Clinical Infectious Diseases

BRIEF REPORT

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

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Antibody decline occurred from 2 weeks to 6 months post-BNT162b2 mRNA vaccination in nursing home (NH) residents and healthcare workers. Antispike, receptor-binding domain, and neutralization levels dropped >81% irrespective of prior infection. Notably, 69% of infection-naive NH residents had neutralizing antibodies at or below the assay's limit of detection.

Keywords. COVID-19; vaccine; long-term care; antibody.

The very high overall coronavirus disease 2019 (COVID-19) morbidity and mortality among nursing home (NH) residents led to their prioritization for early vaccination. In the United States, most NH residents received BNT162b2 mRNA vaccination because of its earlier emergency use authorization (EUA) and availability. NH residents who never had severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) before vaccination produced only one-quarter of the antibody compared with ambulatory healthcare workers (HCWs) [1–3]. There have been multiple reports of breakthrough infections in NH residents over time [4–7]. As a result, there is a significant need to characterize the durability of antibody responses following vaccination in NH residents due to their added vulnerability beyond that of the general population to inform public health policy around the need and timing of booster vaccinations. Here, we extend our prior observation in the same cohort from 2 weeks to 6 months after BNT162b2 mRNA vaccination to determine the magnitude of changes in antibody titers and neutralizing activity over time. We find significant reductions in both NH residents and HCWs [1].

METHODS

Study approval was obtained from the New England Institutional Review Board. All participants or their legally authorized representatives provided informed consent prior to participation and were enrolled in the initial study if they were willing to receive the BNT162b2 mRNA vaccine in the EUA regimen of 2 doses over 3 weeks.

Study Design and Population

We sampled 130 NH residents and 95 HCWs 6 months after vaccination who had been previously evaluated 2 weeks following vaccination (Supplementary Table 1). Patients were studied from December 2020 to July 2021 from 4 NHs in northeast Ohio. The HCWs were workers at the NH buildings and Cleveland Veterans Affairs medical center who all had access to the same vaccine at the same time as the NH residents. All participants received 2 doses of vaccine regardless of prior SARS-CoV-2 infection. Patients with a known prior infection date were vaccinated at a median of 67 days post-infection. Patients had post-vaccination samples drawn within 14 ± 3 days and 6 months (94% ±7 days, 2% ±14 days, and 4% at −21 days) after receiving the second dose. Participants were deemed to have a "prior infection" if they had a diagnostic polymerase chain reaction (PCR) or antigen test that confirmed acute SARS-CoV-2 infection and/or positive antibody levels to the SARS-CoV-2 spike and receptor-binding domain (RBD) prior to vaccination and deemed "infection-naive" if otherwise.

Antispike and Anti-RBD Assay

Immune response to the vaccine was assessed using immunoglobulin G (IgG) to spike protein and its RBD by bead-multiplex immunoassay using the Wuhan strain [1]. Stabilized full-length S protein (aa 16–1230, with furin site mutated) and RBD (aa 319–541) were conjugated to magnetic microbeads (Luminex) and Magpix assay system (BioRad, Inc). The mean fluorescent index was recorded after detection of antigen-specific IgG in

Received 29 September 2021; editorial decision 12 November 2021; published online 19 November 2021.

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Clinical Infectious Diseases® 2022;75(1):e884–7

https://doi.org/10.1093/cid/ciab963

participant serum using phycoerythrin-conjugated donkey F(ab)2 anti-human IgG, with Fcγ (Jackson Immunological). A secondary standard from the Frederick National Laboratory calibrated to the WHO standard 20/136 was used to express antibodies to the spike protein in binding arbitrary units (BAU) per milliliter.

SARS-CoV-2 Pseudovirus Neutralization Assay

To determine the neutralizing activity of vaccine recipients' sera against coronaviruses, we produced lentiviral particles pseudotyped with spike protein based on the Wuhan strain as previously described [8]. Briefly, neutralization assays were performed using a Fluent 780 liquid handler (Tecan) in 384-well plates (Grenier). Three-fold serial dilutions that ranged from 1:12 to 1:8748 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 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.

Statistical Analyses

Geometric mean levels of immune response assays were compared across 4 participant groups: infection-naive NH residents, NH residents with prior infection, infection-naive HCWs, and HCWs with prior infection. Changes within participants from 2 weeks to 6 months were assessed using paired *t* tests on the log-transformed assay values. To compare immune responses at 2 weeks and 6 months across participant groups, regression models for each time point predicting log-transformed assay values with participant groups provided least-squares estimates. In instances of significant group differences, post hoc pairwise tests of group means were implemented with Tukey *P* value adjustments. As the LLD for neutralization titers of 1:12 titer was frequently observed, limiting the validity of variance estimates in regression models, LLD in the neutralizing titer was summarized and analyzed as a binary outcome. Rates of neutralization titer LLD in NH and HCW groups, stratified by prior infection, were compared using Fisher exact tests. All analyses were performed in R version 4.0.3.

