Durability of Immune Responses After Boosting in Ad26.COV2.S-Primed Healthcare Workers

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The emergence of SARS-CoV-2 variants raised questions regarding the durability of immune responses after homologous or heterologous boosters after Ad26.COV2.S priming. We found that SARS-CoV-2–specific binding antibodies, neutralizing antibodies, and T cells are detectable 5 months after boosting, although waning of antibodies and limited cross-reactivity with Omicron BA.1 was observed.

Keywords. SARS-CoV-2; Ad26.COV2.S; waning immunity.

A previous phase 3 clinical trial showed that a single dose of Ad26.COV2.S coronavirus disease 2019 (COVID-19) vaccination provides 52.9% protection against moderate to severe–critical COVID-19 [1]. Bearing in mind the potential emergence of novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants, booster vaccination after Ad26.COV2.S priming is recommended [2]. We recently reported that Ad26.COV2.S, messenger RNA (mRNA)-1273, and BNT162b2 boosters are safe and immunogenic in Ad26.COV2.S-primed healthcare workers (HCW) 28 days after priming [3]. Although all 3 booster regimens significantly increased SARS-CoV-2–specific immune responses, boosting with a heterologous vaccination regimen (either mRNA-1273 or BNT162b2) resulted in a larger increase in antibody and T-cell responses than boosting with a homologous vaccination regimen (Ad26.COV2.S) [3]. To gain insight into the durability of immune responses after homologous vs heterologous booster vaccination, we aimed to conduct long-term follow-up sampling (at 6 and 12 months after boosting) to assess vaccine-induced immunity to SARS-CoV-2. However, the emergence of SARS-CoV-2 variants with immune evasive potential raised urgent questions regarding the durability of immune responses elicited by homologous and heterologous booster vaccination after Ad26.COV2.S priming. We therefore expedited follow-up sampling and analyses to 5 months after booster vaccination. Here, we present data on S-specific binding antibodies, S-specific T-cell responses, and neutralizing antibodies (against ancestral virus, Delta variant, and Omicron BA.1 variant) 5 months after booster vaccination.

METHODS

The SWITCH study is a single-blind, multicenter, randomized, controlled trial that involved HCW from 4 academic hospitals in the Netherlands. Ad26.COV2.S-primed HCW were randomized to 1 of the following 4 groups: no boost, Ad26.COV2.S boost, mRNA-1273 boost, or BNT162b2 boost, and immune responses were initially measured pre- and 28 days post-booster vaccination. During the study period, the government of the Netherlands based their advice [4] on our study results [3] to provide everyone vaccinated with a single dose of Ad26.COV2.S with an mRNA-based booster vaccination (ie, mRNA-1273 or BNT162b2). The “no boost” group is therefore no longer part of this analysis for durability of immune responses. An overview of the study design is given in Supplementary Figure 1.

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Figure 1. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–specific immune responses. (A) Levels of SARS-CoV-2 spike (S) protein–specific IgG antibodies at baseline (pre-boost) and 28 days and 5 months after booster vaccination with Ad26.COV2.S, mRNA-1273, or BNT162b2. The lower limit of detection (LLoD) was set at 4.81 binding antibody units (BAU) per milliliter. The cutoff value for response was set at 33.8 BAU/mL (dotted line). (B) Interferon-γ levels in plasma after stimulation of whole blood with overlapping peptide pool spanning the S protein at baseline (pre-boost) and 28 days and 5 months after booster vaccination in the 3 groups. The LLoD was set at 0.01 IU/mL. The cutoff value for response was set at 0.15 IU/mL (dotted line). (C) Neutralizing antibody PRNT50 at baseline (pre-boost) and 28 days and 5 months after booster vaccination in the 3 groups. The LLoD was set at an antibody titer of 20, and samples that did not neutralize virus were set at an antibody titer of 10. (D) PRNT50 against the ancestral SARS-CoV-2 and the Delta and Omicron (BA.1) variants at 5 months after booster vaccination. Detection limits are identical to those in panel C. Data are presented in box-and-whisker plots. The whiskers indicate the range, the top and bottom of the boxes indicate the interquartile range, and the horizontal line within each box indicates the median. Geometric mean titers are indicated above the box plot. Abbreviations: IgG, immunoglobulin G; mRNA, messenger RNA; PRNT50, plaque reduction neutralization titer-50.
vs Ad26.COV2.S/BNT162b2, and Ad26.COV2.S/mRNA-1273 vs Ad26.COV2.S/BNT162b2 (Figure 1A) [3]. This analysis was repeated for the log-transformed S-specific T-cell responses (measured as interferon-gamma [IU/mL] in plasma after stimulation with overlapping S peptides) and for neutralizing antibody titers to the ancestral virus (Figure 1B and 1D) [5]. We performed a separate analysis that included participants who had a SARS-CoV-2 infection (Supplementary Figure 2). For a description of our laboratory assays, see the supplemental methods section. In line with our original protocol [6], a P value < .01 was considered statistically significant.

