

## Statement on the third dose of COVID-19 vaccines (16/09/2021)

### Multidisciplinary Collaborative Group for the Scientific Monitoring of COVID-19

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### COVID-19 vaccines: Do we need a booster dose now?

One key open question regarding COVID-19 vaccines is the duration of protection conferred by vaccines, mainly against disease but also against infection. The probability that the general population will need a third vaccine dose in the near future has been recently and repeatedly raised, particularly in the context of the more transmissible Delta variant. However, this notion is not fully supported by the scientific evidence to date. The Delta variant has magnified the non-sterilizing nature of COVID-19 vaccines, revealing their dicotomic behavior, i.e. a waning effectiveness against SARS-CoV-2 infection but a sustained and high effectiveness against the development of severe disease and death.

### What does the scientific evidence say?

- **Immunity to SARS-CoV-2 is robust and will likely be long-lasting**

A growing amount of studies show that both natural and vaccine-elicited immunity to SARS-CoV-2 are robust and in both cases immunological memory will probably last for several years.

To start with, Spike-specific neutralising antibodies have been detected for over 7-15 months after infection in most (>90%) COVID-19 recovered individuals [1][2]. In addition, antibodies are only one part of the immune response: while antibodies are expected to wane over time, memory B and T cells are key for ensuring long-lived immunity. In this regard, recent studies provide encouraging results. Quiescent, long-lived plasma cells (responsible for secreting Spike-binding antibodies) were detected in the bone marrow of convalescent patients 7-8 months after infection [3], suggestive of a long-lived humoral immune response even in those patients who experienced mild symptoms. Similarly, memory T cells, responsible for destroying infected cells, are also detectable for at least 8-9 months after infection [4].

In vaccinated individuals, in which shorter follow-up periods have been analyzed, lymph node biopsies of individuals having received mRNA vaccines show active germinal centers (places where antibody-producing B cells are trained to recognise the Spike protein) up to 15 weeks after receiving the second vaccine dose [5]. These findings are indicative of a robust response that will produce a large number of long-lasting memory

B cells, despite the reported waning of antibody levels [6]. Moreover, T cell responses seem to be robust for both RNA- and adenovirus-based vaccines [7].

On top of this, numerous studies show that vaccinated individuals who previously recovered from COVID-19 have significantly higher antibody titers than those fully vaccinated without prior infection, and these individuals could therefore be protected for an even longer period of time [7]. Many groups are trying to identify correlates of vaccine protection, which would be very useful for assessing whether and when a third dose may be needed [8][9].

- **For the general population, vaccines remain effective against currently circulating variants**

Several studies in the laboratory point to a decrease in the ability of sera from vaccinated individuals to neutralise some of the currently circulating variants of concern. Notably, the Beta (B.1.351) variant shows the greatest potential of immune escape, both in the laboratory (up to a 10-fold reduction in neutralising titers) as in the field (considerable reduction in efficacy against symptomatic infections). However, all vaccines currently approved in the US and/or Europe remain highly effective in protecting against COVID-19 hospitalization, ICU admission and death, regardless of the variant. The highly transmissible Delta (B.1.617.2) variant, which has now become dominant in Europe and many other countries in the world, is no exception.

From the epidemiological point of view, the number of reinfections in patients recovered from COVID-19 and the number of 'breakthrough infections' in fully vaccinated individuals remains low. Even in areas where the Delta variant has become predominant, most infections and hospitalizations are observed in non fully-vaccinated individuals [10].

Laboratory studies [11] as well as epidemiological data from England [12] clearly show that, while one dose of the Pfizer or AstraZeneca vaccines protect less effectively from the Delta variant as compared to Alpha, two doses remain protective against symptomatic infection (around 88% for the Pfizer vaccine and 67% for the AstraZeneca vaccine) and highly protective against severe disease or death (above 90% for both), emphasizing the relevance of complete vaccination schedule for effective protection against delta variant.

