Clinical Infectious Diseases
MAJOR ARTICLE

Effectiveness of COVID-19 Vaccination and Prior Infections to Reduce Long COVID Risk During the Pre-Omicron and Omicron Periods

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Background. We estimated vaccine effectiveness (VE) against COVID-19 and long COVID during pre-Omicron and Omicron periods, by number of doses and prior infection history.

Methods. We combined survey information from a cohort of healthcare workers in Quebec, Canada, with immunization registry and laboratory administrative data. We defined COVID-19 cases as symptomatic laboratory-confirmed infections and long COVID as self-reported symptoms persisting ≥12 weeks. We assessed VE against COVID-19 and long COVID, stratified by infection history, using a test-negative design where vaccinated participants were compared to unvaccinated participants during the pre-Omicron period or to those twice vaccinated ≥6 months before laboratory testing during the Omicron period.

Results. Analyses included 8230 COVID-19 participants and 43 361 tested specimens. During the pre-Omicron period, 1- and 2-dose VE was 75% (95% CI: 64–83) and 95% (95% CI: 84–98) against COVID-19, respectively, and 91% (95% CI: 79–96) and 87% (95% CI: 22–98) against long COVID, respectively. During the Omicron period, booster dose VE was 41% (95% CI: 34–47) against COVID-19 and 57% (95% CI: 46–66) against long COVID, waning by 6 months. Hybrid VE in vaccinated and previously infected individuals ranged from 81% (95% CI: 38–94) to 92% (95% CI: 87–95) regardless of number of doses, prior infecting variant or median time since last immunological event up to 9 months.

Conclusions. COVID-19 vaccination prevented long COVID during the pre-Omicron period and reduced the risk by more than half post-Omicron. With most of the population by now both vaccinated and infected, repeated booster doses may add little incremental value against long COVID, an observation with important public health, immunization program, and cost implications.

Keywords. long COVID; vaccine effectiveness; SARS-CoV-2; hybrid immunity.

Long COVID is a chronic post-infectious condition, generally impacting daily functioning that may affect over 400 million people worldwide [1,2].

Most studies evaluating the protective effect of vaccination on long COVID risk assessed it exclusively among COVID-19 cases, ignoring earlier (upstream) risk reduction through the prevention of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, including severe COVID-19, in the first place [3,4]. Since the emergence of Omicron, vaccine effectiveness (VE) against infections appears lower and shorter lasting [5]. While the few studies for which long COVID was considered a severe COVID-19 outcome found low to moderate protection against long COVID, data on the effectiveness of hybrid (vaccine-plus-infection induced) immunity are scarce [6–8].

In Canada, as in other jurisdictions, COVID-19 vaccination program's goal has been to prevent severe illness and, due to short-lived vaccine protection, booster doses have been administered every 6–12 months [9, 10]. In the current context of ongoing transmission of new Omicron subvariants and the high frequency of reinfections, it remains essential to measure ongoing booster dose protection against long COVID.

In spring 2023, we conducted an online survey within a cohort of Quebec healthcare workers (HCW) to evaluate long COVID frequency, risk, and protective factors [11]. Combining survey data with administrative registries, we

Received 30 June 2025; accepted 21 September 2025; published online 29 September 2025

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Clinical Infectious Diseases® 2026;82(3):e436–45

https://doi.org/10.1093/cid/ciaf549

estimated VE against COVID-19 and against long COVID by number of doses (1–5), prior infection history and circulating SARS-CoV-2 variants. For comparability with other studies, we also measured vaccine-associated risk reduction among COVID-19 cases.

METHODS

Study Design

We evaluated VE against COVID-19 using the test-negative design (TND) and estimated vaccine-associated reduction in long COVID risk using a retrospective cohort design (RCD).

Population

Adult HCWs residing in the province of Quebec, Canada, were invited to participate in an on-line survey if working in the health and social services public network and/or registered with a professional order for physicians, nurses, nursing assistants, respiratory therapists, pharmacists, or midwives during the pandemic and able to communicate in French or English. The study population consisted of survey participants who were tested for SARS-CoV-2 by nucleic acid amplification test (NAAT) between 3 January 2021 (3 weeks after vaccine campaign launch in Quebec) and 20 February 2023 (allowing 12-week follow-up for long COVID case ascertainment). We excluded participants with COVID-19: (1) if their first self-reported COVID-19 was not confirmed by a positive NAAT in the laboratory registry (allowing a lag of 60 days between self-reported and laboratory date); (2) if survey responses did not allow long COVID identification or attribution to a COVID-19 episode; (3) if vaccinated with >5 doses, or if last dose was not an mRNA vaccine, or if <3 months between doses. For hybrid immunity analyses, participants were also excluded if their second self-reported COVID-19 infection was not confirmed by a positive NAAT in the laboratory registry or if they reported long COVID after their first infection.

