Real-world Effectiveness of the SARS-CoV-2 mRNA Vaccines in Preventing Confirmed Infection in Patients on Chronic Hemodialysis

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Short summary: Vaccine effectiveness for the currently available mRNA vaccines ≥14 days after the second dose was 68.2%. The effectiveness was 68.9% for the Pfizer-BNT-162b2 and 66.7% for the Moderna-mRNA-1273 vaccine.

Abstract:

Background: Persons on chronic hemodialysis have a significantly diminished humoral immune response to SARS-CoV-2 vaccines. Whether this translates to reduced vaccine effectiveness (VE) is unknown.

Methods: We used the US Department of Veterans Affairs COVID-19 Shared Data Resource to identify all Veterans who were tested for SARS-CoV-2 between January 26, 2021 and August 31, 2021. Using International Classification of Diseases, 10th edition codes and attendance at a dialysis clinic or center, we identified those who were on chronic hemodialysis. We used a test-negative, case-control design using a doubly-robust logistic regression model to determine the VE of the BNT-162b2 (Pfizer) or mRNA-1273 (Moderna) vaccines in preventing confirmed SARS-CoV-2 infection.

Results: Among 847,199 Veterans tested for SARS-CoV-2 between January 26, 2021 and August 31, 2021, there were 6,076 Veterans on chronic hemodialysis. Among those, we identified 1,270 cases (580 fully vaccinated) and 2,959 controls (2,120 fully vaccinated). The overall VE ≥14 days after the second dose in preventing documented infection was 68.2% (95% CI:62.6,72.9). VE was 68.9% (95% CI:61.9,74.7) for Pfizer-BNT-162b2 and 66.7% (95% CI:58.9,73.0) for Moderna-mRNA-1273 vaccine. There was no difference in VE by age (<70 vs. ≥70 years), race or sex. There were no events recorded in persons with a Charlson's comorbidity index score of <2.

Conclusion: VE of two doses of current mRNA vaccines in preventing SARS-CoV-2 infection in persons on chronic hemodialysis is lower than historic VE rates in the general population. Effect of additional doses in improving VE in this special population needs further study.

Key words: SARS-CoV-2; vaccines; vaccine effectiveness; Veterans; Pfizer BNT-162b2; Moderna mRNA-1273; dialysis; end stage renal disease;

In randomized, placebo controlled clinical trials, mRNA vaccines developed by Pfizer (BNT-162b2) and Moderna (mRNA-1273) demonstrated 94%-95% efficacy against symptomatic infection and nearly 100% efficacy against severe disease or death.[1, 2] Subsequent effectiveness studies in the real-world settings have reported similarly high rates of effectiveness in preventing confirmed infection and nearly 100% effectiveness in preventing severe disease or death.[3, 4] However, the effectiveness wanes with the passage of time and in patients infected with certain variants of concern.[5] Patients with chronic kidney disease who are on chronic hemodialysis constitute a particularly challenging group due to significant immune suppression. While being at a higher risk of adverse outcomes including intensive care unit admission and mortality, they have a diminished humoral response to SARS-CoV-2 vaccination.[6-9] They also have a higher rate of SARS-CoV-2 breakthrough infections after vaccination.[10] Despite such risk, during the time this study was conducted, persons on chronic hemodialysis were not included in the list of immunocompromised persons recommended for an additional dose of the vaccine.[11] Vaccine effectiveness of the SARS-CoV-2 vaccines in patients on chronic hemodialysis in the real-world setting is unknown. This information is critical in determining the optimal prevention strategies in this population. To address this gap in knowledge, we determined the effectiveness of the Pfizer-BNT-162b2 and Moderna-mRNA-1273 vaccines among Veterans in care in the United States Department of Veterans Affairs healthcare system (VA) who were on chronic hemodialysis.

Methods

Study Population

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 Veterans in the VA COVID-19 Shared Data Resource who underwent SARS-CoV-2 testing between January 26, 2021 and August 31, 2021, excluding those with confirmed infections prior to January 26, 2021. Among those tested, we identified persons who were receiving chronic hemodialysis based on presence of 2 or more International Classification of Diseases, 10th edition (ICD-10) codes or at least 2 attendances in a dialysis clinic more than 30 days apart. Cases were defined as patients testing positive (taking the date of first positive test result), while controls had only negative tests.

