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BRIEF REPORT

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Adverse events following third dose of mRNA COVID-19 vaccination among nursing home residents who received the primary series

Barbara H. Bardenheier PhD, MPH, MA[1] | Elizabeth M. White APRN, PhD[1] | Carolyn Blackman MD[2] | Stefan Gravenstein MD, MPH[1,3,4] | Roee Gutman PhD[1] | Indra Neil Sarkar PhD, MLIS[1,4,5] | Richard A. Feifer MD, MPH[2] | Kevin McConeghy PharmD[1,3] | Aman Nanda MD[4] | Matthew Duprey PharmD, PhD[1] | Vincent Mor PhD[1,3]

[1]Health Services, Policy, and Practice Department, Brown University School of Public Health, Providence, Rhode Island, USA

[2]Genesis Physicians Services, Kennett Square, Pennsylvania, USA

[3]Center on Innovation in Long-Term Services and Supports, Providence Veterans Administration Medical Center, Providence, Rhode Island, USA

[4]Warren Alpert Medical School Department of Medicine, Brown University, Providence, Rhode Island, USA

[5]Rhode Island Quality Institute, Providence, Rhode Island, USA

Correspondence
Barbara H. Bardenheier and Stefan Gravenstein, Brown University School of Public Health, 121 S. Main Street Box G-S121-6, Providence, RI 02912, USA.
Email: barbara_bardenheier@brown.edu and stefan_gravenstein@brown.edu

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Abstract

Background: We sought to compare rates of adverse events among nursing home residents who received an mRNA COVID-19 vaccine booster dose with those who had not yet received their booster.

Methods: We assessed a prospective cohort of 11,200 nursing home residents who received a primary COVID-19 mRNA vaccine series at least 6 months prior to September 22, 2021 and received a third "booster dose" between September 22, 2021 and February 2, 2022. Residents lived in 239 nursing homes operated by Genesis HealthCare, spanning 21 U.S. states. We screened electronic health records for 20 serious vaccine-related adverse events that are monitored following receipt of COVID-19 vaccination by the CDC's Vaccine Safety Datalink. We matched boosted and yet-to-be boosted residents during the same time period, comparing rates of events occurring 14 days after booster administration with those occurring 14 days prior to booster administration. To supplement previously reported background rates of adverse events, we report background rates of medical conditions among nursing home residents during 2020, before COVID-19 vaccines were administered in nursing homes. Events occurring in 2021–2022 were confirmed by physician chart review. We report unadjusted rates of adverse events and used a false discovery rate procedure to adjust for multiplicity of events tested.

Results: No adverse events were reported during the 14 days post-booster. A few adverse events occurred prior to booster (ischemic stroke: 49.4 per 100,000 residents, 95% CI: 21.2, 115.7; venous thromboembolism: 9.9 per 100,000 residents, 95% CI: 1.7, 56.0), though differences in event rates pre- versus post-booster were not statistically significant ($p < 0.05$) after adjusting for multiple comparisons. No significant differences were detected between post-booster vaccination rates and prior year 14-day background rates of medical conditions.

Conclusions: No safety signals were detected following a COVID-19 mRNA vaccine booster dose in this large multi-state sample of nursing home residents.

KEYWORDS
adverse events after vaccination, booster COVID-19 vaccination, nursing home

INTRODUCTION

Although studies have demonstrated the safety of the primary series of mRNA COVID-19 vaccines in the general population[1] and among nursing home residents,[2,3] none have monitored for vaccine-related adverse events following booster doses among nursing home residents. Depending on the vaccine and the outcome, some adverse effects might increase with repeated exposure (i.e., number of doses) whereas other effects might diminish. Thus, continual monitoring of response to additional vaccine doses is necessary to understand whether repeated exposure to more doses may increase or decrease the risk of particular adverse events, particularly in a vulnerable population of nursing home residents. This surveillance is critical to ensure safety, maintain trust, and inform policy.[1]

We observed in a prior study that, compared to yet-to-be vaccinated nursing home residents, vaccinated residents experienced similar adverse events rates following the first and second COVID-19 mRNA vaccine doses.[2] Here we use a similar matched strata approach to compare rates of adverse events 14 days pre-booster versus 14 days post-booster among nursing home residents who received a two dose mRNA primary vaccine series at least 6 months prior.

