Protection against omicron (B.1.1.529) BA.2 reinfection conferred by primary omicron BA.1 or pre-omicron SARS-CoV-2 infection among health-care workers with and without mRNA vaccination: a test-negative case-control study

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Summary

Background There is a paucity of data on vaccine-induced or infection-induced (hybrid or natural) immunity against omicron (B.1.1.529) subvariant BA.2, particularly in comparing the effects of previous SARS-CoV-2 infection with the same or different genetic lineage. We aimed to estimate the protection against omicron BA.2 associated with previous primary infection with omicron BA.1 or pre-omicron SARS-CoV-2, among health-care workers with and without mRNA vaccination.

Methods We conducted a test-negative case-control study among health-care workers aged 18 years or older who were tested for SARS-CoV-2 in Quebec, Canada, between March 27 and June 4, 2022, when BA.2 was the predominant variant and was presumptively diagnosed with a positive test result. We identified cases (positive test during study period) and controls (negative test during study period) using the provincial laboratory database that records all nucleic acid amplification testing for SARS-CoV-2 in Quebec, and used the provincial immunisation registry to determine vaccination status. Logistic regression models compared the likelihood of BA.2 infection or reinfection (second positive test ≥30 days after primary infection) among health-care workers who had previous primary infection and none to three mRNA vaccine doses versus unvaccinated health-care workers with no primary infection.

Findings 258 007 SARS-CoV-2 tests were done during the study period. Among those with a valid result and that met the inclusion criteria, there were 37 732 presumed BA.2 cases (2521 [6·7%] reinfections following pre-omicron primary infection and 659 [1·7%] reinfections following BA.1 primary infection) and 73 507 controls (7360 [10·0%] had pre-omicron primary infection and 12 315 [16·8%] had BA.1 primary infection). Pre-omicron primary infection was associated with a 38% (95% CI 19–53) reduction in BA.2 infection risk, with higher BA.2 protection among those who had also received one (56%, 95% CI 47–63), two (69%, 64–73), or three (70%, 66–74) mRNA vaccine doses. Omicron BA.1 primary infection was associated with greater protection against BA.2 infection (risk reduction of 72%, 95% CI 65–78), and protection was increased further among those who had received two doses of mRNA vaccine (96%, 95–96), but was not improved with a third dose (96%, 95–97).

Interpretation Health-care workers who had received two doses of mRNA vaccine and had previous BA.1 infection were subsequently well protected for a prolonged period against BA.2 reinfection, with a third vaccine dose conferring no improvement to that hybrid protection. If this protection also pertains to future variants, there might be limited benefit from additional vaccine doses for people with hybrid immunity, depending on timing and variant.

Funding Ministère de la Santé et des Services Sociaux du Québec.

Introduction

Since December, 2021, omicron (B.1.1.529) has been the dominant SARS-CoV-2 variant globally, responsible for the highest COVID-19 incidence to date due to its greater transmissibility and escape from natural immunity and vaccine-induced immunity.[1,2] The initial omicron BA.1 sublineage has been replaced by the phylogenetically distinct and even more transmissible BA.2 sublineage.[3,4] In Quebec, Canada, omicron BA.2 became dominant at the end of March, 2022, accounting for more than 90% of sequenced viruses during the ensuing weeks.[5]

The intense omicron BA.1 surge that occurred among the population of Quebec, despite a high proportion of people having been vaccinated, between December, 2021, and February, 2022,[6] resulted in a considerable pool of people with potential hybrid immunity induced by the combination of vaccination and infection. In the context of previous reports of reduced and rapidly waning

Lancet Infect Dis 2023; 23: 45–55

Published Online September 21, 2022 https://doi.org/10.1016/S1473-3099(22)00578-3

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Research in context

Evidence before this study

We searched Medline and the preprint servers medRxiv and SSRS on June 15, 2022, using the term "omicron BA.2", with no language or date restrictions. We found 16 studies reporting cross-immunity or cross-protection against omicron BA.2 among people who had previous BA.1 infection. Several immunological studies found robust neutralising antibody titres against BA.2 in sera of people who had previous omicron BA.1 infection, which were improved among people who had also been vaccinated. However, we did not identify any published peer-reviewed epidemiological studies that estimated the protection against omicron BA.2 infection in people with previous omicron primary infection with or without vaccination. Two preprint reports estimated cross-sublineage protection against BA.2 reinfection of 95% for people with previous BA.1 infection 35–95 days earlier (adjusted for vaccination) and of about 70% for unvaccinated people who had previous infection during the omicron-dominant period 30–59 days earlier. Data on hybrid immunity (combined protection from vaccination and previous infection) are scarce, particularly in comparing the effects of previous infection with the same or different genetic lineage (eg, pre-omicron infection *vs* omicron BA.1 infection).

Added value of this study

We conducted a test-negative case-control study to estimate the protection against omicron BA.2 reinfection conferred by previous pre-omicron or omicron BA.1 primary infection, with and without mRNA vaccination, in the population-based cohort of health-care workers aged 18 years or older in Quebec, Canada.

Previous omicron BA.1 infection alone was the single most protective factor against BA.2 reinfection (risk reduction of 72%), and was associated with higher protection than pre-omicron primary infection alone (38%) or even than three doses of mRNA vaccine in people with no previous infection (46%). Hybrid immunity conferred by previous omicron BA.1 primary infection plus vaccination increased estimated protection against BA.2 reinfection, similarly to 96% with two or three vaccine doses, and this protection was maintained for at least 5 months after primary infection.

Implications of all the available evidence

In the context of hundreds of millions of people worldwide who have already had SARS-CoV-2 infection, and with over half having accrued since omicron emergence, our results have important implications for preparedness and response to future epidemic waves. If also applicable to other populations and emerging omicron subvariants, our findings of substantial and sustained omicron BA.1 hybrid protection against BA.2 among health-care workers suggest that people who have had previous omicron infection and two vaccine doses might be well protected. For such individuals, additional doses might provide only marginal added benefit against subsequent omicron infections and severe outcomes. Therefore, available vaccine doses might be better prioritised for protecting people who are more vulnerable globally.

vaccine effectiveness against omicron and its sub-lineages,[1,7,8] the potential benefit of third (booster) vaccine doses requires updated understanding compared with within-lineage cross-protection. In particular, the protection against omicron BA.2 conferred by natural and hybrid immunity associated with primary infection with pre-omicron SARS-CoV-2 or omicron BA.1 virus warrants comparison.

We aimed to estimate the protection against omicron BA.2 infection conferred by previous primary infection with omicron BA.1 or pre-omicron SARS-CoV-2, among a population-based cohort of health-care workers with and without mRNA vaccination.

