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MAJOR ARTICLE

Antibody and T-cell response to bivalent booster SARS-cov-2 vaccines in people with compromised immune function (COVERALL-3)

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Background: Bivalent mRNA vaccines, designed to combat emerging SARS-CoV-2 variants, incorporate ancestral strains and a new variant. Our study assessed the immune response in previously vaccinated individuals of the Swiss HIV Cohort Study (SHCS) and the Swiss Transplant Cohort Study (STCS) following bivalent mRNA vaccination.

Methods: Eligible SHCS and STCS participants received approved bivalent mRNA SARS-CoV-2 vaccines (mRNA-1273.214 or BA.1–adapted BNT162b2) within clinical routine. Blood samples were collected at baseline, 4 weeks, 8 weeks, and 6 months post vaccination. We analyzed the proportion of participants with anti-spike protein antibody response≥1642 units/ml (indicating protection against SARS-CoV-2 infection), and in a subsample T-cell response (including mean concentrations), stratifying results by cohorts and population characteristics.

Results: In SHCS participants, baseline anti-spike antibody concentrations ≥1642 were observed in 87% (96/112), reaching nearly 100% at follow-ups. Among STCS participants, 58% (35/60) had baseline antibodies ≥1642, increasing to 80% at 6 months. Except for lung transplant recipients, all participants showed a five-fold increase in geometric mean antibody concentrations at 4 weeks and a reduction by half at 6 months. At baseline, T-cell responses were positive in 96% (26/27) of SHCS participants and 36% (16/45) of STCS participants (moderate increase to 53% at 6 months). Few participants reported SARS-CoV-2 infections, side-effects, or serious adverse events.

Conclusions: Bivalent mRNA vaccination elicited a robust humoral response in individuals with HIV or solid organ transplants, with delayed responses in lung transplant recipients. Despite a waning effect, antibody levels remained high at 6 months and adverse events were rare.

Keywords: SARS-CoV-2; COVID-19; HIV; Organ transplant; Vaccine; SARS-CoV-2 vaccine; bivalent vaccine

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) vaccines have substantially altered the course of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic by preventing an estimated 20 million deaths within the first year of vaccination programs (1). According to the World Health Organization (WHO), over 13 billion vaccine doses have been administered worldwide (2). In the European Union and the United States of America the by far most commonly used COVID-19 vaccines are the mRNA vaccines BNT162b2 (Comirnaty) produced by Pfizer-BioNTech (~1 billion doses) and mRNA-1273 (Spikevax) produced by Moderna (~400 million doses) (3, 4). Both vaccines were tested in large randomized clinical trials among the general population where they have proven to be safe and effective in terms of preventing COVID-19 infections (5, 6).

Evidence on the immune response to SARS-CoV-2 vaccines among people with compromised immune function is of crucial importance for these frail patient populations, that were underrepresented or excluded from these vaccines licensing trials (5, 6). For these reasons, we have established the Corona VaccinE tRiAL pLatform (COVERALL) (7, 8), nested into the Swiss HIV Cohort Study (SHCS) (9) and the Swiss Transplant Cohort Study (STCS) (10) to investigate immune response and vaccine safety in immunocompromised hosts. COVERALL-1, a randomized trial, found comparable antibody responses after basic immunization with mRNA-1273 by Moderna and BNT162b2 by Pfizer-BioNTech, with solid organ transplant (SOT) recipients exhibiting lower responses than people with HIV (PWH) (11). COVERALL-2, an observational extension study, revealed similar outcomes for booster vaccines (mRNA-1273 vs BNT162b2), showing a substantial increase in antibody response among SOT recipients compared to basic immunization (12, 13). Moreover, lower CD4 cell counts and ongoing HIV-1 replication in PWH were associated with diminished immune responses (14).

With the rapid decrease in COVID-19 vaccine effectiveness against emerging variants (15-21), bivalent vaccines incorporating Omicron BA.1 spike mRNA alongside the original wildtype mRNA (mRNA-1273.214 by Moderna and BA.1–adapted BNT162b2 by Pfizer-BioNTech) were approved by Swiss authorities in August and October 2022 (22, 23). In response, the Swiss Federal Office of Public Health recommended these bivalent vaccines for the adult population, prioritizing high-risk individuals and health professionals (24). Consequently, we conducted COVERALL-3 to evaluate the safety and immune response, including T-cell response, of these bivalent SARS-CoV-2 vaccines over six months in previously vaccinated individuals from the SHCS and the STCS, who exhibited varying levels of immunosuppression.

METHODS

Study design

COVERALL-3 was a prospective, longitudinal, multicentric observational study. The study was approved by the ethics committee Nordwest- and Zentralschweiz, Switzerland (BASEC Nr. 2022-01760). The COVERALL platform was registered (https://clinicaltrials.gov/ct2/show/NCT04805125; registration 18. March 2021) and the full protocols for all COVERALL studies are available in the trial registry. Study data were collected using the REDCap electronic data capture database which was set up for the COVERALL-platform (8), including risk-based centralized data monitoring throughout the study.

