Protection Against the Omicron Variant Offered by Previous SARS-CoV-2 Infection: A Retrospective Cohort Study

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Abstract

Background Previous infection with SARS-CoV-2 provides strong protection against future infection. There is limited evidence on whether such protection extends to the Omicron variant.

Methods This retrospective cohort study included 635,341 patients tested for SARS-CoV-2 via polymerase chain reaction (PCR) from 09 March 2020 to 01 March 2022. Patients were analyzed according to the wave in which they were initially infected. The primary outcome was reinfection during the Omicron period (20 December 2021, to 01 March 2022). We used a multivariable model to assess the effects of prior infection and vaccination on hospitalization.

Results Among the patients tested during the Omicron wave, 30.6% tested positive. Protection of prior infection against reinfection with Omicron ranged from 18.0% (95% confidence interval [CI], 13.0-22.7) for patients infected in wave 1 to 69.2% (95% CI, 63.4-74.1) for those infected in the Delta wave. In adjusted models, previous infection reduced hospitalization by 28.5% (95% CI, 19.1-36.7), while full vaccination plus a booster reduced it by 59.2% (95% CI, 54.8-63.1).

Conclusions

Previous infection offered less protection against Omicron than was observed in past waves. Immunity against future waves will likely depend on the degree of similarity between variants.

Keywords: COVID-19; SARS-CoV-2; Omicron; reinfection; immunity.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has been perpetuated by the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants. In November 2021, a new SARS-CoV-2 variant, B.1.1.529 (Omicron), was detected in Botswana and South Africa. Since its identification, the Omicron variant has spread rapidly across the globe, with the first reported case in the United States on 01 December 2021. In just over three weeks, the highly transmissible Omicron variant quickly surpassed the preceding B.1.617.2 (Delta) variant to become the dominant strain of SARS-CoV-2 in the United States. With over 30 mutations in the spike protein, the key mediator of host cell entry and primary target of neutralizing antibodies, the Omicron variant has raised significant concern for immune escape.[1–3]

Previous COVID-19 infection has been shown to be protective against reinfection and symptomatic disease with Omicron's predecessors – the Alpha (B.1.1.7), Beta (B.1.351), and Delta (B.1.617.2) variants.[4–11] However, compared to the previously dominant Delta variant, *in vitro* studies have reported a reduction in the neutralization efficacy against Omicron of antibodies generated by natural infection[3,12,13] and vaccination,[2,14,15] and protection against infection provided by prior infection appeared to be greatly diminished with the arrival of the Omicron variant.[9,16]

Recent population-level analyses from the United Kingdom,[17] Qatar,[16] and South Africa[18] all reported a high risk of reinfection with the Omicron variant, with some describing protective estimates as low as 19%. However, it remains unclear whether reinfections with Omicron are the result of waning immunity or viral evolution. One recent phylogenetic analysis showed that the Omicron lineage does not directly derive from any of its predecessors.[12] Given that the various waves of the COVID-19 pandemic have been driven by different variants of concern in the U.S.,

it is important to understand whether the protection offered by prior SARS-CoV-2 infection differs based on the wave during which the initial infection occurred.

Furthermore, there is an ongoing debate about the degree of protection offered by previous SARS-CoV-2 infection as compared to vaccination. Early during the pandemic, preventive measures were assessed by infection rates. Recently, the focus has shifted towards prevention of hospitalization and Intensive Care Unit (ICU) utilization. Therefore, we designed our study to address two aims: (1) to determine whether previous SARS-CoV-2 infection during different waves of the pandemic offers protection against reinfection with Omicron, and (2) to compare the preventable fractions due to previous SARS-CoV-2 infection and vaccination for prevention of hospitalization and ICU utilization for SARS-CoV-2 infected individuals during the Omicron surge.

Methods

Study design.

We conducted a retrospective cohort study within the Cleveland Clinic Health System in Ohio, USA. The study was approved by the Cleveland Clinic Institutional Review Board.

