CORONAVIRUS

Divergent SARS-CoV-2 Omicron–reactive T and B cell responses in COVID-19 vaccine recipients

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The severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) Omicron variant is spreading rapidly, even in vaccinated individuals, raising concerns about immune escape. Here, we studied neutralizing antibodies and T cell responses targeting SARS-CoV-2 D614G [wild type (WT)] and the Beta, Delta, and Omicron variants of concern in a cohort of 60 health care workers after immunization with ChAdOx-1 S, Ad26.COV2.S, mRNA-1273, or BNT162b2. High binding antibody levels against WT SARS-CoV-2 spike (S) were detected 28 days after vaccination with both mRNA vaccines (mRNA-1273 or BNT162b2), which substantially decreased after 6 months. In contrast, antibody levels were lower after Ad26.COV2.S vaccination but did not wane. Neutralization assays showed consistent cross-neutralization of the Beta and Delta variants, but neutralization of Omicron was significantly lower or absent. BNT162b2 booster vaccination after either two mRNA-1273 immunizations or Ad26.COV2 priming partially restored neutralization of the Omicron variant, but responses were still up to 17-fold decreased compared with WT. SARS-CoV-2–specific T cells were detected up to 6 months after all vaccination regimens, with more consistent detection of specific CD4+ than CD8+ T cells. No significant differences were detected between WT- and variant-specific CD4+ or CD8+ T cell responses, including Omicron, indicating minimal escape at the T cell level. This study shows that vaccinated individuals retain T cell immunity to the SARS-CoV-2 Omicron variant, potentially balancing the lack of neutralizing antibodies in preventing or limiting severe COVID-19. Booster vaccinations are needed to further restore Omicron cross-neutralization by antibodies.

INTRODUCTION

The severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) Omicron variant (B.1.1.529) is characterized by a high number of mutations in the spike (S) protein that have immune evasive potential. On the basis of transmission characteristics and immune evasion, the World Health Organization (WHO) designated Omicron as a novel variant of concern (VOC). The Omicron variant has been identified worldwide, and models have predicted rapid surges of cases that could surpass earlier peaks (*1*). More data are needed to understand the Omicron disease severity profile and how severity is affected by vaccination and preexisting immunity (*2*).

The large number of mutations and deletions in the Omicron S protein includes alterations in the receptor binding domain (RBD), the main target of neutralizing antibodies responsible for host cell entry (*3–5*). It was previously shown for the Beta (B.1.351) and Omicron variant that mutations within the RBD (*6–8*) and the

N-terminal domain (*5, 9*) can lead to partial escape from neutralizing antibodies. There is a concerning reduction in neutralizing antibody titers against Omicron compared with D614G in convalescent and vaccinated individuals, which can be partially restored by booster vaccination (*10–14*). In addition, initial data show that Omicron is resistant to most antibodies authorized for clinical use (*15, 16*).

Thus far, neutralizing antibodies are regarded the main correlate of protection against severe coronavirus disease 2019 (COVID-19) (*17, 18*). The relative contribution of virus-specific T cells is more difficult to decipher. SARS-CoV-2–specific T cells clear infected cells, thereby contributing to the reduction of viral replication, potentially limiting pathogenicity (*19*). Previous studies on the impact of mutations in the S protein on T cell recognition show that VOC S proteins are equally recognized by S-specific T cells induced by mRNA-based (*8, 20, 21*) and adenovirus-based (*22*) vaccines. Recent studies on T cell recognition of the Omicron variant show similar results (*23–26*). Although the numerous mutations in the S protein in the Omicron variant potentially disrupt multiple T cell epitopes (*27*), this negative impact is likely to be significantly smaller than the effect on neutralizing antibody epitopes.

Five vaccines have now been authorized for use in Europe by the European Medicines Agency (EMA): mRNA-based [mRNA-1273 (Moderna) and BNT162b2 (Pfizer)], adenovirus vector–based [ChAdOx-1 S (AstraZeneca) and Ad26.COV2.S (Janssen)], and the protein-based NVX-CoV2373 (Novavax). These vaccines all use the SARS-CoV-2 S protein of the ancestral strain as template for design, induce robust immune responses, and protect from developing

severe COVID-19 (*28–32*). However, vaccine efficacy differs and is affected by waning of antibodies and the emergence of variants (*18, 33–35*). In general, boosting immune responses by additional vaccinations restores antibody and T cell responses, but clinical efficacy and protection against Omicron remain to be determined.

Here, we analyzed humoral and cellular immune responses early and late (up to 6 months) after vaccination with ChAdOx-1, S, Ad26.COV2.S, mRNA-1273, or BNT162b2 and performed in-depth analyses of cross-reactivity of neutralizing antibodies and T cells against the D614G [wild type (WT)], B.1.351 (Beta), B.1.617.2 (Delta), and B.1.1.529 (Omicron) variants. In addition, we assessed cross-recognition of variants by neutralizing antibodies and T cells after booster vaccination. We found cross-neutralization of the Delta and Beta variants in all vaccinated and convalescent individuals, but neutralization of Omicron was consistently lower or even absent. Booster vaccination restored Omicron-specific neutralization, but still at significantly lower levels compared with WT. All VOCs, including Omicron, were equally recognized by both CD4+ and CD8+ T cells.

RESULTS

Cohort description

To assess binding antibody and T cell responses after different vaccination regimens, we collected serum and peripheral blood mononuclear cells (PBMCs) from $n = 400$ participants, of which $n = 26$ received two doses of ChAdOx-1 S, $n = 75$ received a single dose of Ad26.COV2.S, $n = 199$ received two doses of mRNA-1273, and $n = 100$ received two doses of BNT162b2. In addition, we measured responses in $n = 23$ plasma donors with a confirmed WT SARS-CoV-2 infection (convalescent). Binding antibodies were assessed early (28 days after second-dose BNT162b2, mRNA-1273, or ChAdOx-1 or 56 days after single-dose Ad26.COV2.S) and late (6 months) after vaccination. T cell responses in whole blood were assessed at 56 days and 6 months after vaccination (Ad26.COV2.S, $n = 31$), 28 days and 6 months after second vaccination (mRNA-1273, $n = 39$), or exclusively at 6 months after vaccination (ChAdOx-1 S, $n = 14$). Variant-specific virus neutralization and T cells were performed in a selection of $n = 15$ participants from each vaccination group at the early and late time point. The study design is shown in Fig. 1A; participant characteristics are summarized in Table 1.

Participants in the ChAdOx-1 S group were significantly older than participants in other groups ($P < 0.0001$, Kruskal-Wallis with multiple comparisons); other groups were comparable. In addition, the intervals between first and second vaccination were different for all groups that received two vaccines: median interval for (i) ChAdOx-1 S was 56 days, (ii) mRNA-1273 was 28 days, and (iii) BNT162b2 was 21 days.