Participants

During routine cohort study visits, study participants were recruited by treating physicians at the University Hospital Basel, Zurich, Bern and, Lausanne. Targeting individuals with varying levels of immunosuppression, we aimed to enroll participants of the following groups: (i) PWH with

CD4 cell counts <350 cells/µl; (ii) PWH with CD4 cell counts ≥350 cells/µl; (iii) lung transplant recipients; and (iv) kidney transplant recipients. SHCS and STCS participants were eligible for COVERALL-3 if they received the bivalent vaccines (mRNA-1273.214 or BA.1–adapted BNT162b2) according to local clinical guidelines as part of routine care, i.e., with a minimum of two previous shots of either mRNA-1273 or BNT162b2. Of note, previous participation in COVERALL-1 and COVERALL-2 was not required (detailed eligibility criteria in Appendix 1).

Data and blood sample collection

Data collection commenced in October 2022 with the clinical routine rollout of both vaccines. Whole blood samples (3 ml ethylenediamine tetraacetic acid [EDTA]) were obtained at baseline (up to 2 weeks before bivalent vaccination) and follow-up visits at 4 weeks (±1 week), 8 weeks (±2 weeks) and 6 months (±4 weeks). A sub-sample of participants provided an additional 8 ml heparinized blood at baseline, 4 weeks, and 6 months for anti-spike T-cell response measurement. Samples for the T-cell sub-study were collected at the University Hospitals Basel and Zurich and were sent via courier within 6 hours at room temperature to the main laboratory in Zurich (Institute of Medical Virology). At baseline, study staff collected history of SARS-CoV-2 vaccination, seasonal flu vaccination, and treatment with SARS-CoV-2 specific monoclonal antibodies. Furthermore, anti-SARS-CoV-2 nucleocapsid (N) antibodies were assessed and all sociodemographic and clinical data (age, sex, history of cardiovascular or metabolic disease, CD4 T-cell counts, HIV viral load, and immunosuppressive therapy) were directly retrieved from the cohort databases. Clinical outcomes and serious adverse events were assessed at follow-up visits, with data on vaccine-specific side effects collected 4 weeks post vaccination.

Laboratory measurements

Pan-Ig antibody response against the SARS-CoV-2 spike (S1) protein receptor binding domain was measured using the Elecsys Anti-SARS-CoV-2 S assay (Roche Diagnostics, Rotkreuz, Switzerland) at two different laboratories. The main laboratory in Zurich used 1:50 dilutions by default and further dilutions for samples with values above the measuring range until exact values were obtained. The second laboratory site at the University Hospital Basel conducted default repeat measurements of ≤1:10 diluted samples. Pan-Ig antibody response against the SARS-CoV-2 nucleocapsid (N) antigen was assessed with the Elecsys Anti-SARS-CoV-2 assay. Spike protein-specific T-cell response was determined by the Quan-T-Cell SARS-CoV-2 interferon (IFN)-γ release assay from EUROIMMUN (Medizinische Labordiagnostica, Lübeck, Germany) (25). The kit included stimulation tubes for no T-cell stimulation (BLANK), specific T-cell stimulation (S1-based antigens; TUBE) and unspecific T-cell stimulation (STIM). Data were analyzed based on manufacturer-defined criteria for negative (BLANK) and positive (STIM) controls, with samples having non-valid controls labelled as "non evaluable”.

Outcomes

We defined several immunological outcomes: the proportion of participants with an anti-spike protein (pan-Ig) antibody response of (a) ≥1642 units/ml (b) ≥100 units/ml, (c) ≥0.8 units/ml, at 4 weeks, 8 weeks, and 6 months. Additionally, we assessed (d) geometric mean concentrations of the anti-spike protein (pan-Ig) antibody response at these time points. Geometric mean concentrations were calculated as the anti-logs of the means and address anticipated right-skewness of the data. A value of ≥0.8 units/ml was considered a positive response according to the manufacturer's instructions. The cut-off of 100 units/ml was chosen to allow a comparison with previous COVERALL studies (11, 12), and the cut-off of 1642 units/ml was used as a surrogate marker to predict protection against SARS-CoV-2 infection with Omicron strains based on Chen et al. (26). Of note, 1689 binding antibody units (BAU)/ml as described as a protective concentration by Chen et al. are equal to 1642 units/ml using the WHO standardization formula (1 unit/ml=0.972×BAU/ml) based on the Elecsys Anti-SARS-CoV-2 S assay (26).

For the T-cell sub-sample, we determined spike protein-specific T-cell responses using IFN-γ concentrations according to the manufacturer's instructions (positive: >200 mIU/ml, borderline: 100-200 mIU/ml, negative: <100 mIU/ml) (25). Additionally, we quantitatively assessed the response on an IFN-γ concentration scale.

Clinical outcomes were the proportion of patients who reported a PCR or antigen test-confirmed (a) asymptomatic and (b) symptomatic SARS-CoV-2 infection, as well as (c) severe COVID-19 requiring hospitalization or resulting in death.

Safety outcomes encompassed: (a) any local symptom (such as redness or swelling, or prolonged pain at injection site) impeding normal daily activities; (b) any systemic symptom (e.g., fever, generalised muscle or joint pain) impeding normal daily activities; and (c) any vaccine-related symptom prompting contact with a physician within the initial 7 days post vaccination.