Study populations and exposures

The study population included patients tested for SARS-CoV-2 via polymerase chain reaction (PCR) between 09 March 2020 and 01 March 2022. Reasons for PCR testing included symptomatic infection, hospitalization for any reason, preprocedural screening, and international travel clearance.

Exposure was defined as previous SARS-CoV-2 infection confirmed by at least one positive PCR. To compare the strength of association of SARS-CoV-2 infection driven by 3 different

strains, we created 3 exposure cohorts, based on CDC reporting of predominance in Ohio.[9] We excluded patients with a positive PCR detected in more than one wave prior to Omicron.

The initial cohort included patients tested from March 9, 2020, to March 28, 2021. After excluding patients who retested positive prior to December 19, 2021, there were 362,800 individuals who were tested during the first wave. The Alpha (B.1.1.7) cohort included patients tested from March 29, 2021, to June 27, 2021. After exclusions, there were 104,856 individuals tested during the second wave. Finally, the Delta (B.1.617.2) cohort included patients tested from June 28, 2021, to September 21, 2021. After exclusions, there were 98,605 individuals tested during the third wave. Patients tested between 9/22/21 and 12/19/21 were not included in this analysis, because they would not qualify as a reinfection at the beginning of the Omicron period.

Vaccination status by any COVID-19 vaccine product was verified in the electronic medical record (EMR). We considered three vaccination groups, based on CDC criteria. Unvaccinated status was defined as receiving no COVID-19 vaccine doses. Fully vaccinated status was defined as ≥ 14 days after the second dose in a 2-dose series of mRNA Pfizer or Moderna vaccines or ≥ 14 days after a single-dose vaccine (Johnson & Johnson's Janssen or Astra Zeneca vaccine). Boosted status was defined as ≥ 14 days after the third dose of mRNA Pfizer (full dose) or Moderna (either booster or full dose) vaccines or ≥ 14 days after the dose of mRNA Pfizer (full dose) or Moderna (either booster or full dose) vaccines after a single-dose vaccine (Johnson & Johnson's Janssen or Astra Zeneca vaccine).

For the second aim of the study, we included only patients with a positive SARS-CoV-2 PCR test during the period of Omicron dominance – from December 20, 2021, to March 1, 2022.

Data collection and the definitions of covariates.

Data were extracted from the electronic medical record. Covariates collected were age, sex, the reason for PCR testing, and the exposure time between the date of the first positive PCR test during one of the previous waves (1^{st}, 2^{nd}, or 3^{rd}) and the date of the PCR test during the Omicron wave. If a patient had no previous SARS-CoV-2 infection and had negative PCR test results during several COVID-19 waves, the exposure time was calculated between the date of the first negative PCR test during one of the previous waves and the date of the PCR test during the Omicron wave. Symptomatic infection was identified based on the mandatory questionnaire accompanying SARS-CoV-2 infection test orders.

Study outcomes

For the first aim, the primary outcome was a positive PCR retest during the period of Omicron dominance – from December 20, 2021, to March 1, 2022. Omicron constituted 80% of test positive cases on December 20, and 100% of cases by December 26. According to CDC criteria, reinfection is defined as occurring $\geq$90 days after initial testing.[19] Therefore, because the period between each wave and the start of the Omicron period was $\geq$90 days, for patients with a positive PCR test during the first, second, or the third wave, any positive PCR test during the Omicron period was defined as a reinfection.

For the second aim, the primary outcome was hospitalization during the period of Omicron dominance – from December 20, 2021, to March 1, 2022. ICU admission during the index hospitalization was the secondary outcome.

Statistical analysis

For the first aim, we conducted an unadjusted analysis and calculated preventable fraction (PF)[20,21] of the Omicron risk under the unexposed (SARS-CoV-2 PCR negative) condition that could be prevented by SARS-CoV-2 infection exposure during each of 3 previous waves as:

$$PF_{reinfection} = 100 \times (1 - \text{Risk Ratio}) = 100 \times \left(1 - \frac{\text{Omicron Incidence proportion in exposed}}{\text{Omicron Incidence proportion in unexposed}}\right)$$

Incidence proportion was calculated by dividing the number of patients who retested positive by the total number of patients in that cohort. Patients who were not retested during the Omicron period were assumed to be negative. We reported the total preventable fraction for each wave, and stratified it by age (0-17 years, 18-34 years, 35-50 years, 51-64 years, 65-74, and ≥75 years).

