Vaccine Effectiveness Against Hospitalization Among Adolescent and Pediatric SARS-CoV-2 Cases in Ontario, Canada

Alison E. Simmons PhD(c) MPH[1], Afia Amoako MScPH[1], Alicia A. Grima MPH(c)[1], Kiera R. Murison MPH(c)[1], Ashleigh R. Tuite PhD MPH MSc[1,2], David N. Fisman MD MPH[1]

[1]Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada
[2]Centre for Immunization Readiness, Public Health Agency of Canada, Ottawa, Ontario, Canada

Address reprint requests and correspondence to:
David N. Fisman MD MPH FRCP(C)
Room 686, 155 College Street, Toronto, Ontario, Canada M5T 3M7
Email: david.fisman@utoronto.ca

Funding Statement: AES is supported by the University of Toronto Connaught International Doctoral Scholarship. This research is supported by a grant to DNF from the Canadian Institutes for Health Research (2019 COVID-19 rapid researching funding OV4-170360).

Declaration of Competing Interests: DNF has served on advisory boards related to influenza and SARS-CoV-2 vaccines for Seqirus, Pfizer, Astrazeneca and Sanofi-Pasteur Vaccines, and has served as a legal expert on issues related to COVID-19 epidemiology for the Elementary Teachers Federation of Ontario and the Registered Nurses Association of Ontario.
ART was employed by the Public Health Agency of Canada when the research was conducted. The work does not represent the views of the Public Health Agency of Canada.

Acknowledgements: The authors wish to thank Dr. Sarah A. Buchan for valuable feedback on this manuscript, and the staff at Public Health Ontario and Ontario's public health units for collecting, sequencing, analyzing, and providing access to the data used for this analysis.

Background: Vaccines to prevent SARS-CoV-2 infection and severe outcomes were approved in 2021 for adolescent and subsequently pediatric populations. With the emergence of variants of concern, it is important to continue to assess vaccine effectiveness against both infection and severe disease manifestations.

Methods: Using an age and time-matched nested case-control design, we estimated the vaccine effectiveness of SARS-CoV-2 vaccination at preventing hospitalization among adolescent and pediatric patients infected with SARS-CoV-2. We linked SARS-CoV-2 cases ages 4 to 17 years in Ontario's reportable diseases database to SARS-CoV-2 vaccination records. We included 1,441 incident SARS-CoV-2 cases occurring between May 28, 2021 and January 10, 2022. We used multivariable logistic regression to estimate the effectiveness of one and two mRNA vaccine doses against hospitalization among adolescent and pediatric SARS-CoV-2 cases. We quantified and mitigated the impact of unmeasured confounding by calculating an E-value and by applying instrumental variable methods.

Results: We included *n*=131 hospitalized SARS-CoV-2 cases and *n*=1,310 non-hospitalized SARS-CoV-2 cases. One vaccine dose was shown to be 37% effective against hospitalization among SARS-CoV-2 cases (adjusted odds ratio [aOR] = 0.63 [95% CI: 0.33, 1.13]). In contrast, two doses were 59% (aOR = 0.41 [95% CI: 0.21, 0.77]) effective at preventing hospitalization among SARS-CoV-2 cases.

Conclusions: Even with immune evasion by SARS-CoV-2 variants, two vaccine doses continue to provide protection against hospitalization among adolescent and pediatric patients, even when the vaccines do not prevent infection. SARS-CoV-2 vaccines remain a safe and effective intervention to prevent severe outcomes.

Introduction

Severe Acute Respiratory Syndrome (SARS-CoV-2) has caused more than 5.5 million deaths globally since its emergence in 2019.[1] Safe and effective vaccines to prevent SARS-CoV-2 infection and severe outcomes have been approved since late 2020.[2] With the emergence of B.1.617 (Delta) in May 2021 and B.1.1.529 (Omicron) in November 2021, decreased vaccine effectiveness against infection was observed.[3-6] Given that the goal of vaccination is to prevent death, severe disease, and overall disease burden, it is important to consider how well vaccines achieve these goals among individuals with SARS-CoV-2 infections.[7]

Few studies have focused on the real-world effectiveness of SARS-CoV-2 vaccination against severe outcomes among children and adolescents. Prior estimates of vaccine effectiveness against hospitalization among adolescent and pediatric populations have used uninfected controls. Resulting effectiveness estimates reflect the joint risk of infection and the risk of hospitalization conditional on infection.[8] Three recent studies examined vaccine effectiveness against hospitalization among pediatric patients using uninfected controls. These studies showed that BNT162b2 was 94% effective against hospitalization among adolescents infected with the Delta variant (B.1.617).[9] After the emergence of the Omicron variant (B.1.1.529), vaccine effectiveness against hospitalization was estimated to be 73% among adolescents ages 12 to 17 and 48% among pediatric patients ages 5 to 11.[10] In a recent Morbidity and Mortality Weekly Report (MMWR), two dose vaccine effectiveness against hospitalization was between 73% and 94% among pediatric and adolescent populations.[11]

The Canadian province of Ontario represents a large (population 14.6 million) and diverse jurisdiction, with high levels of adolescent and pediatric SARS-CoV-2 vaccine coverage.[12] Approximately 87% of Ontario residents ages 12 to 17 and 53% of Ontario residents ages 5 to 11 received at least one SARS-CoV-2 dose as of January 2022.[13] The BNT162b2 (Pfizer-BioNTech, “Comirnaty”) vaccine was administered to healthy individuals ages 12 to 17 beginning on May 28, 2021, and ages 5 to 11 beginning on November 28, 2021.[14,15] Robust public health surveillance systems in Ontario enable individual-level linkage of the SARS-CoV-2 vaccination database and the reportable disease database. Data include individual-level demographic factors that can be used to reduce bias in our vaccine effectiveness estimates. We calculated the effectiveness of one and two SARS-CoV-2 vaccine doses against hospitalization in adolescent and pediatric patients who tested positive for SARS-CoV-2.