Methods

Study design

We conducted a test-negative case-control study among health-care workers who had SARS-CoV-2 nucleic acid amplification testing in Quebec, Canada, between March 27 and June 4, 2022 (epidemiological weeks 13–22), when BA.2 was the predominant variant and was presumptively diagnosed with a positive test result.

This study was conducted under the legal mandate of the National Director of Public Health of Quebec under the Public Health Act, granting a participant consent waiver. It was approved by the Research Ethics Board of the Centre Hospitalier Universitaire de Québec-Université Laval.

Participants

We included in the study all health-care workers aged 18 years or older who were paid by the Quebec publicly funded health-care system or were registered as members of a health college (physicians, nurses, nursing assistants, respiratory therapists, midwifes, and pharmacists). We compared participants who had a positive SARS-CoV-2 test during the study period (cases) with those who had a negative test (controls). We defined mRNA vaccination as receipt of one dose at least 14 days before specimen collection or two or three doses at least 7 days before specimen collection, with the first and second doses administered at least 21 days apart. People who had a SARS-CoV-2 test within these intervals, who had an invalid vaccination date, or who received a non-mRNA vaccine were excluded. In Quebec, shorter intervals between doses were recommended for people who were immuno-compromised.[9] There, we included only participants who had the second and third doses administered at least 90 days apart, and had not received a fourth dose of vaccine before specimen collection.

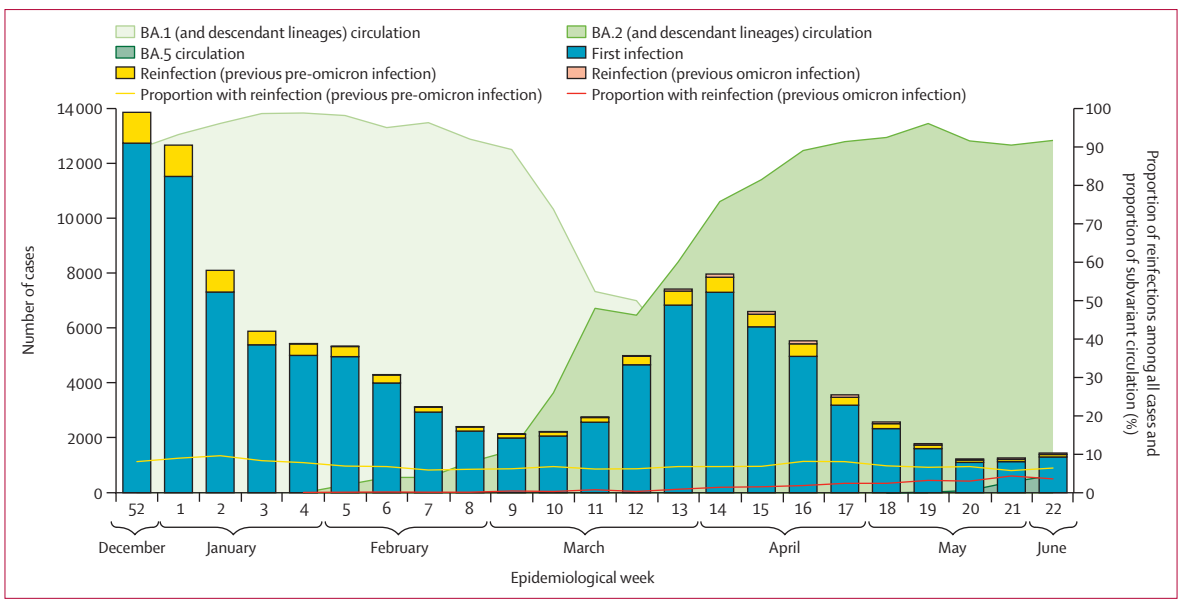

Figure 1: **Weekly distribution of SARS-CoV-2 infections by infection history and weekly proportion of reinfections among all infections during the omicron BA.1 and BA.2 waves, December, 2021–June, 2022**

Reinfection was defined as two positive specimens collected at least 30 days apart. Consequently, tests that were done within 30 days of a previous positive result were excluded. Health-care workers with a reinfection documented before the study period were also excluded. Negative tests collected within 7 days before a positive test were excluded, to avoid misclassifying potential cases within their incubation period as controls. We additionally excluded cases without nucleic acid amplification test confirmation.

Data sources

We identified cases and controls using the provincial laboratory database that records all nucleic acid amplification testing for SARS-CoV-2 in Quebec, including the date of specimen collection, the result, and testing indication. Indications for testing were being symptomatic in assessment centres, symptoms during consultation at the emergency room or hospitalisation, asymptomatic during outbreaks, hospital pre-admission screening, contact with case(s), confirmation of a rapid antigen detection testing positive result, confirmation of recovery, and other reasons combined. Publicly funded nucleic acid amplification testing was broadly accessible to all health-care workers in Quebec throughout the pandemic. We defined symptomatic infection as a positive test result in the presence of symptoms during consultation at an assessment centre, at the emergency room, or at hospitalisation, recognising a broad clinical spectrum for COVID-19.

Using a unique personal identifying number, the cohort of health-care workers was linked with the laboratory database; the provincial immunisation registry, which is a population-based database including all unvaccinated and vaccinated people with their dates of vaccination and the type of vaccine administered; the provincial database of all COVID-19 cases, including demographics and clinical information; and the administrative hospitalisation database.

Procedures

We defined exposure by a combination of previous infection and vaccination history. We defined primary infection as a SARS-CoV-2-positive specimen collected at least 30 days before a specimen collected during the study period. The 30-day interval was chosen to capture all potential BA.2 reinfections following previous BA.1 primary infection, because early reinfections during SARS-CoV-2 variant replacement periods have been documented.[10–12] In a sensitivity analysis, we defined reinfection using the more standard 90-day interval.[13–15]

We defined a pre-omicron primary infection as any SARS-CoV-2-positive specimen collected between Feb 20, 2020, and Nov 27, 2021. The strategy for variant of concern identification in Quebec during this period has been detailed elsewhere.[16] Based on provincial genomic surveillance, we assumed omicron BA.1 attribution for cases between Dec 26, 2021, and March 26, 2022; during this period, all sequenced viruses were omicron and more than 90% overall were characterised as omicron BA.1 between Dec 26, 2021, and March 5, 2022, decreasing but remaining predominant (>50% overall) through March 26, 2022.[5] To separately ascribe and analyse the protection associated with pre-omicron versus omicron primary infection, we excluded