Key points

- Our study suggests that frail, nursing home residents are not at higher risk of adverse events following booster vaccination than those who had not yet received it.

Why does this paper matter?

Monitoring safety of novel vaccines, after each dose, is critical to ensure safety, maintain trust, and inform policy, all of which are imperative to keep vaccination coverage above threshold levels needed to sustain herd immunity.

METHODS

Our study population included 11,200 residents of 239 nursing homes operated by Genesis HealthCare across 21 U.S. states. All residents completed their primary two dose mRNA COVID-19 vaccine series (those receiving one dose of Johnson & Johnson's Janssen COVID-19 vaccine were excluded) at least 6 months prior to September 22, 2021 and received a third booster dose between September 22, 2021 and February 2, 2022. Using de-identified electronic health record (EHR) data, we identified residents' daily disposition, vaccination history, clinical diagnoses, SARS-CoV-2 testing history, and other clinical data. The Brown University Institutional Review Board approved this study.

Study design

This study had a matched prospective cohort design. To ensure comparison in adverse event rates pre- and post-booster during the same time period, we matched residents in strata by date of booster. For example, we matched residents who received their booster September 22–29, 2021 with residents boosted at least 14 days later, from October 6–13, 2021. Residents boosted during the September period were followed 14 days from the booster and served as the "post-booster" group. Residents boosted during the October dates were observed for the 14 days prior to booster and served as the "pre-booster" comparators. As such, the observation window for adverse events overlapped between groups. A total of 15 strata of residents, post-booster ($N = 10{,}862$) and pre-booster ($N = 10{,}115$) were included. We excluded residents who were not boosted as of February 3, 2022 since those who chose not to receive the booster dose may have systematically differed from those who did. For consistency, residents in both groups had to be in the facility at least 14 days prior to receiving the booster dose. We also excluded residents with a positive SARS-CoV-2 test within 20 days prior to booster, as well as those treated with SARS-CoV-2 monoclonal antibodies for 90 days prior to booster, to prevent detection of adverse events attributable to viral infection or treatment.

TABLE 1 Adverse events monitored

Acute Disseminated Encephalomyelitis (ADEM)
Acute Myocardial Infarction (AMI)
Acute Respiratory Distress Syndrome (ARDS)
Anaphylaxis
Appendicitis
Bell's Palsy
Convulsions/Seizures
Disseminated Intravascular Coagulation
Encephalitis/Myelitis/Encephalomyelitis/Encephalopathy
Guillain-Barré syndrome (GBS)
Thrombotic thrombocytopenic purpura (TTP)
Immune thrombocytopenia (ITP)
Multisystem Inflammatory Syndrome in Adults (MIS-A)
Myocarditis/pericarditis
Narcolepsy and cataplexy
Stroke, hemorrhagic
Stroke, ischemic
Transverse myelitis (TM)
Venous thromboembolism (VTE)
Pulmonary Embolism (PE)

Note: This list includes 20 serious vaccine-related adverse events that are monitored following receipt of COVID-19 vaccination by the CDC's Vaccine Safety Datalink.[4]

Outcomes

Serious adverse events were monitored for 14 days using ICD-10-CM codes included in residents' EHR problem or diagnosis lists. Those events, listed in Table 1, were classified using the Brighton Collaboration[5] which identifies diagnoses and exclusions by ICD-10-CM codes, and is available from the CDC's Vaccine Safety Datalink.[4]

Physician chart reviews

Physician chart reviews were conducted on all flagged cases of pre- or post-booster adverse events to confirm diagnoses and to ensure all adverse events were incident cases. To do this, the de-identified EHR record was shared back with Genesis for secure linkage to the original medical record number, so that a physician could review the resident's chart directly in the nursing home's EHR. The chart reviews were used to identify whether events were incident (new onset) conditions, prevalent conditions (documented within the prior year), or incorrectly coded diagnoses.

