Factors Associated With COVID-19 Breakthrough Infections in Large Midwestern Healthcare System

Implications for Vulnerable Healthcare Personnel

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Objective: The aim of the study is to identify factors associated with breakthrough infection among a cohort of Midwestern healthcare personnel (HCP). **Methods:** SARS-CoV-2–positive test results between March 1, 2020, and July 31, 2021, were collected from electronic medical records of HCP to identify breakthrough infections. **Results:** Healthcare personnel who were younger than 35 years, received the Pfizer vaccine, and worked in COVID clinical units had greater adjusted odds of breakthrough infection. COVID infection before full vaccination was associated with reduced odds of breakthrough infection. **Conclusions:** Our study concluded that the most vulnerable HCP are younger, working in COVID-19 clinical units, and received Pfizer-BioNTech primary series vaccines. Healthcare personnel who had COVID before vaccination were at reduced risk of breakthrough infection, indicating that supplemental immunity could better protect at-risk HCP groups.

Keywords: healthcare personnel, COVID-19, SARS-CoV-2, vaccination, breakthrough infection, electronic health records

Learning Objectives

- Identifies factors associated with COVID-19 breakthrough infections in the first seven months after primary vaccine series administration, when immunity was presumably highest.
- Describes relative magnitude of breakthrough infection risk among the most vulnerable healthcare personnel.
- Provides median months to breakthrough infection by factors via survival curves.

Since early in the COVID-19 pandemic, healthcare personnel (HCP) have remained a main concern group for COVID-19 vaccination in efforts to mitigate their risk of occupational infection and ensure the continuation of essential societal functions.[1–3] Research has evidenced that frontline HCP have a significantly increased risk of COVID-19 infection compared with the general community.[1] Those in high transmission areas experience higher rates of infections, likely due to community exposure compounding work exposure.[4,5] Furthermore, fully vaccinated individuals who received their primary vaccine series 5 or more months in the past have also demonstrated greater risk of breakthrough infection.[6] Because HCP were among the earliest groups to be vaccinated,[7–9] they are now the largest and potentially one of the most at-risk groups for vaccine breakthrough infections.[10]

Vaccine breakthrough infections are formally defined as the detection of SARS-CoV-2 RNA or antigen in a respiratory specimen collected from a person more than or 14 days after full vaccination with the primary series,[11] defined as 2 doses of an approved mRNA vaccine (Pfizer-BioNTech ["Pfizer"] or Moderna) or 1 dose of Janssen's Johnson & Johnson vector vaccine.[12,13] Despite more than 212 million people in the United States (US) being fully vaccinated with a primary series,[14] breakthrough cases are becoming more common.[15] Healthcare personnel, as a whole, have been identified as an at-risk group for breakthrough infection,[16] but little is known about groups of HCP most vulnerable to breakthrough infection.[17] A closer look at factors associated with breakthrough cases among fully vaccinated HCP is critical to identify the most vulnerable HCP, prioritize funding, guide policies and practices, and ensure continuous, high-quality care.[1]

Arguably, the most pressing issue related to potential breakthrough cases moving forward is the renewed strain on HCP as they continue to balance increased demands at work and various disruptions at home and in their communities.[15] Since the start of the pandemic, HCP have experienced overall systemic changes to care delivery while simultaneously dealing with daily changes to direct patient care.[18] Throughout the pandemic, HCP have worked longer hours and in different capacities than they did before the pandemic, sometimes covering shifts up to 24 hours a day in uncomfortable and often reused protective equipment.[18,19] Outside of work, HCP in all capacities have faced increased financial and logistic pressures due to unreliable childcare and/or partners who have lost jobs.[15,18,19] Reports show that up to 30% of HCP left healthcare since the pandemic started, contributing to staff shortages and the inability of remaining HCP to work safely and satisfy patient needs.[18,20] Such challenges have exacerbated hospitals' existing financial hardships.[20] Furthermore, 60% to 75% of clinicians recently reported symptoms of exhaustion, depression, sleep disorders, and posttraumatic stress disorder[18,21]; these symptoms have been shown to lead to medical errors, lack of empathy, lower productivity, and higher turnover rates within hospitals.[22] As Omicron sweeps through an already-overburdened US healthcare system and breakthrough cases continue to rise,[23] keeping HCP workforce healthy is critical.[15,24] This starts with identifying those most at risk and implementing solutions to protect them.

