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International Journal of Infectious Diseases 123 (2022) 183–191

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Comparison of antibody response durability of mRNA-1273, BNT162b2, and Ad26.COV2.S SARS-CoV-2 vaccines in healthcare workers

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ARTICLE INFO

Article history:
Received 1 April 2022
Revised 22 August 2022
Accepted 23 August 2022

Keywords:
COVID-19
SARS-CoV-2
Anti-spike antibody
Antibody responses
Vaccine effectiveness

ABSTRACT

Objectives: There are limited comparative immunologic durability data post COVID-19 vaccinations.
Methods: Approximately 8.4 months after primary COVID-19 vaccination, 647 healthcare workers completed surveys about COVID-19 vaccinations/infections and blood draws. The groups included participants vaccinated with mRNA-1273 (n = 387), BNT162b2 (n = 212), or Ad26.COV2.S (n = 10) vaccines; unvaccinated participants (n = 10); and participants who received a booster dose (n = 28). The primary outcome was immunoglobin anti-spike titer. Secondary/tertiary outcomes included neutralizing antibodies (enzyme-linked immunosorbent assay-based pseudoneutralization) and vaccine effectiveness (VE). Antibody levels were compared using analysis of variance and linear regression.
Results: Mean age was 49.7 and 75.3% of the participants were female. Baseline variables were balanced except for immunosuppression, previous COVID-19 infection, and post-primary vaccination time. Unadjusted median (interquartile range [IQR]) anti-spike titers (AU/ml) were 1539.5 (876.7-2626.7) for mRNA-1273, 751.2 (422.0-1381.5) for BNT162b2, 451.6 (103.0-2396.7) for Ad26.COV2.S, 113.4 (3.7-194.0) for unvaccinated participants, and 31898.8 (21347.1-45820.1) for participants administered with booster dose (mRNA-1273 vs BNT162b2, P <.001; mRNA-1273, BNT162b2, or boosted vs unvaccinated, P <.006; mRNA-1273, BNT162b2, Ad26.COV2.S, or unvaccinated vs boosted, P <.001). Unadjusted median (IQR) pseudoneutralization was as follows: 90.9% (80.1-95.0) for mRNA-1273, 77.2% (59.1-89.9) for BNT162b2, 57.9% (36.6-95.8) for Ad26.COV2.S, 40.1% (21.7-60.6) for unvaccinated, and 96.4% (96.1-96.6) for participants administered with booster dose (mRNA-1273 vs BNT162b2, P <.001; mRNA-1273, BNT162b2, or boosted vs unvaccinated, P <.028; mRNA-1273, BNT162b2, Ad26.COV2.S, or unvaccinated vs boosted, P <.001). VE was 87-89% for participants administered mRNA-1273 vaccine, BNT162b2 vaccine, and booster dose, and 33% for Ad26.COV2.S (none significantly different).
Conclusion: Antibody responses 8.4 months after primary vaccination were significantly higher with mRNA-1273 than those observed with BNT162b2.

Introduction

Vaccination with Food and Drug Administration (FDA)–approved/authorized COVID-19 vaccines is imperative to control the ongoing pandemic. Several studies have demonstrated robust similar or higher early anti-spike (anti-S), anti-S-receptor binding domain (RBD), and neutralizing antibody (nAb) responses after primary vaccination with mRNA-1273 compared with BNT162b2 and higher responses with both mRNA vaccines compared with Ad26.COV2.S (Collier *et al.*, 2021; Debes *et al.*, 2021; Naranbhai *et al.*, 2022; Richards *et al.*, 2021; Self *et al.*, 2021; Steensels *et al.*, 2021; Wang *et al.*, 2021; Wheeler *et al.*, 2021). The pattern for early vaccine effectiveness (VE) is similar (Naranbhai *et al.*, 2022;

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https://doi.org/10.1016/j.ijid.2022.08.022

Pilishvili *et al.*, 2021; Rosenberg *et al.*, 2022; Self *et al.*, 2021; Tenforde *et al.*, 2021; Thompson *et al.*, 2021). Individual vaccine durability studies have shown waning immunity, with decreasing antibody titers and VE (breakthrough infections) (Baden *et al.*, 2021; Baden *et al.*, 2021; Barouch *et al.*, 2021; Boyarsky *et al.*, 2021; Chemaitelly *et al.*, 2021; Corchado-Garcia *et al.*, 2021; Doria-Rose *et al.*, 2021; Eliakim-Raz *et al.*, 2021; Falsey *et al.*, 2021; Hall *et al.*, 2021; Levin *et al.*, 2021; Polack *et al.*, 2020; Sadoff *et al.*, 2021; Shrotri *et al.*, 2021; Stephenson *et al.*, 2021; Thomas *et al.*, 2021; Widge *et al.*, 2021).

