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Congenital anomalies following antenatal exposure to dolutegravir: a Canadian surveillance study

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Objective Dolutegravir is recommended worldwide as a first-line antiretroviral therapy (ART) for individuals living with HIV. A recent study reported increased rates of neural tube defects in infants of dolutegravir-treated women. This study examined rates of congenital anomalies in infants born to women living with HIV (WLWH) in Canada.

Design The Canadian Perinatal HIV Surveillance Programme captures surveillance data on pregnant WLWH and their babies and was analysed to examine the incidence of congenital anomalies.

Setting Paediatric HIV clinics.

Population Live-born infants born in Canada to WLWH between 2007 and 2017.

Methods Data on mother–infant pairs, including maternal ART use at conception and during pregnancy, are collected by participating sites.

Main outcome measures Congenital anomalies.

Results Of the 2423 WLWH, 85 (3.5%, 95% CI 2.85–4.36%) had non-chromosomal congenital anomalies. There was no evidence of a significant difference in rates of congenital anomalies between women who were on ART in their first trimester (3.9%, CI 1.7–7.6%) or later in the pregnancy (3.9%, 95% CI 2.6–5.6%). Four of the 80 (5.0%, 95% CI 1.4–12.3%) neonates born to WLWH on dolutegravir during the first trimester had congenital anomalies, none were neural tube defects (95% CI 0.00–3.10%).

Conclusion Despite recent evidence raising a safety concern, this analysis found no signal for increased congenital anomalies.

Keywords Antiretroviral therapy, congenital anomalies, dolutegravir, HIV.

Tweetable abstract Five percent of the infants of Canadian women living with HIV on dolutegravir at conception had congenital anomalies; none had neural tube defects.

Linked article This article is commented on by RM Zash, p. 1346 in this issue. To view this mini commentary visit https://doi.org/10.1111/1471-0528.15864.

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Introduction

Dolutegravir, an integrase strand transfer inhibitor, was recently recommended by the World Health Organization as the preferred first-line antiretroviral treatment (ART) for all people living with HIV.[1–3] Recent years have seen a dramatic increase in dolutegravir use internationally. In Botswana, it has been used as a first-line agent since 2016, including among women of reproductive potential and in pregnancy,[4–6] although dolutegravir has a relatively short history of clinical use and limited pregnancy safety data.[7] Initial studies on dolutegravir were generally reassuring, with data demonstrating no evidence of teratogenicity or developmental toxicity in animal studies and in early

clinical trials, where women had unplanned pregnancies while on dolutegravir.[8]

In May 2018, new data from an interim analysis of a National Institute of Health funded birth surveillance study found that, of 11 558 women living with HIV in Botswana who became pregnant, 0.9% of babies born to the women taking dolutegravir at conception had a neural tube defect (NTD) (4/426), compared with 0.1% of babies born to mothers taking other antiretroviral combinations (14/11 173).[9,10] The most up-to-date data, presented in July 2018, suggested a prevalence of 4/596 (0.67%, 95% CI 0.26–1.7%).[12] Based on these data, cautionary statements on the use of dolutegravir in pregnancy have been issued with many jurisdictions recommending against its use in early pregnancy.[9,10,13]

Among the general population in Canada, 4–5% of infants have major congenital anomalies, including NTDs.[13] Such NTDs occur at variable rates across different populations, geographic locations and jurisdictions. The incidence of NTDs in Canada is approximately 4 per 10 000 live births; this decreased from 7.6 per 10 000 births following the initiation of folate fortification of grain products in 1998 to prevent folate-deficiency-related NTDs.[13] Although data are limited, studies globally have shown substantial geographic variability in rates of NTDs from 5.2 per 10 000 live births to more than 120 per 10 000 live births in African countries.[14–16]

The objective of this study was to examine the rates of congenital anomalies in infants born to women living with HIV (WLWH) and their potential associations with dolutegravir and other ART combinations using data from the Canadian Perinatal HIV Surveillance Program (CPHSP).

