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BRIEF REPORT

Reduced BNT162b2 Messenger RNA Vaccine Response in Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)–Naive Nursing Home Residents

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After BNT162b2 messenger RNA vaccination, antibody levels to spike, receptor-binding domain, and virus neutralization were examined in 149 nursing home residents and 110 healthcare worker controls. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–naive nursing home residents' median post–second vaccine dose antibody neutralization titers are one-quarter that of SARS-CoV-2–naive healthcare workers.

Keywords. SARS-CoV-2; geriatrics; vaccine; COVID-19.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has severely affected nursing home (NH) residents, prompting their prioritization for early vaccination. Recent reports show the BNT162b2 messenger RNA (mRNA) vaccine reduces coronavirus disease 2019 (COVID-19) hospitalization and mortality [1–4]. BNT162b2 mRNA vaccine immunogenicity has been reported in some healthy 65- to 85-year-olds [1], however no immunogenicity data exist for NH residents to this vaccine. NH residents often have multiple morbidities, medications, and advanced age that individually and collectively can blunt immune response. Here, we examined antibody response to BNT162b2 mRNA vaccine in NH residents who were SARS-CoV-2 naive where the vaccine is presumed to be neoantigen-like and individuals who had prior SARS-CoV-2 infection where the vaccine would be boosting prior responses.

METHODS

Regulatory Approval and Study Subjects

We obtained New England Independent Review Board study approval and consented subjects per protocol. We approached nursing home leadership to gain entry to 4 NH buildings and recruit residents for vaccination with and without prior SARS-CoV-2 infection and healthcare workers as controls. Controls included vaccinated individuals with and without prior SARS-CoV-2 infection, and unvaccinated individuals convalescent from prior SARS-CoV-2 infection. Prior SARS-CoV-2 infection was determined by polymerase chain reaction, antigen test, and/or high antibody titer to SARS-CoV-2 spike and receptor-binding domain (RBD).

Anti-Spike and Anti-RDB Assay

Stabilized full-length S protein (aa 16–1230, with furin site mutated) and RBD (aa 319–541) were conjugated to magnetic microbeads (Luminex). Antigen-specific immunoglobulin G (IgG) is detected in patient serum/plasma using Phycoerythrin-conjugated Donkey F(ab)2 anti-human IgG, with Fcγ (Jackson Immunological) added. Using the Magpix assay system (BioRad), the mean fluorescent index (MFI) is recorded. To provide an internal standard and control for plate-to-plate variation, a pool of convalescent plasma was generated from people with known prior SARS-CoV-2 infection and ran a standard curve of half log-dilutions starting at a 1:100 dilution on each plate. A relative antibody unit (AU) value of 4000 was ascribed to the 1:100 dilution. MFI values were interpolated from this curve to generate the AU values presented. A receiver operating curve was generated using 167 pre–SARS-CoV-2 serum control samples and 66 SARS-CoV-2 convalescent samples to determine cutoff values for a convalescent antibody levels with a specificity of 99% and sensitivity of 98% using antibodies to both S and RBD.

SARS-CoV-2 Pseudovirus Neutralization Assay

To compare the neutralizing activity of vaccine recipients' sera against coronaviruses, we produced lentiviral particles pseudotyped with vaccine strain spike protein as previously described [5]. Neutralization assays and readout were performed

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on a Fluent Automated Workstation (Tecan) liquid handler using 384-well plates (Grenier) [6]. Three-fold serial dilutions ranging from 1:12 to 1:8748 were performed for each serum sample before adding 50–250 infectious units of pseudovirus for 1 hour. Percentage neutralization was determined by subtracting background luminescence measured in cell control wells (cells only) from sample wells and dividing by virus control wells (virus and cells only). pseudovirus neutralization titers (pNT_{50}) 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.

We used R version 4.0.3 software for all statistical analyses. Unless otherwise specified, presented *P* values are unadjusted.

RESULTS

We recruited 149 NH residents (median age, 76 [range, 48–99] years), 110 healthcare worker controls (median age, 48 [range, 26–78] years), and 22 unvaccinated convalescent controls (median age, 53 [range, 25–61] years), 29–94 days after SARS-CoV-2 infection with asymptomatic or mild disease (Supplementary Table 1). All NH residents and 71 of 110 healthcare worker controls provided baseline blood samples 1–14 days before BNT162b2 mRNA vaccination and all subjects 14 ± 3 days after their second dose.