Statistical Analyses

We used test-negative design to determine the effectiveness of vaccination against confirmed SARS-CoV-2 infection. This design is a widely accepted standard to determine vaccine effectiveness in a population after the introduction of a vaccine.[12-14] We have also used this design to report SARS-CoV-2 vaccine effectiveness in the real-world settings.[4, 5, 15-17] We modeled the effect of vaccines on testing positive using a doubly robust approach, which protects against the misspecification of the propensity score model or the model for the vaccine's effect, by adjusting for covariates in both models separately.[18-20] The probability of vaccination is modeled using gradient-boosted regression models using age, sex, race, body mass index, testing facility and Charlson score as input variables.[21] We estimated the adjusted odds ratios (95% confidence

intervals) from a logistic regression model weighted by inverse probability of vaccination weights, controlling for age, sex, race, body mass index, testing facility and Charlson score. Vaccine effectiveness (VE) was determined using the following formula:

$$VE = 1 - OR_{adj}.$$

We determined overall vaccine effectiveness ≥14 days after the second dose of the vaccine as our primary outcome of interest. We also determined vaccine effectiveness separately for patients who were only partially vaccinated by identifying partially vaccinated cases to controls never testing positive. Finally, we determined VE among subgroups by age, sex, race and Charlson's comorbidity index score. For all point estimates of VE, we calculated the corresponding 95% confidence intervals.[22, 23]

Nearly 97% of the patients in our final study group received the Pfizer-BNT-162b2 or the Moderna-mRNA-1273. We excluded those who received any other vaccine for our main analyses. As a sensitivity analysis, we performed a 1:1 propensity score matched analysis followed by conditional logistic regression (accounting for strata of matched pairs) to estimate VE. Details of propensity score modeling and imbalance evaluation are provided in **supplementary materials, appendices 1 and 2.** Propensity score matching was performed using the same propensity scores estimated for the weighted analysis. Nearest-neighbors type matching with caliper 0.25 was performed using R package matchit.

Ethical Considerations

The study was approved by the Institutional Review Board at the VA Pittsburgh Healthcare System. A waiver of informed consent was granted for the study.

Results

We identified 847,199 Veterans who were tested for SARS-CoV-2 between January 26, 2021 and August 31, 2021. Among them, there were 6,076 Veterans who were on chronic hemodialysis, of whom 1,843 were excluded from further analyses (1,788 tested positive prior to January 26, 2021; 4 due to missing covariate data; 51 because they were vaccinated at sites that were only associated with cases or only controls). The vaccination status of the remaining 4,229 cases and controls (prior to the date of first positive test result for cases) are reported in **Figure 1**, with additional details on propensity score modeling and imbalance evaluation provided in the **Supplementary materials, appendix 3 and figures S1-S4**. Among the 1,270 cases, 580 were fully vaccinated with an mRNA vaccine at least 14 days prior to testing positive, 573 were unvaccinated, and 117 either received the Janssen vaccine, only one dose of an mRNA vaccine, or tested positive prior to the 14th day following receipt of their second dose. Among the 2,959 controls, 2,120 were fully vaccinated with an mRNA vaccine at least 14 days prior to testing positive, 700 were unvaccinated, and 139 either received the Janssen vaccine, only one dose of an mRNA vaccine, or tested positive prior to the 14th day following receipt of their second dose. Patients in the latter groups were excluded from the study group for the primary analysis.

The median age was 69 years (IQR 62,73) for the vaccinated and 67 year (IQR 60,73) for the unvaccinated persons in the primary study group, 97.0% of the vaccinated and 96.0% of the unvaccinated persons were male, 49.7% of the vaccinated and 46.9% of the unvaccinated persons

were Black. **(Table 1)** Common comorbidities included hypertension in 93.0%, cardiovascular disease in 83.7%, and diabetes mellitus in 74.4%. Among the vaccinated group, 56.5% had received the Pfizer-BNT-162b2 vaccine, 43.5% had received the Moderna-mRNA-1273 vaccine. There was a significant association between testing facility and vaccination status (Chi-square $p<0.001$).

The overall vaccine effectiveness $\geq$14 days after the second dose in preventing documented infection was 68.2% (95% CI: 62.6, 72.9). The effectiveness was 68.9% (95% CI: 61.9, 74.7) for the Pfizer-BNT-162b2 and 66.7% (95% CI: 58.9, 73.0) for the Moderna-mRNA-1273 vaccine. **(Table 2)** The overall vaccine effectiveness was 51.5% (95% CI: 19.6, 70.7) after only 1 dose of the Pfizer-BNT-162b2 or Moderna-mRNA-1273, and 64.4% any time after the second dose of the mRNA vaccines. There was no difference in vaccine effectiveness by age group (<70 vs. $\geq$70 years), race or sex. **(Table 3)** There were no events recorded in persons with a Charlson's comorbidity index score of <2.

