

# What do we know about Immunity to SARS-CoV-2? Implications for Public Health Policies

A Report of the Multidisciplinary Collaborative  
Group for the Scientific Monitoring of  
COVID-19 (GCMSC)

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# What Do We Know about Immunity to SARS-CoV-2? Implications for Public Health Policies

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## Summary

The magnitude, quality and durability of immune responses against SARS-CoV-2 will define the epidemiological dynamics of COVID-19 and the strategies put in place to protect individuals and populations.

The **induction of humoral immune responses** against different viral proteins is **rapid** and occurs in most individuals after infection, although **its magnitude is highly variable** and positively correlates with disease severity. **Neutralizing antibodies**, mostly against the domain of the Spike protein that interacts with the cellular receptor ACE2 (the receptor binding domain, RBD), are present in most infected individuals and are able to block viral entry and infectivity. Less information is available on **T cell** responses, which play a key role in the control of viral replication and the generation of immunological memory, but recent studies indicate that T cells recognizing Spike and other viral proteins are detected in almost all infected individuals, even in those without detectable levels of antibodies.

Although some cases of **reinfection** have been described, cohort studies analysed to date are showing that these immune responses can successfully protect most individuals from subsequent disease and may be long-lasting, with both T and B cells reaching **a stable plateau after six months**. **Vaccines** targeting the Spike protein have been shown to elicit high titers of neutralizing anti-RBD antibodies and T cell responses, explaining their high reported efficacy and potentially contributing to the duration of vaccine protection.

One concern raised by recently identified SARS-CoV-2 **variants** is the selection of “fitter” variants under immune pressure. The duration of immune responses (natural or vaccine-elicited) and the emergence of immune-escape variants are key issues that will impact the management of the pandemic, since they will determine the utility of **seroconversion studies**, the level of **herd immunity**, and the need for **revaccination**.

# Conclusions

1

In the vast majority of cases, natural infection by SARS-CoV-2 induces a protective immunity that lasts for at least **six months**.



In a context of limited vaccine availability, **individuals with past infection** should not be prioritized for immunization.

2

3

The **innate and adaptive immune components** (antibodies, B cells, CD4+ and CD8+ T cells) contribute to protection from disease or reinfection.



**Parallel studies of B and T cell responses** in different cohorts are necessary to define correlates and mechanisms of protection.

4

5

To date, no quantitative cut-offs of protection exist to monitor **natural or vaccine-induced immunity**.



Decisions on **revaccination** will be driven by proactive studies of viral evolution and clinical/epidemiological data.

6

7

These data should allow for the identification of **correlates of protection**, which will simplify future vaccine trials.



Changes in vaccine dosage and **schedule of currently approved vaccines** are not recommended until further evidence is available.

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The emergence of **new viral variants** could compromise vaccine efficacy in the future. Molecular surveillance of circulating virus should be a priority.



**Global vaccination campaigns** are ethically and epidemiologically necessary.

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# ¿Qué sabemos de la inmunidad frente al SARS-CoV-2?

## Implicaciones para políticas de salud

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### Resumen

La magnitud, calidad y duración de la respuesta inmune frente al SARS-CoV-2 definirá la dinámica de la epidemia de COVID-19 y las estrategias implementadas para proteger a personas y poblaciones.

La **inducción de respuestas inmunes** humorales (anticuerpos) frente a diferentes proteínas virales es **rápida** y ocurre en la mayoría de las personas tras la infección, aunque **la magnitud es variable** y mayor cuanto más grave es la enfermedad. Los **anticuerpos neutralizantes**, la mayoría de los cuales están dirigidos contra el dominio que se une al receptor celular ACE2 (llamado dominio de unión al receptor o RBD), están presentes en la gran mayoría de personas infectadas y pueden bloquear la infección por el virus. Hay menos información disponible sobre la respuesta de los **linfocitos T**, que tienen un papel clave en el control de la replicación viral y la generación de memoria inmunológica, pero estudios recientes indican que en prácticamente todas las personas infectadas se detectan células T que reconocen Spike y otras proteínas virales, incluso en aquellas que no tienen niveles detectables de anticuerpos.

Se han descrito algunos casos de **reinfección**, pero los estudios de cohorte analizados hasta ahora indican que esta inmunidad protege contra la enfermedad en caso de reinfección y que es **duradera**, con células B y T que alcanzan **un nivel estable tras seis meses**. Las **vacunas** dirigidas contra la proteína Spike inducen niveles elevados de anticuerpos anti-RBD neutralizantes y respuestas T, lo cual explica su eficacia elevada y contribuye a la duración de la protección mediada por la vacuna.

Las **variantes** recientemente identificadas plantean el riesgo de selección de variantes “más aptas” al aumentar la presión inmune. La duración de la respuesta inmune (natural o inducida por vacuna) y la aparición de variantes capaces de escapar a la misma son cuestiones clave que afectarán la gestión de la pandemia, ya que determinarán la utilidad de los **estudios serológicos**, el nivel de **inmunidad de grupo** y la necesidad de **revacunar**.

# Conclusiones

1

En la gran mayoría de casos, la infección natural por SARS-CoV-2 induce una inmunidad protectora que dura por lo menos **seis meses**.



En caso de dosis limitadas, las **personas que ya han pasado la infección** no deben ser consideradas prioritarias para la vacunación.

2

3

El **componente innato y adaptativo** (anticuerpos, células B, T CD4+ y T CD8+) contribuyen a proteger contra la enfermedad o la reinfección.



Es necesario realizar **estudios paralelos de respuestas T y B** en diferentes cohortes para definir marcadores y mecanismos de protección.

4

5

A día de hoy, no existen valores cuantitativos de protección para el seguimiento de la **inmunidad natural o mediada por vacuna**.



Las decisiones relativas a la necesidad de **revacunar** se tomarán basadas en estudios proactivos de evolución viral y datos clínicos y epidemiológicos.

6

7

Dichos estudios permitirán identificar **marcadores de protección** que simplificarán futuros ensayos clínicos con vacunas.



No se recomiendan cambios en **las dosis o el régimen de las vacunas** actualmente aprobadas hasta que no se cuente con más evidencia.

8

9

La aparición de **nuevas variantes** virales podría comprometer la eficacia de las vacunas en un futuro. La vigilancia molecular del virus debe ser una prioridad.



Las campañas de **vacunación global** son una necesidad ética y epidemiológica.

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# Què sabem de la immunitat davant del SARS-CoV-2?

