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Editorial

Impact of spike genetic variants in vaccines against SARS-CoV-2☆

Impacto de las variantes genéticas de la espícula en las vacunas frente al SARS-CoV-2

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The natural process of evolution and mutation of SARS-CoV-2, in its aim to adapt to the human species, has established the appearance of multiple genetic variants (antigenic drift). Most of them pose no important changes in the biological properties of the virus. However, some involve a significant increase in their spread and ineffectiveness and, to a lesser degree, in mortality (*variants of concern* [VOC]). The onset of massive populational immunization has escalated the concern surrounding the possible impact of these variants on the efficacy of the various of the different vaccines.[1,2] Given that most of these variants exhibit highly specific mutations that affect the amino acids at the binding site of the virus (*receptor-binding domain* [RBD]) and that, in general, the vaccines induce a broad response on all the S protein epitopes, one might initially think that their impact would not be particularly significant.

In addition to this natural evolution of the SARS-CoV-2, the beginning of massive vaccination programs will determine an increase of the selective pressure by the neutralizing antibodies of the people that could facilitate the emergence of escape mutants. These mutants are produced when the antibodies of a vaccinated person limit, but do not eliminate, the viral replication. Although these people do not develop the disease, the infection they suffer enables those viral populations that are not eliminated to be selected by the humoral immune system, such that they become dominant and spread to other people, thereby escaping the immune response to the vaccine.[3] These escape mutants will join the natural mutants that result from the viral evolution and will determine a change in the transmissible viral populations, which could make regular changes in the SARS-CoV-2 vaccine composition necessary, as we see with the flu.[4]

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The first VOC reported was the British one (VOC202012/01, N501Y.V1) that belongs to the B.1.1.7 line and exhibits the N501Y mutation on the RBD. It was described for the first time in September 2020 in the south of the United Kingdom where, within a few weeks, it displaced the strains that had been circulating prior to then, becoming the predominant line across the globe in a short time. The location of the N501Y mutation does not appear to affect the efficacy of the neutralizing antibodies targeting the RBD.[5] Thus, the 2 mRNA vaccines (mRNA-1273; Moderna and BNT162b2; Pfizer) appear to be capable of neutralizing and protecting from this type of variant, with only slightly lower efficacy rates and with adequate populational effectiveness.[4–7] Furthermore, compared to the flu, titer decreases of less than 20% do not appear to signify a significant loss of their populational efficacy.[1] The viral vector-based vaccine ChAdOx1 (AstraZeneca) appears that it would also maintain its effectiveness against this variant, although in one study, a 74% efficacy rate is observed against this variant *versus* 84% against conventional strains.[7] Because they were the first, the 3 previously[-mentioned] vaccines have been developed from the original Wuhan-Hu-1 strain and its genetic sequence, that does not include this variant.[2,6] For its part, the protein subunit vaccine NVX-CoV2373 (Novavax) has demonstrated 86% efficacy against this variant compared to 89% of the conventional strains.[5,6]

The variant South African VOC (N501Y.V2) belongs to the B.1.351 line and is currently the leading cause of the greatest outbreak to occur in this country, where it was first reported in October 2020.[8] There is reasoned concern regarding this variant, inasmuch as it displays important changes in the area of the RBD (mutation of escape E484K, N501Y, and K417N), in addition to modifications that affect the N-terminal domain of this [variant] (another target of the neutralizing antibodies).[6,8] The of mRNA vaccines reveal a significant reduction in their efficacy and neutralizing capacity *in vitro* against the SARS-CoV-2 pseudovirus with these mutations.[1–5] Therefore, the mRNA-1273 and BNT162b2 vaccines display a 6-fold efficacy rate against the strains of this variant,[8,9] although the clinical relevance of this decrease should be prospectively assessed, given that the intense immune response they induce determines a «reserve capacity» that would not overly affect the infection.[2,10] The ChAdOx1 vaccine has proven scant efficacy, close to 10%–25%, against this variant and approximately 9 times lower titers, so that some countries, like South Africa, have announced that they will stop using it.[8] In one study, this vaccine has been seen to be less efficacious against mild or moderate disease; however, it is unknown what it means in severe disease caused by this variant.[5,6] For its part, the viral vector-based vaccine Ad26.COV2.S (Janssen) has demonstrated an efficacy rate of only 57% to protect against moderate/ severe disease compared to 66%–72% in countries in which this variant is not circulating; although it maintains 85% efficacy severe disease.[3–5] Likewise, the NVX-CoV2373 vaccine has been reported to be less than 50% efficacious against this South African variant compared to 89% against conventional strains.[5,6] The studies conducted by Wang et al.[11] with sera from infected and vaccinated patients indicate that there is a 10- to 13-fold decrease in the concentration of neutralizing antibodies against this variant.

