CORRESPONDENCE

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,[1,2] 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 (53), pseudovirus neutralizing antibody titer (160), and RBD-specific binding antibody titer (755) elicited by the vaccine 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 (5848), pseudovirus neutralizing antibody titer (1569), and RBD-specific binding antibody titer (25,677). By 8 months after mRNA-1273 vaccination, the median live-virus neutralizing antibody titer was 133, the pseudovirus neutralizing antibody titer was 273, and the median RBD-specific binding antibody titer was 1546; these titers were lower than the peak titers by a factor of 44, 6, and 17, respectively.

The Ad26.COV2.S vaccine induced substantially lower median titers than the mRNA vaccines at peak immunity. At 4 weeks after single-shot Ad26.COV2.S immunization, the median live-virus neutralizing antibody titer was 146, 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.[3] 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 titers 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-

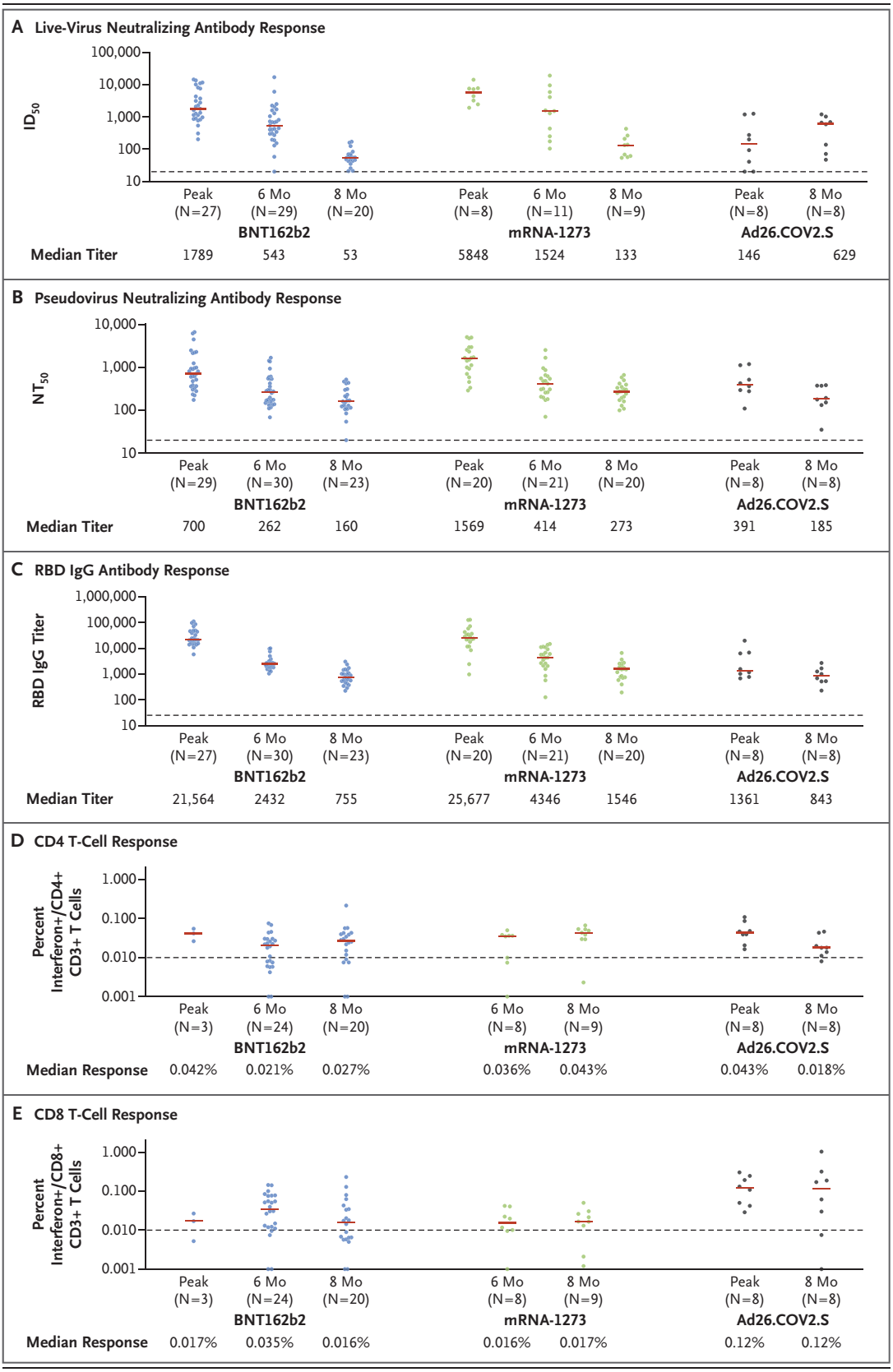
A Live-Virus Neutralizing Antibody Response
ID50
100,000
10,000
1,000
100
10
Peak (N=27)
6 Mo (N=29)
8 Mo (N=20)
Peak (N=8)
6 Mo (N=11)
8 Mo (N=9)
Peak (N=8)
8 Mo (N=8)
BNT162b2
mRNA-1273
Ad26.COV2.S
Median Titer 1789 543 53 5848 1524 133 146 629
B Pseudovirus Neutralizing Antibody Response
NT50
10,000
1,000
100
10
Peak (N=29)
6 Mo (N=30)
8 Mo (N=23)
Peak (N=20)
6 Mo (N=21)
8 Mo (N=20)
Peak (N=8)
8 Mo (N=8)
BNT162b2
mRNA-1273
Ad26.COV2.S
Median Titer 700 262 160 1569 414 273 391 185
C RBD IgG Antibody Response
RBD IgG Titer
1,000,000
100,000
10,000
1,000
100
10
Peak (N=27)
6 Mo (N=30)
8 Mo (N=23)
Peak (N=20)
6 Mo (N=21)
8 Mo (N=20)
Peak (N=8)
8 Mo (N=8)
BNT162b2
mRNA-1273
Ad26.COV2.S
Median Titer 21,564 2432 755 25,677 4346 1546 1361 843
D CD4 T-Cell Response
Percent Interferon+/CD4+ CD3+ T Cells
1.000
0.100
0.010
0.001
Peak (N=3)
6 Mo (N=24)
8 Mo (N=20)
6 Mo (N=8)
8 Mo (N=9)
Peak (N=8)
8 Mo (N=8)
BNT162b2
mRNA-1273
Ad26.COV2.S
Median Response 0.042% 0.021% 0.027% 0.036% 0.043% 0.043% 0.018%
E CD8 T-Cell Response
Percent Interferon+/CD8+ CD3+ T Cells
1.000
0.100
0.010
0.001
Peak (N=3)
6 Mo (N=24)
8 Mo (N=20)
6 Mo (N=8)
8 Mo (N=9)
Peak (N=8)
8 Mo (N=8)
BNT162b2
mRNA-1273
Ad26.COV2.S
Median Response 0.017% 0.035% 0.016% 0.016% 0.017% 0.12% 0.12%

