Necessity of COVID-19 Vaccination in Persons Who Have Already Had COVID-19

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Summary: Individuals previously infected with COVID-19 are substantially protected against COVID-19 for several months in the absence of vaccination. Beyond that time, vaccination protects against symptomatic COVID-19 among those previously infected, probably by boosting of waning natural immunity.

ABSTRACT

Background. The purpose of this study was to evaluate the necessity of COVID-19 vaccination in persons with prior COVID-19.

Methods. Employees of Cleveland Clinic working in Ohio on Dec 16, 2020, the day COVID-19 vaccination was started, were included. Anyone who tested positive for COVID-19 at least once before the study start date was considered previously infected. One was considered vaccinated 14 days after receiving the second dose of a COVID-19 mRNA vaccine. The cumulative incidence of COVID-19, symptomatic COVID-19, and hospitalizations for COVID-19, were examined over the next year.

Results. Among 52238 employees, 4718 (9%) were previously infected, and 36922 (71%) were vaccinated by the study's end. Cumulative incidence of COVID-19 was substantially higher throughout for those previously uninfected who remained unvaccinated than for all other groups, lower for the vaccinated than unvaccinated, and lower for those previously infected than those not. Incidence of COVID-19 increased dramatically in all groups after the Omicron variant emerged. In multivariable Cox proportional hazards regression, both prior COVID-19 and vaccination were independently associated with significantly lower risk of COVID-19. Among previously infected subjects, a lower risk of COVID-19 overall was not demonstrated, but vaccination was associated with a significantly lower risk of symptomatic COVID-19 in both the pre-Omicron (HR 0.60, 95% CI 0.40–0.90) and Omicron (HR 0.36, 95% CI 0.23–0.57) phases.

Conclusions. Both previous infection and vaccination provide substantial protection against COVID-19. Vaccination of previously infected individuals does not provide additional protection against COVID-19 for several months, but after that provides significant protection at least against symptomatic COVID-19.

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

INTRODUCTION

We previously reported that individuals who previously had coronavirus disease of 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome (SARS)-associated Coronavirus-2 (SARS-CoV-2), had a very low cumulative incidence of COVID-19 over 5.5 months of follow up, regardless of whether or not they were vaccinated, thereby concluding that previously infected individuals are unlikely to benefit from vaccination against COVID-19 during this time period [1]. Since then, a new variant, the Delta variant spread worldwide, and more recently a newer one, the Omicron variant has taken over as the predominant variant in many parts of the world. Questions have been raised about whether prior COVID-19 continues to protect against reinfection over a longer duration than was examined earlier, and whether prior infection provides adequate protection against newer variants. It was also important to correct an unnecessarily restrictive definition of prior infection in our previous study, which misclassified persons infected in the recent past as previously uninfected.

The purpose of this study was to re-examine whether individuals with prior COVID-19 benefit from getting vaccinated, with a longer follow-up period, and during the Delta and Omicron phases of the pandemic.

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 as exempt research (IRB no. 21-985). A waiver of informed consent and waiver of HIPAA authorization were approved to allow access to de-identified health information by the research team.

Setting

PCR testing for SARS-CoV-2 at Cleveland Clinic began on March 12, 2020, and a streamlined process for testing of health care personnel was begun shortly thereafter. All employees who tested positive were interviewed, and symptoms monitored remotely by Occupational Health for non-hospitalized employees. Voluntary vaccination for COVID-19 began on December 16, 2020. Almost all employees received an mRNA vaccine, either the Pfizer-BioNTech vaccine or the Moderna vaccine, with the second dose scheduled 28 days after the first, regardless of which vaccine was given. Documentation of COVID-19 vaccination and all SARS-CoV-2 tests in the Occupational Health database, made the employee cohort a suitable one to examine the protective effect of vaccination and prior COVID-19 against future infection.

Participants

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

Variables

COVID-19 was defined as a positive nucleic acid amplification test (NAAT) for the SARS-CoV-2 virus, with the date of the first positive test for that episode of illness considered the date of infection. A person was considered "vaccinated" 14 days after receipt of the second dose of the vaccine. A person who tested positive for SARS-CoV-2 any time before the study start date (December 16, 2020, the date vaccination was begun at Cleveland Clinic), was considered to have had prior COVID-19 (or had been previously infected). Other covariates collected were age, aggregated job title (to maintain anonymity for rare job titles), and job location. Job type categorization into patient-facing or non-patient facing was done, and subjects assigned to one or the other based on aggregated job title and job location. Protected health information identifiers were not included in the extracted data, and institutional data governance rules related to employee data limited our ability to supplement our dataset with additional clinical variables.

