mRNA COVID-19 vaccine safety among children and adolescents: a Canadian National Vaccine Safety Network cohort study

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Summary

Background The Canadian National Vaccine Safety Network conducted active safety surveillance for COVID-19 vaccines. This study aimed to characterize the short-to-medium term safety of mRNA COVID-19 vaccines across the pediatric age spectrum.

Methods In this cohort study, vaccinated and unvaccinated children and adolescents aged 6 months to 19 years from eight Canadian provinces and territories were invited to participate. The outcome was a health event preventing daily activities, resulting in school absenteeism, or requiring medical consultation. Age-stratified multivariable regression models were used to examine health events associated with first and second doses of mRNA COVID-19 vaccines across different age groups: children under 5, children aged 5–11 years and adolescents aged 12–19 years.

Findings From January 2021 through February 2023, a total of 259,361 individuals from the dose one survey, 131,032 from the dose 2 survey, and 1179 from the control survey were included. In the week following dose two, vaccinated adolescents showed a higher proportion of health events [794 (4.6%) of 17,218 BNT162b2 recipients, 98 (8.5%) of 1153 mRNA-1273 recipients, 49 of (10.6%) of 464 heterologous schedule recipients] than unvaccinated adolescents [9 (3.7%) of 242 controls], but most events were self-limited and resolved within 7 days. No significant differences in proportion of health events following mRNA COVID-19 vaccines were observed between vaccinated and unvaccinated groups among adolescents after dose 1, or among children under 5 or those aged 5–11 years after any dose. Reported myocarditis/pericarditis cases within 0–28 days peaked among male adolescents following dose 2, in three of (0.037%) 8088 homologous BNT162b2 recipients, and two of (0.529%) 378 homologous mRNA-1273 recipients.

Interpretation Our findings suggest that reported health events, including myocarditis/pericarditis, vary by pediatric age group. Vaccinated adolescents reported health events more frequently following the second mRNA COVID-19 vaccine dose, while younger age groups did not report events more frequently than their unvaccinated counterparts.

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Research in context

Evidence before this study

We searched the peer-reviewed (PubMed) and pre-print (medRxiv) literature through September 4, 2024, focusing on the safety of COVID-19 vaccines in infants, children and adolescents. In addition to COVID-19 article filters from PubMed, we included search terms "COVID-19" AND "Vaccine", AND "child* OR infant* OR adolescent*" AND "safe* OR reactogenicity OR adverse event* OR tolerability OR adverse events of special interest OR myocarditis OR pericarditis." We found several clinical and observational studies that described adverse events after first and second doses or booster doses of mRNA vaccines in children and adolescents. Most studies focused on specific pediatric age groups separately, including a few that reported adverse events among children aged 5 years and above, and adolescents. Some post-marketing studies, with vaccinated children and adolescents reported adverse events but did not conduct multivariable adjusted analyses to evaluate the health event risk associated with specific COVID-19 vaccine products. Another study included a broader age range of 6 months–17 years, and aimed to specifically detect rare outcomes or adverse event of special interest. We found only one study that examined vaccine-related serious adverse events over a follow-up period of up to 14 months, but it did not include children under 5 years of age.

Added value of this study

Findings from our cohort study contribute to a better understanding of mRNA COVID-19 vaccine safety in the youngest populations eligible for vaccination worldwide. Our results offer valuable insights for clinicians, adolescents and parents regarding what to expect following COVID-19 vaccination. These findings can be utilized to effectively communicate with adolescents and parents about the risks associated with COVID-19 infection and vaccination, thus supporting them in making informed decisions.

Implications of all the available evidence

Our findings show mRNA COVID-19 vaccines are generally safe and the risk of adverse events, including adverse events of special interest, following mRNA COVID-19 vaccination varies by pediatric age group and vaccine dose number. These findings provide critical evidence to inform vaccination policies in pediatric populations, in Canada and globally. Continuous monitoring of vaccine safety, with separate evaluations for children and adolescents, remains essential.

Introduction

In Canada, severe cases of SARS-CoV-2 infection among children and adolescents have been reported since the early stages of the pandemic.[1] Additionally, the potential for severe post-infectious complications, including multisystem inflammatory syndrome in children and post-COVID syndrome (i.e., "long COVID"), have had significant impact on these populations.[2] This underscores the importance of vaccination for these groups. Canadian COVID-19 vaccination programs in these populations were introduced in a stepwise manner: adolescents 12–17 years in May 2021; children 5–11 years in November 2021; and children 6 months-4 years in July 2022.[3] Canada primarily utilized two mRNA vaccines in these age groups, BNT162b2 and mRNA-1273, each with different authorized timing and dosage regimens across various age groups.[3]

The safety and efficacy of mRNA COVID-19 vaccines in these populations were assessed in clinical trials and post-marketing studies.[4–7] However, evidence is limited from post-marketing studies that have examined mRNA-COVID-19 vaccine safety in both older and younger children including infants. A systematic review and meta-analysis of COVID-19 vaccine safety among individuals aged 3–17 years emphasized the urgent need for multicenter, large-sample studies, particularly in younger children and infants, with long-term follow-up data.[8] Thus, evidence from large post-marketing studies with longer follow-up data is required to provide a full understanding of mRNA COVID-19 safety among pediatric populations.

The Canadian National Vaccine Safety (CANVAS) network has been providing real-time vaccine safety information to public health authorities in Canada since 2009.[9,10] The network has been active for COVID-19 vaccine safety since the COVID-19 vaccine rollout in 2020.[11] This study aimed to profile adverse events within seven days and seven months following each mRNA product and dose, and to evaluate the association between mRNA COVID-19 vaccination and health events within seven days following vaccination in infants, children and adolescents.

Methods

Study design and participants

This was a cohort study, and the safety surveillance in the pediatric population used the same methodology as

in adults.[11] CANVAS employed a multi-pronged recruitment strategy to engage a larger sample. Vaccinated participants were recruited through auto-invitation via the vaccine booking system and auto-enrolment through vaccine registries. Additional channels such as posters, information cards, and pamphlets at vaccination clinics were utilized, along with promotion campaigns through local mass media and social media platforms. For unvaccinated controls, traditional methods were primarily used, including distribution of posters, information cards, and pamphlets, complemented by media outreach and invitations sent to previous CANVAS participants who had consented to future contact. It is important to note that not all provinces and territories employed all these methods for both groups. Except for auto-enrolled participants, all other interested participants were directed to the CANVAS website for self-registration. Details of these recruitment methods have been previously published.[12]

From January 2021 through February 2023, we enrolled participants aged 15–20 years or parents/guardians of children 6 months to 14 years of age, with an active email address and telephone number, who were able to communicate in English or French, had received a COVID-19 vaccine and resided in one of eight Canadian provinces and territories (Alberta, British Columbia, Nova Scotia, Ontario, Prince Edward Island, Quebec, Yukon, Northwest Territories). Individuals were able to participate as controls if they were unvaccinated and met the above inclusion criteria.

Study procedure

This was a retrospective analysis of data collected prospectively. Unvaccinated participants completed one online control survey, which captured health problems, including events occurring within 7 days prior to the survey and emergency department visits or hospitalizations in the previous six months. Vaccinated participants completed three online surveys: one each eight days after the first and second doses, and one 7 months after the first dose (Supplementary Fig. S1). The second dose survey captured events experienced between dose one and two surveys, and 7 days after dose two. All individuals completing the dose one survey were sent both dose two and the 7-month follow-up survey irrespective of dose two survey completion.

Our study protocol followed the earliest authorized 28-day interval between COVID-19 doses,[13] and the follow-up survey for vaccinated individuals was scheduled to be sent six months after the second dose, aligning with the six-month observational period for the unvaccinated groups. However, due to challenges in vaccine supply and distribution across Canada, subsequent public health recommendation extended the interval between dose one and dose two,[14] and participants were not provided the second dose survey in a standardize way. As a result, the follow-up survey was administered seven months after the first dose to ensure standardized follow-up of the vaccinated cohort at an interval close to the unvaccinated group's follow-up. Additionally, this allowed inclusion of all participants, irrespective of the receipt or timing of a second dose. This follow-up survey only examined whether vaccinated participants visited an emergency department or were hospitalized during the 7-month follow-up period.

The survey captured demographic data (age group, sex assigned at birth, ethnicity), general health status, pregnancy and lactation status, previous SARS-CoV-2 infection, vaccine product, occurrence or worsening of health events among controls or events following immunization. For adolescents, the ethnicity question was only included in the dose two survey. Participants who reported medically attended health events received a follow-up call for more details. We used Medical Dictionary for Regulatory Activities terminology (MedDRA) to code diagnoses from surveys and phone follow-ups. Research Ethics Board approval was obtained at all sites (British Columbia and Yukon: University of British Columbia Children's & Women's, Ref: H20-03704; Quebec: Centre Intégré univrsitaire de santé et de services sociaux de l'Estrie, Ref: MP-31-2021-4044; Nova Scotia and Prince Edward Island: Health Prince Edward Island and IWK Health Research, Ref: 1026400; Alberta: Conjoint Health REB, University of Calgary, Ref: REB20-2177; Ontario: Unity Health Toronto, Ref: 20–334). All participants, or parents/guardians, provided informed consent electronically.