Empirical data on factors associated with breakthrough cases among HCP will allow healthcare systems to better protect their employees, patients, and institutions. This is especially pertinent in the Midwest, as it is particularly strained with many hospitals having lost more than 10% of their staffed hospital and intensive care unit, meaning a smaller number of COVID-19 patients could overwhelm a hospital.[25–28] To help fill this gap in the literature, this study describes epidemiological data, specifically demographic, work-, and health-related factors associated with breakthrough infection, among a large sample of fully vaccinated Midwestern healthcare workers. These data details breakthrough cases between mid-December 2020, when Food and Drug Administration–approved vaccines were first administered, and July 31, 2021, largely accounting for the Delta emergence timeline in the US.

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These data represent the most immediate aftermath of the initial vaccinations and the period before booster doses were available. This study will also provide time to curves representing time to breakthrough infection across factors determined to be most significantly associated with overall breakthrough infection.

METHODS

Participants

This prospective cohort study recruited employees within a large Midwestern healthcare system consisting of 26 hospitals and more than 500 sites of care across Illinois and Wisconsin. This study includes English- and Spanish-speaking adults 18 years and older employed by the healthcare system as of June 8, 2020 (study initiation) who received an mRNA primary vaccine series between December 15, 2020, when vaccines were first available in the US, and July 31, 2021 (study end). This sample of participants was drawn from the overarching study of 16,357 participants who were tested for SARS-CoV-2 immunoglobulin G assay results between June 8, 2020, and July 10, 2020.[29] For this study, positive SARS-CoV-2 polymerase chain reaction (PCR) test results documented in the system's electronic medical record between March 1, 2020, when tests were first offered, and July 31, 2021, were collected from all participants. It is implicit that team members were vaccinated and also tested at a system-affiliated laboratory, if at all, because of no cost, convenience, and employment implications for both practices. This study obtained approval by the healthcare system institutional review board (#20-168E).

Variables

Data gathered for this study included demographic and work-related factors, vaccination status and type, and all system electronic medical record–documented positive SARS-CoV-2 PCR test results for COVID-19 infection between June 8, 2020, and July 31, 2021, including days between study initiation and second vaccine dose and each positive SARS-CoV-2 PCR test result. Age was collected as continuous and grouped into standard reporting categories and further collapsed as 18 to 24, 25 to 34, 35 to 44, 45 to 54, 55 to 64, and older than 65 years.[30] Race/ethnicity included Hispanic; White, non-Hispanic; Black, non-Hispanic; Asian, non-Hispanic; American Indian, non-Hispanic; or mixed race, non-Hispanic (those who identified as 2 or more races). Sex included male and female. Clinical role category included COVID clinical (participants working in a clinical capacity on COVID-19–designated units), clinical (participants working in a clinical capacity on a non–COVID-19–designated unit), or nonclinical (participants in nonclinical roles, both remote and on-site). Zip code was collected and recoded as urban (Chicago, Milwaukee) versus suburban/rural.

In this study, full vaccination was defined as the receipt of 2 Pfizer or Moderna vaccine doses, as these were the only vaccine types offered within the healthcare system during the study period. The primary outcome in this study is breakthrough infection (yes/no). Breakthrough infection was determined by the presence or absence of a documented SARS-CoV-2–positive PCR result for COVID-19 more than or 14 days after the second primary series vaccine. Time to breakthrough infection was determined by days between full vaccination status (14 days after second vaccine dose) and SARS-CoV-2–positive PCR results. For participants with more than one documented SARS-CoV-2–positive PCR result after full vaccination, time to the first documented positive PCR result after full vaccination was included. During the study period, hospital policy required SARS-CoV-2 PCR tests performed among individuals who were symptomatic, regardless of clinical role, or possibly/knowingly exposed to a known COVID case at work or in the community were required to be tested for SARS-CoV-2 using a PCR test, so breakthrough infection cases are presumably most represented by these scenarios.

Statistical Methods

Data management and analysis were performed by the study research team using SAS statistical software (Version 9.4; SAS Institute, Cary, NC).

