Clinical Infectious Diseases

BRIEF REPORT

Coronavirus Disease 2019 Vaccine-Breakthrough Infections Requiring Hospitalization in Mayo Clinic Florida Through August 2021

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We characterized coronavirus disease 2019 (COVID-19) breakthrough cases admitted to a single center in Florida. With the emergence of delta variant, an increased number of hospitalizations was seen due to breakthrough infections. These patients were older and more likely to have comorbidities. Preventive measures should be maintained even after vaccination.

Keywords. COVID-19; breakthrough infection; vaccine-breakthrough; vaccine; hospitalizations.

The messenger RNA (mRNA) vaccines available in the United States, BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna), have both shown ≥94% efficacy in preventing hospitalization in observational data [1, 2]. Previous studies in high-risk groups (eg, transplant recipients) have shown lower seroconversion rates after vaccination compared to immunocompetent patients [3, 4]. Data from Israel on 152 hospitalized breakthrough cases found that a minority of fully mRNA-vaccinated patients may still develop severe disease, especially in those with higher rate of comorbidity and immunosuppression [5]. In the United States, a total of 10 262 US vaccine breakthrough infections were reported to the Centers for Disease Control and Prevention (CDC) as of 30 April 2021: 27% were asymptomatic, while 10% required hospitalization [6]. By 23 August 2021, 171 million people had been fully vaccinated against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-)2, and breakthrough cases resulting in hospitalization or death in the United States increased by 11-fold [7]. In this brief report, we aim to describe the trend and the clinical characteristics of hospitalized patients with coronavirus disease 2019 (COVID-19) breakthrough infections.

METHODS

Data were extracted from the Mayo Clinic electronic health records on 1 September 2021 and included cases through 28 August 2021. Institutional Review Board approval was obtained. Patient-level vaccination status data were queried from the Florida state COVID-19 registry database. In this retrospective study, patients with the following characteristics were identified and included: (a) at least 18 years of age, (b) positive polymerase chain reaction for SARS-CoV-2 requiring hospitalization, and (c) available vaccination status data on admission. The eligible patients were classified in 2 groups: vaccine breakthrough infections and unvaccinated infections, which required hospital admission. By the CDC definition, a vaccine breakthrough infection is the detection of SARS-CoV-2 RNA or antigen in a respiratory specimen collected from a person ≥14 days after they have completed all recommended doses of a US Food and Drug Administration (FDA)-authorized COVID-19 vaccination. Patients that did not meet the definition were classified as unvaccinated.

Descriptive statistics were used to summarize the clinical data. Tests for differences between breakthrough and non-breakthrough admissions were 2-sample *t* tests for continuous variables and Pearson χ^2 tests for categorical variables. For the analysis of a monotonic increase in the percentage of cases classified as breakthrough admission over months, multiple statistical approaches were used. For a simple tabulated summary, the Cochran-Armitage trend test was used to test for a change in the percentage of breakthroughs by month. Next, to support analyses that examined temporal changes in the breakthrough admissions, time was divided into 2 epochs on the date of the presumed appearance of the delta variant in Northeast Florida: 2 May 2021. To test for differences in the percentage of breakthrough admissions before and after the presumed emergence of the variant, a Pearson χ^2 test was used. Finally, a graphical trend in breakthrough admissions and vaccination by week was also constructed. For this analysis, data were aggregated into weeks beginning on the first Sunday of 2021 (1 March 2021). The percentage of the COVID-19 cases that met the definition of breakthrough were plotted and a LOESS smoothed curve was fit to the data to provide a graphical visual of the trend over time. No statistical testing was performed for the LOESS curve, but the fit was estimated using the total number of COVID-19

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admissions in the week as a weight in the regression model. All data analysis was conducted using R version 4.0.3.

