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COVID-19 vaccine effectiveness against SARS-CoV-2 infection in the United States prior to the Delta and Omicron-associated surges: a retrospective cohort study of repeat blood donors

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Running title: Vaccine effectiveness in repeat blood donors

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ABSTRACT

To inform public health policy, it is critical to monitor COVID-19 vaccine effectiveness (VE), including against acquiring infection. We estimated VE using self-reported vaccination in a retrospective cohort of repeat blood donors who donated during the first half of 2021, demonstrating a viable approach for monitoring of VE via serological surveillance. Using Poisson regression, we estimated an overall VE of 88.8% (95% CI: 86.2–91.1), adjusted for demographic covariates and variable baseline risk. Time since first reporting vaccination, age, race-ethnicity, region, and calendar time were statistically significant predictors of incident infection.

Key words: COVID-19, SARS-CoV-2; vaccines; vaccine effectiveness; blood donors

INTRODUCTION

COVID-19 vaccines have a critical role in preventing symptomatic and serious disease caused by SARS-CoV-2 [1], and in reducing viral transmission [2]. Vaccines approved or authorized for emergency use in the US by the Food and Drug Administration had high efficacy against severe disease in Phase III trials, ranging from 67% to 95% [1, 3-5]. However, long-term management of the SARS-CoV-2 pandemic remains a substantial challenge, especially as variants of concern emerge. To inform public health policy, it is critical to monitor effectiveness, as differentiated from vaccine efficacy, of COVID-19 vaccines at the population-level over longer periods of time [6]. Numerous individual-level and environmental factors (e.g., mitigation practices, vaccine types, and vaccination coverage) impact vaccine effectiveness (VE), underscoring the importance of and need for population-based studies of VE against SARS-CoV-2 infection.

Evaluating VE is challenging given the multitude of endpoints relevant to SARS-CoV-2 infection. Many COVID-19 VE studies have evaluated severe endpoints, such as mortality and hospitalizations, often in higher risk populations. Mild and asymptomatic infections account for the vast majority of SARS-CoV-2 infections, with serosurveys indicating that many more infections occur than diagnosed cases [7]. Vaccine breakthrough infections are frequently asymptomatic with one study finding that among >10,000 breakthrough infections, over a quarter were asymptomatic [8]. Asymptomatic individuals (including with vaccine breakthrough infections) can transmit SARS-CoV-2 to others, and thus preventing asymptomatic infection is important to decrease widespread community transmission [9]. It is therefore important to monitor VE against acquiring infection to inform COVID-19 vaccine policy.

Constraints on large-scale population-level monitoring of VE include the cost and logistical challenges of enrolling and following cohorts of vaccinated and unvaccinated individuals. Case control study designs may be subject to bias if controls are not representative of the population from which cases are drawn. Molecular assays, applied to respiratory swab samples, are the gold standard for diagnosing SARS-CoV-2 infection. However, molecular assays have a limited detection window, necessitating frequent follow-up that reduces the feasibility of ongoing large-scale surveillance, higher cost, and lower throughput. In contrast, serological assays that detect binding antibodies (Abs) against the Spike (S) and Nucleocapsid (NC) viral proteins are lower cost, higher throughput, and can identify SARS-CoV-2 infections after resolution.

We estimated VE using a retrospective cohort of repeat blood donors who donated during the first half of 2021 at Vitalant, a major US blood collection organization (BCO). This proof-of-concept study demonstrates a viable approach for continued near real-time monitoring of VE via serological surveillance among repeat blood donors.