	Cases (n=37 732)		Controls (n=73 507)	
	Previous primary infection	No primary infection	Previous primary infection	No primary infection
Total	3180	34 552	19 675	53 832
Sex				
Female	2643 (82·8%)	28 235 (81·7%)	16 566 (84·2%)	44 401 (82·5%)
Male	546 (17·2%)	6317 (18·3%)	3109 (15·8%)	9431 (17·5%)
Age, years				
18–39	1750 (55·0%)	16 473 (47·7%)	10 833 (55·1%)	24 383 (45·3%)
40–59	1341 (42·2%)	16 161 (46·8%)	8106 (41·2%)	25 629 (47·6%)
≥60	89 (2·8%)	1918 (5·6%)	736 (3·7%)	3820 (7·1%)
Type of employment				
Physician	104 (3·3%)	1653 (4·8%)	465 (2·4%)	3014 (5·6%)
Nursing staff or respiratory therapist	1220 (38·4%)	10 736 (31·1%)	7706 (39·2%)	18 051 (33·5%)
Other health-assisting occupation	980 (30·8%)	8319 (24·1%)	6048 (30·7%)	13 857 (25·7%)
Social worker	569 (17·9%)	8317 (24·1%)	3464 (17·6%)	11 131 (20·7%)
Pharmacist	24 (0·8%)	505 (1·5%)	160 (0·8%)	974 (1·8%)
Management and administrative staff	283 (8·9%)	5022 (14·5%)	1832 (9·3%)	6805 (12·6%)
Facility				
Hospital or health centre	1712 (53·8%)	18 798 (54·4%)	10 927 (55·5%)	29 557 (54·9%)
Long-term health facility	605 (19·0%)	3705 (10·7%)	3736 (19·0%)	7020 (13·0%)
Rehabilitation centre	141 (4·4%)	1689 (4·9%)	712 (3·6%)	2248 (4·2%)
Childhood and youth centre	89 (2·8%)	1547 (4·5%)	561 (2·9%)	1569 (2·9%)
Home care	182 (5·7%)	2057 (6·0%)	1023 (5·2%)	2640 (4·9%)
Other	451 (14·2%)	6756 (19·6%)	2716 (13·8%)	10 798 (20·1%)
Time of specimen collection, epidemiological weeks (calendar date)				
13–14 (March 27–April 9)	1102 (34·7%)	13 789 (39·9%)	4737 (24·1%)	19 310 (35·9%)
15–16 (April 10–23)	1001 (31·5%)	10 676 (30·9%)	5141 (26·1%)	14 515 (27·0%)
17–18 (April 24–May 7)	563 (17·7%)	5284 (15·3%)	4271 (21·7%)	8995 (16·7%)
19–20 (May 8–21)	264 (8·3%)	2556 (7·4%)	2862 (14·6%)	5983 (11·1%)
21–22 (May 22–June 4)	250 (7·9%)	2247 (6·5%)	2664 (13·5%)	5029 (9·3%)
Indication for testing				
Symptomatic, emergency room	52 (1·6%)	445 (1·3%)	820 (4·2%)	1636 (3·0%)
Symptomatic, health-care worker	1765 (55·5%)	21 058 (60·9%)	7374 (37·5%)	20 588 (38·2%)
Asymptomatic, closed setting outbreak	252 (7·9%)	1523 (4·4%)	4617 (23·5%)	10 767 (20·0%)
Asymptomatic, hospital pre-admission	41 (1·3%)	318 (0·9%)	1417 (7·2%)	3880 (7·2%)
Asymptomatic contact	283 (8·9%)	3710 (10·7%)	1955 (9·9%)	8749 (16·3%)
Asymptomatic other	177 (5·6%)	915 (2·6%)	1973 (10·0%)	4758 (8·8%)
Confirmation of positive rapid antigen test	562 (17·7%)	6324 (18·3%)	938 (4·8%)	2277 (4·2%)
Other reasons combined	48 (1·5%)	259 (0·7%)	581 (3·0%)	1177 (2·2%)
Variant of concern of primary infection by calendar period				
Before variant of concern (before Feb 1, 2021)	2081 (65·4%)	NA	5996 (30·5%)	NA
Before variant of concern or alpha (Feb 1–April 10, 2021)	185 (5·8%)	NA	503 (2·6%)	NA
Alpha (April 11–June 26, 2021)	98 (3·1%)	NA	280 (1·4%)	NA
Alpha or delta (June 27–Sept 4, 2021)	53 (1·7%)	NA	141 (0·7%)	NA
Delta (Sept 5–Nov 27, 2021)	104 (3·3%)	NA	440 (2·2%)	NA
Omicron BA.1 (Dec 26, 2021–March 26, 2022)	630 (19·8%)	NA	11 585 (58·9%)	NA
Omicron BA.2 (March 27–May 7, 2022)	29 (0·9%)	NA	730 (3·7%)	NA
Time between primary infection and specimen collection, days	487 (246–572)	NA	120 (95–483)	NA

Data are n (%) or median (IQR). NA=not applicable.

Table 1: **Characteristics of cases and controls stratified by SARS-CoV-2 primary infection history**

participants with past infection during the period of delta and omicron cocirculation (Nov 28–Dec 25, 2021).

We defined vaccination as the administration of BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna) mRNA vaccines. Health-care workers were a prioritised group for vaccination throughout the pandemic, earlier for high-risk facilities (long-term and acute-care facilities), and without geographical differences in the province. Health-care workers with pre-omicron or omicron BA.1 subvariant primary infection who had received no vaccine, or one, two, or three vaccine doses were compared with health-care workers who had no previous primary infection and had not been vaccinated.

The main outcomes were any nucleic acid amplification test-positive SARS-CoV-2 infection or symptomatic infection during the study period, in the context of omicron BA.2 subvariant dominance when 86% (weekly range 60–93) of viruses from sentinel laboratories characterised by sequencing were BA.2 (figure 1).[5] Other outcomes were the number of deaths and COVID-19 hospitalisations within 30 days of sample collection by infection history and vaccination status.

Statistical analysis

The odds of pre-omicron or omicron BA.1 primary infection with or without vaccination and of vaccination alone without primary infection were compared among cases and controls. The comparator group for all analyses were health-care workers who had no previous primary vaccination and had not been vaccinated. Adjusted odds ratios (ORs) and their 95% CIs were computed using the maximum likelihood estimator. Logistic regression models were adjusted for age (18–39, 40–59, and ≥60 years), sex, type of employment (as a proxy for socioeconomic status), facility (associated with infection risk and prioritisation for vaccination), testing indication (as a proxy for disease severity), and epidemiological week (to address vaccine roll-out and potential differential in virus exposure opportunities over time between cases and controls). Vaccine effectiveness or protection (ie, BA.2 infection risk reduction) was derived as 1 – adjusted OR.[17] ORs were not estimated for exposure categories with fewer than five participants because the statistical uncertainty would be too large. Analyses were also stratified by time since last primary infection or vaccine exposure. We did post-hoc sensitivity analyses stratifying by age group and epidemiological weeks 15–22 (April 10–June 4, 2022), when 76–96% of SARS-CoV-2 viruses detected by sentinel laboratories were BA.2.