Procedures

Between 16 May 2023 and 15 June 2023, participants self-reported sociodemographic and clinical data. Questions included the number, date, laboratory confirmation, and severity of COVID-19 episodes, as well as persistence of at least one symptom beyond 12 weeks post-COVID-19 infection [11]. Using a unique identifier, survey data were linked to provincial health administrative databases, including: the immunization registry; the Quebec integrated chronic disease surveillance system (QICDSS), containing population-based information on comorbidities [12]; and the laboratory registry containing all SARS-CoV-2 NAAT performed since pandemic onset, with reasons for testing. In Quebec, HCWs were extensively tested by NAAT the first year of the pandemic and they continued to have easy access to NAAT during the Omicron period.

Variant dominant periods pre-Omicron (from 3 January 2021 to 18 December 2021) and Omicron (from 19 December 2021 to 20 February 2023) were assigned based on Quebec viral genetic surveillance as described elsewhere [13]. During the study period, the main circulating Omicron subvariants were BA.1, BA.2, BA.4/5, BQ.1, and XBB.1.5 (Figure 1).

Exposure and Outcome Definitions

Vaccination status was defined relative to the date of specimen collection. Participants (or tests) were considered vaccinated with 1 to 5 doses (V1 to V5) if they received a dose of mRNA vaccine (BNT-162b2 [Pfizer-BioNTech] or mRNA-1273 [Moderna]) ≥14 days (V1) or ≥7 days (V2-V5) before the NAAT date, and not-vaccinated (NV) if no COVID-19 vaccination was administered. Hybrid immunity was defined by the number of vaccine doses received (V2-V5) and a prior NAAT-confirmed pre-Omicron or Omicron infection, without long COVID.

COVID-19 cases were HCW-positive on NAAT performed for COVID-19 symptoms as recorded at testing. First reinfection was defined as a positive NAAT performed ≥90 days after first positive NAAT. Long COVID cases for all analyses were defined as individuals self-reporting persistence of post-COVID-19 symptom(s) (among a list of 21) attributed to COVID-19 (first infection or first reinfection) that was NAAT-confirmed in the laboratory registry. Moderate or severe long COVID was defined by the presence of ≥1 persistent moderate or severe symptom.

For TND estimation of VE against COVID-19 and long COVID, eligible test-negative controls were symptomatic NAAT-negative participants before a first (if any) positive NAAT. Negative tests performed ≥90 days post-first infection before the first (if any) reinfection were also eligible for the hybrid protection's evaluation. For RCD estimation of vaccine-associated risk reduction among COVID-19 cases, controls were individuals with a SARS-CoV-2 infection (first infection or first reinfection) without long COVID (COVID-19 controls). A summary of methods is presented in Supplementary Figure 1.

Statistical Analyses

Based on vaccine doses administered and variant evolution, 1- and 2-dose VEs were assessed during the pre-Omicron period and booster VE during the Omicron period, in accordance with each dose availability (Figure 1) [14, 15]. We evaluated V1 (vs NV) using specimens tested between January 3 (epi-week W2021-01) and 12 June 2021 (W2021-23) when ancestral strain and Alpha variants circulated. We evaluated V2 (vs NV) using specimens tested between March 28 (W2021-13) and 11 December 2021 (W2021-49), when the ancestral strain, Alpha and Delta variants circulated. We evaluated booster doses (V3-V5) and hybrid immunity (vs V2 ≥6 months before test

