Immunogenicity of bivalent omicron (BA.1) booster vaccination after different priming regimens in health-care workers in the Netherlands (SWITCH ON) results from the direct boost group of an open-label, multicentre, randomised controlled trial
Tan, N.H.; Geers, D.; Sablerolles, R.S.G.; Rietdijk, W.J.R.; Goorhuis, A.; Postma, D.F.; ... ; SWITCH ON Res Grp

Citation
Tan, N. H., Geers, D., Sablerolles, R. S. G., Rietdijk, W. J. R., Goorhuis, A., Postma, D. F., … Kuy, P. H. M. van der. (2023). Immunogenicity of bivalent omicron (BA.1) booster vaccination after different priming regimens in health-care workers in the Netherlands (SWITCH ON): results from the direct boost group of an open-label, multicentre, randomised controlled trial. *The Lancet Infectious Diseases*, *23*(8), 901-913. doi:10.1016/S1473-3099(23)00140-8

Version: Publisher's Version
License: Creative Commons CC BY 4.0 license
Downloaded from: https://hdl.handle.net/1887/3715378

Note: To cite this publication please use the final published version (if applicable).

Immunogenicity of bivalent omicron (BA.1) booster vaccination after different priming regimens in health-care workers in the Netherlands (SWITCH ON): results from the direct boost group of an open-label, multicentre, randomised controlled trial

Ngoc H Tan, Daryl Geers*, Roos S G Sablerolles*, Wim J R Rietdijk, Abraham Goorhuis, Douwe F Postma, Leo G Visser, Susanne Bogers, Laura L A van Dijk, Lennert Gommers, Leanne P M van Leeuwen, Annemarie Boerma, Sander H Nijhof, Karel A van Dort, Marion P G Koopmans, Virgil A S H Dalm, Melvin Lafeber, Neeltje A Kootstra, Anke L W Huckriede, Debbie van Baarle, Luca M Zaeck, Corine H GeurtsvanKessel*, Rory D de Vries*, P Hugo M van der Kuy*, for the SWITCH ON Research Group†*

Summary

Background Bivalent mRNA-based COVID-19 vaccines encoding the ancestral and omicron spike (S) protein were developed as a countermeasure against antigenically distinct SARS-CoV-2 variants. We aimed to assess the (variant-specific) immunogenicity and reactogenicity of mRNA-based bivalent omicron (BA.1) vaccines in individuals who were primed with adenovirus-based or mRNA-based vaccines encoding the ancestral spike protein.

Methods We analysed results of the direct boost group of the SWITCH ON study, an open-label, multicentre, randomised controlled trial. Health-care workers from four academic hospitals in the Netherlands aged 18–65 years who had completed a primary COVID-19 vaccination regimen and received one booster of an mRNA-based vaccine, given no later than 3 months previously, were eligible. Participants were randomly assigned (1:1) using computer software in block sizes of 16 and 24 to receive an omicron BA.1 bivalent booster straight away (direct boost group) or a bivalent omicron BA.5 booster, postponed for 90 days (postponed boost group), stratified by priming regimen. The BNT162b2 OMI BA.1 boost was given to participants younger than 45 years, and the mRNA-1273.214 boost was given to participants 45 years or older, as per Dutch guidelines. The direct boost group, whose results are presented here, were divided into four subgroups for analysis: (1) Ad26.COV2.S (Johnson & Johnson) prime and BNT162b2 OMI BA.1 (BioNTech–Pfizer) boost (Ad/P), (2) mRNA-based prime and BNT162b2 OMI BA.1 boost (mRNA/P), (3) Ad26.COV2.S prime and mRNA-1273.214 (Moderna) boost (Ad/M), and (4) mRNA-based prime and mRNA-1273.214 boost (mRNA/M). The primary outcome was fold change in S protein S1 subunit-specific IgG antibodies before and 28 days after booster vaccination. The primary outcome and safety were assessed in all participants except those who withdrew, had a SARS-CoV-2 breakthrough infection, or had a missing blood sample at day 0 or day 28. This trial is registered with ClinicalTrials.gov, NCT05471440.

Findings Between Sept 2 and Oct 4, 2022, 219 (50%) of 434 eligible participants were randomly assigned to the direct boost group; 187 participants were included in the primary analyses; exclusions were mainly due to SARS-CoV-2 infection between days 0 and 28. From the 187 included participants, 138 (74%) were female and 49 (26%) were male. 42 (22%) of 187 participants received Ad/P and 44 (24%) mRNA/P (those aged <45 years), and 45 (24%) had received Ad/M and 56 (30%) mRNA/M (those aged ≥45 years). S1-specific binding antibody concentrations increased 7 days after bivalent booster vaccination and remained stable over 28 days in all four subgroups (geometric mean ratio [GMR] between day 0 and day 28 was 1·15 [95% CI 1·12–1·19] for the Ad/P group, 1·17 [1·14–1·20] for the mRNA/P group, 1·20 [1·17–1·23] for the Ad/M group, and 1·16 [1·13–1·19] for the mRNA/M group). We observed no significant difference in the GMR between the Ad/P and mRNA/P groups (p=0·51). The GMR appeared to be higher in the Ad/M group than in the mRNA/M group, but was not significant (p=0·073). Most side-effects were mild to moderate in severity and resolved within 48 h in most individuals.

Interpretation Booster vaccination with mRNA-1273.214 or BNT162b2 OMI BA.1 in adult healthcare workers resulted in a rapid recall of humoral and cellular immune responses independent of the priming regimen. Monitoring of SARS-CoV-2 immunity at the population level, and simultaneously antigenic drift at the virus level, remains crucial to assess the necessity and timing of COVID-19 variant-specific booster vaccinations.

Funding The Netherlands Organization for Health Research and Development (ZonMw).

Copyright © 2023 Elsevier Ltd. All rights reserved.

Lancet Infect Dis 2023; 23: 901–13

Published Online April 20, 2023 https://doi.org/10.1016/S1473-3099(23)00140-8

See Comment page 880

*Contributed equally

†Members listed in the appendix (p 3)

Department of Hospital Pharmacy (N H Tan MPharm, R S G Sablerolles MD, W J R Rietdijk PhD, Prof P H M van der Kuy PhD), **Department of Viroscience** (D Geers MSc, S Bogers MSc, L L A van Dijk MSc, L Gommers BSc, L P M van Leeuwen MD, Prof M P G Koopmans DVM, L M Zaeck PhD, C H GeurtsvanKessel MD, R D de Vries PhD), **Department of Internal Medicine, Division of Allergy and Clinical Immunology and Department of Immunology** (V A S H Dalm MD), **and Department of Internal Medicine** (M Lafeber MD), **Erasmus Medical Center, Rotterdam, Netherlands; Center of Tropical Medicine and Travel Medicine, Department of Infectious Diseases** (A Goorhuis MD), **and Department of Experimental Immunology** (K A van Dort MSc, N A Kootstra PhD), **Amsterdam University Medical Centers, Amsterdam, Netherlands; Infection and Immunity, Amsterdam Public Health, University of Amsterdam, Amsterdam, Netherlands** (A Goorhuis); **Department of Internal Medicine and Infectious Diseases**

(D F Postma MD) **and Department of Medical Microbiology and Infection Prevention** (A Boerma MSc, S H Nijhof MSc, Prof A L W Huckriede PhD, Prof D van Baarle PhD)**, University Medical Center Groningen, Groningen, Netherlands; Department of Infectious Diseases, Leiden University Medical Center, Leiden, Netherlands** (Prof L G Visser PhD)**; Center for Infectious Disease Control, National Institute for Public Health and the Environment, Bilthoven, Netherlands** (Prof D van Baarle)

Correspondence to: Prof P Hugo M van der Kuy, Department of Hospital Pharmacy, Erasmus Medical Center, Rotterdam, 3015 GD, Netherlands **h.vanderkuy@erasmusmc.nl**

See **Online** for appendix

Research in context

Evidence before this study

We searched PubMed for relevant articles on Aug 31, 2022 using the search terms "((COVID-19) AND (Vaccination)) AND (bivalent) AND (mRNA)", without date and language restrictions. Exclusion criteria included papers that did not report on the general healthy human population (ie, age, comorbidities, and pre-clinical animal studies), behavioural studies, reviews, protocols, commentaries, safety reports, and studies that did not report on approved mRNA-based bivalent booster vaccines against BA.1. All other articles were included. We found no study reporting on immunogenicity of mRNA-based omicron BA.1 bivalent booster vaccination. We updated our PubMed search on Jan 20, 2023, using the same search strategy and found four relevant articles. One perspective article summarised the current state of omicron BA.1 and omicron BA.5 bivalent vaccination strategies. The remaining three articles assessed vaccine efficacy, safety, and immunogenicity of omicron BA.1 bivalent booster vaccination. All three articles reported on cross-neutralising antibodies against various omicron sublineages including BA.1, BA.4, BA.5, BA.2.75, and BQ.1.1. These studies heavily rely on neutralizing antibody data and do not consider other aspects of the immune response such as T cells. Comparative studies have been released on the evaluation of omicron BA.1 bivalent booster vaccines and no studies have addressed the effect of primary vaccination.

