptomatic COVID-19 disease	149	37/5807 (0·6%)	54·4 (248 299)	112/5829 (1·9%)	165·5 (247 228)	67·1% (52·3 to 77·3)
Asymptomatic or symptoms unknown (COV002)	69	29/3288 (0·9%)	69·8 (151 673)	40/3350 (1·2%)	96·0 (152 138)	27·3% (−17·2 to 54·9)
LD/SD recipients	24	7/1120 (0·6%)	41·4 (61 782)	17/1127 (1·5%)	100·6 (61 730)	58·9% (1·0 to 82·9)‡
SD/SD recipients	45	22/2168 (1·0%)	89·4 (89 891)	23/2223 (1·0%)	92·9 (90 408)	3·8% (−72·4 to 46·3)
Any NAAT-positive swab	221	68/5807 (1·2%)	100·0 (248 299)	153/5829 (2·6%)	226·0 (247 228)	55·7% (41·1 to 66·7)

Voysey M et al, *Lancet,* **2020**
doi : 10.1016/ S0140-6736(20)32661-1

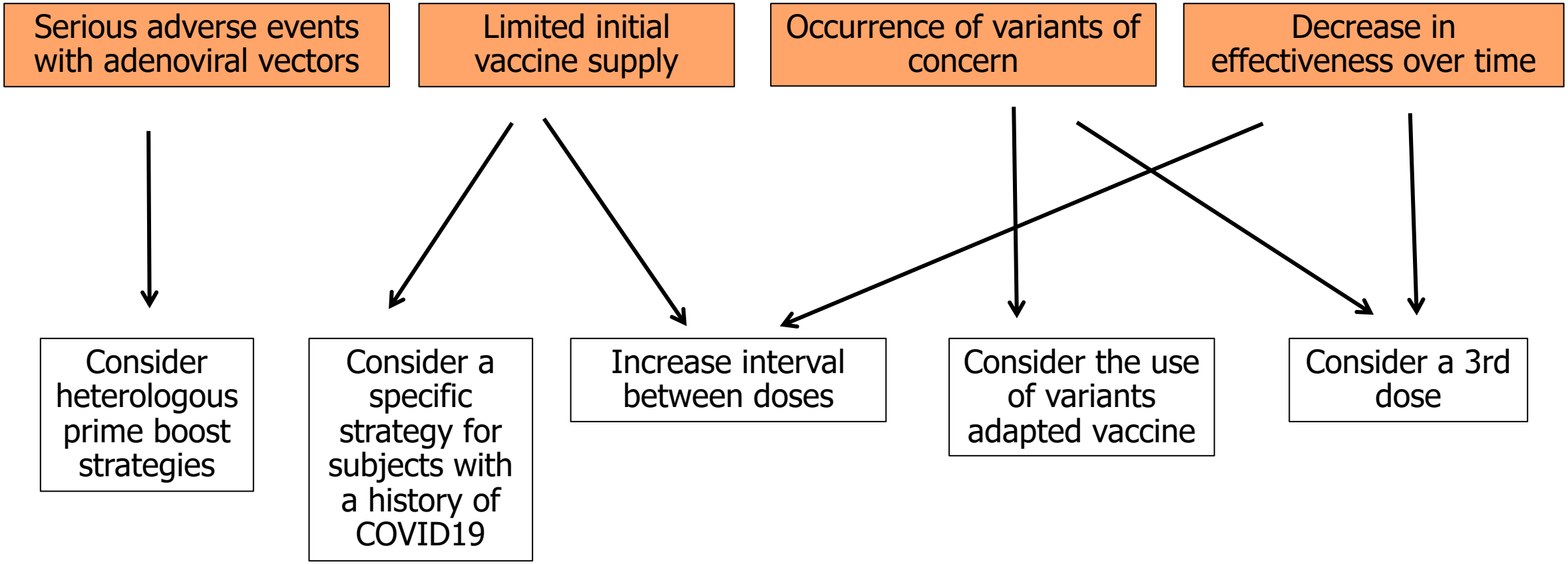
Results from Phase 3 trials showed that an initial strategy with two vaccine doses appears to be effective



Covid-19 Onset	Placebo (N=14,598)	mRNA-1273 (N=14,550)
Randomization to 14 days after dose 1	11	5
14 Days after dose 1 to dose 2	35	2
Dose 2 to 14 days after dose 2	19	0
Starting 14 days after dose 2	204	12
Total (any time after randomization)	269	19

Baden LR et al, *NEJM,* **2020**
doi :10.1056/NEJMoa2035389

Several parameters questioned a universal two-dose strategy with a fixed interval



Impact of heterologous prime-boost strategies

1. Circumvent the problem of pre-existing - or vaccine-induced - immunity to an adenoviral vector when this type of vaccine is used (Mast C et al, *Vaccine,* **2010**, doi:10.1016/j.vaccine.2009.10.145)

