EClinicalMedicine 40 (2021) 101117

Contents lists available at ScienceDirect

EClinicalMedicine

journal homepage: https://www.journals.elsevier.com/eclinicalmedicine

Research paper

Outcomes among patients with breakthrough SARS-CoV-2 infection after vaccination in a high-risk national population

Adeel A. Butt[a,b,c,*], Peng Yan[a], Obaid S. Shaikh[a,d], Florian B. Mayr[a,d]

[a] VA Pittsburgh Healthcare System, Pittsburgh, PA, USA
[b] Weill Cornell Medical College, New York, NY and Doha, Qatar
[c] Hamad Medical Corporation, Doha, Qatar
[d] University of Pittsburgh Medical Center, Pittsburgh, PA, USA

ARTICLE INFO

Article History:
Received 15 May 2021
Revised 16 August 2021
Accepted 16 August 2021
Available online 28 August 2021

Keywords:
Sars-CoV-2
Vaccination
Outcomes
Breakthrough infection

ABSTRACT

Background: Breakthrough infections after SARS-CoV-2 infection have been reported. Clinical outcomes among persons with breakthrough infection are not known.
Methods: We retrospectively identified all Veterans with a confirmed SARS-CoV-2 infection >14 days after the second dose of either Pfizer-BNT-162b2 or Moderna-mRNA-1273 vaccine between December 15, 2020 and March 30, 2021, and age, race, sex, body mass index, Charlson comorbidity index, geographical location, and date of positive test matched unvaccinated controls with SARS-CoV-2 infection. Our primary endpoint was the rate of severe disease or death defined as hospitalization, admission to ICU, mechanical ventilation, or death in both groups.
Findings: Among 258,716 persons with both doses of vaccines and 756,150 without any vaccination, we identified 271 (0.1%) vaccinated persons with breakthrough infection and 48,114 (6.4%) unvaccinated matched controls with infection between December 15, 2020 and March 30, 2021. Among 213 matched pairs, symptoms were present in 33.3% of those with breakthrough infection and 42.2% of the controls. A total of 79 persons met the definition of severe disease or death (42 in the breakthrough infection group and 37 in the control group). Rate of severe disease or death per 1,000 person-days (95% CI) was 4.08 (2.84,5.31) among those with breakthrough infection and 3.6 (2.53,4.73) among the controls ($P = 0.58$). Rate was similar among both groups regardless of age-group, race, BMI or presence of comorbidities. Among persons with breakthrough infection and matched controls with infection, vaccination was not associated with a lower risk of severe disease or death in the main analyses but was associated with a lower risk when matching did not include geographic location (HR 0.62, 95% CI 0.43,0.91).
Interpretation: Demographic or clinical factors are not associated with a lower risk of severe disease or death in persons with breakthrough SARS-CoV-2 infection.
Funding: None

1. Introduction

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% [1,2]. In the real-world setting, effectiveness of these vaccines is similarly very high, ranging from 90–95% [3]. 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 [4]. Despite such remarkable efficacy and effectiveness, breakthrough infections have been reported among fully vaccinated persons. We found the rate of breakthrough infection among fully vaccinated persons to be 0.66 per 1000 person-days after full vaccination [5]. However, certain subgroups are at a higher risk. These include older persons, those with multiple comorbidities, and residents of rural areas [5]. 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]. Real-world vaccine effectiveness studies have also demonstrated >95% effectiveness of the mRNA vaccines in preventing confirmed infection [6]. However, the comparative severity of illness and outcomes in persons with breakthrough infection versus infection in unvaccinated

* Corresponding author: Weill Cornell Medical College, New York, NY and Doha, Qatar.
E-mail address: aab2005@qatar-med.cornell.edu (A.A. Butt).

https://doi.org/10.1016/j.eclinm.2021.101117

Research in context

Evidence before this study

There are emerging data regarding the effectiveness of SARS-CoV-2 vaccines. However, very little is known about the characteristics, risk factors and outcomes of breakthrough infection after full vaccination.

