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Commentary

COVID-19 vaccines: Keeping pace with SARS-CoV-2 variants

Muge Cevik,[1,*] Nathan D. Grubaugh,[2,3,4] Akiko Iwasaki,[2,5,6] and Peter Openshaw[7]
[1]Division of Infection and Global Health, School of Medicine, University of St Andrews, Fife, UK
[2]Department of Epidemiology of Microbial Diseases, Yale School of Public Health, New Haven, CT, USA
[3]Department of Ecology and Evolutionary Biology, Yale University, New Haven, CT, USA
[4]Yale Institute for Global Health, Yale University, New Haven, CT, USA
[5]Department of Immunobiology, Yale University School of Medicine, New Haven, CT 06520, USA
[6]Howard Hughes Medical Institute, Chevy Chase, MD 20815, USA
[7]National Heart and Lung Institute, Imperial College London, London, UK
*Correspondence: mc349@st-andrews.ac.uk
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As the SARS-CoV-2 pandemic evolves, new variants continue to emerge. Some highly transmissible variants, such as Delta, also raised concerns about the effectiveness provided by current vaccines. Understanding immunological correlates of protection and how laboratory findings correspond to clinical effectiveness is imperative to shape future vaccination strategies.

The emergence of variants of concern and assessment of vaccine efficacy

SARS-CoV-2—like all RNA viruses—is prone to introducing random errors in its genetic code during replication. Many of these mutations are corrected by proofreading mechanisms, but advantageous sequence variations are accumulating as the virus continues its global spread. As of August 2021, the World Health Organization (WHO) has designated four SARS-CoV-2 variants as "variants of concern" (VOCs): Alpha (B.1.1.7, first detected in the UK), Beta (B.1.351, first detected in South Africa), Gamma (P.1, first detected in Brazil), and Delta (B.1.617.2, first detected in India). Public health agencies around the world have their own lists, which also include "variants of interest" or "variants under investigation" that could be upgraded to a VOC if there is evidence of enhanced transmission, immune escape, or pathogenicity. Most concerningly, a "variant of high consequence" that has strong evidence of significantly reducing the effectiveness of preventative measures—a status that no SARS-CoV-2 variant has yet achieved.

National regulators have given emergency use authorizations for 21 COVID-19 vaccines; 6 of those have been approved by at least one WHO-recognized authority. These include mRNA vaccines (Pfizer-BioNTech BNT162b2 and Moderna mRNA-1273), viral vector vaccines (Oxford/AstraZeneca AZD1222 and J&J/Janssen's Ad26.COV2.S), recombinant spike vaccines (Novavax NVX-CoV2373), and inactivated vaccines (Sinovac [CoronaVac] and Sinopharm). While these vaccines, based on wild-type virus (sequenced in January 2020) are remarkably efficacy against early variants, their effectiveness against some new variants is being established.

While vaccine efficacy (applies to specific clinical outcomes in a controlled environment) has been established in clinical trials, it is impossible to make direct comparisons between different vaccines due to different clinical endpoints, location, population studied, and circulating SARS-CoV-2 variants at the time of the trial. It is also highly challenging to assess the real-time vaccine effectiveness (performance of vaccines at limiting infections or disease in the real world) against newly emerging variants, considering other pressures influencing the epidemic dynamics such as variant transmissibility, human behavior, and immunity status of the population. In addition, while early preliminary laboratory data primarily based on antibody responses could be helpful, they only provide a limited understanding of clinical effectiveness, especially considering that immunological correlates of protection are poorly understood. Furthermore, T cell responses triggered by vaccines contribute significantly to protection from viral replication and symptomatic disease, maintaining immunological memory and assisting in viral clearance. Therefore, decreased *in vitro* neutralizing activity does not on its own predict that vaccines will be completely ineffective.

When considering vaccine effectiveness against new variants, there are at least three elements to consider: (1) whether antibodies triggered by current vaccines can recognize and neutralize these new variants, (2) whether there are cross-reactive cellular immune responses to these variants, and (3), most importantly, the real-world impact of variants on the clinical protection provided by vaccines. This commentary discusses what we know about these three elements for SARS-CoV-2 VOCs and other emerging elements that factor into effectiveness with the aim of informing vaccination strategies in an evolving pandemic.

