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Original Study

Adverse Events Following One Dose of mRNA COVID-19 Vaccination Among US Nursing Home Residents With and Without a Previous SARS-CoV-2 Infection

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A B S T R A C T

Objectives: To compare rates of adverse events following Coronavirus Disease 2019 (COVID-19) vaccination among nursing home residents with and without previous severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Design: Prospective cohort.

Setting and Participants: A total of 20,918 nursing home residents who received the first dose of messenger RNA COVID-19 vaccine from December 18, 2020, through February 14, 2021, in 284 facilities within Genesis Healthcare, a large nursing home provider spanning 24 US states.

Methods: We screened the electronic health record for adverse events, classified by the Brighton Collaboration, occurring within 15 days of a resident’s first COVID-19 vaccine dose. All events were confirmed by physician chart review. To obtain risk ratios, multilevel logistic regression model that accounted for clustering (variability) across nursing homes was implemented. To balance the probability of prior SARS-CoV-2 infection (previous positive test or diagnosis by the International Classification of Diseases, 10th Revision, Clinical Modification) more than 20 days before vaccination, we used inverse probability weighting. To adjust for multiplicity of adverse events tested, we used a false discovery rate procedure.

Results: Statistically significant differences existed between those without (n = 13,163) and with previous SARS-CoV-2 infection (symptomatic (n = 5617) and asymptomatic (n = 2138)) for all baseline characteristics assessed. Only 1 adverse event was reported among those with previous SARS-CoV-2 infection (asymptomatic), venous thromboembolism [46.8 per 100,000 residents 95% confidence interval (CI) 8.3 –264.5], which was not significantly different from the rate reported for those without previous infection (30.4 per 100,000 95% CI 11.8 –78.1). Several other adverse events were observed for those with no previous infection, but were not statistically significantly higher than those reported with previous infection after adjustments for multiple comparisons.

Conclusions and Implications: Although reactivity increases with preexisting immunity, we did not find that vaccination among those with previous SARS-CoV-2 infection resulted in higher rates of adverse
Little is known about vaccine-related adverse events following Coronavirus Disease 2019 (COVID-19) vaccination among adults with prior severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. One study found that adults with preexisting natural immunity at time of vaccination more frequently reported side effects such as injection site pain, swelling, and erythema as well as systemic symptoms such as fatigue and headaches, after the first dose of either of the messenger RNA (mRNA) vaccines, compared with those without a previous infection.\(^1\) Given that reactogenicity increases with pre-existing immunity, such side effects are biologically plausible. However, age-related declines in immune system function might suggest that we would not observe the same reactogenicity in the nursing home population. Regardless, no studies have assessed significant adverse events, such as acute myocardial infarction or stroke, following COVID-19 vaccination among older adults with previous SARS-CoV-2 infection.

We observed in a prior study that, compared with unvaccinated nursing home residents, vaccinated residents experienced similar adverse events rates following the first or second COVID-19 mRNA vaccine dose.\(^2\) In that study, residents were classified as vaccinated or unvaccinated, regardless of previous SARS-CoV-2 infection, except those who had tested positive for SARS-CoV-2 within 20 days before vaccination who were excluded to be consistent with Centers for Disease Control and Prevention (CDC) guidelines.\(^3\) Here we compare rates of adverse events following vaccination for nursing home residents with the following: (1) no prior infection; (2) symptomatic infection before vaccination, excluding within 20 days of vaccination; and (3) asymptomatic infection before vaccination, excluding within 20 days of vaccination.

**Methods**

Our study population included 20,918 nursing home residents of 284 facilities within Genesis Healthcare, a large nursing home provider spanning 24 US states. De-identified electronic health record (EHR) data from January 2020 to present were collected from the study population containing daily residents’ admissions, diagnoses, SARS-CoV-2 testing records, nursing documentation on symptoms, and other clinical data. Genesis coordinated with the CDC’s Pharmacy Partnership of Long-term Care Program to provide each of their nursing homes with 3 COVID-19 vaccine clinics carried out over a 3-month period to vaccinate residents and staff. The vaccine received (eg, Moderna or Pfizer-BioNTech) varied by state. The Brown University Institutional Review Board approved this study.

**Study Design**

The study residents received their first dose of mRNA vaccine between December 18, 2020, and February 14, 2021. Consistent with CDC guidelines,\(^3\) we excluded residents with a positive SARS-CoV-2 diagnostic test within 20 days before vaccination, as well as those treated with SARS-CoV-2 monoclonal antibodies for 90 days before vaccination.

