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ORIGINAL ARTICLE

Broad immunogenicity to prior SARS-CoV-2 strains and JN.1 variant elicited by XBB.1.5 vaccination in nursing home residents

Yasin Abul · Clare Nugent · Igor Vishnepolskiy · Tiffany Wallace · Evan Dickerson · Laurel Holland · Iva Esparza · Mandi Winkis · Kazi Tanvee Wali · Philip A. Chan · Rosa R. Baier · Amy Recker · Matthew Kaczynski · Shreya Kamojjala · Alexander Pralea · Hailee Rice · Olubunmi Osias · Oladayo A. Oyebanji · Olajide Olagunju · Yi Cao · Chia Jung Li · Alex Roederer · Walther M. Pfeifer · Jürgen Bosch · Christopher L. King · Aman Nanda · Lynn McNicoll · Nadia Mujahid · Sakeena Raza · Rohit Tyagi · Brigid M. Wilson · Elizabeth M. White · David H. Canaday · Stefan Gravenstein · Alejandro B. Balazs

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Abstract SARS-CoV-2 vaccination has reduced hospitalization and mortality for nursing home residents (NHRs) but emerging variants and waning immunity challenge vaccine effectiveness. This study assesses the immunogenicity of the most recent XBB.1.5 monovalent vaccine to variant strains among NHRs. Participants were subset of a longitudinal study of consented NHRs and Healthcare workers (HCWs) who have received serial blood draws to assess immunogenicity with each SARS-CoV-2 mRNA vaccine dose. We report data on participants who received the XBB.1.5 monovalent vaccine post-FDA approval in Fall 2023. NHRs were categorized by whether they had an interval SARS-CoV-2 infection between their first bivalent vaccine dose and their XBB.1.5 monovalent vaccination. The sample included 61 NHRs [median age 76 (IQR 68–86), 51% female] and 28 HCWs [median age 45 (IQR 31–58), 46% female). After XBB.1.5 vaccination, a robust geometric mean fold rise (GMFR) in XBB.1.5-specific neutralizing antibody titers was observed:17.3 (95% confidence interval [CI] 9.3, 32.4) and NHRs with interval infection and 11.3 (95% CI 5, 25.4) in those without and 13.6 (95% CI 8.4,22) in HCWs. For JN.1-specific titers, GMFRs were 14.9

Alejandro B. Balazs, Stefan Gravenstein, and David H. Canaday contributed equally to this work.

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Y. Abul · I. Vishnepolskiy · S. Gravenstein
Center On Innovation in Long-Term Services & Supports, Providence Veterans Administration Medical Center, Providence, RI, USA

Y. Abul · I. Vishnepolskiy · I. Esparza · M. Kaczynski · S. Kamojjala · A. Pralea · O. Osias · A. Nanda · L. McNicoll · N. Mujahid · S. Raza · R. Tyagi · S. Gravenstein
Division of Geriatrics and Palliative Medicine, Warren Alpert Medical School of Brown University, Providence, RI, USA

Y. Abul (✉) · O. A. Oyebanji · O. Olagunju · J. Bosch · C. L. King · B. M. Wilson · D. H. Canaday (✉)
Case Western Reserve University School of Medicine, Cleveland, OH, USA
e-mail: yasin_abul@brown.edu

D. H. Canaday
e-mail: dxc44@case.edu

Y. Abul · P. A. Chan · R. R. Baier · A. Recker · E. M. White · S. Gravenstein
Brown University School of Public Health, Providence, RI, USA

(95% CI 7.9, 28) and 6.5 (95% CI 3.3, 13.1) in NHRs with and without interval infection, and 11.4 (95% CI 6.2, 20.9) in HCWs. NHRs with interval SARS-CoV-2 infection had higher titers across all analyzed strains analyzed. The XBB.1.5 vaccine significantly elevates Omicron-specific neutralizing antibody titers to XBB.1.5 and JN.1 strains in both NHRs and HCWs with more pronounced in those previously infected with SARS-CoV-2 since bivalent vaccination.