2. Increase the intensity of immune responses (Cox KS et al, *J Virol,* **2008**, doi:10.1128/JVI.00620-08)

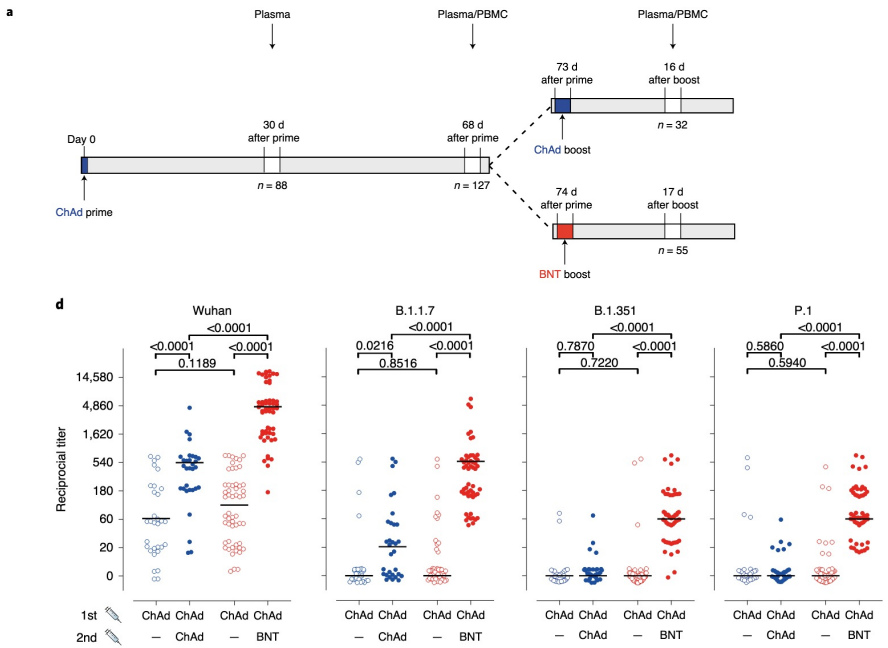
3. Provide a CD4+ T-cell response delivered through the prime vaccine to obtain an optimal humoral response to a protein vaccine used as a boost (Rerks-Ngarm S et al, *N Engl J Med,* **2009,** doi: 10.1056/NEJMoa0908492)

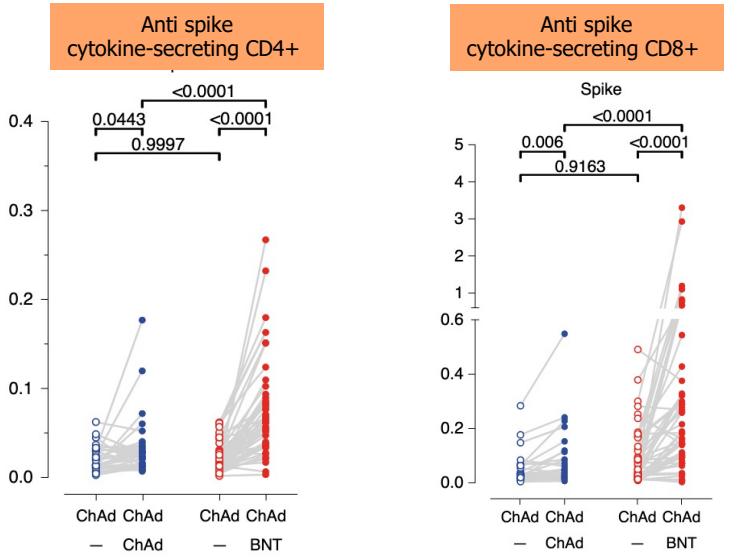
4. Diversify the response against viral strains while increasing the intensity of immune responses against a particular strain (Pollard A et al, *Lancet Infectious Diseases,* **2020**, doi: 10.1016/ S1473-3099(20)30476-X)

Outside COVID-19 :

1) Strategies widely used in settings where the immune response is complex to achieve: HIV, Influenza, TB (Lu S, *Curr Opin Immunol,* **2009**, doi:10.1016/j.coi.2009.05.016.)
2) Large number of publications on their advantages in terms of immunogenicity and even clinical efficacy, no particular safety issues
3) Vaccine with MA: J&J Ebola vaccine is an HBPS combining an Ad 26 vaccine to a second injection with MVA vaccine

Heterologous boost strategies improve B and T responses





Barros-Martins J et al, *Nature Medicine* **2021**, doi : 10.1038/s41591-021-01449-9.

Borobia AM et al, *Lancet,* **2021** , doi: 10.1016/ S0140-6736(21)01420-3

Liu X et al, *Lancet,* **2021** , doi: 10.1016/ S0140-6736(21)01694-9

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Immunological data have shown the value of heterologous prime boost regimens with an antibody response equivalent to the homologous mRNA vaccine-containing regimen and a superior T response.

Real-life data have confirmed the positive impact of these strategies (Shroti M et al, *Lancet,* **2021,** doi: 10.1016/ S1473-3099(21)00289-9 - Nordstöm P et al, *Lancet Regional Health*, **2021**, doi: 10.1016/j.lanepe.2021.100249)

However, as shown in animal models (He Q et al, *Emerging Microbes & Infections,* **2021,** doi: 10.1080/22221751.2021.1902245) or with other vaccines (Kardani K et al, *Vaccine,* **2016**, doi: 10.1016/j.vaccine.2015.11.062*)*, the sequence is important with currently a vaccination by adenoviral vector then mRNA vaccine