Vaccine-induced antibodies wane after 6 months, except in Ad26.COV2.S-vaccinated HCW

Highest levels of S-specific binding antibodies were detected 28 days after full vaccination with mRNA-1273 or BNT162b2 [geometric mean titer (GMT) of 3985 and 3030 binding arbitrary units (BAU)/ml, respectively]. A significant reduction in GMT was observed after 6 months in both groups (Fig. 1B). Both adenovirus vector–based vaccines induced significantly lower binding antibody titers at 28 days (ChAdOx-1 S) or 56 days (Ad26.COV2.S) after vaccination (GMT of 127 and 163 BAU/ml). Whereas a substantial drop in antibody

levels was observed in ChAdOx-1 S–vaccinated health care workers (HCWs), the levels remained stable in Ad26.COV2.S-vaccinated HCW. Despite the levels being stable in Ad26.COV2.S-vaccinated HCW, after 6 months, the antibody levels were still higher in HCW vaccinated with an mRNA-based vaccine. Interferon-γ (IFN-γ) levels were analyzed in ChAdOx-1 S–, Ad26.COV2.S-, and mRNA-1273–vaccinated participants after stimulation of whole blood as a measure for T cell activity. mRNA-1273–vaccinated HCW had the highest T cell responses, but significant decreases were observed 6 months after vaccination. T cell responses remained stable up to 6 months after Ad26.COV2.S vaccination (Fig. 1C).

Significant reduction in Omicron neutralization in convalescent and vaccinated participants

Antibody functionality was measured using an infectious virus neutralization assay with passage 3 SARS-CoV-2 viruses D614G (WT), B.1.351 (Beta), B.1.617.2 (Delta), and B.1.1.529 (Omicron) (Fig. 2A). Human airway Calu-3 cells were used for virus propagation and neutralization assays because SARS-CoV-2 enters these cells using the TMPRSS2-mediated entry pathway (*36–39*). This entry pathway is used in vivo and prevents adaptations in S, commonly observed in Vero cells. At 28 days after vaccination, mRNA-1273 vaccination elicited highest plaque reduction neutralization titers-50% (PRNT50) against WT and all variants, followed by BNT162b2, ChAdOx-1 S, and Ad26.COV2.S vaccination. Delta and Beta variants were neutralized at slightly lower PRNT50, especially after vaccination with mRNA-based vaccines, and a significant reduction of PRNT50 to Omicron was observed in all groups. Notably, 13 of 15 participants in the Ad26.COV2.S group did not neutralize the Omicron variant (Fig. 2C).

At 6 months after vaccination, neutralizing antibodies against WT waned after ChAdOx-1 S, mRNA-1273, and BNT162b2 vaccination but remained stable after Ad26.COV2.S vaccination (Fig. 2, C and D). Differences in GMT PRNT50 values for the different vaccine groups were smaller at this point. An 11- to 15-fold reduction in PRNT50 to Omicron led to low or completely absent neutralizing antibody levels in all groups. An eightfold reduction in Omicron neutralization was observed in the selection of 15 convalescent (after WT SARS-CoV-2 infection) sera (Fig. 2B). Neutralizing antibodies to the WT, Beta, and Delta variants correlated well to measured binding antibody levels, whereas a lower correlation was observed between Omicron-specific neutralizing antibodies and binding antibody levels (fig. S1).

Vaccination-induced S-specific T cells equally recognized VOC including Omicron

Besides neutralizing antibodies, we assessed the presence of S-specific CD4+ and CD8+ T cells in the selected participants early and late after vaccination (Fig. 3). For the selected BNT162b2-vaccinated individuals, a limited set of PBMC was available ($n = 5$ of 15). PBMCs were stimulated with either overlapping peptide pools representing the full-length WT S protein or peptide pools based on the S proteins of the Beta, Delta, or Omicron variants (Fig. 3A). After stimulation, the specific production of 13 different cytokines was measured in cell culture supernatants, and AIM (activation-induced markers) expression on CD4+ (OX40 and CD137) and CD8+ (CD69 and CD137) T cells was measured by flow cytometry (Fig. 3B). On the basis of the production of interleukin-2 (IL-2), IFN-γ, IL-10, and IL-22 in culture supernatants [upon S-specific peptide
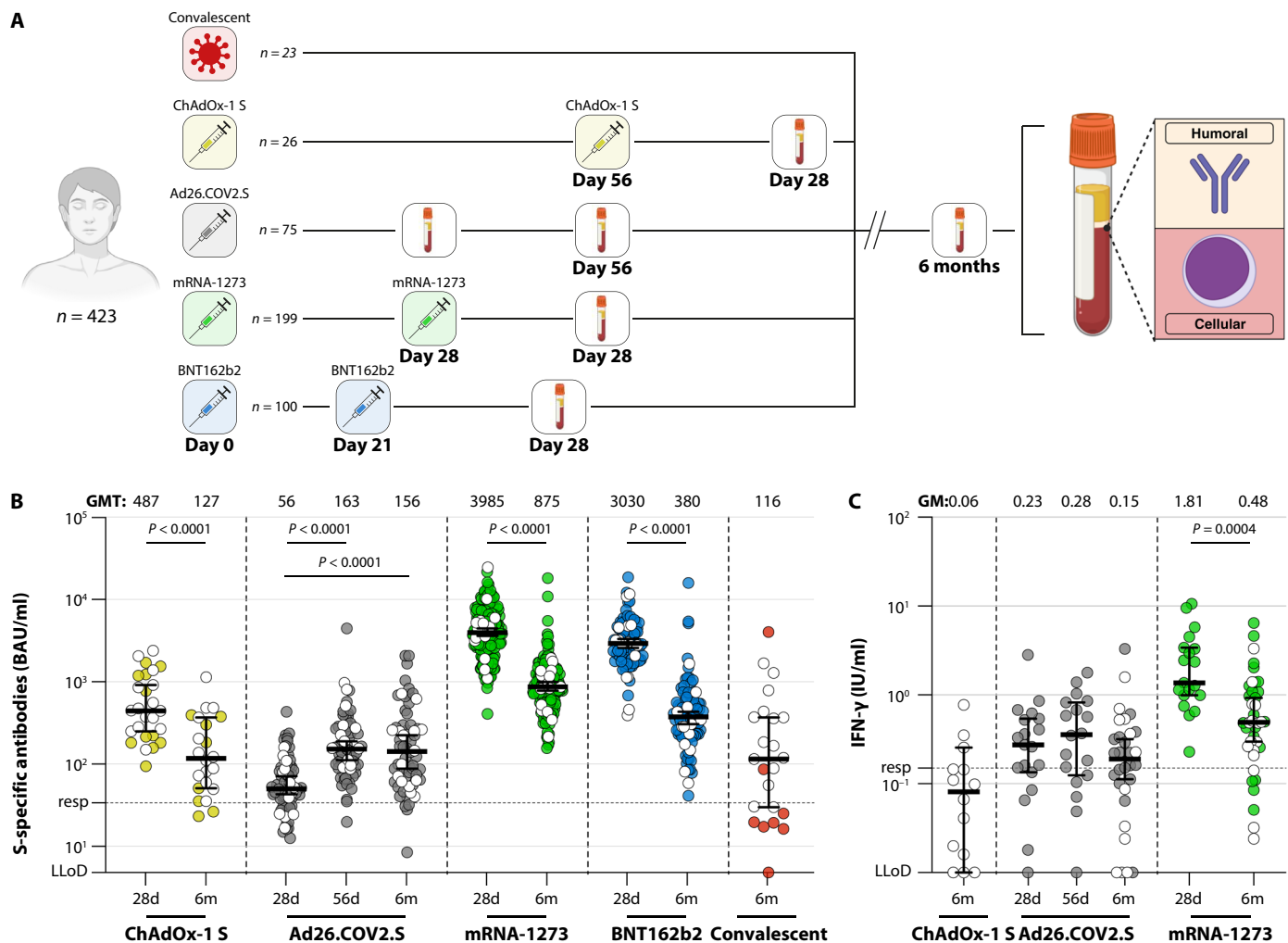
Fig. 1. Study design and detection of virus-specific binding antibodies and T cells. (**A**) Diagram of the number of included participants and study groups. A total of $n = 423$ participants were included for the analysis of binding antibodies, and T cell responses were measured early and late after completion of the vaccination regimen. Binding antibodies were also assessed in $n = 23$ convalescent participants. (**B**) Levels of binding S-specific antibodies early (28 days after second vaccination or 56 days after Ad26.COV2.S vaccination) and late (6 months after completion of vaccination regimen) after vaccination or infection. LLoD is 4.81 BAU/ml; responder (resp) cutoff is 33.8 BAU/ml (dotted line). GMTs are indicated above the graph. (**C**) IFN-γ levels in plasma after stimulation of whole blood with peptide pools spanning the S protein (Ag2, Qiagen) early and late after ChAdOx-1 S, Ad26.COV2.S, or mRNA-1273 vaccination (ChAdOx-1 S responses were exclusively measured at 6 months). LLoD is 0.01 IU/ml; responder cutoff is 0.15 IU/ml. Geometric means are indicated above the graph. Comparisons of time points within study groups were performed by paired t test. White symbols represent samples selected for in-depth analyses. d, days; m, months.

