Coronavirus Disease 2019 (COVID-19) Vaccine Boosting in Previously Infected or Vaccinated Individuals

Nabin K. Shrestha,[1] Priyanka Shrestha,[2] Patrick C. Burke,[3] Amy S. Nowacki,[4] Paul Terpeluk,[5] Steven M. Gordon[1]

[1]Department of Infectious Diseases, Cleveland Clinic, Cleveland, Ohio, USA; [2]Department of Computer Science, Stanford University, Palo Alto, California, USA; [3]Department of Infection Prevention, Cleveland Clinic, Cleveland, Ohio, USA; [4]Department of Quantitative Health Sciences, Cleveland Clinic, Cleveland, Ohio, USA; and [5]Department of Occupational Health, Cleveland Clinic, Cleveland, Ohio, USA.

Correspondence: N. K. Shrestha, 9500 Euclid Avenue / G-21, Cleveland, OH 44195, USA (shrestn@ccf.org)

Running Title: COVID-19 vaccine booster effectiveness

ABSTRACT

Background. The purpose of this study was to evaluate whether boosting previously infected or vaccinated healthcare personnel with a vaccine developed for an earlier variant of SARS-CoV-2 protects against the Omicron variant.

Methods. Employees of Cleveland Clinic previously infected with or vaccinated against COVID-19, and working in Ohio the day the Omicron variant was declared a variant of concern, were included. The cumulative incidence of COVID-19 was examined over two months during an Omicron variant surge. Protection provided by boosting (analyzed as a time-dependent covariate) was evaluated using Cox proportional hazards regression. Analyses were adjusted for time since proximate SARS-CoV-2 exposure as a time-dependent covariate.

Results. Among 39 766 employees, 8037 (20%) previously infected and the remaining previously vaccinated, COVID-19 occurred in 6230 (16%) during the study. Risk of COVID-19 increased with time since proximate SARS-CoV-2 exposure, and boosting protected those >6 months since prior infection or vaccination. In multivariable analysis, boosting was independently associated with lower risk of COVID-19 among those vaccinated but not previously infected (HR, .43; 95% CI, .41-.46) as well as those previously infected (HR, .66; 95% CI, .58-.76). Among those previously infected, receiving 2 compared to 1 dose of vaccine was associated with higher risk of COVID-19 (HR, 1.54; 95% CI, 1.21-1.97).

Conclusions. Administering a COVID-19 vaccine not designed for the Omicron variant, >6 months after prior infection or vaccination, protects against Omicron variant infection in those previously infected or vaccinated. There is no evidence of an advantage to administering more than 1 dose of vaccine to previously infected persons.

Keywords: SARS-CoV-2; COVID-19; incidence; vaccines; immunity;

INTRODUCTION

By the time the Delta variant of severe acute respiratory syndrome-associated coronavirus 2 (SARS-CoV-2) became the predominant strain in the United States, it was already several months after the majority of early vaccine recipients had received their vaccines. A small proportion of vaccinated individuals experienced breakthrough infections, and vaccine boosters began to be administered in some resource-rich countries, with an expectation that waning vaccine-induced immunity might be boosted by an additional dose of vaccine. Nationwide studies from Israel showed that a booster dose did indeed provide significant protection against coronavirus disease 2019 (COVID-19) [1–3].

The Omicron variant was first reported in South Africa in mid-November 2021, and was declared a variant of concern on 26 November 2021. This was more contagious than the Delta variant [4], was first detected in the United States on 1 December 2021, and became the predominant strain within 3 weeks. By this time it was known that this variant had a large number of mutations, including several on the spike protein itself [5,6], the target of COVID-19 vaccines, raising the possibility that vaccine effectiveness against the new variant might be seriously compromised. Corroborating this concern, a surprisingly large proportion of previously infected individuals experienced reinfections with the Omicron variant [7,8], and breakthrough infections in vaccinated individuals also became very common [9,10], including among those in our own practice who had received a vaccine booster. These observations raised questions about the utility of boosting with a vaccine not specifically designed for the new variant.

The purpose of this study was to evaluate whether boosting previously infected or vaccinated individuals with a vaccine developed for an earlier variant of SARS-CoV-2, protects against infection with the Omicron variant.

METHODS

Study design

This was a retrospective cohort study conducted at the Cleveland Clinic Health System (CCHS) in Ohio, United States. The study was approved by the Cleveland Clinic Institutional Review Board as exempt research (IRB no. 21-1163). 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

Beginning in March 2020, all employees at Cleveland Clinic with a positive SARS-CoV-2 test were interviewed and symptoms monitored remotely by Occupational Health while the employees were isolated at home. Voluntary vaccination for COVID-19 began on 16 December 2020. Most employees were vaccinated with two doses of an mRNA vaccine, either the Pfizer-BioNTech vaccine or the Moderna vaccine. Individuals began receiving booster vaccine of their own accord in August 2021, and the healthcare system officially began offering vaccine boosters on 5 October 2021. Antibody testing was not done within our health system.

Participants

CCHS employees in employment in Ohio on December 16, 2020, the day employee COVID-19 vaccination was started, were screened for inclusion in the study. Those previously infected or vaccinated, and who remained in employment as of 26 November 2021, the day the Omicron variant was declared a variant of concern, were included. An individual was considered previously infected 14 days after testing positive for SARS-CoV-2 by a nucleic acid amplification test (NAAT). If not previously infected, a person was considered vaccinated 14 days after receipt of the second dose of an mRNA vaccine. By only screening individuals who had been in employment since vaccination started almost a year prior to the study start date, we could ensure accurate prior vaccination data and be reasonably assured of not having missed a prior COVID-19 diagnosis, at least up to a year in the past.

