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Effect of the incremental protection of previous infection against Omicron infection among individuals with a hybrid of infection- and vaccine-induced immunity: a population-based cohort study in Canada

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ABSTRACT

Objectives: We examined the incremental protection and durability of infection-acquired immunity against Omicron infection in individuals with hybrid immunity in Ontario, Canada.
Methods: We followed up 6 million individuals with at least one multiplex reverse transcriptase–polymerase chain reaction test before November 21, 2021, until an Omicron infection. Protection via infection-acquired immunity was assessed by comparing Omicron infection risk between previously infected individuals and those without documented infection under different vaccination scenarios and stratified by time since the last infection or vaccination.
Results: A previous infection was associated with 68% (95% CI 61-73) and 43% (95% CI 27-56) increased protection against Omicron infection in individuals with two and three doses, respectively. Among individuals with two-dose vaccination, the incremental protection of infection-induced immunity decreased from 79% (95% CI 75-81) within 3 months after vaccination or infection to 27% (95% CI 14-37) at 9-11 months. In individuals with three-dose vaccination, it decreased from 57% (95% CI 50-63) within 3 months to 37% (95% CI 19-51) at 3-5 months after vaccination or infection.
Conclusion: Previous SARS-CovV-2 infections provide added cross-variant immunity to vaccination. Given the limited durability of infection-acquired protection in individuals with hybrid immunity, its influence on shield-effects at the population level and reinfection risks at the individual level may be limited.

Introduction

Immunity conferred by previous SARS-CoV-2 infections and COVID-19 vaccination plays a critical role in building immunity among populations, which may help regions transition to COVID-19 endemicity [1]. Data from earlier in the pandemic suggested that infection-acquired immunity provided 80-95% protection against reinfection with minimal waning within 1 year post-infection [2–7]. As new variants emerged with increased transmission potential and immune evasion properties, the magnitude and durability of infection- and vaccine-acquired immunity may vary. Four

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observational studies reported lower and waning protection of infection-acquired immunity against diagnosed Omicron infections, ranging between 40-70% [8–11]. Observational data on vaccine effectiveness suggest lower protection against the Omicron variant compared to earlier variants [12–17].

Hybrid immunity, defined as immunity acquired from both prior infections and vaccination, reduced diagnosed infections by over 80% during the pre-Omicron period [18–20]. Recent immunological studies observed superior neutralization responses against the Omicron variant following a total of three spike antigen exposures that were achieved by a previous infection and two-dose vaccination [21]. Evidence from existing observational studies shows that a prior infection was able to boost immunity against all diagnostic Omicron infections and symptomatic infection by an additional 10-40% in individuals vaccinated with two and three doses [8–11]. Of these few studies, one found that the effectiveness of hybrid immunity decreased by more than 40% at 9-11 months post-infection or vaccination in individuals vaccinated with two doses, while in those with three doses, it was maintained at 80% within 6 months [10]. In addition to the limited evidence on the durability of hybrid immunity, previous studies that explored this topic did not adjust for important risk factors for SARS-CoV-2 infection such as individuals' socioeconomic status and comorbidities. Therefore, more evidence is needed to address questions regarding the sustainability of infection-acquired immunity in preventing Omicron infection, how this immunity changes with increasing doses, and how a SARS-CoV-2 infection in vaccinated individuals should be considered in public health policies moving forward.

In this study, we aim to examine the effectiveness and durability of immunity acquired from past SARS-CoV-2 infections and how it modifies vaccine protection against Omicron infection, using a population-based cohort in Ontario, Canada.

Methods

Study population, design, and data sources

Among 14.9 million Ontario residents who are covered by the Ontario Health Insurance Plan, we selected individuals who had at least one reverse-transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 between January 15, 2020, and November 21, 2021. Each individual was then followed from November 22, 2021, when the first Omicron case was identified in Ontario, until the end of the study period (December 31, 2021) or the primary outcome - Omicron infection at least 90 days after a previous infection - was observed. We ended the follow-up on December 31, 2021, because starting in 2022 eligibility for PCR testing was restricted to symptomatic individuals in high-risk groups (with those not eligible encouraged to use rapid antigen tests instead), and we wished to ensure consistency of test eligibility during the follow-up period to avoid selection bias [22]. We excluded participants who had a SARS-CoV-2 infection within 90 days before November 22, 2021, and those who died before the start of follow-up.

