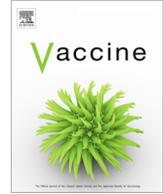




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Short communication

Second monovalent SARS-CoV-2 mRNA booster restores Omicron-specific neutralizing activity in both nursing home residents and health care workers

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ABSTRACT

We examined whether the second monovalent SARS-CoV-2 mRNA booster increased antibody levels and their neutralizing activity to Omicron variants in nursing home residents (NH) residents and healthcare workers (HCW). We sampled 376 NH residents and 63 HCW after primary mRNA vaccination, first and second boosters, for antibody response and pseudovirus neutralization assay against SARS-CoV-2 wild-type (WT) (Wuhan-Hu-1) strain, Omicron BA.1 and BA.5 variants. Antibody levels and neutralizing activity progressively increased with each booster but subsequently waned over 3–6 months. NH residents, both those without and with prior infection, had a robust geometric mean fold rise (GMFR) of 8.1 (95% CI 4.4, 14.8) and 7.8 (95% CI 4.8, 12.9) respectively in Omicron-BA.1 subvariant specific neutralizing antibody levels following the second booster vaccination ($p < 0.001$). These results support the ongoing efforts to ensure that both NH residents and HCW are up-to-date on recommended SARS-CoV-2 vaccine booster doses.

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1. Introduction

The Omicron SARS-CoV-2 variant and its sub-lineages including BA.1, BA.2, BA.2.12.1, BA.4 and BA.5 are more transmissible [1–3].

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SARS-CoV-2 continues to impact nursing home (NH) residents disproportionately. To date, more than 1.3 million NH residents in the US have been infected with SARS-CoV-2 and over 160,000 have died [4]. Vaccination is the best intervention to reduce both mortality and morbidity in NH residents [5–7]. However, in the setting of new SARS-CoV-2 variants, there is still some uncertainty as to the optimal timing and frequency of consecutive booster vaccinations in this frail population.

In previous studies, six months following the two-dose BNT162b2 mRNA monovalent primary vaccine series, vaccine-induced antibody and neutralization titers in NH residents declined by more than 80%, and neutralization antibodies became undetectable in 57% of NH residents [8].

Interestingly, a first monovalent booster dose significantly enhanced vaccine-specific anti-spike and anti-receptor binding domain (RBD) antibody levels and neutralization activity above the pre-booster levels in NH residents [9]. In this study, we assessed anti-spike, anti-RBD antibody levels and neutralizing activity for Wuhan, Omicron BA.1 and BA.5 following a second monovalent booster in NH residents.

2. Methods

2.1. Ethical approval.

This study was approved by the WCG Institutional Review Board. All participating individuals or their legally authorized representatives provided informed consent to be recruited into the study.

2.2. Study design and study population

The current analysis is part of an ongoing study [9,10] in which NH residents and healthcare workers (HCWs) are consented and serially sampled before and after each SARS-CoV-2 vaccine dose. This analysis includes data collected between August 23, 2021, and September 8, 2022.

We recruited HCW and NH residents for this study. HCWs worked at 4 NH buildings, 2 Cleveland area hospitals, and Case Western Reserve University; they had access to the same vaccines as the NH residents from 18 nursing homes in Ohio and 16 nursing homes in Rhode Island. Residents who received SARS-CoV-2 mRNA vaccines [(BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna))] were included, and those who received the Ad26.COV2.S (Janssen) vaccine were excluded. Participants received their first booster dose 8–9 months after the primary vaccination series, and their second booster 4 to 6 months after the first booster. We report results from blood samples obtained at time points prior to and following the two booster doses. Participants were sampled at five time points: (1) pre-first booster (8–9 months post-primary series); (2) approximately 14 days post-first booster; (3) 4–6 months post-first booster; (4) approximately 14 days post-second booster; and (5) approximately 3 months post-second booster. In the setting of breakthrough infection during the study, the timepoints from their breakthrough and through the post-vax of the next dose were excluded from this analysis. Participants were included in the analysis if 2 or more included samples across these five time points were available.

