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Adverse events following mRNA SARS-CoV-2 vaccination among U.S. nursing home residents

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Abstract

Background: The devastating impact of the SARS-CoV-2 pandemic prompted the development and emergency use authorization of two mRNA vaccines in early 2020. Vaccine trials excluded nursing home (NH) residents, limiting adverse event data that directly apply to this population.

Methods: To prospectively monitor for potential adverse events associated with vaccination, we used Electronic Health Record (EHR) data from Genesis HealthCare, the largest NH provider in the United States. EHR data on vaccinations and pre-specified adverse events were updated daily and monitored for signal detection among residents of 147 facilities who received the first dose of vaccine between December 18, 2020 and January 3, 2021. For comparison, unvaccinated residents during the same time period were included from 137 facilities that started vaccinating at least 15 days after the vaccinating-facilities.

Results: As of January 3, 2021, 8553 NH residents had received one dose of SARS-CoV-2 vaccine and by February 20, 2021, 8371 residents had received their second dose of vaccine; 11,072 were included in the unvaccinated comparator group. No significant associations were noted for neurologic outcomes, anaphylaxis, or cardiac events.

Conclusions: No major safety problems were detected following the first or second dose of the vaccine to prevent COVID-19 in the study cohort from December 18, 2020 through March 7, 2021.

1. Introduction

The SARS-CoV-2 pandemic has had a devastating impact on the nursing home (NH) and residential care population in the United States and globally. Less than 1% of the U.S. population lives in long-term care facilities, but by March 2021, 34% of US SARS-CoV-2 deaths occurred in the long-term care population [1]. Accordingly, frail older adults living in congregate settings ranked in the top priority group for distribution of the vaccine [2]. However, both the Pfizer-BioNTech and Moderna vaccine trials excluded NH residents [3,4]. Because considerable evidence indicates immune system responsiveness declines with age and frailty, and such individuals were excluded from vaccine trials on which these vaccines were tested [5], we especially need safety monitoring after vaccination for this population.

By March 10, 2021, over 2.7 million long-term care facility residents and staff were fully vaccinated against SARS-CoV-2 [6]. Reports of fatal adverse events following mRNA-based vaccination (Pfizer-BioNTech) for SARS-CoV-2 in Norwegian NH residents raised concern regarding vaccine safety in very old and frail persons [7]. Those reports lacked contemporaneous control groups, a significant limitation given the high baseline mortality in this population. Moreover, no studies assessed adverse events of special interest following immunization in the NH population such as Guillain-Barre syndrome or Bell’s Palsy, as distinguished by the Brighton Collaboration [8]. Prior to the SARS-CoV-2 pandemic, only passive surveillance captured suspected adverse events after vaccination among the NH population [9]. To address this gap, Brown
University partnered with Genesis HealthCare, a large NH provider spanning 24 U.S. states, to conduct active, prospective surveillance of adverse events after vaccination of NH residents. Herein, we report results of active surveillance for signal detection after vaccination of NH residents from December 18, 2020 through March 7, 2021.

2. Methods

Our study population included 21,222 NH residents of 284 facilities within Genesis Healthcare, a large NH provider spanning 24 U.S. states. One of two long-term care pharmacy chains administered SARS-CoV-2 vaccine at these NHs on specific days or “clinics” temporally spaced according to the recommended vaccination schedule. Genesis coordinated with pharmacy chains to offer vaccine to residents and staff during three vaccine clinics over a three-month period.

2.1. Study design

Genesis HealthCare transferred daily electronic health record (EHR) data to Brown for analysis. These data included the Minimum Data Set (MDS), daily resident census, vital signs, diagnoses, immunizations, SARS-CoV-2 testing records, nursing documentation, medication records and other core EHR elements. To ensure comparison in rates of adverse events during the same time period and with the same duration of follow-up, we identified late-vaccinating facilities based on the date of their first vaccination clinic (e.g., at least 15 days after early-vaccinating facilities). Between December 18, 2020 and January 3, 2021 147 NHs (‘early-vaccinating facilities’) administered the first dose of vaccine and between January 8 through February 20, 2021 those facilities held 2nd clinics, administering the 2nd dose of vaccine. The vaccine received (e.g., Moderna or Pfizer-BioNTech) varied by state. The comparison group included residents from the 137 Genesis facilities that did not start vaccinating until January 4, 2021 (‘late-vaccinating facilities’). Early- and late-vaccinating facilities were partitioned into 12 strata by the date of their first vaccination clinic. This ensured that residents in the late-vaccinating facilities were vaccinated at least 15 days after the early vaccinating facilities. Residents included in the analysis were present in the facility on the day the vaccinating facility had its first vaccination clinic. Follow-up for the first dose and the unvaccinated groups was between December 18, 2020 and January 18, 2021, and follow-up for the second dose was between January 8 and March 7, 2021. For example, in the first stratum, residents of facilities that vaccinated on December 18, 2020 were included and unvaccinated residents of NHs that held their first vaccination clinic on January 4, 2021 who were present in those NHs on December 18, 2020 were included as the comparator group. All in stratum 1 were followed from December 18, 2020 through January 2, 2021.

