

Antibody Response After Third Vaccination With mRNA-1273 or BNT162b2: Extension of a Randomized Controlled SARS-CoV-2 Noninferiority Vaccine Trial in Patients With Different Levels of Immunosuppression (COVERALL-2)

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Extension of the COVERALL (COrona VaccinE tRiAl pLatform) randomized trial showed noninferiority in antibody response of the third dose of Moderna mRNA-1273 vaccine (95.3% [95% confidence interval {CI}, 91.9%–98.7%]) compared to Pfizer-BioNTech BNT162b2 vaccine (98.1% [95% CI, 95.9%–100.0%]) in individuals with different levels of immunosuppression (difference, –2.8% [95% CI, –6.8% to 1.3%]).

Keywords. SARS-CoV-2; HIV; Organ transplant; Vaccine; randomized trial.

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The COrona VaccinE tRiAl pLatform (COVERALL) [1] is a randomized trial nested into 2 national cohort studies, the Swiss HIV Cohort Study (SHCS) [2] and the Swiss Transplant Cohort Study (STCS) [1, 3]. The first COVERALL study (COVERALL-1) determined the noninferiority of the Moderna mRNA-1273 vaccine to the Pfizer-BioNTech BNT162b2 vaccine in terms of antibody response after basic immunization, with 2 vaccine doses in patients with different levels of immunosuppression [4]. While people with human immunodeficiency virus (PWH) showed adequate antibody response, solid organ transplant (SOT) recipients showed insufficient antibody responses [4] as also shown in other studies [4–6]. A third vaccine dose was recommended for this population in winter 2021/2022 by the Swiss Federal Office of Public Health to ensure basic immunization and to accommodate for genetic drift, prevent the emergence of new variants, and provide prolonged protection of patients [7].

We invited all participants from COVERALL-1 to an extension of the COVERALL study (COVERALL-2) to investigate the noninferiority of antibody response of Moderna mRNA-1273 compared to Pfizer-BioNTech BNT162b2 after the third vaccine dose.

METHODS

The methods are explained in detail in the protocols (master protocol, protocol COVERALL-1, protocol COVERALL-2) and were approved by the ethical committee of Northwestern and Central Switzerland (BASEC [Business Administration System for Ethics Committees] number 2021-000593). These documents are publicly available on the trial registration site (<https://clinicaltrials.gov/ct2/show/NCT04805125>). In short, we included participants from the SHCS and STCS who received a third dose of Moderna vaccine (Spikevax; 50 µg [SHCS] or 100 µg [STCS] of mRNA-1273 in 0.5 mL) or Pfizer-BioNTech vaccine (Comirnaty; 30 µg of BNT162b2 in 0.3 mL) as part of their clinical routine following national recommendations in Switzerland [7]. Only patients who were previously randomized into COVERALL-1 (see [Supplementary Material](#) for detailed inclusion and exclusion criteria and flow-chart) were included. Blood samples (ethylenediaminetetraacetic acid tubes; 2 × 7.5 mL) were collected at baseline (up to 2 weeks prior to the third vaccination) and 8 weeks (±2 weeks) after receiving the third vaccination. Patients were recruited from December 2021 to March 2022.

The primary outcome was the proportion of patients with a positive antibody response to SARS-CoV-2 spike (S1) protein receptor-binding domain (RBD) in human serum or plasma, assessed by the commercial immunoassay Elecsys