Testing data were retrieved from the laboratory (Ontario Laboratories Information System and Distributed Labs) and public health surveillance (Public Health Case and Contact Management Solution) databases. The study cohort was linked to population-based provincial health administrative databases to ascertain baseline information on socio-demographic and geographic characteristics and chronic conditions. Vaccination data, including dates of administration and dosage, were retrieved from COVaxON, a centralized COVID-19 vaccine information system. These datasets were linked using unique encoded identifiers and analyzed at ICES (formerly the Institute for Clinical Evaluative Studies). ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement.

Exposures

The main exposure was prior SARS-CoV-2 infection, which was determined by any positive test at least 90 days before an Omicron infection. Individuals without any positive tests and with at least one negative test since January 2020 were considered unexposed. Prior infection status was treated as a time-varying variable during follow-up: individuals infected with non-Omicron variants between November 21 and December 31, 2021 were moved from unexposed to exposed.

BNT162b2 (Pfizer-BioNTech Comirnaty), messenger RNA-1273 (Moderna Spikevax), and ChAdOx1 (Astra-Zeneca Vaxzevria, COVIDSHIELD) were the primary COVID-19 vaccines provided in Ontario [12]. Vaccination roll-out in Ontario started in December 2020, and by July 2021, all Ontarian residents aged $\geq$12 years were eligible for vaccination. Third doses were rolled out starting in August 2021, initially to immunocompromised individuals and long-term care home residents. All individuals aged $\geq$70 years and healthcare workers became eligible on November 6, followed by individuals aged $\geq$50 years on December 13 and individuals aged $\geq$18 years on December 18 [12]. Vaccination status, determined based on the number of doses received before an Omicron infection regardless of vaccine product, changed 14 days after receipt of the first and second doses and 7 days after receipt of the third dose. Vaccination status was treated as a time-varying variable during follow-up.

Outcomes

The primary outcome was infection with the Omicron variant, which was identified by whole genome sequencing (WGS) as the B.1.1.529 lineage or having S-gene target failure (SGTF) detected before December 21, 2021. From December 21, 2021, onwards, any positive SARS-CoV-2 infection cases were classified as Omicron cases (unless confirmed as other variants by WGS or SGTF screening), based on projections that more than 80% of cases were likely to be Omicron by this date [23]. SGTF had been used to identify Omicron in Ontario starting on December 6, 2021 [23]. Between December 6 and 24, 2021, all specimens with a positive PCR result (and a cycle threshold [Ct] value $\leq$35) were sent for SGTF testing using the Thermofisher Taqpath^{TM} COVID-19 PCR. Before December 20, SGTF-positive specimens with Ct values $\leq$30 also underwent WGS. SGTF is a reliable proxy for Omicron identification, with 98.9% sensitivity and 99.9% specificity during December 2021 and January 2022 in Ontario [23].

Covariates

We extracted patients' demographic and residential information, including age, sex, rural residence, and long-term care facility residence. From the 2016 Canadian census data, we obtained area-level information on household income quintile, the proportion of the working population employed as non-health essential workers, the percentage of individuals considered to have lower education, the percentage of unmarried individuals, mean number of persons in private households, proportion of the population who self-identify as a visible minority, and proportion of individuals who reported having immigrated in the past 5 years [24]. Individuals' pre-existing comorbidities were identified using health administrative databases and existing ICES chronic disease cohorts that were created using validated algorithms that have high sensitivity and specificity. The number of comorbidities was assigned to each individual. Definitions of all covariates and their respective databases are listed in Supplementary Tables 1 and 2.