Keywords SARS-CoV-2 · COVID-19 · XBB.1.5 monovalent vaccine · JN.1 variant · Nursing homes · Older adults

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remains the most consequential respiratory virus in broad circulation [1]. As of July 2024, SARS-CoV-2 has infected over 2.0 million NHRs and 1.9 million nursing home staff in the USA, contributing to at least 171,588 residents deaths [2]. Nursing home residents (NHRs) are at particularly high risk for severe disease and adverse health outcomes. The burden and risks of disease are also important for the healthcare workers (HCW) who provide care in these settings. Unlike early in the pandemic, when SARS-CoV-2 vaccine coverage exceeded 50% for both staff and residents, only 8% of NH staff and 20% of NHRs have received the most recent XBB 1.5 monovalent vaccine when first offered, and in only 31% NHRs and 10% HCWs by the end of June 2024 [2]. The evolution of highly immune evasive variants of SARS-CoV-2, waning immunity, immunosenescence, and variations in vaccine efficacy may compromise vaccine effectiveness in NHRs.

Given the rapid evolution of SARS-CoV-2 variants, it is crucial to characterize the breadth of antibody response elicited by vaccines and breakthrough infections against evolving circulating strains as well as the ancestral strain. The lineage BA.2.86, first identified in August 2023, evolved into the descendant, JN.1(BA.2.86.1.1) first identified in September 2023 and then KP.2 and KP.3 that are descendants of JN.1 [3, 4]. JN.1 has more than 30 mutations compared to XBB [5]. Both XBB and JN.1 variants, descendants from the Omicron BA.2 line, have amino acid substitutions that might augment escape from neutralizing antibodies. XBB and JN1 variants show significant differences. JN1 variant has a higher number of unique mutations compared to XBB variant especially in the spike protein that is crucial for infectivity and immune evasion. Higher immune evasion features of JN.1 are reflected in its decreased sensitivity to neutralization which differentiate it from XBB lineage and contribute to its rapid spread and dominance [6]. Despite common ancestry with the BA.2, the XBB lineage differs substantially from JN.1, and that raises the concern whether an XBB-based vaccine will provide adequate cross-protective immunity to JN.1. In the USA, from the end of October, when JN.1 made up less than 0.1% of COVID-19 cases to March 2024, JN.1 had spread to account for 98% of all COVID-19 cases [7].

Our understanding of the durability and nature of antibody protection against SARS-CoV-2 infection is still evolving. In the nursing home population, prior work has demonstrated a waning of SARS-CoV-2 mRNA vaccine immunity in the 3 to 6 months following each vaccine dose [8–10]. The first and second monovalent boost and bivalent SARS-CoV-2 mRNA vaccine augmented immunity and demonstrated a significant reduction in risk of infection, hospitalization, and death at four months following vaccine administration [11, 12]. The newer monovalent XBB.1.5 vaccine has demonstrated adequate immunogenicity and cross-reactivity with current circulating strains in healthier, younger populations [13–15], but it is unknown whether this broader protection is also afforded to NHRs. The motivation of the present study is to demonstrate neutralizing antibody responses against evolving strains in addition to

C. Nugent · T. Wallace · E. Dickerson · L. Holland · M. Winkis · K. T. Wali · H. Rice
Division of Geriatrics and Palliative Medicine, Rhode Island Hospital, Providence, RI, USA

P. A. Chan
Division of Infectious Diseases, Warren Alpert Medical School of Brown University, Providence, RI, USA

Y. Cao · C. J. Li · A. Roederer · A. B. Balazs
Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA

W. M. Pfeifer
East Side Clinical Laboratory, East Providence, RI, USA

B. M. Wilson · D. H. Canaday
Geriatric Research, Education and Clinical Center, VA Northeast Ohio Healthcare System, Cleveland, VA, USA

historical Wuhan ancestral strain and BA.4/5 strain in NHRs. We also included neutralizing antibody responses in a small sample of HCWs to provide complementary and chronologically comparable data to the larger NHRs cohort, to enhance overall understanding of the current vaccine performance. This highlights the importance of assessing cross-reactive antibody response not just against the original strain targeted by the initial vaccine but also against newly emerging variants that may escape existing immunity.

Methods

Ethical approval

This study was approved by the WCG Institutional Review Board. All participants or their legally authorized representatives provided informed consent.

Study design and participants

The current study is part of a longitudinal cohort study that has monitored immunological response to each SARS-CoV-2 mRNA vaccine dose in consented NHRs in Ohio and Rhode Island since SARS-CoV-2 vaccination began in December 2020 [8–10, 12, 16]. We have measured neutralizing antibody titers on serum samples collected from 447 unique NHR over the study period. Participants are sampled roughly 2–4 weeks before and after each vaccine dose and at 3–6-month intervals [8–10]. Not all study participants are sampled at each timepoint.

