Rate and Risk Factors for Severe/Critical Disease Among Fully Vaccinated Persons with Breakthrough SARS-CoV-2 Infection in a High-risk National Population

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Short Summary: SARS-CoV-2 breakthrough infections occurred in 0.5% of vaccinated persons but were less severe than infections in propensity-score matched unvaccinated persons.

Abstract

Background: Breakthrough SARS-CoV-2 infections after vaccination have been reported. Outcomes among persons with breakthrough infection are poorly understood.

Methods: We identified all Veterans with a confirmed SARS-CoV-2 infection >14 days after the second dose of an mRNA vaccine between December 15, 2020 and June 30, 2021, and propensity-score matched unvaccinated controls with SARS-CoV-2 infection. Primary outcome was severe/critical disease, defined as admission to an intensive care unit, mechanical ventilation, or death within 28 days of diagnosis or during index hospitalization.

Results: Among 502,780 vaccinated and 599,974 unvaccinated persons, there were 2,332 (0.5%) breakthrough infections in the vaccinated group and 40,540 (6.8%) infections in the unvaccinated group over a follow up period of 69,083 person-days in each group. Among these groups, we identified 1,728 vaccinated persons with breakthrough infection (cases) and 1,728 propensity-score matched unvaccinated controls with infection. Among the former, 95 (5.5%) persons met the criteria for severe/critical disease, while 200 (11.6%) persons met the criteria among the latter group. Incidence rate for severe/critical disease per 1,000 person-days (95% CI) was 0.55 (0.45-0.68) among the former and 1.22 (1.07-1.41) among the latter group (P<0.0001). Risk was higher (HR, 95% CI) with increasing age (per 10-year increase 1.25; 1.11-1.41), and those with ≥4 comorbidities (2.85; 1.49-5.43), while being vaccinated was associated with strong protection against severe/critical disease (HR 0.41; 0.32-0.52).

Conclusion: Rate of severe/critical disease is higher among older persons and those with ≥4 comorbidities, but lower among fully vaccinated persons with breakthrough infection compared with unvaccinated controls who develop infection.

Key words: SARS-CoV-2; vaccination; outcomes; breakthrough infection;
Effective vaccines against the SARS-CoV-2 infection are now available. The efficacy of the first two authorized vaccines, the Pfizer-BNT-162b2 and the Moderna-mRNA-1273 vaccines, in randomized phase 3 clinical trials was 94-95% in preventing symptomatic disease.[1, 2] In the real-world setting, effectiveness of these vaccines is similarly very high, consistently exceeding 90%.[3, 4] The Pfizer-BNT-162b2 vaccine retains high level of effectiveness even in the Alpha (previously known as the B1.1.7 variant) and Beta (previously known as the B1.351 variant) variants, with 89% effectiveness against the former and 75% effectiveness against the latter variant.[5] Current vaccines have also been found to be highly effective against the Delta (previously known as the B1.617 variant) variant, particularly in preventing severe and critical disease, though their effectiveness is somewhat lower compared with their effectiveness against the previous variants.[6-10] Despite such remarkable efficacy and effectiveness, breakthrough infections have been reported among fully vaccinated persons.

In a previous study, we found the rate of breakthrough infection among fully vaccinated persons to be 0.66 per 1,000 person-days after full vaccination.[11] In an earlier study of the Veterans in the United States, breakthrough infections were reported in 0.1% of the fully vaccinated Veterans.[12] However, certain subgroups are at a higher risk. These include older persons, those with multiple comorbidities, and residents of rural areas.[11] Clinical trials for vaccine efficacy have shown the vaccines to be highly protective against severe disease and death, with efficacy approaching 100% for these outcomes.[1, 2] However, the comparative severity of illness and outcomes in persons with breakthrough infection versus infection in unvaccinated persons in the real-world is not well known.