Statistical analysis

Following descriptive analysis, we estimated the hazard ratio (HR) for Omicron infection using Cox proportional hazards regression models. We first fitted a model including prior infection as the main exposure with no interactions between vaccination and prior infection and adjusted for all listed covariates (including vaccination status). The cohort was stratified by time since the last infection, which was categorized by 3-month intervals, to examine the durability of infection-acquired immunity. We then fitted a model with an interaction term of prior infection and vaccination status to examine if the effect of infection-acquired immunity varied among participants vaccinated with different doses. To assess the incremental protection of infection-acquired immunity within each vaccination group and its durability in individuals with hybrid immunity relative to vaccination only, we conducted subgroup analysis by vaccination status and by 3-month intervals since the latest antigenic exposure (achieved by either vaccination or infection) to compare the risk of Omicron infection between previously infected and infection-naïve individuals under three vaccination scenarios (unvaccinated, vaccinated with two doses, and vaccinated with three doses) and at different time intervals. We adjusted for all listed covariates in all models. We calculated the estimated protection as (1 - adjusted HR) x 100%. Both adjusted HR and corresponding protection were reported. Missing values for covariates were less than or equal to 1%. They were imputed using the median of the variable for continuous variables. For categorical variables, they were randomly imputed based on the distribution of existing non-missing values. The Cox model proportionality assumptions were tested using Schoenfeld residuals.

In a sensitivity analysis, we repeated the above analysis but used a more restrictive definition of Omicron to allow for a more accurate classification of cases. From November 22 to December 31, 2021, only positive specimens identified through WGS as B.1.1.529 lineage or found to have SGTF were considered Omicron infections. Specimens sequenced as B.1.617 lineage or found to be negative for SGTF were classified as Delta infections and excluded from the analysis.

We conducted all analyses in R version 3.6.1 (R foundation for statistical computing) and reported the findings in accordance with the Strengthening the reporting of observational studies in epidemiology guidelines for cohort study. All tests were two-sided and used $P < 0.05$ as the level of statistical significance.

Results

Of 14.9 million Ontario residents, we identified 6,231,942 individuals, who had at least one SARS-CoV-2 PCR test between January 25, 2020, and November 21, 2021. After excluding 48,392 individuals who had a non-Omicron SARS-CoV-2 infection within 90 days of the start of follow-up and 11,107 individuals who died before November 22, 2021, we included a total of 6,172,443 participants in the analysis (Figure 1). At the baseline, 495,657 participants had a prior confirmed infection, and 5,676,786 participants