Added value of this study

Among 258,716 persons with both doses of vaccines and 756,150 without any vaccination, we identified 271 (0.1%) vaccinated persons with breakthrough infection and 48,114 (6.4%) unvaccinated matched controls with infection. Among 213 persons with breakthrough SARS-CoV-2 infection after vaccination compared with infection in 213 unvaccinated matched controls, a total of 79 persons met the definition of severe disease or death (42 in those with breakthrough infection and 37 in the control group). Rate of severe disease or death per 1000 person-days (95% CI) was 4.08 (2.84,5.31) among those with breakthrough infection and 3.6 (2.53,4.73) among the controls (P = 0.58). Among persons with breakthrough infection and matched controls with infection, vaccination was not associated with a lower risk of severe disease or death in the main analyses but was associated with a lower risk when matching did not include geographic location (HR 0.62, 95% CI 0.43,0.91).

Implications of all the available evidence

Among persons with breakthrough infection, vaccination offers protection against severe disease or death.

persons in the real-world is unknown. 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 [7]. Our aim was to compare the severity of illness and clinical outcomes of SARS-CoV-2 breakthrough infection in fully vaccinated persons compared with infection in appropriately matched unvaccinated infected persons.

2. Methods

2.1. Study population and participants

This study was conducted in the Veterans Health Administration (VA) healthcare system. The VA is the largest provider of integrated health services in the USA providing care to over 9 million enrolled Veterans at 170 VA medical centers and 1074 outpatient sites [8]. 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 first identified all vaccinated and unvaccinated persons between December 15, 2020 and March 30, 2021. Cases (i.e. persons with breakthrough infection) 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 created two matched groups of controls, matched 1:1 to each case. First group was matched on age, race, sex, body mass index, Charlson comorbidity score, date of first positive test, and 4 geographic regions as defined by the US Census Bureau [9]. Second group was matched on all above criteria except matching on geographic regions. Both groups were also matched on the date of the first positive test (within +/- 7 days) of the corresponding case. It should be noted that group 2 contains cases and controls included in group 1.

2.2. 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 [10-14].

Disease severity was defined using modified World Health Organization criteria [15]. Our primary outcome of interest was severe disease or death in persons with breakthrough infection >14 days after the second dose of vaccination and in matched controls with infection who were never vaccinated. Severe disease was defined as hospitalization, admission to an intensive care or monitored setting, invasive or non-invasive mechanical ventilation, or death. Specific directed treatment for SARS-CoV-2 was defined as use of ≥4 days of remdesivir and/or corticosteroids, at least one administration of convalescent plasma or at least one dose of tocilizumab, each prescribed after the first diagnosis date for SARS-CoV-2.

2.3. Statistical analyses

Baseline characteristics of persons with SARS-CoV-2 breakthrough infection after vaccination and in matched unvaccinated controls with infection were compared using Chi-squared test for categorical and students t-test for continuous variables. We determined the rate/1000 person-days of severe disease or death 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 disease. A two-sided p-value for <0.05 was considered statistically significant.

2.4. Ethical approval

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

2.5. Role of funding

There was no external funding for this study.

3. Results

We identified 258,716 persons who had received both doses of vaccines and 756,150 persons who had not received any vaccination. Among those, we identified 271 (0.1%) vaccinated persons with breakthrough infection and 48,114 (6.4%) unvaccinated persons with confirmed infection after December 20, 2020. (Fig. 1)