2.3. Definitions and description of data

2.3.1. Prior or breakthrough infection

We defined a participant as having had a prior SARS CoV-2 infection at the time of each vaccine dose based on (1) prior documentation in their medical chart of a positive polymerase chain reaction or antigen test; or (2) a significant increase in SARS-CoV-2 antibody levels that could not be explained by vaccination. Laboratory criteria supporting recent, or interval infection were a rise outside of lab variance of anti-spike, anti-RBD, nucleocapsid, or neutralizing assay results not accounted for by vaccination history.

2.3.2. Infection naive

We defined participants as “infection naive” at each time point if they did not meet the above criteria for prior infection. The prior infection/naive classification could change over time with infection history, i.e., individuals who had a SARS-CoV-2 infection between

their first & second booster would be in the naive category for the first booster & ‘prior infection’ category for the second booster.

2.3.3. Antispike and anti-RBD assay

We assessed vaccine-induced immune response using bead-multiplex immunoassay for anti-spike and RBD for SARS-CoV-2 wild-type (WT) (Wuhan-Hu-1) strain and Omicron BA.1 and BA.5 variants variant as previously described [9]. Stabilized full-length spike protein (aa 16–1230, with furin site mutated), RBD (aa 319–541) from SARS-CoV-2 wild-type (WT) (Wuhan-Hu-1) strain and Omicron BA.1 variant and BA.5 variants, 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.1, BA.5 and anti-RBD from both strains are arbitrary units (AU)/ml.

2.3.4. SARS-Cov-2 pseudovirus neutralization assay

We produced lentiviral particles pseudotyped with spike protein based on the Wuhan and BA.1 and BA.5 strains as previously described to define the neutralizing activity of vaccine recipients’ sera against coronaviruses [11]. We performed three-fold serial dilutions that ranged from 1:12 to 1:8748 and added to 50–250 infectious units of pseudovirus for 1 h. pNT50 values were calculated by taking 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. The lower limit of detection (LLD) of this assay is 1:12 dilution.

2.4. Statistical analysis

All analyses were performed in R version 4.2.2. Distributions of assays at the 5 time points were presented in boxplots. For all subjects with consecutive timepoints available, we assessed the geometric mean titer and its 95% confidence interval for all assays, strains, and time points, stratifying subjects at each booster by HCW vs. NH residents and infection naive vs. prior infection. We then calculated the geometric mean fold change (GMFC) from pre to post-boost for each booster dosing and from 2 weeks post-boost to 3–6 months post-boost and performed t-tests on log-transformed titer fold change comparing the observed fold rise or fall to a null value of 1. All p values are shown without adjustment. Tests were not performed with 5 or fewer subjects.

3. Results

The analytic sample that met criteria for inclusion included 439 volunteers including 376 NH residents (median age 75, 42% female, 78% white non-Hispanic) and 63 HCW (median age 51, 54% female, 83% white non-Hispanic) for comparison.

Prior data and the current study show a significant increase in anti-Omicron titers from the prior time point to the post-first boost that was similarly observed in this study. There is then subsequent waning at 4–6 months after the first booster ranging between 70% and 95% for both binding antibody and neutralizing antibody titers. Most notable and robust declines of Omicron-BA.5 subvariant specific anti-spike titers were from GMT 2490 to 240 AU/ml in NH residents without prior infection [geometric mean fold change (GMFC) of 0.1 (95% CI 0.1, 0.2)] (Table 1) and a decline of Wuhan specific anti-RBD levels from GMT 17640(11728,26531) to 384 (249,592) AU/ml in NH residents with prior infection [GMFC of 0.02 (95% CI 0.01, 0.04)] (Supplementary Table 1). These types of declines provided rationale that prompted the CDC recommendation for a second booster in older individuals.

Table 1

Waning of Wuhan and Omicron-specific antibody response after 4 to 6 months of first booster and second booster vaccination before the upcoming dose.

