COVID-19 vaccine booster dose needed to achieve Omicron-specific neutralisation in nursing home residents

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Summary

Background Nursing home (NH) residents have borne a disproportionate share of SARS-CoV-2 morbidity and mortality. Vaccines have limited hospitalisation and death from earlier variants in this vulnerable population. With the rise of Omicron and future variants, it is vital to sustain and broaden vaccine-induced protection. We examined the effect of boosting with BNT162b2 mRNA vaccine on humoral immunity and Omicron-specific neutralising activity among NH residents and healthcare workers (HCWs).

Methods We longitudinally enrolled 85 NH residents (median age 77) and 48 HCWs (median age 51), and sampled them after the initial vaccination series; and just before and 2 weeks after booster vaccination. Anti-spike, anti-receptor binding domain (RBD) and neutralisation titres to the original Wuhan strain and neutralisation to the Omicron strain were obtained.

Findings Booster vaccination significantly increased vaccine-specific anti-spike, anti-RBD, and neutralisation levels above the pre-booster levels in NH residents and HCWs, both in those with and without prior SARS-CoV-2 infection. Omicron-specific neutralisation activity was low after the initial 2 dose series with only 28% of NH residents' and 28% HCWs' titres above the assay's lower limit of detection. Omicron neutralising activity following the booster lifted 86% of NH residents and 93% of HCWs to the detectable range.

Interpretation With boosting, the vast majority of HCWs and NH residents developed detectable Omicron-specific neutralising activity. These data provide immunologic evidence that strongly supports booster vaccination to broaden neutralising activity and counter waning immunity in the hope it will better protect this vulnerable, high-risk population against the Omicron variant.

Key words: COVID-19; Vaccination; Booster; Omicron; Geriatrics; Long-term care

Introduction

The SARS-CoV-2 Omicron variant has rapidly become the dominant variant worldwide. Illness from the Omicron strain is reportedly less virulent, resulting in less severe illness and hospitalisation than previous strains, but more transmissible.[1,2] As has been seen in the overall population, US nursing homes (NH) have experienced a significant increase in infections among residents and staff due to Omicron.[3] Much of the

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Research in context

Evidence before this study

Pre-print and published data in PubMed, medRxiv, bioRxiv concerning COVID-19 vaccine boosting in general and also specific to the nursing home space were reviewed. The authors determined that there is limited longitudinal data concerning immunologic response to COVID-19 vaccine boosting in the nursing home population.

Added value of this study

These findings illustrate in detail the Omicron-specific response to boosters in nursing home residents, a frail and vulnerable population. These findings also inform our understanding of how tens of millions of community-dwelling frail older adults with similar clinical and functional limitations may respond to boosters.

Implications of all the available evidence

Currently, with widespread vaccine breakthrough infections and outbreaks in nursing homes, these novel Omicron-specific data strongly support a campaign to increase vaccine booster administration in nursing homes. These data also indicate that a three-dose COVID-19 mRNA vaccine series against wild-type virus may be needed to obtain adequate serologic response to Omicron and potentially other variants. These data provide strong rationale for further clinical studies to determine the optimal timing of the third dose that could lead to changes in the practice patterns and guidelines.

enormous morbidity and mortality experienced at the start of the pandemic occurred in NHs, and that was significantly mitigated by early and widespread vaccination of NH residents and staff.[4,5] How to optimally vaccinate this population and maintain immunity in the face of new SARS-CoV-2 variants remains a critical question.

Vaccine-induced antibody levels and neutralisation titres in NH residents completing the two-dose BNT162b2 mRNA vaccine series fell by more than 80% in the 6 months following vaccination, and neutralisation antibodies became undetectable in 57% of residents.[6] In the same paper, healthcare workers (HCWs) experienced a similar decline in antibody levels, even if they had prior infection. The increasing incidence of breakthrough SARS-CoV-2 infections in vaccinated individuals coincident with the marked post-vaccination antibody decline,[7-10] especially among frail older adults, helped inform the decision by the Centers for Disease Control and Prevention (CDC) to recommend booster doses. This was prescient given the emergence of the highly infectious Omicron variant, notable for its mutations conferring potential immune evasion.[11,12] Current reports on post-booster vaccination titres are limited to

healthier older adults where higher titres were elicited with a third dose[13,14] and one cross sectional nursing home study showing a 3rd dose increase neutralisation to wild type and beta variant.[15] Recent studies in primarily younger populations have shown initial poor neutralisation titres to Omicron following a two-dose mRNA vaccine series, but significant increases with boosting.[16-18] This study sought to determine if the booster dose of vaccine afforded a similar increase in antibody levels to spike and receptor binding domain (RBD) as well as neutralising antibody titres to Wuhan and Omicron variants in the NH population.

