

Necessity of COVID-19 vaccination in previously infected individuals

Nabin K. Shrestha,¹ Patrick C. Burke,² Amy S. Nowacki,³ Paul Terpeluk,⁴ Steven M. Gordon¹

From the Departments of ¹Infectious Diseases, ²Infection Prevention, ³Quantitative Health Sciences, and ⁴Occupational Health, Cleveland Clinic, Cleveland, Ohio.

Keywords: SARS-CoV-2; COVID-19; Incidence; Vaccines; Immunity;

Running Title: COVID-19 vaccination if already infected

Corresponding author:

Nabin K. Shrestha, MD, MPH

9500 Euclid Avenue / G-21

Cleveland, OH 44195

Phone: 216-636-1873 / Fax: 216-445-9446 / Email: shrestn@ccf.org

Summary: Cumulative incidence of COVID-19 was examined among 52238 employees in an American healthcare system. COVID-19 did not occur in anyone over the five months of the study among 2579 individuals previously infected with COVID-19, including 1359 who did not take the vaccine.

ABSTRACT

Background. The purpose of this study was to evaluate the necessity of COVID-19 vaccination in persons previously infected with SARS-CoV-2.

Methods. Employees of the Cleveland Clinic Health System working in Ohio on Dec 16, 2020, the day COVID-19 vaccination was started, were included. Any subject who tested positive for SARS-CoV-2 at least 42 days earlier was considered previously infected. One was considered vaccinated 14 days after receipt of the second dose of a SARS-CoV-2 mRNA vaccine. The cumulative incidence of SARS-CoV-2 infection over the next five months, among previously infected subjects who received the vaccine, was compared with those of previously infected subjects who remained unvaccinated, previously uninfected subjects who received the vaccine, and previously uninfected subjects who remained unvaccinated.

Results. Among the 52238 included employees, 1359 (53%) of 2579 previously infected subjects remained unvaccinated, compared with 22777 (41%) of 49659 not previously infected. The cumulative incidence of SARS-CoV-2 infection remained almost zero among previously infected unvaccinated subjects, previously infected subjects who were vaccinated, and previously uninfected subjects who were vaccinated, compared with a steady increase in cumulative incidence among previously uninfected subjects who remained unvaccinated. Not one of the 1359 previously infected subjects who remained unvaccinated had a SARS-CoV-2 infection over the duration of the study. In a Cox proportional hazards regression model, after adjusting for the phase of the epidemic, vaccination was associated with a significantly lower risk of SARS-CoV-2 infection among those not previously infected (HR 0.031, 95% CI 0.015 to 0.061) but not among those previously infected (HR 0.313, 95% CI 0 to Infinity).

Conclusions. Individuals who have had SARS-CoV-2 infection are unlikely to benefit from COVID-19 vaccination, and vaccines can be safely prioritized to those who have not been infected before.

INTRODUCTION

The two FDA-approved (BNT162b2 mRNA [Pfizer-BioNTech] and mRNA-1273 [Moderna]) mRNA vaccines have been shown to be very efficacious in protecting against Severe Acute Respiratory Syndrome (SARS) – associated Coronavirus-2 (SARS-CoV-2) infection [1,2]. The effectiveness of the Pfizer-BioNTech vaccine in a real-world setting has also been shown to be comparable to the efficacy demonstrated in clinical trials [3,4]. Given these, there has been an understandable desire to vaccinate as many people as possible.

The ability to vaccinate a large part of the population is limited by the supply of vaccine. As of March 21, 2021, 78% of 447 million doses of the coronavirus disease 2019 (COVID-19) vaccines that had been deployed had gone to only ten countries [5]. The COVAX initiative was borne out of the recognition that equitable distribution of vaccines worldwide was essential for effective control of the COVID-19 pandemic. However, the reality is that there is great disparity in the availability of vaccines across countries. Countries with limited supplies of vaccine have to prioritize how their supply of vaccines will be allocated within their populations. Criteria used for such prioritization have included profession, age, and comorbid conditions. Data that inform prioritization criteria with help maximize the benefits of whatever vaccine is available.

