Effectiveness of previous infection-induced and vaccine-induced protection against hospitalisation due to omicron BA subvariants in older adults: a test-negative, case-control study in Quebec, Canada

Sara Carazo, Danuta M Skowronski, Marc Brisson, Chantal Sauvageau, Nicholas Brousseau, Judith Fafard, Rodica Gilca, Denis Talbot, Manale Ouakki, Yossi Febriani, Geneviève Deceuninck, Philippe De Wals, Gaston De Serres

Summary

Background Older adults (aged ≥60 years) were prioritised for COVID-19 booster vaccination due to severe outcome risk, but the risk for this group is also affected by previous SARS-CoV-2 infection and vaccination. We estimated vaccine effectiveness against omicron-associated hospitalisation in older adults by previously documented infection, time since last immunological event, and age group.

Methods This was a population-based test-negative case-control study done in Quebec, Canada, during BA.1 dominant (December, 2021, to March, 2022), BA.2 dominant (April to June, 2022), and BA.4/5 dominant (July to November, 2022) periods using provincial laboratory, immunisation, hospitalisation, and chronic disease surveillance databases. We included older adults (aged ≥60 years) with symptoms associated with COVID-19 who were tested for SARS-CoV-2 in acute-care hospitals. Cases were defined as patients who were hospitalised for COVID-19 within 14 days after testing positive; controls were patients who tested negative. Analyses spanned 3–14 months after last vaccine dose or previous infection. Logistic regression models compared COVID-19 hospitalisation risk by mRNA vaccine dose and previous infection versus unvaccinated and infection-naive participants.

Findings Between Dec 26, 2021, and Nov 5, 2022, we included 174 819 specimens (82 870 [47·4%] from men and 91 949 [52·6%] from women; from 8455 cases and 166 364 controls), taken from 2951 cases and 48 724 controls in the BA.1 period; 1897 cases and 41 702 controls in the BA.2 period; and 3607 cases and 75 938 controls in the BA.4/5 period. In participants who were infection naive, vaccine effectiveness against hospitalisation improved with dose number, consistent with a shorter median time since last dose, but decreased with more recent omicron subvariants. Four-dose vaccine effectiveness was 96% (95% CI 93–98) during the BA.1 period, 84% (81–87) during the BA.2 period, and 68% (63–72) during the BA.4/5 period. Regardless of dose number (two to five doses) or timing since previous infection, hybrid protection was more than 90%, persisted for at least 6–8 months, and did not decline with age.

Interpretation Older adults with both previous SARS-CoV-2 infection and two or more vaccine doses appear to be well protected for a prolonged period against hospitalisation due to omicron subvariants, including BA.4/5. Ensuring that older adults who are infection naive remain up to date with vaccination might reduce COVID-19 hospitalisations most efficiently.

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For the French translation of the abstract see Online for appendix 1

Biological Risks Unit, Institut National de Santé Publique du Québec, Quebec, QC, Canada (S Carazo PhD, C Sauvageau MD, N Brousseau MD, R Gilca PhD, M Ouakki MSc, Prof P De Wals PhD, Prof G De Serres PhD); **Social and Preventive Medicine Department, Faculty of Medicine, Laval University, Quebec, QC, Canada** (S Carazo, Prof M Brisson PhD, C Sauvageau, N Brousseau, R Gilca, Prof D Talbot PhD, Prof P De Wals, Prof G De Serres); **Communicable Diseases and Immunization Services, British Columbia Centre for Disease Control, Vancouver, BC, Canada** (D M Skowronski MD); **Centre Hospitalier Universitaire de Québec–Université Laval Research Center, Quebec, QC, Canada** (Prof M Brisson, C Sauvageau, N Brousseau, R Gilca, Prof D Talbot, Y Febriani MSc, G Deceuninck MD, Prof P De Wals, Prof G De Serres); **Laboratoire de Santé Publique du Québec, Institut National de Santé Publique du Québec, Sainte-Anne-de-Bellevue, Quebec, QC, Canada** (J Fafard MD)

Correspondence to: Dr Sara Carazo, Biological Risks Unit, Institut National de Santé Publique du Québec, Quebec, QC G1E 7G9, Canada **sara.carazo@inspq.qc.ca**

Introduction

Since December, 2021, omicron (B.1.1.529) has been the dominant SARS-CoV-2 variant globally. Omicron subvariants have rapidly evolved from the initial BA.1 strain to more transmissible and immune evasive subvariants BA.2, BA.4, BA.5 (BA.4/5), and BQ.1, with XBB the predominant strain by April, 2023.[1] The more recent subvariants, including BA.4/5, have shown substantial capacity to escape from vaccine-only-induced or infection-only-induced neutralising antibodies, but this appears less pronounced in individuals with vaccine-induced and infection-induced hybrid immunity.[2,3]

Vaccine effectiveness against SARS-CoV-2 is reduced and shorter lasting for omicron compared with the delta (B.1.617.2) variant,[4–6] and for the BA.4/5 subvariant compared with BA.1 or BA.2.[7–9] Vaccine effectiveness against BA.4/5-associated hospitalisation in adults was 60–80% within 4–6 months of vaccination, declining thereafter in studies in non-infected individuals or with adjustment for previous infection history,[7–11] similar to the reported vaccine effectiveness in the small number of trials assessing people aged 60 years or older.[9,10] As reported during BA.1 and BA.2 periods,[12,13] stronger and longer lasting vaccine effectiveness was expected in

Research in context

Evidence before this study

We searched MEDLINE, medRxiv, and SSRN from Jan 1, 2020, to Dec 6, 2022 using the terms "omicron BA.5" or "omicron BA.4", with no language restrictions. References of identified papers were also reviewed. We identified 14 relevant epidemiological studies, which reported estimates on vaccine effectiveness (ten studies), or protection from previous infection-induced immunity (two studies) or hybrid immunity (infection and vaccine; four studies) against infection or severe disease caused by omicron, including the BA.4/5 subvariants, in adults or the general population. Vaccine effectiveness against hospitalisation was 60–80% within 4–6 months of vaccination, declining afterwards. Vaccine effectiveness did not increase with number of booster doses when considering the interval since vaccination, but most studies presented estimates adjusted for (rather than stratifying for) previous infection history or had no information on previous infections. Previous infection was associated with moderate protection against symptomatic BA.4/5 reinfection, but higher protection when the primary infection was caused by the omicron variant. When the protection from previous infection was evaluated in vaccinated populations, the incremental effectiveness ranged between 65% and 93% against BA.4/5 reinfection and 96% against BA.4/5-associated severe outcomes. The only study assessing vaccine protection stratified by previous infection status during the omicron period found that booster doses did not improve protection against infections in adults with hybrid immunity who had already received two vaccine doses, but the study did not have a sufficient number of hospitalisations to evaluate severe outcomes and did not stratify by omicron subvariant (BA.1, BA.2, BA.4/5, and BA.2.75). In summary, there remains a paucity of data about protection against omicron BA.4/5 stratified by type of immunity (infection-induced, vaccine-induced, or both), especially against severe outcomes.

Added value of this study

With both methodological and clinical implications, our study separately assesses and directly compares protection against omicron hospitalisation due to omicron BA.1, BA.2, and BA.4/5 subvariants in older adults conferred by previous infection (pre-omicron or omicron), monovalent mRNA vaccination (by number of doses), or both (hybrid immunity), stratified by interval since the last immunological event. Our findings suggest that mRNA vaccine effectiveness against hospitalisation due to omicron was lower for BA.4/5 than for BA.1 or BA.2 subvariants, and was modified mainly by previous infection history rather than number of vaccine doses. Although protection from vaccination alone waned with time, hybrid immunity in those with both previous infection and at least two vaccine doses was more robust, exceeding 90% for at least 6–8 months regardless of type of previous infection or number of booster doses received.

