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Original Study - Brief Report

Antibody Responses After mRNA-Based COVID-19 Vaccination in Residential Older Adults: Implications for Reopening

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A B S T R A C T

Objective: COVID-19 disproportionately impacts residents in long-term care facilities. Our objective was to quantify the presence and magnitude of antibody response in vaccinated, older adult residents at assisted living, personal care, and independent living communities.
Design: A cross-sectional quality improvement study was conducted March 15 – April 1, 2021 in the greater Pittsburgh region.
Setting and Population: Participants were older adult residents at assisted living, personal care, and independent living communities, who received mRNA-based COVID-19 vaccine. Conditions that impair immune responses were exclusionary criteria.
Methods: Sera were collected to measure IgG anti-SARS-CoV-2 antibody level with reflex to total anti-SARS-CoV-2 immunoglobulin levels, and blinded evaluation of SARS-CoV-2 pseudovirus neutralization titers. Descriptive statistics, Pearson correlation coefficients, and multiple linear regression analysis evaluated relationships between factors potentially associated with antibody levels. Spearman correlations were calculated between antibody levels and neutralization titers.
Results: All participants (N = 70) had received two rounds of vaccination and were found to have antibodies with wide variation in relative levels. Antibody levels trended lower in males, advanced age, current use of steroids, and longer length of time from vaccination. Pseudovirus neutralization titer levels were strongly correlated ($P < .001$) with Beckman Coulter antibody levels [D614 G NT50, $r_s = 0.91$; B.1.1.7 (UK) NT50, $r_s = 0.91$].
Conclusions and Implications: Higher functioning, healthier, residential older adults mounted detectable antibody responses when vaccinated with mRNA-based COVID-19 vaccines. Data suggests some degree of immunity is present during the immediate period following vaccination. However, protective effects remain to be determined in larger studies as clinical protection is afforded by ongoing adaptive immunity, which is known to be decreased in older adults. This study provides important preliminary results on level of population risk in older adult residents at assisted living, personal care, and

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Brief summary: All participants mounted antibodies to SARS-CoV-2. As compared to residents in nursing homes, older adults in residential communities are more vaccine responsive and protected, thus indicating less stringent reopening strategies.

Conflicts of interest: None of the authors report any potential conflicts of interest.

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independent living communities to inform reopening strategies, but are not likely to be translatable for residents in nursing homes.

COVID-19 disproportionately impacts older adults and frail individuals residing in long-term care facilities. As of May 2021, there are over 1.2 million cases of COVID-19 in U.S. nursing homes. Of these, over 134,000 COVID-19 related deaths have occurred, representing 23% of all U.S. COVID-19 deaths.[1] Advanced-age, high rates of frailty, comorbid conditions, and close physical contact between residents and staff facilitate spread of the virus in nursing homes. Visitor restrictions, curtailing of community dining, and other social activities have been crucial to limiting spread of the virus. Between December 20, 2020 and March 7, 2021, the number of new nursing home cases decreased by 96% and deaths by 91%, due in part to COVID-19 vaccinations.[2] Given the reductions in cases and severity, residents and families are now calling for reopening of long-term care facilities to reduce the negative impacts of social isolation on residents. The Centers for Medicare and Medicaid Services released guidance for reopening of nursing homes on March 10, 2021,[3] but so far, no consensus exists around reopening strategies for independent living, personal care, and assisted living residential communities.

While current COVID-19 vaccines appear to be effective in reducing severe illness, breakthrough cases do occur including symptomatic and asymptomatic infections.[4] Information regarding antibody response to COVID-19 vaccines is limited. As part of an effort to assess level of risk in reopening strategies, the Society for Post-Acute and Long-Term Care Medicine (AMDA), is recommending a measured, stepwise approach to resuming visitation and group activities in post-acute and long-term care settings, while acknowledging gaps in clinical knowledge about COVID-19.[5] Although recommendations regarding reopening have been published,[6–8] these focus on the process for reopening and not risk assessment of the resident population. Antibody measurement may help inform level of risk, particularly if significant numbers of individuals fail to demonstrate antibody response to vaccination. Therefore, the objective of this study was to quantify the presence and magnitude of antibody responses in vaccinated, older adult residents at assisted living, personal care, and independent living communities, including those with and without prior COVID-19 infection.