METHODS

Beginning in June 2020, Vitalant tested all donors for anti-S and anti-NC Abs using the Ortho VITROS anti-SARS-CoV-2 S Total Ig and Roche Elecsys® NC Anti-SARS-CoV-2 assays. For this analysis, we included donations from donors who donated at least twice between January 1 to July 6, 2021, with anti-S and anti-NC test results and no evidence of past infection. Donors self-reported any COVID-19 vaccination at each donation and each interdonation interval was categorized as vaccinated or unvaccinated time at risk, based on serological status and COVID-19 vaccination report. Specifically, we defined an interdonation interval as vaccinated time at risk if the donor was vaccinated and had anti-S Abs but not anti-NC Abs at the first timepoint and unvaccinated time at risk if the donor was not vaccinated at both timepoints and had no anti-S Abs at the first timepoint. Interdonation intervals during which vaccination took place were excluded because the proportion of vaccinated versus unvaccinated time could not be determined. A single donor could contribute both unvaccinated and vaccinated time at risk. Exact dates of vaccination and vaccine manufacturer were not recorded at donation. (Preliminary data from a survey of Vitalant blood donors conducted subsequently indicates that more than 90% received a Moderna or Pfizer-BioNTech mRNA vaccine.) Survey data further indicate that approximately 30% of intervals classified as vaccinated exposure time started when donors were partially vaccinated (i.e., less than 14 days after the final dose), but that most of the vaccinated exposure time accumulated after being fully vaccinated. Incident SARS-CoV-2 infections were identified using anti-NC seroconversion; vaccine breakthrough infection defined as seroconversion after self-report of COVID-19 vaccination. The demographic composition of the donor population is shown in Supplementary Table 1.

We used multivariable Poisson regression to evaluate the association between incident SARS-CoV-2 infection rate and COVID-19 vaccination and reported adjusted incidence rate ratio (IRR). The final model adjusted for the calendar month during which a donor's follow-up ended (to control for changing baseline risk over time), accumulated time vaccinated at the start of the final observation interval, sex, age, race-ethnicity, and the Vitalant-defined region in which donations were collected. Time at risk was treated as an offset in the regression analysis, with uninfected donors contributing the full interval, and infected donors contributing half of the interval during which infection occurred. A log

link function was used, and analysis conducted in R version 4.1.2. VE was defined as 1-IRR. Since a single donor could contribute both unvaccinated and vaccinated exposure time, and to account for within-donor correlation we computed 95% confidence intervals (CIs) using 10,000 iterations of donor-level bootstrapping (resampling donors with replacement). As a comparator, we used naïve person-time methods to estimate incidence (number of events/time-at-risk) in vaccinated and unvaccinated donors and reported unadjusted IRRs and VE.

We conducted a simulation study to evaluate VE estimation methods and data inclusion rules with respect to bias and precision, with a particular focus on the bias that may arise when both incidence and the proportion of the population vaccinated changes rapidly during the study period, resulting in unvaccinated follow-up time accumulating disproportionately during a period of higher incidence. We simulated 1,020 datasets similar to the Vitalant repeat donor cohort, with varying rates of declining incidence, increasing vaccination, and proportions of the population vaccinated by the end of the period. We evaluated unadjusted IRRs based on conventional person-time methods, Cox proportional hazards regression on a calendar timescale, and Poisson regression adjusted for calendar time; methods were assessed for absolute and relative bias and precision (see Supplementary Appendix).

RESULTS

In total, 61,618 donors who donated in 18 geographic regions across the United States contributed 407,449 unvaccinated person-weeks and 326,752 vaccinated person-weeks of time at risk during the study period (January 1 to July 6, 2021). Most donors (77%) contributed a single interval (median 1, range 1–25), and the median interval length was 56 days (IQR: 28–71). Poisson regression adjusted for the calendar time when a particular donor's follow-up ends (either with an infection event or still at risk) had low bias, good precision, and confidence interval coverage >95% (see Supplementary Appendix).

We identified 1,653 incident infections in unvaccinated donors, and 100 vaccine breakthrough infections. Kaplan-Meier survival curves for both groups are shown in Figure 1. Using multivariable Poisson regression, we estimated overall VE was 88.8% (95% CI: 86.2–91.1), derived from an IRR of 0.11 (0.09–0.14), adjusted for demographic covariates and variable baseline risk (Table 1). The number of days that the donor had been vaccinated at the start of the final interval was significant and protective, with a 2% reduction in incidence associated with a 1-day increase in time since vaccination (IRR 0.98 [0.97,0.99]). Age (1% reduced incidence associated with an additional year of life), Asian or Pacific Islander race (IRR 0.56 [0.31,0.84]), several geographic regions, and the month during which a donor's follow-up ended, from

March onwards, were statistically significant predictors of incident infection, though sex was not (Table 1). The naïve analysis yielded an unadjusted VE estimate of 92.5% (90.8%–93.8%, Table 1).