stimulation compared with a dimethyl sulfoxide (DMSO) control stimulation], S-specific T cells were detected in most vaccinated individuals, early and late after vaccination (fig. S3). No differences in cytokine production were detected after stimulation with either the WT or Omicron S peptide pool.

On the basis of AIM expression (OX40⁺CD137⁺) after WT S peptide pool stimulation of samples obtained at 28 days after any vaccination, we detected S-specific CD4⁺ T cells in 94% of the vaccine recipients (46 of 49). We did not observe significant differences between CD4⁺ T cell responses to WT, Delta, Beta, or Omicron S peptide pools early or late after vaccination with any vaccine (Fig. 3C). When considering the vaccine regimens separately, significant differences between variant-specific T cell responses were not detected (fig. S4).

S-specific CD8⁺ T cells were more difficult to detect, likely because we used peptide pools containing overlapping 15-mer peptides [whereas 8- to 10-mers would be optimal for human leukocyte antigen (HLA) class I binding]. On the basis of AIM expression (CD69⁺CD137⁺) after WT S peptide pool stimulation of samples obtained at 28 days after any vaccination, we detected S-specific CD8⁺ T cells in 63% of the vaccine recipients (31 of 49). We did not observe significant differences between CD8⁺ T cell responses to WT, Delta, Beta, or Omicron S peptide pools early or late after vaccination (Fig. 3D). There was one exception: Delta-specific CD8⁺ T cells were significantly lower compared with WT-specific CD8⁺ T cell responses in samples obtained 28 days after vaccination. When considering the vaccine regimens separately, significant differences between variant-specific T cell responses were not observed (fig. S5).

Table 1. Participant characteristics. CI, confidence interval; N/A, not available.

Cohort	n	Age (median years, 95% CI)	Female (n, %)	Vaccination interval (median days, 95% CI)
Convalescent	23	48 (42–58)	4 (17%)	N/A
In-depth	15	53 (42–62)	1 (7%)	N/A
ChAdOx-1 S	26	63 (62–64)	17 (61%)	56 (56–70)
In-depth	15	63 (62–64)	9 (60%)	56 (56–70)
Ad26.COV2.S	75	37 (32–43)	62 (83%)	N/A
In-depth	15	38 (32–50)	13 (87%)	N/A
mRNA-1273	199	41 (39–44)	156 (78%)	28 (28–28)
In-depth	15	34 (27–40)	12 (80%)	25 (25–28)
BNT162b2	100	40.5 (37–45)	66 (66%)	21 (21–21)
In-depth	15	46 (36–53)	11 (73%)	22 (21–25)

Increased cross-reactivity of neutralizing antibodies and T cells against Omicron after boost

Last, we performed an analysis of neutralizing antibody and T cell responses to the different SARS-CoV-2 variants after booster vaccination. HCWs vaccinated with either one dose of Ad26.COV2.S (n = 15) (40) or two doses of mRNA-1273 (n = 9) were included; both groups were boosted with BNT162b2, either at 85 days after primary vaccination (Ad26.COV2.S) or at 214 days after completion of the primary vaccination series (mRNA-1273) (Fig. 4A). Specimens were collected 28 days (Ad26.COV2.S/BNT162b2) or 14 days (2× mRNA-1273/BNT162b) after boost. Participant characteristics are described in Table 2.

Boosting with BNT162b led to rapid recall responses in both Ad26.COV2.S-primed and mRNA-1273–primed individuals, and a significant increase in binding antibody levels was observed (Fig. 4B). Binding antibody levels in the mRNA-1273 boosting regimen reached the highest levels (GMT of 9331 versus 3328 in the Ad26.COV2.S-primed individuals). PRNT50 after boost was also higher in the mRNA-1273–primed individuals compared with the Ad26.COV2.S-primed individuals (Fig. 4C). When comparing neutralization of the different VOC, no drop in neutralization of Delta, a twofold drop in neutralization of Beta, but a substantial 17- and 12-fold drop in neutralization of Omicron was still observed. However, neutralization of Omicron was observed or restored in all boosted individuals (Fig. 4C). Similar to the observations upon primary vaccination regimens, no reduced T cell responses to variants (including Omicron) were detected after boost (Fig. 4D).

DISCUSSION

Here, we demonstrate the resistance of the SARS-CoV-2 Omicron (B.1.1.529) variant to neutralizing antibodies induced by mRNA-based or adenovirus vector–based vaccination. We observed up to 30-fold reductions of Omicron neutralizing titers when compared with WT SARS-CoV-2. Lower neutralizing antibody levels were previously associated with an increased risk of SARS-CoV-2 infection (18) and a higher burden of disease. In contrast, we show that SARS-CoV-2–specific T cell responses were minimally affected by mutations in the Omicron S protein. T cell activity is thought to confer protection from severe disease, but it remains to be determined whether this is sufficient in the absence of a potent neutralizing antibody response.

A single BNT162b2 booster immunization induced a substantial increase in Omicron-specific neutralization after priming with either Ad26.COV2.S or mRNA-1273 in the short term. Neutralization of Omicron was partially restored in individuals without cross-reactive neutralizing antibodies before boosting, and cross-recognition of the different variants by CD4$^+$ and CD8$^+$ T cells was maintained after booster vaccination.

