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Original Article

A Study on the Incidence and Prevalence of 5q Spinal Muscular Atrophy in Canada Using Multiple Data Sources

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ABSTRACT: ***Objectives:*** Spinal muscular atrophy (SMA) is a leading genetic cause of infant death and represents a significant burden of care. An improved understanding of the epidemiology of SMA in Canada may help inform strategies to improve the standard of care for individuals living with SMA. ***Methods:*** We employed a multisource approach to estimate the minimal incidence and prevalence of 5q SMA and to gain greater insight into recent clinical practices and treatment trends for the Canadian SMA population. Data sources included the Canadian Paediatric Surveillance Program (CPSP), Canadian Neuromuscular Disease Registry (CNDR), and molecular genetics laboratories in Canada. ***Results:*** The estimated annual minimum incidence of 5q SMA was 4.38, 3.44, and 7.99 cases per 100,000 live births in 2020 and 2021, based on CPSP, CNDR, and molecular genetics laboratories data, respectively, representing approximately 1 in 21,472 births (range 12,516–29,070) in Canada. SMA prevalence was estimated to be 0.85 per 100,000 persons aged 0–79 years. Delay in diagnosis exists across all SMA subtypes. Most common presenting symptoms were delayed milestones, hypotonia, and muscle weakness. Nusinersen was the most common disease-modifying treatment received. Most patients utilized multidisciplinary clinics for management of SMA. ***Conclusion:*** This study provides data on the annual minimum incidence of pediatric 5q SMA in Canada. Recent therapeutic advances and newborn screening have the potential to drastically alter the natural history of SMA. Findings underline the importance of ongoing surveillance of the epidemiology and long-term health outcomes of SMA in the Canadian population.

RÉSUMÉ : Étude sur l'incidence et la prévalence de l'amyotrophie spinale liée au chromosome 5q [AS 5q] au Canada, fondée sur différentes sources de données. ***Objectif :*** L'amyotrophie spinale (AS) est une cause importante de mortalité infantile, d'origine génétique, et impose un lourd fardeau de soins. Une compréhension accrue de l'épidémiologie de la maladie au Canada pourrait guider l'élaboration de stratégies visant à améliorer la norme de prestation de soins aux personnes atteintes d'AS. ***Méthode :*** L'équipe s'est appuyée sur une recherche multisource, notamment sur le Programme canadien de surveillance pédiatrique (PCSP), le Canadian Neuromuscular Disease Registry (CNDR) et des laboratoires de génétique moléculaire au Canada, pour estimer l'incidence et la prévalence minimales de l'AS 5q et avoir une meilleure idée des pratiques cliniques récentes et des nouvelles tendances en matière de traitement dans la population touchée par cette maladie au Canada. ***Résultats :*** D'après les données du CPSP, du CNDR et des laboratoires de génétique moléculaire, l'incidence minimale annuelle de l'AS 5q était estimée respectivement à 4,38, à 3,44 et à 7,99 cas pour 100 000 naissances vivantes en 2020 et 2021, ce qui correspond à environ 1 cas pour 21 472 naissances (plage : 12 516-29 070) au Canada. Quant à la prévalence de l'AS, elle était estimée à 0,85 pour 100 000 personnes âgées de 0 à 79 ans. Des poses tardives de diagnostic sont observées dans tous les sous-types d'AS. Les motifs les plus fréquents de consultation étaient des symptômes jalons retardés, l'hypotonie et la faiblesse musculaire. Le médicament utilisé le plus souvent dans le traitement de fond était le nusinersen. La plupart des patients fréquentaient des centres de soins pluridisciplinaires pour la prise en charge de l'AS. ***Conclusion :*** L'étude a permis de recueillir des données sur l'incidence minimale annuelle de l'AS 5q chez les enfants au Canada. Les progrès récents en matière de traitement et le dépistage de la maladie chez les nouveau-nés offrent le potentiel de changer fondamentalement l'évolution naturelle de l'AS. Les constatations qui se dégagent de l'étude font ressortir l'importance d'une surveillance continue de l'épidémiologie et des résultats éloignés de l'AS sur le plan de la santé dans la population canadienne.

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Keywords: Spinal muscular atrophy; Neuromuscular disease; Minimum incidence; Prevalence; Clinical epidemiology

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Background

5q spinal muscular atrophy (SMA) is a severe progressive neuromuscular disease caused by biallelic mutations of the *survival motor neuron* (*SMN*) *1* gene on chromosome 5q13.2.[1] Higher copy number of a nearby *SMN2* gene is associated with a milder phenotype.[2,3] 5q SMA is historically classified into 5 main subtypes (types 0 to IV), based on age of symptom onset and maximal attained motor function.[4,5] Prenatal onset (type 0) SMA is rare.[6] Historically, type I accounts for about 50% of SMA cases, with onset < 6 months of age and death within first two years of life if untreated. Children with type II SMA present between 6 and 18 months of age; they can sit unaided but cannot walk unassisted if untreated. Those with type III SMA present after 18 months of age with ability to walk unassisted; however, progressive weakness may lead to loss of independent ambulation without treatment.[7] Individuals with type IV SMA present after 18 years of age, with preserved ambulation and normal life expectancy.[8] Globally, the incidence of 5q SMA has been estimated to be 1 per 10,000 newborns, with a prevalence of 1–2 per 100,000 persons.[9]

