Antibody response in immunocompromised patients after the administration of SARS-CoV-2 vaccine BNT162b2 or mRNA-1273: A randomised 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], 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[5], Alexandra Trkola[3], Matthias Briel[1,12, §], Katharina Kusejko[3,4 §], Heiner C. Bucher[11, §], and 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, 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, Basel, Switzerland

[11] Swiss Transplant Cohorts Study, University Hospital Basel, Basel, Switzerland

[12] Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Canada

[§]Shared last author

*Corresponding author:

Benjamin Speich, PhD,
Basel Institute for Clinical Epidemiology and Biostatistics, Department of Clinical Research, University Hospital Basel, University of Basel, Basel, Switzerland,
Spitalstrasse 12
4031
Basel Switzerland
Email: benjamin.speich@usb.ch

Summary:

This randomised trial confirmed the non-inferiority of the SARS-CoV-2 vaccine mRNA-1273 compared to BNT162b2 in terms of antibody response in immunocompromised patients. While HIV patients had a sufficient antibody response, a high proportion of transplant recipients had no antibody response.

Abstract

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

Methods: Parallel, two-arm (allocation 1:1), open-label, non-inferiority randomised clinical trial nested into the Swiss HIV Cohort Study and the Swiss Transplant Cohort Study. Patients living with HIV (PLWH) or solid organ transplant recipients (SOTR; i.e. lung and kidney) from these cohorts were randomised 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; cut-off ≥0.8 units/ml) 8 weeks after second vaccination. In addition, antibody response was measured with the Antibody CORonavirus Assay 2 (ABCORA 2).

Results: 430 patients were randomised 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 non-inferiority 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), while for SOTR only 60.6% (95% CI 49.2-71.9%; 43/71) had titres above the cut-off.

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

Keywords: SARS-CoV-2; Randomised controlled trial, HIV; Organ transplant; Platform trial; Vaccine

Background

Coronavirus disease 2019 (COVID-19) has emerged in late 2019 in Wuhan, China, and was declared a pandemic by the World Health Organization (WHO) 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 ten-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 few patients living with HIV (PLWH), with no information on CD4 cell counts, and no solid organ transplant recipients [5, 6]. To date there is no randomised evidence on the comparative effectiveness of BNT162b2 and mRNA-1273 in immunocompromised patients.

Having two Swiss national cohort studies with immunocompromised patients in Switzerland (i.e. the Swiss HIV Cohort Study [SHCS] [7] and the Swiss Transplant Cohort Study [STCS] [8, 9]) a COrona VaccinE tRiAL pLatform (COVERALL) nested in these cohorts was established. We aimed to assess the non-inferiority of mRNA-1273 to BNT162b (the first in Switzerland licensed SARS-CoV-2 vaccines) in a randomised trial with respect to antibody response and safety in immunocompromised patients 12 weeks after the first vaccination (i.e. 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 two-arm (allocation 1:1), open-label, non-inferiority randomised clinical trial (RCT) comparing the two 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, randomisation and blinding

Individuals who were enrolled in the SHCS or the STCS (i.e. lung transplant and kidney transplant recipients; heart and liver transplant centres could not join the trial due to organisational 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 last 3 months, and persons with any emergency condition requiring immediate hospitalisation. In addition, we excluded organ transplant recipients who received the new organ within the last month, had received T-cell depleting agents within the last 3 months, pulse corticosteroids (within the last months), rituximab (within the last 6 months), or if they were in need of chemotherapy treatment. The three cohort centers University Hospital Basel (SHCS + STCS), University Hospital Zürich (SHCS + STCS), and University Hospital Bern (SHCS) recruited all participants.

Randomisation was performed in the Research Electronic Data Entry (REDCap) system [10] separately for the two cohorts stratified by study center, age group, sex, and presence of comorbidities. We used minimisation 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 day 0 and 28 into the deltoid muscle (30µg of BNT162b2 in 0.3ml or 100µg of mRNA-1273 in 0.5ml).

