Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

furin landing site (QTQTNS). Further studies are required to characterize the interaction of bona fide bat-borne CoVs with cells derived from their specific bat hosts.

Multiple bat species can roost together, facilitating the transmission and recombination of bat-borne CoVs. Previous studies have demonstrated that nutritional and reproductive stress can lead to increased Hendra virus replication in *Pteropus scapulatus* (Plowright et al., 2008). Using ecological measurements, Zhou et al. (2021) speculate that temperature seasonality, evapotranspiration, and continentality could affect the distribution of bat species. Most importantly, the authors identified a high richness of rhinolophid bats across much of Southeast Asia and southern China. This high density of *Rhinolophus* bats could potentially facilitate intra- and inter-species transmission and recombination of bat-borne sarbecoviruses. As sampling of bat populations and additional wildlife species intensify, research will highlight the true diversity of CoVs that exist in our wildlife population.

While debate on the origin of SARS-CoV-2 continues, this recent study by Zhou et al. (2021) further bolsters the natural existence of SARS-CoV-2-related viruses in *Rhinolophus* bats.

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Beyond neutralization for BNT162b2 mRNA vaccination

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Mounting a robust immune response against SARS-CoV-2 requires neutralization as well as effector T cell functions. In this issue of *Cell Host Microbe*, Tauzin et al. characterize the humoral and T cell responses after a single dose of BNT162b2 mRNA vaccine in individuals with or without previous exposure to SARS-CoV-2.

We are entering into the 18th month of the ongoing global severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic that has claimed over 3.8 million reported deaths. As of May 2021, over 600 million people have been at least partially vaccinated against coronavirus disease 2019 (COVID-19), yet billions are still left vulnerable without access to an approved vaccine worldwide. We are facing unprecedented times where more than 6 billion people will require immunization against this virus. If two or multiple booster doses (against potential new variants) are required, this

would mean more than 12 billion doses will be necessary to protect against COVID-19. Therefore, there is an urgent need for rapid and efficacious vaccine strategies in order to bring an end to this worldwide epidemic.

Our knowledge of the precise immunological parameters that are required for protection against SARS-CoV-2 is still evolving, and several recent studies have provided important clues with respect to correlates of protection after either infection or following vaccination. Antibody-mediated viral neutralization has been considered the gold-standard in determining immune protection against COVID-19. However, there is no consensus on the timing and strength of neutralizing antibodies generated following vaccination and their ability to predict immune protection against COVID-19. Despite a weak neutralization following a single dose, recent studies have shown that the antibody response improves after second vaccination (Goel et al., 2021). Additionally, a full vaccine regimen may not be sufficient in generating strong neutralizing antibodies against emerging mutations of the virus such as B.1.3.5 (Planas et al., 2021). Moreover, neutralization assays have shown poor viral neutralization *in vitro* after one dose of BNT162b2 mRNA vaccine, although, recent data show nearly 90% efficacy 2 weeks following a single dose of mRNA vaccine. Cumulatively, these studies suggest that we have insufficient knowledge of the immunological parameters required for prediction of protection against SARS-CoV-2 infection.

In this issue, Tauzin et al. (2021) expand our knowledge about the correlates of immune protection beyond just the neutralizing antibodies that contribute toward vaccine efficacy after a single dose administration of an mRNA vaccine, Pfizer/BioNtech BNT162b2, which encodes for a membrane-anchored SARS-CoV-2 full-length spike (S). In this comprehensive study, authors use cohorts of SARS-CoV-2 naive donors or those previously infected (PI) and examine their immunological features prior to and after a single dose of BNT162b2 vaccine.

