IDSA · Infectious Diseases Society of America   hivma · hiv medicine association   OXFORD

Antibody Response in Immunocompromised Patients After the Administration of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Vaccine BNT162b2 or mRNA-1273: A Randomized Controlled Trial

Benjamin Speich,[1,2] Frédérique Chammartin,[1] Irene A. Abela,[3,4] Patrizia Amico,[5] Marcel P. Stoeckle,[6] Anna L. Eichenberger,[7] Barbara Hasse,[4] Dominique L. Braun,[3,4] Macé M. Schuurmans,[8] Thomas F. Müller,[9] Michael Tamm,[10] Annette Audigé,[3] Nicolas J. Mueller,[4] Andri Rauch,[7] Huldrych F. Günthard,[3,4] Michael T. Koller,[11] Alexandra Trkola,[3] Matthias Briel,[1,12,a] Katharina Kusejko,[3,4,a] and Heiner C. Bucher[1,a]; for the Swiss HIV Cohort Study and the Swiss Transplant Cohort Study

[1]Basel Institute for Clinical Epidemiology and Biostatistics, Department of Clinical Research, University Hospital Basel, University of Basel, Basel, Switzerland; [2]Centre for Statistics in Medicine, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom; [3]University of Zurich, Institute of Medical Virology, Zurich, Switzerland; [4]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, Zurich, Switzerland; [5]Clinic for Transplantation Immunology and Nephrology, University Hospital Basel, University of Basel, Basel, Switzerland; [6]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, University of Basel, Switzerland; [7]Department of Infectious Diseases, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; [8]Division of Pulmonology, University Hospital Zurich, Zurich, Switzerland; [9]Nephrology Clinic, University Hospital Zurich, Zürich, Switzerland; [10]Clinic of Respiratory Medicine and Pulmonary Cell Research, University Hospital Basel, University of Basel, Basel, Switzerland; [11]Swiss Transplant Cohorts Study, University Hospital Basel, University of Basel, Basel, Switzerland; and [12]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Canada

Background. BNT162b2 by Pfizer-BioNTech and mRNA-1273 by Moderna are the most commonly used vaccines to prevent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. Head-to-head comparison of the efficacy of these vaccines in immunocompromised patients is lacking.

Methods. Parallel, 2-arm (allocation 1:1), open-label, noninferiority randomized clinical trial nested into the Swiss HIV Cohort Study and the Swiss Transplant Cohort Study. People living with human immunodeficiency virus (PLWH) or solid organ transplant recipients (SOTR; ie, lung and kidney) from these cohorts were randomized to mRNA-1273 or BNT162b2. The primary endpoint was antibody response to SARS-CoV-2 spike (S1) protein receptor binding domain (Elecsys Anti-SARS-CoV-2 immunoassay, Roche; cutoff ≥0.8 units/mL) 12 weeks after first vaccination (ie, 8 weeks after second vaccination). In addition, antibody response was measured with the Antibody Coronavirus Assay 2 (ABCORA 2).

Results. A total of 430 patients were randomized and 412 were included in the intention-to-treat analysis (341 PLWH and 71 SOTR). The percentage of patients showing an immune response was 92.1% (95% confidence interval [CI]: 88.4–95.8; 186/202) for mRNA-1273 and 94.3% (95% CI: 91.2–97.4; 198/210) for BNT162b2 (difference: -2.2%; 95% CI: -7.1 to 2.7), fulfilling noninferiority of mRNA-1273. With the ABCORA 2 test, 89.1% had an immune response to mRNA-1273 (95% CI: 84.8–93.4; 180/202) and 89.5% to BNT162b2 (95% CI: 85.4–93.7; 188/210). Based on the Elecsys test, all PLWH had an antibody response (100.0%; 341/341), whereas for SOTR, only 60.6% (95% CI: 49.2–71.9; 43/71) had titers above the cutoff level.

Conclusions. In immunocompromised patients, the antibody response of mRNA-1273 was noninferior to BNT162b2. PLWH had in general an antibody response, whereas a high proportion of SOTR had no antibody response.

Clinical Trials Registration. NCT04805125.

Keywords. SARS-CoV-2; randomized controlled trial; HIV; organ transplant; platform trial; vaccine.

Coronavirus disease 2019 (COVID-19) emerged in late 2019 in Wuhan, China, and was declared a pandemic by the World Health Organization on March 11, 2020 [1–3]. Since January

2021, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines by Pfizer-BioNTech (BNT162b2; Comirnaty) and Moderna (mRNA-1273; Spikevax) have been approved in Switzerland and are used to vaccinate the Swiss population [4]. Both vaccines were tested in largescale placebo-controlled approval studies including tens of thousands of individuals [5, 6]. Vaccines were found to be safe with excellent efficacy of 95% and 94%, respectively, in terms of preventing COVID-19 illness 14 days after the second vaccination. However, data for immunocompromised patients who have a high risk of COVID-19 infection with adverse outcome are still limited. The approval studies included only a few patients living with human immunodeficiency (PLWH), with no information

on CD4 cell counts and no solid organ transplant recipients [5, 6]. To date, there is no randomized evidence on the comparative effectiveness of BNT162b2 and mRNA-1273 in immunocompromised patients.

Having 2 Swiss national cohort studies with immunocompromised patients in Switzerland (ie, the Swiss HIV Cohort Study [SHCS] [7] and the Swiss Transplant Cohort Study [STCS] [8, 9]) a Corona Vaccine Trial Platform nested in these cohorts was established. We aimed to assess the noninferiority of mRNA-1273 to BNT162b (the first in Switzerland licensed SARS-CoV-2 vaccines) in a randomized trial with respect to antibody response and safety in immunocompromised patients 12 weeks after the first vaccination (ie, 8 weeks after second vaccination).