The literature for comparative vaccine antibody durability after primary SARS-CoV-2 vaccination is limited to only three studies we are aware of. One showed a marked decrease in anti-S-RBD and nAb titers over 6-8 months for mRNA-1273 and BNT162b2 which contrasted with relatively durable responses for Ad26.COV2.S; because early Ad26.COV2.S responses were lower, 6-8 months responses ended up comparable (Collier *et al.*, 2021). Another study showed decrease in anti-S and anti-S-RBD titers over 4 months with mRNA-1273 and BNT162b2, but mRNA-1273 titers were threefold higher at both time points (Bajema *et al.*, 2021). Another showed higher anti-S and nAb titers at about 4 months with mRNA-1273 vs. BNT162b2 vs. Ad26.COV2.S (Atmar *et al.*, 2022). Numerous comparative VE durability studies showed decreases to 80-95% at 3-7 months for mRNA-1273, 65-90% for BNT162b2, and 60-70% for Ad26.COV2.S (Andrews *et al.*, 2022; Bajema *et al.*, 2021; Dickerman *et al.*, 2022; Grannis *et al.*, 2021; Rosenberg *et al.*, 2022; Self *et al.*, 2021; Tenforde *et al.*, 2021).

Due to the dearth of comparative vaccine antibody durability studies, we sought to compare medium-range durability (at 8.4 months) of antibody responses in a cohort of healthcare workers (HCWs) in the Bassett Healthcare Network (New York, USA) vaccinated with FDA-approved/authorized COVID-19 vaccines. Our primary objective was to compare SARS-CoV-2 anti-S titers in HCWs at a median of 8.4 months after primary vaccination with mRNA-1273, BNT162b2, or Ad26.COV2.S, or unvaccinated, or vaccine-boosted HCWs. Our secondary objective was a similar comparison for immunoglobin (IgG)-S-RBD competitive antibody blocking enzyme-linked immunosorbent assay (ELISA) pseudoneutralization semiquantitative inhibition percentages against the USA-WA1/2020 strain. Tertiary objectives included comparisons of COVID-19 infection rates and VE; antibody responses stratified by covariates; and assessments of correlation between anti-S and pseudoneutralization results.

Methods

This observational study was a follow-up to a seroprevalence study conducted among Bassett HCWs during May-August 2020 (Institutional Review Board #1597947). Primary steps included securing consent, online surveys, blood drawing/processing, and antibody assays. Mary Imogene Bassett Institutional Review Board approved the follow-up study as an amendment to the original study. Informed consent was obtained from HCWs before participation in the follow-up study.

HCWs were eligible if they originally consented to storage of their plasma samples for future research and were available for blood drawing. Of 2056 HCWs, 1806 were invited to participate; 903 (50%) consented and completed the survey. Among them, 653 HCWs (72%) had blood drawn from 23 September-16 November 2021, 238 did not have blood drawn because of scheduling/logistics challenges, 12 declined, and 6 were excluded because of incomplete primary vaccination, yielding 647 HCWs for inclusion (Supplementary Figure 1), stratified into four groups: (1) mRNA-1273-vaccinated, (2) BNT162b2-vaccinated, (3) Ad26.COV2.S-vaccinated, and (4) unvaccinated. A fifth group,boosted (regardless of vaccine type),was added upon FDA/CDC recommendations for HCW boosting in October 2021. Primary vaccination was defined as two mRNA or one Ad26.COV2.S vaccine dose(s); "boosted" was defined as primary vaccination plus an additional vaccine. Among the 647 HCWs, 594 (92%) HCWs had specimens from 2020 available for testing.

The survey included questions on medical history (comorbidities, immunosuppression), COVID-19 history, and COVID-19 primary/booster vaccinations (type and timing). COVID-19 vaccination and infection status were updated upon blood drawing. HCWs were considered immunosuppressed if they self-reported that their doctor considered them immunocompromised, took chronic steroids for a month or longer since March 2020, or had a splenectomy. We contacted HCWs to verify chronic steroid use. Medical record reviews were conducted to verify immunosuppression for HCWs who were uncertain whether they were immunocompromised.

Laboratory-confirmed COVID-19 infection was based on medical record evidence of positive polymerase chain reaction or anti-N assays. COVID-19-related hospitalizations were confirmed in medical records. Breakthrough infection rates were calculated from 14 days after primary vaccination through the day of blood drawing. Unvaccinated HCWs were assessed for infection any time from 241 days before their blood draw (the median time from vaccination in the overall cohort [255 days] minus 14 days to the day of blood drawing).

Anti-S antibody tests were performed on both 2021 and 2020 (when available) specimens by Bassett's Laboratory using Abbott AdviseDx SARS-CoV-2 IgG II semiquantitative assay with dilution if necessary (Abbott Laboratories, Abbott Park, Illinois). Anti-N antibody tests were also performed by Bassett using SARS-CoV-2 IgG Abbott Architect assay (Abbott Laboratories, Abbott Park, IL).

Neutralization antibodies to spike protein RBD were measured using ELISA-based pseudoneutralization (competitive antibody blocking) COVID-19 assays (cPASS^{TM}, GenScript, Piscataway, NJ) using USA-WA1/2020 strain and performed by Biodesix (Boulder, CO). The α-RBD nAb test measures a subset of antibodies that block interaction between SARS-CoV-2 spike protein RBD and human host receptor angiotensin-converting enzyme 2 (ACE2). Methods for the cPASS surrogate virus neutralization test were previously published, validated, and shown to be 100% sensitive and specific when compared to gold standard, plaque reduction neutralization test, with qualitative analysis results 100% in agreement (Taylor *et al.*, 2021). The nAb assay readout was percent signal inhibition by neutralizing antibodies, calculated as optical density (OD) value of the sample relative to the OD of the negative control subtracted from one. The cPASS assay has an EUA for qualitative interpretation of results, but here we prioritized presenting numeric semiquantitative percent signal inhibition to compare groups.