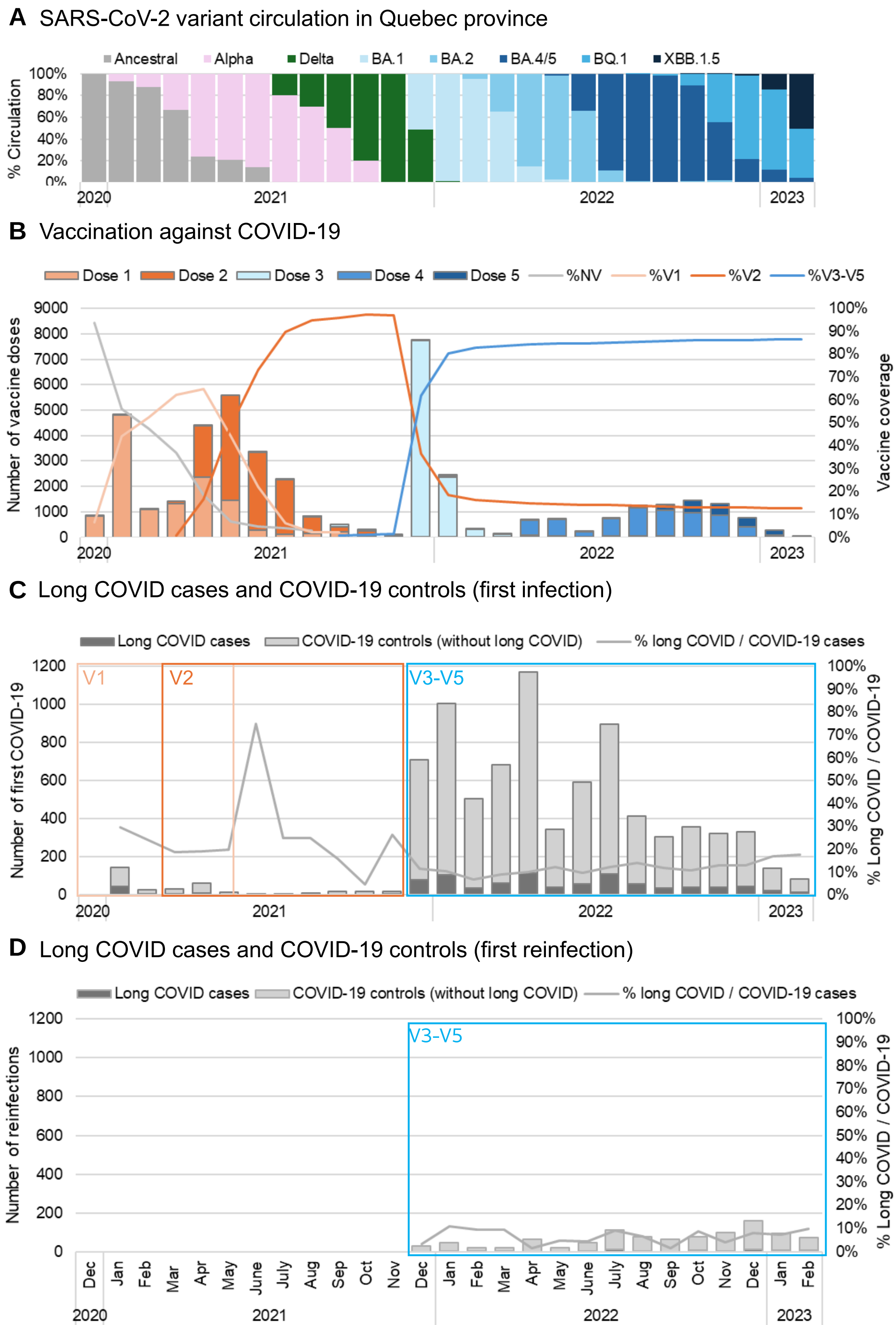

Figure 1. Temporal distribution of SARS-CoV-2 variant circulation (A), COVID-19 vaccination (B), long COVID cases and first COVID-19 infections (C) and reinfections (D). Abbreviations: NV, not vaccinated; V1-V5, vaccination with 1 to 5 doses.

date, without documented or self-reported prior infection) using specimens tested between 19 December 2021 (W2021-51) and 20 February 2023 (W2023-08), when Omicron circulated. The V2 comparison group was chosen for booster dose evaluation given paucity of unvaccinated participants by the Omicron period and waned protection against Omicron by 6 months post-vaccination [16]. Successive booster dose protection was assessed by comparing each dose with the previous dose administered ≥6 months before the test date. These subanalyses included tests conducted since W2021-51 (V3), W2022-14 (V4), and W2022-35 (V5). We further stratified by time since last booster vaccination in 2-month intervals.

For TND VE estimation [17], we used incidence density sampling to randomly select ten test-negative controls (V1 and V2 analyses) or up to 5 test-negative controls (V3-V5 analysis) per case for each 2-week period. Matching by calendar time controlled for potential confounding associated with changes in the distributions of cases and controls and COVID-19 vaccination within the study period [18]. Odds ratio (OR) and 95% confidence intervals (95% CI) were estimated by conditional logistic regression comparing test-positive COVID-19 and long COVID cases to test-negative controls, adjusting for sex, age group, region of residence, occupation, workplace, material and social deprivation indexes, and number of pre-existing comorbidities. For RCD estimation of long COVID risk reduction [19, 20], OR and 95% CI were estimated by logistic regression models comparing long COVID cases and COVID-19 controls (ie, COVID-19 cases without long COVID) adjusting for the same abovementioned variables and for 4-week periods. Absolute (V1 and V2 vs NV) and relative (V3-V5 vs V2) VE and risk reduction were calculated as: $(1\text{-}OR_{adjusted})*100$.

Ethical Considerations

This study was conducted under the legal mandate of the National Director of Public Health of Quebec under the Public Health Act and was approved by the Research Ethics Board of the Centre hospitalier universitaire de Québec-Université Laval.

RESULTS

Among 400 222 Quebec HCWs invited, 22 496 (5.6%) responded to the survey. Among them, 10 281 (45.7%) SARS-CoV-2 infected individuals were linked to a corresponding NAAT in the laboratory registry, 7679 (34.1%) were not linked, and 4536 (20.2%) were uninfected individuals (Supplementary Figure 2). After exclusions, 43 361 and 38 653 NAAT were, respectively, eligible for COVID-19 and long COVID VE analyses by TND, while 8230 individuals with a first infection and 923 with a first reinfection were included in the RCD risk reduction analyses.

For all analyses, case and control characteristics were globally similar, with most participants being white and middle-aged women (Table 1, Supplementary Table 1). Among test-negative controls, 45.1% and 43.0% had at least one comorbidity in the pre-Omicron and Omicron periods, while among long COVID cases the respective proportions where 45.3% and 48.6% (Table 1). Similar proportions were observed by vaccination status (Supplementary Table 2).