Outcomes

All outcomes were assessed 12 weeks (±7 days) after the first vaccination. In cases where patients were not available within this time window (e.g. due to 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 IgG, IgA and IgM responses to SARS-CoV-2 receptor binding domains, S1, S2 and N [15]. The following clinical outcomes were chosen : (i) Newly PCR-confirmed asymptomatic COVID-19 infections; (ii) newly confirmed symptomatic COVID-19 infections; (iii) severe COVID-19 infections (see study protocol for more details [9]); (iv) COVID-19 burden of diseases (BOD; 0 for no COVID-19; 1 for non-severe COVID-19; 2 for severe COVID-19); (v) 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): (i) 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; (ii) any systemic symptom (fever, generalised muscle or joint pain) limiting continuation of normal daily activities during the first 7 days after vaccination; and (iii) any vaccine-related symptom leading to contacting a physician during the first 7 days after vaccination. Serious adverse events (SAE; (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 non-inferiority in terms of immune response (antibodies to SARS-CoV-2 spike (S1) protein receptor binding domain) between the two SARS-CoV-2 vaccines BNT162b2 or mRNA-1273. Data in the general population showed that titres were high in nearly 100 percent after the second vaccination, however, no data was 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 non-inferiority trial so that a 95% two-sided confidence interval excludes a difference in favour 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% confidence interval (CI) or medians and interquartile range (IQR). Non-inferiority of the primary outcome is established if the lower limit of a 95% two-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 pre-defined non-inferiority margin. Trial participants were primarily analysed according to their allocated randomisation 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 pre-specified interval of

± 1 week; results only presented in the appendix). 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 cut-off values of IgG, IgA, IgM) a threshold of 17 to predict neutralisation activity against the vaccine strain Wuhan-Hu-1 in sera. The prediction is based on a head-to-head measurement of pseudovirus neutralisation and ABCORA 2 binding. It was shown that 100% of the sera with a threshold above 17 had measurable neutralisation activity (above a titre of 1:100) in our pseudovirus neutralisation tests [15]. Sub-group analyses were conducted by cohort, as well as for specific sub-populations such as PLWH with less and more than 200 CD4 cells/µl, with a suppressed and unsuppressed HIV viral load (i.e. >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 (below 60, 60 to 69, 70 or above) 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 randomised, and 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 data-set for immunological outcomes, 415 in the intention-to-treat data set for clinical outcomes, and 404 in the per-protocol data set (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). Out 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 randomised 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) randomised to BNT162b2. With a difference of 2.2% (95% CI, -7.1 to 2.7%) the vaccine mRNA-1273 from Moderna was non-inferior 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 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). While 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 pre-specified sub-group analyses (Table S4, S5 and S6) suggest that fewer patients with a lung transplant had an immune response (48.7%; 95% CI 33.0-64.1%; 19/39) compared to 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, while 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 cut-off of 100 units/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 and 23.9% (95% CI 14.0-33.9%; 17/71) for transplant recipients (Table S4, S5 and S6). Sensitivity analyses excluding patients with a reactive antibody test to the protein at baseline were in line with the above mentioned results (Table S7, S8 and S9).

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 titre 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 neutralisation 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 to 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 neutralisation 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 five patients reported that they were 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 to vaccination with BNT162b2 (10.7%; 6.8-15.8%; 22/205). A total of 18 patients had at least one SAE requiring hospitalization and two of these patients died. None of the SAEs were classified as clearly related to study medication (see judgment from treating physicians and data safety monitoring board in Table S13). The clinical outcomes reported separately for the SHCS and the STCS are listed in Table S14 and S15.

Discussion

This randomised head-to-head comparison showed non-inferiority of the mRNA-1273 (Moderna) compared to 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]). While all patients from the HIV cohort (with one 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 above 17 allowed to predict whether sera harbour neutralisation activity 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 neutralisation 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]. An RCT 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 PLWH found high antibody titres 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 to BNT162b2 (Pfizer-BioNTech) due to its higher mRNA content and the longer interval (4 vs 3 weeks) [25]. Our conducted post-hoc analysis found indeed more PLWH with neutralisation activity (according to ABCORA 2 sum S1) after receiving mRNA-1273 compared to BNT162b2. In addition, the assessed titre levels were somewhat higher with mRNA-1273 by Moderna (Figure 2), but due to the large variance in the data (i.e. 95% CI) we cannot conclusively confirm a difference between the two 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 (e.g. severe COVID-19; mortality).