Descriptive statistics are reported as counts (percentages) or means (standard deviations) and median (interquartile ranges [IQR]). Univariate and bivariate analyses were conducted to examine the distributions of each variable, overall and by breakthrough infection. Reported measures of association include mean differences between breakthrough infection cases and nonbreakthrough infection cases for the following continuous variables: age, days from study initiation to first vaccine dose, and days between vaccine doses. For categorical variables, the odds ratio (OR) describes the relative odds of breakthrough infection among participants of a given variable category relative to the reference category of that variable. Variable reference levels were chosen based on lowest presumed risk. Corresponding P values were generated from independent-samples t tests and Wald tests, as appropriate, to represent differences in experiencing a breakthrough infection. An α value of $P < 0.05$ was used to determine statistical significance.

Simple/crude logistic regression was used to investigate the crude relationship between factors and breakthrough infection. Multivariable logistic regression was used to investigate the adjusted association of potential contributing factors and breakthrough infection and to account for confounding and/or effect modification. All variables found to be statistically significant in crude analyses were added to the adjusted logistic regression model during model building. Kaplan-Meier estimator curves describe median time to breakthrough infection across variables from the final logistic regression model.

RESULTS

Overall

Of 12,754 fully vaccinated HCP participants, 101 (0.79%) experienced a breakthrough infection. Overall, the participants had a mean age of 42.70 years (12.24 years), and the majority were female (84.72%), White (87.51%), non-Hispanic (93.88%), and worked in a rural/suburban hospital (77.79%). Most had clinical roles within the healthcare system (56.28%) and received the Pfizer vaccine (59.73%). The median time to first vaccine dose was 199.00 days (189–213 days, approximately 6.5 months) from study initiation (June 8, 2020), indicating that the majority of the sample was vaccinated between mid-December 2020 and early February 2021. Among those who experienced a breakthrough infection, the median time to breakthrough infection was 128.00 days (52–199 days, approximately 4.21 months) after full vaccination status (Table 1).

Bivariate/Crude Analysis

Bivariate analyses revealed independent, statistically significant factors associated with breakthrough infections were:

- Age (binary; see hereinafter, $P < 0.0001$)
- Ethnicity ($P = 0.0479$)
- Clinical role category ($P < 0.0001$)
- Vaccine type ($P < 0.0001$)
- COVID infection before fully vaccinated ($P < 0.0001$)

The HCP who experienced a breakthrough infection were younger (mean age difference, −5.39 [−7.78 to −2.99]; $P < 0.0001$). Categorically, relative to the HCP who were aged 18 to 24 years, odds of breakthrough infections were similar among those aged 25 to 34 years (OR, 1.00 [0.47 to 2.13]; $P = 0.0015$) and reduced among those aged 35 to 44, 45 to 54, and 55 to 64 years (OR, 0.57 [0.26 to 1.27]; $P = 0.9054$; OR, 0.36 [0.15 to 0.88]; $P = 0.0539$; and OR, 0.33 [0.13 to 0.82]; $P = 0.0290$, respectively). Because of similarity in

TABLE 1. Demographics of the Fully Vaccinated Midwestern Healthcare Employees, Overall and by Breakthrough Status