Outcome variables were compared by five prespecified characteristics that impact immune responses to COVID-19 vaccination: age, number of comorbidities, immunosuppression, time from completion of primary vaccination (days), and prior COVID-19 infection.

Statistical analysis

Categorical variables were compared between groups using chi-square. Fisher's exact test was used with small cell sizes. Continuous variables were compared using one-by-five analysis of variance (ANOVA). For continuous variables with skewed distributions, including time from primary vaccination and pseudoneutralization percentages, we were unable to find a suitable transformation of the data to achieve normality. In these cases, data were converted to ranks before being analyzed using ANOVA. For anti-S titers, it was found that a natural log transformation resulted in a normal distribution that could be analyzed in the ANOVA model. All post-hoc tests were performed using Scheffe's method.

A second set of analyses comparing only mRNA-1273 and BNT162b2 groups was done (the other groups were excluded due to small sample sizes). In addition to the main effect of vaccine group, these analyses included an additional dimension for age group (<50 vs. ≥50 years), number of comorbidities (0-1 vs. ≥2), immunosuppression, time from completion of primary vaccination to blood draw (<8.4 vs. ≥ 8.4 months), and ever infected with COVID-19. Multiple linear regression was also performed on the natural log of anti-S titers and the ranks of the pseudoneutralization percentages, including adjustment for the above covariates. Age, comorbidities, and time since vaccination were modeled as continuous variables. A sub-analysis was performed for changes in anti-S (subtracting the 2020 anti-S value from the 2021 anti-S value) among participants who provided blood samples in 2020 and 2021. Values for change in anti-S were converted to ranks and were compared between mRNA-1273 and BNT162b2 groups using multiple linear regression adjusting for the same covariates.

Spearman's correlation coefficients were calculated for anti-S levels and pseudoneutralization percentages. VE was estimated by calculating ([infection rate among the unvaccinated - the infection rate among the vaccinated)/infection rate among the unvaccinated])*100.

Missing data on key variables (COVID-19 infection status, vaccination dates, immunosuppression) were confirmed directly with participants or medical record review. Other missing values were left as missing. Statistical significance was defined as $P < .05$. Analyses were performed using SAS version 9.4 (Cary, North Carolina).

Results

Overall, 75.3% of the patients were female, 93.5% were white, and 4.3% were immunosuppressed. The mean number of comorbidities was 0.7/patient, mean age was 49.7 years and the median interval from completion of primary vaccination to blood drawing was 255 days (8.4 months). Baseline variables were balanced by age, sex, race, and comorbidities ($P > .05$), and not immunosuppression ($P = .047$), previous COVID-19 infection ($P < .001$), or time post primary vaccination ($P < .001$) (Table 1).

Among the boosted HCWs, 19 patients (67.9%) received BNT162b2 (primary)-BNT162b2 (booster), 5 patients (17.9%) received mRNA-1273-mRNA-1273 third dose, 2 patients (7.1%) received mRNA-1273-mRNA-1273 booster, and 2 patients (7.1%) received mRNA-1273-BNT162b2.

Anti-S antibodies

Unadjusted median (IQR) anti-S titers were highest in group 5 (31898.8 AU/ml [21347.1-45820.1]) and lowest in group 4 (113.4 AU/ml [3.7-194.0]); significantly higher in group 1 (1539.5 AU/ml [876.7-2626.7]) than group 2 (751.2 AU/ml [422.0-1381.5]); and not significantly higher in groups 1 and 2 than group 3 [451.6 AU/ml (103.0-2396.7)] (overall, $P < .001$; $P < .001$ for groups 1 vs 2; $P < .006$ for groups 1, 2, or 5 vs 4; $P < .001$ for groups 1, 2, 3, or 4 vs 5; for all other comparisons, $P > .05$) (Table 2 /Figure 1). In multivariable analysis, adjusted median anti-S titers for groups 1 and 2 remained significantly different ($P < .001$) (Table 3). All covariates were independently associated with anti-S titers except for number of comorbidities ($P = .93$).

Upon accounting for 2020 anti-S titers in the subgroup for which those values were available, there was no difference between groups 1 and 2. There were 542 subjects with available values for anti-S from 2020. Multiple linear regression indicated a reduced change in anti-S associated with BNT162b2 (group 2) compared to mRNA-1273 (group 1).

Pseudoneutralization antibodies

Unadjusted median (IQR) pseudoneutralization signal inhibition percentages were highest in group 5 (96.4% [96.1-96.6]) and lowest in group 4 (40.1% [21.7-60.6]), significantly higher in group 1 (90.9% [80.1-95.0]) than group 2 (77.2% [59.1-89.9]) and not significantly higher in groups 1 and 2 compared with group 3 (57.9% [36.6-95]) (overall, $P < .001$; $P < .001$ for group 1 vs 2; $P < .028$ for groups 1, 2, or 5 vs 4; $P < .001$ for groups 1, 2, 3, or 4 vs 5; for all other comparisons, $P > .05$) (Table 2). In multivariable analysis, adjusted median pseudoneutralization percentages for groups 1 and 2 remained significantly different ($P < .001$). Time since vaccination and age were significantly associated with lower percentages of pseudoneutralization ($P < .001$). Previous infection was associated with higher percentages of pseudoneutralization ($P < .001$). Immunosuppression ($P = .51$) and comorbidities ($P = .63$) were not associated with pseudoneutralization.