A recent report from skilled nursing facilities reported 22 breakthrough infections among 627 residents with SARS-CoV-2 infection over a 3 month period. Two-thirds of these persons were asymptomatic,
while 2 (9%) required acute hospitalization and one person died.[13] Our aim was to compare the rate of SARS-CoV-2 breakthrough infection among fully vaccinated persons, and to determine the rate of severe/critical disease among fully vaccinated persons who developed breakthrough infection compared with appropriately matched unvaccinated persons who developed infection. Identifying those at the highest risk of severe consequences of breakthrough infection is critical in optimal utilization of the approved and emerging therapeutic agents and improving outcomes.

Methods

Study Population and Participants

This study was conducted in the United States Veterans Health Administration (VA) healthcare system. The VA is one of the largest provider of integrated health services in the United States providing care to over 9 million enrolled Veterans at 170 VA medical centers and 1,074 outpatient sites.[14] In response to the SARS-CoV-2 pandemic, the VA rapidly created a national VA COVID-19 Shared Data Resource. Using case definitions and data mapping which were validated collaboratively across the VA, it contains information on all Veterans with a confirmed laboratory diagnosis of SARS-CoV-2 infection within the VA and those who tested outside the VA with a VA clinical note confirming the diagnosis. Updated regularly, the VA COVID-19 Shared Data Resource contains extensive demographic, clinical, pharmacologic, laboratory, vital signs and clinical outcomes information which is derived from multiple validated sources including the Corporate Data Warehouse and the VA electronic medical records.

For the current study, we identified all vaccinated and unvaccinated Veterans in the VA COVID-19 Shared Data Resource between December 15, 2020 and June 30, 2021. Cases were persons who had
received both doses of either the Pfizer-BNT-162b2 or the Moderna-mRNA-1273 vaccine and had at least one positive SARS-CoV-2 PCR test >14 days after the second dose. We excluded those with a positive SARS-CoV-2 PCR test up to 7 days before the second dose of the vaccine. Controls were persons who had not received any vaccine for SARS-CoV-2 infection, had not had any positive test prior to December 15, 2020 and had at least one positive test after December 15, 2020. Among this group, we identified propensity score matched controls (1:1 ratio), matched by age, sex, race, body mass index, Charlson comorbidity score, testing location, and the date of first positive test (within +/- 7 days of the corresponding case).[4] We used nearest neighbor matching using a caliper of 0.25 standard deviation. The Charlson Comorbidity Index is a validated and widely used score that identifies persons at the highest risk for mortality over a period of time based on the presence and severity of comorbidities.[15, 16] For testing location, we used the VA facility where the index test was performed to account for geographic variation in disease incidence and testing patterns. Data retrieved included demographic characteristics, clinical diagnoses, presence of symptoms at presentation, anthropometric measurements and vital signs, all pharmacologic interventions, and select laboratory results. Data on vaccine administration date and the type of vaccine used were also retrieved. Comorbidities were defined according to the definitions used in the VA Corporate Data Warehouse, which uses the International Classification of Diseases (Ninth or 10th Revision, as appropriate) for classifying comorbidities.[17-19] Baseline diagnoses included all diagnoses recorded in the 2 years before the index date.


*Definitions*

Presence of SARS-CoV-2 infection was defined as a clinical sample positive for the virus by RT-PCR. Comorbidities were defined as per the definition of the VA COVID-19 Shared Data Resource, which in turn uses validated definitions extracted from the VA Corporate Data Warehouse. These definitions have been used in numerous previous publications related to SARS-CoV-2 infection.[4, 17-23] Our primary outcome was severe/critical disease, defined as admission to an intensive care unit, mechanical ventilation, or death within 28 days of the index positive test date or hospitalization (whichever was longer). Moderate disease was defined as admission to the hospital and/or need for supplemental oxygen, but no intensive care unit admission, mechanical ventilation, or death.

