EDITORIAL

# Interplay between Emerging SARS-CoV-2 Variants and Pandemic Control

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a member of a diverse family of enveloped, nonsegmented RNA viruses. The coronavirus genomic RNA is unusually large, the RNA polymerase is error-prone, and mutations accumulate with increasing frequency during infections. With continued uncontrolled transmission and viral replication, mutations that give the virus a fitness advantage will emerge. A SARS-CoV-2 variant of concern has one or more mutations that confer worrisome epidemiologic, immunologic, or pathogenic properties.[1]

From early in the pandemic, South Africa has been a global leader in the use of intensive genomic sequencing to identify and track emerging SARS-CoV-2 mutations. It has been hypothesized that key detected mutations in the spike protein emerged under conditions of extensive and prolonged viral replication and intrahost evolution.[2] The B.1.351 variant, first identified in South Africa, has shown evidence of increased transmissibility, a considerable reduction in neutralization by convalescent and postvaccination serum, and significantly decreased neutralization by monoclonal antibodies.[3,4]

Investigators now report in the *Journal* the results of two peer-reviewed trials evaluating the efficacy of two vaccines — a replication-deficient chimpanzee adenovirus vector vaccine (ChAdOx1 nCoV-19)[5] and an adjuvanted, recombinant nanoparticle vaccine (NVX-CoV2373)[6] — against the B.1.351 variant. Both trials enrolled predominantly younger adults with high seropositivity to SARS-CoV-2 at trial entry. The trials were conducted with a backdrop of high symptomatic attack rates in the placebo group and a high prevalence of the B.1.351 variant among sequenced strains. Both of these factors reflected the intensity of the outbreak in South Africa in late 2020, so these vaccines were tested in similar, challenging epidemiologic circumstances. However, the two trials differed with respect to the populations that were enrolled and in the trial designs and outcome definitions, factors that undermine a direct comparison of the results.[7]

In the trial by Madhi et al.,[5] two doses of the ChAdOx1 nCoV-19 vaccine conferred no efficacy (point estimate, 10.4%; 95% confidence interval [CI], −76.8 to 54.8) against mild-to-moderate disease caused by the B.1.351 variant in previously seronegative participants. No severe cases of Covid-19 were identified in either the vaccine group or the placebo group, so efficacy against that important end point could not be determined. The authors emphasize that although neutralizing-antibody responses to the B.1.351 variant were substantially diminished, broadly reactive T-cell responses were preserved, which potentially offered a mechanism of protection from severe disease. However, the lack of efficacy against nonsevere disease caused by the B.1.351 variant is disappointing, because the ChAdOx1 nCoV-19 vaccine has highly favorable stability and storage characteristics, can be produced by multiple global manufacturers to supply billions of doses, and is well positioned for global vaccine distribution. Thus, this vaccine remains a critical tool for pandemic control on the basis of efficacy that has been shown in other epidemiologic settings.[8] Countries will need to

weigh the extent of circulating virus variants among other factors, including rare adverse events, when considering vaccine choice.[9]

In the second trial, Shinde et al.[6] found that two doses of the NVX-CoV2373 vaccine had an efficacy of 49.4% (95% CI, 6.1 to 72.8) against symptomatic Covid-19 caused by the B.1.351 variant. A press release that included additional data from this trial reported high efficacy against the original strain of Covid-19 and confirmed the finding of modest efficacy against symptomatic Covid-19 from the B.1.351 variant. Furthermore, the trial sponsor, Novavax, reported that all five cases of severe disease that were observed in the South Africa trial occurred in the placebo group.[10] Although at the time of the trial, the NVX-CoV2373 vaccine had not received regulatory approval, factors that include the safety and efficacy profile, favorable storage conditions, and global manufacturing partnerships also make it an attractive vaccine candidate for global distribution.

At the time of this report, data were publicly available from two other trials that included participants from South Africa. In the first of these trials, the recombinant, replication-incompetent adenovirus serotype 26 vector SARS-CoV-2 vaccine (Ad26.COV2.S) showed significant efficacy among South African participants against moderate-to-severe disease (64.0%; 95% CI, 41.2 to 78.7) with higher efficacy against severe-to-critical disease (81.7%; 95% CI, 46.2 to 95.4) when the B.1.351 variant was the predominant circulating strain.[11] In the second trial, which included 800 participants in South Africa, the use of the BNT162b2 messenger RNA vaccine also showed efficacy, with no cases of Covid-19 in the vaccine group and nine cases in the placebo group. Of the nine cases, six strains were confirmed to be of the B.1.351 lineage.[12]

SARS-CoV-2 will continue to replicate in humans, mutations will continue to occur, and variants of concern will continue to emerge. From a public health perspective, limiting viral transmission through widespread use of vaccines, masking, social distancing, and other control measures will reduce new viral mutations. Effective antiviral drugs (particularly those with oral formulations) would be an important adjunct to vaccines to treat disease and to reduce prolonged viral shedding and the accumulation of new viral mutations.

Vaccine evaluations against new variants will be more challenging going forward as data from randomized, placebo-controlled clinical trials become less common owing to enhanced availability of vaccines. A global scientific agenda that encompasses extensive genomic surveillance, detailed "correlate of protection" evaluations, and robust postintroduction surveillance and sequencing is necessary to measure the effect of new and current vaccines against SARS-CoV-2 variants. Development and testing of second-generation vaccines (including those that target specific variant strains, multiple strains, and antigens other than spike proteins) are under way. Even though faster production timelines will facilitate the manufacturing of new vaccines, such factors as the operational difficulty of replacing current vaccines with new ones, manufacturing regionally specific vaccines, and adding booster doses of a vaccine must be considered in the risk–benefit context.[13]

The emergence of variant strains is arguably the greatest threat to control of the Covid-19 pandemic. A coordinated global prevention-and-control plan is the only way forward. Global investments in vaccine science and technology must be accompanied by investments in public health, genomic and disease surveillance, and programmatic immunization infrastructure to mitigate the effects of Covid-19 and future pandemics.

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