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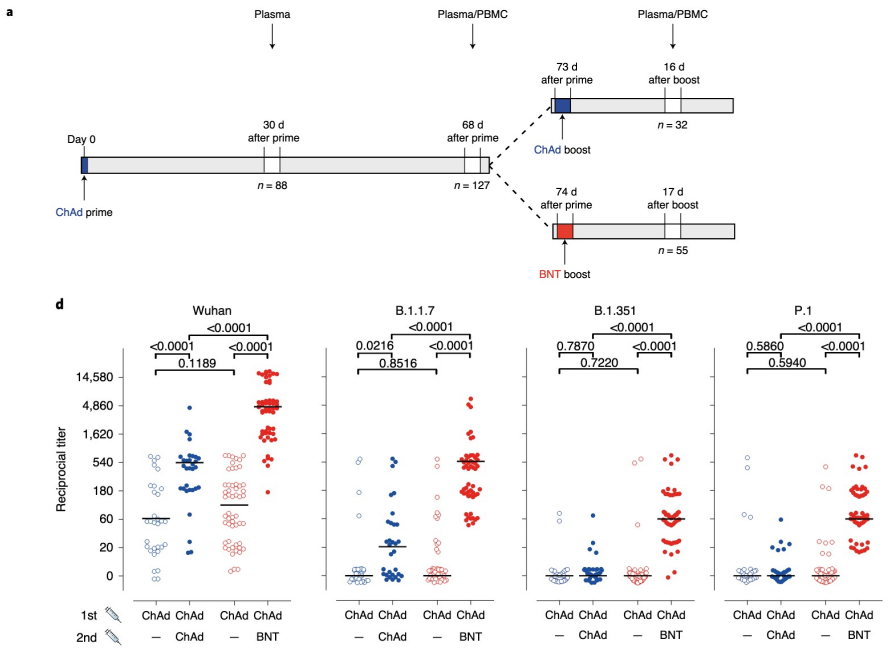

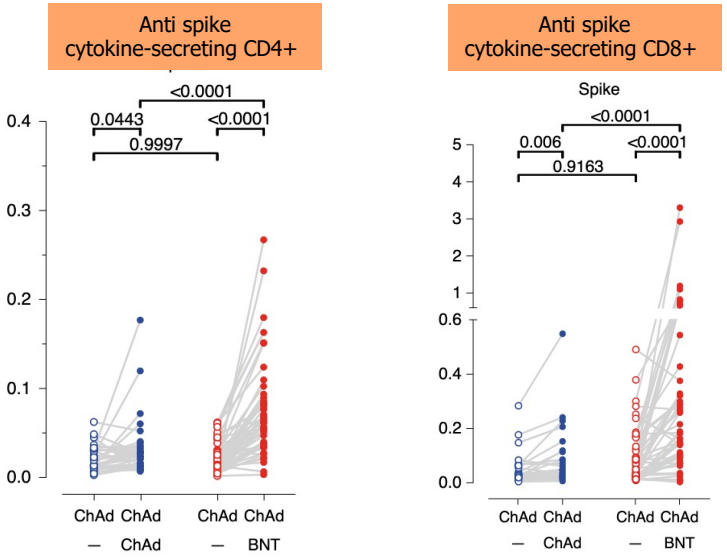

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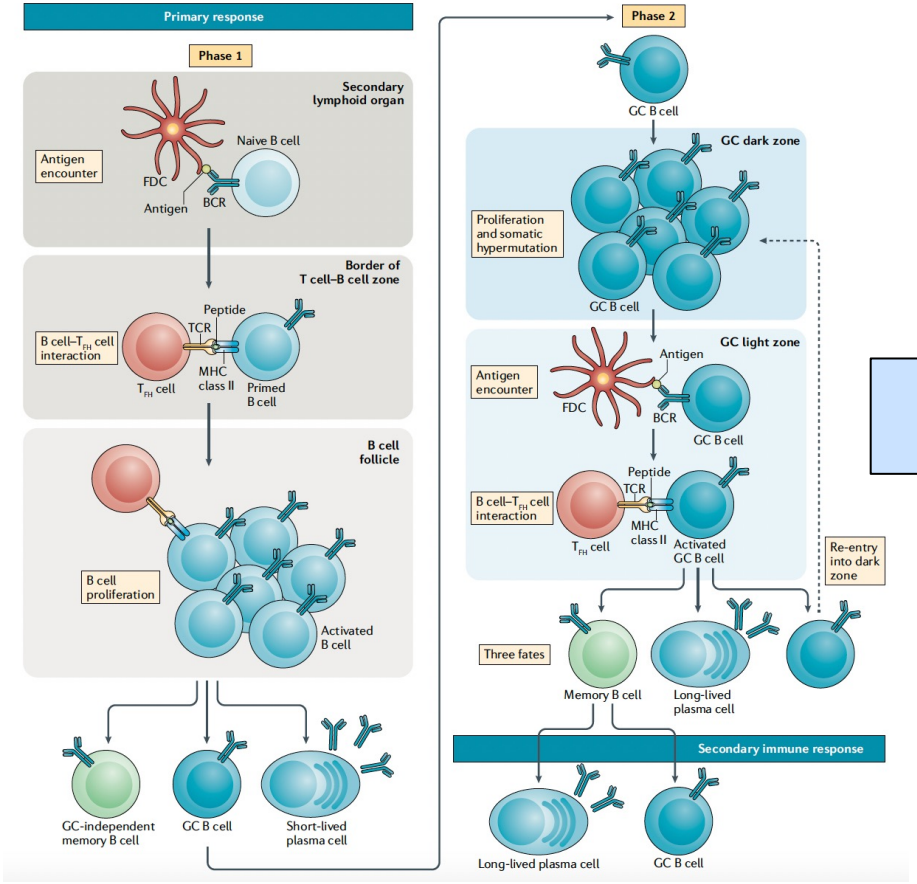
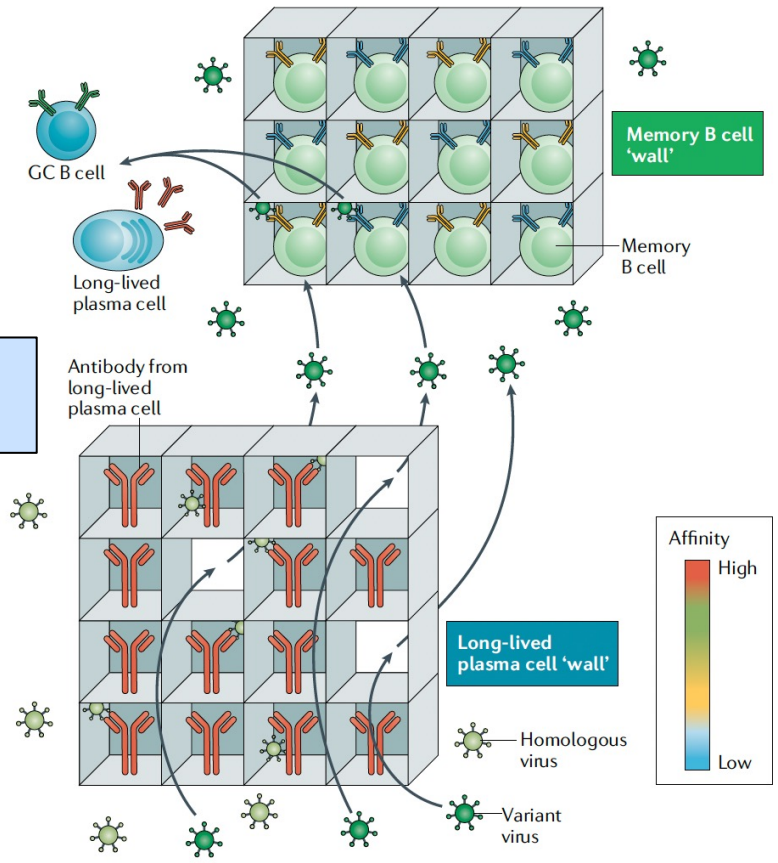
Maturation and mobilization of memory B cells is key

