Commentary

Vaccination after prior COVID-19 infection: Implications for dose sparing and booster shots

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Immunity elicited by both COVID-19 infection and SARS-CoV-2 vaccination effectively primes the immune system and provides protection from future re-infection. Analysis of multiple phase 3 clinical trials has suggested that neutralizing antibody titres are a strong correlate of protection against re-infection [1]. As time passes, neutralizing antibodies wane [2] and reinfections of individuals with prior COVID-19 are increasingly being reported [3]. Re-infections are generally clinically mild with lower levels of virus and reduced transmission. SARS-CoV-2 variants of concern, in particular Beta and Delta, are more infectious and evade a substantial proportion of the neutralizing antibody response from prior infection [4]. There is increasing interest in vaccination of subjects with prior COVID-19 to prevent re-infections.

In this article, Zollner et al. study antibody and T cell responses in a cohort of 14 subjects with prior mild-moderate COVID-19 who received the BioNTech/Pfizer BNT162b2 (Comirnaty) vaccine compared to 27 uninfected subjects [5]. In concordance with prior studies, a remarkable boost in Spike-specific neutralizing antibodies was observed in vaccinated subjects with prior COVID-19, with levels ~20-fold higher after the first dose and ~6-fold higher after the second dose compared to uninfected controls. Importantly, the added benefit of a 2nd vaccine dose at the standard 3-week interval was modest in previously infected subjects (< 2- fold rise). These data suggest that deferring the second vaccination of individuals with prior infection may be a more cost-effective strategy to re-boost neutralizing antibody titres in some populations. Although it comes with logistic challenges (confirming prior infection), such a vaccine-

sparing strategy could help the roll out of the vaccine in the current environment where global supply is limited.

The benefit of T cell immunity in prevention of SARS-CoV-2 is less certain, with a more likely role for T cells in reducing rates of severe infection. CD4 and CD8 T cells to SARS-CoV-2 antigens also wane over time following infection and the benefit of boosting T cell responses by vaccination is not yet clear. T cell responses to the Spike antigen, the only SARS-CoV-2 antigen in most vaccines, represent only a fraction of T cell responses across the SARS-CoV-2 proteome, with Nucleocapsid being a common target of T cell immunity. Zollner et al. studied T cell responses using IFN-gamma release assays and intracellular cytokine staining assays and found that IFN-gamma release responses to Spike were ~2-fold higher in previously infected subjects compared to uninfected subjects after vaccination. T cells responses measured by intracellular cytokine staining assays were similar, albeit in a small subset of subjects.

Several groups have argued that improving the capacity of vaccine to induce or boost SARS-CoV-2 specific T cells could be an important addition to current vaccine efficacy [6]. Improving vaccine-induced T cell responses could act through cytotoxic CD8 T cells to reduce disease severity in the context of vaccine breakthrough infections, or could promote CD4 T cells capable of promoting neutralizing antibody responses. Zollner et al. also posit that persistent N-specific T cell responses in the previously infected cohort could point to their utility as a T cell vaccine target [5]. Studies in small animal models suggest that such an approach may provide additional benefit when combined with existing spike-based vaccines [7]. T cells most critical in assisting the induction of neutralizing antibodies are CD4+ T-follicular helper (TFH) cells present in lymph nodes. Particular phenotypes of TFH may be more efficient at assisting germinal center B cells to undergo the necessary somatic mutations to produce neutralizing antibodies [8]. Understanding how best to induce or boost effective TFH by vaccination, rather than only total CD4 or CD8 T cells, may be an efficient pathway to induce more potent neutralising antibody responses.

Several questions remain regarding T cell responses following vaccination of either uninfected or previously infected individuals. First, it will be important to understand whether CD4 or CD8 T cells contribute to the differences observed between vaccine groups. Furthermore, determining the relationship between cTFH responses and neutralising titres after vaccination of infected subjects will give

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greater insight into the requirement for *T* cell help during recall of memory *B* cell responses.

A major current issue is that all vaccines express the ancestral SARS-CoV-2 Spike, whereas currently circulating variants such as Delta have several mutations that evade much of the response. Neutralizing antibody responses are typically ~4-fold lower to Delta than to the ancestral strain [4]. The current vaccines boost neutralizing responses to all strains but the responses to the variants typically remain proportionally lower. Reformulated vaccines expressing variant Spike are undergoing evaluation and are likely to improve the neutralizing response to variants [9]. However, such vaccines may boost responses to conserved epitopes rather than preferentially induce responses to the new variants, a phenomenon known as immune imprinting or "original antigenic sin" [10]. This is observed with the relatively poorly protective reformulated annual influenza vaccine. Improved strategies to specifically induce responses to new epitopes in the variant spike may be needed to overcome this issue.

Funding

Contributions

Jointly written by SK and JJ.

Declaration of Competing Interest

The authors declare no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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