Our simulation study showed substantial bias with a naïve analysis, and that Poisson regression controlling for calendar time effectively addresses confounding arising from changing baseline hazard over time.

DISCUSSION

VE against acquiring any serologically identifiable SARS-CoV-2 infection, was high in blood donors during the first half of 2021 at 88.8%. Our VE estimate was comparable to previous VE estimates in studies evaluating protection against SARS-CoV-2 infection based on detection of viral RNA in swab samples, which ranged from 73% to 98.2% [10-12], and mostly lower than estimates of protection against hospitalization, which ranged from 88.0% to 95.1% [10, 13, 14]. Evidence of increasing protection with longer times since vaccination in these data are consistent with maturing immune responses during the early period of vaccine implementation, but over longer timescales waning protection would be expected, as has been observed in other studies [10].

A major strength of this study was the broad assessment of a large number of repeat blood donors residing in 18 states during universal screening for SARS-CoV-2 Abs. Our model accounted for spatiotemporal factors and provided a more generalizable estimate of VE in the US population compared to previous studies in clinical populations. Our simulation-based exploration of estimation methods identified a robust statistical approach, specifically based on the criterion of having low bias in situations of time-varying infection and vaccination dynamics. The study constitutes an important proof of concept for the use of serological surveillance of blood donors to monitor VE over time as variants have and continue to emerge and vaccine-induced Ab responses wane or are enhanced through booster vaccinations. This approach further facilitates larger sample sizes and consequently improved precision in VE estimates at lower cost than clinical cohort studies.

Several limitations need to be considered when interpreting these results. The serological assays employed in this study have high sensitivity and specificity for past infection and vaccination-induced Abs, but lower sensitivity than molecular assays for acute infection. From the DHQ responses, we did not have detailed information on COVID-19 vaccination timing, number of doses, or vaccine type, and there is the potential for misreporting of vaccination status by donors.. To limit the impact of potential misclassification of vaccination status, we required serological evidence of an

immunological response (presence of anti-S Abs and absence of anti-NC Abs) to corroborate self-reported vaccination, although donors could still have been classified as vaccinated after receiving only the first of a two-dose series or not long enough after receiving a single-dose vaccine or the second dose of a two-dose series to have developed robust Ab responses and be considered fully vaccinated. Sporadic presentation for donation, which for some donors may be very infrequent, is inherent to repeat blood donor datasets. We developed methods to account for interval censoring of both vaccination and infection events, but some data were excluded because vaccination status or the ordering of vaccination and infection events was uncertain during the interval. We used Vitalant collection region as a proxy geographic variable, however this may not capture with adequate granularity the heterogeneity in local transmission.

Blood donors are not representative of the US population, e.g., racial/ethnic minorities are underrepresented, which may introduce bias if VE differs in underrepresented population groups. Overall, donors are healthier than the general population, but this is unlikely to bias VE estimates since the healthy donor effect is likely present in both vaccinated and unvaccinated donors. Vaccinated donors were disproportionately female and older, potential confounders we controlled for in the analysis. These data were collected before widespread circulation of Delta and Omicron variants of SARS-CoV-2. Anti-NC seroconversion may be less likely in vaccine breakthrough infections [15], although our analysis of survey respondents reporting swab-confirmed breakthrough infections who were tested with the NC assay indicated sensitivity of >90%.

Our results showed a high VE against acquiring SARS-CoV-2 infection during the first half of 2021, although data collection preceded epidemic surges driven by spread of Delta and Omicron variants during the second half of 2021. We have established repeat donor cohorts for continued monitoring in partnership with another large BCO and the US Centers for Disease Control and Prevention for long-term serosurveillance, including comparison of VE during periods of Delta and Omicron predominance. SARS-CoV-2 antibody assays will be complemented with more detailed donor surveys regarding COVID-19 vaccinations (primary and booster), COVID-19 diagnoses, and symptoms. This next study phase will also include estimation of VE by vaccine manufacturer and timing of primary and booster doses, as well as assessment of the severity of vaccine breakthrough infections.