## Implicacions per a polítiques de salut pública

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### Resum

La magnitud, qualitat i durada de la resposta immunitària davant del SARS-CoV-2 definirà la dinàmica de l'epidèmia de COVID-19 i les estratègies implementades per protegir persones i poblacions.

La **inducció de respostes immunes** humorals (anticossos) davant de diferents proteïnes virals és **ràpida** i passa en la majoria de les persones després de la infecció, tot i que la **magnitud és variable** i més gran com més greu és la malaltia. Els **anticossos neutralitzants**, la majoria dels quals estan dirigits contra el domini que s'uneix al receptor cel·lular ACE2 (anomenat domini d'unió al receptor o RBD), estan presents a la gran majoria de persones infectades i poden bloquejar la infecció pel virus. Hi ha menys informació disponible sobre la resposta dels **limfòcits T**, que tenen un paper clau en el control de la replicació viral i la generació de memòria immunològica, però estudis recents indiquen que en gairebé totes les persones infectades es detecten cèl·lules T que reconeixen Spike i d'altres proteïnes virals, fins i tot en aquelles que no tenen nivells detectables d'anticossos.

S'han descrit alguns casos de **reinfecció**, però els estudis de cohort analitzats fins ara indiquen que aquesta immunitat protegeix contra la malaltia en cas de reinfecció i que és **duradora**, amb cèl·lules B i T que assoleixen un **nivell estable després de sis mesos**. Les **vacunes** dirigits contra la proteïna Spike indueixen nivells elevats d'anticossos anti-RBD neutralitzants i respostes T, la qual cosa n'explica l'eficàcia elevada i contribueix a la durada de la protecció mediada per la vacuna.

Les **variants** recentment identificades plantegen el risc de selecció de variants "més aptes" en augmentar la pressió immune. La durada de la resposta immune (natural o induïda per vacuna) i l'aparició de variants capaces d'escapar-hi són qüestions clau que afectaran la gestió de la pandèmia, ja que determinaran la utilitat dels **estudis serològics**, el nivell d'**immunitat de grup** i la necessitat de **revacunar**.

# Conclusions

1

En la gran majoria de casos, la infecció natural per SARS-CoV-2 indueix una immunitat protectora que dura almenys **sis mesos**.



En cas de dosis limitades, les **persones que ja han passat la infecció** no han de ser considerades prioritàries per a la vacunació.

2

3

El **component innat i adaptatiu** (anticossos, cèl·lules B, T CD4+ i T CD8+) contribueixen a protegir contra la malaltia o la reinfecció.



Cal dur a terme **estudis paral·lels de respostes T i B** en diferents cohorts per definir marcadors i mecanismes de protecció.

4

5

Ara per ara, no hi ha valors quantitius de protecció per al seguiment de la **immunitat natural o induïda per vacuna**.



Les decisions relatives a la necessitat de **revacunar** es prendran basades en estudis proactius d'evolució viral i dades clíniques i epidemiològiques.

6

7

Aquests estudis permetran identificar **marcadors de protecció** que simplificaran futurs assajos clínics amb vacunes.



No es recomanen canvis en **les dosis o el règim de les vacunes** actualment aprovades fins que no es compti amb més evidència.

8

9

L'aparició de **noves variants** virals podria comprometre l'eficàcia de les vacunes en un futur. La vigilància molecular del virus ha de ser una prioritat.



Les campanyes de **vacunació global** són una necessitat ètica i epidemiològica.

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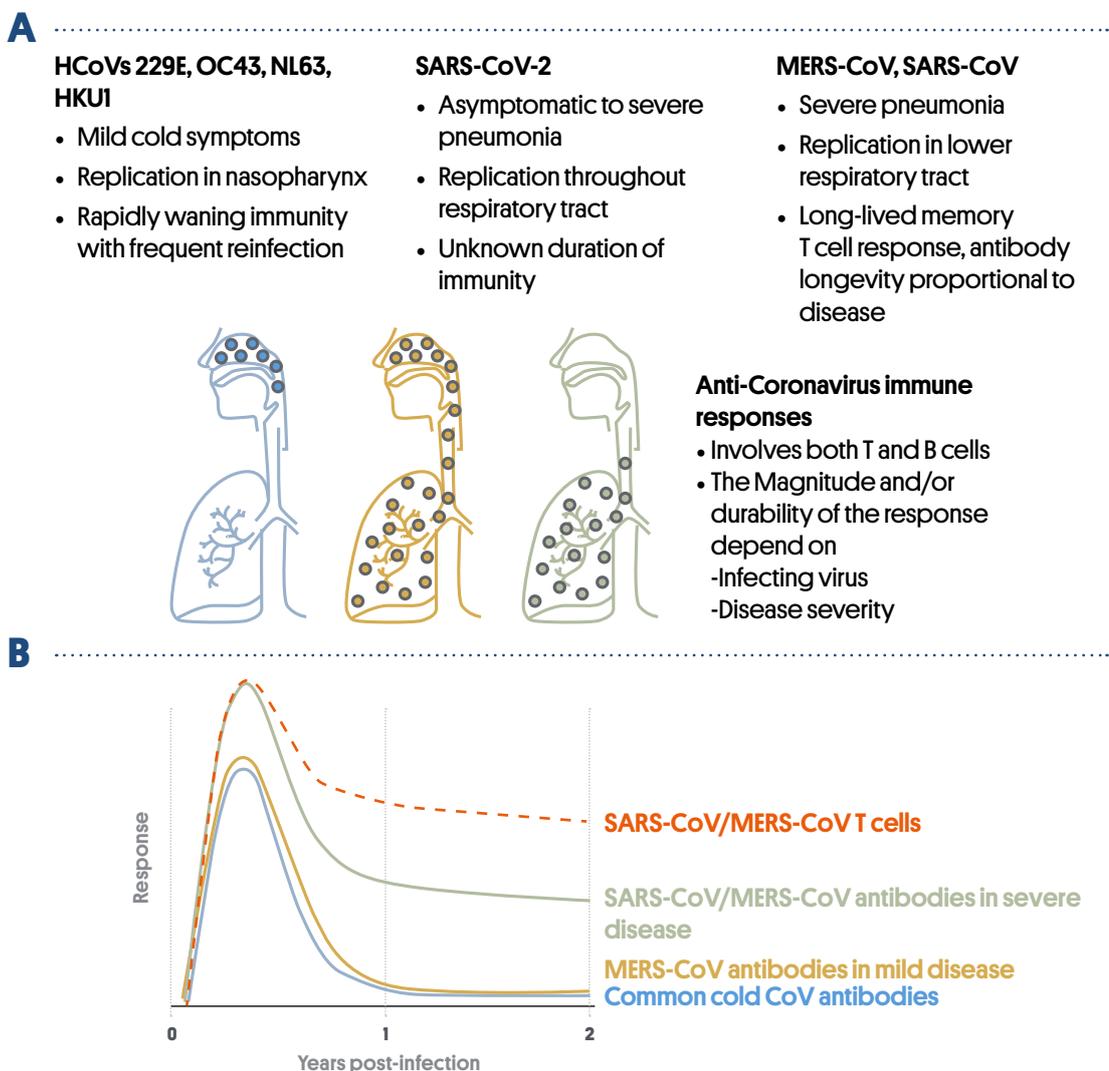
# 01 Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) zoonotic infection causing Coronavirus disease-19 (COVID-19) was first described one year ago in China and rapidly spread worldwide, modifying our established societal, economic and scientific priorities (“Science in the Time of Coronavirus” 2020). The rapid scientific response to tackle this new infection has focused on the development of specific treatments and vaccines to reduce the clinical impact and spread of the disease (Thorlund et al. 2020; Krammer 2020), and additionally on the understanding of the interplay between the new virus and the human immune system (Vabret et al. 2020). This latter aspect is a key piece of information that will help guide public health decisions related to achieving and maintaining herd immunity, both naturally acquired and vaccine-induced.

