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## CORONAVIRUS

# AZD1222/ChAdOx1 nCoV-19 vaccination induces a polyfunctional spike protein-specific T<sub>H</sub>1 response with a diverse TCR repertoire

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AZD1222 (ChAdOx1 nCoV-19), a replication-deficient simian adenovirus–vectored vaccine, has demonstrated safety, efficacy, and immunogenicity against coronavirus disease 2019 in clinical trials and real-world studies. We characterized CD4<sup>+</sup> and CD8<sup>+</sup> T cell responses induced by AZD1222 vaccination in peripheral blood mononuclear cells from 296 unique vaccine recipients aged 18 to 85 years who enrolled in the phase 2/3 COV002 trial. Total spike protein-specific CD4<sup>+</sup> T cell helper type 1 (T<sub>H</sub>1) and CD8<sup>+</sup> T cell responses were increased in AZD1222-vaccinated adults of all ages after two doses of AZD1222. CD4<sup>+</sup> T<sub>H</sub>2 responses after AZD1222 vaccination were not detected. Furthermore, AZD1222-specific T<sub>H</sub>1 and CD8<sup>+</sup> T cells both displayed a high degree of polyfunctionality in all adult age groups. T cell receptor β (TCRβ) sequences from vaccinated participants mapped against TCR sequences known to react to SARS-CoV-2 revealed substantial breadth and depth across the SARS-CoV-2 spike protein for both AZD1222-induced CD4<sup>+</sup> and CD8<sup>+</sup> T cell responses. Overall, AZD1222 vaccination induced a polyfunctional T<sub>H</sub>1-dominated T cell response, with broad CD4<sup>+</sup> and CD8<sup>+</sup> T cell coverage across the SARS-CoV-2 spike protein.

## INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is continuing to cause substantial widespread morbidity and mortality worldwide (1). Cellular immunity may be critical in an individual's response to SARS-CoV-2 infection, particularly in the face of neutralizing antibody (nAb) escape by emerging variants, and for reducing the severity of COVID-19 disease. Cases of asymptomatic COVID-19 have been associated with T cell responses without seroconversion, suggesting a role for T cell responses after SARS-CoV-2 exposure in the absence of nAbs (2). Furthermore, studies of patients with COVID-19 show that the presence of SARS-CoV-2-specific CD4<sup>+</sup> and CD8<sup>+</sup> T cells is associated with lower disease severity (3–5). SARS-CoV-2 vaccines have also been shown to elicit T cell responses (6–10), but more in-depth analyses of the functionality and breadth of vaccine-specific T cells could provide valuable information about potential determinants of protection.

AZD1222 (ChAdOx1 nCoV-19) is a replication-deficient simian adenovirus–vectored vaccine indicated for the prevention of COVID-19.

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The safety, efficacy, and immunogenicity of AZD1222 have been extensively demonstrated in a global clinical development program, supporting regulatory submissions for conditional or emergency use of AZD1222 (11–14). In a phase 1/2 trial conducted in the United Kingdom, COV001, AZD1222 induced marked increases in SARS-CoV-2 spike protein-specific effector T cell responses in adults aged 18 to 55 years, which peaked at day 14 after vaccination. These responses were reported as early as day 8 and were maintained through day 56, which was the latest time point analyzed (12). Similar responses were reported in adults aged 18 to ≥70 years in a phase 2/3 study conducted in the United Kingdom, COV002, in which SARS-CoV-2 spike protein-specific effector T cell responses peaked at day 14 after vaccination (13). Peak responses in adults 18 to 55 years old were characterized by interferon-γ (IFN-γ)–, interleukin-2 (IL-2)–, and tumor necrosis factor (TNF)–producing T cell helper type 1 (T<sub>H</sub>1) CD4<sup>+</sup> T cells and CD8<sup>+</sup> T cells (11). However, the cytokine profile of AZD1222-induced T cell responses beyond day 14 in younger adults or after a second dose of AZD1222 remains unknown. Furthermore, a full characterization of AZD1222-induced T cell cytokine responses in adults older than 55 is also undetermined (11).

Here, we aimed to characterize functional CD4<sup>+</sup> and CD8<sup>+</sup> T cell responses after the first and second doses of AZD1222 in healthy adults aged 18 to 85 years enrolled in phase 1 to 3 trials conducted in the United Kingdom. Furthermore, we describe the breadth and depth of unique SARS-CoV-2 spike protein-specific T cell responses induced by AZD1222 vaccination. These data provide a comprehensive analysis of the AZD1222 T cell response in an adult population.

## RESULTS

### Study participants

Evaluable samples were obtained from 296 participants enrolled in the COV001 and COV002 studies. Participant samples analyzed in this study were selected from three different age cohorts who received

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two doses of either  $5 \times 10^{10}$  virus particles of AZD1222 or control meningococcal conjugate vaccine (MenACWY) (Table 1). Of the 296 participants, 83 participants were analyzed for spike protein-specific cytokine secretion by intracellular cytokine staining (ICS), and 233 were analyzed by T cell receptor (TCR) sequencing. Twenty participants had samples in both sets of analyses.