Statistical analyses were performed using SAS (version 9.4).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

	All infections analysis		Symptomatic infections analysis*	
	Cases (n=37 732)	Controls (n=73 507)	Cases (n=23 371)	Controls (n=30 542)
Pre-omicron primary infection				
Overall	2521 (6·7%)	7360 (10·0%)	1495 (6·4%)	2643 (8·7%)
Non-vaccinated	109 (0·3%)	265 (0·4%)	57 (0·2%)	41 (0·1%)
One vaccine dose	342 (0·9%)	729 (1·0%)	214 (0·9%)	285 (0·9%)
Primary infection, first dose	340 (0·9%)	722 (1·0%)	212 (0·9%)	283 (0·9%)
First dose, primary infection	2 (<0·1%)	7 (<0·1%)	2 (<0·1%)	2 (<0·1%)
Two vaccine doses	897 (2·4%)	2665 (3·6%)	540 (2·3%)	987 (3·2%)
Primary infection, two doses	815 (2·2%)	2376 (3·2%)	486 (2·1%)	860 (2·8%)
First dose, primary infection, second dose	39 (0·1%)	107 (0·1%)	24 (0·1%)	56 (0·2%)
Two doses, primary infection	43 (0·1%)	182 (0·2%)	30 (0·1%)	71 (0·2%)
Three vaccine doses	1173 (3·1%)	3701 (5·0%)	684 (2·9%)	1330 (4·4%)
Primary infection, three doses	1028 (2·7%)	3177 (4·3%)	594 (2·5%)	1118 (3·7%)
First dose, primary infection, second and third doses	83 (0·2%)	271 (0·4%)	52 (0·2%)	99 (0·3%)
Two doses, primary infection, third dose	62 (0·2%)	253 (0·3%)	38 (0·2%)	113 (0·4%)
Omicron BA.1 primary infection				
Overall	659 (1·7%)	12315 (16·8%)	330 (1·4%)	5600 (18·3%)
Non-vaccinated	125 (0·3%)	727 (1·0%)	43 (0·2%)	119 (0·4%)
One vaccine dose	9 (<0·1%)	109 (0·1%)	3 (<0·1%)	33 (<0·1%)
Primary infection, first dose	1 (<0·1%)	6 (<0·1%)	1 (<0·1%)	2 (<0·1%)
First dose, primary infection	8 (<0·1%)	103 (<0·1%)	2 (<0·1%)	31 (<0·1%)
Two vaccine doses	262 (0·7%)	5322 (7·2%)	147 (0·6%)	2519 (8·2%)
Two doses, primary infection	262 (0·7%)	5314 (7·2%)	147 (0·6%)	2517 (8·2%)
First dose, primary infection, second dose	0	8 (<0·1%)	0	2 (<0·1%)
Three vaccine doses	263 (0·7%)	6157 (8·4%)	137 (0·6%)	2929 (9·6%)
Three doses, primary infection	243 (0·6%)	5679 (7·7%)	124 (0·5%)	2716 (8·9%)
Two doses, primary infection, third dose	20 (0·1%)	478 (0·7%)	13 (0·1%)	213 (0·7%)
No previous SARS-CoV-2 infection				
Overall	34 552 (91·6%)	53 832 (73·2%)	21 546 (92·2%)	22 299 (73·0%)
Non-vaccinated	672 (1·8%)	1043 (1·4%)	343 (1·5%)	125 (0·4%)
One vaccine dose	136 (0·4%)	193 (0·3%)	68 (0·3%)	45 (0·1%)
Two vaccine doses	6717 (17·8%)	8939 (12·2%)	4387 (18·8%)	3839 (12·6%)
Three vaccine doses	27 027 (71·6%)	43 657 (59·4%)	16 748 (71·7%)	18 290 (59·9%)

*Including only participants who had symptoms at the time of specimen collection according to the indication for testing.

Table 2: **Vaccination status of presumed omicron BA.2 cases and controls stratified by SARS-CoV-2 primary infection (pre-omicron or omicron BA.1)**

Results

258 007 tests were performed among health-care workers in Quebec during the study period, 256 636 (99·5%) of which had valid results and were merged with other databases. 39 955 (15·5%) of tests were excluded (appendix p 4). In total, 37 732 presumed omicron BA.2 cases were compared with 73 507 randomly selected controls. Most participants were aged 18–59 years (n=104 677 [94·1%]) and female (n=91 845 [82·6%]; table 1). A previous SARS-CoV-2 primary infection was