Vaccine delivery and outcomes

For this analysis, we included vaccinated children and adolescents who received BNT162b2 or mRNA-1273 and were not pregnant or breastfeeding at time of survey completion. The authorized doses of BNT162b2 were 30 μg for adolescents, 10 μg for those aged 5–11 years, and 3 μg for children under 5 years of age. For mRNA-1273, the authorized doses were 100 μg for adolescents, 50 μg for those aged 6–11 years, and 25 μg for children under 6 years.[3] We included unvaccinated individuals who were not pregnant or breastfeeding at the time of survey completion. The COVID-19 vaccine product for each dose was collected either by electronic transfer from the vaccination registry or entered by the participants from their vaccine records. For dose two, three different vaccine groups were evaluated: homologous BNT162b2, homologous mRNA-123, and heterologous (mixed) vaccine regimens. The outcome variable was a composite outcome, defined as a new health event or worsening of a pre-existing condition sufficient to cause school absenteeism, require a medical consultation and/or prevent daily activities in the previous 7 days (for controls) or within 7 days following vaccination for vaccinated individuals.

We examined two adverse events of special interest (myocarditis/pericarditis and anaphylaxis) within 7 days

following first and second doses, as well as during the interval between the doses, and over the 7-month period following dose one. These analyses followed the Brighton Collaboration guidelines for adverse events of special interest case definitions and reporting.[15,16] Individuals with self-reported diagnoses of myocarditis/pericarditis/anaphylaxis from inpatient or outpatient hospital care were defined as cases. Since CANVAS relied on participant-based reporting, medical chart review was not done and the results of laboratory and imaging studies were not available. Therefore, myocarditis/pericarditis or anaphylaxis diagnoses were at Brighton Collaboration level 4 certainty (insufficient evidence to meet levels 1–3, where key data are 'unknown' or 'unobtainable').[15,16]

Statistical analysis

We estimated age specific proportions of health events, including events requiring emergency department visit or hospitalization, injection site reactions (vaccinated group only), common and uncommon specific symptoms, onset and duration of health events within 7 days following vaccination by vaccine exposure and dose, or prior 7 days for controls. The frequency of reported health events was classified as common (<1/10 to ≥1/100), uncommon (<1/100 to ≥1/1000), rare (<1/1000 to ≥1/10,000), and very rare (<1/10,000) as specified by European Medicines Agency.[17] Further, we assessed health events requiring emergency department visit or hospitalization within 7-months following dose one or prior six months for controls. We also examined information on participants' characteristics, medical consultation, and level of care received for those with myocarditis, pericarditis, and anaphylaxis.

To examine the association between vaccine exposure and health events within 7 days following vaccination, age-stratified multivariable generalized linear regression models with a log link were built for each vaccine product and dose. The estimated relative risk (RR) and 95% confidence intervals (CIs) were reported. In the multivariable models, we adjusted for potential confounders and risk factors, including sex assigned at birth (male or female), health status (five-level categorical variable: excellent, very good, good, fair/poor, or unknown), province, and previous COVID-19 infection (yes or no). We did complete case analysis as no variable had more than 5% missing data. Since the reported health status could have been affected by vaccination in the vaccinated group, we conducted sensitivity analyses by fitting multivariable models without the health status variable. Data cleaning was done in SAS version 9.4 (SAS Institute) and analysis was completed in R software version 4.1.1 (R foundation for Statistical Computing, Vienna, Austria).

Role of funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors had full access to the data in the study and had final responsibility for the decision to submit for publication.

Results

Overall survey completion among enrolled participants was 23% for unvaccinated controls and 47% for vaccinated participants in the Dose 1 survey. A total of 259,361 and 131,032 children and adolescents were included in the dose 1 and 2 analyses, respectively (Fig. 1). Most children aged 5–11 years and adolescents aged 12–19 years received the BNT162b2 vaccine for their first and second doses, whereas most children under 5 years received the mRNA-1273 vaccine for both doses. Less than 10% of vaccinated individuals in each pediatric age group received a heterologous series. A total of 1179 participants were included in the control sample (Fig. 2).

Risk of health events

Vaccinated and control participants' characteristics and vaccine products are shown in Table 1 for dose one and Supplementary Table S1 for dose two. Most vaccine recipients were children aged 5–11 years of age and reported excellent/very good/good health (≥90%). In the week following dose one, the occurrence of a health event severe enough to prevent daily activities, result in school absenteeism, or require a medical consultation among vaccinated individuals, regardless of age group, was similar or lower than in controls except mRNA-1273 recipients aged 5–11 years (Table 2). In the multivariable analysis, adjusting for sex, health status, province, and previous SARS-CoV-2 infection, mRNA COVID-19 vaccines were not associated with an increased risk of health events in all age groups within 7 days following dose one (Fig. 3).

In the week following dose two, the proportion of health events were generally higher than after dose 1 (Table 2). For children (6 months-4 years and 5–11 years), the incidence of health events after dose two was not significantly higher than controls, and there was no association between health events and either mRNA COVID-19 vaccine product (Fig. 3). Among the children aged 5–11 years, only three received homologous mRNA-1273, with one reporting a health event within 7 days following vaccination. Due to the limited sample size, regression analyses were not performed for this group. However, adolescents reported more health events after dose 2 and this significant increase in health events was observed with both mRNA vaccines and heterologous regimes (Fig. 3). In the sensitivity analysis, multivariable models that did not adjust for the health status variable produced estimates similar to those in the main analysis for all vaccine products and doses (Supplementary Table S2).

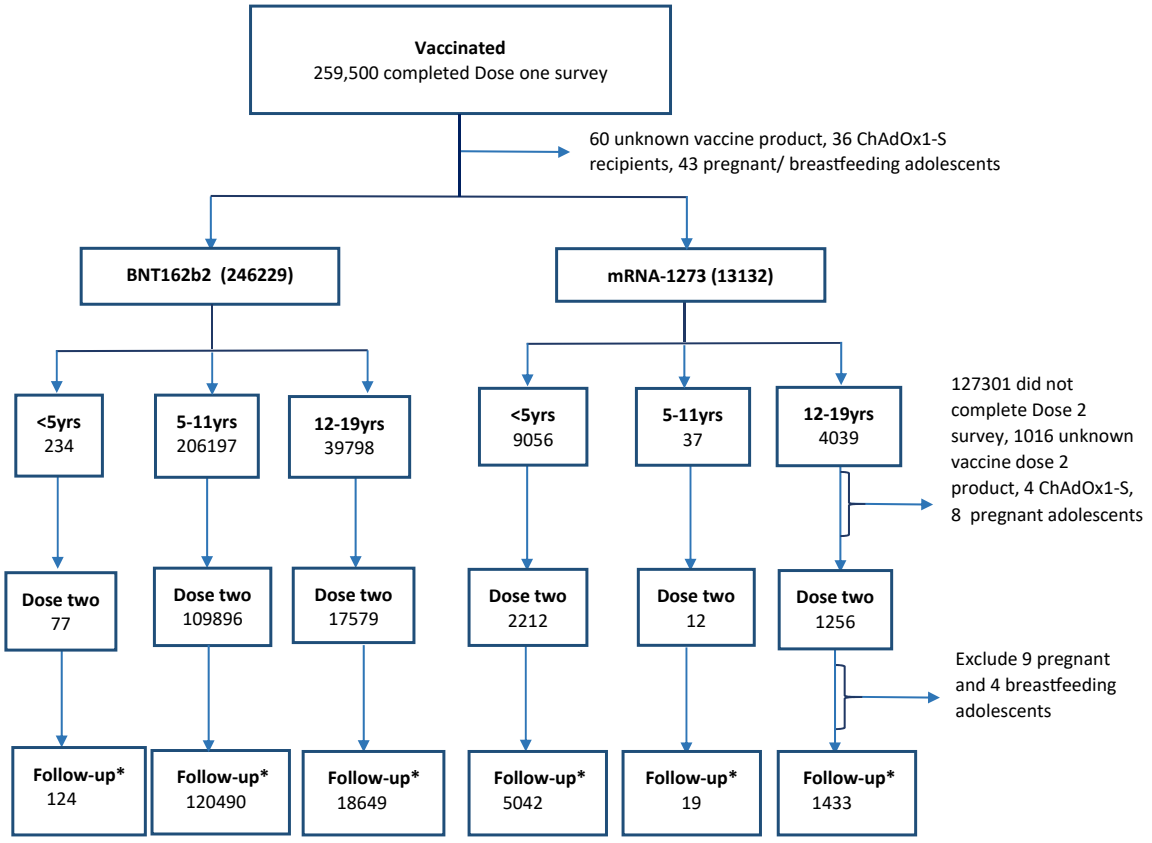

Fig. 1: Analytic sample for vaccinated children and adolescents (aged 6 months to 19 years). The participants in Dose two included individuals who received both homologous and heterologous (mixed) vaccine regimens. *Dose 1 vaccine product presented. The number of participants refers to those who completed three surveys (Dose 1, Dose 2, and the 7-month follow-up), as well as those who completed only the Dose 1 and 7-month follow-up surveys but not the Dose 2 survey.