Implications of all the available evidence

Overall, we show that older adults with a history of both previous SARS-CoV-2 infection and at least two vaccine doses appear well protected against hospitalisation due to omicron, including BA.4/5, for a prolonged period. The risk of hospitalisation due to COVID-19 in older adults mainly varies based on previous infection history, and booster dose recommendations should take this important consideration into account. In individuals with previous SARS-CoV-2 infection, the plateauing of hybrid protection after two vaccine doses calls into question the incremental value of additional booster doses in preventing COVID-19 hospitalisation, whereas in people who are infection naive, waning vaccine protection over time justifies additional booster doses. Immunisation programmes aiming to prevent hospitalisations should prioritise efforts to administer booster doses to people who are infection naive; in September to November, 2022, this group still constituted about half of the older adult population in high-income countries. Ensuring older adults who are infection naive remain up to date with vaccination might reduce COVID-19 hospitalisations most efficiently.

individuals (including adults aged ≥60 years) with hybrid immunity, but evidence for protection against BA.4/5-associated severe outcomes by type of previous infection and duration since the last immunological event remains scarce.

Due to their higher risk of severe outcomes, older adults (≥60 years) have been prioritised for COVID-19 vaccination. Seroprevalence data show an age-related decrease in cumulative SARS-CoV-2 infection across the pandemic, with about half of older adults having been infected by November, 2022.[14] Previous SARS-CoV-2 infection and repeat booster vaccination probably decreased the overall risk of severe COVID-19 in older populations. However, most vaccine effectiveness analyses and booster dose policies have not taken into account this relevant and evolving immuno-epidemiological context.[15,16]

In this study, we aimed to estimate the protection against omicron-associated hospitalisation in older adults conferred by vaccination (one to five doses), by previous infection (pre-omicron or omicron), and by hybrid immunity during the BA.1, BA.2, and BA.4/5 periods.

Methods

Study design and population

In this population-based test-negative case-control study we recruited adults aged 60 years or older living in the province of Quebec, Canada, who had symptoms associated with COVID-19 and had a SARS-CoV-2 nucleic

acid amplification test (NAAT) in acute-care hospitals between Dec 26, 2021, and Nov 5, 2022.

In Quebec, the clinical indication for SARS-CoV-2 NAAT was recorded for all specimens (appendix 2 p 2). NAAT access was restricted during the first pandemic wave (February to June, 2020), but became widely available from July, 2020. The omicron surge in December, 2021, occurred as rapid antigen detection tests (RADTs) became broadly available free of charge to the general population. Due to laboratory capacity, NAAT access has been restricted since Jan 5, 2022 to individuals aged 70 years or older with symptoms associated with COVID-19, patients who attend emergency rooms or are admitted to hospital, and individuals living in closed settings (eg, long-term care facilities or prisons).[17] The mitigation measures in place at the beginning of the omicron wave (Dec 5, 2021) to contain transmission (eg, physical distancing, limited numbers of people gathering, and mask use requirements) were lifted in March, 2022.

For this study, eligible participants were those who were tested in acute-care hospitals with symptoms associated with COVID-19, not specified otherwise (clinical indication M1).[17] Cases were defined as patients who were hospitalised with a positive SARS-CoV-2 NAAT result admitted within 14 days after specimen collection with COVID-19 as primary diagnosis at discharge or respiratory illness as the reason for admission. Controls were defined as patients who had symptoms of COVID-19 with a negative SARS-CoV-2 NAAT result, with or without subsequent hospitalisation. All negative tests were included as controls.

We excluded specimens from individuals who lived in long-term care facilities (because their baseline characteristics and hospital referral indications largely differed from the general population), those with missing comorbidity data, those with documented reinfection before the study period, those who received more than five vaccine doses or a non-mRNA vaccine dose, those vaccinated outside provincial minimum dosing intervals (specified as 21 days between first and second doses and 90 days between subsequent booster doses), those who were tested less than 14 days after their first vaccine or less than 7 days after any subsequent vaccine dose, those who had specimens collected less than 60 days after a positive result (according to reinfection definition), and those with negative specimens collected within 7 days before a positive result. In sensitivity analyses we also excluded individuals identified as being immunosuppressed.

The study was done with the legal mandate of the National Director of Public Health of Quebec under the Public Health Act and approved by the Research Ethics Board of the Centre Hospitalier Universitaire de Québec-Université Laval, who waived the requirement to obtain informed consent.

Procedures

Four Quebec population databases (provincial laboratory database, provincial immunisation registry, administrative hospitalisation database [MED-ECHO], and provincial chronic disease surveillance database [SISMACQ]) were linked through a unique identifying number. The provincial laboratory database comprised all individual-level NAAT results, including testing indication, since pandemic start. The provincial immunisation registry included all residents of Quebec and their COVID-19 vaccine doses and dates administered since immunisation campaign start. MED-ECHO included information on inpatient discharges from Quebec hospitals that provide general or specialised care. SISMACQ links pharmaceutical, medical consultation, and hospitalisation administrative databases to monitor 21 chronic diseases.

See Online for appendix 2

Between Dec 26, 2021, and March 13, 2022, the Quebec laboratory-based surveillance system used single nucleotide polymorphism genotyping of viruses collected from designated sentinel sites for the omicron subvariant attribution. From March 14, 2022, whole-genome sequencing was done on a randomly selected sample of all NAAT-positive specimens. On the basis of this viral genetic surveillance, three periods were defined by predominant omicron subvariants: BA.1 (74–99% of characterised viruses weekly) spanning Dec 26, 2021, to March 12, 2022; BA.2 (74–99% of characterised viruses weekly) spanning April 3 to June 11, 2022; and BA.4/5 spanning July 3 to Nov 5, 2022 (BA.4 comprised 15–21% of characterised viruses weekly and BA.5 and descendant variants, including BQ.1.1, comprised 61–81% of characterised viruses weekly (figure 1). BQ.1.1 subvariant detection increased from 4% to 15% during the final 4 weeks of the study. Weeks of more than one subvariant cocirculation at high levels were excluded.

We used similar dominance periods to ascribe the variant before infection, assigning the initially circulating variant or subvariant to weeks with cocirculation as follows: pre-omicron before Dec 26, 2021; BA.1 from Dec 26, 2021, to April 2, 2022; BA.2 from April 3 to July 2, 2022; and BA.4/5 from July 3 to Nov 5, 2022.

We defined exposure by previous infection and vaccination history. Vaccination with one to five doses of BNT162b2 (Pfizer–BioNTech) or mRNA-1273 (Moderna) mRNA vaccines needed to be administered at least 14 days (for first dose) or 7 days (for second to fifth dose) before specimen collection. We defined patients with previous infection as those with a first positive SARS-CoV-2 NAAT result (because RADT results were not available) at least 60 days before the current specimen collection. A 60-day interval was chosen to capture most reinfections, balancing improved sensitivity to detect early reinfections against imperfect specificity due to prolonged viral shedding, which is more frequent in older adults.[18,19] We used the less sensitive but more specific 90-day interval in sensitivity analyses.