In this report, we focus on a subset of 61 NHR study participants who received both bivalent and XBB.1.5. monovalent vaccine doses. We additionally collected serum samples on 28 HCWs in Ohio as a reference group. XBB.1.5 vaccine administration started in September 2023 following FDA approval. Post-XBB.1.5. samples were collected 2–4 weeks after XBB.1.5 monovalent vaccine administration.

We analyzed NHR serum samples tested for neutralizing antibody titers against multiple SARS-CoV-2 strains, including ancestral Wuhan, Omicron BA.4/5, XBB.1.5, JN.1 using bead-based ELISA methods and pseudovirus neutralization assays, as detailed elsewhere [8, 9].

For data points related to bivalent vaccination and earlier vaccine doses, we defined a NHR as having had a "prior SARS-CoV-2 infection" at the time of each collected sample based on clinical criteria (any prior positive polymerase chain reaction or antigen test documented in the medical chart) or lab criteria. Lab criteria were a substantial increase either in anti-N or in multiple other SARS-CoV-2 assays (anti-spike (S) antibodies, anti-receptor-binding domain antibodies, or neutralizing titers) that could not be explained by vaccination. We defined participants as "infection naive" at each time point if they did not meet the above criteria for prior infection [8–10]. For data points related to the XBB.1.5 monovalent vaccine, we further classified NHR as having had an "interval SARS-CoV-2 infection" if they had a new SARS-CoV-2 infection between their prior bivalent vaccine dose and their XBB.1.5 monovalent vaccine dose. Interval infection was determined based on the same clinical and lab criteria described above. We did not stratify HCWs in this way because infection history was not available for the majority of HCWs with post-XBB.1.5 draws.

Statistical analysis

We analyzed NHRs and HCW results separately. Within the longitudinal NHR cohort, we summarized the distributions of neutralizing titers over all vaccine doses for Wuhan and Omicron BA.4/5 strains, stratifying results at each sample time by infection naive vs. prior. Within the cohort of NHRs and HCW sampled following XBB.1.5 vaccine, we assessed the geometric mean titers with 95% confidence interval before and after XBB.1.5 monovalent vaccination for all strains and calculated the geometric mean fold rise (GMFR) from pre- to post-XBB.1.5 monovalent vaccine. We performed *t*-tests on log transformed titer fold change comparing the observed fold rise to a null value of 1. For the fold change analysis, we required participants to have blood samples collected at least 6 months after their prior XBB.1.5.vaccine dose and excluded participants who received a second bivalent vaccine.

We provide all *p* values without adjustment. All analyses were performed in R (version 4.2.2).

Results

Sample characteristics are presented in Table 1. The longitudinal cohort included 447 NHRs [median age

75 (IQR 69–86, 49% female, 19% Black). The subset of study participants sampled following the XBB.1.5 monovalent booster included 61 NHRs [median age 76 (IQR 68–86), 51% female, 20% Black] and 28 HCWs [median age 45 (IQR 31–58), 46% female)] (Supplementary Fig. 1).

To provide a longitudinal contrast of neutralizing titers from the start of the cohort through the XBB vaccination, Fig. 1 presents antibody levels against Wuhan and BA.4/5 in NHRs from before the primary SARS-CoV-2 vaccine series until after XBB.1.5 vaccination; BA.4/5 titers were first measured beginning 9 months after the primary series was completed. Over the 3 months following vaccination with both monovalent and bivalent vaccinations, neutralizing antibody levels fell to Wuhan and BA.4/5, and absent intercurrent infection or additional boosting, continued to wane through to 12 months post-vaccination. Both the bivalent and XBB.1.5 monovalent vaccinations, at least initially, boosted neutralizing antibody titers against Wuhan and BA.4/5. At virtually all time points, NHRs with prior SARS-CoV-2 infections had higher neutralizing antibody titers after each vaccine administration dose than infection-naive NHRs.

There were many individuals who experienced a SARS-CoV-2 infection in the interval between the bivalent and XBB vaccinations. We therefore examined the effect of boosting separately between these groups. Within the NHR cohort sampled following XBB.1.5 monovalent vaccination, we noticed waning neutralizing antibody levels for Wuhan and BA.4/5 strains over the 3-, 6-, and 12-month time points after bivalent vaccination in NHRs (Fig. 2). The Wuhan and BA4/5 titers fall and again boost also after XBB vaccination (Figs. 1, 2, and 3).