COVID-19 infection rates and vaccine effectiveness against infection (Overall)

COVID-19 infection rates as measured by anti-N antibody and/or clinical laboratory-confirmed COVID-19 infection data during this approximately 8.4-month period were 3.4% (13/387) in group 1, 3.8% (8/212) in group 2, 20% (2/10) in group 3, 30% (3/10) in group 4, and 3.6% (1/38) in group 5 (overall, $P = .004$; $P < .05$ for groups 1, 2, or 5 vs 4; $P = .05$ for group 1 vs 3; $P = .07$ for group 2 vs 3; for all other comparisons, $P > .10$). All were treated as outpatients (no hospitalizations or deaths). Estimated VE rates were 89% (95% CI 67%-96%) in group 1, 87% (95% CI 60%-96%) in group 2, 33% (95% CI 0%-86%) in group 3, and 88% (95% CI 0%-99%) in group 5. Most breakthrough infections were in summer/fall 2021, suggesting Delta variant infections (Supplementary Figure 2).

Stratification by age showed different effects by vaccine type on anti-S antibody titers and pseudoneutralization percentages at 8.4 months, with older HCWs having significantly lower response to BNT162b2 ($P = .002$) but not mRNA-1273 ($P = .40$). Stratification by number of comorbidities, immunosuppression, and time since primary vaccination did not show significant differences. Stratification by previous COVID-19 infection status showed significant effects on anti-S antibody titers and pseudoneutralization percentages for both mRNA-1273 and BNT162b2 (all $P < .001$) (Table 2).

Correlation between anti-S antibody titers and pseudoneutralization percentages in the overall population was high ($\rho = .947$, $P < .001$). Correlation coefficients were.926,.934,.903,.867, and.397 for groups 1 through 5, respectively (all $P < .05$).

Discussion

This COVID-19 vaccine comparative immune response durability cohort study showed that medium-range antibody responses at a median of 8.4 months post primary vaccination were higher after vaccination with mRNA-1273 compared with BNT162b2. Ad26.COV2.S antibody responses were lower but not significantly different than mRNA-1273 and BNT162b2. Specifically, both the median anti-S antibody titers and median anti-USA-WA1/2020 strain RBD pseudoneutralization inhibition percentages were significantly higher for mRNA-1273 than BNT162b2. Median anti-S and pseudoneutralizing antibodies were significantly higher in boosted HCWs and much lower in unvaccinated HCWs (antibodies were not nil suggesting natural infections). As previously reported anti-S titers and pseudoneutralization percentages were strongly correlated. (Taylor *et al.*, 2021). Differences in antibody responses of mRNA-1273 and BNT162b2 persisted in adjusted analyses. Estimated VE against COVID-19 infection was similarly high with both mRNA vaccines, but not significantly different than Ad26.COV2.S,

Table 1
Demographics and clinical characteristics of participants by COVID-19 vaccine status

Characteristic	Total	Group 1(mRNA-1273)	Group 2 (BNT162b2)	Group 3 (Ad26.COV2.S)	Group 4 (Un-vaccinated)	Group 5 (Boosted)	*P* value[a]
No. (%)	647	387 (59.8)	212 (32.8)	10 (1.5)	10 (1.5)	28 (4.3)	
Age (years)							
Mean (SD)	49.7(12.8)	50.1 (12.7)	49.3 (12.6)	49.7 (10.0)	40.6 (13.8)	50.8 (15.4)	.21
<50	304 (47.0)	181 (46.8)	98 (46.2)	5 (50)	8 (80)	12 (43)	.33
≥50	343 (53.0)	206 (53.2)	114 (53.8)	5 (50)	2 (20)	16 (57)	
Sex[b]							
Men	148 (22.9)	95 (24.5)	42 (19.8)	2 (20)	0 (0)	9 (32)	.19
Women	487 (75.3)	284 (73.3)	167 (78.8)	7 (70)	10 (100)	19 (68)	
Race[b,c]							
Asian	10 (1.6)	7 (1.8)	2 (0.9)	0 (0)	0 (0)	1 (4)	.51
Black	6 (0.9)	4 (1.0)	2 (0.9)	0 (0)	0 (0)	0 (0)	.99
White	605 (93.5)	356 (92.0)	205 (96.7)	7 (70)	10 (100)	27 (96)	.067
American Indian/Alaskan Native	3 (0.5)	2 (0.5)	0 (0.0)	1 (10)	0 (0)	0 (0)	.054
Other	11 (1.7)	6 (1.6)	4 (1.9)	1 (10)	0 (0)	0 (0)	.35
Comorbidities							
Mean # conditions per person (SD)	.7 (1.0)	.8 (1.0)	.7 (1.0)	1.1 (1.2)	.4 (1.0)	.8 (1.1)	.60
0-1	525 (81.1)	315 (81.4)	171 (80.7)	7 (70)	9 (90)	23 (82)	.85
2+	122 (18.9)	72 (18.5)	41 (19.3)	3 (30)	1 (10)	5 (18)	
Immunosuppression[b]							
Yes	28 (4.3)	16 (4.1)	7 (3.3)	0 (0)	0 (0)	5 (19)	.047
No	608 (94.0)	366 (94.6)	201 (94.8)	10 (100)	9 (90)	22 (82)	
Ever infected with COVID-19[d]							
Yes	57 (8.8)	32 (8.3)	15 (7.1)	3 (30)	6 (60)	1 (4)	<.001
No	590 (91.2)	355 (91.7)	197 (92.9)	7 (70)	4 (40)	27 (96)	
Time since vaccination							
Median interval between primary vaccination and blood draw (days)	255.0	255.0	254.0	185.0	–	285.0	<.001
Mean	251.9	255.2	246.0	158.9	–	283.6	
Standard Deviation	37.8	28.3	43.8	71.2	–	29.9	
Minimum	13	39	13	57	–	202	
25th Percentile	248	249	246	62	–	272	
75th Percentile	267	270	262	208	–	295	
Maximum	387	308	304	237	–	387	
<8.4 months	316 (48.8)	193 (49.9)	110 (51.9)	10 (100)	–	3 (11)	<.001
≥8.4 months	321 (49.6)	194 (50.1)	102 (48.1)	0 (0)	–	25 (89)	
Chose vaccine type[b,e]							
Yes	178 (27.5)	114 (29.5)	47 (22.2)	10 (100)	–	7 (25)	<.001
No	455 (70.3)	271 (70.0)	163 (76.9)	0 (0)	–	21 (75)	