Outcomes

The main outcome was vaccine effectiveness against hospitalisation associated with BA.1, BA.2, and BA.4/5

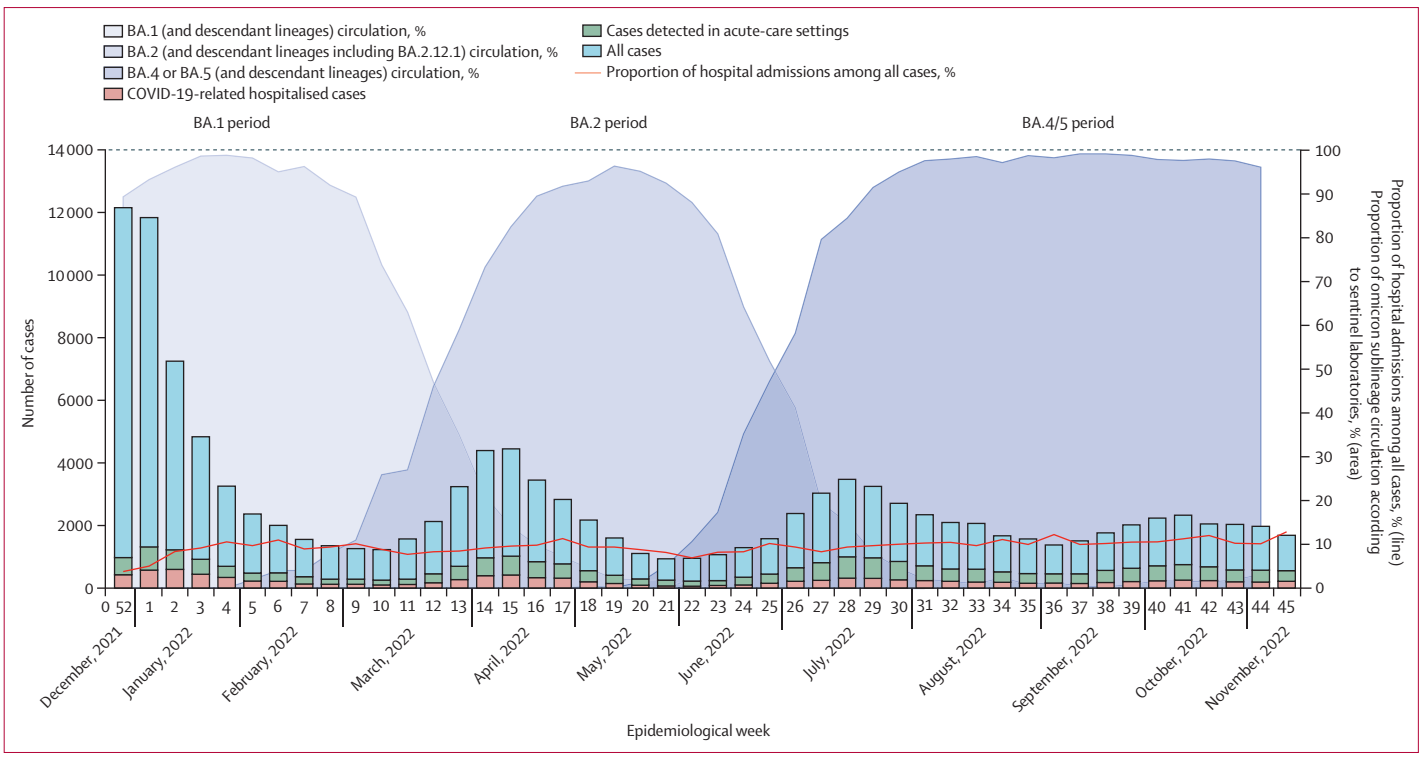

Figure 1: **Number of weekly COVID-19 cases, emergency department consultations and hospitalisations, and omicron sublineage circulation in the province of Quebec, Canada**

infection. As secondary outcomes, we evaluated protection by time since last immunological event and by age.

Statistical analysis

For each period, logistic regression models estimated the odds ratio (OR) for hospitalisation due to omicron by vaccine dose and previous infection history relative to unvaccinated, infection-naive individuals. Models were adjusted for age (60–69 years, 70–79 years, 80–89 years, and ≥90 years old), sex, place of residence (home, private homes for older people, and other), presence of chronic respiratory disease, chronic heart disease, cancer, obesity, immunosuppressive condition, and neurological disease, multimorbidity, and epidemiological week of sampling. We defined multimorbidity as two or more of 21 predefined conditions (hypertension, diabetes, obesity, cardiovascular, respiratory, kidney, and liver diseases, cancer, immunosuppression, neurological disorder, anaemia, hypothyroidism, fluid and electrolyte disorders, coagulopathy, weight loss, psychosis, drug misuse, alcohol misuse, ulcer, and paralysis).[20] Model assumptions, including multicollinearity, were examined and satisfied for each analysis. We derived protection or vaccine effectiveness as (1–OR)×100. We estimated the relative protection comparing individuals who received three to five mRNA doses with those vaccinated with two doses at least 6 months earlier.

Protection was stratified by age (5-year categories for vaccine effectiveness and 10-year categories for hybrid protection) and by time since last immunological event (vaccination or primary infection). For the last immunological event analysis, we pooled previously infected individuals who received two to five doses, given the small number of hospitalised cases and previous results showing similar protection by time since last dose, regardless of dose number.[9,12] In sensitivity analyses, we estimated effectiveness restricted to community-dwelling individuals and excluding immunosuppressed individuals. Statistical analyses were done 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.

Results

293 722 NAATs were done in people with symptoms associated with COVID-19 who had linked information from all source databases and were tested in acute-care hospitals between Dec 26, 2021, and Nov 5, 2022, with 247 292 collected during specified omicron analysis periods. The proportion of excluded NAATs was similar during the BA.1 (19 906 [26·5%]), BA.2 (15 010 [24·4%]), and BA.4/5 (24 094 [21·8%]) periods. The most frequent reason for exclusion was residence in long-term care facilities (15 907 [6·4%]) followed by non-mRNA vaccination (15 116 [6·1%]), with 222 (<1·0%) overall being excluded due to missing data (appendix 2 p 7). After

exclusions, there were 2951 hospitalised cases and 48 724 controls during the BA.1 period, 1897 hospitalised cases and 41 702 controls during the BA.2 period, and 3607 hospitalised cases and 75 938 controls during the BA.4/5 period.

In all periods, cases were more likely than controls to be in men (4637 [54·8%] of 8455 cases *vs* 78 233 [47·0%] of 166 364 controls), among older people (4405 [52·1%] cases *vs* 66 684 [40·1%] controls ≥80 years old), and in people with multimorbidities (6919 [81·8%] cases *vs* 123 824 [74·4%] controls), but cases and controls had similar social and material deprivation index distribution (table 1). Information on race and ethnicity was not available. 1327 (15·7%) cases and 7346 (4·4%) controls were unvaccinated. 4040 (56·7%) of 7128 vaccinated cases and 77 812 (48·9%) of 159 018 vaccinated controls received