Observational studies have found very low rates of reinfection among individuals with prior SARS-CoV-2 infection [6–8]. This brings up the question about whether it is necessary to vaccinate previously infected individuals. These studies notwithstanding, there remains a theoretical possibility that the vaccine may still provide some benefit in previously infected persons. A prior large observational study concluded that immunity from natural infection cannot be relied on to provide adequate protection and advocated for vaccination of previously infected individuals [9]. The CDC website recommends that persons previously infected with SARS-CoV-2 still get the vaccine [10]. Despite these recommendations, credible reports of previously infected persons getting COVID-19 are rare. The rationale often provided for getting the COVID-19 vaccine is that it is safer to get vaccinated than to get the disease. This is

certainly true, but it is not an explanation for why people who have already had the disease need to be vaccinated. A strong case for vaccinating previously infected persons can be made if it can be shown that previously infected persons who are vaccinated have a lower incidence of COVID-19 than previously infected persons who did not receive the vaccine.

The purpose of this study was to attempt to do just that, and thereby evaluate the necessity of the COVID-19 vaccine in persons who were previously infected with SARS-CoV-2.

METHODS

Study design

This was a retrospective cohort study conducted at the Cleveland Clinic Health System in Ohio, USA. The study was approved by the Cleveland Clinic Institutional Review Board. A waiver of informed consent and waiver of HIPAA authorization were approved to allow access to personal health information by the research team, with the understanding that sharing or releasing identifiable data to anyone other than the study team was not permitted without additional IRB approval.

Setting

PCR testing for SARS-CoV-2 at Cleveland Clinic began on March 12, 2020, and a streamlined process dedicated to the testing of health care personnel (HCP) was begun shortly thereafter. All employees with a positive SARS-CoV-2 test were interviewed by Occupational Health, with date of onset of symptoms of COVID-19 being one of the questions asked. Vaccination for COVID-19 began at Cleveland Clinic on December 16, 2020. When initially started it was the Pfizer-BioNTech vaccine that was administered, until the Moderna vaccine became available, from which time employees received one or the other. All employees were scheduled to receive their second vaccine dose 28 days after the first one, regardless of which vaccine was given. The employee cohort was chosen for this study because of documentation of their COVID-19 vaccination and of any SARS-CoV-2 infection in the Occupational Health database.

Participants

All employees of the Cleveland Clinic Health System, working in Ohio, on Dec 16, 2020, were screened for inclusion in the study. Those who were in employment on December 16, 2020, were included.

Variables

SARS-CoV-2 infection was defined as a positive nucleic acid amplification test. The date of infection was taken to be the date of onset of symptoms when available, and the date of specimen collection when not. A person was considered vaccinated 14 days after receipt of the second dose of the vaccine (which would have been 42 days after receipt of the first dose of the vaccine for most subjects). For the sake of consistency in the duration assumed for development of natural and vaccine immunity, any person who tested positive for SARS-CoV-2 at least 42 days before the vaccine rollout date, was considered previously infected. Other covariates collected were age, job location, job type (patient-facing or non-patient facing), and job category. The job location variable could be one of the following: Cleveland Clinic Main Campus, regional hospital (within Ohio), ambulatory center, administrative center, or remote location. The job category was one of the following: professional staff, residents/fellows, advance practice practitioners, nursing, pharmacy, clinical support, research, administration, and administration support.

Outcome

The study outcome was time to SARS-CoV-2 infection, the latter defined as a positive nucleic acid amplification test for SARS-CoV-2 on or after December 16, 2020. Time to SARS-CoV-2 infection was calculated as number of days from December 16, 2020 (vaccine rollout date) to SARS-CoV-2 infection. Employees that had not developed a SARS-CoV-2 infection were censored at the end of the study follow-up period (May 15, 2021). Those who received the Johnson & Johnson vaccine (81 subjects) without having had a SARS-CoV-2 infection were censored on the day of receipt of the vaccine, and those whose employment was terminated during the study period before they had SARS-CoV-2 infection (2245 subjects) were censored on the date of termination of employment. The health system never had a requirement for asymptomatic employee test screening. Most of the positive tests, therefore, would have

been tests done to evaluate suspicious symptoms. A small proportion would have been tests done as part of pre-operative or pre-procedural screening.