Ethics and informed consent: Blood donors provided consent for the use of donation data and biospecimens in research at the time of donation. Consistent with the policies and guidance of the University of California San Francisco

Institutional Review Board, Vitalant Research Institute self-certified that use of the deidentified data in this study does not meet the criteria for human subjects research. Centers for Disease Control and Prevention (CDC) investigators reviewed and relied on this determination as consistent with applicable federal law and CDC policy (45 C.F.R. part 46, 21 C.F.R. part 56; 42 U.S.C. § 241[d]; 5 U.S.C. § 552a; 44 U.S.C. § 3501).

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC.

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TABLES AND FIGURES

Table 1: Vaccine effectiveness estimates against anti-nucleocapsid antibody seroconversion* using multivariable regression and person-time approaches among US blood donors, January-July 2021

Model	Incidence in vaccinated donors *infections/10^4 person-weeks* (95% CI)	Incidence in unvaccinated donors *infections/10^4 person-weeks* (95% CI)	Predictors / covariates**	(adjusted) Incidence Rate Ratio (95% CI)	Vaccine Effectiveness *%* (95% CI)
Poisson regression			*Vaccination status*		88.8 (86.2–91.1)
			Unvaccinated	*ref*	
			Vaccinated	**0.11 (0.09,0.14)**	
			Days vaccinated at start of final interval	**0.98 (0.97,0.99)**	
			Sex		
			Female	*ref*	
			Male	0.99 (0.90,1.09)	
			Age (in years at first donation)	**0.99 (0.99,0.99)**	
			Race-ethnicity		
			White, Non-Hispanic	*ref*	
			Black, Non-Hispanic	0.67 (0.34,1.06)	
			Asian/Pacific Islander, Non-Hispanic	**0.56 (0.31,0.84)**	
			Native American/Alaskan, Non-Hispanic	0.70 (0.22,1.27)	
			Hispanic ethnicity	0.93 (0.76,1.11)	
			Missing/Unknown/Refused	1.24 (0.88,1.65)	
			*Vitalant Regional Center****		
			Albuquerque, NM (ALB)	*ref*	
			Billings, MT (BIL)	1.3 (0.92,1.85)	
			Cheyenne, WY (CYS)	1.28 (0.78,1.91)	
			Denver, CO (DEN)	**1.39 (1.10,1.80)**	
			El Paso, TX (ELP)	1.42 (0.95,2.06)	
			Fargo, ND (FAR)	**2.00 (1.56,2.63)**	
			Lafayette, LA (LAF)	**1.55 (1.13,2.12)**	
			Las Vegas, NV (LAS)	1.16 (0.86,1.59)	
			Lubbock, TX (LBB)	1.25 (0.88,1.77)	
			McAllen, TX (MCA)	0.90 (0.38,1.59)	
			Memphis, TN (MEM)	1.38 (0.94,1.98)	
			Phoenix, AZ (PHX)	1.08 (0.85,1.49)	
			Rapid City, SD (RAP)	1.48 (0.98,2.04)	
			Reno, NV (RNO)	0.82 (0.56,1.18)	
			Sacramento, CA (SAC)	**0.59 (0.44,0.79)**	
			San Francisco, CA (SFO)	**0.30 (0.17,0.47)**	
			Spokane, WA (SPK)	**1.51 (1.14,2.03)**	
			Ventura, CA (VTA)	**0.43 (0.27,0.62)**	
			End of follow-up		
			January 2021	*ref*	
			February 2021	0.55 (0.32,1.20)	
			March 2021	**0.31 (0.19,0.65)**	
			April 2021	**0.39 (0.24,0.83)**	
			May 2021	**0.36 (0.22,0.76)**	

			June/July 2021	**0.26 (0.16,0.55)**	
Naïve person-time	3.1 (2.5–3.7)	40.6 (38.6,42.6)	N/A	0.075 (0.062–0.092)	92.5 (90.8–93.8)

* Vaccine breakthrough infections defined as anti-nucleocapsid seroconversion after any self-report of previous COVID-19 vaccination. Number of vaccine doses not collected. Analysis included 100 vaccine breakthrough infections.