Methods

Information on management and health outcomes of pregnant WLWH was abstracted from the CPHSP, a public health surveillance program for vertical transmission of HIV.[17,18] The CPHSP consists of 22 sites, 19 HIV referral health centres and three health departments from all Canadian provinces and territories. It is estimated to capture 95% of all pregnancies in WLWH, and 100% of those where the infant is infected with HIV. Data management and analysis were provided by the Canadian Institutes of Health Research – Canadian HIV Trials Network (CTN). Support for the program is provided by the Public Health Agency of Canada (PHAC). Ethics approval was obtained from the research ethics boards of the participating sites. Summary data are submitted annually to the HIV/AIDS Surveillance Section, Surveillance and Risk Assessment Division at PHAC and reported in its regularly published technical reports entitled *HIV and AIDS in Canada*.[19] No specific funding was secured for this analysis. PHAC had no role in this study's conduct and design; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication. There was no individual patient involvement in the design or analysis of this study.

Data on mother–infant pairs, including maternal ART use at conception and during pregnancy, are collected by the participating sites upon obstetric or paediatric referral; all mother–infant pairs meeting inclusion criteria are included. Retrospective chart reviews of identified mothers and live-born infants are collated annually and clinical, demographic and HIV outcome data are submitted. In most sites, the treating physician or clinic nurse abstracts the data from the clinical record; in the largest sites, trained research assistants abstract the data with physician support. Given the nature of data collection primarily by paediatric providers, information on pregnancy losses, terminations of pregnancy for fetal anomaly and stillbirths is not available, because care for women with these outcomes is most often conducted by primary-care providers. Maternal data collected include their country of birth, self-reported race/ethnicity, according to national surveillance definitions, suspected mode of maternal HIV acquisition, antiretroviral regimen and duration of therapy in pregnancy (including dates of ART commencement and changes), mode of delivery, gestational age and birthweight. Maternal treatment is categorised according to ART regimens, defined as combinations of nucleoside reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors, protease inhibitors and/or integrase strand transfer inhibitors.

Congenital anomaly data are recorded as a free text field and authors who were blinded to antiretroviral exposures (DM, LJS) reviewed the text field and categorised data using the International Classification of Diseases, tenth revision. Major and minor congenital anomalies were included, although birth marks and positional deformities were not included. Infants are followed until 18 months of age, and congenital anomalies that were identified by 18 months of age are included. Additional information was requested from the individual sites when required to categorise the anomaly in specific cases. Congenital anomalies are classified by organ system involved.[20] The subsequent HIV status of the infant is reported with confirmation by virological testing for HIV by polymerase chain reaction. Data from each centre are reported to the CTN, using a secure web-based Oracle database. Only de-identified data are available for analysis to the CTN and the study investigator group.

This analysis was restricted to live-born infants born in Canada to WLWH, with data available on both congenital anomalies and ART in pregnancy, which included 2423 of 2591 infants born from 2007 to 2017.

Summary statistics were used to describe the demographic characteristics of the population and occurrence of congenital anomalies for different anomalies. Rates of

congenital anomalies are compared with the general population rate in Canada,[13] based on data from 1998 to 2007 in the Canadian Congenital Anomalies Surveillance System using exact binomial test. Proportions of affected infants between groups are compared using chi-squared or Fisher's exact test, as appropriate. Exact confidence intervals based on binomial distribution are computed for proportions. Firth logistic regression was used to compare congenital anomaly rate across groups. Analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

From 2007 to 2017, there were 2591 live infants born to WLWH in the CPHSP, of which 2423 had congenital anomaly data. Ethnic origin and birthplace of the mother are listed in Table 1. The majority of deliveries were at term (81.9%), with a mean gestational age of 38.2 weeks.

The timing of HIV diagnosis was known for 2306 of the mothers; 272 (11.8%) were diagnosed with HIV during their pregnancy and 40 (1.7%) were diagnosed at or after childbirth; the remainder (n = 1994; 86.5%) were aware of their diagnosis before the pregnancy. In all, 1311 women (56.4%) were on antiretrovirals at the time of conception, and another 204 (8.8%) started in the first trimester (Table 2).

Types of congenital anomalies are described in Table 3, and listed in the Supplementary material (Appendix S1). There were 98 total cases of anomalies (4.04%, 95% CI 3.30–4.91%), 12 of which were chromosomal abnormalities (0.5%, 95% CI 0.26–0.86%), and 86 were non-chromosomal congenital anomalies (3.5%, 95% CI 2.85–4.36%). The prevalence of congenital anomalies did not significantly differ across gestational age exposure timing groups (P = 0.915; Table 2) nor by dolutegravir exposure during pregnancy (P = 0.746; Table 2). The rate of congenital anomalies did not differ by maternal ethnic origin or background (P = 0.683; Table 2).

