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Durability of immune responses after boosting in Ad26.COV2.S-primed healthcare workers

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ABSTRACT

The emergence of SARS-CoV-2 variants raised questions regarding the durability of immune responses after homologous or heterologous booster vaccination 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

INTRODUCTION

A previous phase 3 clinical trial showed that a single dose Ad26.COV2.S COVID-19 vaccination provides 52.9% protection against moderate to severe–critical COVID-19. [1] Bearing in mind the potential emergence of novel SARS-CoV-2 variants, booster vaccination after Ad26.COV2.S priming is recommended. [2] We recently reported that Ad26.COV2.S, mRNA-1273 and BNT162b2 boosters are safe and immunogenic in Ad26.COV2.S-primed health care workers (HCW) 28 days after priming. [3] Although all three booster regimens significantly increased SARS-CoV-2-specific immune responses, boosting with a heterologous vaccination regimen (with either mRNA-1273 or BNT162b2) resulted in a larger increase in antibody and T-cell responses than boosting with a homologous vaccination regimen (with Ad26.COV2.S). [3] To gain insight into the durability of immune responses after homologous versus 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 or 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 AND DATA

The SWITCH study is a single-blind, multicenter, randomized, controlled trial involving HCW from four academic hospitals in the Netherlands. Ad26.COV2.S-primed HCW were randomized to four groups: (1) no boost, (2) Ad26.COV2.S boost, (3) mRNA-1273 boost, or (4) 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 (i.e., 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 **Figure S1**.

We included all participants from whom samples at all study visits were obtained and who did not report a PCR-confirmed SARS-CoV-2 infection. The primary outcome (i.e., S-specific binding antibodies) is presented as the geometric mean titer (GMT) and interquartile range (IQR) for each study group. We analyzed the differences in log-transformed S-specific binding antibody titers 28-days and 5 months after boost using a Mann Whitney U test with the following contrasts:

Ad26.COV2.S/Ad26.COV2.S vs. Ad26.COV2.S/mRNA-1273, Ad26.COV2.S/Ad26.COV2.S 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 IFNγ (IU/ml) in plasma after stimulation with overlapping S peptides) and for neutralizing antibody titers to the ancestral virus **(Figure 1B and D)**. [5] We performed a separate analysis including participants who had a SARS-CoV-2 infection **(Figure S2)**. In line with our original protocol [6], a p-value below 0.01 was considered statistically significant.

RESULTS

We included 279 individuals of the original 461 participants **(Figure S1)** 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 **Table S1**. In two randomly drawn sub-samples, 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), respectively. S-specific binding antibody levels were significantly higher 5 months (median of 153.2 days, IQR 140.2-162.1 days) after mRNA-based booster vaccination compared to Ad26.COV2.S boost vaccination **(Figure 1A)**. Boosting with mRNA-1273 yielded higher antibody levels compared to BNT162b2 booster vaccination. Neutralizing antibodies were also significantly higher 5 months after mRNA-based booster vaccination compared to Ad26.COV2.S boost 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 this time-point (**Figure 1C**, original data in **Figure S3**). Although S-specific T-cell responses measured in whole blood were higher 28 days after mRNA-based booster vaccination compared to 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 **(Figure S4A to S4C)**, 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 **(Figure S4D to S4F)**.

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 to 6.1 and 5.3 fold after mRNA-1273 or BNT162b2 booster vaccination, respectively **(Figure S5A)**. Table S2 provides the geometric means of all groups at all study visits. Between 28 days and 5 months after receiving booster

vaccination, the S-specific T-cell responses declined towards similar levels as detected pre-booster vaccination **(Figure S5B)**. For the neutralizing antibodies, this is also the case for the Ad26.COV2.S boost, however the neutralizing antibodies remain higher 5 months after an mRNA-based boost versus pre-boost. 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 including 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 **(Figure S2)**.

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 to 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). Especially, in the absence of cross-neutralization of immune-evasive SARS-CoV-2 variants, preserved T-cell responses could play an important role in protecting 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 further boosters in the future trajectory of the pandemic.