Variables

A vaccine booster was defined as at least 1 dose of any COVID-19 vaccine at least 90 days following COVID-19 for those previously infected, or a third dose of a COVID-19 vaccine at least 90 days following the second dose of an mRNA COVID-19 vaccine for those vaccinated but not previously infected. Individuals were considered boosted 7 days after receipt of a qualifying vaccine booster. Covariates collected were age, aggregated job title (to maintain anonymity for rare job titles), job location, and job type categorization into patient-facing or non-patient facing, as described in an earlier study [11]. 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, the latter defined as a positive NAAT for SARS-CoV-2 any time after 26 November 2021, the study start date. The date of infection for any episode of COVID-19 was the date of the first positive test for that episode of illness. Subsequent positive tests within 90 days were considered part of the same episode of illness. The health system never had a requirement for systematic asymptomatic employee test screening. Most of the positive tests would have been tests done to evaluate suspicious symptoms or as part of quarantine and return-to-work testing of employees exposed to patients with COVID-19. A small proportion would have been tests done as part of pre-operative or pre-procedural screening.

Time to symptomatic COVID-19 and time to hospitalization for COVID-19 were planned as secondary outcomes. Unfortunately, employee health monitoring processes had to be stopped about 21 days after the study start date due to inability to keep up with a very large number of cases, preventing us from evaluating these secondary outcomes.

Statistical analysis

Boosting status of a study subject was treated as a time-dependent covariate whose value changed from "non-boosted" to "boosted" 7 days after receipt of a vaccine booster. Since risk of COVID-19 would be influenced by how recently an individual was exposed to the causative pathogen or its antigens, and since this could change on any day for any study subject, time (in days) since the proximate exposure to SARS-CoV-2 by infection or vaccination (hereinafter referred to as "proximate SARS-CoV-2 exposure"), was also treated as a time-dependent covariate.

A Simon-Makuch hazard plot [12] was created to compare the cumulative incidence of COVID-19 among subjects classified by type of prior SARS-CoV-2 exposure on the study start date (prior infection, or prior vaccination but no prior infection) and boosting status (boosted or non-boosted, as a time-dependent covariate). Employees who had not developed COVID-19 were censored at the end of the study follow-up period (28 January 2022). Those whose employment was terminated during the study period before they had COVID-19 (216 subjects) were censored on the date of termination of employment. Curves for the non-boosted were based on data for as long as the booster status remained "non-boosted". Curves for the boosted were based on data from the date the booster status changed to "boosted", until the study end date.

To evaluate the effect of time since proximate SARS-CoV-2 exposure on risk of COVID-19, Simon-Makuch hazard plots comparing the cumulative incidence of COVID-19 for groups stratified by time since proximate SARS-CoV-2 exposure were plotted separately for those previously infected and those vaccinated but not previously infected. Subjects were censored on the date they were terminated as in the primary analysis. Time since proximate SARS-CoV-2 exposure could change for any subject any day over the course of the study if they received a vaccine during the study, and subjects moved from one subgroup to another as they crossed the limits of the time group strata.

Among those previously infected, the effect of timing of vaccine administration, and the effect of number of doses of vaccine, on risk of COVID-19, were examined in separate Simon-Makuch hazard

plots. For the former, groupings were based on time since prior infection and boosting status as separate time-dependent covariates. For the latter, the number of vaccine doses was evaluated as a time-dependent covariate (as it could change for any subject on any day of the study).

Multivariable Cox proportional hazards regression models were fitted to examine associations of various variables with time to COVID-19, separately for those previously infected and those vaccinated but not previously infected. Where included, boosting, time since proximate SARS-CoV-2 exposure, time since prior infection, and number of vaccine doses were included as time-dependent covariates [13]. These models were also explored in subsets divided by time since prior infection (for those previously infected) and time since second vaccine dose (for those vaccinated but not previously infected).

The analysis was performed by N. K. S. and A. S. N. using the *survival* package and R version 4.1.2 (R Foundation for Statistical Computing) [13–15].

RESULTS

Of 39 766 employees included in the study, 8037 (20%) were previously infected and 31 729 (80%) vaccinated but not previously infected. By the end of the study, 26 176 (66%) were boosted. Altogether, 6230 employees (16%) acquired COVID-19 during the 9 weeks of the study.

Baseline characteristics

Table 1 shows the characteristics of subjects grouped by type of prior SARS-CoV-2 exposure at the start of the study. The median duration since prior SARS-CoV-2 exposure was, 331 days (IQR 228-363 days) for those previously infected, and 275 days (IQR 228-283 days) for those vaccinated but not previously infected.

Table 2 shows the characteristics of subjects grouped by their boosting status by the end of the study. For those boosted, the median time to being boosted was 16 days prior to the study start date (IQR -38 to 6 days).

Cumulative incidence of COVID-19 among boosted and non-boosted individuals who were either previously infected, or vaccinated but not previously infected

Figure 1 compares the cumulative incidence of COVID-19 stratified by type of prior SARS-CoV-2 exposure and vaccine boosting status. Among persons vaccinated but not previously infected, the cumulative incidence of COVID-19 was significantly lower for those boosted compared to those not boosted. However, among those previously infected, the cumulative incidence of COVID-19 did not differ between the boosted and the non-boosted in an unadjusted comparison.

Time since proximate SARS-CoV-2 exposure

Figure 2 shows the risk of COVID-19 stratified by time since proximate SARS-CoV-2 exposure, separately for those previously infected, and those vaccinated but not previously infected.

For those previously infected, the risk of COVID-19 was lowest for proximate SARS-CoV-2 exposure within the preceding 6 months. Proximate SARS-CoV-2 exposure between 6-9 months had a higher risk, and proximate SARS-CoV-2 exposure 9 months or longer in the past had an even higher risk.

For those vaccinated but not previously infected, the risk of COVID-19 was higher for proximate SARS-CoV-2 exposure 3-6 or 6-9 months previously compared to proximate SARS-CoV-2 exposure within the preceding 3 months, suggesting that protection against the Omicron variant from two doses of an mRNA vaccine wanes after 3 months. Surprisingly, proximate SARS-CoV-2 exposure 9-12 months previously had a lower risk of COVID-19 than proximate SARS-CoV-2 exposure 3-9 months previously, and a similar risk to proximate SARS-CoV-2 exposure within the preceding 3 months.