**Exposure Groups**

The 3 groups compared included those who, at time of vaccination, had (1) no previous diagnosis of SARS-CoV-2, (2) previous infection with symptoms (more than 20 days before vaccination), and (3) previous infection without symptoms (more than 20 days before vaccination). For residents with prior SARS-CoV-2 infection, we obtained symptom data from change in condition notes that nurses complete when residents present with any new symptoms. We classified residents as having asymptomatic or symptomatic infection based on whether they had any SARS-CoV-2—related symptoms from 5 days before up to 14 days after a positive test or diagnosis.

**Outcomes**

Serious outcomes, such as mortality, were monitored for 7 days post-vaccination. If a resident died in the hospital shortly after transfer, or when they were expected to return to a Genesis facility, Genesis was notified of the death, and thus the death was captured in this analysis. Other adverse events that could manifest somewhat longer post-vaccination were monitored for 15 days using International Classification of Diseases, 10\(^{th}\) Revision, Clinical Modification (ICD-10-CM) codes included in residents’ EHR problem list. Those events, listed in Table 1, were classified by the Brighton Collaboration\(^4\) using ICD-10-CM codes for diagnoses and exclusions available from the CDC’s Vaccine Safety Datalink.\(^5\) For most events, prevalent cases were excluded to ensure capturing only incident cases.

**Physician Chart Reviews**

Physician chart review was conducted on all flagged cases of adverse events to confirm the diagnoses. To do this, the de-identified EHR record was shared back with Genesis for secure linkage to the original medical record number, so that the physician could review the resident’s chart directly in the nursing home’s EHR. The purposes of the chart reviews were to identify whether events were incident (new onset), recent prevalent conditions (within the past 30 days), or incorrectly coded diagnoses.

**Statistical Analysis**

We used SAS version 9.4 software (SAS Institute, Inc., Cary, NC) for data management and to compute frequencies and \(\chi^2\) tests to assess statistical differences in baseline characteristics of residents. Adverse events identified, and their rates and 95% Wilson’s confidence intervals (CIs) were calculated per 100,000 residents.\(^6\) We used STATA version 16 software (StataCorp, College Station, TX) for the adjusted analysis, using multilevel logistic regression that adjusted for clustering (variability) across nursing homes. To balance the probability of prior SARS-CoV-2 infection more than 20 days before vaccination, we used inverse probability weighting. This was incorporated into the logistic regression model to adjust for the baseline probability of prior SARS-CoV-2 infection. A sandwich estimator was used to account for correlation within facilities.\(^7,8\) Variables in the propensity score model included age, sex, race/ethnicity, diabetes, chronic obstructive pulmonary disease, chronic kidney disease, congestive heart failure,
December 18, 2020, through February 14, 2021. 

Symptoms, we included all residents who received the

enough sample of residents with previous infection, with and without 

100,000; 95% CI: 1.3

ICD-10-CM codes. One case occurred within 15 days after vaccination 

infection [symptomatic (n 

¼

5617) and asymptomatic (n 

2138)]

and mortality remained statistically significantly lower among those 

with previous SARS-CoV-2 infection, symptomatic or asymptomatic, 

than those with no previous infection (results not presented). More-

had no previous SARS-CoV-2 infection than female residents. Similarly, residents younger than 65 years were more likely 

to have had no previous SARS-CoV-2 infection than were older resi-

and cognitively intact residents were also more likely to have 

had no previous infection compared with cognitively impaired resi-

those with previous symptomatic infection were more likely to 

have comorbidities than the other 2 groups.

Adverse Events

Chart reviews were conducted to verify events identified using 

ICD-10-CM codes. One case occurred within 15 days after vaccination 

among those who had no previous SARS-CoV-2 infection (7.6 per

Table 1

Adverse Events Monitored

| Acute disseminated encephalomyelitis |
| Acute myocardial infarction |
| Acute respiratory distress syndrome |
| Anaphylaxis |
| Appendicitis |
| Bell's palsy |
| Convulsions/Seizures |
| Disseminated intravascular coagulation |
| Encephalitis/Myelitis/Encephalomyelitis/Encephalopathy |
| Guillain-Barré syndrome |
| Thrombotic thrombocytopenic purpura |
| Immune thrombocytopenia |
| Multisystem inflammatory syndrome in adults |
| Myocarditis/Pericarditis |
| Narcolepsy and cataplexy |
| Stroke, hemorrhagic |
| Stroke, ischemic |
| Transverse myelitis |
| Venous thromboembolism |
| Pulmonary embolism |
| Death |

Sensitivity Analysis

Although the focus of this study was to determine whether adverse event rates after vaccination differed between those with and without previous SARS-CoV-2 infection, we also compared the incidence of adverse events among the vaccinated and unvaccinated groups. Because our population was mostly vaccinated by mid-February 2021, the best unvaccinated comparator group was the “yet-to-be vaccinated,” unvaccinated population from our previous study.2 Details on the unvaccinated group are published elsewhere.2 To obtain a large enough sample of residents with previous infection, with and without symptoms, we included all residents who received the first dose from December 18, 2020, through February 14, 2021.