METHODS

Trial Oversight

The full version of the study protocol as approved by the ethical committee Nordwest- and Zentralschweiz, Switzerland (BASEC Nr. 2021-000593), is available on the trial registration site (https://clinicaltrials.gov/ct2/show/NCT04805125); a condensed version has been published [9]. In brief, we conducted a parallel 2-arm (allocation 1:1), open-label, noninferiority randomized clinical trial comparing the 2 in Switzerland-approved SARS-CoV-2 mRNA vaccines that are used to vaccinate the Swiss population. Treating cohort physicians or delegated staff contacted potentially eligible cohort participants from the SHCS and the STCS and obtained written informed consent.

Participants, Randomization, and Blinding

Individuals who were enrolled in the SHCS or the STCS (ie, lung transplant and kidney transplant recipients; heart and liver transplant centers could not join the trial for organizational reasons) were eligible for trial participation if they were aged 18 years or older, and if the COVID-19 vaccination was recommended by the treating physician. We excluded pregnant women, patients with any acute respiratory tract infection, SARS-CoV-2-positive patients with an infection occurring in the past 3 months, and persons with any emergency condition requiring immediate hospitalization. In addition, we excluded organ transplant recipients who received the new organ within the past month, had received T-cell-depleting agents within the past 3 months, pulse corticosteroids (within the past few months), rituximab (within the past 6 months), or if they were in need of chemotherapy treatment. The 3 cohort centers—University Hospital Basel (SHCS + STCS), University Hospital Zürich (SHCS + STCS), and University Hospital Bern (SHCS)—recruited all participants.

Randomization was performed in the Research Electronic Data Entry system [10] separately for the 2 cohorts stratified by study center, age group, sex, and presence of comorbidities. We used minimization with a random element across stratification factors to control for imbalances in treatment arms.

Participants, treating physicians, and outcome assessors for clinical outcomes were not blinded. Laboratory staff who assessed immunological parameters was blinded to treatment allocation. Serious adverse events were adjudicated by the data safety monitoring board that was blinded to intervention allocation.

Interventions

BNT162b2 licensed by Pfizer-BioNTech (Comirnaty) and mRNA-1273 licensed by Moderna (Spikevax) were stored and applied according to the recommendation of the manufacturers [9, 11–13]. Both vaccines were administered on days 0 and 28 into the deltoid muscle (30 μg of BNT162b2 in 0.3 mL or 100 μg of mRNA-1273 in 0.5 mL).

Outcomes

All outcomes were assessed 12 weeks (±7 days) after the first vaccination. In cases in which patients were not available within this time window (eg, because of vacations), outcome data were collected on the closest possible date.

The primary outcome was a positive antibody response to SARS-CoV-2 spike (S1) protein receptor-binding domain in human serum or plasma assessed by the commercial immunoassay Elecsys Anti-SARS-CoV-2 S (Elecsys S) from Roche Diagnostics [14]. The outcome is binary using a threshold of ≥0.8 units/mL as defined by the manufacturer. Further immunological outcomes were positive antibody response using the Antibody CORonavirus Assay (ABCORA) 2 that assesses seropositivity by measuring specific immunoglobulin G (IgG), IgA, and IgM responses to SARS-CoV-2 receptor binding domains, S1, S2, and N [15]. The following clinical outcomes were chosen: (1) newly polymerase chain reaction–confirmed asymptomatic COVID-19 infections; (2) newly confirmed symptomatic COVID-19 infections; (3) severe COVID-19 infections (see study protocol for more details [9]); (4) COVID-19 burden of diseases (0 for no COVID-19; 1 for nonsevere COVID-19; 2 for severe COVID-19); and (5) COVID-19 infection of a household member. Safety outcomes were assessed during the 12-week study visit and were reduced for feasibility and relevance reasons to the following (asked separately after the first and second vaccine): (1) any local symptom (redness or swelling or prolonged pain at injection site) limiting continuation of normal daily activities during the first 7 days after vaccination; (2) any systemic symptom (fever, generalized muscle or joint pain) limiting continuation of normal daily activities during the first 7 days after vaccination; and (3) any vaccine-related symptom leading to contacting a physician during the first 7 days after vaccination. Serious adverse events (SAEs; see study protocol for more details [9]) were documented throughout the trial and routinely assessed during the 12-week study visit.

Sample Size

This study is powered to assess the noninferiority in terms of immune response (antibodies to SARS-CoV-2 spike (S1) protein receptor binding domain) between the 2 SARS-CoV-2 vaccines BNT162b2 or mRNA-1273. Data in the general population showed that titers were high in nearly 100% after the second vaccination; however, no data were available for immunocompromised patients when this study was planned [16, 17]. We assumed an immune response in 90% of patients in both groups and powered our noninferiority trial so that a 95% 2-sided confidence interval (CI) excludes a difference in favor of the reference group of more than 10%. In total, 380 patients (190 in each treatment arm) were required for a statistical power of 90% and a type I error of 0.025. The sample size was increased to 430 patients to account for losses to follow-up. Sample size was calculated using the "ssc_propcomp" function of the R statistical software package SampleSize4ClinicalTrials [18].

Analysis

Trial participants' baseline characteristics, secondary outcomes regarding antibody response, clinical outcomes, SAEs, and safety outcomes are described as frequencies and percentages with 95% CIs or medians and interquartile range (IQR). Noninferiority of the primary outcome is established if the lower limit of a 95% 2-sided Wald CI for the difference in antibody response proportion between participants receiving mRNA-1273 and BNT162bs vaccines is above –10%, where 10% is the predefined noninferiority margin. Trial participants were primarily analyzed according to their allocated randomization group (intention to treat) but also according to a per-protocol principle that was defined as restricting the analysis to participants who received both vaccine doses they were allocated to. An additional "strict" per-protocol analysis was conducted restricted to individuals who received both dosages of their allocated vaccine (within the interval of 4 weeks ± 1 week) and had available outcome data at week 12 week (within the prespecified interval of ± 1 week; results presented in the appendix only). We performed sensitivity analyses by excluding participants with positive antibody response to the nucleocapsid protein at baseline as indicated by the Elecsys Anti-SARS-CoV-2 test Elecsys N test (sign of previous infection).