*Statistical Analyses*

Baseline characteristics of persons with SARS-CoV-2 infection with and without prior vaccination were compared using Chi-squared test for categorical and students t-test for continuous variables. We determined the rate/1,000 person-days of severe/critical infection by various baseline characteristics. We used Cox proportional hazards model to calculate the hazards ratios and 95% confidence intervals for factors associated with development of severe/critical disease. Assumptions for proportional hazards were checked using Schoenfeld residuals. For variables not meeting the proportional hazards assumptions, we stratified our analyses by those variables and conducted additional analyses after removing those variables.

A two-side p-value of <0.05 was considered statistically significant.
Ethical Approval

The study was approved by the Institutional Review Board at VA Pittsburgh Healthcare System with waiver of informed consent requirement.

Results

We identified 502,780 persons who had received both doses of vaccines. Among these, a total of 2,332 (0.46%) persons developed confirmed SARS-CoV-2 infection >14 days after the second dose. We identified 599,974 persons who had not received any vaccine dose. Among these, a total of 40,540 (6.76%) persons developed infection during the study follow up period. (Figure 1) Our final evaluable dataset consisted of 1,728 vaccinated persons with breakthrough infection and 1,728 propensity score matched unvaccinated controls who developed infection during the study follow up period. (Figure 1) Among the vaccinated persons with breakthrough infection, median age was 71 (IQR 63-76) years, 93.9% were male, 23.4% were Black, and the mean body mass index (SD) was 30.2 (6.8) kg/m$^2$. Among the unvaccinated controls who developed infection, the median age was 68 (IQR 60-74) years, 92.3% were male, 25.0% were Black, and the median body mass index (SD) was 30.6 (6.7) kg/m$^2$. Comorbidities were more common among the vaccinated persons with breakthrough infection, but they were less likely to be symptomatic at baseline (19.4% vs. 33.1%; P<0.0001) compared with unvaccinated matched controls who developed infection. (Table 1) Other baseline characteristics including the prevalence of various comorbidities are also provided in table 1.
A total of 295 persons met the definition of severe/critical disease (95 [5.5%] among vaccinated persons with breakthrough infection, and 200 [11.6%] in the unvaccinated matched controls who developed infection). *(Figure 1 and table 2)* Rate of severe/critical disease per 1,000 person-days (95% CI) was 0.55 (0.45,0.68) among vaccinated persons with breakthrough infection and 1.22 (1.07,1.41) among the unvaccinated matched controls who developed infection (P<0.0001). *(Table 2)* Within the vaccinated persons with breakthrough infection, rate of severe/critical disease was not higher among older persons or those with comorbidities, while among the unvaccinated matched controls who developed infection, the rate was higher among those >70 years old (compared with those 40-60 years old) and those with 4 or more comorbidities (compared with none). *(Figure 2)* When comparing vaccinated persons with breakthrough infection with unvaccinated matched controls who developed infection in the same stratum, rates were consistently higher among the unvaccinated matched controls who developed infection. *(Table 2)*

Kaplan-Meier curves comparing event-free survival for severe/critical disease revealed significantly better survival among vaccinated persons with breakthrough infection compared with infection among unvaccinated matched controls who developed infection. *(logrank p<0.0001; Figure 2)* In Cox proportional hazards analysis, increasing age (HR per 10-year increase in age 1.25; 95% CI 1.11-1.41), and presence of 4 or more comorbidities (HR 2.85; 95% CI 1.49-5.43) were associated with a significantly higher risk of developing severe/critical disease. Being vaccinated was associated with a significantly reduced risk of severe/critical disease (HR 0.41; 95% CI 0.32-0.52). *(Table 3)*
Additional Analyses

To understand the impact of matching upon the balance of baseline characteristics, we compared the baseline characteristics of all vaccinated persons with breakthrough infection (N=2,332) with all unvaccinated persons who developed infection during the study follow up period (N=40,540).

(Supplementary table 1) Box plots to show the effect of propensity score matching upon select variables are provided in supplementary figure 1.