Results

We included 20,918 residents across 284 nursing homes who received their first mRNA vaccine dose between December 18, 2020, and February 14, 2021. Statistically significant differences existed between those without (n = 13,163) and with previous SARS-CoV-2 infection [symptomatic (n = 5617) and asymptomatic (n = 2138)] for all baseline characteristics assessed (Table 2). For example, higher proportions of residents with prior infection, symptomatic or asymptomatic, were long-stay (lived in the nursing home 100 or more days) than those with no prior infection. Male residents were more likely to have had no previous SARS-CoV-2 infection than female residents. Similarly, residents younger than 65 years were more likely to have had no previous SARS-CoV-2 infection than were older residents; and cognitively intact residents were also more likely to have had no previous infection compared with cognitively impaired residents.

Those with previous symptomatic infection were more likely to have comorbidities than the other 2 groups.

Discussion

Although reactogenicity increases with preexisting immunity,10 we did not observe higher rates of adverse events among nursing home residents with versus without prior natural infection. In fact, our study suggests that SARS-CoV-2 infection, regardless of whether it was symptomatic or asymptomatic, did not increase the risk of adverse events following COVID-19 vaccination. Although we identified some adverse events following vaccination among those with no previous SARS-CoV-2 infection that did not occur among the unvaccinated, no differences in rates were statistically significant after adjustment for multiplicity using a false discovery rate procedure.9

One reason for the lower mortality among those with previous SARS-CoV-2 infection, symptomatic or asymptomatic, compared with those with no previous infection could be selective survival, or immortal time bias.11 In other words, those who survived SARS-CoV-2 infection and were healthy enough to get vaccinated months later may have been less likely to die than those coming into the nursing home with no previous infection, even after adjustments for comorbidities. Because of the disparity in long-stay (ie, those with previous infection were more likely to be long-stay than those with no previous infection), we ran the mortality analyses excluding short-stay residents, and mortality remained statistically significantly lower among those with previous SARS-CoV-2 infection, symptomatic or asymptomatic, than those with no previous infection (results not presented). Moreover, younger (<65 years) residents were more likely to have had no previous infection, whereas older (aged 85 years and older) residents were more likely to have had a previous asymptomatic infection. Thus, those older adults with previous asymptomatic infection may have been “healthier” than the younger adults who entered the nursing home without a previous infection.

Our study had a few key limitations. First, there were significant differences in baseline characteristics between those with no previous SARS-CoV-2 infection and those with previous symptomatic or asymptomatic infection. We used inverse probability weighting to adjust for the baseline probability of previous SARS-CoV-2 infection based on observed values. However, there are still indications that there may be other unobserved factors that may influence the lack of significant evidence for differences in adverse events rates among 

Table 2

Baseline Characteristics of Nursing Home Residents With and Without Previous SARS-CoV-2 Infection

| Characteristic | Without Previous SARS-CoV-2 Infection | With Previous SARS-CoV-2 Infection |
|---------------|---------------------------------------|-----------------------------------|
| Median Age    | 81 years                               | 84 years                           |
| Median Length of Stay | 2 years                               | 5 years                            |
| Previous SARS-CoV-2 Infection | 46.8 per 100,000 (95% CI: 11.8–78.1) | 0.61 per 100,000 (95% CI: 0.49–0.76) |

Table 3

Adverse Events Occurring Among Nursing Home Residents With and Without Previous SARS-CoV-2 Infection

| Event Category | Without Previous SARS-CoV-2 Infection | With Previous SARS-CoV-2 Infection |
|---------------|---------------------------------------|-----------------------------------|
| Acute Myocardial Infarction | 0.46 (95% CI: 0.35–0.61) | 0.51 (95% CI: 0.35–0.73) |
| Bell's Palsy | 0.51 (95% CI: 0.49–0.51) | |
these populations. Second, to conduct timely analyses, adverse events were included only if they were diagnosed by the medical provider with a supporting ICD-10-CM code. Third, the relatively small sample size to assess rare adverse events resulted in an inability to generate precise estimates. However, the extremely low number of suspected adverse events was reassuring and an important finding of the study.