RESULTS

We analyzed 6161 patients with a positive nasopharyngeal SARS-CoV-2 PCR, 965 of which were hospitalized with COVID-19 infection, from 3 January 2021 through 28 August 2021 at Mayo Clinic in Florida. Data were split into 2-time epochs on 2 May 2021, approximately 1 month prior to known circulation of delta variant in Northeast Florida [7]. There were 1120 (18%) total vaccine breakthrough infections: 97% (n = 1089) of which occurred after 2 May 2021 of these 12% (n = 126) required hospitalization. Mean (standard deviation [SD]; range) duration from vaccination immunity to infection was 121.3 (48.5; 15–210) days. Results available on 23 cases show most infections (91%, n = 21) were identified as the delta variant.

In the 126 vaccine breakthrough admissions, the manufacturer was known in 105 cases: Pfizer, Inc (n = 59), Moderna US, Inc (n = 36), and Janssen (n = 10). The percentage of hospitalized breakthrough infections was 2.1% before 2 May 2021 and later rose to 19.1%. During that period, CDC changed masking guidance for vaccinated individuals (Figure 1).

When compared to unvaccinated COVID-19 admissions, vaccine breakthrough admissions were older in age (mean [SD]) (69.1 [13.9] vs. 59.6 [16.0] years, $P < .001$), more likely to be immunocompromised (42/126 [33.3%] vs. 124/839 [14.8%]; $P < .001$) and had a higher (4.9 [2.0] vs. 3.5 [2.0]; $P < .001$) COVID-19 complication risk scores [8]. In addition, this vaccinated cohort was more likely to have diabetes (39/126 [31.0%] vs 190/839 [22.7%]; $P < .043$), hypertension (80/126 [63.5%] vs 433/839 [51.7%]; $P < .014$), coronary artery disease (40/126 [31.7%] vs 147/839 [17.6%]; $P < .001$), and chronic kidney disease (25/126 [19.8%] vs 55/839 [6.6%]; $P < .001$) (see Supplementary Table 1).

DISCUSSION

In this study, a higher percentage of breakthrough hospitalizations was seen after 2 May 2021 compared to before. Multiple changes occurred around this time, which contributed to increasing breakthrough infections. First, May 2021 represented the presumed circulation date of the delta variant in Florida with higher infectivity and modest reduction in response to available vaccines. Second, CDC masking guidance was lifted from 13 May through 27 July [9, 10], which may have contributed to higher rates of community spread. Third, vaccination

