

**Real-world incidence of breakthrough COVID-19 hospitalization after vaccination versus natural infection in a large, local, empaneled primary care population using time-to-event analysis**

Benjamin D. Pollock<sup>1</sup>, PhD, Curtis B. Storlie<sup>2</sup>, PhD, Aaron J. Tande<sup>3</sup>, MD, Priya Sampathkumar<sup>3</sup>, MD

1 – Division of Health Care Delivery Research, Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic, Jacksonville, FL, USA

2 – Division of Data Science, Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic, Rochester, MN, USA

3 – Division of Infectious Diseases, Mayo Clinic, Rochester, MN, USA

**Corresponding Author:**

Ben Pollock, PhD, MSPH

Assistant Professor of Health Services Research

Mayo Clinic – Stable 750N

4500 San Pablo Road, Jacksonville, FL 32224

Email: Pollock.Benjamin@Mayo.Edu

**Abstract**

We followed 106,349 primary care patients for 22,385,309 person-days across 21 calendar months. There were 69 breakthrough COVID-19 hospitalizations: 65/102,613(0.06%) among fully vaccinated, 3/11,047(0.03%) among those previously infected, and 1/7,313(0.01%) among those with both statuses. This data gives primary care providers real-world context regarding breakthrough COVID-19 hospitalization risk.

**Keywords:** COVID-19; breakthrough; vaccination; natural immunity

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## Background

Available data present contrasting results as to whether vaccine induced immunity (VI) or natural immunity (NI) induced by infection with the SARS-COV-2 virus provide greater protection against 'breakthrough' infections leading to hospitalization. An Israeli pre-print showed that NI from initial SARS-COV-2 infections occurring in January-February 2021 was 7x more effective than VI at preventing breakthrough COVID-19 hospitalization<sup>1</sup> from June-August 2021. Conversely, an American study found that VI was 5x more effective at preventing breakthrough COVID-19 hospitalization compared to NI in the 90-179 days following initial infection<sup>2</sup>. A systematic review from October 2021 identified seven studies [3 randomized controlled trials (RCT) and 4 observational studies] estimating effectiveness of VI versus NI in preventing hospitalization, with mixed results<sup>3</sup>. The RCTs favored VI, though not significantly. The observational studies significantly favored NI by a factor of nearly 4x. When pooled, NI was favored by approximately 2x, although this was not statistically significant. Critically, none of the 4 observational studies included a time-to-event analysis within an American population. Further, RCTs may be limited in their ability to reflect the real-world experiences of COVID-19 infection, vaccination, and follow-up in primary care populations.

Here we sought to compare the incidence of breakthrough hospitalization after natural infection versus vaccination using time-to-event analysis in a real-world setting among empaneled primary care patients at a large academic healthcare institution in the US Midwest.

## Methods

### *Study data and population*

We included consecutive patients who met all of the following inclusion criteria:

- 1.) Age  $\geq$  18 years;
- 2.) Empaneled for primary care at our institution with a home address within our institution's hospital referral region (HRR)

3.) Active Minnesota research authorization;

4) Had a documented COVID infection (positive PCR/antigen test for COVID-19) and/or full vaccination defined as 1 dose of Johnson & Johnson or 2 doses of mRNA vaccine.

From the EHR, we collected PCR/antigen test dates and results, vaccination dates, manufacturer, dose sequence (1<sup>st</sup> dose, 2<sup>nd</sup> dose, etc.), monoclonal antibody infusion dates, patients' counties of residence, age, gender, death dates, and COVID-19 hospitalization dates. The study period for positive tests, vaccinations, and hospitalizations included 3/1/2020 through 11/3/2021.

### *Outcome*

The outcome for time-to-event analysis was breakthrough hospitalization for COVID-19, which was defined as any COVID-19 hospitalization occurring more than 14 days after full vaccination or 90 days after an initial positive PCR/antigen test. We used the 90-day cut off for defining re-infection based on CDC guidance for investigation of re-infections<sup>4</sup>. We right-censored on November 3, 2021 for those not hospitalized. We also right-censored on date of death as a competing risk. All cases of hospitalization flagged for COVID-19 were adjudicated by chart review to confirm COVID-19 as the reason for hospitalization.