Statistical analysis

A Simon-Makuch hazard plot [11] was created to compare the cumulative incidence of SARS-CoV-2 infection among previously infected subjects who were vaccinated, with those of previously infected subjects who remained unvaccinated, previously uninfected subjects who were vaccinated, and previously uninfected subjects who remained unvaccinated. Previous infection was treated as a time-independent covariate (SARS-CoV-2 infection at least 42 days before Dec 16, 2020), and vaccination (14 days after receipt of the second dose of the vaccine) was treated as a time-dependent covariate (Figure 1). Curves for the unvaccinated were based on data for those who did not receive the vaccine over the duration of the study, and for those who did until the date they were considered vaccinated, from which point onwards their data were recorded into the corresponding vaccinated set. A Cox proportional hazards regression model was fitted with time to SARS-CoV-2 infection as the outcome variable against vaccination (as a time-dependent covariate whose value changed on the date a subject was considered vaccinated)[12]. Previous infection (as a time-independent covariate) and an interaction term for previous infection and vaccination were included as covariates. The phase of the epidemic was adjusted for by including the slope of the epidemic curve as a time-dependent covariate whose value changed continuously with the slope of the epidemic curve. The analysis was performed by NKS and ASN using the *survival* package and R version 4.0.5 [12–14].

RESULTS

Of 52238 employees included in the study, 2579 (5%) were previously infected with SARS-CoV-2.

Baseline characteristics

Those previously infected with SARS-CoV-2 were significantly younger (mean $\pm$ SD age; 39 ± 13 vs. 42 ± 13 , $p < 0.001$), and included a significantly higher proportion with patient-facing jobs (65% vs. 51%, $p < 0.001$). Table 1 shows the characteristics of subjects grouped by whether or not they were previously infected. A significantly lower proportion of those previously infected (47%, 1220 subjects) were vaccinated by the end of the study compared to 59% (29461) of those not previously infected ($p < 0.001$). Of those vaccinated, 63% received the Moderna vaccine. Twelve percent of subjects with previous SARS-CoV-2 infection did not have a symptom onset date, suggesting they may possibly have been identified on pre-operative or pre-procedural screening, and may not have had symptomatic infection. When vaccination was begun, the epidemic in Ohio was at the peak of its third wave (Figure 2).

Cumulative incidence of COVID-19

Figure 3 is a Simon-Makuch plot showing that SARS-CoV-2 infections occurred almost exclusively in subjects who were not previously infected with SARS-CoV-2 and who remained unvaccinated. The cumulative incidence of SARS-CoV-2 infection among previously infected unvaccinated subjects did not differ from that of previously infected subjects who were vaccinated, and that of previously uninfected subjects who were vaccinated. For all three of these groups, the cumulative incidence of SARS-CoV-2 infection was much lower than that of subjects who were not previously infected and who remained unvaccinated. Of the 2154 SARS-CoV-2 infections during the study period, 2139 (99.3%) occurred among those not previously infected who remained unvaccinated or were waiting

to get vaccinated, and 15 (0.7%) occurred among those not previously infected who were vaccinated. Not one of the 2579 previously infected subjects had a SARS-CoV-2 infection, including 1359 who remained unvaccinated throughout the duration of the study.

Association of vaccination with occurrence of COVID-19

In a Cox proportional hazards regression model, after adjusting for the phase of the epidemic, vaccination was associated with a significantly lower risk of SARS-CoV-2 infection among those not previously infected (HR 0.031, 95% CI 0.015 – 0.061) but not among those previously infected (HR 0.313, 95% CI 0 – Infinity). The absence of events among those who were previously infected, whether they received the vaccine or not, precluded accurate or precise estimates for the latter effect size.