Quantitative SARS-CoV-2 S protein receptor binding domain with values ≥0.80 U/mL were considered "positive" for anti-SARS-CoV-2 S antibodies. In a first post hoc analysis setting the threshold for predicting a protective immune response was changed to 100 U/mL as indicated by Hall et al [19] and Khoury and colleagues [20].

In a second post hoc analyses, we chose for the ABCORA 2 sum S1 (sum of S1 signal over cutoff values of IgG, IgA, IgM) a threshold of 17 to predict neutralization activity against the vaccine strain Wuhan-Hu-1 in sera. The prediction is based on a head-to-head measurement of pseudovirus neutralization and

ABCORA 2 binding. It was shown that 100% of the sera with a threshold above 17 had measurable neutralization activity (above a titer of 1:100) in our pseudovirus neutralization tests [15]. Subgroup analyses were conducted by cohort, as well as for specific subpopulations such as PLWH with less and more than 200 CD4 cells/μL, with a suppressed and unsuppressed HIV viral load (ie, >50 copies/mL), for transplanted patients under intense (triple or quadruple immunosuppressive regimen) or less intense immunosuppressive therapy (dual immunosuppressive regimen) and for study participants according to sex (male/female), age group (<60, 60 to 69, ≥70 years) and history of cardiovascular diseases or metabolic syndrome (see appendix for definition). No interim analysis was conducted. All analysis were done in R Project for Statistical Computing (version 4.0.3) software [21].

RESULTS

A total of 430 patients were randomized; of those, 419 received a first vaccination dose in the frame of this study between April 19 and June 9, 2021; 412 patients received a second dose. We included 412 patients in the intention-to-treat dataset for immunological outcomes, 415 in the intention-to-treat dataset for clinical outcomes, and 404 in the per-protocol dataset (Figure 1).

Trial participants had a median age of 53 years (IQR: 43–61), the majority was male (75.8%; 326/430) and from the SHCS (81.9%; 352/430; Table 1). Of the 352 included PLWH, 2.0% (7/352) had CD4 cell counts below 200/μL and 5.7% (20/352) had an unsuppressed viral load (>50 copies/mL). Of the 78 organ transplant recipients, 79.5% (62/78) were on an intensive immunosuppressive therapy; 41 (52.6%) had received a lung and 37 (47.4%) a kidney transplantation. A total of 39 (9.1%) patients had a reactive antibody test to the nucleocapsid protein at baseline as determined by the Elecsys N test (mRNA-1273: 4.2%; 9/215; BNT162b2: 14.0%; 30/215) indicating a prior SARS-CoV-2 infection. Baseline data stratified by cohort are presented in the supplementary appendix (Table S1 and Table S2). The duration between the first and the second vaccine was a median of 28 days (IQR: 28–28) and the 12-week follow-up was conducted after a median of 84 days after the first vaccination (IQR: 84–86; Table S3).

Overall, 92.1% of participants randomized to mRNA-1273 (95% CI: 88.4–95.8; 186/202) had an antibody response (Elecsys S test) compared with 94.3% (95% CI: 91.2–97.4; 198/210) randomized to BNT162b2. With a difference of -2.2% (95% CI: -7.1 to 2.7), the vaccine mRNA-1273 from Moderna was noninferior to BNT162b2 from Pfizer-BioNTech (Table 2). This result was confirmed by the ABCORA 2 test for which a total of 89.3% (95% CI: 86.3–92.3; 368/412) had an antibody response (mRNA-1273: 89.1%; 95% CI: 84.8–93.4; 180/202 vs BNT162b2: 89.5%; 95% CI: 85.4–93.7; 188/210). When assessing the ABCORA 2
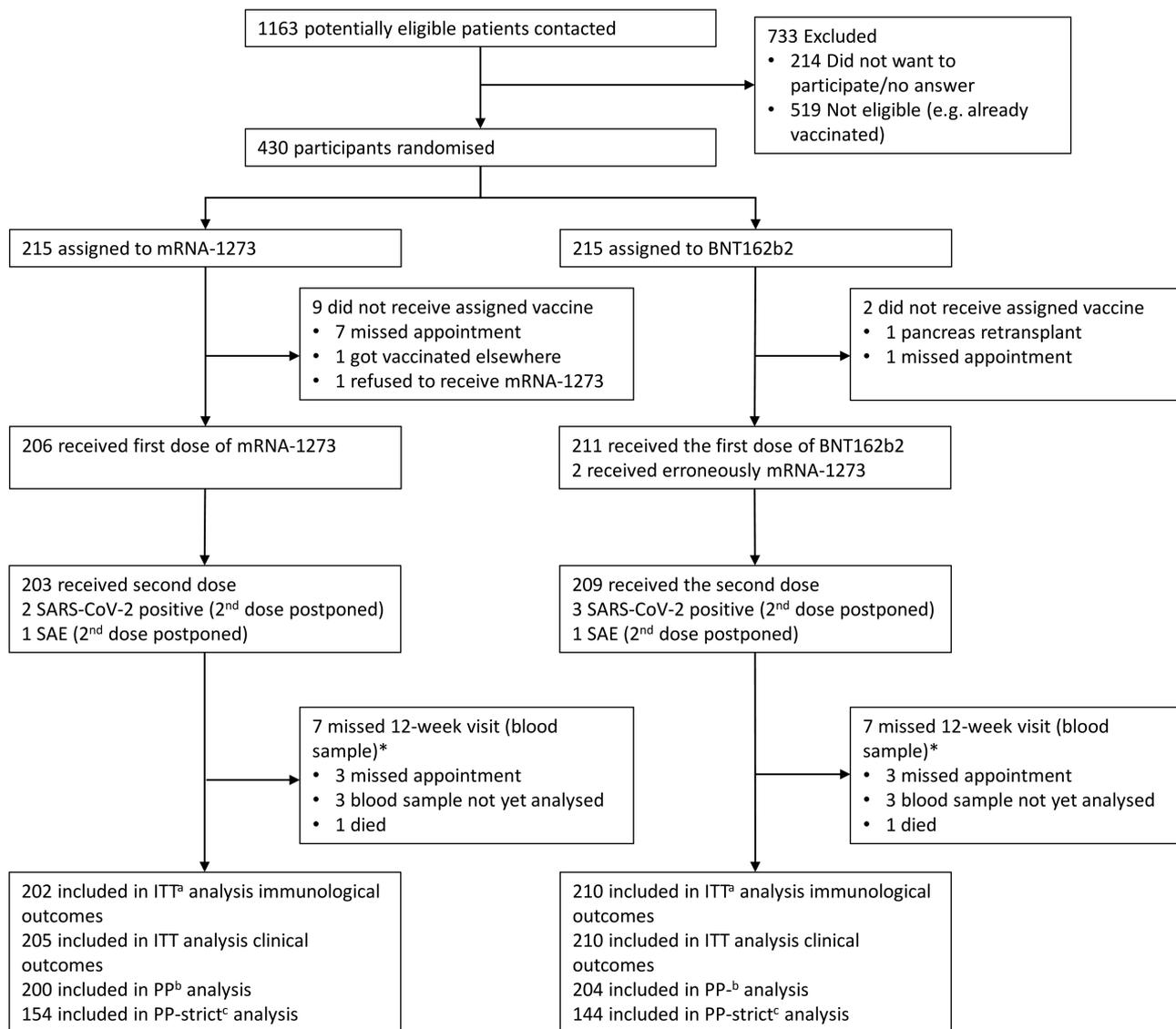
Figure 1. Flow chart.
*3 patients who missed the study visits could be contacted by phone to assess clinical outcomes.
[a]Including all patients because they were randomized and have available outcome data.
[b]Including patients who received the intervention they were allocated to and have available outcome data.
[c]Including patients who received the intervention they were allocated to, with an interval of 4 weeks (± 1 week) between first and second vaccination dose and provided outcome data at 12 weeks (± 1 week). Results only presented within appendix.
Abbreviations: ITT, intention to treat; pp, per-protocol; SAE, serious adverse event.