We observed high, but transient, levels of SARS-CoV-2–specific binding antibodies after mRNA-based vaccination. Despite the waning of binding antibody levels in vaccinees, affinity maturation of antibodies and a continued increase in SARS-CoV-2–specific memory B cells were previously described between 3 and 6 months after mRNA vaccination (41). These memory B cells are generated in prolonged germinal center reactions (42) and are capable of mounting a rapid recall response upon re-encountering the S protein, by either natural infection or booster vaccination. In contrast, we observed that Ad26.COV2.S vaccination led to antibody responses, which showed minimal waning at 6 months, in line with recent findings by Barouch et al. (43). This suggests that upon Ad26.COV2.S vaccination, maturation of B cells occurs without further short-term boosting. Neutralizing antibodies are regarded the main correlate of protection against infection with SARS-CoV-2 (17, 18). The capacity of sera from vaccinated individuals to cross-neutralize the Omicron variant in our study was reduced up to 30-fold (9, 10, 13–16, 44, 45). To be protected against symptomatic COVID-19 caused by Omicron, affinity maturation will be essential for the acquisition of broader neutralizing activity of RBD-binding antibodies that were previously formed (46, 47). Booster vaccination of Ad26.COV2.S-primed and mRNA-1273–primed individuals quickly increased S-specific antibodies and restored Omicron neutralization (11, 12, 48); however, these levels were still significantly lower than neutralization of WT. Whether booster vaccinations increase the breadth of the response remains to be determined, as well as whether antibody responses targeting variants are maintained long-term (43).

Multiple assays to determine the neutralizing capacity of sera are currently used (49), and the variety of protocols hinders a direct head-to-head comparison of different studies. We studied VOC-specific neutralization using infectious virus plaque reduction assays. It is known that SARS-CoV-2 propagation on VeroE6 cells, a cell line routinely used for SARS-CoV-2 neutralization assays, can lead
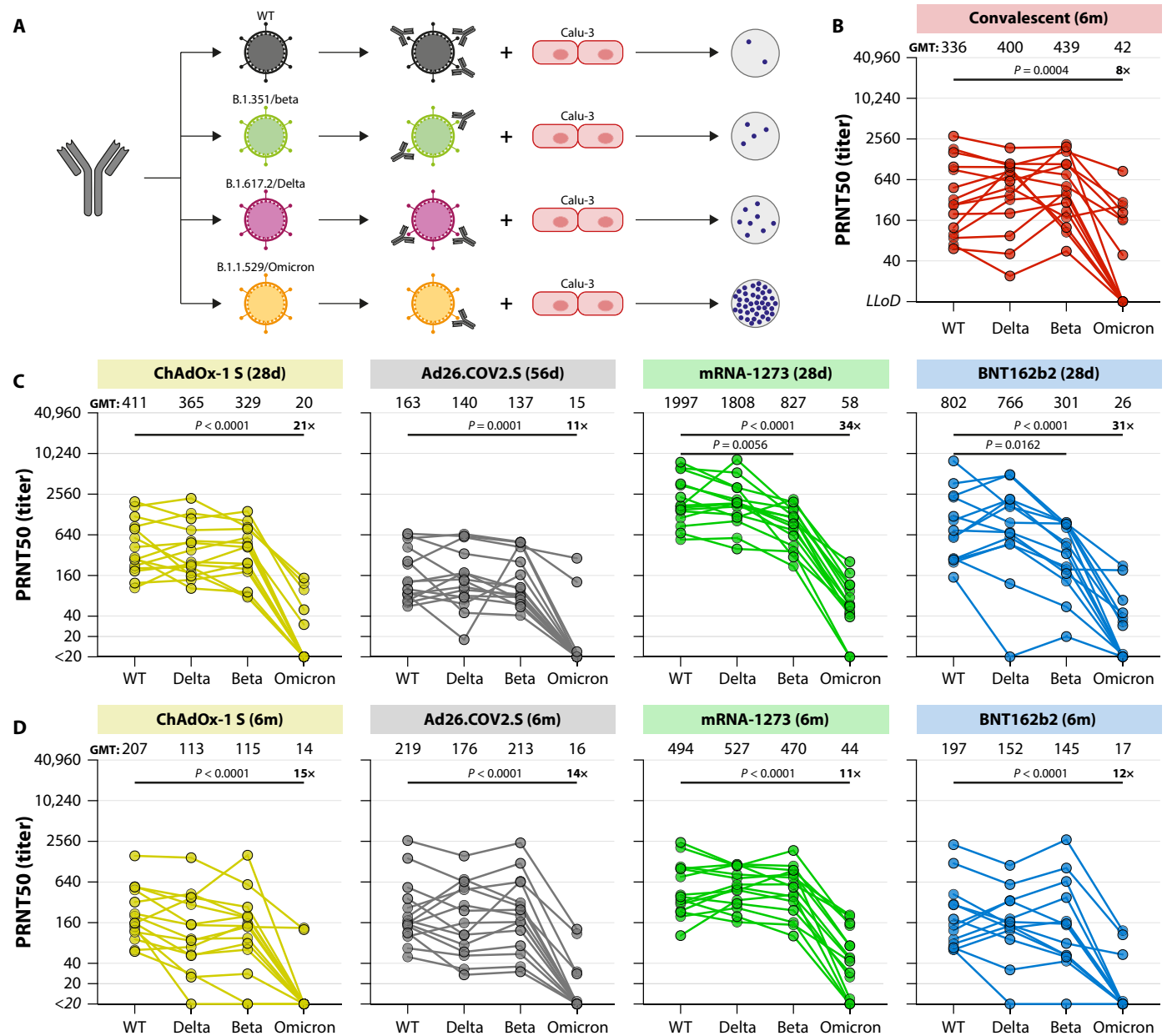
Fig. 2. SARS-CoV-2 variant–specific neutralizing antibody responses. (**A**) Schematic overview of the infectious virus PRNT50 assay. Serum samples were preincubated with 400 plaque-forming units of infectious virus for 1 hour and transferred to Calu-3 cells, and N-positive plaques were counted after 8 hours. A PRNT50 (50% reduction of plaques) value was calculated by a proportionate distance formula. (**B** to **D**) Levels of neutralizing antibodies in convalescent donors after 6 months (B), early after completion of the vaccination regimen (C), and late after completion of the vaccination regimen (D). $n = 15$ participants were included per vaccination regimen. The lowest serum dilution tested was 1:20; undetectable PRNT50 values (<20) were set at a PRNT50 value of 10. GMTs are indicated above the graphs, and fold change reductions are indicated and calculated by dividing the D614G GMT by the Omicron GMT. Comparisons of VOC-specific responses within study groups were performed by Friedman test with multiple comparisons.

to mutations or deletions in the multibasic cleavage site in the S protein (*36–39*). We therefore grew the viral stocks and performed the neutralization assays on the TMPRSS2-expressing human airway cell line Calu-3.