Vaccination status varied with time (Figure 1). In December 2021, 96.9% of participants were 2-dose vaccinated and <1% were unvaccinated. Booster vaccine coverage achieved 82.2% by February 2022 with 13.7% of HCWs not receiving any booster dose during the study period. Overall, most first infections were due to Omicron among long COVID cases (849 [89.0%]) and test-positive COVID-19 cases (5306 [93.7%]; Figure 1). During the Omicron period, 18 (2.1%) and 43 (5.1%) long COVID cases had, respectively, pre-Omicron and Omicron prior NAAT-confirmed infections, being 267 (3.6%) and 589 (8.0%) for COVID-19 controls (Supplementary Table 3).

During the pre-Omicron period, absolute one-dose VE estimated by TND was 75% (95% CI: 64–83) against COVID-19, increasing to 91% (95% CI: 79–96) against long COVID, with RCD-estimated reduction in the long COVID risk among COVID-19 infected HCWs of 77% (95% CI: 38–82) (Table 2). Two-dose VE by TND was 95% (95% CI: 84–98) against COVID-19 and 87% (95% CI: 27–98) against long COVID, without signs of waning during the 7-month follow-up (Supplementary Tables 4 and 5). There was no RCD evidence of long COVID risk reduction among infected 2-dose vaccinated HCWs.

During the Omicron period, booster-dose VE (V3-V5 relative to V2) by TND was 41% (95% CI: 34–47) against first COVID-19 and 57% (95% CI: 46–63) against long COVID post-first infection (Table 2). It was higher within 2 months of administration, at 53% (95% CI: 46–58) against COVID-19 and 72% (95% CI: 62–79) against long COVID (Supplementary Tables 4 and 5). However, unlike V1 and V2 VE during the pre-Omicron period, booster VE steadily decreased over time, becoming low and non-significant at 6 months post-vaccination (13% [95% CI: −6 to 28] against COVID-19 and 29% [95% CI: −1 to 50] against long COVID) (Figure 2). Pre-Omicron prior infection was associated with hybrid VE against COVID-19 reinfection of 60% (95% CI: 51–67); hybrid VE for Omicron prior infection ranged 76% (95% CI: 69–81) to 79% (95% CI: 75–83) (Figure 3, Supplementary Table 6). Prior Omicron infection was associated with similar hybrid VE against long COVID for 2-dose (87% 95% CI: 72–94) or booster-dose recipients (85% [95% CI: 73–91] to 92% [95% CI: 87–95]) (Figure 3, Supplementary Table 7). For different combinations of prior infection and vaccine doses, risk reduction of long COVID post-reinfection varied between 65% and 79%, with large confidence intervals (Figure 3, Supplementary Table 8).

Although the number of long COVID cases post-reinfection was too limited to stratify for time since last immunological event, VE estimates were similar regardless of median time since last vaccination, which ranged from 2 to 9 months (Supplementary Table 3).

In all scenarios, estimated VE against long COVID with moderate or severe symptoms were similar to the protection against long COVID overall (Supplementary Table 9).

DISCUSSION

In this analysis of vaccine protection against long COVID, that combined survey data from more than 14 000 HCWs with

Table 1. Characteristics of Cases and Controls Included in Test-negative Design Study, by Variant Period