RESULTS

Of 225 participants with available 6-month follow-up, 13 (6%) were excluded for presumed or known SARS-CoV-2 infection between the 2-week and 6-month draws (Supplementary Table 2). All of these participants were in buildings or workspaces with known outbreaks. Those with presumed infection had an increase in titer greater than 100% at 6 months from the 2 week post-vaccine level in at least 1 of the immune assays. Five participants had known PCR-confirmed diagnoses; the other presumed cases were clinically undetected.

Among the remaining participants with both 2-week and 6-month data available (n = 212), anti-spike, anti-RBD, and neutralization titers were determined. Significant decreases were observed at 6 months in all assays for all participant groups (paired *t* test $P < .001$ for all). Geometric mean titers (GMTs) dropped 82%–95% over time in all groups (Figure 1A–C and Supplementary Table 3) irrespective of prior SARS-CoV-2 infection status.

At both 2 weeks and 6 months post-vaccination, infection-naive NH residents had significantly lower anti-spike, RBD, and neutralization GMTs than NH residents with prior infection, HCWs with prior infection, and infection-naive HCWs ($P < .01$ for all comparisons; Figure 1A–C, Supplementary Table 2). Interestingly, the anti-spike and RBD antibody levels across the naive HCWs and both NH residents and HCWs who had prior SARS-CoV-2 infection were not significantly different at either time point. At 6 months post-vaccination, 69% of the infection-naive NH residents had neutralization titers at or below the LLD compared with 16% at 2 weeks after full vaccination (Supplementary Table 4). No HCWs and NH residents who were vaccinated after prior infection had neutralizing levels at or below the LLD at 2 weeks post-vaccination; however, by 6 months, those at or below the LLD increased to 19% and 35%, respectively. Among infection-naive HCWs, the rate of those at or below the LLD increased from 2% to 16% from 2 weeks to 6 months.

DISCUSSION

An improved understanding of the clinical consequences of this drop in antibody levels that mediate humoral immunity is urgently needed to inform boosting strategies and policies. NH residents and HCWs were among those vaccinated earliest, resulting in the longest time for immunity to wane. In particular, infection-naive NH residents had lower initial antibody levels and the lowest at 6 months post-vaccination. HCWs, given their younger age and fewer comorbidities, achieved higher initial antibody levels yet also experienced similarly large declines in antibody levels. In addition, the initial advantage of being vaccinated following infection was blunted by 6 months, at which time the anti-spike and RBD antibody levels were similar to those in HCWs not previously infected. Van Praet et al also noted a similar decline in NH residents and infection-naive HCWs over time, but they did not include HCWs with prior infection as a comparator nor an assessment of neutralizing activity [9].

Recent data suggest that neutralization activity correlates with protection from symptomatic infection prior to the emergence of the delta variant [10, 11]. Those individuals with undetectable neutralizing antibodies had lower protection from symptomatic infection. The loss in neutralizing activity may therefore translate to a clinically important difference between