Data analysis

All conducted analyses were of exploratory nature, without *a priori* power calculation. In the primary analysis set, all patients were included regardless of the time window. As a sensitivity analysis, we only included patients with results available within the pre-specified time window ("strict time window"; i.e., baseline sample maximum up to 2 weeks before vaccination, 4 weeks after vaccination ±1 week, 8 weeks ±2 weeks, and 6 months ±4 weeks).

Descriptive statistics were used to present immunological and safety outcomes (i.e. frequencies, percentages and 95% confidence intervals [CI]).

For the geometric mean concentration of antibody response, we excluded samples analyzed at the University Hospital of Basel due to absence of reruns for antibody concentrations >2500 units/ml. Results are presented stratified by cohort study (SHCS vs STCS), population of interest (SHCS participants with CD4 below vs above 350 cells/µl; STCS participants receiving a kidney vs lung transplant) and prior immune response status (participants with any evidence of immunization [positive nucleocapsid antibodies or SARS-CoV-2 vaccination in the past 6 months] vs participants with no evidence of prior immunization) and not by vaccine type, given significant baseline characteristics differences. All data processing, graphing, and statistical analyses were performed using R Project for Statistical Computing (version 4.1.3) (27).

RESULTS

Baseline characteristics of participants

Between October 2022 and January 2023, 174 participants were enrolled (112 SHCS; 62 STCS) with 58% (101/174) receiving mRNA-1273.214 and 42% (73/174) receiving BA.1–adapted BNT162b2 vaccines (Table 1). The majority of participants were male (78.7% overall, 64.5% in STCS and 86.6% in SHCS, Table 1). The overall median age was 56 years (interquartile range [IQR] 45-64), with 59 years (IQR 47-65) in the STCS and 55 years (IQR 44-63) in the SHCS (Table 1). Among SHCS participants, 82% (92/112) had CD4 cell counts of 350 cells/µl or above, with the majority (93.8%; 105/112) having a suppressed viral load (i.e. <50 copies/ml). One-third of the STCS participants were kidney transplant recipients (35%; 22/62), while two-thirds received a lung transplant (65%; 40/62). Considering all participants, at baseline 59% (102/174) had a reactive antibody test to the nucleocapsid protein suggesting a previous SARS-CoV-2 infection (44% [27/62] among STCS and 67% [75/112] among SHCS participants). Most participants had received three (87%; 151/174) or four (10%; 17/174) doses of the respective monovalent vaccines before receiving the bivalent vaccine dose and only 4% (7/174) have received a SARS-CoV-2 vaccine in the 6 months prior receiving the bivalent vaccine. None of the SHCS participants had received SARS-CoV-2 specific monoclonal antibodies within the 6 months prior to vaccination. From the STCS, three kidney transplant (14%; 3/22) and one lung transplant recipients (3%; 1/40) had received SARS-CoV-2 specific monoclonal antibodies (all sotrovimab). Most STCS participants were receiving intensive immunosuppressive therapy, defined as more than two regimens (87%; 54/62), whereas only 13% (8/62) were taking a less intense regimen (Table 1).

Baseline stratification by vaccine type revealed notable differences (Table S1). Specifically, 65% (40/62) of STCS participants received the mRNA-1273.214 vaccine, while only 54% (61/112) of SHCS participants did so. Of the 40 STCS participants receiving mRNA-1273.214 vaccine, 73% (29/40) were lung transplant recipients compared to 50% (11/22) in the BA.1–adapted BNT162b2 group. Further baseline characteristics of participants stratified by vaccine type and cohort study are presented in supplementary Table S2.

Antibody status and response

At baseline, 87% (96/112) of SHCS participants had anti-spike antibody concentrations ≥1642 units/ml, increasing to 97% (95% CI: 94-100%; 103/106) at 4 weeks, 98% (95% CI: 95-100%; 99/101) at 8 weeks, and 96% (95% CI: 92-100%; 96/100) at 6 months (Table 2). Among STCS participants, 58% (35/60) had anti-spike antibody concentrations ≥1642 units/ml at baseline, reaching 75% (95% CI: 64-87%; 43/57) at 4 weeks, 74% (95% CI: 63-85%; 43/58) at 8 weeks, and 80% (95 % CI: 70-91%; 45/56) at 6 months (Table 2).

All groups except for lung transplant recipients exhibited a 5-fold increase in geometric mean antibody concentrations at 4 weeks (i.e. SHCS participants with CD4 <350 cells/µl: baseline 4,398 [IQR 1,406-13,764]; 4 weeks 32,342 [IQR 12,638-82,766]; SHCS participants with CD4 ≥350 cells/µl: baseline 8,992 [IQR 6,899-11,721]; 4 weeks 53,461 [IQR 44,474-62,264]; kidney transplant recipients: baseline 5,102 [IQR 1,819-14,310], 4 weeks 23,956 [IQR 8,098-70,872]; lung transplant recipients: baseline 1,226 [95% CI: 491-3,061], 4 weeks 3,108 [95% CI: 1,137-8,499]; Table 2 and Figure 1). At 6 months, geometric mean antibody concentrations decreased to 12,426 (IQR 5,846-26,412) for SHCS participants with CD4 <350 cells/µl, to 18,088 (IQR 14,577-22,446) in SHCS participants with CD4 ≥350 cells/µl, to 12,899 (IQR 4,535-36,695) in kidney transplant recipients and increased to 5,722 (IQR 3,142-10,421) for lung transplant recipients (Table 2 and Figure 1). For other cut-offs (≥100 units/ml and ≥0.8 units/ml), nearly all participants had reached these levels already at baseline (Table 2). The sensitivity analysis using the strict time window yielded similar findings (Table S3).