In a first encounter with a virus, the innate arm of the immune system responds using non-specific mechanisms that control initial viral replication and prepares the adaptive response to generate specific and long-lasting immunity. Key contributors to adaptive immunity are CD4+ T cells (helper T cells) that coordinate immune responses by helping B and CD8+ T cells to generate strong antiviral responses. B cells produce antibodies able to block infectivity and to clear viruses and infected cells; while CD8+ T cells contribute to killing infected cells. Both the innate and adaptive arms of immunity are relevant and must work co-ordinately to protect against viral infections (Rydzynski Moderbacher et al. 2020).

Human coronaviruses, including common cold viruses (229E, OC43, NL63 and HKU1) and those causing more severe respiratory disease (MERS and SARS), are not an exception and elicit both B and T cell immune responses in infected individuals. However, the magnitude and the extent of these responses are highly variable, thus limiting our capability to predict the evolution of anti-SARS-CoV-2 immunity (*Figure 1*).

**Figure 1 Summary of immune responses against different human coronaviruses. Common-cold coronaviruses induce a transient B and T-cell immune response that explains reinfections; conversely former SARS & MERS-CoV generate a durable response that is higher in severe patients. (Sariol and Perlman 2020)**



Sariol&Stanley 2020 Immunity. <https://doi.org/10.1016/j.immuni.2020.07.005>

In this document, we have summarized the current knowledge on SARS-CoV-2 immunity and the implications in our understanding of disease, specifically in the development of optimal immune-based diagnostic and therapeutic tools, vaccine strategies and epidemiologic surveillance.

# 02 Natural immune responses to SARS-CoV-2 infection

## a) Do we develop a protective immune response upon infection?

The answer, in short, is yes. Both SARS-CoV-2-specific antibodies and T cells are induced upon natural infection. However, much remains to be understood regarding the type, magnitude, kinetics and thus durability of the immune response required to protect against infection and/or severe disease.

First, our immune system responds to the virus activating the innate arm of defence against infection. This innate response, vastly dominated by Type-1 interferons, shows a double function: to minimize viral replication and to organize adaptive immune responses. In this sense, two relevant studies identify defects in the type I interferon response, due to either genetic mutations or autoantibodies that block the response, which may lead to severe COVID-19 (Bastard et al. 2020). Despite the relevance of innate responses, in this document we will focus on the adaptive arm of the immune response (T cells, B cells and antibodies) since they are central to ensuring viral clearance and immunological memory.

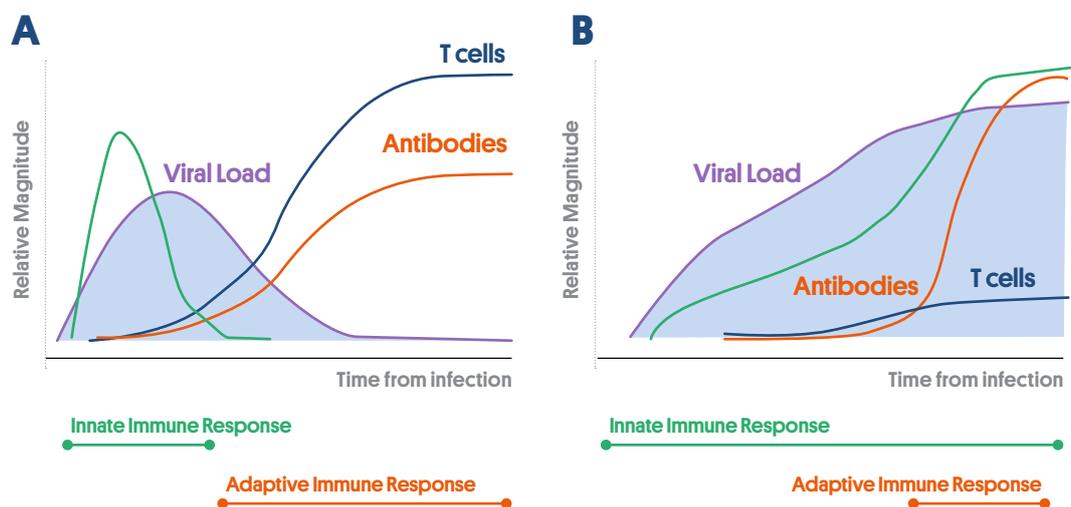
## i) Antibody responses (humoral immunity)

A large amount of relevant information on antibody responses to SARS-CoV-2 has been generated, excellently reviewed by Sette & Crotty (Vabret et al. 2020). The seroconversion rate induced by natural infection is higher than 90% (Figure 2) with an average time of 11 days after symptom's onset (Zhao et al. 2020). The antibody response peaks between the second and third week after infection and is characterized by the presence of IgA, IgM and IgG isotypes in plasma and saliva (Carrillo et al. 2020). Although IgM is the first line of humoral response, one particularity of SARS-CoV-2 infection is that all three antibody isotypes can be detected in a narrow time frame upon seroconversion.