	BA.1 period (n=51 675)		BA.2 period (n=43 599)		BA.4/5 period (n=79 545)	
	Cases (n=2951)	Controls (n=48 724)	Cases (n=1897)	Controls (n=41 702)	Cases (n=3607)	Controls (n=75 938)
Sex						
Female	1290 (43·7%)	25 417 (52·2%)	869 (45·8%)	21 989 (52·7%)	1659 (46·0%)	40 725 (53·6%)
Male	1661 (56·3%)	23 307 (47·8%)	1028 (54·2%)	19 713 (47·3%)	1948 (54·0%)	35 213 (46·4%)
Age, years	78 (71–86)	77 (69–84)	81 (75–88)	76 (68–84)	80 (73–87)	77 (69–84)
Age group, years						
60–69	644 (21·8%)	13 232 (27·2%)	254 (13·4%)	11 812 (28·3%)	517 (14·3%)	20 363 (26·8%)
70–79	931 (31·5%)	15 612 (32·0%)	542 (28·6%)	13 919 (33·4%)	1162 (32·2%)	24 742 (32·6%)
80–89	968 (32·8%)	14 568 (29·9%)	755 (39·8%)	11 847 (28·4%)	1391 (38·6%)	22 183 (29·2%)
≥90	408 (13·8%)	5312 (10·9%)	346 (18·2%)	4124 (9·9%)	537 (14·9%)	8650 (11·4%)
Place of residence						
Home	2194 (74·3%)	36 030 (73·9%)	1104 (58·2%)	32 330 (77·5%)	2774 (76·9%)	57 198 (75·3%)
Private homes for older people	684 (23·2%)	11 615 (23·8%)	755 (39·8%)	8527 (20·4%)	772 (21·4%)	17 068 (22·5%)
Other	73 (2·5%)	1079 (2·2%)	38 (2·0%)	845 (2·0%)	61 (1·7%)	1672 (2·2%)
Material deprivation index*						
Upper quintile	7419 (18·0%)	301 (12·1%)	6426 (17·9%)	220 (15·2%)	11266 (17·5%)	452 (14·7%)
Three middle quintiles	23 852 (58·0%)	1423 (57·3%)	20 501 (57·2%)	868 (59·8%)	37 308 (57·8%)	1812 (58·8%)
Lower quintile	9879 (24·0%)	761 (30·6%)	8892 (24·8%)	364 (25·1%)	15 958 (24·7%)	817 (26·5%)
Social deprivation index*						
Upper quintile	7047 (17·1%)	403 (16·2%)	6194 (17·3%)	178 (12·3%)	11148 (17·3%)	504 (16·4%)
Three middle quintiles	24 223 (58·9%)	1459 (58·7%)	21 149 (59·0%)	874 (60·2%)	38 199 (59·2%)	1872 (60·8%)
Lower quintile	9880 (24·0%)	623 (25·1%)	8476 (23·7%)	400 (27·5%)	15 188 (23·5%)	705 (22·9%)
Comorbidity†						
At least two of the 21 comorbidities considered‡	2405 (81·5%)	37 155 (76·3%)	1595 (84·1%)	30 909 (74·1%)	2919 (80·9%)	55 760 (73·4%)
Chronic heart disease	1578 (53·5%)	24 279 (49·8%)	1077 (56·8%)	19 513 (46·8%)	1896 (52·6%)	34 938 (46·0%)
Chronic lung disease	1178 (39·9%)	17304 (35·5%)	798 (42·1%)	14831 (35·6%)	1379 (38·2%)	26 560 (35·0%)
Cancer	640 (21·7%)	10713 (22·0%)	444 (23·4%)	8916 (21·4%)	792 (22·0%)	15 277 (20·1%)
Neurological disease or dementia	515 (17·5%)	6564 (13·5%)	386 (20·3%)	5598 (13·4%)	660 (18·3%)	10 519 (13·9%)
Obesity	420 (14·2%)	5656 (11·6%)	228 (12·0%)	4799 (11·5%)	404 (11·2%)	8225 (10·8%)
Immunosuppressive condition	262 (8·9%)	3486 (7·2%)	148 (7·8%)	2910 (7·0%)	331 (9·2%)	5184 (6·8%)
Previous infection history						
No previous infection	2918 (98·9%)	46323 (95·1%)	1845 (97·3%)	37 292 (89·4%)	3440 (95·4%)	63 927 (84·2%)
Pre-omicron previous infection (March 1, 2020, to Dec 25, 2021)	32 (1·1%)	2322 (4·8%)	35 (1·8%)	1840 (4·4%)	51 (1·4%)	3012 (4·0%)
Omicron previous infection (Dec 26, 2021, to Aug 8, 2022)	1 (<0·1%)	79 (0·2%)	17 (0·9%)	2570 (6·2%)	116 (3·2%)	8999 (11·9%)
Omicron BA.1 (Dec 26, 2021, to April 9, 2022)	1 (<0·1%)	79 (0·2%)	16 (0·8%)	2549 (6·1%)	69 (1·9%)	5316 (7·0%)
Omicron BA.2 (April 10 to July 9, 2022)	NA	NA	1 (0·1%)	21 (0·1%)	32 (0·9%)	2825 (3·7%)
Omicron BA.4/5 (July 10 to Sept 6, 2022)§	NA	NA	NA	NA	15 (0·4%)	858 (1·1%)

(Table 1 continues on next page)

only Pfizer–BioNTech vaccine, 1992 (27·9%) cases and 55 002 (34·6%) controls received a mixed Pfizer–BioNTech and Moderna schedule, and 1096 (15·4%) cases and 26 204 (16·5%) controls received Moderna only. During the BA.4/5 period, 3307 (4·4%) of 76 005 vaccinated participants (both cases and controls) had received a bivalent booster vaccine (table 1). The proportion of controls with repeat vaccine doses increased during the

	BA.1 period (n=51 675)		BA.2 period (n=43 599)		BA.4/5 period (n=79 545)	
	Cases (n=2951)	Controls (n=48 724)	Cases (n=1897)	Controls (n=41 702)	Cases (n=3607)	Controls (n=75 938)
(Continued from previous page)						
Vaccination status and type of vaccine						
Unvaccinated	776 (26·3%)	2289 (4·7%)	221 (11·6%)	1847 (4·4%)	330 (9·1%)	3210 (4·2%)
Vaccinated with ≥1 dose	2175 (73·7%)	46 435 (95·3%)	1676 (88·4%)	39 855 (95·6%)	3277 (90·9%)	72 728 (95·8%)
BNT162b2 (Pfizer–BioNTech)	1552 (52·6%)	28 576 (58·6%)	992 (52·3%)	18 526 (44·4%)	1496 (41·5%)	30 710 (40·4%)
mRNA-1273 (Moderna)	359 (12·2%)	7523 (15·4%)	227 (12·0%)	6870 (16·5%)	510 (14·1%)	11 811 (15·6%)
Mixed mRNA schedule	264 (8·9%)	10 336 (21·2%)	457 (24·1%)	14 459 (34·7%)	1271 (35·2%)	30 207 (39·8%)
Bivalent booster¶	NA	NA	NA	NA	105 (3·2%)	3202 (4·4%)
Interval in months between previous infection and specimen collection	12 (11–14)	13 (11–15)	15 (4–17)	4 (3–15)	7 (4–17)	7 (5–10)
Interval in months between last vaccine dose and specimen collection	4 (2–6)	2 (1–4)	4 (3–5)	3 (2–5)	5 (3–8)	5 (3–7)

Data are n (%) or median (IQR). NA=not applicable. *148 519 (81·7%) of 181 874 participants with data on material and social deprivation index. †Categories of comorbidity are not mutually exclusive. ‡The 21 medical conditions considered were: hypertension, cardiovascular disease, neurological disorder, anaemia, respiratory diseases, diabetes, hypothyroidism, fluid and electrolyte disorders, cancer, kidney disease, obesity, psychosis, liver disease, immune system problem, coagulopathy, weight loss, drug abuse, alcohol abuse, ulcer, and paralysis. §BA.4/5 previous infections considered until Sept 6, 2022, 60 days before the end of the study period. ¶At least one bivalent booster dose (Pfizer–BioNTech BA.4/5 bivalent vaccine or Moderna BA.1 bivalent vaccine)

Table 1: **Characteristics of cases hospitalised due to omicron and test-negative controls stratified by omicron subvariant period**

For more on the **social deprivation index** see https://www.inspq.qc.ca/sites/default/files/publications/2639_material_social_deprivation_index.pdf