Methods

Ethics

Study approval was obtained from the WCG institutional review board, study numbers 1316159 and 1283160. All participants or their legally authorised representatives provided informed consent.

Participants

Participants who were previously evaluated over 6 months following initial SARS-CoV-2 BNT162b2 mRNA vaccination were eligible for inclusion.[6,19] Residents and HCWs were sampled from 3 community NH and one state Veterans Home. Additionally, HCWs were recruited from the Cleveland Department of Veterans Affairs Medical Center. All sites administered the BNT162b2 mRNA vaccine between December 2020 and January 2021 followed by a second dose 3 weeks later during the emergency use authorization period, and then a booster dose with the same vaccine 6 to 9 months after primary series. The mean time from 2nd dose to booster was 264 days and >85% of our population was vaccinated within 7 days of this mean interval. Minimum interval was 239 days and maximum interval was 309 days.

At the time of initial vaccination, participants were deemed to have a "*prior infection*" if they had a known history of SARS-CoV-2 infection confirmed by PCR or antigen test, and/or detectable antibody levels to SARS-CoV-2 spike, RBD, and Nucleocapsid (N protein) from serum collected prior to their first dose. Otherwise, participants were classified as "*infection-naive.*" Throughout the course of the longitudinal study, if a subject was PCR, antigen positive and or developed anti-N protein positivity they were removed from the analysis. Cut-off for positive antibody response to the S, RBD and N proteins are described below. In our prior study,[6,19] participants with prior infection achieved and sustained higher antibody levels after vaccination than those who were infection-naive. For this reason we have continued to study these four groups separately: NH residents

with and without prior infection; and HCWs with and without prior infection.

Serum samples were obtained at three time points: 2 weeks after completion of the primary series; 0-14 days before booster (generally 8-9 months after primary series); and 14±3 days after booster.

Anti-spike, anti-RBD and anti-N assay

Immune response to the vaccine was assessed using a bead-multiplex immunoassay using Wuhan strain.[19] Anti-spike IgG generated a result of Binding Antibody Units (BAU/ml) based on the Frederick National Laboratory standard which was calibrated to the WHO 20/136 standard, and anti-RBD generated a result in arbitrary units (AU). Stabilised full-length spike protein (aa 16-1230, with furin site mutated), RBD (aa 319-541), and full length N (aa1-419) were conjugated to magnetic microbeads (Luminex) and Magpix assay system (Bio-Rad, Inc). The mean fluorescent index was recorded after detecting antigen-specific IgG in participant serum using PE-conjugated Donkey F(ab)2 anti-human IgG, with Fcγ (Jackson Immunological). Thresholds for establishing infection based on seroconversion were determined using serum samples collected from Northeast Ohio adults pre-pandemic (N=167) and serum samples collected from individuals in early 2020 prior to significant SARS-CoV-2 infections in the area (N=161 for a total of N=328 negative controls). Cut-off for a negative response were based on values falling below the mean plus three standard deviations of N, spike and RBD of the Wuhan strain of the negative controls. Using WHO standardised BAU/ml for Wuhan spike protein, this corresponds to 3.8 BAU/ml. For RBD this corresponds to 6.0 AU/ml. For the full-length N protein, we did not normalise values to AUs. We ran all samples at a 1:400 dilution. If the mean fluorescent index (MFI) is >866 for N protein we consider this a positive response to the N protein. If a participant had elevated antibodies to the N protein (prior exposed individuals), we considered a new SARS-CoV-2 exposure to have at least a 2 fold rise in antibody levels to the N protein.

SARS-CoV-2 pseudovirus neutralisation assay

To determine the neutralising activity of vaccine recipients' sera against coronaviruses, we produced lentiviral particles pseudotyped with spike protein based on the Wuhan and Omicron strains as previously described.[16,20] Briefly, neutralisation assays were performed using a Fluent 780 liquid handler (Tecan) in 384-well plates (Grenier). Three-fold serial dilutions ranging from 1:12 to 1:8,748 were performed and added to 50−250 infectious units of pseudovirus for 1 hour. pNT50 values were calculated by taking the inverse of the 50% inhibitory concentration value for all samples

with a pseudovirus neutralisation value of 80% or higher at the highest concentration of serum. The lower limit of detection (LLD) of this assay is 1:12 dilution.