Outcome

The primary study outcome was time to COVID-19, defined as a positive NAAT for SARS-CoV-2 on or after December 16, 2020. Events were followed until December 27, 2021. Time to COVID-19 was the number of days from December 16, 2020 to a subsequent positive SARS-CoV-2 test. For those previously infected, positive tests within 90 days of the first positive test were considered part of the initial episode of illness [2]. The health system never had a requirement for systematic asymptomatic employee test screening. Most of the positive tests, therefore, were tests done to evaluate suspicious symptoms or, since June 21, 2021, quarantine and return-to-work testing of employees exposed to COVID-19, to remain in compliance with the Occupational Safety and Health Administration (OSHA) Healthcare Emergency Temporary Standard (final rule June 21, 2021). A small proportion would have been tests done for pre-operative or pre-procedural screening.

Secondary outcomes were time to symptomatic COVID-19 and time to COVID-19 that required hospitalization. Documentation of at least one symptom by Occupational Health during remote home monitoring, from among fever (>100.4 F), cough, shortness of breath, worsening appetite, vomiting, diarrhea, weakness, or a peripheral oxygen saturation (SpO2) < 95%, within 7 days of a positive SARS-CoV-2 NAAT, was considered symptomatic COVID-19. Time to symptomatic COVID-19 was defined as number of days from Dec 16, 2020 to the first positive SARS-CoV-2 NAAT of an episode of symptomatic COVID-19. Hospitalization within 3 days before or 14 days after any positive SARS-CoV-2 NAAT, and associated occurrence of at least one symptom of COVID-19, was considered hospitalization for COVID-19. Time to COVID-19 that required hospitalization was defined as number of days from December 16, 2020 to the first positive SARS-CoV-2 NAAT of an episode of COVID-19 that required hospitalization.

Statistical analysis

A Simon-Makuch hazard plot [3] was created to compare the cumulative incidence of COVID-19 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. Vaccination was treated as a time-dependent covariate whose value changed from "unvaccinated" to "vaccinated" 14 days after receipt of a second dose of either the Pfizer or Moderna vaccine (Figure 1). Those who received the Johnson & Johnson vaccine (344 subjects) or the Novavax vaccine (1 subject) without having had COVID-19 were censored on the date they received the vaccine, and those whose employment was terminated during the study period before they had COVID-19 (7368 subjects) were censored on the date of termination of employment. Curves for the unvaccinated were based on data for those who remained unvaccinated, and until the date the vaccination status changed from "unvaccinated" to "vaccinated" for those who received the vaccine. Curves for the vaccinated were based on their data from the date their vaccination status changed to "vaccinated", until the study end date.

Simon-Makuch hazard plots were similarly constructed for time to symptomatic COVID-19 and time to hospitalization for COVID-19.

Multivariable Cox proportional hazards regression models were fitted to examine associations of various variables with time to COVID-19, time to symptomatic COVID-19, and time to COVID-19 that required hospitalization. Time-dependent covariates were used for covariates whose values changed with time and time-dependent coefficients used for covariates whose effects changed with time. Prior COVID-19, vaccination (as a time-dependent covariate whose value changed 14 days after receipt of the second dose of vaccine), age, gender, and job type, were included as explanatory variables. An interaction term for prior COVID-19 and vaccination was included as a covariate. Time-dependent coefficients were used for prior COVID-19 and vaccination, cut off by the date on which the Omicron variant was first detected in the USA, to separate their effects in the pre-Omicron and Omicron phases of the pandemic [4,5].

The effect of time since prior infection on risk of COVID-19 and symptomatic COVID-19, was explored in the subset of previously infected subjects, using multivariable Cox proportional hazards regression, with vaccination analyzed as a time-dependent covariate whose value changed 14 days after receipt of the second dose of vaccine, and time-dependent coefficients used for vaccination, to account for the pre-Omicron and Omicron phases of the pandemic. Age and job type were included as covariates.