For the second aim, we calculated the adjusted PF[20,21] of hospitalizations and ICU admissions using logistic regression, comparing the odds of having versus not having prior SARS-CoV-2 infection, as well as odds of being vaccinated versus not among patients with Omicron SARS-CoV-2 infection as:

$$Adjusted\ PF = 100 \times (1 - \text{Adjusted Odds Ratio})$$

Separate logistic regression models were constructed for hospitalizations and ICU admissions. Each model included an indicator variable for infection during the ancestral, Alpha, or Delta wave, and an indicator variable for vaccination group (unvaccinated, fully vaccinated, or boosted); the model was adjusted for age, sex, the reason for testing, and the exposure time. To compare adjusted preventable fractions among individuals with different vaccination status, and among patients previously infected during different waves, we performed post hoc pairwise comparisons across the levels of factor variables, using a two-sided significance level of $P<0.002$. We corrected significance level for testing 26 hypotheses. Finally, we conducted these same analyses in a subgroup of elderly individuals (age ≥ 65y).

Analyses were conducted using R v4.1.0 (R Core Team, Vienna) and STATA MP 17.0 (StataCorp LP, College Station, TX).

Results

During the study period, 1,218,684 PCR tests were collected from 635,341 individuals (average age, 47.3 ± 24.2 years; 54.0% female), of whom, 129,878 (20.4%) tested positive. During the Omicron period, 126,772 PCR tests were collected from 104,705 individuals, of whom 32,059 (30.6%) tested positive.

Protection against reinfection with Omicron by the previous SARS-CoV-2 infection

Comparison of patient characteristics by exposure group is shown in Table 1. Overall, demographic characteristics of patients tested during each wave of SARS-CoV-2 infection were similar. Only a small proportion (8-15%) of these patients were retested during the Omicron wave. In unadjusted analysis, previous SARS-CoV-2 infection offered protection against Omicron SARS-CoV-2 infection. The preventable fraction gradually increased from the first to the third wave. Results were similar when limited to symptomatic Omicron infection (Supplementary Table 1).

Results stratified by age group are shown in Table 2. Among those infected during the first and third waves, the oldest (≥75y) patients were subsequently protected against SARS-CoV-2 infection to a significantly greater degree than patients aged 18-64 years. However, testing frequency also varied by age and previous infection status. In general, older patients who had been previously infected were less likely than their peers to be retested, whereas younger patients who had been previously infected were more likely than their peers to be retested.

Prevention of hospitalization and ICU admission

Clinical and demographic characteristics of patients with Omicron SARS-CoV-2 infection are summarized in Table 3. Out of 13,179 patients with Omicron SARS-CoV-2 infection, 1,467 patients (11.1%) had a documented history of previous SARS-CoV-2 infection. Patients with previous SARS-CoV-2 infection were younger and less likely to be vaccinated. They were also significantly less likely to be hospitalized during the Omicron wave or admitted to ICU.

Table 4 shows the results of adjusted analyses. After adjustment for age, sex, the reason for Omicron SARS-CoV-2 testing, time between previous SARS-CoV-2 infection exposure and Omicron SARS-CoV-2 infection detection, and vaccination status, a previous SARS-CoV-2 infection offered small (approximately 30%) but statistically significant protection against hospitalization and ICU admission during the Omicron wave. There were no differences in the strength of protection offered by previous infection during the different waves.