Timing of vaccine administration after COVID-19

Among previously infected persons who did not subsequently get vaccinated, the risk of COVID-19 was substantially higher for those infected at least 6 months previously than those infected within 6 months (Figure 3). Among those infected at least 6 months previously, those vaccinated (1 or more doses) after COVID-19 had lower risk of COVID-19 than those not. Among those previously infected within 6

months, risk of COVID-19 for those subsequently vaccinated did not differ significantly from those who remained unvaccinated. A single infection within the <6 months and vaccinated group would make the cumulative incidence of COVID-19 in that group the same as that of the <6 months and unvaccinated group (note the small at risk sample size). Notably, those previously infected within the preceding 6 months and subsequently unvaccinated still had a risk of COVID-19 that was significantly lower than that of those previously infected more than 6 months earlier and subsequently vaccinated.

Number of vaccine doses after COVID-19

Among previously infected individuals, those who received 1 dose of vaccine had a significantly lower risk of COVID-19 than those who received no vaccine, but those who received 2 doses had a higher risk of COVID-19 than those who received a single dose and a risk that was no lower than those who received no vaccine (Figure 4). Those who received 3 doses appeared to have a lower risk than those who received no vaccine, but a higher risk than those who received a single dose.

Effect of a vaccine booster on occurrence of COVID-19 in multivariable analyses

Boosting with a COVID-19 vaccine designed for an earlier variant was associated with significantly reduced risk of infection with the Omicron variant in multivariable Cox proportional hazards regression analyses, among people vaccinated but not previously infected (Table 3) or previously infected (Table 4), for whom it was more than 6 months past their prior infection or vaccination.

When the effect of number of vaccine doses in previously infected individuals was analyzed in multivariable analysis, there was no advantage to more than 1 dose of vaccine, and those who received 2 doses were at significantly higher risk of getting COVID-19 than those who received a single dose (Table 5), supporting the findings of the unadjusted comparison visually depicted in figure 4.

DISCUSSION

This study corroborates findings from earlier studies that natural immunity from prior infection is more robust than immunity acquired through vaccination [11,17,18], and additionally finds that

individuals previously infected with a pre-Omicron variant of SARS-CoV-2 retain substantial protection against the Omicron variant for at least 6 months in the absence of vaccination.

This study found that time since proximate SARS-CoV-2 exposure was an important risk factor for COVID-19 among both previously infected and previously vaccinated individuals. Individuals previously infected with a pre-Omicron variant enjoy some protection against the Omicron variant for up to 6 months, with subsequent waning of protection. Among those vaccinated but not previously infected, time since proximate SARS-CoV-2 exposure greater than 3 months was associated with a higher risk of COVID-19 than time since proximate SARS-CoV-2 exposure less than 3 months, suggesting waning of vaccine-induced immunity after 3 months. The association of lower risk of COVID-19 with time since proximate SARS-CoV-2 exposure of 9-12 months compared to 3-9 months requires careful interpretation. Given the time period in which the study was conducted, this anomalous finding could possibly be explained by the fact that those with proximate SARS-CoV-2 exposure (i.e. vaccination) 9-12 months previously were those who would have faced the Delta variant within the preceding 3 months with waning vaccine-induced immunity (being past 6 months from their original vaccination) [11]. Many of them may have been inadvertently boosted by an unrecognized asymptomatic or pauci-symptomatic infection with the Delta variant. Those vaccinated 3-6 and 6-9 months prior to the start of this study (and hence with time since SARS-CoV-2 exposure of 3-6 and 6-9 months, respectively) would have been within 6 months of their vaccination during the Delta variant surge, thereby protected from a Delta variant infection at the time [11,16], and thus would not have had the benefit of a boost to their immunity from a Delta variant infection.

This study also found that among previously infected individuals, receipt of a single dose of vaccine provides protection against COVID-19 compared to receipt of no doses of vaccine, but that receipt of more than 1 dose of vaccine provides no additional protection beyond that acquired by receipt of a single dose. Surprisingly, receipt of 2 doses of vaccine was associated with higher risk of COVID-19 than receipt of a single dose. This last finding raises the intriguing possibility that a second dose of vaccine given shortly after the first in persons with pre-existing natural immunity might nullify the

protection that a single dose of vaccine would otherwise provide. If so, it will have to bear out in other studies that can adequately evaluate this association.

The strengths of our study include its large sample size and a study start date that resulted in all prior infections being pre-Omicron variant infections and the vast predominance of incident infections being Omicron variant infections. Given that this was a study among employees of a health system, that recognized very early the critical importance of maintaining an effective workforce during the pandemic, 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 time-to-event analysis design allowed for important covariates that change over time to be adjusted in a time-dependent manner.

The study has its limitations. Individuals with unrecognized asymptomatic prior infections would have been misclassified as previously uninfected, resulting in underestimating the protective effect of prior infection. Many asymptomatic incident infections were probably missed. There is little reason to suppose, however, that they would have been missed in the various groups at rates disproportionate enough to change the directionality of the study's findings. Because our employee health symptom-monitoring processes were overwhelmed by disease volume during the Omicron phase of the pandemic, we were unable to distinguish between symptomatic and asymptomatic infections and had to limit our analyses to all detected infections. We did not have a way to adjust for behavioral differences and household exposures, both of which can strongly influence risk of COVID-19. Our study of healthcare personnel included no children and few elderly subjects, and the majority would not have been immunocompromised. Lastly, knowing that the Omicron variant causes milder infection than the Delta variant, the clinical impact of protection from severe infection with vaccine boosting would be smaller than the protective effect on infections overall that this study found.