The analysis was performed by NKS and ASN using the *survival* and *rms* packages and R version 4.1.2 [4–7].

RESULTS

Of 52238 employees included in the study, 4718 (9%) had prior COVID-19, and 36922 (71%) were vaccinated by the end of the study. A total of 7851 (15%) employees acquired COVID-19 during the study, of which 4675 (60%) were symptomatic infections and 133 (1.7%) required hospitalization for COVID-19.

Baseline characteristics

Table 1 shows the characteristics of subjects grouped by whether or not they had prior COVID-19. For those previously infected the median duration since prior infection at the start of the study was 33 days (IQR 16-120 days). A significantly lower proportion of those previously infected (63%, 3002 subjects) were vaccinated by the end of the study compared to those not previously infected (71%, 33920 subjects, $p<0.001$).

Table 2 shows the characteristics of subjects grouped by whether or not they were vaccinated by the end of the study. For those vaccinated, the median time to being vaccinated was 71 days from the study start date.

The epidemic in Ohio was at the peak of its third wave when the study started, another wave (the Delta wave) peaked around 9 months later, and another wave (the Omicron wave) occurred about a year into the study (Figure 2).

Cumulative incidence of COVID-19

Of the 7851 COVID-19 infections during the study period, 4936 (63%) occurred in the 11 months before, and 2915 (37%) in the one month after, the Omicron variant was first detected in the USA.

Figure 3 shows that the cumulative incidence of COVID-19 was highest for those without prior COVID-19 who remained unvaccinated, and was substantially lower for all others. Among those previously infected, until the emergence of the Omicron variant, the cumulative incidence of COVID-19 was not significantly different between those vaccinated and unvaccinated, even at almost a year of follow-up. Among those not previously infected, the cumulative incidence of COVID-19 remained negligible for those vaccinated up to 8 months into the study (by which time it was 5 months since being fully vaccinated for the majority of such subjects), following which there was a steady increase in infections. The incidence of COVID-19 increased dramatically with the Omicron variant's emergence, regardless of whether subjects were previously infected or not, and vaccinated or not.

Figure 4 shows the cumulative incidence of symptomatic COVID-19 across the various groups, and figure 5 shows the cumulative incidence of COVID-19 that required hospitalization. Findings for both are similar to that of COVID-19 infection overall, in that the group at highest risk was previously uninfected subjects who remained unvaccinated. Eighty-eight (2.9%) of the 4585 symptomatic

COVID-19 infections, and two of the 133 hospitalizations for COVID-19 (1.5%) occurred among those with prior COVID-19.

Association of prior COVID-19 and vaccination with occurrence of COVID-19

In a Cox proportional hazards regression model, both prior COVID-19 and vaccination were independently associated with significantly lower risk of COVID-19, in both the pre-Omicron and Omicron phases. Unadjusted and adjusted associations with time to COVID-19 are shown in table 3. Among those without prior COVID-19, vaccination was associated with significantly lower risk of COVID-19 in both the pre-Omicron (HR 0.26, 95% C.I. 0.24-0.28) and the Omicron (HR 0.48, 95% C.I. 0.44-0.53) phases. However, among those with prior COVID-19, vaccination was not associated with significantly lower risk of COVID-19 in either the pre-Omicron (HR 0.78, 95% C.I. 0.31-1.96) or the Omicron phase (HR 0.77, 95% C.I. 0.53-1.12).

Unadjusted and adjusted associations with time to symptomatic COVID-19 in a Cox proportional hazards regression model are shown in table 4. Among those without prior COVID-19, vaccination was associated with significantly lower risk of symptomatic COVID-19 in both the pre-Omicron (HR 0.24, 95% C.I. 0.22-0.26) and the Omicron (HR 0.22, 95% C.I. 0.20-0.24) phases. Similarly, among those with prior COVID-19, vaccination was associated with significantly lower risk of symptomatic COVID-19 in both the pre-Omicron (HR 0.60, 95% C.I. 0.40-0.90) and the Omicron phase (HR 0.36, 95% C.I. 0.23-0.57).

