Durability of immunity and clinical protection in nursing home residents following bivalent SARS-CoV-2 vaccination

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eBioMedicine
2024;105: 105180
Published Online 10 June 2024
https://doi.org/10.1016/j.ebiom.2024.105180

Summary

Background Bivalent SARS-CoV-2 vaccines were developed to counter increasing susceptibility to emerging SARS-CoV-2 variants. We evaluated the durability of immunity and protection following first bivalent vaccination among nursing home residents.

Methods We evaluated anti-spike and neutralization titers from blood in 653 community nursing home residents before and after each monovalent booster, and a bivalent vaccine. Concurrent clinical outcomes were evaluated using electronic health record data from a separate cohort of 3783 residents of Veterans Affairs (VA) nursing homes who had received at least the primary series monovalent vaccination. Using target trial emulation, we compared VA residents who did and did not receive the bivalent vaccine to measure vaccine effectiveness against infection, hospitalization, and death.

Findings In the community cohort, Omicron BA.5 neutralization activity rose after each monovalent and bivalent booster vaccination regardless of prior infection history. Titers declined over time but six months post-bivalent vaccination, BA.5 neutralization persisted at detectable levels in 75% of infection-naive and 98% of prior-infected individuals. In the VA nursing home cohort, bivalent vaccine added effectiveness to monovalent booster vaccination by 18.5% for infection (95% confidence interval (CI) −5.6, 34.0%), and 29.2% for hospitalization or death (95% CI −14.2, 56.2%) over five months.

Interpretation The level of protection declined after bivalent vaccination over a 6 month period and may open a window of added vulnerability before the next updated vaccine becomes available, suggesting a subset of nursing home residents may benefit from an additional vaccination booster.

Funding CDC, NIH, VHA.

Keywords: COVID-19; Vaccine; Long-term care; Antibodies; Effectiveness

Introduction

SARS-CoV-2 continues to cause disproportionately higher morbidity and mortality in older adults.[1] Although vaccines effectively reduce this burden, immunity wanes in the months following vaccination[2,3] and the virus continues to evolve to escape population immunity.[4,5] As newer versions of vaccines are adapted to recent SARS-CoV-2 variants (i.e., bivalent vaccines and

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Research in context

Evidence before this study

Little is known about durability of response to bivalent SARS-CoV-2 vaccine and clinical protection for vulnerable populations like nursing home residents. We evaluated two cohorts of nursing home residents following bivalent SARS-CoV-2 vaccination: 1) a community nursing home population of 653 residents with and without evidence of prior infection for production of antibodies and neutralizing activity to vaccine strains of SARS-CoV-2; and, 2) a clinical cohort for evidence of infection and severe outcomes using electronic health records.

Added value of this study

Most nursing home residents generate an immune response to a single dose of the bivalent SARS-CoV-2 vaccine that includes substantial functional antibody that persists for up to six months after vaccination. Nursing home residents also have a lower but not statistically significant reduced risk of infection and severe outcomes over 20 weeks following vaccination.

Implications of all the available evidence

The bivalent SARS-CoV-2 vaccine can benefit many nursing home residents by reducing near term consequences of exposure to SARS-CoV-2 infection during the early Omicron period.

XBB1.5),[6] we must continue to determine how effective these vaccines are over time against emerging variants and especially in vulnerable populations.

Nursing home residents are a particularly vulnerable population in which it is important to monitor ongoing immunologic and clinical response to the SARS-CoV-2 vaccines. Nursing home residents and staff have suffered among the most significant morbidity and mortality from SARS-CoV-2 infection.[7] The close proximity of living arrangements and significant care needs that increase person-to-person contact and transmission risk, coupled with the inherent vulnerability of residents due to multiple comorbidities, frailty, and senescent immunity make this population highly susceptible to adverse outcomes.[8] It is therefore critical to evaluate both immunologic correlates of immunity and clinical outcomes such as infection, hospitalization and death following vaccination in this population.

Our cross-institution collaboration has provided a unique opportunity to evaluate these outcomes concurrently in two separate populations: first, a cohort of residents from community nursing homes in two U.S. states who have consented to serial blood draws to monitor immunologic response; and second, a nationally-representative cohort of residents from Veterans Affairs (VA) nursing homes for whom we have complete electronic health record data to monitor clinical outcomes. Our objective is to report on durability of protection following the first bivalent SARS-CoV-2 vaccine initially offered in September 2022, as measured by immunity in the community nursing home cohort, and by clinical outcomes in the VA cohort.

Methods

Ethical approval

The immunology study (Study #1316159) was approved by the Western Copernicus Group national institutional review board (IRB). All participants or their legally authorized representatives provided informed consent. Verbal consenting was IRB approved for this minimal risk study to facilitate recruitment. The Providence VA Healthcare System IRB approved the effectiveness evaluations using VA nursing home data (RDC-2020-017-E) and waived informed consent as the protocol met criteria for minimal harm.

Immunology

Participants

For the immunology studies, residents were sampled from 40 community nursing homes in Ohio and Rhode Island. All sites administered the BNT162b2 or mRNA-1273 SARS-CoV-2 vaccines, with the vast majority of subjects receiving the former. Participants generally received vaccines shortly after they were authorized by the FDA and as recommended by the Centers for Disease Control and Prevention. Supplementary Figure S1 depicts the blood sampling scheme. Follow-up blood sampling was performed two weeks after each dose for a peak response and then three and six months following each vaccine dose to determine how sustained the response was. Not all participants were drawn or followed for all time points. We also received clinical information in the follow-up intervals to assess for prior SARS-CoV-2 infection detected either clinically or from our serologic studies. When infection was confirmed, we excluded subsequent antibody data until after their next vaccine dose, and then categorized those values in the prior infection category. After the bivalent vaccine was approved in the U.S., it was the only booster that any subject was able to receive.

Participants were deemed to have a "*prior infection*" if they had a history of SARS-CoV-2 infection confirmed by PCR or antigen test, and/or detectable antibody levels to SARS-CoV-2 spike, receptor binding domain (RBD), and nucleocapsid (N protein) prior to their first dose in the initial study.[9,10] Otherwise, participants were classified as "*infection-naive*." Also, we re-classified subjects

when we identified PCR/antigen confirmation of infection and/or a rise outside of laboratory variance of anti-spike, RBD, N-protein, and neutralizing assay results not accounted for by vaccination history as "*prior infection*" from that time point onward. In our recent initial report on the bivalent vaccination, 77% of the nursing home cohort had evidence of prior infection.[10]

Immunology assays

Anti-spike was assessed with a bead-multiplex immunoassay using Wuhan strain and BA.5 as previously described.[10,11] Anti-N used full length Wuhan, N-protein to assess prior infection or breakthrough as done previously.

All SARS-CoV-2 proteins were purchased from the Frederick National Lab. There are stabilized full-length spike protein (aa 16-1230, with furin site mutated and recombinant SARS-CoV-2 S (1-1208)-2P-3C-His8-TwinStrep), and full-length N (aa1-419) from Wuhan were conjugated to magnetic microbeads (Luminex) and Magpix assay system (BioRad, Inc). Anti-Wuhan spike IgG levels were in Binding Antibody Units (BAU)/mL based on the Frederick National Laboratory standard, and anti-spike BA.4/5 are arbitrary units (AU)/mL. SARS-CoV-2 pseudovirus neutralization assay used lentiviral particles pseudotyped with spike protein based on the Wuhan and Omicron BA.5 strain as previously described .[10,12] The lentiviral pseudoviruses where sequenced in their entirety to confirm the integrity of the constructs. Briefly, serial dilutions of serum ranging from lower limit of detection of 1:12 to 1:8748. pNT50 values are defined as the inverse of the 50% inhibitory concentration value for all samples with a pseudovirus neutralization value of 80% or higher at the highest concentration of serum. Not all samples were tested for pNT50 due to resource limits, samples were prioritized from persons where multiple longitudinal samples were available.