Consistent with CDC guidelines, we excluded residents with a laboratory confirmed SARS-CoV-2 infection in the 20 days prior to the vaccine clinic, as well as those who had received monoclonal antibody treatment for their SARS-CoV-2 infection during the 90 days prior to the vaccine clinic.

2.2. Outcomes

Serious outcomes such as mortality and hospital transfers post-vaccination were monitored for 7 days. If a resident died in the
hospital shortly after transfer or they were expected to return to the Genesys facility. Genesis was notified of the death, and the outcome was therefore captured in this analysis. Other serious outcomes that could manifest somewhat longer post-vaccination were monitored for 15 days. We monitored for events identified by the Brighton Collaboration [8] using ICD-10-CM codes for diagnoses and exclusions from the Center for Disease Control and Prevention’s Vaccine Safety Datalink [10]. For most events, we excluded prevalent cases to ensure capturing only incident cases.

2.3. Medical record reviews

We prospectively conducted an EHR record review on each case with a potential adverse event identified in the 15-day risk interval after SARS-CoV-2 vaccination. These reviews parsed potential adverse events between an incident (new onset) condition, a recent prevalent condition (duration varied by event) or incorrectly coded diagnosis within a 2-week period after identification. In order to estimate comparable unvaccinated rates, we also conducted record reviews on cases among the unvaccinated for the risk interval period identified by the vaccination date of their respective stratum.

2.4. Statistical analysis

We used SAS version 9.4 software for data management and to compute frequencies, and used chi-squared tests to assess statistical differences in baseline characteristics of residents. Adverse event rates and 95% Wilson’s confidence intervals (CI) were calculated per 100,000 residents [11]. To identify the risk ratios of adverse events between vaccinated and unvaccinated residents, we estimated average treatment effects (presented as risk ratios) weighted by the conditional inverse probability of vaccination (or not if not given) (IPW). The weights were estimated with logistic regression and included the following variables: age, sex, race/ethnicity, diabetes, chronic obstructive pulmonary disease (COPD), chronic kidney disease, congestive heart failure, coronary artery disease, dementia, hypertension, and MDS measures of physical and cognitive function. Physical function was measured using the Morris Activities of Daily Living (ADL) scale, which ranges from 0 to 28, with higher scores indicating more impairment [12]. Cognitive function was measured using the Cognitive Function Scale which classifies residents as cognitively intact; or has having mild, moderate, or severe cognitive impairment [13]. Standard errors were estimated using a Huber-White covariance (“sandwich”) estimator clustered by strata. STATA version 16 (StataCorp, College Station, TX) software was used for the IPW-adjusted analysis [14,15].

The Brown University Institutional Review Board approved this study.

3. Results

In the 147 early-vaccinating facilities, 8553 residents received the first dose of vaccine and 8371 residents received the second dose of vaccine. Of the 8275 vaccinated for whom the vaccine manufacturer was known, 70.6% received Pfizer vaccine. Among the 137 late-vaccinating facilities, 11,072 residents were followed to assess for background event rates among the unvaccinated. There were no baseline significant differences among the vaccinated