After adjustment for age, sex, the reason for Omicron SARS-CoV-2 testing, history of previous SARS-CoV-2 infection, and time between previous SARS-CoV-2 infection and Omicron SARS-CoV-2 infection detection, full SARS-CoV-2 vaccination offered substantial, statistically significant protection against hospitalization and ICU admission. Furthermore, there was a statistically significant difference in the strength of protection offered by boosting (approximately 60%) compared to full vaccination (approximately 40%). Importantly, full vaccination and especially boosting provided substantial (≥50%) protection against ICU admission. Patients with and without previous infection appeared to derive similar benefits from vaccination and boosting (Supplementary Table 2). Results for older patients appear in Supplementary Table 3. Neither previous infection nor vaccination without boosting reduced hospitalizations or ICU admissions in older patients, whereas boosting reduced both.

Discussion

In this observational cohort study of more than 600,000 individuals who were tested for COVID-19 in the past 2 years, we found that previous infection with SARS-CoV-2 provided varying protection against infection with the Omicron variant, depending on the most likely original infecting virus strain and time since the previous infection. Infection during the Delta wave provided the strongest protection. Interestingly, protection varied by age; unexpectedly, older patients generally had the greatest protection against infection. Lastly, we found that once patients were infected with Omicron, previous infection provided a small, additional benefit against severe disease. Vaccination provided much greater protection against severe disease, with boosters providing the greatest protection against both hospitalization and ICU admission, regardless of previous infection status.

Our findings differ from those of past analyses, which found that previous infection provided 80-90% protection against reinfection (with pre-Omicron variants) in subsequent waves.[4–11,22] Moreover, such protection did not appear to wane over 8-13 months.[7,11,22–25] The reduced protection against Omicron is most likely due to the variant's multiple mutations, which allow it to evade immune defenses. The higher rate of protection afforded by infection in the Delta wave may be due to the strains' characteristics or recency of infection, although our past analyses using similar methods did not find that protection waned over time.[4,7]

One other analysis also found that past infection provided less protection against Omicron than against other strains.[16] Using a national SARS-CoV-2 database from Qatar, they found that previous infection provided 56% protection against Omicron. However, they did not stratify by past waves, and it appears that most of their previous infections were from the Delta wave.

Theirs was a predominantly young, healthy population with too few hospitalizations to accurately assess the impact of past infection on severity of disease.

Our analysis stratified by age also contradicts previous studies, which generally found that protection from natural infection declined with age.[5,7,26] In contrast, we found that the oldest patients derived the greatest protection. This finding most likely reflects differences in social or testing behavior by age and previous infection status. The fact that previously infected younger patients were more likely to be retested suggests that their behavior may have exposed them to other respiratory pathogens, leading them to be tested for symptoms. The opposite was true for older patients. The differential testing by age could have biased our results, causing previous infection to appear less protective in younger patients and more protective among older ones.

Previous infection offered some additional protection against severe disease, reducing hospitalization by about 30%. However, this was substantially less than that seen with vaccination, even among those who had not received a booster, and was not seen with older patients. Therefore, previously infected patients, especially those who had COVID-19 prior to Delta and those over 65 years of age, may wish to be vaccinated as an additional safeguard against severe disease. Others have observed that vaccination and COVID-19 infection together provide the greatest level of protection.[9,27,28] However, because COVID-19 is dangerous, people should not expose themselves purposefully in order to gain protection against future variants.

Lastly, our data are sobering regarding the development of herd immunity. Following the Omicron wave, close to 80 million Americans have had documented cases of COVID-19. It is likely that an overwhelming majority of Americans have now had some exposure to the virus or have been vaccinated. Cases of Omicron have declined rapidly and should leave behind a temporary barrier of herd immunity, allowing for some return to normal life. However, neither

vaccination nor previous infection was very effective in stopping the spread of Omicron, suggesting that a sufficiently mutated strain could cause another pandemic cycle. Indeed, achieving herd immunity against SARS-CoV2 may not be possible.

Strengths and Limitations

The strengths of our study include a large population of patients with validated, nucleic acid amplification test (NAAT)-confirmed SARS-CoV-2 infection and documented vaccination status. This allowed us to stratify patients based on the timing of infection, as well as by age, and to study the interaction of vaccination and previous infection for protection against severe disease.

