Received: 18 July 2023 | Accepted: 20 July 2023

DOI: 10.1111/jgs.18557

RESEARCH LETTER

Journal of the American Geriatrics Society

Neutralization and binding antibody response to second bivalent COVID-19 vaccination in nursing home residents

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Funding information
Center for Integrated Healthcare, U.S. Department of Veterans Affairs, Grant/Award Number: BX005507-0; National Center for Preparedness, Detection, and Control of Infectious Diseases, Grant/Award Numbers: 200-2016-91773, U01 CA260539-03; National Institute of Allergy and Infectious Diseases, Grant/Award Number: AI129709-03S1

INTRODUCTION

To date, SARS-CoV-2 has infected more than 1.6 million U.S. nursing home (NH) residents and killed more than 160,000.[1] Vaccination plays a vital role in preventing SARS-CoV-2 infection and reducing morbidity and mortality burden in this population. A single bivalent COVID-19 mRNA vaccine broadens SARS-CoV-2 immunity and reduces infection, hospitalization, and death beyond that from monovalent vaccination.[2,3] We extend our work here by evaluating the immune response following a second bivalent vaccine dose.

METHODS

The current analysis extends our longitudinal data evaluating serial blood draws from consented NH residents vaccinated with the COVID-19 mRNA vaccines.[2–5] We

Oladayo A. Oyebanji and Yasin Abul shared first authorship.

Stefan Gravenstein and David H. Canaday shared last authorship.

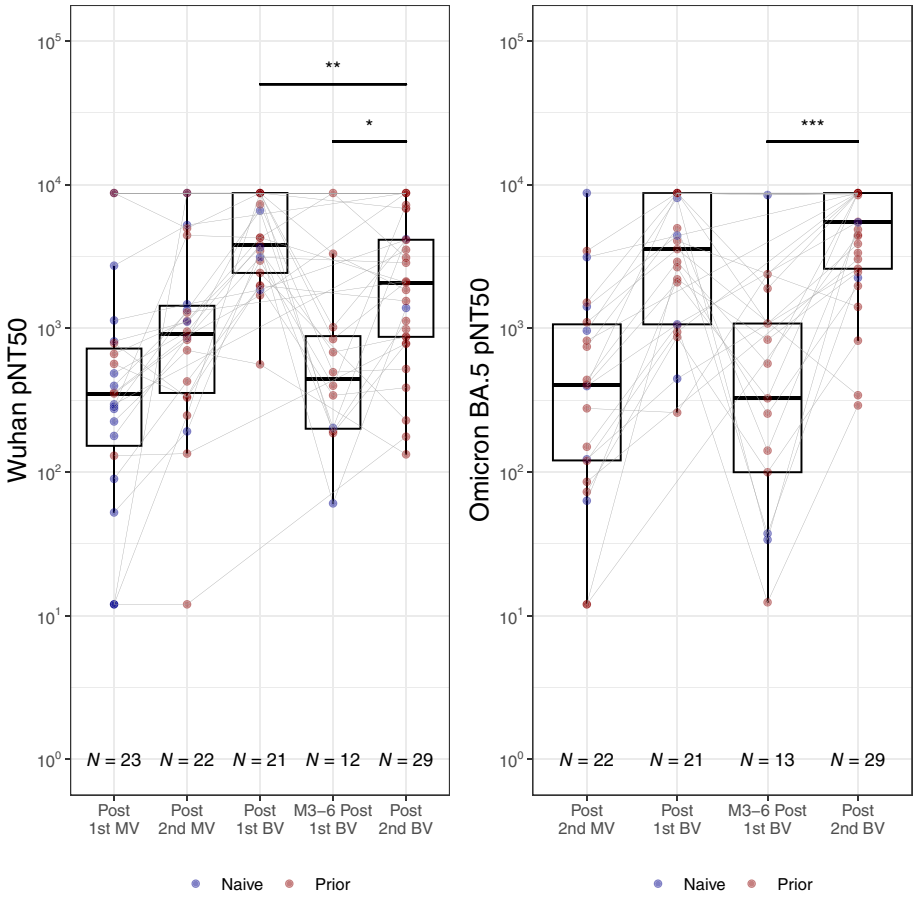

FIGURE 1 Neutralization titers for Wuhan and Omicron BA.5 in nursing home residents up to the second bivalent dose. Geometric mean titers and their 95% confidence intervals were calculated for each time point, strain, and assay. Two pairs of time points, post-1st bivalent vs post-2nd bivalent and 3–6 month post-1st bivalent vs post-2nd bivalent were compared for each titer using paired *t*-tests on the log-transformed titer values to compare the geometric mean fold change to 1. Blue dots represent pNT50 for serum from those without prior infection, red dots from those with prior infection. Significant fold-change differences indicated above, *corresponding to $p < 0.05$, ** to $p < 0.01$, and *** to $p < 0.001$. *p*-Values were unadjusted. Other statistical comparisons are not shown. The M3-6 month post-1st BV draw was obtained with a median of 180 days after vaccination (range 97–189 days). All analyses were performed using R Version 4.2.2. Abbreviations. MV Monovalent, BV Bivalent.