AssayNeut	Group	n	Pre-waning1* GMT(CI)	Post-waning1* GMT(CI)	GMFC (CI)	p-value	n	Pre-waning2** GMT(CI)	Post-waning2** GMT(CI)	GMFC (CI)	p-value
Wu	HCW naive	16	744 (527, 1052)	156 (89, 276)	0.21 (0.13, 0.4)	<0.001	NA	NA	NA	NA	NA
Wu	HCW prior	10	1400 (616, 3183))	191 (80, 459)	0.1 (0.1, 0.3)	<0.001	NA	NA	NA	NA	NA
Wu	NH naive	50	640 (435, 943)	116 (77,175)	0.2 (0.1, 0.3)	<0.001	12	1262 (584, 2723)	549 (262, 1151)	0.4 (0.3, 0.7)	<0.001
Wu	NH prior	58	1035 (731, 1465)	205 (144, 292)	0.2 (0.2, 0.3)	<0.001	16	1378 (684, 2778)	764 (437, 1337)	0.6 (0.4, 0.7)	<0.001
BA.1	HCW naive	16	101 (55, 184)	29 (16, 52)	0.3 (0.1, 0.6)	0.002	NA	NA	NA	NA	NA
BA.1	HCW prior	10	325 (173, 610)	42 (12, 153)	0.13 (0.1, 0.5)	0.008	NA	NA	NA	NA	NA
BA.1	NH naive	50	162 (100, 262)	28 (19, 42)	0.2 (0.1, 0.3)	<0.001	12	448 (182, 1104)	107 (32, 362)	0.2 (0.2, 0.4)	<0.001
BA.1	NH prior	55	304 (195, 474)	58 (39, 87)	0.2 (0.1, 0.3)	<0.001	16	876 (360, 2129)	403 (158, 1031)	0.5 (0.3, 0.6)	0.001
BA.5	NH naive	30	100 (52, 192)	28 (16, 47)	0.3 (0.2, 0.4)	<0.001	12	464 (162, 1329)	115 (40, 333))	0.3 (0.1, 0.4)	<0.001
BA.5	NH prior	37	259 (126, 532)	85 (48, 150)	0.3 (0.2, 0.5)	<0.001	16	781 (350, 1745)	362 (151, 866)	0.5 (0.4, 0.6)	<0.001
AssaySpike	Group	n	Pre-waning1 GMT(CI)	Post-waning1 GMT(CI)	GMFC (CI)	p-value	n	Pre-waning2 GMT(CI)	Post-waning2 GMT(CI)	GMFC (CI)	p-value
Wu	HCW naive	20	4779 (3209, 7116)	484 (294, 796)	0.1 (0.1, 0.2)	<0.001	NA	NA	NA	NA	NA
Wu	HCW prior	16	5716 (2634, 12405)	635 (323, 1250)	0.1 (0.1, 0.3)	<0.001	NA	NA	NA	NA	NA
Wu	NH naive	68	3705 (2844, 4826)	422 (298, 599)	0.1 (0.1, 0.2)	<0.001	9	6138 (1879, 20047)	1217 (517, 2863)	0.2 (0.1, 0.7)	0.019
Wu	NH prior	88	7000 (5483, 8938)	814 (592, 1118)	0.1 (0.1, 0.2)	<0.001	18	5351 (3398, 8428)	887 (519, 1516)	0.2 (0.1, 0.3)	<0.001
BA.1	HCW naive	14	3698 (2147, 6371)	210 (129, 341)	0.1 (0, 0.1)	<0.001	NA	NA	NA	NA	NA
BA.1	HCW prior	13	8490 (2994, 24075)	370 (210, 651)	0 (0, 0.1)	<0.001	NA	NA	NA	NA	NA
BA.1	NH naive	58	1860 (1292, 2678)	269 (176, 410)	0.1 (0.1, 0.2)	<0.001	9	3027 (898, 10209)	558 (213, 1460)	0.2 (0, 0.8)	0.031
BA.1	NH prior	69	2568 (1757, 3753)	465 (309, 701)	0.2 (0.1, 0.3)	<0.001	18	2214 (1380, 3551)	276 (190, 402)	0.1 (0.1, 0.2)	<0.001
BA.5	NH naive	17	2490 (1464, 4236)	240 (131, 439)	0.1 (0.1, 0.2)	<0.001	3
BA.5	NH prior	16	3841 (2328, 6337)	418 (200, 875)	0.1 (0.1, 0.2)	<0.001	5