In sensitivity analyses using a 1:1 propensity score matched approach, covariate imbalance was higher than for the primary analysis **(supplementary table S1)**, and the estimated overall vaccine effectiveness was somewhat lower than the primary estimate **(supplementary table S2)**. We also estimated the vaccine effectiveness over time by calculating the vaccination effectiveness for each month after completion of the primary vaccine series. **(Supplementary table S3)** These results should be interpreted independent of the primary analysis since the controls needed an assigned test negative date and a look-back at the vaccination status. (See footnote for supplementary table S3 for details)

Discussion

To our knowledge, this is the first large scale study of SARS-CoV-2 vaccine effectiveness in persons on chronic hemodialysis. We found the mRNA based vaccines were effective in preventing documented infection in this group, though their effectiveness was lower than what has been reported for the general population.

Patients on chronic hemodialysis are at a higher risk of SARS-CoV-2 infection, and when infected, are more likely to experience poorer clinical outcomes. This is compounded by the suboptimal humoral response to the currently available SARS-CoV-2 vaccines in these patients. While our results provide reassurance regarding the effectiveness of the mRNA vaccines in preventing documented infection, the observed vaccine effectiveness of 68% is lower than the 95% effectiveness in the general VA population[17] and observed in randomized clinical trials,[1, 2] it is sufficiently high to significantly impact the course of disease in this highly vulnerable population. Two factors that significantly reduce vaccine effectiveness of the mRNA vaccines against documented infection are passage of time[5] and infection with the Delta variant.[24] The study period for the current study extended through August 2021, when the Delta variant accounted for the overwhelming majority of infections and a substantial proportion of the study population had been vaccinated several months earlier.[25]

An overwhelming majority of our study population had comorbidities, the most common being hypertension, diabetes, and cardiovascular disease. Presence of these comorbidities is an independent risk factor for poor clinical outcomes. Vaccine effectiveness among persons with these comorbidities has not been studied. It is unclear whether the lower vaccine effectiveness rate in our chronic hemodialysis population was due to these comorbidities, the resultant renal failure, or being

on hemodialysis itself. Recently, a third dose of the Pfizer-BNT162b2 vaccine has been approved for certain high-risk populations. Early data also demonstrate a significant increase in neutralization of the Beta and the Delta variants after the third dose,[26] and recent studies have demonstrated a significant increase in vaccine effectiveness in reducing infections and mortality among in persons who receive a third dose compared with those who only received two dose.[27, 28] Whether a booster will enhance vaccine effectiveness in persons on chronic hemodialysis requires further study.

A limitation of our study is the lack of information on SARS-CoV-2 variants of concern. We have previously demonstrated a somewhat lower effectiveness of the Pfizer-BNT-162b2 vaccine against the Beta and Delta variants.[4, 24] However, with an overall effectiveness of 68%, the benefit of the vaccine supports its use regardless of the variant type at this time. It is possible that future variants may be less amenable to the current vaccine, which would necessitate altering the vaccines to protect against such potential future variants. We also did not study clinical outcomes like severe disease or death. Again, with a vaccine effectiveness of 68% in preventing documented infection necessarily means that a large proportion of complications would be prevented. Varying testing and vaccination practices in different geographic region can impact the results of such studies. We mitigated this by matching the cases and control on the geographic location of testing. This matching was done to the level of the center or facility where testing was performed. Since we did not include patients on peritoneal dialysis in our study, our findings cannot be generalized to those patients. Nearly 97% of the study subjects were male, therefore the results cannot be generalized to females. Our study population was predominantly male and older compared with the general population, and the results should not be generalized to the larger national population.

In conclusion, two doses of currently available mRNA vaccines are effective in preventing confirmed SARS-CoV-2 infection in patients on chronic hemodialysis, though the effectiveness is lower than that observed in the general population. Despite the concerns of diminished humoral response, these patients should be prioritized for SARS-CoV-2 vaccination to reduce the risk of infection and its complications.

NOTES

Author Contributions:

Study concept: AAB

Study design: AAB, VBT, FBM, SBO

Acquisition and analysis of data: AAB, FBM, PY

Drafting of the manuscript: AAB

Critical revision of the manuscript for important intellectual content: AAB, VBT, PY, OSS, SBO, FBM

Authorship Statement: Dr. Butt and Mr. Yan had complete access to data at all times and accept the responsibility of the integrity of this article.

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Data Availability Statement

Requests for data must be directed to the Veterans Health Administration at the Department of Veterans Affairs. Any request must fulfil all requirements for data sharing according the existing laws, regulations, and policies of the Department of Veterans Affairs.

Diagnosis Codes

International Classification of Diseases (ICD) 9th and 10th edition codes related to dialysis are provided in **supplementary materials appendix 4.**

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Table 1. Baseline characteristics of fully vaccinated persons and non-vaccinated persons.