Several studies have explored different factors that can be associated with antibody responses; however, no clear correlation has been observed between antibody levels and gender, age, or viral load (Zhao et al. 2020). In contrast, they positively correlate with disease severity. Hospitalized patients with severe COVID-19 present higher titers of IgG and IgA than mild cases, in which lower or even undetectable antibody levels have been reported (Trinité et al. 2021). This paradoxical observation suggests that T cells could be the major players in the control of disease progression. An effective T cell response may rapidly control viral replication, making antibodies unnecessary. Conversely, ongoing viral replication, as a consequence of poor or delayed T cell responses, would lead to an increase in antibody titers. (Figure 2)

## 02 Natural immune responses to SARS-CoV-2 infection

**Figure 2** Suggested model for early dynamics of immune responses in SARS-COV-2 infection. A proper transient innate response and a coordinated adaptive response (including T cells) allows for viral clearance in most cases (A). However, persistent innate responses may result in delayed adaptive responses and persistent VL associated with severe infection (B). Adapted from (Sette and Crotty 2021)



Antibody responses can be directed against all viral proteins, although Spike and nucleocapsid are considered the main targets (Sette and Crotty 2021). Antibodies against the RBD of Spike appear earlier in the course of infection than anti-nucleocapsid antibodies. Moreover, anti-RBD antibodies may provide a higher sensitivity and specificity for diagnosis than anti-nucleocapsid responses and show low cross-reactivity with other coronaviruses (Suthar et al. 2020; Chia et al. 2020).

### Neutralizing humoral response

For several pathogens, neutralizing antibodies are considered a major correlate of protective immunity and vaccine success (Plotkin 2008). In SARS-CoV-2 infection, these antibodies recognize several regions within the Spike glycoprotein, mainly but not exclusively the RBD, and inhibit viral infectivity by several mechanisms including the blockade of initial Spike binding to ACE2 (Sette and Crotty 2021). Two main regions of vulnerability have been identified in the Spike: the RBD and the adjacent N-terminal domain (NTD) (Ju et al. 2020). SARS-CoV and SARS-CoV-2 have 80% homology and share approximately 75% of the Spike

## 02 Natural immune responses to SARS-CoV-2 infection

glycoprotein sequence. Although, few antibodies with cross-neutralizing activity of SARS-CoV and SARS-CoV-2 have been identified, the existence of potentially cross-reactive antibodies opens new avenues for the potential development of a pan-neutralizing vaccines against various coronaviruses (Ju et al. 2020).

Neutralizing antibodies are detected in 40-90% of infected individuals, depending on the criteria and the cohort studied (Sette and Crotty 2021), around 6-15 days after symptom onset. As with total antibody titers, the amount of neutralizing antibodies associates with clinical severity of COVID-19 (Legros et al. 2020).

### Potential therapeutic and pathogenic roles of antibodies

Neutralizing monoclonal antibodies (mAbs) protect from SARS-CoV-2 lung infection and weight loss in mice, rhesus macaques and other animal models (Carrillo et al. 2020). Accordingly, early administration of convalescent plasma to infected individuals can improve their clinical status, at least in those treated with high neutralizing plasma within the first days after symptom onset (Dagotto, Yu, and Barouch 2020; Xia et al. 2020). No clinical benefit of plasma or antibody treatment has been observed in hospitalized patients (Xia et al. 2020).

Beyond their beneficial effects, antibodies can also be deleterious, promoting infection through a mechanism called antibody-dependent enhancement (ADE) of the disease, a potentially life-threatening phenomenon documented for other pathogens such as dengue or respiratory syncytial virus (RSV). Current evidence support the hypothesis that ADE events in COVID-19 will be extremely sporadic:

- 1) The infusion of convalescent plasma in COVID19 patients has not revealed any adverse effect (Dagotto, Yu, and Barouch 2020);
- 2) Vaccinated non-human primates develop antibodies against SARS-CoV-2 and are resistant to reinfection without signs of ADE (Deng et al. 2020); and
- 3) Vaccinated animals do not show signs of ADE after challenge (Yu et al. 2020). Furthermore, no ADE effects have been noticed in the large number of clinical trials for the different COVID-19 vaccine candidates.

To minimize the potential risk of ADE in COVID-19, CEPI and the Brighton Collaboration Safety Platform for Emergency vACCines (SPEAC) proposed a series of guidelines to assess and reduce the risk of enhanced disease during SARS-CoV-2 vaccine development (Lambert et al. 2020).

## 02 Natural immune responses to SARS-CoV-2 infection

### ii) Cellular immune responses to SARS-CoV-2

As mentioned in the introduction, the adaptive immune response to a virus is not limited to antibodies. Upon infection, CD4+ T cells activate antibody-producing B cells as well as cytotoxic CD8+ T cells, which recognize and destroy cells infected by the virus. A small portion of these T cells become long-lived memory cells capable of responding rapidly upon re-exposure to the pathogen. Therefore, T cells play a key role not only in clearing the virus but also in maintaining long-term protection against it.

T cell responses are more laborious to measure and therefore received less attention than antibodies during the first months of the pandemic. However, recent studies have revealed the presence of SARS-CoV-2-specific CD4+ and CD8+ T cells in the great majority of individuals recovering from SARS-CoV-2 infection (Grifoni et al. 2020). These T cells respond strongly to the viral Spike protein as well as to other viral proteins (M and N). Importantly, SARS-CoV-2 specific T cells were consistently detected even in those patients who no longer had detectable antibodies (Schulien et al. 2021). In fact, these authors proposed that CD8+ T-cell responses might serve as a more precise correlate of antiviral immunity than antibodies.

Identifying the type of T cell responses associated with protection from severe disease remains a central issue. The magnitude and kinetics of the T cell responses do not seem to be associated with viral clearance or COVID-19 survival (Thieme et al. 2020). Rather, the clue seems to lie in the diversity. A greater diversity of SARS-CoV-2 T cell responses (i.e. the recognition of multiple epitopes from different viral proteins) was associated with mild symptoms of COVID-19 (Nelde et al. 2021), whereas SARS-CoV-2 T cells from severe cases showed low functional avidity and clonality, despite increased frequencies (Bacher et al. 2020).

Unconventional T cells -namely, mucosal-associated invariant T (MAIT) cells and invariant natural killer T (iNKT) cells- may also play a beneficial role in severe COVID-19. Patients with highly activated MAIT and iNKT cells at the time of their admittance to the ICU were less susceptible to hypoxemia and were discharged sooner than patients whose MAIT and iNKT cells were less active (Jouan et al. 2020).