Immunology statistical methods

Subjects with Wuhan or BA.5 spike antibody or neutralizing titers measured at least once from pre-first monovalent booster to six months post-bivalent vaccination were included. If sample volume permitted, BA.5 titres were measured but not all samples were tested against BA.5. Samples collected following a breakthrough infection were excluded. Demographics were summarized overall and separately for each vaccine dose. For each sample time, assay, and strain, the geometric mean titer (GMT) was calculated among infection-naive and prior infection participants. Given the repeated sampling of participants over time and differences in available time points per participant, we employed mixed-effects modeling methods similar to those implemented in other recent studies of longitudinal serologic response to SARS-CoV-2 infection or vaccination.[13–16] Conditional means across days of follow-up were estimated with a linear model regressing log-transformed titers on a non-linear function of days since vaccine dose, and normally distributed random-intercept term for person to account for intra-correlation due to repeated sampling. Days since last dose was modeled as a continuous variable with a 2nd-degree polynomial function. Each model was evaluated separately; for vaccine dose, COVID-19 strain, assay, and the prior versus naive infection status of the participant at the time of draw. For all models, assumptions of homoskedasticity and independence of residual error by observation, normally distributed random intercepts were checked. Models and contrasts were estimated using the nlme and emmeans packages in R Statistical Software (v4.2.2).[17,18]

Clinical outcomes

Participants

For the vaccine effectiveness analysis, the sample included residents of 129 U.S. VA nursing homes who met the study inclusion and exclusion described below.

Target trial emulation methods

Because a randomized trial was infeasible, we emulated a target trial using observational data from a cohort of nursing home residents from the Veterans Health Administration. We deployed a target trial emulation approach similar to our prior vaccine effectiveness studies of the monovalent vaccines,[19,20] to evaluate the effectiveness of bivalent SARS-CoV-2 vaccination compared to no additional vaccination in residents with a prior monovalent vaccination series. A series of sequential calendar dates between September 18, 2022 and November 30, 2022 were included as index dates for assessing individual eligibility and baseline for follow-up. From each index date follow-up was continued until either 6 months accrued or residents were either non-adherent to their assigned treatment strategy or otherwise loss to follow-up (died). On each index date, we evaluated residents inclusion eligibility. Residents were included if they resided in a VA nursing home for at least 100 days with a non-resident gap of no more than ten days and had received the primary SARS-CoV-2 vaccination series. We excluded those with test-confirmed SARS-CoV-2 infection within 90 days prior to the index date, any SARS-CoV-2 vaccine in the 134 days prior to the index date (4 months + 14 days as a grace period), and those receiving hospice care. On each index date those residents receiving vaccine on that date were considered as "assigned" to the bivalent vaccination strategy, while those who met eligibility criteria but did not receive the vaccine were "assigned" to the no bivalent vaccination strategy. Individuals could be eligible on multiple days, so we randomly selected only one date for inclusion.[19,20] Residents under the no vaccination strategy

were censored when they received the bivalent vaccine. Additionally, all residents were censored when they were out of the facility for more than 10 days and thus lost to follow-up, death (when death is not the outcome), or the administrative end date of May 31, 2023. Clinical outcomes included a test-confirmed SARS-CoV-2 infection (with or without symptoms), death within 30 days of infection, hospitalization within 14 days of infection, and a composite outcome of death or hospitalization.

Statistical analysis

Failure time analyses are used to evaluate each outcome using methods that are described in detail in prior work.[20] The hazard is approximated using pooled logistic regression models and longitudinal person-period datasets. Cumulative incidence curves (i.e., risk: 1 minus the probability of event-free survival at each person trial day) for the bivalent vaccination and no vaccination groups are estimated and relative risk differences between groups reported as vaccine effectiveness at weeks 12, 16, and 20. To address informative censoring and confounding, analyses utilized probability weighting. The first component of the probability weights is a treatment weight estimating probability of vaccination on the index date (i.e., inverse probability-of-treatment weight [IPTW]). The second weight is the probability of remaining uncensored (inverse probability-of-censoring weight [IPCW]), and the product of both is used to adjust results.

The weighted models are designed to emulate the "per protocol" effect of a randomized clinical trial with no informative censoring and no confounding. Variables included in the final models included known and observable confounders of vaccination status and clinical outcomes and predictors of the outcome not deemed to introduce bias (e.g. via collider stratification). The IPCW were estimated separately by treatment group. For all comorbidities we used a one year look-back from index for valid ICD-10 determined by the Elixhauser comorbidity classification system.[21] Refer to Supplementary Appendix for model specification, weights were truncated at their 99% upper quantile. Sampling with replacement by resident (i.e., bootstrapping) with 500 replications was used to generate percentile-based 95th % confidence intervals accounting for the estimated probability weights and crossover of treatment groups by resident. A complete case analysis was performed in all regressions. All target trial emulation analyses were performed using R Statistical Software (v4.2.2).

Role of funders

The funders had no role in the in study design, data collection, data analyses, interpretation, decision to publish, or writing of report.

Results

Immunology results

Table 1 describes the numbers and demographics of participants in the immunology study (n = 653). The median age of participants was 76 years, which trended downward to 74 for those receiving the bivalent vaccine. The proportion of men to women was evenly split 51:49, with more women sampled for the bivalent analysis (53%). The proportion of white participants was 80% and remained similar across vaccination doses. Among those receiving any bivalent vaccine (n = 340), 6 (1.7%) had received no monovalent booster, 89 (26%) had received one monovalent booster, and 245 (72%) had received two. Supplementary Figure S1 and Table S1 provide details on sampling timeframes, time since last vaccine and number of samples at each timepoint.

The primary focus of this study was the six-month post-bivalent vaccination time point. Fig. 1 and Table 2 summarize neutralizing and anti-spike titers to BA.5 and Wuhan, the two strains in the bivalent vaccines. At virtually all time points, the prior-infected individuals had higher titers than the naive group (Fig. 1). The levels declined three and six months following all vaccination time points (Fig. 1). The neutralizing assays demonstrate that after each vaccine dose, from the first two monovalent vaccinations and then the bivalent vaccination, both BA.5 and Wuhan neutralization titers rose in both the infection-naive and prior infection groups. However, there is also significant long-term decline in titres following vaccination, the ratio in neutralizing geometric mean titres (GMT) against BA.5 six months post-bivalent vaccination versus two weeks was 0.10 (95% Confidence Interval [95% CI]: 0.04–0.22) and 0.14 (95% CI: 0.08–0.25) in those infection-naïve versus with prior infection respectively. For anti-spike titres, the relative GMT ratio was 0.32 (95% CI: 0.20, 0.53) and 0.57 (95% CI: 0.43, 0.76) for infection-naïve and prior history of infection respectively. The reductions in titers from 2 weeks to 6 months post-bivalent vaccination were statistically significant across all assays for both infection-naive and prior-infected individuals (Table 2).