### AZD1222 induced strong $T_H1$ -biased T cell responses to the SARS-CoV-2 spike protein

SARS-CoV-2 spike protein-specific T cell responses from all participants vaccinated with AZD1222 or MenACWY were assessed by measuring intracellular cytokine production in peripheral blood mononuclear cells (PBMCs) after in vitro stimulation with two separate overlapping peptide pools covering the entire SARS-CoV-2 spike protein sequence. Total spike protein-specific  $T_H1$  responses significantly increased from a median frequency of 0.01% [interquartile range (IQR), 0.00 to 0.03] at day 0 to 0.063% (IQR, 0.04 to 0.11) in AZD1222-vaccinated participants at day 28 after vaccination and 0.062% (IQR, 0.04 to 0.10) at day 56 after vaccination (4 weeks after the second dose) ( $P < 0.0001$ ; Fig. 1A and table S1). In MenACWY-vaccinated participants, no increases in the median frequencies of spike protein-specific  $T_H1$  responses were observed over time.  $T_H1$  responses in AZD1222-vaccinated participants were significantly greater than the median frequencies from those who received MenACWY at both day 28 (0.01% median frequency; IQR, 0.00 to 0.02;  $P < 0.0001$ ) and day 56 (0.02% median frequency; IQR, 0.01 to 0.02;  $P < 0.0001$ ) after vaccination although lower than the responses observed in convalescent patients with COVID-19 (0.13% median frequency; IQR, 0.12 to 0.21) (fig. S1A). The  $T_H1$  response followed a hierarchical pattern of cytokine production, with most spike protein-specific  $T_H1$  cells producing TNF (0.06% median frequency; IQR, 0.03 to 0.08), followed by IL-2 (0.04% median frequency; IQR, 0.02 to 0.07) and IFN- $\gamma$  (0.03 median frequency; IQR, 0.01 to 0.04) at day 56 after vaccination (Fig. 1B and fig. S1B). Spike protein-specific  $T_H2$  responses were near absent after AZD1222 vaccination (Fig. 1, C and D, and fig. S1C).

In comparison with the  $T_H1$  response, total spike protein-specific  $CD8^+$  T cells were detected at lower frequencies at day 28 and day 56 after vaccination. However, at day 56 after AZD1222 vaccination, the 0.34% (IQR, 0.02 to 0.07) median frequency of spike protein-specific  $CD8^+$  T cells was significantly elevated compared with the 0.04% median frequency (IQR, 0.00 to 0.02;  $P < 0.0001$ ) at day 0 and compared with the median frequency of 0.01% (IQR, 0.00 to 0.06;  $P = 0.0296$ ) at day 56 in participants vaccinated with MenACWY

(Fig. 1E and table S1). Spike protein-specific  $CD8^+$  T cell responses induced by AZD1222 were also equivalent to those observed in convalescent patients with COVID-19 (0.04% median frequency; IQR, 0.02 to 0.10) (fig. S2A). In contrast to the  $T_H1$  response, at day 56, most spike protein-specific  $CD8^+$  T cells produced IFN- $\gamma$  with a median frequency of 0.03% (IQR, 0.01 to 0.07), followed by TNF (0.02% median frequency; IQR, 0.01 to 0.05) and IL-2 (0.01% median frequency; IQR, 0.00 to 0.03) (Fig. 1F and fig. S2B). Using a twofold increase in any spike protein-specific  $CD4^+$  and  $CD8^+$  T cell responses, study participants vaccinated with AZD1222 induced response rates of 79.2 and 68.6%, respectively, 28 days after a second dose (table S2). These data demonstrate that AZD1222 elicited a robust  $T_H1$ -dominated T cell response with an expanded  $CD8^+$  T cell response after vaccination compared with day 0 albeit at a smaller magnitude than the  $CD4^+$  response.

### AZD1222 vaccination generated a polyfunctional $CD4^+$ T cell cytokine response across adult age groups

To determine whether  $CD4^+$  T cell responses to AZD1222 vaccination varied by age, we performed subgroup analyses according to participants' age (18 to 55, 56 to 69, and  $\geq 70$  years). Significant increases in spike protein-specific  $CD4^+$  T cell responses at day 28 over day 0 were observed for participants within each age group (18 to 55,  $P < 0.0001$ ; 56 to 69,  $P = 0.0015$ ;  $\geq 70$  years,  $P = 0.0024$ ; Fig. 2A). The median frequency of spike protein-specific  $CD4^+$  T cells producing any  $T_H1$  cytokine increased from 0.00% (IQR, 0.00 to 0.02) at day 0 to 0.05% (IQR, 0.03 to 0.10) at day 56 for 18- to 55-year-olds, 0.02% (IQR, 0.01 to 0.05) at day 0 to 0.08% (IQR, 0.04 to 0.11) at day 56 for 56- to 69-year-olds, and 0.01% (IQR, 0.00 to 0.02) at day 0 to 0.06% (IQR, 0.04 to 0.08) at day 56 in  $\geq 70$ -year-olds. Individual  $T_H1$  cytokine production followed a similar hierarchical pattern within each age group (TNF > IL-2 > IFN- $\gamma$ ) (Fig. 2A, fig. S3A, and table S3). However, the kinetics of the AZD1222-specific  $T_H1$  cell response differed by age. In participants aged 18 to 55 years, the median frequency of spike protein-specific  $CD4^+$  T cells producing any  $T_H1$  cytokine increased to 0.06% (IQR, 0.04 to 0.09) at day 28 and remained at a consistent frequency through day 56 after vaccination (Fig. 2A). In participants aged 55 to 69 years, any response median frequency of the spike protein-specific  $T_H1$  peaked at 0.13% (IQR, 0.07 to 0.16) on day 28 and declined by day 56 despite receiving a second vaccine dose. Although  $T_H1$  cell responses observed at day 28 after vaccination were at a lower frequency in participants aged  $\geq 70$  years compared with other age groups (0.04% median frequency; IQR, 0.02 to 0.06), spike protein-specific responses