A current working model is that disease severity is associated with an imbalance or improper sequential development of the different arms of the immune system (figure 2) from (Sette and Crotty 2021)

## 02 Natural immune responses to SARS-CoV-2 infection

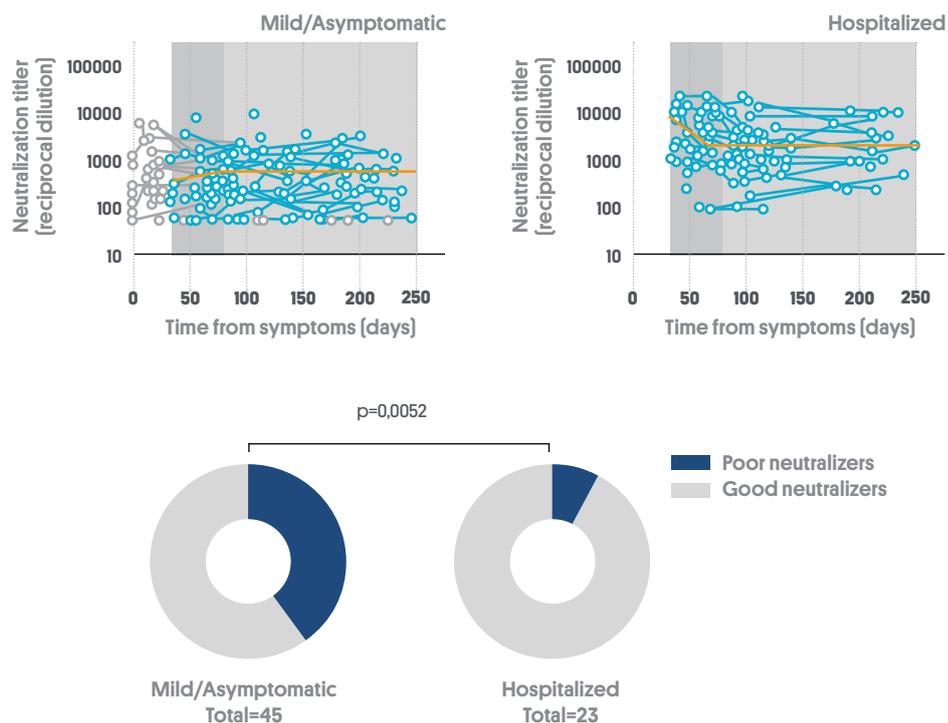
### b) How long does natural immunity last?

A few initial reports suggested a rapid decay of SARS-CoV-2-specific IgG antibody levels, particularly in patients with mild symptoms (Chen et al. 2020), raising concerns that immunity following natural infection may be short-lived and that this could lead to reinfections in the short to mid-term. However, a growing number of recent studies indicate that immunity to SARS-CoV-2 could last several months, even years, regardless of symptom severity. A longitudinal assessment of individuals recovered from mild COVID-19 showed SARS-CoV-2-specific IgG antibodies, neutralizing plasma, memory B and memory T cells that persisted for at least three months, and IgG memory B cells that even increased over time (Rodda et al. 2021). Accordingly, another recent study shows that spike-specific memory B cells were more abundant at 6 months than at 1 month after infection, and that the half-life for SARS-CoV-2-specific CD4+ T cells and CD8+ T cells is of 3-5 months (Dan et al. 2020). Finally, a small UK study has found that T cell immunity to SARS-CoV-2 is present after six months in people who had mild or asymptomatic COVID-19, suggesting they might have some level of protection for at least that time (Mahase 2021).

Two recent studies confirm the durability of neutralizing antibody responses and define its kinetics overtime. The results from these independent studies show a stabilization of the titer of neutralizing antibodies three months after infection, with half lives of more than one year, suggesting that immunity could be long lived. However, titers of neutralizing antibodies remain higher in individuals that required hospitalization, while a high portion of mild symptomatic participants show low neutralization titers after six months of infection (*Figure 3*) (Pradenas et al. 2021).

## 02 Natural immune responses to SARS-CoV-2 infection

**Figure 3** Longitudinal analysis of neutralizing activity in 210 SARS-CoV-2 infected individuals in Catalonia. **a**, Individual measurements (dots) and linear mixed model (solid orange line) of the longitudinal analysis for mild or asymptomatic individuals beyond day 30 (single-phase slope -0.00014;  $p=0.75$ , likelihood ratio test; estimated half-life 2,134 days). Time points preceding day 30 are shown but greyed out. **b**, the corresponding analysis for hospitalized individuals (the half-life of the linear fit for the first and second phase were half-life 31 days and half-life 753 days, respectively. **c**, Frequency of long-term neutralizers (i.e., individuals with mean neutralizing activity >250 after 6 months of infection) in each severity subgroup (Chi square test  $p$  value is shown). (Pradenas et al. 2021)



In addition to the pure immunological follow up, a recent epidemiological study confirmed immune protection. This study analysed SARS-COV-2 infections among 12 364 healthcare workers with a median age of 38 years for a maximum of 31 weeks. The presence of antibodies was associated with a 90% protection from PCR positivity during the study period, confirming the existence of protective im-

## 02 Natural immune responses to SARS-CoV-2 infection

munity and its relationship with seroconversion (Mahase 2021). Although further research is needed in other cohorts (children, older adults), these data are consistent with antibody evolution and support the recommendation that people with evidence of past COVID-19 should not be prioritized in vaccination campaigns (Sanjose et al. 2020). Recent evidence also suggests that a single dose of vaccine could be sufficient to achieve neutralizing antibody titers as high or higher than two doses in patients without prior infection (Kramer et al. 2021).

### **c) Can cross reactivity with common cold coronaviruses protect from infection or disease?**

Human common cold coronaviruses share extensive sequence homology with SARS-CoV-2, particularly in the S2 subunit of the Spike protein (Wec et al. 2020). Therefore, it has been postulated that previous infections with these endemic viruses may confer some degree of protection against COVID-19. Accordingly, one study in hospitalized COVID-19 patients suggested that recent endemic coronavirus infection was associated with less severe COVID-19 (Sagar et al. 2021). Indeed, a considerable percentage (20-50%) of healthy donors unexposed to SARS-CoV-2 have been shown to harbour memory CD4+ T cells capable of recognizing epitopes shared by SARS-CoV-2 and common cold coronaviruses, although these cross-reactive T cells are normally found at very low frequencies - under 0.1% - (Weiskopf et al. 2020).

However, the presence of SARS-CoV-2 reactive T cells in unexposed humans does not necessarily imply protective immunity. One study for example found that CD8+ T cells recovered from COVID-19 patients showed almost no cross-reactivity with epitopes from seasonal coronaviruses (Ferretti et al. 2020), while another study found the same for CD4+ T cells (Bacher et al. 2020). At the moment it is not clear whether these pre-existing cross-reactive T-cells ameliorate or worsen COVID-19.