Statistical analysis

For each of the 4 groups at each time point, we determined the anti-spike, anti-RBD, and neutralisation geometric mean titres. We then assessed the geometric mean fold rise (GMFR) from 2 weeks pre- to 2 weeks post-booster, and from 2 weeks post-initial vaccination to 2 weeks post-booster within each group using a two-sided t-test on the log-transformed fold changes. The log transformation reduces the dispersal and distribution of the log (fold rise) values. These were checked for finite variance and extreme values towards meeting the t-test assumptions. We present the t-test as its assumptions are met, it is robust to non-normality, and it provides familiar 95% confidence intervals. To assess changes in detectable Omicron neutralising titres, we performed McNemar's test comparing detectable titres after the post-initial vaccination and post-booster paired within the subject and separately for each group. All p-values are presented without adjustment. All analyses were performed in R version 4.0.3.

Role of the funding source

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Results

We sampled 85 NH residents (median age 77, 34% female, 84% White) and 48 HCWs (median age 51, 48% female, 79% White). More detailed demographics for each subpopulation are summarised in Table 1. Table 2 presents the geometric mean titres (GMT) at each timepoint for all groups and all immunologic tests, along with the GMFR comparing levels pre vs. post-booster, and post-initial vaccine series versus post-booster. In all groups, the Wuhan anti-spike, anti-RBD, and neutralisation GMT declined from 2 weeks after the initial series to the pre-booster timepoint, with titres being the lowest among infection-naive NH residents (Table 2, Figures1 and 2).

We previously reported loss of antibody and neutralisation titers to Wuhan strain at 6 month post initial vaccine series of 82-95%.[6] The preboost samples here were drawn 2-3 months later and as a group they still have continued losses in antibody titers (Table 2). Two naive HCW and 5 naive NH residents had seroreverted their anti-spike by the pre-boost time point to below detectable anti-spike levels but were successfully boosted

	HCW prior SARS-CoV-2	HCW SARS-CoV-2 naive	NH residents prior SARS-CoV-2	NH residents SARS-CoV-2 naive
nSubjects	18	30	36	49
Age Median (IQR)	47 (38,55)	53 (46,58)	82 (75,89)	74 (68,84)
Age Years (Range)	30-63	31-67	63-96	48-99
Male (%)	10 (56%)	15 (50%)	23 (64%)	33 (67%)
Female	8 (44%)	15 (50%)	13 (36%)	16 (33%)
Race/ethnicity				
White (%)	15 (83%)	23 (77%)	27 (75%)	44 (90%)
Black (%)	3 (17%)	1 (3%)	9 (25%)	5 (10%)
Hispanic (%)	0 (0%)	2 (7%)	0 (0%)	0 (0%)
Asian (%)	0 (0%)	4 (13%)	0 (0%)	0 (0%)

Table 1: Subject Demographics.

while one 95 year old NH resident never achieved anti-spike titers even after boosting (Figure 2).

Figure 1 demonstrates the titer results of the pseudo-virus neutralisation assay with Wuhan and Omicron strains for individual subjects at all three time points studied. Figure 3 reports the proportion of individuals with a neutralising titer above the lower limit of detection of the assay. Across all four groups, Omicron neutralisation GMT markedly increased following the booster dose compared to levels after the initial 2-dose series (t-test p<0.001 in all, Table 2 and Figure 1a). Specifically, in the infection-naive NH resident group Omicron-specific neutralisation GMT increased from 12.6 to 69.5, a GMFR of 5.5 from the post-primary vaccine series to post-booster (Table 2). This produced detectable Omicron neutralisation titres above the lower limits of detection (LLD) in 73% of individuals, compared to 4% after the primary series (Table 2 and Figure 3 lower right panel). In the prior infected NH resident group, GMT increased from 44.9 to 293, a GMFR of 6.5 with 97% of individuals reaching detectable Omicron neutralisation titres compared to 47% after the primary series (Table 2 and Figure 3 lower left panel). In the infection-naive HCW group, Omicron-specific neutralisation increased from a GMT of 30.6 to 173, a GMFR of 5.6 with 93% of individuals achieving detectable titres vs. 29% after the primary series (Table 2 and Figure 3 upper right panel). In the prior infected HCW group, GMT increased from 20.6 to 372, a GMFR of 18 with 94% of individuals reaching detectable Omicron neutralisation titres vs. 28% after the primary series (Table 2 and Figure 3 upper left panel). The proportion of subjects with detectable Omicron neutralisation levels from primary series to post-booster is significant in all four groups (Figure 3, McNemar p < 0.001).