Background rates

We report background rates of medical conditions during 2020, before COVID-19 vaccines were available, in two metrics. First, we report 14-day rates per 100,000 residents, similar to our primary analyses, for comparison. We included residents who were in the facility the year before booster doses were authorized, September 22, 2020 and followed them for 14 days. The other requirements for eligibility included that they were in the facility at least 14 days and that they did not have a positive COVID-19 test within 20 days of September 22, 2020 and were not on monoclonal antibodies 90 days prior to September 22, 2020.

The second analysis of background rates included 21 medical events in the Brighton criteria (including death)[5] in this nursing home population. Although U.S. population-based background incidence rates of medical events used in safety assessment of COVID-19 vaccines have been published, they only included some information on Medicare beneficiaries but not the nursing home population specifically.[6] This sub-analysis was done to supplement previous publications and to understand annual incidence (rates per 100,000 person-years) of these conditions, regardless of vaccine exposure. We followed residents who lived in the nursing home at least 1 day during the same months of the prior year (September 22, 2020 – December 15, 2020), truncating the window mid-December following the initial administration of the Pfizer vaccine among nursing home residsents. Residents were followed from September 22, 2020 or nursing home admission date (after September 22), until December 15, contributing person-time for their days in the facility. Residents were censored at time of diagnosis with one of the adverse events, upon discharge from facility, or at death. To be consistent with COVID-19 vaccine safety studies, we excluded residents with a positive SARS-CoV-2 test in the 20 days prior to adverse event diagnosis, and residents who received monoclonal antibodies during the 90 days before September 22, 2020 or their nursing home admission date. We calculated overall, annual background rates per 100,000 person years to be comparable with previously published adverse event rates for use in safety assessment of COVID-19 vaccines.[6] By annualizing rates of events, we assumed that events would occur similarly as was observed from September 22 – December 15 throughout the year. We also report rates stratified by prior SARS-CoV-2 diagnosis (occurring more than 20 days prior to study start date), and by immunocompromised status. Diagnoses and medications that can cause immunosuppression were identified from ICD-10-CM codes on the EHR problem or diagnosis lists and medication orders

TABLE 2 Nursing home residents monitored for adverse events 14 days pre- and post- mRNA COVID-19 vaccine booster dose from September 22, 2021 through February 16, 2022.

	14-day Rates			
	Pre-Booster, $n = 10,116$		Post-Booster, $n = 10,863$	
	n	Per 100,000 residents	*n*	Per 100,000 residents
Total				
Acute Myocardial Infarction (AMI)	2	19.8 (5.4,72.1)	0	No cases
Stroke, ischemic	5	49.4 (21.2115.7)	0	No cases
Seizure	1	9.9 (1.7, 56.0)	0	No cases
Venous thromboembolism (VTE)	1	9.9 (1.7, 56.0)	0	No cases
Pulmonary Embolism (PE)	1	9.9 (1.7, 56.0)	0	No cases

Note: Residents with a positive COVID-19 test within 20 days of vaccination or on monoclonal antibodies within 90 days of booster to prevent detection of adverse events attributable to viral infection or treatment were excluded (to be comparable rates with boosted rates) and to prevent detection of adverse events attributable to viral infection or treatment.

(except steroids) that the CDC has recommended to get a third primary dose of the COVID-19 vaccine.[7]

Statistical analysis

We computed unadjusted frequencies of incident adverse events per 100,000 residents, along with 95% Wilson's confidence intervals.[8] Because of the large number ($n = 20$) events monitored and the fact that some events were identified in the pre-booster group that were not identified in the post-booster group, we used a false discovery rate procedure to adjust for multiplicity of tests to assess statistical significance of differences between the pre- and post- booster rates of events.[9] For background rates, we used Poisson regression to obtain incidence rates of adverse events and 95% confidence intervals. SAS version 9.4 software (SAS Institute, Cary, NC) was used for all data management and analyses.

RESULTS

Overall, among those with known vaccine manufacturer ($n = 631$ [2.9%] had unknown vaccine manufacturer), 36.6% of boosted residents received the Moderna vaccine and 63.4% received Pfizer.