[a] *P* value for overall comparison across all groups. X^2 test was used for comparisons of categorical variables and 1-by-5 analysis of variance for continuous variables.
[b] Percentage does not add to 100% due to missing data.
[c] Race was self-reported from five fixed non-mutually exclusive categories. "Other" race indicates the healthcare workers provided a response different from the five categories. Ethnicity data were excluded due to a low response rate (54%).
[d] Self-reported and/or laboratory-confirmed infection. Self-reported COVID-19 infection was identified by a positive response to the survey question: "To your knowledge, do you have or have you ever had COVID-19?" Laboratory-confirmed infection was based on medical record evidence of a positive polymerase chain reaction test or a positive anti-N antibody test from the original 2020 or this follow-up study.
[e] Response to survey question: "Did you choose your vaccination site/time-based on which vaccine was being offered?"

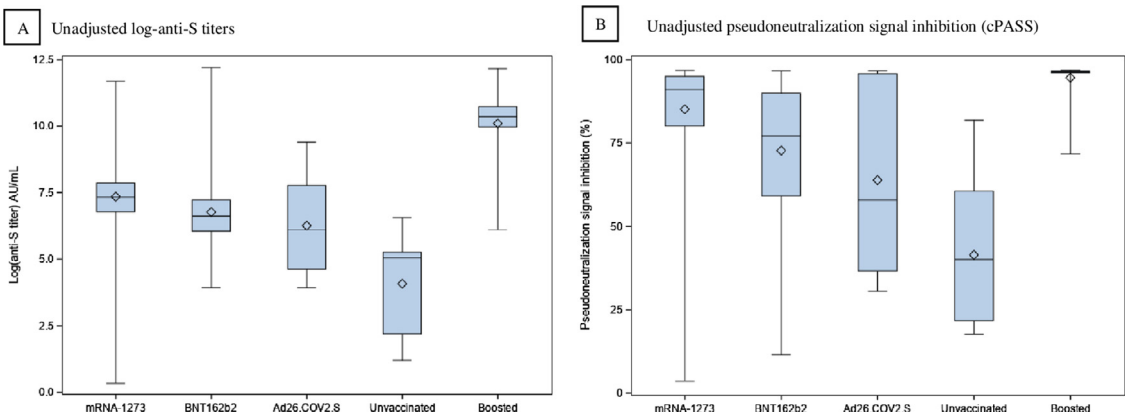

Figure 1. Boxplots showing antibody levels by study group at a median of 8.4 months since complete vaccination.
The bar inside each box represents the median and the diamond represents the mean antibody level. A, Difference in unadjusted log-anti-S antibodies by vaccine type. B, Difference in unadjusted pseudoneutralization signal inhibition percentages by vaccine type. Note: Sixty percent (6/10) of the unvaccinated HCWs reported a COVID-19 infection before antibody testing.

