



Antigenic evolution will lead to new SARS-CoV-2 variants with unpredictable severity

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The comparatively milder infections with the Omicron variant and higher levels of population immunity have raised hopes for a weakening of the pandemic. We argue that the lower severity of Omicron is a coincidence and that ongoing rapid antigenic evolution is likely to produce new variants that may escape immunity and be more severe.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is set for continuous circulation in humans owing to its ease of transmission, waning immunity, antigenic evolution and an array of potential animal reservoirs¹. A key question is predicting the epidemiological and clinical parameters of this continuous circulation² and the future population burden of coronavirus disease 2019 (COVID-19).

The comparatively milder levels of disease produced by Omicron, the most recent variant of concern (VOC), in relation to previous VOCs rekindled a variety of wishful narratives about the epidemiology and evolution of the virus. These ideas range from misconceived and premature theories about 'harmless' endemicity³, to expectations that widespread immunity renders epidemic waves safe and to hopes that the virus will evolve to be benign.

The notion that viruses will evolve to be less virulent to spare their hosts is one of the most persistent myths surrounding pathogen evolution. Unlike viral immune escape and transmissibility, which are under strong evolutionary pressure, virulence is typically a by-product, fashioned by complex interactions between factors in both the host and the pathogen. Viruses evolve to maximize their transmissibility and sometimes this may correlate with higher virulence, for example, if high viral loads promote transmission but also increase severity. If so, pathogens may evolve towards higher virulence. If severity manifests late in infection, only after the typical transmission window, as in SARS-CoV-2, but also influenza virus, HIV, hepatitis C virus and many others, it plays a limited role in viral fitness and may not be selected against. Forecasting virulence evolution is a complex task, and the lower severity of Omicron is hardly a good predictor for future variants. The prospect of future VOCs featuring the potentially disastrous combination of the ability to reinfect due to immune escape along with high virulence is unfortunately very real.

Another common belief banks on widespread vaccine or infection-induced immunity to guarantee mild SARS-CoV-2 infections in the future. This idea, however, ignores a central feature of SARS-CoV-2 biology — antigenic evolution, that is, an ongoing modification of the viral antigenic profile in response to host immune pressures. High rates of antigenic evolution can result in immune escape, that is, reduced capacity of the immune system to prevent reinfection and potentially severe disease thereupon. On a population level, antigenic evolution and escape can increase burden through increasing the rates of reinfections and rates of severe illness (FIG. 1).

Omicron demonstrated clearly that SARS-CoV-2 is capable of considerable antigenic escape over a relatively short period of time. The variant features at least 50 amino acid mutations compared with the ancestral Wuhan-Hu-1 reference strain⁴ and is highly antigenically divergent from earlier VOCs⁵. Its explosive spread in highly immune populations revealed that these mutations enable the variant to easily infect individuals with immunity due to previous infection or vaccination. Genetic divergence is considerable amongst sub-lineages of omicron, and the functional importance of this divergence is being illustrated by the proportional increase of the BA.2 lineage.

In September 2020, after an initial period of relative evolutionary stability, SARS-CoV-2 variants with considerable antigenic divergence from the ancestral virus started to emerge⁶. At least three earlier VOCs, Beta, Gamma and Delta, featured immune escape mutations⁷, and nothing currently suggests that antigenic evolution will slow down in the future. On the contrary, VOCs are just the tip of the 'evolutionary iceberg'. Hundreds of SARS-CoV-2 lineages continuously diverge from each other over time and evolutionary theory predicts increasing chances of immune escape variants in the future.