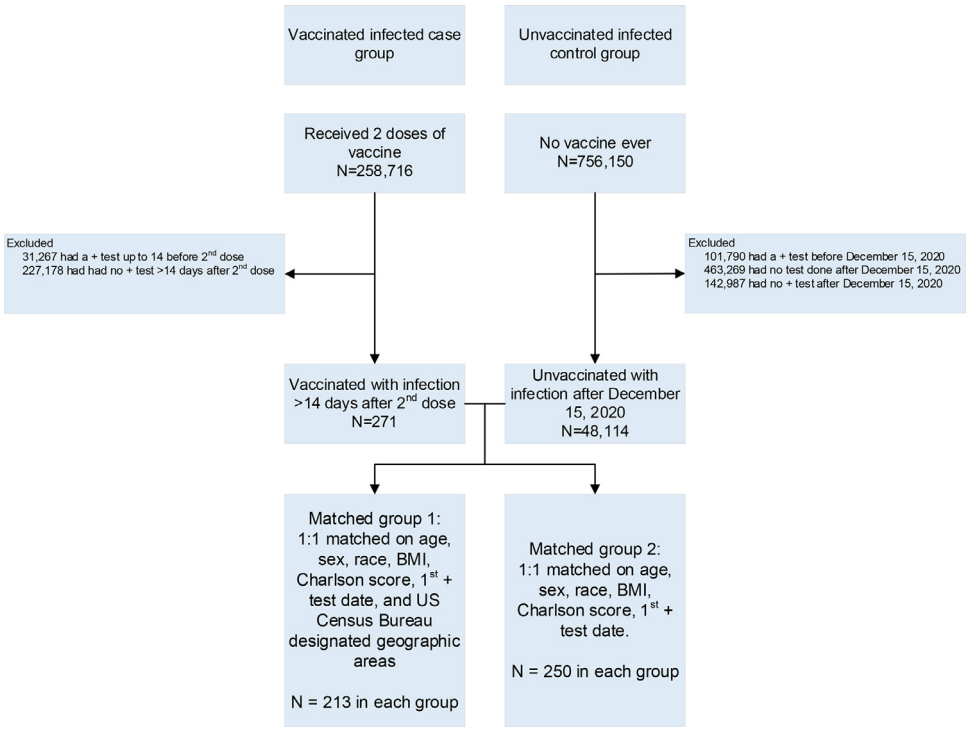

Fig. 1. Construction of the study data-set.

3.1. Matched group 1

For matched group 1 (matched on age, race, sex, body mass index, Charlson comorbidity score, date of first positive test, and 4 geographic regions as defined by the US Census Bureau), we were able to find 213 vaccinated persons who developed infection >14 days after their second dose of vaccination and 213 unvaccinated matched persons who developed infection. (Fig. 1) The median age was 73 years, 95% were males, and 84% were White. The median body mass index was 29.5 kg/m^2 in those with breakthrough infection and 30.4 kg/m^2 in the control group (P = 0.23). Symptoms were present in 33.3% of those with breakthrough infection and 42.2% of the controls (P = 0.06). (Table 1) Other baseline characteristics including the prevalence of various comorbidities are also provided in Table 1.

A total of 79 persons met the definition of severe disease or death (42 in those with breakthrough infection and 37 in the controls). Rate of severe disease or death per 1000 person-days (95% CI) was 4.08 (2.84,5.31) among those with breakthrough infection and 3.60 (2.53,4.73) among the controls (P = 0.58). (Table 2) Rates among the two groups were similar in various age categories and by race, body mass index and presence of comorbidities. (Table 2)

Kaplan-Meier curves comparing event-free survival for severe disease or death did not reveal any significant difference among those with breakthrough infection vs. the controls. (Fig. 2, Panel A) In Cox proportional hazards analysis, presence of anemia was the only factor associated with higher risk of severe disease or death (HR 2.89, 95% CI 1.58,5.28). Being vaccinated was not associated with a lower risk of severe disease or death (HR 0.88, 95% CI 0.57,1.36). (Table 3)

3.2. Matched group 2

For matched group 2 (matched on all previous criteria except the 4 geographic regions), we identified 250 vaccinated persons who developed infection >14 days after their second dose of vaccination and 250 unvaccinated matched controls who developed infection. The median age was 73.5 for those with breakthrough infection and 72.5 years for the controls, and 94% were males, 80% were White and the median body mass index was 29 kg/m^2 for both groups. Symptoms were present in 31.2% of those with breakthrough infection and 41.2% of the controls (P = 0.02). (Table 1) Other baseline characteristics including the prevalence of various comorbidities are also provided in Table 1.