Across all groups, we observed the highest lifetime neutralisation, anti-spike, and anti-RBD titres to the Wuhan (vaccine) strain 2 weeks following booster vaccination (Table 2, Figures 1 and 2). Differences in neutralisation levels to the Wuhan strain from 2 weeks after the initial series to 2 weeks post-booster were statistically significant for infection-naive NH residents (GMFR = 5.6; 95% CI 3.5-8.8; t-test p=<0.001); and infection-naive HCWs (GMFR = 2; 95% CI 1.1-3.6; p=0.021); but did not achieve statistical significance for prior-infected NH residents or HCWs (Table 2, Figure 1). Differences in anti-spike levels from 2 weeks after the initial series to 2 weeks post-booster were statistically significant across groups: infection-naive NH residents GMFR 9.3 (95% CI 6-14.4; p<0.001); prior-infected NH residents GMFR 3.1 (95% CI 1.9-5.1; p<0.001); infection-naive HCWs GMFR 3.3 (95% CI 2.5-4.3; p<0.001); and prior-infected HCWs GMFR 3.3 (95% CI 1.3-8.4; p=0.015) (Table 2, Figure 2a). A similar pattern was observed for GMFR in anti-RBD from 2 weeks after the initial series to 2 weeks post-booster (Table 2, Figure 2b).

The sample size limitation does not give us the power to readily detect differences between the sexes. We have however included a figure differentiating the male and female subjects for all of the immunology assays (sup. Figure 1). With this sample size there are no differences between the sexes in any group.

Discussion

We report significant increases in Omicron neutralisation titres in NH residents following booster vaccination. This is similar to what we and others observed in younger, healthier HCWs.[16-18] Our study extends this observation to the more frail NH population because of their much greater risk for morbidity and mortality from SARS-CoV-2. Previous studies have shown that SARS-CoV-2-specific B cells persist following vaccination and/or SARS-CoV-2 infection with comparatively little decline compared to antibody levels that continue to undergo affinity maturation.[21] Thus boosting increases the breadth and levels of antibodies to more effectively neutralise Omicron and potentially future variants. There are mechanistic data showing increased B-cell maturation and higher avidity antibodies over time after mRNA vaccination.[22-24] Three exposures to

Group	Ab	Subjects n	GMT (95%) 2W post	GMT (95%) pre-boost	GMT (95%) post-boost	GMFR, (95%) pre- to post- boost	p-value	GMFR, (95%) 2W to post-boost	p-value
HCW	Spike	16	815 (351, 1891)	163 (91.7, 288)	2705 (1995, 3669)	16.6 (9.9, 28.1)	< 0.001	3.3 (1.3, 8.4)	0.015
prior	RBD	16	6817 (2842, 16352)	832 (408, 1696)	23072 (15689, 33928)	27.7 (14.8, 52.1)	< 0.001	3.4 (1.3, 8.7)	0.015
SARS-CoV-2	Neut	18	1073 (475, 2426)	39.6 (17.7, 88.3)	1095 (623, 1927)	27.7 (13.1, 58.8)	< 0.001	1.0 (0.6, 1.9)	0.944
	Neut Omicron	18	20.6 (11.8, 36.1)	28.1 (16.5, 47.8)	372 (202, 683)	13.2 (6.0, 29.3)	< 0.001	18 (8.7, 37.6)	< 0.001
HCW	Spike	25	745 (596, 931)	50.4 (28.4, 89.4)	2432 (2081, 2843)	48.2 (27.1, 85.9)	< 0.001	3.3 (2.5, 4.3)	< 0.001
SARS-CoV-2 naive	RBD	27	5194 (3854, 7001)	292 (167, 509)	18824 (15745, 22504)	64.6 (37.3, 112)	< 0.001	3.6 (2.5, 5.2)	< 0.001
	Neut	28	431 (265, 699)	15.8 (11.6, 21.5)	870 (668, 1132)	55.1 (37, 81.9)	< 0.001	2 (1.1, 3.6)	0.021
	Neut Omicron	28	30.6 (16.2, 57.8)	17.8 (11.9, 26.5)	173 (102, 293)	9.7 (6.1, 15.5)	< 0.001	5.6 (2.6, 12.2)	< 0.001
NH residents prior	Spike	33	957 (630, 1453)	79.9 (40.7, 157)	2980 (2030, 4376)	37.3 (17.6, 79.3)	< 0.001	3.1 (1.9, 5.1)	< 0.001
SARS-CoV-2	RBD	33	7497 (4316, 13022)	279 (105, 739)	24065 (15211, 38073)	86.2 (30.3, 246)	< 0.001	3.2 (1.7, 6.2)	0.001
	Neut	32	1311 (697, 2469)	34.6 (19.2, 62.1)	1159 (722, 1862)	33.5 (18.7, 60.2)	< 0.001	0.9 (0.5, 1.6)	0.659
	Neut Omicron	32	44.9 (23.8, 84.8)	29.3 (17.7, 48.4)	293 (162, 529)	10 (6.1, 16.3)	< 0.001	6.5 (3.7, 11.6)	< 0.001
NH residents SARS-CoV-2 naive	Spike	46	196 (114, 337)	15.6 (10.7, 22.6)	1821 (1183, 2804)	117 (79.3, 172)	< 0.001	9.3 (6, 14.4)	< 0.001
	RBD	46	1018 (600, 1730)	38.5 (22.3, 66.5)	12540 (6992, 22491)	326 (205, 519)	< 0.001	12.3 (7.3, 20.7)	< 0.001
	Neut	43	89.7 (59.2, 136)	14.7 (11.1, 19.4)	500 (305, 817)	34 (20.6, 56.1)	< 0.001	5.6 (3.5, 8.8)	< 0.001
	Neut Omicron	26	12.5 (11.5, 13.7)	12.6 (11.7, 13.6)	69.5 (36.2, 134)	5.5 (2.9, 10.3)	< 0.001	5.5 (2.8, 10.9)	< 0.001