Table 2
Unadjusted antibody levels by COVID-19 vaccine type

	Group 1 (mRNA-1273)	Group 2 (BNT162b2)	Group 3 (Ad26.COV2.S)	Group 4 (Unvaccinated)	Group 5 (Boosted)	Pairwise *P* values
Anti-S antibody titer (AU/mL)						
No.	387	212	10	10	28	
Percent positive (≥50 AU/mL)	99.5	100	100	60	100	*P* <.001
Median (IQR)[a]	1539.5 (876.7-2626.7)	751.2 (422.0-1381.5)	451.6 (103.0-2396.7)	113.4 (3.7-194.0)	31898.8 (21347.1-45820.1)	Group 1 vs. 2: *P* <.001 Group 1 vs. 3: *P* =.10 Group 1 vs. 4: *P* <.001 Group 2 vs. 3: *P* =.99 Group 2 vs. 4: *P* =.006 Group 3 vs. 4: *P* =.23 Group 5 vs. all: *P* <.001
Age (years)						
<50	1668.9	989.4	915.2	82.7	32855.0	Group 1 vs. 2: *P* <.001
≥50	1414.8	662.3	273.7	186.7	30684.8	Group 1 vs. 2: *P* <.001
***P*-value**[b]	.40	.002				
Comorbidities						
0-1	1487.4	709.3	477.5	156.4	30374.2	Group 1 vs. 2: *P* <.001
2+	1783.7	800.8	425.7	3.3	49840.0	Group 1 vs. 2: *P* <.001
***P*-value**[b]	.74	.97				
Immunosuppressed						
Yes	2093.7	423.1	–	–	22299.8	Group 1 vs. 2: *P* =.002
No	1506.2	758.8	451.6	156.4	32491.0	Group 1 vs. 2: *P* <.001
***P*-value**[b]	.71	.25				
Time between vaccination and testing						
<8.4 months	1672.7	869.4	451.6	–	22299.8	Group 1 vs. 2: *P* <.001
≥8.4 months	1500.8	694.6	–	–	32411.6	Group 1 vs. 2: *P* <.001
***P*-value**[b]	.073	.42				
Ever infected with COVID-19 (immunologic and/or clinical)						
Infected	3604.4	5838.8	2653.4	184.6	192509.0	Group 1 vs. 2: *P* =.98
Uninfected	1487.4	692.4	273.7	3.5	31385.9	Group 1 vs. 2: *P* <.001
***P*-value**[b]	<.001	<.001				
Pseudoneutralization signal inhibition (cPASS) (%)						
No.	387	211	10	10	28	
Percent positive (≥30%)	99.0	97.2	100	60	100	*P* <.001
Median (IQR)[a]	90.9 (80.1-95.0)	77.2 (59.1-89.9)	57.9 (36.6-95.8)	40.1 (21.7-60.6)	96.4 (96.1-96.6)	Group 1 vs. 2: *P* <.001 Group 1 vs. 3: *P* =.25 Group 1 vs. 4: *P* <.001 Group 2 vs. 3: *P* =.99 Group 2 vs. 4: *P* =.028 Group 3 vs. 4: *P* =.24 Group 5 vs. all: *P* <.001
Age (years)						
<50	92.0	84.7	85.5	31.1	96.4	Group 1 vs. 2: *P* <.001
≥50	90.3	68.8	45.6	53.4	96.4	Group 1 vs. 2: *P* <.001
***P*-value**[b]	.19	<.001				
Comorbidities						

(*continued on next page*)

Table 2 (*continued*)

	Group 1 (mRNA-1273)	Group 2 (BNT162b2)	Group 3 (Ad26.COV2.S)	Group 4 (Unvaccinated)	Group 5 (Boosted)	Pairwise *P* values
0-1	90.8	77.2	61.3	40.5	96.5	Group 1 vs. 2: *P* <.001
2+	92.1	77.3	45.6	22.5	96.4	Group 1 vs. 2: *P* <.001
***P*-value**[b]	.93	.91				
Immunosuppressed						
Yes	93.1	60.7	–	–	96.1	Group 1 vs. 2: *P* =.004
No	90.8	77.3	57.9	40.5	96.5	Group 1 vs. 2: *P* <.001
***P*-value**[b]	.95	.19				
Time between vaccination and testing						
<8.4 months	92.5	77.7	57.9	–	96.0	Group 1 vs. 2: *P* <.001
≥8.4 months	90.6	77.1	–	–	96.5	Group 1 vs. 2: *P* <.001
***P*-value**[b]	.10	.74				
Ever infected with COVID-19 (immunologic and/or clinical)						
Infected	95.8	96.0	96.5	52.1	96.7	Group 1 vs. 2: *P* >.99
Uninfected	90.4	75.8	45.6	20.9	96.4	Group 1 vs. 2: *P* <.001
***P*-value**[b]	<.001	<.001				

[a] Overall (across all vaccine groups) *P* <.001.
[b] Within-vaccine group comparison across levels of covariates.

Table 3
Multivariable linear regression model of anti-S antibody levels (log-transformed)

	Regression coefficient (95% CI)	*P*-value
Vaccine type		
BNT162b2 (vs. mRNA-1273)	-0.645 (-0.819, -0.472)	<.001
Age, per year	-0.012 (-0.019, -0.005)	<.001
Comorbidities, per condition	-0.004 (-0.087, 0.080)	.93
Immunosuppression		
Yes	-0.568 (-0.996, -0.140)	.009
No	Reference	
Previous COVID-19 infection		
Yes	1.444 (1.138, 1.750)	<.001
No	Reference	
Time between vaccination and blood draw, per day	-0.008 (-0.011, -0.006)	<.001

although conclusions are limited by high statistical uncertainty because of low event rates, small sample sizes for Ad26.COV2.S, boosted groups, and insufficient post-boosting time to assess its VE.

Prespecified subgroup analyses, restricted to unadjusted comparisons between mRNA-1273 and BNT162b2 groups, found no significant differences in anti-S titers or pseudoneutralization percentages by the number of comorbidities, immunosuppression status (in contrast with others' findings for COVID-19 mRNA vaccines) (Deepak *et al.*, 2021; Levin *et al.*, 2021), or the time since primary vaccination.