In Table 3, relative ratios for bivalent versus prior vaccinations in geometric mean antibody titers are summarized. Across time points and assays, we observed the steepest change in BA.5 neutralization titers following bivalent vaccination relative to 2nd monovalent vaccination (relative change of 4.36 [95% CI: 2.26, 8.44] in infection naïve, and 2.20 [95% CI: 1.32, 3.68] with prior history of infection). BA.5 neutralization levels decreased by >90% (fold change = 0.098) in naive and >85% (fold change = 0.14) in prior-infected participants six months after the bivalent vaccination. However, 75% (15/20) of infection-naive persons and 98% (45/46) of those with prior infection still had detectable BA.5 neutralization activity at 6 months.

Subjects	All (n = 653)	First monovalent booster (n = 450)	Second monovalent booster (n = 256)	Bivalent booster (n = 340)
Age				
Median, IQR	76 (68, 86)	76 (69, 85)	76 (68, 86)	74 (67, 85)
Male	335 (51%)	254 (56%)	114 (45%)	161 (47%)
Female	318 (49%)	196 (44%)	142 (55%)	179 (53%)
Race				
White	518 (79%)	352 (78%)	205 (80%)	268 (79%)
Black	118 (18%)	86 (19%)	43 (17%)	65 (19%)
Hispanic	8 (1%)	6 (1%)	5 (2%)	2 (1%)
Asian	2 (0%)	2 (0%)	0 (0%)	0 (0%)

Description. This table includes residents who had serology analyzed before and after vaccinations to determine immune response. The number in the Bivalent booster column includes those who had 0+ monovalent boosters. IQR, interquartile range, SD, Standard Deviation.

Table 1: **Demographics of residents participating in the immunology analysis.**

A focused examination of neutralization titer decay in the six months after each vaccine dose is shown in Fig. 2. Those with prior-infection have more sustained titer levels versus infection-naive individuals through the six months after each vaccination. The decay curves in both groups from the three-to six-month timepoints after bivalent vaccination have a relative flattening over time with the anti-BA.5 spike (Table 2 and Fig. 3), maintaining readily detectable levels that provide some degree of BA.5-specific neutralization through at least

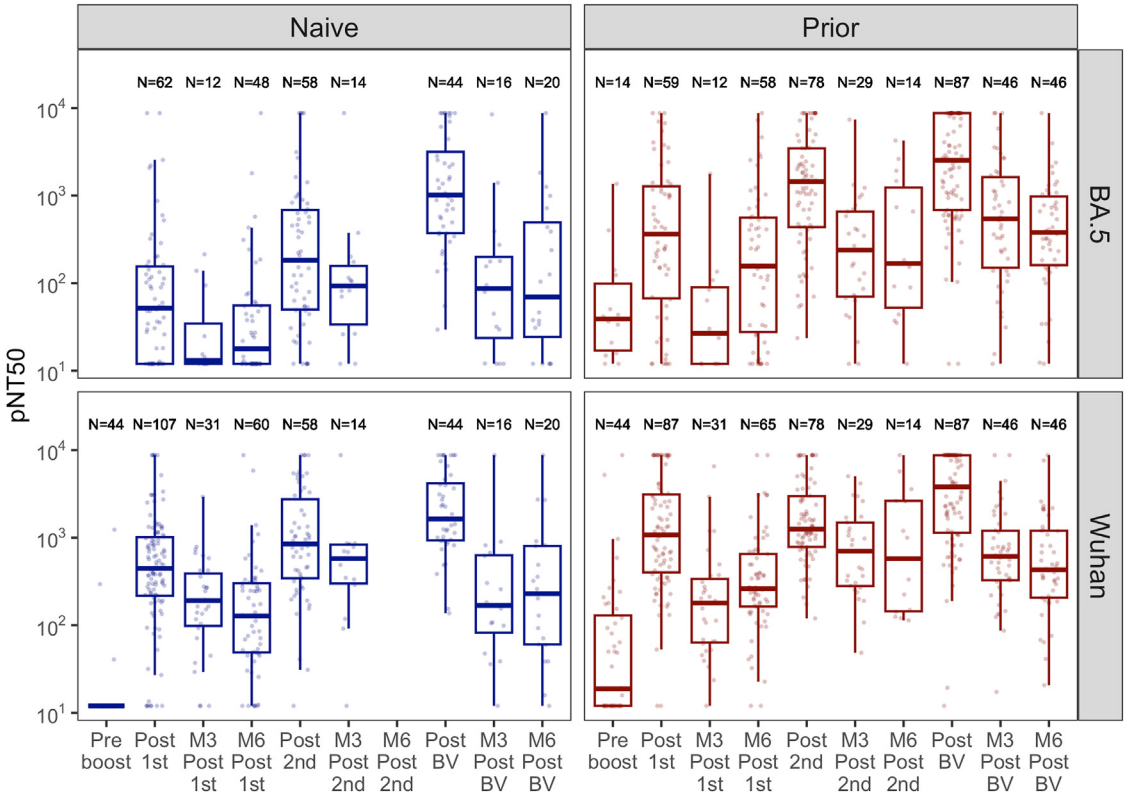

Fig. 1: **Pseudovirus neutralization results pre- and post-vaccination with COVID-19 booster vaccinations in a convenience sample of nursing home residents**. The blue panels are COVID-19 infection-naive residents and the red panels include those prior history of COVID-19 infection. N refers to the number of samples for that group, not all subjects had available data for all timepoints. The boxplot represents the median (solid line), 25 and 75% quantiles (box) and 95% quantiles (tails). pNT50 = inverse of titre concentration where 50% pseudovirus neutralization. The limits of detection for the assay are 1:12 to 1:8748. See Figure S1 for further description of sampling timepoints and x-axis labels.

Strain	Infection status	2 weeks post 1st GMT (CI)	2 weeks post 2nd GMT (CI)	2 weeks post BV GMT (CI)	6 months post BV GMT (CI)	Adjusted Ratio: 6 months/2 weeks post BV[a]
Neutralization						
BA.5	Naive	68 (43, 109)	195 (120, 318)	1107 (705, 1739)	114 (45, 290)	0.10 (0.04, 0.22)
BA.5	Prior	299 (174, 514)	1133 (806, 1592)	2026 (1483, 2767)	353 (230, 542)	0.14 (0.08, 0.25)
Wuhan	Naive	425 (313, 578)	818 (555,1206)	1881 (1355, 2610)	224 (98, 513)	0.13 (0.06, 0.27)
Wuhan	Prior	1073 (778, 1479)	1457 (1152, 1843)	2677 (2014, 3557)	481 (330, 703)	0.17 (0.10, 0.29)
Spike						
BA.5	Naive	2228 (1397, 3552)	968 (679, 1379)	1223 (950, 1574)	458 (273, 770)	0.32 (0.20, 0.53)
BA.5	Prior	3500 (2301, 5324)	2093 (1683, 2602)	1393 (1184, 1639)	850 (662, 1092)	0.57 (0.43, 0.76)
Wuhan	Naive	1954 (1430, 2672)	1577 (1009, 2465)	3248 (2356, 4478)	402 (241, 669)	0.10 (0.05, 0.23)
Wuhan	Prior	6429 (5210, 7934)	3655 (2984, 4475)	3251 (2713, 3896)	639 (494, 826)	0.19 (0.12, 0.29)

Description. GMT, Geometric mean titer, CI, 95% Confidence interval, 1st, First monovalent booster, 2nd, Second monovalent booster, BV, Bivalent Vaccine. [a]All reports ratio statistics are statistically significant with p-values <0.001. Adjusted Ratio of Month 6 Post BV: 2 weeks Post BV calculation will be slightly different from the crude ratios of the presented GMTs because the mixed-effects model adjusts for correlated values within subject when >1 sample is present from the same person. The GMT columns ignore repeated sampling and consider all values as independent of each other. Infection Status refers to a history of COVID-19 infection prior to vaccination, "Naive" means individuals who have not been infected with SARS-CoV-2 before vaccination and "Prior" had been infected before vaccination.