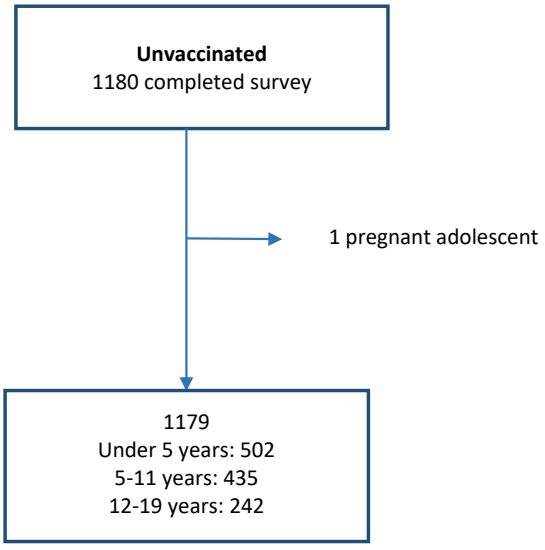

Fig. 2: Analytic sample for unvaccinated children and adolescents (aged 6 Months to 19 Years).

In the week following doses 1 and 2, the proportion of health events requiring an emergency department visit or hospitalization among vaccinated individuals ranged from 0% to 0.9%. No hospitalizations were reported among unvaccinated children and adolescents (Table 2).

Injection-site reactions and specific symptoms: reported within 7 days after doses 1 and 2

Tables 2–4 present the occurrence of local reactions, and other reported specific symptoms following the first and second doses of mRNA COVID-19 vaccines compared with controls. The proportion of individuals with local reaction was highest among vaccinated adolescents (61.3–77.8%), followed by vaccinated children aged 5–11 years (48.2–62.2%) and children under 5 years of age (19.2–31.9%). By comparing vaccine product, injection site reactions occurred more frequently among mRNA-1273 recipients than BNT162b2 recipients (Table 2). Commonly reported systemic symptoms included feeling unwell, fever, vomiting or diarrhea, cough, headache, sore throat, and rhinorrhea. Vaccinated

	Children (6 months–4 years)			Children (5–11 years)			Adolescent (12–19yrs)		
	Controls N = 502	BNT162b2 N = 234	mRNA-1273 N = 9056	Controls N = 435	BNT162b2 N = 206,197	mRNA-1273 N = 37	Controls N = 242	BNT162b2 N = 39,798	mRNA-1273 N = 4039
Median age in years (Interquartile range)	2 (1–4)	2 (1–3)	2 (1–3)	7 (6–9)	8 (6–10)	9 (6–11)	NA	NA	NA
Sex assigned at birth									
Male	284 (56.6%)	119 (51%)	4705 (52%)	234 (53.8%)	105,643 (51.2%)	17 (45.9%)	124 (51.2%)	18,552 (46.6%)	1485 (36.8%)
Female	218 (43.4%)	115 (49%)	4338 (47.9%)	201 (46.2%)	100,316 (48.7%)	19 (51.4%)	118 (48.8%)	21,111 (53%)	2542 (62.9%)
Other[a]	0 (0%)	0 (0%)	0 (0%)	0 (0%)	224 (0.1%)	0 (0%)	0 (0%)	130 (0.3%)	1 (<0.1%)
Decline	0 (0%)	0 (0%)	13 (0.1%)	0 (0%)	14 (<0.1%)	1 (2.7%)	0 (0%)	5 (<0.1%)	12 (0.3%)
Province									
Alberta	63 (12.5%)	30 (12.8%)	480 (5.3%)	96 (22.1%)	3125 (1.5%)	2 (5.4%)	75 (31%)	4766 (12%)	376 (9.3%)
BC/Yukon/NWT	296 (59%)	15 (6.4%)	5343 (59%)	173 (39.8%)	64,747 (31.4%)	20 (54.1%)	65 (26.9%)	10,502 (26.4%)	1042 (25.8%)
Nova Scotia/PE	9 (1.8%)	2 (0.9%)	118 (1.3%)	4 (0.9%)	196 (0.1%)	0 (0%)	11 (4.5%)	394 (1%)	27 (0.7%)
Ontario	134 (26.7%)	37 (15.8%)	308 (3.4%)	156 (35.9%)	1231 (0.6%)	5 (13.5%)	87 (36%)	3595 (9%)	291 (7.2%)
Quebec	0 (0%)	150 (64.1%)	2807 (31%)	6 (1.4%)	136,898 (66.4%)	10 (27%)	4 (1.7%)	20,541 (51.6%)	2303 (57%)
Health status									
Excellent	341 (67.9%)	156 (67%)	5894 (65.1%)	269 (61.8%)	114,738 (55.6%)	16 (43.2%)	96 (39.7%)	13,713 (34.5%)	944 (23.4%)
Very good	119 (23.7%)	68 (29%)	2648 (29.2%)	142 (32.6%)	76,042 (36.9%)	16 (43.2%)	87 (36%)	15,763 (39.6%)	1608 (39.8%)
Good	35 (7.0%)	10 (4.3%)	443 (4.9%)	21 (4.8%)	13,399 (6.5%)	4 (10.8%)	49 (20.2%)	7901 (19.9%)	1155 (28.6%)
Fair or poor	6 (1.2%)	0 (0%)	39 (0.4%)	3 (0.7%)	1337 (0.6%)	0 (0%)	9 (3.7%)	792 (2%)	138 (3.4%)
Unknown	1 (0.2%)	0 (0%)	32 (0.4%)	0 (0%)	681 (0.3%)	1 (2.7%)	1 (0.4%)	1629 (4.1%)	194 (4.8%)
Race and ethnicity									
Black	1 (0.2%)	3 (1.3%)	44 (0.5%)	4 (0.9%)	2770 (1.3%)	0 (0%)	NA	NA	NA
White	346 (68.9%)	158 (67.5%)	5838 (64.5%)	301 (69.2%)	140,645 (68.2%)	15 (40.5%)	NA	NA	NA
Indigenous	6 (1.2%)	2 (0.9%)	118 (1.3%)	10 (2.3%)	2521 (1.2%)	2 (5.4%)	NA	NA	NA
Latino	3 (0.6%)	6 (2.6%)	171 (1.9%)	5 (1.1%)	3706 (1.8%)	0 (0%)	NA	NA	NA
Middle Eastern	3 (0.6%)	4 (1.7%)	104 (1.1%)	8 (1.8%)	3315 (1.6%)	0 (0%)	NA	NA	NA
Mixed	80 (15.9%)	29 (12.4%)	1202 (13.3%)	56 (12.9%)	13,224 (6.4%)	3 (8.1%)	NA	NA	NA
East Asian	24 (4.8%)	10 (4.3%)	682 (7.5%)	9 (2.1%)	10,576 (5.1%)	2 (5.4%)	NA	NA	NA
South Asian	9 (1.8%)	7 (3.0%)	277 (3.1%)	8 (1.8%)	4896 (2.4%)	1 (2.7%)	NA	NA	NA
Southeast Asian	6 (1.2%)	4 (1.7%)	216 (2.4%)	3 (0.7%)	4027 (2%)	0 (0%)	NA	NA	NA
Other	10 (2.0%)	7 (3.0%)	181 (2.0%)	5 (1.1%)	7626 (3.7%)	0 (0%)	NA	NA	NA
Unknown/Decline	14 (2.8%)	4 (1.7%)	223 (2.5%)	26 (5.9%)	12,891 (6.2%)	14 (37.8%)	NA	NA	NA
Previous SARS-COV-2 infection									
Yes	144 (28.2%)	83 (35.5%)	3711 (40.9%)	147 (33.8%)	11,723 (5.7%)	5 (13.5%)	47 (19.4%)	2622 (6.6%)	233 (5.8%)
Immunocompromised									
Yes	4 (0.8%)	0 (0%)	15 (0.2%)	4 (0.9%)	630 (0.3%)	1 (2.7%)	3 (1.2%)	338 (0.8%)	54 (1.3%)
Autoimmune condition									
Yes	3 (0.6%)	1 (0.4%)	29 (0.3%)	9 (2.1%)	1379 (0.7%)	1 (2.7%)	5 (2.1%)	583 (1.5%)	99 (2.5%)

Data are n (%). [a]Intersex or other, UK: Unknown, BC/YK/NWT: British Columbia, Yukon, Northwest Territories, PE: Prince Edward Island, NA: Age information for adolescents was collected only in categorical format. The question regarding ethnicity among adolescents was only in Dose 2 survey.

Table 1: **Participants' characteristics: Unvaccinated and vaccinated individuals by product (dose 1).**

adolescents reported these symptoms more frequently than vaccinated children did in the week following dose two. Other symptoms were uncommon and occurred in similar proportions across vaccinated and unvaccinated groups (Tables 3 and 4). Among vaccine recipients, around 65–80% of adolescents with health events experienced onset within 1–24 h of vaccination, whereas about 67–86% of younger age groups had onset of health events within 3 days after vaccination (Fig. 4). Most symptoms resolved within the 7 days after vaccination (Fig. 5), regardless of vaccine product, dose or age group.