It was previously shown that vaccine-induced T cells targeting the ancestral S protein demonstrate minimal reductions in frequency and magnitude against the Alpha, Beta, Gamma, and Delta variants (*8, 21, 22, 25, 41, 50*). Recently, preservation of T cell reactivity with the Omicron S protein was also demonstrated (*23–26*). Here, we performed a comprehensive analysis of SARS-CoV-2–specific T cell responses in vaccinated individuals early and late after receiving ChAdOx-1 S, Ad26.COV2.S, mRNA-1273, or BNT162b2 vaccination.
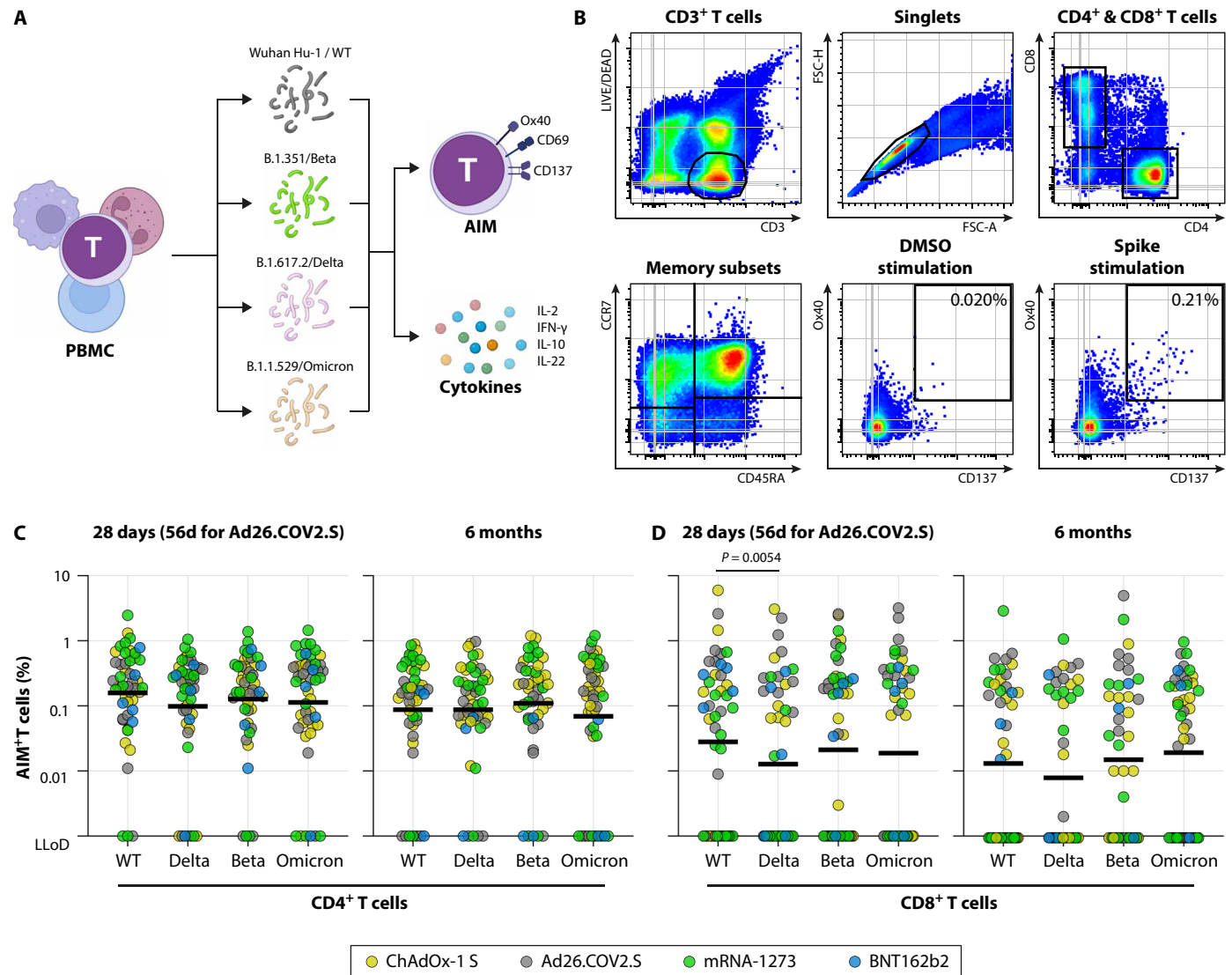
Fig. 3. SARS-CoV-2 variant–specific T cell responses. (**A**) Schematic overview of AIM assay. PBMCs were stimulated with different overlapping peptide pools for 20 hours, followed by measurement of up-regulation of activation markers by flow cytometry and cytokines in cell culture supernatant. (**B**) SARS-CoV-2–specific T cells were detected by flow cytometry. (**C** and **D**) Up-regulation of AIM early and late after completion of the vaccination regimen on CD4+ (C) and CD8+ (D) T cells. Percentages indicate the percentage of AIM+ T cells after subtraction of observed background in a DMSO stimulation; bars indicate the means. n = 49 participants were analyzed over various time points. Comparisons of VOC-specific responses within study groups were performed by Friedman test with multiple comparisons.

In contrast to the humoral response, we showed durable cellular immune responses that persisted for at least 6 months after either mRNA-based or adenovirus vector–based vaccination. Vaccine-induced S-specific CD4+ T cells were detected in 94% of the vaccine recipients, whereas we could detect S-specific CD8+ T cell responses in 63% of the vaccine recipients. In line with previous studies into VOC-specific T cell responses, vaccine-induced T cells equally recognized the WT, Beta, Delta, and Omicron variant independent of timing or vaccination regimen, although we only included five BNT162b2-vaccinated participants, so these results were interpreted with caution. After peptide pool stimulation, we detected production of typical T helper 1 (T_H1) (IFN-γ and IL-2), T_H2 (IL-10), and T_H17 (IL-22) cytokines, without differences between WT and Omicron S stimulation. This fits well with the observation that although

Omicron has numerous mutations in the S protein, T cell epitopes are minimally affected. Variant-specific CD4+ and CD8+ T cell responses were maintained after booster vaccination.

