# Alternatives for vaccination of individuals under 60 years of age having received one dose of Astra-Zeneca vaccine (10/05/2021)

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

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## The current situation requires a rapid and scientifically sound response

There are ~2 million people in Spain under the age of 60 who received a first dose of Astra-Zeneca vaccine three months ago and who are, according to national health authorities' guidelines, no longer eligible for a second dose of Astra-Zeneca due to the risk of unusual blood clots with thrombocytopenia.

Different suboptimal alternatives have been discussed to fully vaccinate these individuals:

1. Administer a second dose of a different vaccine (mRNA). A hypothetically solid option that lacks safety, immunogenicity and efficacy data
2. Administer a second dose of the same vaccine (Astra-Zeneca). An option based on clinical data available, with a potential minimal risk of thrombotic events.
3. Wait until evidence for one of the previous options is generated. This option relies on a still unknown parameter: the durability of protective immune responses generated after a single dose.

## What is the evidence to support or discard these options?

### 1. The risk of giving a second dose of an mRNA vaccine

Although there is some preclinical evidence in mice, there is still very limited clinical data combining both vaccines in humans.

The UK has launched a trial in 820 individuals combining Astra-Zeneca and Pfizer vaccines with different intervals and should have results soon. A second study in UK is also ongoing (https://comcovstudy.org.uk/)

The Instituto de Salud Carlos III (ISCIII, Madrid Spain) has also started a trial to test the vaccination with Pfizer/BioNTech mRNA vaccine in 600 individuals vaccinated with Astra-Zeneca.

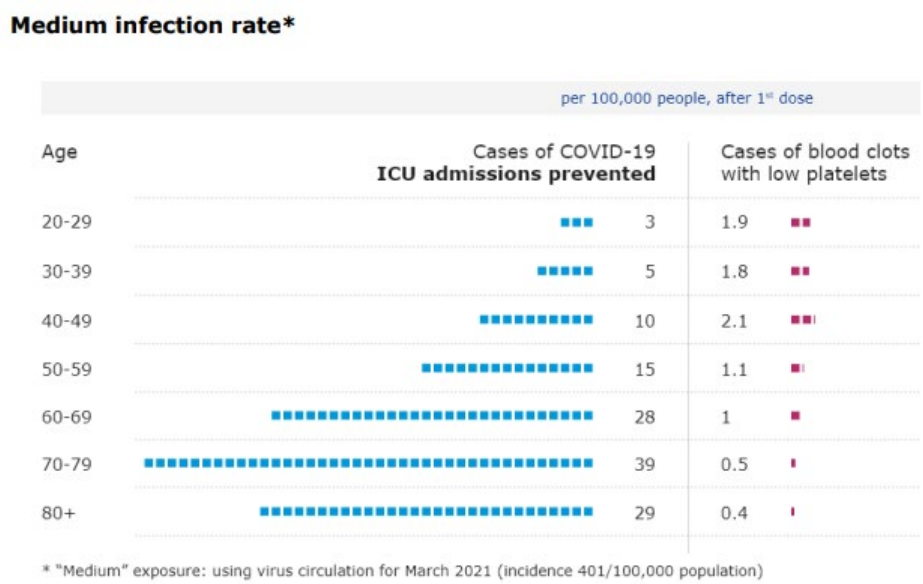
However, these studies are powered to determine immunogenicity of heterologous prime/boost COVID-19 vaccine schedules but not to provide sufficient information on the safety or efficacy of this strategy (due to the low number of recruited individuals). Moreover, in the case of the ISCIII study, the design lacks a control group vaccinated with a second dose of Astra-Zeneca to compare humoral and cellular immune response.

## 2. The risk of developing vaccine-induced immune thrombotic thrombocytopenia (VITT) vs the risk of severe COVID-19

For the Astra-Zeneca vaccine, the estimated risk of VITT is of 1 in 100,000, after the first dose, according to the EMA (1). After the second dose the risk seems to be 10 times lower (around 0.1 in 100,000, according to MHRA reports (2). About 1 in 5 cases proved fatal, but the condition can be treated if quickly identified.