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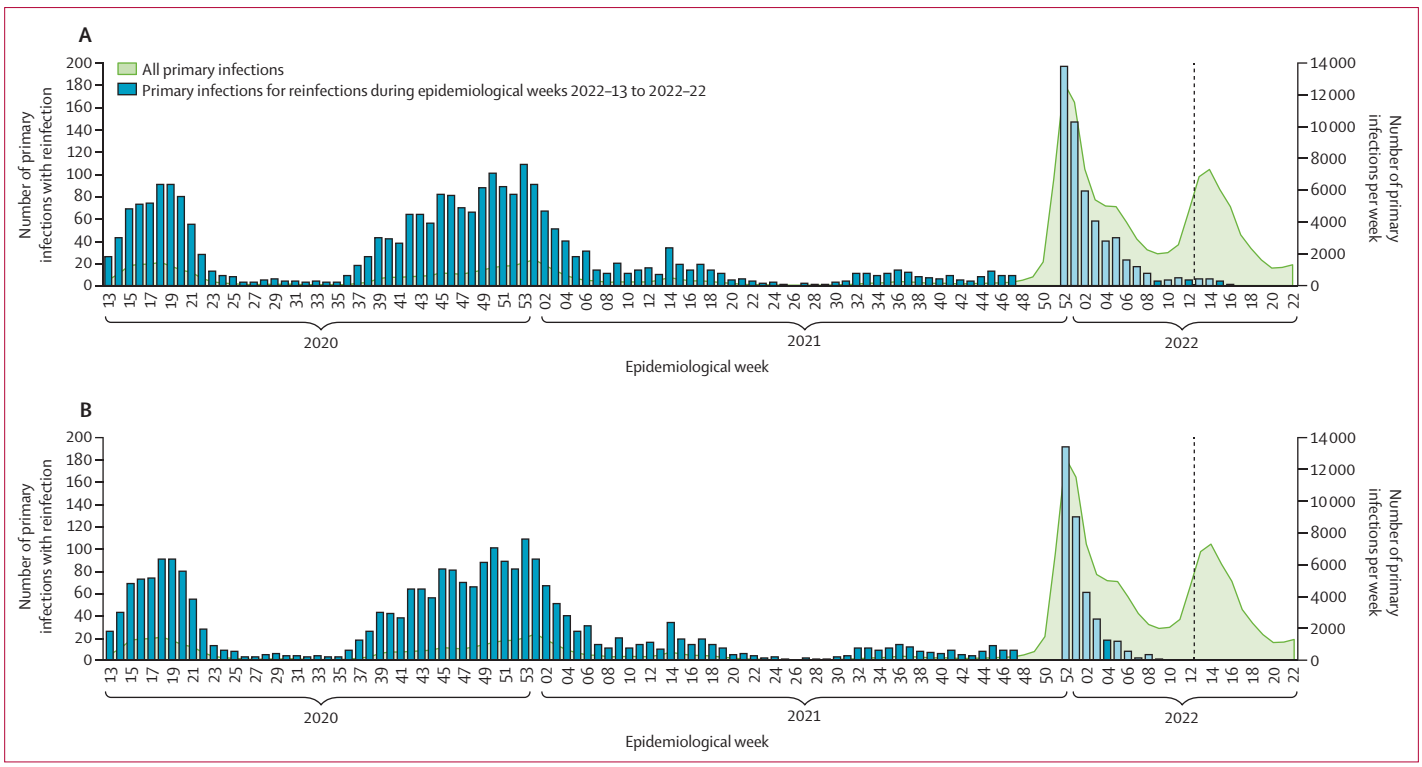

Figure 2: **Distribution of primary infections relative to reinfections during the study period, by definition of reinfection (≥30-day interval *vs* ≥90-day interval)**
Distribution of primary infections associated with a reinfection using the 30-day or longer interval definition (A) and using the 90-day or longer interval definition (B). Vertical dotted lines show start of study period.

observed in 3180 (8·4%) of 37 732 cases and 19 675 (26·8%) of 73 507 controls (table 2). Among cases, 1159 (3·1%) had primary infection combined with two vaccine doses and 1436 (3·8%) had primary infection and three vaccine doses. Among controls, 687 (10·9%) had primary infection combined with two vaccine doses and 821 (13·4%) had primary infection and three vaccine doses.

COVID-19 hospitalisations within 30 days following specimen collection were recorded for 58 vaccinated cases: 51 (0·1%) of 34 552 cases without primary infection, four (0·2%) of 2521 cases with pre-omicron primary infection, and three (0·6%) of 659 cases with BA.1 primary infection. Only one COVID-19-attributable death was documented in a participant with no previous primary infection who had received three doses of vaccine (data not shown).

Among the 2521 (6·7%) cases who had reinfection following pre-omicron primary infection, most had been vaccinated following their primary infection (815 [32·3%] had received two vaccine doses and 1028 [40·8%] had received three vaccine doses) and 109 (4·3%) remained unvaccinated. Among the 659 (1·7%) cases who had reinfection after a presumed omicron BA.1 primary infection, 125 (19·0%) were unvaccinated, 262 (39·8%) had received two vaccine doses, and 263 (36·9%) had received three vaccine doses (table 2).

Reinfections in participants who had a previous pre-omicron primary infection mostly (in 2081 [82·5%] of 2521 participants) occurred before February, 2021, during the time before the variant-of-concern period, with a median primary infection to reinfection interval of 515 days (IQR 461–682; figure 2). Reinfections in participants who had a previous omicron primary infection mostly (in 429 [65·1%] of 659 participants) occurred during the 3 peak weeks of the omicron BA.1 wave, with a median primary infection to reinfection interval of 100 days (IQR 87–116). Of these, 49 (6·5%) reinfections occurred at 30–59 days after primary infection and 151 (20·8%) occurred at 60–89 days after primary infection (figure 2). The proportion of reinfections following a BA.1 primary infection increased from 0·9% to 3·6% of the reported cases from epidemiological weeks 13–22 of 2022 (figure 1).

Pre-omicron primary infection alone (without vaccination) was associated with a BA.2 reinfection risk reduction of 38% (95% CI 19–53) and a symptomatic reinfection risk reduction of 51% (22–69). In participants who had received two vaccine doses and had pre-omicron primary infection hybrid exposure, the estimated BA.2 reinfection risk reduction was 69% (95% CI 64–73), similar to in participants who had received three vaccine doses and had pre-omicron primary infection exposure (70%, 66–74). Protection against symptomatic BA.2 reinfection was also similar in participants who had