Methods

Data Sources

Confirmed SARS-CoV-2 cases were identified in Ontario’s Public Health Case and Contact Management Solution (CCM).[16,17] The CCM includes patient demographics (i.e., sex, age, comorbidities), geographic location (i.e., public health unit), and SARS-CoV-2 case characteristics (i.e., test date, symptom onset date, hospital admission and discharge dates) for all laboratory-confirmed cases in Ontario. SARS-CoV-2 vaccination information was identified from the provincial COVaxON database. COVaxON data includes vaccine administration information (i.e., dose dates, dose locations, dose indication, vaccine product) for Ontario residents. The CCM and COVaxON data were linked through a unique “pseudo-health card number” identifier present in both datasets.

Study Design

We conducted a nested case-control study from a cohort of individuals aged 4-17 years who tested positive for SARS-CoV-2 in Ontario, Canada. These individuals had provincial health insurance and a positive reverse transcription real-time polymerase chain reaction (PCR) test between May 28, 2021 and January 10, 2022. For each hospitalized patient, we matched 10 non-hospitalized patients by case onset date and age using the near-neighbor matching procedure to improve precision.[18,19]

We restricted our analysis to incident SARS-CoV-2 infections. We excluded SARS-CoV-2 cases where individuals had received three vaccine doses, as this population was not eligible for third doses during the study period. We extracted the data on January 19, 2022, but only included test dates up to January 10, 2022, to account for delays between testing and hospitalization. SARS-CoV-2 cases aged 4 years were included in the analysis because cases among pediatric patients aged 4 and aged 5 were grouped in these data, and pediatric patients who turned 5 in the calendar year were eligible for vaccination. In total, 131 hospitalized SARS-CoV-2 cases were matched with 1,310 non-hospitalized SARS-CoV-2 cases (**Figure 1**).

Measures

The outcome was hospitalization due to SARS-CoV-2. Hospitalizations were identified by a reported hospital admission date, or a reported hospitalization or ICU admission. The exposure was SARS-CoV-2 vaccination. We considered individuals one dose vaccinated 14 or more days after the date the first vaccine dose was administered; individuals were considered two dose vaccinated 14 or more days after the date the second vaccine dose was administered. During the first 13 days after the date the first vaccine dose was administered, individuals were considered unvaccinated.[20]

Covariates were selected based on the literature and the theory of Directed Acyclic Graphs (DAGs).[21] Case onset date, age, sex, asthma, and immunocompromising condition were selected as confounders.[3,22,23] Case onset date was defined as the date of symptom onset for symptomatic cases and the specimen collection date for asymptomatic cases. Additionally, the proportion of two dose vaccinated individuals less than age 18 years within each public health unit was included as an instrumental variable in a sensitivity analysis. A DAG outlining the hypothesized relationships between the variables is presented in **Figure 2**.

Statistical Analysis

We calculated frequencies of baseline characteristics and compared SARS-CoV-2 cases by hospitalization status. Standardized mean differences (SMD) were used in addition to statistical tests (Chi-square and unpaired t-tests) to compare differences in covariates between hospitalized and non-hospitalized groups. Standardized mean differences are not impacted by sample size, in contrast to the common statistical tests used in descriptive tables. A standardized difference greater than 0.10 represents a lack of covariate balance.[24] We used multivariable logistic regression to calculate the effectiveness of one and two vaccine doses against hospitalization among adolescent (ages 12-17) and pediatric (ages 4-11) SARS-CoV-2 cases, while adjusting for sex, asthma, immunocompromising condition, age, and case onset

date.[25] Subsequently, we examined potential effect measure modification by age group and case onset date. To assess effect measure modification by age-group, we used two multivariable logistic regression models to separately calculate vaccine effectiveness among those ages 4-11 and ages 12-17 while adjusting for sex, asthma, immunocompromising condition, age, and case onset date. To assess effect measure modification by infecting variant (i.e., Delta and Omicron), we included an interaction term between vaccination status and case onset data (May 28, 2021 – December 14, 2021 compared to December 15, 2021 – January 10, 2022) in a multivariable logistic regression model among adolescents. Ontario residents under age 12 were ineligible for SARS-CoV-2 vaccination during most of the former time-period and were thus excluded from the analysis. Dates were chosen to align with the rise in the prevalence of the Omicron variant in Ontario. Vaccine effectiveness (VE) was calculated using the formula VE = (1-aOR)*100%.

We performed sensitivity analyses to quantify and mitigate the impact of unmeasured confounding. First, we calculated an E-value based on the results of the non-instrumented multivariable conditional logistic regression model.[26] An E-value quantifies how strong an unmeasured confounder would need to be to explain away the association between SARS-CoV-2 vaccination and hospitalization.[27] Second, we used instrumented-multivariable logistic regression to estimate the average impact of two doses of vaccination on SARS-CoV-2 hospitalization risk with additional control for unmeasured confounders. Instrumental variable methods can be used to estimate the average causal effect of vaccination on hospitalization in the presence of unmeasured confounders under the following assumptions: (i) the instrument causes the exposure, (ii) affects the outcome only through the exposure, and (iii) shares no common causes with the outcome.[28] We used the proportion of individuals under age 18 vaccinated with two doses of SARS-CoV-2 vaccine in each public health unit (hereby referred to as PHU vaccine proportion) as a measure of vaccine acceptance, and as an instrument to predict individual-level vaccination.