The response dynamic in terms of anti-spike antibody concentration ≥1642 units/ml was similar among SHCS participants receiving the mRNA-1273.214 (87% at baseline; 96% at 4 weeks, 8 weeks, and at 6 months) and those receiving the BA.1–adapted BNT162b2 (86% at baseline; 98% [95% CI: 94-100%] at 4 weeks; 100% at 8 weeks; and 96% [95% CI: 90-100] at 6 months; Table S4). A higher proportion of STCS participants vaccinated with BA.1–adapted BNT162b2 had antibody concentrations of ≥1642 units/ml already at baseline (75%) compared to those vaccinated with mRNA-1273.214 (53%) (Table S5). Subsequently, across both vaccine groups, 15% more participants had an anti-spike antibody response of ≥1642 units/ml at 4 weeks (BA.1–adapted BNT162b2: 89% [95% CI: 76-100%]; mRNA-1273.214: 68% [95% CI: 54-83%]) and remained similarly high at 6 months (BA.1–adapted BNT162b2: 95% [95% CI: 85-100%]; mRNA-1273.214: 72% [95% CI: 58-87%]) (Table S5). Further stratification showed that baseline antibodies were higher amongst individuals with evidence of prior immunization, but subsequent response dynamic was similar across both groups (Table S6). Details about the 17 cases who did not mount a sufficient humoral immune response at 8 weeks are provided in Table S7.

T-cell status and response

From 81 of the 174 participants, T-cell response was assessed after vaccination with mRNA-1273.214 (n=54) or BA.1–adapted BNT162b2 (n=27; see baseline characteristics in Table S8).

Among SHCS participants, all had evaluable results, with 96% (26/27) having a positive status and one (4%; 1/27) having a borderline status at baseline. The geometric mean concentration increased for both SHCS groups at 4 weeks (i.e., CD4 <350: baseline 1,193 [IQR 448-3,179]; 4 weeks 1,500 [IQR 664-3,386]; CD4 ≥350: baseline 2,202 [IQR 1,234-3,931]; 4 weeks 4,189 [IQR 2,671-6,571]) and decreased at 6 months (CD4 <350: 507 [IQR 218-1,180]; CD4 ≥350: 1,939 [IQR 1,123-3,347]; Table 3 and Figure 2).

Among STCS participants, 36% (16/45) had a positive status at baseline and 40% (18/45) were not evaluable due to a non-valid control (primarily in lung transplant recipients; 50% [17/34] not evaluable; Table 3). The proportion with a positive reaction remained relatively low at 4 weeks (40%; 17/43) and at 6 months (53%; 20/38) after vaccination. On a quantitative scale, geometric mean concentrations were low at baseline (kidney recipients: 247 [IQR 86-710]; lung recipients: 45 [IQR 3-674]). After vaccination, they remained low at 4 weeks (kidney recipients: 221 [IQR 74-659]; lung recipients: 28 [IQR 1-642]) and 6 months (kidney recipients: 368 [IQR 118-1,152]; lung recipients: 185 [IQR 36-962]; Table 3, Figure 2). The proportion of not evaluable samples among SOT recipients was 35% at 4 weeks and 24% at 6 months. The analyses using the strict time window and stratified by evidence of previous immunization are presented in Table S9, and S10, showing similar response results.

Clinical outcomes

Until 6 months of follow-up, eight symptomatic antigen- or PCR-confirmed SARS-CoV-2 infections occurred (Table 4). Among the 8 infected participants, one was from the SHCS and seven from the STCS (1 kidney transplant recipient, 6 lung transplant recipients), seven had anti-spike antibody concentrations ≥1642 units/ml and three a reactive T-cell test at the study visit before acquiring a SARS-CoV-2 infection. Details about the 8 clinical cases are provided in Table S11. No severe COVID-19 cases (requiring hospitalization or leading to death) occurred. Four serious adverse events were reported, including one death in an SHCS participants due to cancer, and three STCS participants hospitalized for infectious diseases, all not related to COVID-19. The local investigator judged that all four serious adverse events were not related to the vaccination. Systemic and local symptoms limiting daily activities occurred infrequently (7-8% with mRNA-1273.214 and 4-8% with BA.1–adapted BNT162b2; Table 4).