Currently, there are three available disease-modifying therapies (DMTs) for 5q SMA. Nusinersen (Spinraza®) was first approved by Health Canada in June 2017; it is an antisense oligonucleotide that binds to *SMN2* pre-mRNA to increase expression of SMN protein.[10] Other DMTs, including onasemnogene abeparvovec (Zolgensma®), a viral-mediated *SMN* gene replacement therapy, and risdiplam (Evrysdi®), an oral *SMN2* splicing modulator, were subsequently approved by Health Canada in December 2020 and April 2021, respectively.[11,12] Notably, the best outcomes were seen in infants who received early pre-symptomatic treatment.[13–15]

Surveillance is an integral aspect of public health. Active surveillance of rare diseases, like SMA, leads to a greater understanding of the epidemiology of the disease. Accordingly, the objectives of the study were to: (1) determine the minimum incidence of 5q SMA from 3 independent Canadian sources; (2) determine the prevalence of 5q SMA in Canada; and (3) describe the clinical features and current treatment approaches for 5q SMA patients across Canada.

Methods

Data Sources

To estimate the minimum annual incidence of pediatric (<18 years old) 5q SMA in Canada, we used data available through the Canadian Paediatric Surveillance Program (CPSP), the Canadian Neuromuscular Disease Registry (CNDR), and Canadian molecular genetics laboratories between January 2020 and December 2021. SMA type IV (adult-onset) cases were excluded from the minimum annual incidence estimates. The total number of pediatric patients with new diagnoses of 5q SMA who were enrolled in the CNDR during the 24-month study period were compared to the numbers of new cases confirmed from the CPSP and from Canadian molecular genetics laboratories. Prevalence estimates were determined from CNDR data as of July 1, 2022. To identify baseline demographics, clinical characteristics, and treatment approaches, we used data from both the CPSP and CNDR.

Canadian Paediatric Surveillance Program (CPSP)

The CPSP is a joint project of the Canadian Paediatric Society and the Public Health Agency of Canada (PHAC).[16] Data are gathered monthly from more than 2800 pediatricians and pediatric subspecialists throughout Canada; these physicians cover a population of over 7 million children and youth in Canada.[16] Monthly reporting forms were sent out by mail/secure weblink to pediatricians during the 24-month reporting period. A case definition and protocol providing background information on SMA were mailed to all CPSP participants. SMA was defined as any patient with a new, genetically confirmed case of 5q SMA from birth to 18 years of age (up to the 18th birthday). The complete protocol can be accessed at https://cpsp.cps.ca/surveillance. After identifying a case, participating physicians were asked to complete a separate questionnaire detailing the baseline demographics for each case, along with clinical presentation and initial treatment received. Follow-up reminders were sent to ask the physicians to complete the questionnaires and return them to the CPSP staff upon completion. The CPSP staff, who had security clearance from the Government of Canada, then performed a check on every completed questionnaire to ensure that any personal identifying information was removed. The questionnaire was then uploaded into a protected and secure PHAC file transfer site for downloading and subsequent data analysis.

Canadian Neuromuscular Disease Registry (CNDR)

The CNDR is a national, pan-Canadian, consent-based neuromuscular disease registry working closely with 37 affiliated adult and pediatric neuromuscular clinics across 10 provinces.[17] Since its inception in 2010, the CNDR has enrolled over 4,500 participants across Canada with neuromuscular diseases.[18] In order to register with CNDR, patients must provide informed consent and are required to have a confirmed diagnosis according to the World Federation of Neurology classification.[19] The CNDR collects patient registration information, demographics, and disease-specific clinical characteristics. For the purposes of incidence reporting, SMA was defined as any pediatric patient with a new, genetically confirmed case of 5q SMA based on both date of birth and date of diagnosis during the study period. Aggregate nonidentifiable results were provided via secure file download directly from CNDR staff.

Canadian Molecular Genetics Laboratories

Molecular genetics laboratories providing clinical *SMN1* genetic testing were identified using publicly available sources and expert input from the Canadian College of Medical Geneticists. Data from the identified Canadian molecular genetics laboratories were collected via an online survey to determine the method of *SMN1* testing as well as the number of new pediatric patients with a

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genetically confirmed diagnosis of 5q SMA. The standardized survey was sent using personalized emails to identify the total number of positive SMA cases from birth to 18 years of age based on biallelic *SMN1* gene mutations during the 24-month study period, excluding prenatal cases. Only the total number of cases were provided to minimize risk of identifying any individual patient. Four molecular genetics laboratories in three provinces (British Columbia, Alberta, and Ontario) responded to the online survey; there were no responses from other provincial laboratories.