Our study has several limitations: First, the sample size for which in-depth T cell profiling was performed was limited to 15 donors per vaccination regimen, and we measured lower levels of CD8+ T cells likely due to the use of 15-mer peptides. Additional studies with smaller peptides (8- to 10-nucleotide oligomers) predicted or shown to bind HLA class I are advised to specifically study VOC cross-reactive CD8+ T cell responses. Furthermore, the data after booster vaccination are limited, and longevity of variant-specific immune responses after booster vaccination remains to be determined. Last, this study is skewed toward healthy young-adult participants (with the exception of ChAdOx-1 S–vaccinated individuals).
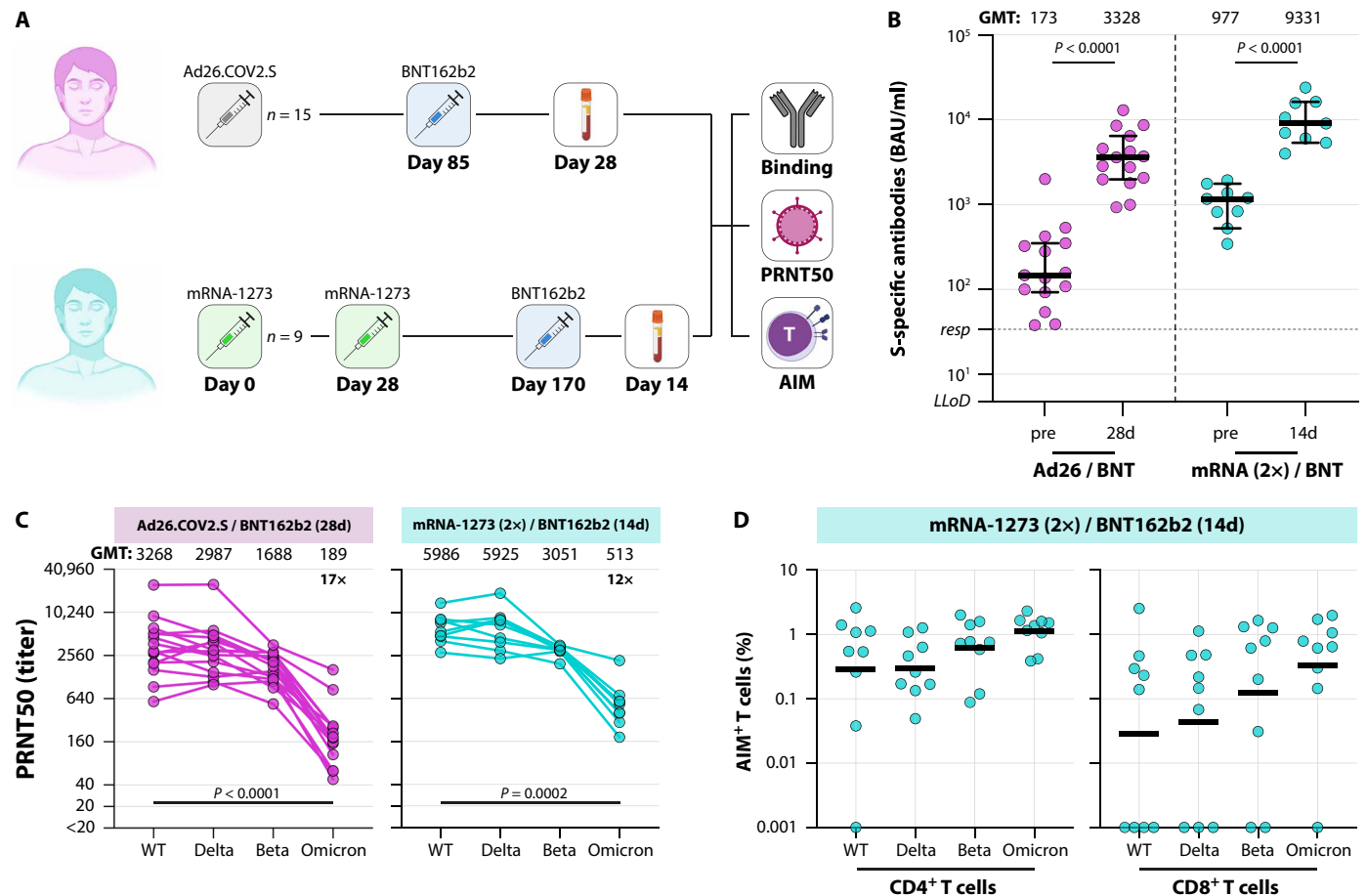
Fig. 4. Variant-specific immune responses early after booster vaccination. (**A**) Diagram of the number of included participants in the booster analysis. A total of $n = 24$ participants were included for the analysis of binding antibodies, variant-specific neutralizing antibodies, and variant-specific T cell responses. $n = 15$ participants were primed with one-shot Ad26.COV2.S; $n = 9$ participants were primed with two-shot mRNA-1273; all participants were analyzed throughout the panels. Responses were measured early after BNT162b2 booster vaccination. (**B**) Levels of binding S-specific antibodies early after booster vaccination. LLoD is 4.81 BAU/ml; responder (resp) cutoff is 33.8 BAU/ml (dotted line). GMTs are indicated above the graph. Comparisons of time points within study groups were performed by paired t test. (**C**) Levels of neutralizing antibodies in boosted donors. The lowest serum dilution tested was 1:20; undetectable PRNT50 values (<20) were set at a PRNT50 value of 10. GMTs are indicated above the graphs; fold change reductions are indicated and calculated by dividing the D614G GMT by the Omicron GMT. (**D**) Up-regulation of AIM on CD4$^+$ T cells (left) and CD8$^+$ T cells (right) in boosted donors. Percentages indicate the percentage of AIM$^+$ cells after subtraction of observed background in a DMSO stimulation; bars indicate the means. Comparisons of VOC-specific responses within study groups were performed by Friedman test with multiple comparisons.

Table 2. Booster participant characteristics.

Cohort	n	Age (median years, 95% CI)	Female (n, %)	Vaccination interval (median days, 95% CI)
Ad26.COV2.S/BNT162b2	15	37 (28–44)	10 (67%)	88 (79–88)
2× mRNA-1273/BNT162b2	9	29 (27–40)	7 (78%)	214 (214–219)

Although in-depth analyses were performed in a relatively small number of subjects, we show that vaccinated individuals retain T cell immunity to the Omicron variant, potentially balancing the lack of neutralization antibodies in preventing or limiting severe COVID-19. Furthermore, the fact that booster vaccinations restored and increased the neutralizing capacity against Omicron supports the call for immediate booster campaigns. In the near future, variant-specific booster vaccines may be required to optimally skew the immune responses toward emerging viruses.

MATERIALS AND METHODS
Study design
A prospective cohort study of HCWs at Erasmus MC was initiated in 2020, with a focus on immunity against SARS-CoV-2 after symptomatic presentation to the occupational health services. From January 2021, HCWs in The Netherlands were offered vaccination with one of the four approved vaccines in The Netherlands (ChAdOx-1 S, Ad26.COV2.S, mRNA-1273, and BNT162b2), and participants of the HCW study were invited for the follow-up study

in which immune responses upon vaccination were studied. From December 2021, HCWs in the study were invited for a follow-up study after booster vaccination with BNT162b2. A single-blind, multicenter, randomized controlled trial (SWITCH trial) was performed to study immune responses after heterologous booster vaccination following a priming vaccination with Ad26.COV2.S (40). Last, we performed a study in which polymerase chain reaction (PCR)–confirmed patients with COVID-19 were recruited to participate as plasma donors (ConCOVID) (51). A combination of samples was used for a complete immunological assessment of SARS-CoV-2–specific immune responses after vaccination targeting different VOCs.

Ethics statement

Samples from three different trials (HCW, ConCOVID, and SWITCH) were analyzed in the scope of this study (table S1). The HCW study was approved by the institutional review board of the Erasmus MC (medical ethical committee, MEC-2020-0264) (8). The ConCOVID trial was also approved by the institutional review board of the Erasmus MC (MEC 2020-0228). The study was registered at ClinicalTrials.gov (NCT04342182) (51). The SWITCH trial was approved by the institutional review board of the Erasmus MC (MEC 2021-0132) and local review boards of participating centers. The study was registered at ClinicalTrials.gov (NCT04927936) (40). All studies adhere to the principles of the Declaration of Helsinki, and written informed consent was obtained from every participant, patient, or legal representative.