Added value of this study

In the first part of the SWITCH ON trial (the direct boost arm), we present the data in which health-care workers primed with Ad26.COV2.S (Johnson & Johnson), BNT162b2 (BioNTech–Pfizer), or mRNA-1273 (Moderna) received either a BNT162b2 OMI BA.1 or mRNA-1273.214 booster vaccination. This is the first study, to our knowledge, to evaluate the immunogenicity and reactogenicity of bivalent COVID-19 boosters against the background of different priming vaccinations. Vaccination with a bivalent booster resulted in a rapid recall of humoral and cellular immune responses independent of the initial priming regimen. The largest proportion of (neutralising) antibodies and virus-specific T cells were recalled within 7 days of booster vaccination across all four study groups within the direct boost group. Although no preferential boosting of variant-specific responses was observed, the induced antibodies and T cells cross-reacted with omicron BA.1, which was included in the vaccine, and with the more antigenically distinct omicron BA.5.

Implications of all the available evidence

There have been multiple vaccine platforms used as priming regimens worldwide, which have differed in their efficacy and immunogenicity. Several studies have shown that bivalent booster vaccination leads to an increase in neutralising antibody levels. However, priming history is not taken into consideration in most studies. Heterologous and homologous boosting with monovalent COVID-19 vaccines after different priming regimens are reported to induce antibody and T-cell responses differently. Therefore, the effect of a different priming history needs to be taken into consideration when assessing vaccine immunogenicity. Our study showed that bivalent booster vaccination was associated with a fast antibody response independent of priming with either Ad26.COV2.S, BNT162b2, or mRNA-1273, suggesting that a similar recall of immunological memory will occur during SARS-CoV-2 breakthrough infection. The data from our study contributes to the discussion about the necessity and timing of COVID-19 booster vaccinations in the healthy population and the need for continuous monitoring of immunity at the population level.

Introduction

The ongoing spread of SARS-CoV-2 remains a public health emergency of international concern. Immunological memory is crucial in the prevention of severe COVID-19, because sterilising immunity against SARS-CoV-2 infection cannot be brought about by vaccination or infection.[1,2] Although vaccination against COVID-19 initially provided high amounts of protection from both infection and severe disease,[3,4] the emergence of variants has resulted in escape from protection against infection. Frequent breakthrough infections can be explained by waning antibodies in combination with (partial) evasion from neutralising antibodies, especially since the emergence of omicron sublineages.[5–9] The shift in key epitopes to those that were more characteristic of omicron variant viruses than ancestral viruses[10] resulted in the recommendation by the WHO advisory group on vaccinations to update the vaccines.[11] This recommendation led to vaccination campaigns with bivalent booster vaccines targeting the spike (S) protein of omicron sub-variants.

The first generation of licensed bivalent vaccines consisted of mRNAs encoding the S protein from both the ancestral SARS-CoV-2 and the omicron BA.1 variant.[12,13] A study with the bivalent mRNA-1273.214 vaccine (Moderna) showed that this vaccine induced higher amounts of omicron BA.1 neutralising antibodies than the monovalent mRNA-1273 vaccine (Moderna), when given as a second booster in adults who had previously received a primary vaccination series and first booster with the mRNA-1273 vaccine.[12] Partly as a result of this finding, many countries introduced bivalent vaccines into their booster campaigns.

The COVID-19 pandemic has now entered a phase in which repeated boosters are available for high-risk groups and the general population in many countries, and a relatively low number of severe COVID-19 cases and a low mortality rate are being observed, but in which SARS-CoV-2 continues to display antigenic drift.[10] By the time updated bivalent vaccines were introduced, increasingly different omicron sublineages had become

dominant. To ascertain the immunological benefit of additional (bivalent) booster vaccinations and provide scientific evidence for decision makers, in-depth evaluations of immunogenicity are crucial.

The SWITCH ON trial,[14] which is still ongoing, aims to evaluate the bivalent booster vaccines BNT162b2 OMI BA.1 (BioNTech-Pfizer) and mRNA-1273.214 in a cohort of health-care workers in the Netherlands. The SWITCH-ON trial is investigating three main topics: immunogenicity of omicron BA.1 bivalent vaccines after adenovirus-based or mRNA-based vaccine priming; rapid immunological recall responses, indicative of preserved immunological memory; and cross-reactivity with relevant variants after booster vaccination. To assess the effect of timing on the induction of immune responses, we randomly assigned participants to a direct boost group or a postponed boost group. These data will aid in the discussion on the necessity of future booster vaccinations in the healthy general population and aim to facilitate more personalised vaccination approaches in future public health interventions against COVID-19. In this Article, we report the data from the direct boost group of the trial only, because relatively few data are currently available about the immunogenicity of bivalent booster vaccination in the general healthy population.

Methods

Study design and participants

The SWITCH ON study is an ongoing open-label, multicentre, randomised controlled trial involving health-care workers from four academic hospitals in the Netherlands.[14] The SWITCH ON trial consists of two randomised treatment groups (ie, a direct boost group with omicron BA.1 bivalent vaccines and a postponed boost group with omicron BA.5 bivalent vaccines). The present Article covers only the data from the direct boost group. The trial protocol was approved by the medical ethics committee of Erasmus Medical Centre (Rotterdam, the Netherlands), the sponsor site, and the local review boards of the other participating centres. The study adheres to the principles of the Declaration of Helsinki and the CONSORT guidelines. All eligible participants provided written informed consent before their participation in the study.

Health-care workers, independent of sex and gender, were eligible to participate in the SWITCH ON study if they were between the ages of 18 and 65 years and had completed a primary COVID-19 vaccination regimen with either one shot of the adenovirus-based vaccine Ad26.COV2.S (Johnson & Johnson) or two shots of an mRNA-based vaccine (BNT162b2 or mRNA-1273). All participants had also received at least one booster dose with an mRNA-based vaccine, given no later than 3 months before the start of the SWITCH ON study. Participants with severe comorbidities such as dialysis dependence, or participants with an immunodeficiency due to treatment with immunosuppressants or cancer therapy, were excluded from the study. Participants with a known history of previous SARS-CoV-2 infection were eligible, unless the infection occurred less than 3 months before the start of the study (based on self-reporting). At baseline, SARS-CoV-2 nucleocapsid-specific antibodies were measured to establish the distribution of infection history across groups. Participants with a positive nucleocapsid test, who did not report having contracted SARS-CoV-2 less than 3 months before the start of the study, were included in the analyses. The full list of inclusion and exclusion criteria was published previously.[14]

Randomisation and masking

Block randomisation in block sizes of 16 and 24 was used to randomly assign participants (1:1) to the direct boost group or the postponed boost group, with stratification for Ad26.COV2.S priming or mRNA-based priming. Block randomisation was completed by the research assistants who were not involved in the data analysis using Castor software (version 2022.5.1.0). Participants in the direct boost group received a bivalent omicron BA.1 booster vaccine in October, 2022, whereas participants in the postponed boost group received a bivalent omicron BA.5 booster vaccine in December, 2022. It was not possible to conceal the group allocation due to timing of the different bivalent boosters. Participants were informed about their allocated group after randomisation. Laboratory personnel were not masked from the study allocation of participants.

Procedures

In the direct (omicron BA.1) boost group, participants aged at least 45 years were administered mRNA-1273.214 50 μg intramuscularly, and participants younger than 45 years received BNT162b2 OMI BA.1 30 μg intramuscularly; the decision to vaccinate the age groups differently was in response to guidelines from the Dutch National Institute for Public Health and the Environment, released in September, 2022.[15] On the basis of their respective priming regimens, participants in the direct boost group were further divided into four subgroups: (1) Ad26.COV2.S prime and BNT162b2 OMI BA.1 boost (Ad/P); (2) mRNA-based prime and BNT162b2 OMI BA.1 boost (mRNA/P); (3) Ad26.COV2.S prime and mRNA-1273.214 boost (Ad/M); and (4) mRNA-based prime and mRNA-1273.214 boost (mRNA/M). Blood samples were collected on the day of booster vaccination (day 0, study visit 1), on day 7 (study visit 2), and day 28 (study visit 3) after booster vaccination (appendix p 8). Additionally, 25% of the samples in each group were randomly selected using Castor software for in-depth immunological analyses. Participants in the postponed boost group had their first blood sample taken in September 2022 as safety baseline. In December 2022, participants in this group received their booster vaccination and blood was sampled in a similar way to the direct boost group.

After randomisation, participants were sent the baseline characteristics questionnaires to gather information about biological sex, age, height, weight, ancestry, occupation, comorbidities, and the date of last booster. The options provided for sex in the questionnaire were female and male.

SARS-CoV-2-specific antibodies and T-cell responses were measured in all participants at baseline, and 7 and 28 days after booster vaccination. Concentrations of IgG antibodies specific to the ancestral S protein S1 subunit (S1) were measured using the quantitative LIAISON SARS-CoV-2 TrimericS IgG assay (DiaSorin, Saluggia, Italy) as previously described.[4] The lower limit of detection was set at 4·81 BAU/mL. The cutoff responder value was set at 33·8 BAU/mL. S-protein-specific binding antibodies to ancestral SARS-CoV-2 and omicron subvariants BA.1 and BA.5 were assessed by ELISA as previously described.[16,17] Neutralising antibodies targeting ancestral SARS-CoV-2 and omicron subvariants BA.1 and BA.5 were assessed by the 50% plaque reduction neutralisation test (PRNT50) as previously described.[16,18] SARS-CoV-2-specific T-cell responses were measured by IFNγ release assay using the QuantiFERON SARS-CoV-2 kit (QIAGEN, Hilden, Germany).[5,6] A lower limit of detection was set at 0·01 IU/mL as per manufacturer's instructions. Additionally, SARS-CoV-2-specific T cells were phenotyped in an activation-induced marker (AIM) flow cytometry assay.[5] In these AIM assays, cross-reactive variant-specific T-cell responses targeting ancestral SARS-CoV-2 and omicron subvariants BA.1 and BA.5 were measured.[5,16,17]

Participants received an online electronic questionnaire on day 8 after booster vaccination, which asked participants questions about adverse reactions (ie, side-effects).[6,19] The severity of adverse reactions was described in accordance with the US Food & Drug Administration Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.[20] Any serious adverse reactions, both local and systemic, were additionally reported via email and phone calls. The final question of the questionnaire was open to report any reactions that were not listed in our questionnaire. Side-effects known for the products were asked in the questionnaire in the form of multiple choice questions.