Duration of protection provided by natural immunity

In a subset including only those with prior COVID-19, a significant risk with time since prior infection was not found for either COVID-19 (HR 1.003, 95% C.I. 0.9999-1.0052) or symptomatic COVID-19 (HR 1.002, 95% C.I. 0.9998-1.0037). Unadjusted and adjusted associations with time to COVID-19 and symptomatic COVID-19, in multivariable Cox proportional hazards regression models, are shown in supplementary tables 1 and 2.

Notably, most of the incident infections occurred near the tail end of the study when duration since prior infection was a year or longer for every previously infected person. Inability to find a significant association with days since prior infection in these models is probably because natural immunity provides protection for at least several months and the duration of follow-up was not long enough beyond such protection to detect an association. Based on figures 3, 4, and 5, duration of protection by natural immunity in the absence of vaccination appeared to be at least a year in the pre-Omicron period. Duration of protection by natural immunity in the Omicron period will need to be determined by future studies.

DISCUSSION

This study shows that prior to the Omicron variant's emergence, both previously infected individuals and those vaccinated were at much lower risk of getting COVID-19 than those without prior COVID-19 who remained unvaccinated. With the Omicron variant's emergence however, early findings suggest a substantial increase in risk of infection for all individuals, including those previously infected and those vaccinated.

Earlier observational studies found very low rates of reinfection over several months among survivors of COVID-19 [8–16]. A single study conducted by the CDC concluded that prior vaccination was more protective against future COVID-19 than was prior COVID-19 [17]. This finding has not been replicated elsewhere. Multiple observational studies in different continents found that both prior infection and vaccination provided similar levels of protection against subsequent COVID-19 [18–20]. A large nationwide study in Israel found that unvaccinated individuals with prior COVID-19 actually had significantly lower risks of COVID-19, symptomatic COVID-19, and hospitalization, than vaccinated individuals without prior COVID-19 [21], a finding also observed in our study. Observations in our own and others' clinical practices also concurred that while both reinfections in persons with prior COVID-19 and breakthrough infections in vaccine recipients occurred, the latter were far more common.

A single study conducted by the CDC concluded that vaccination protects against subsequent COVID-19 among persons with prior infection [22]. This case-control study was biased in that protection from subsequent COVID-19 could be easily explained by better adherence to masking and social distancing recommendations among those who chose to receive the vaccine, which was extremely likely in the population that was studied, rather than vaccination. Our earlier study failed to find a benefit of vaccination in previously individuals for up to 5.5 months of follow-up [1], and a study in a healthcare worker cohort in India also did not find evidence of additional protection with vaccination among 1449 individuals with prior COVID-19 over a 45-day period during a surge [23]. Immunity acquired from prior infection wanes with time, but data that quantified waning of natural immunity showed that during a surge of Delta variant infection in Israel, the risk of COVID-19 for those previously infected was similar 8-10 months after infection in the absence of vaccination as it was 0-2 months after vaccination among those not previously infected [24].

The strengths of our study include its large sample size, follow-up duration exceeding one year, and a follow-up period that included the Alpha, Delta, and Omicron variants surges. Study within a single healthcare system would have minimized bias from heterogeneity of masking patterns and other risk factors in cohorts gathered from multiple sites. Given the critical importance of keeping track of the pandemic among its employees, our healthcare system had procedures and policies in place to allow an accurate accounting of who had COVID-19 and when, and who received a COVID-19 vaccine and when. Additionally, the organization continued to emphasize the need to seek testing if suspicious symptoms occurred, even in those vaccinated, through intranet home page messages and organization-wide email reminders.

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, thereby underestimating the protective effect of prior infection. Similarly,

incident asymptomatic infections would have been missed due to lack of testing. Any difference in rates of testing across the comparison groups would likely be from comparatively less testing of vaccinated individuals, because of a sense of being protected by vaccination, thereby overestimating the protective effect of vaccination. Our healthcare employee cohort included no children and few elderly subjects, and only a small minority would have been immunocompromised. Data governance policies in our institution precluded us from obtaining detailed clinical information on employees. Prior infection in our previously infected individuals occurred before monoclonal antibody treatment was available. Administering monoclonal antibodies during COVID-19 might interfere with the mounting of a normal immunologic response. Given this possibility, it may not be wise to extrapolate this study's findings to persons who received monoclonal antibody treatment for their prior COVID-19 infection.

