COVID-19 Vaccine Effectiveness Against Omicron Infection and Hospitalization

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abstract

OBJECTIVES: This study aimed to provide real-world evidence on coronavirus disease 2019 vaccine effectiveness (VE) against symptomatic infection and severe outcomes caused by Omicron in children aged 5 to 11 years.

METHODS: We used the test-negative study design and linked provincial databases to estimate BNT162b2 vaccine effectiveness against symptomatic infection and severe outcomes caused by Omicron in children aged 5 to 11 years between January 2 and August 27, 2022 in Ontario. We used multivariable logistic regression to estimate VE by time since the latest dose, compared with unvaccinated children, and we evaluated VE by dosing interval.

RESULTS: We included 6284 test-positive cases and 8389 test-negative controls. VE against symptomatic infection declined from 24% (95% confidence interval [CI], 8% to 36%) 14 to 29 days after a first dose and 66% (95% CI, 60% to 71%) 7 to 29 days after 2 doses. VE was higher for children with dosing intervals of ≥56 days (57% [95% CI, 51% to 62%]) than 15 to 27 days (12% [95% CI, −11% to 30%]) and 28 to 41 days (38% [95% CI, 28% to 47%]), but appeared to wane over time for all dosing interval groups. VE against severe outcomes was 94% (95% CI, 57% to 99%) 7 to 29 days after 2 doses and declined to 57% (95%CI, −20% to 85%) after ≥120 days.

CONCLUSIONS: In children aged 5 to 11 years, 2 doses of BNT162b2 provide moderate protection against symptomatic Omicron infection within 4 months of vaccination and good protection against severe outcomes. Protection wanes more rapidly for infection than severe outcomes. Overall, longer dosing intervals confer higher protection against symptomatic infection, however protection decreases and becomes similar to shorter dosing interval starting 90 days after vaccination.

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Drs Piché-Renaud and Kwong conceptualized and designed the study, contributed to the analysis plan, interpreted the results, and drafted the initial manuscript; Ms Swayze contributed to the analysis plan, obtained the data and conducted the analyses, and interpreted the results; Drs Buchan and Sarah Wilson conceptualized and designed the study, contributed

WHAT'S KNOWN ON THIS SUBJECT: Coronavirus disease 2019 vaccination has been estimated to be 29% to 65% effective against infection and 68% to 100% effective against hospitalization from Omicron in children 5 to 11 years old. Less is known on the effectiveness of extended versus shorter dosing intervals.

WHAT THIS STUDY ADDS: Two doses of BNT162b2 initially retained effectiveness against Omicron infection in children 5 to 11 years, although this decreased steadily over time. The extended 8-week dosing interval was associated with higher effectiveness against symptomatic infection during the first 3 months after vaccination.

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For children aged 5 to 11 years, 2 doses of the BNT162b2 (Pfizer-BioNTech Comirnaty) coronavirus disease 2019 (COVID-19) vaccine were 90.7% efficacious against symptomatic SARS-CoV-2 infection when administered at a 3-week dosing interval.[1] However, the Omicron variant has greatly impacted real-world vaccine effectiveness (VE) because of significant immune evasion.[2] Early studies from the United States have estimated VE to be 31% against Omicron infection and 68% to 74% against hospitalization for this age group.[3–5]

In Ontario, Canada, Omicron was first detected on November 22, 2021, and became predominant within a few weeks.[6] Administration of BNT162b2 (10mcg) in children aged 5 to 11 years began on November 23, 2021.[7,8] Aligning with recommendations from Canada's National Advisory Committee on Immunization, the vaccine program used an 8-week interval for routine scheduling of second doses, but with informed consent, parents could request shorter intervals (minimum 3 weeks, as per the product monograph).[9]

For children aged 5 to 11 years, data on VE against Omicron beyond 2 months after vaccination remains scarce, and how VE varies by dosing interval is unknown. We aimed to provide real-world evidence on COVID-19 VE against symptomatic infection and severe outcomes caused by Omicron over time and by dosing interval in this age group.

METHODS

Study Population, Setting, and Design

We included community-dwelling children aged 5 to 11 years who had COVID-19-relevant symptoms or a severe outcome attributable to COVID-19 and who were tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by reverse-transcription polymerase chain reaction (RT-PCR) between January 2 and August 27, 2022, as recorded in the Ontario Laboratories Information System. Children who tested positive at least once during the study period were considered cases. For those with multiple positive tests, the first was used. Once an individual became a case, they could not re-enter the study. The index date was the date of specimen collection. Children who were asymptomatic at the time of testing, who had symptoms that were unrelated to COVID-19 (incidental SARS-CoV-2 infection), or who had no information on their symptoms at the time of testing were excluded. The list of COVID-19-related symptoms has been described elsewhere.[10,11]

Severe outcomes attributable to Omicron infection were defined as either hospitalization or death from COVID-19, identified from the Public Health Case and Contact Management Solution (CCM).[10–14] CCM records hospitalizations only if cases are admitted because of COVID-19, and not if admitted for other reasons with incidental detection of SARS-CoV-2. The index date for severe cases was the earliest of specimen collection, hospitalization, or death. Cases of multisystem inflammatory syndrome in children were not included because they are inadequately captured by CCM.