Our study also has limitations. As a retrospective COVID-19 study, there may have been confounding due to unmeasured differences in exposures between individuals who were or were not previously infected. Behaviors that led to avoidance of infected individuals would be misinterpreted as immunity to infection. Alternatively, patients who were previously infected may have been more or less likely to seek out testing when symptomatic. Alternatively, one group may have been more prone to perform rapid testing at home or in an urgent care center. If so, we would have underestimated infections in that group. Similarly, we assessed only hopsitalizations within the Cleveland Clinic Health System. If one group of patients were more likely to seek care outside that system, it would have biased our estimates.

In conclusion, previous infection with SARS-CoV-2 offered limited protection against reinfection with the Omicron variant, with infection during the Delta wave offering the greatest subsequent protection. The age distribution of protection suggests that immunity may be overcome with a larger dose of virus. Most importantly, previous infection offered only mild

protection against severe disease. Vaccination remains the best way to protect against severe COVID-19.

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Potential conflicts of interest

M.B.R. has owned stock in Moderna. All other authors report no potential conflicts of interests. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References:

1. Cao Y, Wang J, Jian F, et al. Omicron escapes the majority of existing SARS-CoV-2 neutralizing antibodies. *Nature*. Published online 2021. doi:10.1038/s41586-021-04385-3
2. Garcia-Beltran WF, St. Denis KJ, Hoelzemer A, et al. mRNA-based COVID-19 vaccine boosters induce neutralizing immunity against SARS-CoV-2 Omicron variant. *Cell*. 2022;185(3):457. doi:10.1016/J.CELL.2021.12.033
3. Wang Y, Zhang L, Li Q, et al. The significant immune escape of pseudotyped SARS-CoV-2 variant Omicron. *Emerg Microbes Infect*. 2022;11(1):1. doi:10.1080/22221751.2021.2017757
4. Sheehan MM, Reddy AJ, Rothberg MB. Reinfection Rates among Patients who Previously Tested Positive for COVID-19: a Retrospective Cohort Study. *Clin Infect Dis An Off Publ Infect Dis Soc Am*. 2021;73(10):1882-1886. doi:10.1093/CID/CIAB234
5. 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 (London, England)*. 2021;397(10280):1204. doi:10.1016/S0140-6736(21)00575-4
6. 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(6):533-540. doi:10.1056/NEJMOA2034545
7. Kim P, Gordon SM, Sheehan MM, Rothberg MB. Duration of SARS-CoV-2 Natural Immunity and Protection against the Delta Variant: A Retrospective Cohort Study. *Clin Infect Dis An Off Publ Infect Dis Soc Am*. Published online December 2021.

doi:10.1093/CID/CIAB999

8. 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(6529). doi:10.1126/SCIENCE.ABF4063

9. 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*. Published online January 13, 2022. doi:10.1093/CID/CIAC022

10. Grant R, Charmet T, Schaeffer L, et al. Impact of SARS-CoV-2 Delta variant on incubation, transmission settings and vaccine effectiveness: Results from a nationwide case-control study in France. *Lancet Reg Heal - Eur*. 2022;13:100278. doi:10.1016/J.LANEPE.2021.100278

11. Leidi A, Koegler F, Dumont R, et al. Risk of reinfection after seroconversion to SARS-CoV-2: A population-based propensity-score matched cohort study. *Clin Infect Dis*. Published online May 27, 2021. doi:10.1093/CID/CIAB495

12. Planas D, Saunders N, Maes P, et al. Considerable escape of SARS-CoV-2 Omicron to antibody neutralization. *Nat 2021*. Published online December 2021:1-7. doi:10.1038/s41586-021-04389-z

13. Eggink D, Andeweg SP, Vennema H, et al. Increased risk of infection with SARS-CoV-2 Omicron BA.1 compared with Delta in vaccinated and previously infected individuals, the Netherlands, 22 November 2021 to 19 January 2022. *Euro Surveill*. 2022;27(4). doi:10.2807/1560-7917.ES.2022.27.4.2101196

