Rapid Reviews COVID-19

RR:C19 Editorial: Immune Escape and Viral Evolution

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Published on: Feb 17, 2021

DOI: 10.1162/2e3983f5.660ac656

Immune Escape and Viral Evolution

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Introduction

Scientists have monitored the SARS-CoV-2 genome because mutations that normally occur through replication might alter the virus' ability to infect and survive in a host. Because the spike protein of SARS-CoV-2 mediates entry into human cells, significant resources have been dedicated to vaccine and therapeutic antibody candidates that target those spike proteins. Monitoring of viral evolution has focused on identifying mutations in spike protein genes that could alter viral transmissibility and effectiveness of both vaccines and therapies. At least three independent SARS-CoV-2 variants that emerged in the United Kingdom, Brazil, and South Africa have rapidly increased in prevalence in their respective geographic regions. This increase suggests that the genetic changes in the spike protein provide some advantage to the virus, likely in human-to-human transmission. These variants all have an unusually high number of mutations, including multiple mutations in the spike protein.

Many critical questions remain that scientific and public health communities must answer. It is not

known if these variants alter the efficacy of current vaccines and therapeutics. It also remains unclear how the viral variants will change during the next phase of the pandemic, with selective pressure from increased global vaccination. *Rapid Reviews: COVID-19* has invited peer reviews of preprints that describe studies examining what spike mutations emerge under persistent immune pressure (or in the presence of highly neutralizing polyclonal antibodies). One of the studies is *in vitro* using convalescent plasma serum, whereas another is an *in vivo* study during clinical treatment.

Viral Evolution and Immune Escape of SARS-CoV-2 Strains

Andreano et al[1] track the emergence of spike mutations when SARS-CoV-2 is serially passaged in the presence of high-neutralizing convalescent serum over 100 days. The study provides insight into how combinations of mutations can facilitate immune escape for SARS-CoV-2 and demonstrates how quickly the virus can adapt to selective pressure despite a relatively slow rate of evolutionary mutation. The study finds that three mutations—all in the S1 domain of the spike protein—were sufficient to completely resist neutralization by the original polyclonal antibodies. Fortunately, other convalescent sera tested retained at least partial neutralization activity, demonstrating that additional viral epitopes can be targeted for neutralization. These three mutations have relevance to the recently identified variants of interest: B.1.351 (South Africa), P.1 (Brazil), and B.1.1.7 (UK). The E484K mutation in the receptor-binding domain (RBD) is present in variants B.1.351 and P.1 and the mutation was previously reported to reduce neutralization by monoclonal and polyclonal antibodies.[2–4] The two other changes occurred in the N-terminal domain (NTD), a site where numerous deletions have been found in circulating isolates,[5] including Δ69/Δ70, which is found in B.1.1.7. Although it remains to be determined if there is a benefit to updating current vaccines for new variants, this and other studies demonstrate the potential for SARS-CoV-2 adaption under immune pressure and there should be ongoing surveillance for mutations that could alter vaccine efficacy.

Therapeutics, such as convalescent plasma, impose evolutionary pressure on pathogens. In another preprint, Kemp et al document the evolution of SARS-CoV-2 in a single immunosuppressed individual over 101 days.[6] The patient was treated early in the disease course with dexamethasone and two courses of remdesivir (administered days 41 and 54) and later in the disease course with convalescent plasma (days 63 and 65). After collecting 23 sequential respiratory samples, the authors generated whole-genome sequences to assess viral evolution. Viral load remained consistent with no sustained change in cycle threshold through the 101 days. However, a significant evolution occurred after the administration of convalescent plasma, with the joint linkage of Δ69/Δ70 and the D796H on the S2 domain of the spike protein mutations becoming dominant. These mutations together are less

sensitive to convalescent plasma. Although the isolated mutant Δ69/Δ70 did not impact neutralization, this paper suggests that joint linkage of mutations could affect clinical strategies for preventing and treating COVID-19 in patients. Though this case report only uncovered ties to the B.1.1.7. variant, our knowledge remains limited on how other mutations contribute to *in vivo* viral escape in the B.1.351 and P.1 variants. Further research is needed to assess if this individual case report is consistent with population-level studies.

