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1 **Durability of immune responses after boosting in Ad26.COVID.S-primed healthcare workers**

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1 **ABSTRACT**

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

7

8 **KEYWORDS:** SARS-CoV-2, Ad26.COV2.S, waning immunity

ACCEPTED MANUSCRIPT

1 INTRODUCTION

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

19 20 METHODS AND DATA

21 The SWITCH study is a single-blind, multicenter, randomized, controlled trial involving HCW from
22 four academic hospitals in the Netherlands. Ad26.COVID.S-primed HCW were randomized to four
23 groups: (1) no boost, (2) Ad26.COVID.S boost, (3) mRNA-1273 boost, or (4) BNT162b2 boost, and
24 immune responses were initially measured pre- and 28 days post-booster vaccination. During the
25 study period, the government of the Netherlands based their advice [4] on our study results [3] to
26 provide everyone vaccinated with a single dose of Ad26.COVID.S with an mRNA-based booster
27 vaccination (i.e., mRNA-1273 or BNT162b2). The “no boost” group is therefore no longer part of this
28 analysis for durability of immune responses. An overview of the study design is given in **Figure S1**.

29
30 We included all participants from whom samples at all study visits were obtained and who
31 did not report a PCR-confirmed SARS-CoV-2 infection. The primary outcome (i.e., S-specific binding
32 antibodies) is presented as the geometric mean titer (GMT) and interquartile range (IQR) for each
33 study group. We analyzed the differences in log-transformed S-specific binding antibody titers 28-
34 days and 5 months after boost using a Mann Whitney U test with the following contrasts:

1 Ad26.COVS/Ad26.COVS vs. Ad26.COVS/mRNA-1273, Ad26.COVS/Ad26.COVS vs
2 Ad26.COVS/BNT162b2, and Ad26.COVS/mRNA-1273 vs. Ad26.COVS/BNT162b2 (**Figure 1A**). [3]
3 This analysis was repeated for the log-transformed S-specific T-cell responses (measured as IFN γ
4 (IU/ml) in plasma after stimulation with overlapping S peptides) and for neutralizing antibody titers
5 to the ancestral virus (**Figure 1B and D**). [5] We performed a separate analysis including participants
6 who had a SARS-CoV-2 infection (**Figure S2**). In line with our original protocol [6], a p-value below
7 0.01 was considered statistically significant.

8

9 RESULTS

10 We included 279 individuals of the original 461 participants (**Figure S1**) for the analyses of S-specific
11 antibodies (Ad26.COVS: N=85, mRNA-1273: N=93, BNT162b2: N=101). The baseline demographics
12 of the included participants are presented in **Table S1**. In two randomly drawn sub-samples, we
13 analyzed T-cell responses in 112 participants (Ad26.COVS: N=36, mRNA-1273: N=37, BNT162b2:
14 N=39) and neutralizing antibodies in 35 participants (Ad26.COVS: N=12, mRNA-1273: N=11,
15 BNT162b2: N=12), respectively. S-specific binding antibody levels were significantly higher 5 months
16 (median of 153.2 days, IQR 140.2-162.1 days) after mRNA-based booster vaccination compared to
17 Ad26.COVS boost vaccination (**Figure 1A**). Boosting with mRNA-1273 yielded higher antibody
18 levels compared to BNT162b2 booster vaccination. Neutralizing antibodies were also significantly
19 higher 5 months after mRNA-based booster vaccination compared to Ad26.COVS boost vaccination
20 (**Figure 1B**). We detected neutralizing antibodies against the ancestral virus and Delta variant at 5
21 months post-boost, but no cross-neutralization of Omicron (BA.1) at this time-point (**Figure 1C**,
22 original data in **Figure S3**). Although S-specific T-cell responses measured in whole blood were higher
23 28 days after mRNA-based booster vaccination compared to Ad26.COVS booster vaccination, this
24 difference was no longer apparent 5 months after booster vaccination (**Figure 1D**). We observed
25 significant positive correlations between neutralizing antibodies against the ancestral SARS-CoV-2
26 variant and the presence of S-specific binding antibodies pre- and post-boost (**Figure S4A to S4C**),
27 and between S-specific binding antibodies and S-specific T-cell responses pre-boost and 28 days
28 post-boost, but not 5 months post-boost (**Figure S4D to S4F**).

29

30 Waning of binding antibodies, neutralizing antibodies and T-cell responses was observed in
31 all groups. Between 28 days and 5 months after booster, the GMT of S-specific antibodies was
32 reduced 3.4 fold after Ad26.COVS booster vaccination, compared to 6.1 and 5.3 fold after mRNA-
33 1273 or BNT162b2 booster vaccination, respectively (**Figure S5A**). Table S2 provides the geometric
34 means of all groups at all study visits. Between 28 days and 5 months after receiving booster

1 vaccination, the S-specific T-cell responses declined towards similar levels as detected pre-booster
2 vaccination (**Figure S5B**). For the neutralizing antibodies, this is also the case for the Ad26.COVS.S
3 boost, however the neutralizing antibodies remain higher 5 months after an mRNA-based boost
4 versus pre-boost. Despite waning of immune responses at 5 months, the fact that immune
5 responses were detected in almost all participants 28 days after booster vaccination, indicates
6 proper formation of immunological memory. [7] The intention to treat analysis including participants
7 with a self-reported PCR confirmed SARS-CoV-2 infection (n=22) yielded similar results as the
8 analysis presented above. The participants who developed infection during follow-up yielded high S-
9 specific binding antibody levels (**Figure S2**).

11 CONCLUSION

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

22
23 We speculate that recall responses upon exposure to SARS-CoV-2 are likely to protect
24 healthy vaccinated individuals against developing severe COVID-19. Understanding the durability of
25 antibody and T-cell responses will guide the need for further boosters in the future trajectory of the
26 pandemic.