Anti-SARS-CoV-2 S from Roche Diagnostics at the follow-up visit 8 weeks after the third vaccination [8]. The primary outcome was binary and was considered positive if a threshold ≥ 100 units/mL was reached. This threshold has been shown to be predictive of 50% protective neutralization [9, 10]. We calculated the difference in antibody response between the 2 vaccines with a 2-sided 95% Wald confidence interval (CI). We chose a noninferiority design, assessing if the vaccines have a similar efficacy (in terms of antibody response) as the storage and handling of Moderna mRNA-1273 was supposed to be easier [1]. As previously described [4], we assumed noninferiority if the lower limit of the 95% 2-sided CI was above -10% in the intention-to-treat (ITT) and the per-protocol (PP) populations. The ITT population included all randomized patients who agreed to participate in the study extension and provided follow-up data at any time point. The PP population was restricted to participants who received the 3 vaccine doses in line with their randomized allocation (ie, 3 doses of Moderna vs 3 doses of Pfizer) and provided follow-up data within the prespecified time at 8 ± 2 weeks after the third vaccine dose. Secondary outcomes (see detailed definition in [Supplementary Material](#)) included (1) using a threshold of ≥ 0.8 units/mL for the primary outcome (Elecsys); (2) the proportion of patients with a positive antibody response using the Antibody CORonavirus Assay (ABCORA) 2 [11]; (3) the proportion of patients with neutralization activity against the vaccine strain Wuhan-Hu-1 in sera, defined as having an ABCORA sum S1 > 17 [11]; (4) mean pan-immunoglobulin antibodies against the RBD in the S1 subunit of the spike protein (pan-immunoglobulin anti-S1-RBD) of SARS-CoV-2; (5) mean immune response of immunoglobulin M (IgM), immunoglobulin A (IgA), and immunoglobulin G (IgG) to the subunit S1 using ABCORA 2; (6) newly polymerase chain reaction (PCR)-confirmed SARS-CoV-2 infection; (7) newly PCR-confirmed asymptomatic SARS-CoV-2 infection; (8) newly PCR-confirmed symptomatic SARS-CoV-2 infection; (9) severe COVID-19 infection; (10) SARS-CoV-2 infection of a household member; (11) local symptoms limiting normal daily activities during the first 7 days after vaccination; (12) symptoms limiting normal daily activities during the first 7 days after vaccination; (13) any symptoms leading to contacting a physician during the first 7 days after vaccination; and (14) serious adverse events (SAEs). All analyses were additionally stratified by cohort (SHCS and STCS; [Supplementary Table S4](#)). Detailed information on statistical analyses are presented in the [Supplementary Material](#).

RESULTS

A total of 312 of 430 (72.6%) participants from the previous COVERALL study agreed to participate in the extension study (154 received Moderna mRNA-1273 and 158 Pfizer-BioNTech

BNT162b2; [Supplementary Figure 1](#)). We included 303 patients (277 SHCS and 26 STCS) in the ITT analysis and 234 patients (228 SHCS and 6 STCS) in the PP analysis. In the ITT dataset, 5 patients who were originally allocated to Moderna mRNA-1273 received Pfizer-BioNTech BNT162b2 and 17 who were originally allocated to Pfizer-BNT162b2 received Moderna mRNA-1273 as a third vaccine.

The majority of the patients were male (234/312 [75.0%]), had a median age of 54 years (interquartile range, 44–60 years), and were PWH (283/312 [90.7%]); [Supplementary Tables 1 and 2](#). PWH generally had CD4 cell counts > 350 cells/ μ L (262/312 [84.0%]) and a suppressed HIV RNA load (269/312 [95.1%]). Baseline characteristics were similar among COVERALL participants enrolled in COVERALL-2 and those who were not participating ([Supplementary Table 1](#)).

For patients randomized to Moderna mRNA-1273, 142 of 149 (95.3% [95% CI, 91.9%–98.7%]) had a sufficient antibody response (ie, Elecsys S test ≥ 100 units/mL) after the third SARS-CoV-2 vaccination. For patients randomized to Pfizer-BioNTech BNT162b, 151 of 154 (98.1% [95% CI, 95.9%–100.0%]) had an adequate antibody response (difference, -2.8% [95% CI, -6.8% to 1.3%]), fulfilling the noninferiority of Moderna mRNA-1273 (based on the ITT dataset; [Table 1](#)). According to the ABCORA 2 test, 143 of 149 (96.0% [95% CI, 92.8%–99.1%]) patients randomized to Moderna mRNA-1273 and 149 of 152 (98.0% [95% CI, 95.8%–100.0%]) randomized to Pfizer-BioNTech BNT162b2 showed a seroconversion (based on the ITT dataset; [Table 1](#)). Mean immunoglobulin values were comparable between groups ([Table 1](#)). Based on the Elecsys S test, 276 of 277 (99.6% [95% CI, 98.9%–100.0%]) PWH showed an adequate antibody response ([Supplementary Table 4](#)), whereas only 17 of 26 (65.4% [95% CI, 47.1%–83.7%]) SOT recipients had antibody levels above the Elecsys S test ≥ 100 units/mL cutoff ([Supplementary Table 4](#)). Further prespecified immunological outcomes are listed in [Table 1](#). The PP results are in line with the ITT analysis ([Supplementary Table 3](#)).