Statistical Analysis

An observed minimum incidence rate was calculated as the total number of new diagnosed cases of 5q SMA per year per 100,000 live births. The denominators used for the Canadian incidence estimates and province-specific estimates were derived from 2020 and 2021 Statistics Canada (https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1710001601) using the total number of live births during the 24-month study period. It was assumed that the estimates remained stable over the study period. Confidence intervals (CIs) were calculated using Poisson distributions following standard statistical methods. 5q SMA point prevalence estimates were calculated based on data obtained from the CNDR; the numerator represented the number of registered SMA cases as of July 1, 2022, and the denominator was the total population of individuals by age category based on July 1, 2022, Canadian population census data (https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1710000501). Descriptive statistics, including median and interquartile range (IQR), were used to describe patient demographics and clinical characteristics. Frequency tables were created to summarize data from ordinal or binary measurements. Statistics were calculated using SAS, Version 9.4 (Cary, NC).

Statement of Ethics

Ethical approval was obtained from the University of Calgary Conjoint Research and Ethics Board as well as the PHAC Research Ethics Board.

Results

Over the 24-month surveillance period, a total of 32, 25, and 37 incident pediatric cases were reported by the CPSP, CNDR, and molecular genetics laboratories, respectively. An overview of the case reporting by the three Canadian data sources is detailed in the following paragraphs.

The CPSP received a total of 38 reports (24 in 2020 and 14 in 2021) of 5q SMA. Six were duplicate reports determined from review of the available data, including date (month/year) of birth and gender (male/female) of cases and geographic location (by province) of the reporting physicians. Of the remaining 32 cases, 6 (18.8%) were from British Columbia, 8 (25%) were from Alberta, 12 (37.5%) from Ontario, and 6 (18.8%) were from Quebec and Atlantic Canada. Nineteen (59.4%) cases had detailed questionnaires completed by reporting physicians; the remaining 13 (40.6%) cases did not have completed reports for unknown reasons. Of the 19 completed reports, 10 (52.6%) cases were from Ontario, 7 (36.8%) cases were from Western Canada, and the remaining were from other parts of Canada.

The total number of pediatric patients with new diagnosis of 5q SMA who were enrolled in the CNDR during the 24-month study period were included in the annual incidence estimation. The CNDR received a total of 25 reports (12 in 2020 and 13 in 2021), including 6 (24.0%) from British Columbia, 5 (20.0%) from Alberta, 6 (24.0%) from Quebec, and the remaining 8 (32.0%) from Saskatchewan, Manitoba, and Ontario.

Four molecular genetics laboratories in three provinces reported a total of 37 pediatric cases of 5q SMA during 2020–2021, including 7 (18.9%) cases from British Columbia, 27 (73.0%) cases from Ontario, and the remaining from Alberta. Only the total number of cases over the combined study period by geographic distribution were provided; therefore, a breakdown of cases by study year was unavailable.

Table 1: Minimum incidence rates of 5q SMA in Canadian children aged < 18 years by data source during 2020 and 2021

Study Period and Data Source	Number of 5q SMA cases	Population estimates of births[a]	Incidence rates (95% CI), per 100,000 live births per year
2020			
CPSP	20	361,613	5.53 (3.38–8.54)
CNDR[b]	12	359,705	3.34 (1.72–5.83)
2021			
CPSP	12	368,792	3.25 (1.68–5.68)
CNDR[b]	13	367,030	3.54 (1.88–6.06)
Combined 2020–2021			
CPSP	32	730,405	4.38 (3.00–6.19)
CNDR[b]	25	726,735	3.44 (2.23–5.08)
Genetics Labs[c,d]	37	463,021	7.99 (5.63–11.01)

CNDR = Canadian Neuromuscular Disease Registry; CPSP = Canadian Paediatric Surveillance Program; SMA = spinal muscular atrophy; CI = confidence interval.
[a]Data from 2020 and 2021 population census, Statistics Canada. Table 17-10-0016-01 Estimates of births, by sex, annual https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1710001601 accessed 24Nov2022.
[b]The population denominator used for CNDR was based on Statistics Canada population estimates for the 10 participating provinces.
[c]Only the total number of cases across the combined study period were available from participating molecular genetics laboratories.
[d]Data from only four molecular genetics laboratories in three provinces (British Columbia, Alberta, and Ontario) were available.

Minimum Incidence of Pediatric SMA in Canada

Table 1 outlines the observed minimum incidence of pediatric 5q SMA by data source and study period year; the minimal incidence rates during 2020–2021 by participating provinces are summarized in Table 2.