summarize findings from 2 weeks after each of four vaccination time points (first and second monovalent boosters, first and second bivalent boosters) and an intermediate draw 3–6 months after the first bivalent booster. We exclude data points from subjects with an interval infection (positive polymerase chain reaction or antigen test) and/or laboratory criteria [positive nucleocapsid (N) protein or a rise outside of lab variance of anti-spike (S), N, or neutralizing assay results not accounted for by vaccination history] until their next vaccine dose. We tested each sample for anti-S and neutralizing antibodies against SARS-CoV-2 Omicron BA.5 and the ancestral Wuhan strains using a bead-based ELISA method and pseudovirus neutralization assays as previously reported.[4,5]

RESULTS

One NH in our parent longitudinal cohort had 29 NH residents who received a 2nd bivalent vaccine and were not excluded by recent infection. They had a median age of 75 (range 63–97) with 62% female and 34% Black. All subjects received the primary series and first bivalent booster; 14% had only one prior monovalent booster and 86% received two prior monovalent boosters.

Neutralization titers declined 3–6 months after the first bivalent vaccine with geometric mean titers (GMT) decreasing from 3925 (2805, 5492) to 659 (265, 1636) for Wuhan and from 2877 (1761, 4701) to 319 (102, 1002) for BA.5. Among these subjects with the intermediate draw, titers were restored with the receipt of a second bivalent vaccine (Figure 1) with a geometric fold rise of 2.80 for Wuhan and a remarkable 11.1 for BA.5. Similarly, declining anti-S titers were boosted significantly following the administration of the second bivalent dose (Figure 2). Notably, BA.5 anti-S levels boosted to a level significantly higher than that attained after the first bivalent dose ($p = 0.002$).

DISCUSSION

This study investigated the impact of a second bivalent vaccine on neutralization titers and anti–S antibodies among NH residents. Our findings revealed that the administration of a second bivalent vaccine restored declining neutralization and anti-spike S, with a higher magnitude noted for the Omicron BA.5 compared to the ancestral Wuhan strain.

The ability of the Omicron variant to evade immunity conferred by a previous SARS-CoV-2 infection or vaccination