Eight weeks after receiving the third vaccine, 24 of 307 (7.8%) patients reported that they had tested positive for SARS-CoV-2 (mRNA-1273: 14/151 [9.3%]; BNT162b2: 10/156 [6.4%]) ([Table 1](#)). No patients had severe COVID-19 infections leading to hospitalization. Furthermore, 15 of 307 (4.9%) patients reported household members who tested positive for SARS-CoV-2 (mRNA-1273: 7/151 [4.6%]; BNT162b2: 8/156 [5.1%]; [Table 1](#)). After receiving the third vaccine, 31 patients (10.1%) had reported systemic symptoms (13.3%; [20 of 150 patients] after receiving the third dose of Moderna mRNA-1273 and 7.1% [11 of 156 patients] after receiving the Pfizer-BioNTech BNT162b2 vaccine ([Table 1](#)). Two patients had at least 1 SAE, requiring hospitalization for (1) worsening of general condition, fever, and dyspnea and (2) simultaneous viral pulmonary and gastrointestinal infection (both SARS-CoV-2 negative), but no deaths occurred. None of the SAEs were classified as related to vaccines received (see SAE classification and reasons for hospitalization in [Supplementary Table 5](#)).

Table 1. Outcomes Based on the Intention-to-Treat Dataset

Outcomes	mRNA-1273 (Moderna)	BNT162b2 (Pfizer-BioNTech)	Total	Difference
Immune response (Elecys S, cutoff ≥ 100 units/mL)	95.3% (91.9%–98.7%); 142/149	98.1% (95.9%–100.0%); 151/154	96.7% (94.7%–98.7%); 293/303	–2.8% (–6.8% to 1.3%)
Immune response (Elecys S, cutoff ≥ 0.8 units/mL)	96.6% (93.8%–99.5%); 144/149	98.7% (96.9%–100.0%); 152/154	97.7% (96.0%–99.4%); 296/303	–2.1% (–5.5% to 1.3%)
Immune response (ABCORA 2) [11]	96.0% (92.8%–99.1%); 143/149	98.0% (95.8%–100.0%); 149/152	97.0% (95.1%–98.9%); 292/301	–2.1% (–5.9% to 1.8%)
Neutralization (ABCORA 2) [11], cutoff 17	92.6% (88.4%–96.8%); 138/149	96.7% (93.9%–99.6%); 147/152	94.7% (92.2%–97.2%); 285/301	–4.1% (–9.2% to 1.0%)
Immunoglobulins, mean (95% CI)				
IgG RBD	208.4 (195.7–221.1)	202.4 (192.9–212.0)	205.5 (197.5–213.5)	...
IgG S1	230.5 (214.7–246.3)	220.2 (207.2–233.1)	225.5 (215.2–235.7)	...
IgA S1	5.3 (4.8–5.8)	5.765 (5.4–6.3)	5.5 (5.2–5.9)	...
IgM S1	0.2 (.1–.2)	0.2 (.1–.3)	0.2 (.1–.2)	...
Clinical outcomes ^a				
Confirmed SARS-CoV-2 infection	9.3% (4.6%–13.9%); 14/151	6.4% (2.6%–10.3%); 10/156	7.8% (4.8%–10.8%); 24/307	...
Asymptomatic SARS-CoV-2 infection	0.7% (0.0–2.0%); 1/151	0.6% (0.0–1.9%); 1/156	0.7% (0.0–1.6%); 2/307	...
Symptomatic SARS-CoV-2 infection	8.6% (4.1%–13.1%); 13/151	5.8% (2.1%–9.4%); 9/156	7.2% (4.3%–10.1%); 22/307	...
Severe COVID-19 infection ^b	0.0% (0.0–0.0); 0/151	0.0% (0.0–0.0); 0/156	0.0% (0.0–0.0); 0/307	...
Confirmed SARS-CoV-2 infection of household members	4.6% (1.3%–8.0%); 7/151	5.1% (1.7%–8.6%); 8/156	4.9% (2.5%–7.3%); 15/307	...
Serious adverse events	0.7% (0.0–2.0%); 1/151	0.6% (0.0–1.9%); 1/156	0.7% (0.0–1.6%); 2/307	...
Death	0.0% (0.0–0.0); 0/151	0.0% (0.0–0.0); 0/156	0.0% (0.0–0.0); 0/307	...
Safety outcomes ^c				
Any symptoms at injection site limiting continuation of normal daily activities during the first 7 d following third vaccination	7.3% (3.2%–11.5%); 11/150	5.8% (2.1%–9.4%); 9/156	6.5% (3.8%–9.3%); 20/306	...
Any systemic symptoms (e.g. fever, muscle pain, joint pain) limiting continuation of normal daily activities during the first 7 d following third vaccination	13.3% (7.9%–18.8%); 20/150	7.1% (3.0%–11.7%); 11/156	10.1% (6.7%–13.5%); 31/306	...
Any vaccine-related symptoms leading to consultation 7 d following third vaccination	1.3% (0.0–3.2%); 2/150	0.0% (0.0–0.0); 0/156	0.7% (0.0–1.6%); 2/306	...