	BA.1 period		BA.2 period		BA.4/5 period	
	Cases (n=2951)	Controls (n=48 724)	Cases (n=1897)	Controls (n=41 702)	Cases (n=3607)	Controls (n=75 938)
No previous infection	2918 (98·9%)	46 323 (95·1%)	1845 (97·3%)	37 292 (89·4%)	3440 (95·4%)	63 927 (84·2%)
Unvaccinated	772 (26·2%)	2154 (4·4%)	218 (11·5%)	1610 (3·9%)	316 (8·8%)	2584 (3·4%)
One dose	72 (2·4%)	477 (1·0%)	23 (1·2%)	263 (0·6%)	33 (0·9%)	386 (0·5%)
Two doses	1099 (37·2%)	11 110 (22·8%)	197 (10·4%)	3286 (7·9%)	329 (9·1%)	4648 (6·1%)
Three doses	964 (32·7%)	31 804 (65·3%)	1136 (59·9%)	21 432 (51·4%)	1030 (28·6%)	19 325 (25·4%)
Four doses	11 (0·4%)	778 (1·6%)	271 (14·3%)	10 701 (25·7%)	1460 (40·5%)	30 533 (40·2%)
Five doses	NA	NA	NA	NA	272 (7·5%)	6451 (8·5%)
Previous pre-omicron infection	32 (1·1%)	2322 (4·8%)	35 (1·8%)	1840 (4·4%)	51 (1·4%)	3012 (4·0%)
Unvaccinated	4 (0·1%)	133 (0·3%)	2 (0·1%)	104 (0·2%)	7 (0·2%)	154 (0·2%)
One dose	5 (0·2%)	177 (0·4%)	4 (0·2%)	86 (0·2%)	1 (<0·1%)	122 (0·2%)
Two doses	14 (0·5%)	990 (2·0%)	13 (0·7%)	480 (1·2%)	5 (0·1%)	440 (0·6%)
Three doses	9 (0·3%)	969 (2·0%)	13 (0·7%)	840 (2·0%)	19 (0·5%)	1003 (1·3%)
Four doses	0	53 (0·1%)	3 (0·2%)	330 (0·8%)	16 (0·4%)	1043 (1·4%)
Five doses	NA	NA	NA	NA	3 (0·1%)	250 (0·3%)
Previous omicron infection	1 (<0·1%)	79 (0·2%)	17 (0·9%)	2570 (6·2%)	116 (3·2%)	8999 (11·9%)
Unvaccinated	0	2 (<0·1%)	1 (0·1%)	133 (0·3%)	7 (0·2%)	472 (0·6%)
One dose	0	0	1 (0·1%)	36 (0·1%)	3 (0·1%)	87 (0·1%)
Two doses	1 (<0·1%)	32 (0·1%)	1 (0·1%)	525 (1·3%)	12 (0·3%)	981 (1·3%)
Three doses	0	45 (0·1%)	10 (0·5%)	1229 (2·9%)	35 (1·0%)	2961 (3·9%)
Four doses	0	0	4 (0·2%)	647 (1·6%)	48 (1·3%)	3541 (4·7%)
Five doses	NA	NA	NA	NA	11 (0·3%)	957 (1·3%)

Data are n (%). NA=not applicable.

Table 2: **Previous infection history and vaccination status in cases and controls stratified by omicron subvariant period**

three subvariant periods in line with public health recommendations for booster doses 6 months after the last dose for adults aged 60 years or older in December, 2021, and August, 2022, with an additional dose recommended for adults aged 80 years or older in March, 2022 (table 2; appendix 2 p 8). Consequently, few older adults had only one or two doses, contributing to reduced precision of vaccine effectiveness estimates, especially during BA.2 and BA.4/5 periods.

The proportion of participants with a documented previous infection increased from 33 (1·1%) of 2951 cases and 2401 (4·9%) of 48724 controls during the BA.1 period, to 52 (2·7%) of 1897 cases and 4410 (10·6%) of 41702 controls during the BA.2 period and 167 (4·6%) of 3607 cases and 12011 (15·8%) of 75938 controls during the BA.4/5 period (table 2). Overall, most previous infections were due to omicron, increasing with subvariant periods. Conversely, the proportion of cases

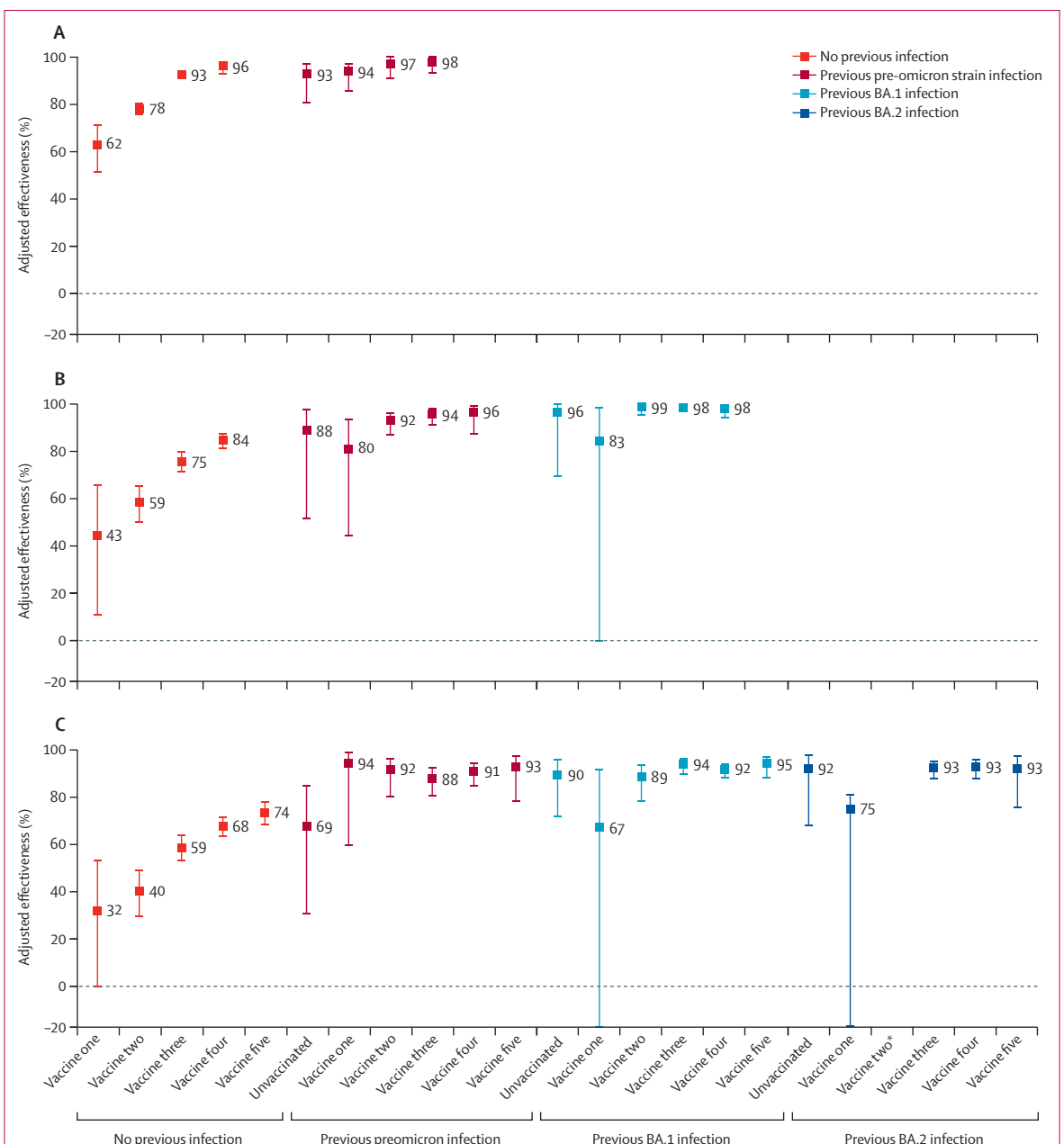

Figure 2: **Estimated protection against hospitalisation due to omicron**
(A) BA.1 period. (B) BA.2 period. (C) BA.4/5 period. Error bars are 95% CI. Logistic regression models adjusted for sex, age (60–69 years, 70–79 years, 80–89 years, and ≥90 years), place of residence (home, private homes for older people, or other), epidemiological week, multimorbidity (two or more conditions), chronic respiratory disease, chronic heart disease, cancer, obesity, immunosuppressive condition, and neurological disease. *Effectiveness was not estimable.

