THE BEST OF THE WEEK (22 mag – 28 mag 2023)

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SARS-CoV-2 variant transition dynamics are associated with vaccination rates, number of co-circulating variants, and convalescent immunity

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Abstract

Throughout the COVID-19 pandemic, the SARS-CoV-2 virus has continued to evolve, with new variants outcompeting existing variants and often leading to different dynamics of disease spread.

Methods

In this paper, we performed a retrospective analysis using longitudinal sequencing data to characterize differences in the speed, calendar timing, and magnitude of 16 SARS-CoV-2 variant waves/transitions for 230 countries and sub-country regions, between October 2020 and January 2023. We then clustered geographic locations in terms of their variant behavior across several Omicron variants, allowing us to identify groups of locations exhibiting similar variant transitions. Finally, we explored relationships between heterogeneity in these variant waves and time-varying factors, including vaccination status of the population, governmental policy, and the number of variants in simultaneous competition.

Findings

This work demonstrates associations between the behavior of an emerging variant and the number of co-circulating variants as well as the demographic context of the population. We also observed an association between high vaccination rates and variant transition dynamics prior to the Mu and Delta variant transitions.

Interpretation

These results suggest the behavior of an emergent variant may be sensitive to the immunologic and demographic context of its location. Additionally, this work represents the most comprehensive characterization of variant transitions globally to date.

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Bivalent COVID-19 Vaccines: Can the Original Antigenic Sin Be Forgiven?

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Abstract

On 31 August 2022, the United States (US) Food and Drug Administration authorized bivalent formulations of the Moderna and Pfizer-BioNTech coronavirus disease 2019 (COVID-19) vaccines [1]. These modified vaccines contain messenger RNA (mRNA) encoding for both the ancestral WA1/2020 and the Omicron BA.4/BA.5 spike proteins. The hope was that they would provide immunity to the BA.5 virus, which differs from WA1/2020 by >30 mutations in the spike protein and was the predominant variant in circulation at the time. Unfortunately, studies have shown

that the levels of neutralizing antibodies to the BA.5 variant were not significantly higher in patients who received the bivalent vaccine than those who received the monovalent vaccine with WA1/2020 mRNA [2, 3]. In other words, vaccination with BA.5 spike protein did not lead to an appreciably better antibody response. The reason for this disappointing result has not yet been determined, but antigenic imprinting, also known as the “original antigenic sin,” has been invoked as a potential cause for these results.

To fully explain this tenant of immunotheology, one has to review some basic principles. While there are some notable exceptions [4], the process of extensive gene segment recombination leads to the production of diverse T- and B-cell receptors that should be capable of recognizing almost any conceivable pathogen we will ever encounter. The drawback is that there are very few cells with any given receptor and so when we first see a pathogen, naive cells with receptors specific for the pathogen's antigens have to proliferate extensively before we can mount an effective primary adaptive immune response. Some of these naive cells will become memory cells that circulate at higher levels so that if the same antigen is encountered again, a faster, more effective secondary adaptive immune response will occur.

Unfortunately, by the time 2 bivalent booster shots are given to a significant part of the population—an unlikely prospect given the limited uptake of the bivalent vaccine and the vaccine weariness of the US population—the variant in question will probably no longer be the dominant variant in circulation. The question then becomes should we periodically modify the bivalent vaccines to target the spike protein from the most prevalent circulating variant, or can we just rely on a monovalent vaccine to expand preexisting memory cells with cross-reactive receptors?

It is likely that we have low frequencies of naive B and T cells with high-affinity receptors specific for every SARS-CoV-2 variant that will emerge. So, if we continue to vaccinate with different spike proteins and generate more cells with cross-reactive receptors, will we be able to prime the rare naive cells with the high-affinity receptors we want, or will we just amplify cells with less effective cross-reactive receptors that are circulating at much higher levels? The good news is that if new variants escape to a point where there is little cross-recognition by preexisting memory B and T cells, then it should be possible to prime an effective primary immune response against the emerging spike protein. This phenomenon is routinely seen in untreated human immunodeficiency virus infection where there is a much higher degree of virologic escape [10]. At this point, hopefully the original antigenic sin will be forgiven