Specific review of NTDs reveals that there have been three cases of NTDs since 2007, an overall incidence rate of 0.12% (95% CI 0.03–0.36%). This was not significantly higher than the Canadian population rate of 0.04% (P = 0.075). These specific defects included a closed lumbar lipomeningocele, a lipomyelomeningocele and an open myelomeningocele. Two women were taking ART at conception; one was on tenofovir, emtricitabine and ritonavir-boosted atazanavir, whereas the other was on zidovudine, lamivudine, abacavir and ritonavir-boosted atazanavir. The third woman did not start ART until week 16 and was on zidovudine, lamivudine and nelfinavir. The rate of NTDs in those exposed to ART at conception was 2/1311 (0.15%, 95% CI 0.02–0.55%) compared with a rate of 1/690 (0.14%, 95% CI 0.00–0.80%) for those who had no ART exposure in the first trimester. Of note, no NTDs occurred with dolutegravir (0/117; 95% CI 0.00–3.10%) or other integrase inhibitor exposures (0/324, 95% CI 0.00–1.13%) in pregnancy.

Of the 2423 mother–infant pairs in the cohort with complete congenital anomaly data, 1515 had first-trimester ART exposure. There were 80 cases with dolutegravir exposure in the first trimester (69 cases with dolutegravir at conception) with four cases of non-chromosomal congenital anomalies, giving a rate of 5.0% (95% CI 1.4–12.3%) (Table 4). These included anomalies in the following systems: urinary tract (n = 2), circulatory system (n = 1) and musculoskeletal system (isolated polydactyly, n = 1). Of the other integrase inhibitors, 76 neonates had first-trimester raltegravir exposure and three of these had non-chromosomal anomalies, in either the respiratory, genital or urinary system (4.0% 95% CI 0.82–11.1%). Three of the 28 infants who had first-trimester elvitegravir exposure had congenital anomalies; systems affected were urinary system (polycystic kidneys), musculoskeletal system (isolated polydactyly) and multiple systems (including polycystic kidney, imperforate anus and hydronephrosis) (10.7% 95% CI 2.3–28.2%).

Discussion

This review presents a population level analysis of congenital anomalies for women who have ART exposure in pregnancy, focusing on integrase strand transfer inhibitor data. Dolutegravir has recently been recommended as the preferred first-line antiretroviral for treatment of adults with HIV, due to its tolerability, efficacy and cost.[1] In this context, the safety signal suggesting potential association with increased NTDs is of concern when prescribing ART to women of reproductive potential.[11] HIV care providers for WLWH who may become pregnant, and obstetric care providers for pregnant WLWH need access to medication safety data, to provide guidance to their patients on the risks and benefits of specific ARTs in pregnancy. Data on congenital anomaly risk related to use of antiretroviral regimens are also crucial to inform guidelines and regional policies for treatment of WLWH with reproductive potential.

Main findings

Using the Canadian cohort data from the CPHSP, despite modest numbers of women exposed to dolutegravir, we did not observe an increased rate of non-chromosomal congenital anomalies among the 80 neonates born to mothers on dolutegravir during the first trimester of pregnancy (4/80; 5.0%, 95% CI 1.4–12.3%), compared with the baseline rate of congenital anomalies in the Canadian population. It is reassuring that this analysis found no NTDs in the small number (69) of women on dolutegravir at conception