Symptomatic children with a negative SARS-CoV-2 RT-PCR test were considered controls. For children with multiple negative tests during the same calendar week, a randomly selected negative test was used. Children with multiple negative tests in different calendar weeks during the study period could be considered controls multiple times. Controls could later be considered cases if they subsequently tested positive.

Because of overwhelming volumes, diagnostic RT-PCR testing was restricted to certain populations, including hospitalized patients, patients seen in emergency departments, outpatients for whom COVID-19 treatment was being considered, household members of patient-facing healthcare workers, and symptomatic students who received a RT-PCR self-collection kit through their school.[15] At-home SARS-CoV-2 rapid antigen detection tests could be accessed by those not among these groups. By January 2, 2022, >95% of circulating SARS-CoV-2 cases in Ontario were determined by representative surveillance to be B.1.1.529 (Omicron) sublineage BA.1/BA.2, and starting on July 2, 2022 the majority were BA.4/BA.5.[6] Thus, cases were assumed to be Omicron throughout the study period, unless they were determined by whole genome sequencing or S-gene target failure screening to be B.1.617 (Delta), in which case they were excluded.

We excluded immunocompromised children (defined as solid organ or hematopoietic stem cell transplant recipients, taking any immunosuppressive medication, or those with HIV, cancer, sickle cell disease, or any other immunocompromising conditions);[16,17] those who received Moderna's mRNA-1273 vaccine (because of limited use in this age group), a non-Health Canada-authorized COVID-19 vaccine, or three doses of COVID-19 vaccine within a span of 12 weeks (suggesting an immunocompromising condition); those who were tested after their third dose; and those tested <14 days after their first dose, or tested

positive <90 days before testing (for cases).

Exposure (COVID-19 vaccination) and Covariates

COVID-19 vaccination status, vaccine product, dose administered, date of administration, dose number, and dosing interval were obtained from COVaxON, a centralized information system that includes comprehensive documentation of all COVID-19 vaccination events in Ontario.

Age, sex, and postal code were obtained from the Ontario Registered Persons Database. Comorbidities were determined from various databases using validated algorithms and commonly accepted diagnostic codes, as described elsewhere.[16] Receipt of influenza vaccination (as a measure of health behaviors) during the 2019 to 2020 or 2020 to 2021 influenza seasons was obtained using physician and pharmacist billing claims from the Ontario Health Insurance Plan and Ontario Drug Benefit databases, respectively. COVID-19 vaccination of the child's mother was retrieved using COVaxON and the MOMBABY database, an ICES-derived dataset linking children born in Ontario hospitals to their mothers using birth hospitalization records.[18] Maternal COVID-19 vaccination before April 1, 2021 was used as a proxy to identify children of healthcare workers, given that only individuals aged ≥80 years, long-term care home residents and staff, Indigenous adults, and healthcare workers were eligible for COVID-19 vaccines in Ontario before that date.[19] The public health unit of residence was determined using the postal code and Statistics Canada Postal Code Conversion File Plus (version 7B). Neighborhood-level information on household income quintile, household density quintile, and essential workers quintile was obtained from 2016 Census data using residential postal codes.

All datasets were linked using unique encoded identifiers and analyzed at ICES (formerly the Institute for Clinical Evaluative Sciences).[10–14]

Statistical Analyses

Means (continuous variables) and frequencies (categorical variables) of participants' baseline characteristics were calculated. Standardized differences were used to compare test-positive cases and test-negative controls and vaccinated (≥1 dose) and unvaccinated children.

Multivariable logistic regression models were employed to calculate adjusted odds ratios of vaccination in test-positive cases versus test-negative controls after adjusting for potential confounders. Confounders included week of test, age, sex, medical comorbidities, prior influenza vaccination, being a child of a healthcare worker, positive SARS-CoV-2 RT-PCR test ≥90 days before specimen collection date, household income quintile, household density quintile, essential workers quintile, and public health region.[20–22]

We calculated vaccine effectiveness (VE) using the formula: VE = (1–adjusted odds ratio) x 100%. We estimated VE against infection and severe outcomes caused by Omicron by the number of vaccine doses received; for children who had received only 1 dose by the index date, we estimated VE ≥14 days after the first dose, whereas for children who had received 2 doses, we estimated VE ≥7 days after the second dose.[1,23] VE was also estimated by varying time periods after vaccination. For children who had received 2 doses, we estimated VE by dosing interval and by both dosing interval and time since second dose receipt. Characteristics of children with different dosing intervals were compared using analysis of variance for continuous variables and χ^2 tests for categorical and dichotomous variables.

All analyses were conducted using SAS Version 9.4 (SAS Institute). All tests were 2-sided and used $P < .05$ as the level of statistical significance.

Ethics Approval

Use of data were authorized under section 45 of Ontario's Personal Health Information Protection Act; research ethics board review was not required.