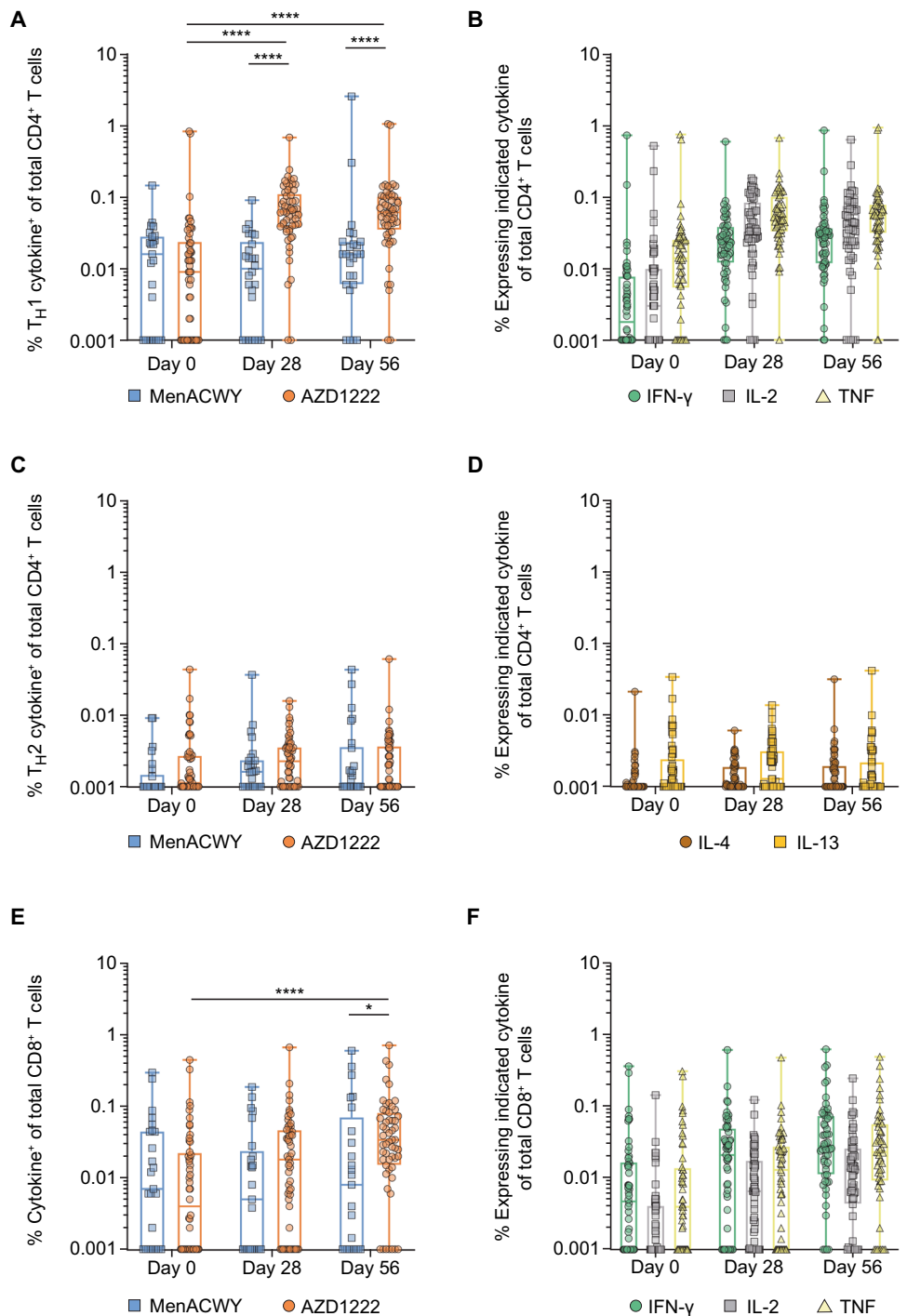
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**Table 1. Details of participants included in this analysis.**

		Patients all ages	Patients aged 18 to 55	Patients aged 56 to 69	Patients aged $\geq 70$	Patients with paired samples (day 0 and day 28 after dose 2)
ICS flow	MenACWY	26	9	7	10	26
	AZD1222	57	20	17	20	55
	Total	83	29	24	30	81
TCRseq	MenACWY	26	18	2	6	14
	AZD1222	207	130	26	51	114
	Total	233	148	28	57	128

**Fig. 1. T<sub>H</sub>1 and CD8<sup>+</sup> T cell responses are elicited after vaccination with AZD1222 or MenACWY.**

PBMCs from human participants vaccinated with AZD1222 or MenACWY at the indicated time point after vaccination were stimulated with SARS-CoV-2 spike peptide pools, and the intracellular cytokine response was measured. (A) Frequencies of total spike protein-specific CD4<sup>+</sup> T cells producing any combination of T<sub>H</sub>1 (IFN-γ, IL-2, or TNF) cytokines are shown. (B) Frequencies of total spike protein-specific CD4<sup>+</sup> T cells producing individual T<sub>H</sub>1 cytokines at the indicated time points are shown. (C) Frequencies of total spike protein-specific CD4<sup>+</sup> T cells producing any combination of T<sub>H</sub>2 (IL-4 or IL-13) cytokines are shown. (D) Frequencies of total spike protein-specific CD4<sup>+</sup> T cells producing individual T<sub>H</sub>2 cytokines at the indicated time points are shown. (E) Frequencies of total spike protein-specific CD8<sup>+</sup> T cells producing any combination of IFN-γ, IL-2, or TNF after vaccination with AZD1222 or MenACWY. (F) Frequencies of individual CD8<sup>+</sup> T cell cytokines at the indicated time points in participants vaccinated with AZD1222. For all data, responses to each peptide pool were combined to determine the total spike protein-specific response. In the box and whisker plots, the horizontal line represents median, boxes represent IQR, whiskers extend to the minimum and maximum, and symbols represent each participant. Significant differences between AZD1222 and MenACWY at each time point were determined by two-tailed Mann-Whitney tests. Significant differences between time points within each vaccine group were determined by Kruskal-Wallis test with Dunn's test to correct for multiple comparisons. All comparisons are not significant unless stated as significant; \**P* < 0.05 and \*\*\*\**P* < 0.0001.



demonstrated an increased frequency at day 56, potentially aided by the second vaccine dose at day 28. No age-specific differences in AZD1222-specific T<sub>H</sub>1 cell responses were observed at day 56.