In conclusion, natural immunity from prior COVID-19 provides substantial protection against the Omicron variant for at least 6 months even in the absence of a vaccine. There is little to be gained by vaccinating those who are within 6 months of SARS-CoV-2 infection. Among individuals with waning immunity, boosting with a COVID-19 vaccine not designed for the Omicron variant protects against

Omicron variant infection in both previously vaccinated and previously infected individuals. There is no advantage to administering more than 1 dose of vaccine to previously infected persons. The elderly, children, and the immunocompromised, were not represented or inadequately represented in this study, and caution should be exercised in extrapolating these findings to those populations.

Notes

Author contributions. N. K. S.: Conceptualization, methodology, validation, investigation, data curation, software, formal analysis, visualization, writing- original draft preparation, writing- reviewing and editing, supervision, project administration. P. S.: Data curation, validation, formal analysis, visualization, writing- reviewing and editing. P. C. B.: Resources, investigation, validation, writing- reviewing and editing. A. S. N.: Methodology, formal analysis, visualization, validation, writing- reviewing and editing. P. T.: Resources, writing- reviewing and editing. S. M. G.: Project administration, resources, writing- reviewing and editing.

Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Funding. None.

REFERENCES

1. Bar-On YM, Goldberg Y, Mandel M, et al. Protection of BNT162b2 vaccine booster against COVID-19 in Israel. N Engl J Med **2021**; 385:1393–1400.

2. Barda N, Dagan N, Cohen C, et al. Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study. Lancet **2021**; 398: 2093-2100.

3. Bar-On YM, Goldberg Y, Mandel M, et al. Protection against COVID-19 by BNT162b2 Booster across Age Groups. N Engl J Med **2021**; 385: 2421-2430.

4. Gozzi N, Chinazzi M, Davis JT, et al. Preliminary modeling estimates of the relative transmissibility and immune escape of the Omicron SARS-CoV-2 variant of concern in South Africa. medRxiv, doi: 2022.01.04.22268721v1, preprint: not peer reviewed. Accessed 7 February 2022.

5. Kannan SR, Spratt AN, Sharma K, Chand HS, Byrareddy SN, Singh K. Omicron SARS-CoV-2 variant: Unique features and their impact on pre-existing antibodies. J Autoimmun **2022**; 126:102779.

6. Willett BJ, Grove J, MacLean OA, et al. The hyper-transmissible SARS-CoV-2 Omicron variant exhibits significant antigenic change, vaccine escape and a switch in cell entry mechanism. medRxiv, doi: 2022.01.03.21268111v1, preprint: not peer reviewed. Accessed 7 February 2022.

7. Pulliam JRC, Schalkwyk C van, Govender N, et al. Increased risk of SARS-CoV-2 reinfection associated with emergence of the Omicron variant in South Africa. medRxiv, doi: 2021.11.11.21266068v2, preprint: not peer reviewed. Accessed 7 February 2022.

8. Altarawneh H, Chemaitelly H, Tang P, et al. Protection afforded by prior infection against SARS-CoV-2 reinfection with the Omicron variant. medRxiv, doi: 2022.01.05.22268782v1, preprint: not peer reviewed. Accessed 7 February 2022.

9. Goga A, Bekker L-G, Garrett N, et al. Breakthrough COVID-19 infections during periods of circulating Beta, Delta and Omicron variants of concern, among health care workers in the Sisonke Ad26.COV2.S vaccine trial, South Africa. medRxiv, doi: 2021.12.21.21268171v2, preprint: not peer reviewed. Accessed 7 February 2022.

10. Christensen PA, Olsen RJ, Long SW, et al. Signals of significantly increased vaccine breakthrough, decreased hospitalization rates, and less severe disease in patients with COVID-19 caused by the Omicron variant of SARS-CoV-2 in Houston, Texas. medRxiv, doi: 2021.12.30.21268560v4, preprint: not peer reviewed. Accessed 7 February 2022.

11. Shrestha NK, Burke PC, Nowacki AS, Terpeluk P, Gordon SM. Necessity of COVID-19 vaccination in persons who have already had COVID-19. Clin Infect Dis **2022**; :ciac022.

12. 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.

13. Therneau TM, Crowson C, Atkinson E. Using time dependent covariates and time dependent coefficients in the Cox model. 2021; Available at: https://cran.r-project.org/web/packages/survival/vignettes/timedep.pdf. Accessed 8 May 2021.

14. Therneau TM, Grambsh, PM. Modeling survival data: extending the Cox model. New York, NY: Springer International Publishing, 2000.

15. R Core Team. R: A Language and environment for statistical computing. Vienna, Austria: R Foundation for Statisical Computing, 2021.

16. Chen X, Wang W, Chen X, et al. Prediction of long-term kinetics of vaccine-elicited neutralizing antibody and time-varying vaccine-specific efficacy against the SARS-CoV-2 Delta variant by clinical endpoint. medRxiv, doi: 2021.09.23.21263715v1, preprint: not peer reviewed. Accessed 7 February 2022.

17. Gazit S, Shlezinger R, Perez G, et al. Comparing SARS-CoV-2 natural immunity to vaccine-induced immunity: reinfections versus breakthrough infections. medRxiv, doi: 2021.08.24.21262415v1, preprint: not peer reviewed. Accessed 25 August 2021.

18. León TM, Dorabawila V, Nelson L, et al. COVID-19 Cases and hospitalizations by COVID-19 vaccination status and previous COVID-19 diagnosis — California and New York, May–November 2021. MMWR Morb Mortal Wkly Rep **2022**; 71:125–131.