| Table 1 | Demographic and clinical characteristics of nursing home residents by vaccination status. |
|---------|------------------------------------------------------------------------------------------|
| 284 Facilities | 147 Facilities | 2 doses | 137 Facilities | \( p \) |
| Gender | | | | |
| Male | 8092 (38.1) | 3191 (37.6) | 3072 (37.3) | 4128 (38.0) | 0.41 |
| Female | 13,123 (61.9) | 5301 (62.4) | 5161 (62.7) | 6731 (62.0) | |
| Age Group (years) | | | | |
| <65 | 4001 (18.8) | 1611 (19.0) | 1593 (19.3) | 2041 (18.8) | 0.98 |
| 65–74 | 4981 (23.5) | 1988 (23.4) | 1916 (23.3) | 2571 (23.7) | |
| 75–84 | 5912 (27.9) | 2341 (27.6) | 2281 (27.7) | 3006 (27.7) | |
| ≥85 | 6328 (29.8) | 2552 (30.1) | 2443 (29.7) | 3241 (29.8) | |
| Race/Ethnicity | | | | |
| African-American | 2768 (13.1) | 952 (11.2) | 969 (11.8) | 1600 (14.7) | 0.01 |
| Latinx | 1027 (4.9) | 333 (3.9) | 311 (3.8) | 614 (5.7) | 0.01 |
| Comorbidities | | | | |
| COPD | 5503 (26.3) | 2309 (27.2) | 2251 (27.3) | 2742 (25.3) | 0.01 |
| Dementia | 9203 (43.9) | 3884 (45.7) | 3836 (46.6) | 4667 (43.0) | 0.01 |
| Coronary artery disease | 5315 (25.4) | 2247 (26.5) | 2171 (26.4) | 2850 (24.4) | 0.01 |
| Diabetes | 8056 (38.3) | 3222 (37.9) | 3096 (37.6) | 4173 (38.4) | 0.49 |
| Congestive heart failure | 4779 (22.8) | 1984 (23.4) | 1897 (23.0) | 2433 (22.4) | 0.20 |
| Chronic kidney disease | 5629 (26.9) | 2254 (26.5) | 2157 (26.2) | 2903 (26.7) | 0.72 |
| Hypertension | 16,529 (78.9) | 6755 (79.5) | 6519 (79.2) | 8521 (78.5) | 0.15 |
| Cognitive Function Scale | | | | 0.01 |
| Cognitively Intact | 6372 (29.6) | 2435 (28.7) | 2300 (27.9) | 3433 (31.6) | 0.01 |
| Mildly Impaired | 5003 (23.9) | 2058 (24.2) | 2017 (24.1) | 2563 (23.6) | 0.01 |
| Moderately Impaired | 6775 (33.3) | 2874 (33.8) | 2883 (35.0) | 3415 (31.4) | 0.01 |
| Severely Impaired | 2748 (13.2) | 1125 (13.2) | 1063 (12.9) | 1448 (13.3) | 0.01 |
| ADL score, mean (SD) | | | | 0.01 |
| ADL dependency quartile | | | | |
| 0–17 | 5917 (28.1) | 2334 (27.5) | 2215 (26.9) | 3153 (29.0) | 0.01 |
| 18–20 | 5798 (27.5) | 2225 (26.6) | 2211 (26.9) | 3016 (27.8) | 0.01 |
| 21–22 | 4219 (20.1) | 1702 (20.7) | 1709 (20.8) | 2124 (19.6) | 0.01 |
| 23–28 | 5106 (24.3) | 2141 (25.2) | 2098 (25.5) | 2566 (23.6) | 0.01 |

Note: Residents who received two doses vaccine are among those who received the first dose of vaccine in the same 147 facilities.

Indicates chi-squared test p-value.
Fig. 2. A, Proportion of study participants in the 147 early vaccinating facilities in the state who received one dose of COVID-19 vaccine from December 18, 2020 through January 3, 2021. B, Proportion of study participants in the 147 early vaccinating facilities in the state who received the second dose of COVID-19 vaccine from January 8-February 20, 2021. C, Proportion of study participants in the 137 late vaccinating facilities in the state who were not vaccinated from December 18, 2020 through January 3, 2021 by state.
and unvaccinated groups by age, sex, concurrent diabetes, history of congestive heart failure or chronic kidney disease [Table 1]. However, vaccinated residents were less likely than unvaccinated comparator group residents to identify as Black/African-American (one dose: 11.2%, two doses: 11.8%, unvaccinated 14.7%), or Hispanic/Latinx residents (one dose: 3.9%, two doses: 3.8%, unvaccinated 5.7%). Vaccinated residents were also more likely than unvaccinated residents to have COPD (one dose: 27.2%, two doses: 27.3%, unvaccinated 25.3%). Coronary artery disease, cognitive impairment and dementia were also more frequent among the vaccinated than among the unvaccinated (p < 0.01). In addition, the proportion vaccinated and unvaccinated residents varied by the state in which the facility was located. (p < 0.01) [Fig. 2a-c].

3.1. Adverse events

Chart reviews were conducted to verify events identified using ICD-10-CM codes. Among the vaccinated, five events were verified during the 15-day risk interval post-vaccination; and among the unvaccinated, two events were verified during the 15-day risk interval [Tables 2a and 2b].

Unadjusted 15-day rates of adverse events per 100,000 residents following the first dose of vaccine were the same for Bell’s Palsy, ischemic stroke, and pulmonary embolism (12 (95% CI: 2, 66)); the rate for venous thromboembolism was 23 (95% CI: 6, 85). The unadjusted 7-day rate of mortality per 100,000 residents following first dose of vaccine was 374 (95% CI: 265, 528) and of hospital transfer was 1,497 (95% CI: 1,260, 1,777). The unadjusted rate of mortality was similar following the second dose of vaccine, though the rate of hospital transfers per 100,000 residents was lower (1,003 95% CI: 811, 1,241) than after the first dose (see Table 3).