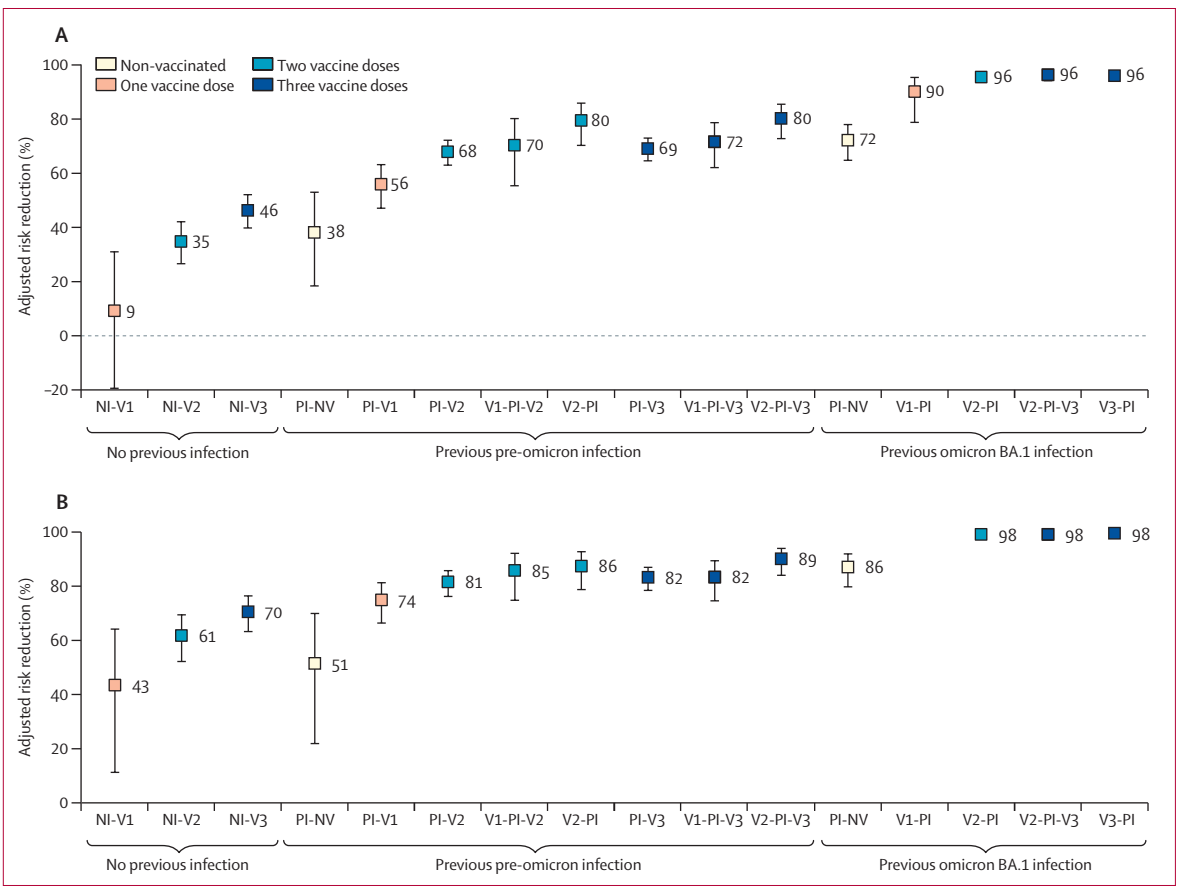

Figure 3: **Protection against omicron BA.2 infection (any infection or symptomatic infection) conferred by pre-omicron or omicron BA.1 primary infection with or without vaccination**

Protection against any BA.2 infection (A) and symptomatic BA.2 infection (B). Logistic regression models compared participants with previous primary infection or vaccination, or both, versus unvaccinated participants without previous primary infection. All estimates were adjusted for age, sex, type of employment, facility, indication for testing, and epidemiological week. Error bars are 95% CI. NI-V1=no previous infection, one vaccine dose. NI-V2=no previous infection, two vaccine doses. NI-V3=no previous infection, three vaccine doses. PI-NV=primary infection non-vaccinated. PI-V1=primary infection before one vaccine dose. PI-V2=primary infection before two vaccine doses. PI-V3=primary infection before three vaccine doses. V1-PI=primary infection after one vaccine dose. V1-PI-V2=primary infection after first but before second vaccine dose. V1-PI-V3=primary infection after first but before second and third vaccine doses. V2-PI=primary infection after two vaccine doses. V2-PI-V3=primary infection after second but before third vaccine dose. V3-PI=primary infection after three vaccine doses.

pre-omicron primary infection and two vaccine doses (risk reduction of 81%, 95% CI 76–85) or three vaccine doses (83%, 78–86; figure 3; appendix p 2).

Omicron BA.1 primary infection alone (without vaccination) was associated with a BA.2 reinfection risk reduction of 72% (95% CI 65 to 78) and a symptomatic reinfection risk reduction of 86% (79 to 91). This protection was similar to that of hybrid pre-omicron primary infection plus two or three vaccine doses and higher than the estimated risk reduction with three vaccine doses among participants with no previous primary infection (46%, 95% CI 40 to 52; figure 3). This difference was not explained by time since last exposure. At a similar interval since primary infection (3 to <6 months), omicron BA.1 primary infection without vaccination was associated with a BA.2 risk reduction of 70% (95% CI 61 to 77) compared with 42% (–47 to 77) for pre-omicron primary infection without vaccination (table 3). At a similar interval since last exposure (30–89 days), omicron BA.1 primary infection without vaccination was associated with a BA.2 risk reduction of 78% (95% CI 66 to 86), compared with 63% (57 to 68) conferred by three vaccine doses without previous primary infection (data not shown).

Omicron BA.1 primary infection with two mRNA vaccine doses was associated with 96% (95% CI 95–96) reduced risk of any omicron BA.2 reinfection and 98% (97–98) reduced risk of symptomatic omicron BA.2 reinfection. As observed with pre-omicron primary infection, the estimated hybrid protection associated with BA.1 primary infection was not improved with a third vaccine dose against any BA.2 reinfection (risk reduction of 96%, 95% CI 95–97) or symptomatic BA.2 reinfection (98%, 98–99; appendix p 2). The timing of the third dose (ie, before or after the primary infection) did not modify the observed protection (figure 3). Sensitivity

	Pre-omicron primary infection		Omicron BA.1 primary infection	
	Unadjusted risk reduction* (95% CI)	Adjusted risk reduction*† (95% CI)	Unadjusted risk reduction* (95% CI)	Adjusted risk reduction*† (95% CI)
Time since primary infection among unvaccinated participants				
30–59 days (1 to <2 months)	NE	NE	78% (43 to 91)	82% (49 to 94)
60–89 days (2 to <3 months)	NE	NE	72% (59 to 82)	76% (63 to 85)
90–182 days (3 to <6 months)	13% (–99 to 62)	42% (–47 to 77)	73% (66 to 79)	70% (61 to 77)
183–364 days (6 to <12 months)	38% (5 to 60)	39% (0 to 63)	NE	NE
365–757 days (≥12 months)	37% (16 to 53)	42% (17 to 60)	NE	NE
Time since primary infection among participants with two vaccine doses				
30–59 days (1 to <2 months)	NE	NE	94% (88 to 97)	97% (94 to 98)
60–89 days (2 to <3 months)	NE	NE	93% (90 to 95)	97% (96 to 98)
90–159 days (3 to <6 months)	NE	NE	92% (91 to 94)	96% (95 to 96)
Time since primary infection among participants with three vaccine doses				
30–59 days (1 to <2 months)	NE	NE	93% (89 to 95)	96% (94 to 98)
60–89 days (2 to <3 months)	NE	NE	93% (91 to 95)	97% (96 to 98)
90–158 days (3 to <6 months)	NE	NE	94% (92 to 95)	96% (95 to 97)
Time since second vaccine dose among participants with two vaccine doses				
7–59 days (<2 months)	71% (48 to 84)	89% (78 to 94)	NE	NE
60–89 days (2 to <3 months)	42% (18 to 59)	73% (60 to 82)	NE	NE
90–182 days (3 to <6 months)	59% (50 to 66)	77% (71 to 82)	NE	NE
183–364 days (6 to <12 months)	41% (32 to 48)	68% (62 to 74)	NE	NE
Time since third vaccine dose among participants with three vaccine doses				
7–59 days (<2 months)	71% (55 to 80)	88% (81 to 92)	94% (90 to 97)	98% (96 to 99)
60–89 days (2 to <3 months)	49% (39 to 57)	80% (75 to 84)	90% (78 to 96)	95% (89 to 98)
90–182 days (3 to <6 months)	50% (44 to 56)	72% (67 to 76)	NE	NE
183–305 days (6 to <10 months)	74% (–115 to 97)	82% (–109 to 98)	NE	NE

NE=not estimable. *Logistic regression models comparing participants with previous primary infection with or without vaccination versus unvaccinated participants without previous primary infection. †Estimates adjusted for age, sex, type of employment, facility, indication for testing, and epidemiological week.