Figure 3 and Table 2 next show the GMFR rises in titers to Wuhan, BA.4/5, XBB1.5, and JN.1 strains in NHR and HCW pre-and post XBB vaccination. NHRs with and without interval SARS-CoV-2 infection had robust GMFR of 17.3 (95% CI:9.3–32.4, $p<0.001$) and 11.3 (95% CI: 5–25.4, $p<0.001$), respectively, in XBB.1.5 subvariant specific neutralizing antibody titer levels following the XBB.1.5 monovalent vaccination. The XBB.1.5 monovalent dose also induced substantial rises in neutralizing antibodies not only in NHRs but also in HCWs with a GMFR of 13.6 (95% CI: 8.4–22, $p<0.001$) (Table 2, Fig. 3). The GMFR after XBB.1.5 monovalent vaccination was notably higher in XBB.1.5-specific neutralizing antibody levels compared to those of Wuhan and BA.4/5 specific neutralizing antibody levels (11.3 and 17.3 in XBB.1.5 subvariant, 6.5 and 6.3 in BA.4/5 subvariant, and 3.7 and 3.4 in Wuhan ancestral strain, respectively) (Table 2). Comparing to XBB.1.5 titers among NHRs with and without interval SARS-CoV-2 infection, a similarly robust GMFR in JN.1 subvariant specific neutralizing antibody titer levels were noted following the XBB.1.5 monovalent vaccination (14.9, 95%

Table 1 Sample demographics and interval SARS-CoV-2 infection history

	Longitudinal cohort of NHRs	NHRs sampled after XBB.1.5 monovalent vaccine	HCWs sampled after XBB.1.5 monovalent vaccine
Subjects, *n*	447	61	28
Age at consent, median (IQR)	75 (69, 86)	75 (66, 84)	55 (25, 58)
Age at consent, range	33–104	48–104	21–64
Male, *n* (%)	229 (51%)	30 (49%)	15 (54%)
Female, *n* (%)	218 (49%)	31 (51%)	13 (46%)
White, *n* (%)	357 (80%)	47 (77%)	22 (79%)
Black, *n* (%)	83 (19%)	12 (20%)	1 (4%)
Hispanic, *n* (%)	3 (1%)	0	1 (4%)
Asian, *n* (%)	2 (< 1%)	0	4 (14%)
Other race or ethnicity, *n* (%)	2 (< 1%)	2 (3%)	0
Interval infection, *n* (%)	98 (22%)	42 (69%)	NA

Race and ethnicity unavailable for healthcare workers. *HCW*, health care worker; *NHR*, nursing home resident