Outcomes

The primary outcome was fold change (ie, the gemoetric mean ratio [GMR] between day 0 and day 28) in antibody response between day 0 and day 28, in which we compared groups primed by Ad26.COV2.S and mRNA-based vaccine (Ad/P *vs* mRNA/P and Ad/M *vs* mRNA/M) by calculating the GMR from the log-transformed data. Secondary outcomes were fast response, levels of neutralising antibodies, S-protein-specific T-cell responses, and reactogenicity. A fast response was defined as having reached an immune response on day 7 equal to or higher than a 65% increase of the response 28 days after booster vaccination. Post-hoc analyses of S-protein-specific binding antibodies measured by ELISA, and S-protein-specific cross-reactive T-cell responses measured by AIM provided an overview of the variant-specific immunogenicity after bivalent vaccination.

Statistical analysis

For the SWITCH ON trial, an initial power calculation was performed for the combined direct boost and postponed boost groups. We calculated that the study required 91 participants in each of four groups (direct boost group: priming with (1) adenovirus-based or (2) mRNA-based vaccine; postponed boost group: priming with (3) adenovirus-based or (4) mRNA-based vaccine) to reach 80% power at a two-sided 5% significance level to detect a $\log_{10}$-transformed difference of 0·2 in the fold change in antibody concentration 28 days after booster vaccination. This difference is based on data from the Erasmus MC health-care worker study,[5] in which the mean fold changes in the individuals primed with an adenovirus-based vaccine and individuals primed with an mRNA-based vaccine were 1·344 (SD 0·451) and 1·151 (0·449), respectively. Considering 10% loss to follow-up, we planned to include 102 participants per group, resulting in a total sample size of 408 participants. These participants consisted of 204 (50%) participants primed with Ad26.COV2.S and 204 (50%) participants primed with BNT162b2 or mRNA-1273, equally divided over the direct boost and postponed boost groups. In this Article, we only report the results of the participants from the direct boost group. During study recruitment in September, 2022, an updated COVID-19 booster policy by the national government of the Netherlands[15] was implemented with the introduction of different vaccine strategies for the two available vaccines according to age (older than or younger than 45 years), which was not part of the initial power calculation. Therefore, we deviated from the original study protocol and the sample size in each study group of the direct boost group was adjusted to fit the new groups (Ad/M, Ad/P, mRNA/M, and mRNA/P).

Descriptive analysis was used to report baseline characteristics of participants. For continuous variables, mean and SD were used if data were normally distributed. If data were not normally distributed, median and IQR were reported. Normality was assessed using the Shapiro-Wilk test for numerical outcome data and the quantile-quantile (Q-Q) plot for log-transformed outcome data. Categorical variables were presented as numbers and percentages. Immunogenicity data were presented as geometric mean titre (GMT) or geometric mean. For the primary outcome, the fold change in antibody response was presented as a GMR and 95% CI. The GMRs in each group were compared using the two-sided ratio *t* test. For the secondary outcomes reported in this Article (apart

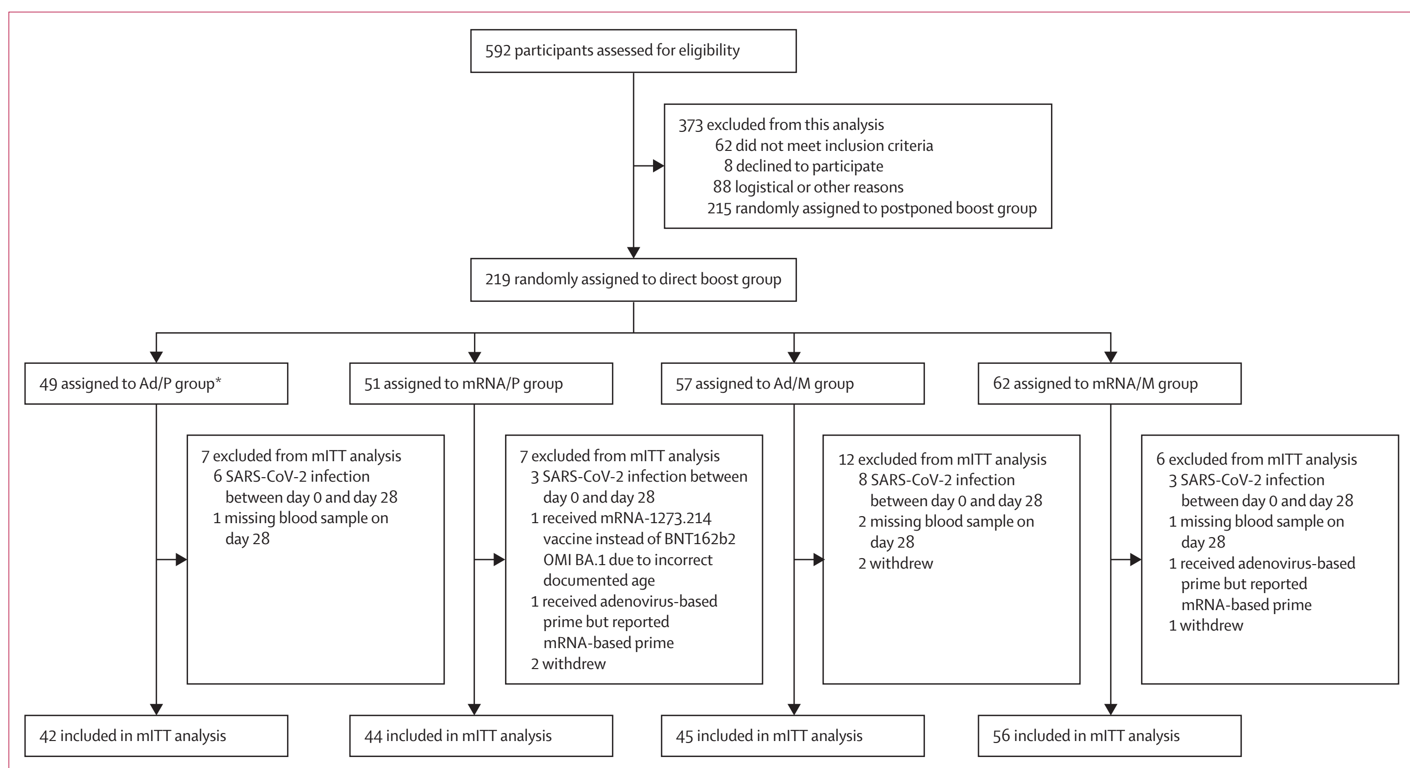

Figure 1: **Trial profile**

Ad/P=Ad26.COV2.S prime and BNT162b2 OMI BA.1 boost (in participants aged <45 years). mRNA/P=mRNA-based prime and BNT162b2 OMI BA.1 boost (in participants aged <45 years). Ad/M=Ad26.COV2.S prime and mRNA-1273.214 boost (in participants aged >45 years). mRNA/M=mRNA-based prime and mRNA-1273.214 boost (in participants aged >45 years). mITT=modified intention-to-treat.

from fast response) and post-hoc analyses we used similar statistical analyses as for the primary outcome. Fast response was reported as the proportion of participants per priming regimen and booster vaccination. All other data are presented as geometric means with 95% CIs. We used p values of less than 0·01 as the statistical significance threshold. The data were analysed for all outcomes and safety analyses in a modified intention-to-treat (mITT) population, which consisted of all randomly assigned participants except those who withdrew from the study, had a SARS-CoV-2 breakthrough infection between study visits, had a missing blood sample at day 0 (study visit 1) or day 28 (study visit 3), received incorrect booster vaccine, or misreported priming history. Missing values were reported when applicable (appendix p 23), and no imputation was used because the number of missing values was low. All statistical analyses were conducted using GraphPad Prism software (Dotmatics; version 9.4.1) and RStudio (version 4.2.1). The study is registered with ClinicalTrials.gov, number NCT05471440.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Sept 2 and Oct 4, 2022, of the 592 health-care workers who were screened for eligibility, 434 (73%) were included in the SWITCH ON study. 62 (10%) participants were excluded because they did not meet the inclusion criteria, eight (1%) withdrew before randomisation, and 88 (15%) were excluded for logistical reasons (eg, unable to attend baseline or day 28 blood sampling due to planned holiday). The representativeness of the study participants is described in the appendix (p 22). Of the 434 included participants, 219 (50%) were randomly assigned to the direct boost group discussed in this Article. 32 (7%) participants were excluded from the mITT analysis because of withdrawal from the study, SARS-CoV-2 breakthrough infection between study visits, or missing blood samples across study visits, or because they received a different prime than orginally thought (figure 1). All 187 participants included in the mITT analysis adhered to the defined timing intervals in between study visits. All continuous variables displayed non-normal distribution as assessed by the Shapiro-Wilk test (appendix p 24). All results from the LIAISON IgG assay were log-transformed, and Q-Q plots displayed normality of the fold change (appendix p 9). The median interval between study visit 1 and study visit 2 was 7·0 days (IQR 7·0–7·0) and the median interval between