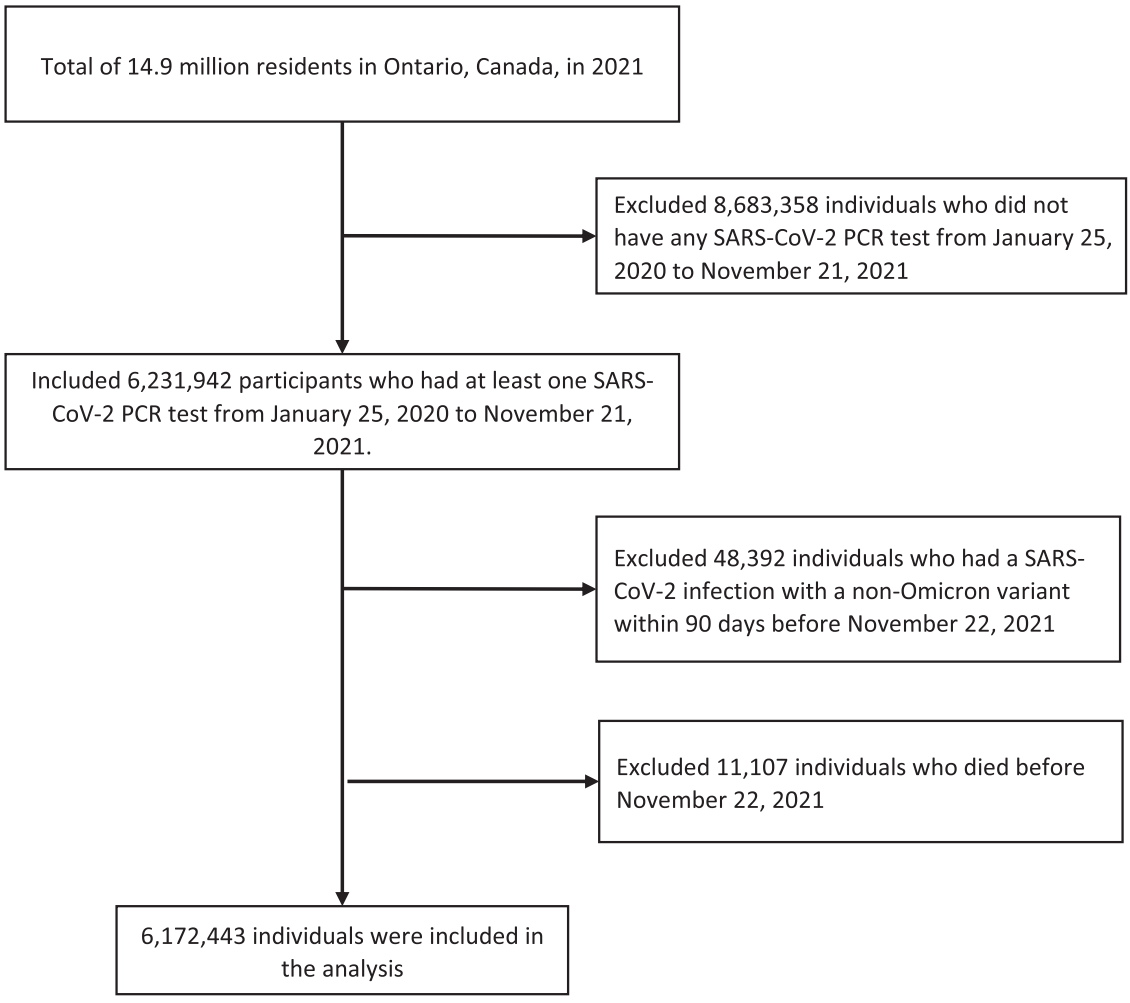

Figure 1. Flow chart of participants in the cohort. PCR, polymerase chain reaction

Table 1
Demographic characteristics and vaccination status at baseline[a].

Characteristics	Prior infection		
	No (n = 5,676,786)	Yes (n = 495,657)	Total individuals (N = 6,172,443)
Age group, N (%) (years)			
<=4	334,394 (5.9)	15,870 (3.2)	382,183 (5.7)
5-11	457,333 (8.1)	26,295 (5.3)	541,756 (8.1)
12-19	485,033 (8.5)	50,210 (10.1)	592,165 (8.9)
20-29	830,170 (14.6)	92,894 (18.7)	998,906 (14.9)
30-39	845,234 (14.9)	80,457 (16.2)	999,321 (14.9)
40-49	724,627 (12.8)	75,175 (15.2)	867,916 (13.0)
50-59	762,251 (13.4)	74,274 (15.0)	902,561 (13.5)
60-69	597,505 (10.5)	42,843 (8.6)	686,474 (10.3)
70-79	368,622 (6.5)	20,234 (4.1)	41,2917 (6.2)
80+	271,617 (4.8)	17,405 (3.5)	300,938 (4.5)
Sex, N (%)			
Male	2,640,516 (46.5)	243,597 (49.1)	2,884,113 (46.7)
Female	3,036,270 (53.5)	252,060 (50.9)	3,288,330 (53.3)
Long-term care resident, N (%)			
No	5,616,428 (98.9)	485,973 (98.0)	6,102,401 (98.9)
Yes	60,358 (1.1)	9684 (2.0)	70,042 (1.1)
Neighborhood income quintile[b]			
1 (lowest)	1,049,528 (18.5)	122,335 (24.7)	1,171,863 (19.0)
2	1,068,463 (18.8)	105,849 (21.4)	1,174,312 (19.0)
3	1,131,437 (19.9)	105,473 (21.3)	1,236,910 (20.0)
4	1,180,713 (20.8)	88,842 (17.9)	1,269,555 (20.6)
5 (highest)	1,230,656 (21.7)	71,714 (14.5)	1,302,370 (21.1)
Number of comorbidities, N (%)			
0	3,289,811 (58.0)	296,473 (59.8)	3,586,284 (58.1)
1	1,414,685 (24.9)	122,944 (24.8)	1,537,629 (24.9)
2	516,414 (9.1)	42,769 (8.6)	559,183 (9.1)
≥3	455,876 (8.0)	33,471 (6.8)	489,347 (7.9)
Essential workers quintile [b]			
1 (0-32.5%)	1,274,879 (22.5)	78,784 (15.9)	1,353,663 (21.9)
2 (32.5-42.3%)	1,285,535 (22.6)	104,512 (21.1)	1,390,047 (22.5)
3 (42.3-49.8%)	1,119,557 (19.7)	98,921 (20.0)	1,218,478 (19.7)
4 (50.0-57.5%)	1,044,468 (18.4)	104,775 (21.1)	1,149,243 (18.6)
5 (57.5-100%)	925,090 (16.3)	106,281 (21.4)	1,031,371 (16.7)
Vaccination status at baseline			
Unvaccinated	1,204,646 (21.2)	89,105 (18.0)	1,293,751 (21.0)
Vaccinated with one dose	123,977 (2.2)	16,156 (3.3)	140,133 (2.3)
Vaccinated with two doses	4,068,233 (71.7)	372,007 (75.1)	4,440,240 (71.9)
Vaccinated with three doses	279,930 (4.9)	18,389 (3.7)	298,319 (4.8)