	Pre-Omicron			Omicron		
	Test-Positive COVID-19 Cases	Long COVID Cases	Test-Negative Controls[a]	Test-Positive COVID-19 Cases	Long COVID Cases	Test-Negative Controls[a]
N	310	95	16 663	5306	849	20 414
Characteristics	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Sex						
Female	270 (87.1)	81 (85.3)	14 295 (85.8)	4537 (85.5)	743 (87.5)	17 734 (86.9)
Male	40 (12.9)	14 (14.7)	2368 (14.2)	769 (14.5)	106 (12.5)	2680 (13.1)
Age, years						
Median (IQR)	43 (35–50)	45 (36–53)	42 (35–51)	44 (36–52)	45 (38–53)	43 (36–52)
18–39	129 (41.6)	34 (35.8)	6806 (40.9)	2018 (38.0)	252 (29.7)	8271 (40.5)
40–49	98 (31.6)	30 (31.6)	5316 (31.9)	1716 (32.3)	298 (35.1)	6120 (30.0)
50–59	59 (19.0)	20 (21.1)	3173 (19.0)	1130 (21.3)	216 (25.4)	4435 (21.7)
≥60	24 (7.7)	11 (11.6)	1366 (8.2)	442 (8.3)	83 (9.8)	1588 (7.8)
Race/ethnicity						
White	246 (79.4)	73 (76.8)	14 658 (88.0)	4706 (88.7)	730 (86.0)	18 406 (90.2)
Black	24 (7.7)	7 (7.4)	682 (4.1)	168 (3.2)	34 (4.0)	753 (3.7)
Asiatic	12 (3.9)	1 (1.1)	314 (1.9)	129 (2.4)	23 (2.7)	336 (1.6)
Hispanic	9 (2.9)	4 (4.2)	714 (4.3)	84 (1.6)	18 (2.1)	237 (1.2)
Other/not reported	19 (6.1)	10 (10.5)	295 (1.7)	219 (4.1)	44 (5.2)	682 (3.3)
Comorbidity[b]						
None	171 (55.2)	52 (54.7)	9142 (54.9)	3094 (58.3)	436 (51.4)	11 630 (57.0)
One	71 (22.9)	20 (21.1)	4326 (26.0)	1305 (24.6)	222 (26.1)	5019 (24.6)
Two or more	68 (21.9)	23 (24.2)	3195 (19.2)	907 (17.1)	191 (22.5)	3765 (18.4)
Profession						
Nursing staff, physicians, other health professionals	181 (58.4)	48 (50.5)	10 893 (65.4)	3341 (63.0)	481 (56.7)	14 082 (60.9)
Health-assisting occupations	72 (23.2)	30 (31.6)	3704 (22.2)	994 (18.7)	208 (24.5)	4150 (20.3)
Management and administrative staff	57 (18.4)	17 (17.9)	2066 (12.4)	971 (18.3)	160 (18.8)	2182 (10.7)
Workplace						
Hospital	133 (42.9)	50 (52.6)	8736 (52.4)	2602 (49.0)	384 (45.2)	12 434 (60.9)
LTCF	58 (18.7)	13 (13.7)	3021 (18.1)	589 (11.1)	133 (15.7)	3140 (15.4)
Clinics	37 (11.9)	11 (11.6)	1865 (11.2)	813 (15.3)	123 (14.5)	1862 (9.1)
Other[c]	82 (26.5)	21 (22.1)	3041 (18.3)	1302 (24.5)	209 (24.6)	2978 (14.6)
Variant of infection						
Ancestral	125 (40.3)	43 (45.3)	NA	NA	NA	NA
Alpha	133 (42.9)	38 (40.0)	NA	NA	NA	NA
Delta	52 (16.8)	14 (14.7)	NA	NA	NA	NA
Omicron BA.1	NA	NA	NA	1811 (34.1)	231 (27.2)	NA
Omicron BA.2	NA	NA	NA	1580 (29.8)	231 (27.2)	NA
Omicron BA.4/5	NA	NA	NA	1475 (27.8)	288 (33.9)	NA
Omicron BQ.1	NA	NA	NA	411 (7.7)	91 (10.7)	NA
Omicron XBB.1.5	NA	NA	NA	29 (0.5)	8 (0.9)	NA
Type of last mRNA vaccine dose						
Monovalent	123 (39.7)	29 (30.5)	12 557 (75.4)	5086 (95.9)	810 (95.4)	19 928 (97.6)
Bivalent	0 (0.0)	0 (0.0)	0 (0.0)	197 (3.7)	37 (4.4)	445 (2.2)

Abbreviations: IQR, interquartile range; LTCF, long-term health facilities; NA, not applicable.

[a]Test negative controls eligible for density sampling matched with COVID-19 test-positive or long COVID cases.

[b]Included comorbidities: depressive disorder, alcohol and drug abuse, hypertension, chronic lung disease, hypothyroidism, kidney disease, fluid and electrolyte disorders, peripheral vascular disorders, obesity, dementia, cerebrovascular disease, neurological disorders, liver disease, psychosis, pulmonary circulation disorders, rheumatoid arthritis, coagulopathy, weight loss, paralysis, ulcerative disease, AIDS/HIV, anemia, cardiovascular disease, diabetes, immune system problems, cancer.

[c]Rehabilitation centers, patients' homes, telework, other.

registry-confirmed vaccination and SARS-CoV-2 infections, we extend earlier findings by revealing the important benefit of preventing COVID-19 infection in the first place. While seemingly obvious to consider in quantifying vaccine benefit against long COVID, most prior analyses have overlooked this critical aspect, considering only the prevention of long COVID among those already infected. During the pre-Omicron period, we show that COVID-19 vaccination

Table 2. Participants, Vaccine Effectiveness and Long COVID Risk Reduction During First COVID-19 Episode

	Participants			
	Cases	Controls	Months Since Vaccination (Median (IQR))	Adjusted VE (%) or Risk Reduction (%) (95% CI) [a,b]
COVID-19 VE analysis, TND				
Case and control definition	COVID-19 cases	Test-negative	…	…
NV (pre-Omicron period)[c]	180 (80.4)	1254 (56.0)	NA	Reference
V1	44 (19.6)	986 (44.0)	1.6 (0.8–2.8)	75% (64–83)
NV (pre-Omicron period)[d]	44 (36.7)	299 (24.9)	NA	Reference
V2	76 (63.3)	901 (75.1)	5.4 (3.8–6.8)	95% (84–98)
V2_6m (Omicron period)[e]	702 (14.3)	1190 (11.3)	7.9 (7.0–9.5)	Reference
V3-V5	4219 (85.7)	9376 (88.7)	2.7 (1.1–4.4)	41% (34–47)
Long COVID VE analysis, TND				
Case and control definition	Long COVID cases	Test-negative	…	…
NV (pre-Omicron period)[c]	65 (89.0)	426 (58.4)	NA	Reference
V1	8 (11.0)	304 (41.6)	1.6 (0.8–2.7)	91% (79–96)
NV (pre-Omicron period)[d]	14 (40.0)	109 (31.1)	NA	Reference
V2	21 (60.0)	241 (68.9)	5.4 (3.6–6.9)	87% (27–98)
V2_6m (Omicron period)[e]	138 (17.5)	369 (9.4)	9.0 (7.5–12.5)	Reference
V3-V5	652 (82.5)	3559 (90.6)	3.7 (2.0–6.4)	57% (46–66)
Long COVID risk reduction analysis, RCD				
Case and control definition	Long COVID cases	COVID-19 controls	…	…
NV (pre-Omicron period)[c]	65 (89.0)	158 (73.8)	NA	Reference
V1	8 (11.0)	56 (26.2)	2.5 (1.4–3.0)	77% (38–92)
NV (pre-Omicron period)[d]	14 (40.0)	42 (38.5)	NA	Reference
V2	21 (60.0)	67 (61.5)	5.6 (4.2–6.9)	−122% (−2119–78)
V2_6m (Omicron period)[e]	138 (17.5)	773 (11.9)	8.0 (6.9–10.5)	Reference
V3-V5	652 (82.5)	5747 (88.1)	3.7 (2.0–6.2)	47% (33–57)