In contrast, stratification by age showed lower anti-S antibody titers and pseudoneutralization percentages in older (≥ 50 years old) vs younger (< 50 years old) HCWs vaccinated with BNT162b2 but not mRNA-1273. Other studies have shown a similar age effect for the mRNA vaccines (Doria-Rose *et al.*, 2021; Pilishvili *et al.*, 2021; Richards *et al.*, 2021; Rosenberg *et al.*, 2022; Tenforde *et al.*, 2021; Thompson *et al.*, 2021; Widge *et al.*, 2021) suggesting that primary vaccination with mRNA-1273 rather than BNT162b2 should be prioritized for older individuals.

Stratification by previous COVID-19 infection status also showed significant effects, with higher anti-S antibody titers and pseudoneutralization percentages in HCWs vaccinated with mRNA-1273 and BNT162b2 and had previous COVID-19 infection. Notably, increased antibody responses with previous COVID-19 infection were more pronounced with BNT162b2 compared with mRNA-1273, particularly for anti-S antibodies (8.4-fold vs 2.4-fold; and 1.27-fold vs 1.06-fold, respectively). Other studies have also shown higher antibody responses in previously COVID-19-infected vs naive individuals with both mRNA vaccines (Naranbhai *et al.*, 2022; Steensels *et al.*, 2021).

A synopsis of the current literature shows many more studies reporting antibody and VE results for individual vaccines rather than comparative analyses, particularly for durability comparisons.

Individual mRNA-1273 antibody studies show high anti-S, anti-S-RBD, and nAb titers post-vaccination that were durable for 3-6 months earlier in the pandemic and increased even in immunosuppressed adults upon boosting (Doria-Rose *et al.*, 2021; Hall *et al.*, 2021; Widge *et al.*, 2021); low to undetectable nAb levels against Omicron 4-7 months after primary vaccination increase with boosting but less than with other variants and with faster decay 6 months post-boosting (Pajon *et al.*, 2022). VE studies showed high protection against infection and severe disease after vaccination (95%), but declined by 36-46% between 7-9 and 12 months later in the pandemic when Delta predominated(Baden *et al.*, 2021; Baden *et al.*, 2021).

Individual BNT162b2 antibody studies have shown that high antibody titers (same antibodies as above) decline 2-6 months after vaccination (more rapidly with immunosuppression) and increase with boosting (Boyarsky *et al.*, 2021; Eliakim-Raz *et al.*, 2021;

Falsey *et al.*, 2021; Levin *et al.*, 2021; Shrotri *et al.*, 2021). Undetectable nAb titers against Omicron, 5.5 months after the primary vaccination increased 100-fold post-boosting (Nemet *et al.*, 2022). VE studies show high protection against infection with durability for 6 months (90-95%) earlier in the pandemic when Alpha and Beta variants predominated, but decreased to 20% when Beta and Delta variants predominated. VE against severe disease (hospitalization and death) remained high (>90%) throughout the pandemic (Chemaitelly *et al.*, 2021; Polack *et al.*, 2020; Thomas *et al.*, 2021). VE against infection, severe infection, and mortality in Israel when Delta predominated was much higher with boosting (Arbel *et al.*, 2021)Bar-On et al., 2021.

Individual Ad26.COV2.S antibody studies show high titers post-vaccination (albeit lower than with both mRNA vaccines) that are relatively durable for 8 months (only 1.8-fold decrease) (Barouch *et al.*, 2021; Stephenson *et al.*, 2021). VE studies show protection against infection and severe disease of 64-85% after vaccination (Corchado-Garcia *et al.*, 2021; Sadoff *et al.*, 2021).

Comparative antibody studies, soon after primary vaccination, show titers that are similar or (more commonly) higher for mRNA-1273 vs BNT162b2 and higher with either vs Ad26.COV2.S (Collier *et al.*, 2021; Debes *et al.*, 2021; Naranbhai *et al.*, 2022; Richards *et al.*, 2021; Self *et al.*, 2021; Steensels *et al.*, 2021; Wang *et al.*, 2021; Wheeler *et al.*, 2021). Higher antibody response to mRNA-1273 compared with BNT162b2 after primary vaccination might, at least in part, be related to its approximately 3-fold higher dose formulation. Higher antibody response of both mRNA vaccines compared with Ad26.COV2.S after primary vaccination might be due, at least in part, to its single vs double primary vaccination schedule; one study showed similar antibody responses with all three vaccines 4-5 weeks after a single dose of each (Naranbhai *et al.*, 2022).

Our results are consistent with the three other comparative COVID-19 vaccine immunologic durability studies we are aware of (Atmar *et al.*, 2022; Bajema *et al.*, 2021; Collier *et al.*, 2021). One showed a marked decrease in anti-S-RBD and nAb titers for mRNA-1273 and BNT162b2 at 6-8 months. Initial lower titers of Ad26.COV2.S were more durable such that by 6-8 months titers were similar for all the three vaccines (Collier *et al.*, 2021). Another study showed about 3-fold higher peak (< 4 months) anti-S and anti-S-RBD titers with mRNA-1273 vs BNT162b2 with similar 3-fold decreases after 4 months, such that after 4 months, both antibody levels remained 3-fold higher with mRNA-1273 (Bajema *et al.*, 2021). Another study showed anti-spike and nAb titers at about 4 months with mRNA-1273 to be about 2-3-fold and 9-10-fold higher than with BNT162b2 and Ad26.COV2.S, respectively (Atmar *et al.*, 2022). Likewise, our results show significantly higher anti-S titers and pseudoneutralization percentages at 8.4 months for mRNA-1273 vs BNT162b2, and higher (but not significantly different) results for mRNA-1273 and BNT162b2 vs Ad26.COV2.S. However, we cannot draw conclusions about relative diminution of these titers as we did not complete sequential antibody assays.