[a] Full list of demographic characteristics is provided in the Appendix Table S3. Continuous variables were presented as mean (± SD). Categorical variables were presented as number of individuals and percentages. Standardized differences between the two groups were also presented with 95% confidence interval.
[b] The sum of counts does not equal the column total because of individuals with missing information (≤1.0%) for this characteristic.

were considered infection-naïve. Compared to the infection-naïve group, previously infected individuals were more likely to be adolescents or working-age adults, male, long-term care residents, have no comorbidities, and reside in areas with lower household income and higher proportions of essential workers. As of November 22, 2021, 21% (1,293,751) of the cohort was unvaccinated, 71.9% (4,440,240) was vaccinated with two doses, and 4.8% (298,319) was vaccinated with three doses; only 2.3% (140,133) was vaccinated with a single dose. The proportions of individuals with one or two doses among previously infected individuals were greater than among infection-naïve individuals (Table 1). The full list of demographic characteristics is given in Supplementary Table 3.

From November 22 to December 31, 2021, we observed 110,026 Omicron infections, with a median follow-up time of 39 days and an incidence rate of 139.5 (95% CI 138.6-140.3) per 10,000 person-months. A total of 106,070 Omicron infections occurred in individuals without a prior infection, compared to 3956 observed among those previously infected, most of which occurred at least 6 months after the previous infection. After adjusting for all covariates, including vaccination status, the HR for Omicron infection among previously infected individuals compared to infection-naïve individuals was 0.33 (95% CI 0.32-0.35), corresponding to an overall estimated protection of 67% (95% CI 65-68). In the cohort, the overall protection of infection-acquired immunity against Omicron infection was 73% (95% CI 67-78) at 3-5 months, 70% (95% CI 69-72) at 6-8 months, 64% (95% CI 62-66) at 9-11 months, and 64% (95% CI 61-66) 12-14 months post-infection. The trend was maintained until ≥15 months post-infection when the overall protection declined to 54% (95% CI 49-58) (Supplementary Table 5).

Among unvaccinated individuals, infection-acquired immunity provided 63% (95% CI 59-66) overall protection against Omicron infection. The protection was 67% (95% CI 50-78) at 3-5 months, was maintained at 58% (95% CI 49-66) 12-14 months post-infection, and declined to 45% (95% CI 26-59) ≥15 months post-infection (Figure 2).

In individuals vaccinated with two doses, a prior infection was associated with 68% (95% CI 61-74) higher overall protection against Omicron infection compared to infection-naïve individuals. The incremental protection of infection-induced immunity in individuals with a prior infection and two-dose vaccination was highest at 79% (95% CI 75-81) 0-2 months since the last antigenic exposure, compared to immunity induced by two vaccine doses alone

