Hot News

New SARS-CoV-2 Variants Challenge Vaccines Protection

By the end of February 2021, roughly 115 million people worldwide had been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and more than 2.5 million had died. Uneasily, the coronavirus disease 2019 (COVID-19) pandemic is increasingly resembling the tragic 1918 influenza pandemic that killed more than 50 million people a century ago.

In an unprecedented race, COVID-19 vaccines have been developed and began to be distributed by Christmas 2020, rising the expectations for achieving herd immunity within a couple of months. Despite large numbers of hospitalizations and deaths, immunity as a result of natural infections had only been reached by 20-25% of the population by the end of 2020, even in hotspot places such as Madrid or New York (Soriano et al. *Int J Infect Dis* 2021; Sanchez-Romero et al. *PLoS One* 2021).

The recognition that inhalation of large viral inoculum accounts for increased infection risk and more severe COVID-19 (Guallar et al. *Int J Infect Dis* 2020) has strongly supported social distancing as the most effective intervention for halting SARS-CoV-2 transmissions. While wearing face masks are protective, prolonged indoor gatherings with poor ventilation are risky. Of course, inadvertent household transmission is frequent, especially during the incubation period or from asymptomatic carriers (Thompson et al. *Clin Infect Dis* 2021). On the other hand, contacts with surfaces are no longer considered a significant source of contagion (Lewis D. *Nature* 2021).

Global dispersal and increasing frequency of the SARS-CoV-2 spike protein variant D614G during the fall of 2020 was suggestive of a selective advantage, mainly, in terms of increased transmissibility (Volz et al. *Cell* 2021). More recently, the recognition of N501Y mutants associated with superspreading events and outbreaks mostly reflect increased transmissibility. Interestingly, this variant was originally recognized among infected minks in Denmark, although emergence in other places suggest that it could arise independently from those animals (Fig. 1).

More worrisome has been the recent recognition in South Africa and the Brazilian Amazon of new variants harboring a E484K spike mutant that reduces the activity of neutralizing antibodies, accounting for more reinfections and that might render vaccines less effective. These variants have already spread elsewhere, despite the implementation of travel restrictions for people coming from those regions.

The current scenario is that the coronavirus is actively propagating elsewhere while facing significant immune pressure from vaccines and naturally infected and recovered people. This is the perfect storm for allowing the emergence of immune escape mutants, initially with partial resistance but with potential for greater resistance if coronavirus variants evolve further. Thus, it seems crucial to accelerate the vaccination process to reach as soon as possible a threshold of susceptible individuals that would really impact on viral transmissions. Massive vaccination campaigns should be prioritized elsewhere.

For other RNA viruses that cause global pandemics, such as HIV or hepatitis C, we do not have vaccines but we have been successful using antivirals. In the absence of HIV eradication, antiretroviral treatment as prevention of carriers has represented a powerful tool to avert new infections (Rodger et al. *JAMA* 2016). Furthermore, the use of antiretrovirals by HIV uninfected people at risk as pre-exposure prophylaxis has drastically reduced contagions in certain risk populations (Benitez-Gutierrez et al. *Expert Rev Clin Pharmacol*. 2018; 11: 507-17). Based on these lessons, the development of antivirals against SARS-CoV-2 must be considered as a priority and complementary to vaccines. In this regard, pioneer studies using experimental molecules such as plitidepsin (Aplidin) must be encouraged (White et al. *Science*. 2021; 371: 926-31).

Direct antivirals against SARS-CoV-2 might be beneficial in two scenarios. First, during the earlier stages of the disease, when the virus replicates at high titers in the respiratory tract and immune responses are still being mounted. Blocking viral replication will soften the triggering of the cytokine storm that typically worsens the second phase of the disease (Griffin et al. *AIDS Rev* 2021).

Figure 1. Emergence of new SARS-CoV-2 variants.

A second indication for antivirals against SARS-CoV-2 could be as prophylaxis. Imagine that we can access formulations that could be administered intranasally and act locally, preventing from acquiring new infections. A similar strategy has proven to be very successful using long-acting antiretrovirals to prevent HIV infection and is being investigated using further long-extended release nanoformulations (Kulkarni et al. *Nat Mater.* 2020; 19: 910-20). This use of long-acting antivirals as “chemovaccines” (Soriano et al. *Nat Mater.* 2020; 2020; 19: 826-7) could be appealing for certain individuals at risk for developing severe COVID-19

– even as result of reinfections – including the elderly and obese; or health professionals directly caring for COVID-19 patients.

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Received in original form: 22-02-2021

Accepted in final form: 01-03-2021

DOI: 10.24875/AIDSRev.M21000040