Clinical Infectious Diseases

BRIEF REPORT

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

Roos S. G. Sablerolles,[1,2,a] Wim J. R. Rietdijk,[2,a] Abraham Goorhuis,[3,4] Douwe F. Postma,[5] Leo G. Visser,[6] Katharina S. Schmitz,[7] Daryl Geers,[7] Susanne Bogers,[7] Eva van Haren,[2] Marion P. G. Koopmans,[7] Virgil A. S. H. Dalm,[8] Neeltje A. Kootstra,[9] Anke L. W. Huckriede,[10] Renate Akkerman,[10] Martin Beukema,[10] Melvin Lafeber,[1] Debbie van Baarle,[10,11] Rory D. de Vries,[7,b] P. Hugo M. van der Kuy,[2,b] and Corine H. GeurtsvanKessel[7b]; for the SWITCH Research Group

[1]Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands; [2]Department of Hospital Pharmacy, Erasmus Medical Center, Rotterdam, The Netherlands; [3]Center of Tropical Medicine and Travel Medicine, Department of Infectious Diseases, Amsterdam University Medical Centers, Amsterdam, The Netherlands; [4]Infection & Immunity, Amsterdam Public Health, University of Amsterdam, Amsterdam, The Netherlands; [5]Department of Internal Medicine and Infectious Diseases, University Medical Center Groningen, Groningen, The Netherlands; [6]Department of Infectious Diseases, Leiden University Medical Center, Leiden, The Netherlands; [7]Department of Viroscience, Erasmus Medical Center, Rotterdam, The Netherlands; [8]Department of Internal Medicine, Division of Allergy & Clinical Immunology and Department of Immunology, Erasmus Medical Center, Rotterdam, The Netherlands; [9]Department of Experimental Immunology, Amsterdam University Medical Centers, Amsterdam Infection and Immunity Institute, University of Amsterdam, Amsterdam, The Netherlands; [10]Department of Medical Microbiology and Infection Prevention, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; and [11]Center for Infectious Disease Control, National Institute for Public Health and the Environment, Bilthoven, The Netherlands

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 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.

We included all participants from whom samples at all study visits were obtained and who did not report a polymerase chain reaction (PCR)-confirmed SARS-CoV-2 infection. The primary outcome (ie, 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

Received 15 April 2022; editorial decision 08 June 2022; published online 20 June 2022

[a]R. S. G. S. and W. J. R. R. are equal first author contributors.

[b]R. D. d. V., P. H. M. v. d. K., and C. H. G. v. K. are equal senior author contributors.

Correspondence: C. H. GeurtsvanKessel, Department of Viroscience, Erasmus Medical Center, 3015GD, Rotterdam, The Netherlands (c.geurtsvankessel@erasmusmc.nl).