Of the cases reported by the CPSP and based on annual birth rates in Canada, the observed minimum incidence of 5q SMA in Canadian children < 18 years old was 5.53 and 3.25 cases per 100,000 live births per year, in 2020 and 2021, respectively. Overall, the combined minimum incidence rate was 4.38 cases per 100,000 live births per year, or approximately 1 in 22,831 births.

Of the cases reported by CNDR and based on annual birth rates in 8 of the participating provinces, the observed minimum incidence of 5q SMA in Canadian children was 3.34 and 3.54 cases per 100,000 live births per year, in 2020 and 2021, respectively. Overall, the combined minimum incidence rate was 3.44 cases per 100,000 live births per year, or approximately 1 in 29,070 live births.

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Table 2: Minimum incidence rates of 5q SMA in Canadian children aged < 18 years by data source and geographic distribution during 2020 and 2021

Participating Centers (by Provinces) and Data Source	Number of 5q SMA cases	Incidence rates (95% CI), per 100,000 live births per year[a]
British Columbia (2020–2021)		
CPSP	6	7.01 (2.56–15.25)
CNDR	6	7.01 (2.56–15.25)
Genetics lab[b,c]	7	8.17 (3.28–16.84)
Alberta (2020–2021)		
CPSP	8	8.01 (3.48–15.90)
CNDR	5	5.04 (1.63–11.77)
Genetics lab[b,c]	<5	3.03 (0.61–8.84)
Saskatchewan (2020–2021)		
CPSP	0	–
CNDR	<5	7.08 (0.80–25.57)
Manitoba (2020–2021)		
CPSP	0	–
CNDR	<5	6.39 (0.72–23.07)
Ontario (2020–2021)		
CPSP	12	4.31 (2.23–7.53)
CNDR	<5	1.44 (0.39–3.68)
Genetics lab[b,c]	27	9.70 (6.39–14.12)
Quebec (2020–2021)		
CPSP	<5	2.42 (0.65–6.19)
CNDR	6	3.63 (1.33–7.90)
Atlantic Canada[d] (2020–2021)		
CPSP	<5	5.15 (0.58–18.60)
CNDR	0	–

CNDR = Canadian Neuromuscular Disease Registry; CPSP = Canadian Paediatric Surveillance Program; SMA = spinal muscular atrophy; CI = confidence interval. Note: Cells with counts smaller than 5 were indicated as < 5, per data source reporting requirements.
[a]Population estimates of birth for each province were based on data from 2020 and 2021 population census, Statistics Canada. Table 17–10–0016–01 Estimates of births, by sex, annual https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid = 1710001601 accessed 24Nov2022.
[b]Only the total number of cases across the combined study period were available from participating molecular genetics laboratories.
[c]Data from only four molecular genetics laboratories in three provinces (British Columbia, Alberta, and Ontario) were available.
[d]Includes Newfoundland and Labrador, Prince Edward Island, Nova Scotia, and New Brunswick. '–' represents no data to report.

The minimum incidence rate from four participating molecular genetics laboratories in three provinces was 8.17, 3.03 and 9.70 cases per 100,000 live births per year for British Columbia, Alberta, and Ontario, respectively. Overall, the combined minimum incidence rate was 7.99 cases per 100,000 live births per year, or approximately 1 in 12,516 live births.

Prevalence of SMA in Canada

As of July 1, 2022, CNDR reported a total of 299 cases of 5q SMA. Table 3 provides an overview of prevalence of SMA by age category corresponding to Canadian population estimates. A 5q SMA point prevalence of 0.85 cases per 100,000 persons aged 0–79 years was observed, or approximately 1 in 118,026 persons. Prevalence estimates were higher among the younger age groups (0–29 years of age) with a point prevalence range of 1.1 to 2.12 cases per 100,000 persons (Table 3).

Table 3: Prevalence of 5q SMA based on CNDR data and Canadian population 2022 census data, by age categories

Age category	No. of 5q SMA Cases	Population estimates[a]	Cases per 100,000 persons
Total			
0–79 years	299	37,169,132	0.85
Age Group[b]			
0–4 years	40	1,881,099	2.12
5–9 years	38	2,062,572	1.85
10–14 years	45	2,126,905	2.12
15–19 years	37	2,124,972	1.74
20–24 years	29	2,520,278	1.15
25–29 years	30	2,703,647	1.11
30–34 years	9	2,782,998	0.32
35–39 years	21	2,718,849	0.77
40–44 years	7	2,573,624	0.27
45–49 years	10	2,405,593	0.42
50–54 years	8	2,423,627	0.33
55–59 years	5	2,635,125	0.19
60–64 years	9	2,640,008	0.34
65–79 years	9	5,569,835	0.16
Unknown	<5	–	–

CNDR = Canadian Neuromuscular Disease Registry; SMA = spinal muscular atrophy. Cells with counts smaller than 5 were indicated as < 5, per data source reporting requirements.
[a]Data from 2022 population census, Statistics Canada. Table 17-10-0005-01 Population estimates on July 1st, by age and sex https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid = 1710000501 accessed 28May2023.
[b]Age group corresponds–the age groupings provided by Canadian population estimates. SMA cases within the CNDR range from less than 1 year–a maximum of 79 years of age. '–' represents no data–report.

