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The Third Dose of the SARS-CoV-2 Vaccine: Why and for Whom?

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Abstract

The authors of this brief commentary give an update on the results of the last studies on the antibody response to the so-called "booster" administration of the Severe Acute Respiratory Syndrome (SARS)-CoronaVirus (CoV)-2 vaccines, with particular reference to the new "omicron" variant. A brief overview of the immunological response to this infection is also provided, with the advise that a serological test before the third dose of the vaccine is not recommended, as stated by the Food and Drug Administration (FDA).

Keywords: SARS-CoV-2; CoVID-19; Vaccine.

It seems that there is no way out of this CoronaVirus (CoV) epidemic. There are nations like Austria that has decided to confine the unvaccinated, so that they cannot block the economy, and vaccinations have restarted with many adhesions [1]. In Italy, infections are 10 thousand, and in Germany 52 thousand cases and 300 deaths. Fortunately, the victims are much less thanks to vaccines than seven months ago [2].

But are these vaccines effective? The protection offered by anti-Severe Acute Respiratory Syndrome (SARS)-CoV-2 vaccines decreases over time. We are told by the data coming from countries that started to administer them before us, such as Israel, where the third booster dose has been shown to restore a very high protection against the virus, decreasing the risk of hospitalization by 93%, the risk to develop a severe form of the disease by 92%, and to die by 89%, compared to those who have completed the first vaccination course five months or more before. This fits to some other data showing a correlation between antibodies and neutralizing antibody titers and protection from infection. This also confirms that antibody titers are higher after vaccination than after natural infection [3].

The antibody level can only be used to say whether someone is at risk for an infection, but there is no guarantee. Problem is lack of standardization and rapid drop of titers. The only way to get at least a little protection against the new variants such as omicron is the booster (or, next year, the updated vaccine) [4]. However, it is not certain that the booster is necessary for

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everyone: the dangers, we have learned, are very different based on age, state of health, and the working activity. For this reason, it has currently been decided to reserve the booster dose for the over 60s, patients at risk, and medical staff, pending more precise data on its usefulness for the rest of the population. In such a situation, there are those who ask to use an objective test, such as the dosage of antibodies, to evaluate more precisely who needs the booster, and those who can do without it: if the antibodies have decreased – this is the thought – the vaccine can be used again to restore the disappearing protection; if they are still tall, it is better to avoid the administration. A reasoning that may seem logical, but which is actually unfounded on a scientific level. The American Food and Drug Administration (FDA) explained this precisely in a note last May, in which it reminded the United States of America (US) population that the use of serological tests is not recommended to evaluate the efficacy of vaccination in individual patients [5]. The tests currently available, in fact, have not been studied to verify individual protection against SARS-CoV-2: a serological test can tell us if we have come into contact with the virus (or if we have carried out a vaccination) in the previous months, consequently developing antibodies capable of neutralizing it, but nothing more. It does not therefore tell us whether the levels of antibodies present in our body are sufficient to prevent infection, or the development of the disease in a severe form. And making decisions based on scientifically inconclusive data can have serious consequences, for example by prompting a person in whom the vaccine does not give the desired results to let their guard down, or by causing unwarranted concern in people who have low levels of antibodies, but are perfectly safe from CoV disease 2019 (CoVID-19).

The reason for this diagnostic ineffectiveness has several explanations. The first, as we have said, is that the tests on the market have not been designed for this use. On average, they have an excellent ability to identify antibodies produced following an infection. But as the FDA itself recalls, not all kits on the market recognize with the same effectiveness even those produced following vaccination, and therefore it may happen that a person perfectly immunized by the vaccine results negative to a serological test. The second problem is related to the fact that the protection provided by antibodies, called humoral immunity, is not so simple to assess. It has been shown, for example, that the amount of neutralizing antibodies (i.e., those actually able to bind to the spike protein of the virus and prevent it from replicating) is related to protection against infection. This, however, in a very general sense, because no one has yet identified a precise threshold at which the level of antibodies present in the body becomes sufficient to prevent infection, or the development of a severe form of CoVID-19. For this reason, the antibody dosage is used in some clinical studies as an indicator of vaccination efficacy, but with the awareness that it is an indirect relationship: a clue, but certainly not a proof. In fact, the immune system is not reduced to just the antibodies present in the blood at a given moment. For example, there is a type of B-lymphocytes called long-lasting plasma cells, which once a virus is identified during an infection, or following vaccination, settle in the bone marrow, surviving for years, ready to produce again the antibodies that have proved useful earlier, in case of new invasions. After months of recovery or vaccination, the levels of antibodies present in the blood can therefore also drop, but in the right conditions the body can still be ready to replenish them when needed. Similarly, there are other immune cells called T-lymphocytes, which have the task of recognizing cells infected by a virus, to destroy them and prevent it from spreading throughout the body. This type of immunity, defined as cell-mediated, is particularly important against CoV, such as SARS-CoV-2. And again, its effectiveness cannot be deduced from the result of a serological test, because it is not linked to the presence of specific antibodies [6].