Study design and sample collection

Serum and PBMC samples from all vaccinated participants of the HCW study were obtained 28 days and 6 months after second vaccination (with the exception of Ad26.COV2.S-vaccinated HCW, samples were obtained 56 days after first vaccination). HCWs were vaccinated with (i) ChAdOx-1 S/ChAdOx-1S (56-day interval), (ii) Ad26.COV2.S, (iii) mRNA-1273/mRNA-1273 (28-day interval), or BNT162b2/BNT162b2 (21-day interval) (Fig. 1A). Additional serum and PBMC samples were obtained from nine mRNA1273/mRNA-1273–primed participants at 14 days after booster vaccination with BNT162b2. Participants of the SWITCH trial were vaccinated with Ad26.COV2.S, followed by a BNT162b2 boost (85-day interval) (40). Serum samples were obtained 28 days after the booster vaccination (Fig. 4A). Participants of the HCW and SWITCH trial had no history of previous SARS-CoV-2 infection, as confirmed by the absence of N-specific antibodies and/or S-specific antibodies before vaccination at baseline. Serum samples from convalescent PCR-confirmed patients with COVID-19 were obtained 6 months after infection in the scope of the ConCOVID study, in which study participants were recruited to participate as plasma donors (51). These patients were infected during the first wave in 2020, all with a D614G SARS-CoV-2. In-depth neutralization and T cell assays were performed on a selection of $n = 15$ participants from each group (Tables 1 and 2). The selection of participants for in-depth analyses was based on availability of longitudinal PBMC samples and the distribution of antibody responses (Fig. 1, B and C).

Serum and PBMC isolation

Serum was collected in 10-ml tubes without anticoagulant, centrifuged at 2500 rpm for 15 min, aliquoted, and stored at −20°C for further experiments. PBMCs were isolated from blood collected in K_3EDTA

or lithium heparin tubes by density gradient centrifugation. Briefly, blood was layered on a density gradient (Lymphoprep, STEMCELL Technologies), and PBMCs were separated by centrifuging at 2000 rpm for 30 min. PBMCs were washed four times in phosphate-buffered saline and subsequently frozen in liquid nitrogen in 90% fetal bovine serum (FBS) with 10% DMSO (Honeywell) until use in stimulation assays.

Detection of S-specific binding antibodies

Binding antibodies against the SARS-CoV-2 S protein were measured by Liaison SARS-CoV-2 TrimericS immunoglobulin G (IgG) assay (DiaSorin, Italy), with a lower limit of detection (LLoD) of 4.81 BAU/ml and a cutoff for positivity at 33.8 BAU/ml. The assay was performed following the manufacturer's instructions.

IFN-γ release assay

The SARS-CoV-2–specific T cell response was measured by commercially available IFN-γ Release Assay (QuantiFERON, Qiagen) in whole blood as previously described and following the manufacturer's description (52). In short, heparinized whole blood was incubated with three different SARS-CoV-2 antigens for 20 to 24 hours using a combination of peptides stimulating both CD4$^+$ and CD8$^+$ T cells (Ag1, Ag2, and Ag3, QuantiFERON, Qiagen). After incubation, plasma was obtained and IFN-γ production in response to the antigens was measured by enzyme-linked immunosorbent assay (ELISA). Results are expressed in IU IFN-γ/ml after subtraction of the negative control values as interpolated from a standard calibration curve. LLoD in this assay is set at 0.01 IU/ml, and responder cutoff is 0.15 IU/ml. IFN-γ production after stimulation with Ag2, containing peptides covering the S protein, was shown in this study.

Virus culture and deep sequencing

SARS-CoV-2 isolates were grown to passage 3 on Calu-3 (American Type Culture Collection, HTB-55) cells in Advanced DMEM/F12 (Gibco), supplemented with Hepes, GlutaMAX, penicillin (100 IU/ml), and streptomycin (100 IU/ml) at 37°C in a humidified CO_2 incubator. Infections were performed at a multiplicity of infection (MOI) of 0.01, and virus was harvested after 72 hours. The culture supernatant was cleared by centrifugation at 1000g for 5 min and stored at −80°C in aliquots. Stock titers were determined by incubating 10-fold dilutions of virus stock in Opti-MEM at 37°C for 1 hour, after which they were transferred onto Calu-3 cells and incubated for 8 hours at 37°C in a humidified CO_2 incubator. Next, cells were fixed with 4% formalin and permeabilized in 70% ethanol, after which infected cells were stained with polyclonal rabbit anti–SARS-CoV-2 nucleocapsid antibody (Sino Biological) and a secondary goat anti-rabbit IgG AF488 (Invitrogen). Stained plates were scanned on the Amersham Typhoon Biomolecular Imager (channel Cy2; resolution, 10 μm; GE Healthcare), and the number of infected cells was determined to calculate the stock titer per milliliter. All work with infectious SARS-CoV-2 was performed in a Class II Biosafety Cabinet under biosafety level–3 conditions at Erasmus Medical Center.

Viral genome sequences were determined using Illumina deep sequencing. RNA was extracted using AMPure XP beads, and complementary DNA (cDNA) was generated using ProtoScript II reverse transcriptase enzyme (New England BioLabs) according to the manufacturer's protocol (53). Samples were amplified using the QIAseq SARS-CoV-2 Primer Panel (Qiagen). Amplicons were purified with 0.8× AMPure XP beads, and 100 ng of DNA was

converted to paired-end Illumina sequencing libraries using the KAPA HyperPlus library preparation kit (Roche) with the KAPA unique dual-indexed adapters (Roche) as per the manufacturer's recommendations. The barcode-labeled samples were pooled and analyzed on an Illumina sequencer V3 MiSeq flowcell (2 × 300 cycles). Sequences were analyzed using CLC Genomics Workbench 21.0.3. The 614G virus (clade B; isolate Bavpat-1; European Virus Archive Global #026V-03883) passage 3 sequence was identical to passage 1 (provided by C. Drosten), and no minor variants >20% were detected. The Beta variant (clade B.1.351) passage 3 sequence contained two mutations compared with the original respiratory specimen: one synonymous mutation C13860T (Wuhan-1 position) in ORF1ab and an L71P change in the E gene (T26456C, Wuhan-1 position). No other minor variants >20% were detected. The Delta (clade B.1.617.2) and Omicron (clade B.1.1.529) variant passage 3 sequences were identical to the original respiratory specimens, and no minor variants >20% were detected. Because of primer mismatches in the S1 region of the Omicron S gene, amplicons 72, 73, 75, and 76 were sequenced at low coverage. Therefore, the S1 regions of the original respiratory specimen and passage 3 virus were confirmed to be identical by Sanger sequencing. The Beta, Delta, and Omicron sequences are available on GenBank under accession numbers OM286905, OM287123, and OM287553, respectively.

The Beta variant contained the following S changes: L18F, D80A, D215G, del241-243, K417N, E484K, N501Y, D614G, and A701V. The Delta variant contained the following S changes: T19R, G142D, del156-157, R158G, A222V, L452R, T478K, D614G, P681R, and D950N. The Omicron variant contained the following S mutations: A67VS, del69-70, T95I, G142-, del143-144, Y145D, del211, L212I, ins215EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, and L981F.