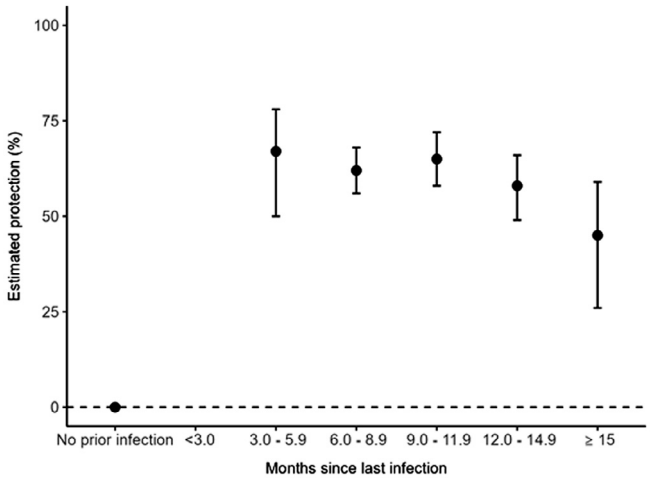

Figure 2. Protection and durability of infection-acquired immunity against Omicron infection among unvaccinated individuals. We assessed the protection of infection-acquired immunity in unvaccinated individuals at 3-5, 6-8, 9-11, 12-14, and ≥15 months since last infection. Individuals without a prior SARS-CoV-2 infection and unvaccinated serve as the reference group. Since a prior SARS-CoV-2 infection was determined by any positive polymerase chain reaction test at least 90 days before an Omicron infection, protection of infection-acquired immunity <3 months since last infection was not applicable. Specific estimates and their 95%CI are shown in Supplementary Table 6.

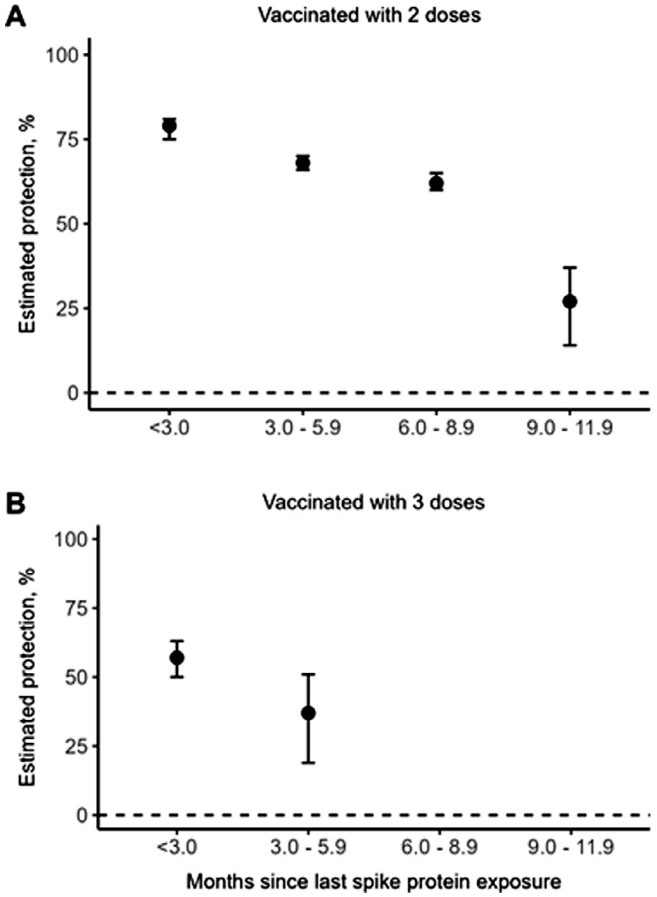

Figure 3. The incremental protection of infection-acquired immunity against Omicron infection and its durability in individuals with hybrid immunity. In Figure 3(a), we assessed the incremental protection of infection-acquired immunity against Omicron infection in individuals with hybrid immunity (acquired from a prior infection and two-dose vaccination) in comparison to those with two-dose vaccination only at 0-2, 3-5, 6-8, and 9-11 months since last antigenic exposure. Individuals with two-dose vaccination only at each time interval served as the reference group. In Figure 3(b), we assessed the incremental protection of infection-acquired immunity against Omicron infection in individuals with hybrid immunity (acquired from a prior infection and three-dose vaccination) in comparison to those with three-dose vaccination only at 0-2, 3-5, 6-8, and 9-11 months since last spike protein exposure. Individuals with three-dose vaccination only at each time interval served as the reference group. Specific estimates and their 95%CI are shown in Supplementary Table 7.

0-2 months after vaccination. However, it declined over time to 27% (95% CI 14-37) 9-11 months since the last antigenic exposure (Figure 3a).