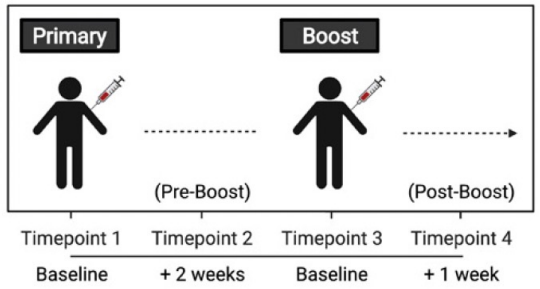


Akkaya M et al,
Nat Rev Immunol , **2020,**
doi: 10.1038/s41577-019-0244-2

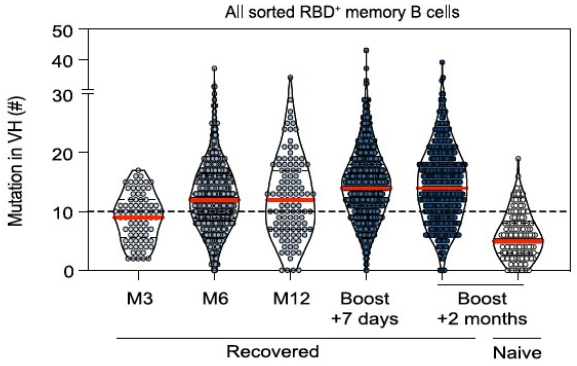


Indeed the stimulation at the end of these populations through vaccination will allow the production of more avid antibodies and having a greater diversity of activity against different strains

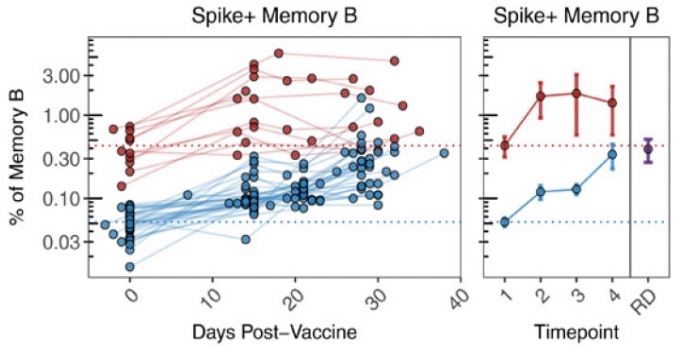
Memory B cell continue to mature post infection and post vaccination



	SARS-CoV-2 Naive	SARS-CoV-2 Recovered
N	33	11
Age	37.3 [23-67]	34.7 [23-58]
Sex	15 M (46%) / 18 F (54%)	7 M (64%) / 4 F (36%)