For all these reasons, it is currently impossible to establish with a test how much an individual is actually protected against CoVID-19. And the only viable alternative for administering the third booster dose of the vaccine is the one chosen by the health authorities of our country:

proceed to groups of the population, starting with those who present a greater danger of contracting the disease in a severe form, or of becoming a vector of contagion for other patients at risk. If the situation in the coming months makes it necessary, the audience will gradually expand, as happened for the first cycle of the vaccine. And in due course, we will all be able to undergo the third recall, without fear: the experts agree that the vaccine is absolutely safe, even for those who already have high levels of antibodies in their bodies.

According to the rate of neutralizing antibodies, it takes a third dose to fight against omicron. Omicron, first detected in South Africa in November 2021, is now dominant in Europe. This "variant of concern" of SARS-CoV-2 presents 32 mutations, insertions or deletions of the Spike protein, including the N501Y mutation associated with the increase in the transmissibility of the alpha, beta, and gamma variants (for comparison, the delta variant had only two mutations) [7]. However, it is not yet known to what extent its very rapid spread was favored by the increase in the transmissibility of the virus or by an escape from the immunity induced by a previous infection or vaccination. To find out, a London team measured the titers of neutralizing antibodies against the omicron variant in blood samples from 364 participants in the Legacy study. This study, conducted on healthy volunteers, was set up in January 2021 to monitor serological responses to vaccination or following a positive test for CoVID-19. Antibody levels against omicron were compared to those measured against alpha and delta variants, for which vaccine efficacy had been shown to be closely correlated with neutralizing antibody levels. Three times less neutralizing antibodies against omicron than against delta two to six weeks after two doses of the Pfizer-BioNtech vaccine, neutralizing antibodies against omicron are detectable in 83% of participants, but at a median concentration seven times lower than that found against the alpha variant and three times lower than that against the delta variant. Twelve to 16 weeks after the second dose of vaccine, neutralizing antibodies against omicron are only detectable in one to two individuals, while almost all still have neutralizing antibodies against alpha (96%) and delta (97%). The same assays were done on participants vaccinated with the Astra-Zeneca vaccine. They show that two to six weeks after the second dose, only 36% of people have quantifiable antibodies against omicron, and there are only 19% at 12-16 weeks. In comparison, two to six weeks after vaccination, the majority have quantifiable neutralizing antibodies against the alpha variant (87%) and against the delta variant (76%). The data also show that, among people who received the Astra-Zeneca vaccine, the presence of neutralizing antibodies strongly depends on whether or not they report a history of symptoms of CoVID-19: the absence of neutralizer antibodies is more common when there have been no symptoms of CoVID-19. This association is also found, but more rarely, with the Pfizer-BioNtech vaccine. It rises in the rate with the third dose but it remains lower against omicron [8]. In September 2021, the injection of a third dose was decided in the United Kingdom (UK), for certain priority groups. The study was therefore continued in a certain number of participants, with a determination of neutralizing antibodies at the time of the injection of the third dose and about 20 days later. All participants in this section were vaccinated with Pfizer-BioNtech, for the three doses. While only 42% of participants still had detectable neutralizing antibodies at the time of their third injection, the percentage rose to 96% three weeks later. But their level of neutralizing antibodies against omicron is three times lower than that of antibodies against the alpha variant and two times lower than the level of antibodies against the delta variant. It should be added that, in the process, in vitro tests were carried out on the monoclonal antibody treatments available in the UK, sotrovimab and the combination casirivimab and imdevimab. Only the first succeeds in proving its effectiveness. Note that sotrovimab is six to eight times less effective on omicron than on delta or alpha, but the concentrations used in these in vitro tests are much lower than those measured 29 days after an infusion of 500 mg of sotrovimab. This study confirms the interest of the third dose of vaccine to fight against the omicron variant. It also shows the importance of continuing the titration of

neutralizing antibodies, over time and on different cohorts. These data constitute an important source of information for the development of vaccine strategies [9-11].

Authors and contributors

The authors contributed equally to the manuscript.

Competing Interests

The authors state that any financial and personal relationships with other people or organizations, even if it does not directly relate to the submitted manuscript, exist.

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