### *Exposure*

Patients contributed person-time in the following immune statuses:

- 1.) Vaccine immunity (VI), beginning 14 days after the 2<sup>nd</sup> dose of mRNA vaccine or 1<sup>st</sup> dose of Johnson & Johnson
- 2.) Natural immunity (NI), beginning 90 days after the initial positive PCR/antigen test
- 3.) Double immunity (VI-NI), beginning 14 days after the 2<sup>nd</sup> dose of mRNA vaccine or 1<sup>st</sup> dose of Johnson & Johnson and 90 days after the initial positive PCR/antigen test

A patient could contribute person-time to one or two immune statuses over the follow-up period.

For example, a patient achieving VI on 3/1/2021, having a positive COVID-19 PCR test on 5/1/2021, and right-censored on 11/3/2021 would have contributed 151 person-days of VI status (from 3/1/2021 until 90 days past the positive test, which would be 7/29/2021) and 96 person-days of VI-

NI status (from 7/29/2021 through 11/3/2021). This study was deemed exempt by the Mayo Clinic Institutional Review Board.

### *Statistical analysis*

We tabulated patient demographic characteristics by immune status and compared using chi-squared test for sex and ANOVA for age. Within each status we calculated unadjusted incidence rates (and 95% confidence intervals) of breakthrough COVID-19 hospitalization per 1,000,000 person-days. We calculated incidence rate ratios (IRR) with VI as the reference group using Fisher's exact tests with a significance level of  $p < .05$ .

### *Sensitivity analysis*

We conducted two sensitivity analyses: 1.) Restricted main analysis to patients aged 50+; 2.) Restricted main analysis to patients aged 65+.

## **Results**

A total of 106,349 unique patients were included, contributing 22,385,309 person-days of follow-up. Mean(SD) age was 52.3(19.3) and 60,143 (56.6%) patients were female. 102,613 patients contributed 19,650,843 person-days of VI status, 11,047 patients contributed 1,514,386 person-days of NI status, and 7,313 patients contributed 1,220,080 person-days of VI-NI status. Among VI-NI patients, 4,144 received Pfizer (57%), 507 J&J (7%), and 2,662 Moderna (36%). Among VI patients, 64,776 received Pfizer (63%), 4,948 J&J (5%), and 32,889 Moderna (32%). There were 108 breakthrough infections in hospitalized patients. Of these 69 cases were adjudicated as hospitalizations for COVID-19: 65/102,613 (.06%) among those with VI, 3/11,047 (.03%) among those with NI, and 1/7,313 (0.01%) among those with VI-NI status. Incidence rates (95% CI) per 1,000,000 person-days were 3.31(2.55,4.22) for VI, 1.98(0.40,5.79) for NI, and 0.82(0.01,4.56) for VI-NI. The IRR comparing NI to VI was 0.60 (95% CI: 0.12,1.83;  $p=0.55$ ) and the IRR comparing VI-NI to VI was 0.25 (95% CI: 0.01,1.43;  $p=0.19$ ) (**Table 1**). 17/7,313 (0.23%) of VI-NI, 8/11,047 (0.07%) of NI, and 6/102,613 (0.01%) of VI patients were right-censored via death. In sensitivity analyses restricting

to patients aged 50+ or 65+, results were consistent with the main analysis indicating the highest incidence rate in the VI group and lowest incidence for VI-NI (**Table 1**).