There is solid evidence for the maintained high levels of protection against severe COVID-19 conferred by current vaccines, despite a reduced protection against infection. Highly consistent data have been generated in different countries (Bahrain, Qatar, Israel and USA), with different vaccines (RNA-based or Adenovirus-based), and different times since vaccination (up to 6 months). Importantly, the level of protection against severe COVID-19 is mostly independent of the infecting SARS-CoV-2 variant and reaches more than 90% even six months after vaccination [13–15]. However, the effectiveness of vaccines against symptomatic infections by Delta drops to 88% and 67% for the Pfizer/BioNTech and AstraZeneca/Oxford vaccines respectively, according to data from England (2) and to 66% according to a study in mRNA-vaccinated healthcare workers [16]. Lower effectiveness of Pfizer/BioNTech vaccine against both asymptomatic and symptomatic SARS-CoV-2 infection has been also reported in a nationwide study in Israel [17]. However, the exact contribution of waning immunity, new viral variants, non-pharmacological measures and virus circulation at the population level to these observations are still under discussion.

Finally, although booster doses have been shown to result in a transient increase in systemic neutralizing antibodies and may therefore better protect against Delta infections, this effect might be short-lived, with a minimal impact on the memory B and T cell compartment [7].

- **Elderly individuals may need a booster dose this winter**

There is still limited data on the duration of vaccine-mediated protection in the elderly population, and to date there are no vaccine effectiveness studies published with the Delta variant in residents of long-term care facilities. However, it has been observed that individuals over 80 vaccinated with mRNA vaccines show reduced somatic hypermutation of B cells, lower T-cell responses, and lower neutralisation titers than younger participants [18]. Moreover, [unpublished data](#) point to low neutralizing responses in nursing home residents in Catalonia unless they have been previously infected.

Whether this translates into reduced vaccine effectiveness against severe COVID-19 or death remains to be seen, but one study found that the risk of post-vaccination SARS-CoV-2 infection seems to be higher in frail elderly individuals [13] with a reduced protection against severe disease overtime [17]. Importantly, a recent study in the US shows that among the few fully vaccinated patients admitted to hospital with severe COVID-19 (14 out of a total of 969 patients), the median age was 80.5 years [19].

Therefore, measures to boost vaccine responses in the elder population may be necessary in the near future, and one alternative would be to offer a booster dose to elderly individuals with frail health during the flu vaccination campaign this coming winter. The current lack of detailed data does not allow for the definition of a clear prioritization according to age or frailty in the elderly population. It will be important to monitor the frequency and severity of breakthrough infections in elderly populations in order to determine whether these are due to waning immunity or to the spread of viral variants with greater immune escape potential. Catalunya, for example, is closely monitoring the most vulnerable populations (including nursing home residents) through weekly PCR tests in order to identify and study breakthrough infections.

- **Some groups of immunocompromised patients need a third dose to reach protective levels**

Contrasting with the high level of protection of the general population, there are certain groups of individuals who, due to a compromised immune system, may require specific schedules with additional dose(s) of SARS-CoV-2 vaccines. This situation is reminiscent of other vaccines such as hepatitis B or pneumococcus, among others, that are administered at specific schedules in immunocompromised individuals [20].

In these individuals, standard vaccine doses, including COVID-19 vaccines, are unable to elicit an adequate titer of antibodies or T-cell responses upon vaccination, that can be increased by an additional dose [21]. These immunocompromised individuals include, but are not limited to, patients with solid organ transplants, treated neoplasms, patients in haemodialysis, advanced non-virologically suppressed HIV-infected individuals. Altogether, they represent around 0.5% of the population in Catalonia (approximately 40,000 individuals). In contrast, primovaccination with two vaccine doses seem to be enough for patients who have received stem cell transplants [22] or immunocompetent HIV-treated individuals [23].

- **Additional specific groups**

Other specific groups may require specific monitoring owing to their higher exposure to virus. In the particular case of health care workers, most recent data indicate a higher incidence of breakthrough infections six months after vaccination, concomitant with the emergence of delta variant and waning immunity [16]. However, the reported cases were mild and without secondary infections but with persistent symptoms in a non-negligible percentage (19%) of cases [24].

This situation is probably similar in our country. However, no definitive data on the follow-up studies that are being conducted in different hospitals in Catalonia is available yet. These data will be key to define the potential impact of breakthrough infections in our Health-Care System, both for the workforce and the patients.

The effectiveness of COVID-19 vaccines has been tested in pregnant women, with protection rates comparable to the general population [25]. Therefore, current data do not support changes in vaccine schedule in this population.

