SARS-CoV-2 variants of concern and vaccine escape, from Alpha to Omicron and beyond

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\textbf{ARTICLE HISTORY} Received 28 December 2021; Accepted 21 March 2022

\textbf{KEYWORDS} COVID-19; SARS-CoV-2; vaccination; breakthrough infection

1. Background

More than nine billion Coronavirus Disease-2019 (COVID-19) vaccine doses were administered worldwide in 2021, and $\sim$58% of the global population has received at least one dose [1]. The rapid development of safe and effective COVID-19 vaccines was heralded as the beginning of the end of the pandemic. However, these hopes have dimmed with the emergence of SARS-CoV-2 Variants of Concern (VOC) such as Delta (B.1.617.2) and Omicron (B.1.1.529), which have caused large outbreaks among highly vaccinated populations. We review the impact of VOCs on vaccine effectiveness (VE) and immune escape and outline potential future directions to optimize vaccination regimens.

2. Immune evasion by VOCs

In vaccinated individuals, SARS-CoV-2 needs to overcome a coordinated immune response to cause infection and early host-virus interactions are critical for determining the initial rate of viral replication [2]. Multiple viral structural and nonstructural proteins have been associated with evasion of host innate immune sensing pathways such as interferon signaling or altering expression of surface MHC-I [3,4]. Adaptations in these proteins have also been associated with more effective innate immune evasion and may contribute to the higher virus levels and transmissibility observed with Alpha and other VOCs [5,6].

The SARS-CoV-2 spike protein mediates viral entry into the host cell and is the key immunogenic target for all vaccines currently approved by the World Health Organization (WHO). Studies on the effect of amino acid substitutions in the spike protein on vaccine/convalescent sera and monoclonal antibody binding can allow prediction of the phenotypic (and public health) effects of combinations that emerge in different VOCs (Supplementary Table S1). However, there is at present a lack of \textit{in vitro} data in $>50\%$ of signature spike protein mutations.

Furthermore, while changes in the spike protein, which alter antibody neutralization through binding to the receptor binding domain (RBD), have received much attention, the spike antibody response induced by infection and vaccination is broad. Other binding antibodies may play functional roles, which are important for determining the severity of infection, for example, through modulation of the inflammatory response by activation of Fc receptors [7]. Modeling of SARS-CoV-2 vaccine breakthrough infections utilizing data from multiple patient cohorts, vaccinated with a variety of mRNA and non-mRNA vaccines, has estimated neutralization level correlates for 50% protection (i.e. half the chance of developing the event compared to an unvaccinated person) at 20.2% of mean convalescent level against detectable SARS-CoV-2 infection, but much lower at only 3% for severe disease [8].

This situation is distinct from therapeutic monoclonal antibodies, which typically bind to a single epitope and thus are more susceptible to viral immune evasion – as was observed with Bamlanivimab/LY-CoV555 and $>100$-fold reduced neutralizing susceptibility against Beta, Gamma, and Delta compared with wild type [9,10]. Evasion of mRNA vaccine-induced neutralizing antibodies is much less pronounced with early VOCs, ranging from 1.2 to 4.0-fold, with greater reductions for Beta than Delta [11]. Omicron, on the other hand, escapes the majority of neutralizing antibodies \textit{in vitro} and has been associated with an 11.4-fold reduction in neutralization titer by postvaccination sera [12,13].

Resolution of infection and clearance of virus is generally considered to rely on the cellular rather than humoral immune response [14]. An early T-cell response limits SARS-CoV-2 replication and protects against severe infection [15]. There is limited evidence for viral immune escape from T-cell recognition, and \textit{in silico} analysis predicts that substitutions in Omicron have left 73% of T-cell epitopes unaffected, compared with 88.5–91.5% for other VOCs [16]. This suggests that immune memory from prior SARS-CoV-2 infection and vaccination will continue to offer protection against severe COVID-19 with Omicron and future variants, and this likely explains in large part the observed lower proportion of severe disease with Omicron infection.
3. Real-world evaluation of vaccine effectiveness (VE)

Extrapolating from *in vitro* studies to predict the clinical consequences of different spike mutations is complicated by a number of factors. First, a range of different vaccines are in clinical use worldwide, and these induce antibody and cellular immune responses of varying quality and quantity [17]. Messenger RNA and viral vector vaccines have been associated with stronger and more sustained immunogenicity compared to inactivated vaccines, particularly with respect to T-cell responses. Correspondingly, the rate of waning immunity post-vaccination also varies greatly. Second, there are also important host factors, which determine the strength of immune response to vaccination, rate of waning, and susceptibility to symptomatic and severe infection [18]. These are highly correlated, such that advanced age, male sex, and comorbid conditions place individuals at highest risk of both severe infection intrinsically and a weaker vaccine-induced immune response, which further increases disease severity. Third, two years into the pandemic, successive outbreaks of ancestral and SARS-CoV-2 VOCs mean that immunity from prior infection varies in different regions of the world. Finally, vaccination has effects beyond the immune response. This includes reducing the viral loads and therefore transmissibility of SARS-CoV-2 in breakthrough infections. Vaccination may also modify behavior post-vaccination and hence increase risk of exposure to SARS-CoV-2, for example, through public health measures, which privilege access to crowded indoor venues to vaccinated individuals.