RESULTS

Study Population

A total of 114 637 SARS-CoV-2 RT-PCR testing episodes occurred in children aged 5 to 11 years between January 2 and August 27, 2022. We excluded 9792 episodes based on predefined exclusion criteria (Fig 1). An additional 90 193 episodes were also excluded, with 10 261 testing episodes occurring in children who were asymptomatic, and 79 932 testing episodes with no information on symptoms or symptoms unrelated to COVID-19. We included 14 673 testing episodes, with 1004 children (7.5%) having multiple testing episodes eligible for inclusion during the study period. Among the included episodes, 6284 (45.4%) were considered symptomatic test-positive cases and 8389 (54.6%) were considered symptomatic test-negative controls.

Compared with test-negative controls, test-positive cases were older, more likely to reside in areas with more persons per dwelling, less likely to be vaccinated against COVID-19, less likely to have had a positive SARS-CoV-2 RT-PCR test >90 days before index date, less likely to have received prior influenza vaccination, and less likely

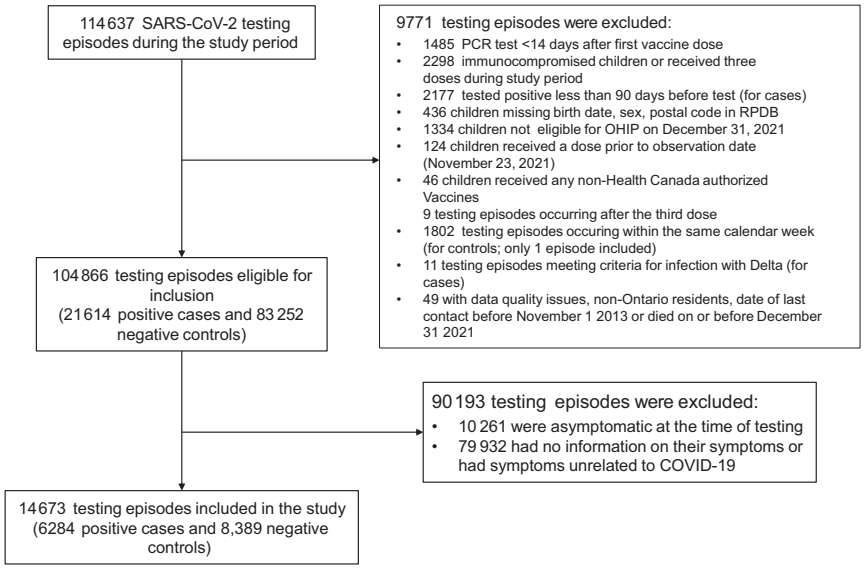

FIGURE 1
Flowchart of children aged 5 to 11 years old tested for SARS-CoV-2 during the study period from January 2 to August 27, 2022, and who were excluded from the study.

to be the child of a healthcare worker (Table 1). Among children who had received 2 doses, the mean dosing interval was longer for test-negative controls than for test-positive cases (52.3 [standard difference (SD) 17.7] days versus 47.2 [SD 15.2] days).

Compared with unvaccinated children, vaccinated children were older, more likely to reside in the highest neighborhood income quintile, more likely to have received prior influenza vaccination or to be the child of a healthcare worker, and less likely to reside in lower income areas (Table 2).

Vaccine Effectiveness Against Symptomatic Infection

Overall, VE against symptomatic infection was 9% (95% CI, 0% to 18%) ≥14 days after a first dose, and 49% (95% CI, 43% to 54%) ≥7 days after a second dose. VE declined over time after each dose, from a peak of 24% (95% CI, 8% to 36%) 14 to 29 days after a first dose to −1% (95% CI, −17% to 13%) ≥60 days after a first dose, and from a peak of 66% (95% CI, 60% to 71%) 7 to 29 days after a second dose to −4% (95% CI, −30% to 17%) ≥120 days after a second dose (Fig 2A, Supplemental Table 3).

VE was notably higher for children with longer dosing intervals. Children with a dosing interval of ≥56 days had a VE of 57% (95% CI, 51% to 62%), compared with children with a dosing interval of 15 to 27 days (12% [95% CI, −11% to 30%]) and 28 to 41 days (38% [95% CI, 28% to 47%]) (Fig 3A, Supplemental Table 3).

However, when stratifying VE by dosing interval and time since second dose receipt, we observed declining VE over time within each dosing interval group, although confidence intervals frequently overlapped (Fig 3B, Supplemental Table 4). We also noted higher VE for children with longer dosing intervals for some time-since-second-dose periods but not others. For example, 30 to 59 days after a second dose, VE was only 6% (95% CI, −47% to 40%) for children with a dosing interval of 15 to 27 days, compared with 60% (95% CI, 52% to 67%) for children with a dosing interval of ≥56 days. However, VE estimates became comparable between all dosing intervals at 90 to 119 days after vaccination, with confidence intervals overlapping 0% ≥120 days after vaccination.

Children with a shorter dosing interval were more likely to have received prior influenza vaccination ($P < .001$), be the child of a healthcare worker ($P < .001$), reside in Toronto ($P < .001$), and reside in higher income areas ($P < .001$) or more persons per dwelling ($P < .001$) compared with children with an extended dosing interval (Supplemental Table 5).

Vaccine Effectiveness Against Hospitalization or Death

We identified 138 cases of severe outcomes (COVID-19-related hospitalization or death), with ≤5 deaths. Compared with test-negative controls, cases of severe COVID-19 were older, more likely to reside in lower income areas, more likely to have comorbidities, less likely to be vaccinated against COVID-19, less likely to have received prior influenza vaccination, and less likely to be the child of a healthcare worker.