The first assumption can be verified by quantifying the association between PHU vaccine proportion and vaccination status using a correlation coefficient (r^2). The latter two assumptions can be verified theoretically and based on our causal structure presented in **Figure 2**. Because overall PHU vaccine proportion is unlikely to be related to individual level hospitalization risk among individuals infected with SARS-CoV-2 and any factors that cause PHU vaccination are unlikely to also be causes of individual hospitalization, PHU vaccine proportion is a valid instrument to mitigate the impact of unmeasured confounding on the relationship between vaccination and hospitalization. We used a two-stage model to calculate the adjusted odds ratio (aOR) of the average impact of 2-dose SARS-CoV-2 vaccination on hospitalization under the assumption of homogeneity (i.e., no effect measure modification).[29] The first model used multivariable probit regression to calculate predicted levels of vaccination conditional on PHU vaccine proportion and the measured covariates. The second model used logistic regression with hospitalization as the outcome, and the predicted levels of vaccination from the probit model and the measured confounders, including case onset date, as predictors. Robust standard errors were calculated with the Sandwich estimator. [30] Analyses were conducted in R version 4.0.3.

Ethics

We received ethics approval for this study from the Research Ethics Board at the University of Toronto (#00031358).

Results

We included 131 hospitalized SARS-CoV-2 cases and 1,310 nonhospitalized SARS-CoV-2 cases in our analysis, with test report dates between May 28, 2021 and January 10, 2022 (**Figure 1**). Individuals hospitalized with SARS-CoV-2 were more likely to be unvaccinated, immunocompromised, and have an asthma diagnosis compared to those who were not hospitalized. There were no differences by age or case onset date because the distribution is identical across hospitalization status due to the age and time-matched study design.

In our main analysis, after adjustment for sex, asthma, immunocompromising condition, age, and case onset date, we observed that one SARS-CoV-2 vaccine dose was 37% effective (aOR = 0.63 [95% CI: 0.33, 1.13]) against hospitalization among adolescent and pediatric SARS-CoV-2 cases (**Table 2**). In contrast, two SARS-CoV-2 vaccine doses were 59% effective (aOR = 0.41 [95% CI: 0.21, 0.77]) at preventing hospitalization among SARS-CoV-2 cases. In our stratified analysis, we found that one SARS-CoV-2 vaccine dose 32% effective (aOR = 0.68 [95% CI: 0.28, 1.49]) at preventing hospitalization among pediatric SARS-CoV-2 cases ages 4-11. One SARS-CoV-2 vaccine dose was 38% effective (adjusted odds ratio (aOR) = 0.62 [95% CI: 0.21, 1.51]) and two SARS-CoV-2 vaccine doses were 63% effective (adjusted odds ratio (aOR) = 0.37 [95% CI: 0.18, 0.77]) at preventing hospitalization among adolescent patients ages 12-17 years. We found evidence of non-statistically significant effect measure modification by case onset date among SARS-CoV-2 cases ages 12-17 (likelihood ratio test, p=0.18) (**Figure 3**).

In our primary analysis, the E-value for the adjusted association between vaccination with two doses and the risk of hospitalization (i.e., aOR = 0.41) was 4.66.[26] An unmeasured confounder would need to be independently associated with vaccination and hospitalization by a 4.66-fold risk ratio to result in a null risk ratio, after adjusting for sex, asthma, immunocompromising condition, age, and case onset date. Similarly, the E-value for the upper 95% CI bound (i.e., 95% CI upper bound = 0.77) is 1.92. A set of unmeasured confounders would need to be independently associated with vaccination and hospitalization by a 1.92-fold risk ratio for the 95% CI to encompass the null value after controlling sex, asthma, immunocompromising condition, age, and case onset date. The validity of the first assumption in our instrumental variable analysis was confirmed with a modest correlation between PHU vaccine proportion and two dose vaccination status (r^2 = 0.31). In our instrumental variable analysis, which accounts for unmeasured confounding, two SARS-CoV-2 vaccine doses were 36% effective (adjusted OR (aOR) = 0.64 [95% CI: 0.54, 1.87]) at preventing hospitalization among pediatric SARS-CoV-2 cases (Table S1).

Discussion

Among pediatric SARS-CoV-2 cases, one vaccine dose was 37% effective, and two vaccine doses were 59% effective at preventing SARS-CoV-2 hospitalization. Unadjusted hospitalization proportions in this population during the study time-period were 29 hospitalizations/10,000

SARS-CoV-2 cases among unvaccinated cases, 19 hospitalizations/10,000 SARS-CoV-2 cases among one-dose vaccinated cases, and 10 hospitalizations/10,000 SARS-CoV-2 cases among two-dose vaccinated cases. We found no evidence of effect modification by age-group. One SARS-CoV-2 vaccine dose was 38% effective, and two SARS-CoV-2 vaccine doses were 63% effective at preventing hospitalization among cases ages 12-17 years, and one SARS-CoV-2 dose was 32% effective against hospitalization among cases ages 5-11 years. The effectiveness of two SARS-CoV-2 vaccine doses could not be examined in the pediatric population due to a small number of two-dose vaccinated hospitalized cases. Our vaccine effectiveness estimates are robust to unmeasured confounding, as evidenced by the high E-value for the estimates. Similarly, two doses of SARS-CoV-2 vaccine remained efficacious against hospitalization after additional control for unmeasured confounding in our instrumental variable analysis. Our study demonstrates that among adolescent and pediatric SARS-CoV-2 cases, vaccination provides additional protection against hospitalization independent of protection provided against infection.