	Direct boost group (N=187)	Ad/P group (n=42)	mRNA/P group (n=44)	Ad/M group (n=45)	mRNA/M group (n=56)
Sex					
Female	138 (74%)	27 (64%)	34 (77%)	28 (62%)	49 (88%)
Male	49 (26%)	15 (36%)	10 (23%)	17 (38%)	7 (12%)
Age, years	47·0 (36·0–53·0)	32·0 (28·0–40·5)	35·0 (28·0–40·0)	52·0 (50·0–55·0)	53·0 (50·0–57·0)
BMI, kg/m^2	24·2 (22·5–27·0)	23·8 (22·2–24·8)	23·8 (21·7–26·3)	25·0 (23·0–27·5)	24·8 (23·0–27·7)
Ethnicity					
African	2 (1%)	0	1 (2%)	1 (2%)	0
Asian	6 (3%)	0	3 (7%)	0	3 (5%)
European	173 (93%)	40 (95%)	39 (89%)	44 (98%)	50 (89%)
North American	1 (<1%)	0	1 (2%)	0	0
South American	0	0	0	0	0
Other	5 (3%)	2 (5%)	0	0	3 (5%)
Occupation in hospital					
Administrative or policy maker	27 (14%)	6 (14%)	3 (7%)	10 (22%)	8 (14%)
Medical doctor	15 (8%)	2 (5%)	4 (9%)	0	9 (16%)
Facility services	3 (2%)	1 (2%)	1 (2%)	1 (2%)	0
Management	24 (13%)	5 (12%)	3 (7%)	9 (20%)	7 (13%)
Supportive staff clinic or emergency department	2 (1%)	1 (2%)	0	0	1 (2%)
Supportive staff outpatient clinic	1 (<1%)	0	0	0	1 (2%)
Researcher	45 (24%)	17 (40%)	15 (34%)	5 (11%)	8 (14%)
Nurse	11 (6%)	0	4 (9%)	0	7 (13%)
Other	59 (32%)	10 (24%)	14 (32%)	20 (44%)	15 (27%)
Comorbidities					
Cardiovascular diseases	2 (1%)	0	0	0	2 (4%)
Pulmonary diseases	9 (5%)	1 (2%)	2 (5%)	2 (4%)	4 (7%)
Diabetes	3 (2%)	0	1 (2%)	2 (4%)	0
Liver diseases	2 (1%)	0	0	0	2 (4%)
Kidney diseases	3 (2%)	1 (2%)	1 (2%)	0	1 (2%)
None	168 (90%)	40 (95%)	40 (91%)	41 (91%)	47 (84%)
S1-specific* binding antibodies, BAU/mL†	2660 (1530–6920)	1950 (1253–3423)	2725 (1560–7928)	2130 (1210–4760)	5665 (2008–11 050)
Geometric mean titre of S1-specific* binding antibodies, BAU/mL	2790 (2514–3508)	1959 (1392–2757)	3198 (2333–4384)	2032 (1481–2789)	5196 (3828–7053)
Nucleocapsid					
Negative	151 (81%)	33 (79%)	39 (89%)	41 (91%)	38 (68%)
Positive	36 (19%)	9 (21%)	5 (11%)	4 (9%)	18 (32%)
Original centre					
Amsterdam University Medical Center	22 (12%)	6 (14%)	8 (18%)	3 (7%)	5 (9%)
Erasmus Medical Center	130 (70%)	23 (55%)	34 (77%)	23 (51%)	50 (89%)
Leiden University Medical Center	16 (9%)	9 (21%)	0	7 (16%)	0
University Medical Center Groningen	19 (10%)	4 (10%)	2 (5%)	12 (27%)	1 (2%)
Time between SV1 and SV2, days	7·0 (7·0–7·0)	7·0 (7·0–7·0)	7·0 (7·0–7·0)	7·0 (7·0–7·0)	7·0 (7·0–7·0)
Time between SV1 and SV3, days	28·0 (28·0–28·0)	28·0 (28·0–28·0)	28·0 (28·0–28·0)	28·0 (28·0 - 28·0)	28·0 (28·0–28·0)
Time between last booster and bivalent booster, days	298·0 (266·0–309·5)	266·5 (260·5–305·3)	303·0 (297·0–309·3)	266·0 (263·0–293·0)	307·0 (302·3–310·3)

Data are n (%), median (IQR), or geometric mean titre (95% CI). Percentages might not sum to 100 because of rounding. Participants in the direct boost group were divided into four groups: (1) Ad26.COV2.S prime and BNT162b2 OMI BA.1 boost (Ad/P), (2) mRNA-based prime and BNT162b2 OMI BA.1 boost (mRNA/P), (3) Ad26.COV2.S prime and mRNA-1273·214 boost (Ad/M), and (4) mRNA-based prime and mRNA-1273·214 boost (mRNA/M). The BNT162b2 BA.1 boost was given to participants younger than 45 years, and the mRNA-1273·214 boost was given to participants 45 years or older, as per Dutch guidelines. BAU=binding antibody units. SV1=study visit 1. SV2=study visit 2. SV3=study visit 3. *S1 is a subunit of the spike protein. †Measured by quantitative LIAISON SARS-CoV-2 TrimericS IgG assay (DiaSorin, Saluggia, Italy).

Table 1: **Baseline characteristics of participants in the direct boost group of the SWITCH ON trial**

study visit 1 and study visit 3 was 28·0 days (28·0–28·0). The median interval between the last vaccination and the bivalent booster vaccination was 298 days (266·0–309·5; table 1). Notably, the distribution of biological sex was different to that of the general population, with a higher number of female participants than male participants across all groups. Table 1 presents all baseline characteristics.

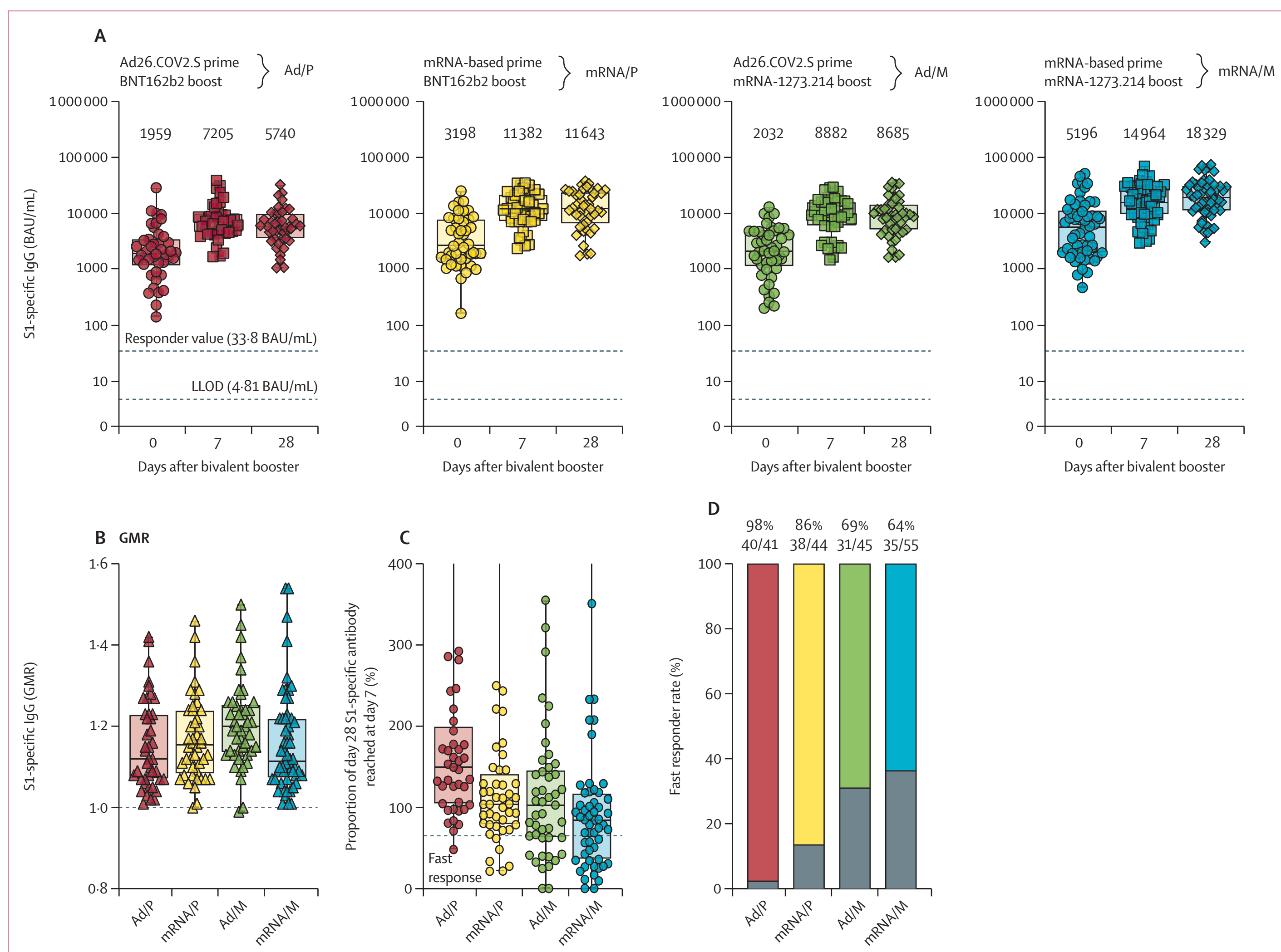

Figure 2: **Spike-protein-specific binding antibodies and fast response after bivalent booster vaccination**