Abbreviations: GMT; geometric mean titer, GMFC; geometric mean fold change, CI: Confidence Interval NH: Nursing Home, HCW: Health Care Worker.

*Pre-waning1: 2 weeks after the 1st booster; Post-waning1: 3-6 months after the 1st booster**Pre-waning2: 2 weeks after the 2nd booster; Post-waning 2: 3-6 months after the 2nd booster

Table 2
Neutralization and anti-spike titers against Wuhan and Omicron for NH residents and HCW with and without prior infection history.

Assay	Neut	Group	Boost 1 GMT (CI)			Boost 1 GMFR	p-value	Boost 2 GMT (CI)			Boost 2 GMFR	p-value
			n	Pre	Post			n	Pre	Post		
Wu	HCW naive	23	14	804	59.3	<0.001	4	
Wu	HCW prior	23	(11, 17)	(609, 1063)	(45.6, 77.1)	<0.001	3	
Wu	NH naive	42	13	497	37.3	<0.001	27	144	895	6.2	<0.001	
Wu	NH prior	43	(11, 16)	(313, 788)	(23.8, 58.4)	<0.001	41	(75, 277)	(510, 1570)	(3.6, 10.9)	<0.001	
BA.1	HCW naive	23	14	143	10.2	<0.001	4	
BA.1	HCW prior	23	(11, 18)	(81, 254)	(5.6, 18.5)	<0.001	3	
BA.1	NH naive	42	14	124	9.1	<0.001	27	45	362	8.1	<0.001	
BA.1	NH prior	43	(11, 17)	(71, 217)	(5.4, 15.4)	<0.001	41	(23, 88)	(190, 688)	(4.4, 14.8)	<0.001	
BA.5	NH naive	3	21	318	14.8	<0.001	13	155	1214	7.8	<0.001	
BA.5	NH prior	12	(15, 30)	(184, 548)	(8.6, 25.5)	<0.001	29	(87, 277)	(826, 1783)	(4.8, 12.9)	<0.001	
BA.5	NH prior	12	13	68	420	6.2	0.004	
BA.5	NH prior	12	46	815	17.7	<0.001	29	(19, 238)	(124, 1423)	(2, 18.9)	<0.001	
BA.5	NH prior	12	(20, 108)	(204, 3263)	(4.6, 67.8)	<0.001	29	264	2470	9.4	<0.001	
BA.5	NH prior	12	29	(137, 509)	(1677, 3637)	(4.9, 17.7)	<0.001	
Assay	Spike	Group	Boost 1 GMT (CI)			Boost 1 GMFR	p-value	Boost 2 GMT (CI)			Boost 2 GMFR	p-value
n	Pre	Post	n	Pre	Post							
Wu	HCW naive	27	87	4820	55.7	<0.001	5	
Wu	HCW prior	27	(57, 133)	(3381, 6871)	(37.8, 81.9)	<0.001	3	
Wu	NH naive	96	145	4188	28.9	<0.001	30	864	1575	1.8	0.08	
Wu	NH prior	125	(85, 248)	(2582, 6792)	(15.8, 52.9)	<0.001	30	(458, 1630)	(873, 2841)	(0.9, 3.6)	<0.001	
BA.1	HCW naive	17	19	2980	155.3	<0.001	5	1517	5429	3.6	<0.001	
BA.1	HCW prior	21	(14, 26)	(2276, 3901)	(114.2, 211.1)	<0.001	5	(947, 2430)	(4144, 7111)	(2.5, 5.2)	<0.001	
BA.1	NH naive	38	67	3819	57.2	<0.001	3	
BA.1	NH prior	46	(41, 109)	(2326, 6271)	(32.6, 100.5)	<0.001	30	441	778	1.8	0.09	
BA.5	NH naive	2	192	11,844	61.6	<0.001	50	(241, 806)	(449, 1351)	(0.9, 3.4)	<0.001	
BA.5	NH prior	1	(87, 426)	(5941, 23610)	(27.7, 136.6)	<0.001	50	615	2066	3.4	<0.001	
BA.5	NH prior	1	26	2827	109.6	<0.001	4	(382, 988)	(1487, 2872)	(2.3, 4.9)	<0.001	
BA.5	NH prior	1	(14, 49)	(1718, 4651)	(55.2, 217.8)	<0.001	11	1163	4963	4.3	<0.001	
BA.5	NH prior	1	128	3138	24.5	<0.001	11	(605, 2236)	(3219, 7653)	(2.8, 6.6)	<0.001	
BA.5	NH prior	1	(72, 229)	(1802, 5464)	(13.4, 44.7)	<0.001	11	