Few studies have focused on SARS-CoV-2 vaccine effectiveness in pediatric and adolescent populations. Our estimated two dose vaccine effectiveness against hospitalization is slightly lower than studies in the United States.[9-11,31] In a case-control study conducted between May and October 2021 (i.e., prior to widespread infection with Omicron) with test-negative and syndrome-negative controls, vaccine effectiveness against hospitalization was 94% among those with two doses, and 97% among those with one dose.[9] A study with 164 hospitals in the United States from April 2021 to January 2022 found that two dose vaccine effectiveness against hospitalization was 74% among children ages 5-11 years and between 73% and 94% among adolescents.[11] In contrast to these studies, our control group consisted of non-hospitalized SARS-CoV-2 cases, not uninfected individuals. This allowed us to isolate the effectiveness of vaccination against hospitalization independent of infection risk, which explains our lower vaccine effectiveness estimates against hospitalization.[8] Related, we were able to match our non-hospitalized and hospitalized cases on case onset date to maximize our ability to control for time, and thus circulating SARS-CoV-2 variant.[19]

Our study has several notable strengths. Due to Ontario's high quality public health surveillance data, we isolated the direct impact of vaccination on hospitalization risk with control for individual level demographic and health related factors. Our study includes a diverse population in a region with publicly funded healthcare.[32,33] Additionally, we used a quantitative bias analysis to demonstrate the susceptibility of our results to unmeasured confounding.[26] Finally, we conducted an instrumental variable analysis to enable adjustment for unmeasured confounders.[28] Our study also had a few limitations. First, we did not consider time since vaccination in our analysis. In a recent study in the United States, time since vaccination was not shown to significantly impact SARS-CoV-2 vaccine effectiveness estimates against hospitalization in this population.[11] We were unable to assess two dose effectiveness against hospitalization specifically among cases ages 5-11 years due to few hospitalizations among two-dose vaccinated individuals. The availability of testing, and the propensity to get tested may have differed between vaccinated and unvaccinated individuals, and the reporting of comorbidities may have been more common among hospitalized SARS-CoV-2 cases. Finally,

there may be misclassification because we used time as proxy for infecting variant among adolescents in our evaluation of effect measure modification.

With the continued emergence of variants that may further decrease SARS-CoV-2 vaccine effectiveness against infection, it is vital to consider how effective these vaccines are at preventing severe outcomes.[34] Given that two dose vaccine effectiveness against hospitalization following infection is approximately 63% in adolescents, and may be lower in youth ages 5-11 years, it is important to continue non-pharmaceutical interventions to prevent infection risk in these populations. Given that SARS-CoV-2 is primarily an airborne infection, this study supports the continued use of high-quality masks, increased ventilation, and accessible rapid antigen tests.[35,36]

In this evaluation of the effectiveness of SARS-CoV-2 vaccination in pediatric patients ages 4 to 17 in Ontario, Canada, we found that vaccination is moderately effective at preventing hospitalization, even when the vaccines do not prevent infection. SARS-CoV-2 vaccines remain a safe and effective intervention to prevent severe outcomes in pediatric populations.