Similarly, many individuals, particularly children and adolescents, possess antibodies to common cold coronaviruses, and some of these antibodies can cross-react with the SARS-CoV-2 spike protein (mainly the S2 subunit, which is highly conserved among coronaviruses), as well as with nucleocapsid proteins (Ng et al. 2020). However, cross-reactive antibodies were not associated with protection against SARS-CoV-2 infections or hospitalizations (Poston et al. 2020) and one study suggests they could even have a negative impact (Westerhuis et al. 2020) probably associated with the development of cross reactive antibodies that preclude proper targeting of specific regions of the SARS-CoV-2 Spike, in particular the RBD.

## 03 Vaccine-mediated immunity

Historically, most vaccines against infectious diseases have elicited immune responses that are at least comparable or greater in magnitude than the response to natural infection. Therefore, we should expect that a COVID-19 vaccine elicits high titer neutralizing antibody titers and T cell responses conferring protection from the disease. Available data confirm that current vaccines fulfil these requirements. However, it is unclear whether vaccines confer sterilizing immunity or whether vaccinated individuals can undergo subclinical infection and transmit the virus. Experiments in non-human primates indicate that most vaccines protected against lung pathology but did not completely prevent viral replication in the upper respiratory tract. Recent studies show that symptomatic individuals are more infectious than asymptomatic ones (Sayampanathan et al. 2021) and therefore one could reasonably expect that, even if vaccines do not completely prevent infection of the upper respiratory tract, they may still reduce viral transmission, as recently reported (Mallapaty 2021).

Most leading candidate vaccines are based on the expression of the SARS-CoV-2 Spike protein, and have been shown to elicit good levels of neutralizing antibodies, CD4+ and- to a lesser extent- CD8+ T cell responses. No evidence for ADE has been observed with any of the vaccine candidates tested in non-human primates or in clinical trials (Carrillo et al. 2020). The SARS-CoV-2 vaccines currently in development and the challenges for determining their efficacy have been excellently reviewed elsewhere (Amanat and Krammer 2020; Hodgson et al. 2021). Key messages include the need of standardised approaches for measuring and comparing vaccine efficacy, and the need of ensuring pharmacovigilance studies once vaccines are deployed. Most relevant data are summarized in Table 1. Briefly, approved vaccines in our geographical EU context (Pfizer/Biontech, Moderna and Oxford/Astra-Zeneca) elicit robust neutralizing antibody and T cell responses. Antibody titers after the second dose of these vaccines appear to be roughly 5-fold higher than values observed in convalescent individuals. Protection from mild or moderate disease is excellent for mRNA-based vaccines (>90%) and lower for Astra-Zeneca (62-90%, depending on dosage and intervals). Despite these apparent differences, no hospitalization or deaths have been observed among people immunised with any of these vaccines. Protection from severe disease/death has been reported to be 100% for Johnson & Johnson or Astra-Zeneca vaccines (<https://www.astra-zeneca.com/media-centre/press-releases/2021/covid-19-vaccine-astrazeneca-confirms-protection-against-severe-disease-hospitalisation-and-death-in-the-primary-analysis-of-phase-iii-trials.html>) and is expected to be similar for mRNA vaccines. No information is available on the mid- or long-term durability of antibody or T cell immune responses induced by these vaccines.

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**Table 1 Vaccines approved by the EU**

Platform	Company	Phase III	Reported Efficacy	Doses	Storage	Approval	More information
mRNA	Pfizer/ BioNTech	NCT04368728	>90%	2x (21 days)	-70°C	EU, UK, US, CAN...	<a href="https://www.pfizer.com">https://www.pfizer.com</a>
	Moderna	NCT04470427	94%	2x (28 days)	-20°C	EU, UK, US, CAN...	<a href="https://www.modernatx.com">https://www.modernatx.com</a>
Viral vector	Astra Zeneca	NCT04516746	62-90%	2x (28 days)	2-8°C	EU, UK, ARG, BRA	<a href="https://www.astrazeneca.com">https://www.astrazeneca.com</a>

Other vaccine candidates are being tested in China, Russia or South America, with much less available data. Different vaccines are needed to help ensure global vaccine coverage. Nevertheless, not all candidates will be successful- several vaccine candidates have been stopped, due to cross reactivity with HIV serological tests (Queensland University vaccine programme) or to insufficient responses (measles and VSV vectored vaccines developed by Merk-Sharp and Dome), among other.

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**Table 2** Leading COVID-19 vaccines or have already been approved in at least one country

Platform	Company	Phase III	Reported Efficacy	Doses	Storage	Approval	More information
mRNA	CureVac	NCT04652102	?	2x (28 days)	2-8°C		<a href="https://www.curevac.com/en/covid-19">https://www.curevac.com/en/covid-19</a>
DNA	Anges	NCT04655625	?	2x (14 ó 28 días)	T amb		<a href="https://www.anges.co.jp/en/">https://www.anges.co.jp/en/</a>
	Inovio	NCT04642638	?	2x (28 days)	T amb	EU, UK, ARG, BRA	<a href="https://www.inovio.com/">https://www.inovio.com/</a>
Viral vector	Gameleya	NCT04530396	91%	2x, (21 days)	-18°C	RUS, ARG, ...	<a href="https://sputnikvaccine.com/">https://sputnikvaccine.com/</a>
	Johnson & Johnson	NCT04505722	60-70	1x	2-8°C		<a href="https://www.jnj.com/coronavirus">https://www.jnj.com/coronavirus</a>
	CanSinoBio	NCT04526990	?	1x	2-8°C	CHINA	<a href="http://www.cansinotech.com/">http://www.cansinotech.com/</a>
Protein	Novavax	NCT04611802	60-89%	2x (21 days)	2-8°C		<a href="https://ir.novavax.com/">https://ir.novavax.com/</a>
	GSK/Medicago	NCT04636697	?	2x (21 days)	2-8°C		<a href="https://www.medicago.com/en/">https://www.medicago.com/en/</a>
	China Acad Sci	ChiC-TR2000040153	?	?	?		<a href="http://en.zhifeishengwu.com/">http://en.zhifeishengwu.com/</a>
	Vector	?	?	2x (21 days)	2-8°C	RUS	<a href="http://www.vector.nsc.ru/">http://www.vector.nsc.ru/</a>
Inactivated virus	Sinopharm/pekin	NCT04510207	79%	2x (21 days)	2-8°C	CHINA, UAE	<a href="http://www.sinopharm.com/1156.html">http://www.sinopharm.com/1156.html</a>
	Sinopharm/Wuhan	NCT04510207	79-86%	2x (21 days)	2-8°C	CHINA, UAE	<a href="http://www.sinopharm.com/1156.html">http://www.sinopharm.com/1156.html</a>
	China Acad Sci	NCT04659239	?	2x (14 days)	?		<a href="https://www.dynavax.com/">https://www.dynavax.com/</a>
	Sinovac	NCT04582344	50%	2x (14 days)	2-8°C	CHINA, BRA	<a href="http://www.sinovac.com/">http://www.sinovac.com/</a>
	Bharat	NCT04641481	?	2x (21 days)	2-8°C	INDIA	<a href="https://www.bharatbiotech.com/">https://www.bharatbiotech.com/</a>