Demographics, Clinical Characteristics, and Treatment Approaches in Patients with SMA

Figure 1 and Figure 2 present select demographics, clinical characteristics, and treatment approaches in Canadian patients with 5q SMA by data source (see Table 4 for expanded results). Of the 32 incidence cases reported by CPSP during the study period, 19 cases had detailed questionnaires completed. As of July 1, 2022, CNDR reported a total of 299 cases of 5q SMA enrolled in the registry; 265 of these cases had detailed clinical and disease-specific information relevant to our study.

Of the 19 cases from the CPSP with detailed questionnaires completed, 63.2% ($n = 12$) of the cases were male and 78.9% ($n = 15$) had no family history of SMA. Ten (52.6%) cases had SMA type I, 26.3% ($n = 5$) had type III, and the rest (21.1%) had type II disease. For patients with type I SMA, the median (IQR) age at diagnosis was 5.0 (3.0, 6.0) months, with a delay of 3.0 (2.5, 3.0) months between symptom onset and diagnosis. For patients with type II and type III SMA, the median (IQR) age at diagnosis was 13.0 (9.0, 22.0) and 37.5 (28.5, 41.0) months, respectively, with a

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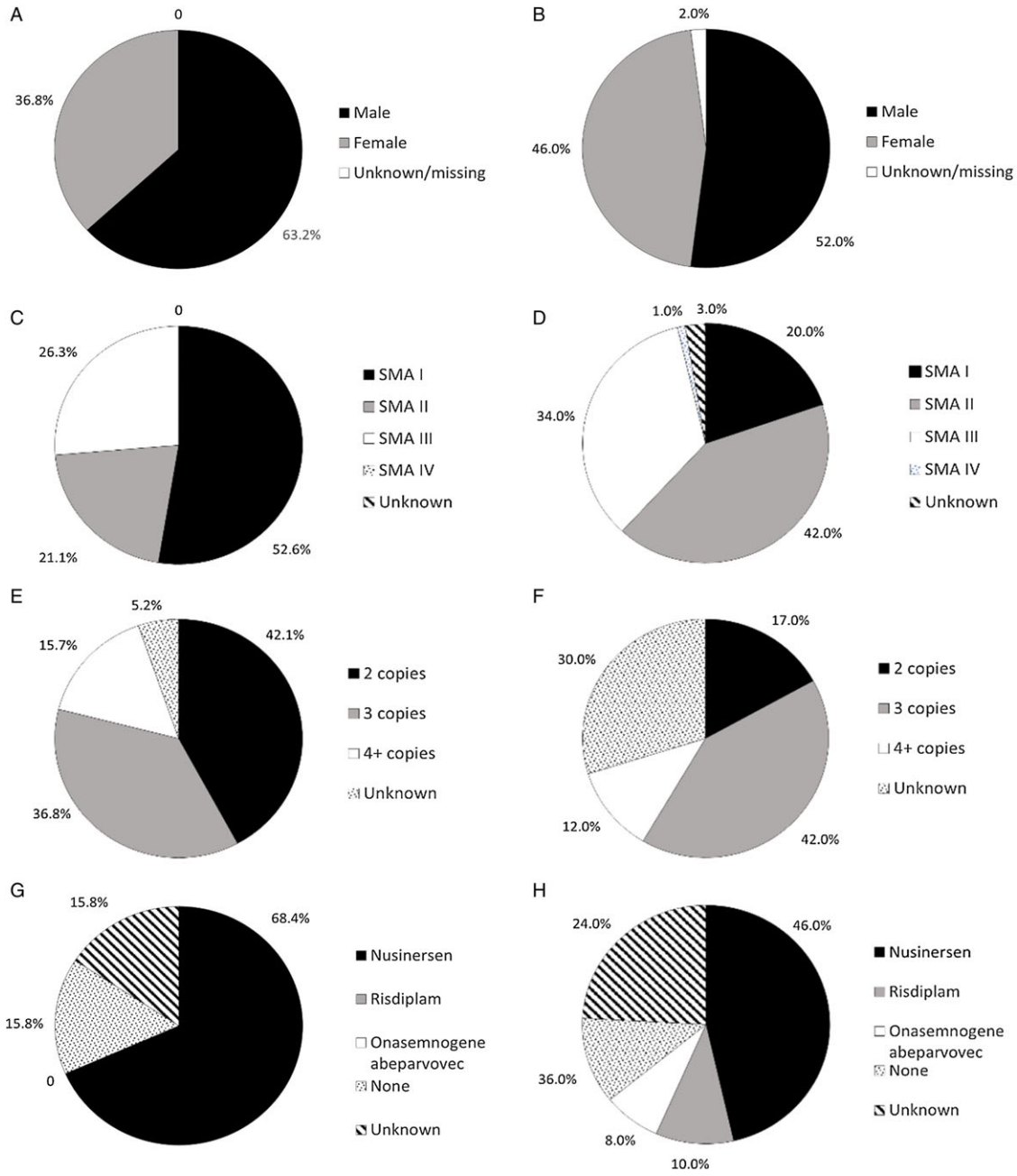