Figure 1. Flow Diagram for Creation of Nested Case-Control Study Population

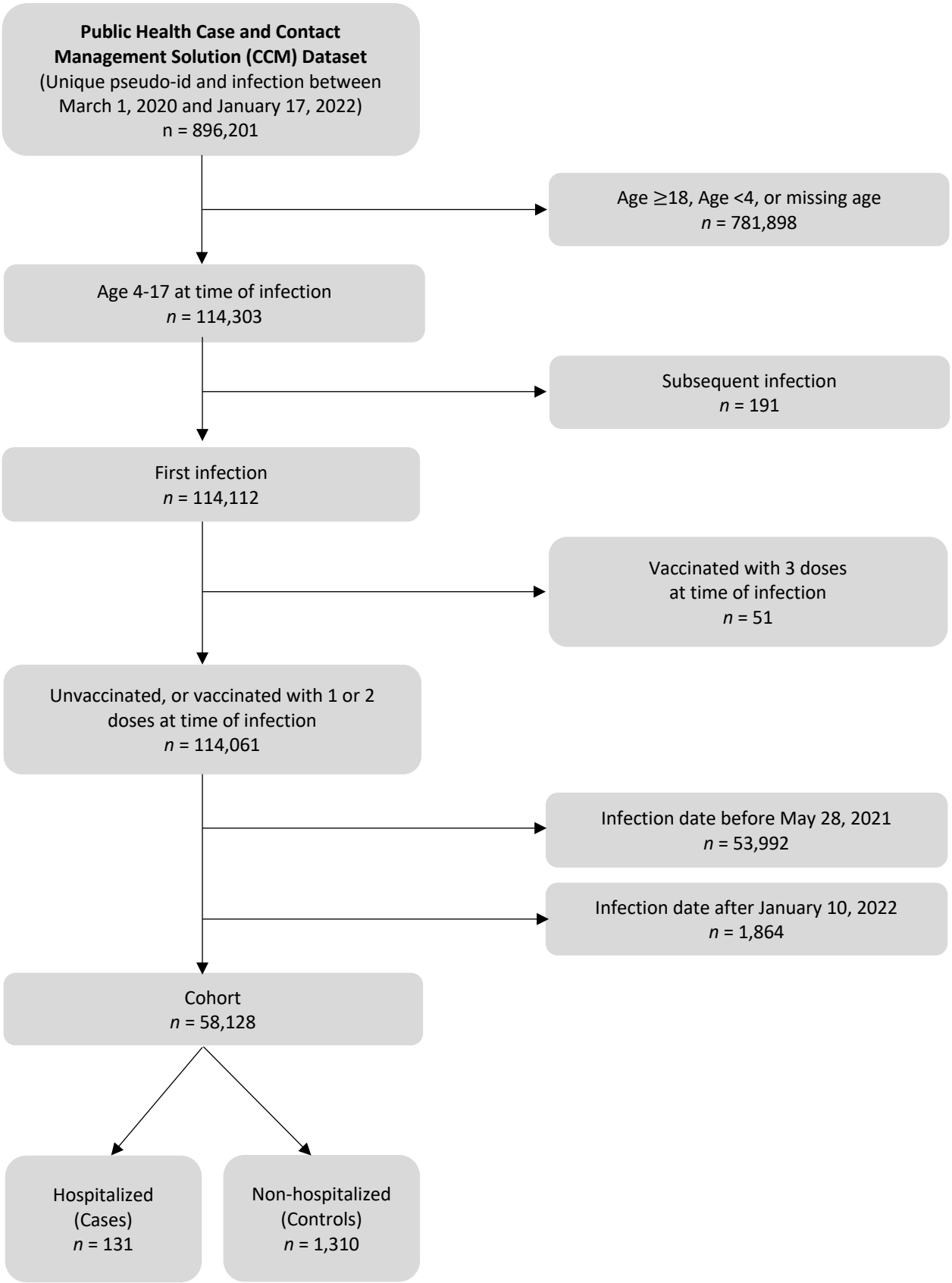


Figure 2. Directed Acyclic Graph (DAG) of the relationship between vaccination status and hospitalization among pediatric SARS-CoV-2 cases

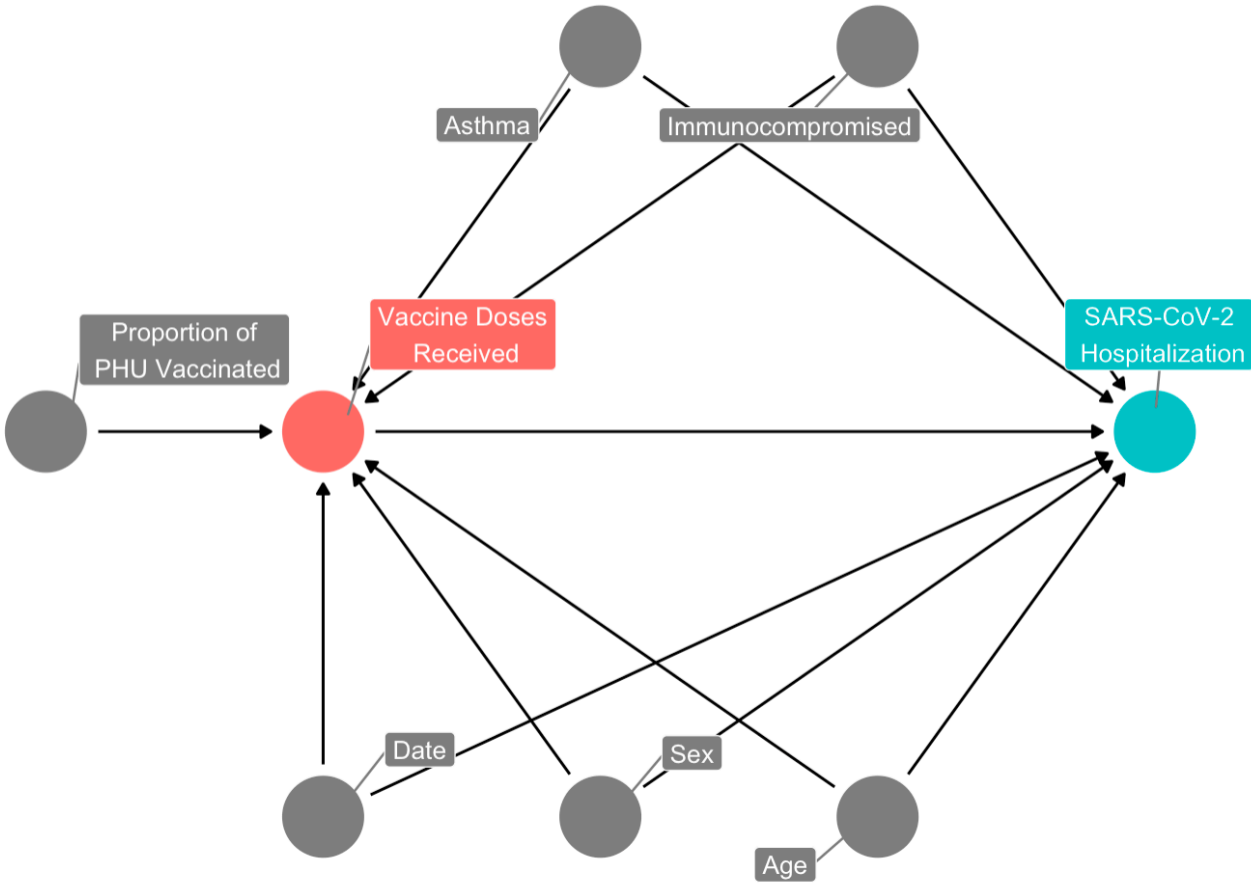


Table 1. Description of adolescent and pediatric SARS-CoV-2 cases by hospitalization status (*n* = 1,441)