Table 3: **Protection against any omicron BA.2 reinfection associated with pre-omicron or omicron BA.1 primary infection with or without vaccination, by time since last immunogenic event (vaccination or primary infection)**

analyses stratified by age group showed risk reduction estimates higher than in the primary analysis for two and three vaccine doses with pre-omicron primary infection, but the 95% CIs were overlapping between age groups (appendix p 3). We found no differences when using the more standard 90-day interval for defining reinfection (appendix p 4), or when the period was restricted to epidemiological weeks 15–22 (appendix p 5).

Pre-omicron primary infection without vaccination, occurring 4–25 months before omicron BA.2 circulation, was associated with BA.2 reinfection risk reduction of 42% (95% CI –47 to 77) after 4–5 months, 39% (0 to 63) after 6–11 months, and 42% (17 to 60) after 12 months or longer (table 3). When the last vaccine dose followed the pre-omicron primary infection, two and three doses of vaccine were associated with similar protection during the 7–59-day period after vaccination (risk reduction of 89% [95% CI 78 to 94] with two doses and 88% [81 to 92] with three doses) and the 60–89-day period after vaccination (73% [60 to 82] and 80% [75 to 84]).

Over the 5-month follow-up of participants with history of previous omicron BA.1 primary infection, a non-significant decline in BA.2 reinfection protection was observed among unvaccinated participants (from risk reduction of 82% [95% CI 49–94] at 30–59 days to 70% [61–77] at 90–160 days), but not among those who had received two or three doses before their primary infection, whose protection remained between 96% and 97% for the 30–159 days of follow-up (table 3).

Estimated protection against BA.2 reinfection when the third dose was instead administered after an omicron BA.1 primary infection was similarly high at 98% (95% CI 96–99) at 7–59 days after the third dose and 95% (89–98) at 60–89 days after the third dose. No participants who had received two vaccine doses had received their second dose after omicron BA.1 primary infection (table 3).

Discussion

Hybrid immunity resulting from previous omicron BA.1 infection plus two or three mRNA vaccine doses conferred the highest protection against any BA.2 infection (risk reduction of 96%) or symptomatic BA.2 infection (98%) among health-care workers. Protection was maintained for at least 5 months after primary infection. Previous omicron BA.1 primary infection alone was associated with greater protection against BA.2 infection than pre-omicron primary SARS-CoV-2 infection alone, or even three doses of mRNA vaccine in health-care workers who had no previous primary infection. When the primary infection was pre-omicron SARS-CoV-2, the reduction in risk of BA.2 reinfection was 38% in unvaccinated individuals, but was greater than 85% in those who had received their second or third vaccine dose less than 2 months earlier, and 70% when these doses were administered 2–6 months earlier.

In this population of health-care workers, 1·7% of cases detected during the study period, where BA.2 was the dominant variant, had previous primary infection with omicron BA.1; their odds of reinfection was four times lower than among those who had previous pre-omicron primary infection, but was still higher than the reported reinfection rates before the omicron surge.[18,19] The omicron BA.2 sublineage shares multiple mutations with BA.1, but with genetic differences conferring growth advantage and resulting in BA.1 displacement.[3] Omicron BA.2 reinfections had been documented using whole genome sequencing as early as 20 days after an omicron BA.1 primary infection, although such occurrences appeared to be rare.[10,11]

We observed a moderate protection against any BA.2 infection (risk reduction of 38%) and symptomatic BA.2 infection (51%) by heterologous pre-omicron primary infection without vaccination. Persistent cross-protection extending to different lineages might be explained by a T-cell response recognising epitopes across multiple viral proteins and other non-structural proteins that are less susceptible to mutations.[20] We found higher effectiveness

for hybrid immunity with primary infection and two vaccine doses (risk reduction of 81%) than for natural immunity from primary infection alone. This pattern was also reported in a study from Qatar, with 46% effectiveness against symptomatic BA.2 infection in people who had pre-omicron primary infection and 55% if combined with two vaccine doses and 77% with three doses.[14] Protection was greater than 70% against any severe outcome.[14] Their lower estimate for hybrid immunity with primary infection and two vaccine doses compared with our results might be explained by a longer time since second dose. Andeweg and colleagues[12] reported in a preprint that protection against BA.2 infection for people with previous (pre-omicron or omicron) infection was 60–80% for those who had received two vaccine doses within 1–7 months earlier, and 75–80% for those who had received three vaccine doses within 1–4 months earlier. Studies examining protection against omicron reinfection (BA.1 or any sublineage) have reported that previous pre-omicron SARS-CoV-2 infection was associated with moderate protection against infection (25–47%), but stronger protection against severe outcomes (>80%), which was improved further with vaccination.[12,14–16,21,22] As reported in our study, a third vaccine dose among health-care workers with previous infection was associated with only a transient increase in protection both against omicron BA.1 and BA.2 subvariants.[12,15,16]

Despite antigenic differences among omicron sublineages, immunological data show robust neutralising antibody titres against BA.2 in the sera of people who have had previous infection with BA.1, with broader neutralising responses across variants in people who have also been vaccinated.[23,24] Few studies to date have estimated real-word cross-protection. We found that previous omicron infection alone was associated with 72% protection against BA.2 reinfection, and 82% when primary infection occurred 30–59 days earlier. In a preprint, Chemaitelly and colleagues[25] evaluated cross-sublineage protection against BA.2 reinfection 35 days or longer after primary infection and reported that BA.1 was 95% protective against BA.2 reinfection during 1–60 days of follow-up. The authors adjusted for, but did not stratify by, vaccine status, and did not show the difference in protection with natural immunity versus hybrid immunity. In their preprint, Andeweg and colleagues[12] reported an estimated protection of about 70% against BA.2 reinfection when the primary infection (without vaccination) occurred 30–59 days earlier, during omicron-dominant SARS-CoV-2 circulation, and thus indirectly measuring BA.1 and BA.2 cross-sublineage protection.[12] The authors did not, however, report protection from hybrid immunity with two or three vaccine doses for primary infections that occurred during the omicron period.