Abbreviations: GMT; geometric mean titer, GMFR; geometric mean fold rise, CI: Confidence Interval NH: Nursing Home, HCW: Health Care Worker.

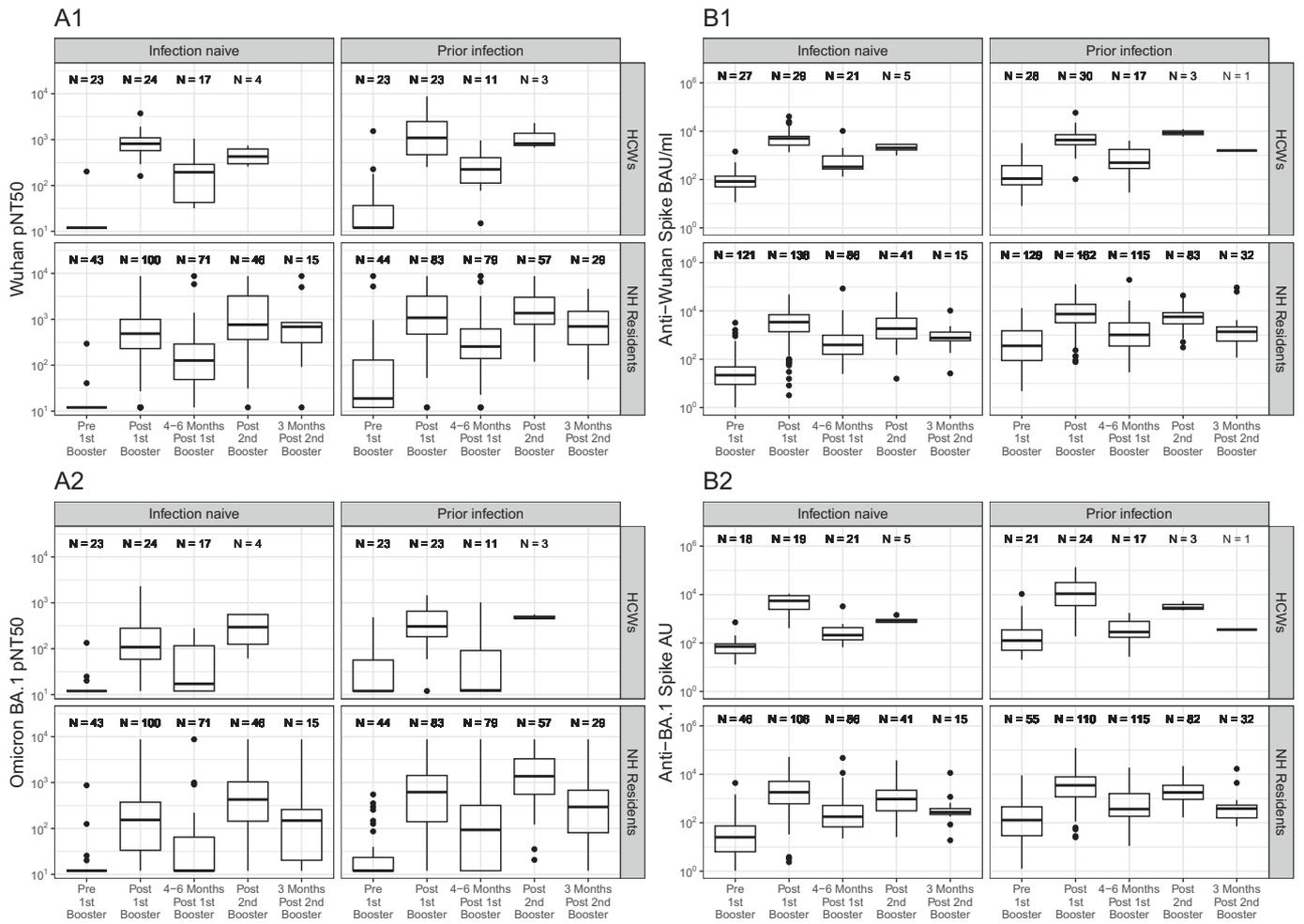


Fig. 1. Neutralization titers (Panel A1:Wuhan; A2: Omicron BA.1) and anti-spike levels (Panel B1:Wuhan; B2:Omicron BA.1) over time pre and post-boost with mRNA vaccination in healthcare workers (HCWs) and nursing home(NH) residents, with and without prior SARS-CoV-2 infection.