RESULTS

We included 279 of the original 461 participants (Supplementary Figure 1) for the analyses of S-specific antibodies (Ad26.COV2.S: n = 85, mRNA-1273: n = 93, BNT162b2: n = 101). The baseline demographics of the included participants are presented in Supplementary Table 1. In 2 randomly drawn subsamples, we analyzed T-cell responses in 112 participants (Ad26.COV2.S: n = 36, mRNA-1273: n = 37, BNT162b2: n = 39) and neutralizing antibodies in 35 participants (Ad26.COV2.S: n = 12, mRNA-1273: n = 11, BNT162b2: n = 12). S-specific binding antibody levels were significantly higher 5 months (median, 153.2 days; IQR, 140.2–162.1) after mRNA-based booster vaccination compared with Ad26.COV2.S booster vaccination (Figure 1A). Boosting with mRNA-1273 yielded higher antibody levels compared with BNT162b2 booster vaccination. Neutralizing antibodies were also significantly higher 5 months after mRNA-based booster vaccination compared with Ad26.COV2.S booster vaccination (Figure 1B). We detected neutralizing antibodies against the ancestral virus and Delta variant at 5 months post-boost but no cross-neutralization of Omicron (BA.1) at that time point (Figure 1C, original data in Supplementary Figure 3). Although S-specific T-cell responses measured in whole blood were higher 28 days after mRNA-based booster vaccination compared with Ad26.COV2.S booster vaccination, this difference was no longer apparent 5 months after booster vaccination (Figure 1D). We observed significant positive correlations between neutralizing antibodies against the ancestral SARS-CoV-2 variant and the presence of S-specific binding antibodies pre- and post-boost (Supplementary Figure 4A–4C) and between S-specific binding antibodies and S-specific T-cell responses pre-boost and 28 days post-boost but not 5 months post-boost (Supplementary Figure 4D–4F).

Waning of binding antibodies, neutralizing antibodies, and T-cell responses was observed in all groups. Between 28 days and 5 months after booster, the GMT of S-specific antibodies was reduced 3.4 fold after Ad26.COV2.S booster vaccination compared with 6.1 fold and 5.3 fold after mRNA-1273 and BNT162b2 booster vaccination, respectively (Supplementary Figure 5A). Supplementary Table 2 provides the geometric means of all groups at all study visits. Between 28 days and 5 months after receipt of booster vaccination, the S-specific T-cell responses declined toward similar levels as detected pre-booster vaccination (Supplementary Figure 5B). For the neutralizing antibodies, this is also the case for the Ad26.COV2.S boost; however, the neutralizing antibodies remained higher 5 months after an mRNA-based boost vs pre-boost (Supplementary Figure 5C). Despite waning of immune responses at 5 months, the fact that immune responses were detected in almost all participants 28 days after booster vaccination indicates proper formation of immunological memory [7]. The intention-to-treat analysis that included participants with a self-reported PCR-confirmed SARS-CoV-2 infection (n = 22) yielded similar results as the analysis presented above. The participants who developed infection during follow-up yielded high S-specific binding antibody levels (Supplementary Figure 2).

DISCUSSION AND CONCLUSION

To conclude, we showed that SARS-CoV-2–specific binding antibodies, neutralizing antibodies, and T-cell responses are detectable 5 months after boosting of Ad26.COV2.S-primed individuals with an Ad26.COV2.S, mRNA-1273, or BNT162b2 vaccination, although waning of responses was observed. In general, immune responses after heterologous mRNA-based booster vaccination remained higher compared with Ad26.COV2.S booster vaccination, similar to observations 28 days after booster [3]. Five months after boosting, the majority of participants still had antibodies that neutralized the ancestral SARS-CoV-2 and Delta variants, but almost none of the participants cross-neutralized Omicron (BA.1). Of note, in the absence of cross-neutralization of immune-evasive SARS-CoV-2 variants, preserved T-cell responses could play an important role in providing protection from (severe) COVID-19. Cross-reactivity of T cells with the Omicron variant was previously demonstrated [5, 8, 9].

We speculate that recall responses upon exposure to SARS-CoV-2 are likely to protect healthy vaccinated individuals against developing severe COVID-19. Understanding the durability of antibody and T-cell responses will guide the need for additional boosters in the future trajectory of the pandemic.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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