DISCUSSION

This study examined the antibody and T-cell response to bivalent SARS-CoV-2 vaccines (Moderna's mRNA-1273.214 or Pfizer-BioNTech's BA.1–adapted BNT162b2) in PWH and SOT recipients who had received at least two prior SARS-CoV-2 vaccine doses. Both bivalent vaccines increased the proportion of individuals achieving a humoral immune response of ≥1642 units/ml, suggesting protection from COVID-19, and at six months a waning effect was observed. However, lung transplant recipients showed a delayed and lower humoral response throughout. T-cell-mediated immune response among SHCS participants remained consistently high, while STCS participants showed low baseline activity, and only a minor increase at 6 months. Seven out of eight breakthrough infections were observed among SOT recipients (5 lung and 2 kidney recipients), however, not a single case of severe COVID-19 disease, requiring hospitalization or leading to death, was observed. During the study period SARS-CoV-2 infections, side-effects, and serious events were rare. In immunocompetent individuals, the bivalent mRNA vaccines have demonstrated high immunogenicity against Omicron and Omicron sublineages (28), including effectiveness on clinical outcomes (20, 29). However, limited data exist among immunocompromised individuals receiving these bivalent vaccines.

Similar to our findings, an observational cohort study on 48 PWH revealed a significant humoral response increase post-bivalent mRNA vaccination, irrespective of CD4 cell count, while T-cell-mediated response remained unchanged (30). This aligns with previous research indicating a robust T-cell response in PWH after two doses of SARS-CoV-2 vaccines, which remained stable after the third dose (31). Earlier studies in the same setting (i.e. COVERALL 1 and 2), also demonstrated solid immune response in PWH after basic immunization (11) and after a third vaccine dose (13).

SOT recipients are a critical population in terms of vaccine-induced immune response (32). Unlike in PWH, 9% of kidney transplant recipients and 50% of lung transplant recipients had a non-evaluable T-cell response and among the evaluable ones, only a minor increase in T-cell response was observed, most likely due to the concurrent intense immunosuppressive therapy as shown in previous mRNA vaccine studies (33-35). A study among kidney transplant recipients concluded that a better antibody response after receiving the bivalent vaccine was associated with a lower drug-related immunosuppression (36).

A recent study explored cell-mediated responses against the BA.4/BA.5 spike receptor-binding domain at baseline and 2 weeks after the mRNA-based bivalent vaccination among 30 kidney or liver transplant recipients and compared the immune responses against a healthy control group (37). In contrast to our results, kidney transplant recipients had a significant increase in T-cell activity already at 2 weeks. A recent meta-analysis summarized the humoral immune response rates among SOT recipients, showing increased immunogenicity with booster vaccinations and weakest response among lung transplant recipients, in line with our findings (37). Ninety-five percent of the lung transplant recipients in our study were taking a 3- or 4-drug intense immunosuppressive therapy versus 73% of the kidney transplant recipient participants. None of the included studies in the meta-analysis evaluated any bivalent vaccine. We are not aware of further evidence about immune response elicited by the mRNA-based bivalent vaccines in SOT nor PWH. However, several studies have assessed the immunogenicity of the bivalent mRNA vaccines among immunocompetent but frail populations such as nursing home residents, all showing a markedly increased humoral and cellular response post-vaccination (38-40).

Previous studies observed significant differences in vaccine-induced immune response between different non-bivalent mRNA SARS-CoV-2 vaccines (32, 41). Our study, while not designed for statistical power in comparing immune responses between the two bivalent vaccines, did not indicate any clear differences from descriptive analyses. Of note, such differences were often attributed to the varying concentration of mRNA in previous vaccines (e.g., the mRNA-1273 vaccine had 3-fold greater concentration than the BNT162b2 vaccine (32)).

Prior immunization has been shown to elicit an even stronger immune response across SARS-CoV-2 vaccine studies (30, 42, 43). Nearly 60% of our participants had a positive nucleocapsid antibody test at baseline, suggestive of previous infection and 4% additionally received a recent vaccination (within 6 months prior to baseline). Participants with evidence of prior immunization had higher baseline immune response, without marked differences in the immune response dynamic in the follow-up (Table S6 and Table S10).Our study has several limitations. First, we acknowledge that interpreting the anti-spike antibody level cut-off of 1642 units/ml requires caution. While at the beginning of the COVID-19 pandemic antibody responses were more straightforward to interpret, the emergence of several variants as well as repeated exposure to the virus have made the interpretation more difficult (44, 45). Second, we do not have information on neutralizing antibodies for the new variants nor data systematically collected on prior COVID-19 episodes except nucleocapsid antibodies as a proxy. Last, for the geometric mean concentration of the humoral response, we excluded all patients from the University Hospital Basel site (n= 32) due to variations in the local laboratory protocol for diluting high values compared to other laboratories.

In conclusion, this is the largest study on immune response in PWH and SOT recipients after receiving an mRNA-based bivalent COVID-19 vaccine. Despite a waning effect, antibody levels remained high at six months. SOT recipients, particularly lung transplant recipients, showed lower and delayed immune responses. Further research is required to understand the clinical implications of these immune response patterns.

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Authors' contribution: AAm, FC, AAu, AG, NDL, HCB, HFG, IAA, MB, and BS designed the study. KK developed the database structure and link between the SHCS and COVERALL study. FC conducted the statistical analyses. AAm, FC, CMS, and BS were responsible for monitoring. AAm, and BS coordinated the study. ALE, DLB, PA, MPS, BH, MPO, OM, CB, MMS, RH, DD, MT, NJM, AR, HFG, were responsible for patient recruitment and follow-up at local centres. KK, MTK, RK and IAA managed the data matching with the cohort studies. AAu conducted all laboratory analyses. AAm, FC, AAu, AG, IAA, MB, and BS interpreted the data. AAm and BS wrote the first draft of the manuscript. All authors read and approved the final version of the manuscript.