Factors of Interest	Overall Sample ($N = 12,754$)	Breakthrough[a] ($n = 101$, 0.79%)	No Breakthrough[a] ($n = 12,653$, 99.21%)	Measure of Association[b] (95% CI)	P
Days from study initiation to first dose, mean (SD), median (IQR)	208.22 (33.54), 199.00 (189–213)	197.40 (23.00), 192.00 (186–199)	208.30 (33.59), 199.00 (189–213)	−10.91 (−15.49 to −6.33)	<0.0001**
Days between vaccine doses, mean (SD), median (IQR)	24.74 (6.52), 23.00 (21–28)	22.47 (3.42), 21.00 (20–23)	24.76 (6.54), 23.00 (21–28)	−2.29 (−2.98 to −1.61)	<0.0001**
Days to breakthrough, mean (SD), median (IQR)	—	125.25 (73.61), 28.00 (52–199)	—	—	—
Age ($n = 12,753$), mean (SD), median (IQR)	42.70 (12.24), 2.00 (21.00)	37.36 (10.97), 34.00 (16.00)	42.74 (12.24), 2.00 (20.00)	−5.39 (−7.78 to −2.99)	<0.0001**
Standardized categories					
18–24	605 (4.74%)	8 (1.32%)	597 (98.68%)	REF	0.0007*
25–34	3343 (26.21%)	44 (1.32%)	3299 (98.68%)	1.00 (0.47 to 2.13), $P = 0.0015$*	
35–44	3297 (25.85%)	25 (0.76%)	3272 (99.24%)	0.57 (0.26 to 1.27), $P = 0.9054$	
45–54	2686 (21.06%)	13 (0.48%)	2673 (99.52%)	0.36 (0.15 to 0.88), $P = 0.0539$	
55–64	2508 (19.67%)	11 (0.44%)	2497 (99.56%)	0.33 (0.13 to 0.82), $P = 0.0290$*	
>65[c]	314 (2.46%)	0 (0.00%)	314 (100.00%)	—	
Binary categories					
>35	8805 (69.04%)	49 (48.51%)	8756 (69.21%)	REF	<0.0001**
<35	3948 (30.96%)	52 (51.49%)	3896 (98.68%)	2.39 (1.61 to 3.53)**	
Sex ($n = 12,753$)					
Male	1949 (15.28%)	87 (86.14%)	10,717 (84.71%)	REF	0.6904
Female	10,804 (84.72%)	14 (13.86%)	1935 (15.29%)	1.12 (0.64 to 1.98)	
Race ($n = 12,575$)					
White only	11,005 (87.51%)	89 (0.81%)	10,916 (99.19%)	REF	0.7609
Black only	449 (3.57%)	1 (0.22%)	448 (99.78%)	0.27 (0.04 to 1.97)	
Asian only	743 (5.91%)	7 (0.94%)	736 (99.06%)	1.17 (0.54 to 2.53)	
American Indian only	38 (0.30%)	0 (0.00%)	38 (100.00%)	—	
Multiracial	340 (2.70%)	3 (0.88%)	337 (99.12%)	1.09 (0.34 to 3.47)	
Ethnicity					
Non-Hispanic	11,974 (93.88%)	90 (0.75%)	11,884 (99.25%)	REF	0.0479*
Hispanic	780 (6.12%)	11 (1.41%)	769 (98.59%)	1.89 (1.01 to 3.55)*	
Clinical role category					
Nonclinical	3864 (30.30%)	6 (0.16%)	3858 (99.84%)	REF	<0.0001**
Clinical	7178 (56.28%)	65 (0.91%)	7113 (99.09%)	5.87 (2.54 to 13.56), $P = 0.0317$*	
COVID clinical	1712 (13.42%)	30 (1.75%)	1682 (98.25%)	11.46 (4.76 to 27.59), $P < 0.0001$**	
Urban status ($n = 12,753$)					
Rural/suburban	9920 (77.79%)	75 (0.76%)	9845 (99.24%)	REF	0.3924
Urban	2833 (22.21%)	26 (0.92%)	2807 (99.08%)	1.22 (0.78 to 1.90)	
Vaccine type					
Moderna	5136 (40.27%)	18 (0.35%)	5118 (99.65%)	REF	<0.0001**
Pfizer-BioNTech	7618 (59.73%)	83 (1.09%)	7535 (98.91%)	3.13 (1.88 to 5.22)**	
COVID infection before fully vaccinated					
No	10,701 (83.90%)	63 (0.59%)	10,638 (99.41%)	REF	<0.0001**
Yes	2053 (16.10%)	38 (1.85%)	2015 (98.15%)	3.18 (2.12 to 4.78)**	

*Statistically significant at $P < 0.05$.

**Statistically significant at $P < 0.0001$.

[a]Represents column percentages.

[b]Represents mean differences with Student t test P values for continuous variables or ORs with Wald test P values for direct differences between the variable level relative to the variable reference level for categorical variables.

[c]Variable level was removed for bivariate effects.

