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Previews

Of variants and vaccines

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In this issue of *Cell*, Bushman et al. show how more transmissible variants, even if they do not escape immunity, can be strongly selected during the early pandemic. This explains the dynamics of past SARS-CoV-2 variants, but as immunity increases, it is difficult to predict what will emerge next.

Introduction

The emergence of SARS-CoV-2 variants, in particular Delta (lineage B.1.617.2 & AY.x; first detected in India), Alpha (B.1.1.7; UK), Beta (B.1.351; South Africa), and Gamma (P.1; Brazil/Japan), changed the trajectory of the COVID-19 pandemic. There is still debate on which evolutionary forces drove their emergence and how the selective landscape may change in the future. We use the insights provided by Bushman et al., 2021 in this issue of *Cell* to describe the influences of these forces on variant dynamics and their implications for vaccination strategies.

Intrinsic transmissibility versus immune escape

In the simplest view, two primary traits influence variant success: intrinsic transmissibility and immune escape. Transmissibility is the ability to cause secondary infections in susceptible hosts, which we can quantify by the intrinsic reproductive number (R0). SARS-CoV-2 has evolved to better transmit in humans through mutations that enhance receptor binding and increase replication. The impacts of these adaptations to increase transmission, a proxy for fitness, have been opposed by a decline in the susceptible population through infection and vaccination. For the virus to transmit well in an immune population, it must evolve mechanisms to circumvent protective immunity. Neutralizing antibodies targeting the outer SARS-CoV-2 spike protein are a potent form of protection, and similar antibodies impose strong selection in other viruses (e.g., influenza). Mutations to the spike protein, especially in the receptor binding domain, can lead to partial immune escape, thus making part of the population susceptible to infection again.

Early in the pandemic, when a small fraction of the population had some protection against SARS-CoV-2 infection, it was unclear which trait provides the greater advantage. To motivate intuition, Bushman et al., 2021 created mathematical models to simulate the dynamics of variants with 60% enhanced transmissibility, 40% immune escape, or both, compared to the wild type. In their initially susceptible population (experiencing their first "wave" of infections), they find that enhanced transmissibility provides a strong advantage and can considerably increase the size of the epidemic. Even with vaccination, partial immune escape alone is unlikely to be efficiently selected unless coupled with enhanced transmissibility. Such a variant could limit the effectiveness of vaccination to bring the pandemic under control. Their models provide an important framework to study the drivers of variant emergence and the effectiveness of mitigation strategies in a pandemic.

Emergence of past variants

In late 2020, the pandemic transitioned into a new phase dominated by variants Alpha, Beta, and Gamma, followed by several others. These variants co-circulated at least briefly, and there was much debate over which would most impact the pandemic. While Alpha tended to dominate in frequency, Beta and Gamma tended to dominate concern. Vaccine effectiveness against symptomatic infection was lower for Beta and Gamma than Alpha (Cevik et al., 2021), the result of spike mutations leading to a significant reduction in antibody neutralization (Lucas et al., 2021). Thus, as vaccination programs started in early to mid-2021, the concern was that Beta and Gamma would have a growing selective advantage. In response, Moderna constructed a prototype vaccine matched to Beta's spike (mRNA-1273.351).

Ultimately, Beta and Gamma never exceeded 10% of the global sequenced COVID-19 cases and have now fallen to < 0.1%. The reason is, as concluded by Bushman and colleagues, the selective advantage of partial immune escape is easily dwarfed by the advantage of increased intrinsic transmissibility. Although Alpha, Beta, and Gamma were all more transmissible than the original genotype (Davies et al., 2021; Faria et al., 2021; Tegally et al., 2021), Delta is at least 50% more transmissible than all other variants (Campbell et al., 2021). This has allowed Delta to quickly rise to dominance despite only moderately impacting immune escape (Lucas et al., 2021).

Emergence of future variants

As the fraction of the population immune to SARS-CoV-2 increases, selective pressure for immune escape (relative to intrinsic transmissibility) should increase. This is not fully modeled by Bushman and colleagues, who simulate self-limiting epidemics in an initially susceptible population. There is little evidence or theory to suggest that SARS-CoV-2 will die out as it does in the model. This could lead to recurrent epidemics driven by a combination of new susceptible populations (namely, young children) and individuals who might maintain enough immunity to

prevent severe disease but who can transmit partial immune escape variants. Evolutionary models show that the number of co-circulating immune escape variants and their rate of evolution are sensitive to the viral mutation rate, prevalence, degree of immune escape, structure of cross-immunity between variants, host movement, seasonality, and other factors (Georgieva et al., 2019). Endemic respiratory viruses demonstrate a broad range of patterns, from minimal immune escape (e.g., measles) to serial turnover of new immune escape variants (e.g., influenza A/H1N1) to complex patterns of diversification over time (e.g., rhinoviruses). Although the endemic evolutionary dynamics of SARS-CoV-2 remain unknown, Beta and Gamma demonstrate that some degree of immune escape is possible and can be advantageous. We might expect similar variants, descended from Delta, to be selected for in the future.

What is to stop SARS-CoV-2 from becoming ever more transmissible, not only from immune escape but also from enhanced intrinsic transmissibility? The history of life is studded with large and small evolutionary innovations whose bases can be dissected retrospectively but whose occurrences remain challenging to predict. It is perhaps comforting that common pathogens have not shown conspicuous increases in their transmissibility that were not associated with changes in human behavior, drug resistance, or immune escape, although poor surveillance makes quantitative estimates challenging. In the short term, we should not be surprised if more transmissible lineages emerge from within Delta, like AY.4.2.

Impact on vaccination strategy

The evolution of more transmissible variants directly impacts vaccination strategies. In the case of Delta, improved viral replication amounts to a simple form of immune escape that can justify a more aggressive approach (e.g., more immunogenic vaccines or boosters) in vulnerable populations. The emergence of variants that escape adaptive immunity might warrant updates to the vaccine strain or a shift to vaccines with greater breadth. Notably, non-pharmaceutical interventions can be powerfully effective against both.

Bushman and colleagues suggest how the timing of vaccination might in turn affect viral evolution. An important result of their model is that even an imperfect vaccine, given early enough, can suppress the spread of variants with higher intrinsic transmissibility or moderate to low immune escape. It is well established that the rate of adaptive evolution is generally higher in expanding populations (Otto and Whitlock, 1997), and early vaccination slows adaptation by limiting the growth of both founder and variant strains. These benefits of early vaccination are compounded when considering that the rate of emergence of beneficial mutations is lower in smaller populations. This work aligns with evidence that expanding vaccination coverage globally could pay longer-term dividends in the form of reduced rates of viral evolution (Wen et al., 2020).

Conclusions

During the first waves of the pandemic, increases in intrinsic transmissibility drove variant success. Currently, for a variant to replace Delta, it must be significantly more transmissible, whether through immune evasion or increased intrinsic transmissibility (R0). As the pandemic progresses, immune escape may provide the most accessible selective advantage, which could force a change in our vaccination strategies.

DECLARATION OF INTERESTS

N.D.G. is a paid consultant for Tempus Labs and the National Basketball Association and has received speaking fees from Goldman Sachs.

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