Therefore, as both the WHO and the EMA have clearly stated, in a situation of ongoing viral transmission, the benefits of the vaccine largely outweigh the risks for all age groups as can be seen in the ICU admission prevention *vs.* VITT (Figure 1) as per the visual risk contextualisation published by EMA (3).

Figure 1. Benefit / risk visualization in a transmission setting similar to that currently observed in Spain. ICU admissions prevented and risk of VITT per age group.




*Has VITT been reported for other vaccines?*

VITT has also been reported after a single Ad26.COV2.S vaccination (Janssen). The estimated risk is around 0.2 in 100,000 according to recent CDC data (4).

The risk of VITT also exists with mRNA vaccines although it seems much lower (0.02 in 100,000 for Pfizer/BionTech and 0.04 in 100,000 for Moderna, according to data given by the EMA.[1]

### 3. The risk of leaving people with only one single dose beyond three months

Efficacy data from clinical trials (5) and effectiveness data from vaccination in UK show that one single dose of the Astra-Zeneca vaccine confers good protection against symptomatic disease (around 70%) and hospitalisation (around 80%) from 20 days onwards, after the first dose (6,7). However, antibody levels are not optimal after one dose of Astra Zeneca, and seem to be lower compared to Pfizer and Moderna's vaccines (8). This may leave people more susceptible to infections by new viral variants, as suggested by a study showing that people receiving one vaccine dose without prior infection showed reduced immunity against B1.1.7 (British) and B1.351 (South African) variants (9). Similarly, recent effectiveness data from Qatar show that, while two doses confer very good protection against both the B1.1.7 and B1.351 variants, one single dose confers much lower protection to the former and almost none to the latter (10). This is further supported by a modelling approach showing that a one-dose strategy may increase the potential for antigenic evolution if immune responses are suboptimal and the virus continues to circulate and replicate in some vaccinated people (11).

The impact on mortality and severe cases in the UK was the result of a combined effect of a high coverage of people receiving a first dose together with strict non pharmaceutical measures.

Importantly, there are no data on how long the protection lasts beyond 3 months after the first dose and there is no clinical trial where the interval between doses was spaced beyond the 12 weeks. Therefore, leaving people a longer time period without a vaccine boost could potentially expose them unnecessarily to infection, particularly in a situation where emerging variants are circulating and vaccines for a second dose are available.

[1] In this regard, The Joint Committee on Vaccination and Immunisation (JCVI) has issued advice to the UK government on the use of the coronavirus (COVID-19) Oxford/AstraZeneca vaccine for people aged under 40 (https://www.gov.uk/government/news/jcvi-advises-on-covid-19-vaccine-for-people-aged-under-40 ) maintains the recommendation that "Everybody who has already had a first dose of the Oxford/AstraZeneca vaccine should receive a second dose of the same jab, irrespective of age, except for the very small number of people who experienced blood clots from their first vaccination." Unrelated to the clear strategy to complete vaccination with second doses of Astra-Zeneca vaccines, and considering the above mentioned risk/benefit balance (Figure 1), the document opens the door to the possibility that adults aged 18 to 39 years are offered an alternative to the Oxford/AstraZeneca vaccine as the first dose of vaccine, if available and if it does not cause delays in having the vaccine.

## Recommendations

- A **second dose should be offered no later than 3 months after** the first dose
- The **administration of a second dose of Astra-Zeneca to individuals under age 60 who already received a first dose of Astra-Zeneca vaccine** should be considered, given the strong evidence for efficacy, and the very low risk of blood clots with thrombocytopenia.
- To date, **there is no safety/efficacy evidence for the administration of a second dose of mRNA vaccines** to Astra-Zeneca vaccinated individuals.

## References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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/gcmsc