In Quebec, as in many countries with high vaccine coverage, most cases during the omicron BA.1 surge were in people who had received two vaccine doses, as third-dose (booster) campaigns for the general population grew only in response to signals of omicron immune evasion and surge.[6] This created a pool of recently infected or recently vaccinated people with hybrid immunity that was more closely homologous for the infection-induced component. In our population of health-care workers, previous omicron infection combined with two or three vaccine doses was associated with 96% protection against BA.2. Estimated protection was slightly higher against symptomatic infections, and only three hospitalisations were recorded. No other studies to date have directly examined the effect and duration of protection from hybrid BA.1 immunity against descendant omicron sublineages.

Reported protection against omicron reinfection conferred by previous pre-omicron infection waned with time since the last immunogenic event (primary infection or vaccination),[15,16,26] with faster and more substantial waning among vaccinated people who had no previous primary infection.[1] However, data interpretation is challenging due to overlapping changes in SARS-CoV-2 variant circulation, vaccination deployment, and time since the priming event (primary infection or vaccination). In our study, we observed waning in the first 6 months following receipt of the second or third vaccine dose among people with a previous pre-omicron primary infection (from 88–89% to 72–77%), but not for those with previous omicron BA.1 primary infection during the shorter 5-month follow-up period (stable at 96–97%). To our knowledge, no studies with longer follow-up have examined the duration of protection from natural or hybrid immunity conferred by omicron BA.1 primary infection.

Our study has some limitations. We assigned BA.1 and BA.2 sublineages based on calendar time and provincial phylogenetic analysis and surveillance.[5] We excluded weeks of delta and omicron cocirculation to specifically measure the effect of previous omicron infection, but still about 14% of infections during the study period might have been due to the omicron BA.1 sublineage,[5] which might have led to overestimation of omicron primary infection protection against BA.2 reinfection. We defined reinfections on the basis of a 30-day or longer interval between positive tests, because of data documenting early BA.2 reinfections.[10,11] Prolonged viral shedding might have been misclassified as reinfection,[13] but this would tend to underestimate the protection associated with previous BA.1 infection. Reassuringly, sensitivity analysis using the standard 90-day or longer interval did not change our estimates. Asymptomatic or pauci-symptomatic infections might have been undetected before or during omicron waves, which would also lead to underestimation of the protection induced by previous infection. Infection ascertainment bias should be low among the prioritised and repeatedly tested health-care workers who had easy and continuous

access to testing. Due to the low COVID-19 hospitalisation rate among health-care workers, the effect of primary infection severity as well as effectiveness against severe outcomes could not be estimated. Previous data indicate that protection should be higher and longer lasting against severe omicron disease.[15,16] The proportion of health-care workers who were unvaccinated and had no previous primary infection, the comparator group for all analyses, was low (<2%), and unmeasured characteristics or exposure behaviours could have differed from the other groups, leading to residual confounding. Reassuringly, our estimates of vaccine and pre-omicron primary infection protection are in line with published evidence. Finally, the study was conducted among health-care workers, such that results might not be generalisable to children, older people, or immunocompromised adults. Extrapolation of our results to newly circulating omicron BA.4 and BA.5 or other sublineages requires caution. BA.4 and BA.5 differ antigenically from BA.2 and are even more distant from BA.1.[24] BA.1 infection-induced neutralising immunity seems less protective against newly dominating omicron BA.5 than BA.2,[27] but preprints from epidemiological studies in Portugal and Qatar suggest that hybrid protection against BA.4 and BA.5 conferred by omicron primary infection and vaccination also remains high at 76–80%.[28,29] Ongoing evaluation of heterologous cross-protection (infection and infection plus vaccine-induced hybrid immunity) against emerging dominant variants and subvariants, including within and between lineages, remains important in informing real-time vaccination programme adjustments.

Hundreds of millions of people worldwide have already been infected with SARS-CoV-2, with over half having accrued since omicron emergence alone, and much of the global population have by now also received two vaccine doses.[30] In that context, our findings have important implications for preparedness and response to future epidemic waves, including immunisation programme recommendations. If also applicable to other populations and emerging omicron subvariants, our findings of substantial and sustained omicron BA.1 hybrid protection against BA.2 among health-care workers suggest that people with previous omicron infection who have received two vaccine doses might be well protected against omicron reinfection. For such individuals, additional vaccine doses might provide only marginal added benefit against subsequent omicron infections and severe outcomes. In that context, available vaccine doses might be better prioritised for protecting people who are more vulnerable globally.

Contributors

GDS and SC conceptualised the study. All authors contributed to the study design. GDS, SC, and MO developed the statistical analysis plan. SC and MO accessed and verified the data, did the data linkage, and conducted the formal analysis. GDS supervised the analyses and verified the data. All authors contributed to data interpretation. SC created the figures and wrote the first draft of the manuscript. All authors critically revised and edited the manuscript and approved the final version for submission. SC and NB contributed to the literature search. GDS obtained funding for the study. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

SC, MO, and GDS report financial support from the Ministère de la Santé et des Services Sociaux du Québec to their institution for this work, during the conduct of the study. GDS reports a grant from Pfizer for a "Meningococcal B antibody seroprevalence study", outside of the submitted work. RG reports personal fees from AbbVie honorary for a conference on respiratory syncytial virus burden in children, outside of the submitted work. DT is supported by a research career award from the Fonds de Recherche du Québec–Santé. JF reports grants from the Ministry of Health of Quebec for sequencing of SARS-CoV-2 positive samples and grants from Cancogen (Génome Canada) for sequencing of SARS-CoV-2-positive samples, outside of the submitted work; and is chair of the provincial genomic surveillance committee of SARS-CoV-2 (INSPQ, Quebec). DMS reports grants paid to their institution from Public Health Agency of Canada, Michael Smith Foundation for Health Research, Canadian Institutes of Health Research, and BCCDC Foundation for Public Health, outside of the submitted work. All other authors declare no competing interests.

Data sharing

The databases used in this study are a property of the Ministère de la Santé et des Services Sociaux du Québec, which were shared with the researchers under the legal mandate of the National Director of Public Health of Quebec under the Public Health Act, precluding data sharing with a third party. Aggregate data are available within the manuscript and in the appendix.

Acknowledgments

This work was supported by the Ministère de la Santé et des Services Sociaux du Québec. We thank Radhouene Doggi and Abakar Idriss-Hassan (Institut National de Santé public du Québec) for their contribution in the literature search.

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