Methods

Setting and Population

Enrollment for this cross-sectional quality improvement study occurred March 15 − April 1, 2021 at University of Pittsburgh Medical Center (UPMC) Senior Communities for assisted living, personal care, and independent living in the greater Pittsburgh region. To maximize external validity and limit recruitment bias, all residents were invited to participate. Volunteers were screened for study eligibility following verbal consent. Participant eligibility criteria were residents who have received one or more doses of a COVID-19 vaccine. Conditions that impair immune responses were exclusionary criteria (eg, hematologic malignancies, solid organ transplants, active chemotherapy, and active immunosuppressive therapies). Individuals receiving steroids for self-limited conditions such as skin rashes at doses equivalent to less than 20 mg of prednisone daily or for less than 10 days duration were not excluded. This project underwent formal review and was granted ethical approval (Project ID: 3250) as a quality improvement study by the UPMC Quality Improvement Review Committee, the ethics, regulatory, and legal oversight body for protecting patient and participant rights, confidentiality, consent (including waiver of consent), and the analysis and dissemination of de-identified data within the UPMC system.

Data Collection

Study data were collected by the project coordinator and managed using the Research Electronic Data Capture (REDCap) hosted at UPMC.[9] REDCap is a secure, web-based software platform designed to support data capture for research and quality improvement studies.[10] Data was collected on vaccination status (dates, number of doses, and type of vaccine), medical conditions, and current medications. Level of frailty was assessed in participants using self-reported activities of daily living and instrumental activities of daily living measures.[11–13]

Study Outcomes

To quantify the presence and magnitude of antibody response in this population, trained phlebotomists collected blood samples from each participant to provide sera for measurement of IgG anti-SARS-CoV-2 antibody levels with reflex to total anti-SARS-CoV-2 immunoglobulin levels; the first assay is a high throughput assay that assesses established antibody response to the RBD (receptor binding domain) of SARS-CoV-2 after either infection or vaccination, with the second assay being orthogonal for IgG and IgM antibody responses to different epitopes of the RBD and rules out false positive binding.14,15 SARS-CoV-2 antibody assays were performed in the CLIA-88 accredited UPMC Clinical Laboratories. Specimens were initially assessed using the Beckman Coulter SARS-CoV-2 IgG Access assay (AU5800 analyzer, Brea, CA, USA), and then confirmed orthogonally using the Siemens Healthineers SARS-CoV-2 Total assay (ADIVA Centaur XP analyzer, Munich, Germany; Siemens-C).14,15 The Beckman Coulter assay uses S1 Spike antigens as capture and anti-IgG as reporter; the Siemens uses S1 Spike antigens as both capture and reporter and thus IgM antibodies are detected and at a higher molar 'index value' than IgG antibodies. Both assays were run according to the manufacturer's instructions. Both assays use units that are generated by comparison to an internal calibrator or standard, when referring to assay results collectively we refer to these units as 'index values' for simplicity; both use an index of >1.0 for positivity.

SARS-CoV-2 pseudovirus neutralization titer levels were evaluated blinded to Beckman Coulter antibody levels; this assay was used to correlate the patient antibody levels to actual virus neutralization. SARS-CoV-2 pseudovirus (PSV) was generated in 293T cells by co-transfection of pFC37K-CMV-S, an enhanced expression plasmid encoding for codon-optimized full-length SARS-CoV-2 S (Wuhan-1 sequence containing D614 G substitution or from the B.1.1.7 variant) with the N-term HiBit tag removed, and pNL4-3.luc.R-E-mCherry-luciferase, an envelope deficient HIV-1 dual reporter construct that was cloned by recombination of the pNL.luc.R-E− plasmid (NIH AIDS Reagent Program) and the fully infectious pNL4-3 mCherry luciferase plasmid (Addgene).[16–19] After harvest, PSV was centrifuged at 400 units of gravity (xg) for 10 mins and supernatant removed and filtered with a 0.45 micron syringe filter to remove producer cells. For neutralization assays, 10^4 293T-hACE2 cells were plated in 100 microliters (μL) media per well in 96 well white-wall white-bottom plates (Perkin Elmer) and incubated overnight at 37°C. Sera was diluted 1:2, then serially diluted 5-fold and incubated with 50 μL of