Nonetheless, several large community surveillance cohort studies have attempted to disentangle these confounders by evaluating VE after correction for time post-vaccination, age, and demographics. Tartof and colleagues analyzed VE of BNT162b2 in a large cohort of 3,436,957 patients in California and demonstrated waning of VE from one to five months post-vaccination independent of VOC type. VE against Delta variant infection remained >90% in the first month post-vaccination, and VE for hospitalization remained preserved throughout the six-month study period against all VOCs including Delta [19]. Similar findings were seen in Qatari surveillance data, demonstrating decline in VE across all variants after five months from vaccination, but preserved effectiveness against severe disease and mortality, with a robust protection of >90% for these clinically significant outcomes [20]. Other studies in multiple settings, although not accounting for waning, have reliably demonstrated preserved VE for the first four VOCs in the early post-vaccination period, with at most modest declines in VE for Delta variant, but without an impact on severe disease or mortality [21–23]. As such, it seems more likely that, for the first four VOCs, resurgences of COVID-19 incidence despite broad vaccine coverage in multiple settings might have been driven in larger part by waning immunity rather than variant-specific immune escape.

With Omicron, however, emerging evidence paints a different picture of immune escape and high transmissibility driving large outbreaks in countries with high vaccination coverage and preexisting immunity [24]. Surveillance data from the United Kingdom at a period of Delta and Omicron co-circulation showed that Omicron was associated with a significantly higher risk of reinfection (5.41; 95% CI 4.87–6.00) compared to Delta [25], suggesting that immunity from previous infection conferred less protection. Similarly, calculated vaccine efficacy was lower for Omicron compared to Delta for both Pfizer and AstraZeneca vaccines and both boosted and unboosted individuals. These findings are corroborated by South African data demonstrating a significantly higher risk of reinfection with Omicron compared to Beta and Delta variants [26]. Hybrid immunity from previous infection and vaccination is more robust than vaccine-induced immunity alone, and the increased reinfection risk in settings with significant vaccination and previous infection rates is concerning for the significant immune-evading potential of Omicron.

Evaluating the intrinsic severity of Omicron is also challenging given the significant extent of preexisting immunity in the majority of settings with large Omicron outbreaks, and retrospective adjustment for vaccination and prior infection has to be interpreted carefully [27]. In *in vitro* data suggest reduced replication competence in lung tissue compared to upper airway epithelia, providing a potential biologic basis for reduced severity, which will need to be evaluated in larger epidemiologic or potentially even *in vivo* human challenge studies.

4. Strategies to bolster vaccine efficacy

COVID-19 vaccination programmes are unfortunately not complete once the primary vaccine series has been administered, particularly for more vulnerable individuals. Third-dose boosters have been shown to reduce rates of infection, severe disease, and mortality [28,29], and these should be rapidly implemented in the short-to-medium term to mitigate the impact of Omicron. However, the durability of a three-dose regimen remains to be seen, and waning immunity may still be observed further in the future. We will need ways to bolster vaccine-derived immune responses to achieve both durability and broad-range cross-protection.

SARS-CoV-2 vaccines, which contain spike protein from VOCs, have been in development since the emergence of Alpha in 2020. These efforts have been given fresh impetus by the emergence of Omicron given its clear ability to evade postvaccination and infection antibody, and several manufacturers have committed to releasing an Omicron vaccine in the first half of 2022. Such vaccines are likely to play an important role in protecting individuals at risk of severe COVID-19, however, with the inevitable waning of antibody levels postvaccination and potential for further variants to emerge, the durability of this approach is unclear.

The use of heterologous prime-boost regimens shows promise in further optimizing VE and may be able to induce cross-protective immunity against future variants or other emerging related coronaviruses. Tan and colleagues demonstrated that SARS-CoV-1 survivors vaccinated with BNT162b2 vaccine developed broad-spectrum cross-clade neutralizing antibodies against all VOCs and also related animal sarbecoviruses [30]. Flipping this concept, it may be feasible that individuals immune to SARS-CoV-2 may develop cross-protecting antibodies using a heterologous booster vaccine based on SARS-CoV-1 or another related sarbecovirus. The optimal interdose duration is another important research question that
needs to be studied to better design vaccine regimens. A longer duration between first and second doses has been shown to stimulate more robust antibody responses with both the ChAdOx1 nCoV-19 (AZD1222) and BNT162b2 vaccines [31,32].

5. Conclusion

The emergence and rapid spread of the Omicron variant has demonstrated that the COVID-19 pandemic is far from over, even if the virus may be evolving toward an endemic seasonal upper respiratory tract virus infection. Vaccination remains a key part of the pandemic control strategy even in the presence of an immune escape variant, but strategies to optimize vaccination regimens and development of next-generation vaccines will be key to counter novel variants and reduce COVID-19 morbidity and mortality and should be a priority for future research.

Funding

Barnaby Young was supported by grants from the National Medical Research Council (REF: COVID19RF-018, COVID19RF-0008).

Declaration of Interests

Barnaby Young reports personal fees from AstraZeneca, Gilead, Novacyte, Roche, and Sanofi, which are outside the scope of this work. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers of this manuscript have no relevant financial or other relationships to disclose.

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