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COMMENTARY

The Time for COVID-19 Vaccination

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ABSTRACT Studying the composition and dynamics of viral mutant spectra in infected individuals shows us that to avoid selection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) escape mutants, vaccination campaigns for coronavirus disease 2019 (COVID-19) should be launched when disease incidence is low.

KEYWORDS SARS-CoV-2, escape mutants, vaccination campaign

The protective efficacy of a coronavirus disease 2019 (COVID-19) vaccine will be influenced by the ability of the circulating virus to overcome the immune response evoked. This requirement depends on the amount of virus confronted by the vaccinated population when the latter is in the process of mounting a protective response. The rapid rate of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) evolution (averaging 1×10^{-3} mutations introduced per genomic residue and year), together with the genetic heterogeneity of the virus inside each infected individual (1), provides fertile terrain for selection of vaccine escape mutants or vaccination-driven virus evolution (2). The problem is not a mere theoretical conjecture given the occurrence in the SARS-CoV-2 genome not only of point mutations but also of insertions-deletions (indels, gains and losses of pieces of genetic material) in the region encoding the spike (S) protein (several data bases) whose expression is relied upon for evoking the immune response. S alterations may abolish antigenic determinants and promote selection of antibody escape virus mutants (3). The variability of RNA viruses is due to the limited fidelity of their replicases and the absence of error-correcting activities. However, coronaviruses include in their replication complex a 3′–5′ exonuclease domain that may decrease about 15-fold their mutation rate. In the case of SARS-CoV-2, it is not clear if the fidelity of the core polymerase is comparable to that of other RNA viruses, if the 3′–5′ exonuclease lowers the mutation rate and to what extent, and if the copying fidelity is influenced by other subunits of the replication complex (4, 5). Whatever the mechanism, the capacity of SARS-CoV-2 to generate variant genomes seems remarkable.

Viral dynamics implies that the probability of any potential escape mutant being present is higher the higher the number of circulating viral populations. That is, even if mutation frequency is independent of the population size (intrinsic property), the probability of an individual mutation or indel to be found is proportional to the total size of circulating virus (extrinsic property) (6). This concept validates at the public health level the classic Phil Anderson dictum "more is different" (7) regarding the significance of cumulative viral population size in the supply of individual mutant types. Therefore, despite understandable current urgencies, it would be highly advisable to consider the epidemiological context at the time of initiation of a vaccination campaign. Specifically, for countries where vaccination plans are still pending, vaccination campaigns should be implemented when COVID-19 is at an incidence valley.

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