In individuals vaccinated with three doses, a prior infection was associated with 45% (95% CI 29-57) higher overall protection against Omicron infection compared to infection-naïve individuals. The incremental protection of infection-induced immunity in individuals with a prior infection and three-dose vaccination was 57% (95% CI 50-63) 0-2 months since the last antigenic exposure and declined to 37% (95% CI 19-51) 3-5 months since the last antigenic exposure (Figure 3b).

Discussion

We conducted a cohort study of 6 million Ontario residents to examine the effectiveness and durability of infection-acquired immunity and how it modifies vaccine-induced immunity in preventing Omicron infection. By comparing to individuals protected by vaccination only, we found that on top of immunity induced by COVID-19 vaccines, a prior infection was associated with 68% and 43% incremental protection against Omicron infection in individuals vaccinated with two and three doses respectively. Among individuals with hybrid immunity acquired from prior infection and two-dose vaccination, the incremental protection of infection-acquired immunity decreased from 79% within 3 months after vaccination or infection to 27% at 9-11 months, whereas for individuals with hybrid immunity acquired from prior infection and three-dose vaccination, it decreased from 57% within 3 months to 37% at 3-5 months post vaccination or infection.

Consistent with previous studies, we observed that past SARS-CoV-2 infections provide added cross-variant immunity in vaccinated populations, indicating that hybrid immunity acquired from both infections and vaccines achieved higher protection against Omicron infection than vaccination only. Furthermore, we observed lower incremental protection of infection-induced immunity in individuals vaccinated with three doses compared to those with two doses. The extent to which infection-acquired immunity adds to vaccine-induced immunity varies between populations with different vaccine dosages and across studies. For example, in the previous studies, a past SARS-CoV-2 infection was associated with 20-40% overall incremental protection against Omicron infection in individuals with two doses, and 10-30% in those with three doses [8,10,11]. The improved protection against Omicron infection following SARS-CoV-2 infections among vaccinated individuals can be supported by immunological evidence that antigenic exposure achieved through either vaccination or infection strengthens the magnitude of the serum antibody-neutralizing response [25]. However, it is important to note that our analysis focuses on the relative protection of hybrid immunity to vaccines, as we quantified the additional preventive benefit of infection-acquired immunity among vaccinated populations in comparison to vaccinated individuals only. Therefore, our estimated incremental protection of infection-acquired immunity should be interpreted with an understanding that the comparison groups have residual protection from vaccines and may depend on absolute vaccine effectiveness, which is often calculated in comparison to unvaccinated individuals and can vary substantially across settings due to different populations, epidemiological situation, and public health policies implemented for containing COVID-19 transmission [26,27].

We observed evidence of waning protection from infection-acquired immunity in individuals with hybrid immunity within one year from the last antigenic exposure. Our findings are consistent with existing immunological studies that antibodies from past infections and vaccination are all projected to wane, leading to decreased protection against future infections [28]. In contrast to pre-Omicron studies that observed minimal waning of protection provided by infection-induced immunity and hybrid immunity even more than 15 months after infection or vaccination [19,29,30], we observed that the additional benefit of past infections declined substantially after 3 months post-infection or vaccination in individuals with three vaccine doses and after 9 months in those with two doses, suggesting that SARS-CoV-2 infections contracted before the Omicron wave may not provide immunity against Omicron infection that is as durable as against the previous variant of concerns (VOCs). This may be attributed to the immunity evasion properties of the Omicron variant, as researchers observed considerably lower neutralizing antibody responses to Omicron compared with previous VOCs ([31–33]), owing to key mutations in the spike protein of the Omicron variant [34–36]. Furthermore, we observed a faster decline of the incremental protection acquired from the previous infection in individuals with three doses compared with two doses. It should be noted that individuals in our cohort with a third dose were among the priority groups, which, compared to the general population, were older and had a higher proportion of long-term care residents and individuals living with at least one comorbidity (Supplementary Table 4). Pre-Omicron studies observed faster decay of and lower peak neutralization antibody titers following vaccination and/or infection in persons aged 65 years or older compared to persons younger than 65 years [37,38]. A recent study reported significantly lower antibody concentrations in response to Omicron measured 1 month after the booster dose among older adults compared to those among healthcare workers [39]. This suggests that infection- and/or vaccine-induced immunity may provide limited and transient protection against Omicron infection in the elderly.