sum S1 threshold of 17, 83.5% (95% CI: 79.9–87.1; 344/412) had neutralizing antibodies (mRNA-1273: 84.7%; 95% CI: 79.7–89.6; 171/202 vs BNT162b2: 82.4%; 95% CI: 77.2–87.5; 173/210; Table S4). The analyses conducted on the per-protocol dataset were in line with the findings from the intention-to-treat dataset (Table 2 and Table S4). Although all PLWH (341/341) showed an immune response, only 60.6% (95% CI: 49.2–71.9; 43/71) of solid organ transplant recipients had an immune response (Elecsys S test). This number decreased to 39.4% (95% CI: 28.1–50.8; 28/71) among organ transplant recipients when using the more stringent ABCORA 2 test and to 21.1% (95% CI: 11.6–30.6; 15/71) when using the ABCORA 2 sum S1 threshold.

Results from prespecified subgroup analyses (Tables S4–6) suggest that fewer patients with a lung transplant had an immune response (48.7%; 95% CI: 33.0–64.1; 19/39) compared with kidney transplant recipients (75.0%; 95% CI: 60.0–90.0; 24/32). Furthermore, 85.7% (95% CI: 67.4–100.0; 12/14) of transplant recipients with less intensive immunosuppressive therapy had an immune response, whereas this was only the case for 54.4% (95% CI: 41.5–67.3; 31/57) of transplant patients with an intensive immunosuppressive therapy. When using a cutoff of 100 U/mL for Elecsys S, the proportion of patients with an immune response decreased to 86.4% (95% CI: 83.1–89.7; 356/412) for all patients, 99.4% (95% CI: 98.6–100.0; 339/341) for PLWH,

Table 1.   Demographics and Clinical Characteristics of the Study Population at Baseline

Characteristic	mRNA-1273 (Moderna) N = 215	BNT162b2 (Pfizer-BioNTech) N = 215	Total N = 430
Median age (IQR)	53 (43, 60)	53 (43, 61)	53 (43, 61)
Sex			
Male	161 (74.9%)	165 (76.7%)	326 (75.8%)
Female	54 (25.1%)	50 (23.3%)	104 (24.2%)
Cohort			
SHCS	177 (82.3%)	175 (81.4%)	352 (81.9%)
STCS	38 (17.7%)	40 (18.6%)	78 (18.1%)
Centers			
University Hospital Basel	77 (35.8%)	81 (37.7%)	158 (36.7%)
University Hospital Bern	53 (24.7%)	49 (22.8%)	102 (23.7%)
University Hospital Zurich	85 (39.5%)	85 (39.5%)	170 (39.5%)
History of cardiovascular disease or metabolic syndrome			
Yes	75/215 (34.9%)	77/215 (35.8%)	152/430 (35.3%)
No	140/215 (65.1%)	138/215 (64.2%)	278/430 (64.7%)
CD4 cell count (cells/µL)[a]			
<200	3/177 (1.7%)	4/175 (2.3%)	7/352 (2.0%)
200–350	13/177 (7.3%)	10/175 (5.7%)	23/352 (6.5%)
350–500	18/177 (10.2%)	26/175 (14.9%)	44/352 (12.5%)
>500	143/177 (80.8%)	135/175 (77.1%)	278/352 (79.0%)
Unsuppressed viral load (≥200 copies/mL)[a]			
Yes	7/177 (4.0%)	13/175 (7.4%)	20/352 (5.7%)
No	170/177 (96.0%)	162/175 (92.6%)	332/352 (94.3%)
Transplanted organ[b]			
Lung transplant	20/38 (52.6%)	21/40 (52.5%)	41/78 (52.6%)
Kidney transplant	18/38 (47.4%)	19/40 (47.5%)	37/78 (47.4%)
Immunosuppressive therapy[b]			
Less intense (<2 regimen)	5/38 (13.2%)	11/40 (27.5%)	16/78 (20.5%)
Intense (3 or 4 regimen)	33/38 (86.8%)	29/40 (72.5%)	62/78 (79.5%)
Antibody test to the nucleocapsid protein[c]			
Nonreactive	197 (91.6%)	181 (84.2%)	378 (87.9%)
Reactive	9 (4.2%)	30 (14.0%)	39 (9.1%)
Missing	9 (4.2%)	4 (1.9%)	13 (3.0%)

Abbreviations: IQR, interquartile range; SHCS, Swiss HIV Cohort Study; STCT, Swiss Transplant Cohort Study.

