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

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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 immunoglobulin anti-spike titer. Secondary/tertiary outcomes included neutralizing antibodies (enzyme-linked immunosorbent assay-based pseudonutralization) 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 pseudonutralization 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.

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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; Narainbhai 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 (Narainbhai et al., 2022; 2021).
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; Elakim-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 infection 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 three-fold 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 immunoglobulin (IgG)-S-RBD competitive antibody blocking enzyme-linked immunosorbent assay (ELISA) pseudo-neutralization 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 pseudo-neutralization 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 boost-
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 pseudonutralization 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 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 pseudonutralization percentages. VE was estimated by calculating (1-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 43% 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 (7512.4 AU/ml [422.0-1381.5]); and not significantly different in groups 1 and 2 vs. group 3 (4516.4 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 2). 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).

Pseudonutralization antibodies

Unadjusted median (IQR) pseudonutralization signal inhibition percentages were highest in group 5 (96.4% [96.1-96.6]) and lowest in group 4 (40.1% [217.6-60.6]), significantly higher in group 1 (90.9% [90.1-95.0]) 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 pseudonutralization percentages for groups 1 and 2 remained significantly different (P < .001). Time since vaccination and age were significantly associated with lower percentages of pseudonutralization (P < .001). Previous infection was associated with higher percentages of pseudonutralization (P < .001). Immunosuppression (P = .51) and comorbidities (P = .63) were not associated with pseudonutralization.

COVID-19 infection rates and vaccine effectiveness against infection

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 67.6-96.0) in group 1, 87% (95% CI 60.6-96.0) 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 pseudonutralization 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 pseudonutralization percentages for both mRNA-1273 and BNT162b2 (all P < .001) (Table 2).

Correlation between anti-S antibody titers and pseudonutralization percentages in the overall population was high (ρ = .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 pseudonutralization inhibition percentages were significantly higher for mRNA-1273 than BNT162b2. Median anti-S and pseudonutralizing 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 pseudonutralization 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 (Unvaccinated) | Group 5 (Boosted) | P value<sup>a</sup> |
|----------------------------------------|---------|---------------------|--------------------|-----------------------|------------------------|-------------------|-------------------|
| 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<sup>b</sup>                        |         |                     |                    |                       |                        |                  |                   |
| 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<sup>c</sup>                       |         |                     |                    |                       |                        |                  |                   |
| 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                          | .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<sup>b</sup>          |         |                     |                    |                       |                        |                  |                   |
| 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<sup>d</sup> |         |                     |                    |                       |                        |                  |                   |
| 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 |                   |
| 25<sup>th</sup> Percentile            | 248 | 249 | 246 | 62 | – | 272 |                   |
| 75<sup>th</sup> 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<sup>e</sup>         |         |                     |                    |                       |                        |                  |                   |
| 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) |                   |

<sup>a</sup> P value for overall comparison across all groups. X<sup>2</sup> test was used for comparisons of categorical variables and 1-by-5 analysis of variance for continuous variables.

<sup>b</sup> Percentage does not add to 100% due to missing data.

<sup>c</sup> 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%).

<sup>d</sup> 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.

<sup>e</sup> Response to survey question: "Did you choose your vaccination site/time-based on which vaccine was being offered?"

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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                           | 187                 | 212                | 10                    | 10                     | 28               |                  |
| Percent positive (≥50 AU/mL) | 99.5                | 100                | 100                   | 60                     | 100              | P < .001         |
| Median (IQR)*                | 1539.5              | 751.2              | 451.6                 | 113.4                  | 31898.8          | Group 1 vs. 2: P < .001 |
|                             | (876.7-2626.7)      | (422.0-1381.5)     | (103.0-2396.7)        | (3.7-194.0)            | (21347.1-45820.1) | Group 1 vs. 3: P = .99 |
|                             |                     |                    |                        |                        |                  | Group 2 vs. 3: P = .99 |
|                             |                     |                    |                        |                        |                  | Group 2 vs. 4: P = .006 |
|                             |                     |                    |                        |                        |                  | Group 2 vs. 4: P = .02 |
|                             |                     |                    |                        |                        |                  | 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*                     | .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*                     | .74                 | .97                |                       |                        |                  |                  |
| **Immunosuppressed**         |                     |                    |                        |                        |                  |                  |
| Yes                          | 2093.7              | 423.1              | –                     | –                     | 22298.9          | Group 1 vs. 2: P < .001 |
| No                           | 1506.2              | 758.8              | 451.6                 | 156.4                  | 32491.0          | Group 1 vs. 2: P < .001 |
| P-value*                     | .71                 | .25                |                       |                        |                  |                  |
| **Time between vaccination and testing** |                     |                    |                        |                        |                  |                  |
| <8.4 months                  | 1672.7              | 869.4              | 451.6                 | –                     | 22298.9          | Group 1 vs. 2: P < .001 |
| ≥8.4 months                  | 1500.8              | 694.6              | –                     | –                     | 32411.6          | Group 1 vs. 2: P < .001 |
| P-value*                     | .073                | .42                |                       |                        |                  |                  |
| **Ever infected with COVID-19** |                     |                    |                        |                        |                  |                  |
| 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*                     | < .001              | < .001             |                       |                        |                  |                  |
| **Pseudoneutralization signal inhibition (cPASs) (%)** |                     |                    |                        |                        |                  |                  |
| No                           | 387                 | 211                | 10                    | 10                     | 28               | Group 1 vs. 2: P < .001 |
| Percent positive (≥30%)      | 99.0                | 97.2               | 100                   | 60                     | 100              | Group 1 vs. 3: P = .25 |
| Median (IQR)*                | 90.9                | 77.2               | 57.9                  | 40.1                   | 96.4             | Group 1 vs. 3: P = .001 |
|                             | (80.1-95.0)         | (59.1-89.9)        | (36.6-95.8)           | (21.7-60.6)            | (96.1-96.6)      | Group 1 vs. 4: P = .028 |
|                             |                     |                    |                        |                        |                  | Group 2 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*                     | .19                 | < .001             |                       |                        |                  |                  |

(continued on next page)
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 pseudonutralization 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 pseudonutralization 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; Pillishvili 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 pseudonutralization 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 naïve 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 (Nemeth 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 (Chenaitelly 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 pseudneutralization 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 pseudneutralization inhibition percentages against SARS-CoV-2 USA-WA1/2020 were significantly higher with mRNA-1273 than BNT162b2, 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.

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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.
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