	Overall	Vaccinated[a]	Unvaccinated[b]	P-value
	N=3,973	N=2,700	N=1,273	
Median age (IQR), years	69 (62, 73)	69 (62, 73)	67 (60, 73)	<0.01
Sex, % male	96.7%	97.0%	96.0%	0.12
Race				
White	42.3%	41.9%	43.7%	0.19
Black/African American	48.8%	49.7%	46.9%	
Other/unknown	8.9%	9.7%	8.5%	
Median body mass index (IQR), kg/m^2	27.8 (24, 32)	28.1 (24,32)	27.3 (24, 32)	0.31
Comorbidities				
Hypertension	93.0%	93.1%	92.6%	0.50
Diabetes	74.4%	75.9%	71.4%	<0.01
Cardiovascular disease	83.7%	84.6%	81.7%	0.03
Chronic obstructive pulmonary disease	29.6%	27.8%	29.6%	0.90
Cancer	35.3%	36.5%	32.9%	0.03
Vaccine type[c]				
Pfizer-BNT-162b2	-	56.5%	-	N/A
Moderna-mRNA-1273	-	43.5%	-	
Solid organ transplant	73.2%	73.5%	72.6%	<0.01

[a] Fully-vaccinated status is defined ≥14 days following the second dose of an mRNA vaccine.

[b] Non-vaccinated status is defined as never having received any doses of an mRNA vaccine.

[c] Patients who received a non-mRNA vaccine, or had not reached fully-vaccinated status prior to testing positive, were excluded from the primary analysis.

Table 2. Vaccine effectiveness estimates using the test-negative case-control design for the Pfizer-BNT-162b2 and Moderna-mRNA-1273 vaccines. Those who received any other vaccine were excluded from these analyses.

	Test-positive, N			Test-negative, N			Vaccine Effectiveness (%)		
	BNT-162b2	mRNA-1273	Not Vaccinated	BNT-162b2	mRNA-1273	Not Vaccinated	Overall	BNT-162b2	mRNA-1273
Primary analysis									
≥14 days after the 2nd dose[a]	302	278	573	1224	896	700	68.2 (62.6, 72.9)	68.9 (61.9, 74.7)	66.7 (58.9, 73.0)
Secondary analyses									
Only 1 dose[b]	13	16	573	40	31	700	51.5 (19.6, 70.7)	60.6 (25.5, 79.2)	37.2 (-27.1, 69.0)
Anytime after the 2nd dose[c]	331	320	573	1224	896	700	64.4 (58.2, 70.0)	66.9 (60.9, 71.9)	61.7 (53.0, 68.8)

[a] Analysis of the primary study group comparing the 580 and 2,120 fully vaccinated cases and controls, respectively, against the 573 and 700 unvaccinated cases and controls, respectively.

[b] Analysis comparing the 29 and 71 partially vaccinated cases and controls respectively (see supplement), against the 560 unvaccinated cases and 700 unvaccinated controls.

[c] Analysis includes all patients from the original study group, in addition to 71 cases testing positive between 0 and <14 days after their second dose.

Table 3. Vaccine effectiveness (%) by population subgroups.

	Anytime after the second dose			≥ 14 days after the second dose		
	N	Vaccine Effectiveness (%, 95% CI)	P-value[a]	N	Vaccine Effectiveness (%, 95% CI)	P-value[a]
By age group						
< 70	2,197	65.0 (56.5, 71.9)	0.82	2,155	69.2 (61.6, 75.4)	0.60
≥ 70	1,847	64.4 (54.5, 72.1)		1,818	67.3 (58.1, 74.5)	
By race						
White	1,712	65.0 (55.0, 72.7)	0.92	1,682	69.4 (60.6, 76.3)	0.89
Black	1,973	64.4 (54.8, 71.9)		1,938	67.9 (59.2, 74.8)	
Other	359	74.9 (51.0, 87.1)		353	79.0 (57.9, 89.5)	
History of solid organ transplant						
Yes	1081	71.4 (60.0, 79.6)	0.22	1064	74.4 (63.9, 81.8)	0.34
No	2963	64.3 (57.0, 70.4)		2909	68.5 (61.9, 74.0)	

[a] From a test of differential vaccine effectiveness across subgroups.

Figure Legend.

Study flowsheet.

[a] 71 persons tested positive <14 days after their second dose; 17 persons were vaccinated with a non-mRNA vaccine; 29 patients received only 1 dose of the vaccine (13 with BNT-162b2 and 16 with mRNA-1273) and tested positive prior to second dose.

[b] 71 persons received only 1 dose of the vaccine (40 with BNT-162b2 and 31 with mRNA-1273); 68 persons were vaccinated with a non-mRNA vaccine.

(See appendix 3 for more details on these exclusions)

Figure 1