Table 2: **Neutralizing and spike antibody titers 2 weeks following 1st and 2nd monovalent booster vaccination; and 2 weeks and 6 months following bivalent vaccination.**

six months in most individuals, including those that are infection-naive.

With the exception of serum from infection-naïve individuals tested against Wuhan virus, anti-spike titers reached a peak level after the first monovalent booster and did not rise higher with subsequent booster doses, in contrast to neutralization titers (Table 3). The anti-spike binding assay titers reveal that all participants regardless of their prior infection status had readily detectable levels of anti-BA.5 and Wuhan spike titers (Fig. 3).

Overall, the immunology data show significant anti-BA.5 neutralizing and binding antibody titres present prior to receiving the Bivalent booster regardless of prior infection status. Significant declines in the neutralizing and binding antibody titres of both Wuhan and BA.5 titers occur over time. The BA.5 neutralizing titers in particular drop more than binding antibody titers, regardless of prior infection status.

Vaccine effectiveness results

The full cohort of residents in the VA nursing home cohort eligible from September 18, 2022 to November 30, 2022 included 3374 persons with 5181 observations (person-trials), across 129 VA nursing homes. 3264 veteran-trials in our control group 1917 received the bivalent vaccine after their trial start date. Supplement Figure S2 describes inclusion and exclusion in further detail. Table 4 presents baseline covariates of the sample, and shows that most residents had received at least one monovalent booster dose. Disproportionately more of those who received a bivalent vaccine also had two prior booster vaccinations, and influenza vaccination (Table 4).

Comparisons by assay	Relative ratio (95% CI) infection Naïve	Relative ratio (95% CI) Prior infection
Neutralization BA.5 contrast		
Post Bivalent versus 2nd monovalent booster	4.36 (2.26, 8.44)	2.20 (1.32, 3.68)
Post 2nd versus 1st monovalent boosters	2.95 (1.56, 5.55)	3.15 (1.71, 5.81)
Anti-Spike BA.5 contrast		
Post Bivalent versus 2nd monovalent booster	0.95 (0.62, 1.46)	0.64 (0.48, 0.84)
Post 2nd versus 1st monovalent boosters	0.54 (0.31, 0.96)	0.59 (0.35, 1.00)
Neutralization Wuhan contrast		
Post Bivalent versus 2nd monovalent booster	1.84 (1.03, 3.27)	1.89 (1.20, 2.96)
Post 2nd versus 1st monovalent boosters	1.88 (1.16, 3.06)	1.11 (0.69, 1.77)
Anti-Spike Wuhan contrast		
Post Bivalent versus 2nd monovalent booster	1.91 (1.05, 3.50)	0.91 (0.62, 1.33)
Post 2nd versus 1st monovalent boosters	0.75 (0.44, 1.27)	0.54 (0.36, 0.80)

Each cell contains a ratio of the relative change in geometric mean antibody titres from pre vaccination to post-vaccination. Higher (>1) ratio values indicate a greater vaccine response while lower (<1) values indicate a lower response. Ratios are computed from the conditional mean estimates of linear models with a random intercept for person to account for serial correlation of samples. "Naive", no known infection history, "Prior", infection history before vaccination.

Table 3: **Ratio of change in geometric mean titres relative to vaccination timing and infection history.**