The majority of severe COVID-19 cases occurred in unvaccinated children ($n = 84$, 60.9%), with few cases occurring in children who had received 1 dose ($n = 30$, 21.7%) or 2 doses ($n = 24$, 17.4%). VE against severe outcomes was 79% (95% CI, 63% to 88%) ≥7 days after a second dose. VE against severe outcomes also showed suggestions of waning, declining from 94% (95% CI, 57% to 99%) 7 to 29 days after a second dose to 57% (95% CI, −20% to 85%) ≥120 days after a second dose, but confidence intervals overlapped (Fig 2B, Supplemental Table 3).

TABLE 1 Descriptive Characteristics of Children Tested for SARS-CoV-2 With COVID-19-Related Symptoms Between January 2 and August 27, 2022, Comparing Test-Positive Cases to Test-Negative Controls

Subject Characteristics	Test-Positive Cases, *n* (%)[a]	Test-Negative Controls, *n* (%)[a]	SD[b]
Total	*N* = 6284	*N* = 8389	
Age in years, mean ± SD	8.02 ± 2.03	7.29 ± 2.08	0.35
Male sex	3322 (52.9)	4450 (53.0)	0
Any comorbidity[c]	1439 (22.9)	1982 (23.6)	0.02
Receipt of 2019–2020 and/or 2020–2021 influenza vaccine	2083 (33.1)	3512 (41.9)	0.18
Child of a healthcare worker	1232 (19.6)	2236 (26.7)	0.17
Positive SARS-CoV-2 test >90 d before index date	80 (1.3)	407 (4.9)	0.21
Public health unit region			
Central East	324 (5.2)	490 (5.8)	0.03
Central West	874 (13.9)	1086 (12.9)	0.03
Durham	598 (9.5)	654 (7.8)	0.06
Eastern	289 (4.6)	411 (4.9)	0.01
Northern	672 (10.7)	1139 (13.6)	0.09
Ottawa	117 (1.9)	106 (1.3)	0.05
Peel	796 (12.7)	773 (9.2)	0.11
Southwest	725 (11.5)	862 (10.3)	0.04
Toronto	1321 (21.0)	2315 (27.6)	0.15
York	538 (8.6)	529 (6.3)	0.09
Neighborhood income quintile[d,e]			
1 (lowest)	998 (15.9)	1266 (15.1)	0.02
2	1054 (16.8)	1455 (17.3)	0.02
3	1286 (20.5)	1638 (19.5)	0.02
4	1317 (21.0)	1797 (21.4)	0.01
5 (highest)	1602 (25.5)	2207 (26.3)	0.02
Essential workers quintile[d,f]			
1 (0%–32.5%)	1340 (21.3)	2093 (24.9)	0.09
2 (32.5%–42.3%)	1668 (26.5)	2093 (24.9)	0.04
3 (42.3%–49.8%)	1245 (19.8)	1641 (19.6)	0.01
4 (50.0%–57.5%)	1073 (17.1)	1382 (16.5)	0.02
5 (57.5%–100%)	888 (14.1)	1122 (13.4)	0.02
Persons per dwelling quintile[d,g]			
1 (0–2.1)	708 (11.3)	1140 (13.6)	0.07
2 (2.2–2.4)	919 (14.6)	1373 (16.4)	0.05
3 (2.5–2.6)	817 (13.0)	1221 (14.6)	0.05
4 (2.7–3.0)	1574 (25.0)	2194 (26.2)	0.03
5 (3.1–5.7)	2193 (34.9)	2403 (28.6)	0.13
Week of testing			
January 2, 2022 to January 8, 2022	959 (15.3)	365 (4.4)	0.37
January 9, 2022 to January 15, 2022	537 (8.5)	249 (3.0)	0.24
January 16, 2022 to January 22, 2022	399 (6.3)	259 (3.1)	0.15
January 23, 2022 to January 29, 2022	481 (7.7)	331 (3.9)	0.16
January 30, 2022 to February 5, 2022	375 (6.0)	338 (4.0)	0.09
February 6, 2022 to February 12, 2022	351 (5.6)	371 (4.4)	0.05
February 13, 2022 to February 19, 2022	269 (4.3)	294 (3.5)	0.04
February 20, 2022 to February 26, 2022	242 (3.9)	279 (3.3)	0.03
February 27, 2022 to March 5, 2022	282 (4.5)	332 (4.0)	0.03
March 6, 2022 to March 12, 2022	236 (3.8)	292 (3.5)	0.01
March 13, 2022 to March 19, 2022	189 (3.0)	194 (2.3)	0.04
March 20, 2022 to March 26, 2022	170 (2.7)	222 (2.6)	0
March 27, 2022 to April 2, 2022	288 (4.6)	427 (5.1)	0.02
April 3, 2022 to April 9, 2022	310 (4.9)	542 (6.5)	0.07
April 10, 2022 to April 16, 2022	277 (4.4)	569 (6.8)	0.1
April 17, 2022 to April 23, 2022	194 (3.1)	400 (4.8)	0.09
April 24, 2022 to April 30, 2022	134 (2.1)	369 (4.4)	0.13
May 1, 2022 to May 7, 2022	82 (1.3)	356 (4.2)	0.18
May 8, 2022 to May 14, 2022	79 (1.3)	301 (3.6)	0.15
May 15, 2022 to May 21, 2022	46 (0.7)	281 (3.3)	0.19
May 22, 2022 to May 28, 2022	30 (0.5)	213 (2.5)	0.17
May 29, 2022 to June 4, 2022	22 (0.4)	176 (2.1)	0.16
June 5, 2022 to June 11, 2022	25 (0.4)	184 (2.2)	0.16