Clinical Infectious Diseases®

https://doi.org/10.1093/cid/ciac495

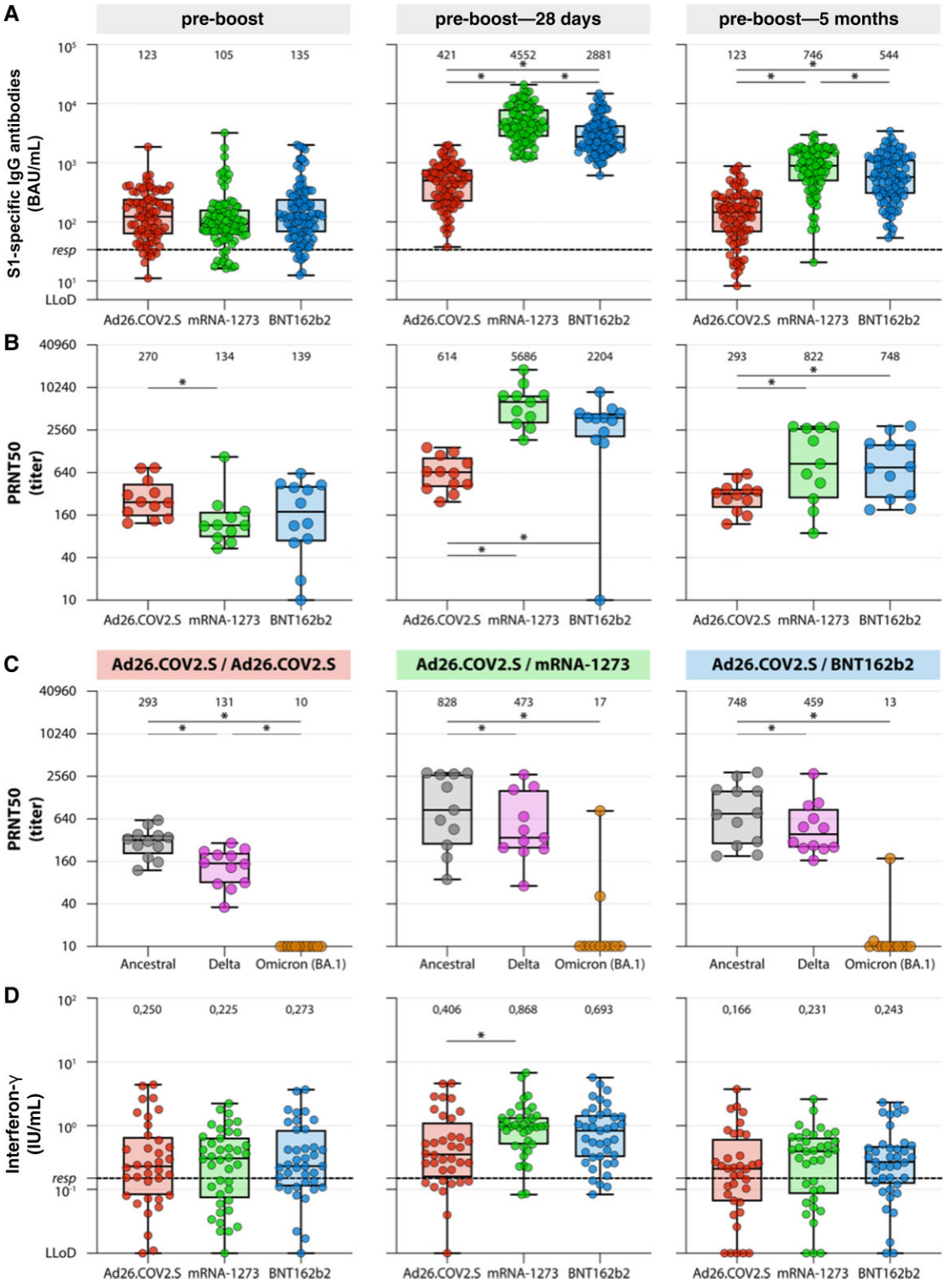

Figure 1. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–specific immune responses. *(A)* Levels of SARS-CoV-2 spike (S) protein–specific IgG antibodies at baseline (pre-boost) and 28 days and 5 months after booster vaccination with Ad26.COV2.S, mRNA-1273, or BNT162b2. The lower limit of 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 1*A*) [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 1*B* and 1*D*) [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 1*A*). 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 1*B*). 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 1*C*, 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 1*D*). 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 4*A*–4*C*) 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 4*D*–4*F*).

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 5*A*). 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 5*B*). 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 5*C*). 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

Financial support. The SWITCH trial was funded by a grant (10430072110001) from ZonMw.

Potential conflicts of interest. L. G. V. reports research grants from U Needle, MyLife Technologies, and Bavarian Nordic, all outside of the submitted work; consulting fees from Emergent for expert meeting travel vaccines; participation on a scientific advisory board for Geosentinel; and serving as committee member for the National Board Guideline Development Travel Medicine. A. G. reports participation on a data and safety monitoring board (DSMB) IDSCOVA (Establishing the tolerability, safety and immunogenicity of intradermal delivery of mRNA SARS-CoV-2 vaccine in healthy adults) study on intradermal COVID vaccinations and serving as member of national advisory board on coronavirus disease vaccinations for immunocompromised patients. A. L. W. H. reports support for the present research from the Dutch Research Council (ZonMw) to their organization. D. F. P. reports participation on the DSMB of the COBRA-KAI trial (COVID-19 vaccination in patients with reduced B-cell and T-cell immunity: response after vaccination in a kaleidoscopic group of hematologic patients: what's the impact?). V. A. S. H. D. reports research funding outside of the submitted work from ZonMw and EU Horizon 2020, consulting fees for an advisory board meeting from GSK, and honoraria for lectures from Pharming, Takeda. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Sadoff J, Gray G, Vandebosch A, et al. Final analysis of efficacy and safety of single-dose Ad26.COV2.S. New Engl J Med **2022**; 386:847–60. doi:10.1056/NEJMoa2117608.
2. Gray G, Collie S, Goga A, et al. Effectiveness of Ad26. COV2. S and BNT162b2 vaccines against Omicron variant in South Africa. N Engl J Med **2022**; 386:2243–5. doi:10.1056/NEJMc2202061.
3. Sablerolles RSG, Rietdijk WJR, Goorhuis A, et al. Immunogenicity and reactogenicity of vaccine boosters after Ad26.COV2.S Priming. N Engl J Med **2022**; 386:951–63. doi:10.1056/NEJMoa2116747.
4. Gezondheidsraad. Advies boostervaccinatie tegen COVID-19 bij personen van 18 tot 60 jaar. 3289333/3289394/PVL/ym/087, 2021.
5. GeurtsvanKessel CH, Geers D, Schmitz KS, et al. Divergent SARS CoV-2 Omicron-reactive T- and B cell responses in COVID-19 vaccine recipients. Sci Immunol **2022**; 7:eabo2202. doi:10.1126/sciimmunol.abo2202.
6. Sablerolles RSG, Goorhuis A, GeurtsvanKessel C, et al. Heterologous Ad26.COV2.S prime and mRNA-based boost COVID-19 vaccination regimens: the SWITCH trial protocol. Front Immunol **2021**; 12:753319. doi:10.3389/fimmu.2021.753319.
7. Goel RR, Painter MM, Apostolidis SA, et al. mRNA vaccines induce durable immune memory to SARS-CoV-2 and variants of concern. Science **2021**; 374: abm0829. doi:10.1126/science.abm0829.
8. Liu J, Chandrashekar A, Sellers D, et al. Vaccines elicit highly conserved cellular immunity to SARS-CoV-2 Omicron. Nature **2022**; 603:493–6. doi:10.1038/s41586-022-04465-y.
9. Tarke A, Coelho CH, Zhang Z, et al. SARS-CoV-2 vaccination induces immunological T cell memory able to cross-recognize variants from Alpha to Omicron. Cell **2022**; 185:847–59.e11. doi:10.1016/j.cell.2022.01.015.