It is clear that the group at highest risk of contracting COVID-19 is still individuals who never had COVID-19 and remain unvaccinated. Categorizing the population as "vaccinated" and "unvaccinated" is a less accurate way of expressing risk of COVID-19 than classifying into "protected" (anyone who's either had COVID-19 or has been vaccinated) and "vulnerable" (anyone who has neither had COVID-19 nor been vaccinated). As it's become increasingly obvious that natural immunity from prior COVID-19 protects against reinfection, vaccine recommendations that do not factor in prior infection should be re-examined [25]. Until the Omicron variant emerged, there was no tenable evidence that previously infected individuals benefited substantially from a COVID-19 vaccine for up to 8-10 months. Given the increased risk of infection from the Omicron variant, a practical and useful message at this time would be that people need not be vaccinated immediately after contracting COVID-19, but would likely benefit from a vaccine 6 months or more later.

In conclusion, both previously infected individuals and those who've been vaccinated are substantially protected against COVID-19 infection, but protection from both natural and vaccine-induced immunity wanes with time and is inherently less potent against the Omicron variant. Vaccination does not provide additional protection against COVID-19 among previously infected individuals for several months, but after that, protects at least against symptomatic COVID-19. Previous infection should be factored into COVID-19 vaccination recommendations.

TRANSPARENCY DECLARATION

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Author contributions

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

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

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

PT: Resources, Writing- Reviewing and Editing.

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

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.

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TABLES

Table 1. Study Subject Characteristics Compared by Previously Infected Status

Characteristic	Previously Infected[1] (N = 4718)	Not Previously Infected (N = 47520)	*P* Value
Age, y, mean ± SD	39±13	42±13	<0.001
Gender			<0.001
Female	3694 (78)	31405 (66)	
Male	1024 (22)	10613 (22)	
Unknown[2]	0	5502 (12)	
Patient-facing job	2838 (60)	23152 (49)	<0.001
Job location			<0.001
Cleveland Clinic Main Campus	1724 (37)	18887 (40)	
Regional hospitals	2019 (43)	15515 (33)	
Ambulatory centers	615 (13)	7402 (16)	
Administrative centers	305 (7)	4304 (9)	
Remote location	55 (1)	1412 (3)	
Job category			<0.001
Professional staff	184 (4)	3671 (8)	
Residents and fellows	133 (3)	1607 (3)	
Advanced practice practitioners	287 (6)	2672 (6)	
Nursing	1951 (41)	12809 (27)	
Pharmacy	68 (1)	1248 (2)	
Research	42 (<1)	1169 (3)	
Clinical support	622 (13)	6481 (14)	
Administration	237 (5)	3388 (7)	
Administration support	1194 (25)	14475 (31)	

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

[1]Any person with at least one positive SARS-CoV2 nucleic acid amplification test prior to the study start date was considered previously infected

[2]The gender variable was not available in the Occupational Health dataset. This was obtained by queries to clinical databases without extracting identifiers. Those without entries in clinical databases were classified as having an unknown gender.

Table 2. Study Subject Characteristics Compared by Vaccine Receipt Status

Characteristic	Vaccinated[1] (N = 36922)	Not Vaccinated (N = 15316)	*P* Value
Age, y, mean ± SD	44±13	39±13	<0.001
Gender			<0.001
Female	24768 (67)	10678 (70)	
Male	8703 (24)	3072 (20)	
Unknown[2]	3451 (9)	1566 (10)	
Patient-facing job	18031 (49)	7959 (52)	<0.001
Job location			<0.001
Cleveland Clinic Main Campus	14911 (40)	5700 (37)	
Regional hospitals	11752 (32)	5782 (38)	
Ambulatory centers	5841 (16)	2176 (14)	
Administrative centers	3350 (9)	1259 (8)	
Remote location	1068 (3)	399 (3)	
Job category			<0.001
Professional staff	3463 (9)	392 (3)	
Residents and fellows	1259 (3)	481 (3)	
Advanced practice providers	2220 (6)	739 (5)	
Nursing	9767 (27)	4993 (33)	
Pharmacy	982 (3)	334 (2)	
Research	894 (2)	317 (2)	
Clinical support	4474 (12)	2629 (17)	
Administration	2908 (8)	717 (5)	
Administration support	10955 (30)	4714 (31)	

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

[1]A person was considered vaccinated 14 days after receipt of a second dose of a mRNA COVID-19 vaccine

[2]The gender variable was not available in the Occupational Health dataset. This was obtained by queries to clinical databases without extracting identifiers. Those without entries in clinical databases were classified as having an unknown gender.