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17 board meeting from Glaxo Smith Kline; and honoraria for lectures from Pharming, Takeda.

18

19

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3 Dose Ad26.COVID.S. *New England Journal of Medicine* **2022**.
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1 **FIGURE CAPTION**

2 **Figure 1. SARS-CoV-2-specific immune responses.** (A) Levels of SARS-CoV-2 spike protein (S)-specific IgG antibodies at
3 baseline (pre-boost), and 28 days and 5 months after booster vaccination with either Ad26.COV2.S, mRNA-1273 or
4 BNT162b2. The lower limit of detection (LLoD) was set at 4.81 binding antibody units (BAU) per milliliter. The cut-off value
5 for response was set at 33.8 BAU per milliliter (dotted line). (B) Interferon- γ levels in plasma after stimulation of whole
6 blood with overlapping peptide pool spanning the S protein at baseline (pre-boost), and 28 days and 5 months after
7 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
8 0.15 IU per milliliter (dotted line). (C) Neutralizing antibodies (plaque reduction neutralization titer-50 [PRNT50]) at
9 baseline (pre-boost), and 28 days and 5 months after booster vaccination in the three groups. The LLoD was set at an
10 antibody titer of 20, and samples that did not neutralize virus were set at an antibody titer of 10. (D) PRNT50 against the
11 ancestral SARS-CoV-2, and the Delta and Omicron (BA.1) at 5 months after booster vaccination. Detection limits are
12 identical to panel C. Data are presented in box-and-whisker plots. The whiskers indicate the range, the top and bottom of
13 the boxes indicate the interquartile range, and the horizontal line within each box indicates the median. Geometric mean
14 titers are indicated above the boxplot.
15

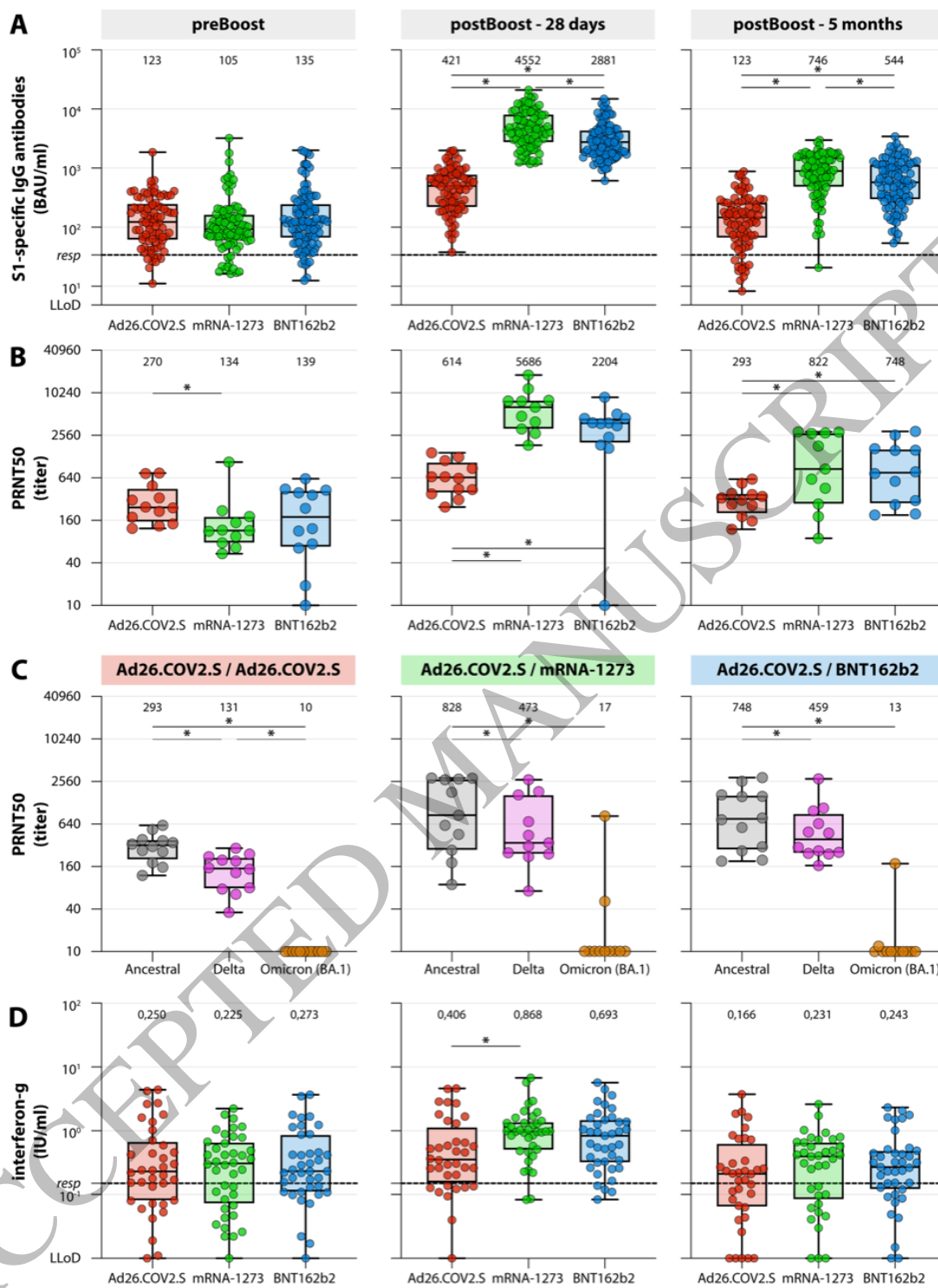


Figure 1
24x33 mm (.49 x DPI)

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