Table 2: **Antibody and neutralisation titres.**
Anti-spike in BAU/ml, Anti-RBD in AU, Neut is Wuhan (vaccine) strain Neut Omicron stain both in pNT50. Abbreviations: 2W post; 2 weeks post-primary vaccination series, pre-boost; pre-booster dose, post-boost; 14-days post-booster dose, GMT; geometric mean titre, GMFR; geometric mean fold rise.
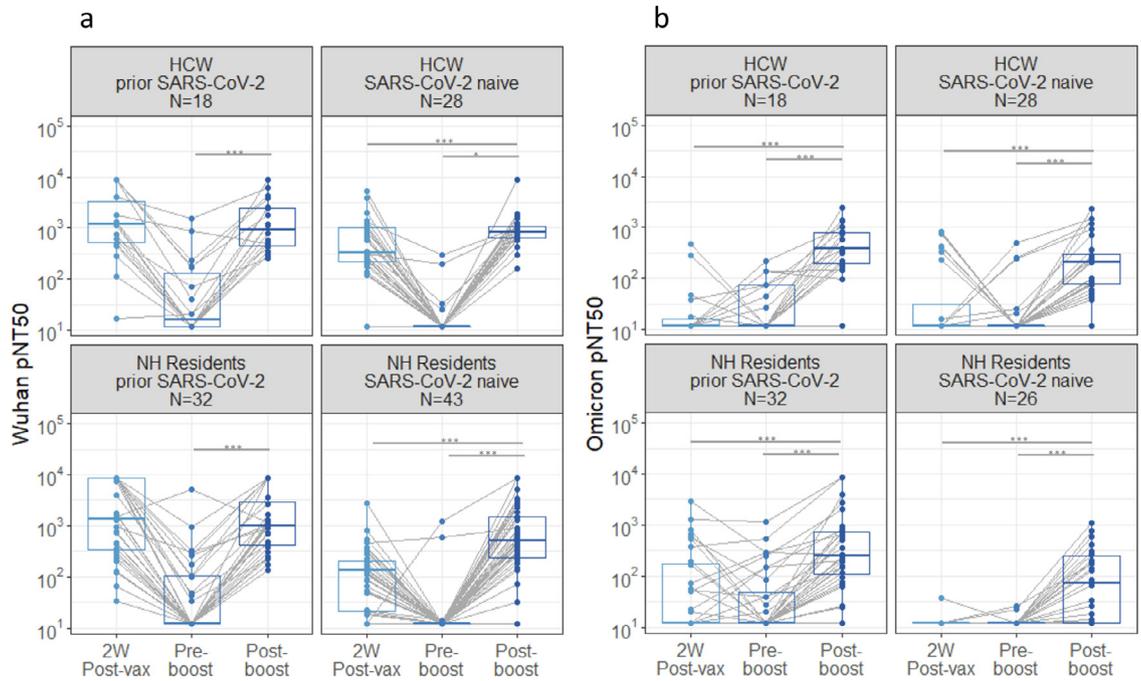
Articles