TABLE 1 Continued

Subject Characteristics	Test-Positive Cases, *n* (%)[a]	Test-Negative Controls, *n* (%)[a]	SD[b]
June 12, 2022 to June 18, 2022	23 (0.4)	181 (2.2)	0.16
June 19, 2022 to June 25, 2022	30 (0.5)	152 (1.8)	0.13
June 26, 2022 to July 2, 2022	24 (0.4)	95 (1.1)	0.09
July 3, 2022 to July 9, 2022	29 (0.5)	112 (1.3)	0.09
July 10, 2022 to July 16, 2022	39 (0.6)	93 (1.1)	0.05
July 17, 2022 to July 23, 2022	40 (0.6)	81 (1.0)	0.04
July 24, 2022 to July 30, 2022	34 (0.5)	75 (0.9)	0.04
July 31, 2022 to August 6, 2022	28 (0.4)	64 (0.8)	0.04
August 7, 2022 to August 13, 2022	19 (0.3)	60 (0.7)	0.06
August 14, 2022 to August 20, 2022	22 (0.4)	65 (0.8)	0.06
August 21, 2022 to August 27, 2022	19 (0.3)	67 (0.8)	0.07
Vaccination status			
Unvaccinated	2488 (39.6)	2383 (28.4)	0.24
14–29 d after first dose	394 (6.3)	256 (3.1)	0.15
30–59 d after second dose	1057 (16.8)	702 (8.4)	0.26
≥60 d after first dose	474 (7.5)	666 (7.9)	0.01
0–6 d after second dose	118 (1.9)	123 (1.5)	0.03
7–29 d after second dose	279 (4.4)	603 (7.2)	0.12
30–59 d after second dose	536 (8.5)	932 (11.1)	0.09
60–89 d after second dose	468 (7.4)	1145 (13.6)	0.20
90–119 d after second dose	239 (3.8)	801 (9.5)	0.23
≥120 d after second dose	231 (3.7)	778 (9.3)	0.23
Dosing interval			
15 to 27 d between doses	192 (3.1)	234 (2.8)	0.02
28 to 41 d between doses	493 (7.8)	945 (11.3)	0.12
42 to 55 d between doses	416 (6.6)	910 (10.8)	0.15
≥56 d after second dose	770 (12.3)	2293 (27.3)	0.39
Dosing interval in days, mean ± SD	47.20 ± 15.15	52.33 ± 17.73	0.31

[a] Proportion reported, unless stated otherwise.

[b] Standardized differences of >0.10 are considered clinically relevant. Comparison of *o* cases and SARS-CoV-2 negative controls.

[c] Comorbidities include asthma, diabetes, immunocompromising conditions caused by underlying diseases or therapy, autoimmune diseases, active cancer, or pediatric complex chronic conditions.

[d] The sum of counts does not equal the column total because of individuals with missing information (≤2.0%) for this characteristic.

[e] Household income quintile has variable cut-off values in each city or Census area to account for cost of living. A dissemination area (DA) being in quintile 1 means it is among the lowest 20% of DAs in its city by income.

[f] Percentage of people in the area working in the following occupations: sales and service occupations; trades, transport and equipment operators and related occupations; natural resources, agriculture, and related production occupations; and occupations in manufacturing and utilities. Census counts for people are randomly rounded up or down to the nearest number divisible by 5, which causes some minor imprecision.

[g] Range of persons per dwelling.

DISCUSSION

We found that for children aged 5 to 11 years, VE against symptomatic Omicron infection was low after 1 dose of BNT162b2, and moderate after 2 doses, with waning VE over time after each dose. Against severe outcomes, VE was very high initially after a second dose (94%) but may also wane over time. These findings have important implications for recommendations on the use of COVID-19 vaccines in children.

Data on COVID-19 VE in children aged 5 to 11 years are still emerging. A test-negative design study employing data from a US pharmacy-based network found that VE against symptomatic infection during Omicron predominance decreased from 60.1% (95% CI, 54.7% to 64.8%) 2 to 4 weeks after a second dose to 28.9% (95% CI, 24.5% to 33.1%) 2 months after a second dose.[24] Similar decreasing trends in VE were observed in cohort studies, including in New York state, where the incidence rate ratio of Omicron infection in unvaccinated versus vaccinated children decreased from 3.1 (95% CI, 2.7 to 3.6) within 13 days after vaccination to 1.1 (95% CI, 1.1 to 1.2) 42 to 48 days after vaccination, and in Italy, where VE against infection peaked at 38.7% (95% CI, 37.7% to 39.7%) 0 to 14 days after vaccination and decreased to 21.2% (95% CI, 19.7% to 22.7%) 43 to 84 days after vaccination.[25,26] Another cohort study from Israel reported VE against symptomatic infection to be 48% (95% CI, 29% to 63%) at 7 to 21 days after the second dose, but longer-term trends were not provided.[27] The overall VE seen in our study seems comparable to these previously published estimates, yet the VE observed at 60 to 89 days after a second dose (51% [95% CI, 43% to 58%]) was higher than what has been previously described, with significant decreases occurring only starting 90 days after vaccination (35% [95% CI, 21% to 46%]). It is possible that this slower