Surveillance Policy

Few countries have invested in building sequencing capacity.

Many countries are unable to collect and sequence a large number of samples from infected individuals. Limiting constraints include insufficient sequencing infrastructure and training, inadequate financial resources, and fragmented surveillance systems. Certain national teams have made exceptional progress toward genomic surveillance, such as the United Kingdom's COVID-19 Genomics Consortium (COG-UK), which sequences a large proportion of samples collected on a national scale. In South Africa, the Network for Genomic Surveillance in South Africa has been able to sequence 50-100 genomes per week and can serve as an excellent model for other research groups and countries with sequencing capacity limitations.

In the United States, countering variants will require coordination on federal and local levels.

In countries like the United States, a key challenge has been that only about 0.3% of confirmed cases have been sequenced and submitted to GISAID,[7] with uneven representation across states. Recent efforts to ramp up genomic surveillance includes the CDC-led SARS-CoV-2 Sequencing for Public Health Emergency Response, Epidemiology, and Surveillance (SPHERES) project, which partners with academic centers, industry, and nongovernmental organizations to increase sequencing capacity. The National SARS-CoV-2 Strain Surveillance (NS3) program sends weekly submissions from public health departments to the Centers for Disease Control and Prevention (CDC) for sequencing and characterization. These partnerships, with additional financial support under coordinated federal and state leadership, *could* get the United States where it needs to be. Costs should decrease over time as vaccination reduces the pool of susceptible hosts.

Managing novel variants requires global cooperation.

National surveillance systems must also coordinate as part of a global surveillance system. We must invest in strengthening national and global genomic surveillance that can characterize emergent

mutations, track the speed of their spread, and both predict and monitor the effectiveness of immunotherapies and vaccines against the new strains. Although the World Health Organization (WHO) has released a guide for countries to implement genomic sequencing in response, more resources and training need to be mobilized to support nations with limited capacity to support genomic sequencing. US health authorities should approach this situation with humility as the United States has consistently had the highest case counts of COVID-19 in the world and has not adequately systematized genomic surveillance. There may be more highly transmissible strains or strains that are resistant to some monoclonal antibodies or vaccines circulating within US communities that have yet to be identified. Our knowledge of the existence of novel strains might have as much to do with the robustness of the local surveillance infrastructure as with the actual prevalence and threat of these new variants.

Communication with the public is key.

At a community level, it is imperative that public health authorities communicate what the variants mean for people's day-to-day risk and explain why masking and physical distancing remain the best strategy for preventing disease and viral evolution. Fortunately, preliminary assessment of spike variants with sera from vaccinated individuals shows at least partial neutralization activity is retained against B.1.1.7 and B.1.351 variants.[8–11] Studies are underway to assess vaccine efficacy for these variants and the benefit of a variant-specific booster dose that targets these emerging mutants.[8]

Conclusion

Global efforts to sequence and share SARS-CoV-2 isolates throughout the pandemic has progressively improved our understanding of how the virus is evolving as it transmits through the population. This work has been complemented by *in vitro* and *in vivo* studies on viral escape that hint at what additional changes we might expect. As the world works to vaccinate, isolate, and treat to choke off the transmission, the virus is working to evade our powerful tools. Coordinated international efforts in genomic surveillance and phenotypic characterization of new strains will be critical if we hope to stay one step ahead of the virus.

Acknowledgments

The authors are grateful for the thoughtful comments and suggestions from our colleagues at the *Rapid Reviews: COVID-19* Editorial Office, in particular Raphael Frankfurter, UCSF-UC Berkeley Joint Program in Medical Anthropology, Bryan Tegomoh, MD, MPH, UC Berkeley School of Public Health, and Hildy Fong Baker, PhD, from the UC Berkeley-UCSF Center for Global Health Delivery, Diplomacy and

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