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Table 1: Baseline characteristics of participants before receiving a bivalent mRNA SARS-CoV-2 vaccine

Bivalent mRNA SARS-CoV-2							
mRNA-1273.214 vaccine by	6 (30.0%)	55	61	11	29	40	101
BA.1-adapted BNT162b2 vaccine	14	37	51	11	11	22	73
Median age (IQR)	57 (44-	55 (44-	55 (44-63)	61 (48-	57 (48-64)	59 (47-	56 (45-64)
Sex							
Male	19	78	97	17	23	40	137/174
Female	1 (5.0%)	14	15	5 (22.7%)	17	22	37/174
Antibody test to the							
Non-reactive	6 (30.0%)	30	36	12	21	33	69/174
Reactive	14	61	75	10	17	27	102/174
Missing	0	1 (1.1%)	1 (0.9%)	0	2 (5.0%)	2 (3.2%)	3/174
History of cardiovascular disease	8 (40.0%)	31	39	22	34	56	95/174
Previous Sars-CoV-2 vaccine in	1 (5.0%)	0 (0.0%)	1 (0.9%)	2 (9.1%)	4 (10.0%)	6 (9.7%)	7/174
Number of previously received							
2	0 (0.0%)	2 (2.2%)	2 (1.8%)	2 (9.1%)	1 (2.5%)	3 (4.8%)	5/174
3	18	89	107	18	26	44	151/174
4	2 (10.0%)	1 (1.1%)	3 (2.7%)	2 (9.1%)	12	14	17/174
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)	1 (1.6%)	1/174
Seasonal flu vaccine (2022/2023)	9 (45.0%)	60	69	15	25	40	109/174
Suppressed HIV viral load[a,b]	18	87	105	-	-	-	105/112
Current Immunosuppressive							
Less intense (≤2 drug regimen)[d]	-	-	-	6 (27.3%)	2 (5.0%)	8	8/62
Intense (3 or 4 drug regimen)[d]	-	-	-	16	38	54	54/62
Median days since transplant	-	-	-	671 (245-	1,219	859	859 (462-
SARS-CoV-2 specific monoclonal antibodies received within the	0	0	0	3 (13.6%)	1 (2.5%)	4 (6.5%)	4/174 (2.3%)

[a] Only considering participants from the Swiss HIV Cohort Study

[b] Suppressed HIV viral load defined as <50 copies/ml

[c] Only considering participants from the Swiss Transplant Cohort Study

[d] Intense treatment defined as triple or quadruple immunosuppressive regimen vs. less intense immunosuppressive therapy defined as dual immunosuppressive regimen

Abbreviations: IQR=Interquartile range

Table 2: Antibody status before and after vaccination with bivalent mRNA SARS-CoV-2 vaccines in participants with different levels of immunosuppression, measured with the Elecsys Anti-SARS-CoV-2 S assay from Roche

Baseline						
Antibody response (cut-	75% (15/20)	89% (81/91)	87% (96/111)	77% (17/22)	47% (18/38)	58% (35/60)
Antibody response (cut-	90% (18/20)	100% (91/91)	98%	100%	84% (32/38)	90% (54/60)
Antibody response (cut-	100% (20/20)	100% (91/91)	100%	100%	92% (35/38)	95% (57/60)

Geometric mean	4,398 (1,406-	8,992 (6,899-	7,955 (5,965-	5,102 (1,819-	1,226 (491-	1,865 (907-
4 weeks follow-up						
Antibody response (cut-	85% (69-	100% (NA)	97% (94-	95% (86-	64% (49-	75% (64-
Antibody response (cut-	95% (85-	100% (NA)	99% (97-	100% (NA)	83% (71-	89% (82-
Antibody response (cut-	100% (NA)	100% (NA)	100% (NA)	100% (NA)	92% (83-	95% (89-
Geometric mean	32,342	53,461	48,837	23,956	3,108	5,772
8 weeks follow-up						
Antibody response (cut-	94% (84-	99% (96-	98% (95-	95% (87-	61% (45-	74% (63-
Antibody response (cut-	100% (NA)	100% (NA)	100% (NA)	100% (NA)	89% (79-	93% (87-
Antibody response (cut-	100% (NA)	100% (NA)	100% (NA)	100% (NA)	92% (83-	95% (89-
Geometric mean	27,852	36,581	34,939	23,462	4,216	7,208
6 months follow-up						
Antibody response (cut-	82% (64-	99% (97-	96% (92-	95% (86-	71% (56-	80% (70-
Antibody response (cut-	100% (NA)	100% (NA)	100% (NA)	100% (NA)	91% (82-	95% (89-
Antibody response (cut-	100% (NA)	100% (NA)	100% (NA)	100% (NA)	94% (86-	96% (92-
Geometric mean	12,426	18,088	17,036	12,899	5,722	7,438

[a]Excluding study samples from the University Hospital Basel center as the measuring range was up to 2500 units/ml (i.e. patients living with HIV: n=2 with CD4 <350 CD4; n=4 with CD4 ≥350; n=12 kidney transplant recipients; and n=14 lung transplant recipients).