NOTES

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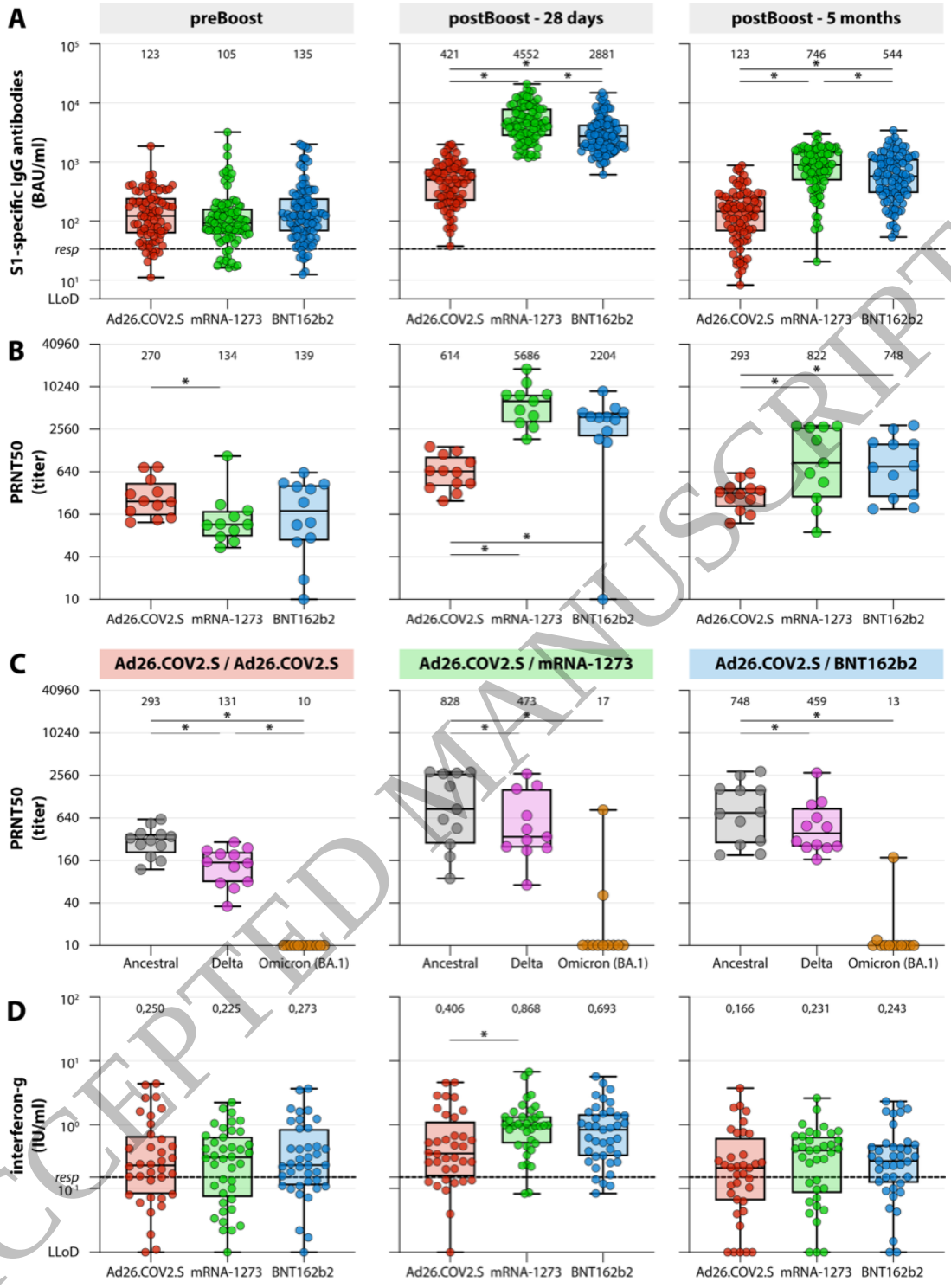
FIGURE CAPTION

Figure 1. SARS-CoV-2-specific immune responses. (A) Levels of SARS-CoV-2 spike protein (S)–specific IgG antibodies at baseline (pre-boost), and 28 days and 5 months after booster vaccination with either 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 cut-off value for response was set at 33.8 BAU per milliliter (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 three groups. The LLoD was set at 0.01 IU per milliliter. The cut-off value for response was set at 0.15 IU per milliliter (dotted line). (C) Neutralizing antibodies (plaque reduction neutralization titer-50 [PRNT50]) at baseline (pre-boost), and 28 days and 5 months after booster vaccination in the three 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) at 5 months after booster vaccination. Detection limits are identical to 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 boxplot.



1

2 **Figure 1**

3 **24x33 mm (.49 x DPI)**