TABLE 2 Descriptive Characteristics of Children Tested for SARS-CoV-2 With COVID-19-Related Symptoms Between January 2 and August 27, 2022, Comparing Vaccinated and Unvaccinated Children

Subject Characteristics	Vaccinated *n* (%)[a]	Unvaccinated *n* (%)[a]	SD[b]
Total	*N* = 9802	*N* = 4871	
Age in years, mean ± SD	7.77 ± 2.06	7.27 ± 2.13	0.24
Male sex	5251 (53.6)	2521 (51.8)	0.04
Any comorbidity[c]	2290 (23.4)	1131 (23.2)	0
Receipt of 2019–2020 and/or 2020–2021 influenza vaccine	4749 (48.4)	846 (17.4)	0.70
Child of a healthcare worker	2860 (29.2)	608 (12.5)	0.42
Positive SARS-CoV-2 test >90 d before index date	279 (2.8)	208 (4.3)	0.08
Public health unit region			
Central East	564 (5.8)	250 (5.1)	0.03
Central West	1257 (12.8)	703 (14.4)	0.05
Durham	834 (8.5)	418 (8.6)	0
Eastern	525 (5.4)	175 (3.6)	0.09
Northern	1201 (12.3)	610 (12.5)	0.01
Ottawa	150 (1.5)	73 (1.5)	0
Peel	864 (8.8)	705 (14.5)	0.18
Southwest	906 (9.2)	681 (14.0)	0.15
Toronto	2759 (28.1)	877 (18.0)	0.24
York	715 (7.3)	352 (7.2)	0
Neighborhood income quintile[d,e]			
1 (lowest)	1202 (12.3)	1062 (21.8)	0.26
2	1509 (15.4)	1000 (20.5)	0.13
3	1871 (19.1)	1053 (21.6)	0.06
4	2166 (22.1)	948 (19.5)	0.06
5 (highest)	3021 (30.8)	788 (16.2)	0.35
Essential workers quintile[d,f]			
1 (0%–32.5%)	2802 (28.6)	631 (13.0)	0.39
2 (32.5%–42.3%)	2588 (26.4)	1173 (24.1)	0.05
3 (42.3%–49.8%)	1862 (19.0)	1024 (21.0)	0.05
4 (50.0%–57.5%)	1482 (15.1)	973 (20.0)	0.13
5 (57.5%–100%)	1004 (10.2)	1006 (20.7)	0.29
Persons per dwelling quintile[d,g]			
1 (0–2.1)	1197 (12.2)	651 (13.4)	0.03
2 (2.2–2.4)	1440 (14.7)	852 (17.5)	0.08
3 (2.5–2.6)	1455 (14.8)	583 (12.0)	0.08
4 (2.7–3.0)	2654 (27.1)	1114 (22.9)	0.10
5 (3.1–5.7)	2992 (30.5)	1604 (32.9)	0.05
Week of testing			
January 2, 2022 to January 8, 2022	595 (6.1)	729 (15.0)	0.29
January 9, 2022 to January 15, 2022	367 (3.7)	419 (8.6)	0.2
January 16, 2022 to January 22, 2022	364 (3.7)	294 (6.0)	0.11
January 23, 2022 to January 29, 2022	495 (5.0)	317 (6.5)	0.06
January 30, 2022 to February 5, 2022	466 (4.8)	247 (5.1)	0.01
February 6, 2022 to February 12, 2022	494 (5.0)	228 (4.7)	0.02
February 13, 2022 to February 19, 2022	394 (4.0)	169 (3.5)	0.03
February 20, 2022 to February 26, 2022	395 (4.0)	126 (2.6)	0.08
February 27, 2022 to March 5, 2022	475 (4.8)	139 (2.9)	0.10
March 6, 2022 to March 12, 2022	404 (4.1)	124 (2.5)	0.09
March 13, 2022 to March 19, 2022	282 (2.9)	101 (2.1)	0.05
March 20, 2022 to March 26, 2022	293 (3.0)	99 (2.0)	0.06
March 27, 2022 to April 2, 2022	539 (5.5)	176 (3.6)	0.09
April 3, 2022 to April 9, 2022	634 (6.5)	218 (4.5)	0.09
April 10, 2022 to April 16, 2022	639 (6.5)	207 (4.2)	0.10
April 17, 2022 to April 23, 2022	437 (4.5)	157 (3.2)	0.06
April 24, 2022 to April 30, 2022	352 (3.6)	151 (3.1)	0.03
May 1, 2022 to May 7, 2022	320 (3.3)	118 (2.4)	0.05
May 8, 2022 to May 14, 2022	255 (2.6)	125 (2.6)	0
May 15, 2022 to May 21, 2022	238 (2.4)	89 (1.8)	0.04
May 22, 2022 to May 28, 2022	153 (1.6)	90 (1.8)	0.02
May 29, 2022 to June 4, 2022	130 (1.3)	68 (1.4)	0.01
June 5, 2022 to June 11, 2022	144 (1.5)	65 (1.3)	0.01