In vitro assessment of neutralization response

SARS-CoV-2 contains four major structural proteins: spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. S proteins are responsible for recognizing the host cellular receptor to initiate virus entry and are the primary target for most COVID-19 vaccines (exceptions being for inactivated and live-attenuated virus vaccines that use the whole virus). Compared

to the evolution of resistance to therapeutic agents like antimicrobials or antivirals, the emergence of immune escape variants in direct response to vaccines is different and expected to occur more slowly. This is because vaccines prevent infection, while (most) drugs are used to treat established infections. In addition, even some vaccines that only encode S proteins still produce a range of antibody and T cell responses recognizing different parts of the protein, making it less likely that single mutational changes will substantially reduce protection. This means that the opportunity for variants to emerge under within-host selection from vaccines is many orders of magnitude smaller than drugs. Nevertheless, the accumulation of mutations in the S protein that evolve through a variety of mechanisms, including for enhanced transmission, could influence vaccine effectiveness.

It has been shown that some amino acid substitutions in the S receptor-binding domain and N-terminal domain result in a more significant reduction of virus neutralizing capacity in laboratory assays. E484K is one such mutation, which has emerged repeatedly across many different SARS-CoV-2 lineages, including Beta, Gamma, and Iota (B.1.526; variant of interest in the US). The most significant decline in neutralization was measured against Beta, much less so against Gamma and Iota. On the other hand, most sequenced Alpha variants do not have the E484K mutation, which is one potential reason it is more susceptible to the current COVID-19 vaccines. Oxford/AstraZeneca vaccine (AZD1222; viral vector) and Pfizer-BioNTech vaccine (BNT162b2; mRNA) show only a slight decrease in *in vitro* antibody neutralization against Alpha. Delta, which also does not have the E484K or a related E484Q mutation, has a modest ability to avoid neutralizing activity induced by the Pfizer-BioNTech and Oxford/AstraZeneca vaccines and is neutralized by inactivated vaccines (Tregoning et al., 2021). While some studies showed a significant reduction in peak neutralizing antibodies induced by the Pfizer-BioNTech against Delta that is similar to that seen with Beta, others only showed a marginal decline. According to a comprehensive analysis, variants with E484K and N501Y mutations, like Beta and Gamma, had the most significant reduction in neutralization capacity (Lucas et al., 2021).

Decreased neutralizing activity *in vitro* does not on its own predict that vaccines will be ineffective

Despite a decline in *in vitro* neutralization response, all vaccinated individuals retained neutralization capability against the Beta variant. This is likely due to vaccination stimulating cross-variant neutralizing antibodies and cellular response. For instance, mRNA vaccines enhance neutralizing activity against Gamma and Beta (Stamatatos et al., 2021). While no sufficient neutralizing antibodies against Beta were detected after the first dose, immunization with the second dose of the Pfizer-BioNTech and Moderna (mRNA-1273) mRNA vaccines achieve sufficient immunity that controls replication (Corbett et al., 2021). In comparison, neutralizing antibody response to Gamma is much better than Beta after vaccination with Pfizer-BioNTech and AstraZeneca vaccines (Dejnirattisai et al., 2021). Furthermore, antibodies induced by the Pfizer-BioNTech and Moderna vaccines generate durable neutralizing antibody response against Beta as well as Gamma, Iota, and Epsilon (B.1.429, which does not have E484K), at least 8 and 6 months later, respectively.

Neutralizing antibodies are likely not the only mechanism of protection

The emerging evidence supports the importance of neutralizing antibodies for preventing infection, demonstrating an association between neutralizing antibody levels and breakthrough infections (Khoury et al., 2021). However, neutralizing antibodies are likely not the only mechanism of protection, and T cells and non-neutralizing antibodies are likely also playing a significant role especially in regard to protection against symptomatic infection and severe disease. For instance, T cells appear to be the major contributors to controlling SARS-CoV-2 infection (Tan et al., 2021). Vaccines can also elicit cross-protective B and T cell responses, which has been found for the Pfizer-BioNTech and Moderna mRNA vaccines (Reynolds et al., 2021; Stamatatos et al., 2021). Importantly, B and T cells can recognize different SARS-CoV-2 variants and are minimally affected by S mutations (Tarke et al., 2021). In addition, current evidence suggests that Alpha and Beta do not escape T cell responses induced by vaccines (Geers et al., 2021). Therefore, despite reduced antibody titers against some of these variants, vaccine-induced immunity will likely be conserved against currently circulating variants, supported by clinical data (Table 1).