[a]Only considering patients from the Swiss HIV Cohort Study.

[b]Only considering patients from the Swiss Transplant Cohort Study.

[c]Elecsys N test [14] reactive to nucleocapsid protein indicates previous contact to severe acute respiratory syndrome coronavirus 2.

and 23.9% (95% CI: 14.0–33.9; 17/71) for transplant recipients (Tables S4–6). Sensitivity analyses excluding patients with a reactive antibody test to the protein at baseline were in line with the previously mentioned results (Tables S7–9).

Based on per-protocol data, mean ABCORA 2 sum S1 levels were 107.2 (95% CI: 96.7–117.9) for mRNA-1273 and 90.6 (95% CI: 80.0–101.3) for BNT162b2 (Figure 2, Table S10; per-protocol strict in Table S11). Results for Elecsys S titer levels are presented in the appendix (Figure S1; Table S12). For PLWH, the ABCORA 2 sum S1 titers were 123.5 (95% CI: 113.5–133.4) and 102.3 (95% CI: 91.2–113.4) for mRNA-1273 and BNT162b2, respectively, and the proportion of patients with a neutralization activity defined by the ABCORA 2 sum S1 threshold was higher with mRNA-1273 (98.8%; 95% CI: 97.2–100.0; 176/169) compared with BNT162b2 (94.2%; 95% CI: 90.7–97.7; 176/169; Table S5). Organ transplant recipients mean ABCORA 2 sum S1 levels were 22.1 (95% CI: 0.0–48.4) after receiving

mRNA-1273 and 32.1 (95% CI: 7.5–56.7) following vaccination with BNT162b2 (Figure 2, Table S10), and the proportion of patients with a neutralization activity (ABCORA 2 sum S1) was 12.1% (95% CI: 1.0–23.4; 4/33) for mRNA-1273 and 29.0% (95% CI: 14.0–43.4; 11/38) for BNT162b2; Table S5)

At 12-week follow-up, a total of 5 patients reported that they tested SARS-CoV-2 positive (all before receiving the second dose of vaccine). No severe COVID-19 infections occurred, and no household members were reported as SARS-CoV-2 positive (Table 3). Symptoms limiting the normal daily activities occurred frequently after the second vaccination and systemic symptoms appeared more frequently after the second dose of mRNA-1273 (21.8%; 95% CI: 16.3–28.1; 44/202) compared with vaccination with BNT162b2 (10.7%; 6.8–15.8; 22/205). A total of 18 patients had at least 1 SAE requiring hospitalization and 2 of these patients died. None of the SAEs were classified as clearly related to study medication (see judgment from treating

Table 2. Proportion of Patients With an Immune Response 12 Weeks After the First SARS-CoV-2 Vaccination

	SHCS and STCS				SHCS			STCS		
	mRNA-1273 (Moderna)	BNT162b2 (Pfizer-BioNTech)	Total	Difference	mRNA-1273 (Moderna)	BNT162b2 (Pfizer-BioNTech)	Total	mRNA-1273 (Moderna)	BNT162b2 (Pfizer-BioNTech)	Total
Intention to treat										
Immune response (Elecsys S [14])[a]	92.1% (88.4; 95.8%) 186/202	94.3% (91.2; 97.4%) 198/210	93.2% (90.8; 95.6%) 384/412	−2.2% (−7.1; 2.7%)	100.0% (-) 169/169	100.0% (-) 172/172	100.0% (-) 341/341	51.5% (34.5; 68.6%) 17/33	68.4% (53.6; 83.2%) 26/38	60.6% (49.2; 71.9%) 43/71
Immune response (ABCORA2 [15])	89.1% (84.8; 93.4%) 180/202	89.5% (85.4; 93.7%) 188/210	89.3% (86.3; 92.3%) 368/412	−0.4% (−6.4; 5.6%)	100.0% (-)169/169	99.4% (98.3; 100.0%) 171/172	99.7% (99.1–100.0) 340/341	33.3% (17.3; 49.4%) 11/33	44.7% (28.9; 60.6%) 17/38	39.4% (28.1; 50.8%) 28/71
Per-protocol[b]										
Immune response (Elecsys S [14])[a]	92.0% (88.2; 95.8%) 184/200	94.6% (91.5; 97.7%) 193/204	93.3% (90.9; 95.8%) 377/404	−2.6% (−7.5; 2.3%)	100.0% (-) 168/168	100.0% (-) 170/170	100.0% (-) 338/338	50.0% (32.7; 67.3%) 16/32	67.7% (51.9; 83.4%) 23/34	59.1% (47.2; 71.0%) 39/66
Immune response (ABCORA 2 [15])	89.0% (84.7; 93.3%) 178/200	89.7% (85.5; 93.9%) 183/204	89.4% (86.4; 92.4%) 361/404	−0.7% (−6.7; 5.3%)	100.0% (-) 168/168	99.4% (98.3; 100.0%) 169/170	99.7% (99.1; 100.0%) 337/338	31.3% (15.2; 47.3%) 10/32	41.2% (24.6; 57.7%) 14/34	36.4% (24.8; 48.0%) 24/66

Sensitivity analysis for the per-protocol estimate, including only patients who received the intervention they were allocated to, with an interval of 4 weeks (± 1 week) between first and second vaccination dose and provided outcome data at 12 weeks (± 1 week) is available in the Supplementary Appendix.