TABLE 2 Continued

Subject Characteristics	Vaccinated *n* (%)[a]	Unvaccinated *n* (%)[a]	SD[b]
June 12, 2022 to June 18, 2022	151 (1.5)	53 (1.1)	0.04
June 19, 2022 to June 25, 2022	143 (1.5)	39 (0.8)	0.06
June 26, 2022 to July 2, 2022	84 (0.9)	35 (0.7)	0.02
July 3, 2022 to July 9, 2022	93 (0.9)	48 (1.0)	0
July 10, 2022 to July 16, 2022	86 (0.9)	46 (0.9)	0.01
July 17, 2022 to July 23, 2022	81 (0.8)	40 (0.8)	0
July 24, 2022 to July 30, 2022	77 (0.8)	32 (0.7)	0.02
July 31, 2022 to August 6, 2022	64 (0.7)	28 (0.6)	0.01
August 7, 2022 to August 13, 2022	49 (0.5)	30 (0.6)	0.02
August 14, 2022 to August 20, 2022	53 (0.5)	34 (0.7)	0.02
August 21, 2022 to August 27, 2022	56 (0.6)	30 (0.6)	0.01

[a] Proportion reported, unless stated otherwise.

[b] Standardized differences of >0.10 are considered clinically relevant. Comparison of *o* cases and SARS-CoV-2 negative controls.

[c] Comorbidities include asthma, diabetes, immunocompromising conditions caused by underlying diseases or therapy, autoimmune diseases, active cancer, or pediatric complex chronic conditions.

[d] The sum of counts does not equal the column total because of individuals with missing information (≤2.0%) for this characteristic.

[e] Household income quintile has variable cut-off values in each city or Census area to account for cost of living. A dissemination area (DA) being in quintile 1 means it is among the lowest 20% of DAs in its city by income.

[f] Percentage of people in the area working in the following occupations: sales and service occupations; trades, transport and equipment operators and related occupations; natural resources, agriculture, and related production occupations; and occupations in manufacturing and utilities. Census counts for people are randomly rounded up or down to the nearest number divisible by 5, which causes some minor imprecision.

[g] Range of persons per dwelling.

decline in VE against Omicron infection relates to the extended dosing interval that was employed for a significant proportion of our study population. Although the previously referenced studies did not provide specific information on the dosing intervals that were employed, a 3-week dosing interval was preferentially recommended in Israel, Italy, and the United States.[28–30] Our study revealed low VE at ≥120 days after vaccination with 95% confidence intervals overlapping 0% (−4% [95% CI, −29% to 17%]), which may relate to waning protection with time and lower VE against BA.4/BA.5 compared with BA.1/BA.2. Although VE against severe outcomes also showed signs of waning at ≥90 days after vaccination, confidence intervals overlapped.

Direct comparisons with other jurisdictions are challenging because of differences in study methodology, outcome definitions, sensitivity of administrative and surveillance data, and criteria for hospitalization. Compared with studies from Ontario that used the same databases to assess VE against Omicron infection in other age groups, we found that VE in children aged 5 to 11 years 7 to 59 days after a second dose was comparable to estimates for adolescents aged 12 to 17 years (51% [95% CI, 38% to 61%]), and higher than estimates reported for adults (36% [95% CI, 24% to 45%]).[12,31]

In our study, VE was overall higher for children with longer dosing intervals, with slower waning after a second dose following an interval of ≥56 days, although VE became comparable ≥90 days after vaccination. Multiple immunogenicity studies have demonstrated that extended dosing intervals result in higher spike antibodies, receptor-binding domain antibodies, neutralizing antibodies, and specific T-cell responses compared with shorter intervals, likely reflecting immune maturation between prime-boost events.[32,33] However, very few studies have directly compared the clinical effectiveness of varying dosing intervals; moreover, they are limited to adults and are from a limited number of jurisdictions that have allowed varying dosing intervals. A study from the Canadian provinces

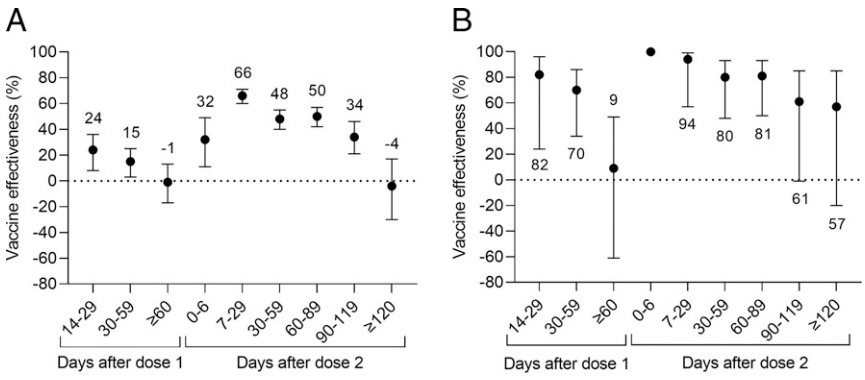

FIGURE 2
Vaccine effectiveness estimates in children aged 5 to 11 years old against (A) symptomatic infection and (B) severe outcomes from *o* between January 2 and August 27, 2022, by time since last dose.