We conducted additional analyses using moderate disease as the primary outcome of interest. Unlike severe/critical disease, rates of moderate disease were not higher among the older age groups or those with comorbidities. The rates were also not different when same strata of persons with breakthrough infection after vaccination were compared with unvaccinated matched controls who developed infection. (Supplementary table 2) In Cox proportional hazards analyses, BMI did not meet the assumptions of proportional hazards and the results were stratified by BMI. Among those with BMI <30 kg/m², vaccination did not have a protective effect against moderate disease, while among those with BMI ≥ 30 kg/m², being vaccinated was associated with lower hazards of moderate infection. (Supplementary table 3) Kaplan-Meier curves did not demonstrate a significant difference in the probability of remaining free of moderate disease among persons with breakthrough infection after vaccination versus those with infection in unvaccinated propensity score matched controls. (Supplementary figure 2)

We also reanalyzed factors associated with severe/critical disease using a Cox proportional hazards model with individual comorbidities as covariates instead of a comorbidity count. Coronary artery
disease diagnosis did not meet the assumptions of proportional hazards; therefore, results were stratified by presence or absence of this diagnosis. In both models, vaccinated persons had a similarly low hazards of developing severe/critical disease as in the main model. (Supplementary table 4)

Since we did not have the data on variants of concern, we plotted the number of diagnosis during each week of follow up for both groups to approximate trends of increase in the proportion of infection with the delta variant across the United States. The proportion of infection with the delta variant increased rapidly from 1.4% to 83.7% between May 8, 2021 and July 17, 2021. [24] By the end of our study date (June 30, 2020), Delta variant accounted for approximately 61% of all tested samples in the US. (Supplementary table 5)

Discussion

There are increasing reports of breakthrough infection among persons who have been fully vaccinated against the SARS-CoV-2 virus. However, an accurate picture of the scope of the problem and its consequences is not available. We present results from the largest study of breakthrough infections among fully vaccinated persons with appropriate propensity score matched controls to help answer some of these critical questions. The central finding of this study is the lower risk of severe/critical disease associated with vaccination among persons with breakthrough infection. This is an extension of the numerous studies of vaccine effectiveness in preventing infection and severe disease. Our study provides strong evidence that even when breakthrough infections occur, the prior vaccination may offer substantial protection against severe/critical disease.
The proportion of persons who developed breakthrough SARS-CoV-2 infection after being fully vaccinated was much lower than the proportion of unvaccinated persons who developed infection in the same time period (0.5% vs. 6.8%). While this provides strong reassurance of the effectiveness of the vaccines, these results should be interpreted with caution since these are crude numbers and were not adjusted for various factors that may affect the rate of infection. Nonetheless, in a large national population, it is expected that some or many of those factors would be somewhat balanced between the two groups. The crude proportion of persons with severe/critical disease was similarly lower among the vaccinated persons with breakthrough infection compared with propensity score matched controls with infection during the same follow up period (5.5% vs. 11.6%), again underscoring the positive impact of vaccination upon clinical outcomes. In a recent large national study from the United Kingdom, 4% of COVID-19 related deaths and 3.7% of COVID-19 related hospitalizations occurred 14 or more days after the second dose of the vaccine.[25] In the United States, 84% of the hospitalizations related to COVID occur in unvaccinated persons.[26] These date provide further compelling evidence regarding the benefit of vaccination in preventing severe outcomes.

Rate of severe/critical disease was significantly lower among vaccinated persons with breakthrough infection compared with infection among unvaccinated persons (0.55 vs. 1.22 per 1,000 person-days; \( P<0.0001 \)). Among vaccinated persons who developed breakthrough infection, the risk was not higher among the traditional high risk groups, including older persons, those with higher BMI, or those with comorbidities. However, among unvaccinated matched controls who developed infection, these traditional risk factors for poorer clinical outcomes were significantly associated with a higher risk of
severe/critical disease. Our results provide strong support to the value of vaccination in preventing serious complications of breakthrough infection.