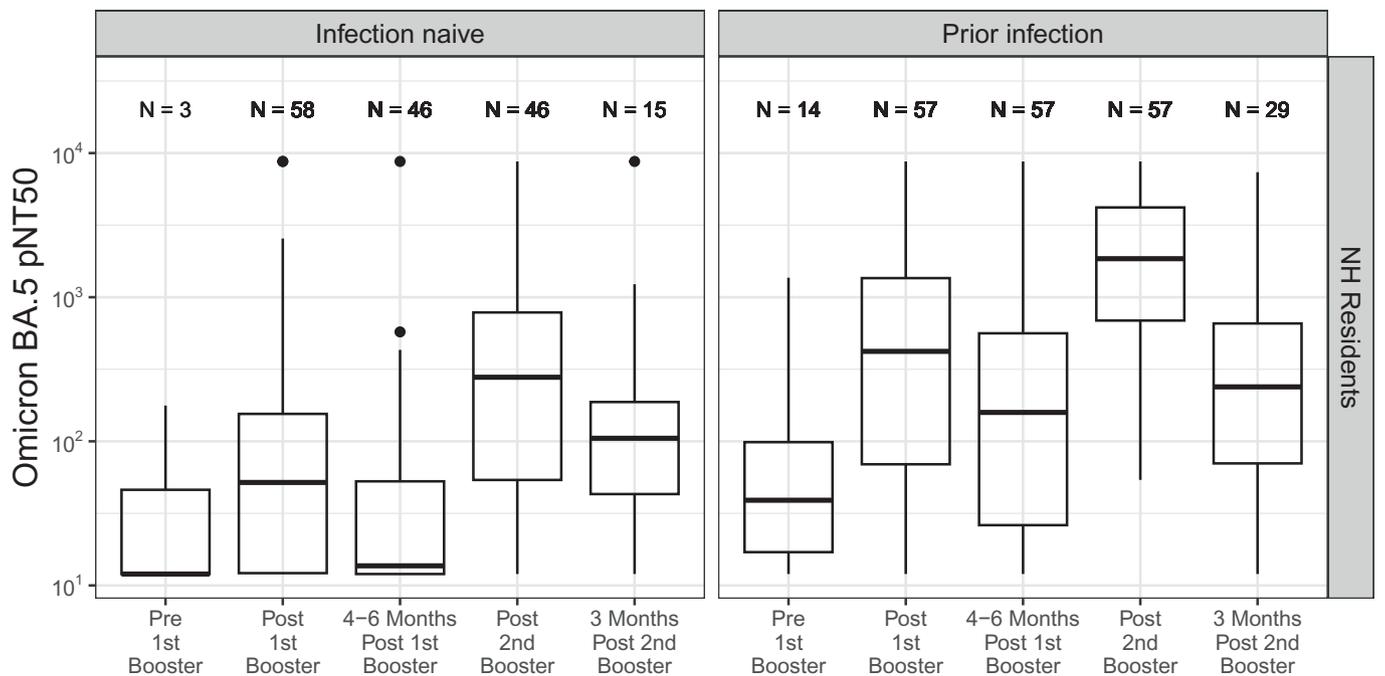


Fig. 2. The rise and waning in pseudovirus neutralization(pNT50) antibody titers against Omicron BA.5 strain in naïve NH residents and NH residents with prior infection after 1st and 2nd boosters.

NH residents, both those with and without prior infection, had a robust geometric mean fold rise (GMFR) of 8.1 (95% CI 4.4, 14.8) and 7.8 (95% CI 4.8, 12.9) respectively in Omicron-BA.1 subvariant specific neutralizing antibody levels following the second booster vaccination ($p < 0.001$). For infection-naïve and prior infection their Omicron-BA.1 subvariant specific GMFR was 1.8 (95% CI 0.9, 3.4) and 3.4 (95% CI 2.3, 4.9) for anti-spike antibody (Table 2) and 1.8 (95% CI 0.9, 3.7) and 2.2 (95% CI 1.2, 4) for anti-RBD antibody levels, respectively (Supplementary Table 2). We also observed a robust GMFR in Omicron-BA.5 subvariant specific neutralizing antibody levels [6.2 (95% CI 2, 18.9) and 9.4 (95% CI 4.9, 17.7) in each group, NH naïve and NH prior] after second booster vaccination (Fig. 2 and Table 2). Similar trends were observed in relatively smaller sample sizes of infection-naïve HCWs and HCW with prior infection (Table 2, Supplementary Table 2, Fig. 1 and Supplementary Figure 1).

Subjects were then sampled 3 months after the second booster and, across all titers and groups, we also observed a notable decline in the geometric mean titers (GMT) from 2 weeks after the second booster to approximately 3 months after the second booster ranging between 50% and 95%. The most notable decline of Omicron-BA.1-specific anti-spike titers was from GMT 2214 (1380,3551) to 276 (190,402) (AU)/ml in NH residents with prior infection [GMFC of 0.12 (95% CI 0.07, 0.22)] (Table 1) and another notable decline was in Wuhan specific anti-Receptor binding domain levels from GMT 2150 (1119,4134) to 309 (163,585) (AU)/ml in NH residents with prior infection [GMFC of 0.14 (95% CI 0.07, 0.29)] (Supplementary Table 1).

4. Discussion

This study presents immunogenicity of the 4th monovalent SARS-CoV-2 mRNA vaccination, comparing NH and HCW populations. Our extensive longitudinal follow up from before and after the first and second boost contrasts subjects with and without a prior infection and resulting BA.5 neutralization activity. NH resident anti-Omicron (BA.1 and BA.5) neutralization titers dropped substantially over the 6 months following the first mRNA monovalent booster. NH residents responded well to the second monovalent booster, achieving similar and in many cases higher levels than obtained after just one booster dose.