Abbreviations: CI, confidence interval; IQR, interquartile range; NA, non-applicable; NV, not vaccinated; RCD, retrospective cohort design; RR, risk reduction; TND, test-negative design; V1-V5, vaccination with 1 to 5 doses; V2_6m, vaccination with 2 doses ≥6 m before testing date; VE, vaccine effectiveness; W, epi-week.

[a]Logistic regression models conditional to biweekly periods compared vaccinated participants without prior infection versus participants not vaccinated (pre-Omicron period) or vaccinated with 2 doses 6 m or more before testing (Omicron period), adjusted for age group, sex, region of residence, occupation, workplace, material and social deprivation index, number of comorbidities.

[b]Vaccine effectiveness and risk reduction calculated as (1—adjusted OR)×100.

[c]W2021-01 to 2021-23.

[d]W2021-13 to 2021-49.

[e]W2021-51 to 2023-08.

reduced the long COVID risk by about 90%, mostly by reducing the risk of COVID-19 disease. During the Omicron period, booster dose VE against long COVID post-first infection was ∼60%, waning at 6 months post-vaccination. Conversely, hybrid VE against long COVID resulting from prior infection and 2–5 vaccine doses was 80% to 90% and did not vary further based upon the number of doses, prior infecting variant or median time since vaccination, up to 9 months.

Although over 80 studies have examined the impact of vaccination on long COVID [3], most included only SARS-CoV-2-infected participants and reported long COVID risk reductions after breakthrough infections that cannot be interpreted as global VE [4, 21, 22]. Our study reports vaccine effects against long COVID not only among COVID-19 cases but also relative to non-cases, capturing the fuller spectrum of vaccine benefit. We also computed VE against COVID-19 per se to contextualize risk reduction estimates.

During the pre-Omicron period, 2 European studies including 4 countries estimated 1-dose effectiveness of 35–58% against long COVID, much lower than our 91% estimate [7,8]. Using administrative health records, they defined long COVID by the presence of ≥1 core long COVID symptoms but without specific COVID-19 attribution. A previous study using the same data source from UK reported one-dose VE against COVID-19 of 57% to 75% [23]. VE against long COVID was paradoxically lower than against COVID-19, suggesting potential underestimation of VE against long COVID. Studies reporting one-dose long COVID risk reduction among COVID-19 cases did not observe vaccine protection with estimates ranging from −4% to 4% [24–26]. Most studies evaluating the additional protection of a second dose among COVID-19 patients reported long COVID risk reductions of <50%, ranging from 22% to 49% [21, 24, 26–28]. Conversely, we observed 77% reduction in the risk of long COVID associated with one vaccine dose for those with pre-Omicron breakthrough infections, without evidence of additional benefit against long COVID among infected patients vaccinated with 2 doses. This result has to be interpreted in the context of a