The frequencies (Fig. 2B) and proportions (Fig. 2C) of AZD1222-specific T<sub>H</sub>1 cells producing each combination of T<sub>H</sub>1 cytokines were compared among age groups at day 28 and day 56 after vaccination. Spike protein-specific T<sub>H</sub>1 cells displayed a high degree of polyfunctionality at day 28 after vaccination in all three age groups, with 50% of the spike protein-specific CD4<sup>+</sup> T cells in 18- to 55-year-olds and 65% of the responses in 56- to 69- and ≥70-year-olds producing two or more T<sub>H</sub>1 cytokines. Spike protein-specific T<sub>H</sub>1 cells remained polyfunctional through day 56 among participants aged 56 to 69 and ≥70 years. However, in participants aged 18 to 55 years, the proportion of polyfunctional spike protein-specific T<sub>H</sub>1 cells increased to 64%. Furthermore, at day 56, spike protein-specific T<sub>H</sub>1 cells producing all three cytokines represented 32% of the response in participants

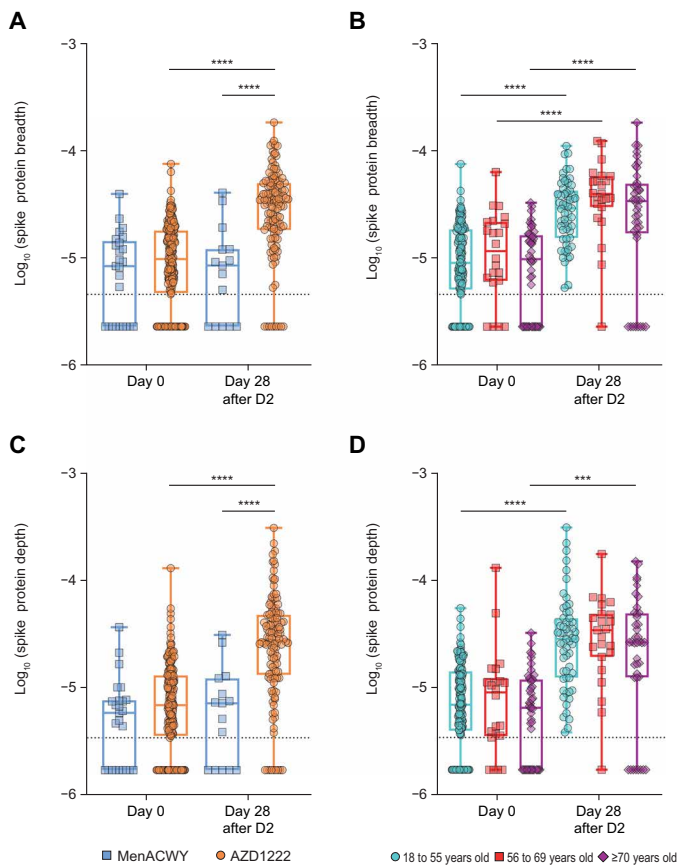
aged 18 to 55, 28% in participants aged 56 to 69 years, and 23% in participants aged ≥70 years. These data show that AZD1222 induces a polyfunctional T<sub>H</sub>1 cell response that is equivalent in frequency and functionality across all adult age groups at day 56 after vaccination.

**Polyfunctional CD8<sup>+</sup> T cell responses are generated after AZD1222 vaccination**

AZD1222-specific CD8<sup>+</sup> T cell responses were generated in all age groups but at lower frequencies compared with the T<sub>H</sub>1 responses.







**Fig. 4. Spike protein-specific TCR breadth and depth increased after vaccination with two doses of AZD1222.** (A) Spike protein-specific TCR breadth after dose two (D2) of vaccination with MenACWY (blue) or AZD1222 (orange) is shown. Breadth indicates SARS-CoV-2-associated unique TCRs of total unique TCRs. (B) Spike protein-specific TCR breadth is shown disaggregated by age. (C) Spike protein-specific TCR depth after vaccination with MenACWY (blue) or AZD1222 (orange) is shown. Depth indicates SARS-CoV-2-associated T cells of total T cells. (D) Spike protein-specific TCR depth is shown disaggregated by age. Data are  $\log_{10}$ -transformed, where all 0 values have been converted to half of the lowest nonzero value. In the box and whisker plots, the horizontal line represents median, boxes represent IQR, whiskers extend to the minimum and maximum, and symbols represent each participant. The dotted lines represent the lower detected value. Significant differences were determined by one-way ANOVA followed by Sidak's multiple comparisons tests. All comparisons are not significant unless stated as significant; \*\*\* $P < 0.001$  and \*\*\*\* $P < 0.0001$ .