The Figure 1 shows antibody levels after vaccination and/or infection. The postvaccination antibodies of NH residents and younger healthcare worker controls are stratified by prior SARS-CoV-2 infection at the time of vaccination. SARS-CoV-2–naive NH residents compared to SARS-CoV-2–naive healthcare workers had significantly lower median postvaccination antibody titer, neutralization titers (135 vs 521, $P < .0001$), geometric mean anti-spike levels (1029 vs 4177, $P < .0001$), and geometric mean anti-RBD levels (768 vs 3894, $P < .0001$). Postvaccination anti-RBD levels and neutralization titers were highly correlated (Spearman rank $r = 0.84$, $P < .0001$).

After vaccination, 19% of SARS-CoV-2–naive NH residents had neutralizing titers at or below the lower limit of detection with only 1.4% of SARS-CoV-2–naive healthcare workers that low. Similarly, fewer vaccinated SARS-CoV-2–naive NH residents compared to vaccinated SARS-CoV-2–naive controls (36% vs 85%) had neutralization titers above the median of the unvaccinated SARS-CoV-2 convalescent younger adults. By contrast, SARS-CoV-2–recovered NH residents' postvaccination neutralization titers, anti-spike, and anti-RBD levels were similar to those SARS-CoV-2–recovered vaccinated healthcare workers.

Increasing age correlated with declining postvaccination antibody titers among SARS-CoV-2–naive subjects (Spearman rank $r = –0.39$, $–0.44$, $–0.45$ for anti-spike, anti-RBD, and neutralization titers, respectively, all $P < .001$), but not SARS-CoV-2–convalescent subjects. We did not detect statistically significant differences by sex in postvaccine anti-spike, anti-RBD, or neutralizing titer levels for either NH resident or control SARS-CoV-2–naive subjects or SARS-CoV-2–recovered subjects. We observed a potential shift toward higher

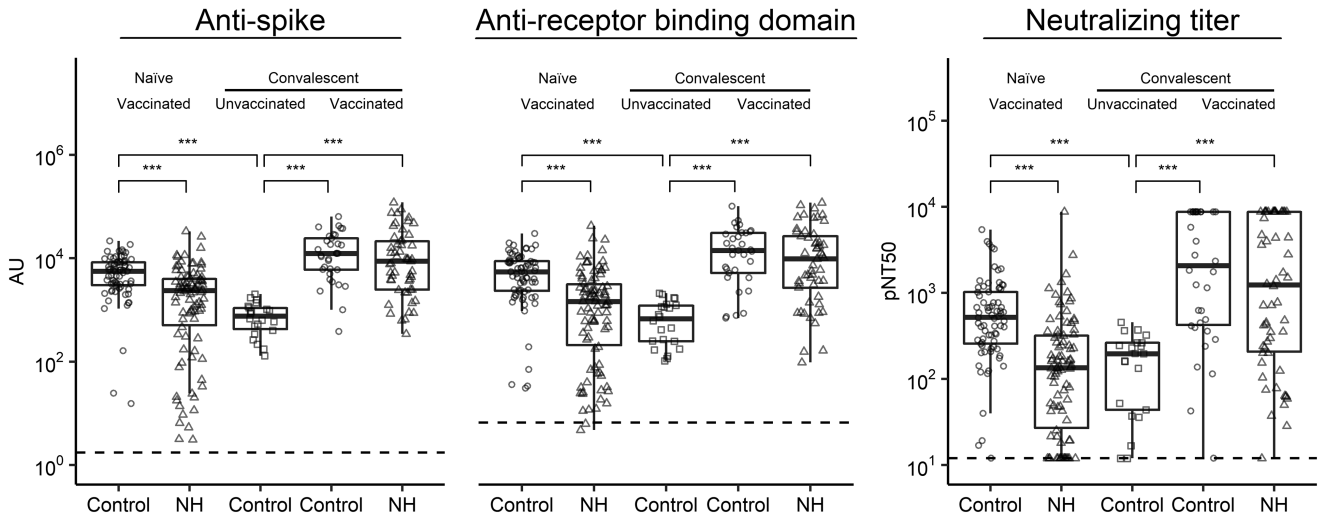

Figure 1. Humoral immune assessment of BNT162b2 messenger RNA (mRNA) vaccine vaccination in nursing home (NH) residents. Postvaccination anti-spike, anti–receptor-binding domain (RBD) and serum neutralization titers are shown. On the x-axis, "NH" refers to NH residents and "control" refers to the vaccinated younger healthcare workers or unvaccinated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–convalescent individuals. The dotted line in each panel is the median preimmunization value in the SARS-CoV-2–naive subjects. Anti-spike and anti-RBD differences in geometric means were assessed using *t* tests of log-transformed values. Given observed points at upper and lower limits of detection in the neutralizing titer assay (12–8748), differences in distribution were assessed using the Wilcoxon rank-sum test. *P* values were adjusted within assay (n = 6 tests per assay, Bonferroni method). ***Adjusted $P < .001$. Abbreviations: AU, antibody unit; NH, nursing home; pNT_{50}, pseudovirus neutralization titer.

postvaccination antibody levels in SARS-CoV-2–recovered female subjects vs male subjects, which requires further study.