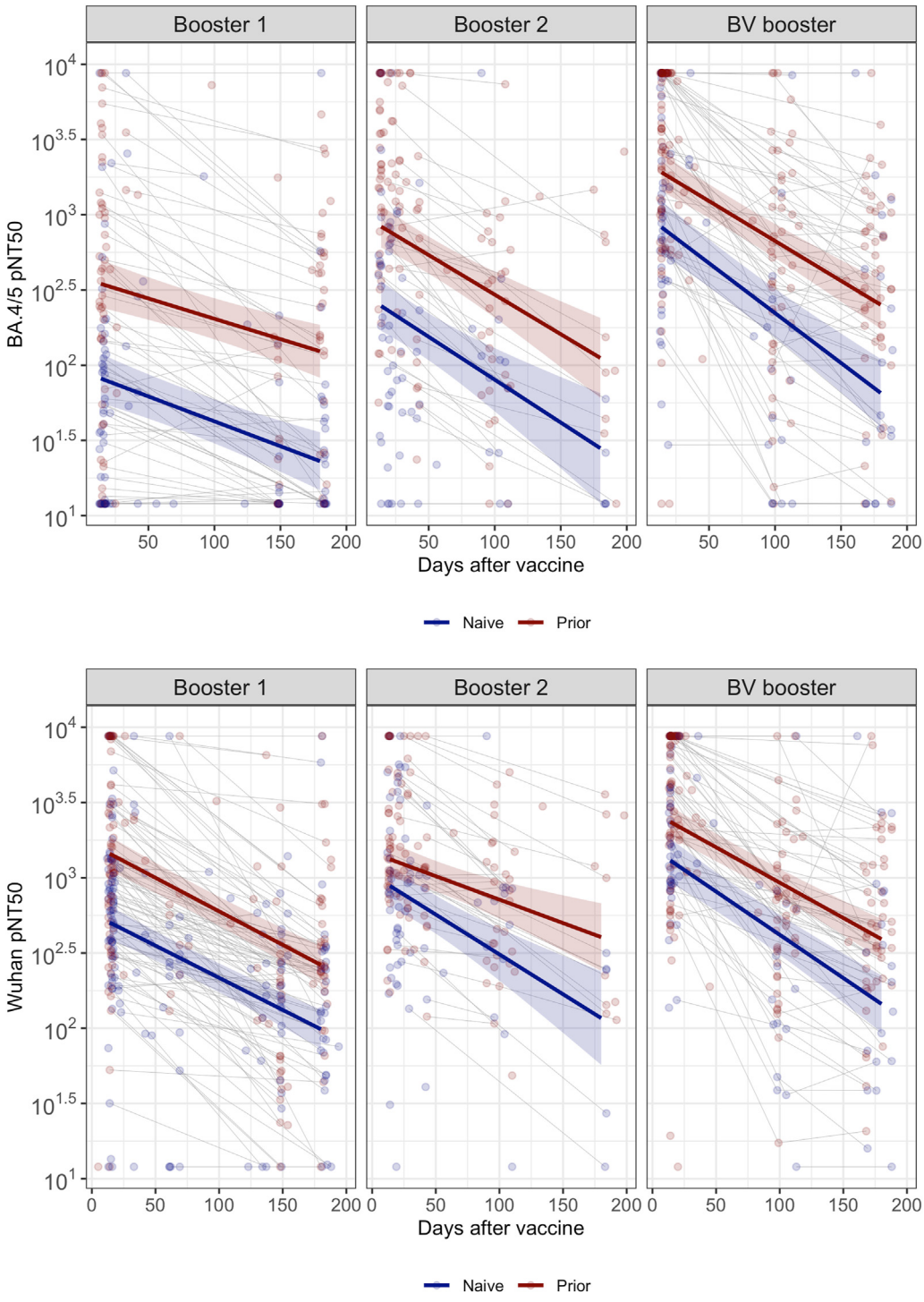

***Fig. 2*: Decline of COVID-19 pseudovirus neutralization titers after vaccination with COVID-19 boosters**. pNT50 neutralization titers of BA.5 (top) and Wuhan (bottom) plotted by days from a COVID-19 booster vaccination. COVID-19 infection naive (blue) and prior history of infection (red) are graphed separately. The lines represent conditional means of the log-transformed neutralization response adjusted for days since last vaccination and random intercepts for each included subject. Shaded regions represent the 95% confidence interval of the linear model prediction fixed effects.

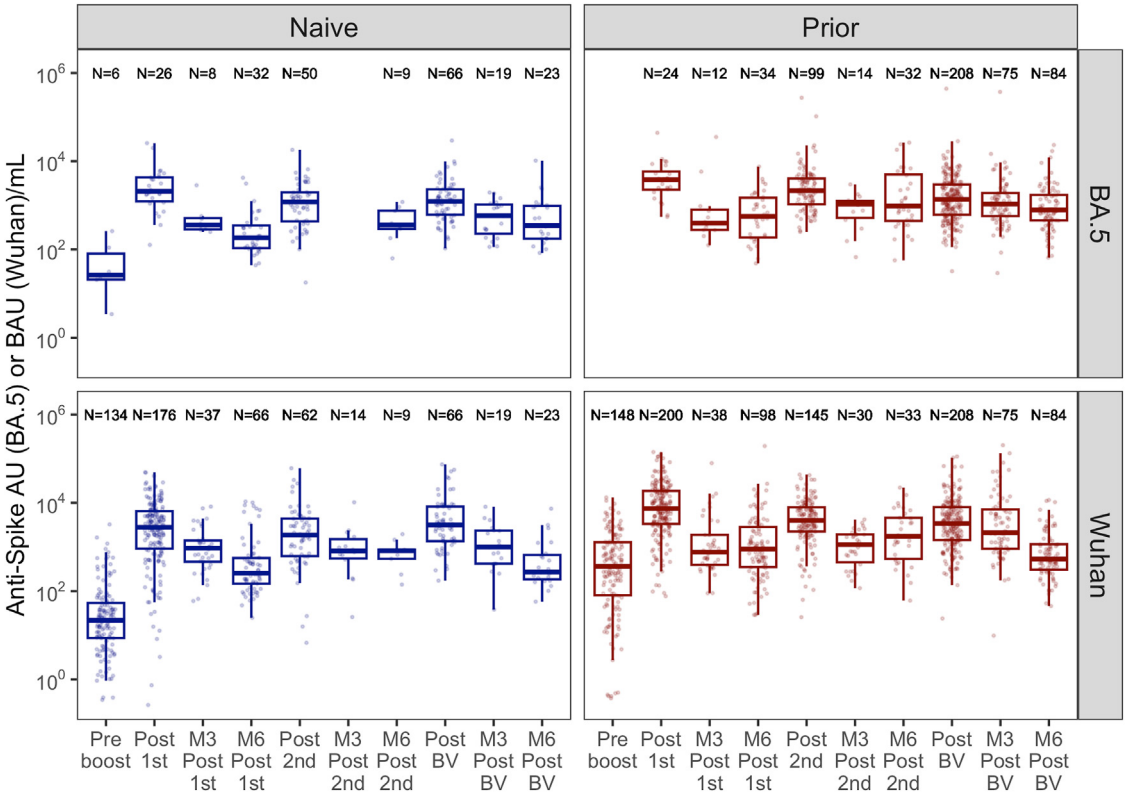

***Fig. 3:* Anti-spike titer results pre- and post- COVID-19 booster vaccination in a convenience sample of nursing home residents**. This figure illustrates anti-spike for BA.5 (top) in AU/ml and Wuhan (bottom) in BAU/ml in nursing home residents before and after COVID-19 booster vaccinations. COVID-19 infection naive (blue) and prior history of infection (red) are graphed separately. N refers to the number of samples for that group, not all subjects had available data for all timepoints. The boxplot represents the median (solid line), 25 and 75% quantiles (box) and 95% quantiles (tails). See Figure S1 for further description of sampling timepoints and x-axis labels.

Fig. 4 and Table 5 summarize the 6-month risk of infection, hospitalization, and death among residents who did and did not receive the bivalent vaccine. Among "treated" individuals (those receiving bivalent vaccination) the follow-up time was 39,906 weeks, while among controls (no bivalent vaccination) it was 18,751 weeks. Censoring limited the number of observations beyond week 20 (Supplement 1). Compared to no bivalent vaccine by week 20, bivalent vaccination had a vaccine effectiveness of 18.5% against infection (95% confidence interval [CI] –5.6, 34.0), 29.2% against hospitalization (95% CI –14.2, 56.2), and 32.6% against the composite outcome of hospitalization or death (95% CI –7.7, 58.4). The risk of death was similar among residents who did and did not receive the bivalent vaccine, but this effect was imprecisely estimated due to small sample size and event rates.

Discussion

This study evaluates immunity and clinical protection of the bivalent SARS-CoV-2 vaccination among nursing home residents. We show immunologic and clinical evidence of protection from two separate nursing home populations. Immunologically, we show evidence of sustained if also waning antibody and neutralizing activity over the six months following the administration of a SARS-CoV-2 bivalent vaccine. The target trial emulation analysis indicates a modest, non-statistically significant reduction in infection and the composite outcome of hospitalization or death over 5 months. The observational evidence lacks statistical power to definitively show adding bivalent vaccination further increases protection to those with a prior monovalent vaccination series. Because of the timing of vaccinations and availability, the specific benefit of a bivalent vaccination versus yet another monovalent vaccine dose cannot be determined. The immunologic data provide evidence for protection lasting four to six months after bivalent vaccination administration, but we do prove reductions in clinical endpoints in an observational study.