Figure 1 (facing page). Kinetics of Humoral and Cellular Immune Responses Elicited by the BNT162b2, mRNA-1273, and Ad26.COV2.S Vaccines.

Shown are immune responses after vaccination with BNT162b2, mRNA-1273, and Ad26.COV2.S at peak immunity (2 to 4 weeks after the second dose in recipients of the messenger RNA vaccines or 4 weeks after one dose in recipients of the Ad26.COV2.S vaccine) and at 6 months, 8 months, or both after the first dose. Panel A shows the serum 50% inhibitory dilution (ID_{50}) titers in the live-virus neutralizing antibody assay. Red bars indicate medians, dashed lines the limit of detection for each assay, and each dot a single participant. Panel B shows the serum dilution for 50% reduction (NT_{50}) expressed in relative light units in the pseudovirus neutralizing antibody assay. Panel C shows the binding IgG antibody titers against the receptor-binding domain (RBD) in the serum enzyme-linked immunosorbent assay. Intracellular cytokine-staining assays were performed to measure the percentage of interferon-γ production in T cells; Panel D shows this percentage in CD4+ T cells, and Panel E shows this percentage in CD8+ T cells. Flow cytometric gating was performed to identify T cells (which are CD3+) rather than other CD4+- or CD8+-expressing immune cells. All assays were performed with the use of the SARS-CoV-2 WA1/2020 strain. The Ad26.COV2.S vaccine data in Panels B through E were published previously[3] and are included here for comparative purposes.

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,[1,2] 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.[3] 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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1. Pegu A, O'Connell SE, Schmidt SD, et al. Durability of mRNA-1273 vaccine-induced antibodies against SARS-CoV-2 variants. Science 2021;373:1372-7.

2. Falsey AR, Frenck RW Jr, Walsh EE, et al. SARS-CoV-2 neutralization with BNT162b2 vaccine dose 3. N Engl J Med. DOI: 10.1056/NEJMc2113468.

3. Barouch DH, Stephenson KE, Sadoff J, et al. Durable humoral and cellular immune responses 8 months after Ad26.COV2.S vaccination. N Engl J Med 2021;385:951-3.

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