Duration of protection

This study was not specifically designed to determine the duration of protection afforded by natural infection, but for the previously infected subjects the median duration since prior infection was 143 days (IQR 76 – 179 days), and no one had SARS-CoV-2 infection over the following five months, suggesting that SARS-CoV-2 infection may provide protection against reinfection for 10 months or longer.

DISCUSSION

This study shows that subjects previously infected with SARS-CoV-2 are unlikely to get COVID-19 reinfection whether or not they receive the vaccine. This finding calls into question the necessity to vaccinate those who have already had SARS-CoV-2 infection.

It is reasonable to expect that immunity acquired by natural infection provides effective protection against future infection with SARS-CoV-2. Observational studies have indeed found very low rates of reinfection over the following months among survivors of COVID-19 [6–8]. Reports of true reinfections are extremely rare in the absence of emergence of new variants. When such reinfections occur, it would be purely speculative to suggest that a vaccine might have prevented them. Duration of protective immunity from natural infection is not known. However, the same also can be said about duration of protective immunity from vaccination. Uncertainty about the duration of protective immunity afforded by natural infection is not by itself a valid argument for vaccinating previously infected individuals. This study provides direct evidence that vaccination with the best available vaccines does not provide additional protection in previously infected individuals.

A prior study concluded that natural infection cannot be relied on to protect against COVID-19 [9]. That study was based on comparison of PCR-positivity rates during a second COVID-19 surge in Denmark between those who tested positive and negative during the first COVID-19 surge, and indirectly calculated that prior infection provided 80.5% protection against repeat infection, and that protection against those older than 65 years was only 47.1%. The study did not compare vaccinated and unvaccinated people, and it is therefore an assumption to consider that a vaccine would have provided better protection in that particular population. Furthermore, there was a gap of only seven weeks between the end of the first surge and the beginning of the second in that study. It is now well-known that a small number of people can continue to have positive PCR test results for several weeks to a few months after infection, one study finding that 5.3% remained positive at 90 days [15]. It is possible that some of the positives picked up in the early part of the second surge were not necessarily new infections but residual

virus from the tail end of the first surge. Since the actual number of infections was small, a few such misclassifications could change the rates substantially. Our study examined rates of SARS-CoV-2 infection in vaccinated and unvaccinated individuals and showed that those previously infected who did not receive the vaccine did not have higher rates of SARS-CoV-2 infection than those previously infected who did, thereby providing direct evidence that vaccination does not add protection to those who were previously infected.

There are several strengths to our study. Its large sample size and follow-up of up to 5 months provide us with an ample degree of confidence in its findings. A major strength of our study is that we adjusted the analyses for the phase of the epidemic at all time points. The risk of acquisition of infection is strongly influenced by the phase of the epidemic at any given time, and it is important to adjust for this for accurate risk analyses. Given that this was a study among employees of a health system, and that the health system had policies and procedures in recognition of the critical importance of keeping track of the pandemic among its employees, we had an accurate accounting of who had COVID-19, when they were diagnosed with COVID-19, who received a COVID-19 vaccine, and when they received it.

The study has its limitations. Because we did not have a policy of asymptomatic employee screening, previously infected subjects who remained asymptomatic might have been misclassified as previously uninfected. Given this limitation, one should be cautious about drawing conclusions about the protective effect of prior asymptomatic SARS-CoV-2 infection. It should be noted though, that 12% of the subjects classified as previously infected did not have a symptom onset date recorded, suggesting that at least some of those classified as previously infected might have been asymptomatic infections. It is reassuring that none of these possibly asymptotically infected individuals developed COVID-19 during the duration of the study. The study follow-up duration was short, being only five months, but this was longer than published mRNA vaccine efficacy studies [1,2], and longer than the follow-up duration of the largest published vaccine effectiveness studies to date [3,4]. Median freedom from reinfection (time from initial infection until end of follow-up) in this study, for those previously infected, of almost 10 months, is consistent with findings in an earlier study that immunoglobulin G (IgG) to the spike protein remained