Figure 1: Comparison of demographics, clinical characteristics, and treatments in Canadian patients with 5q SMA by CPSP ($n = 19$) vs. CNDR ($n = 299$): gender distribution from CPSP (***a***) vs. CNDR (***b***); SMA types from CPSP (***c***) vs. CNDR (d); *SMN2* copy number from CPSP (***e***) vs. CNDR (***f***); disease-modifying therapies from CPSP (***g***) vs. CNDR (***h***).

delay of 7.0 (6.0, 10.0) and 19.5 (12.0, 24.5) months, respectively, between symptom onset and diagnosis. Among the symptomatic cases, the most common presenting symptoms were muscle weakness ($n = 14$), hypotonia ($n = 13$), delayed motor milestones ($n = 11$), and poor head control ($n = 8$). Sixteen (84.2%) cases did not require feeding or respiratory support at the time of CPSP reporting. Thirteen (68.4%) cases received nusinersen as the initial DMT. The majority (94.7%) were followed in pediatric multidisciplinary clinics for management of SMA as part of standard of care.

Of the 299 prevalent cases captured from CNDR, 51.5% ($n = 154$) of the cases were male and 21.1% ($n = 56$) had a family history of SMA. Fifty-nine (19.7%) cases had SMA type I, 42.1% ($n = 126$) had type II, and 34.4% ($n = 103$) had type III. One-hundred and fifty-eight (52.8%) cases provided information on age at symptom onset and age at diagnosis. For patients with type I SMA, the median (IQR) age at diagnosis was 5.0 (2.0, 6.5) months, with a delay of 2.5 (1.0, 4.0) months between symptom onset and diagnosis. For patients with type II and type III SMA, the median (IQR) age at diagnosis was 18.0 (14.0, 24.0) and 48.0 (35.9, 99.0) months, respectively, with a delay of 7.9 (4.0, 12.0) and 16.1 (0.0, 43.5) months, respectively, between symptom onset and diagnosis. Among the symptomatic cases, the most common presenting symptoms were delayed motor milestones ($n = 81$), hypotonia ($n = 57$), weakness ($n = 49$), and motor regression ($n = 30$). Sixty-three (23.8%) cases required feeding tubes, and ninety-two (34.7%) cases

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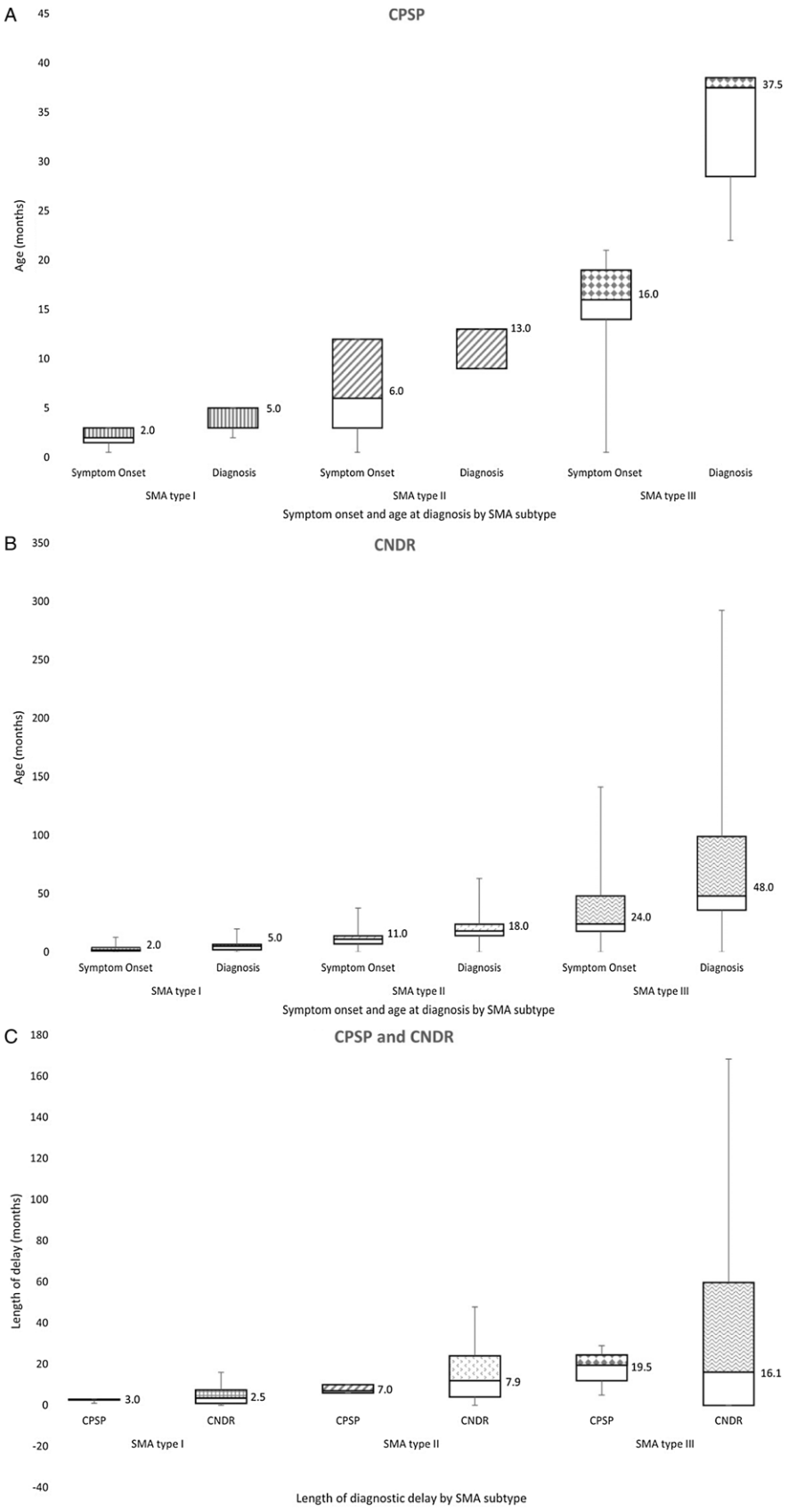