PSV for 1 hour at 37°C. After incubation, media was removed from wells containing 293T-hACE2 cells and replaced with PSV/sera, and spinoculation was performed at 1,000xg for 1 hour at real-time (RT). Plates were then incubated for 48 hours at 37°C. After 48 hours, plates were analyzed for luciferase production by adding 100 μL of BriteLite Plus reagent (Perkin Elmer), incubating at RT for 2 minutes, and reading on a Victor Nivo microplate luminometer (Perkin Elmer). Results are reported as the highest serum dilution that neutralizes >50% of the PSV termed the NT50.

Statistical Methods

Descriptive statistics for baseline population characteristics were calculated as means, standard deviations, and frequencies. Pearson correlation coefficients were calculated between age and antibody level, and between days since vaccination and antibody level. We also performed multiple linear regression modeling using stepwise entry criteria of $P < .20$ to identify factors potentially associated with antibody levels. Based on the distributional properties of the antibody assay variables, Spearman correlations were calculated between antibody levels and neutralization titers. Analysis were performed using SAS, version 9.4 (SAS Institute, Inc., Cary, NC). Methods and results are reported in accordance with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement[20] and Standards for Quality Improvement Reporting Excellence (SQUIRE) guidelines.[21]

Results

Population

A total of 82 potential participants were screened and of these, 12 failed screening due to impaired immunity (14.6%). Presented in Table 1, 70 participants were enrolled in the study, 10 were assisted living residents (14.3%), 28 were personal care residents (40.0%), and 32 were independent living residents (45.7%). The age range was 62-97 years old with almost half in their 80s (49.3%), and the rest split between younger (22.5%) and older (28.2%). Two-thirds were female (60.0%) and almost all participants were white (97.1%). Frailty indices indicated moderate to high functioning and 6 participants (8.6%) were taking low dose (<20 mg daily) or short-term (<10 days) steroid medication to treat mild or temporary conditions (arthritis = 2, chronic obstructive pulmonary disease = 1, skin rash = 1, back pain = 2).

Study Outcomes

All participants had undergone two rounds of vaccination (Moderna 98.6%, Pfizer 1.4%) within the prior 50 days, and one in six had recovered from COVID-19 infection (15.7%). Antibody levels were determined using two FDA Emergency Use assays. All participants were found to have antibodies to SARS-CoV-2; one was deemed nonreactive by the Beckman Coulter assay, having an extinction coefficient < 1, but was assessed as reactive by the more sensitive ADIVA Centaur assay.[14] There was wide variation in relative levels of antibodies as determined by extinction coefficients (mdn = 23.5, m = 23.1, IQR = 10.7-34.0, range = 0.46-61.0). While the sample size is modest, which limits statistical power, we found that antibody levels trended lower in males [standardized beta coefficient (β) = -0.11, $P = .33$] (Figure 1A), advanced age (β = −0.18, $P = .11$), current use of steroids (β = −0.22, $P = .07$), and longer length of time from vaccination (β = −0.13, $P = .28$) (Figure 1B). In participants who previously tested positive for COVID-19 (n = 11), antibody levels trended higher (β = 0.18, $P = .12$), though one participant had very low levels of antibodies suggesting that prior infection does not guarantee a strong response. SARS-CoV-2 pseudovirus NT50 levels ranged from 2 to 8218 (mdn = 135) against the D614 G and B.1.1.7 variants and were strongly correlated ($P < .001$) with Beckman Coulter antibody levels [D614 G NT50, $r_s = 0.91$; B.1.1.7 (UK) NT50, $r_s = 0.91$] (Figure 2). The level of correlation strongly suggests that commercial high throughput assays for antibodies against SARS-CoV-2 RBD reflect ability to neutralize infectivity and present at least partial protection against more severe disease.