- **Vaccine types for booster doses**

The strategy of vaccination in Catalonia, and most European countries, has been different in terms of vaccine types and dose intervals across the age groups. However, immunocompromised, nursing home residents and health care workers were mostly vaccinated with mRNA-based vaccines. Individuals between 60 and 69 years received AstraZeneca/Oxford, and some individuals under 60 received a heterologous prime-boost regimen of AstraZeneca, and Pfizer/BioNTech. Furthermore, the Janssen monodose vaccine was also administered in specific populations although the number of people having received this vaccine in Catalonia is low (341,000 individuals).

With the current range of approved vaccines, the same mRNA-based vaccines should be preferred as booster dose in individuals previously vaccinated with mRNA vaccines, since current data show a safety profile comparable to the second dose [26]. Repeated boosting with Adenovirus-based vaccines can be more complex, and current data report a good safety and immunogenicity profile of heterologous combinations [27,28], suggesting that Pfizer/BioNTech would be the best option for individuals vaccinated with AstraZeneca or heterologous regimens. No data is available with Janssen vaccinees, although studies on booster doses for this vaccine are ongoing. Indeed, well designed clinical trials are urgently required to fill the general lack of information and expand clinical options for booster vaccination.

Finally, different scenarios for booster doses may open in the near future if vaccine prototypes based on new SARS-CoV-2 variants are approved. [Moderna](#) and [Pfizer/BioNTech](#) are testing variant-adapted mRNA vaccines in Phase I clinical trials. Other vaccine platforms based on recombinant proteins are also exploring the variant landscape, such as the HIPRA vaccine candidate based on the RBD from alpha and beta variants which has also started Phase I clinical trials. While these are probably the best options for booster doses, the calendar for their approval remains unclear.

## **Conclusions**

- From an immunological standpoint, all studies to date indicate that two doses of the mRNA or ChAd vaccines will induce long-lasting immunological memory and protection against severe COVID-19 among the general population.
- Breakthrough infections are more common with the Delta variant (due to its high infectiousness), but all data indicate that the great majority of these infections are asymptomatic or mild. All EMA-approved vaccines are highly effective in protecting against hospitalization, ICU admission and death by Delta or other variants of concern.
- From an epidemiological point of view, the lack of full efficacy against infection of current vaccines in the context of evolving viral variants implies that additional non-pharmacological measures are still required to control viral spread.
- The gradual loss of vaccine effectiveness against severe COVID-19 in frail and elderly individuals requires specific attention. A booster dose seems to be the easiest strategy to increase protection in nursing home residents and general elderly population with an age threshold to be defined.
- Certain immunocompromised patients need a specific vaccine dosage (including a three-dose schedule) to reach antibody titers comparable to those observed after two doses in the general population.
- Close monitoring will be needed in order to determine if, and when specific groups such as healthcare workers, would benefit from a booster dose.
- Current data point to mRNA-based vaccines as ideal candidates for additional doses, both in terms of safety and immunogenicity, regardless of the primovaccination regimen.
- The most effective strategy to deal with new viral variants is to nationally increase vaccine coverage instead of providing booster doses to the already vaccinated population.
- To reduce the emergence of new viral variants and vaccine access inequities, there is an urgent need to allocate existing vaccine doses to protect the most vulnerable in countries with low vaccine access as quickly as possible.
- At this timepoint, there is no clinical or epidemiological evidence supporting the need of a booster dose in the near future for the general population.

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### **Multidisciplinary Collaborative Group for the Scientific Monitoring of COVID-19 (GCMSC)**

The GCMSC is a group of experts from different disciplines and research backgrounds, whose specialities are relevant to the COVID-19 context. It was formed by the Barcelona Institute for Global Health (ISGlobal) and the Barcelona Medical Council (COMB) in collaboration with the Catalan Association of Research Centres (ACER)—three complementary institutions dedicated to health research and the translation of research findings to society as a whole.

The group, which came together for the first time in September 2020, aims to follow the scientific evidence regarding the pandemic in order to guide technical and political decisions in the COVID-19 response through reports that can be consulted by authorities, private entities and the society as a whole.

More information: <https://www.isglobal.org/en/gcmsc>