7-Month information on emergency visits or hospitalization

Follow-up information was available for 56% of all vaccinated individuals 7 months after dose one, while 87% of unvaccinated controls responded to the questions regarding emergency department visits/hospitalizations in the previous 6 months. Overall, children under 5 years of age reported visiting the emergency department more often than older children or adolescents (Table 2). Among respondents, the proportion of hospitalizations in both vaccinated and unvaccinated individuals varied between 0% and 0.8%. Of those who

	Children (6 months–4 years)				Children (5–11 years)				Adolescent (12–19yrs)			
	Control	BNT162b2	mRNA-1273	Mixed	Control	BNT162b2	mRNA-1273	Mixed	Control	BNT162b2	mRNA-1273	Mixed
Within 7 days following Dose 1 or previous 7 days (controls)												
Total	N = 502	N = 234	N = 9056		N = 435	N = 206,197	N = 37		N = 242	N = 39,798	N = 4039	
Injection site reactions[a]	NA	45 (19.2%)	2079 (22.9%)		NA	99,428 (48.2%)	23 (62.2%)		NA	24,402 (61.3%)	2995 (74.1%)	
Health event[b]	68 (13.5%)	15 (6.4%)	862 (9.5%)		38 (8.8%)	8072 (3.9%)	6 (16.2%)		9 (3.7%)	1436 (3.6%)	162 (4%)	
Consulted HCP	16 (3.2%)	7 (3%)	197 (2.2%)		6 (1.4%)	1291 (0.6%)	2 (5.4%)		2 (0.8%)	263 (0.7%)	34 (0.8%)	
ED visit	4 (0.8%)	0 (0%)	48 (0.53%)		0 (0%)	301 (0.15%)	0 (0%)		0 (0%)	89 (0.22%)	13 (0.3%)	
Hospitalization	0 (0%)	0 (0%)	4 (0.04%)		0 (0%)	26 (0.01%)	0 (0%)		0 (0%)	10 (0.03%)	1 (0.02%)	
Within 7 days following Dose 2 or previous 7 days (controls)												
Total	N = 502	N = 70	N = 2015	N = 204	N = 435	N = 109,674	N = 3	N = 231	N = 242	N = 17,218	N = 1153	N = 464
Injection site reactions[a]	NA	16 (22.9%)	641 (31.9%)	60 (29.4%)	NA	64,963 (59.2%)	1 (33.3%)	131 (56.7%)	NA	11,351 (65.9%)	881 (76.4%)	361 (77.8%)
Health event[b]	68 (13.5%)	7 (10%)	173 (8.6%)	19 (9.3%)	38 (8.8%)	3420 (3.1%)	1 (33.3%)	10 (4.3%)	9 (3.7%)	794 (4.6%)	98 (8.5%)	49 (10.6%)
Consulted HCP	16 (3.2%)	3 (4.3%)	37 (1.8%)	4 (2%)	6 (1.4%)	333 (0.3%)	1 (33.3%)	2 (0.9%)	2 (0.8%)	95 (0.6%)	12 (1.0%)	7 (1.5%)
ED visit	4 (0.8%)	0 (0%)	11 (0.5%)	1 (0.5%)	0 (0%)	94 (0.09%)	1 (33.3%)	2 (0.9%)	0 (0%)	42 (0.24%)	3 (0.26%)	4 (0.86%)
Hospitalization	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)	9 (0.01%)	0 (0%)	0 (0%)	0 (0%)	5 (0.03%)	3 (0.26%)	0 (0%)
7 months following Dose 1 or previous 6 months among controls[c]												
Total	N = 495	N = 124	N = 5042		N = 420	N = 120,490	N = 19		N = 109	N = 18,649	N = 1433	
ED visit	65 (13.1%)	4 (3.2%)	347 (6.9%)		26 (6.2%)	3047 (2.5%)	1 (5.3%)		7 (6.4%)	411 (2.2%)	43 (3.0%)	
Hospitalization	2 (0.4%)	0 (0%)	41 (0.81%)		1 (0.24%)	300 (0.25%)	0 (0%)		1 (0.92%)	45 (0.24%)	5 (0.35%)	

Data are n(%) HCP: health care providers ED visit: Emergency department visit NA: Not available. [a]All participants were asked about injection site reactions (Redness, pain or swelling at injection site/above and below in the immunized arm). [b]Health event severe enough to result in prevention of daily activities, school absenteeism, or requiring medical consultation. [c]Dose 1 vaccine product presented. The same control groups were used for both doses 1 and 2.

***Table 2*: Self-reported injection site reaction and health events among unvaccinated (previous 7 days, last 6 months) and vaccinated groups (within 7 days after doses 1 and 2, 7 months after dose 1).**

visited the emergency department or were hospitalized in the follow-up period or in the prior 6 months, the median number of visits was 1, with an interquartile range of 1 to 1 in both vaccinated and unvaccinated groups.

Myocarditis/pericarditis

Following dose one, eight individuals (children aged 5–11 years: two [0.001%] of 206,197 BNT162b2 recipients; adolescents: six [0.015%] of 39,798 BNT162b2 recipients), received a physician diagnosis of myocarditis or pericarditis within 0–28 days after BNT162b2 (Supplementary Table S3). Among these cases, two were diagnosed with pericarditis, one with perimyocarditis, and the remaining five with myocarditis. Symptoms such as chest tightness, palpitations occurred within 24–120 h after vaccination in four cases. Four of the eight cases were hospitalized, with one male adolescent in the intensive care unit for one day. Symptoms resolved within 7 days of onset for four individuals, while they persisted for more than 7 days in the remaining cases.

Following dose two a myocarditis or pericarditis diagnosis within 0–28 days was reported for nine new cases (children 5–11years: two [0.002%] of 109,674 BNT162b2 recipients, adolescents: four [0.023%]of 17,218 BNT162b2 recipients, three [0.185%] of 1617 mRNA-1273 recipients including one heterologous series recipient) (Supplementary Table S3). Of nine cases, only two cases were diagnosed with pericarditis, and the remaining seven with myocarditis. The highest incidence occurred among males aged 12–19 years old following dose 2, with three (0.037%) of 8088 BNT162b2 recipients, and two (0.529%) of 378 mRNA-1273 recipients. For male adolescents, the incidence after the second dose of homologous BNT162b2 was significantly lower than that of homologous mRNA-1273. Five of the nine cases presented with symptoms such as chest tightness and/or palpitation within 3 days of vaccination. Four of the nine cases were hospitalized, with one male adolescent in intensive care unit for 4 days. Four of the nine cases had their symptoms resolve within 7 days of vaccination while symptoms persisted for more than 7 days in the rest.

Of the 140,591 vaccinated adolescents and children aged 5–11 years in the 7-month follow-up survey, twelve (0.008%) new diagnoses of myocarditis or pericarditis were reported (Supplementary Table S3). These individuals visited the emergency department or were hospitalized a mean of 143 days (median 142 days) after receiving dose one (range 82–210 days), and 94 days (median 83 days) after receiving dose two (range 42–166 days). No cases of myocarditis or pericarditis were detected in vaccinated children under 5 years of age or in the control group.