Although there is yet to be a definitely established immune correlate of protection against SARS-CoV-2 of the immune assays, it is generally held that higher titers indicate better protection.[22,23] We show a continued rise in peak neutralization titers with each boost that wanes

Variable	No bivalent (n = 3264)	Bivalent (n = 1917)	SMD	Weighted SMD[a]
Male, %	3121 (95.6%)	1831 (95.5%)	0.01	0.02
White, %	2121 (65.0%)	1193 (62.2%)	0.06	0.04
Black, %	855 (26.2%)	539 (28.1%)	0.04	0.05
Race (other), %	288 (8.8%)	185 (9.7%)	0.03	0.01
Age, mean (SD) in years	74.56 (10.1)	74.60 (9.4)	0.00	0.00
Time since last vaccination	162 (144, 214)	169 (155, 187)	0.09	0.14
SARS-CoV-2 monovalent booster:				
[9] [10] At least 1, %[a]	2917 (89.4%)	1842 (96.1%)	0.26	0.20
[11] [12] At least 2, %[a]	2210 (67.7%)	1522 (79.4%)	0.27	0.27
[13] [14] Influenza vaccine last year, %[a]	2975 (91.2%)	1841 (96.0%)	0.20	0.11
Comorbidities				
Diabetes mellitus, %[a]	1237 (37.9%)	797 (41.6%)	0.08	0.07
Major adverse cardiovascular events, %	847 (26.0%)	515 (26.9%)	0.02	0.07
Pulmonary disease, %	693 (21.2%)	463 (24.2%)	0.07	0.01
Hypertension, %	1632 (50.0%)	1056 (55.1%)	0.10	0.08
Neurologic, %	1229 (37.7%)	782 (40.8%)	0.06	0.02
Psychoses, %	980 (30.0%)	688 (35.9%)	0.13	0.06
Immunocompromised, %	450 (13.8%)	285 (14.9%)	0.03	0.05
ADRD, %	1650 (50.6%)	1047 (54.6%)	0.08	0.04
Current smoker, %	376 (11.5%)	198 (10.3%)	0.04	0.04
SARS-CoV-2 testing				
Per resident, in prior 14 days				
Median (IQR)	2 (0, 4)	2 (1, 4)	–	–
Per resident, in prior 90 days				
Median (IQR)	15 (7, 22)	17 (8, 23)	–	–
Per facility, in prior 14 days				
Median (IQR)	99 (30, 203)	109 (29, 211)	–	–
(+) SARS-CoV-2 tests in facility, prior 14 days				
Mean (SD)	1.4 (2.8)	1.2 (2.2)	0.07	0.07
Median (IQR)	0 (0, 2)	0 (0, 2)	–	–

ADRD, Alzheimer's and related dementias; SMD, standardized mean difference, IQR, intraquartile range. SD, standard deviation. [a]Adjusted with weights for probability of treatment and censoring.

Table 4: **Baseline characteristics of a cohort of Veteran nursing home residents included in a target trial emulation of 2022–2023 Bivalent COVID-19 vaccination.**

between booster doses. In our recent initial report on the bivalent vaccination, 77% of the nursing home cohort had evidence of prior infection.[10] The current study also included a group of residents that appeared to have never been infected, allowing us to perform a subgroup analysis of naive and prior infected residents. Those without prior SARS-CoV-2 infection get a larger relative titer rise with each boost than those with prior infection, but the previously infected achieve even higher peak titers. The neutralization assay is a more functional assay. Interestingly even though anti-spike levels did not rise appreciably, the neutralization titer still rises with each vaccine dose. Also, the relative difference between the naive and prior infected group in anti-spike titers is small compared to the differences noted in neutralization titers.

Even from the prior two monovalent boosters, the BA.5 neutralization activity increases with each boost suggesting a further broadening of immunity to Omicron strains. In the period of the study, September through July 2022 the circulating US strains were Omicron, transitioning from lineages BA.1 to XBB. Qu et al. show that those persons who received bivalent vaccine had more cross reactivity and anti-XBB activity than those who only received monovalent vaccine.[24] Thus, we find no evidence that another vaccination similarly spaced will undermine further broadening neutralization activity.

The observational data emulating a target trial of vaccination suggest protective benefits, with lower rates of infection, hospitalization and/or death, but we cannot rule out chance findings with significant statistical precision. Follow-up time and event rates allowed assessment of vaccine effectiveness up to 20 weeks following the bivalent vaccination. Several other studies have initial effectiveness data after the bivalent vaccination. Lin et al. published in the general population[25] and Arbel et al. and Johnson et al. in persons over age 65[26,27] and

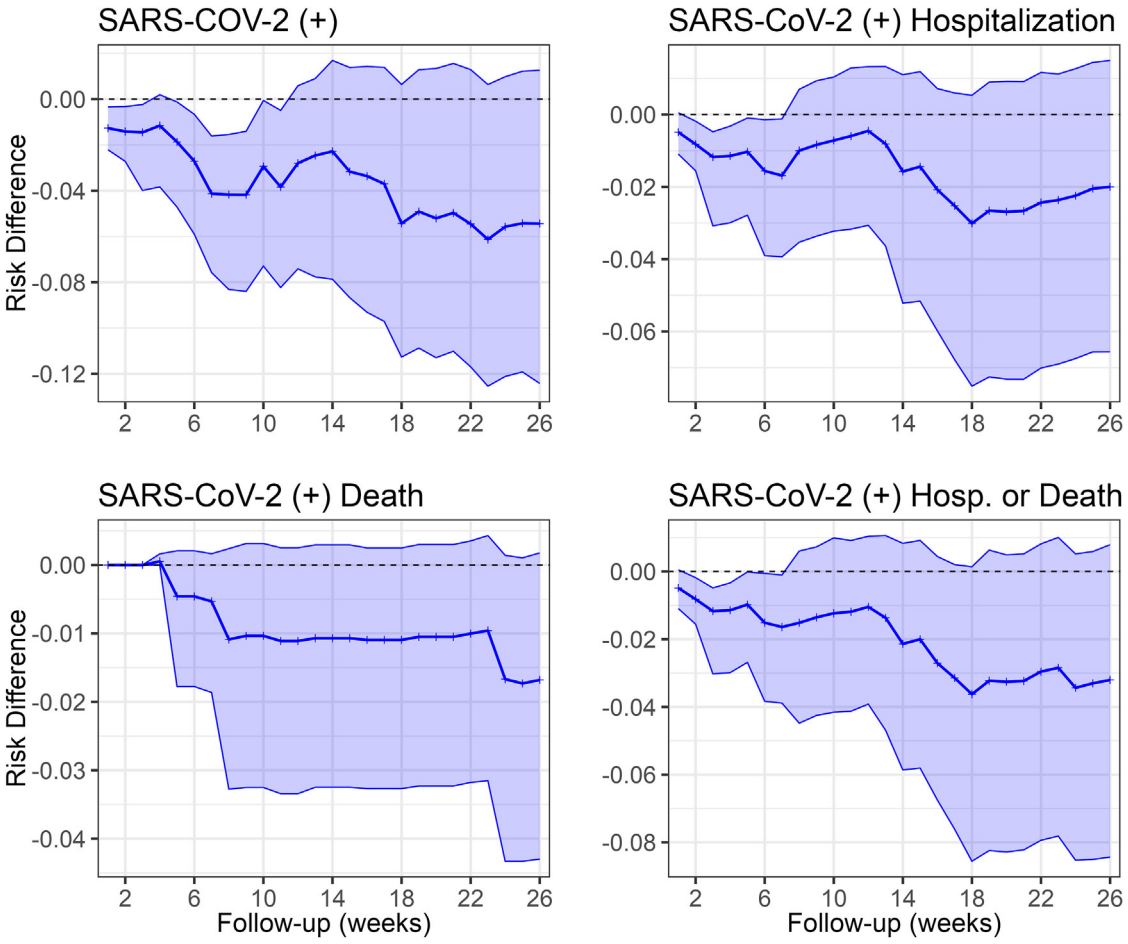

***Fig. 4:* Differences in cumulative incidence by bivalent vaccination for SARS-CoV-2 clinical outcomes up to 26 weeks.** Each solid blue line represents the difference in cumulative incidences by vaccination status with a corresponding 95% confidence interval (light blue shading) across weeks of follow-up. A vertical dashed line at 0 for reference.

both found significant benefit from bivalent vaccinations. Arbel et al.'s study population was data from one of Israel's large public health services and Johnson's data used mortality rates across the US and neither specifically focused on long-term care residents. Wong et al., published on nursing home residents in the US and showed a modest prevention of infection after bivalent boosting but was only able to focus only on infection and not specifically on severe outcomes.[28] Our data focuses on long stay nursing home residents with outcomes of infection, hospitalization and death but has limited generalizability due to few women represented in the Veteran population.