Table 1. Maternal and neonatal characteristics

Variable	All (*n* = 2423)	Congenital anomaly outcome		*P*
		Absent (*n* = 1325)	Present (*n* = 98)	
Maternal region of birth, *n* (%)				
Canada	975 (41.2)	944 (41.6)	31 (32.3)	0.087
Africa	1088 (46.0)	1041 (45.9)	47 (49.0)	
Other	303 (12.8)	285 (12.6)	18 (18.8)	
Unknown	57	55	2	
Ethnicity, *n* (%)				
Black	1285 (53.9)	1227 (53.6)	58 (59.8)	0.614
Indigenous	481 (20.2)	463 (20.2)	18 (18.6)	
White	456 (19.1)	440 (19.2)	16 (16.5)	
Asian	75 (3.1)	71 (3.1)	4 (4.1)	
Hispanic	32 (1.3)	32 (1.4)	0 (0.0)	
Other	56 (2.3)	55 (2.4)	1 (1.0)	
Unknown	38	37	1	
Mode of acquisition, *n* (%)				
Sexual contact	1663 (75.3)	1587 (75.0)	76 (82.6)	0.310
Injection drug use	432 (19.6)	421 (19.9)	11 (12.0)	
Vertical transmission	50 (2.3)	48 (2.3)	2 (2.2)	
Blood products	42 (1.9)	40 (1.9)	2 (2.2)	
Other	21 (1.0)	20 (0.9)	1 (1.1)	
Unknown	215	209	6	
Viral load closest to delivery, *n* (%)				
<50	1959 (84.8)	1875 (84.7)	84 (87.5)	0.237
50–999	226 (9.8)	221 (10.0)	5 (5.2)	
>1000	125 (5.4)	118 (5.3)	7 (7.3)	
Unknown	113	111	2	
Mode of delivery, *n* (%)				
Caesarean section – elective	551 (23.1)	529 (23.1)	22 (22.9)	0.949
Caesarean section – emergency	346 (14.5)	331 (14.4)	15 (15.6)	
Vaginal	1491 (62.4)	1432 (62.5)	59 (61.5)	
Unknown	35	33	2	
Gestational age at delivery, mean (SD)	38.2 (2.46)	38.2 (2.42)	37.8 (3.29)	0.152
Gestational age at delivery, *n* (%)				
<34 weeks	289 (12.2)	273 (12.0)	16 (16.7)	0.196
34–36 weeks	138 (5.8)	130 (5.7)	8 (8.3)	
≥37 weeks	1936 (81.9)	1864 (82.2)	72 (75.0)	
Unknown	62	59	3	
Birthweight (kg), mean (SD)*	3.04 (0.66)	3.05 (0.66)	2.93 (0.77)	0.086
Child sex, *n* (%)				
Female	1164 (48.1)	1129 (48.6)	35 (35.7)	0.012
Male	1257 (51.9)	1194 (51.4)	63 (64.3)	
Unknown	2	2	0	
Childbirth province, *n* (%)				
BC/Yukon	266 (11.0)	260 (11.2)	6 (6.1)	0.002
Alberta	361 (14.9)	348 (15.0)	13 (13.3)	
Saskatchewan	255 (10.5)	250 (10.8)	5 (5.1)	
Manitoba	156 (6.4)	152 (6.5)	4 (4.1)	
Ontario	887 (36.6)	854 (36.7)	33 (33.7)	
Quebec	487 (20.1)	451 (19.4)	36 (36.7)	
Atlantic	11 (0.5)	10 (0.4)	1 (1.0)	

*Missing for 111 infants (107 versus 4).
Table includes women with congenital anomaly data only (2423 of 2591 live-born infants). *P* value was based on Chi-squared test, Fisher's exact test or *t*-test as appropriate.

Table 2. Association between congenital anomaly outcomes, ART exposure during pregnancy and maternal ethnic origin

Variable	*n*	Presence of congenital anomaly, *n* (rate [95% CI])	*P*	Odds ratio (95% CI)	*P*
Timing of ART exposure during pregnancy					
No ART exposure	118	6 (5.1% [1.9–10.7%])	0.915	1	
ART at conception	1311	55 (4.2% [3.2–5.4%])		0.76 (0.33–1.77)	0.530
ART started in first trimester	204	8 (3.9% [1.7–7.6%])		0.75 (0.26–2.14)	0.589
ART started from 14 weeks onwards	690	27 (3.9% [2.6–5.6%])		0.72 (0.30–1.73)	0.459
ART timing Unknown	100	2		–	
ART exposure during pregnancy					
No ART exposure	118	6 (5.1% [1.9–10.7%])	0.746	1	
Non-dolutegravir	2173	87 (4.0% [3.2–4.9%])		0.73 (0.32–1.65)	0.444
Dolutegravir	117	4 (3.4% [0.94–8.5%])		0.69 (0.20–2.36)	0.549
Unknown	15	1		–	
Ethnicity					
Black	1285	58 (4.5% [3.4–5.8%])	0.683	1	
Indigenous	481	18 (3.7% [2.2–5.9%])		0.84 (0.49–1.43)	0.515
White	456	16 (3.5% [2.0–5.6%])		0.79 (0.45–1.37)	0.397
Asian	75	4 (5.3% [1.5–13.1%])		1.32 (0.49–3.57)	0.584
Hispanic	32	0 (0% [0.0–10.9%])		0.32 (0.02–5.57)	0.437
Other	56	1 (1.8% [0.05–9.6%])		0.57 (0.11–2.97)	0.502
Unknown	38	1		–	

This includes exposure to all ARTs.