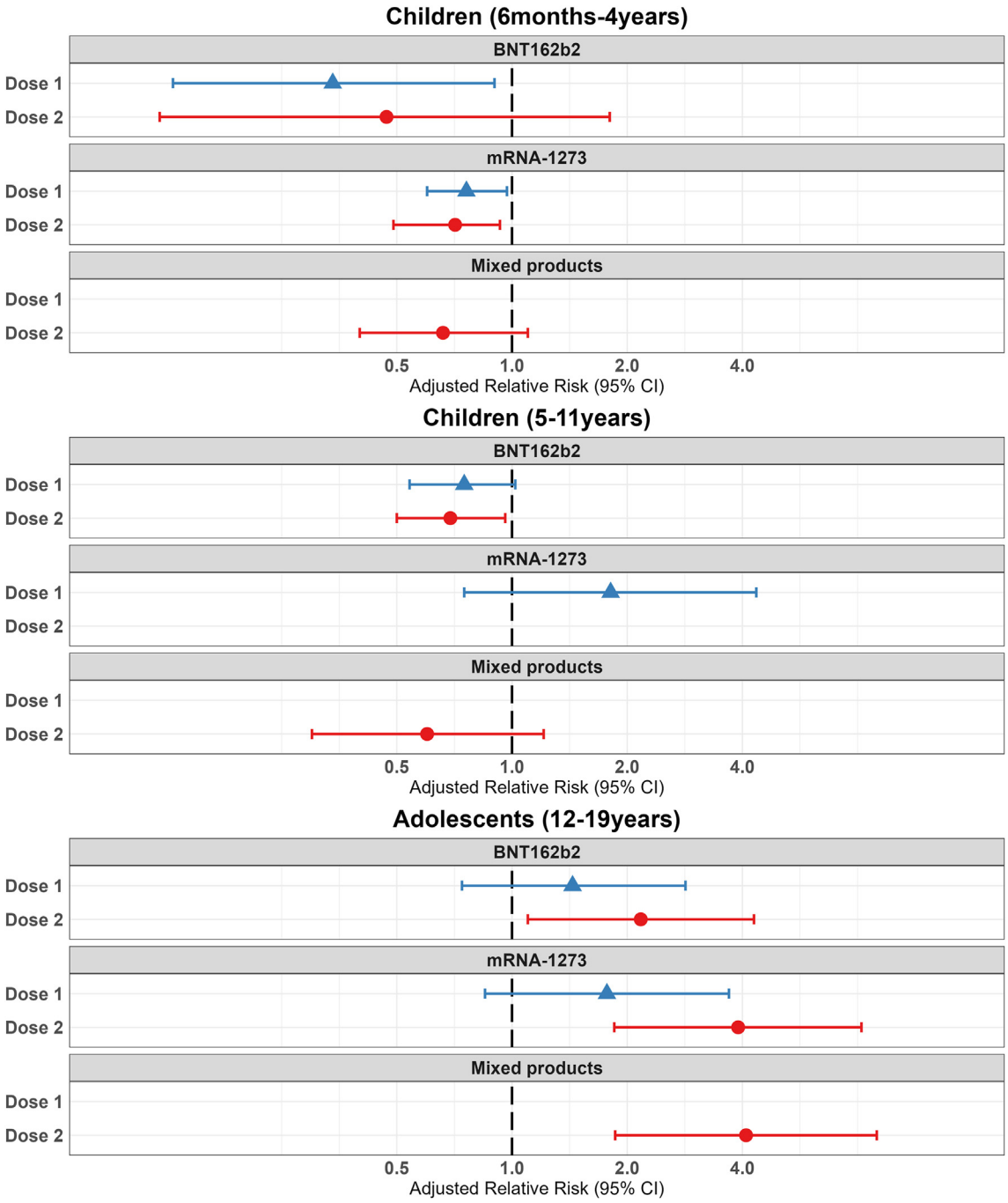

Fig. 3: Relative risk of health events within 7 days following vaccination, by vaccine product and dose, between children and adolescents, compared to unvaccinated controls. The graph represents three age groups: children (6 months–4 years), (5–11 years), and adolescents (12–19 years). Outcome: health event severe enough to result in prevention of daily activities, school absenteeism, or requiring medical consultation. Blue triangles and red circles represent adjusted Relative risk (RR) for vaccine dose 1 and 2, with 95% confidence interval (95% CIs). The reference groups are unvaccinated participants in the same age group. RRs are adjusted for sex assigned at birth, health status, province, and previous SARS-CoV-2 infection. The x-axis of each graph is a log-scale. Since only 3 children aged 5–11 years received homologous mRNA-1273, regression analyses were not performed for this group.

	Children (6 months–4 years)			Children (5–11 years)			Adolescent (12–19yrs)		
	Controls N = 502	BNT162b2 N = 234	mRNA-1273 N = 9056	Controls N = 435	BNT162b2 N = 206,197	mRNA-1273 N = 37	Controls N = 242	BNT162b2 N = 39,798	mRNA-1273 N = 4039
Injection site reactions reported with health events[a]	NA	6 (2.6%)	263 (2.9%)	NA	4768 (2.3%)	5 (13.5%)	NA	1110 (2.8%)	140 (3.5%)
General symptoms									
Unwell[b]	39 (7.8%)	10 (4.3%)	609 (6.7%)	29 (6.7%)	5343 (2.6%)	5 (13.5%)	6 (2.5%)	1175 (3%)	148 (3.7%)
Fever (≥38¤C)	35 (7%)	13 (5.6%)	530 (5.9%)	20 (4.6%)	2869 (1.4%)	3 (8.1%)	2 (0.8%)	386 (1%)	59 (1.5%)
Febrile convulsion	0 (0%)	0 (0%)	4 (0.1%)	0 (0%)	3 (<0.1%)	0 (0%)	0 (0%)	3 (0%)	0 (0%)
GI symptoms[c]	31 (6.2%)	5 (2.1%)	291 (3.2%)	10 (2.3%)	3080 (1.5%)	3 (8.1%)	3 (1.2%)	610 (1.5%)	87 (2.2%)
Joint pain/stiffness	1 (0.2%)	1 (0.4%)	17 (0.2%)	2 (0.5%)	433 (0.2%)	2 (5.4%)	0 (0%)	291 (0.7%)	56 (1.4%)
Earache/ear pain/ear symptoms	3 (0.6%)	3 (1.3%)	66 (0.7%)	3 (0.7%)	421 (0.2%)	0 (0%)	0 (0%)	97 (0.2%)	18 (0.4%)
Nasal congestion/sinus congestion	42 (8.4%)	3 (1.3%)	436 (4.8%)	14 (3.2%)	2908 (1.4%)	4 (10.8%)	3 (1.2%)	373 (0.9%)	38 (0.9%)
Runny nose	48 (9.6%)	6 (2.6%)	523 (5.8%)	13 (3%)	2809 (1.4%)	2 (5.4%)	2 (0.8%)	326 (0.8%)	40 (1%)
Sore throat	18 (3.6%)	2 (0.9%)	178 (2%)	13 (3%)	2956 (1.4%)	3 (8.1%)	4 (1.7%)	440 (1.1%)	48 (1.2%)
Neurologic symptoms									
Headache or migraine	10 (2%)	2 (0.9%)	126 (1.4%)	11 (2.5%)	3722 (1.8%)	5 (13.5%)	5 (2.1%)	924 (2.3%)	118 (2.9%)
Dizziness/light-headedness	1 (0.2%)	0 (0%)	7 (0.1%)	2 (0.5%)	486 (0.2%)	0 (0%)	1 (0.4%)	369 (0.9%)	54 (1.3%)
Fainting	0 (0%)	0 (0%)	1 (<0.1%)	0 (0%)	52 (<0.1%)	0 (0%)	0 (0%)	56 (0.1%)	4 (0.1%)
Loss of taste/smell	0 (0%)	0 (0%)	12 (0.1%)	2 (0.5%)	147 (0.1%)	0 (0%)	1 (0.4%)	67 (0.2%)	4 (0.1%)
Paresthesia	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)	72 (<0.1%)	0 (0%)	1 (0.4%)	87 (0.2%)	21 (0.5%)
Seizure or convulsion	0 (0%)	0 (0%)	4 (<0.1%)	0 (0%)	14 (<0.1%)	0 (0%)	0 (0%)	16 (<0.1%)	1 (<0.1%)
Other neurologic symptoms[d]	0 (0%)	0 (0%)	5 (0.1%)	0 (0%)	52 (<0.1%)	0 (0%)	0 (0%)	42 (0.1%)	10 (0.2%)
Coagulation symptoms									
Symptoms of blood clot/bleeding[e]	0 (0%)	0 (0%)	2 (<0.1%)	0 (0%)	30 (<0.1%)	0 (0%)	0 (0%)	21 (0.1%)	3 (0.1%)
Bruising or pinpoint dark red rash[f]	0 (0%)	0 (0%)	7 (0.1%)	0 (0%)	44 (<0.1%)	0 (0%)	0 (0%)	18 (<0.1%)	4 (0.1%)
Allergic-like									
Rash or hives	4 (0.8%)	0 (0%)	69 (0.8%)	3 (0.7%)	334 (0.2%)	0 (0%)	0 (0%)	70 (0.2%)	19 (0.5%)
Itchy or painful eyes	2 (0.4%)	1 (0.4%)	52 (0.6%)	2 (0.5%)	388 (0.2%)	2 (5.4%)	0 (0%)	157 (0.4%)	29 (0.7%)
Tearing or eye discharge	6 (1.2%)	1 (0.4%)	116 (1.3%)	1 (0.2%)	287 (0.1%)	0 (0%)	0 (0%)	77 (0.2%)	12 (0.3%)
Swelling of the throat/tongue	0 (0%)	0 (0%)	17 (0.2%)	0 (0%)	114 (0.1%)	1 (2.7%)	1 (0.4%)	84 (0.2%)	9 (0.2%)
Cardiorespiratory									
Chest tightness/discomfort/pain	0 (0%)	0 (0%)	21 (0.2%)	0 (0%)	272 (0.1%)	1 (2.7%)	2 (0.8%)	218 (0.5%)	29 (0.7%)
Rapid heart rate/palpitations	1 (0.2%)	0 (0%)	19 (0.2%)	0 (0%)	183 (0.1%)	0 (0%)	2 (0.8%)	139 (0.3%)	22 (0.5%)
Cough	47 (9.4%)	4 (1.7%)	475 (5.2%)	20 (4.6%)	3038 (1.5%)	2 (5.4%)	3 (1.2%)	294 (0.7%)	37 (0.9%)
Difficulty breathing	1 (0.2%)	2 (0.9%)	66 (0.7%)	2 (0.5%)	313 (0.2%)	1 (2.7%)	0 (0%)	181 (0.5%)	24 (0.6%)

Data are n(%). [a]Participants who reported both injection site reaction and health events severe enough to result in prevention of daily activities, school absenteeism, or requiring medical consultation. Only those who indicated a health event were asked to provide details of their symptoms. As symptoms are not mutually excluded, participants can report more than one symptoms. [b]Tiredness, weakness, muscle aches, fatigue, or chills. [c]GI symptoms: Gastrointestinal symptoms such as nausea, vomiting, diarrhea, or stomach pain. [d]Weakness or paralysis of the arms or legs, confusion, change in personality or behavior, or difficulty with urination or defecation. [e]Symptoms of blood clot or bleeding, including swelling, pain in legs, or bruising or pinpoint dark rash; GI symptoms: nausea, vomiting, diarrhea, or stomach pain. [f]Bruising or pinpoint dark red rash (NOT at injection site).

