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

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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

Naïve B cells

Naïve CD4+ T cells

Naïve CD8+ T cells

Plasma cells

Tfh

Th1 CD4+ T cells

Effector CD8+ T cells

Memory CD8+ T cells

Memory B cells

Neutralizing Ab

CONTROL INFECTION

CONTROL REPLICATION
Immune responses that control infection

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- Memory CD8+ T cells
- Memory B cells

Neutralizing Ab

Plasma cells

CONTROL INFECTION

CONTROL REPLICATION
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.

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

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

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

doi : 10.1016/S0140-6736(20)32661-1

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

Baden LR et al, *NEJM*, 2020
doi : 10.1056/NEJMoa2035389
Several parameters questioned a universal two-dose strategy with a fixed interval

- Serious adverse events with adenoviral vectors
- Limited initial vaccine supply
- Occurrence of variants of concern
- Decrease in effectiveness over time

- 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
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 )


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

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.


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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Maturation and mobilization of memory B cells is key

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

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


Extend the delay between doses may improve Ab responses

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: 10.1101/2021.05.15.21257017).

Therefore a booster dose is immunologically relevant

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

The realization of a second early dose post infection had

- no effect on B cell response (see before)


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

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

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

Vaccines given systemically have an impact on the mucosal response

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.


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Although not a substitute for clinical efficacy data obtained in clinical trials and in real life, immunological data have provided 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