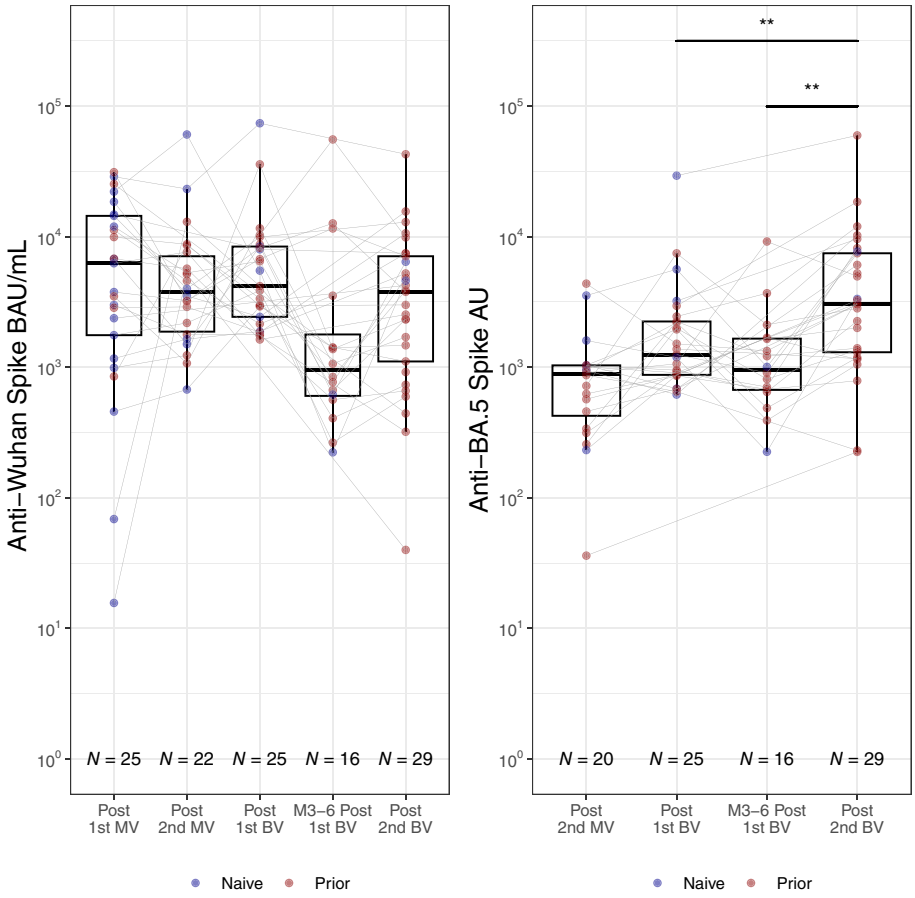

FIGURE 2 Anti-spike antibody titers for Wuhan and Omicron BA.5 in nursing home residents up to the second bivalent dose. Geometric mean titers and their 95% confidence intervals were calculated for each time point, strain, and assay. Two pairs of time points, post-1st bivalent vs post-2nd bivalent and 3–6 month post-1st bivalent vs post-2nd bivalent were compared for each titer using paired *t*-tests on the log-transformed titer values to compare the geometric mean fold change to 1. Blue dots represent anti-S titers for serum from those without prior infection, red dots from those with prior infection. Significant fold-change differences indicated above, **corresponding to $p < 0.01$. *p*-Values were unadjusted. Other statistical comparisons are not shown. The M3-6 month post-1st bivalent draw has obtained a median of the day 180 days after vaccination (range 97–189 days). All analyses were performed using R Version 4.2.2. Abbreviations. MV Monovalent, BV Bivalent.

led to the development and emergency use of the bivalent vaccines and subsequently authorized for an additional boost in older and other at-risk populations.[6] The increase in neutralization titers and anti-S antibodies in this study indicates a robust immune response induced by the second bivalent vaccine. Even as specific vaccine-induced immune correlates of protection continue to evolve, higher neutralization titers and anti-S antibodies are suggestive of a more effective immune response and have been associated with reduced disease severity and transmission.[7,8] Thus, by boosting neutralization titers and anti-S antibodies further, the second bivalent vaccine can enhance protection against the Omicron variants, reducing the risk of breakthrough infections and severe disease among this vulnerable population.

Remarkably, while we observed a ceiling anti-S response to Wuhan strain across two bivalent doses, the Omicron BA.5 response still increased. This suggests that the initial bivalent immunization with the new BA.5 antigen recruited additional memory T and B cells that could be further boosted with a second bivalent immunization. Interestingly, this was not observed with neutralization titers which represent a more limited epitope repertoire and more often cross-react with the ancestral Wuhan strain. We hypothesize this inability to boost beyond what imprinting allows is due to original antigenic sin.[9] These findings are particularly significant as they support and anticipate success with implementing Omicron-containing monovalent vaccines.[10]

Despite being limited by its small sample size, this is the first study, to our knowledge, characterizing the immunological response to the second bivalent vaccine among NH residents. Moreso, these findings have important implications for public health policy, supporting the recommendation for a second bivalent vaccine dose for NH residents as well as the proposed Omicron-containing monovalent vaccines to mitigate the impact of emerging variants and improve overall population health.

AUTHOR CONTRIBUTIONS

Oladayo A. Oyebanji, Yasin Abul, Stefan Gravenstein, and David H. Canaday: Concept and Design. Oladayo A. Oyebanji, Yasin Abul, Brigid M. Wilson, David H. Canaday, Elizabeth M. White, Christopher L. King, and Stefan Gravenstein: Preparation of manuscript. Brigid M. Wilson: Data analysis. Oladayo A. Oyebanji and Debbie Keresztesy: Recruitment of subjects. Elise M. Didion, Alexandra N. Paxitzis, Nicholas Sundheimer, Vaishnavi Ragavapuram, Htin Aung, Yi Cao, Alejandro B. Balazs, Jurgen Bosch, and Christopher L. King:

Data collection. Jurgen Bosch, Christopher L. King, Alejandro B. Balazs, Elizabeth M. White, David H. Canaday, and Stefan Gravenstein: Interpretation and funding.

CONFLICT OF INTEREST STATEMENT

Stefan Gravenstein (S.G.) and David H. Canaday (D.H.C.) receive investigator-initiated grants to their universities from Pfizer to study pneumococcal vaccines and Sanofi Pasteur to study influenza vaccines. S. G. also consults for GlaxoSmithKline, Janssen, Moderna, Novavax, Pfizer, Sanofi, Seqirus, and Vaxart and has served on the speakers' bureaus for Seqirus and Sanofi.

SPONSOR'S ROLE

This work was supported by NIH AI129709-03S1, CDC 200-2016-91773, U01 CA260539-03, and VA BX005507-0. The sponsors had no role in the decision for publication or the message presented.

FINANCIAL DISCLOSURE

This work was supported by grants from the National Institute of Health (NIH AI129709-03S1), Centers for Disease Control and Prevention (CDC 200-2016-91773, U01 CA260539-03), and Veteran's Affairs merit benefit (VA BX005507-0).

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How to cite this article: Oyebanji OA, Abul Y, Wilson BM, et al. Neutralization and binding antibody response to second bivalent COVID-19 vaccination in nursing home residents. *J Am Geriatr Soc*. 2023;1-4. doi:10.1111/jgs.18557