Clinical efficacy and effectiveness of vaccines against variants of concerns

Alpha

There is a growing body of evidence that Alpha has only a limited ability to escape from vaccine-induced immunity, and vaccines remain clinically effective against this variant. Interim results of the Novavax vaccine (NVX-CoV2373; recombinant spike) shows 86% efficacy against Alpha (Tregoning et al., 2021). Likewise, when Alpha was dominant in Israel, the Pfizer-BioNTech vaccine showed 92% protection against asymptomatic infection, 97% against symptomatic, and 97% against severe disease. In Scotland, AstraZeneca and Pfizer-BioNTech vaccines demonstrated a 94% and 85% reduction in hospitalizations, respectively, against Alpha. In Qatar, the effectiveness of the Pfizer-BioNTech vaccine against any documented infection with the Alpha variant was 89.5% and against the severe disease was 97.4%. Early real-world data also suggest these vaccines significantly reduce transmission of Alpha.

Beta

An exploratory analysis of the Pfizer-BioNTech vaccine trial demonstrated high efficacy against symptomatic infection in South Africa, where Beta is dominant, with no cases of COVID-19 in the vaccine group. In Qatar, while protection after first dose of the Pfizer-BioNTech vaccine was reduced, after the second dose, it provided 75.0% protection against any documented infection with the Beta and 97.4% protection against severe disease (Abu-Raddad et al., 2021). Interim results of J&J/Janssen's vaccine (Ad26.COV2.S; viral vector) clinical trial showed 65%–66% protection against hospitalization and 91%–95% against mortality in South Africa, similar to the reported efficacy in the United States (Tregoning et al., 2021). In a phase 2a/b study, the efficacy

Table 1. Vaccine effectiveness in % (95% CI) or mean

Outcome	Alpha	Delta	Beta/Gamma
Symptomatic infection			
Pfizer-BioNTech	90 (85–95)	85 (80–90)	85 (70–93)
Oxford	80 (70–85)	70 (60–75)	<70 [−76.8–54.8] (mild COVID-19 only)[b]
Moderna	91 (84, 95)	70 (45–85)	78 (60–88) [1 dose]
J&J	N/A	N/A	52 (30.3–67.4)
Novavax	86	60	60
Sinovac	N/A	N/A	65.9 (65.2–66.6)?
Severe disease			
Pfizer-BioNTech	95 (90–99)	95 (90–99)	98 (82–100)
Oxford	95 (80–99)	95 (80–99)	N/A
Moderna	94 (90, 97)	96 (72–99) [1 dose]	94 (75–99) [1 dose]
J&J	N/A	71	65–66 (hospitalization) 91–95 (mortality)
Sinovac	N/A	N/A	87.5 (86.7–88.2)
Infection			
Pfizer-BioNTech	Variable[a]	Variable[a]	Variable[a]
Oxford	55–80	50–87	70–79 (limited data)
Moderna			

[a]Vaccine effectiveness against infection is a dynamic figure that varies by setting, testing criteria, behavior, community prevalence, exposure risk, immunity status, and time from vaccination.
[b]Please see the text for detailed explanation of this study.

of the Novavax vaccine against mild-to-moderate disease due to Beta was modestly reduced (Tregoning et al., 2021).

On the other hand, the AstraZeneca vaccine trial in South Africa did not achieve efficacy greater than 60% (the hypothesis being tested and for which the study was powered to address) against mild and moderate disease when Beta was in circulation (Madhi et al., 2021). However, this small phase 1/2a study was not designed to address clinical efficacy against severe disease and was primarily aimed at assessing safety. Hence, the actual clinical efficacy of the AstraZeneca vaccine against Beta requires further investigation. For example, in a hamster model, sera from non-human primates after inoculation with the AstraZeneca vaccine neutralized Beta, and this provided complete protection against disease caused by Beta. Additionally, it is unknown whether an enhanced antibody response resulting from a longer interval between the first and second doses of AstraZeneca might confer better clinical efficacy against the Beta variant.