This is important to people living in close proximity and receiving frequent contact from caregivers. One problem with vaccine effectiveness estimates in the community is that vaccination status influences SARS-CoV-2 testing patterns. However, the nursing home population lives in a closed setting with more frequent testing that is not driven solely by symptom presentation. This reduces the probability that many asymptomatic or symptomatic infections were missed.

The target trial emulation approach provides a useful tool for addressing major concerns of immortal time bias to estimate vaccine effectiveness. Probability weighting is used to account for confounding by indication, and censoring weights adjust for informative censoring. Causal interpretation of these results requires strong assumptions about consistency of treatment effects of a well-defined intervention, and no residual confounding or informative censoring after adjustment. If we failed to adjust for all relevant factors, those factors were not measured properly (e.g. smoking history), or incorrectly weighted estimates, then results may be biased. Also, the use of community nursing home and Veteran nursing home populations in the same paper could mislead readers into directly contrasting results from one to the other. Broadly similar findings of vaccine effectiveness in community and Veteran populations may be expected but the Veteran

Outcome	Cumulative incidence per 1000 residents (95% CI)		Relative vaccine effectiveness, % (95% CI)*	Risk difference in cumulative incidence (95% CI)
	Bivalent vaccination	No bivalent vaccination		
Infection				
Week 12	128.5 (112.6, 144.5)	156.5 (126.7, 200.6)	17.9 (−4.4, 38.0)	−28.0 (−74.1, 5.9)
Week 16	189.7 (170.2, 209.3)	223.3 (179.3, 278.7)	15.1 (−7.8, 34.3)	−34 (−93.1, 14.3)
Week 20	230.1 (208.6, 252.9)	282.2 (225.6, 337.3)	18.5 (−5.6, 34.0)	−52.1 (−113, 13.4)
Hospitalization				
Week 12	37.8 (27.3, 50.6)	42.3 (29.5, 64.7)	10.6 (−43.7, 49.2)	−4.5 (−30.6, 13.2)
Week 16	54.2 (41.9, 67.9)	75.0 (49.2, 114.1)	27.7 (−12.8, 54.6)	−20.8 (−59.8, 7.2)
Week 20	65.3 (51.1, 80.1)	92.2 (60.3, 134.0)	29.2 (−14.2, 56.2)	−26.9 (−73.2, 9.2)
Death				
Week 12	2.4 (0.5, 5.1)	13.5 (0.7, 34.7)	82.4 (−414.6, 97.6)	−11.1 (−33.4, 2.5)
Week 16	3.2 (1.0, 6.1)	14.2 (0.8, 35.3)	77.2 (−271.0, 95.0)	−11.0 (−32.7, 2.5)
Week 20	3.7 (1.4, 7.0)	14.2 (0.8, 35.3)	74.0 (−286.7, 93.7)	−10.5 (−32.3, 3.0)
Composite				
Week 12	39.1 (28.8, 51.8)	49.6 (32.7, 76.1)	21.1 (−32.9, 55.0)	−10.5 (−39.2, 10.4)
Week 16	55.9 (43.2, 70.1)	82.9 (54.7, 124.3)	32.6 (−7.8, 56.4)	−27.1 (−67.5, 4.4)
Week 20	67.4 (53.6, 82.8)	100.0 (66.5, 145.3)	32.6 (−7.7, 58.4)	−32.6 (−82.8, 4.9)

*Relative Vaccine Effectiveness is 1 minus the Cumulative Incidence Ratio Multiplied by 100.
Cumulative risk differences persist to week 20 for the outcome of infection and composite outcome of hospitalization or death.

Table 5: **Estimated vaccine effectiveness among VA nursing home residents who did versus did not receive a bivalent vaccine.**

population is a distinctly separate healthcare system, with a differing distribution of confounders (e.g. gender, chronic conditions). Therefore the same target trial emulation in a community cohort may yield somewhat different effectiveness estimates.

As of September 11, 2023, the bivalent Pfizer-BioNTech and Moderna COVID-19 vaccines are no longer available for use in the United States. The current vaccine is a monovalent Omicron XBB1.5 vaccine that was recommended for the Fall 2023. On March 7, 2024 CDC recommended that persons over age 65 should receive 1 additional dose of the XBB1.5 vaccine if they are at least 4 months after the previous updated dose.[29] Our current and prior studies on nursing home residents including published work and one recent preprint also support this recommendation.[2,3,9–11,30] Both natural infection and vaccinations have continued to raise the lowest titers in the population over time. Yet, we will still need to confront new variants with immune-evasive properties as they continue to arise. Also, SARS-CoV-2, unlike other beta coronaviruses and influenza, has circulated widely throughout warmer months outside of the typical respiratory viral season. This complicates any decision to recommend waiting for a seasonal SARS-CoV-2 vaccine update in the fall using the seasonal influenza model for vaccination.

In summary, we report three findings. First, a monovalent or bivalent boost, both increased antibody and neutralization titers against omicron independent of prior infection history. Second, titers to vaccine and infection decay over time, but less with each boost. Third, VA nursing home residents evaluated in a similar timeframe may have benefited clinically from bivalent boost, but statistical analysis does not rule out observed differences are due to random chance.

Contributors

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KWM oversaw the response to reviewer comments.
SG, DC, KWM had access and verified the underlying data. All authors read and approved the final version of the manuscript.

Data sharing statement

The observational data using in this analysis included protected health information that cannot be publicly disseminated, however at request investigators can share the programming code which generated study results for transparency and reproducibility by others.

Declaration of interests

Stefan Gravenstein (S. G.) and David H. Canaday (D. H. C.) are recipients of investigator-initiated grants to their universities from Pfizer to study pneumococcal vaccines, Moderna to study respiratory infections, and Sanofi Pasteur and Seqirus to study influenza vaccines, and S.G. from Genentech on influenza antivirals. S. G. also receives consulting fees from GlaxoSmithKline, Icosavax, Janssen, Merck, Moderna, Novavax, Pfizer, Reviral, Sanofi, Seqirus, and Vaxart, and has received fees for speaking for Janssen, Pfizer, Moderna, GlaxoSmithKline, Sanofi, and Seqirus. KWM Investigator initiated research support from Seqirus pharmaceuticals, Sanofi-Pasteur, Genentech and Pfizer.

Acknowledgements

This work was supported by National Institute of Health AI129709-03S1 and U01 CA260539-01, Centers for Disease Control and Prevention 200-

2016-91773, Veteran Affairs Health Services Research & Development CIN 13-419 and VA BX005507-0.

The views and opinions expressed are those of the authors and do not represent the policy of the US Dept of Veterans Affairs.

Thank-you for these individuals for their substantial assistance in various parts of the study.