Abbreviations: ABCORA 2, Antibody Coronavirus Assay 2; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SHCS, Swiss HIV Cohort Study; STCT, Swiss Transplant Cohort Study.

[a]Using the threshold of at 0.8 U/mL.

[b]Including patients who received the intervention they were allocated to and have available outcome data.

physicians and data safety monitoring board in Table S13). The clinical outcomes reported separately for the SHCS and the STCS are listed in Tables S14 and S15.

DISCUSSION

This randomized head-to-head comparison showed noninferiority of the mRNA-1273 (Moderna) compared with the BNT162b2 (Pfizer-BioNTech) vaccine in terms of antibody response at 12 weeks. An antibody response was seen in the majority of the included patients independently of the antibody test (Elecsys S [14] or ABCORA 2 [15]). Although all patients from the HIV cohort (with 1 exception using the ABCORA 2 test) had an immune response after vaccination, only 61% of the patients from the transplant cohort had an immune response using the Elecsys S test. An ABCORA 2 sum S1 value >17 allowed the prediction of whether sera harbor neutralization activity was based on a previous established algorithm [15]. Based on this analysis, we found that nearly 80% of organ transplant recipients had with high certainty not developed neutralization activity.

Our results confirmed the findings from a published observational study reporting that immune response in solid organ transplant recipients was detectable in 54% of patients (357/658) [22]. A randomized clinical trial conducted by Hall et al has shown that solid organ transplant recipients have a higher immune response after a third SARS-CoV-2 vaccination; hence, a third vaccine should be considered in this population [19]. Two recently published case reports in 14 and 12 virologically suppressed PLWHs found high antibody titers after the second vaccination with mRNA-1273 [23, 24]. These results are in line with our findings, which provide now more robust evidence for mRNA-1273 and for BNT162b2 in PLWH with a suppressed viral load.

Current research indicates that the immune response is stronger in immunocompetent individuals when applying the mRNA-1273 vaccine (Moderna) compared with BNT162b2 (Pfizer-BioNTech) because of its higher mRNA content and the longer interval (4 vs 3 weeks) [25]. Our conducted post hoc analysis found more PLWHs with neutralization activity (according to ABCORA 2 sum S1) after receiving mRNA-1273 compared with BNT162b2. In addition, the assessed titer levels were somewhat higher with mRNA-1273 by Moderna (Figure 2), but because of the large variance in the data (ie, 95% CI), we cannot conclusively confirm a difference between the 2 vaccines. A retrospective study in more than 50 000 vaccinated individuals found fewer breakthrough infections when the mRNA-1273 vaccine was used [26]. Further high-quality evidence is needed to assess if the mRNA-1273 might be superior for specific clinical endpoints (eg, severe COVID-19, mortality).

The study has the following limitations. First, sample size for transplant patients and for subgroup analyses was small. Therefore, suggested differences (eg, between kidney and lung
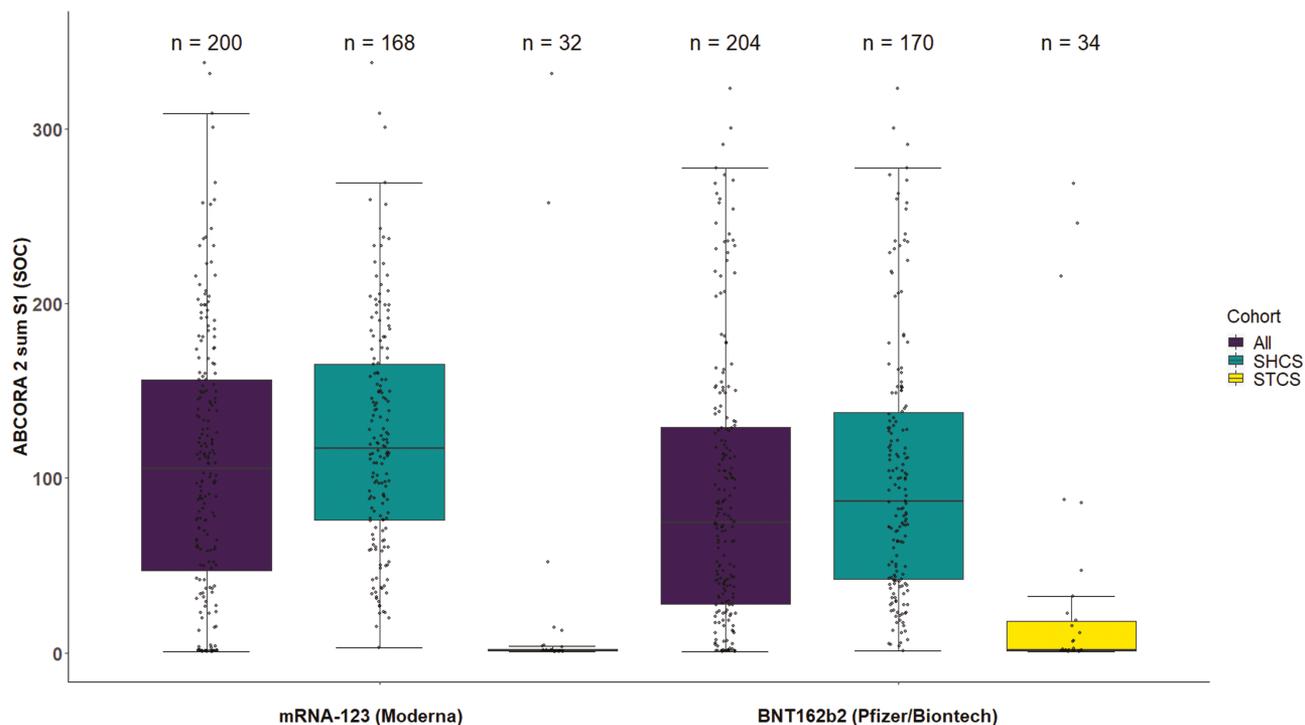
Figure 2. Antibody response in immunocompromised patients after receiving 2 doses of SARS-CoV-2 vaccines (per-protocol data set) using ABCORA 2 [15]. Figure shows combined reactivity of IgM, IgA, and IgG to the subunit S1 in patients who received the allocation they were randomized to and provided a blood sample at follow-up (per-protocol). Depicted are sum S1 (sum of S1 signal over cutoff values IgG, IgA, IgM) off all patients, patients from Swiss HIV Cohort Study (SHCS), Swiss Transplant Cohort Study (STCS). Box plots indicate the interquartile ranges with vertical lines representing the minimum and maximum values. ABCORA 2, Antibody Coronavirus Assay 2; Ig, immunoglobulin; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 3. Clinical Outcomes and Adverse Events