TABLES

Table 1

Table 1. Study Subject Characteristics Compared by Prior Infection Status

Characteristics	Previously Infected[a] (n = 8037)	Vaccinated but Not Previously Infected[b] (n = 31 729)	*P*
Age, mean ± SD, years	41±12	45±13	<.001
Gender			<.001
Female	6395 (80)	20 888 (66)	
Male	1640 (20)	7574 (24)	
Unknown[c]	2 (< 1%)	3267 (1%)	
Patient-facing job	4474 (56)	14 944 (47)	<.001
Job location			<.001
Cleveland Clinic Main Campus	2784 (35)	12 962 (41)	
Regional hospitals	3239 (40)	9763 (31)	
Ambulatory centers	1293 (16)	5013 (16)	
Administrative centers	572 (7)	3003 (10)	
Remote location	149 (2)	988 (3)	
Job category			<.001
Professional staff	326 (4)	3247 (10)	
Residents and fellows	139 (2)	1006 (3)	
Advanced practice practitioners	617 (8)	2009 (6)	
Nursing	2860 (36)	7587 (24)	
Pharmacy	137 (2)	889 (3)	

Research	102 (1)	803 (3)
Clinical support	1109 (14)	3788 (12)
Administration	528 (7)	2774 (9)
Administration support	2219 (28)	9626 (30)

Data are presented as no. (%) unless otherwise indicated. Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Any person with at least 1 positive SARS-CoV-2 nucleic acid amplification test at least 14 days prior to the study start date was considered previously infected.

[b]Any person who had received at least 2 doses of an mRNA COVID-19 vaccine at least 14 days prior to the study start date was considered vaccinated.

[c]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

Table 2. Study Subject Characteristics Compared by Boosting Status by the End of the Study

Characteristics	Boosted[a] (n = 26 176)	Not Boosted (n = 13 590)	*P*
Age, mean ± SD, years	45±13	42±13	<.001
Gender			<.001
Female	17 664 (67)	9619 (71)	
Male	6429 (25)	2785 (20)	
Unknown[b]	2083 (8)	1186 (9)	
Patient-facing job	12 562 (48)	6856 (50)	<.001
Job location			<.001
Cleveland Clinic Main Campus	11 467 (44)	4279 (32)	
Regional hospitals	7856 (30)	5146 (38)	
Ambulatory centers	3950 (15)	2356 (17)	
Administrative centers	2263 (9)	1312 (10)	
Remote location	640 (2)	497 (4)	
Job category			<.001
Professional staff	2988 (11)	585 (4)	
Residents and fellows	922 (4)	223 (2)	
Advanced practice providers	1746 (7)	880 (7)	
Nursing	6484 (25)	3963 (29)	
Pharmacy	689 (3)	337 (3)	
Research	713(3)	192 (1)	
Clinical support	2772 (11)	2125 (16)	
Administration	2407 (9)	895 (7)	
Administration support	7455 (29)	4390 (32)	

Data are presented as no. (%) unless otherwise indicated. Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Any person who, by the study end date, had received at least 1 doses of an mRNA COVID-19 vaccine at least 90 days following COVID-19 or completion of a 2-dose COVID-19 mRNA vaccine series.

[b]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

Table 3. Unadjusted and Adjusted Associations with Time to COVID-19 for Vaccinated but not Previously Infected Individuals

Characteristics	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)[a]	*P*
Boosting[b]	.40 (.38-.42)	<.001	.43 (.41-.46)	<.001
Age	.98 (.98-.98)	<.001	.98 (.98-.98)	<.001
Male gender[c]	.66 (.62-.71)	<.001	.71 (.66-.76)	<.001
Patient facing job[d]	1.22 (1.15-1.29)	<.001	1.09 (1.03-1.15)	.002
Time since proximate SARS-CoV-2 exposure[c,e]				
3-6 months	1.71 (1.49-1.96)	<.001	.92 (.80-1.05)	.20
6-9 months	1.70 (1.55-1.86)	<.001	1.14 (1.04-1.26)	.006
≥ 9 months	1.15 (1.07-1.24)	<.001	1.07 (1.00-1.16)	.02
Hazard ratio for boosting among subsets defined by time since second vaccine dose				
Time since second vaccine dose				
<6 months (n^f = 3302)	.75 (.40-1.40)	.36	.71 (.38-1.32)	.28
6-9 months (n^f = 6010)	.37 (.32-.42)	<.001	.40 (.35-.46)	<.001
>=9 months (n^f = 25369)	.37 (.35-.40)	<.001	.40 (.37-.43)	<.001

Abbreviation: CI, confidence interval; HR, hazard ratio; proximate SARS-CoV-2 exposure, proximate exposure to SARS-CoV-2 by infection or vaccination.

[a]From a multivariable Cox-proportional hazards regression model with boosting and time since proximate SARS-CoV-2 exposure treated as time-dependent covariates.

[b]Time-dependent covariate

[c]Reference is female gender

[d]Reference is non-patient facing job

[e]Reference is <3 months

[f]Number of subjects who were in the study when this was their time since proximate SARS-CoV-2 exposure. Individuals could contribute data to more than one subset if their time since proximate SARS-CoV-2 exposure crossed the time subset cutoff points during the study.

Table 4

Table 4. Unadjusted and Adjusted Associations with Time to COVID-19 for Previously Infected Individuals

Characteristics	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)[a]	*P*
Boosting[b]	.80 (.70-.91)	<.001	.66 (.58-.76)	<.001
Age	.98 (.97-.98)	<.001	.98 (.97-.98)	<.001
Male gender[c]	.68 (.57-.82)	<.001	.70 (.58-.84)	<.001
Patient facing job[d]	1.34 (1.17-1.53)	<.001	1.14 (1.00-1.31)	.05
Time since proximate SARS-CoV-2 exposure[e]				
3-6 months	.95 (.65-1.40)	.81	.76 (.51-1.12)	.16
6-9 months	2.12 (1.33-3.37)	.002	1.84 (1.15-2.93)	.01
9-12 months	3.52 (2.78-4.47)	<.001	3.38 (2.67-4.30)	<.001
≥12 months	3.63 (2.97-4.44)	<.001	3.73 (3.05-4.57)	<.001
Hazard ratio for boosting among subsets defined by time since prior infection				
Time since prior infection				
< 6 months (n^f = 1718)	Undefined[g]		Undefined[g]	
6-9 months (n^f = 397)	.24 (.11-.53)	<.001	.25 (.11-.54)	<.001
9-12 months (n^f = 3146)	.40 (.33-.49)	<.001	.42 (.35-.50)	<.001
>=12 months (n^f = 2776)	.50 (.40-.61)	<.001	.53 (.43-.65)	<.001

Abbreviations: CI, confidence interval; HR, hazard ratio; proximate SARS-CoV-2 exposure, proximate exposure to SARS-CoV-2 by infection or vaccination.