Sokal A et al, *Immunity,* **2021**
doi :10.1016/j.immuni.2021.09.011



Goel et al., S*ci Immunol,* **2021**,
doi: 10.1126/sciimmunol.abi6950

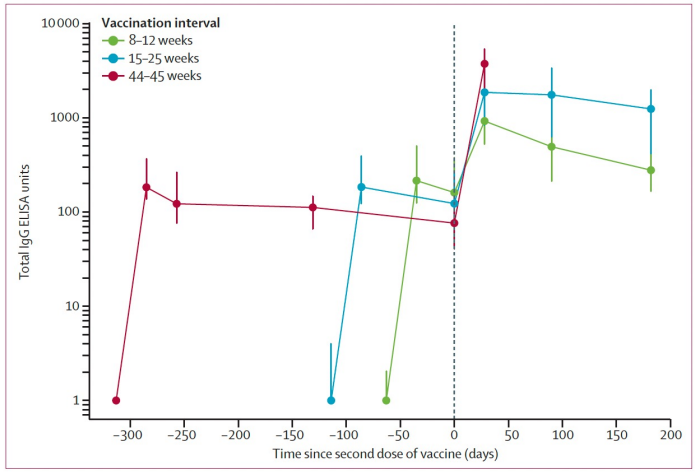
Number of memory B cells increases after vaccination but the rate of memory cells is lower after vaccination than after infection

Increase in hypersomatic mutations (MHS) over time suggestive of B Memory cell maturation.

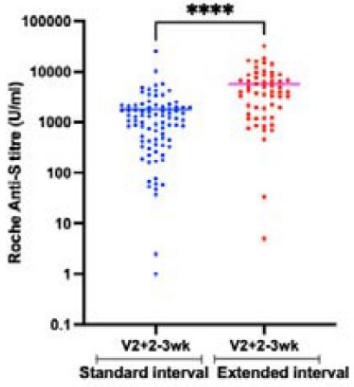
Frequency is lower in post-vaccination than in post-vaccination

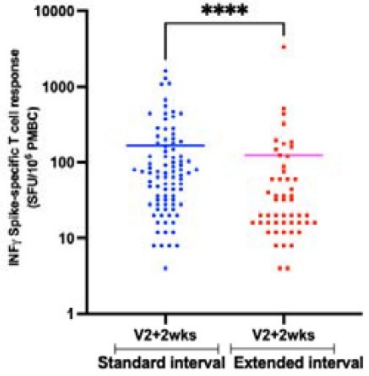
Angyal A et al , **2021**, https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3820576.
Bradley T et al, *medRxiv,* **2021** , doi: 10.1101/2021.02.03.21251078.
Camara C et al, *bioRxiv* , **2021** doi: 10.1101/2021.03.22.436441;
Ebinger J et al, *Nature Medicine* **2021**, doi: 10.1038/s41591-021-01325-6
Goel et al., S*ci. Immunol.* **2021**, doi: 10.1126/sciimmunol.abi6950
Krammer, F. et al. *N. Engl. J. Med.* **2021** 384, 1372–1374
Mazzoni A, et al, *J Clin Invest,* **2021**, doi10.1172/JCI149150.
Saadat, S., et al, *medRxiv,* **2021**, doi: 10.1101/ 2021.01.30.21250843
Samanovic, M.I., et al *medRxiv*, **2021**, doi: 10.1101/ 2021.2002.2007. 21251311.

Extend the delay between doses may improve Ab responses



Flaxman A et al, *Lancet,* **2021**
doi: 10.1016/ S0140-6736(21)01699-8





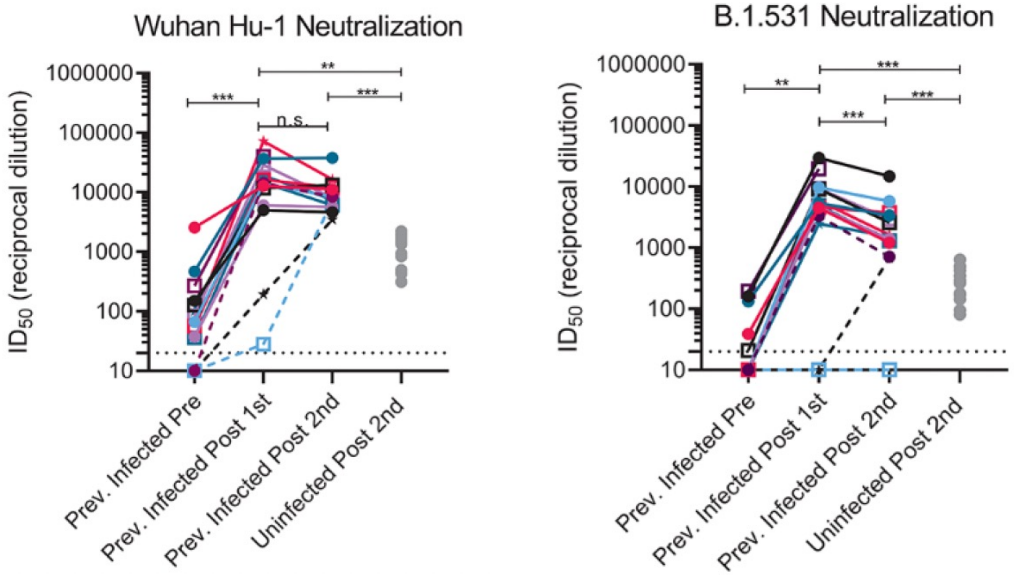
Parry H et al , *medRxiv,* **2021**
doi: 10.1101/2021.05.15.21257017

The question of the optimal interval between primary vaccination doses has been the subject of much debate. The issue is the maturation of B cells and the formation of germinal centers.