### a) Defining a protective cut-off. Is it possible?

An obvious risk associated with a fast decay or a poor elicitation of neutralizing antibodies is the possibility of reinfection. Although animal models and epidemiological data suggest that infection induces protective immunity (Deng et al. 2020), several cases of reinfection have been reported in humans. A close surveillance of reinfection events accompanied by serological surveys will inform on the relevance of this phenomenon.

To date, no clear cut-off for a neutralizing activity that protects against reinfection has been established. Nevertheless, data gathered from high attack rate events suggest that neutralizing activities between 1:161 and 1:3,082 are strong enough to prevent infection (Addetia et al. 2020).

The analysis of reinfections by SARS-CoV-2 is a potential source of information to improve our understanding of the correlates of protection, a critical factor when trying to define vaccine efficacy endpoints in future clinical trials. However, reinfection with SARS-CoV-2 after primary infection can be confounded by the prolonged viral RNA shedding described in some patients. In the absence of viral sequence analysis, both events cannot be properly categorized, thus limiting our capacity to assess the real frequency of reinfections. Although more than 6,000 suspected reinfections have been reported, this figure remains anecdotal compared with the total number of cases, and to date, only 39 reinfections have been appropriately-documented and microbiologically confirmed (<https://bnonews.com/index.php/2020/08/covid-19-reinfection-tracker/>).

In general, most reinfections were associated with lack of seroconversion during the first COVID-19 episode and induced a mild disease, although severe cases have also been reported. The definition of specific correlates of protection will need larger numbers of well-defined reinfections.

### b) Viral escape to immune responses.

The durability of SARS-CoV-2 immunity -whether naturally acquired or vaccine-dependent- will also depend on how quickly the virus is changing, particularly in its Spike protein, the sole protein included in most vaccine candidates, to which neutralizing antibodies and a high proportion of T cell responses are directed. Vaccines including other viral proteins (such as inactivated viruses) and therefore inducing a wider range of T cell responses could be less affected by Spike mutations, although viral evolution has been described outside the Spike gene.

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Coronaviruses have a molecular machinery that results in a higher replication fidelity than other RNA viruses. Indeed, genomic analyses performed in the first months of the pandemic revealed a relatively low mutation rate (estimated at 1-2 mutations per month) and no evidence of adaptive selection. The D614G mutation in the Spike protein became dominant early in the pandemic, a phenomenon that could be explained partly by a founder effect and partly by a potential increase in infective capacity as suggested by *in vitro* experiments (Plante et al. 2020). Other recently identified variants have raised more concern among the scientific community, not only because they accumulate a larger number of mutations than previously observed, but also because some of these mutations, particularly those near or in the RBD of Spike, could have a biological impact and thus potential public health adverse consequences. Current investigations are addressing three main questions regarding these variants: are they more transmissible, do they cause more severe disease, can they escape from natural or vaccine-elicited immunity?

A variant called B.1.1.7 or 501Y.V1 has rapidly spread across England, replacing all other circulating variants. This variant has accumulated 14 non-synonymous mutations and three deletions. Three changes in the Spike protein are particularly worrying: i) the mutation N501Y, which occurs in other independent variants, is within the RBD and may increase the binding affinity to its human ACE2 receptor; ii) a deletion of two amino acids (69,70 del), which was also detected in a variant isolated from a mink farm in Denmark, could reduce the effect of certain antibodies; iii) mutation P681H is next to the furin cleavage site and could potentially enhance viral infectivity.

An analysis by Public Health England indicates that B.1.1.7 has a higher secondary attack rate (15% versus 11% for other variants) and that this increased transmissibility is observed across all age groups (children included). Epidemiological data from Ireland and Denmark confirm that this viral variant is 30-50% more transmissible. There is, however, no clinical evidence that it causes more severe disease, although the indirect impact of a more transmissible variant is of concern in relation to an increased pressure to the health system. Importantly, preliminary results indicate that this variant remains susceptible to antibodies in sera of convalescent individuals or of people immunized with the Pfizer vaccine (Haynes et al. 2021; Wang et al. 2021).

A variant detected in South Africa (501Y.V2) and another independent variant detected in Manaus, Brazil (P.1 or 501Y.V3) raise more particular concerns regarding possible escape from immunity. Both harbour a mutation in Spike (E484K), which, according to preliminary experiments *in vitro*, may reduce the potency of convalescent sera up to 10-fold (Greaney et al. 2021; Wibmer et al. 2021). The 501.YV2 variant also contains two other mutations in the RBD: N501Y and

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K417N. These 3 mutations, particularly when combined, can reduce in a variable but significant manner the neutralizing activity of convalescent plasma (Wibmer et al. 2021) or of plasma from individuals immunized with the Pfizer and Moderna mRNA vaccines (Wang et al. 2021).

It is believed that these variants may have emerged in immunocompromised hosts where prolonged viral replication occurs. For example, several mutations observed in the B.1.1.7 variant were detected in an immunosuppressed individual treated with convalescent plasma (Kemp et al. 2020) and in another Italian patient with persistent infection (Fiorentini et al. 2021).

It is probable that more SARS-CoV-2 variants will arise as an increasing number of people are infected or vaccinated and immune pressure on the virus grows. The key to good surveillance will rely on the prompt sequencing and sharing of enough genomes to detect them as they arise. Furthermore, surveillance must go beyond focusing on single point mutations and consider the combined effect of mutations in these variants. Evaluating their impact will require integrating genomic sequence data with epidemiological, clinical and laboratory data. In any case, the best way to approach the emergence of new variants is to ensure a very high and fast coverage of vaccination, because this will minimize the number of viruses circulating, and as a result, their potential to evolve.

Finally, the emergence of a SARS-CoV-2 variant harbouring the 69,70 deletion in a mink farm in Denmark is a warning call to implement measures that reduce transmission to this and other animals susceptible of infection, and to implement a broader, One Health surveillance approach.