A total of 103 persons met the definition of severe disease or death (50 in those with breakthrough infection and 53 in the controls). Rate of severe disease or death per 1000 person-days (95% CI) was 4.15 (3.00,5.30) among those with breakthrough infection and 4.50 (3.37,5.70) among the controls (P = 0.68). (Table 2) Rate was significantly higher among Blacks in the control group (7.43 [4.11,13.41]) compared with Blacks with breakthrough infection (1.19 [0.30,4.78]; P = 0.02) and among controls with a body mass index <30 kg/m^2 (7.41 [4.84,10.20]) compared with those with breakthrough infection in the same body mass index category (4.33 [2.63,6.03]; P = 0.05). The latter comparison was borderline statistically significant. There was no difference based on the number of comorbidities in the two groups. (Table 2)

Kaplan-Meier curves comparing event-free survival for severe disease or death did not reveal any significant difference among those with breakthrough infection and controls. (Fig. 2, Panel B) In Cox proportional hazards analysis, presence of anemia was the only factor associated with higher risk (HR 4.92, 95% CI 2.63,9.20), while being vaccinated was associated with a lower risk of severe disease or death (HR 0.62, 95% CI 0.43,0.91). (Table 3)

4. Discussion

With the emergency use authorization of several highly effective vaccines against the SARS-CoV-2 virus infection, there is a critical need to define the outcomes in persons with breakthrough infection. We provide information on a large number of confirmed breakthrough infections and infection in well-matched unvaccinated controls. Our data suggests being vaccinated offers significant protection

Table 1
Baseline characteristics of persons with documented SARS-CoV-2 infection ≥14 days after vaccination compared with infection in those who were not vaccinated.

	Matched group 1[1]			Matched group 2[2]		
	Breakthrough infections among vaccinated *N* = 213	Infection among unvaccinated *N* = 213	P-value	Breakthrough infections among vaccinated *N* = 250	Infection among unvaccinated *N* = 250	P-value
Median age (IQR) years	73 (69,78)	73 (67,78)	0.28	73.5 (69,79)	72.5 (67,77)	0.09
Male sex	95.31%	95.31%	1.00	94.00%	94.00%	1.00
Race						
White	84.04%	84.04%	1.00	80.00%	80.00%	1.00
Black	10.33%	10.33%		14.00%	14.00%	
Other/unknown	5.63%	5.63%		6.00%	6.00%	
Body mass index, kg/m^2, mean (SD)						
Mean, SD	29.5 (6.5)	30.4 (6.4)	0.23	29.5 (6.4)	29.2 (6.8)	0.71
Comorbidities						
Diabetes	46.48%	51.17%	0.33	48.40%	53.60%	0.24
Hypertension	75.59%	78.87%	0.42	76.40%	79.20%	0.45
Coronary artery disease	37.56%	37.09%	0.92	37.20%	38.40%	0.78
Chronic kidney disease	27.70%	21.60%	0.14	30.80%	28.80%	0.62
Chronic lung disease (COPD)	44.60%	48.83%	0.38	44.00%	44.00%	1.00
Anemia	69.01%	58.22%	0.02	72.00%	57.60%	0.001
Cancer diagnosis	34.27%	37.56%	0.48	36.40%	39.20%	0.52
Current smoker	11.74%	9.86%	0.53	11.20%	10.40%	0.77
Symptomatic at baseline	33.33%	42.25%	0.06	31.20%	41.20%	0.02
Geographical location			0.53			0.18
Urban	72.77%	70.89%		74.80%	68.80%	
Rural	26.76%	29.11%		24.80%	31.20%	
Unknown	0.47%	0.00%		0.40%	0.00%	
Median annual income (IQR), x10^3 US dollars	25,453 (12,582,40,152)	24,820 (12,864,36,211)	0.75	23,654 (12,090,38,400)	25,246 (12,456,36,211)	0.95
Treatment received after infection						
Remdesivir	2.82%	7.04%	0.04	2.40%	6.40%	0.03
Steroids	0.00%	0.47%	0.32	0.00%	0.80%	0.50
Tocilizumab	0.47%	1.41%	0.32	0.40%	1.20%	0.62

[1] Matched group 1 was matched on age, race, sex, body mass index, Charlson comorbidity score, date of first positive test, and 4 geographic regions as defined by the US Census Bureau.
[2] Matched group 2 was matched on all of the above except 4 geographic regions as defined by the US Census Bureau.