Case Western Reserve University: Debbie Keresztesy, Dennis Wilk, Alexandra Paxitzis, Vaishnavi Ragavapuram, Nicholas Sundheimer, Htin Aung. Brown University & Lifespan: Rosa Baier, Amy Recker, Joyce Sunday, Igor Vishnepolskiy, Evan Dickerson, Laurel Holland, Shreya Kamojjala, Alex Pralea, Aman Nanda, Tiffany Wallace. Houston Methodist Academic Institute: Eleftherios Mylonakis.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ebiom.2024.105180.

References

1 *Risk for COVID-19 infection, hospitalization, and death by age group*; 2023. https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-age.html.
2 Canaday DH, Oyebanji OA, Keresztesy D, et al. Significant reduction in vaccine-Induced antibody levels and neutralization activity among healthcare workers and nursing home residents 6 months following coronavirus disease 2019 BNT162b2 mRNA vaccination. *Clin Infect Dis*. 2022;75(1):e884–e887.
3 Nugent C, Abul Y, White EM, et al. Second monovalent SARS-CoV-2 mRNA booster restores Omicron-specific neutralizing activity in both nursing home residents and health care workers. *Vaccine*. 2023;41(22):3403–3409.
4 Markov PV, Ghafari M, Beer M, et al. The evolution of SARS-CoV-2. *Nat Rev Microbiol*. 2023;21(6):361–379.
5 Ao D, He X, Hong W, Wei X. The rapid rise of SARS-CoV-2 Omicron subvariants with immune evasion properties: XBB.1.5 and BQ.1.1 subvariants. *MedComm*. 2023;4(2):e239.
6 Zou J, Kurhade C, Patel S, et al. Neutralization of BA.4-BA.5, BA.4.6, BA.2.75.2, BQ.1.1, and XBB.1 with bivalent vaccine. *N Engl J Med*. 2023;388(9):854–857.
7 CDC. Nursing home covid-19 data dashboard. https://www.cdc.gov/nhsn/covid19/ltc-report-overview.html. Accessed April 21, 2023.
8 Ouslander JG, Grabowski DC. COVID-19 in nursing homes: calming the perfect storm. *J Am Geriatr Soc*. 2020;68(10):2153–2162.
9 Canaday DH, Carias L, Oyebanji OA, et al. Reduced BNT162b2 messenger RNA vaccine response in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-naive nursing home residents. *Clin Infect Dis*. 2021;73(11):2112–2115.
10 Canaday DH, Oyebanji OA, White EM, et al. SARS-CoV-2 antibody responses to the ancestral SARS-CoV-2 strain and omicron BA.1 and BA.4/BA.5 variants in nursing home residents after receipt of bivalent COVID-19 vaccine–Ohio and Rhode Island, September-November 2022. *MMWR Morb Mortal Wkly Rep*. 2023;72(4):100–106.
11 Canaday DH, Oyebanji OA, White E, et al. COVID-19 vaccine booster dose needed to achieve Omicron-specific neutralisation in nursing home residents. *eBioMedicine*. 2022;80:104066.
12 Garcia-Beltran WF, St Denis KJ, Hoelzemer A, et al. mRNA-based COVID-19 vaccine boosters induce neutralizing immunity against SARS-CoV-2 Omicron variant. *Cell*. 2022;185(3):457–466.e4.
13 Anastassopoulou C, Antoni D, Manoussopoulos Y, et al. Age and sex associations of SARS-CoV-2 antibody responses post BNT162b2 vaccination in healthcare workers: a mixed effects model across two vaccination periods. *PLoS One*. 2022;17(4):e0266958.
14 Eyran T, Vaisman-Mentesh A, Taussig D, et al. Longitudinal kinetics of RBD+ antibodies in COVID-19 recovered patients over 14 months. *PLoS Pathog*. 2022;18(6):e1010569.
15 Perez-Alos L, Armenteros JJA, Madsen JR, et al. Modeling of waning immunity after SARS-CoV-2 vaccination and influencing factors. *Nat Commun*. 2022;13(1):1614.
16 Xia W, Li M, Wang Y, et al. Longitudinal analysis of antibody decay in convalescent COVID-19 patients. *Sci Rep*. 2021;11(1):16796.
17 Pinheiro J, Bates D, Team RC. *nlme: linear and nonlinear mixed effects models. R package version 3.1-162*; 2023. https://CRAN.R-project.org/package=nlme. Accessed April 23, 2023.
18 Lenth RV. *Emmeans: estimated marginal means, aka least-squares means_. R package version 1.8.2*; 2023. https://CRAN.R-project.org/package=emmeans. Accessed April 23, 2023.
19 McConeghy KW, Bardenheier B, Huang AW, et al. Infections, hospitalizations, and deaths among US nursing home residents with vs without a SARS-CoV-2 vaccine booster. *JAMA Netw Open*. 2022;5(12):e2245417.
20 McConeghy KW, White EM, Blackman C, et al. Effectiveness of a second COVID-19 vaccine booster dose against infection, hospitalization, or death among nursing home residents–19 states, March 29-July 25, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(39):1235–1238.
21 Moore BJ, White S, Washington R, Coenen N, Elixhauser A. Identifying increased risk of readmission and in-hospital mortality using hospital administrative data: the AHRQ elixhauser comorbidity index. *Med Care*. 2017;55(7):698–705.
22 Feng S, Phillips DJ, White T, et al. Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection. *Nat Med*. 2021;27(11):2032–2040.
23 Gilbert PB, Montefiori DC, McDermott AB, et al. Immune correlates analysis of the mRNA-1273 COVID-19 vaccine efficacy clinical trial. *Science*. 2022;375(6576):43–50.
24 Qu P, Faraone JN, Evans JP, et al. Enhanced evasion of neutralizing antibody response by Omicron XBB.1.5, CH.1.1, and CA.3.1 variants. *Cell Rep*. 2023;42(5):112443.
25 Lin DY, Xu Y, Gu Y, Zeng D, Sunny SK, Moore Z. Durability of bivalent boosters against omicron subvariants. *N Engl J Med*. 2023;388(19):1818–1820.
26 Arbel R, Peretz A, Sergienko R, et al. Effectiveness of a bivalent mRNA vaccine booster dose to prevent severe COVID-19 outcomes: a retrospective cohort study. *Lancet Infect Dis*. 2023;23(8):914–921.
27 Johnson AG, Linde L, Payne AB, et al. Notes from the field: comparison of COVID-19 mortality rates among adults aged >/=65 Years who were unvaccinated and those who received a bivalent booster dose within the preceding 6 Months–20 U.S. Jurisdictions, September 18, 2022-April 1, 2023. *MMWR Morb Mortal Wkly Rep*. 2023;72(24):667–669.
28 Wong E, Barbre K, Wiegand RE, et al. Effectiveness of up-to-date COVID-19 vaccination in preventing SARS-CoV-2 infection among nursing home residents–United States, November 20, 2022-January 8, 2023. *MMWR Morb Mortal Wkly Rep*. 2023;72(25):690–693.
29 CDC. Stay up to date with COVID-19 vaccines. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/stay-up-to-date.html. Accessed March 27, 2024.
30 Abul Y, Nugent C, Vishnepolskiy I, et al. Broad immunogenicity to prior SARS-CoV-2 strains and JN.1 variant elicited by XBB.1.5 vaccination in nursing home residents. *medRxiv*. 2024:24303684.