14. Wilhelm A, Widera M, Grikscheit K, et al. Reduced Neutralization of SARS-CoV-2 Omicron Variant by Vaccine Sera and monoclonal antibodies. *medRxiv*. Published online December 2021:2021.12.07.21267432. doi:10.1101/2021.12.07.21267432

15. Rössler A, Riepler L, Bante D, von Laer D, Kimpel J. SARS-CoV-2 Omicron Variant Neutralization in Serum from Vaccinated and Convalescent Persons. *N Engl J Med*. Published online January 2022. doi:10.1056/NEJMC2119236

16. Altarawneh HN, Chemaitelly H, Hasan MR, et al. Protection against the Omicron Variant from Previous SARS-CoV-2 Infection. *N Engl J Med*. Published online February 9, 2022. doi:10.1056/NEJMC2200133

17. Ferguson N, Ghani A, Cori A, Hogan A, Hinsley W, Volz E. Report 49: Growth, population distribution and immune escape of Omicron in England. *Imp Coll London*. Published online December 2021. doi:10.25561/93038

18. Pulliam JRC, van Schalkwyk C, Govender N, et al. Increased risk of SARS-CoV-2 reinfection associated with emergence of the Omicron variant in South Africa. *medRxiv*. Published online December 2021:2021.11.11.21266068. doi:10.1101/2021.11.11.21266068

19. Centers for Disease Control and Prevention. Investigative Criteria for Suspected Cases of SARS-CoV-2 Reinfection (ICR). Published online October 2020. Accessed February 11, 2022. https://www.cdc.gov/coronavirus/2019-ncov/php/invest-criteria.html

20. Gargiullo PM, Rothenberg RB, Wilson HG. Confidence intervals, hypothesis tests, and sample sizes for the prevented fraction in cross-sectional studies. *Stat Med*. 1995;14(1):51-72. doi:10.1002/SIM.4780140107

21. Greenland S, Drescher K. Maximum likelihood estimation of the attributable fraction from logistic models. *Biometrics*. 1993;49(3):865-872.

22. Vitale J, Mumoli N, Clerici P, et al. Assessment of SARS-CoV-2 Reinfection 1 Year After Primary Infection in a Population in Lombardy, Italy. *JAMA Intern Med*.

2021;181(10):1407-1408. doi:10.1001/JAMAINTERNMED.2021.2959

23. Jeffery-Smith A, Rowland TAJ, Patel M, et al. Reinfection with new variants of SARS-CoV-2 after natural infection: a prospective observational cohort in 13 care homes in England. *Lancet Heal Longev*. 2021;2(12):e811-e819. doi:10.1016/S2666-7568(21)00253-1

24. Breathnach AS, Riley PA, Cotter MP, Houston AC, Habibi MS, Planche TD. Prior COVID-19 significantly reduces the risk of subsequent infection, but reinfections are seen after eight months. *J Infect*. 2021;82(4):e11-e12. doi:10.1016/J.JINF.2021.01.005

25. 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(4):125-131. doi:10.15585/MMWR.MM7104E1

26. Spicer KB, Glick C, Cavanaugh AM, Thoroughman D. Protective Immunity after Natural Infection with Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) - Kentucky, USA, 2020. *Int J Infect Dis*. 2022;114:21-28. doi:10.1016/J.IJID.2021.10.010

27. Gazit S, Shlezinger R, Perez G, et al. The Incidence of SARS-CoV-2 Reinfection in Persons With Naturally Acquired Immunity With and Without Subsequent Receipt of a Single Dose of BNT162b2 Vaccine : A Retrospective Cohort Study. *Ann Intern Med*. Published online February 15, 2022. doi:10.7326/M21-4130

28. Cavanaugh AM, Spicer KB, Thoroughman D, Glick C, Winter K. Reduced Risk of Reinfection with SARS-CoV-2 After COVID-19 Vaccination - Kentucky, May-June 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(32):1081-1083. doi:10.15585/MMWR.MM7032E1