Table 2
Disease severity (severe disease or death) rate per 1000 person-days by subgroups among those who were vaccinated.

	Matched group 1[1]					Matched group 2[2]				
	N	Vaccinated	N	Unvaccinated	P-value	N	Vaccinated	N	Unvaccinated	P-value
Severe disease rate, overall	42	4.08 (2.84,5.31)	37	3.60 (2.53,4.73)	0.58	50	4.15 (3.00,5.30)	53	4.5 (3.37,5.70)	0.68
By age										
<=40	0		0			0		0		
>40 – 60	2	1.96 (0.49,7.85)	4	3.43 (1.29,9.13)	0.52	2	1.68 (0.42,6.70)	3	2.10 (0.68,6.51)	0.80
>60 – 70	8	3.40 (1.04,5.76)	4	1.75 (0.48,3.16)	0.28	9	3.02 (1.05,5.00)	13	4.51 (2.40,6.83)	0.36
>70	32	4.75 (3.11,6.4)	29	4.37 (2.93,5.92)	0.75	39	5.07 (3.48,6.66)	37	5.10 (3.59,6.70)	0.98
By race										
White	39	4.58 (3.14,6.02)	30	3.46 (2.34,4.67)	0.25	44	4.59 (3.23,5.94)	40	4.2 (3.00,5.48)	0.69
Black	0		5	5.09 (1.65,8.93)		2	1.19 (0.30,4.78)	11	7.43 (4.11,13.41)	0.02
Other/Unknown	3	4.41 (1.42,13.68)	2	3.15 (0.79,12.61)	0.71	4	5.10 (0.10,10.10)	2	2.61 (0.32,4.82)	0.44
By sex										
Female	0		1	1.18 (0.17,8.36)		0		1	0.85 (0.12,6.01)	
Male	42	4.46 (3.11,5.81)	36	3.82 (2.67,5.04)	0.49	50	4.62 (3.34,5.89)	52	4.91 (3.67,6.23)	0.75
By BMI, kg/m^2										
<30	20	3.97 (2.23,5.72)	20	5.86 (3.58,8.34)	0.22	25	4.33 (2.63,6.03)	26	7.41 (4.84,10.20)	0.05
>=30	20	5.39 (3.03,7.75)	11	3.58 (1.79,5.56)	0.28	21	4.81 (2.75,6.87)	15	6.06 (3.39,8.98)	0.49
By comorbidities										
None	2	2.04 (0.51,8.18)	0			2	1.87 (0.47,7.47)	0		
1–3	23	3.37 (2.00,4.75)	24	4.12 (2.64,5.72)	0.49	28	3.60 (2.27,4.93)	31	4.54 (3.08,6.09)	0.37
4 or more	17	6.79 (3.56,10.00)	13	3.64 (1.94,5.51)	0.09	20	6.25 (3.51,8.99)	22	6.24 (3.91,8.77)	1.00

[1] Matched group 1 was matched on age, race, sex, body mass index, Charlson comorbidity score, date of first positive test, and 4 geographic regions as defined by the US Census Bureau.
[2] Matched group 2 was matched on all of the above except 4 geographic regions as defined by the US Census Bureau.

against severe disease or death in persons with breakthrough infection.

We performed two sets of complementary analyses to determine the rate and risk factors for severe disease or death among vaccinated persons with breakthrough infection compared with well-matched unvaccinated persons with confirmed infection. First analysis matched for demographic and clinical factors as well as geographic location where the infection was diagnosed, while the second analysis matched for all previous factors except the geographical location. The reason for second analysis was the low number of matched pairs