Table 3: **Self-reported health events within 7 Days after dose 1 vaccination among vaccinated or during previous 7 Days among unvaccinated children and adolescents.**

Anaphylaxis

In the week following dose one, six adolescents (five [0.002%] of 246,229 BNT162b2 recipients, one [0.008%] of 13,132 mRNA-1273 recipients) were diagnosed with anaphylaxis. All of them were female and presented with urticarial rash, with or without swelling of the throat/face, chest tightness, and difficulty breathing. Half developed symptoms within 24 h (two within 60 min, one within 24 h), but all resolved within 7 days without requiring hospitalization. In the week following dose two, one adolescent female reported "anaphylactic reaction" within 24 h after receiving a mixed schedule and symptoms resolved on the day of onset.

No cases of anaphylaxis were reported within 7 days following dose 1 and 2 among vaccinated children, nor in the unvaccinated controls.

Discussion

Findings from our cohort study provide reassuring real-world evidence of the safety of mRNA COVID-19 vaccines (BNT162b2, mRNA-1273, mixed schedules) in children and adolescents while also confirming some known risks. The occurrence of health events among children and adolescents within 7 days following the first dose of an mRNA-COVID vaccine

	Children (6 months–4 years)			Children (5–11 years)		Adolescent (12–19yrs)		
	BNT162b2 N = 70	mRNA-1273 N = 2015	Mixed N = 204	BNT162b2 N = 109,674	Mixed N = 231	BNT162b2 N = 17,218	mRNA-1273 N = 1153	Mixed N = 464
Injection site reactions reported with health event[a]	1 (1.4%)	89 (4.4%)	8 (3.9%)	2522 (2.3%)	7 (3.0%)	659 (3.8%)	86 (7.5%)	42 (9.1%)
General symptoms								
Unwell[b]	5 (7.1%)	119 (5.9%)	17 (8.3%)	2671 (2.4%)	10 (4.3%)	705 (4.1%)	90 (7.8%)	48 (10.3%)
Fever (≥38¤C)	5 (7.1%)	106 (5.3%)	14 (6.9%)	1420 (1.3%)	5 (2.2%)	351 (2%)	59 (5.1%)	27 (5.8%)
Febrile convulsion	0 (0%)	0 (0%)	0 (0%)	4 (<0.1%)	0 (0%)	2 (<0.1%)	0 (0%)	0 (0%)
GI symptoms[c]	2 (2.9%)	53 (2.6%)	6 (2.9%)	1324 (1.2%)	4 (1.7%)	324 (1.9%)	47 (4.1%)	23 (5.0%)
Arthritis/joint pain/stiffness	1 (1.4%)	6 (0.3%)	0 (0%)	222 (0.2%)	2 (0.9%)	139 (0.8%)	28 (2.4%)	16 (3.4%)
Earache/ear pain/ear symptoms	1 (1.4%)	7 (0.3%)	0 (0%)	80 (0.1%)	0 (0%)	37 (0.2%)	5 (0.4%)	2 (0.4%)
Nasal congestion/sinus congestion	3 (4.3%)	72 (3.6%)	8 (3.9%)	754 (0.7%)	3 (1.3%)	139 (0.8%)	9 (0.8%)	10 (2.2%)
Runny nose	4 (5.7%)	77 (3.8%)	9 (4.4%)	736 (0.7%)	3 (1.3%)	112 (0.7%)	8 (0.7%)	2 (0.4%)
Sore throat	1 (1.4%)	13 (0.6%)	4 (2%)	984 (0.9%)	5 (2.2%)	166 (1%)	16 (1.4%)	7 (1.5%)
Neurologic symptoms								
Headache or migraine	0 (0%)	28 (1.4%)	3 (1.5%)	2011 (1.8%)	6 (2.6%)	589 (3.4%)	76 (6.6%)	41 (8.8%)
Dizziness/vertigo/light-headedness	0 (0%)	4 (0.2%)	0 (0%)	240 (0.2%)	4 (1.7%)	187 (1.1%)	28 (2.4%)	18 (3.9%)
Fainting	0 (0%)	0 (0%)	0 (0%)	6 (<0.1%)	0 (0%)	18 (0.1%)	0 (0%)	3 (0.6%)
Loss of taste/smell	0 (0%)	2 (0.1%)	0 (0%)	42 (<0.1%)	0 (0%)	19 (0.1%)	2 (0.2%)	1 (0.2%)
Paresthesia	0 (0%)	1 (<0.1%)	0 (0%)	37 (<0.1%)	0 (0%)	40 (0.2%)	4 (0.3%)	5 (1.1%)
Seizure or convulsion	0 (0%)	0 (0%)	0 (0%)	9 (<0.1%)	0 (0%)	3 (<0.1%)	0 (0%)	0 (0%)
Other neurologic symptoms[d]	0 (0%)	0 (0%)	0 (0%)	23 (<0.1%)	0 (0%)	11 (0.1%)	1 (0.1%)	0 (0%)
Coagulation symptoms								
Symptoms of blood clot or bleeding[e]	0 (0%)	0 (0%)	0 (0%)	11 (<0.1%)	0 (0%)	2 (<0.1%)	1 (0.1%)	0 (0%)
Bruising or pinpoint dark red rash[f]	0 (0%)	1 (<0.1%)	0 (0%)	22 (<0.1%)	0 (0%)	5 (<0.1%)	0 (0%)	0 (0%)
Allergic-like symptoms								
Rash or hives	0 (0%)	13 (0.6%)	0 (0%)	128 (0.1%)	0 (0%)	27 (0.2%)	5 (0.4%)	1 (0.2%)
Itchy or painful eyes	0 (0%)	10 (0.5%)	0 (0%)	134 (0.1%)	0 (0%)	58 (0.3%)	7 (0.6%)	2 (0.4%)
Tearing or eye discharge	1 (1.4%)	15 (0.7%)	0 (0%)	68 (0.1%)	0 (0%)	19 (0.1%)	2 (0.2%)	0 (0%)
Swelling of the throat and/or tongue	0 (0%)	1 (<0.1%)	0 (0%)	33 (<0.1%)	0 (0%)	17 (0.1%)	2 (0.2%)	1 (0.2%)
Cardiorespiratory								
Chest tightness/discomfort/pain	0 (0%)	1 (<0.1%)	0 (0.0%)	115 (0.1%)	1 (0.4%)	95 (0.6%)	24 (2.1%)	7 (1.5%)
Rapid heart rate/palpitations	0 (0%)	1 (<0.1%)	1 (0.5%)	73 (0.1%)	1 (0.4%)	71 (0.4%)	14 (1.2%)	3 (0.6%)
Cough	4 (5.7%)	74 (3.7%)	10 (4.9%)	675 (0.6%)	3 (1.3%)	85 (0.5%)	10 (0.9%)	4 (0.9%)
Difficulty breathing	0 (0%)	6 (0.3%)	2 (1.0%)	104 (0.1%)	1 (0.4%)	79 (0.5%)	14 (1.2%)	5 (1.1%)

Data are n(%). [a]Participants who reported both injection site reaction and health events severe enough to result in prevention of daily activities, school absenteeism, or requiring medical consultation. Only those who indicated a health event were asked to provide details of their symptoms. As symptoms are not mutually excluded, participants can report more than one symptoms. [b]Tiredness, weakness, muscle aches, fatigue, or chills. [c]GI symptoms: Gastrointestinal symptoms such as nausea, vomiting, diarrhea, or stomach pain. [d]Weakness or paralysis of the arms or legs, confusion, change in personality or behavior, or difficulty with urination or defecation. [e]Symptoms of blood clot or bleeding, including swelling, pain in legs, or bruising or pinpoint dark rash; GI symptoms: nausea, vomiting, diarrhea, or stomach pain. [f]Bruising or pinpoint dark red rash (NOT at injection site). Since only three children aged 5–11 years received the homologous mRNA-1273 vaccine, the results were not included in the table.

Table 4: **Self-reported health events reported within 7 Days after dose 2 vaccination among vaccinated children and adolescents.**

was similar to or lower than their unvaccinated counterparts. Health events were generally reported more often after dose two than dose one. The risk of developing health events severe enough to prevent daily activities, result in school absenteeism, or require a medical consultation following the second dose was higher among vaccinated adolescents (4.6 — 10.6%) compared to unvaccinated adolescents (3.7%), and this pattern was consistent across different vaccine products. When restricted to events resulting in emergency department visits or hospitalizations, the proportions of emergency care utilization among children and adolescents were uncommon or rare across all vaccine products and doses.