[a]From a multivariable Cox-proportional hazards regression model with number of vaccine doses and time since proximate SARS-CoV-2 exposure treated as time-dependent covariates.

[b]Time-dependent covariate

[c]Reference is female gender

[d]Reference is non-patient facing job

[e]Reference is <3 months

[f]Number of subjects who were in the study when this was their time since proximate SARS-CoV-2 exposure. Individuals could contribute data to more than one subset if their time since proximate SARS-CoV-2 exposure crossed the time subset cutoff points during the study.

[g]Could not be calculated because there were zero events among the very small number of individuals who were boosted.

Table 5

Table 5. Effect of Number of Vaccine Doses on Risk of COVID-19 for Previously Infected Individuals

Characteristics	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)[a]	*P*
Number of vaccine doses[b,c]				
0	1.99 (1.54-2.57)	<.001	2.44 (1.88-3.15)	<.001
2	2.36 (1.85-3.00)	<.001	1.54 (1.21-1.97)	<.001
3	1.52 (1.17-1.98)	.002	1.01 (.77-1.32)	.96
Age	.98 (.97-.98)	< .001	.98 (.98-.99)	<.001
Male gender[d]	.68 (.57-.81)	< .001	.73 (.60-.87)	<.001
Patient facing job[e]	1.33 (1.17-1.53)	< .001	1.13 (.99-1.30)	.07
Time since prior infection[b,f]				
3-6 months	1.97 (1.06-3.66)	.03	2.19 (1.28-4.08)	.01
6-9 months	4.14 (2.12-8.08)	<.001	4.73 (2.41-9.26)	<.001
9-12 months	7.52 (4.37-12.93)	<.001	10.27 (5.92-17.81)	<.001
≥12 months	7.87 (4.63-13.37)	<.001	11.29 (6.58-19.40)	<.001

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]From a multivariable Cox-proportional hazards regression model with number of vaccine doses and time since prior infection treated as time-dependent covariates.

[b]Time-dependent covariate

[c]Reference is 1 dose

[d]Reference is female gender

[e]Reference is non-patient facing job

[f]Reference is <3 months

FIGURE LEGENDS

Figure 1. Simon-Makuch plot showing the cumulative incidence of COVID-19 stratified by type of prior SARS-CoV-2 exposure (infection or vaccination) and boosting status. Day zero was 26 November 2021, the day the Omicron variant was first declared a variant of concern. Point estimates and 95% confidence intervals are jittered along the x-axis to improve visibility. Those previously infected are represented in blue and those vaccinated but not previously infected in red. Boosting was a time-dependent covariate whose value changed from "non-boosted" to "boosted" 7 days after receipt of a vaccine booster. Those boosted are represented by bold lines and those who remained non-boosted by dashed lines.

Figure 2. Simon-Makuch plot showing the cumulative incidence of COVID-19 among subjects stratified by time since proximate SARS-CoV-2 exposure as a time-dependent covariate. The left panel shows the cumulative incidence for those previously infected and the right one for those vaccinated but not previously infected. Day zero was 26 November 2021, the day the Omicron variant was declared a variant of concern. Point estimates and 95% confidence intervals are jittered along the x-axis to improve visibility. Receipt of a vaccine booster (as a time-dependent covariate) was considered an exposure to SARS-CoV-2 and would result in data for that subject to move to the '<3 m' group 7 days after the date of the booster.

Figure 3. Simon-Makuch plot comparing the cumulative incidence of COVID-19 among previously infected subjects, stratified by boosting status and time since prior infection. Day zero was 26 November 2021, the day the Omicron variant was declared a variant of concern. Point estimates and 95% confidence intervals are jittered along the x-axis to improve visibility. Strata of time since prior infection (as a time-dependent covariate) are represented by different colors. Those boosted (as a time-dependent covariate) are represented by bold lines and those who remained non-boosted by dashed lines.

Figure 4. Simon-Makuch plot comparing the cumulative incidence of COVID-19 among previously infected individuals stratified by number of vaccine doses received (as a time-dependent covariate). Day zero was 26 November 2021, the day the Omicron variant was declared a variant of concern. Point estimates and 95% confidence intervals are jittered along the x-axis to improve visibility.