(A) Detection of (ancestral) spike protein S1 subunit-specific binding IgG antibodies at baseline before bivalent booster (0 days; circles), 7 days (squares) after booster, and 28 days (diamonds) after booster in the four subgroups. The LLOD was set at 4·81 BAU/mL. The cutoff responder value was set at 33·8 BAU/mL (horizontal dashed line). The bold numbers above the box-and-whisker plots indicate the geometric mean titre per timepoint. (B) GMR of S1-specific binding antibody concentrations between baseline and 28 days after bivalent booster vaccination in the four subgroups. The horizontal dashed line indicates a GMR of 1, which corresponds to no increase or decrease in S1-specific binding antibody concentrations after vaccination. (C) Fast response based on S1-specific antibody concentrations in the four subgroups. The horizontal dashed line indicates the fast responder cutoff, which was defined as having reached an antibody concentration on day 7 after vaccination that was equal to or higher than 65% of the total spike-protein-specific binding antibody response on day 28. (D) Percentage of fast responders per subgroup. Data in panels A, B, and C are presented in box-and-whisker plots. The horizontal lines of the box-and-whisker plots indicate the median, the whiskers indicate the range, and the bounds of the boxes indicate the IQR. All datapoints are shown for the individuals in the modified intention to treat population. BAU=binding antibody units. GMR=geometric mean ratio. LLOD=lower limit of detection.

S1-specific binding antibody concentrations increased 7 days after bivalent booster vaccination and remained stable over 28 days in all four subgroups (figure 2A). No significant difference was observed between the fold change in antibody concentrations from day 0 to day 28 in the Ad/P (GMR 1·15 [95% CI 1·12–1·19]) and mRNA/P (1·17 [1·14–1·20]) groups (p=0·51). The fold change after bivalent booster vaccination appeared to be higher in the Ad/M group (GMR 1·20 [95% CI 1·17–1·23]) than the mRNA/M group (1·16 [1·13–1·19]), but this difference was also not significant (p=0·073; figure 2B). However, higher baseline concentrations of S1-specific binding IgG antibodies were detected in individuals who had received an mRNA-based primary vaccine (GMT 5196 binding antibody units [BAU] per mL [95% CI 3828–7053] in the mRNA/M group and 3198 BAU/mL [2333–4384] in the mRNA/P group) compared with individuals who had received Ad26.COV2.S primary vaccination (2032 BAU/mL [1481–2789] in the Ad/M group and 1959 BAU/mL [1392–2757] in the Ad/P group; table 1, figure 2A). Similarly, at 28 days after bivalent booster vaccination, S1-specific binding IgG antibody concentrations were higher in the mRNA/M (18 329 BAU/mL [14 933–22 498])

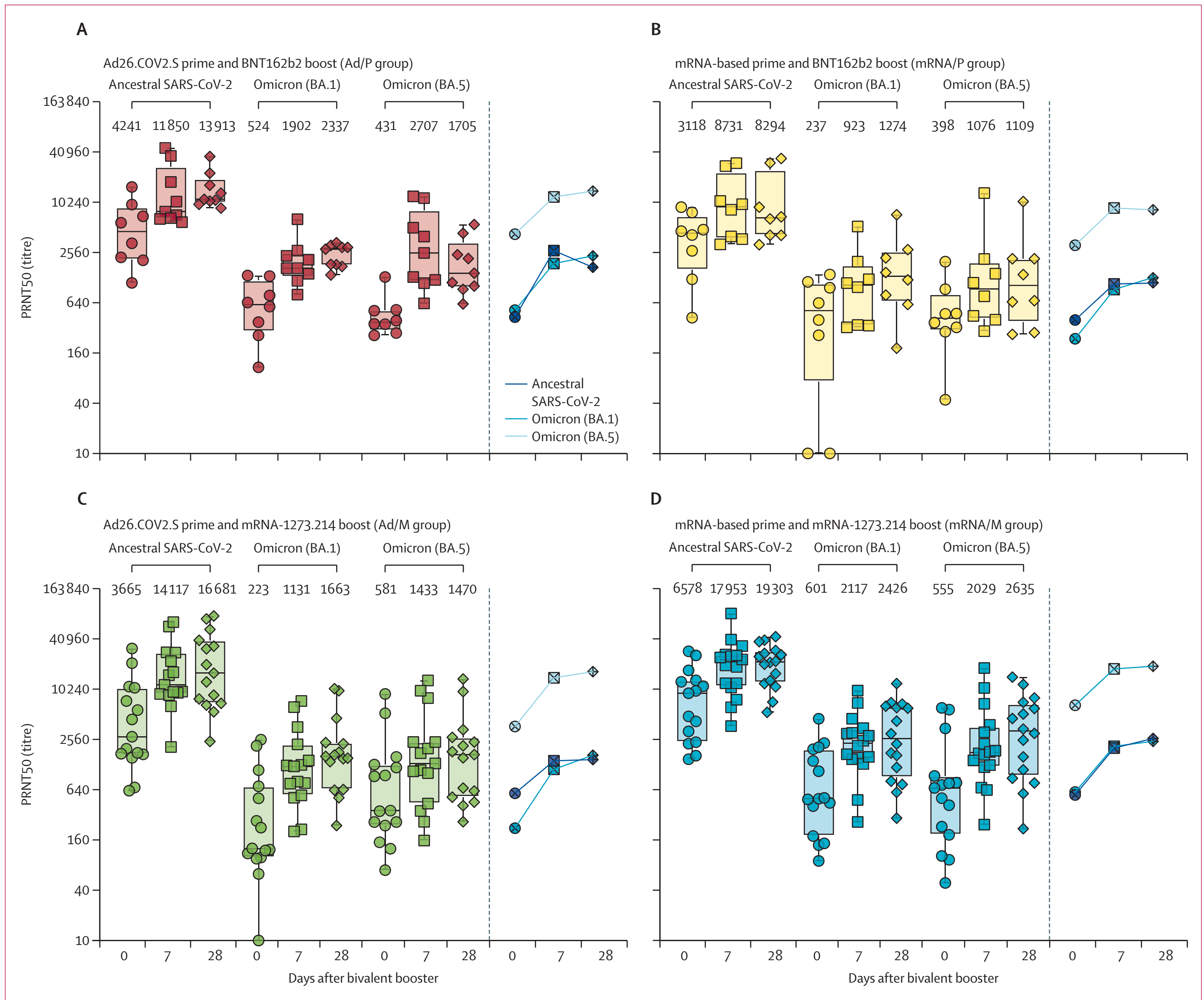

Figure 3: **Variant-specific neutralisation after bivalent booster vaccination in randomly selected serum samples**
Detection of SARS-CoV-2-neutralising antibodies targeting ancestral SARS-CoV-2 and omicron subvariants (BA.1 and BA.5) at baseline (0 days; circles), 7 days (squares) after bivalent booster vaccination, and 28 days (diamonds) after vaccination for the Ad/P group (n=9; A), mRNA/P group (n=8; B), Ad/M group (n=15; C), and mRNA/M group (n=16; D). The bold numbers above the box-and-whisker plots indicate the geometric mean titre per timepoint and variant. The line graphs next to each panel represent the median neutralising titre against ancestral SARS-CoV-2 and omicron subvariants (BA.1 and BA.5) at baseline (0 days), 7 days after bivalent booster vaccination, and 28 days after vaccination. When no neutralisation was observed, the PRNT50 was given a value of 10. The horizontal lines of the box-and-whisker plots indicate the median, the whiskers indicate the range, and the bounds of the boxes indicate the IQR. All datapoints are shown for the individuals randomly selected for this analysis. PRNT50=50% plaque reduction neutralisation test.

and mRNA/P (11 643 BAU/mL [9058–14 966]) subgroups than in the Ad/M (8685 BAU/mL [6831–11 042]) and Ad/P (5740 BAU/mL [4526–7279]) subgroups (figure 2A). Among individuals primed with an mRNA-based vaccine (44 in the mRNA/P group and 56 in the mRNA/M group), no differences in fold change of S1-specific antibody concentrations were observed after bivalent booster vaccination between those primed with mRNA-1273 or BNT162b2 (appendix p 10).