Detection of neutralizing antibodies by plaque reduction assay

Plaque reduction neutralization tests (PRNTs) were performed as described previously (8, 54). Briefly, heat-inactivated sera were two-fold diluted in Opti-MEM medium starting at a dilution of 1:10 (or 1:80 for sera known to have more than 2500 BAU/ml S-specific binding antibodies) in 60 μl. Four hundred plaque-forming units of different SARS-CoV-2 variants was added to each well in 60 μl of virus suspension incubated at 37°C for 1 hour. After 1 hour of incubation, the virus-antibody mixtures were transferred onto the human airway cell line Calu-3 and incubated for 8 hours. After incubation, cells were fixed and plaques were stained with polyclonal rabbit anti–SARS-CoV-2 nucleocapsid antibody (Sino Biological) and a secondary peroxidase-labeled goat anti-rabbit IgG (Dako). Signal was developed by using a precipitate-forming 3,3′,5,5′-tetramethylbenzidine substrate (TrueBlue; Kirkegaard & Perry Laboratories), and the number of infected cells was counted per well by using the ImmunoSpot Image Analyzer (CTL Europe GmbH). The dilution that would yield 50% reduction of plaques (PRNT50) compared with the infection control was estimated by determining the proportionate distance between two dilutions from which an endpoint titer was calculated. Raw data for neutralizing antibodies early after vaccination (fig. S2, A and B), late after vaccination (fig. S2, C and D), 6 months after positive PCR (fig. S2, E and F), or early after booster vaccination (fig. S2, G and H) are included in the

supplementary figures. Infection controls and positive serum controls were included on each plate, and the National Institute for Biological Standards for Control (NIBSC) standard was included in three separate experiments. When no neutralization was observed, we set the PRNT50 one dilution step below the dilution series, i.e., a PRNT50 value of 10.

Overlapping SARS-CoV-2 S peptide pools

SARS-CoV-2 peptides were synthesized as crude material (TC Peptide Lab, San Diego, CA). Overlapping 15-mer by 10 amino acids covering the full-length S proteins from the WT, Beta (B.1.351), Delta (B.1.617.2), and Omicron (B.1.1.529) variants was synthesized and individually resuspended in DMSO at a concentration of 10 to 20 mg/ml. Megapools for each S variant were generated by pooling aliquots of these individual peptides, undergoing another lyophilization, and resuspending in DMSO at 1 mg/ml (21).

Stimulations for detection of SARS-CoV-2–specific CD4^{+} and CD8^{+} T cells

PBMCs were thawed in RPMI 1640 medium (Gibco) supplemented with 10% human serum (Sanquin, Rotterdam), penicillin (100 IU/ml; Lonza, Belgium), streptomycin (100 μg/ml; Lonza, Belgium), and 2 mM L-glutamine (Lonza, Belgium; R10H medium) and treated with benzonase (50 IU/ml; Merck) at 37°C for 30 min. Subsequently, 1×10^6 PBMCs were stimulated with SARS-CoV-2 variant peptide pools at 1 μg/ml per peptide in 200 μl in a 96-well U-bottom plate at 37°C for 20 hours. Cells were additionally stimulated with an equimolar concentration of DMSO (negative control) or a combination of phorbol 12-myristate 13-acetate (50 μg/ml) and ionomycin (500 μg/ml) (positive control). In addition, PBMCs were stimulated with a peptide pool consisting of 176 known peptides for a broad range of HLA subtypes and different infectious agents (including human herpesviruses and influenza virus) as peptide positive control (PepMix CEFX Ultra SuperStim Pool, JPT). After stimulation, cells were stained for phenotypic lymphocyte markers.

Multiplex detection of cytokines

Cytokines in cell culture supernatants from ex vivo stimulations were quantified using a human T_H cytokine panel (13-plex) kit (LEGENDplex, BioLegend) as described previously (55). Briefly, cell culture supernatants were mixed with beads coated with capture antibodies specific for IL-5, IL-13, IL-2, IL-6, IL-9, IL-10, IFN-γ, TNF-α (tumor necrosis factor–α), IL-17A, IL-17F, IL-4, IL-21, and IL-22. After staining, cytokines were detected by flow cytometry on FACSLyric (BD Biosciences). IL-2, IFN-γ, IL-10, and IL-22 were found specifically produced after peptide pool stimulation, and other cytokines are not shown.

Detection of AIM by flow cytometry

Detection of AIM was performed as described previously (8). Briefly, cells were stained with the following antibodies in their respective dilutions: anti–CD3-PerCP (1:25, clone SK7; BD Biosciences), anti–CD4-V50 (1:50, clone L200; BD Biosciences), anti–CD8–fluorescein isothiocyanate (1:25, clone DK25; Dako), anti–CD45RA–phycoerythrin (PE)–Cy7 (1:50, clone L48; BD Biosciences), anti–CCR7-BV711, anti–CD69–allophycocyanin (APC)–H7 (1:50, clone FN50; BD Biosciences), anti–CD137-PE (1:50, clone 4B4-1; Miltenyi Biotec), and anti–OX40-BV605 (1:25, clone L106; BD Biosciences). LIVE/DEAD Fixable Aqua Dead Cell staining was included (1:100, AmCyan; Invitrogen) and acquired

on FACSLyric (BD Biosciences). After setting a time gate, LIVE $CD3^+$ T cells were gated, singlets were selected, and T cells were subtyped into $CD3^+CD4^+$ and $CD3^+CD8^+$ cells. Within the $CD4^+$ and $CD8^+$ T cells, T_{naive} were defined as $CD45RA^+CCR7^+$, T_{CM} as $CD45RA^-CCR7^+$, T_{EM} as $CD45RA^-CCR7^-$, and T_{EMRA} as $CD45RA^+CCR7^-$. S-specific T cells were detected by coexpression of AIM on $CD4^+$ (OX40 and CD137) or $CD8^+$ (CD69 and CD137) T cells in the combination of memory subsets (Fig. 3A). The DMSO-stimulated sample was used to set the cutoff gate for activation markers. On average, 500,000 cells were acquired per sample.

Statistical analysis

A comparison of the baseline characteristics age and interval between vaccinations between groups was performed by Kruskal-Wallis with multiple comparisons. Reduction in binding and neutralizing antibody levels over time within groups was analyzed by paired t test. Different groups were compared by unpaired t test. Differences in PRNT50 and T cell responses to VOC were estimated by Friedman test with multiple comparisons, and data were not normally distributed. Multiple comparisons were always performed as the variants versus WT, and variants were not compared between themselves. Spearman R was calculated for the correlation between binding and neutralizing antibodies. All statistical analyses were performed on log-transformed data.

Software

Statistical analyses were performed with GraphPad Prism version 9.1.2. Expression of AIM was analyzed with FlowJo software version 10.8.1.

SUPPLEMENTARY MATERIALS

www.science.org/doi/10.1126/sciimmunol.abo2202
Figs. S1 to S5
Table S1
Data S1
MDAR Reproducibility Checklist

View/request a protocol for this paper from *Bio-protocol*.

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Divergent SARS-CoV-2 Omicron–reactive T and B cell responses in COVID-19 vaccine recipients

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T cells stand strong against Omicron

The severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) Omicron variant of concern (VOC) caused an unprecedented rise in COVID-19 cases, even among vaccinated individuals. Omicron has a high number of mutations in the spike protein, probably aiding its evasion of immune responses. GeurtsvanKessel *et al.* studied humoral and cellular immune responses to Omicron and other VOCs to understand how vaccinated individuals are protected against Omicron. They found that antibody cross-neutralization of Omicron was very low or absent compared with WT, Beta, and Delta variants, but could be partially restored by a third booster vaccination. T cells recognized Omicron just as effectively as other VOCs, suggesting that vaccinated individuals maintain T cell immunity, which could provide protection in the absence of neutralizing antibodies, limiting severe disease.

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