Figure 2: Median age with interquartile range (IQR) in months at symptom onset and diagnosis from CPSP (***a***) and CNDR (***b***) by SMA subtypes, and median length of diagnostic delay with interquartile range (IQR) in months for CPSP and CNDR (***c***) by SMA subtypes. CPSP $n = 19$, CNDR $n = 158$.

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Table 4: Overview of the demographic, clinical characteristics, and treatment patterns in patients with 5q SMA based on data from the CPSP and CNDR

Characteristics	CPSP	CNDR[a]
	n (%)	
Gender	*n* = 19	*n* = 299[b]
Male	12 (63.2)	154 (51.5)
Female	7 (36.8)	139 (46.5)
Unknown/missing	0	6 (2.0)
Family history		*n* = 265
Yes	<5	56 (21.1)
No	15 (78.9)	149 (56.2)
Unknown/Missing	<5	60 (22.6)
SMA type		
Type I	10 (52.6)	59 (19.7)
Type II	<5	126 (42.1)
Type III	5 (26.3)	103 (34.4)
Type IV	0	<5
Unknown	<5	8 (2.7)
Genetic Confirmation		*n* = 246
Genetic test result	19 (100.0)	213 (86.6)
SMN2 copy number		*n* = 265
2	8 (42.1)	45 (17.0)
3	7 (36.8)	110 (41.5)
4+	<5	31 (11.7)
Unknown	<5	79 (29.8)
Most common presenting symptoms[c]		*n* = 208
Hypotonia	13	57
Delayed milestones	11	81
Poor head control	8	15
Weakness (including flaccid and limb weakness)	14	49
Motor regression	DNDC	30
Other	18	34
Median (IQR) of age at symptom onset (months)		*n* = 158
Overall	3.0 (2.0, 13.0)	12.0 (4.0, 20.0); *n* = 158
Type I	2.0 (1.5, 3.0)	2.0 (1.0, 4.0); *n* = 45
Type II	6.0 (3.0, 12.0)	11.0 (7.0, 13.8); *n* = 62
Type III	16.0 (14.0, 19.0)	24.0 (17.8, 48.0); *n* = 48
Type IV	0	204.0 (198.0, 264.0); *n* < 5
Median (IQR) age at diagnosis (months)		*n* = 158
Overall	7.5 (5.0, 22.0)	18.0 (7.1, 37.6); *n* = 158
Type I	5.0 (3.0, 6.0)	5.0 (2.0, 6.5); *n* = 45
Type II	13.0 (9.0, 22.0)	18.0 (14.0, 24.0); *n* = 62
Type III	37.5 (28.5, 41.0)	48.0 (35.9, 99.0); *n* = 48
Type IV	0	384.0 (294.0, 438.0); *n* < 5
Median (IQR) length of diagnostic delay (months)		*n* = 158
Overall	4.0 (3.0, 10.0)	5.0 (1.0, 14.0); *n* = 158
Type I	3.0 (2.5, 3.0)	2.5 (1.0, 4.0); *n* = 45
Type II	7.0 (6.0, 10.0)	7.9 (4.0, 12.0); *n* = 62
Type III	19.5 (12.0, 24.5)	16.1 (0.0, 43.5); *n* = 48