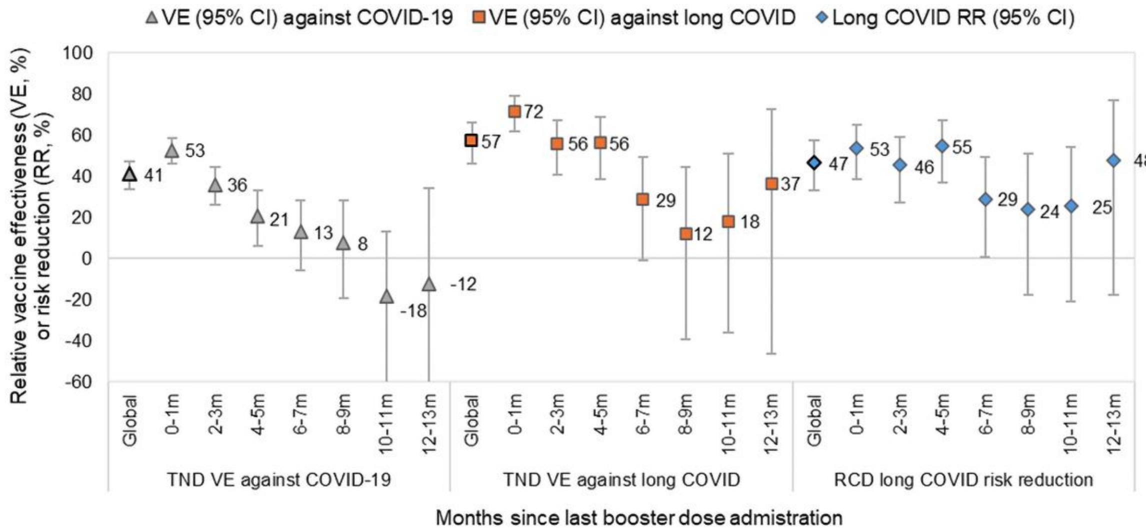

Figure 2. Protection against COVID-19 and long COVID associated with booster vaccination without prior infection, by time since vaccination. Logistic regression models compared participants vaccinated with a booster dose without prior infection versus participants vaccinated with 2 doses 6 m or more before testing, stratified by time since last booster vaccination. Abbreviations: CI, confidence interval; M, month; RCD, retrospective cohort design; RR, risk reduction; TND, test-negative design; VE, vaccine effectiveness.

delayed administration of the second vaccine dose in Quebec and a very high 2-dose VE against COVID-19, leaving few individuals 2-dose vaccinated and infected to assess the additional protection against long COVID among COVID-19 cases [29].

During the Omicron period, a Czech nation-wide study based on administrative data and physician-diagnosed long COVID reported low booster VE against long COVID of 20%, contrasted with their estimated VE against severe COVID-19 of 50% to 80%, and declining over the 10-month post-vaccination follow-up [6]. We observed higher VE, at 72% for long COVID, and 53% for COVID-19, during the first 2 months post-vaccination, but a similar temporal waning pattern. Among Omicron-infected cases, long COVID risk was reduced by half for booster vaccination, but decreasing to 24%–29% by 6–11 months post-vaccination. This is consistent with most published studies reporting long COVID risk reduction of 15%–70% associated with booster doses [19, 30–32], while other studies reported no protection [20, 26, 28].

The protection conferred by hybrid immunity is now the most relevant given most individuals have already experienced SARS-CoV-2 infections. In our study, hybrid immunity was associated with high effectiveness (>80%) against long COVID during Omicron reinfections, independent of the number of vaccine doses and the likely variant of prior infection. This was higher than estimates from the Czeck study [6]. In another study, prior infection was also associated with 86% long COVID risk reduction after adjustment for vaccination status and circulating variant [33]. Our study overcomes important limitations of previous studies with its exclusion of pre-vaccination periods [34–37], accurate timing of vaccination relative to infection [38–40], and more specific long COVID definitions (eg with post-COVID symptoms attributed to laboratory-confirmed COVID-19) [7]. The inclusion of the pre-vaccination period overestimates VE because variants during the pre-vaccination period are recognized to be associated with higher long COVID risk [33]. Most studies based on administrative data use non-specific definitions, with long COVID rarely diagnosed with ICD-10 codes [41]. Those using specific physician diagnosis may also be confounded by health-seeking behaviour, the latter correlated with the likelihood of both vaccination and long COVID diagnosis [6, 42].

Cohort survey-based studies like ours also have limitations. To mitigate misclassification associated with self-reported COVID-19 attributed persistent symptoms, we included only cases prevalent at the time of the survey, with limited recall bias, and laboratory-confirmed COVID-19 episodes and performed a secondary analysis against moderate or severe long COVID, which increases outcome specificity. Low survey participation may be associated with lack of representativeness for the outcome (eg severe long COVID cases may be more interested to participate), but protection against moderate/severe long COVID was similar to overall estimates. There were insufficient unvaccinated participants to measure absolute VE during the Omicron period. Based on other studies, individuals last vaccinated ≥6 months earlier were likely unprotected and thus provided a valid comparison group [16, 43], although limiting our capacity to measure 2-dose VE during the Omicron period.