Table 3. Frequency of types of congenital anomalies by organ system among all neonates (*n* = 2423)

Type of anomaly by system	Frequency	Rate
Chromosomal	12	0.5%
Non-chromosomal		
Cardiac	17	0.7%
Isolated polydactyly	15	0.61%
Urinary	13	0.53%
Musculoskeletal (other than polydactyly)	9	0.37%
Vascular	9	0.37%
Respiratory	7	0.28%
Nervous system (other than NTD)	5	0.2%
Isolated NTD	3	0.12%
Eye, ear, face and neck	2	0.08%
Digestive	1	0.04%
Genital	1	0.04%
Multisystem anomalies (non-chromosomal)	4	0.16%
Total	98	4.0%

(95% CI 0.00–5.21%). These findings are consistent with several other studies, including a small systematic review of six studies evaluating dolutegravir use in pregnancy and possible adverse neonatal outcomes,[13,20,21] which showed similar rates of congenital anomalies among newborns exposed during pregnancy compared with the expected global incidence rate of congenital anomalies (16 newborns had congenital anomalies among 442 women exposed in pregnancy; 3.6%).[14] There was a concerning trend for a threefold higher rate of congenital anomalies among the small number of pregnancies exposed to elvitegravir in the first trimester; however, the confidence interval was wide (3/28; 10.7%, 95% CI 2.3–28.2%).

Strengths

There are several strengths related to these data and methodology that render them unique and comprehensive. Our data are population-level data, as they are from an active national surveillance study, spanning a prolonged period of 10 years, capturing the majority of WLWH giving birth across all Canadian provinces. Additionally, our data distinctly identify women who were started on dolutegravir before conception and those initiated on it after conception, providing an important comparative analysis.

Limitations

There are a few factors related to the CPHSP data that may have produced bias in our results. The most important limitation is the small size of the cohort due to limited use of dolutegravir in women of reproductive age in Canada. Consequently, there are insufficient data to definitively address rare birth defects. With only 80 women exposed to dolutegravir in the first trimester, we would have expected to see at most one case of NTD (if the rate was 0.9%). As the CPHSP data were initially designed to examine vertical transmission and not congenital anomalies specifically, detection of congenital anomalies may not have been as systematic as for a

Table 4. Congenital anomalies associated with different combinations of ART exposure in the first trimester

ART in first trimester	*n*	Congenital anomaly	
		Chromosomal, *n* (%)	Non-chromosomal, *n* (%)
No ART	803	2 (0.25% [0.03–0.90%])	31 (3.9% [2.6–5.4%])
NNRTI + NRTI	221	0 (0.0% [0.0–1.7%])	7 (3.2% [1.3–6.4%])
Efavirenz	46	0 (0.0% [0.0–7.7%])	3 (6.5% [1.4–17.9%])
Nevirapine	124	0 (0.0% [0.0–2.9%])	4 (3.2% [0.89%–8.1%])
Rilpivirine or etravarine	51	0 (0.0% [0.0–7.0%])	0 (0.0% [0.0–7.0%])
PI + NRTI	974	8 (0.82% [0.36–1.6%])	34 (3.5% [2.4–4.8%])
II + NRTI	180	1 (0.56% [0.01–3.1%])	9 (5.0% [2.3–9.3%])
Dolutegravir	80	0 (0.0% [0.0–4.5%])	4 (5.0% [1.4–12.3%])
Elvitegravir	28	0 (0.0% [0.0–12.3%])	3 (10.7% [2.3–28.2%])
Raltegravir	76	1 (1.3% [0.03–7.1%])	3 (4.0% [0.82–11.1%])
Other	131	1 (0.76% [0.20–4.2%])	3 (2.3% [0.47–6.6%])
Unknown	114	0	2