Among the unvaccinated, unadjusted event rates for venous thromboembolism and pulmonary embolism were similar to those observed in the vaccinated. Unlike the vaccinated, no occurrences of Bell’s Palsy, acute myocardial infarction, or ischemic stroke were observed among the unvaccinated during the 15-day period.

In the adjusted analyses, 7-day mortality rates post-vaccination were lower among those who were vaccinated than unvaccinated (one dose: risk ratio (RR) 0.34 (95%CI: 0.22, 0.54); second dose: RR 0.49 (95%CI: 0.34, 0.71)) [Table 2]. Hospital transfers within 7 days post-vaccination were less frequent among those after the second dose of vaccine when compared with residents after the first dose (RR 0.66 (95%CI: 0.51, 0.86) or when compared with the unvaccinated (RR 0.57 (95%CI: 0.43, 0.75).

4. Discussion

We conducted active, prospective surveillance for adverse events following SARS-CoV-2 mRNA vaccinations under Emergency Use Authorization in a large multi-state cohort of NH residents. Our analyses did not detect statistically significant safety signals for the pre-specified outcomes including demyelinating disease, Guillain-Barre Syndrome, peripheral nervous system disorders, seizures, encephalomyelitis, ataxia, anaphylaxis, allergic reactions, cranial nerve disorders, or myocarditis. Rates of thromboembolic events were also similar between vaccinated and unvaccinated NH residents. Although cases of anaphylaxis have been reported in adults after the first dose of mRNA SARS-CoV-2 vaccines [16], none were observed in this NH population. Unlike
| Adverse Event | Age (yr) | Sex | Vaccine | Onset after vaccination (days) | Clinical verification of event | PMI |
|---------------|---------|-----|---------|-------------------------------|-------------------------------|-----|
| Bell's Palsy  | 87      | F   | First dose, Pfizer 11 | Verified diagnosis with physician | Heart disease noted | CTA + CT | HypoT, FTT, Obesity |
| Acute MI      | 56      | M   | Second dose, Pfizer 2 | Verified diagnosis by in-hospital cardiac cath showing extensive disease | Heart disease noted | CTA + CT | HypoT, FTT, Obesity |
| Venous Thromboembolism | 78     | F   | First dose, Pfizer 12 | Verified diagnosis at hospital with MS, DM, HTN, HLD, PAF, IBS, Anx/Dep, Migraine | Heart disease noted | CTA + CT | HypoT, FTT, Obesity |

Vascular dementia; AF - Atrial fibrillation; COPD - Chronic obstructive pulmonary disease; ICH - intracranial hemorrhage; TIA - transient ischemic attack; CVA - cerebral vascular accident; SZ - seizure; MDD - major depressive disorder; HL - hyperlipidemia; HTN - Hypertension; PVD - Peripheral vascular disease; OP - Osteoporosis; GERD - Gastroesophageal reflux disease; HypoT - Hypothyroidism; CAD - Coronary artery disease; MI - Myocardial infarction; AKI - Acute kidney injury; CA - Cancer; ThAoAn - Thoracic aortic aneurysm; ITP - Idiopathic thrombocytopenia purpura; TEN - Toxic epidermal necrolysis; CHF - Congestive Heart Failure; PVD - Pulmonary vasculature disease; AD - Alzheimer's disease.

### Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: BHB reports conflicts with vaccine manufacturers Sanofi and GSK.
First dose of vaccine rates of adverse events were among those vaccinated between December 18, 2020 and January 3, 2021 followed 15 days through January 18, 2021 within 90 days of vaccination or start date were excluded.

Second dose of vaccine rates of adverse events are among those vaccinated January 8, 2021 through February 20, 2021.

Adjusted risk ratios: Inverse probability weighting was used to adjust the probability of vaccination by age, gender, race/ethnicity, diabetes, COPD, renal disease, hyper-tension, congestive heart failure, Chronic kidney disease; DVT - Deep venous thrombosis; PE - Pulmonary embolism; FTT - Failure to thrive; MS - Multiple Sclerosis; PAF, - Paroxysmal atrial fibrillation; IBS - Irritable bowel syndrome; Anx - Anxiety; PD - Parkinson’s disease; AD - Alzheimer’s disease.