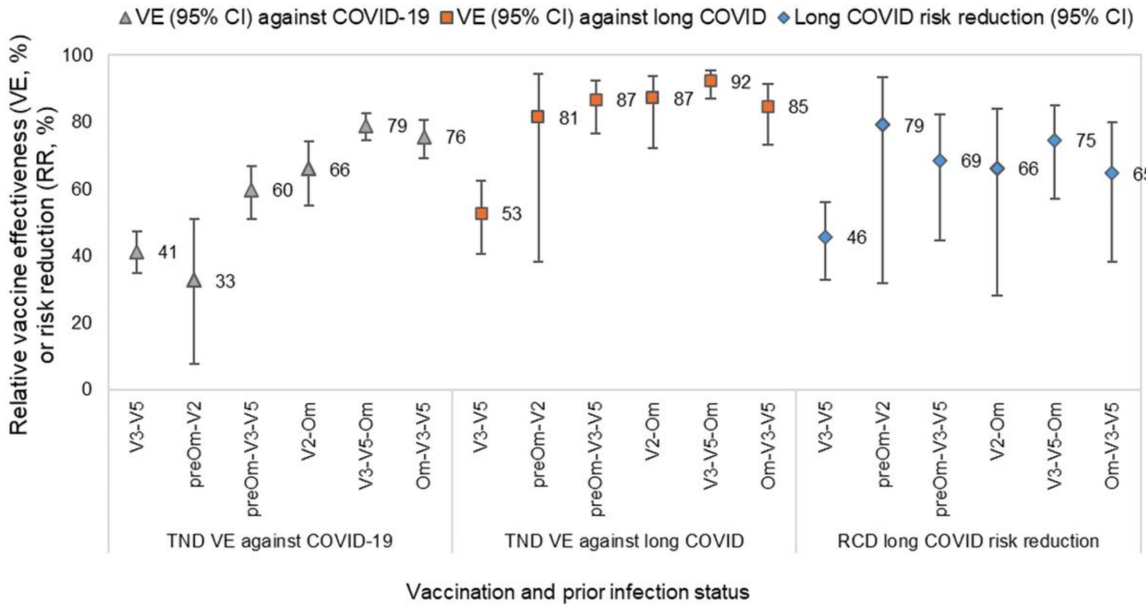

Figure 3. Protection against COVID-19 and long COVID associated with vaccination and prior infection during Omicron period. Logistic regression models compared vaccinated participants with or without prior infection versus participants vaccinated with 2 doses ≥6 m before testing and without documented or self-reported prior infection. Abbreviations: CI, confidence interval; PreOm-V2, prior pre-Omicron infection before 2 vaccine doses; PreOm-V3-V5, prior pre-Omicron infection before 3 to 5 vaccine doses; RCD, retrospective cohort design; RR, risk reduction; TND, test-negative design; V2-Om, prior Omicron infection after 2 vaccine doses; V3-V5, vaccination with 3 to 5 doses without prior infection; V3-V5-Om, prior Omicron infection after 3 to 5 vaccine doses; Om-V3-V5, prior Omicron infection before 3 to 5 vaccine doses; VE, vaccine effectiveness.

Undocumented prior infections may underestimate VE [44], but HCWs had unrestricted access and were systematically tested during the pre-Omicron period; we also excluded those with self-reported prior infection but lacking NAAT confirmation. HCWs were only questioned about first occurrence of long COVID. Consequently, only those without long COVID following their first infection were eligible for the assessment of hybrid immunity. Lower host susceptibility to long COVID, instead of vaccine or prior infection induced immunity, may partially explain the observed protection associated with hybrid immunity. Our population of HCWs had similar regarding demographic characteristics and presence of comorbidities than other cohorts of HCWs reported elsewhere [17, 45], however our findings might not be generalizable to broader populations, including children or older adults.

Overall, our findings strongly reinforce that COVID-19 vaccination protects against long COVID, adding to protection against COVID-19 disease. Vaccination plus prior infection provide the highest protection against long COVID post-Omicron infection. Our study confirms the major role of COVID-19 vaccination programs to reduce long COVID risk, mostly during the pre-Omicron period but moderately also since Omicron emergence with ongoing relevance given Omicron descendants continue to circulate. In the current context of highly vaccinated and infected populations, however, our findings of similar hybrid protection against long COVID regardless of the number of booster doses or time since vaccination suggest that repeated administration is unlikely to provide substantial incremental benefit. This observation warrants further investigation and confirmation by others given the important public health, vaccine program, and cost implications.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. The authors thank Stéphanie Grenier et Josiane Rivard (Centre de Recherche du CHU de Québec—Université Laval) for their work at coordinating and implementing the long COVID survey, and Dr Aissatou Fall (Public Health Agency of Canada) for her contributions in the discussion of the study protocol and the preliminary results. Finally, we thank all healthcare workers who generously participated in the survey.

Author Contributions. All the authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: S. C., G. D. S., D. M. S., C. S., and D. T. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: S. C. Critical revision of the manuscript for important intellectual content: All authors. Statistical analyses: J. P., M. O., and S. C. Supervision: G. D. S. and S. C.

Data availability. The databases used in this study are a property of the "Ministère de la Santé et des Services sociaux du Québec" that was 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 the Supplementary supplementary material. The SAS code for the statistical analyses is shared int the GitHub repository (https://github.com/JoPhi-immun/VE-against-Long-COVID).

Financial support. This work was supported by the Public Health Agency of Canada. The long COVID survey was supported by the Ministère de la Santé et des Services Sociaux du Québec. This work was also supported by the Fonds de recherche du Québec (FRQ) through the Research Centre grant.

Potential conflicts of interest. S. C., J. P., M. O., and K. G. report that the Public Health Agency of Canada and the "Ministère de la Santé et des Services Sociaux du Québec" gave financial support to their institution to conduct the study. D. M. S. reports grants paid to her institution and unrelated to current work from Public Health Agency of Canada, the Pacific Public Health Foundation, the Canadian Institutes of Health Research and the Michael Smith Foundation for Health Research. D. T. is supported by an FRQ research career award. Other authors have no conflicts of interest to declare.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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