Increasing age and presence of 4 or more comorbidities was independently associated with a higher risk of severe/critical illness. In analysis including individual comorbidities, chronic kidney disease and cancer diagnosis were associated with a higher risk of severe/critical disease. Lower antibody levels have been demonstrated in persons with chronic kidney disease on renal replacement therapy and those with hematologic malignancies and could at least partially explain this finding.[27-29] It also suggest higher vigilance for consequences of infection in these subgroups. Whether this is true for other populations and plays a part in mediating outcomes needs further study.

There are several strengths of this study, including a large national and geographically diverse population. The US Veterans population is an especially vulnerable population due to older age and a higher burden of comorbidities. Effectiveness of vaccination in reducing the risk of severe/critical disease in persons with breakthrough infections is particularly reassuring and suggestive of an even larger benefit in the general population. However, certain limitations of our study should be noted. We did not study the effect of different variants of concern upon outcomes. However, we have previously shown that the Pfizer-BNT162b2 vaccine has an effectiveness of 89.5% against the Alpha variant and 74.5% against the Beta variant. The vaccine is nearly 100% effective in preventing critical illness or death against these variants.[5] More recent data have also demonstrated the effectiveness of current vaccines against the Delta variant, with two doses of the Pfizer-BNT-162b2 and the Oxford–AstraZeneca vaccines being 93.7% and 67% protective against symptomatic infection by the delta variant.[8, 30]
Since we only included persons vaccinated with the approved mRNA vaccines, our data cannot be extrapolated to persons vaccinated with other vaccines.

Our population was predominantly male and older, with a higher burden of comorbidities than the general population. This may limit the generalizability of our findings to the larger population. However, demonstration of effectiveness in this high-risk population is critically important in reassuring that the general population may have at least similar level of response.

In conclusion, we found that the rate of severe/critical disease is significantly lower among those with breakthrough infection after vaccination compared with infection in unvaccinated persons. These data further underscore the importance of vaccination in response to the SARS-CoV-2 global pandemic.
NOTES

Author Contributions:

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Data Access: Dr. Butt had complete access to the data at all times and accepts responsibility for the integrity of this article.

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Table 1. Baseline characteristics of persons with breakthrough infection after vaccination compared with infection in unvaccinated propensity score matched controls