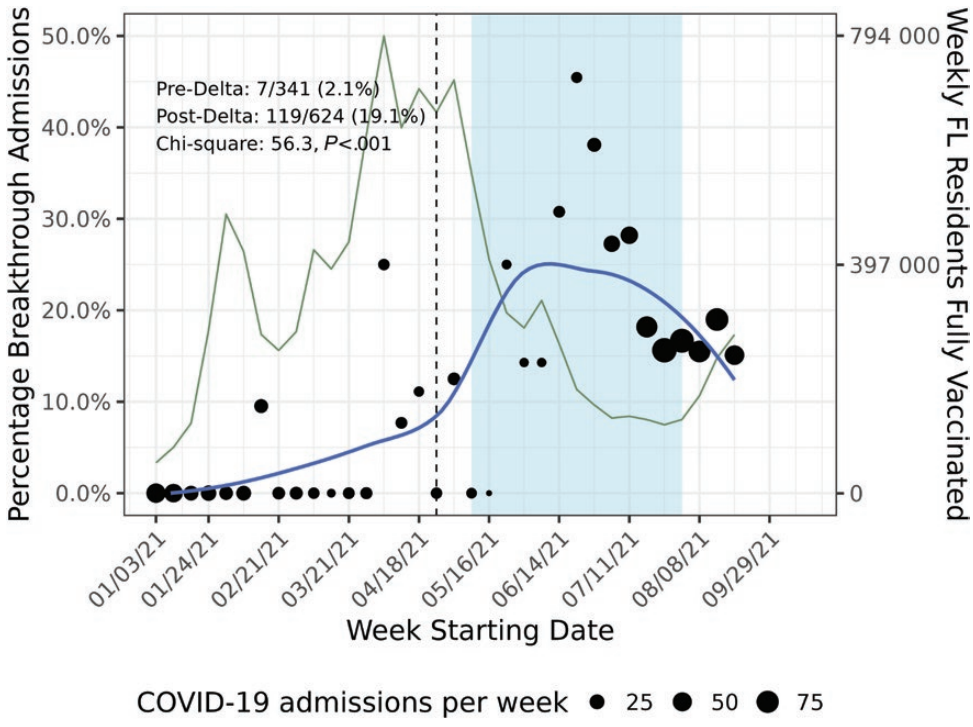

Figure 1. COVID-19 vaccine-breakthrough hospital admissions by week. Figure plots the percentage of weekly COVID-19 admissions that met the definition for a vaccine breakthrough infection, see Supplemental Materials. Size of the points has been scaled based on the total number of COVID-19 admissions in the week. Blue smoothed curve is a LOESS fit based on the data weighted by the number of COVID-19 admissions. (left *y*-axis). Green shaded represents the absolute number of vaccinated individuals by week in Florida, United States (right *y*-axis). Dashed vertical line represents a hypothetical point of onset of the B.1.617.2 (delta) variant in Northeastern Florida, United States. Light blue shaded region covers the time from CDC's masking guidance relaxation for vaccinated people from 13 May 2021 to 27 July 2021. Inset provides the crude percentage of breakthrough admissions pre and post the hypothesized delta variant's arrival to the region. Abbreviations: CDC, Centers for Disease Control and Prevention; COVID-19, coronavirus disease 2019.

against COVID-19 had begun approximately 6 months prior but had leveled off prior to May, leading to concerns of waning immunity among the patients vaccinated earliest in the campaign. Statistically, when community spread is high, more cases will occur in vaccinated individuals, although this might not be the only reason that explains the increase in the percentage of breakthrough cases requiring hospitalization. Further investigation is needed to evaluate the underlying causes of breakthrough infection hospitalization. Based on these results, we recommend continuation of social distancing and protective measures such as masking in fully vaccinated individuals until breakthrough infection dynamics have been better understood.

In the current study, hospitalized COVID-19 breakthrough cases were older and had more comorbidities than unvaccinated hospitalized patients. These findings agree with previously published reports from Israel that showed that hospitalized breakthrough cases have higher rates of comorbid conditions [5]. It is important to mention that the predominant variant was the alpha variant in that cohort while we believe the delta variant was more prevalent in the current study [5]. In contrast, nonhospitalized breakthrough infections in healthcare workers were characterized by a younger (average age of 42 years) and predominantly female patient group (64%) [11]. Our analysis did not include this subgroup of patients. In the Massachusetts outbreak in July 2021, a lower percentage (0.02%) of hospitalization from the 469 breakthrough cases was seen [12].

Several limitations can be noted to this descriptive study. The true rate of breakthrough admissions after presumed emergence of delta variant was not characterized statistically, due to incomplete genomic sequencing of samples and the lack of a population-based sampling frame to quantify all vaccinated people as at risk for breakthrough infection. Also, we did not analyze health outcomes or control for the possibility of waning immunity from early vaccination. These can be addressed in further studies.

In conclusion, our study describes an increased number of vaccine breakthrough COVID-19 infections requiring hospitalization at a single center in Florida after May 2021. This coincided with the more-infectious delta variant, with more high-risk vaccinated individuals, with changes to preventive recommendations, and with the potential for waning immunity from early vaccinations. Although the majority of infections and admissions involved unvaccinated patients, it is important to note that patients admitted with vaccine breakthrough infections were older and had more comorbidities. It remains to be seen how the introduction of additional doses or boosters may impact the need for hospitalization for vaccinated individuals. This work underscores the importance of continued mitigation strategies such as masks, improved indoor ventilation, and social distancing for high-risk patients even after vaccination.

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.

Note

Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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