NRTI: Nucleoside reverse transcriptase inhibitor – for example, zidovudine, lamivudine, abacavir, stavudine, didanosineNNRTI: Non-nucleoside reverse transcriptase inhibitor – for example, efavirenz, nevirapine, rilpivirine, etraverine
PI: Protease inhibitor – for example, atazanavir, darunavir, lopinavir, nelfinavir, ritonavi
II: Integrase inhibitor – for example, dolutegravir, elvitrgravir, raltegravir

study specifically designed to examine this outcome. Ideally, additional information regarding maternal demographics would have been captured, including age of the mother, history of maternal substance use, and maternal use of any other medications. These factors, specifically maternal age, will be important to consider in future studies, as they can impact rates of congenital anomalies.

Of note, we do not have rates for *in utero* diagnosis of congenital anomalies that resulted in stillbirth, pregnancy loss or termination, which is an important limitation as the risk of stillbirth and termination is high in the context of severe congenital anomalies. In the Tsepamo study in Botswana, 25% of NTDs were in infants who were stillborn.[5] The CPHSP captures the majority of outcomes among WLWH with live births in Canada, including all children who have been referred to one of the paediatric HIV centres for care. There may be a small number of infants born to WLWH, particularly in more geographically isolated areas, who have not been seen by a paediatric HIV expert; however, children who have major congenital anomalies are most often seen in paediatric hospitals in Canada. Despite our near-complete ascertainment, the sample size is small. Comparing our data against the Canadian Congenital Anomalies Surveillance System report data provides suboptimal internal comparison. Unlike our data from the CPHSP, the Canadian Congenital Anomalies Surveillance System data include stillbirths after 20 weeks of gestation, which is likely to show higher rates of anomalies than we would have captured, so biasing our data to under-report anomalies.[22] Given the low number of congenital anomalies observed and limited sample size in some groups, comparisons of rates between groups were not adjusted for potential confounders to avoid overfitting.

Interpretation

These population-level surveillance data demonstrate no safety signal for congenital anomalies among the modest number of pregnancies with dolutegravir exposure in the first trimester. The overall rate of NTDs (0.12%, 95% CI 0.03–0.36) is not significantly higher than Canadian population data (0.04%)[13] and is comparable to the baseline rates in Botswana in non-dolutegravir-exposed pregnancies (0.1%).[9] There was, however, a small number pregnancies with elvitegravir first-trimester exposure demonstrating a rate of non-NTD anomalies of 10.7% (3/28). There were no other safety signals for other ART exposure in pregnancy. Due to the small number of WLWH exposed to integrase strand transfer inhibitors, these data will need to be combined with other data sources to allow a more robust assessment of risk; as seen for valproic acid, initial reports had wide confidence intervals for overall congenital anomalies and NTDs but in combining data sets a more accurate assessment was possible.[23]

Conclusions

These data should ideally be combined with other global data to further explore any potential risks of ART exposure in pregnancy. The dolutegravir concern highlights the critical need for ongoing surveillance. It is important to include reproductive potential in consideration of choice of ART for women.

Declarations

Meetings at which the data were presented in part: data from the Canadian Perinatal HIV Surveillance Program are presented annually at the Canadian Conference on HIV/AIDS Research. An abstract with a specific focus on dolutegravir and congenital anomalies was presented at the Glasgow 2018 conference in October 2018 and at the Women and HIV conference in Seattle, Washington, March 2019.

Disclosure of interests

All authors have nothing to disclose other than the funding for the Surveillance Program from the Public Health Agency of Canada and support from teh CIHR Canadian HIV Trials Network. Completed disclosure of interest forms are available to view online as supporting information.

Contribution to authorship

DM and LJS conceived and designed the study, acquired and analysed the data, interpreted the study findings and drafted the manuscript. LJS and AB lead the Canadian Paediatric Surveillance Programme. TL advised on analytical methods, carried out analysis and critically reviewed the manuscript. CO contributed to data analysis and interpretation. JB, AB, FK, IB, AA, WV and JS all contributed to designing the study, acquiring and analysing data, interpretation of the study findings, and critically revising the manuscript. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Details of ethics approval

The procedures of the study received ethics approval from the University of British Columbia (H07-02384); approval for 2018 was granted on 4 July 2018.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. List of congenital anomalies. ■

References

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