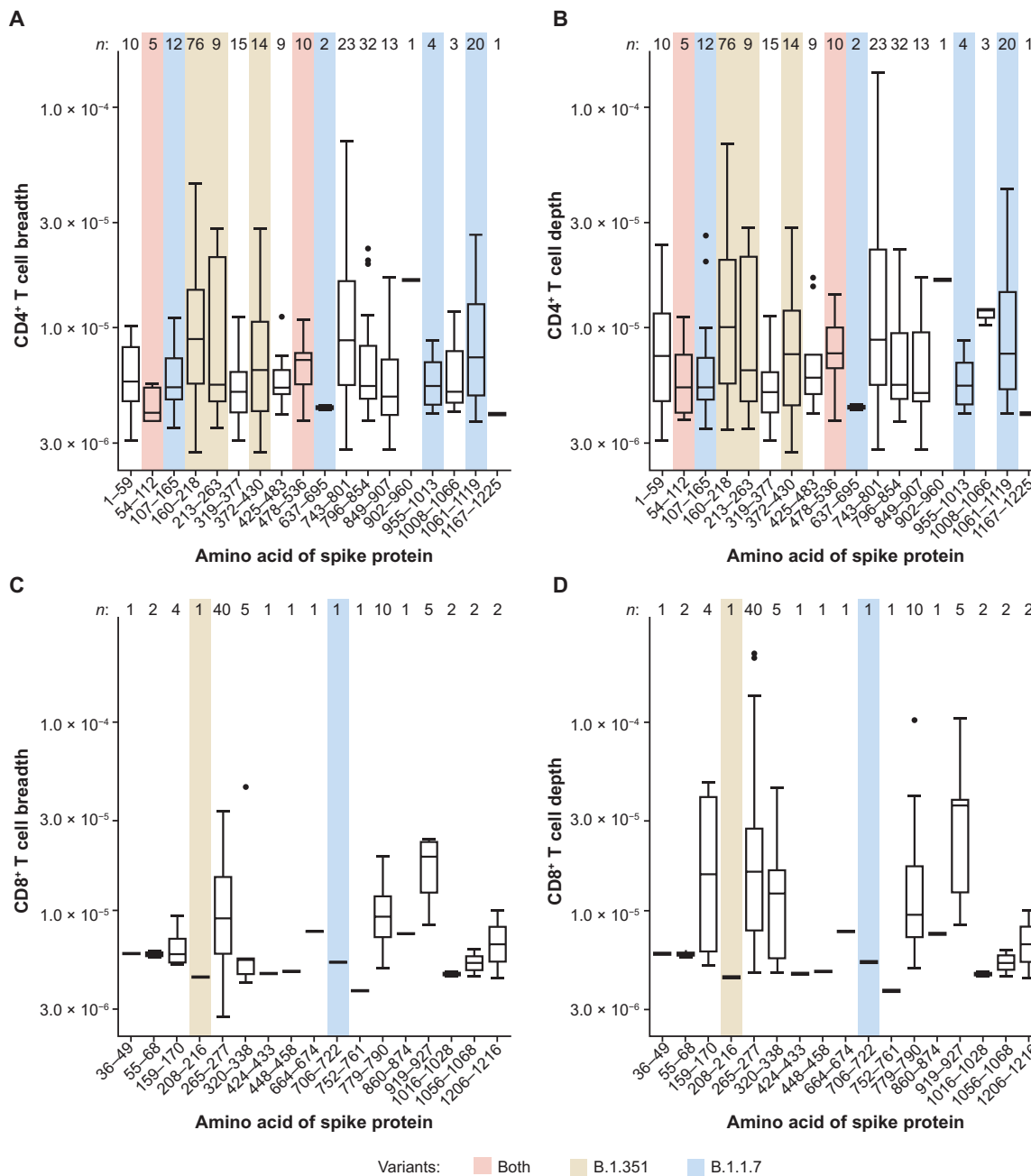
AZD1222- or MenACWY-vaccinated participants (fig. S6A). When participants were separated by age cohorts, all three age groups had a significant increase in spike protein-specific TCR breadth from day 0 to day 28 after the second dose ( $P < 0.0001$ ; Fig. 4B). In addition to TCR breadth, total TCR templates were also quantified for each group. Further confirming the ICS data (Fig. 1), the number of spike protein-specific TCRs, or depth, was significantly increased in AZD1222-vaccinated participants at day 28 after the second dose compared with day 0 and also compared with MenACWY-vaccinated participants ( $P < 0.0001$ ; Fig. 4C). The trends observed with regard to spike protein-specific TCR depth after vaccination were the same across age groups, but in the 56 to 69 years group, these responses did not meet significance for depth of response, likely due to the lower power given the smaller number of analysis points for this age

group ( $P = 0.14$ ). Participants aged 18 to 55 years and  $\geq 70$  years displayed significant increases in spike protein-specific TCR depth after vaccination ( $P < 0.0001$  and  $P = 0.0003$ , respectively; Fig. 4D). In addition, two convalescent patients with COVID-19 were sequenced, and the depth and breadth of spike protein-specific T cells were comparable to patients at day 28 after the second dose (table S4). There were no changes in depth within non-spike protein-specific TCRs in AZD1222- or MenACWY-vaccinated participants (fig. S6B).

To better understand the breadth and depth of the T cell response in AZD1222-vaccinated participants, we mapped each unique spike protein-specific TCR sequence to the region of the spike protein to which it reacted in the MIRA data (15). Spike protein-specific CD4<sup>+</sup> T cell responses spanned the entire spike protein (Fig. 5, A and B, and table S5). Dominant responses (those with the highest frequency) were observed in the N-terminal region 160–218 and the C-terminal side 743–854. Fewer unique spike protein-specific CD8<sup>+</sup> T cell TCRs were sequenced, likely due to the lower response after vaccination at these time points (Fig. 1) and the greater human leukocyte antigen (HLA) restriction of class I peptides. Half of all unique CD8<sup>+</sup> TCRs mapped to a single region of the spike protein, with the other TCRs spread evenly across the other regions (Fig. 5, C and D). Overlaying known mutations in variants of concern, including B.1.1.7 and B.1.351, indicates that although nearly 30% of unique TCRs mapped to a single region of the spike protein that is mutated in the B.1.351 SARS-CoV-2 variant, nearly half of all unique spike protein-specific TCRs recognized epitopes outside of the mutated regions found in the B.1.351 and B.1.1.7 variants. Moreover, the mutation within this single region is a single point mutation, D215G. Therefore, these data demonstrate that AZD1222 vaccination induces an expansion of SARS-CoV-2 spike protein-specific T cells with TCR sequences that map to a number of epitopes across the entire spike protein.

## DISCUSSION

Correlates of protection against COVID-19 are currently undetermined (16); however, cellular immunity is associated with positive outcomes (3–5). Here, we have provided a comprehensive assessment of the T cell response to AZD1222 vaccination. AZD1222 vaccination elicited a robust and polyfunctional T<sub>H</sub>1-dominated T cell response to the SARS-CoV-2 spike protein with a spike protein-specific CD8<sup>+</sup> T cell response across all age groups 28 days after the second dose. These responses may be critical in reducing the clinical symptoms associated with COVID-19 disease, as evidenced by longitudinal follow-up of patients with SARS-CoV-2 infection, where rapid CD4<sup>+</sup> T cell responses in acute COVID-19 were shown to be associated with mild disease and accelerated viral clearance, and early appearance of SARS-CoV-2-specific T cells was associated with shorter duration of infection (17). In a study that measured SARS-CoV-2-specific antibodies, CD4<sup>+</sup>, and CD8<sup>+</sup> T cells in participants with a range of COVID-19 disease severities, severe or fatal disease was shown to be associated with minimal or lacking SARS-CoV-2-specific CD4<sup>+</sup> and CD8<sup>+</sup> T cell responses (3). Furthermore, SARS-CoV-2-specific CD4<sup>+</sup> T cells were associated with less severe disease. SARS-CoV-2-specific CD8<sup>+</sup> T cells were also associated with lower disease severity, reinforcing the potential importance of T cell-mediated immunity for minimizing disease caused by SARS-CoV-2 infection. Last, there is evidence with some vaccinations, such as influenza, that T cell-mediated immunity may be a more reliable correlate of protection than antibody responses in older