stable over more than six months after an episode of infection [16]. Our study included no children and few elderly subjects, and the majority would not have been immunosuppressed. Data governance policies in our institution precluded us from obtaining detailed clinical information on employees. While one cannot generalize this study's findings to assume that prior infection would provide adequate immunity in these groups, there is also no reason to expect a vaccine to provide additional protection in these same groups. Lastly, it is necessary to emphasize that these findings are based on the prevailing assortment of virus variants in the community during the study. It is not known how well these results will hold if or when some of the newer variants of concern become prominent. However, if prior infection does not afford protection against some of the newer variants of concern, there is little reason to suppose that the currently available vaccines would either. Vaccine breakthrough infections with variants have indeed been reported [17].

Our study's findings have important implications. Worldwide, COVID-19 vaccines are still in short supply. As of March 9, 2021, dozens of countries had not been able to administer a single dose of the vaccine [18]. As of May 17, 2021, only 17 countries had been able to reach ten percent or more of their populations with at least the first dose of vaccine [19]. Given such a scarcity of the vaccine, and the knowledge that vaccine does not provide additional protection to those previously infected, it would make most sense to limit vaccine administration to those who have not previously had the infection. In addition to profession, age, and comorbid conditions, previous infection should be an important consideration in deciding whom to prioritize to receive the vaccine. A practical and useful message would be to consider symptomatic COVID-19 to be as good as having received a vaccine, and that people who have had COVID-19 confirmed by a reliable laboratory test do not need the vaccine.

In conclusion, individuals who have laboratory-confirmed symptomatic SARS-CoV-2 infection are unlikely to benefit from COVID-19 vaccination, and vaccines can be safely prioritized to those who have not been infected before.

TRANSPARENCY DECLARATION

Conflict of Interest

Selection of “no competing interests” reflects that all authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Funding

None received.

Author contributions

NKS: Conceptualization, Methodology, Validation, Investigation, Data curation, Software, Formal analysis, Visualization, Writing- Original draft preparation, Writing- Reviewing and Editing, Supervision, Project administration.

ASN: Methodology, Formal analysis, Visualization, Validation, Writing- Reviewing and Editing.

PCB: Resources, Investigation, Validation, Writing- Reviewing and Editing.

PT: Resources, Writing- Reviewing and Editing.

SMG: Project administration, Resources, Writing- Reviewing and Editing.

REFERENCES

1. 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.
2. 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.
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. Haas EJ, Angulo FJ, McLaughlin JM, et al. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. *Lancet* **2021**;397:1819–29.
5. Beyrer C, Allotey P, Amon JJ, et al. Human rights and fair access to COVID-19 vaccines: the International AIDS Society–Lancet Commission on Health and Human Rights. *Lancet* **2021**;397:1524–7.
6. Sheehan MM, Reddy AJ, Rothberg MB. Reinfection Rates Among Patients Who Previously Tested Positive for Coronavirus Disease 2019: A Retrospective Cohort Study. *Clin Infect Dis* **2021**. Available from: <https://doi.org/10.1093/cid/ciab234>. Accessed May 5, 2021.
7. Pilz S, Chakeri A, Ioannidis JP, et al. SARS-CoV-2 re-infection risk in Austria. *Eur J Clin Invest* **2021**;51:e13520.
8. Lumley SF, O'Donnell D, Stoesser NE, et al. Antibody Status and Incidence of SARS-CoV-2 Infection in Health Care Workers. *N Engl J Med* **2021**;384:533–40.
9. Hansen CH, Michlmayr D, Gubbels SM, Mølbak K, Ethelberg S. Assessment of protection against reinfection with SARS-CoV-2 among 4 million PCR-tested individuals in Denmark in 2020: a population-level observational study. *Lancet* **2021**;397:1204–12.
10. Centers for Disease Control and Prevention. Frequently Asked Questions about COVID-19