Our findings provide an understanding of mRNA COVID-19 vaccine safety among pediatric populations and results for short-term follow up were consistent with previous clinical studies,[4,5,18] and post-marketing studies.[6,7,19,20] Most studies focused on the safety of mRNA COVID-19 vaccines in specific age groups. We found one passive surveillance study from South Korea that compared adverse events between children and adolescents receiving the BNT162b2 vaccine, which showed lower adverse event frequencies in children

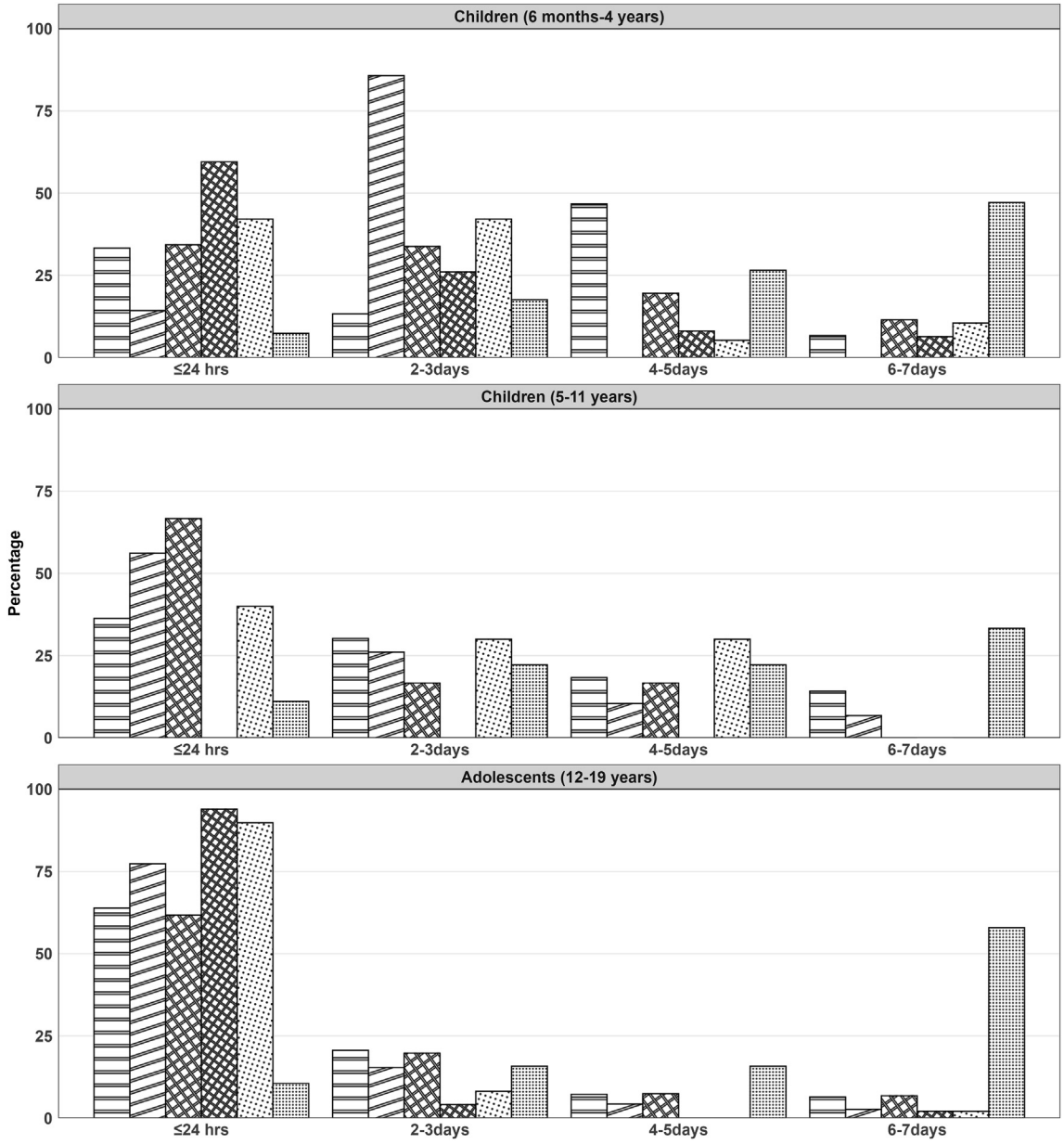

Fig. 4: Onset of Health Events within 7 Days following Vaccination or previous 7 days among Vaccinated and Unvaccinated Children and Adolescents. Since only 3 children aged 5–11 years received homologous mRNA-1273, the results were not included in the figure.

aged 5–11 years than in adolescents aged 12–17 years after either dose.[21] A systematic review and meta-analysis pooled data to examine adverse reaction risks of mRNA vaccine recipients, finding significantly higher risks in adolescents aged 12–17 compared to children aged 5–11.[9] Compared to previous evidence, our findings, supported by a primary study with a diverse pediatric sample, suggest that age-related adverse event risks may be linked to the different mRNA vaccine dosages recommended for children and adolescents.

In our study, participant-reported or parents/guardian reported cases of myocarditis/pericarditis were identified within 0–28 days following vaccination, with the highest incidence observed among male adolescents after the second dose, consistent with the current literature. Although these individuals required emergency care or hospitalization, we have limited

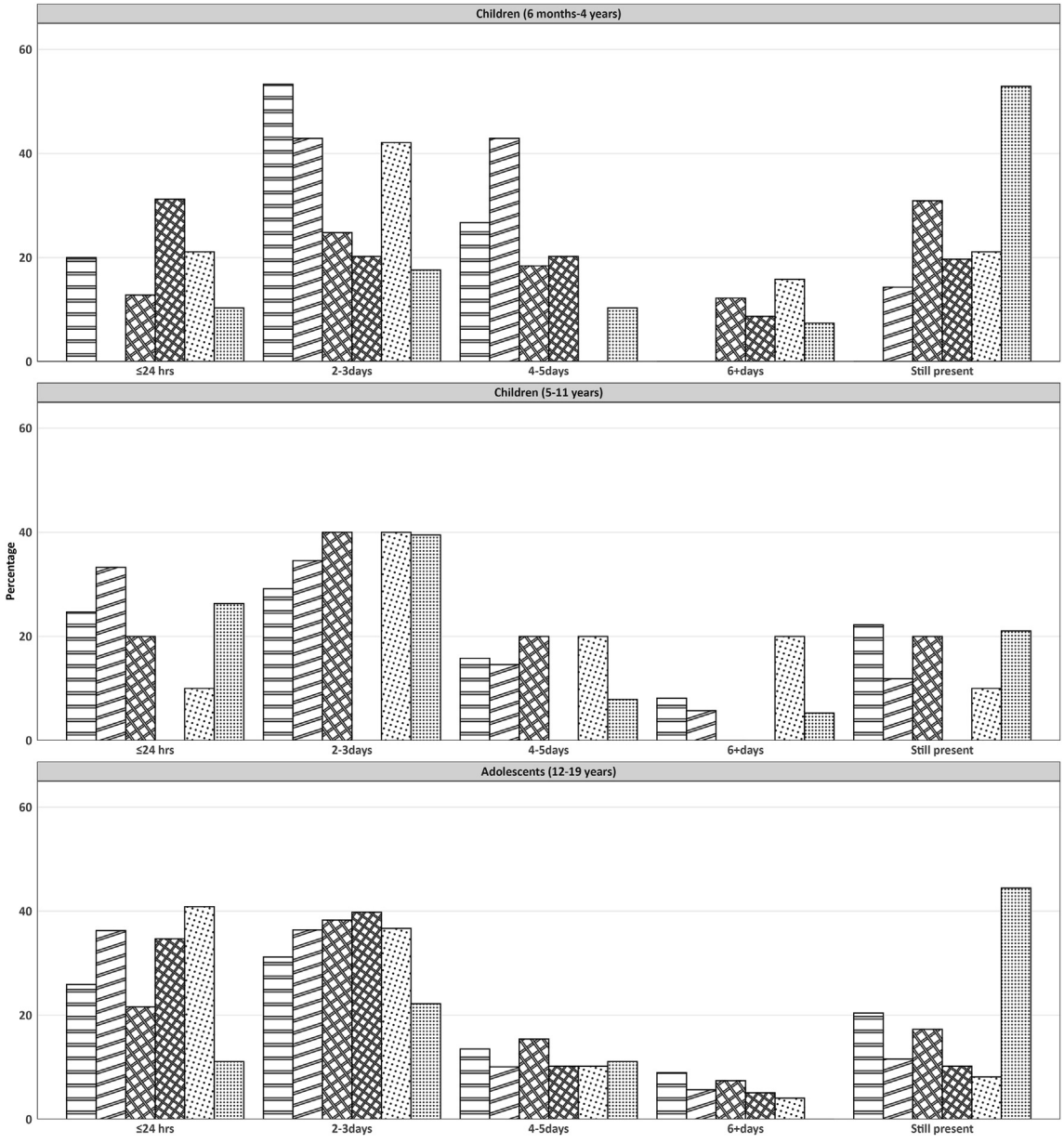

Fig. 5: Duration of health events within 7 days following vaccination or previous 7 days among vaccinated and unvaccinated children and adolescents. Since only 3 children aged 5–11 years received homologous mRNA-1273, the results were not included in the figure.

information on specific laboratory or imagining results. While our data does not confirm these cases, the demographic patterns, symptoms of onset, clinical presentation and resolutions align with findings from a systematic review and meta-analysis study, and large population-based studies.[22–26] In the Canadian context, a population-based study from Ontario reported a higher rate of myocarditis/pericarditis in males aged 12–17 following the second doses of BNT162b2.[27] However, no data were reported for mRNA-1273 recipients in this age group as it was not used.[27] The same study observed the highest reporting rates in males aged 18–24 years following mRNA-1273 as the second dose.[27] Another study[28] using Canadian passive surveillance data confirmed a higher risk of myocarditis and/or pericarditis after mRNA-1273 than BNT162b2 in males aged 18–29 years. Although our study included a limited sample of mRNA-1273 recipients aged 19 and below, we detected three cases following the second dose of mRNA-1273 (two after

homologous mRNA-1273 and one after heterologous BNT162b2-mRNA-1273).