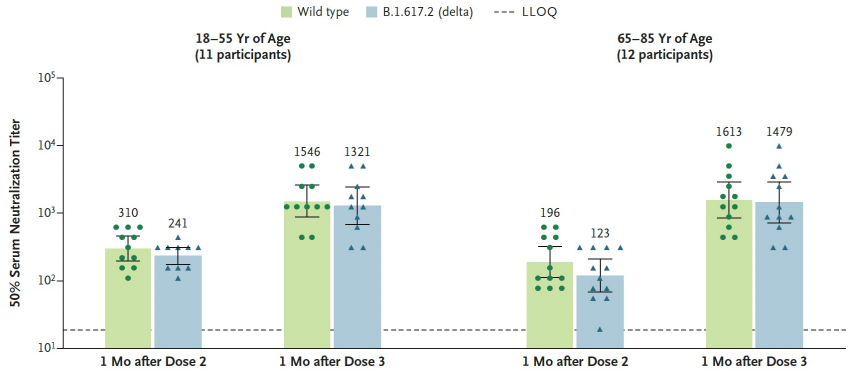
Lower dose prime could increase the selection stringency in GCs due to reduced antigen availability, resulting in the selection of GC B cells with higher affinities or the target antigen. Boost could relax this selection stringency and allow the expansion of the higher affinity GC B cells selected, improving the overall response. With a longer dosing interval, the decay in the antigen with time following the prime could further increase the selection stringency, amplifying this effect (Grag A et al, *medRxiv,* ***2021,*** doi: 10.1101/2021.09.08.21263248).

Distribution and persistence of the current COVID19 vaccine (mRNA and adenoviral vectors) however are poorly deciphered (Coughlan L, *Front Immunol,* **2021,** doi: 10.3389/fimmu.2020.00909 - Liang F et al, *Molecular Therapy*, **2019,** doi 10.1016/j.ymthe.2017.08.006.)

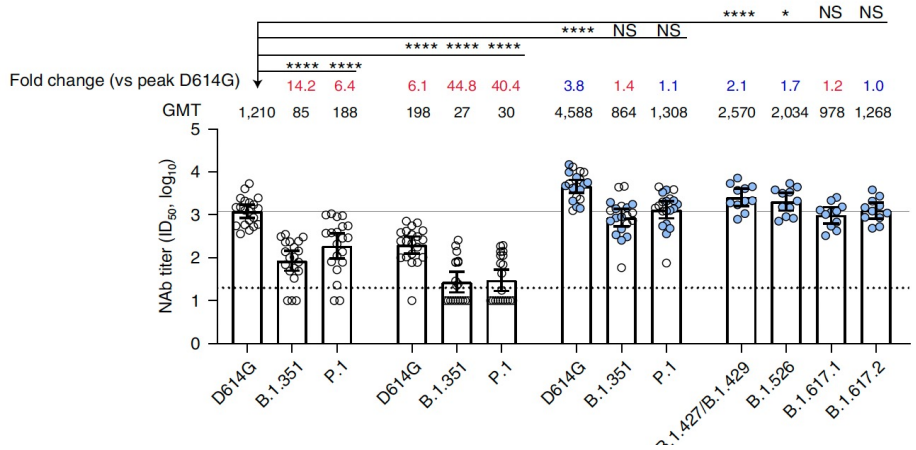
Therefore a booster dose is immunologically relevant



Goel et al, S*ci Immunol,* **2021**,
doi: 10.1126/sciimmunol.abi6950



Falsey AR et al, *N Engl J Med,* **2021**,
DOI: 10.1056/NEJMc2113468



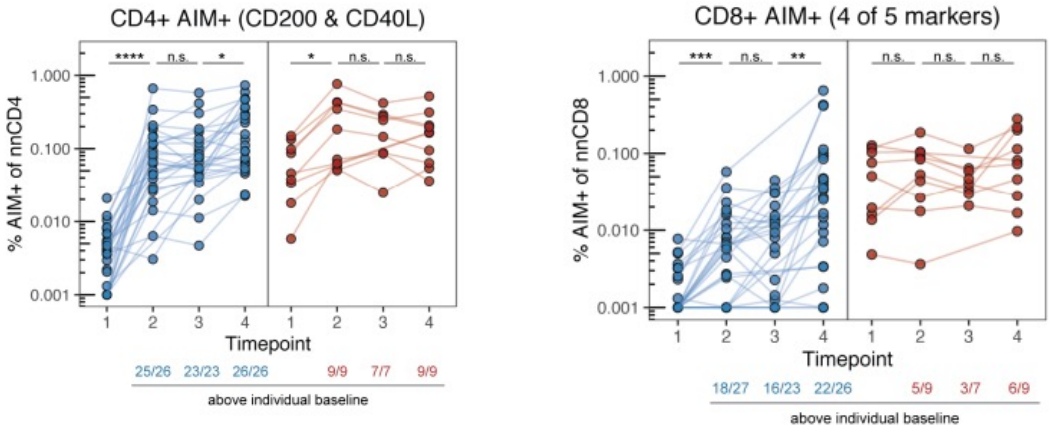
Choi A et al, *Nature Medicine,* **2021**,
Doi: 10.1038/s41591-021-01527-y

The realization of a boost dose, i.e.