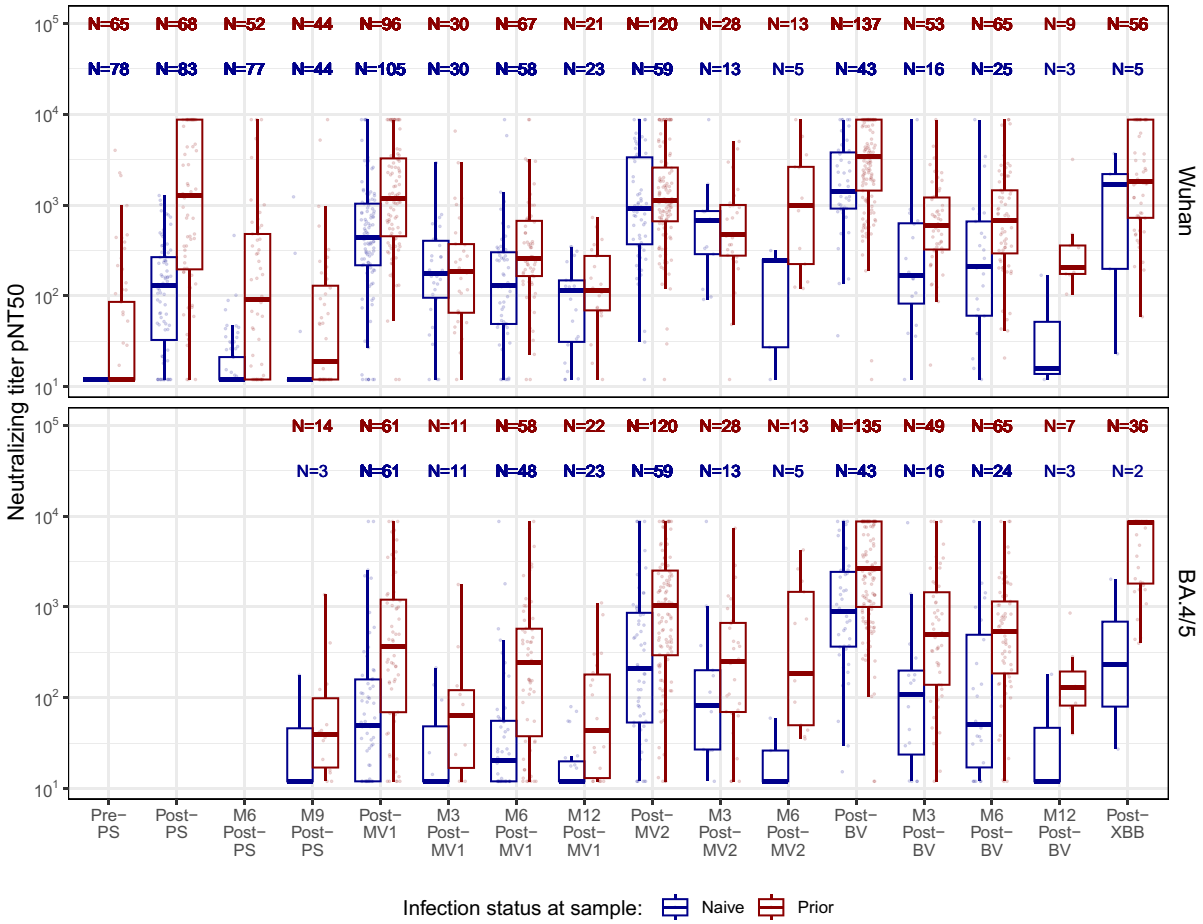

Fig. 1 Neutralizing antibody titers against Wuhan and BA.4/5 in nursing home residents ($n=447$), from SARS-CoV-2 primary vaccine series through XBB.1.5 monovalent vaccination. *Notes*. PS = primary series; MV1 = first monovalent vaccine; MV2 = second monovalent vaccine; BV = bivalent vaccine; XBB = XBB.1.5 monovalent vaccine; M3 = month 3; M6 = month 6, M9 = month 9, M12 = month 12. In cases of SARS-CoV-2 infection, samples within subjects were excluded from the time of breakthrough infection until the next vaccine dose

CI: 7.9–28, $p<0.001$ in NHR with interval; 6.5, 95% CI: 3.3–13.1, $p<0.001$ in NHR without interval; and 11.4, 95% CI: 6.2–20.9, $p<0.001$ in HCWs) (Table 2, Fig. 3).

Within the subset XBB cohort of NHRs, higher neutralizing titers were observed similarly in those with an interval SARS-CoV-2 infection that persisted after XBB.1.5 monovalent vaccination (Fig. 3).

Discussion

This is the first study, to our knowledge, to demonstrate robust neutralizing antibody response specific to NHRs in the XBB.1.5 and JN.1 subvariant era. We report broad immunogenicity to variant strains by XBB.1.5 monovalent SARS-CoV-2 vaccines in both NHRs and HCWs. We find that both groups develop robust neutralizing antibody titers to XBB.1.5 monovalent vaccine, but that Wuhan and anti-omicron BA.4/5 neutralizing antibody titers decreased substantially over the 3 to 12 months following the mRNA bivalent booster. Our findings suggest the new XBB.1.5 monovalent vaccine likely augments the protection against SARS-CoV-2 infection caused by recently circulating XBB.1.5 subvariants in older vulnerable NHRs, may enhance immunity against variant