Figure 1. Neutralisation titres over time pre- and post-boost with BNT162b2 mRNA vaccination in HCW and NH residents, with and without prior SARS-CoV-2 infection. a. Wuhan (vaccine) strain, b. Omicron strain. Pseudovirus neutralisation (pNT50) values are shown. The upper limit of detection of the assay is 1:8748 and the lower limit of detection (LLD) of the neutralisation assay is 1:12. The centre line indicates the median and the bottom and top of the box indicate the first and third quartile, respectively. The lower and upper whiskers extend from the first and third quartile lines, respectively, to the smallest and largest values no more than 1.5 times the interquartile range (height of box) away from the first and third quartile values with ∗ indicating $p < 0.05$ and ∗∗∗ indicating $p < 0.001$. 2 weeks (2W Post-vax) after primary vaccination series and Pre-boost (generally 8-9 months after the first two-dose vaccination series) and Post-boost which is 14±3 days after vaccine boost.

SARS-CoV-2 antigen, whether all vaccines or one being natural infection, results in higher anti-Omicron immunity with a rise in antibody avidity.[25]

As a group, our data show a consistent drop in spike and RBD antibody levels in naive individuals over the 6-9 month period. The magnitude of the drop is more variable, and less pronounced among participants with prior SARS-CoV-2 infection. A few individuals' antibody levels rise during this period who have no other evidence of SARS-CoV-2 infection. These data are consistent with previous studies showing a similar rise in antibodies without apparent new SARS-CoV-2 infection.[23,26] This boosting might occur from cross-reaction to endemic coronaviruses as suggested by Ortega, et al and even by heterologous boosting to other respiratory viruses.[27-29] Another possibility is that these might represent low affinity polyclonal antibodies that cross-react with spike and RBD.

Our data here and in a previous report on these cohorts show that having prior infection and then being vaccinated, even when a NH resident, induces excellent anti-spike and Wuhan specific neutralisation titers.[19] Our Omicron-neutralisation focused data however show that remote prior infection and then the prior vaccine

series is still not adequate compared to vaccine boosting to elicit higher titres of Omicron neutralisation activity. The ramifications of these favourable anti-Omicron immunologic observations after boosting have some clinical substantiation in the general population. Three large metadata studies focused on Omicron outbreaks, with over 70% of the study populations under age 50, reported protection against severe disease with just a two-dose series, but improved protection after a 3rd dose.[30-32] A recent metadata study from Israel in long-term care residents in the pre-Omicron time window, followed residents for 6 weeks after booster and found reduction in both infection rates and hospitalisation.[33]