Gamma

Comparable efficacy to the J&J/Janssen vaccine was reported in Brazil when Gamma was dominant. The Sinovac vaccine (CoronaVac; inactivated virus) and AstraZeneca vaccine showed comparable real-world effectiveness in Brazil against symptomatic COVID-19 during wide Gamma circulation (Tregoning et al., 2021).

Delta

The evidence so far suggests that effectiveness against hospitalizations and symptomatic illness is highly preserved against Delta based on data from England, Scotland, Canada, Qatar, Israel, and the United States. An analysis from England showed sustained protection against hospitalization with Delta compared with Alpha, 96% and 92% after the second doses of BNT162b2 and ChAdOx1. In New York, high effectiveness of mRNA vaccines against hospitalization was shown when Delta was in circulation (91.9%–95.3%). According to the analysis from England and Canada, protection against symptomatic disease was significantly lower after one dose of vaccine with Delta compared to Alpha. Nevertheless, effectiveness was recovered after the second dose with an effectiveness of 85%–90% and 61%–72% with BNT162b2 and ChAdOx1, respectively, with a modest decline seen compared to Alpha (Lopez Bernal et al., 2021). Although the preliminary data published by the Ministry of Health in Israel caused much concern suggesting a significant decline of effectiveness against symptomatic Delta infection, further preprint published did not report effectiveness figures against symptomatic infection as symptoms reporting was not reliable in the national database. Vaccine effectiveness against infection is much harder to measure as these estimates are affected by various biases such as testing criteria, behavior, exposure risk, immunity status of the population, and community prevalence. Studies showed an estimated 55%–80% effectiveness against infection before Delta was dominant, and there is a modest decline seen in prevention against infection with Delta. In Scotland, vaccine effectiveness in preventing RT-PCR-confirmed SARS-CoV-2 Delta infection was 79% with BNT162b2 and 60% with AstraZeneca after two doses. A recent analysis based on systematic testing in England demonstrated that Pfizer-BioNTech and AstraZeneca vaccines remain highly protective against any infection similar to that seen with Alpha, including those with high viral load (Ct < 30). A test-negative case-control study from Qatar demonstrated high effectiveness against swab positivity with Delta, 60% and 86% with Pfizer-BioNTech and Moderna vaccines, respectively. Based on routine surveillance data in the United States, two doses of mRNA vaccines were 75% effective against infection in early 2021, which declined to 53% when Delta predominated, which may also be affected by waning plasma neutralizing titers. However, these analyses did not account for prior infection in the unvaccinated cohort, which could influence effectiveness estimates. It is important to note that effectiveness against infection is a dynamic figure, that is influenced by several factors, making it challenging to compare various studies.

Future considerations

As natural immunity builds in the population, SARS-CoV-2 variants may be increasingly selected as immune escape variants. Vaccination, on the other hand, even when partial, is unlikely to contribute significantly to the emergence of escape variants owing to the vaccines' ability to

strongly restrict the evolutionary and antigenic escape pathways accessible to SARS-CoV-2, reducing the emergence of such variants. It has also been shown that intra-host SARS-CoV-2 genetic diversity remains limited during acute infections in healthy hosts. Thus, the sudden emergence of new SARS-CoV-2 variants, often with several key mutations, is hypothesized to be rare during transmission among primarily healthy individuals (Braun et al., 2021). Instead, SARS-CoV-2 evolution during chronic infections of immunocompromised individuals has been found to drive significantly more genetic diversity, including the generation of mutations commonly found in VOCs, such as E484K. This highlights the importance of vaccinating clinically vulnerable groups as a priority globally, which has the most potential to limit the emergence of new variants that may evolve some immune resistance. Preventing these variants from taking hold will be critically important in the future as immunity developed from natural infection or vaccination is variable and tends to fade over time.