Analysis of the secondary outcome of fast response of S1-specific antibodies after bivalent booster vaccination showed that the increase in S1-specific binding IgG antibodies between day 0 and day 7 after booster vaccination was larger than the increase between day 7 and day 28 in all four subgroups (figure 2C, D). Notably, the proportions of participants who had a fast response after receiving the BNT162b2 OMI BA.1 bivalent booster vaccination were higher than the proportions of

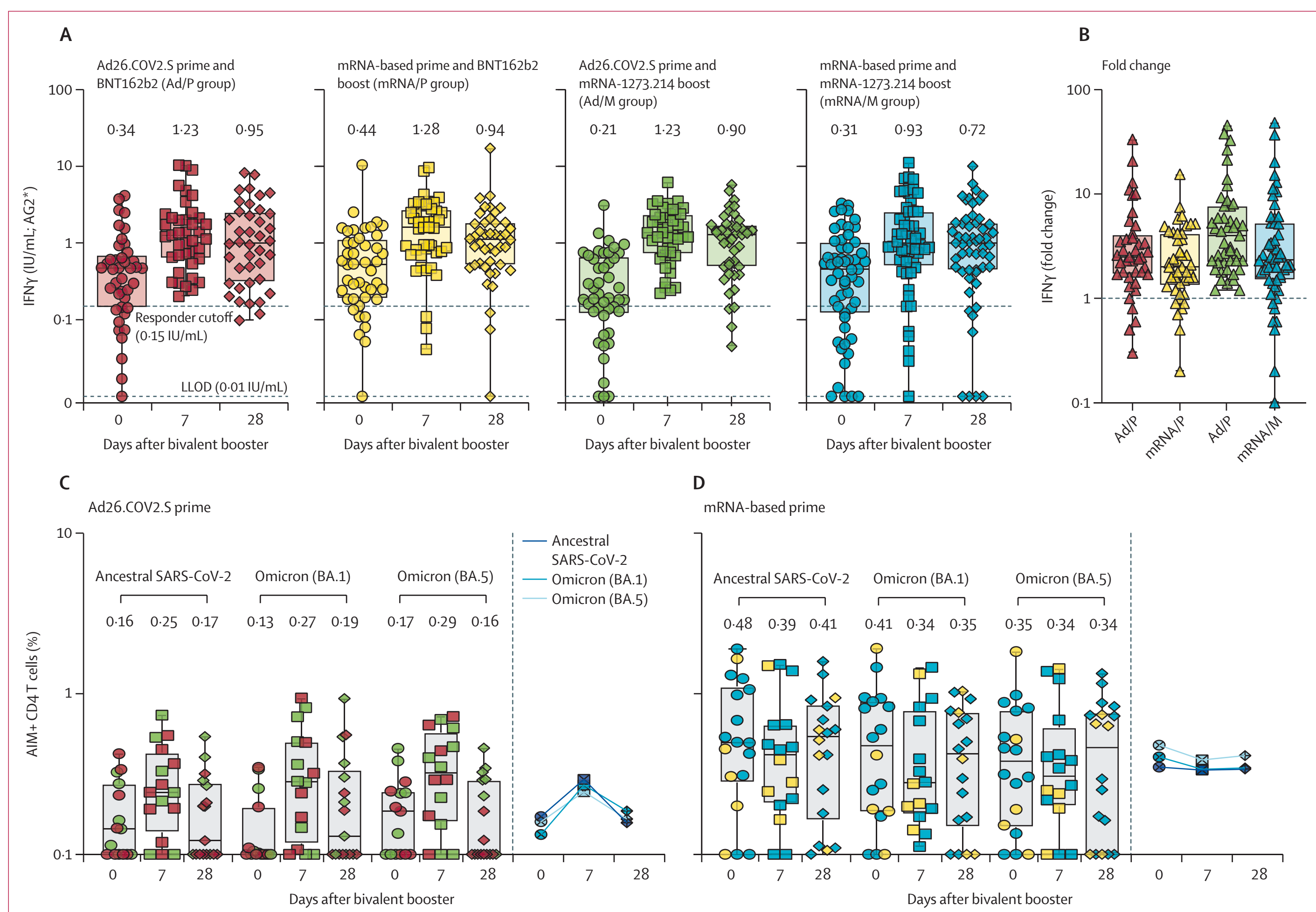

Figure 4: **Variant-specific T-cell responses after bivalent booster vaccination**

(A) Detection of IFNγ (IU/mL) after stimulation of whole blood with overlapping spike (S) protein peptide pools in coated QuantiFERON tubes at baseline (day 0; circles), 7 days (squares) after bivalent booster vaccination, and 28 days (diamonds) after bivalent booster vaccination in the four subgroups (mITT population). An LLOD was set at 0·01 IU/mL as per manufacturer's instructions. The horizontal dotted line indicates a predefined responder cutoff of 0·15 IU/mL. The bold numbers above the box-and-whisker plots indicate the geometric mean IFNγ concentrations per timepoint. (B) Fold change of IFNγ concentrations between baseline and 28 days after bivalent booster vaccination in the four subgroups. The horizontal dashed line indicates a fold change of 1, which corresponds to no increase or decrease. (C, D) Percentages of AIM-positive CD4 T cells after ex-vivo stimulation with an overlapping peptide pool spanning the full S protein of ancestral SARS-CoV-2 or the omicron subvariants BA.1 and BA.5 in randomly selected individuals primed with Ad26.COV2.S (n=17, C) or selected individuals primed with an mRNA-based vaccine (n=19, D). The data used in this analysis were collected from two of the four centres. The bold numbers above the box-and-whisker plots indicate the geometric mean of the percentage of AIM-positive CD4 T cells per timepoint. The line graphs next to each panel represent the median percentage of AIM-positive CD4 T cells for ancestral SARS-CoV-2 and omicron subvariants BA.1 and BA.5 at baseline (0 days), 7 days after bivalent booster vaccination, and 28 days after bivalent booster vaccination. The horizontal lines of the box-and-whisker plots indicate the median, the whiskers indicate the range, and the bounds of the boxes indicate the IQR. All datapoints are shown for the individuals in the mITT population (A, B) or the individuals selected for the AIM analysis (C, D). AG2=antigen 2. AIM=activation induced marker. mITT=modified intention-to-treat. LLOD=lower limit of detection. *The assay uses three different antigen mixes (appendix p 6).

participants who had a fast response after receiving the mRNA-1273.214 bivalent vaccine (figure 2D). Of the 187 participants assessed for the fast response of S1-specific antibodies, two (1%) participants (one in the Ad/P group and one in the mRNA/M group) were excluded due to missing blood samples at day 7 (study visit 2).

To assess boosting of SARS-CoV-2-neutralising antibodies after bivalent booster vaccination, PRNT50 using ancestral SARS-CoV-2 and omicron subvariants BA.1 and BA.5 was performed on a random selection of serum samples (nine participants in the Ad/P group, eight participants in the mRNA/P group, 15 participants in the Ad/M group, and 16 participants in the mRNA/M group; figure 3). Individual S-shaped curves of neutralisation per serum dilution were generated per group for all timepoints and tested variants (appendix pp 12–13). Neutralising antibody titres against ancestral SARS-CoV-2 were similar at baseline across all four subgroups, although participants in the mRNA/M group had higher baseline neutralising antibody titres than participants in all other groups (figure 3). Bivalent booster vaccination increased the neutralising antibody titres against ancestral SARS-CoV-2 in all subgroups at 7 days and 28 days after vaccination.

Similar to the binding antibodies (figure 2), the increase in neutralising antibodies between day 0 and day 7 was larger than that observed between day 7 and day 28 in all groups (figure 3). At baseline, the neutralising antibody response of the participants against omicron subvariants BA.1 and BA.5 was lower than the neutralising antibody titre against ancestral SARS-CoV-2. Neutralising antibody titres against omicron BA.1 and omicron BA.5 increased 7 days after bivalent booster vaccination with a similar pattern of increase to antibodies neutralising ancestral SARS-CoV-2; the magnitude of boosting was similar between the different priming regimens and booster vaccinations at all three study visits.

A similar pattern was observed for S-protein-specific binding antibody titres against ancestral SARS-CoV-2 and the omicron subvariants BA.1 and BA.5 when measured by ELISA (appendix pp 14–15). Individual S-shaped curves per serum dilution were generated per group for all timepoints and tested variants (appendix pp 16–17). S-protein-specific binding antibody titres for ancestral SARS-CoV-2 and omicron subvariants BA.1 and BA.5 were similar at baseline, increased 7 days after bivalent booster vaccination, and remained stable at 28 days for all four subgroups (appendix pp 14–15). S-protein-specific binding antibody titres against omicron subvariants BA.1 and BA.5 were lower (ie, GMT per group) than titres against ancestral SARS-CoV-2 in all four subgroups at all timepoints (appendix pp 14–15).

SARS-CoV-2 S-protein-specific T-cell responses were assessed by measuring IFNγ concentrations after stimulating whole blood with peptides covering the S protein. T-cell responses increased directly after bivalent booster (day 7) and then decreased slightly at day 28 after booster vaccination for all four subgroups (figure 4A, B). T-cell responses were similar at baseline and after bivalent booster (after 7 days and after 28 days) for all four subgroups (figure 4A). No major difference in fold change of IFNγ concentrations was observed between baseline and day 28 between the BNT162b2 OMI BA.1 boosted groups (median IFNγ concentrations were 2·5 times [IQR 1·7–3·9] higher at day 28 than at baseline in the Ad/P group and 2·0 times [1·4–4·2] higher than at baseline in the mRNA/P group); however, a higher fold change in IFNγ concentrations was observed after bivalent booster vaccination with mRNA-1273.214 following Ad26.COV2.S priming (AD/M group; 4·0 times [2·2–7·7] higher than at baseline) than after bivalent booster vaccination with mRNA-1273.214 following mRNA priming (mRNA/M group; 2·2 times [1·2–4·9] higher; figure 4B).