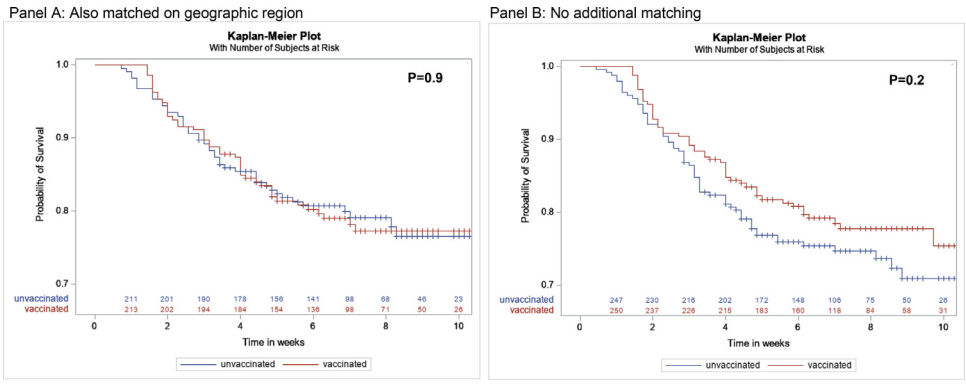

Fig. 2. Kaplan-Meier curves demonstrating the probability of remaining free of severe disease or death among those with breakthrough infection vs. matched unvaccinated controls who developed infection. The groups are matched on age, sex, race, BMI, Charlson comorbidity score, 1st positive test date and additional criteria listed. Breakthrough infection defined as infection after ≥14 days after second vaccine dose. Panel A−Also matched on geographic region Panel B−No additional matching.

Table 3
Factors associated with severe disease or death after vaccination (multivariable Cox proportional hazards analysis).

	Matched group 1[1]		Matched group 2[2]	
	Hazards ratio (95% CI)	P-value	Hazards ratio (95% CI)	P-value
Age (per 10 years increase)	1.22 (0.96,1.55)	0.10	1.24 (1.00,1.54)	0.05
Male sex	2.44 (0.32,18.59)	0.39	4.99 (0.67,36.91)	0.12
Race (comparator: white)				
Black	0.59 (0.24,1.50)	0.27	1.04 (0.58,1.88)	0.90
Other/unknown	1.05 (0.42,2.63)	0.92	0.85 (0.37,1.96)	0.70
Body mass index >30 (comparator: <30)	1.18 (0.74,1.90)	0.49	1.36 (0.89,2.06)	0.16
Comorbidities				
Diabetes	1.29 (0.81,2.07)	0.29	1.25 (0.83,1.87)	0.29
Coronary artery disease	1.01 (0.64,1.58)	0.98	1.03 (0.69,1.53)	0.89
Chronic kidney disease	1.06 (0.64,1.74)	0.83	0.97 (0.65,1.45)	0.89
Chronic lung disease (COPD)	0.88 (0.56,1.37)	0.56	1.01 (0.70,1.48)	0.94
Anemia	2.89 (1.58,5.28)	0.001	4.92 (2.63,9.2)	<0.0001
Cancer diagnosis	0.84 (0.54,1.31)	0.45	0.91 (0.62,1.33)	0.62
Vaccinated (vs. unvaccinated)	0.88 (0.57,1.36)	0.57	0.62 (0.43,0.91)	0.01
Income (comparator: <15,000)				
15,000−30,000	0.58 (0.32,1.04)	0.07	1.11 (0.69,1.78)	0.66
>30,000	0.76 (0.46,1.25)	0.28	0.83 (0.53,1.29)	0.40
Missing	0.88 (0.26,2.97)	0.84	0.60 (0.14,2.54)	0.49
Geographical location (comparator: urban)				
Rural or very rural	0.87 (0.54,1.40)	0.56	0.85 (0.56,1.29)	0.44

[1] Matched group 1 was matched on age, race, sex, body mass index, Charlson comorbidity score, date of first positive test, and 4 geographic regions as defined by the US Census Bureau.
[2] Matched group 2 was matched on all of the above except 4 geographic regions as defined by the US Census Bureau. USD, USA dollars.

with outcome events of interest when matching was done with geographical location, thus decreasing the power to detect meaningful differences between the groups. Using this approach, the incidence rates of infection were quite similar though statistical significance was lost for race and BMI variable when comparing vaccinated persons with unvaccinated persons. In the Cox regression model, vaccination status was associated with a significant decrease in the risk of severe disease or death. The 95% confidence interval range in the second model was entirely within the 95% confidence interval range of the first model, strongly suggesting that the association is a true one, and the lack of statistical significance in the first model was due to the small number of events. It should be noted that geographical location is a possible confounder which is accounted for in the first model, but not in the second model. These results add to the growing literature of vaccine effectiveness in the general population and provides assurance that vaccination is effective in preventing severe consequences among those who experience breakthrough infection after vaccination.