TABLE 2. Logistic Regression Model ORs Predicting Factors Associated With Experiencing a Breakthrough Infection

Factors	OR (95% CI)		
	Crude	Fully Adjusted	Final Adjusted
Intercept	—	−4.97, $P < 0.0001$	−5.17, $P < 0.0001$
Age: <35 vs >35 y	2.39 (1.61–3.53), $P < 0.0001$	1.73 (1.16–2.59), $P = 0.0072$	1.76 (1.18–2.63), $P = 0.0054$
Vaccine type: Pfizer vs Moderna	3.13 (1.88–5.22), $P < 0.0001$	2.29 (1.37–3.84), $P = 0.0017$	2.29 (1.36–3.84), $P = 0.0017$
Role category: clinical vs nonclinical	5.87 (2.54–13.56), $P = 0.0317$	4.45 (1.91–10.37), $P = 0.0531$	4.42 (1.89–10.30), $P = 0.0580$
Role category: COVID clinical vs nonclinical	11.46 (4.76–27.59), $P < 0.0001$	7.31 (2.97–17.96), $P < 0.0001$	7.36 (2.99–18.09), $P < 0.0001$
Ethnicity: Hispanic vs non-Hispanic	1.89 (1.01–3.55), $P = 0.0479$	1.62 (0.86–3.06), $P = 0.1355$	—

relative odds of breakthrough infection and in efforts to simplify groups of the HCP for reporting purposes, age categories were further collapsed as binary to include less than 35 and greater than 35 years of age to be used for all modeling. Relative to the HCP older than 35 years, the HCP younger than 35 years had 2.39 (1.61 to 3.53) times greater odds of breakthrough infection ($P < 0.0001$). Relative to the non-Hispanic HCP, the Hispanic HCP had 1.89 (1.01 to 3.55) times greater odds of breakthrough infection ($P = 0.0479$). Relative to the nonclinical HCP, the clinical HCP and COVID clinical HCP had 5.87 (2.54 to 13.56) times greater odds and 11.46 (4.76 to 27.59) times greater odds of breakthrough infection, respectively ($P = 0.0317$ and $P < 0.0001$, respectively). The HCP who received the Pfizer primary series vaccine had 3.13 (1.88 to 5.22) times greater odds of breakthrough infection ($P < 0.0001$). Finally, the HCP who had COVID before being fully vaccinated had 3.18 (2.12 to 4.78) times greater odds of breakthrough infection ($P < 0.0001$). There were no statistically significant differences in breakthrough infection across level of sex, race, or urban status (Table 1).

Adjusted Analysis

Statistically significant variables—specifically age, ethnicity, clinical role category, vaccine type, and COVID infection before fully vaccinated—were included in the adjusted logistic regression model. Each variable and all interaction pairs were added one by one during model building to assess for confounders and effect modifiers. No interactions were found to be significant, but large changes in ORs of COVID infection before fully vaccinated suggested that it was a confounding factor or effect modifier in the relationship of 1 or more remaining variables and the outcome. Stratified analyses across the COVID infection before fully vaccinated variable were then performed, indicating effect modification (detailed hereinafter). This variable was removed from the model and reported separately.

After removing COVID infection before fully vaccinated, the model was built again with the remaining variables and all interaction pairs. Once again, no interactions were statistically significant and thus were removed. In the fully adjusted model, ethnicity was washed out as a significant variable ($P = 0.1355$) after adjusting for age, clinical role category, and vaccine type; therefore, it was removed. The final adjusted model included age, clinical role category, and vaccine type.

The final adjusted model estimates revealed that the HCP who were younger, received the Pfizer vaccine, and had COVID clinical roles had greater odds of breakthrough infection when adjusting for the other model variables. Specifically, the HCP younger than 35 years had 1.76 (1.18 to 2.63) times greater odds of breakthrough infection relative to the HCP older than 35 years, when adjusting for vaccine type and clinical role category ($P = 0.0054$). The HCP who received the Pfizer vaccine had 2.29 (1.36 to 3.84) times greater odds of breakthrough infection relative to HCP who received the Moderna vaccine, when controlling for age and clinical role category ($P = 0.0017$). Finally, the HCP in COVID clinical roles had 7.36 (2.99 to 18.09) times greater odds of breakthrough infection relative to HCP in nonclinical roles when adjusting for age and vaccine type ($P < 0.0001$). After adjusting for age and vaccine type, significance (by the predetermined α of $P < 0.05$) of relative odds of breakthrough infection of HCP in clinical roles washed out (OR, 4.42 [1.89 to 10.30]; $P = 0.0580$; Table 2).