Abbreviations: IQR=Interquartile range; NA=Not applicable

Table 3: T-cell status before and after vaccination with bivalent mRNA SARS-CoV-2 vaccines in a sub-sample of participants with different levels of immunosuppression, measured with the interferon gamma release assay from Euroimmun

Baseline						
Positive	90%; 9/10	100%;	96%; 26/27	55%; 6/11	29%; 10/34	36%; 16/45
Borderline	10%; 1/10	0%; 0/17	4%; 1/27	9%; 1/11	3%; 1/34	4%; 2/45
Negative	0%; 0/10	0%; 0/17	0%; 0/27	27%; 3/11	18%; 6/34	20%; 9/45
Not evaluable	0%; 0/10	0%; 0/17	0%; 0/27	9%; 1/11	50%; 17/34	40%; 18/45
Geometric mean concentrations (IQR)[a]	1,193 (448-3,179) n=10	2,202 (1,234-	1,755 (1,077-2,859) n=27	247 (86-710) n=10	45 (3-674) n=17	85 (16-464) n=27
4 weeks follow-up						
Positive	73% (46-	96% (88-	89% (78-99%)	50% (19-81%)	36% (20-	40% (25-
Borderline	9% (0-26%)	0% (NA)	3% (0-8%)	10% (0-29%)	3% (0-9%)	5% (0-11%)
Negative	0% (NA)	0% (NA)	0% (NA) 0/35	20% (0-45%)	21% (7-35%)	21% (9-33%)
Not evaluable	18% (0-41%)	4% (0-12%)	9% (0-18%)	20% (0-45%)	39% (23-	35% (21-
Geometric mean concentrations (IQR)[a]	1,500 (664-3,386) n=9	4,189 (2,671-	3,138 (2,088-4,718) n=32	221 (74-659) n=8	28 (1-642) n=20	51 (5-467) n=28
6 months follow-up						
Positive	75% (45-100%) 6/8	100% (NA) 15/15	91% (80-100%) 21/23	50% (19-81%) 5/10	54% (35-72%) 15/28	53% (37-69%) 20/38
Borderline	25% (0-55%) 2/8	0% (NA) 0/15	9% (0-20%) 2/23	30% (2-58%) 3/10	10% (0-22%) 3/28	16% (4-27%) 6/38
Negative	0% (NA) 0/8	0% (NA) 0/15	0% (NA) 0/23	10% (0-29%) 1/10	7% (0-17%) 2/28	8% (0-16%) 3/38

Not evaluable	0% (NA) 0/8	0% (NA) 0/15	0% (NA) 0/23	10% (0-29%) 1/10	29% (12-45%) 8/28	24% (10-37%) 9/38
Geometric mean concentrations (IQR)[a]	507 (208-1,180) n=8	1939 (1,123-3,347) n=15	1,216 (733-2017) n=23	368 (118-1,152) n=9	185 (36-962) n=20	229 (72-724) n=29

[a]Excluding not evaluable patients

Abbreviations: IQR=Interquartile range; NA=Not applicable

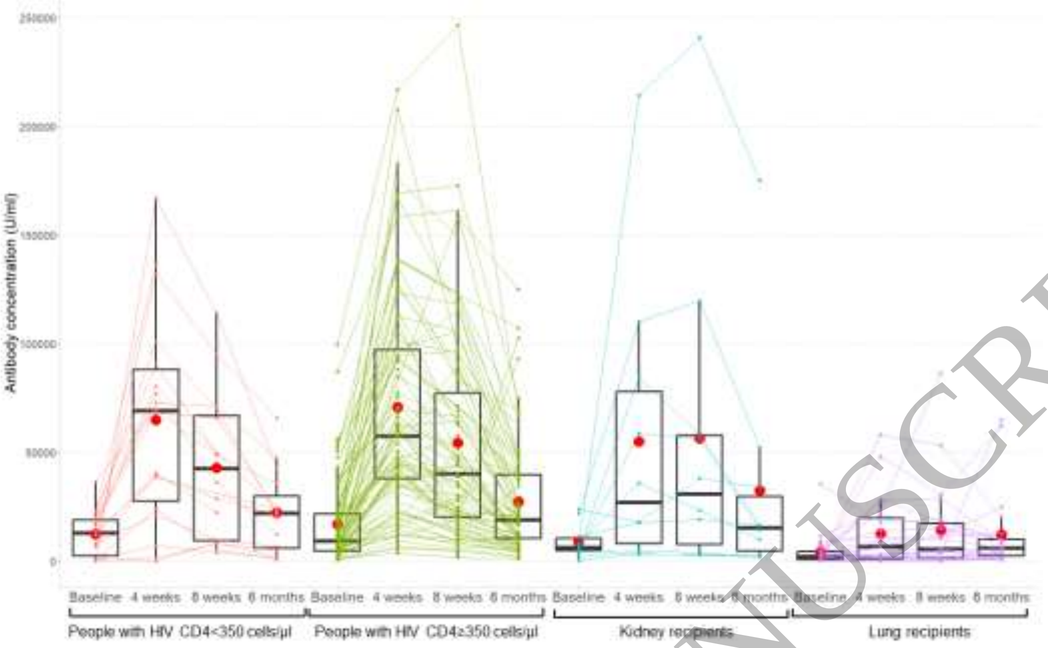
Table 4: Clinical outcomes after vaccination with bivalent mRNA SARS-CoV-2 vaccines in participants with different levels of immunosuppression