Table 1. Patient characteristics and unadjusted preventable fractions (PF) for prevention of SARS-CoV-2 reinfection by the study cohort

Characteristic	Wave 1		Wave 2		Wave 3	
	SARS-CoV-2(+)	SARS-CoV-2(-)	SARS-CoV-2(+)	SARS-CoV-2(-)	SARS-CoV-2(+)	SARS-CoV-2(-)
N	54,233	308,567	5052	99,804	9976	88,629
Age ± SD, y	48.7 ± 21.7	50.9± 22.7	42.2 ± 21.7	51.9 ± 24.1	40.3 ± 23.2	44.0 ± 27.1
Female, n(%)	28,000 (51.6)	169,206 (54.8)	2753 (54.5)	54,539 (54.6)	5270 (52.8)	48,698 (54.9)
N retested during Omicron wave	4719 (8.7)	28,535 (9.2)	482 (9.5)	12,651 (12.7)	818 (8.2)	13,311 (15.0)
Omicron SARS-CoV-2(+), n(%)	1230 (2.3)	8535 (2.8)	107 (2.1)	3417 (3.4)	130 (1.3)	3749 (4.2)
Unvaccinated, n(%)	29,064(53.6)	156,341(50.7)	3,344(66.2)	42,735(42.8)	6,763(67.8)	41,504(46.8)
Fully vaccinated, n(%)	12,339(22.8)	64,425(20.9)	1,105(21.9)	24,934(25.0)	1,777(17.8)	22,980(25.9)
Boosted, n(%)	11,471(21.2)	80,253(26.0)	412(8.2)	28,955(29.0)	1,103(11.1)	21,219(23.9)
Unadjusted PF (95% CI), %	18.0 (13.0 - 22.7)		38.1 (25.2 – 48.9)		69.2 (63.4 – 74.1)	

Table 2. Protection against reinfection with the Omicron variant by age group

Wave	Age group (years)	Total Number of patients		Retested during Omicron, N (%)		Omicron reinfection cases, N		Omicron reinfection incidence proportion, %		Preventable fraction, %	Pairwise *P*-value[a]
		Exposed	Unexposed	Among exposed	Among unexposed	Among Exposed	Among Unexposed	Among Exposed	Among Unexposed		
Wave 1	Overall	54,233	308,567	4719	28,535	1230	8535	2.3%	2.8%	18.0%	--
	0-17	4451	28,224	464 (9.8)	3329 (11.7)	89	978	2.0%	3.5%	42.3%	<0.001
	18-34	11601	54,983	831 (17.6)	3989 (14.0)	306	1513	2.6%	2.8%	4.1%	<0.001
	35-50	12305	57,034	1122 (23.8)	5097 (17.9)	401	1854	3.3%	3.3%	-0.25%	<0.001
	51-64	12442	70,441	1121 (23.8)	6576 (23.0)	287	1931	2.3%	2.7%	15.9%	<0.001
	65-74	6837	54,463	679 (14.4)	5356 (18.8)	93	1273	1.4%	2.3%	41.8%	<0.001
	≥75	6597	43,421	502 (10.6)	4188 (14.7)	54	988	0.8%	2.3%	64.0%	*Ref*
Wave 2	Overall	5052	99,804	482	12,651	107	3417	2.1%	3.4%	38.1%	--
	0-17	777	11795	85 (17.6)	1870 (14.8)	11	504	1.4%	4.3%	66.9%	0.81
	18-34	1222	14338	83 (17.2)	1408 (11.1)	33	481	2.7%	3.3%	19.5%	0.20
	35-50	1183	15542	108 (22.4)	1951 (15.4)	34	617	2.9%	4.0%	27.6%	0.24
	51-64	1075	21841	115 (23.9)	2760 (21.8)	12	771	1.1%	3.5%	68.4%	0.83
	65-74	483	19775	53 (11.0)	2533 (20.0)	13	576	2.7%	2.9%	7.6%	0.19
	≥75	312	16513	38 (7.9)	2129 (16.8)	4	468	1.3%	2.8%	54.8%	*Ref*
Wave 3	Overall	9976	88,629	818	13,311	130	3749	1.3%	4.2%	69.2%	--
	0-17	2158	21298	211 (25.8)	3339 (25.1)	36	953	1.7%	4.5%	62.7%	0.009
	18-34	2250	14086	165 (20.2)	1593 (12.0)	33	578	1.5%	4.1%	64.3%	0.01
	35-50	2132	13021	151 (18.5)	1958 (14.7)	27	683	1.3%	5.2%	75.9%	0.03
	51-64	1681	15159	134 (16.4)	2427 (18.2)	23	652	1.4%	4.3%	68.2%	0.02
	65-74	983	12946	89 (10.9)	2089 (15.7)	8	469	0.8%	3.6%	77.5%	0.09
	≥75	772	12119	68 (8.3)	1905 (14.3)	3	414	0.4%	3.4%	88.6%	*Ref*