Comparative VE studies show higher protection against infection and hospitalization for mRNA-1273 (90-95%) and BNT162b2 (90%) compared with Ad26.COV2.S (70-85%) post-vaccination (Pilishvili *et al.*, 2021; Rosenberg *et al.*, 2022; Self *et al.*, 2021; Tenforde *et al.*, 2021; Thompson *et al.*, 2021). Comparative VE durability studies against infection and severe disease at different pandemic times show decline to 80-95% for mRNA-1273, 65-90% by 3-7 months for BNT162b2, and 60-70% for Ad26.COV2.S (Andrews *et al.*, 2022; Bajema *et al.*, 2021; Dickerman *et al.*, 2022; Grannis *et al.*, 2021; Rosenberg *et al.*, 2022; Self *et al.*, 2021; Tenforde *et al.*, 2021); the higher ranges were for VE against more severe disease for all three vaccines. Two more comparative VE durability studies 6-11 months post primary vaccination showed higher VE against infection and severe disease with mRNA-1273 compared with BNT162b2 (Abu-Raddad *et al.*, 2022; Wang *et al.*, 2022). In contrast, our study showed equivalently high VE against infection at 8.4 months (87-89%) with mRNA-1273 and BNT162b2 despite significantly higher anti-S titers and pseudoneutralization percentages with mRNA-1273 than BNT162b2. VE was higher but not significantly different with both mRNA vaccines than with Ad26.COV2.S (33%).

Study limitations included: (1) Our study was observational. We addressed predicted confounders by adjusting for covariates likely to impact results; however, unmeasured confounders (COVID-19 prevention behavior, vaccine preferences, varying infection rates/exposures, and prevalent variants) may have influenced results. Lack of randomization required standardization of the period during which VE was quantified. (2) We did not complete peak antibody assays post primary vaccination precluding comparisons over time. (3) Analyses of groups 3-5 were limited by small sample sizes. (4) Significant baseline variable group differences included immunosuppression, previous COVID-19 infection rates (not stratified into symptomatic vs asymptomatic participants; 6.5% of self-reported infections were asymptomatic), and time from primary vaccination. (5) The study design (with addition of the boosted group) and statistical analysis plan (primary analysis focused on HCWs who had blood drawn) were modified after enrollment initiation; however, these changes were prespecified before seeing primary outcome data. (6) Antibody inhibition pseudoneutralization assays were completed rather than gold standard plaque reduction neutralization test; however, good correlation has been reported for these tests (Taylor *et al.*, 2021).

Conclusions

In this COVID-19 vaccines comparative immunology durability study, at a median of 8.4 months after primary vaccination, IgG spike protein antibody titers and pseudoneutralization inhibition percentages against SARS-CoV-2 USA-WA1/2020 were significantly higher with mRNA-1273 than BNT162b, both of which were not significantly higher than Ad26.COV2.S. VE against infection remained high with both mRNA vaccines (87-89%), also higher but not significantly different than Ad26.COV2.S (33%). Clinically meaningful differences could not be excluded because of the statistical uncertainty in the small Ad26.COV2.S group. Boosting led to a significant increase in anti-S and pseudoneutralization responses.

Funding

This work was supported by the Stephen C. Clark Research Endowment; E. Donnell Thomas Resident Research Endowment; and Marion Cooper Fund. Funding sources did not have a role in this study.

Ethical approval statement

The study was conducted in accordance with principles of the Code of Ethics of the World Medical Association (Declaration of Helsinki) and Good Clinical Practice (GCP) guidelines of the International Conference on Harmonization, with general principles of protection of humans participating in research. The Mary Imogene Bassett IRB approved this follow-up study as an amendment to the original study. Informed consent was obtained from HCWs prior to participation in the follow-up study.

Conflict of interest

The authors have no competing interests to declare.

CRediT authorship contribution statement

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Acknowledgments

We would like to thank the Bassett Research Institute Center for Clinical Research staff (Melissa Huckabone, Martina King, and Catherine Gilmore) and Casie Collins (New York Center for Agricultural Medicine and Health) for completing the blood draws, Carleen Henderson for processing specimens, the Bassett Healthcare Network Clinical Laboratory staff (Brittany Houghton-Depietro, Kyle Thorn, and Marfas Marakankadavu Parambu) for conducting the anti-S and anti-N antibody assays, and the Biodesix lab staff (Sam Imel and Tristan Finch) for performing the cPass assays. This study would not have been possible without their hard work. We would also like to thank Melinda Hasbrouck for providing logistical support, Tim Dupont for coordinating collaborations between the Bassett Research Institute and Biodesix, and Stephen Clark and Henry Weil for assisting in securing funding to support this study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.08.022.

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