SARS-CoV-2 infection 4 weeks[a]	0%	3% (1/40)	1% (1/91)	0%	5% (1/21)	2%	1%
SARS-CoV-2 infection 4-8 weeks	0%	0% (0/40)	0% (0/95)	0%	0% (0/19)	0%	0%
SARS-CoV-2 infection 8 weeks – 6	0%	13%	5% (5/95)	2%	0% (0/19)	1%	4%
Severe COVID-19 disease (requiring hospitalization or leading to death	0% (0/61)	0% (0/40)	0% (0/101)	0% (0/51)	0% (0/22)	0% (0/73)	0% (0/174)
Serious Adverse Events	0%	8%%	3%	0%	5% (1/22)	1%	2%
Any local symptoms limiting continuation of normal daily	12% (7/60)	0% (0/40)	7% (7/100)	5% (5/50)	5% (1/22)	8% (6/72)	8% (13/172)
Any systemic symptoms limiting continuation of normal daily	12% (7/60)	3% (1/40)	8% (8/100)	6% (3/50)	0% (0/22)	4% (3/72)	6% (11/172)
Any vaccine related symptom leading to contacting a physician	0% (0/60)	0% (0/40)	0% (0/100)	0% (0/50)	0% (0/22)	0% (0/72)	0% (0/172)

[a] both symptomatic with the following symptoms: cough, shortness of breath, muscle aches, sore throat

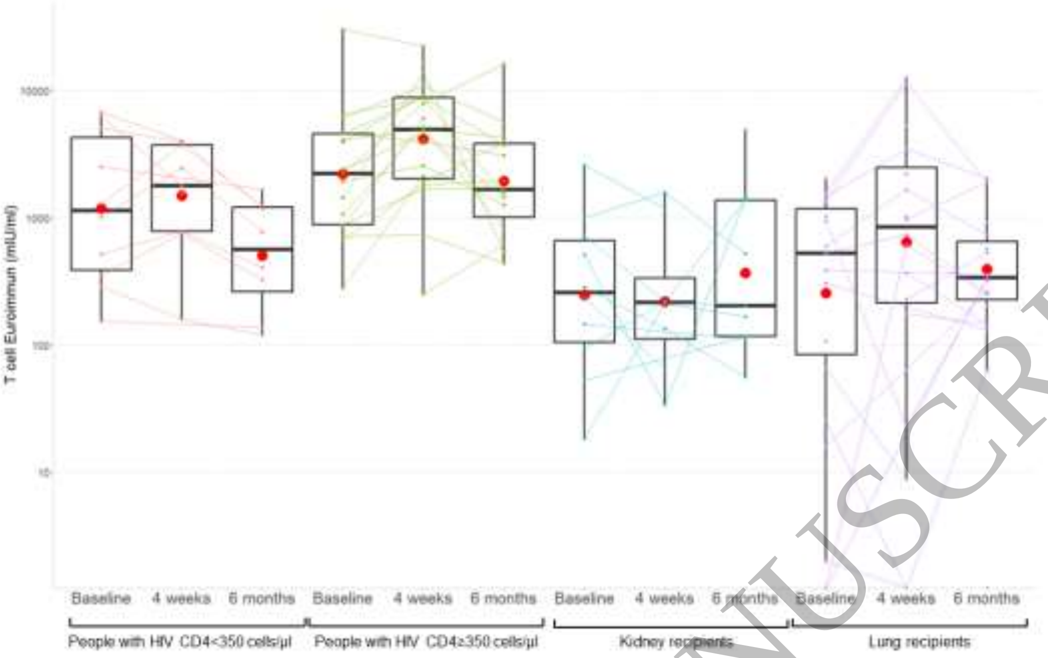
[b] all symptomatic with the following symptoms: fever or chills, cough, shortness of breath, fatigue, muscle or body aches, headache, sore throat, congestion or runny nose, nausea or vomiting

Figure 1: Antibody concentrations before and after vaccination with bivalent mRNA SARS-CoV-2 vaccines in people with HIV (stratified by CD4 cell counts below and above 350 cells/µl) and solid organ transplant recipient (stratified by kidney and lung recipients), measured with the Elecsys Anti-SARS-CoV-2 S assay



Red dots indicate mean values; boxplots indicate median and interquartile range.
The University Hospital Basel center did not perform reruns with further dilutions if the antibody concentrations were >2500 units/ml. Hence, in order not to distort the results, all samples from the University Hospital of Basel were excluded.

Figure 2: T-cell geometric mean concentration before and after vaccination with bivalent mRNA SARS-CoV-2 vaccines in people with HIV (stratified by CD4 cell counts below and above 350 cells/µl) and solid organ transplant recipients (stratified by kidney and lung recipients), measured with the interferon gamma release assay



Red dots indicate mean values; boxplots indicate median and interquartile range.
Participants with a non-evaluable T-cell response were excluded.

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