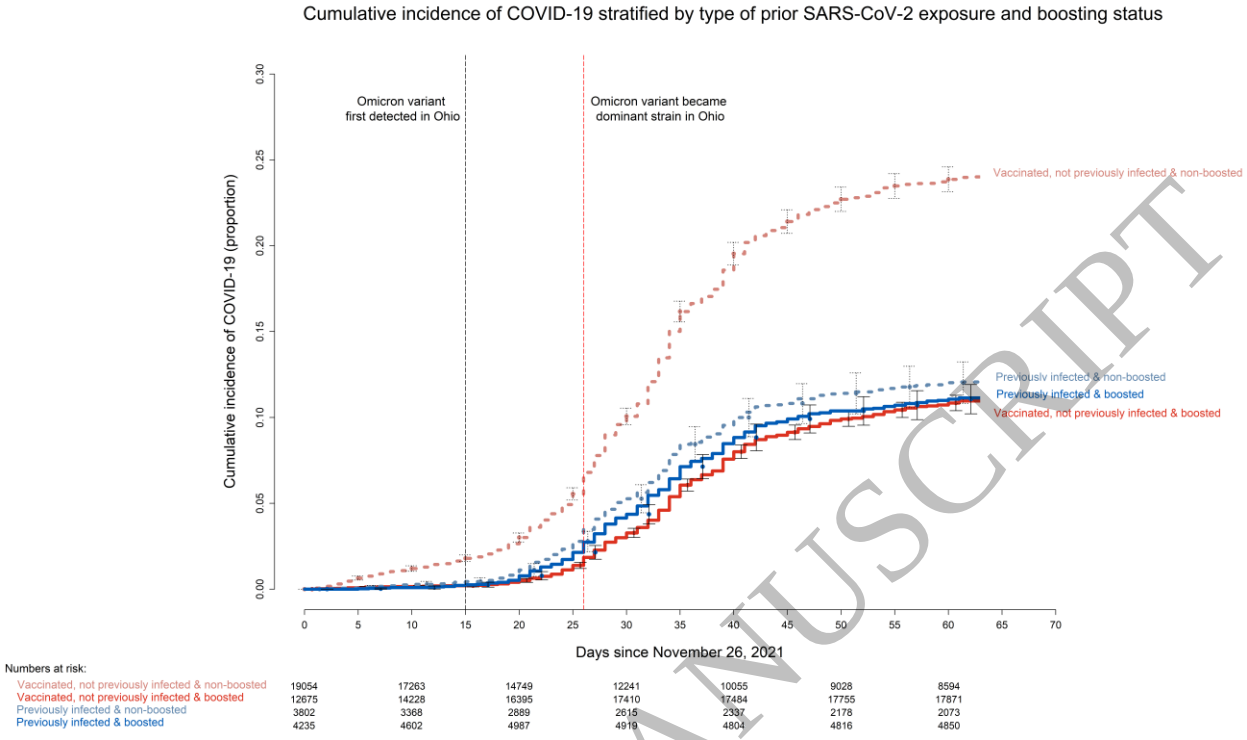

Figure 1
165x99 mm (0.0 x DPI)

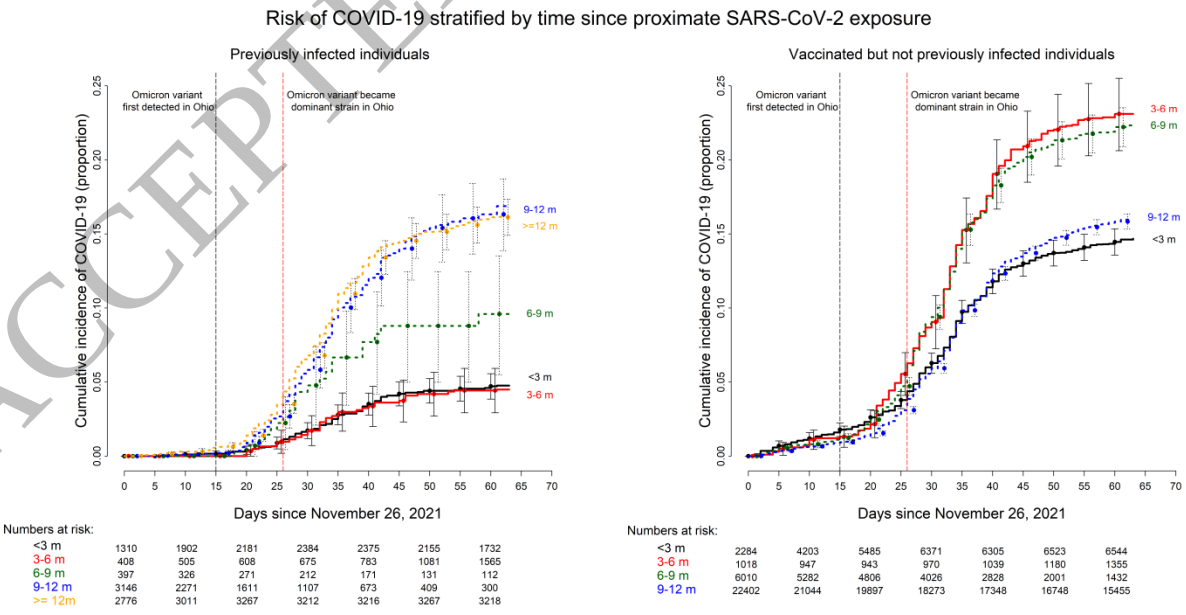

Figure 2
165x99 mm (0.0 x DPI)