Characteristic	**Hospitalized** *n* = 131		**Non-hospitalized** *n* = 1,310		**SMD**	***p*[a]**
	n	**(%)**	***n***	**(%)**		
Vaccination Status[b]					0.19	0.16
Unvaccinated	99	(75.6)	888	(67.8)		
One dose	15	(11.5)	172	(13.1)		
Two doses	17	(13.0)	250	(19.1)		
Male					0.06	0.60
Yes	66	(50.4)	697	(53.2)		
No	65	(49.6)	613	(46.8)		
Immunocompromised					0.43	<0.001
Yes	8	(6.1)	<5	(<0.4)		
No	123	(93.9)	>1305	(>99.6)		
Asthma					0.27	<0.001
Yes	12	(9.2)	15	(1.1)		
No	119	(90.8)	1,295	(98.9)		
	Mean	**(SD)**	**Mean**	**(SD)**		
Age	11.2	(4.3)	11.2	(4.0)	0.01	0.92

Notes: SMD = standardized mean difference; *p* = p-value; SD = standard deviation

[a] Pearson chi-square for categorical variables, and unpaired t-tests for continuous variables

[b] Vaccination status on case onset date

Table 2. Adjusted odds ratios, with 95% confidence intervals, of the relationship between vaccination status and hospitalization among pediatric SARS-CoV-2 cases (*n* = 1,441)

	Overall *n* = 1,441		**Ages 4-11** *n* = 753		**Ages 12-17** *n* = 688	
Characteristic	**aOR**	**(95% CI)**	**aOR**	**(95% CI)**	**aOR**	**(95% CI)**
Vaccination Status[a]						
Unvaccinated	1.00	(ref)	1.00	(ref)	1.00	(ref)
One dose	0.63	(0.33, 1.13)	0.68	(0.28, 1.49)	0.62	(0.21, 1.51)
Two doses	0.41	(0.21, 0.77)	--[d]	--	0.37	(0.18, 0.77)
Male						
Yes	0.87	(0.60, 1.27)	0.94	(0.55, 1.60)	0.81	(0.47, 1.39)
No	1.00	(ref)	1.00	(ref)	1.00	(ref)
Immunocompromised						
Yes	39.26	(0.13, 144.38)	37.4	(8.20, 263.22)	40.25	(8.50, 292.84)
No	1.00	(ref)	1.00	(ref)	1.00	(ref)
Asthma						
Yes	6.30	(2.46, 15.06)	6.21	(1.59, 20.92)	6.26	(1.57, 21.92)
No	1.00	(ref)	1.00	(ref)	1.00	(ref)
Age[b]	1.05	(1.00, 1.10)	1.02	(0.91, 1.14)	1.06	(0.90, 1.26)
Case onset date[c]	1.00	(1.00, 1.01)	1.00	(1.00, 1.01)	1.00	(1.00, 1.01)

Notes: aOR = adjusted odds ratio; CI = confidence interval; ref = reference.