Stratified Analysis

Separately and unexpectedly, stratified analyses across COVID infection before fully vaccinated revealed this to be an effect modifier in the relationship between age, ethnicity, clinical role, vaccine type, ethnicity, and breakthrough infection. Comparing those who had COVID before being fully vaccinated with those who did not have COVID before being fully vaccinated, the crude relative odds of breakthrough infection increased by the following magnitudes:

- Increased from 1.43 (0.75 to 2.71, $P = 0.2779$) to 2.61 (1.59 to 4.29, $P = 0.0001$) among the HCP who were younger than 35 years relative to those older than 35 years;
- Increased from 2.38 (0.93 to 6.14, $P = 0.0716$) to 9.14 (2.83 to 29.47, $P = 0.0226$) among the HCP who were clinical relative to nonclinical;
- Increased from 1.81 (0.51 to 6.41, $P = 0.1705$) to 17.01 (4.98 to 58.16, $P < 0.0001$) among the HCP who were COVID clinical relative to nonclinical;
- Increased from 2.38 (0.93 to 6.14, $P = 0.0716$) to 2.91 (1.58 to 5.37, $P = 0.0006$) among the HCP who received the Pfizer primary series vaccine relative to Moderna;
- Increased from 0.64 (0.15 to 2.66, $P = 0.5351$)—a protective effect—to 2.75 (1.35 to 5.61, $P = 0.0052$) among those who were Hispanic relative to non-Hispanic.

In short, identified vulnerable groups (ie, younger, clinical/COVID clinical, Hispanic, Pfizer vaccine type) were even more vulnerable to breakthrough infection and to a statistically significant effect, if they had not had COVID before vaccination (Table 3).

TABLE 3. Relative Odds of Experiencing a Breakthrough Infection by Factor, Stratified by COVID Status before Vaccination

Factors	ORs	
	COVID+ Before Vaccination	COVID− Before Vaccination
Age category: <35 vs >35 y	1.43 (0.75–2.71), $P = 0.2779$	2.61 (1.59–4.29), $P = 0.0001$
Vaccine type: Pfizer vs Moderna	2.38 (0.93–6.14), $P = 0.0716$	2.91 (1.58–5.37), $P = 0.0006$
Role category: clinical vs nonclinical	1.03 (0.31–3.49), $P = 0.4996$	9.14 (2.83–29.47), $P = 0.0226$
Role category: COVID clinical vs nonclinical	1.81 (0.51–6.41), $P = 0.1705$	17.01 (4.98–58.16), $P < 0.0001$
Ethnicity: Hispanic vs non-Hispanic	0.64 (0.15–2.66), $P = 0.5351$	2.75 (1.35–5.61), $P = 0.0052$

TABLE 4. Kaplan-Meier Estimates of Median Months to Breakthrough Infection, Overall and Across Associated Factors

Group	Median Months (95% CI)
Overall (n = 101)	4.21 (3.06 to 5.52)
Age, y	
<35 (n = 52)	4.54 (3.19 to 6.02)
>35 (n = 49)	3.53 (1.84 to 5.95)
Vaccine type	
Pfizer (n = 83)	4.54 (3.19 to 5.98)
Moderna (n = 18)	3.12 (1.51 to 5.59)
Clinical role category	
Nonclinical (n = 6)	6.61 (2.83 to 7.27)
Clinical (n = 65)	5.52 (4.21 to 6.28)
COVID clinical (n = 30)	1.87 (1.64 to 3.19)
Ethnicity	
Hispanic (n = 11)	3.88 (1.22 to 6.41)
Non-Hispanic (n = 90)	4.44 (3.06 to 5.59)
COVID infection before vaccination	
Yes (n = 38)	5.97 (2.54 to 6.31)
No (n = 63)	3.68 (2.99 to 5.10)

Kaplan-Meier Curves

Kaplan-Meier estimator was performed to describe median time, in months, to breakthrough infection overall and across statistically significant factors. The median time to breakthrough infection among the overall HCP sample was 4.21 months (3.06 to 5.52 months). The median time to breakthrough infection by factor is as follows:

- Age: 4.54 months (3.19 to 6.02 months) among the HCP younger than 35 years and 3.53 months (1.84 to 5.95 months) among the HCP older than 35 years;
- Vaccine type: 4.54 months (3.19 to 5.98 months) among the HCP who received Pfizer vaccine and 3.12 months (1.51 to 5.59 months) among the HCP who received Moderna vaccine;
- Clinical role category: 6.61 months (2.83 to 7.27 months) among the nonclinical HCP, 5.52 months (4.21 to 6.28 months) among the clinical HCP, and 1.87 months (1.64 to 3.19 months) among the COVID-clinical HCP;
- Ethnicity: 3.88 months (1.22 to 6.41 months) among the Hispanic HCP and 4.44 months (3.06 to 5.59 months) among the non-Hispanic HCP;
- COVID before fully vaccinated: 5.97 months (2.54 to 6.31 months) among the HCP who had COVID before vaccination and 3.68 months (2.99 to 5.10 months) among the HCP who did not have COVID before vaccination.

See Table 4 for full details. In addition, Kaplan-Meier estimator curves visually describe months to breakthrough infection by group (Fig. 1).

DISCUSSION

The results of this study contribute noteworthy empirical data regarding factors associated with breakthrough infections among recently vaccinated HCP in the US. These results have important implications in terms of identifying the most vulnerable HCP, despite full