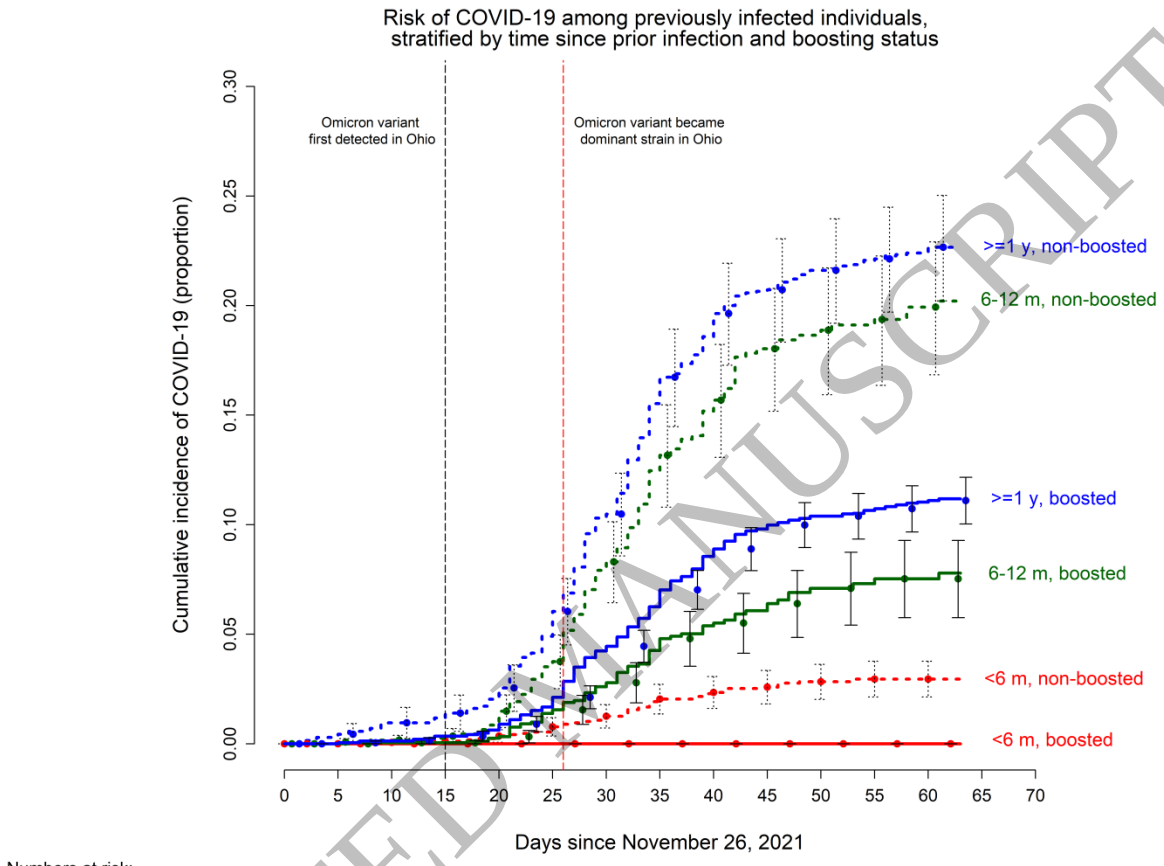

Figure 3
165x99 mm (0.0 x DPI)

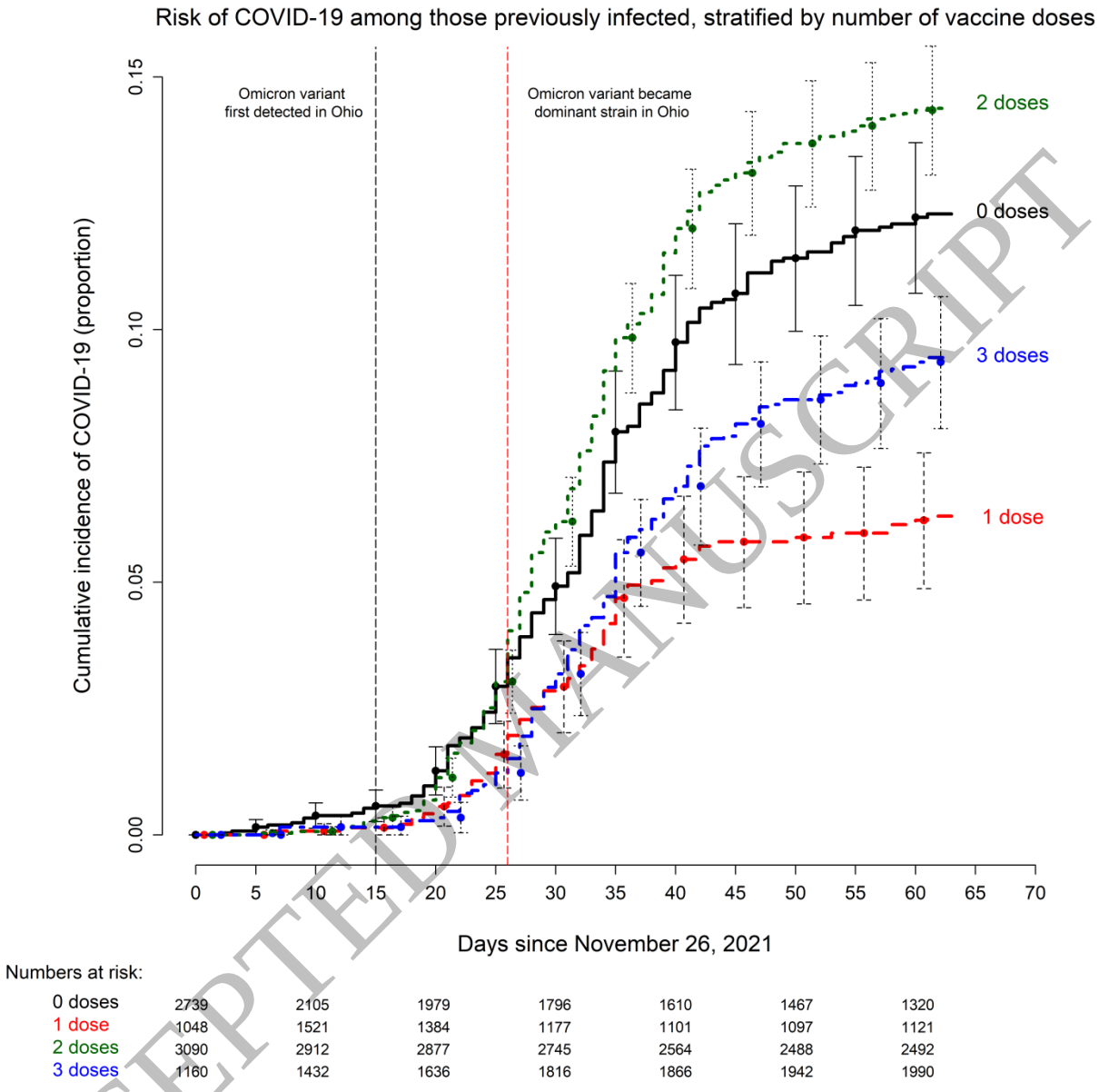

Figure 4
165x99 mm (0.0 x DPI)