S-protein-specific T-cell cross-reactivity to omicron subvariants BA.1 and BA.5 was assessed in 36 individuals (17 for Ad26.COV2.S priming and 19 for mRNA-based priming) from two of the four participating centres (data were not available from the other two centres) by AIM flow cytometry assay, after stimulating peripheral blood mononuclear cells with overlapping S protein peptides. SARS-CoV-2-specific CD4 T-cell responses against the ancestral variant were higher in individuals primed with an mRNA-based vaccine than in individuals primed with Ad26.COV2.S at baseline (geometric mean 0·48 [95% CI 0·42–0·96] for mRNA-based prime and 0·16 [0·12–0·24] for Ad26.COV2.S prime), at 7 days after bivalent booster vaccination (0·39 [0·29–0·81] and 0·25 [0·20–0·40]), and at 28 days after bivalent booster vaccination (0·41 [0·36–0·79] and 0·17 [0·13–0·26]; figure 4C, D). Ancestral S-protein-specific T-cell responses were assessed at all participating centres (appendix p 20). An increase in S-protein-specific T cells between 0 days and 7 days after vaccination was observed in individuals primed with Ad26.COV2.S, but not in individuals primed with an mRNA-based vaccine (figure 4C, 4D). Notably, S-protein-specific T cells were cross-reactive with the omicron subvariants BA.1 and BA.5 variants in all subgroups at all timepoints (figure 4C, D). The geometric means for the omicron subvariants BA.1 and BA.5 are shown in the appendix (p 25). CD8 T-cell responses followed similar

	Ad/P group (n=42)	mRNA/P group (n=44)	Ad/M group (n=45)	mRNA/M group (n=56)
Fatigue				
Not at all	19 (45%)	21 (48%)	21 (47%)	24 (43%)
A little, but it did not hinder my daily activity	16 (38%)	14 (32%)	17 (38%)	20 (36%)
Quite, it hindered my daily activity	6 (14%)	7 (16%)	7 (16%)	10 (18%)
Significantly, I could not perform my daily activity	1 (2%)	2 (5%)	0	2 (4%)
Shiver				
Not at all	35 (83%)	33 (75%)	35 (78%)	42 (75%)
A little, but it did not hinder my daily activity	7 (17%)	10 (23%)	6 (13%)	6 (11%)
Quite, it hindered my daily activity	0	1 (2%)	4 (9%)	4 (7%)
Significantly, I could not perform my daily activity	0	0	0	4 (7%)
Fever				
Not at all	35 (83%)	38 (86%)	35 (78%)	45 (80%)
A little, but it did not hinder my daily activity	5 (12%)	5 (11%)	7 (16%)	7 (13%)
Quite, it hindered my daily activity	2 (5%)	1 (2%)	2 (4%)	2 (4%)
Significantly, I could not perform my daily activity	0	0	1 (2%)	2 (4%)
Nausea				
Not at all	39 (93%)	42 (95%)	39 (87%)	51 (91%)
A little, but it did not hinder my daily activity	3 (7%)	2 (5%)	4 (9%)	3 (5%)
Quite, it hindered my daily activity	0	0	2 (4%)	0
Significantly, I could not perform my daily activity	0	0	0	2 (4%)
Headache				
Not at all	28 (67%)	20 (45%)	25 (56%)	27 (48%)
A little, but it did not hinder my daily activity	10 (24%)	22 (50%)	17 (38%)	17 (30%)
Quite, it hindered my daily activity	4 (10%)	2 (4%)	2 (4%)	9 (16%)
Significantly, I could not perform my daily activity	0	2 (5%)	1 (2%)	3 (5%)
Muscle ache				
Not at all	26 (62%)	20 (45%)	25 (56%)	30 (54%)
A little, but it did not hinder my daily activity	14 (33%)	16 (36%)	17 (38%)	16 (29%)
Quite, it hindered my daily activity	1 (2%)	7 (16%)	3 (7%)	7 (13%)
Significantly, I could not perform my daily activity	1 (2%)	1 (2%)	0	3 (5%)

(Table 2 continues on next page)

kinetics as CD4 T-cell responses for all subgroups (appendix p 21).

The reactogenicity data showed that pain at the vaccination site, muscle aches, headache, or fatigue were the most reported side-effects in all four subgroups (table 2). Most side-effects were mild to moderate in severity (table 2) and resolved within 48 h (appendix pp 26–28). The severity of side-effects was similar between all groups, except for joint pain, which was reported more frequently in participants who received the mRNA-1273.214 vaccine regardless of their priming regimen (table 2).

	Ad/P group (n=42)	mRNA/P group (n=44)	Ad/M group (n=45)	mRNA/M group (n=56)
(Continued from previous page)				
Joint pain				
Not at all	36 (86%)	39 (89%)	30 (67%)	37 (66%)
A little, but it did not hinder my daily activity	6 (14%)	2 (5%)	13 (29%)	15 (27%)
Quite, it hindered my daily activity	0 (0%)	3 (7%)	2 (4%)	3 (5%)
Significantly, I could not perform my daily activity	0	0	0	1 (2%)
Red spot at vaccination site, cm				
0	40 (95%)	40 (91%)	39 (87%)	50 (89%)
2·5–5·0	2	4 (9%)	5 (11%)	5 (9%)
5·1–10·0	0	0	1 (2%)	0
>10·0	0	0	0	1 (2%)
Swelling at vaccination site, cm				
0	39 (93%)	38 (86%)	40 (89%)	46 (82%)
2·5–5·0	3 (7%)	5 (11%)	4 (9%)	8 (14%)
5·1–10·0	0	1 (2%)	1 (2%)	1 (2%)
>10·0 cm	0	0	0	1 (2%)
Pain at vaccination site				
Not at all	10 (24%)	9 (20%)	10 (22%)	13 (23%)
A little, but it did not hinder my daily activity	31 (74%)	33 (75%)	33 (73%)	35 (63%)
Quite, it hindered my daily activity and I took mild painkillers (eg, paracetamol) but not strong painkillers (eg, morphine or oxycodone)	1 (2%)	2 (5%)	2 (4%)	8 (14%)

Data are n (%). Percentages might not sum to 100 because of rounding. Participants in the direct boost group were divided into four groups: (1) Ad26.COV2.S prime and BNT162b2 OMI BA.1 boost (Ad/P), (2) mRNA-based prime and BNT162b2 OMI BA.1 boost (mRNA/P), (3) Ad26.COV2.S prime and mRNA-1273·214 boost (Ad/M), and (4) mRNA-based prime and mRNA-1273·214 boost (mRNA/M). The BNT162b2 BA.1 boost was given to participants younger than 45 years, and the mRNA-1273·214 boost was given to participants 45 years or older, as per Dutch guidelines. Participants were asked in an electronic questionnaire how severely they were affected by these side-effects in the 7 days after booster vaccination.

Table 2: **Severity of side-effects after bivalent booster vaccination**

Discussion

This study reports the results from the direct boost arm of the SWITCH ON trial, which assessed the immunogenicity and reactogenicity of omicron BA.1 bivalent COVID-19 booster vaccines in health-care workers in the Netherlands primed with Ad26.COV2.S, mRNA-1273, or BNT162b2 vaccines. Bivalent booster vaccination increased binding and neutralising antibody concentration in all groups between baseline and day 28, and no differences in so-called boostability were observed between individuals primed with an Ad26.COV2.S-based vaccine or an mRNA-based vaccine.

We observed an increase in antibody titres from day 0 to day 28 after vaccination in all four groups, but no differences between priming regimens were observed. The largest increase in antibody titres was detected within the first 7 days after booster vaccination, indicating a rapid recall of memory responses. This increase was most prominent in groups who received the BNT162b2 OMI BA.1 booster vaccination. As per Dutch policy, participants younger than 45 years received BNT162b2 OMI BA.1, whereas those older than 45 years were boosted with mRNA-1273.214, making it plausible that the lower age of these participants is responsible for the difference in increase of antibody titres within 7 days of vaccination. A similar rapid recall was noticed for T-cell responses measured in whole blood, with kinetics slightly different from the antibody kinetics: after the rapid recall at day 7, IFNγ responses in whole blood decreased at day 28 after booster vaccination. The observation of combined rapid SARS-CoV-2-specific antibody and T-cell recall responses is indicative of efficient induction of immunological memory by previous vaccinations or infections, or both.

The BA.1 bivalent booster vaccination boosted neutralising antibodies targeting both omicron sub-variants BA.1 and BA.5. However, these neutralising antibody concentrations against the omicron sub-variants BA.1 and BA.5 were generally lower than those against ancestral SARS-CoV-2 in all four groups. This result is consistent with previous studies describing the immunogenicity of BA.1 bivalent booster vaccines.[12,21,22] Although our data support the induction of cross-neutralising antibodies by the BA.1 bivalent booster vaccines against the BA.5 variant not contained in the vaccine, we did not observe preferential boosting of neutralising antibodies for omicron BA.1 or omicron BA.5. This observation is consistent with two studies published in 2022 that show that exposure to antigenically distinct omicron variants by either vaccination or infection recalls pre-existing memory B cells specific for epitopes shared by different SARS-CoV-2 variants.[23,24] Real-world data exploring the effectiveness of this increased breadth of the immune response will be essential when evaluating the need for continuous updating of variant-specific booster vaccines.