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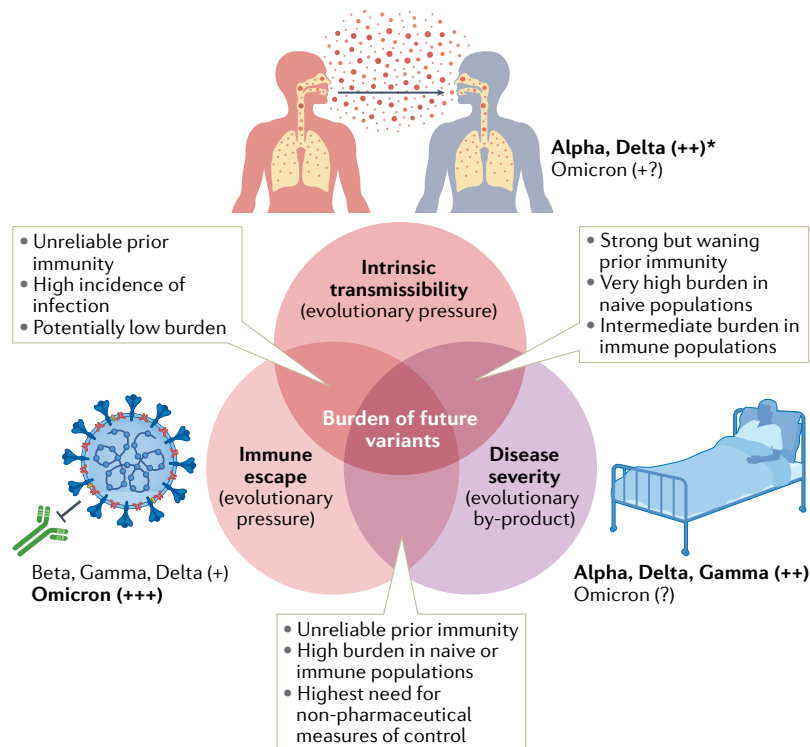


Fig. 1 | **Effects of the interactions between transmissibility, disease severity and immune escape of variants of concern on SARS-CoV-2 population burden.** SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. *All comparisons are with the Wuhan-Hu-1 lineage.

The adaptive fitness of a virus is suitably quantified by its effective reproduction number (R_t). R_t is the total number of secondary infections that an infectious case generates in the population⁸. So, the fittest virus is the one that transmits to the highest number of hosts. In a naive population with everyone susceptible, a virus can best achieve this by becoming more infectious. Early VOCs evolved in this way; Alpha, then Delta were each approximately 50% more infectious than their predecessor, each rapidly displacing it on their way to dominance in the population⁹. In highly immune populations, however, a mere increment in intrinsic infectiousness will contribute relatively little to transmissibility, because the obstacle in this situation is host resistance to infection. Accordingly, as human populations transition to high levels of immunity, SARS-CoV-2 is predicted to increasingly optimize its transmissibility (R_t) through honing its ability to re-infect immune individuals, and less through being highly infectious. Thus, the growing levels of immunity are likely to accelerate the rates of antigenic evolution, raising both the risk of reinfection and potentially the prospect of higher disease severity of reinfections. The rapid spread of Omicron was facilitated by its extraordinary ability to re-infect immune individuals, exemplifying this evolutionary strategy¹⁰.

Omicron is the first VOC that is less virulent than other circulating strains and this has been enthusiastically interpreted to be a sign of the approaching end

of the pandemic. Yet the lower severity of Omicron is nothing but a lucky coincidence — compared with previous VOCs, the majority of which featured increased virulence, Omicron appears like the exception. Immune escape needs to hit constantly changing targets. Once Omicron infects the majority of individuals, the next variant will need to be as antigenically different from Omicron and previous VOCs as possible to overcome immunity against them. None of the VOCs that previously rose to dominance originated from the prevailing lineage at the time, which will also likely be the case for future VOCs. We know little about the circumstances and processes that generated all the antigenically divergent variants so far, and this makes it hard to predict the timing or antigenic and viral properties of future variants. A more pathogenic future VOC would sweep and replace Omicron along with the features that contribute to its lower severity (preference for upper respiratory tract over pulmonary tissue⁹, and reduced tendency to induce cell–cell fusion). Molecular clock analysis dated the split of Omicron from other SARS-CoV-2 lineages to more than a year before its epidemic emergence. This hints at the possibility of other, antigenically divergent variants in existence or currently forming that may be yet to emerge.

To understand the future burden of COVID-19, besides exploring the relationship between antigenic escape and disease severity, we need to scrutinize the mechanisms generating highly antigenically divergent variants and the circumstances underlying their emergence. This includes studying patterns of antigenic evolution in immunodeficient individuals or in SARS-CoV-2-permissive animal species at human proximity. Understanding these factors will enable us to more reliably evaluate the future population risk of disease in humans and to plan and prepare.

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Competing interests

The authors declare no competing interests.

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