The authors found that the naive group elicited antibodies against receptor-binding domain and S at levels that were similar to PI group at 9 months post symptom onset. They further showed that vaccination also elicited cross-reactive antibodies against other betacoronaviruses such as SARS-CoV-1 and Midde East respiratory syndrome (MERS)-CoV in both cohorts, suggesting a broad recognition of mRNA vaccines. While a single dose of BNT162b2 enhanced the potency of the neutralizing response against a number of variants, the overall activity of these neutralizing antibodies at 3 weeks post vaccination was weak. In agreement with other published studies (Collier et al., 2021; Goel et al., 2021), Tauzin et al. (2021) found that while the overall neutralization activity appeared weak in the naive group after one dose of vaccination, Fc-mediated effector functions seemed robust based on the antibody-dependent cell-mediated cytotoxicity (ADCC) assays. This suggests the possibility that the production of antibodies with Fc-mediated effector functions with low neutralizing capacity can still provide effective protection and implicates a role for phagocytes and natural killer cells in mediating protection (Butler et al., 2021). In addition to humoral immunity, by using T cell receptor-dependent activation-induced marker (AIM) assays as well as intracellular cytokine staining (ICS), they found a significant increase in $CD4^+$, cTfh, and $CD8^+$ T cell responses in the naive group following a single dose of vaccine. A further deep profiling of T cells revealed that PI group exhibited elevated S-specific $CD8^+$ T cells and $CD4^+$ T cells that also co-expressed CD40L, IFNγ with sometimes co-expression of tumor necrosis factor alpha, CD107a, and interleukin-2. Finally, authors created prediction models based on humoral responses before vaccination that could provide cues toward inducing and boosting immune responses following a single dose of mRNA vaccine. Interestingly, the humoral and cell mediated immune response in PI individuals immunized by a single dose of mRNA vaccine was comparable to those who received two doses without previous exposure to SARS-CoV-2. Recent studies have shown that a second dose of vaccine in PI group fails to augment B cell or T cell responses (Ebinger et al., 2021; Goel et al., 2021; Saadat et al., 2021; Samanovic et al., 2021). Thus, this finding by Tauzin et al. (2021) and others suggests that providing a second dose of vaccine to previously infected individuals is not necessary with regards to enhancing neutralization, which will make more doses available for nations with limited accessibility to vaccines. However, further clinical studies are required to provide definitive insights into the effectiveness of administering two doses in PI group. This is because a second dose in the PI group may yet help refine the immune repertoire by enhancing memory T, B cells, or plasma cells in a way that are not quantitively boosted.

Overall, Tauzin et al. (2021) provide a framework for investigating effector functions and looking beyond the neutralizing antibodies in response to vaccinations. This study is highly relevant at the moment considering the number of newly emerging variants being identified in different parts of the world such as P.1, B.1.6.1.7, and B.1.617.2 (a.k.a. Delta) variants. In addition to efficacy of mRNA vaccines, there have been no comprehensive clinical reports showing the efficacy of single or two dose regimens of AstraZeneca/Covishield or Covaxin to elicit neutralization or cellular responses against those variants. It is likely that a robust immune protection can be elicited by using a heterologous vaccination approach by combining mRNA and adenovirus-based vaccines with minimal side effects (Shaw et al., 2021).

The road ahead

In this issue of *Cell Host Microbe*, Tauzin et al. (2021) provide a prediction model for detecting humoral and cellular immune protection following a single dose of Pfizer/BioNtech BNT162b2 mRNA vaccine in virus-naive and PI groups. Particularly striking, Tauzin et al. (2021) report the enhancement of cellular responses even with weak detectable neutralization suggesting another parameter to detect immune protection following administration of mRNA vaccines. However, there are still a number of unknowns toward understanding the correlates of immune protection. It is now widely accepted that the majority of COVID-19 pathology stems from an immune overdrive long past viral clearance. To this end, there is a poor understanding of the innate immune response

in the lung and the contributions of phagocytes toward inflammation and persisting tissue damage. It is also unclear which type of antibodies are being generated in response to vaccination, such as the isotypes of immunoglobulin G. This is critical to evaluate characterization of appropriate Fc-dependent effector functions and subsequent curation of anti-viral immune response. There is little clarity about the strength and quality of antibodies generated in those individuals that have previously experienced a severe disease against those with moderate symptoms. This is a critical gap in our understanding regarding the level of protection provided by natural infection and thereby a requirement for a single versus two dose regimen. Studies have also shown that even when the antibody levels were low following a natural infection, a single dose remarkably elevated these levels but did not improve after a second dose, which may be because long-lived bone marrow-derived plasma cells can provide immediate protection against SARS-CoV2 even when antibody levels were low in PI patients (Turner et al., 2021). All these reports collectively suggest that low antibody levels are insufficient to conclude lack of immune protection being afforded since plasma and T cell responses are maintained even with low detectable antibodies.

In order to win the fight against COVID-19, there needs to be unprecedented concert of policy makers and scientists coming together to engineer strategies that are safe and efficacious against the existing and newly emerging mutant variants. With regards to providing broader protection against COVID-19, we will need to extend the use of vaccines in a manner that protects individuals as well as the general populous such that those most vulnerable will be protected. Recent studies have reported about vaccine efficacy, albeit in narrow pools of clinical data from specific geography, with cohorts of patients from selected gender and genetic backgrounds. While these data seem scattered, this is to our advantage considering the cumulative intelligence being accumulated from each individual study that provides impactful insights into cohesively untangling the complexity of the infectivity of viral variants, their transmission rate, and the arsenal of host immune system against them.

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