[a]Pairwise p-values indicate the significance of differences in preventable fractions across age groups, with age group ≥75 years as the reference group for each comparison. The age group ≥75 years was selected as the reference group given the higher risk of severe illness in this population.

Table 3. Demographic and clinical characteristics of patients with Omicron infection

	All (n=13,179)	Previous SARS-CoV-2 infection (n=1,467)	No Previous SARS-CoV-2 infection (n=11,712)	*P*-value
Age, mean ± SD, y	46.2±23.5	43.4±18.7	46.5±24.0	<0.0001
Female, n(%)	7,608(57.7)	829(56.5)	6,779(57.9)	0.566
Vaccination status:				<0.0001
Unvaccinated, n(%)	4,968(37.7)	71348.6)	4,255(36.3)	
Fully vaccinated, n(%)	4,191(31.8)	460(31.4)	3,731(31.9)	
Boosted, n(%)	3,605(27.4)	252(17.2)	3,353(28.6)	
Days between previous SARS-CoV-2 testing and index Omicron SARS-CoV-2 infection, mean ± SD	319.6 ± 154.8	398.7± 124.8	309.6 ± 155.4	<0.0001
Hospitalization, n(%)	5,443 (41.3)	497(33.9)	4,946(42.2)	<0.0001
ICU admission, n(%)	641(4.9)	41(2.8)	600(5.1)	<0.0001

Table 4. Adjusted preventable fractions (PF) for prevention of hospitalizations and ICU admissions in patients with Omicron SARS-CoV-2 infection

	Hospitalization outcome		Pairwise *P*-values		ICU admission outcome matrix		Pairwise *P*-values	
Exposure	Adjusted PF (95%CI),%	*P*-value	*1st*	*2nd*	Adjusted PF (95%CI),%	*P*-value	*1st*	*2nd*
No previous infection	Reference				Reference			
1st wave infection	27.1(16.6-36.2)	<0.001			30.1 (-0.2 to 51.2)	0.051		
2nd wave infection	35.2 (2.7 - 57.8)	0.046	0.602		51.5 (-20.3 to 80.4)	0.427	0.853	
3rd wave infection	34.6 (3.1 - 55.8)	0.034	0.607	0.973	44.9 (-77.7 to 82.9)	0.319	0.703	0.884
Any previous SARS-CoV-2 infection	28.5 (19.1 – 36.7)	<0.0001			32.1 (5.4 - 51.3)	0.022		
Unvaccinated	Reference				Reference			
Fully vaccinated	42.7 (37.1 – 47.7)	<0.0001	<0.0001		31.1 (15.6 – 43.7)	<0.0001	<0.0001	
Boosted	59.2 (54.8 - 63.1)	<0.0001	<0.0001	<0.0001	51.0 (39.5 – 60.3)	<0.0001	<0.0001	0.002

Adjusted for age, sex, time between previous SARS-CoV-2 infection exposure and Omicron SARS-CoV-2 infection outcome, and a reason for Omicron SARS-CoV-2 testing. Both exposures (previous SARS-CoV-2 infection and vaccination) were included in the model.