The study findings are clinically important as neutralizing and binding antibody titers correlate with vaccine protection against many viral diseases [9,11,12]. Anti-spike, anti-RBD and neutralization antibody titers correlate with enhanced protection from symptomatic SARS-CoV-2 infection [13,14]. Feng et al reported that an anti-Wuhan Spike level of 264 BAU/ml achieved 80% protection against symptomatic infection from the now ancestral alpha variant [14]. All the NH residents in our sample achieved this cut off level after their second booster dose. However, Favresse et al proposed an alternative much higher cut-off of 8434 BAU/ml for binding antibodies to predict neutralization of the more recent Omicron BA.1 variant (sensitivity: 83.1%, specificity: 63.4%) [15]. The substantial difference in these results demonstrates the complexity of defining precise antibody immune correlates in the current clinical setting where the evolving viral variants and sub-variants continue to acquire immune evasive mutations. Even as higher antibody titers may add protection, the relative clinical protection and titers decline over time while newer variants and sub-variants produce different thresholds of protection, perhaps especially in the frail older NH when compared to younger adults.

McConeghy et al showed that vaccine effectiveness of a second mRNA COVID-19 booster dose against SARS-CoV-2-associated hospitalization or death was 73.9% and 89.6% for death alone com-

pared to a single booster dose among NH residents [6]. The mechanism for this increased protection is not yet fully defined but this current quantitative antibody response study after the second booster demonstrates that the additional doses for NH residents add to Omicron subvariant humoral immunity in this population. These higher titers likely play a significant role in this increased protection but certainly a contribution of cellular immunity which may be a factor as well. Our study adds longitudinal immunogenicity data and a HCW comparison to the clinical outcomes described by McConeghy et al [6].

There are at least four related studies on clinical effectiveness of 4th dose in NH population [16–19] demonstrating protection but none have immunogenicity data in NH residents and HCWs. Our study offers biologic evidence that these findings arise at least in part from an immune response in a population that suffers from immunosenescence and disease that vaccines help overcome. Benjamini et al assessed the humoral and cellular response to the fourth BNT162b2 mRNA COVID-19 vaccine dose in patients with anticipated blunted response due to CLL. They demonstrated that the fourth SARS-CoV-2 booster enhances serologic response in patients with CLL to a lesser extent than healthy controls [20].

We note several limitations of this study beyond a relatively small sample size and inability to obtain follow-up samples from all participants. While women make up over $\frac{2}{3}$ of US NH residents, our sample of 41% women arises from significant participation of Veterans living in state Veterans homes, most of whom are male. We did not assess vaccine-induced T-cell immunity. Also, we may have misclassified some participants with undetected asymptomatic SARS CoV-2 infection who did not meet the laboratory criteria threshold for prior infection between infection naïve and prior infected groups. The group of our small HCW sample under 50 years old did not meet initial eligibility for a second booster per CDC guidelines. The HCW remaining for analysis therefore skewed towards better representing older individuals in this group. Finally, as the subjects recruited or sampled after prior SARS-CoV-2 infection all survived the infection, their inclusion may introduce survivorship bias to our analysis.

5. Conclusion

In a sample of 376 nursing home residents, anti-Omicron neutralization titers waned significantly over the months following the first and second SARS-CoV-2 mRNA monovalent booster doses. Antibody titers rose significantly with boosting, achieving similar or in many cases higher levels after the second boost than after the first, while also gaining important anti-Omicron neutralizing activity. Subsequent waning of antibody titers with additional boosters and broadening of neutralizing immunity with the second boost provides evidence of the critical need to keep nursing home residents, up to date with SARS-CoV-2 vaccination.

Data availability

Data sharing is restricted by NIH, CDC and VA requirements.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: S. G. and D. H. C. are recipients of investigator-initiated grants to their universities from Pfizer to study pneumococcal vaccines and Sanofi Pasteur and Seqirus to study influenza vaccines, and S.G. from Genentech on influenza antivirals. S. G. also does consulting for Seqirus, Sanofi, Merck, Vaxart, Novavax, Moderna and Janssen; has served on the speaker's bureaus for Seqirus and Sanofi;

and reports personal fees from Pfizer and data and safety monitoring board (DSMB) fees from Longevoron and SciClone.

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Appendix A. Supplementary data

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