Table 2b
Selected clinical findings of adverse events among unvaccinated nursing home residents.

| Event                  | Age(yr) | sex | Onset after start date (days) | Current event          | PMH                                                                 | Illness/other in 4 wks prior to onset |
|------------------------|---------|-----|-------------------------------|------------------------|----------------------------------------------------------------------|---------------------------------------|
| Venous thromboembolism | 69 F    | 12  | Verified                      | VascDem, DM, HTN, HL, anemia, sickle trait, DVT, COVID and pressure ulcers | Fall hip fracture, PE by CTA in hospital |
| Pulmonary Embolism     | 67 F    | 4   | Verified, clot likely due to fracture and repair |                                                                      |                                      |

VascDem - Vascular dementia; AF - Atrial fibrillation; COPD - Chronic obstructive pulmonary disease; ICH - intracranial hemorrhage; TIA - transient ischemic attack; CVA - cerebral vascular accident; SZ - seizure; MDD - major depressive disorder; HL - hyperlipidemia; HTN - Hypertension; PVD - Peripheral vascular disease; OP - Osteoporosis; GERD - Gastroesophageal reflux disease; HypoT - Hypothyroidism; CAD - Coronary artery disease; CABG - Coronary artery bypass graft; DM - Diabetes mellitus; AKI - Acute kidney injury; CA - Cancer; ThAoAn - Thoracic aortic aneurysm; ITP - Idiopathic thrombocytopenia purpura; TKR - Total knee replacement; CHF - Congestive heart failure; Chronic kidney disease; DVT - Deep venous thrombosis; PE - Pulmonary embolism; FTT - Failure to thrive; MS - Multiple Sclerosis; PAF, - Paroxysmal atrial fibrillation; IBS - Irritable bowel syndrome; Anx - Anxiety; PD - Parkinson’s disease; AD - Alzheimer’s disease.

Table 3
Adverse events diagnosed after vaccinated and unvaccinated nursing home residents.

| 147 Facilities | Unadjusted Per 100,000 | 15-day event rates | 7-day event rates | 137 Facilities |
|----------------|------------------------|---------------------|-------------------|----------------|
| n = 8553       |                        |                     |                   | n = 11,072     |
| n = 8571 Unvaccinated Residents | Adjusted Risk Ratio 95%CI | First dose vs unvaccinated | Second dose vs first dose | Second dose vs unvaccinated | Per 100,000 |
| 15-day event rates | 1 12 (2, 68) | 1 19 (2, 68) | 0 0 | 1 19 (2, 68) | 0 0 |
| Acute Myocardial Infarction (AMI) | 0 0 | 0 0 | 0 0 | 0 0 | 0 0 |
| Bell's Palsy | 1 12 (2, 66) | 0 0 | 0 0 | 1 9 (2,51) | 0 0 |
| Stroke, ischemic | 1 12 (2, 66) | 0 0 | 0 0 | 1 9 (2,51) | 0 0 |
| Venous thromboembolism (VTE) | 2 23 (6, 85) | 2.41 (0.22, 26.3) | 0 0 | 1 9 (2,51) | 0 0 |
| Pulmonary Embolism (PE) | 1 12 (2, 66) | 1.14 (0.07, 18.0) | 0 0 | 1 9 (2,51) | 0 0 |
| 7-day event rates | 0.34 (0.22, 0.54) | 0.49 (0.34, 0.71) | 0.57 (0.43, 0.75) | 0.71 |
| Death | 32 374 (265, 528) | 19.0 | 1241 | 126 1138 (957, 1353) | 179 1617 (1398, 1869) |
| Hospital Transfer | 128 1497 (1260, 1777) | 0.95 (0.72, 1.24) | 0.66 (0.51, 0.86) | 0.75 |

First dose of vaccine rates of adverse events were among those vaccinated between December 18, 2020 and January 3, 2021 followed 15 days through January 18, 2021 (except mortality and hospital transfers were within 7 days).

Second dose of vaccine rates of adverse events are among those vaccinated January 8, 2021 through February 20, 2021. Unvaccinated rates of adverse events are during the period before vaccination, including residents in the SNFs that began vaccinating after January 3, 2015, followed for 15 days through January 18, 2021 (except mortality and hospital transfers were followed for 7 days).

Adjusted risk ratios: Inverse probability weighting was used to adjust the probability of vaccination by age, gender, race/ethnicity, diabetes, COPD, renal disease, hypertension, congestive heart failure, coronary heart disease, dementia, cognitive function and physical function.

Note: Residents with a positive COVID-19 test within 20 days of vaccination (since they should not have been vaccinated) or start date, or who were on monoclonal antibodies within 90 days of vaccination or start date were excluded.

1 Wilson’s 95% Confidence Intervals.

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Disclaimer

The content and views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government.

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