

Extending the time between the two injections of the Covid-19 vaccine: what risks for what benefits?

Press release from the French National Academy of Medicine

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The recent marketing authorization (MA) for 2 messenger RNA vaccines against Covid19 (Comirnaty® from Pfizer / BioNTech and COVID-19 Vaccine Moderna®) and the hope of an upcoming validation of the AstraZeneca / Oxford vaccine have changed the strategy of the national vaccination campaign: in addition to the initial objective of reducing morbidity and mortality and preserving the health system [1], has been added, facing the threat of a new upsurge of the epidemic, a goal of obtaining a collective immunity sufficient to stop the spread of SARS-CoV-2 by vaccinating 17 to 27 million people by the summer. But the main factor limiting the achievement of “a” mass vaccination is the availability of sufficient vaccine stocks to achieve such vaccination coverage in less than 6 months. Following the WHO and the European Medicines Agency opinions accepting that the period of 21 days between the administration of the two doses of the Comirnaty® vaccine be delayed by a few weeks in order to increase the number of people who can benefit from a first dose, the National drug and health products safety agency (ANSM) declared itself in favor of extending this period to 42 days [2]. In response, the BioNTech laboratory recalls that the efficacy rate of the vaccine, 52% after the first dose, rises to 95% when the second dose has been administered at 21 days [3], but does not guarantee such a high efficiency rate if the second injection is postponed beyond that point.

Among the countries that have decided to postpone the administration of the second dose, the United Kingdom, facing a major resurgence of the epidemic linked to the spread of a highly transmissible variant, has chosen a 12 weeks period to be able to double the number of people first-vaccinated in the next three months. What are the potential risks induced by this time extension? The experience acquired in vaccinology shows that the late administration of a booster injection does not compromise its effectiveness since it is generally followed by a rapid re-rise in the antibody titer and a lasting strengthening of the protective immunity.

On the other hand, in the current context of a resurgent epidemic, it is the persistence of a low or even insufficient immunity rate during the additional weeks preceding the second injection that must be taken into account. The individual risk of aggravation by "facilitating antibodies" [4] should be considered when the infection occurs in a person with a low level of neutralizing antibodies, as the postponement of the second injection prolongs this state of increased receptivity. At the collective level, obtaining an expanded vaccination coverage, but weakened by a low level of immunity, will constitute a favorable ground for selecting the emergence of one or more variants escaping the immunity induced by the vaccination.

Given the potential benefits and risks associated with the off-label practice of postponing the second injection of the Covid-19 vaccines, **the National Academy of Medicine recommends:**

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- to comply as much as possible with the vaccine schedule prescribed by the manufacturer (21 days for Pfizer / BioNTech, 28 days for Moderna);
- to defer the injection of the second dose only if the circumstances require it (lack of available doses) and without exceeding 3 weeks;
- to restrict this extension of time to people under the age of 50 and not presenting any risk factor of a severe form of Covid-19;

- to prescribe reinforced barrier measures so that any vaccinated person avoids being infected before the administration of the second dose;
- to assess the impact of this extension on the increase in the number of people first-vaccinated each week.

[1] HAS (High health authority). Sars-Cov-2 vaccination strategy Preliminary recommendations on the strategy for prioritizing the populations to be vaccinated. November 27, 2020

[2] ANSM (National Agency for the Safety of Medicines and Health Products). Opinion concerning the second dose of the Comirnaty Pfizer BioNtech vaccine, January 7, 2021

[3] Polack FP et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med, 2020; 383 (27): 2603-15.

[4] Lee WS et al. Antibody-dependent enhancement and SARS-CoV-2 vaccines and therapies. Nat Microbiol. 2020; 5 (10): 1185-91.