Outcomes	mRNA-1273 (Moderna)	BNT162b2 (Pfizer-BioNTech)	Total
Confirmed SARS-CoV-2 infection	2/205[c] (1.0%; 0.0–2.3%)	3/210[c] (1.4%; 0.0–3.0%)	5/415[c] (1.2%; 0.2–2.3%)
Symptomatic	2/205 (1.0%; 0.0–2.3%)	1/210 (0.5%; 0.0–1.4%)	3/415 (0.7%; 0.0–1.5%)
Asymptomatic	0/205 (0.0%)	2/210 (1.0%; 0.1–3.4%)	2/415 (0.5%; 0.0–1.1%)
Severe COVID-19 infection	0/205 (0.0%)	0/210 (0.0%)	0/415 (0.0%)
COVID-19 burden of disease[a] (mean, SD)	0.010 (0.099 SD)	0.014 (0.118 SD)	0.012 (0.109 SD)
Confirmed SARS-COV-2 infection of household members	0/205 (0.0%)	0/210 (0.0%)	0/415 (0.0%)
Safety outcomes after first vaccine			
Any local symptoms limiting continuation of normal daily activities during the first 7 days	13/205 (6.3%; 3.0–9.7%)	14/210 (6.7%; 3.3–10.0%)	27/415 (6.5%; 4.1–8.9%)
Any systemic symptoms limiting continuation of normal daily activities during the first 7 days	14/205 (6.8%; 3.4–10.3%)	12/210 (5.7%; 2.6–8.9%)	26/415 (6.3%; 3.9–8.6%)
Any vaccine related symptom leading to contacting a physician during the first 7 days	2/205 (1.0%; 0.0–2.3%)	1/210 (0.5%; 0.0–1.4%)	3/415 (0.7%; 0.0–1.5%)
Safety outcomes after second vaccine			
Any local symptoms limiting continuation of normal daily activities during the first 7 days	18/202 (8.9%; 5.0–12.8%)	13/205 (6.3%; 3.0–9.7%)	31/407 (7.6%; 5.0–10.2%)
Any systemic symptoms limiting continuation of normal daily activities during the first 7 days	44/202 (21.8%; 16.1–27.5%)	22/205 (10.7%; 6.5–15.0%)	66/407 (16.2%; 12.6–19.8%)
Any vaccine related symptom leading to contacting a physician during the first 7 days	3/202 (1.5%; 0.0–3.2%)	2/205 (1.0%; 0.0–2.3%)	5/407 (1.2%; 0.2–2.3%)
Serious adverse events[b]	9/205 (4.4%; 1.6–7.2%)	9/210 (4.3%; 1.5–7.0%)	18/415 (4.3%; 2.4–6.3%)
Patient died	1/205 (0.5%; 0.0–1.4%)	1/210 (0.5%; 0.0–1.4%)	2/415 (0.5%; 0.0–1.1%)

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation.

[a]The burden of disease was judged as 0 for no SARS-CoV-2 infection, 1 for nonsevere SARS-CoV-2 infections and 2 for severe SARS-CoV-2 infections.

[b]All infections occurred after the first vaccination, but before the second vaccine was administered.

[c]All infections occurred after the first vaccination, but before the second vaccine was administered.

transplant patients) are of exploratory nature and have to be interpreted carefully. Second, the prespecified neutralization cutoff for the primary outcome (ie, of ≥0.8 U/mL) was chosen when little information was available. Now, it is unclear how useful this cutoff from the Elecsys S test is in terms of predictive resistance to infection. Although other studies took the same cutoff (ie, of ≥0.8 U/mL) [23, 27], Hall et al chose a cutoff of 100 U/mL. We believe that by including a second high-quality test (ABCORA 2 antibody response and sum S1) as well as assessing the results with a cutoff of 100 U/mL allows us to make a sensible interpretation of study results. However, these cutoffs will have to be further adjusted in the future (ie, to account for SARS-CoV-2 variants of concern).

In conclusion, the proportion of patients with an immune response was comparable between mRNA-1273 (Moderna) and BNT162b2 (Pfizer-BioNTech). In general, PLWH had a good immune response, whereas solid organ transplant patients had a low immune response. These patients should be prioritized when third ("booster") vaccines are administered.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Members of the Swiss Transplant Cohort Study. Patrizia Amico, Andres Axel, John-David Aubert, Vanessa Banz, Beckmann Sonja, Guido Beldi, Christoph Berger, Ekaterine Berishvili, Isabelle Binet, Pierre-Yves Bochud, Sanda Branca, Heiner C. Bucher, Thierry Carrel, Emmanuelle Catana, Yves Chalandon, Sabina De Geest, Olivier De Rougemont, Michael Dickenmann, Joëlle Lynn Dreifuss, Michel Duchosal, Thomas Fehr, Sylvie Ferrari-Lacraz, Nicola Franscini, Christian Garzoni, Paola Gasche Soccal, Christophe Gaudet, Déla Golshayan, Nicolas Goossens, Karine Hadaya, Jörg Halter, Dominik Heim, Christoph Hess, Sven Hillinger, Hans Hirsch, Patricia Hirt, Günther Hofbauer, Uyen Huynh-Do, Franz Immer, Michael Koller (head of the data center), Mirjam Laager, Bettina Laesser, Roger Lehmann, Alexander Leichtle, Christian Lovis, Oriol Manuel, Hans-Peter Marti, Pierre Yves Martin, Michele Martinelli, Valérie McLin, Katell Mellac, Aurélia Merçay, Karin Mettler, Nicolas Mueller (chair Scientific Committee), Antonia Müller, Ulrike Müller-Arndt, Beat Müllhaupt, Mirjam Nägeli, Graziano Oldani, Manuel Pascual (executive office), Klara Posfay-Barbe, Juliane Rick, Anne Rosselet, Simona Rossi, Silvia Rothlin, Frank Ruschitzka, Thomas Schachtner, Urs Schanz, Stefan Schaub, Aurelia Schnyder, Macé Schuurmans, Thierry Sengstag, Federico Simonetta, Susanne Stampf, Jürg Steiger (head, executive office), Guido Stirniman, Ueli Stürzinger, Christian Van Delden (executive office), Jean-Pierre Venetz, Jean Villard, Julien Vionnet, Madeleine Wick (STCS coordinator), Markus Wilhlem, Patrick Yerly