In the 7-month follow up, reported emergency care utilizations were higher among children under 5 years of age than older children or adolescents. This pattern is consistent between vaccinated and unvaccinated groups, and aligned with emergency department visits from Canadian National Ambulatory Care Reporting System.[29] Reassuringly, hospitalizations within 7 months following the first dose, or within 6 months prior to the survey among controls, were uncommon in both vaccinated and unvaccinated groups. Additionally no considerable increase in emergency care utilization was observed during the longer follow-up period. A population based study from an Italy reported that one or more doses of mRNA COVID-19 vaccines in individuals aged 6 years and above was not associated with an increased risk of death from any cause, or any potentially vaccine-related serious adverse events requiring hospitalization within an average follow-up period of 14 months.[30]

Our findings provide insights into the short- and medium-term safety of mRNA COVID-19 vaccines across the pediatric age spectrum. When assessing vaccine safety, it is crucial to consider both vaccine-associated adverse events as well as the risks and outcomes associated with infection. While our study focused on adverse events following immunization, other research highlights the risk–benefit profile of COVID-19 vaccination in children and adolescents. For instance, a recent population-based study from the US indicated that vaccination against COVID-19 in children aged 5–17 years is associated with a reduced risk of post COVID conditions, with a stronger effect in adolescents.[31] Moreover, a self-controlled case-series study involving linked data of 5.1 million children in England revealed that SARS-CoV-2 infection increased the risk of hospitalization for seven outcomes, including multisystem inflammatory syndrome and myocarditis; however, these risks were absent or reduced in children vaccinated prior to infection.[32] These findings assist in guiding vaccination decision-making by balancing the benefits and risks of vaccinations, especially among adolescents.

Our study participants self-selected to participate, and the majority were White, which may limit the generalizability of our findings to the broader population of children and adolescents. However, our sample had similar characteristics (sex, health status and residence) to the Canadian pediatric population.[33,34] The sex distribution (45.3–49.6% female in our study vs 48.8% nationally)[34] and health status (91–94% in our study vs 90.9% nationally),[33] align closely with national data, for both vaccinated and unvaccinated groups. Additionally, most our data were collected from Canada's most populous provinces: Quebec, Ontario, British Columbia, and Alberta.[34]

CANVAS relies on participant-based reporting without verification from medical records, which is subject to reporting or recall bias. In particular, differential recall bias is a concern; vaccinated participants may be more likely to recall adverse events following vaccination in assessments covering both short and longer periods compared to their unvaccinated counterparts. Furthermore, both groups may have poor recall regarding emergency care utilization in questionnaires interrogating longer periods.

Another important limitation is the limited sample sizes for unvaccinated controls across all age groups and for vaccinated individuals receiving mRNA-1273 vaccines (children aged 5–11), and those who received mixed schedules. The smaller unvaccinated sample size may be due to recruitment strategies. The limited number of children aged 5–11 receiving mRNA-1273 may be related to our recruitment timing, as BNT162b2 was approved for children in November 2021, while mRNA-1273 was only approved in March 2022.[3] Most children in our sample were recruited between December 2021 and February 2022, aligning with the availability of BNT162b2.

Additionally, unvaccinated children and adolescents were recruited a few months earlier than vaccinated groups, which may have reduced comparability between vaccinated and control groups. We observed a high proportion of health events reported in the 7 days prior to the survey among the unvaccinated control groups. This may be related to delayed vaccination and circulating SARS-CoV-2 variants. In general, unvaccinated adolescents were recruited before the Omicron period, while unvaccinated children were recruited during the Omicron period. Although similar proportions of participants reported past SARS-CoV-2 infection in both unvaccinated and vaccinated children under 5 years of age, higher proportions of unvaccinated children aged 5–11 years and adolescents reported past infection compared to their vaccinated counterparts for both doses. Despite adjusting for previous SARS-COV-2 infection status in multivariable models, we did not differentiate whether these infections were recent or distant. This limitation may have led to underestimation of the risk of health events associated vaccination.

Although efforts were made to control for confounders and risk factors in the multivariable regression models, there may be residuals or unmeasured confounders. We also recognized the potential influence of ethnicity on reactogenicity and reporting adverse events. However, the ethnicity question was included in the survey for the second dose among adolescents. Consequently, this information was not available for most unvaccinated and dose 1 adolescent participants, limiting our ability to consistently adjust for this variable in all regression models. Although ethnicity was included in our multivariable models for children under

5 and those aged 5–11, results did not significantly differ with or without this variable (data not shown). Furthermore, to reduce participant burden, our surveys did not collect data on individual-level variables such as body weight, comorbidities for all age groups, or age as a continuous variable for adolescents, limiting their inclusion in our analyses.

Finally, not all participants from the dose one survey completed dose two and follow-up surveys. Attrition was slightly higher among those who reported experiencing health events after dose one. This differential drop-out may have led to underestimations in the estimates from dose two and the follow-up surveys. Despite these limitations, our results complement ongoing vaccine pharmacovigilance systems (passive surveillance) in Canada and elsewhere.

One strength of this study was the inclusion of three pediatric age groups eligible for COVID-19 vaccines. This enabled us to examine the age-stratified risk associated with each vaccine product used in Canada. Another strength was the recruitment of non-vaccinated children and adolescents, which enabled the assessment of events in unvaccinated groups. The longer-term follow-up surveys allowed us to examine emergency care utilization patterns and incidence of pericarditis/myocarditis among pediatric populations through 7 months following dose one.

In conclusion, our findings support the safety of mRNA COVID-19 vaccines for children and adolescents. Similar to vaccinated adults, our findings showed that vaccinated adolescents reported higher proportions of health events after the second dose of mRNA COVID-19 vaccines. Our study detected rare adverse events of special interest, including myocarditis and pericarditis, with similar epidemiology confirmed in multiple large population-based studies. Through 7 months of follow-up, there was no increase in emergency department visit/hospitalization in vaccinated participants compared to controls. Our findings can be used to inform safety profiles of COVID-19 vaccines among the youngest population eligible for COVID-19 vaccines in Canada and globally and help inform adolescents and parents about what to expect following COVID-19 vaccination.

Contributors

JAB designed, implemented, and oversaw the study, supervised PS and shares senior and corresponding authorship. PS developed the analysis plan, contributed to data analysis, produced data tables and figures, interpreted the data and drafted the manuscript. OGV developed the analysis plan, interpreted the data and reviewed the manuscript and shares senior and corresponding authorship. KM and HS cleaned and analyzed the data. Together with JAB, GDS, MPM, JDK, KM, JDK, MS, AM, OGV, LV and KAT implemented study and all contributed equally to this work. HW and MN supervised PS and reviewed the analysis plan and manuscript. All authors read, revised, and approved the manuscript.

Data sharing statement

De-identified data collected for the study (with data dictionary) may be made available upon approval by the study investigators, with relevant agreements (e.g., data sharing agreement) and approvals (e.g., relevant ethics approvals). Requests should be directed to the corresponding author in the first instance.

Declaration of interests

GDS, HS, HW, LV, MN, KM and OGV have no competing interests. PS received personal payments for consulting from the Joint United Nations Programme on HIV/AIDS outside the submitted work. MS has been an investigator on projects funded by GlaxoSmithKline, Merck, Moderna, Pfizer and Sanofi-Pasteur outside the submitted work. All funds were paid to his institute, and he has not received any personal payments. MPM received payment testifying as an expert with respect to mandatory influenza and COVID-19 vaccination in healthcare settings. JDK has been an investigator on projects funded by Moderna Canada and Alberta Children's Hospital Research Institute and Government of Alberta, all outside the submitted work. All funds have been paid to his institute, and he has not received any personal payments. KAT reports grants from Canadian Institute of Health Research and the Coalition of Epidemic Preparedness Innovations for COVID-19 vaccine studies. KAT received personal payments for consulting from World Health Organization. JEI has been an investigator on projects funded by GlaxoSmithKline and Sanofi-Pasteur outside the submitted work. All funds were paid to her institute, and she has not received any personal payment. AM reports grants to her institution from Pfizer, Merck, Sanofi, and Seqirus, as well as personal payments for consulting or honoraria from Sienna Senior Living, AstraZeneca, Merck, Biogen, Sanofi, GlaxoSmithKline, Moderna, Medicago, Janssen, Novavax, Pfizer, and Seqirus. JAB has served on the Research Leadership Committee at BC Children's Hospital Research Institute and the National Advisory Committee on Immunization.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2024.100949.

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