Adverse events among boosted residents

No events were observed during the 14-day post-booster period, therefore unadjusted estimates are presented (Table 2). Five unique medical conditions or types of events among 10 residents were observed during the 14-day pre-booster period: one case each of (1) seizure, (2) venous thromboembolism, and (3) pulmonary embolism (9.9 events per 100,000 residents, 95% confidence interval [CI] 1.7, 56.0); two cases of (4) acute myocardial infarction (19.8 events per 100,000 residents, 95% CI: 5.4, 72.1); and five cases of (5) ischemic stroke (49.4 events per 100,000 residents, 95% CI: 21.2, 115.7). Differences in adverse event rates observed across strata for the pre- vs. post-booster periods were not statistically significant after adjustments for multiple comparisons at the 5% false discovery rate level.

Background rates during the previous year

The 14-day prior year background rates are presented in Table 3. The five unique medical conditions that occurred among residents during the pre-booster period also occurred during the previous year at similar rates, though three additional conditions occurred during the previous year that did not occur during the pre- or post-booster periods including Bell's Palsy (4.1 events per 100,000 residents, 95% CI: 0.7, 23.3); Disseminated Intravascular Coagulation (4.1 events per 100,000 residents, 95% CI: 0.7, 23.3); and hemorrhagic stroke (20.5 events per 100,000 residents, 95% CI: 8.8, 48.0). Differences in adverse event rates observed between the post-booster period and the previous year 14-day background rates were not statistically significant after adjustments for multiple comparisons at the 5% false discovery rate level.

The annual incidence rates of medical conditions that occurred among nursing home residents during 2020 are presented in the Table S1. Of the 43,371 residents in facilities at least 1 day from September 22 to December 15, 2020, 5963 (13.7%) had a previous SARS-CoV-2 infection and

TABLE 3 Background 14-day incidence rates of medical conditions among nursing home residents from September 22–October 6, 2020, prior to administration of the COVID-19 vaccine.

			Previous SARS-CoV-2 infection				Immunocompromise			
		Overall, $N = 24{,}406$	No, $N = 18{,}960$		Yes, $N = 5446$		No, $N = 21{,}658$		Yes, $N = 2748$	
	n	Per 100,000	*n*	Per 100,000	*n*	Per 100,000	*n*	Per 100,000	*n*	Per 100,000
Total										
Acute Myocardial Infarction (AMI)	10	41.0 (22.3, 75.4)	10	52.7 (28.7, 97.1)	0		10	46.2 (25.1, 85.0)	0	
Bell's Palsy	1	4.1 (0.7, 23.3)	1	5.3 (0.9, 29.9)	0		1	4.6 (0.8, 26.2)	0	
Convulsions/Seizures	5	20.5 (8.8, 48.0)	5	26.4 (11.3, 61.7)	0		3	13.9 (4.7, 40.7)	2	72.8 (0.2, 265.0)
Disseminated Intravascular Coagulation	1	4.1 (0.7, 23.3)	1	5.3 (0.9, 29.9)	0		1	4.6 (0.8, 26.2)	0	
Stroke, hemorrhagic	5	20.5 (8.8, 48.0)	5	26.4 (11.3, 61.7)	0		3	13.9 (4.7, 40.7)	2	72.8 (0.2, 265.0)
Stroke, ischemic	23	94.2 (62.8, 141.4)	21	110.8 (72.5, 169.3)	2	36.7 (10.1, 133.8)	21	97.0 (63.4, 148.2)	2	72.8 (0.2, 265.0)
Venous thromboembolism (VTE)	18	73.8 (46.7, 116.6)	15	79.1, (48.0, 130.5)	3	55.1 (18.7, 161.8)	12	55.4 (31.7, 96.8)	6	218.3 (100.1, 475.6)
Pulmonary Embolism (PE)	9	36.9 (19.4, 70.1)	9	47.5 (25.0, 90.2)	0		7	32.3 (15.7, 66.7)	2	72.8 (0.2, 265.0)

Note: Residents who were in a SNF for at least 14 days who were in the facility on September 22, 2020 were followed 14 days to observe incident medical conditions. Residents with a positive COVID-19 test within 20 days of study start date or on monoclonal antibodies within 90 days of study start date were excluded (to be comparable rates with boosted rates) and to prevent detection of adverse events attributable to viral infection or treatment.