Although we did not observe any effect of the respective priming regimen on neutralising and binding antibody titres before or after bivalent booster vaccination, CD4 T-cell responses measured by AIM assay were different between priming regimens. Activation of CD4 T cells after stimulation with overlapping S protein peptide pools at any timepoint was considerably lower in individuals primed with Ad26.COV2.S than in individuals primed with an mRNA-based vaccine, which is in line with other observations after primary vaccination.[5,16]

Nevertheless, the response was rapidly reactivated upon antigen exposure. In all groups, T-cell responses cross-reacted with the omicron subvariants BA.1 and BA.5,[5,16] and no preferential induction of variant-specific T cells was observed after booster vaccination.

Our study has some limitations. Female participants make up a larger proportion of participants in each group than male participants. Although a sex difference in vaccine-induced response has been reported,[25] the composition of our cohort reflects the female-dominated structure of the health-care workforce in the Netherlands.[26] Additionally, most of the study population is of European descent and our participants were aged between 18 and 65 years. Therefore, the translation of our findings to other age groups and ethnic backgrounds should be done with care. We assessed whether participants had previous SARS-CoV-2 infections by both self-reporting and nucleocapsid ELISA. Although these methods could have low sensitivity, participants with previous infections according to our definition were equally distributed over the groups. Finally, due to a change in vaccination policy, we deviated from the original protocol, which resulted in the use of two vaccines instead of one according to the policy's age criterion. Nonetheless, we adhered to the original statistical analysis plan as much as possible. Because of these adaptations, we compromised our power calculation as it was based on the use of one vaccine. However, due to policy change in the Netherlands we had to use two vaccines, one for younger (<45 years) and one for older (≥45 years) age groups.

Our data show that bivalent booster vaccination is associated with a robust recall of memory B-cell and T-cell responses, and that the largest proportion of these responses occurs within the first 7 days after boosting. A similar rapid recall of immune memory is to be expected in the case of a SARS-CoV-2 breakthrough infection. It is therefore not unreasonable to assume that the generally mild disease profile upon infection with variants from the omicron sublineage is partly driven by a broad memory recall response. Although no immunological correlates of protection have been identified after bivalent COVID-19 booster vaccination, our data could also be predictive of mild clinical disease after reinfection with future variants. Our data emphasise the need for a re-evaluation of the necessity and frequency of future COVID-19 booster vaccinations in the general population and risk groups. For specific risk populations, decision making should include a risk evaluation for severe clinical disease, and the monitoring of immunity against the background of antigenic drift at the viral level. After obtaining all data 3 months (study visit 4) after bivalent omicron BA.1 boost (direct boost group), and 3 months after omicron BA.5 boost (postponed boost group), we will publish the full findings of the SWITCH ON trial, in combination with advice for future vaccination policy.

Contributors

PHMvdK, CHG, and RDdV contributed to conceptualisation. NHT, DG, RSGS, WJRR, LMZ, and RDdV did the formal analysis. NHT, RSGS, WJRR, AG, DFP, LGV, MPGK, VASHD, ML, NAK, ALWH, DvB, LMZ, CHG, RDdV, and PHMvdK acquired funding. All authors did the investigation. PHMvdK, CHG, and RDdV supervised the trial. DG, LMZ, and RDdV contributed to visualisation. NHT, DG, RSGS, WJRR, LMZ, RDdV, CGvK, and PHMvdK wrote the original draft. All authors reviewed, wrote, and edited the final draft. NHT, DG, RSGS, WJRR, LMZ, RDdV, and PHMvdK accessed and verified the data. All authors were permitted to access the data used in this study (if they wished). CHG, RDdV, and PHMvdK had final responsibility for the decision to submit for publication. All authors accept responsibility to submit the manuscript for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Deidentified individual participant data, the analytics code, and other supporting documents will be made available when the study is complete, upon requests made to the corresponding author.

Acknowledgments

Assay methodology images were created with Biorender. This study was funded by the Netherlands Organization for Health Research and Development (ZonMw), grant agreement 10430072110001.

References

1 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.

2 European Centre for Disease Prevention and Control. Interim analysis of COVID-19 vaccine effectiveness in healthcare workers; an ECDC multi country study. 2022. https://www.ecdc.europa.eu/en/publications-data/interim-analysis-covid-19-vaccine-effectiveness-healthcare-workers-ecdc-multi (accessed Nov 16, 2022).

3 Watson OJ, Barnsley G, Toor J, Hogan AB, Winskill P, Ghani AC. Global impact of the first year of COVID-19 vaccination: a mathematical modelling study. *Lancet Infect Dis* 2022; **22:** 1293–302.

4 Suthar AB, Wang J, Seffren V, Wiegand RE, Griffing S, Zell E. Public health impact of covid-19 vaccines in the US: observational study. *BMJ* 2022; **377:** e069317.

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.

6 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.

7 Andrews N, Stowe J, Kirsebom F, et al. Covid-19 vaccine effectiveness against the omicron (B.1.1.529) variant. *N Engl J Med* 2022; **386:** 1532–46.

8 Malhotra S, Mani K, Lodha R, et al. COVID-19 infection, and reinfection, and vaccine effectiveness against symptomatic infection among health care workers in the setting of omicron variant transmission in New Delhi, India. *Lancet Reg Health Southeast Asia* 2022; **3:** 100023.

9 Patalon T, Saciuk Y, Peretz A, et al. Waning effectiveness of the third dose of the BNT162b2 mRNA COVID-19 vaccine. *Nat Commun* 2022; **13:** 3203.

10 Mykytyn AZ, Rissmann M, Kok A, et al. Omicron BA.1 and BA.2 are antigenically distinct SARS-CoV-2 variants. *bioRxiv* 2022; published online Feb 24. https://doi.org/10.1101/2022.02.23.481644.

11 WHO. Interim statement on the composition of current COVID-19 vaccines. 2022. https:// www.who.int/news/item/17-06-2022-interim-statement-on--the-composition-of-current-COVID-19-vaccines (accessed Nov 16, 2022).

12 Chalkias S, Harper C, Vrbicky K, et al. A bivalent omicron-containing booster vaccine against Covid-19. *N Engl J Med* 2022; **387:** 1279–91.

13 ClinicalTrials.gov. Study to describe the safety, tolerability, immunogenicity, and efficacy of RNA vaccine candidates against COVID-19 in healthy individuals. 2022. https://clinicaltrials.gov/ct2/show/NCT04368728 (accessed Nov 16, 2022).

14 Tan NH, Sablerolles RSG, Rietdijk WJR, et al. Analyzing the immunogenicity of bivalent booster vaccinations in healthcare workers: the SWITCH ON trial protocol. *Front Immunol* 2022; **13:** 1067749.
15 Dutch National Institute for Public Health and the Environment. COVID-19 vaccinatie uitvoeringsrichtlijn 2022. https://lci.rivm.nl/richtlijnen/covid-19-vaccinatie (accessed Nov 16, 2022).
16 Geers D, Shamier MC, Bogers S, et al. SARS-CoV-2 variants of concern partially escape humoral but not T cell responses in COVID-19 convalescent donors and vaccine recipients. *Sci Immunol* 2021; **6:** eabj1750.
17 Geers D, Sablerolles RSG, van Baarle D, et al. Ad26.COV2.S priming provided a solid immunological base for mRNA-based COVID-19 booster vaccination. *iScience* 2023; **26:** 105753.
18 Okba NMA, Müller MA, Li W, et al. Severe acute respiratory syndrome coronavirus 2-specific antibody responses in coronavirus disease patients. *Emerg Infect Dis* 2020; **26:** 1478–88.
19 Sablerolles RSG, Goorhuis A, GeurtsvanKessel CH, et al. Heterologous Ad26.COV2.S prime and mRNA-based boost COVID-19 vaccination regimens: the SWITCH trial protocol. *Front Immunol* 2021; **12:** 753319.
20 US Food and Drug Administration. Toxicity Grading Scale for Healthy Adults and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. 2007. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/toxicity-grading-scale-healthy-adult-and-adolescent-volunteers-enrolled-preventive-vaccine-clinical (accessed Nov 16, 2022).
21 Chalkias S, Eder F, Essink B, et al. Safety, immunogenicity and antibody persistence of a bivalent beta-containing booster vaccine against COVID-19: a phase 2/3 trial. *Nat Med* 2022; **28:** 2388–97.
22 Hachmann NP, Miller J, Collier A-rY, et al. Neutralization escape by SARS-CoV-2 omicron subvariants BA.2.12.1, BA.4, and BA.5. *N Engl J Med* 2022; **387:** 86–88.
23 Quandt J, Muik A, Salisch N, et al. Omicron BA.1 breakthrough infection drives cross-variant neutralization and memory B cell formation against conserved epitopes. *Sci Immunol* 2022; **7:** eabq2427.
24 Park Y-J, Pinto D, Walls AC, et al. Imprinted antibody responses against SARS-CoV-2 omicron sublineages. *Science* 2022; **378:** 619–27.
25 Klein SL, Jedlicka A, Pekosz A. The Xs and Y of immune responses to viral vaccines. *Lancet Infect Dis* 2010; **10:** 338–49.
26 Centraal Bureau voor de Statistiek. Arbeidsparticipatie naar leeftijd en geslacht. 2022. https://www.cbs.nl/nl-nl/visualisaties/dashboard-arbeidsmarkt/werkenden/beroepen-van-werkenden (accessed March 29, 2023).