** Statistically significant predictors indicated in bold font.

*** Geographic collection areas for Vitalant regional centers are shown in Figure 1 of manuscript Vassallo, RR, Bravo MD, Dumont LJ, Hazegh K, Kamel H. Seroprevalence of Antibodies to SARS-CoV-2 in US Blood Donors. medRxiv 2020.09.17.20195131; doi: 10.1101/2020.09.17.20195131.

Figure 1: Kaplan-Meier survival curves by vaccination status comparing time to anti-nucleocapsid antibody seroconversion among US blood donors, January-July 2021

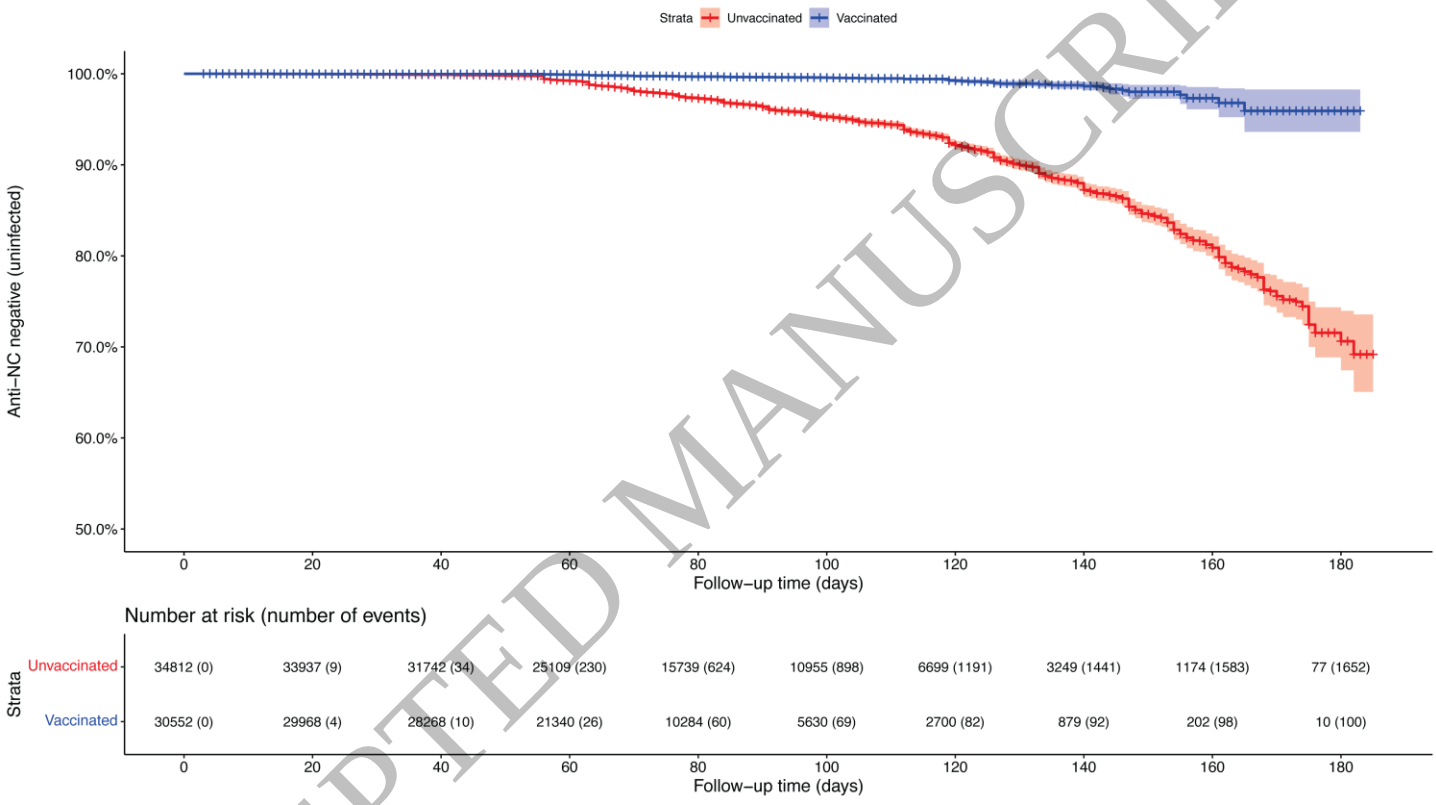

Figure 1
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