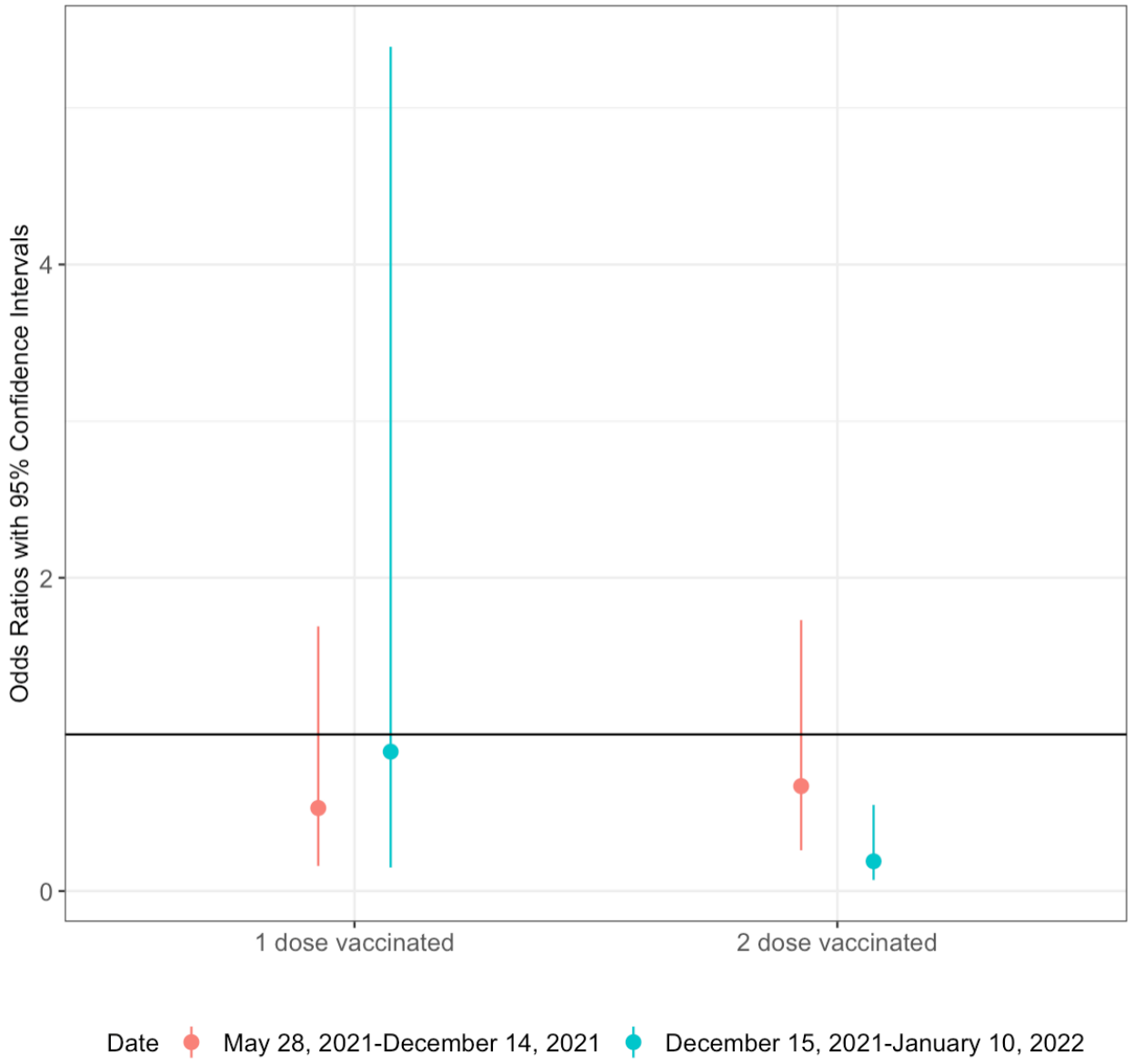
[a] Vaccination status on case onset date

[b] Per 2-year increase in age

[c] Date of symptom onset for symptomatic cases and the specimen collection date for asymptomatic cases

[d] 5 SARS-CoV-2 cases occurred among pediatric patients ages 5-11 vaccinated with two doses, and <5 patients were hospitalized

Figure 3. Adjusted odds, with 95% confidence intervals, of hospitalization among SARS-CoV-2 cases ages 12-17 stratified by vaccination status and case onset date (*n* = 688)



References

1. World Health Organization. *WHO Coronavirus (COVID-19) Dashboard*2021.
2. Higdon MM, Wahl B, Jones CB, et al. A systematic review of COVID-19 vaccine efficacy and effectiveness against SARS-CoV-2 infection and disease. *medRxiv.* 2021:2021.09.17.21263549.
3. Buchan SA, Chung H, Brown KA, et al. Effectiveness of COVID-19 vaccines against Omicron or Delta symptomatic infection and severe outcomes. *medRxiv.* 2022:2021.12.30.21268565.
4. Ontario Agency for Health Protection and Promotion (Public Health Ontario). *COVID-19 Public Health Measures Related to the Delta Variant*2021.
5. Ontario Agency for Health Protection and Promotion (Public Health Ontario). *COVID-19 Variant of Concern Omicron (B.1.1.529): Risk Assessment, February 23, 2022*2022.
6. Fowlkes AL, Yoon SK, Lutrick K, et al. Effectiveness of 2-Dose BNT162b2 (Pfizer BioNTech) mRNA Vaccine in Preventing SARS-CoV-2 Infection Among Children Aged 5–11 Years and Adolescents Aged 12–15 Years — PROTECT Cohort, July 2021–February 2022. *MMWR Morb Mortal Wkly Rep.* 2022;ePub.
7. World Health Organization. WHO, UN set out steps to meet world COVID vaccination targets2021.
8. Chua H, Feng S, Lewnard JA, et al. The Use of Test-negative Controls to Monitor Vaccine Effectiveness: A Systematic Review of Methodology. *Epidemiology.* 2020;31:43-64.
9. Olson SM, Newhams MM, Halasa NB, et al. Effectiveness of BNT162b2 Vaccine against Critical Covid-19 in Adolescents. *N Engl J Med.* 2022;386:713-23.

10. Dorabawila V, Hoefer D, Bauer UE, Bassett MT, Lutterloh E, Rosenberg ES. Effectiveness of the BNT162b2 vaccine among children 5-11 and 12-17 years in New York after the Emergence of the Omicron Variant. *medRxiv.* 2022:2022.02.25.22271454.

11. Klein NP, Stockwell MS, Demarco M, et al. Effectiveness of COVID-19 Pfizer-BioNTech BNT162b2 mRNA Vaccination in Preventing COVID-19–Associated Emergency Department and Urgent Care Encounters and Hospitalizations Among Nonimmunocompromised Children and Adolescents Aged 5–17 Years — VISION Network, 10 States, April 2021–January 2022. *MMWR Morb Mortal Wkly Rep.* 2022;71:352-8.

12. Statistics Canada. Table 17-10-0134-01 Estimates of population (2016 Census and administrative data), by age group and sex for July 1st, Canada, provinces, territories, health regions (2018 boundaries) and peer groups.