## **Discussion**

Our analysis found that both natural infection and vaccination led to low incidence rates of breakthrough COVID-19 hospitalization, with NI providing slightly better (though statistically insignificant) protection than VI alone. Double immunity (both prior natural infection plus vaccination) led to lower incidence rates than either NI or VI alone, though again this did not reach statistical significance. Real-world observational studies such as this may be a key source of data that can be used to guide care delivery. For example, these analyses done at a local level give primary care physicians the ability to inform patients of their risks using evidence from a large cohort of similar, empaneled peers. Instead of trying to translate the results of RCTs to potentially dissimilar settings and subgroups, physicians can seek to glean insight from the documented experiences of their own populations.

Notably, utilizing time-to-event analysis resulted in directionally consistent findings to other published observational studies, which have favored natural immunity over vaccination for preventing COVID-19 hospitalization. Conversely, the published RCTs have indicated that vaccination is more protective. Some of this discrepancy is likely related to the selection of a time frame after initial positive PCR test in which a subsequent hospitalization is considered 'breakthrough' infection as opposed to sequelae of the initial infection. Our use of 90+ days after initial infection is a reasonable cut-off in the absence of confirmed negative testing. Another explanation is that other studies have not considered allocating person-time for 'double immunity' resulting in misclassification of patients as VI or NI only, and potentially patients biasing effectiveness estimates. Limitations of this analysis include lack of adjustment for different SARS-COV-2 variants, age, sex, or potential confounding variables due to low event size, as well as potential for breakthrough hospitalization outside of our institution which we have mitigated by only

including empaneled patients in geographic proximity to our institution. Although testing was readily available, some patients may have skipped testing altogether and would therefore be misclassified as VI only, thereby underestimating the benefit of double immunity. Likewise, though there were very few deaths during follow-up, right-censoring may not be the ideal method for the competing risk of death. As such, this should be interpreted as a novel and descriptive report describing post-immunity time-to-event breakthrough hospitalization risk in a large primary care population as opposed to a comparative effectiveness study.

### **Conclusions**

Large, real-world observational studies are still needed to determine the comparative effectiveness of natural immunity versus vaccination in preventing COVID-19 hospitalization. While breakthrough infections are increasingly reported, infections that result in hospitalization are rare in those with either type of immunity. Primary care physicians should continue to promote COVID-19 vaccination as an evidence-based method of limiting the risks of future COVID-19 hospitalization.

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### **Disclosures**

AJT reports payment from Uptodate.com for writing osteomyelitis treatment section and unpaid role as board member of Musculoskeletal Infection Society.

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**Table 1**

<b>Primary analysis</b>	Natural immunity N=11,047	Vaccine immunity N=102,613	Double Immunity* N=7,313	<i>p</i>
Age, mean(SD)	45.4 (17.7)	53.3 (19.3)	47.8 (17.9)	<.01
Female, n (%)	6,140 (55.6%)	58,205 (56.7%)	4,201 (57.7%)	.03
Unadjusted breakthrough hospitalization Cumulative incidence, n(%) Events/person-days Incidence rate per 1,000,000 person-days	3/11,047 (0.03%) 3 / 1,514,386 1.98 (0.40,5.79)	65/ 102,613 (0.06%) 65 / 19,650,843 3.31 (2.55,4.22)	1 / 7,313 (0.01%) 1 / 1,220,080 0.82 (0.01,4.56)	-
Incidence Rate Ratio for breakthrough COVID-19 hospitalization	0.60 95% CI: 0.12,1.83 <i>p</i> =0.55	Reference	0.25 95% CI: 0.01,1.43 <i>p</i> =0.19	-
<b>Sensitivity Analysis 1</b> Unadjusted breakthrough hospitalization Incidence rate per 1,000,000 person-days ≥50 years old only (n=66,670)	4.02 (0.45,14.53)	5.13 (3.92,6.60)	1.71 (0.02,9.54)	-
<b>Sensitivity Analysis 2</b> Unadjusted breakthrough hospitalization Incidence rate per 1,000,000 person-days ≥65 years old only (n=35,272)	6.03 (0.08,33.57)	7.26 (5.37,9.60)	4.09 (0.05,22.74)	-

\*patient was more than 90 days past a natural infection and more than 14 days past full vaccination status;