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**Figure 4 Main Spike mutations found in SARS-CoV-2 variants of concern and reported impact on disease and immunity.**

	S1										S2				Transmission	Mortality	Escape to vaccines	Identified in Catalonia			
	14	305	319	541	685	778	816	902	1035	1076	1141	1163	1273	FP					HR	CD	HR2/TM/Cyt
	NTD		RBD		Subdomains																
VOC 202012/01 B.1.1.7 (identified in UK)	Δ 69-70	Δ 144-145			N 501	A 570	D 614	P 681	T 716		S 982		D 1118					40% higher	? Preliminary data suggest 30% higher	1-3 fold resistant	Yes
VOC 501YV2 B.1.351 (identified in SA)		D 80			K 417	E 484	N 501		D 614	A 701								? Expected to be high	?	6-10 fold resistant	No yet
B.1.1.248 (identified in Barzil/Japan)	L 18	T 20	P 26	D 138	R 190	K 417	E 484	N 501	D 614	H 655				T 1027				? Expected to be high	?	? Expected similar to B.1.351	No yet
	F	N	S	Y	S	N	K	Y	G	Y				I							F

# 04 Impact on herd immunity and vaccination strategies

The current setting offers a rather complex scenario, defined by the development of effective and safe vaccines and by a worldwide almost uncontrolled spread of the virus. In this setting, the rapid distribution of vaccines is mandatory to reach herd immunity levels, but this objective is strongly limited by the production capacity of pharmaceutical companies.

By herd immunity to SARS-Cov-2, we refer to the proportion of a population that needs to be immune to SARS-Cov-2 (through overcoming natural infection or through vaccination) to stop generating large outbreaks. Several elements are required to estimate the herd immunity threshold. These include the presence and use of non-pharmaceutical interventions (NPIs), vaccine coverage, the percentage of people that have been infected, and the number of infections that one contact can generate ( $R_0$ ).

After few months of the pandemic, Salje et al. in France estimated (using  $R_0=3$ ) that herd immunity against SARS-Cov-2 could be attained if 67% of the population was immune (Salje et al. 2020). Others estimated that at least 75% coverage will be needed with a vaccine efficacy of 70% to reduce the epidemic peak by >99% without other interventions. Other published estimates range from 43% to 90% (Fontanet and Cauchemez 2020).

A preliminary simulation analysis on a US population evaluates the impact on new infections after variations of vaccine efficacy and levels of coverage with and without NPIs. The data indicate that coverage and efficacy can compensate each other. For example, a higher vaccine coverage (i.e., 75% vs. 25%) could lead to a comparatively more significant reduction of infections than higher vaccine efficacy (i.e., 90% vs. 50%) when removing NPIs. But a premature removal of NPIs, while implementing the vaccine program, may result in substantial increases in infections, hospitalizations, and deaths, clearly affecting any potential herd immunity effect (Patel et al. 2021).

Vaccination options will surely increase after the approval of the Astra-Zeneca and other vaccines. Although some of them may confer a lower protection than RNA-based vaccines, recent data support the notion that most vaccines may reduce viral transmission. Meanwhile, different strategies have been suggested to increase vaccine coverage, among them the administration of one single dose or the delay in the second vaccine dose. However, both approaches are not exempt of risk, there is a clear danger of reducing or spacing doses in terms of selecting immune escape variants. Viral evolution could be accelerated under suboptimal immune pressure, as suggested by studies in immunocompromised patients. This risk is particularly relevant in the current context of increasing number of circulating variants that show a relative resistance (up to 6-fold) to current vaccines. To avoid this risk, full

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vaccination doses are recommended, until solid data (currently under analysis) support changes in dosage. In parallel, updating the vaccine to include Spike variants (easier to do with mRNA vaccines) is a current priority of vaccine developers. In parallel, regulatory bodies need to define a clear and simplified path for these new vaccines. Finally, randomized clinical trials have been launched to study the possibility of mixing different vaccines to boost the immune response. Preclinical data in mice showed that a combination of an mRNA coronavirus vaccine and the Oxford-AstraZeneca vaccine induced a better CD8 T cell response as compared to either vaccine alone (Spencer et al. 2021).

An additional consequence of the emergence of new variants is the requirement of a global vaccination campaign. Although ethical consideration should be sufficient to claim for a global access to vaccines, the potential viral evolution in countries with inadequate control of the pandemic further strengthens this message. In a truly globalized world, it makes no sense to protect people living in high-income countries, leaving unprotected other regions. The risk of emergence of resistant variants could make the effort useless in the long-term.

Finally, another open question in the current strategy of vaccination is the durability of protection conferred by the vaccine and the potential need of revaccination. Obviously, no data are yet available on the durability of protective immunity in vaccinees; therefore, the analysis of vaccinated cohorts, at the immunological (neutralizing antibody titers or T cell responses) and the epidemiological level (incidence of new infections) is mandatory to identify immune correlates of protection and to define an evidence-based vaccination/revaccination program.

# 05 Conclusions

- In the vast majority of cases, SARS-CoV-2 natural infection induces a **protective immunity that lasts for at least six months**, and possibly longer.
- Therefore, in a context of limited vaccine availability, **individuals with past infection should not be initially prioritized for immunization**.
- The innate and all the compartments of the **adaptive immune response** (antibodies, B cells, CD4+ and CD8+ T cells) contribute to protection from disease or reinfection, although their exact contribution is still unknown.
- **Parallel studies of B and T cell responses** in different cohorts (infected with different clinical course, exposed and uninfected, reinfected) **are necessary** to define correlates and mechanisms of protection
- To date, **no quantitative cut-offs of protection** (for antibody and T cell responses) exist to monitor natural or vaccine-induced immunity.
- Decisions on **revaccination** will be driven by proactive studies of viral evolution and clinical/epidemiological data.
- These data should allow for the **identification of correlates of protection**, which will simplify future vaccine trials, minimizing their size, length and complexity.
- Changes in vaccine dosage and schedule of currently approved vaccines are not recommended until further evidence is available. The lack of data on protection after one single dose of currently approved vaccines (in naïve individuals), and the risk of accelerating virus adaptation under suboptimal immune responses argue **against modification of tested calendars**.
- The emergence of new viral variants could compromise vaccine efficacy in the future. Again, **molecular surveillance of virus circulating in human and animal populations** (i.e. mink farms) should be an epidemiological priority.
- **Global vaccination campaigns** are ethically and epidemiologically necessary.

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