Table 3. Unadjusted and Adjusted Associations with Time to COVID-19

Characteristic	Unadjusted HR (95% C.I.)	*P* Value	Adjusted HR (95% C.I.)[1]	*P* Value
Prior COVID-19				
Pre-Omicron phase	0.04 (0.03-0.07)	< 0.001	0.02 (0.01-0.04)	
Omicron phase	0.86 (0.75-0.98)	0.02	0.47 (0.37-0.59)	
Vaccination[2]				
Pre-Omicron phase	0.26 (0.24-0.28)	< 0.001	0.26 (0.24-0.28)	
Omicron phase	0.49 (0.45-0.53)	<0.001	0.48 (0.44-0.53)	
Age	0.98 (0.98-0.98)	< 0.001	0.98 (0.98-0.99)	<0.001
Male gender[3]	0.69 (0.65-0.73)	< 0.001	0.73 (0.69-0.77)	<0.001
Unknown gender[3]	0.002 (0.001-0.008)	< 0.001	0.002 (0.000-0.007)	< 0.001
Patient facing job[4]	1.17 (1.12-1.22)	< 0.001	1.09 (1.05-1.14)	< 0.001
Previously infected : vaccination interaction				
Pre-Omicron phase	-	-	3.01 (1.28 - 7.06)	0.01
Omicron phase	-	-	1.60 (1.21-2.13)	0.001
ASSOCIATIONS DERIVED FROM THE MODEL AFTER ADJUSTING FOR INTERACTIONS				
Pre-Omicron phase				
Vaccination for those without prior COVID-19	-	-	0.26 (0.24-0.28)	
Vaccination for those with prior COVID-19	-	-	0.78 (0.31-1.96)	
Omicron phase				

Vaccination for those without prior COVID-19	-	-	0.48 (0.44-0.53)
Vaccination for those with prior COVID-19	-	-	0.77 (0.53-1.12)

[1]From a multivariable Cox-proportional hazards regression model with vaccination treated as a time-dependent covariate, and using time-dependent coefficients, cut by the date of first detection of the Omicron variant in the USA, for vaccination and prior COVID-19 infection.

[2]Time-dependent covariate

[3]Reference is female gender

[4]Reference is non-patient facing job

Table 4. Unadjusted and Adjusted Associations with Time to Symptomatic COVID-19

Characteristic	Unadjusted HR (95% C.I.)	*P* Value	Adjusted HR (95% C.I.)[1]	*P* Value
Prior COVID-19				
Pre-Omicron phase	0.22 (0.19-0.26)	<0.001	0.13 (0.10-0.16)	<0.001
Omicron phase	0.68 (0.57-0.81)	<0.001	0.39 (0.31-0.48)	<0.001
Vaccination[2]				
Pre-Omicron phase	0.25 (0.23-0.26)	<0.001	0.24 (0.22-0.26)	<0.001
Omicron phase	0.23 (0.21-0.25)	<0.001	0.22 (0.20-0.24)	<0.001
Age	0.98 (0.98-0.99)	< 0.001	0.99 (0.99-0.99)	<0.001
Male gender[3]	0.65 (0.61-0.69)	< 0.001	0.71 (0.67-0.75)	<0.001
Unknown gender[3]	0.002 (0.000-0.008)	< 0.001	0.002 (0.000-0.007)	< 0.001
Patient facing job[4]	1.12 (1.07-1.17)	< 0.001	1.11 (1.06-1.16)	< 0.001
Previously infected : vaccination interaction	-	-		
Pre-Omicron phase			2.51 (1.78-3.53)	<0.001
Omicron phase			1.63 (1.13-2.33)	<0.001
ASSOCIATIONS DERIVED FROM THE MODEL AFTER ADJUSTING FOR INTERACTIONS				
Pre-Omicron phase				
Vaccination for those without prior COVID-19	-	-	0.25 (0.22-0.26)	
Vaccination for those with prior COVID-19	-	-	0.60 (0.40-0.90)	
Omicron phase				
Vaccination for those without prior COVID-19	-	-	0.22 (0.20-0.24)	

Vaccination for those with prior COVID-19	-	-	0.36 (0.23-0.57)

[1]From a multivariable Cox-proportional hazards regression model with vaccination treated as a time-dependent covariate, and using time-dependent coefficients, cut by the date of first detection of the Omicron variant in the USA, for vaccination and prior COVID-19 infection.