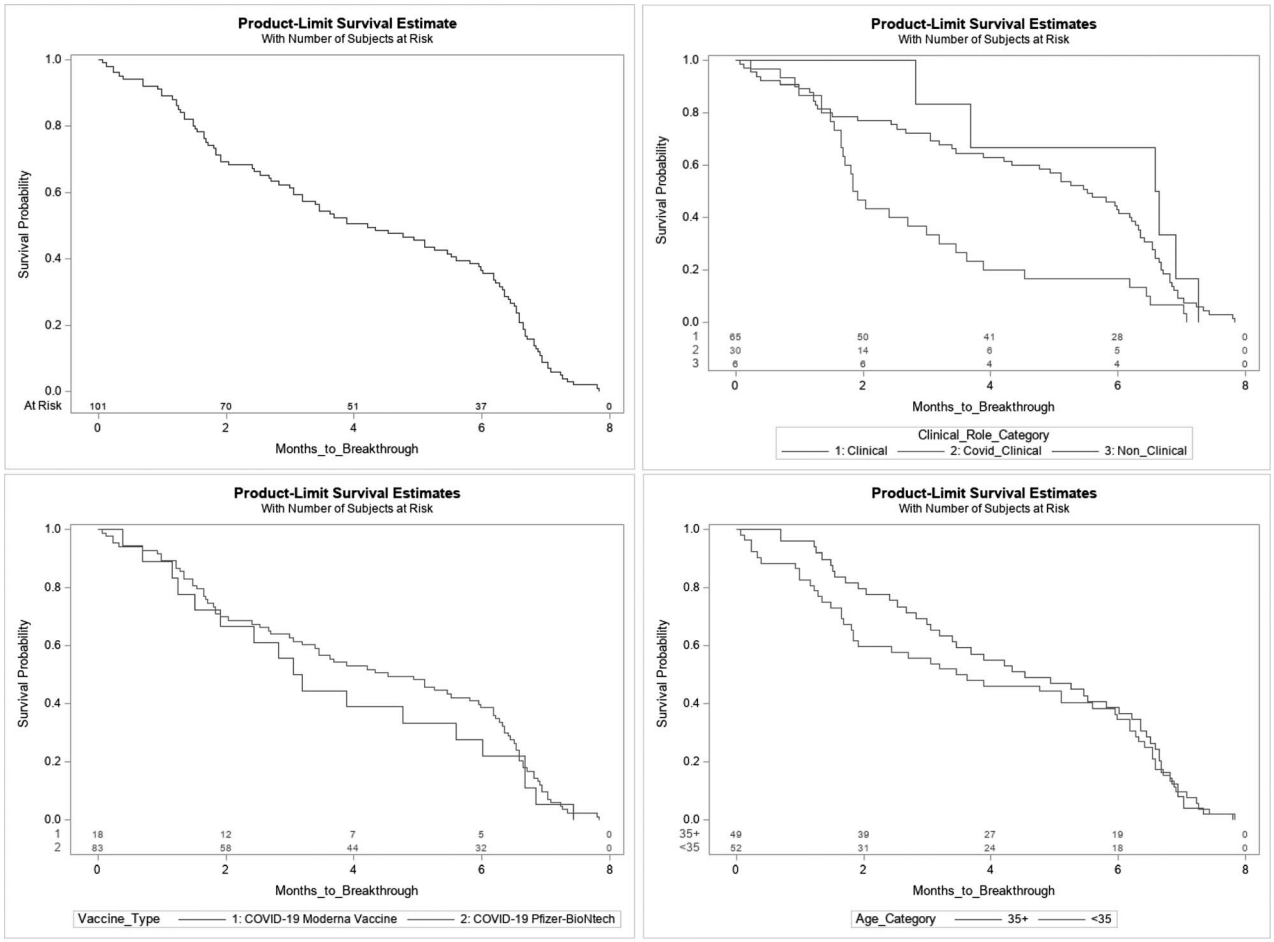

FIGURE 1. Kaplan-Meier curves displaying months to breakthrough among HCP, overall and by associated factors.

vaccination. These data can be used to tailor policies accordingly to better protect HCP, stabilize the healthcare systems in which they work, and serve the influx of patients needing treatment in hospitals right now.

We now know that younger age, a COVID clinical role, and receipt of the Pfizer primary vaccine series are associated with greater adjusted risk of breakthrough infection, despite full vaccination. This study showed fewer breakthrough infections among those who had COVID before full vaccination, in line with other research.[16] This suggests that supplemental immunity may be necessary, as in the form of a booster. We also know that breakthrough infection occurred approximately 4.21 months after full vaccination among this sample of HCP, which is congruent with preliminary research but, more importantly, early given current booster recommendations.[16] Interestingly, crude data show breakthrough infection occurred even sooner among the HCP who were older, received the Moderna vaccine, were Hispanic, worked in COVID clinical roles, or did not have COVID before vaccination. Despite greater overall risk of breakthrough infection, younger HCP and those who received Pfizer vaccine experienced breakthrough infection later in time.

Future research will look at whether factors associated with breakthrough infection during the emergence of Delta variant predicted those who experienced breakthrough infection during that of Omicron. While this study provided a glimpse into time to breakthrough infection by levels of identified risk factors, future research will use Cox proportional hazards models to evaluate the effect of several factors on breakthrough infections over time.

Clinical Significance

Because these data were collected, vaccine protection against infection has further declined, as vaccine-induced immunity has further waned.[31,32] Furthermore, while the Centers for Disease Control and Prevention currently recommends a booster vaccine dose 5 months after the primary series to mitigate risk of breakthrough infection,[11] uptake is currently split in the US, with only approximately half the eligible population receiving a booster.[33] Taken together, these findings underline the significance of initiating booster vaccination among all HCP, but especially groups at higher risk of breakthrough infections, such as younger HCP, those in COVID clinical units, and those who received a Pfizer primary series vaccine. Those most vulnerable to breakthrough infection were less vulnerable if they had COVID before receiving their primary vaccine series, reiterating the importance of supplemental immunity. A booster vaccine dose—particularly sooner than 5 months after full vaccination—would provide necessary supplemental protection for at-risk HCP. In addition, healthcare systems need to continue to support and protect vulnerable HCP in this unpredictable time in healthcare. This includes but is not limited to: appropriate and sufficient personal protective equipment, versatile sick leave and exposure policies, increased testing and symptom monitoring, and potential incentives for booster vaccines. A sick or absent HCP workforce has a significant negative effect on community health and healthcare system stability. This issue needs to be prevented or at least mitigated, accordingly.

Limitations

This study was limited in a few ways. First, this study included fully vaccinated HCP drawn from a larger sample of HCP enrolled in the original study. Differences in this fully vaccinated sample and those excluded/not fully vaccinated were not explored. Second, while hospital policy required SARS-CoV-2 testing among all healthcare workers, it is possible that clinical or COVID clinical groups may have been more likely to pursue testing compared with the nonclinical group. In addition, while COVID infection before vaccination reflected reduced risk of breakthrough infection, time between COVID and breakthrough infections was not examined in this study. Finally, this study did not collect participants' community activities, symptoms, or outcomes related to COVID-19 infections, but the authors recognize that these data points would have provided a more comprehensive assessment of breakthrough infection sources and severity.

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