Table 1
Descriptive Characteristics and Antibody Levels in Older Adult Residents at Assisted Living, Personal Care, and Independent Living Communities

Characteristic/Antibody level	All Participants (N = 70) (100%)	Female (N = 42) (60.0%)	Male (N = 28) (40.0%)
Residential Setting, %, (n)			
Assisted Living	14.3 (10)	19.1 (8)	7.1 (2)
Personal Care	40.0 (28)	33.3 (14)	50.0 (14)
Independent Living	45.7 (32)	47.6 (20)	42.9 (12)
Age in years, mean (SD)	84.8 (7.8)	84.6 (7.6)	85.1 (8.3)
Age in years, %, (n)			
62 to 79 years	21.4 (15)	21.4 (9)	21.4 (6)
80 to 89 years	50.0 (35)	50.0 (21)	50.0 (14)
90 to 97 years	28.6 (20)	28.6 (12)	28.6 (8)
Frailty, mean (SD)			
Katz Index Independence ADL*	5.2 (1.4)	5.2 (1.3)	5.3 (1.5)
Lawton Instrumental ADL†	5.3 (2.4)	5.4 (2.3)	5.1 (2.7)
Previously told had COVID-19, %, (n)	15.7 (11)	11.9 (5)	21,4 (6)
Currently taking a steroid medication, %, (n)	8.6 (6)	9.5 (4)	7.1 (2)
Days from first vaccine to antibody sample, mean (SD)	59.8 (13.5)	58.9 (14.9)	61.1 (11.1)
Days from second vaccine to antibody sample, mean (SD)	32.3 (12.4)	31.8 (13.2)	33.0 (11.3)
ADIVA Centaur antibody determination, %, (n)			
Low responder (ADIVA Centaur ≤10)	7.0 (5)	9.5 (4)	3.4 (1)
High responder (ADIVA Centaur > 10)	93.0 (66)	90.5 (38)	96.6 (28)
Beckman Coulter antibody level, mean (SD)	23.5 (15.4)	24.3 (15.9)	22.3 (14.8)
Beckman Coulter antibody level, %, (n)			
0 to < 5	11.3 (8)	7.1 (3)	17.2 (5)
5 to 10	11.3 (8)	14.3 (6)	6.9 (2)
More than 10	77.5 (55)	78.6 (33)	75.9 (22)

ADL, Activities of Daily Living.
*Katz Index Independence ADL scale: 1-6.
†Lawton Instrumental ADL scale: 1-6.

Discussion

The results indicate that older adult residents at assisted living, personal care, and independent living communities did mount detectable antibody responses—though antibody levels and neutralization titers varied widely among individuals. The Beckman Coulter SARS-CoV-2 antibody assays appear to be reliable due to very strong external validation (correlation) with established SARS-CoV-2 pseudovirus neutralization assays. Demonstration of vaccine response in this population, along with observational data demonstrating reductions of COVID-19 following implementation of vaccination,[2] supports the argument for reopening residential communities in the immediate period following vaccination.

This study has several limitations. Importantly, the presence of antibody levels and neutralization titers does not necessarily confirm immunity. As with other viral infections, immunity to SARS-CoV-2 infection is complex and is influenced by B and T cell responses and the innate immune system.[22] Levels of antibody, quality of antibodies produced, and duration of antibody presence are all important unknowns in this population.[23] Thus, the