[2]Time-dependent covariate

[3]Reference is female gender

[4]Reference is non-patient facing job

FIGURE LEGENDS

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 the study start date. 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 wavy line represents a fitted polynomial curve.

Figure 3. Simon-Makuch plot showing the cumulative incidence of COVID-19 among subjects with and without prior COVID-19, who did and did not receive the vaccine. Day zero was Dec 16, 2020, the day vaccination became available at our institution. Shaded areas represent 95% confidence bands. A few subjects who had received two doses of the vaccine before the study start date were presumed to have been vaccinated earlier as participants in clinical trials. A few subjects, who received their first dose in the first week of the vaccination campaign received their second dose three weeks later, and were thus considered vaccinated earlier than 42 days. The pandemic phases are identified according to which variant accounted for more than 50% of the strains in HHS region 5 (comprising of Illinois, Indiana, Michigan, Minnesota, Ohio, and Wisconsin) on weekly genomic surveillance conducted by the CDC (https://covid.cdc.gov/covid-data-tracker/#variant-proportions).

Figure 4. Simon-Makuch plot showing the cumulative incidence of symptomatic COVID-19 among subjects with and without prior COVID-19, who did and did not receive the vaccine. Day zero was Dec 16, 2020, the day vaccination became available at our institution. Shaded areas represent 95% confidence bands. A few subjects who had received two doses of the vaccine before the study start date were presumed to have been vaccinated earlier as participants in clinical trials. A few subjects, who received their first dose in the first week of the vaccination campaign received their second dose three weeks later, and were thus considered vaccinated earlier than 42 days. The pandemic phases are identified according to which variant accounted for more than 50% of the strains in HHS region 5 (comprising of Illinois, Indiana, Michigan, Minnesota, Ohio, and Wisconsin) on weekly genomic surveillance conducted by the CDC (https://covid.cdc.gov/covid-data-tracker/#variant-proportions).

Figure 5. Simon-Makuch plot showing the cumulative incidence of COVID-19 requiring hospitalization among subjects with and without prior COVID-19, who did and did not receive the vaccine. Day zero was Dec 16, 2020, the day vaccination became available at our institution. Shaded areas represent 95% confidence bands. A few subjects who had received two doses of the vaccine before the study start date were presumed to have been vaccinated earlier as participants in clinical trials. A few subjects, who received their first dose in the first week of the vaccination campaign received their second dose three weeks later, and were thus considered vaccinated earlier than 42 days. The pandemic phases are identified according to which variant accounted for more than 50% of the strains in HHS region 5 (comprising of Illinois, Indiana, Michigan, Minnesota, Ohio, and Wisconsin) on weekly genomic surveillance conducted by the CDC (https://covid.cdc.gov/covid-data-tracker/#variant-proportions).