**Fig. 5. Spike protein-specific CD4<sup>+</sup> and CD8<sup>+</sup> T cell responses demonstrate substantial breadth and depth across the entire spike protein.** TCR sequences from participants vaccinated with AZD1222 at day 28 after the second dose were mapped against TCR sequences known to react to SARS-CoV-2. (A and B) CD4<sup>+</sup> T cell breadth (A) and depth (B) were analyzed for each participant. (C and D) CD8<sup>+</sup> T cell breadth (C) and depth (D) were analyzed for each participant. The number of participants displaying responses for each epitope region is indicated at the top of each plot (n). Sequences of known variants were aligned to known Multiplex Identification of T cell Receptor Antigen Specificity (MIRA) antigen locations, with any mutations observed in B.1.351 (yellow), B.1.1.7 (blue), or both (red) highlighted. In the box and whisker plots, the horizontal line represents median, boxes represent IQR, whiskers extend to the 5th and 95th percentiles, and individual symbols represent outlier samples.

adults (18). The AZD1222-primed T cell responses that formed across all age groups may provide critical protection from severe illness due to COVID-19, as seen in vaccinated participants in these trials.

Strong T<sub>H</sub>1 responses are an important safety indicator for vaccines against respiratory pathogens. Previous whole inactivated virus vaccines for measles (19) and respiratory syncytial virus (20) led to vaccine-associated enhanced respiratory disease. This disease,

characterized by an intense allergic inflammation of the airways, is driven by vaccine-specific T<sub>H</sub>2 cells (21). Furthermore, vaccination of mice with SARS-CoV-1 and Middle East respiratory syndrome coronavirus vaccines has been shown to result in immunopathology that was attributed to T<sub>H</sub>2-biased responses (22, 23). T<sub>H</sub>1-predominant responses and balanced CD4<sup>+</sup> and CD8<sup>+</sup> T cell responses are less likely to induce immunopathology and are therefore preferred



COVID-19 vaccine characteristics. Spike protein-specific  $T_H2$  responses were minimal after AZD1222 vaccination in all age groups. These data are consistent with other SARS-CoV-2 vaccines, in which similar  $T_H1$ -dominated responses have been reported (6–9).

When we further characterized this T cell response, most spike protein-specific  $T_H1$  and  $CD8^+$  T cells were polyfunctional across all age groups. Whereas previous data have suggested that T cells, as analyzed by IFN- $\gamma$  enzyme-linked immunosorbent spot, do not increase after a second dose of AZD1222, the increases in polyfunctionality that are seen after the second dose suggest that the quality, rather than quantity, of the response may be improved by a two-dose regimen. The quality of the T cell response by cytokine characterization can give clues as to how well T cells are performing effector functions and organizing immune responses (24). Numerous studies have demonstrated that both vaccine- and infection-elicited, multicytokine-producing T cells correlate with enhanced protection against cytomegalovirus (CMV), hepatitis C virus, human herpesvirus-8, HIV, influenza virus, yellow fever virus, and *Leishmania major* (25–30). The polyfunctional responses that we observe in our analyses therefore support the contribution of T cell immunity to the protective effect of AZD1222 vaccination. Although there was more limited polyfunctionality of  $CD8^+$  T cell responses after the first dose of AZD1222 in adults aged  $\geq 70$  years, after a second dose,  $CD8^+$  T cells improved in quantity and polyfunctionality. Therefore, two doses of AZD1222 may be required in adults aged  $\geq 70$  years to achieve the same degree of polyfunctionality that is achieved in other age groups after the first dose. Data from clinical trials and emerging real-world evidence in individuals aged  $\geq 65$  have demonstrated the effectiveness of AZD1222 for the protection of COVID-19 disease after one or two doses (13, 31–33).

Although T cells are important for minimizing disease caused by SARS-CoV-2, nAbs have also been found to be associated with protection against reinfection (34). B cells depend on  $CD4^+$  T cell help for the development of pathogen-specific antibody responses (35). Anti-spike protein receptor binding domain antibody responses in patients who have recovered from COVID-19 correlated with the magnitude of spike protein-specific  $CD4^+$  T cell responses (36). Such antibody responses are facilitated specifically by a subset of  $CD4^+$  T cells called T follicular helper (Tfh) cells through the development of germinal centers in secondary lymphoid tissues (37). Circulating Tfh cells have been detected in patients who have recovered from COVID-19 (38) and have even been shown to be prominent among specific  $CD4^+$  T cells in individuals during acute COVID-19 or after convalescence (3). Characterizing the frequency and phenotype of circulating Tfh cells after AZD1222 vaccination may be informative to future studies.

In the present study, AZD1222-expanded T cells were reactive to a variety of epitopes spanning the length of spike protein. Analysis by TCR sequencing (TCRseq) showed an increase in both breadth and depth across multiple epitopes of the SARS-CoV-2 spike protein. Increased T cell breadth is an important protective mechanism against viruses that genetically diverge from parental strains (39–42). Recently, the SARS-CoV-2 spike genome has accumulated mutations, resulting in the emergence of SARS-CoV-2 variants, including the B.1.351 lineage that was first identified in South Africa and the B.1.1.7 lineage that was first identified in the United Kingdom (43, 44). Efficacy of AZD1222 against SARS-CoV-2 variants B.1.351 and B.1.1.7 investigated in Syrian hamsters showed that, despite an observed reduction in nAb titers against B.1.351 in AZD1222-vaccinated

hamsters compared with those against B.1.1.7, there was evidence of protection in the lower respiratory tract against both variants after AZD1222 vaccination (45). AZD1222 vaccination has been shown to provide protection against symptomatic disease in adults aged  $\geq 18$  years caused by the B.1.1.7 lineage, shortening the duration of shedding and viral load, which may result in reduced transmission of disease (46). Although AZD1222 was not able to prevent mild to moderate symptomatic infection against B.1.351 in humans, we believe that the vaccine may still play a protective role against severe disease, and further study is warranted. Recent studies in patients exposed to SARS-CoV-2 demonstrated that  $CD4^+$  and  $CD8^+$  T cell responses were not affected by mutations found in the B.1.351 and B.1.1.7 variants (47, 48). The breadth of T cell responses across multiple viral epitopes spanning the length of SARS-CoV-2 spike protein after vaccination with AZD1222 is similar to the response after Ad26.CoV2.S vaccination (49) and suggests that the cellular immune response to AZD1222 may be resilient to point mutations in SARS-CoV-2.