|                                | Vaccinated persons with breakthrough infection | Unvaccinated persons with infection | P-value |
|--------------------------------|----------------------------------------------|-----------------------------------|---------|
|                                | N=1,728                                      | N=1,728                            |         |
| Median age (IQR) years         | 71 (63,76)                                   | 68 (60,74)                         | <.0001  |
| Male sex                       | 93.87%                                       | 92.30%                             | 0.070   |
| Race                           |                                              |                                   | 0.441   |
| White                          | 68.87%                                       | 66.84%                             |         |
| Black                          | 23.38%                                       | 25.00%                             |         |
| Other/unknown                  | 7.75%                                        | 8.16%                              |         |
| Body mass index, kg/m$^2$, mean (SD) |                                              |                                   |         |
| Mean, SD                       | 30.2 (6.8)                                   | 30.6 (6.7)                         | 0.108   |
| <=25                           | 21.35%                                       | 21.12%                             |         |
| >25 – 30                       | 32.58%                                       | 28.94%                             | 0.040   |
| >30                            | 46.06%                                       | 49.94%                             |         |
| Missing                        |                                              |                                   |         |
| Comorbidities                  |                                              |                                   |         |
| Diabetes                       | 51.68%                                       | 47.86%                             | 0.025   |
| Hypertension                   | 80.15%                                       | 76.39%                             | 0.007   |
| Coronary artery disease        | 38.14%                                       | 33.22%                             | 0.003   |
| Chronic kidney disease         | 29.57%                                       | 24.88%                             | 0.002   |
| Chronic lung disease           | 51.04%                                       | 44.44%                             | 0.0001  |
| Anemia                         | 64.93%                                       | 53.41%                             | <.0001  |
| Cancer diagnosis               | 35.65%                                       | 31.54%                             | 0.011   |
| Human immunodeficiency virus infection | 0.87%                                     | 0.87%                              | 1.00    |
| Current smoker                 | 12.62%                                       | 14.81%                             | 0.060   |
|                          | Group 1  | Group 2  | p-value |
|--------------------------|----------|----------|---------|
| Median Charlson comorbidity index score (IQR) | 3 (1,6)  | 3 (1,5)  | <.0001  |
| Symptomatic at baseline  | 19.39%   | 33.10%   | <.0001  |
| Geographical location    |          |          | <.0001  |
| Urban                    | 76.50%   | 68.69%   |         |
| Rural                    | 23.38%   | 31.31%   |         |
| Unknown                  | 0.12%    | 0.00%    |         |
| Geographical location per US Census Bureau |          |          | 1.00    |
| Continental              | 14.58%   | 14.58%   |         |
| MidWest                  | 23.09%   | 23.09%   |         |
| North Atlantic           | 26.79%   | 26.79%   |         |
| Pacific                  | 14.18%   | 14.18%   |         |
| Southeast                | 21.35%   | 21.35%   |         |
| Total follow up, person-days | 69,083   | 69,083   |         |
Table 2. Rate of severe/critical disease per 1,000 patient-days, overall and within specified subgroups.

| Rate of severe disease or death, overall | N | Vaccinated persons with breakthrough infection | P-value* | N | Unvaccinated persons with infection | P-value* | P-value† |
|-----------------------------------------|---|-----------------------------------------------|----------|---|-------------------------------------|----------|----------|
| N Vaccinated persons with breakthrough infection | 0.553 (0.452,0.676) | N/A | 1 | 0.156 (0.022,1.106) | 0.082 | N/A |
| Unvaccinated persons with infection | 1.224 (1.066,1.406) | <.0001 |

By age

| <=40 | 0 | N/A | N/A | 0.264 (0.066,1.055) | Comparator 4 | 0.443 (0.166,1.181) | Comparator 0.549 |
| >40 – 60 | 10 | 0.353 (0.19,0.657) | Comparator 33 | 0.909 (0.646,1.278) | Comparator 0.009 |
| >60 – 70 | 31 | 0.716 (0.504,1.019) | 0.052 | 0.169 | 0.169 | 0.169 | 0.169 |
| >70 | 54 | 0.567 (0.434,0.74) | Comparator 110 | 0.169 | 0.169 | 0.169 | 0.169 |

By race

| White | 69 | 0.586 (0.463,0.742) | Comparator 128 | 1.152 (0.969,1.37) | Comparator <.0001 |
| Black | 17 | 0.416 (0.259,0.669) | Comparator 57 | 1.481 (1.142,1.919) | Comparator <.0001 |
| Other/Unknown | 9 | 0.684 (0.356,1.315) | Comparator 15 | 1.092 (0.658,1.811) | Comparator 0.267 |

By sex

| Female | 3 | 0.265 (0.085,0.821) | Comparator 8 | 0.647 (0.324,1.295) | Comparator 0.186 |
| Male | 92 | 0.574 (0.468,0.704) | Comparator 192 | 1.272 (1.104,1.465) | Comparator <.0001 |

By BMI, kg/m²

| <30 | 53 | 0.568 (0.434,0.743) | Comparator 103 | 1.256 (1.035,1.523) | Comparator <.0001 |
| >=30 | 42 | 0.535 (0.396,0.725) | Comparator 97 | 1.193 (0.978,1.456) | Comparator 0.718 |

