Differential Kinetics of Immune Responses Elicited by Covid-19 Vaccines

To the Editor: Previous studies have shown that the BNT162b2 (Pfizer–BioNTech), mRNA-1273 (Moderna), and Ad26.COV2.S (Johnson & Johnson–Janssen) vaccines provide robust protective efficacy against coronavirus disease 2019 (Covid-19). Here, we report comparative kinetics of humoral and cellular immune responses elicited by the two-dose BNT162b2 vaccine (in 31 participants), the two-dose mRNA-1273 vaccine (in 22 participants), and the one-dose Ad26.COV2.S vaccine (in 8 participants). We evaluated antibody and T-cell responses from peak immunity at 2 to 4 weeks after the second immunization in recipients of the messenger RNA (mRNA) vaccines or after the first immunization in recipients of the Ad26.COV2.S vaccine to 8 months (Table S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org).

At peak immunity, the BNT162b2 vaccine induced a high median live-virus neutralizing antibody titer (1789), a high median pseudovirus neutralizing antibody titer (700), and a high median binding antibody titer against the receptor-binding domain (RBD) (21,564). However, these titers declined sharply by 6 months after vaccination, as previously reported, and they declined further by 8 months (Figs. 1A through 1C, S1, and S2). By 8 months after BNT162b2 vaccination, the median live-virus neutralizing antibody titer was 53, the median pseudovirus neutralizing antibody titer was 160, and the median RBD-specific binding antibody titer was 755; these titers were lower than the peak titers by a factor of 34, 4, and 29, respectively.

At peak immunity, the mRNA-1273 vaccine also elicited a high median live-virus neutralizing antibody titer (1789), a high median pseudovirus neutralizing antibody titer (700), and a high median binding antibody titer against the receptor-binding domain (RBD) (21,564). However, these titers declined sharply by 6 months after vaccination, as previously reported, and they declined further by 8 months (Figs. 1A through 1C, S1, and S2). By 8 months after mRNA-1273 vaccination, the median live-virus neutralizing antibody titer was 133, the median pseudovirus neutralizing antibody titer was 391, and the median RBD-specific binding antibody titer was 1361; however, these titers remained relatively stable over 8 months. At 8 months, the median live-virus neutralizing antibody titer was 629, the median pseudovirus neutralizing antibody titer was 185, and the median RBD-specific binding antibody titer was 843; these titers were similar to the titers at week 4. With all three vaccines, there were generally stable antibody-dependent cellular phagocytosis and antibody-dependent complement deposition responses (Fig. S3).

Recipients of the BNT162b2 and mRNA-1273 vaccines also had decreases in titers of live-virus neutralizing antibodies, pseudovirus neutralizing antibodies, and RBD- and spike protein (S)-specific binding antibody responses against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants from peak immunity to 8 months; after Ad26.COV2.S vaccination, however, there were stable or in some cases increasing antibody titers against these variants (Figs. S4 and S5). At 8 months, the median pseudovirus neutralizing antibody titer against the SARS-CoV-2 B.1.617.2 (delta) variant were similar with the BNT162b2 vaccine (67), the mRNA-1273 vaccine (76), and the Ad26.COV2.S vaccine (107).

T-cell responses were assessed by CD4+ and CD8+ intracellular cytokine-staining assays that used pooled S peptides for stimulation (Fig. 1D and 1E). At 8 months, the median CD8+ T-cell responses were 0.016% with the BNT162b2 vac-
A  Live-Virus Neutralizing Antibody Response

B  Pseudovirus Neutralizing Antibody Response

C  RBD IgG Antibody Response

D  CD4 T-Cell Response

E  CD8 T-Cell Response

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Percent CD4+ IFN+ CD3+ T Cells

Percent CD8+ IFN+ CD3+ T Cells
cine, 0.017% with the mRNA-1273 vaccine, and 0.12% with the Ad26.COV2.S vaccine. With all three vaccines, T-cell responses showed broad cross-reactivity against SARS-CoV-2 variants (Fig. S6).

These data show differential kinetics of immune responses induced by the mRNA and Ad26.COV2.S vaccines over an 8-month follow-up period. As shown in previous studies, the BNT162b2 and mRNA-1273 vaccines were characterized by high peak antibody responses that declined sharply by 6 months; these responses declined further by 8 months. Antibody titers in recipients of the mRNA-1273 vaccine were generally higher than those in recipients of the BNT162b2 vaccine. The Ad26.COV2.S vaccine induced lower initial antibody responses, but these responses were relatively stable over the 8-month follow-up period, with minimal-to-no evidence of decline. These findings have important implications for waning vaccine immunity, although correlates of protection from SARS-CoV-2 are not yet defined.

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