In the era of Omicron with additional future variants likely on the horizon, our data suggest that the current mRNA vaccine formulation to Wuhan strain may most effectively be given as a 3-dose rather than 2-dose series in the HCW and the frail NH population. The significant outstanding issue remains when to give the third dose. Ours and other published studies in HCWs show a particular boost to Omicron-specific responses following a third dose at least 5 months after the initial 2-dose series.[16,17] The 3rd dose timing could warrant further examination if a regimen that gives the 3rd dose prior to
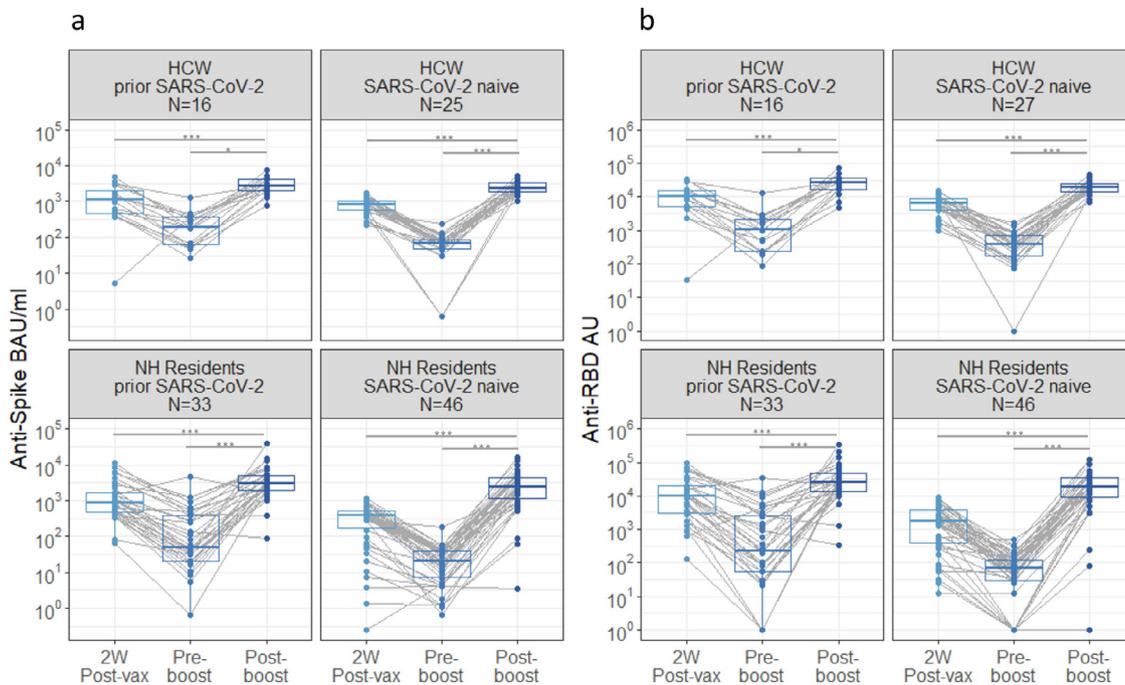
Figure 2. Anti-spike and Anti-Receptor binding domain (RBD) levels over time pre- and post-boost with BNT162b2 mRNA vaccination in healthcare workers (HCWs) and nursing home (NH) residents, with and without prior SARS-CoV-2 infection. a. Anti-spike values depicted in the binding arbitrary units/millilitre (BAU/ml) based on the WHO standard. The cutoff for a positive anti-spike response over pre-pandemic controls is 3.8 BAU/ml. **b.** Anti-RBD values depicted in the arbitrary units (AU) with ∗ indicating $p<0.05$ and ∗∗∗ indicating $p<0.001$. Both proteins are to Wuhan strain. 2 weeks (2W Post-vax) after primary vaccination series and Pre-boost (generally 8-9 months after the first two-dose vaccination series) and Post-boost which is 14±3 days after vaccine boost.

5 months were to be considered. This type of shorter 3-dose regimen has already been previously recommended by CDC for transplant recipients and others with chronic immune suppression and just had expanded approval for those with higher risk conditions or over age 50.

Based on pre-Omicron studies that show strong correlation between immune responses and protection[34,35] and similar patterns of immunologic response to the 3rd dose among HCW and NH residents in our study, we believe the much higher Omicron-specific neutralising activity will result in substantially better protection against severe disease in the NH population as well. In the pre-Omicron era, Feng et al estimated that an anti-spike of 264 BAU/ml achieved 80% protection from symptomatic infection.[35] Using the same WHO standard, we found that 95% of the NH residents reached this anti-spike level after boosting, compared with only 82% 2 weeks after the initial two-dose series. After boosting, the magnitude above this level was substantial with anti-spike GMT increasing to 1821 BAU/ml vs 196 BAU/ml after the primary vaccine series in the infection-naive NH residents (Table 2). These significantly higher levels should extend the time during which titres remain above the 264 BAU/ml "protective"

threshold, at least for the Wuhan strain. Neutralisation titres had a similar GMT increase achieving much higher levels after boosting to 500 pNT50 vs 90 pNT50 after the primary series. Similar Omicron protective titre estimates remain unavailable to date.

A fairly large proportion of infection-naive NH residents proved to be hypo-responders with low anti-spike, anti-RBD and neutralisation levels after the initial 2-dose vaccine series.[19] The booster dose increased the hyporesponsive group's antibody levels closer to the median level of the rest of the population. These data suggest that populations who are immunologically like those living in nursing homes might benefit from much earlier receipt of a third "consolidating" dose, similar to the three-dose strategy recommended by CDC for immunosuppressed individuals. We take encouragement from the finding that most of this frail NH population can eventually mount a substantial antibody response to these vaccines, even if only after three doses.