By comorbidities

| None | 2 | 0.264 (0.066,1.055) | Comparator 4 | 0.443 (0.166,1.181) | Comparator 0.549 |
| 1 - 3 | 38 | 0.388 (0.282,0.533) | Comparator 114 | 1.131 (0.941,1.359) | Comparator 0.066 |
| 4 or more | 55 | 0.83 (0.638,1.082) | Comparator 82 | 1.533 (1.234,1.903) | Comparator 0.015 |

BMI, body mass index

* P-value within group, vs. first row results

† P-value for vaccinated vs. unvaccinated groups.
Table 3. Factors associated with severe/critical disease (multivariable Cox proportional hazards analysis).

| Factor                                      | Hazards ratio (95% CI) | P-value |
|---------------------------------------------|------------------------|---------|
| Age (per 10 years increase)                 | 1.25 (1.11,1.41)       | 0.0002  |
| Male sex                                    | 1.34 (0.72,2.5)        | 0.35    |
| Race (comparator: White)                    |                        |         |
| Black                                        | 1.27 (0.96,1.68)       | 0.10    |
| Other/unknown                               | 1.12 (0.73,1.71)       | 0.61    |
| Body mass index >30 (comparator: <=30)      | 1.02 (0.81,1.3)        | 0.84    |
| Comorbidities (comparator: None)            |                        |         |
| 1 - 3                                       | 1.57 (0.84,2.93)       | 0.16    |
| 4 or more                                   | 2.85 (1.49,5.43)       | 0.002   |
| Vaccinated (vs. unvaccinated)               | 0.41 (0.32,0.52)       | <.0001  |
| Geographical location (comparator: urban)   |                        |         |
| Rural or very rural                         | 0.92 (0.71,1.2)        | 0.54    |
FIGURE LEGENDS

Figure 1. Construction of the study dataset.

Figure 2. Kaplan-Meier curves demonstrating the probability of remaining free of severe/critical disease among persons with breakthrough infection after vaccination compared with infection in unvaccinated propensity score matched controls (shaded areas are Wellner-Hall bands representing 95% confidence intervals).
Figure 1

- Vaccinated infected case group
- Received 2 doses of vaccine
  - Excluded: 75,927 had a + test up to 7 days before 2nd dose, 424,521 had no positive test >14 days after 2nd dose
  - N=502,780

- Unvaccinated infected control group
- No vaccine ever
  - Excluded: 81,757 had a + test before December 15, 2020, 340,353 had no test done after December 15, 2020, 137,324 had no + test after December 15, 2020
  - N=599,974

- Vaccinated with infection >14 days after 2nd dose
  - N=2,332 (0.5%)

- Unvaccinated with infection after December 15, 2020
  - N=40,540 (6.8%)

- Final dataset with available matched control
  - N=1,728

- 1:1 propensity score matched control
  - N=1,728

- Moderate and severe/critical disease
  - N=256 (14.9%)

- Primary Outcome (Severe/critical disease)
  - N=95 (5.5%)

- Primary Outcome (Severe/critical disease)
  - N=200 (11.6%)

- Moderate and severe/critical disease
  - N=370 (21.4%)
Figure 2

Figure 2. Kaplan-Meier curves demonstrating the probability of remaining free of severe/critical disease among persons with breakthrough infection after vaccination compared with infection in unvaccinated propensity score matched controls.

| Number at risk | 2 weeks | 4 weeks | 6 weeks | 8 weeks | 10 weeks | 12 weeks | 14 weeks | 16 weeks | 18 weeks | 20 weeks |
|---------------|---------|---------|---------|---------|----------|----------|----------|----------|----------|----------|
| Unvaccinated  | 1551    | 1516    | 1470    | 1428    | 1370     | 1260     | 1095     | 879      | 614      | 302      |
| Vaccinated    | 1503    | 1554    | 1530    | 1500    | 1449     | 1339     | 1175     | 944      | 674      | 339      |

Logrank p < .0001