The limited magnitude of neutralizing activity after the first dose of vaccines against Beta and Delta underscores the importance of the complete two-dose regimen for protection against these variants. Reassuringly, a significant drop seen in neutralizing data has only been translated to a modest decline in effectiveness against symptomatic illness and severe disease. Beta seems to be the most antigenically distant variant so far, yet vaccines' effectiveness against severe illness is broadly conserved. Similarly, vaccines' effectiveness is conserved against symptomatic illness and severe disease caused by Delta; however, there is a modest decline seen in prevention against infection. Importantly, protection from hospitalization or death due to COVID-19 is easier to achieve than protection against infection and is expected to be long lasting.

Several options could improve the strategies used with current vaccines especially in elderly and immunocompromised. These include late booster dose (i.e., with same vaccine and strain), additional variant-specific booster dose, heterologous prime-boost strategy (HPBS), and varying the time between first and second dose. There are early indications that infection with Beta elicits antibodies that cross-neutralize other variants, which may be a promising target for future vaccines. For example, a booster dose of a modified Moderna vaccine candidate matched to Beta (mRNA-1273.351) achieves higher titers against Beta and Gamma than a prototype booster dose. ChAdOx1-vectored vaccine against Beta (AZD2816) also showed strong immunogenicity against Beta, Delta, and Kappa. However, as the current vaccines offer strong protection against severe and symptomatic disease, there may be a limited return on a new variant booster in the near future. Murine models show better immunogenicity of the HPBS in which different vaccines are given as first and second dose, and their clinical relevance has been demonstrated in a non-human primate model. In the medium term, it seems essential to test additional boosting with HPBS by comparing the efficacy of boosting with currently available vaccines and those expressing variant-specific spike proteins. Future vaccine strategies that elicit mucosal immune responses within the respiratory tract also hold promise for providing broadly cross-reactive protection against variant viruses.

It has been possible to reduce the burden of many infectious diseases by vaccines without significant escape mutations emerging. Nevertheless, viral variation requiring changes in vaccines does occur, most notably necessitating the annual adjustment of influenza vaccines, though the antigenic variation of influenza virus is not driven by vaccine use but by immunity following natural infection. Given that cellular immunity can mitigate severe or prolonged infection, protection against severe-to-critical illness is likely to be conserved against new SARS-CoV-2 variants even in the presence of very low *in vitro* neutralizing titers. In addition, with more transmissible variants like Delta, protection against infection and subsequent transmission may be reduced, influencing the epidemic trajectory, especially in countries where vaccine coverage remains limited.

To help keep pace with future epidemic "waves" driven by emerging variants, there is a need for a solid correlate of protection and clinical tests to determine an individual's response to vaccines. This will be important to help determine when booster doses are needed, both on individual and population levels. While this may be needed to defend against variants with the ability to evade immunity, variants with increased transmission potential might pose a greater challenge to our ability to maintain vaccine effectiveness. Variants like Delta with intrinsic transmissibility advantages can challenge vaccines by increasing SARS-CoV-2 incidence in the community and thus increasing exposure risk to vaccinated individuals. Unless variants with the ability to evade neutralizing antibodies can compete on a population level, transmissibility will always be favored. This is because a variant with intrinsic transmissibility advantage will always compete with other variants, further emphasizing the crucial role that increased transmissibility plays in hospitalizations, irrespective of any direct effect on virulence or vaccine effectiveness.

Conclusion

During the current pandemic, SARS-CoV-2 has surprised some evolutionary virologists in its ability to consistently generate variants that have accumulated 10–20 new mutations during a short period, which encode new phenotypes leading to enhanced transmission, immune escape, or increased pathogenicity. For now, these variants are mainly susceptible to some degree to immunity conferred by infection with original strains of the virus and to current vaccines. While some variants show a degree of escape from protective antibody induced by natural infection (and, to a lesser degree after immunization), T cell responses are retained. This would likely reduce the disease burden in future waves once most of the population, especially clinically vulnerable, is vaccinated. While immune escape mutations will continue to appear, vaccine-induced immunity currently has important benefits in protection against variants. However, a continued adaptation of SARS-CoV-2 to human transmission and immune escape seems inevitable. It is vital that we remain vigilant and monitor and evaluate variants arising around the globe. In the meantime, rapid global deployment of licensed and effective vaccines remains an urgent and vital public health priority.

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