Other than anemia, presence of comorbidities was not associated with a higher risk of severe disease or death. This is likely due to the matching of the two groups by comorbidity burden. We used the widely accepted WHO definition of anemia (hemoglobin <13 g/dL for men and <12 g/dL for women), which is a very permissive definition and picks up even very mild degrees of anemia. We also did not identify the cause of anemia. A more careful analysis of the effect of anemia upon outcomes is warranted. On the other hand, remdesivir use was more common in the unvaccinated group. Remdesivir is indicated in persons with SARS-CoV-2 infection with at least some degree of symptoms or hypoxia. Indeed, persons in the unvaccinated group were more likely to be symptomatic, which may at least partly explain the difference.

Our sensitivity analyses using a more permissive definition of breakthrough infection (>7 days after the second vaccine dose) largely mirrored the main findings in terms of effect size. Due to a larger number of outcome events, certain risk factors which were not statistically significant in the main analyses attained statistical significance. These results need to be interpreted with caution since there may be some biological differences in persons with early vs. late breakthrough infection.

Overall, a comparison of all vaccinated persons with breakthrough infection versus all unvaccinated persons with infection revealed that the vaccinated persons were older, more likely to be White and had a higher burden of comorbidities. These findings are in line with the prioritization of vaccination for these high-risk individuals.

Conversely, vaccinated persons were less likely to have symptoms at the time of diagnosis and less likely to receive remdesivir treatment. Again, this can be explained by the observation that vaccination carries benefits and that remdesivir is approved only for persons with some degree of symptoms.

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. Vaccination effectiveness in 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 [4]. More recent data and news reports have also demonstrated the effectiveness of current vaccines against the delta variant, with the Pfizer-BNT-162b2 and the Oxford–AstraZeneca vaccines being 96% and 92% protective against hospitalization by the delta variant [16,17].

Our population was predominantly male and socioeconomically disadvantaged, as evidenced by the lower median annual income in both groups compared with the US averages. This may limit the generalizability of our findings to the larger population. However, based on demographic and socioeconomic factors, and burden of comorbidities, the Veterans are among the highest risk group for poor outcomes. Therefore, these data are critically important in understanding the course of disease in this high-risk population. Finally, it is possible that the testing strategy and reason for testing may have introduced a bias in those being included in one group. However, it is quite unlikely and would have minimal impact on our results for the following reasons. With the large number of Veterans in each group (258,716 in the vaccinated and 756,150 unvaccinated), we would expect the reason for testing in the two groups to be relatively evenly distributed. In our analyses, we match the groups on demographic and clinical variables, further reducing the risk of bias. We also matched the two groups on the test date and the clinical facility where testing was done, which would minimize any temporal and regional variations in testing.

In conclusion, we found that SARS-CoV-2 vaccination is associated with a lower risk of severe disease or death in persons with breakthrough infection after adjusting for several confounders. These results provide additional evidence and justification for vaccinating the population, particularly those at a high-risk of poor outcomes.

5. Author contributions

Study concept and design: AAB
Acquisition and analysis of data: PY
Interpretation of data: AAB, FM
Drafting of the manuscript: AAB
Critical revision of the manuscript for important intellectual content: AAB, OSS, FM
Dr. Butt had complete access to data at all times and accepts the responsibility of the integrity of this article."

Declaration of competing interest

Dr. Butt has received grants (to the institution) from Gilead Sciences. Dr. Mayr is supported by K23GM132688 from the National Institutes of Health. Other authors have no relevant disclosures.