3405 (7.9%) were immunocompromised. Among the examined adverse events, death was the most common (42,790 events per 100,000 person-years [PY], 95%CI: 41,192, 44,449). Other frequently reported adverse events included ischemic stroke (1068.4 events per 100,000PY 95%CI: 840.9, 1357.4), venous thromboembolism (765.3 events per 100,000PY 95%CI: 576.8, 1015.6), acute myocardial infarction (467.8 events per 100,000PY 95%CI: 325.1, 673.1), and pulmonary embolism (398.4 events per 100,000PY 95%CI: 269.2, 589.6). After stratifying by prior SARS-Cov-2 infection status, we found few adverse events among residents with previous SARS-Cov-2 infection. Because of the small number of events among immunocompromised residents, confidence intervals were wide and no statistically significant differences in rates of adverse events with non-immunocompromised were detected.

DISCUSSION

Similar to data presented to the Advisory Committee for Immunization Practices,[10] we found no safety signals following the booster dose of the mRNA vaccines among nursing home residents. Although we identified some adverse events in the pre-booster time period, differences in event rates compared to the post-booster period were not statistically significant after adjustment for multiplicity using a false discovery rate procedure.[9]

Because serious health outcomes linked to vaccination are rare, knowledge of background incidence rates of those medical conditions is critical to vaccine safety monitoring. For this reason, vaccine safety officials at the U.S. Food and Drug Administration and the U.S. Centers for Disease Control and Prevention have published a collection of incidence rates for the adverse events monitored for COVID-19 vaccines. However, the rates published in that paper were not specific to the nursing home population.[6] Therefore we included those background rates which though uncommon, were higher than the rates occurring in the general population, or even among Medicare beneficiaries in general.[11]

Our study had a few key limitations. First, to conduct timely analyses, adverse events were only included if they were diagnosed by the medical provider with a supporting ICD-10-CM code. This may result in underreporting if such events were not detected by staff or if they were delayed in documentation. Second, 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 encouraging and an important result of the study. Finally, a limitation of the annualized 2020 background rates of medical conditions was that we could not perform chart reviews for the number of cases observed resulting in possible inflation of those rates.

CONCLUSIONS AND IMPLICATIONS

This study contributes new evidence on the safety of booster doses of vaccination in the high-risk nursing home resident population. This research supports previous reports from the original randomized trials of these vaccines that did not include nursing home residents.[12,13] Furthermore, the mRNA-based booster dose offers the potential of being life-saving for nursing home residents who have borne a disproportionate share of morbidity and mortality from COVID-19.[14,15] This study further points to the importance of having an organization that can support near real-time monitoring of adverse events, safety and efficacy of novel vaccines in this vulnerable population.

CONFLICT OF INTEREST

BHB currently received investigator-initiated support from Sanofi Pasteur. KWM currently receives investigator-initiated support from Sanofi-Pasteur, Seqirus pharmaceuticals. SG reports conflicts with vaccine manufacturers related to grants, consulting, and speaking engagements: Sanofi, Seqirus, Pfizer. SG also consults with other pharmaceutical companies such as Longevoron, Janssen, and Merck. SG has grants with Sunovion and Essity.

AUTHOR CONTRIBUTIONS

Barbara H. Bardenheier participated in the study concept and design, data management and analysis, interpretation of data, and preparation of manuscript. All authors participated in the interpretation of data, and editing of manuscript.

SPONSOR'S ROLE

None.

ORCID

Elizabeth M. White https://orcid.org/0000-0003-4175-8662

Kevin McConeghy https://orcid.org/0000-0002-5056-0431

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

Table S1 Background Annual Incidence Rates of Events Among Nursing Home Residents during 2020, Prior to Administration of the COVID-19 Vaccine.

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