Figure 1

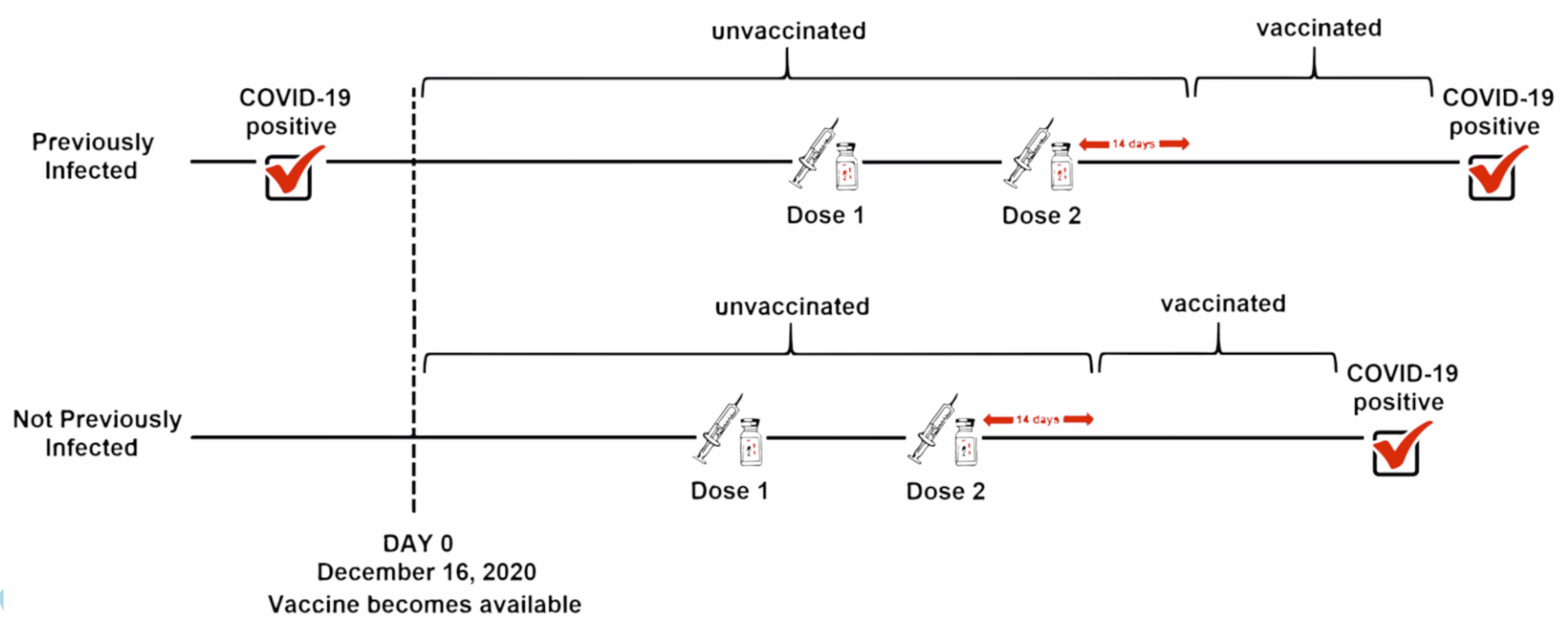

Figure 2

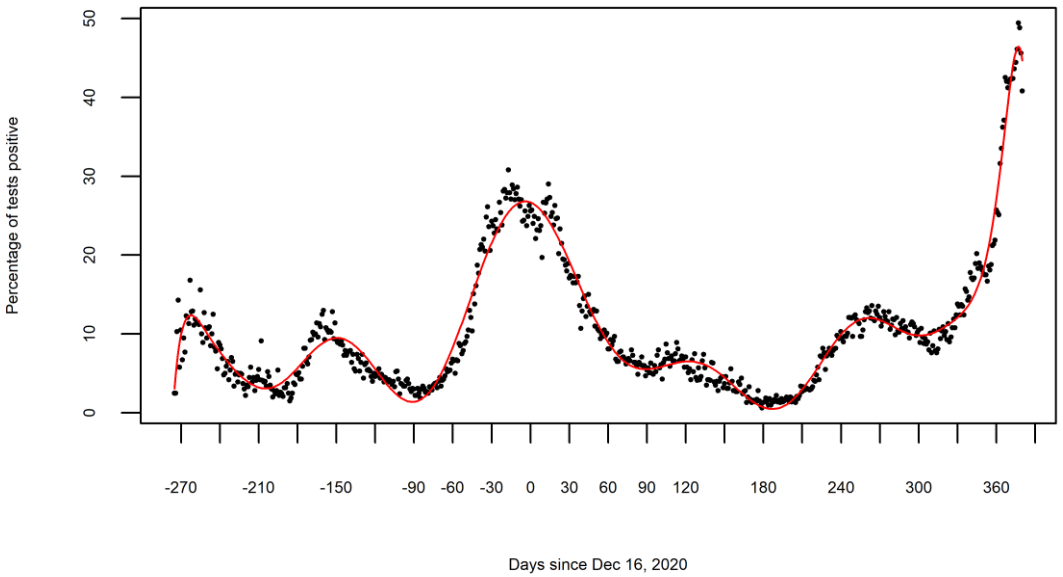

Figure 3