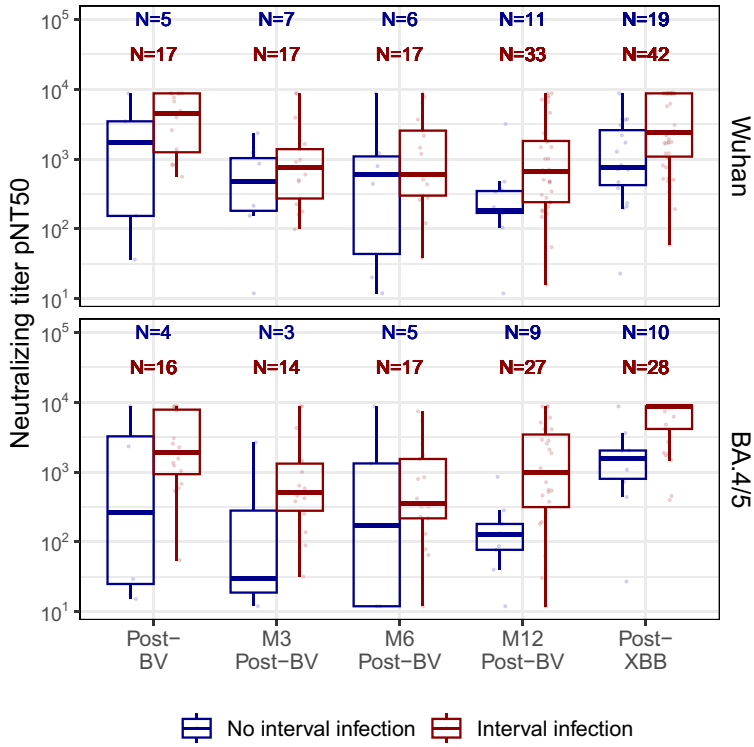

Fig. 2 Neutralization titers against Wuhan and BA.4/5 after bivalent and XBB.1.5 monovalent SARS-CoV-2 mRNA vaccination, among nursing home residents with and without interval infection ($n=61$). *Notes*. Interval SARS-CoV-2 infection is defined as an infection occurring between a participant's prior bivalent vaccine dose and the XBB.1.5 monovalent dose. BV = bivalent vaccine; XBB = XBB.1.5 monovalent vaccine; M3 = month 3; M6 = month 6, M12 = month 12. Post-BV and Post-XBB samples were collected 2–4 weeks after vaccine dose

strains, and may support ongoing efforts to prevent SARS-CoV-2 morbidity and mortality in NHRs.

Preliminary data from phase II–III trials indicate a boost in neutralizing antibody titers against both XBB.1.5 lineages and BA.2.86 [13]. In the most recent immunological data, Marking et al. (2024) reported a significant increase in neutralization activity against all variants tested after XBB.1.5 vaccination, with a more than tenfold increase in GMT 2 weeks after vaccination (84 to 869) in 24 HCWs (median age = 64 years) [15] and Stankov et al. (2024) reported a rise in GMT neutralization from 27 to 967 for XBB.1.5 and from 28 to 906 for XBB.1.16 after the updated monovalent Omicron XBB.1.5 vaccine (median age = 45) [14]. Our study cohort demonstrated 13.6 GMFR (from 88 to 1198) in neutralizing antibodies to XBB.1.5 in HCWs, 11.3 GMFR (from 49 to 555) in NH without known SARS-CoV-2 infection since bivalent vaccine dose, and 17.3 GMFR (from 121 to 2089) in NHRs with known interval infection. The current study provides the first data from NHRs ($n=61$, median age 76). Previously, Chalkias et al. (2023) reported similar GMFRs of neutralizing antibody levels in ancestral, BA.4/5 and XBB.1.5 sub-variants after monovalent XBB.1.5 vaccine in a relatively younger study population ($n=50$, median age 55) [13].

We were encouraged by the finding that a similarly robust GMFR in JN.1 subvariant specific neutralizing antibody to that arising to the XBB.1.5 monovalent vaccination occurred both in NHRs and in HCWs and both with and without interval infection. However, we also note that absolute JN.1 specific neutralizing antibody titers after XBB.1.5 monovalent vaccination were far below those of XBB specific neutralizing titers after XBB.1.5 monovalent vaccination. The most recent early estimates of XBB.1.5 monovalent vaccine effectiveness data while JN.1 was the prevailing circulating strain indicate 54% (95% CI: 46–60%) protection against symptomatic SARS-CoV-2 infection compared to unvaccinated individuals [12, 17, 18].

Previous studies found the most robust and persistent protection against SARS-CoV-2 infection is in individuals with hybrid immunity (i.e., immunity developed by the combination of both infection and vaccination) [19–23]. This study demonstrates that both hybrid immunity and receipt of the XBB.1.5 monovalent vaccine augmented the neutralizing antibody titers to a higher level, compared