	<3 months*	3 to 5 months	6 to 8 months	9 to 11 months	12 to 14 months
BA.1 period					
When vaccination is last event					
Vaccination without PI					
Two doses	86% (78 to 91)	78% (74to 81)	76% (73 to 79)	68% (37 to 84)	NA
Three doses	93% (92 to 94)	87% (84 to 89)	NA	NA	NA
Four doses	96% (92 to 98)	NA	NA	NA	NA
Vaccination after PI					
Two to four doses and pre-omicron PI	95% (92 to 97)	98% (94 to 99)	96% (90 to 99)	NA	NA
When PI is last event					
PI without vaccination					
Pre-omicron PI	NE	NE	NE	NE	NE
PI after vaccination					
Two to four doses and pre-omicron PI	NE	NE	NE	NE	NE
BA.2 period					
When vaccination is last event					
Vaccination without PI					
Two doses	66% (28 to 84)	46% (12 to 66)	58% (43 to 69)	61% (50 to 70)	73 (–13 to 94)
Three doses	85% (81 to 88)	73% (68 to 77)	66% (48 to 78)	NA	NA
Four doses	82% (78 to 86)	85% (69 to 93)	NA	NA	NA
Vaccination after PI					
Two to four doses and pre-omicron PI	95% (88 to 98)	92% (85 to 95)	84% (54 to 94)	87% (46 to 96)	NA
Two to four doses and omicron PI	96% (90 to 98)	NA	NA	NA	NA
When PI is last event:					
PI without vaccination					
Pre-omicron PI	NE	NE	NE	NE	NE
Omicron PI	NE	NE	NE	NE	NA
PI after vaccination					
Two to four doses and pre-omicron PI	NE	NE	NE	NE	NE
Two to four doses and omicron PI	95% (88 to 98)	99% (95 to 100)	NA	NA	NA
BA.4/5 period					
When vaccination is last event					
Vaccination without PI					
Two doses	55% (–95 to 89)	40% (–5 to 66)	40% (5 to 62)	36% (17 to 51)	47 (35 to 57)
Three doses	82% (68 to 90)	67% (60 to 74)	56% (49 to 62)	56% (45 to 66)	NA
Four doses	80% (76 to 83)	64% (58 to 69)	52% (38 to 63)	75% (–7 to 94)	NA
Five doses	73% (67 to 78)	57% (11 to 79)	NA	NA	NA

(Table 3 continues on next page)

and controls with a previous pre-omicron infection was similar across the three omicron subvariant periods. Somewhat counter-intuitively, the proportion of people with previous infections was lower in unvaccinated controls (626 [19·5%] of 3210 during the BA.4/5 period) than in controls who received one vaccine dose (209 [35·1%] of 595) or two vaccine doses (1421 [23·4%] of 6069), and was only slightly higher in those who received three vaccine doses (3964 [17·0%] of 23 289; appendix 2 p 9).

In those without a documented previous infection, estimated vaccine effectiveness against hospitalisation increased with the number of doses (two doses *vs* four doses) and decreased with more recent subvariants, from 78% (95% CI 75–80) to 96% (93–98) during the BA.1 period; from 60% (50–97) to 84% (81–87) during the BA.2 period; and from 40% (30–49) to 68% (63–72) during the BA.4/5 period. The lower vaccine effectiveness for two doses versus four doses was consistent with the longer median time since second dose versus fourth dose (eg, 13 months *vs* 4 months for BA.4/5; figure 2; appendix 2 p 3). After standardising for time since vaccination, two-dose vaccine effectiveness estimates were lower than three-dose vaccine effectiveness estimates during all omicron subvariant periods, at both less than 3 months and 3–5 months after vaccination (table 3). Estimates of vaccine effectiveness at less than 3 months after vaccination were similar for three-dose versus four-dose vaccination schedules during all omicron subvariant periods, and at 3–5 months after vaccination during the BA.4/5 period for participants who received three, four, or five doses (table 3).

Relative vaccine effectiveness of a third dose, compared with a second dose received 6 months or more before specimen collection and thus eligible for a booster dose, decreased with more recent subvariants to 70% (95% CI 67–73) during BA.1, 38% (26–48) during BA.2, and 31% (22–40) during BA.4/5 periods (appendix 2 p 3).

Previous pre-omicron infection alone (without vaccination) was associated with an estimated effectiveness against hospitalisation of 93% (95% CI 80–97) during the BA.1 period, 88% (50–97) during the BA.2 period, and 69% (30–85) during BA.4/5 periods, which was lower than the effectiveness associated with previous omicron infection during BA.2 (96% [68–99]) and BA.4/5 periods (90% [79–95]; figure 2; appendix 2 p 3). Previous omicron infection alone was associated with a BA.4/5 hospitalisation risk reduction of 90% (95% CI 30–99) at less than 3 months (days 60–89) before specimen collection, 93% (90–97) at 3–5 months, and 84% (57–94) at 6–8 months (table 3).

Hybrid immunity, including previous infection and at least two vaccine doses, was associated with higher protection against hospitalisation than vaccination alone during all analysis periods, and higher than pre-omicron infection alone during the BA.4/5 period (figure 2). Regardless of the number of doses (two to five) or

previous infection type (pre-omicron or omicron), hybrid immunity was associated with a hospitalisation risk reduction of about 90% or more, not improved by booster doses compared with two doses during any of the periods (figure 2; appendix 2 p 3).

When vaccination (two to five doses) was the last immunological event, hybrid protection associated with previous pre-omicron infection decreased slightly with time since last dose from 95% (95% CI 90–98) after less than 3 months, an interval after which most controls (739 [81·6%] of 906) had received four or five vaccine doses, to 82% (54–93) at 9–11 months, a period after which controls had received two (90 [51·4%] of 175) or three (85 [48·6%] of 175) vaccine doses (table 3). However, in participants with a previous omicron infection, estimated hybrid protection during the 8 months after the last vaccine dose remained stable at more than 94% (longer follow-up not feasible). When a previous omicron infection was the last immunological event (not estimable for pre-omicron infection), hybrid protection also remained stable at more than 90% during the first 8 months after infection.

Vaccine effectiveness stratified by age group did not suggest decreased protection with older age, although cautious interpretation is required with multiple comparisons (appendix 2 pp 10–11).

In sensitivity analyses, results were similar when reinfection was defined with a 90-day interval (appendix 2 p 4), with restriction to community-dwelling individuals (appendix 2 p 5), and with exclusion of immunosuppressed individuals (appendix 2 p 6).

	<3 months*	3 to 5 months	6 to 8 months	9 to 11 months	12 to 14 months
(Continued from previous page)					
Vaccination after PI					
Two to five doses and pre-omicron PI	95% (90 to 98)	89% (81 to 93)	90% (79 to 95)	82% (54 to 93)	NA
Two to five doses and omicron PI	94% (90 to 96)	94% (90 to 97)	95% (65 to 99)	NA	NA
When PI is last event					
PI without vaccination					
Pre-omicron PI	NE	NE	NE	NE	NE
Omicron PI	90% (30 to 99)	93% (71 to 98)	84% (57 to 94)	NA	NA
PI after vaccination					
Two to five doses and pre-omicron PI	NE	NE	NE	NE	NE
Two to five doses and omicron PI	91% (85 to 95)	94% (90 to 96)	92% (86 to 96)	88% (51 to 97)	NA

Data are adjusted effectiveness (%, 95% CI). Immunogenic event was defined as either vaccination or primary infection. Logistic regression models adjusted for sex, age (60–69 years, 70–79 years, 80-89 years, and ≥90 years old), place of residence (home, private homes for older people, and other), epidemiological week, multimorbidity (two or more conditions), chronic respiratory disease, chronic heart disease, cancer, obesity, immunosuppressive condition, and neurological disease. NA=not applicable considering variant circulations or vaccine recommendations. NE=not estimable. PI=previous infection. *7–90 days when vaccination was the last event and 60–90 days when primary infection was the last event.