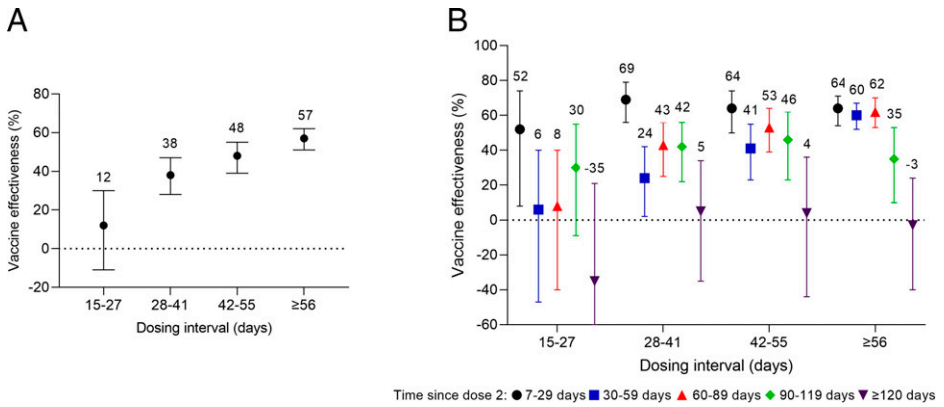

FIGURE 3

Vaccine effectiveness estimates in children aged 5 to 11 years old against symptomatic *o* infection between January 2 and August 27, 2022, by dosing interval (A) overall and (B) by time since last dose.

of Québec and British Columbia revealed higher VE for mRNA vaccines against infection with wild-type SARS-CoV-2 or the Alpha, Beta, or Gamma variants in adults with a dosing interval of 7 to 8 weeks (90% in British Columbia and 87% in Québec) compared with an interval of 3 to 4 weeks (84% in British Columbia and 79% in Québec).[34] A study from England also revealed higher VE for BNT162b2 against COVID-19 in adults aged 50 to 89 years with a dosing interval of >6 weeks compared with 3 weeks.[35] These previously described trends are consistent with our study's findings for children aged 5 to 11 years. Ultimately, decisions about the optimal dosing interval for vaccine programs should balance achieving more rapid versus more sustained protection from vaccination and be guided by jurisdictions' current SARS-CoV-2 epidemiology. Additional considerations on dosing interval include the reduced risk of myocarditis and pericarditis that has been described with longer dosing intervals.[36]

Our study has some limitations. First, there were important restrictions to SARS-CoV-2 RT-PCR testing in Ontario during the study period, and our study did not capture rapid antigen detection tests results, which could have led to residual confounding from undetected SARS-CoV-2 infection, especially in children with longer dosing intervals. Limitations to testing may also restrict the external validity of our findings, as symptomatic and tested children differed from untested children regarding the presence of comorbidities, COVID-19 vaccination, prior influenza vaccination, and being a child of a healthcare worker. We were also unable to measure VE in immunocompromised children and those who received the Moderna vaccine, given their exclusion from the study. Further, because of the small number of testing episodes occurring after BA.4/BA.5 circulation and the limited use of whole genome sequencing, we could not estimate VE against Omicron sublineages. Lastly, we did not assess VE against other COVID-19-related outcomes, such as multisystem inflammatory syndrome in children or long COVID-19. Further studies assessing the impact of vaccination on these outcomes, as well as the duration of protection for longer intervals after vaccination in this age group, are needed.

CONCLUSIONS

Our results suggest that 2 doses of the BNT162b2 COVID-19 vaccine were initially effective against symptomatic infection from Omicron in children aged 5 to 11 years, but VE decreased steadily with time, especially >120 days after vaccination. Although extended dosing intervals were associated with higher effectiveness against symptomatic infection in the first 3 months after vaccination, VE estimates became similar to those of shorter intervals starting 90 days after the second dose. Cases of severe COVID-19 were rare among vaccinated children in this age group, and VE was high against severe outcomes, but with potential waning over time. Further studies are warranted, especially with bivalent COVID-19 vaccines and the potential emergence of other Omicron sublineages and SARS-CoV-2 variants.

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ABBREVIATIONS

CCM: Public Health Case and Contact Management Solution
COVID-19: coronavirus disease 2019
RT-PCR: reverse-transcription polymerase chain reaction
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
VE: vaccine effectiveness

to the analysis plan, and interpreted the results; Dr Austin contributed to the analysis plan and interpreted the results; Dr Nasreen generated the study figures and interpreted the results; Drs Morris, Schwartz, Tadrous, Thampi and Kumanan Wilson interpreted the results; and all authors reviewed, edited, and approved the final version of the manuscript, authorized its submission for publication, and agree to be accountable for all aspects of the work.

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

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