Strength and limitations

Compared to previous studies that examined the effect of previous SARS-CoV2 infection and hybrid immunity, the main strength of our study is the size and completeness of our dataset, which is based on the entire population of Ontario, Canada, and included over 6 million participants who had been tested for COVID-19 since the start of the pandemic among the entire 14·9 million Ontario residents. We followed up individuals over time and captured changes in infection and vaccination status during follow-up by using population-wide databases. Furthermore, a major limitation in the previous studies is that important risk factors for SARS-CoV-2 infections such as residential status and socioeconomic indicators were not adjusted for when assessing the effectiveness of infection-acquired and vaccine-induced immunity. In our study, we adjusted for a comprehensive set of covariates, including comorbidities and indicators for residential and socioeconomic status, that have been identified in the literature to be associated with higher infection risks. Data on the majority of comorbidity variables has been validated and showed high sensitivity and specificity (Supplementary Table 2), so misclassification of comorbidities is minimal.

Our study has some limitations. First, residual confounding may have potentially biased our estimates, including differences between vaccinated and unvaccinated groups and previously infected and infection-naïve groups in terms of mobility and contact levels, compliance with public health measures, and susceptibility to infection [40]. Second, some misclassification of Omicron cases might have occurred. However, the WGS and SGTF screening used to ascertain infection types are believed to be highly accurate, and results from the sensitivity analysis showed that our estimates in the incremental protection of infection-induced immunity against Omicron infection are stable when using a more restrictive definition of Omicron cases (Supplementary Tables 8 and 9). Third, with over 30% of our cohort older than 50 years of age, our findings may not be generalizable to settings with a much younger population. Fourth, we did not calculate the absolute vaccine effectiveness, which is the hybrid immunity in comparison to unvaccinated individuals, because of the substantial difference among the groups, i.e., the unvaccinated group tended to be younger and residents with three doses tended to be much older, thus, our results might be influenced by the residual effect of vaccines. Finally, our study had a relatively short follow-up due to changes in PCR testing policies in 2022. As such, we were unable to estimate the protection of hybrid immunity against Omicron subvariants that emerged in 2022 nor its protection beyond 6 months after a third dose. Therefore, more longitudinal studies among populations with complete testing are needed to assess the long-term effect of a third dose or even a fourth dose, and characterize how vaccines and past infection will influence the risk of infections with Omicron subvariants and their associated severe outcomes.

Conclusion

Our study reaffirms the importance of accounting for hybrid immunity in transmission models to better understand and predict epidemic dynamics. Our findings support prior evidence that a previous SARS-CoV-2 infection provides added immunity to vaccination against Omicron infection. We further addressed an evidence gap by examining the durability of this incremental protection, as we found that it may decline substantially within 1 year since the last antigenic exposure. Given the limited durability of infection-acquired immunity in individuals with hybrid immunity, its influence on shield-effects at the population level and reducing reinfection risks at the individual level may be limited.

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Ethical approval

ICES is a prescribed entity under Ontario's Personal Health Information Protection Act (PHIPA). Section 45 of PHIPA authorizes ICES to collect personal health information, without consent, for the purpose of analysis or compiling statistical information with respect to the management of, evaluation or monitoring of, the allocation of resources to or planning for all or part of the health

system. Projects that use data collected by ICES under section 45 of PHIPA, and use no other data, are exempt from Research Ethics Board (REB) review. The use of the data in this project is authorized under section 45 and approved by ICES' Privacy and Legal Office.

Author contributions

XW and JK conceived the study idea. SW, YL, SM, JK, and XW designed the study and developed the analysis protocol. YL performed data analysis and SW verified the analysis and results. SM, KB, SB, JK, and XW provided inputs to the analysis and methodology. SW wrote the first draft of the manuscript. All authors critically revised the manuscript, approved the final version, and had final responsibility for the decision to submit for publication.

Data availability statement

The dataset from this study is held securely in coded form at ICES. While legal data sharing agreements between ICES and data providers (e.g., healthcare organizations and government) prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS (email: das@ices.on.ca). The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

Declaration of Competing Interest

The authors have no competing interests to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.11.028.

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