Table 3: **Vaccine-induced and hybrid protection against hospitalisation due to omicron by time since last immunogenic event**

Discussion

Our findings suggest that in older adults (≥60 years old), monovalent mRNA vaccine effectiveness against hospitalisation due to omicron decreased with more recent omicron subvariants, and was modified mainly by previous infection history rather than number of vaccine doses. In participants who were infection naive, vaccine effectiveness estimates did not differ for three to five doses during the first 6 months after vaccination during the BA.4/5 period. Infection-induced immunity in unvaccinated individuals was associated with better and longer lasting protection against hospitalisation than vaccination alone (slightly lower protection with previous infection due to a pre-omicron variant than omicron). Whereas protection waned with time since either of these immunological events alone, hybrid immunity induced by both previous infection and two or more vaccine doses was more robust, exceeding 90% for at least 6–8 months regardless of type of previous infection or number of doses received.

In our study, estimated vaccine effectiveness against omicron hospitalisation was more than 90% for BA.1, about 85% for BA.2, and about 80% for BA.4/5 during the 3 months after the last booster dose in infection-naive participants, dropping by about 15% after 3–5 months. These findings are consistent with observations published previously.[8,9,21,22] However, previous studies did not assess all of these omicron subvariants or did not use simultaneous stratification for previous infection history. In adults aged 18 years or older with unknown previous infection status, three-dose vaccine effectiveness in Portugal was 93% against hospitalisation due to BA.2 and 77% against hospitalisation due to BA.4/5,[21] and in the USA three-dose vaccine effectiveness was 98% against hospitalisation due to BA.1, 82% due to BA.2, and 72% due to BA.4/5.[8] Our findings suggest that additional booster doses of monovalent mRNA vaccine did not gradually increase protection but rather reset protection to the levels achieved shortly after a previous dose. This conceptualisation is also supported by two previous studies in which vaccine effectiveness against BA.4/5 hospitalisation was the same shortly after a third or fourth dose in adults without a previous infection (66%) or with an unknown previous infection status (60%).[9,22]

The substantial protection we observed in unvaccinated older adults with a previous infection alone corroborates and extends results from the meta-analysis by Bobrovitz and colleagues,[13] which showed that previous infection reduced the subsequent risk of severe COVID-19 by 83% at 3 months and 75% at 12 months during BA.1 and BA.2 dominant periods.[13] In Qatar, pre-omicron (36%) and omicron (69%) infection without vaccination were associated with a reduced risk of symptomatic BA.4/5 infection,[23] but no study assessed protection against

severe outcomes. We identified no other publication assessing hybrid protection against BA.4/5-associated hospitalisation, but Bobrovitz and colleagues[13] reported that hybrid immunity, including two or three vaccine doses, reduced the risk of severe BA.1 and BA.2 by more than 95% at both the 3-month and 6-month follow-up, similar to our findings for the BA.1, BA.2, and BA.4/5 omicron subvariants.

Ageing has been identified as the strongest risk factor for severe COVID-19,[24] potentially associated with age-related immune dysfunction affecting responses to both infection and vaccine.[25] One study reported lower vaccine effectiveness against severe outcomes for people aged 70 years or older (76–79%) compared with 50–69-year-olds (85–87%) 8 months after vaccination, but similar effectiveness shortly after vaccination.[10] Our findings suggest no decrease in protection, but cautious interpretation is required given the multiple comparisons. Future research should specifically address the effect of chronological ageing and immunosenescence versus other potentially associated factors (eg, frailty and imprinting) on vaccine-associated and infection-associated protection against severe disease.

In our study, outcome ascertainment was comprehensive and specific for COVID-19-related hospitalisations. Cases and controls were individuals tested in acute-care hospitals for the same clinical indication, increasing comparability.[26,27] Because all participants were ill enough to attend a hospital, we do not expect differential health-seeking behaviour, even with the inclusion of controls who were not hospitalised. Moreover, we adjusted for age, comorbidity, and place of residence, which might be associated with disease severity and immunisation behaviour. Nevertheless, our study has several limitations most likely to result in underestimation. Because previous infection was documented only through (reportable) NAAT detection, we will have missed and misclassified some unrecognised or undiagnosed pre-omicron infections, as well as omicron infections, especially since January, 2022, when (non-reportable) RADTs became broadly available. In our BA.4/5 controls, we identified 15% with a previous infection compared with 40% in the same age group in seroprevalence studies done in July to August, 2022, in Quebec and British Columbia, Canada.[14,28] The relatively low proportion of previous infections in unvaccinated compared with vaccinated controls might have been due to more missed infections associated with differential testing behaviour or to fewer exposure opportunities in unvaccinated older adults who might have more rigorously self-isolated. Both explanations would tend to underestimate the protection induced by previous infection and hybrid immunity. Vaccine effectiveness in individuals without a previous detected infection would be underestimated or overestimated depending on the relative proportion of missed previous infections in vaccinated compared with unvaccinated groups. The disproportionately lower rates of previous infection detected in unvaccinated adults might also tend to obscure the incremental value of additional doses in individuals who are infection naive if vaccination and test-seeking behaviour are correlated.

Despite adjustment for several factors, residual confounding is possible; factors such as frailty, race and ethnicity, and education might influence both the uptake and the effect of vaccination. We did not have information on the use of ritonavir-boosted nirmatrelvir in Quebec. It has been available for adults who are immunosuppressed since mid-January, 2022, and for individuals aged 60 years or older with no or one vaccine doses or individuals at higher risk of COVID-19 complications due to comorbidity since mid-March, 2022.[29] Because ritonavir-boosted nirmatrelvir might also reduce the risk of hospitalisation, failure to take it into account might have tended to underestimate vaccine effectiveness. Although our main analyses included immunocompromised individuals with potentially reduced response to vaccination, they represented only 7% of cases and controls and similar estimates were obtained with their exclusion. Our findings might not apply to bivalent vaccines, against less severe COVID-19 or newly emerging subvariants, which will require evaluation. Although our population was representative of community-dwelling adults aged 60 years or older in Quebec, our findings might not be generalisable to excluded residents of long-term care facilities or older adults elsewhere with different care access. Despite these limitations, our data align with and confirm observations from other immunological and epidemiological studies,[4–11] although our analysis of three subvariants simultaneously, including BA.4/5, updates understanding and enables within-lineage comparison and cross-reference with previous studies of vaccine and hybrid immunity against BA.1 and BA.2 only.

Our findings have methodological and clinical implications. Given the substantial effect modification by previous infection and vaccination, estimates of protection should be separately considered for each of these strata (vaccine only, previous infection only, and both) rather than averaged as a global vaccine effectiveness finding adjusted for previous infection as a confounder.[30] For public health authorities and expert advisory committees, the effect modification by previous infection means that recommendations for additional vaccine doses might need to take into account the evolving proportion of the population already previously infected. Older adults with a history of both previous SARS-CoV-2 infection and at least two vaccine doses appear well protected for a prolonged period against omicron hospitalisation, including against hospitalisation due to BA.4/5. The plateauing of hybrid protection after two doses calls into question the incremental value of additional booster doses in preventing COVID-19 hospitalisation. Immunisation programmes aiming to

prevent hospitalisation should prioritise efforts to administer booster doses to individuals who are infection naive, who constituted about half of the older adult population in high-income countries in September to November, 2022.

Contributors

GDS, SC, and MB conceptualised the study. All authors designed the study. GDS, SC, and MO developed the statistical analysis plan. SC and MO had direct access to raw data, verified the data, did the data linkage, and did the formal analysis. GDS supervised the analyses and verified the data. All authors interpreted the data. SC created the figures and wrote the original draft of the manuscript. All authors critically revised and edited the manuscript and approved the final version for submission. SC and YF contributed to the literature search. GDS obtained funding for the study. All the authors had full access to all the data in the study and take responsibility to submit for publication.