Limitations of the study included that it was run in the United Kingdom, with a majority of participants who were white and of British descent and with more females than males in the overall population. This may have therefore resulted in underestimating clonal diversity induced by AZD1222, due to a population with a more limited HLA profile and may be a factor responsible for reduced spike protein-specific  $CD8^+$  T cell clonal diversity and lower frequencies compared with corresponding  $T_H1$  responses. Furthermore, spike protein-specific  $CD8^+$  T cell frequencies may have been reduced because samples were analyzed at day 28 after vaccination, which is 2 weeks past the peak time point of the T cell responses (13), although they were still comparable to  $CD8^+$  T cell responses from convalescent patients with COVID-19. Lack of availability of biospecimens at the day 14 time point in the present study prevented analyses of AZD1222-induced T cell responses against SARS-CoV-2 and characterization of the TCR repertoire at this peak time point. Furthermore, in this study, only six participants vaccinated with AZD1222 were seropositive at day 0, providing limited data for the effect of AZD1222 vaccination on seropositive participants. Despite these study limitations, our observations are still consistent with data that SARS-CoV-2-specific  $CD4^+$  T cell responses are more prominent than  $CD8^+$  T cell responses after infection (36) and vaccination (7, 8, 10).

In summary, a combination of antibody and T cell immunity is likely needed to provide long-term protection against SARS-CoV-2 infection (50). Previous studies have shown that AZD1222 leads to a robust nAb response across multiple age groups (12, 13). Here, we demonstrate that AZD1222 vaccination also induces a polyfunctional  $T_H1$ -dominated T cell response to SARS-CoV-2 spike protein in all adult age groups, including expansion of SARS-CoV-2 spike protein-specific  $CD4^+$  and  $CD8^+$  T cells, with unique TCR sequences that mapped to multiple epitope regions across the entire spike protein, which may provide long-lasting protection from severe disease associated with SARS-CoV-2 variants.

## MATERIALS AND METHODS

### Study design

Healthy adults aged 18 to  $\geq 70$  years were enrolled in a single-blind, randomized, and controlled phase 2/3 trial for the SARS-CoV-2 vaccine, AZD1222 (ChAdOx1 nCoV-19), as described in the previously published safety and immunogenicity report (13). Full

descriptions of the methods of the studies have been previously published, including full study protocols (12, 13). Briefly, participants were enrolled in an age-escalation manner, into 18 to 55, 56 to 69, and  $\geq 70$  years immunogenicity subgroups. Participants were randomly assigned to receive either AZD1222 or control MenACWY, using block randomization. Because of a dosing error in the study, some participants received a low dose ( $2.2 \times 10^{10}$  virus particles) rather than the intended standard dose ( $5 \times 10^{10}$  virus particles) as their first dose. A licensed vaccine comparator such as MenACWY has the potential to provide a benefit to participants (prevention of infection with *Neisseria meningitidis*) and facilitates the participant blinding, who, upon control vaccination, may experience local and general adverse events similar to those experienced by those vaccinated with the experimental vaccine. Participants aged 18 to 55 years were randomly assigned (1:1) to either two doses of AZD1222 or two doses of MenACWY. Participants aged 56 to 69 years were randomly assigned (3:1:3:1) to one dose of AZD1222, one dose of MenACWY, two doses of AZD1222, or two doses of MenACWY. Participants aged  $\geq 70$  years were randomly assigned (5:1:5:1) to one dose of AZD1222, one dose of MenACWY, two doses of AZD1222, or two doses of MenACWY. Prime-booster regimens were given 28 days apart. Participants were then recruited to the standard-dose cohort ( $5 \times 10^{10}$  virus particles of AZD1222), and the same randomization procedures were followed, except participants aged 18 to 55 years were randomly assigned in a 5:1 ratio to two doses of AZD1222 or two doses of MenACWY. Participants, clinical investigators, and the laboratory team, but not the staff administering the vaccine, were masked to vaccine allocation for the duration of the study.

For the analysis performed in this study, participant samples, for whom PBMCs were available at matched time points, were selected from all three age cohorts who received either two doses of AZD1222 ( $5 \times 10^{10}$  virus particles) or control MenACWY (Table 1). In total, samples were obtained from 296 unique participants in studies COV001 and COV002. A windowing convention was applied to ICS and TCRseq data. For ICS, day 28 refers to  $28 \pm 7$  days after the first dose, and day 56 refers to  $28 \pm 7$  days from the second dose (or about 56 days after the first dose). Written informed consent was obtained from all participants, and the trials were performed in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. COV001 was approved in the United Kingdom by the Medicines and Healthcare products Regulatory Agency (reference 21584/0424/001-0001) and the South-Central Berkshire Research Ethics Committee (reference 20/SC/0145). COV002 was sponsored by the University of Oxford and approved in the United Kingdom by the Medicines and Healthcare products Regulatory Agency (reference 21584/0428/001-0001) and the South-Central Berkshire Research Ethics Committee (reference 20/SC/0179). Vaccine use was authorized by Genetically Modified Organisms Safety Committees at each participating site.

Samples from 83 participants were used for ICS analysis and samples from 233 participants for TCR analysis, with 20 participant samples present in both datasets (Table 1). One patient in TCR analysis from the 18 to 55 age group was confirmed to have received a lower first dose ( $2.25 \times 10^{10}$  virus particles) and a standard second dose ( $5 \times 10^{10}$  virus particles) of AZD1222.