DISCUSSION

We show that most NH residents have produced antibodies to the BNT162b2 mRNA vaccine but those without prior SARS-CoV-2 infection have significantly lower antibody levels than younger nonfrail control participants with few exceptions. It is interesting to note that individuals with prior SARS-CoV-2 infection, including NH residents, have higher postvaccination antibody levels than SARS-CoV-2–naive individuals and are similar to those in vaccinated convalescent controls, a trend more noticeable for women. However, it is difficult to disentangle this finding from a survivorship bias for these NH residents; possibly, nonresponders may have been culled from contributing to our sample based on survival or ability to recruit them due to post–COVID-19 outcomes affecting their ability to consent and participate in our study. Therefore, those SARS-CoV-2–naive NH residents' blunted antibody responses have important implications regarding the interpretation of these net high titers of convalescent NH residents, regarding the quality and durability of protection afforded as neoantigen vaccines, and potentially as a breeding ground for vaccine-resistant variants.

The causes for the diminished response are not fully clear, but older adults have reduced vaccine response to many different vaccines [7–9], leading to the development of enhanced vaccines in order to overcome this age handicap such as the adjuvanted and higher-dose influenza vaccines. Of note, individuals without prior SARS-CoV-2 infection were more likely to have reduced antibody responses following vaccination with increasing age. Developing responses in this neoantigen setting are the most demanding for the vaccine. Reduced responsiveness brought on by age, frailty, multimorbidities, and medications are likely key contributing factors.

Lower titers can mean (1) less protection from infection; (2) shorter interval of protective titers; (3) greater likelihood of breakthrough infection with resistant variants; (4) greater likelihood of disease; (5) greater likelihood of asymptomatic or silent infection, posing a risk for transmission to remaining vulnerable/unvaccinated staff, residents and visitors; and (6) among those who have breakthrough infection, those starting with the lowest titers may be the most symptomatic. Early reports of significant reductions in COVID-19 in NH after vaccination are encouraging, but it is not clear how sustained that protection will be. Continued and even increased infection risk in NHs is expected as they relax visitation policies and confront vaccine hesitancy in some residents and especially among NH staff.

There may be differences in responses between the different vaccine platforms in NH residents. Although Walsh et al reported similarities in the antibody responses after BNT162b2 mRNA vaccination in a much healthier older population compared to younger individuals [1], our data suggest that this does not hold in the more frail, older NH population. Poor vaccine immune responses in frail older adults with many multimorbidities could be exacerbated with the somewhat less immunogenic non-mRNA vaccine, such as an adenovirus-vectored vaccine like the Ad26.COV2.S SARS-CoV-2 vaccine [10]. There is still much to do to fully understand how to optimally protect this most frail and vulnerable population from COVID-19. We urgently need better longitudinal evidence on vaccine effectiveness specific to NH resident populations, especially in the context of new, more transmissible variants, to inform best practices for NH infection control measures and outbreak prevention. Vaccine failure with a variant has already been reported in a skilled nursing facility in Kentucky [11]. We do not know if additional booster vaccination will rescue poor responders and nonresponders, making them more fit from the variant matching their vaccine's design, or to other variants of concern. We should presume that a population setting with suboptimal vaccine uptake among staff and visitors and a substantial proportion of poor responders will place selective pressure for the development of new variants of concern. If an additional booster vaccine can improve protection, our results would support an approach in which we screen antibody responses after vaccination in NH residents to determine for whom an additional vaccine boost could be beneficial. Data on immune correlates of protection are needed as well.

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

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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 Sanofi Pasteur and Seqirus to study influenza vaccines. S. G. also does consulting for Seqirus, Sanofi, Merck, 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. D. H. C. has done consulting work for Seqirus. S. D. B. reports royalties from Wolters-Kluwer, lecture fees from Harvard, and DSMB membership for a trial of zoledronic acid in Parkinson's patients, outside the submitted work. C. L. K. reports grants from the Bill & Melinda Gates Foundation, the National Institutes of Health, and Veterans Health Administration, outside the submitted work.

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