Declaration of interests

SC, MO, and GDS report financial support to their institution from Ministère de la Santé et des Services Sociaux du Québec, during the conduct of the study. DT is supported by a research career award from the Fonds de recherche du Québec – Santé. JF reports grants from Ministère de la Santé et des Services Sociaux du Québec, grants and receipt of sequencing consumables from the Public Health Agency of Canada, and grants from Génome Canada, unrelated to the current work. DMS reports grants paid to her institution and unrelated to the current work from the Public Health Agency of Canada, Michael Smith Foundation for Health Research, Canadian Institutes of Health Research, and British Columbia Centre for Disease Control Foundation for Public Health. 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 that 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 appendix 2.

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References

1 WHO. Tracking SARS-CoV-2 variants. 2022. https://www.who.int/activities/tracking-SARS-CoV-2-variants (accessed May 1, 2023).
2 Hachmann NP, Miller J, Collier AY, et al. Neutralization escape by SARS-CoV-2 omicron subvariants BA.2.12.1, BA.4, and BA.5. *N Engl J Med* 2022; **387:** 86–88.
3 Davis-Gardner ME, Lai L, Wali B, et al. Neutralization against BA.2.75.2, BQ.1.1, and XBB from mRNA bivalent booster. *N Engl J Med* 2023; **388:** 183–85.
4 Skowronski DM, Febriani Y, Ouakki M, et al. Two-dose severe acute respiratory syndrome coronavirus 2 vaccine effectiveness with mixed schedules and extended dosing intervals: test-negative design studies from British Columbia and Quebec, Canada. *Clin Infect Dis* 2022; **75:** 1980–92.
5 Andrews N, Stowe J, Kirsebom F, et al. Covid-19 vaccine effectiveness against the omicron (B.1.1.529) variant. *N Engl J Med* 2022; **386:** 1532–46.
6 Carazo S, Skowronski DM, Brisson M, et al. Estimated protection of prior SARS-CoV-2 infection against reinfection with the omicron variant among messenger RNA–vaccinated and nonvaccinated individuals in Quebec, Canada. *JAMA Netw Open* 2022; **5:** e2236670.
7 Tartof SY, Slezak JM, Puzniak L, et al. BNT162b2 vaccine effectiveness against SARS-CoV-2 omicron BA.4 and BA.5. *Lancet Infect Dis* 2022; **22:** 1663–65.
8 Tseng HF, Ackerson BK, Bruxvoort KJ, et al. Effectiveness of mRNA-1273 vaccination against SARS-CoV-2 omicron subvariants BA.1, BA.2, BA.2.12.1, BA.4, and BA.5. *Nat Commun* 2023; **14:** 189.
9 Link-Gelles R, Levy ME, Natarajan K, et al. Estimation of COVID-19 mRNA vaccine effectiveness and COVID-19 illness and severity by vaccination status during omicron BA.4 and BA.5 sublineage periods. *JAMA Netw Open* 2023; **6:** e232598.
10 Grewal R, Nguyen L, Buchan SA, et al. Effectiveness of mRNA COVID-19 vaccine booster doses against omicron severe outcomes. *Nat Commun* 2023; **14:** 1273.
11 Møller Kirsebom FC, Andrews N, Stowe J, et al. Effectiveness of the COVID-19 vaccines against hospitalisation with omicron sub-lineages BA.4 and BA.5 in England. *Lancet Reg Health Eur* 2022; **23:** 100537.
12 Carazo S, Skowronski DM, Brisson M, et al. 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. *Lancet Infect Dis* 2023; **23:** 45–55.
13 Bobrovitz N, Ware H, Ma X, et al. Protective effectiveness of previous SARS-CoV-2 infection and hybrid immunity against the omicron variant and severe disease: a systematic review and meta-regression. *Lancet Infect Dis* 2023; **23:** 556–67.
14 Skowronski DM, Kaweski SE, Irvine MA, et al. Serial cross-sectional estimation of vaccine-and infection-induced SARS-CoV-2 seroprevalence in British Columbia, Canada. *CMAJ* 2022; **194:** E1599–609.
15 Public Health Agency of Canada. COVID-19 vaccine: Canadian immunization guide. 2022. https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines/page-26-covid-19-vaccine.html (accessed Dec 1, 2022).
16 US Centers for Disease Control and Prevention, Advisory Committee on Immunization Practices. ACIP update to the evidence to recommendations for a 2nd COVID-19 booster dose in adults ages 50 years and older and immunocompromised individuals. 2022. https://www.cdc.gov/vaccines/acip/recs/grade/covid-19-second-booster-dose-etr.html (accessed Dec 1, 2022).
17 Québec Ministry of Health and Social Services. Department of Health and Human Services COVID-19 guidelines. 2022. https://publications.msss.gouv.qc.ca/msss/directives-covid-19/sujets/depistage (accessed Dec 1, 2022).
18 Nevejan L, Cuypers L, Laenen L, et al. Early SARS-CoV-2 reinfections within 60 days and implications for retesting policies. *Emerg Infect Dis* 2022; **28:** 1729–31.
19 Cevik M, Tate M, Lloyd O, Maraolo AE, Schafers J, Ho A. SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis. *Lancet Microbe* 2021; **2:** e13–22.
20 Simard M, Boiteau V, Fortin É, et al. Impact of chronic comorbidities on hospitalization, intensive care unit admission and death among adult vaccinated and unvaccinated COVID-19 confirmed cases during the omicron wave. *J Multimorb Comorb* 2023; **13:** 26335652311695567.
21 Kislaya I, Machado A, Magalhães S, et al. COVID-19 mRNA vaccine effectiveness (second and first booster dose) against hospitalisation and death during omicron BA.5 circulation: cohort study based on electronic health records, Portugal, May to July 2022. *Euro Surveill* 2022; **27:** 2200697.
22 Surie D, Bonnell L, Adams K, et al. Effectiveness of monovalent mRNA vaccines against COVID-19-associated hospitalization among immunocompetent adults during BA.1/BA.2 and BA.4/BA.5 predominant periods of SARS-CoV-2 omicron variant in the United States - IVY Network, 18 States, December 26, 2021-August 31, 2022. *MMWR Morb Mortal Wkly Rep* 2022; **71:** 1327–34.
23 Altarawneh HN, Chemaitelly H, Ayoub HH, et al. Protective effect of previous SARS-CoV-2 infection against omicron BA.4 and BA.5 subvariants. *N Engl J Med* 2022; **387:** 1620–22.
24 Pennington AF, Kompaniyets L, Summers AD, et al. Risk of clinical severity by age and race/ethnicity among adults hospitalized for COVID-19-United States, March-September 2020. *Open Forum Infect Dis* 2020; **8:** ofaa638.
25 Tang F, Hammel IS, Andrew MK, Ruiz JG. Frailty reduces vaccine effectiveness against SARS-CoV-2 infection: a test-negative case control study using national VA data. *J Nutr Health Aging* 2023; **27:** 81–88.

26 WHO. Evaluation of COVID-19 vaccine effectiveness in a changing landscape of COVID-19 epidemiology and vaccination: interim guidance, 1 October 2022: second addendum to Evaluation of COVID-19 vaccine effectiveness: interim guidance. 2022. https://apps.who.int/iris/handle/10665/363344 (accessed Nov 3, 2022).

27 Lewnard JA, Patel MM, Jewell NP, et al. Theoretical framework for retrospective studies of the effectiveness of SARS-CoV-2 vaccines. *Epidemiology* 2021; **32:** 508–17.

28 Héma-Québec. Phase 4 de l'étude sur la séroprévalence des anticorps dirigés contre le SRAS-CoV-2 au Québec. 2022. https://https://www.hema-quebec.qc.ca/userfiles/file/coronavirus/Rapport-seroprevalence-phase-4.pdf (accessed Nov 20, 2022).

29 Zheng Q, Ma P, Wang M, et al. Efficacy and safety of paxlovid for COVID-19: a meta-analysis. *J Infect* 2023; **86:** 66–117.

30 Schnitzer ME. Estimands and estimation of COVID-19 vaccine effectiveness under the test-negative design: connections to causal inference. *Epidemiology* 2022; **33:** 325–33.