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Additional Doses of Vaccines against COVID-19 - Attempting to Enhance the Immune Response

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Introduction

Vaccination against COVID-19 with a complete primary series is essential. To date, COVID-19 vaccines have demonstrated high vaccine effectiveness against severe disease, hospitalization and death from COVID-19 in the majority of the properly vaccinated population. No vaccine including the COVID-19 vaccines is 100% effective so some breakthrough infections are possible. Moreover, evidence has been emerging of a "weakening" of immunity after passing the infection as well as a decrease in the effectiveness of the vaccines that have been administered against this infection. For this reason, according to many opinions, it will be necessary to reinforce the immune system through additional doses of the available vaccines. The general purpose of these doses is to restore the protection that has declined over time to an insufficient level in persons who initially responded adequately or less than expected, after a complete series of primary vaccination. Currently, there is some scientific debate regarding whether an additional dose of COVID-19 vaccines really constitutes a suitable booster, especially in the non-elderly population without other underlying risk factors or associated pathologies. It is important to assess the existing scientific contribution to the best way to manage these vaccines and to examine the key differences between primary immunizations able to generate a robust immune memory, versus a booster that potentiates the memory response when the initial protection has really declined.

With this decision made and although it may seem the same thing, it could be necessary to distinguish between the administration of a booster dose for persons with a normal immune system in whom the benefits are more difficult to appreciate, and an extra dose for persons with weakened immune systems or carriers of underlying pathologies in whom such doses will be very important.

Thus, could vaccines provide a true "sterilizing immunity" and primary immunization be sufficient in people without risk factors?

Antibody-dependent enhancement phenomenon

The long-term impact of additional doses on reducing infection, hospital admissions, and disease transmission is not yet clear. Although plasma antibody levels will increase and it is assumed that they may temporarily extend the protection, the magnitude to which they increase T-cell and B-cell memory responses is not yet confirmed. There is optimism that they will achieve long-term protection against severe disease for the majority of the immune competent population. The prediction and demonstration that antibody levels can be increased in the general population should not be interpreted as proof of long-term effectiveness, and conclusive clinical results are needed to justify the indication for these additional doses. A careful and public analysis of the course of the results obtained would appear to be opportune to ensure that decisions on extra or booster doses are based more on reliable scientific data than on political or social motives.

One aspect to keep in mind is the claim that the priority should be the primary vaccination of the greatest possible number of non-immune people before even considering extra or booster vaccines in immune competent persons, and in all countries, especially in those with more limited resources. WHO reminds this in an appeal for global vaccine equity: "The main objective is to increase imperatively the global vaccination coverage with the primary series". Furthermore, and quite relevant, the occurrence of new and frequent infections in countries with low vaccine compliance, due to vaccine shortage (or refusal), represents a risk that higher virus replications may result in mutations and the potential emergence of resistant VOC. The survival of the virus is conditioned to the availability of a sufficient number of persons susceptible to being infected in order to replicate easily. National action is not enough; it must be global because countries that do not control the virus efficiently represent a threat to others. At the time of writing, about 52% of the world population and only 4.2% of people in poor countries have received at least 1 dose of any COVID-19 vaccine.

The role of antibody-dependent enhancement phenomenon. Not all antibody responses are similar. In some viral infections, the antibodies generated in a previous infection or after vaccination can potentiate the recent secondary infection by facilitating the entry and replication of the virus (or its strains and variants) into the cells. This process is known as antibody-dependent enhancement of infection (ADE). These are pre-existing non-neutralizing or sub neutralizing antibodies, especially IgG, which recognize the antigen. In short, the pre-existing antibodies become allied with the newly arrived virus, facilitating infection and potentially worsening the disease. This phenomenon has been described in infections by other viruses, such as Zika and Dengue virus and rarely after early versions of the measles vaccine. It was speculated that a vaccine administered to persons never exposed to the virus could mimic the first infection with the production of antibodies causing that a true exposure to the natural infection of the virus would imply a more severe infectious process due to a hypothetical ADE phenomenon. With regard to SARS-CoV-2 infection, the virus would be able to open another lock on target cells, and also modify the transmission signal. This virus access is independent of the conventional entry pathway via the spike protein and ACE2 receptors. Results of an in vitro study show that a specific type of antibodies generated by SARS-CoV-2 infection can cause an ADE-induced infection and that these antibodies persist for at least six months after infection. It has been suggested that one explanation for the emergence of the SARS-CoV-2-associated multi systemic inflammatory syndrome in children even presenting a good antibody response of SARS-CoV-2 antibodies, maybe due to the ADE phenomenon. These are non-neutralizing nonspecific anti-protein S antibodies with a different activity profile. There is currently no definitive clinical evidence that COVID-19 and its specific vaccines cause the ADE

phenomenon. The existing data are derived basically from theoretical concepts or hypotheses or from in vitro studies.