This study contributes new evidence that older, frail nursing home residents with previous SARS-CoV-2 infection do not seem to be at risk of exhibiting these findings of the study.

Table 2
Demographic and Clinical Characteristics of Vaccinated Nursing Home Residents by Previous SARS-CoV-2 Status

| Age group, y | Race/Ethnicity | Comorbidities | ADL score, mean (SD) | Cognitive function scale | Sex | n Unadjusted Rate Per 100,000* | n Unadjusted Rate Per 100,000* | P-value* |
|--------------|----------------|---------------|----------------------|-------------------------|-----|-----------------------------|-----------------------------|----------|
| <65          | Hispanic       | COPD           | 19.2 (5.5)           | Cognitive intact        | Male| 14681 (73.2)               | 3874 (18.5)                | <.01     |
| 65–74        | Hispanic       | Dementia       | 5614 (27.1)          | Mildly impaired         | Female| 5380 (26.8)               | 4891 (23.4)                | .01      |
| 75–84        | Hispanic       | Coronary artery disease | 9232 (44.6)         | Moderately impaired     | 990 (4.7)  | 3385 (26.0)               | 5918 (28.3)                | .01      |
| ≥85          | Hispanic       | Diabetes       | 6009 (29.0)          | Severely impaired       | 2551 (12.2) | 8124 (38.9)               | 6235 (29.8)                | .01      |
|              | Comorbidities  | ADL dependency quartile | 0.73 (5.5)         | ADL score, mean (SD)    | 980 (4.7)  | 5614 (27.1)               | 5614 (27.1)                | .01      |
|              |                | ADL dependency quartile | 0.56 (5.3)         | ADL score, mean (SD)    | 980 (4.7)  | 5614 (27.1)               | 5614 (27.1)                | .01      |

Table 3
Adverse Events Diagnosed Among Vaccinated Residents by Previous SARS-CoV-2 Status

| 15-day event rates | 7-day event rates | n Unadjusted Rate Per 100,000* | n Unadjusted Rate Per 100,000* |
|--------------------|------------------|-----------------------------|-----------------------------|
| Acute myocardial infarction | 76.4 (1.3–43.0) | 0 — — | — |
| Bell’s palsy | 76.4 (1.3–43.0) | 0 — — | — |
| Convulsions/Seizures | 3.3 (7.6–67.0) | 0 — — | — |
| Stroke, hemorrhagic | 76.4 (1.3–43.0) | 0 — — | — |
| Stroke, ischemic | 76.4 (1.3–43.0) | 0 — — | — |
| Venous thromboembolism | 30.4 (11.8–78.1) | 0 — — | — |
| Pulmonary embolism | 76.4 (1.3–43.0) | 0 — — | — |

15-day event rates

| 7-day event rates | n Unadjusted Rate Per 100,000* | n Unadjusted Rate Per 100,000* |
| Death | 76.4 (1.3–43.0) | 0 — — | — |

Adjusted risk ratios: Inverse probability weighting was used to adjust the probability of previous SARS-CoV-2 diagnosis by age, gender, race/ethnicity, diabetes, chronic obstructive pulmonary disease, renal disease, hypertension, congestive heart failure, coronary heart disease, dementia, cognitive function, mortality risk and physical function.

Note: Residents with a positive SARS-CoV-2 test within 20 days of vaccination (because they should not have been vaccinated), or who were on monoclonal antibodies within 90 days of vaccination were excluded. Previous SARS-CoV-2 diagnosis or positive test were 21 or more days before vaccination. Symptoms presented within the 5 days before or up to 14 days after the previous SARS-CoV-2 diagnosis or positive test.

*Wilson’s 95% CIs.
higher risk of adverse events following the first dose of mRNA vaccine than their vaccinated counterparts with no previous infection, nor do they seem to be at a higher risk of adverse events compared with their unvaccinated counterparts. In addition, it is important to stress the finding in our previous study that mortality rates after vaccination were not higher than mortality rates among the unvaccinated. This research supports previous reports from the original randomized trials of these vaccines, although nursing home residents were not included in those trials. Moreover, the mRNA-based vaccines have demonstrated safety, and offer the prospect of being life-saving for nursing home residents who have borne a disproportionate share of morbidity and mortality from COVID-19.

Conclusions and Implications

Our study suggests that frail, nursing home residents with a previous SARS-CoV-2 infection, whether symptomatic or not, were not at higher risk of adverse events following vaccination, compared with those who had no previous infection. This study further stresses the importance of having the infrastructure to support near real-time monitoring of adverse events, safety, and efficacy of novel vaccines in this vulnerable population.

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