Funding

None

Acknowledgments

This study was supported by data created by the VA COVID-19 Shared Data Resource and resources and facilities of the Department of Veterans Affairs (VA) Informatics and Computing Infrastructure (VINCI), VA HSR RES 13–457. This material is the result of work is also supported with resources and the use of facilities at the VA Pittsburgh Healthcare System and the central data repositories maintained by the VA Information Resource Center, including the Corporate Data Warehouse. The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the funding agencies.

Data sharing statement

This study used data created and maintained by the Veterans Health Administration, Department of Veterans Affairs. These data are freely available to approved individuals upon fulfilling the specified requirements.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2021.101117.

References

[1] Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med 2021;384:403–16.
[2] Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. N Engl J Med 2020;383:2603–15.
[3] Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA COVID-19 vaccine in a nationwide mass vaccination setting. N Engl J Med 2021;384:1412–23.
[4] Abu-Raddad LJ, Chemaitelly H, Butt AA. National study group for C-V. Effectiveness of the BNT162b2 COVID-19 vaccine against the B.1.1.7 and B.1.351 variants. N Engl J Med 2021;385(2):187–9. doi: 10.1056/NEJMc2104974.
[5] Butt AA, Khan T, Yan P, Shaikh OS, Omer SB, Mayr F. Rate and risk factors for breakthrough SARS-CoV-2 infection after vaccination. J Infect 2021;83(2):237–79. doi: 10.1016/j.jinf.2021.05.021.
[6] Butt AA, Omer SB, Yan P, Shaikh OS, Mayr FB. SARS-CoV-2 vaccine effectiveness in a high-risk national population in a real-world setting. Ann Intern Med 2021 10.7326/m21-1577.
[7] Teran RA, Walblay KA, Shane EL, et al. Post vaccination SARS-CoV-2 infections among skilled nursing facility residents and staff members–Chicago, Illinois, December 2020–March 2021. MMWR Morb Mortal Wkly Rep 2021 ePub: 21 April 2021. doi: 10.15585/mmwr.mm7017e1.
[8] VA. https://www.va.gov/health/aboutvha.asp accessed April 7, 2021. 2021.
[9] US Census Bureau. Census regions and divisions of the USA. US Census Bureau 2021 Accessed 6 June 2021 https://www2.census.gov/geo/pdfs/maps-data/maps/reference/us_regdiv.pdf.
[10] Ioannou GN, Green P, Fan VS, et al. Development of COVIDVax Model to estimate the risk of SARS-CoV-2-related death among 7.6 million US veterans for use in vaccination prioritization. JAMA Netw Open 2021; 4:e214347.
[11] Eastment MC, Berry K, Locke E, et al. BMI and outcomes of SARS-CoV-2 among US veterans. Obesity (Silver Spring) 2020. doi: 10.1002/oby.23111.
[12] Ioannou GN, Locke E, Green P, et al. Risk factors for hospitalization, mechanical ventilation, or death among 10 131 US veterans with SARS-CoV-2 infection. JAMA Netw Open 2020;3:e2022310 open.
[13] Butt AA, Yan P. Rates and characteristics of SARS-CoV-2 infection in persons with hepatitis C virus infection. Liver Int 2021;41:76–80.
[14] Butt AA, Yan P, Chotani RA, Shaikh OS. Mortality is not increased in SARS-CoV-2 infected persons with hepatitis C virus infection. Liver Int 2021;41(8):1824–31. doi: 10.1111/liv.14804.
[15] WHO. Clinical management of severe acute respiratory infection when COVID-19 disease is suspected. https://wwwwhoint/publications/i/item/clinical-management-of- COVID -19 Accessed 4 October 2020 2020.
[16] Sheikh A, McMenamin J, Taylor B, Robertson C. SARS-CoV-2 Delta VOC in Scotland–Demographics, risk of hospital admission, and vaccine effectiveness. The Lancet 2021;397:2461–2.
[17] Reuters. UK study finds vaccines offer high protection against hospitalisation from Delta variant. https://wwwreuterscom/business/healthcare-pharmaceuticals/uk-study-finds-vaccines-offer-high-protection-against-hospitalisation-delta-2021-06-14/; accessed 27 June 2021 2021;June 14, 2021.