The study has the following limitation: First, sample size for transplant patients and for sub-group analyses was small. Therefore, suggested differences, e.g. between kidney and lung transplant patients, are of exploratory nature and have to be interpreted carefully. Second, the pre-specified neutralisation cut-off for the primary outcome (i.e. of ≥0.8 units/ml) was chosen when little information was available. Nowadays it is unclear how useful this cut-off from the Elecsys S test is in terms of predictive resistance to infection. While other studies took the same cut-off (i.e. of ≥0.8 units/ml) [23, 27], Hall et al., chose a cut-off of 100 units/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 cut-off of 100 units/ml allows us to make a sensible interpretation of study results. However, these cut-offs will have to be further adjusted in the future (i.e. 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 while solid organ transplant patients had a low immune response. These patients should be prioritised when third ("booster") vaccines are administered.

Notes

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Authors' contribution

HCB, BS, FC, NJM, HFG, MPS, AR, MT, MTK, MB, and KK designed the study; KK was responsible for preparing the data platform; FC conducted sample size calculation and all analyses; BS, HCB, PA, MPS, ALE, BH, DLB, MMS, TFM, MT, AR, HFG coordinated patient recruitment and follow-up at local centres. IAA, AT and AA conducted all laboratory analyses; BS wrote the first draft of the manuscript; all authors read and approved the final version of the manuscript.

Members of the Swiss HIV Cohort Study

Abela I A, Aebi-Popp K, Anagnostopoulos A, Battegay M, Bernasconi E, Braun DL, Bucher HC, Calmy A, Cavassini M, Ciuffi A, Dollenmaier G, Egger M, Elzi L, Fehr J, Fellay J, Furrer H, Fux CA, Günthard HF (President of the SHCS), Hachfeld A, Haerry D (deputy of "Positive Council"), Hasse B, Hirsch HH, Hoffmann M, Hösli I, Huber M, Kahlert CR (Chairman of the Mother & Child Substudy),

Kaiser L, Keiser O, Klimkait T, Kouyos RD, Kovari H, Kusejko K (Head of Data Centre), Martinetti G, Martinez de Tejada B, Marzolini C, Metzner KJ, Müller N, Nemeth J, Nicca D, Paioni P, Pantaleo G, Perreau M, Rauch A (Chairman of the Scientific Board), Schmid P, Speck R, Stöckle M (Chairman of the Clinical and Laboratory Committee), Tarr P, Trkola A, Wandeler G, Yerly S.

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 (Chairman 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, Excecutive 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

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Conflict of interests:

Heiner C. Bucher has received in the 36 months prior to the submission of this manuscript grants, support for travelling, consultancy fees and honorarium from Gilead, BMS, Viiv Healthcare, Roche and Pfizer that were not related to this project. He serves as the president of the Association contre le HIV et autres infections transmissibles. In this function he has received support for the Swiss HIV Cohort Study from ViiV Healthcare, Gilead, BMS, and MSD. He also reports participation on a Data Safety Monitory Board or Advisory Board for Gilead Viiv Health Care and receipt of equipment, materials, drugs, medical writing, gifts or other services for his institution from Roche. Alexandra Trkola received a consultant fee from Roche and Neuroimmune, has received unrestricted research funding from Gilead and Roche not related to this study, reports grants or contract unrelated to this study from the Swiss National Science Foundation, Swiss Federal Office of Public Health, Gilead COVID grant initiative, Pandemiefonds of the UZH Foundation, Swiss Red Cross “Glückskette” Corona Funding, and the University Hospital Zurich, Innovation Pool Project, has received payment or honoraria from Schweizer Lungen Liga for a COVID lecture unrelated to the study, participated on a Data Safety Monitory Board or Advisory Board for Neuroimmune, and received material for COVID-19 diagnostics evaluation unrelated to the study from Roche. Dominique L. Braun received honoraria for advisory boards from the companies Gilead, MSD and ViiV, consulting fees for participation on advisory boards for Gilead, ViiV, and Merck, and payment or honoraria for lectures from Gilead, Merck, ViiV, and Abbvie outside of the study. Huldrych F. Günthard, outside of this study, reports grants from the Swiss National Science Foundation, National Institutes of Health (NIH), and the Swiss HIV Cohort Study, unrestricted research grants from Gilead Sciences, Roche, and Yvonne Jacob Foundation, personal fees from consulting or advisory boards or data safety monitoring boards for Merck, Gilead Sciences, ViiV Healthcare, Mepha, Janssen, Novartis and Sandoz, and payment for lectures, presentations, speakers bureaus, manuscript writing or education events from Medscape. Huldrych F. Günthard’s institution received money for participation in the following clinical COVID-19

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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 nucleocapside protein[c]			
Non-reactive	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%)

[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 SARS-CoV-2.