- Vaccination. **2021**; Available from: <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/faq.html>. Accessed April 26, 2021.
11. Simon R, Makuch RW. A non-parametric graphical representation of the relationship between survival and the occurrence of an event: Application to responder versus non-responder bias. *Stat Med* **1984**;3:35–44.
12. Therneau TM, Crowson C, Atkinson E. Using Time Dependent Covariates and Time Dependent Coefficients in the Cox Model. Available from: <https://cran.r-project.org/web/packages/survival/vignettes/timedep.pdf>. Accessed May 8, 2021.
13. Therneau TM, Grambsch PM. *Modeling Survival Data: Extending the Cox Model*. New York, NY: Springer International Publishing; 2000.
14. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2021.
15. Vibholm LK, Nielsen SSF, Pahus MH, et al. SARS-CoV-2 persistence is associated with antigen-specific CD8 T-cell responses. *EBioMedicine* **2021**;64:103230.
16. Dan JM, Mateus J, Kato Y, et al. Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. *Science* **2021**;371:eabf4063. <https://doi.org/10.1126/science.abf4063>.
17. Hacisuleyman E, Hale C, Saito Y, et al. Vaccine Breakthrough Infections with SARS-CoV-2 Variants. *N Engl J Med* **2021**; <https://doi.org/10.1056/NEJMoa2105000>.
18. The Lancet. Access to COVID-19 vaccines: looking beyond COVAX. *Lancet* **2021**;397:941.
19. Mathieu E, Ritchie H, Ortiz-Ospina E, et al. A global database of COVID-19 vaccinations. *Nat Hum Behav* **2021**; <https://doi.org/10.1038/s41562-021-01122-8>.

TABLES

Table 1. Study Subject Characteristics

Characteristic	Previously Infected (N = 2579)	Not Previously Infected (N = 49659)	P Value
Age, y, mean ± SD	39±13	42±13	<0.001
Patient-facing job	1676 (65)	25504 (51)	<0.001
Job location			<0.001
Cleveland Clinic Main Campus	1011 (39)	19595 (40)	
Regional hospitals	1096 (43)	16433 (33)	
Ambulatory centers	313 (12)	7767 (16)	
Administrative centers	138 (5)	4424 (9)	
Remote location	21 (<1)	1440 (3)	
Job category			<0.001
Professional staff	89 (4)	3775 (8)	
Residents and fellows	72 (3)	1669 (3)	
Advanced practice practitioners	154 (6)	2806 (6)	
Nursing	1142 (44)	13623 (27)	
Pharmacy	44 (2)	1274 (3)	
Research	328 (13)	6776 (14)	
Clinical support	111 (4)	3500 (7)	
Administration	614 (24)	15050(30)	
Administration support	25 (1)	1186 (2)	