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; RBD, receptor-binding domain; S1, S1 subunit of the spike protein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

^aClinical outcomes: 5 missing.

^bSafety outcomes: 9 missing.

^cSymptoms leading to hospitalization.

DISCUSSION

In this extension of the randomized COVERALL study, we confirmed noninferiority of the Moderna mRNA-1273 vaccine to the Pfizer-BioNTech BNT162b2 vaccine in patients with different levels

of immunosuppression, as assessed by the antibody response 8 weeks after receiving a third vaccine dose. Whereas almost all PWH showed an adequate antibody response, this response was still insufficient for 35% of SOT recipients.

Our results are in line with the findings from our previous study where almost all PWH had an adequate antibody response after 2 SARS-CoV-2 vaccinations [4]. It should be noted that the vast majority of PWH in our population had high CD4 cell counts (>350 cells/ μ L) and had a suppressed HIV RNA load (<50 copies/mL; [Supplementary Table 2](#)). For SOT recipients we noticed an improvement in the proportion of patients with antibody response, from 23.9% (17/71) in the first sub-study (COVERALL-1) to 65.4% (17/26) in this extension (COVERALL-2). Due to the small number of participating SOT recipients (ie, only 26 in the ITT and 6 in the PP analysis), these findings need to be interpreted with caution.

The number of SARS-CoV-2 infections increased compared to the previous COVERALL-1 study [4], which is likely due to the emergence of new variants with higher transmissibility, such as Omicron [12]. Continued protection will require new or adapted vaccines such as the bivalent vaccines currently being approved or in the process of approval by Moderna and Pfizer-BioNTech, respectively [12].

Our extension study has the following limitations: First, many SOT recipients were vaccinated with a third dose before national guidelines recommended the third dose for the entire population and before this study could be initiated. Consequently, many SOT recipients who were randomized into COVERALL-1 could not be included in the COVERALL-2 extension study. Second, the event rates for the clinically relevant outcomes were strongly dependent on the progression of the pandemic, which was hard to predict. Hence, we chose a serological primary outcome (ie, antibody response). These 2 limitations also highlight the difficulties of conducting clinical trials in a pandemic setting. Third, since the vaccines were applied during clinical routine and not in the frame of the study, we had several participants who switched the vaccine product after the second vaccination (22/303 [6.7%]; [Supplementary Figure 1](#)). Nevertheless, ITT results are consistent with PP analyses.

In conclusion, the antibody response of Moderna mRNA-1273 compared to Pfizer-BioNTech BNT162b2 after third vaccination was noninferior in patients with different levels of immunosuppression. Additional strategies (eg, new vaccines, monoclonal antibodies) need to be investigated for nonresponders such as SOT recipients.

Supplementary Data

[Supplementary materials](#) are available at *Open Forum 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

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Author contributions. H. C. B., B. S., F. C., H. F. G., A. R., M. T. K., I. A. A., M. B., and K. K. designed the study. K. K. was responsible for managing the data platform. F. C. conducted the statistical analyses and was responsible for monitoring. B. S., A. G., C. M. S., A. T. H., A. Am., and M. B. coordinated the study. H. C. B., P. A., M. P. S., A. L. E., B. H., D. L. B., M. M. S., T. F. M., M. T., A. R., H. F. G., M. T., and N. J. M. were responsible for patient recruitment and follow-up at local centers. I. A. A., A. T., S. E., and A. Au. conducted all laboratory analyses. A. G., B. S., M. B., F. C., A. Am., and C. M. S. interpreted the data, A. G. and B. S. wrote the first draft of the manuscript; all authors read and approved the final version of the manuscript.

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Patient consent. Written informed consent was obtained from all participants. The study conforms to local and international standards (International Conference on Harmonisation Good Clinical Practice).

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revision to the manuscript; however, no changes were proposed by Moderna.

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