In December 2020, a new VOC was reported for the first time in Japan that was related to several cases from Brazil. Similarly, Brazil also subsequently reported a high circulation of this variant in the region of Manaos (some 40% of the strains sequenced).[12] This Brazilian variant (P.1, N501Y.V3) that also contains the E484K mutation, amongst others, appears to be associated with reinfection and, while there are still no definitive data with respect to the efficacy of the current vaccines, one study in Manaos points toward there being a 25%–61% decrease.[2,3] The study carried out by Wang et al.[13] among people inoculated with the of mRNA vaccines has shown a significant decrease in the titer of neutralizing antibodies (by a factor of between 2.2 and 2.8) against this variant, although the elevated titer obtained appears to counteract this effect on the virus, not displaying the same impact as against the South African variant.

At the beginning of February 2021, a new variant was reported in the city of Los Angeles (California) (CAL.20C, B.1.427/B.1.429) that encompasses the B.1.427 and B.1.429 lines. The L452Y mutation, in the area of the RBD, is very similar to the N501Y, such that its effect on the vaccines would be minimal and similar to the British mutation, although there are no conclusive published data.[3,14]

All of these data regarding variants and vaccine efficacy must be interpreted cautiously, insofar as they have largely been obtained from small studies or from *in vitro* analyses of the post-vaccination antibodies against the pseudovirions, chimeric viruses, or recombinant clones, with the antigenic mutations introduced.[15] Moreover, the immune response to the vaccines is a broad spectrum response and not only are specific antibodies induced, but instead, an intense specific cell response (helper T cells and cytotoxic, or killer, T cells) that can, overall, make up for the decrease of the whole of neutralizing antibodies.[4] In convalescents, cell immunity is not only restricted to the S protein epitopes, but acts against other antigenic areas, such as the nucleocapsid. That is why this cell immunity must be considered to remain functional against the news variants.[16] T cells do not come from the infection, but they do prevent the infection of other neighboring cells. In SARS-CoV-2 infection, killer T cells establish the difference between mild/ moderate infection and severe infection requiring hospitalization.[16] Mention must also be made of a study that seems to indicate that the second dose of an mRNA vaccine or of the first dose in an already infected individual would determine an immune response of great magnitude (>1000 greater than the pre-existing one) which would imply a reserve capacity that could easily offset the decreased protective efficacy of the antibodies induced by these vaccines.[17]

What strategies could minimize the impact of these variants on the vaccines? The 2 mRNA vaccines and the virus vector-based vaccine ChAdOx1 require two doses to reach maximum efficacy. Despite being able to detect the presence of neutralizing antibodies after the first dose, the titers increase significantly after the second dose. Consequently, these vaccines are less effective during the interval between doses. Thus, in people infected during this period, SARS-CoV-2 could be capable of replicating, since [these people] are in a suboptimal situation of protection, which would facilitate the selection of variants escaping the vaccine. That is why it would be paramount to avoid unnecessarily and excessively prolong-

ing the interval between doses,[18] to use vaccines that induce a high rate of antibodies already after the first dose (the higher the baseline titer, the greater the neutralizing capacity), and to confirm that this escape process is not occurring in those that only require a single dose, such as the virus vector-based vaccine Ad26.COV2.S.[18] In addition, it is necessary to establish new correlates of protection against these variants in each of the different vaccines, so that their choice is determined by the circulation of these variants in each territory or country.[5,6]

Another possibility would be to update and reformulate the composition of existing vaccines, using the strains with most of the variants that lower their efficacy. The pharmaceutical companies have indicated that they are elaborating second generation mRNA vaccines and virus vector-based vaccines with a view to the worldwide spread of these variants. Nonetheless, if it is necessary to revaccinate people in the future with updates vaccines, we should examine the possible implication of the «original antigenic sin», previously reported as it relates to the flu, and that determines that in a new vaccination with antigenically different strains, the immune system primarily responds with the antibodies already present and, to a lesser degree, with the new antibodies induced by the new vaccine, decreasing the efficacy of this second, different vaccine.[3] A third booster dose could also be introduced to fight against these variants or vaccines could be redesigned to attain a stronger cellular.[2,3,19,20]

In addition to tall this, it is critical that all the strains identified in patients with partial or total vaccination be sequenced and molecular epidemiological surveillance systems must be enhanced to monitor the circulation of these or possible new genetic variants that will most certainly arise from the biological evolution of SARS-CoV-2.

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