Data are presented as no. (%) unless otherwise indicated

FIGURES

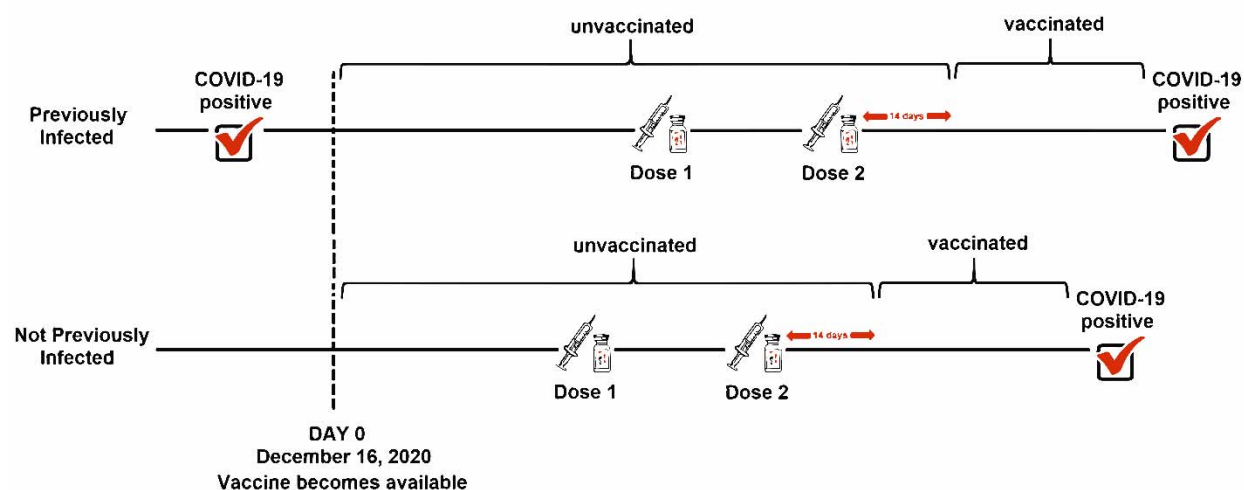


Figure 1. Explanation of “previously infected” analyzed as a time-independent covariate and “vaccinated” treated as a time-dependent covariate.

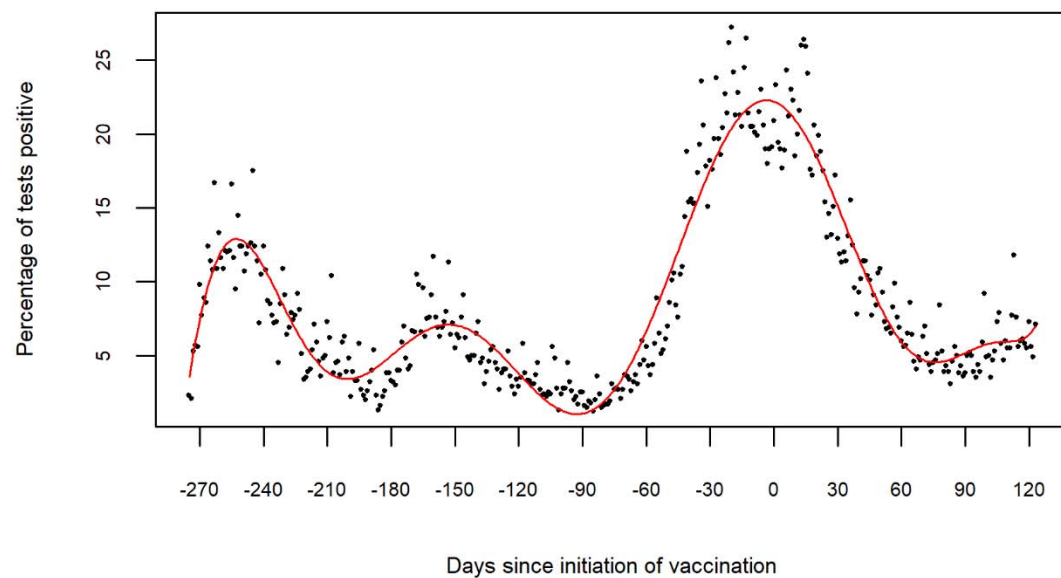


Figure 2. COVID-19 epidemic curve before and after vaccine rollout. Points on the scatter plot represent the proportion of all COVID-19 PCR tests done at Cleveland Clinic that were positive on any given day. The colored line represents a fitted polynomial curve.