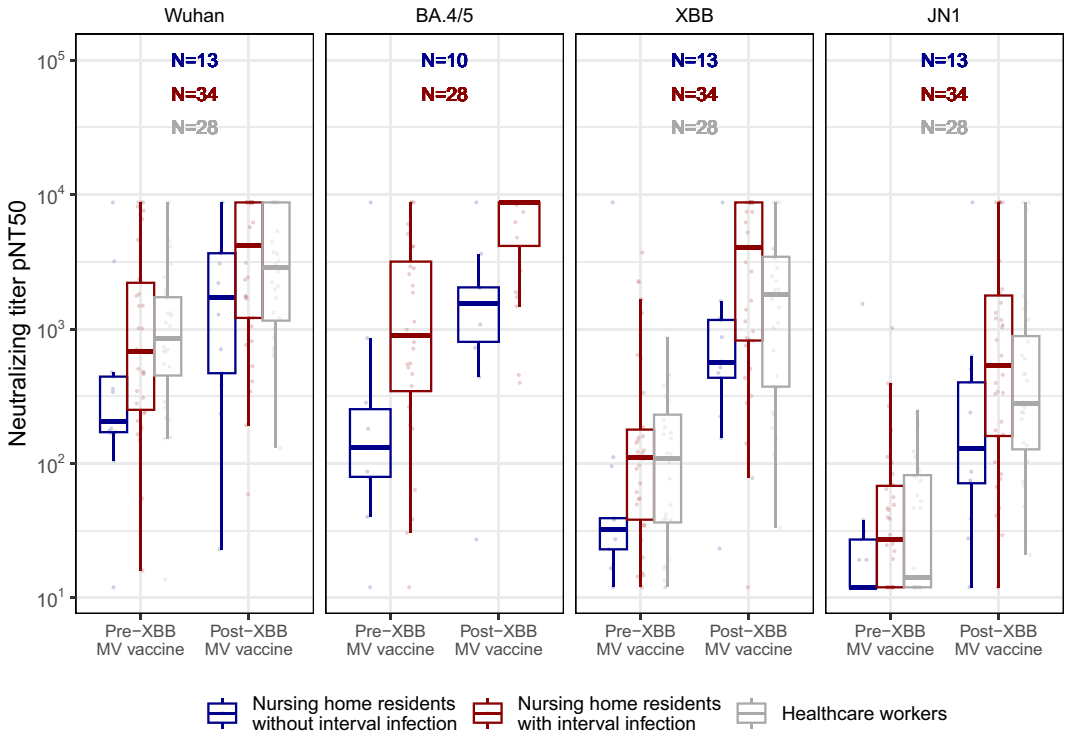

Fig. 3 Neutralization titers against Wuhan, BA.4/5, XBB, and JN1 after XBB.1.5 monovalent SARS-CoV-2 mRNA vaccination among NHRs and HCWs with and without interval infection. *Notes*. Interval SARS-CoV-2 infection is defined as an infection occurring between a participant's prior bivalent vaccine dose and the XBB.1.5 monovalent dose. MV = monovalent vaccine; post-XBB samples were collected 2–4 weeks after vaccine dose. *Healthcare workers' interval infection status combined as insufficient data are available to categorize their infection status

Table 2 Wuhan, BA.4/5, and XBB.1.5 neutralizing antibody response in nursing home residents and health workers with and without interval SARS-CoV-2 infection since bivalent vaccination

Assay Neut	Group	*n*	Pre-XBB.1.5 GMT(CI)	Post-XBB.1.5 GMT(CI)	GMFR (CI)	*p*-value
Wu	HCW*	28	783 (473, 1295)	2513 (1640, 3851)	3.2 (2.1, 4.9)	< 0.001
	$NHRs^{uninfected}$	13	302 (116, 786)	1124 (433, 2916)	3.7 (1.9, 7.1)	< 0.001
	$NHRs^{infected}$	34	807 (463, 1409)	2719 (1698, 4355)	3.4 (1.8, 6.2)	< 0.001
BA.4/5	$NHRs^{uninfected}$	10	171 (48, 614)	1115 (370, 3361)	6.5 (2.5, 16.8)	0.002
	$NHRs^{infected}$	28	823 (410, 1652)	5145 (3601, 7350)	6.3 (3.3, 11.7)	< 0.001
XBB	HCW*	28	88 (53, 147)	1198 (673, 2132)	13.6 (8.4, 22)	< 0.001
	$NHRs^{uninfected}$	13	49 (18, 136)	555 (242, 1275)	11.3 (5, 25.4)	< 0.001
	$NHRs^{infected}$	34	121 (70, 208)	2089 (1160, 3760)	17.3 (9.3, 32.4)	< 0.001
JN.1	HCW*	28	32 (21, 49)	365 (196, 677)	11.4 (6.2,20.9)	< 0.001
	$NHRs^{uninfected}$	13	24 (11,52)	154 (56, 423)	6.5 (3.3, 13.1)	< 0.001
	$NHRs^{infected}$	34	37 (24,57)	552 (289, 1053)	14.9 (7.9, 28)	< 0.001