### ICS assay and analysis

PBMCs were isolated from vaccine recipient blood samples within 6 hours of venipuncture and cryopreserved at below  $-150^\circ\text{C}$  before use in ICS assays. Human convalescent samples were obtained after

symptom onset from adults with previous SARS-CoV-2 infection. Specimens were collected after participants provided written informed consent under an institutional review board–approved protocol at the National Institutes of Health Clinical Center (NCT00067054). PBMCs were isolated and cryopreserved similarly to those from vaccine recipients. ICS was performed on samples obtained at day 0, day 28, second dose (if different from day 28), and day 28 after the second dose.

Antibody titration of all antibodies included in the analysis was performed before the analysis of clinical specimens. The ICS assay was used to evaluate T cell responses, as previously described (10). Briefly, PBMCs were thawed and rested overnight before being stimulated with pools of 15-mer peptides overlapping by 10 amino acids covering the N terminus of SARS-CoV-2 spike protein up to the furin cleavage site (S1 pool) and the C terminus of the SARS-CoV-2 spike protein up to the furin cleavage site (S2 pool) for 6 hours at  $37^\circ\text{C}$  with 5%  $\text{CO}_2$ . Peptide pools were custom-ordered from JPT Peptide Technologies GmbH and were  $>85\%$  pure.

After stimulation, cells were stained and analyzed as described previously (51). Briefly, cells were washed with phosphate-buffered saline (PBS) and stained with viability dye for 20 min at room temperature, followed by surface stain for 20 min at room temperature, cell fixation, and permeabilization with a BD Cytofix/Cytoperm kit (catalog no. 554714) for 20 min at room temperature and then intracellular stain for 20 min at room temperature. All antibody staining was performed in the dark. Surface staining and all pre-fixation washes were performed with fluorescence-activated cell sorting buffer (PBS + 1% fetal bovine serum + 0.02%  $\text{NaN}_3$ ), and intracellular staining and postfixation washes were performed in  $1 \times$  BD Perm/Wash buffer (BD Biosciences, catalog no. 554714). See table S6 for a complete list of antibodies used. Upon completion of staining, cells were collected on a BD FACSymphony flow cytometer. Samples were invalidated if  $<20,000$  live  $\text{CD}3^+$  T cells were collected. On average,  $\geq 280,000$  cells were collected for each sample. Samples were analyzed using FlowJo 10.6.2 (BD Biosciences). Anomalous “bad” events were separated from “good” events using FlowAI (52). “Good events” were used for all downstream gating. Gating strategy can be found in fig. S7. Individual cytokines were plotted on the y axis versus  $\text{CD}69^+$  cells on the x axis, and only  $\text{CD}69^+$  events were used to determine positive responses. No cytokine-positive responses were detected above background in the  $\text{CD}69^-$  gate. Representative flow plots for cytokine gating are shown in fig. S8.  $\text{CD}69^+$  activated cells were increased over baseline after AZD1222 vaccination but did not differ between peptide pools or by age groups (fig. S9). All antigen-specific cytokine frequencies are reported after background subtraction of identical gates from the same sample incubated with negative control stimulation with dimethyl sulfoxide.

Assay qualification was performed by the Vaccine Immunology Program at the Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health. Assay qualification included assessment of  $\text{T}_\text{H}1$  and  $\text{T}_\text{H}2$  specificity,  $\text{T}_\text{H}1$  and  $\text{T}_\text{H}2$  intra-assay precision, inter-assay precision, and SARS-CoV-2 peptide pool validation.  $\text{T}_\text{H}1$  and  $\text{T}_\text{H}2$  specificity was conducted using PBMCs from acutely infected CMV donors (for  $\text{T}_\text{H}1$  specificity) or *Filaria* parasite donors (for  $\text{T}_\text{H}2$  specificity), given the established cytokine profiles of these pathogens.

### TCR $\beta$ chain sequencing

Immunosequencing of the complementarity-determining region 3 (CDR3) regions of human TCR $\beta$  chains was performed using the

ImmunoSEQ Assay (Adaptive Biotechnologies). Extracted genomic DNA was amplified in a bias-controlled multiplex polymerase chain reaction (PCR), followed by high-throughput sequencing. Sequences were collapsed and filtered to identify and quantitate the absolute abundance of each unique TCR $\beta$  CDR3 region for further analysis as previously described (53–55). The fraction of T cells was calculated by normalizing TCR $\beta$  template counts to the total amount of DNA usable for TCRseq, where the amount of usable DNA was determined by PCR amplification and sequencing of several reference genes that are expected to be present in all nucleated cells.

### Mapping of SARS-CoV-2 TCR $\beta$ sequences

TCR sequences from participants receiving AZD1222 were mapped against a set of TCR sequences that are known to react to SARS-CoV-2. Briefly, these sequences were first identified by MIRA (56). TCRs that reacted were further screened for enrichment in COVID-19–positive repertoires collected as part of immuneCODE (15) and compared with COVID-19–negative repertoires to remove TCRs that may be highly public or cross-reactive to common antigens. Individual response could be quantified by the number or frequency of SARS-CoV-2 TCRs seen after vaccination. TCRs were further analyzed to determine position within the spike protein based on the MIRA antigens.

Sequences of known variants were obtained from GISAID (www.gisaid.org) and aligned to known MIRA antigen locations. Antigens that contain any mutations observed in the B.1.1.7 or B.1.351 variants were labeled as potentially affected.

### Statistical analysis

For ICS analysis, significant differences between vaccination groups were determined by Mann-Whitney nonparametric two-tailed *t* tests with a 95% confidence interval. Significant differences between time points within each vaccine group were determined by Kruskal-Wallis nonparametric one-way analysis of variance (ANOVA) with Dunn's test to correct for multiple comparisons. For all TCR analyses, significant differences were determined by one-way ANOVA followed by Sidak's multiple comparisons tests. Raw data are available in data files S1 and S2.

### SUPPLEMENTARY MATERIALS

www.science.org/doi/10.1126/scitranslmed.abj7211

Figs. S1 to S9

Tables S1 to S6

Data files S1 and S2

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

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