13. Public Health Ontario. *COVID-19 Vaccine Uptake in Ontario: December 14, 2020 to January 30, 2022*2022.

14. Ontario Ministry of Health. COVID-19 Vaccine Bookings to Open For All Children Aged Five to 112021.

15. Ontario Ministry of Health. COVID-19 Vaccine Bookings to Open For All Children Aged Five to 11. Families can book appointments through a variety of channels starting November 23rd. Available via the Internet at https://news.ontario.ca/en/release/1001195/covid-19-vaccine-bookings-to-open-for-all-children-aged-five-to-11. Last accessed December 8, 2021. 2021.

16. Fisman DN, Greer AL, Hillmer M, O'Brien SF, Drews SJ, Tuite AR. COVID-19 case age distribution: correction for differential testing by age. *medRxiv.* 2020:2020.09.15.20193862.

17. Fisman DN, Tuite AR. Evaluation of the relative virulence of novel SARS-CoV-2 variants: a retrospective cohort study in Ontario, Canada. *CMAJ.* 2021;193:E1619-E25.

18. Olmos A, Govindasamy P. Propensity scores: a practical introduction using R. *Journal of MultiDisciplinary Evaluation.* 2015;11:68-88.

19. Pearce N. Analysis of matched case-control studies. *BMJ.* 2016;352:i969.

20. Ontario Ministry of Health. COVID-19 Fully Vaccinated Status in Ontario. Available via the Internet at https://www.health.gov.on.ca/en/pro/programs/publichealth/coronavirus/docs/vaccine/COVID-19_fully_vaccinated_status_ontario.pdf. Last accessed December 2, 2021. 2021.

21. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology.* 1999:37-48.

22. Johnson AG, Amin AB, Ali AR, et al. COVID-19 Incidence and Death Rates Among Unvaccinated and Fully Vaccinated Adults with and Without Booster Doses During Periods of Delta and Omicron Variant Emergence - 25 U.S. Jurisdictions, April 4-December 25, 2021. *MMWR Morb Mortal Wkly Rep.* 2022;71:132-8.

23. Graff K, Smith C, Silveira L, et al. Risk Factors for Severe COVID-19 in Children. *The Pediatric Infectious Disease Journal.* 2021;40.

24. Austin PC. Using the Standardized Difference to Compare the Prevalence of a Binary Variable Between Two Groups in Observational Research. *Communications in Statistics - Simulation and Computation.* 2009;38:1228-34.

25. McNutt L-A, Wu C, Xue X, Hafner JP. Estimating the Relative Risk in Cohort Studies and Clinical Trials of Common Outcomes. *American Journal of Epidemiology.* 2003;157:940-3.

26. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. *Annals of Internal Medicine.* 2017;167:268-74.

27. Linden A, Mathur MB, VanderWeele TJ. Conducting sensitivity analysis for unmeasured confounding in observational studies using E-values: The evalue package. *The Stata Journal.* 2020;20:162-75.

28. Hernán MA, Robins JM. Instruments for causal inference: an epidemiologist's dream? *Epidemiology.* 2006;17:360-72.

29. Swanson SA, Hernán MA. Commentary: How to Report Instrumental Variable Analyses (Suggestions Welcome). *Epidemiology.* 2013;24:370-4.

30. Davies NM, Smith GD, Windmeijer F, Martin RM. Issues in the reporting and conduct of instrumental variable studies: a systematic review. *Epidemiology.* 2013;24:363-9.

31. Tartof SY, Slezak JM, Fischer H, et al. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. *The Lancet.* 2021;398:1407-16.

32. Ontario Ministry of Health and Ontario Ministry of Long-Term Care. Ontario Health Insurance Plan. 2021; https://www.health.gov.on.ca/en/public/programs/ohip/ohipfaq_mn.aspx.

33. Ontario Ministry of Finance. Ethnic Origin and Visible Minorities. *2016 Census Highlights* 2017; https://www.fin.gov.on.ca/en/economy/demographics/census/cenhi16-9.html.

34. Callaway E. Why does the Omicron sub-variant spread faster than the original? *Nature.* 2022;602:556-7.

35. Peeling RW, Olliaro PL, Boeras DI, Fongwen N. Scaling up COVID-19 rapid antigen tests: promises and challenges. *The Lancet Infectious Diseases.* 2021;21:e290-e5.

36. Greenhalgh T, Jimenez JL, Prather KA, Tufekci Z, Fisman D, Schooley R. Ten scientific reasons in support of airborne transmission of SARS-CoV-2. *The Lancet.* 2021;397:1603-5.

Table S1. Effect of vaccination on hospitalization among pediatric SARS-CoV-2 cases using instrumental-variable adjusted regression with robust standard errors (*n* = 1,441)

Characteristic	**aOR**	**(95% CI)**
Vaccination Status[a]		
Unvaccinated	1.00	(ref)
Two doses	0.64	(0.22, 1.87)
Male		
Yes	0.82	(0.55, 1.22)
No	1.00	(ref)
Immunocompromised		
Yes	41.11	(10.56, 160.08)
No	1.00	(ref)
Asthma		
Yes	7.11	(2.91, 17.37)
No	1.00	(ref)
Age[b]	1.03	(0.96, 1.10)
Case onset date[c]	1.00	(1.00, 1.01)

Notes: aOR = adjusted odds ratio; CI = confidence interval; ref = reference.

[a] Vaccination status on case onset date

[b] Per 2-year increase in age

[c] Date of symptom onset for symptomatic cases and the specimen collection date for asymptomatic cases