*Interval infection status of HCWs unavailable

$NHRs^{uninfected}$ nursing home residents without interval infection

$NHRs^{infected}$ nursing home residents with interval infection

CI confidence interval, *GMT* geometric mean titer, *GMFR* geometric mean fold rise, *Wu* Wuhan

to individuals without SARS-CoV-2 infection, in the setting of the highly antibody-evasive variant of XBB.1.5. The primary mechanism of action in hybrid immunity involves the generation of an enhanced and diverse antibody response that targets the multiple viral epitopes. The implications of hybrid immunity through associated basic pathways on SARS-CoV-2 infection are important that the immune system can adapt both for recognition and response to viral changes and limits the virus's ability to escape from immune system [24–26]. Future studies will need to determine the durability of hybrid immunity after XBB.1.5 monovalent vaccination and its determinants for potential longer durability in setting of newly evolving highly antibody evasive strains.

It has been suggested that hybrid immunity has helped protect against the highly antibody-evasive variants including XBB.1.5 and EG.5, and substantially contributes to the declining COVID-19 hospitalizations and mortality [23]. We should take hybrid immunity into consideration for booster vaccination strategies since hybrid immunity is so common in the general population. However, NHRs continue to have an elevated risk of severe infection, given their high prevalence of immunosenescence and multiple morbidities, and the substantial exposure risk to infection conferred by the congregate nature of the nursing home living environment.

These study results are clinically important as neutralizing antibodies correlate with enhanced protection against symptomatic SARS-CoV-2 infection [27, 28]. Different studies conducted with various SARS-CoV-2 strains reported variable cutoff levels of neutralizing antibodies to achieve protection against symptomatic SARS-CoV-2 infection so more work needs to be done to determine a precise correlate if that is even possible [28, 29].

Potential limitations of the current study include the small sample size, particularly for HCW participants which may limit generalizability in this group. We did not evaluate the vaccine-induced T-cell immunity. Our longitudinal study design with regular antibody titer assessment enables detection of both clinically apparent and asymptomatic SARS-CoV-2 infections, and we have a method to detect asymptomatic infections by assessing anti-N and other antibody titer changes not corresponding to their vaccination; however, we may have missed a few newly infected resulting in miscategorization if our methods are not sensitive enough or the individuals did not seroconvert to infection. Potential for selection bias is another limitation since our study sample only includes participants who received the XBB1.5 vaccine and survived, and those who opted to receive it are not necessarily generalizable to NHRs and HCWs more broadly since the overall vaccine coverage in this setting is only 42% of NHRs and 4.5% of HCWs [2]. A strength of this study is the longitudinal nature of the data from before the primary vaccine series through the XBB.1.5 monovalent booster, allowing for a comprehensive assessment of vaccine impact over time as new virus variants have emerged.

Conclusion

This is the first study of XBB.1.5 and JN.1-specific neutralizing antibody responses after the XBB.1.5 monovalent vaccine in NHRs and shows comparable results among both NHRs and a comparison group of younger HCWs. This is particularly important in the context of understanding the immunologic interplay between emerging variants, waning immunity, immunosenescence, and variable vaccine effectiveness in NHRs and other older adults.

Author contribution Study concept and design: SG, DHC, EMW, RB, and YA.

Acquisition of subjects and/or data: CN, IV, IE, TW, ED, LH, HR, MK, KTW, AP, OOs, OAO, OO, AR, CJL, YC, AR, AN, LM, RT, SR, NM, ABB, SK, MW, WP, and JB.

Analysis and interpretation of data: BW, OAO, JB, CLK, ABB, DHC, SG, and YA.

Preparation of manuscript: YA, SG, DHC, EMW, BW, RB, ABB, PC, and CLK.

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

Declarations

Conflict of interest S.G. and D.H.C. are recipients of investigator-initiated grants to their Universities from Pfizer, to study pneumococcal vaccines (S.G. and D.H.C.), Sanofi Pasteur and Seqirus, to study influenza vaccines (S.G., D.H.C. and YA, Genentech, to study influenza antivirals (S.G. and YA), GSK to study shingles vaccine (S.G.), and a collaborative grant from

Moderna on respiratory infection in long-term care (S.G., D.H.C., and YA). S. G. also consults for Janssen, Moderna, Novavax, Pfizer, Seqirus, and Sanofi and has received honoraria for speaking for GSK, Novavax, Pfizer, Sanofi, and Seqirus; YA is recipient of a grant from Centers for Disease Control and Prevention on The Kinetics of SARS-CoV-2 Shedding in Nursing Home Staff and Residents.

Disclaimer The sponsor had no role in the design, methods, data analysis, or preparation of the manuscript.

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