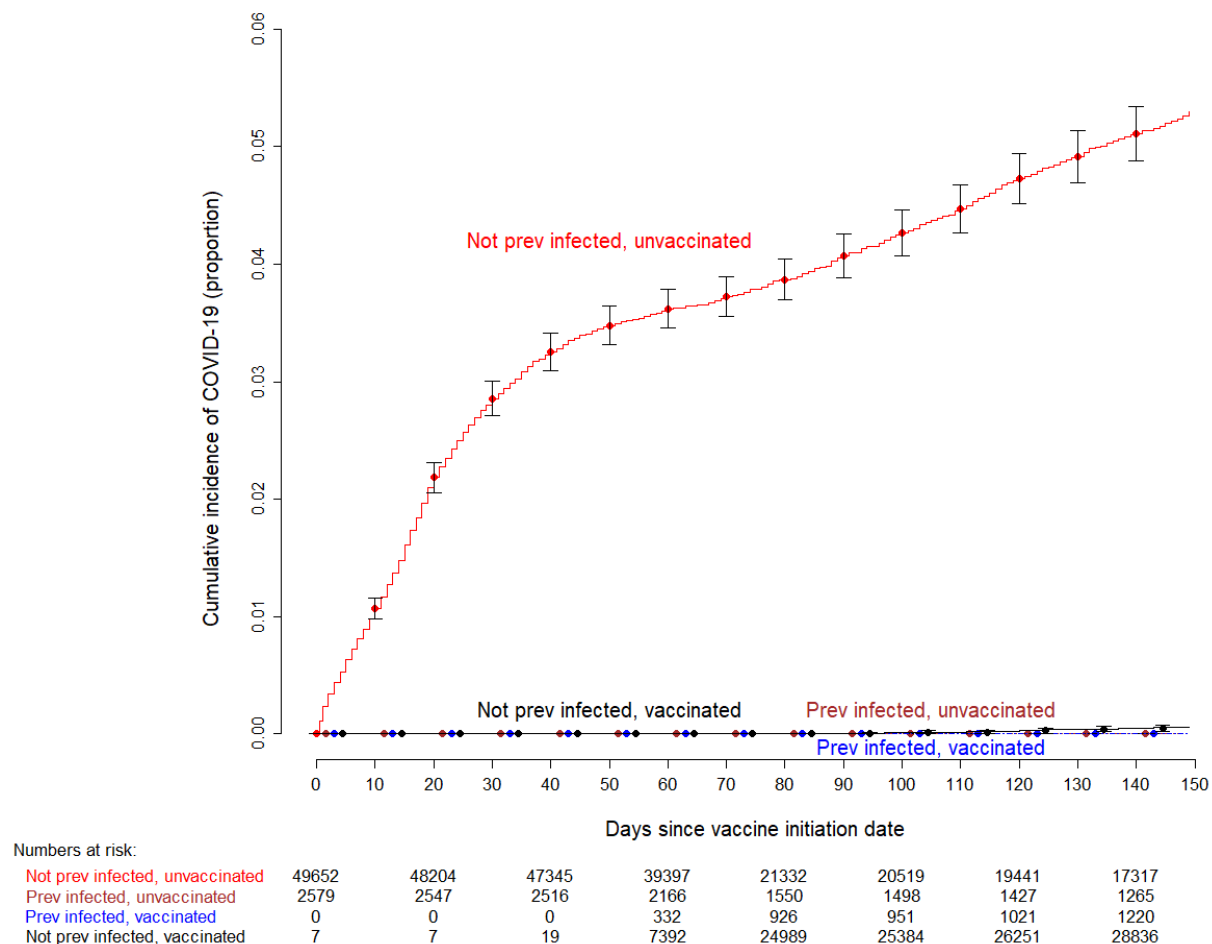


Figure 3. Simon-Makuch plot showing the cumulative incidence of COVID-19 among subjects previously infected and not previously infected with COVID-19, who did and did not receive the vaccine. Curves for the unvaccinated are based on data for those who did not receive the vaccine during the duration of the study, and for those waiting to receive the vaccine. Day zero was Dec 16, 2020, the day vaccination was started in our institution. Error bars represent 95% confidence intervals. Seven subjects who had been vaccinated earlier as participants in clinical trials were considered vaccinated throughout the duration of the study. Twelve subjects who received their first dose in the first week of the vaccination campaign managed to get their second dose three weeks later, and were thus considered vaccinated earlier than 42 days since the start of the vaccination campaign.