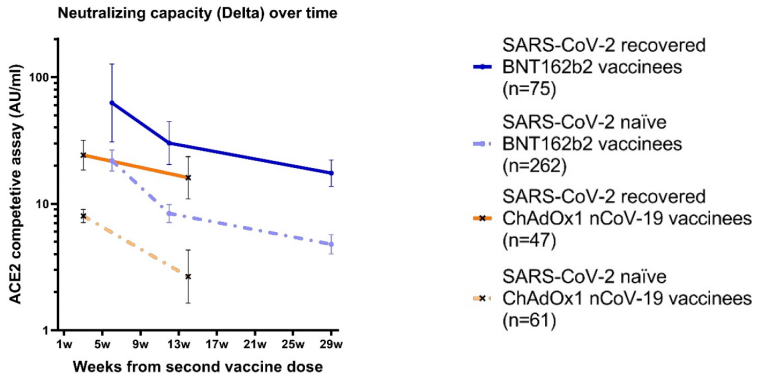
- 1 dose 6 months post infection
- 1 dose 6 months after second dose of RNA vaccine

vaccine increases the rate and diversity of neutralizing antibodies

One dose post infectious seems sufficient



Painter M et al, *bioRxiv,* **2021**
doi: 10.1101/2021.04.21.440862



Havervall S et al, *medRxiv,* **2021**
doi: 10.1101/2021.10.16.21264948

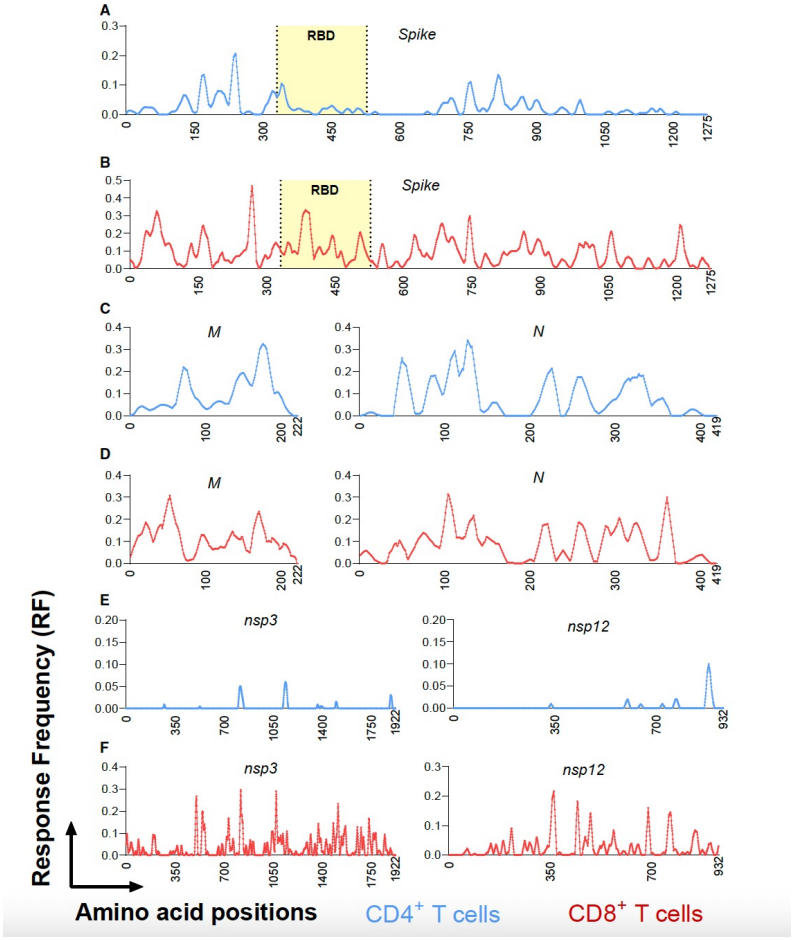
The realization of a second early dose post infection had

- no effect on B cell response (see before)
- no impact (Paine RP et al, *Cell,* **2021**, doi: 10.1016/j.cell.2021.10.011; Reynolds CJ et al, *Science,* **2021**, doi 10.1126/science.abh1282) or even deleterious impact on T cell (Camara C et al, Cell Reports , **2021**, doi:10.1016/j.celrep.2021.109570)

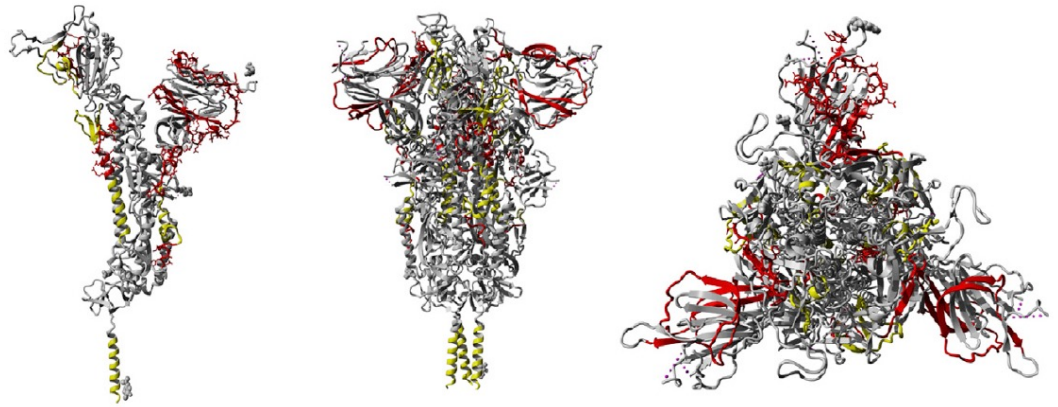
The use of a longer interval could be interesting (Payne RP et al, *Cell,* **2021**, doi: 10.1016/j.cell.2021.10.011 - Tauzin A et al, *medRxiv,* **2021,** doi:10.1101/2021.09.17.21263532) however the antibody level before the second dose remains high, questioning its relevance