References

1. WHO. Pneumonia of unknown cause – China. WHO. https://www.who.int/emergencies/disease-outbreak-news/item/2020-DON229. Accessed: 16 March 2022.

2. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet **2020**; 395:470–3.

3. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 — 11 March **2020**. https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Accessed: 14 February 2022.

4. Federal Office of Public Health. Coronavirus: vaccination. https://www.bag.admin.ch/bag/en/home/krankheiten/ausbrueche-epidemien-pandemien/aktuelle-ausbrueche-epidemien/novel-cov/impfen.html#288501448 Accessed: 14 Feburary 2022.

5. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med **2020**; 383:2603–15.

6. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med **2021**; 384:403–16.

7. Scherrer AU, Traytel A, Braun DL, et al. Cohort profile update: the Swiss HIV Cohort Study (SHCS). Int J Epidemiol **2022**; 51(1):33–4j.

8. Koller MT, van Delden C, Muller NJ, et al. Design and methodology of the Swiss Transplant Cohort Study (STCS): a comprehensive prospective nationwide long-term follow-up cohort. Eur J Epidemiol **2013**; 28:347–55.

9. Speich B, Chammartin F, Smith D, et al. A trial platform to assess approved SARS-CoV-2 vaccines in immunocompromised patients: first sub-protocol for a pilot trial comparing the mRNA vaccines Comirnaty(R) and COVID-19 mRNA Vaccine Moderna(R). Trials **2021**; 22:724.

10. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: BUILDING an international community of software platform partners. J Biomed Inform **2019**; 95:103208.

11. FDA briefing document: Moderna COVID-19 vaccine. vaccines and related biological products advisory committee meeting 17 December **2020**. https://www.fda.gov/media/144434/download Accessed: 14 February 2022.

12. Centers for Disease Control and Prevention (CDC). Pfizer-BioNTech COVID-19 vaccine. Storage and handling summary. https://www.cdc.gov/vaccines/covid-19/info-by-product/pfizer/downloads/storage-summary.pdf Accessed: 14 February 2022.

13. European Medicines Agency (EMA). COVID-19 vaccine Moderna. Annex 1. https://www.ema.europa.eu/en/documents/product-information/spikevax-previously-covid-19-vaccine-moderna-epar-product-information_en.pdf Accessed: 14 February 2022.

14. Roche. Elecsys®Covid-19 solutions. https://diagnostics.roche.com/global/en/products/params/elecsys-anti-sars-cov-2-s.html Accessed: 14 February 2022.

15. Abela IA, Pasin C, Schwarzmuller M, et al. Multifactorial seroprofiling dissects the contribution of pre-existing human coronaviruses responses to SARS-CoV-2 immunity. Nat Commun **2021**; 12:6703.

16. Mulligan MJ, Lyke KE, Kitchin N, et al. Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults. Nature **2020**; 586:589–93.

17. Widge AT, Rouphael NG, Jackson LA, et al. Durability of responses after SARS-CoV-2 mRNA-1273 vaccination. N Engl J Med **2021**; 384:80–2.

18. Chow S, Shao J, Wang H. Sample size calculations in clinical research. 2nd ed. Chapman & Hall/CRC Biostatistics Series **2008**.

19. Hall VG, Ferreira VH, Ku T, et al. Randomized trial of a third dose of mRNA-1273 vaccine in transplant recipients. N Engl J Med **2021**; 385:1244–6.

20. Khoury DS, Cromer D, Reynaldi A, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. Nat Med **2021**; 27:1205–11.

21. R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, **2021**. Available at: https://www.R-project.org/. Accessed: 16 March 2022.

22. Boyarsky BJ, Werbel WA, Avery RK, et al. Antibody response to 2-Dose SARS-CoV-2 mRNA vaccine series in solid organ transplant recipients. JAMA **2021**; 325(21):2204–6.

23. Ruddy JA, Boyarsky BJ, Bailey JR, et al. Safety and antibody response to two-dose SARS-CoV-2 messenger RNA vaccination in persons with HIV. AIDS **2021**; 35(14):2399–401.

24. Woldemeskel BA, Karaba AH, Garliss CC, et al. The BNT162b2 mRNA vaccine elicits robust humoral and cellular immune responses in people living with HIV. Clin Infect Dis **2021**.

25. Steensels D, Pierlet N, Penders J, Mesotten D, Heylen L. Comparison of SARS-CoV-2 antibody response following vaccination with BNT162b2 and mRNA-1273. JAMA **2021**; 326(15):1533–5.

26. Puranik A, Lenehan PJ, Silvert E, et al. Comparison of two highly-effective mRNA vaccines for COVID-19 during periods of Alpha and Delta variant prevalence. medRxiv **2021**.

27. Strauss AT, Hallett AM, Boyarsky BJ, et al. Antibody response to severe acute respiratory syndrome-coronavirus-2 messenger RNA vaccines in liver transplant recipients. Liver Transpl **2021**; 27(12):1852–6.