Abbreviations: IQR=Interquartile range; SHCS=Swiss HIV Cohort Study; STCT= Swiss Transplant Cohort Study

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 (ABCORA 2 [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

[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.

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: SHCS=Swiss HIV Cohort Study; STCT= Swiss Transplant Cohort Study

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%)

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

FIGURE LEGENDS

Figure 1: Flow chart

*****3 patients who missed the study visits could be contacted by phone to assess clinical outcomes.

[a] Including all patients as they were randomised 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: SAE= serious adverse events; ITT= intention to treat; pp= per-protocol

Figure 2: Antibody response in immunocompromised patients after receiving two 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 randomised to and provided a blood sample at follow-up (per-protocol). Depicted are sum S1 (sum of S1 signal over cut-off values IgG, IgA, IgM) off all patients (purple), patients from Swiss HIV Cohort Study (green), Swiss Transplant Cohort Study (STCS; yellow). Box plots indicate the interquartile ranges with vertical lines representing the minimum and maximum values.

Figure 1

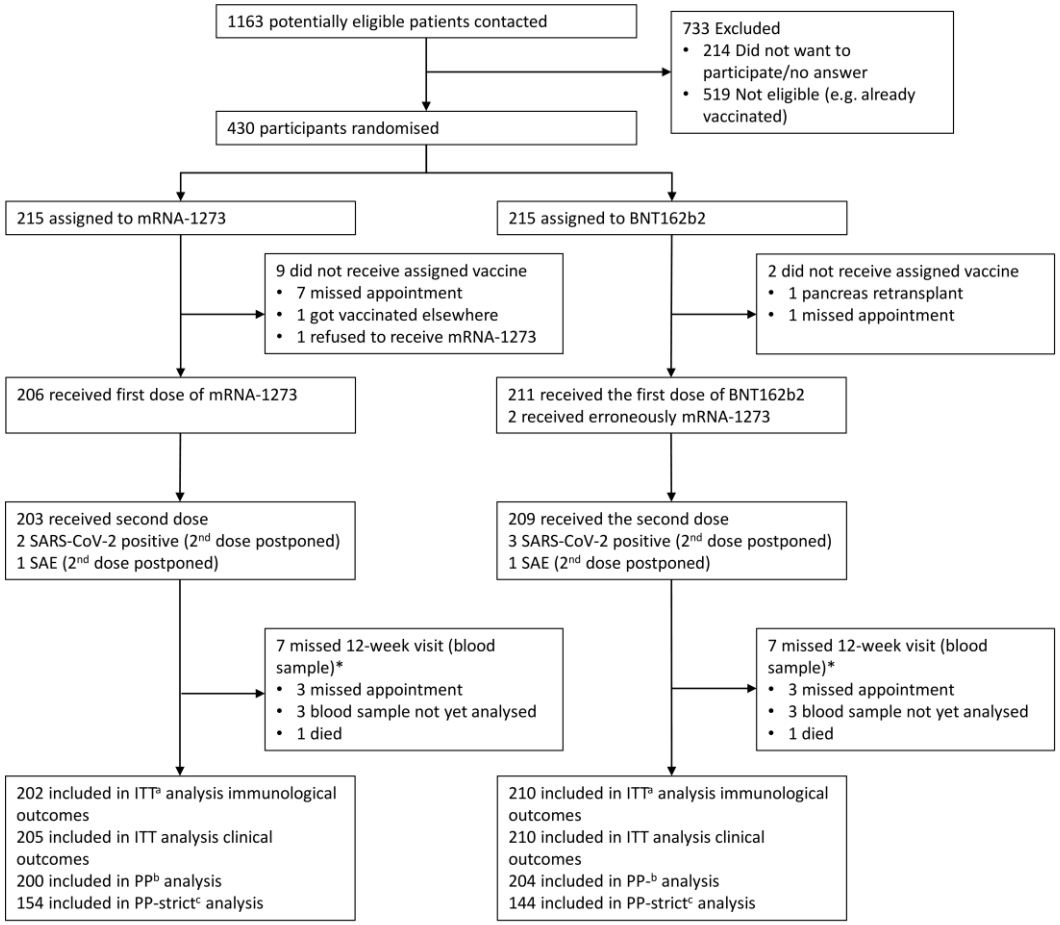

Figure 2