In addition, a high antibody level remains after vaccination in subjects with a history of COVID19

The analysis of the T responses also allows to consider the response to the variants



Grifoni A et al , Ce*ll Host & Microbes* , **2021,**
doi : 10.1038/s41586-020-03041-6



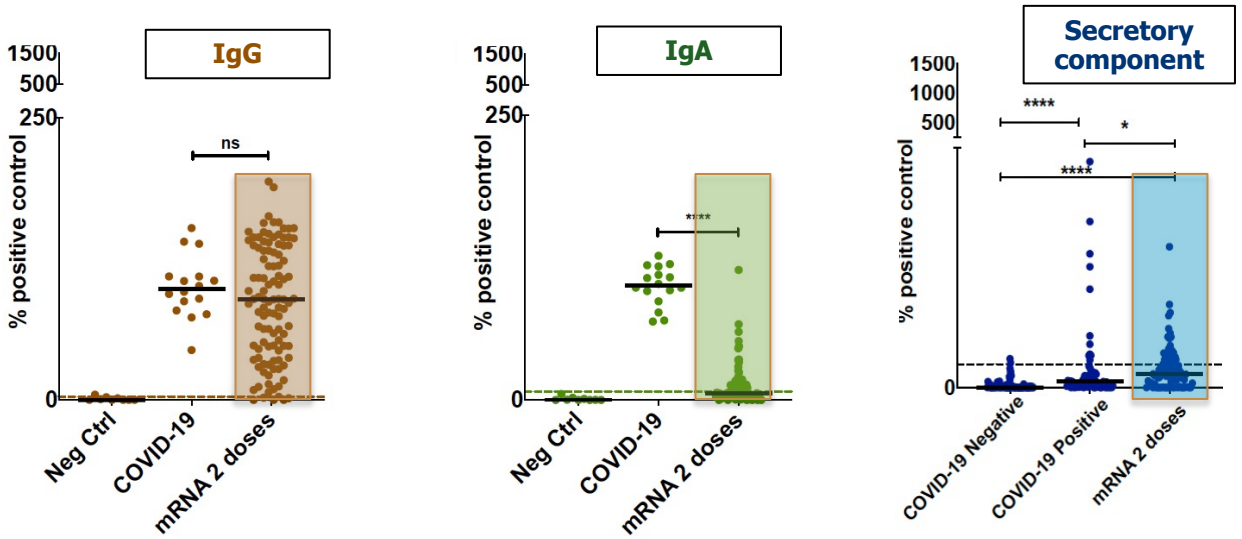
in red the immunodominant regions of CD4+ T cells for each protein with a frequency of positive responses >20% and **in yellow** the immunodominating regions of B cells for each protein

Tarke A et al, *Cell Reports Medicine*, **2021**
doi :10.1016/j.xcrm.2021.100204

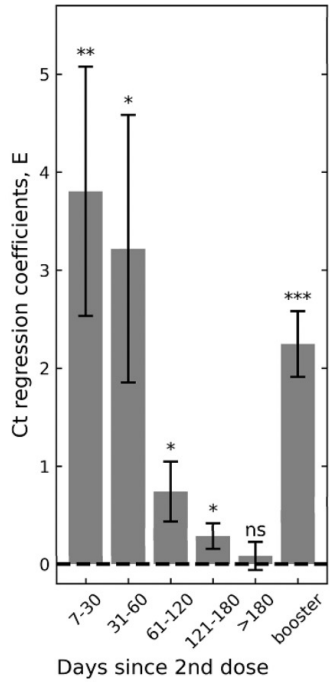
The post-infection T response covers more than 1400 epitopes from several proteins (nsp3, nsp4, nsp6, nsp12, nsp13, S, ORF3a, ORF8, M, and N).

The B and T epitopes of the spike are different, allowing the preservation of an effective T response against VOC

Vaccines given systemically have an impact on the mucosal response



Sheik-Mohamed S et al, *medRxiv,* **2021**, doi:10.1101/2021.08.01.21261297



Association of infection Ct with 2-dose vaccination and with the booster

Levine-Tiefenbrun M et al , *medRxiv* , **2021**, doi : 10.1101/2021.08.29.21262798

The post-vaccination immune response is less studied, but with mRNA vaccines we note the induction of anti IgG but also IgA antibodies

The persistence and functional activity remains to be analysed. However, data on viral replication kinetics following infection after vaccination suggest that this response decreases over time and is boosted by a 3rd dose

Several parameters questioned a universal two-dose strategy with a fixed interval

Consider heterologous prime boost strategies

Consider a specific strategy for subjects with a history of COVID19

Increase interval between doses

Consider the use of variants adapted vaccine

Consider a 3rd dose

Although not a substitute for clinical efficacy data obtained in clinical trials and in real life, immunological data have provide mechanistic support for modulating initial COVID 19 vaccine strategies regarding the use of

- a single dose in subjects with a history of infection
- an extended interval between the two initial doses
- heterologous prime boost strategies
- a late 3rd dose

strategies which for some of them have shown their clinical relevance