Limitations of this study include the small sample size available from our prior cohort. Subjects we could not re-enroll either refused booster vaccination, no longer worked (HCWs) or lived (residents) in the facility, or were lost-to-follow-up due to non-COVID-19 interim mortality. In addition, we had an atypically high proportion of
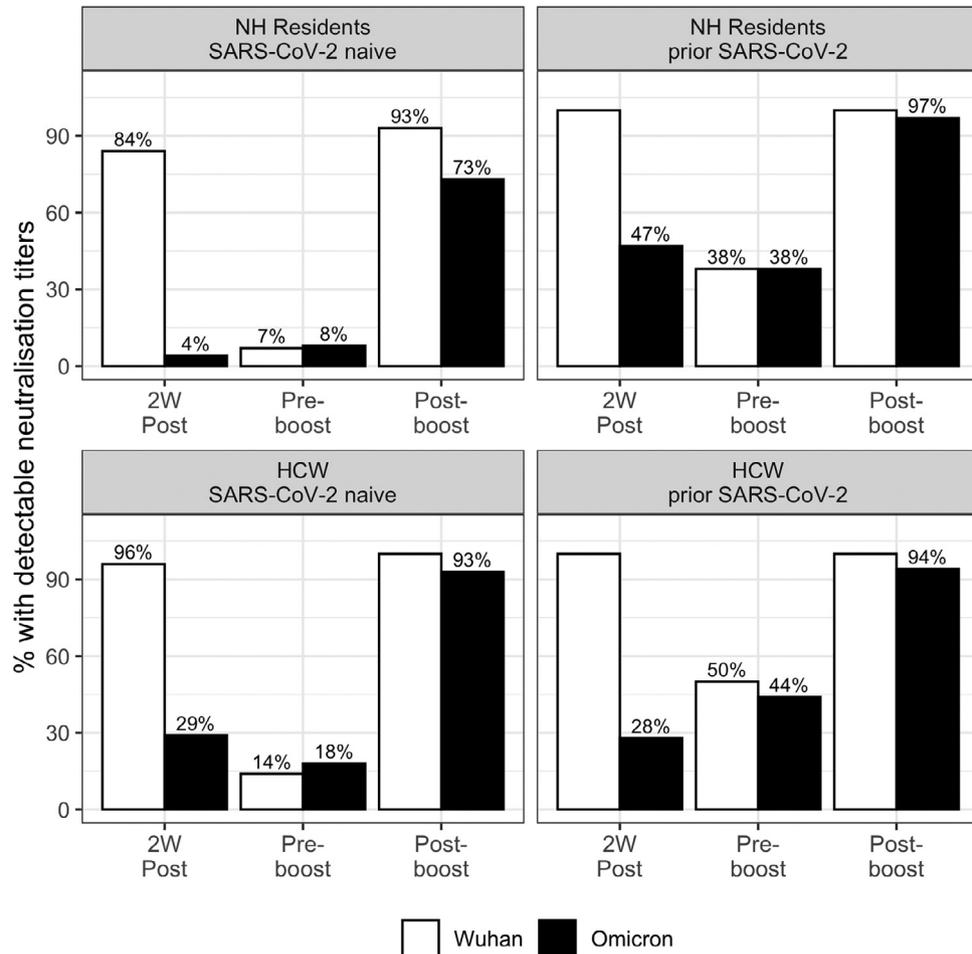
Figure 3. Subjects with detectable Omicron neutralisation titres. Indicates the percentage of subjects in each clinical group with detectable neutralisation titres above LLD for Wuhan (vaccine) vs Omicron strains.

males (66%) for the typical NH population due to many being recruited from the overwhelmingly male population living at the state Veterans home. Although one prior study indicated higher spike antibody to SARS-CoV-2 vaccine in women,[36] another reported higher pre-fusion spike antibody in men,[24] and others have not reported significant differences in SARS-CoV-2 vaccine responses by sex.[37,38] Together, these and our study leave the importance of sex differences unanswered. Also, we did not assess T-cell contribution to vaccine-induced immunity.

In conclusion, our data provide strong immunologic evidence that offers support for booster vaccination for NH residents and staff to counter waning immunity and better protect this population from complications of SARS-CoV-2 infection. Furthermore, while there are now several reports of booster vaccination offering increased clinical protection in the general population even after the emergence of Omicron,[30-32,39-41] our data provide evidence specific to the frail NH population, and may inform decisions to boost immunologically-similar older adults residing in other settings.

Data sharing

The de-identified dataset and related codes for analysis will be made available to researchers on request after publication. Requests for data should be addressed to the corresponding authors.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ebiom.2022.104066.

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