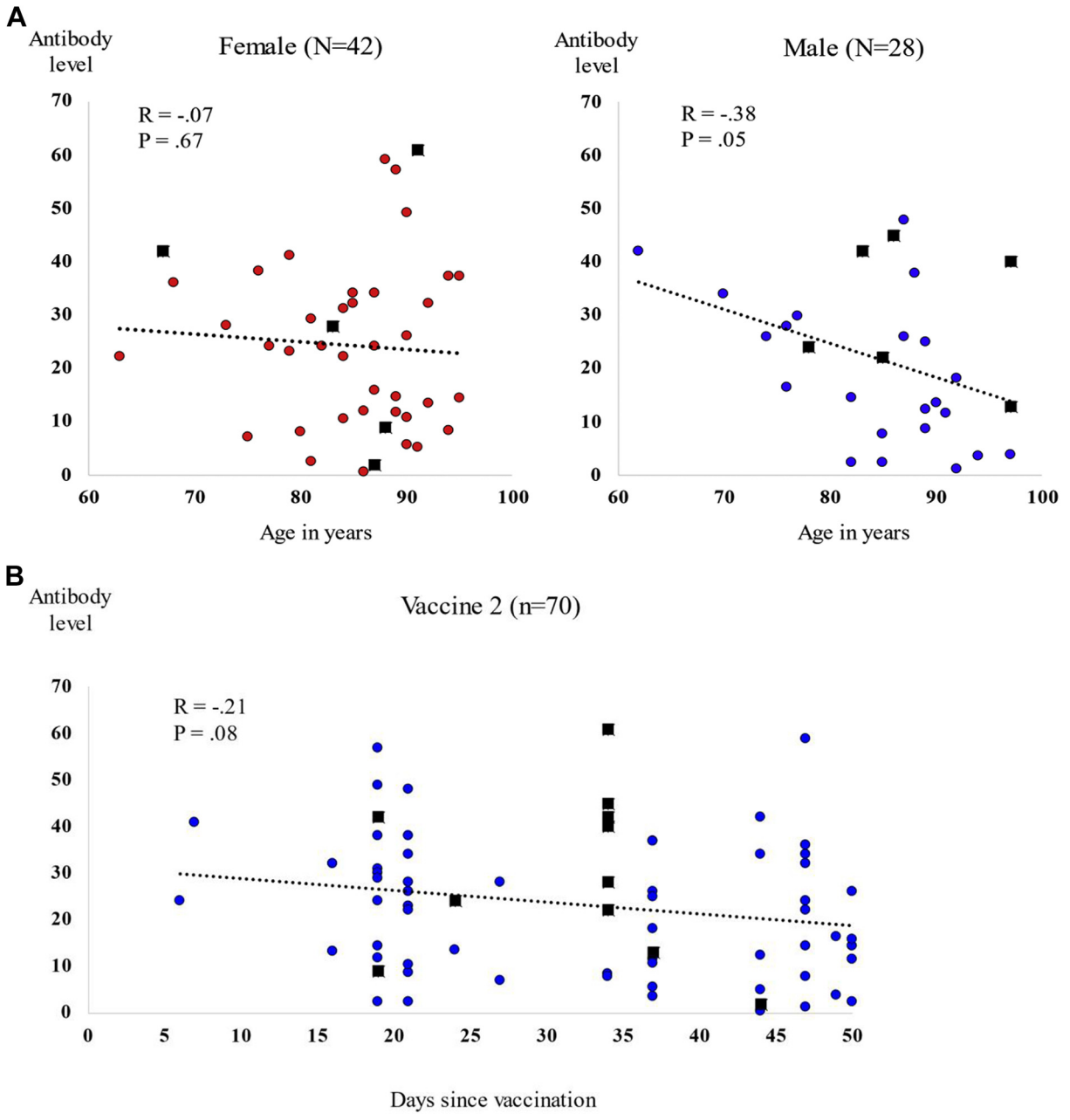

Fig. 1. (A). Scatter plot of participant age (x-axis) by Beckman Coulter antibody level (y-axis). Females (left plot) with red-filled round dots depicting participants without a prior history of COVID-19, and black-filled rectangles depicting participants with a prior history of COVID-19. Males (right plot) with blue-filled round dots depicting participants without a prior history of COVID-19, and black-filled rectangles depicting participants with a prior history of COVID-19. (B). Scatter plot of days since second vaccination (x-axis) by Beckman Coulter antibody level (y-axis). Blue-filled round dots depict participants without a prior history of COVID-19, and black-filled rectangles depict the participants with a prior history of COVID-19.

implications of these levels of antibodies and neutralization titers in preventing COVID-19 disease must be determined by clinical follow-up and incorporated into ongoing risk assessment as recommended.[5] The modest sample size limits the precision in estimates and conclusions that can be drawn, particularly in stratified analysis. The residential older adult participants were volunteers and likely to be healthier than residents who were unable to volunteer or were excluded due to known immunosuppressive conditions (eg, hematologic malignancies, solid organ transplants, active chemotherapy).