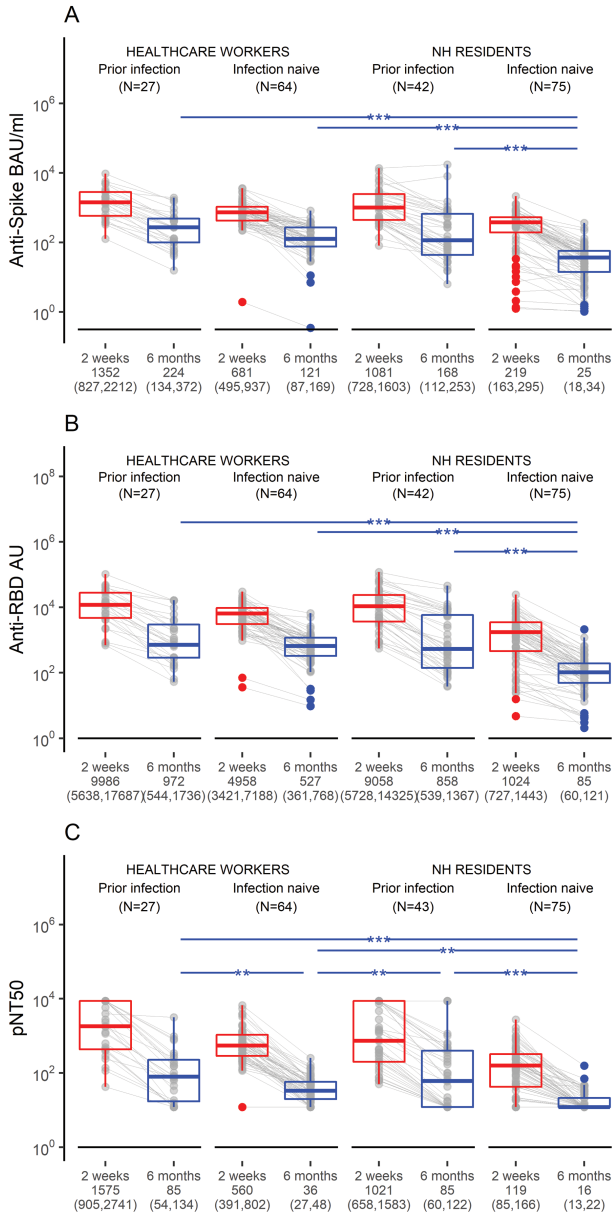

Figure 1. Antibody levels 2 weeks and 6 months after BNT162b2 mRNA vaccination in healthcare workers (HCWs) and NH residents with and without severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection prior to vaccination. Post-vaccination anti-spike in BAU/mL *(A)*, anti-RBD in AUs *(B)*, and pNT50 *(C)* are shown. The lower limit of detection of the neutralization assay is 1:12. N for each assay and group of total participants depicted. Results are stratified by younger HCWs and NH residents. Prior infection refers to antibody levels at the given time points in individuals vaccinated after recovering from earlier SARS-CoV-2 infection, and infection naive refers to individuals vaccinated without prior SARS-CoV-2 infection. Geometric means were compared across groups at 2 weeks and 6 months using least-squares regression on log-transformed assay values. Post-hoc pairwise group differences at 6 months are presented here after Tukey adjustment for 4 group comparisons, with ** indicating $P < .01$ and *** indicating < 0.001. All 2-week to 6-month changes in all panels are significant, with paired *t* test $P < .001$ (not shown). Abbreviations: AU, arbitrary unit; BAU, binding arbitrary unit; NH, nursing home; pNT50, pseudovirus neutralization; RBD, receptor-binding domain.

groups. In our sample, 69% of infection-naive NH residents exhibited serum neutralizing activity at or below the LLD of the assay, suggesting that they are at greater risk for vaccine failure.

Our results show that a marked decline in antibody levels occurred in parallel with the rapid rise of the delta variant and that reported vaccine breakthrough in NHs and the broader community had already taken place [4–7], supporting the Centers for Disease Control and Prevention's (CDC's) recommended boosting of NH residents to curb spread and prevent severe illness.

There are several limitations of the study. T-cell responses that may offer more enduring clinical benefit were not assessed nor was antibody specificity to emerging variants. The study is also of limited size and applies to 1 geographic area.

In conclusion, these results show the significant loss of potentially protective antibody within 6 months among elderly NH residents following BNT162b2 mRNA vaccination, particularly in those individuals without prior SARS-CoV-2 infection. Our results provide support for the current CDC policy recommending boosters in this older population, and the need for ongoing monitoring to evaluate clinical implications and inform future boosting strategies.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Financial support. This work was supported by the National Institutes of Health (AI129709-03S1, 3P01AG027296-11S1, U01 CA260539-01, Centers for Disease Control and Prevention [CDC] 200-2016-91773, and VA BX005507-01).

Potential conflicts of interest. S. G. and D. H. C. are recipients of investigator-initiated grants to their universities from Pfizer to study pneumococcal vaccines and from Sanofi Pasteur and Seqirus to study influenza vaccines, and funding from the CDC to study vaccines in nursing home residents. S. G. does consulting work for Seqirus, Sanofi, Merck, Vaxart, Novavax, Moderna, and Janssen; has served on speaker's bureaus for Seqirus and Sanofi; reports personal fees from Janssen (fees related to non–severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] vaccine development), Longevoron (DSMB), Novavax (consulting fees related to vaccine development), and Pfizer; reports receipt of data and safety monitoring board (DSMB) fees from Longevoron and SciClone; reports grants and personal fees from Pfizer (grant to Brown University and fees related to pneumococcal vaccines), Seqirus (grant to Brown University and fees related to influenza vaccines), and Sanofi (grant to Brown University, fees related to influenza and other vaccines); and grants from the CDC (contract related to post-SARS-CoV-2 vaccination immunity) outside the submitted work. D. H. C. has done paid consulting work for Seqirus (sat on expert panel for advice on their potential coronavirus disease 2019 vaccine construct). S. D. B. reports receiving National Institute of Aging U54 AG063546; reports royalties from Wolters Klewer for a chapter on falls in nursing home for Up-to-Date; reports serving on an advisory board/DSMB for the TOPAZ study (zoledronic acid in participants with Parkinson's disease); and served in a leadership role on an American Geriatrics Society research committee. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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