These considerations suggest that the relatively higher functioning residential older adults do respond to COVID-19 vaccines, but the strength and duration of response may be shortened by sex, age, and other well-documented comorbidities (eg, cardiovascular disease, renal disease, dementia, chronic inflammatory disease).[24,25] Thus, we expect that residents in this population are more vaccine responsive and protected than residents in nursing homes. This is supported by findings of Canaday and colleagues who found vaccine responses absent in a significant fraction of residents in nursing homes.[26]

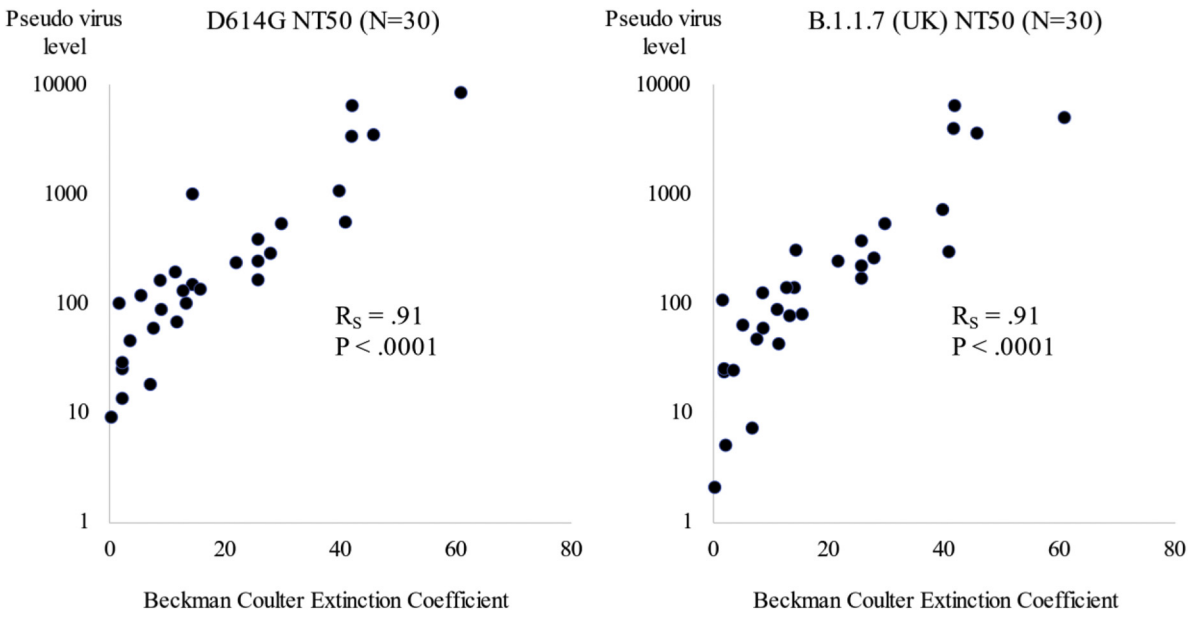

Fig. 2. Spearman correlation scatter plot of Beckman Coulter extinction coefficients (x-axis) by D614 G NT50 pseudovirus (left side, y-axis) and B.1.1.7 (UK) NT50 pseudovirus (right side, y-axis). Black filled round dots depict the first 30 consecutively enrolled participants.

Conclusions/Implications

The data reassures that moderate to higher functioning residential older adults do mount detectable and functionally neutralizing antibody responses when vaccinated with mRNA-based COVID-19 vaccines. These individuals demonstrate IgG within a range considered protective from other studies.[15] This suggests that vaccination is immunogenic and appropriate in this population. The actual protective effects of such vaccination programs in higher functioning, healthier, older adult residents at assisted living, personal care, and independent living communities remain to be determined in larger studies. Published recommendations regarding reopening of post-acute and long-term care facilities focus on the process for reopening.[5–8] Results from this study are part of an effort to assess level of population risk in reopening strategies for older adult residents at assisted living, personal care, and independent living communities, but are not likely to be translatable to residents in nursing homes. These data suggest that protective strategies among relatively healthy older adult residents at assisted living, personal care, and independent living communities can likely be revised to account for the ability to mount protective responses after vaccination, even if these diverge from the more stringent approaches needed for residents in nursing homes, whose comorbid conditions and frailty require skilled nursing level of care.

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