(*Continued*)

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Table 4: (*Continued*)

Characteristics	CPSP	CNDR[a]
Type IV	0	60.0 (36.0, 174.0); $n < 5$
Dysphagia		$n = 265$
Yes	5 (26.3)	60 (22.6)
No	14 (73.7)	172 (64.9)
Unknown/Missing	0	33 (12.5)
Feeding tube use		$n = 265$
Yes	<5	63 (23.8)
No	16 (84.2)	186 (70.2)
Unknown	<5	16 (6.0)
Ventilatory support		$n = 265$
Yes	<5	92 (34.7)
No	16 (84.2)	150 (56.6)
Unknown	<5	23 (8.7)
Scoliosis		$n = 265$
Yes	<5	175 (66.0)
No	18 (94.7)	66 (24.9)
Unknown/Missing	<5	24 (9.1)
Scoliosis surgery		$n = 265$
Yes	0	69 (26.0)
No	19 (100.0)	173 (65.3)
Unknown	0	23 (8.7)
Disease modifying therapy		$n = 265$
Nusinersen	13 (68.4)	123 (46.4)
Risdiplam	<5	27 (10.2)
Onasemnogene abeparvovec	<5	20 (7.5)
None	<5	31 (11.7)
Unknown	<5	64 (24.2)
Followed in multidisciplinary clinics for management of SMA		
Yes	18 (94.7)	DNDC
Number of multidisciplinary clinics being accessed[c]		$n = 168$
Physiotherapy	14	146
Occupational therapy	13	115
Speech therapy	9	64
Dietitian	8	67
Pediatrician	16	95
General practitioner	8	126
Respiratory care	11	90
Respite care	0	46
Palliative care	9	34
Social work	<5	18
Other (including neuromuscular specialist)	18	10

CNDR = Canadian Neuromuscular Disease Registry; CPSP = Canadian Paediatric Surveillance Program; DNDC = data not directly comparable; IQR = Interquartile range (first quartile, third quartile); SMA = spinal muscular atrophy.
Cells with counts smaller than 5 were indicated as < 5 without percentages, per data source reporting requirements.
[a]CNDR data current as of July 1, 2022.
[b]Number of responders from CNDR is 299 unless otherwise specified.
[c]This data element allowed multioption selection by responders, as such, total selection count exceeds total patient count due to ability to make multiple selections per patient. Accordingly, only counts are provided for this variable.

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required respiratory support. Nusinersen was the most common DMT used at the time of reporting ($n = 123$, 46.4%). One-hundred and sixty-eight (56.2%) cases provided information on the multidisciplinary clinics accessed for the management of SMA; the most common of these were physiotherapy, general practitioner, occupational therapy, and pediatrician.

Discussion

5q SMA is a leading genetic cause of infant death and represents a significant healthcare burden in Canada.[20] The recent therapeutic advances with availability of three DMTs and the uptake of SMA newborn screening programs in many provinces including British Columbia, Alberta, Saskatchewan, Manitoba, and Ontario, as well as Yukon, Northwest Territories, and Nunavut, have the potential to drastically changed the prognosis and long-term outcomes for these patients.[21] Information arising from active disease surveillance can help inform strategies to improve the standard of care for individuals living with SMA in Canada.

Our study found variability in the estimated minimum incidence of SMA across the CPSP, CNDR, and molecular genetics laboratories. There are several contributing factors that may explain the differences in the reporting of SMA cases and the corresponding minimum incidence estimates. These factors include geographic variability, timing of reporting to databases, as well as inherent differences in data collection approaches and source populations. Factors such as healthcare accessibility, diagnostic capabilities, and referral patterns likely influence the geographic distribution of reported cases. For example, patients who were diagnosed in clinics outside their province of residence may contribute to the observed variability in reporting across datasets. Second, delay in case reporting by the reporting physicians, delay in data entry, and variations in the frequency of data updates may have resulted in underrepresentation or overrepresentation of SMA cases for a given time period. Finally, the CPSP and CNDR datasets relied on voluntary participation; they yielded lower incidence estimates compared to incidence estimates from molecular genetics laboratories which do not rely on voluntary reporting. Voluntary participation may also have resulted in issues with data completeness and missing information for some of the cases. Furthermore, the voluntary nature of participation also introduces a potential selection bias, particularly toward milder cases, due to reduced life expectancy for those with early onset or severe SMA. The molecular genetics laboratories dataset, while not relying on voluntary participation, pose unique challenges as privacy constraints limit the availability of detailed information for cases within this dataset. These limitations necessitate careful consideration when interpreting the estimates from each of the three data sources.

Published incidence and prevalence estimates of 5q SMA in Canada are currently limited. A study by Chen and colleagues estimated the 5-year (2012–2017) incidence and prevalence of pediatric-onset SMA in Alberta using anonymized data from provincial administrative healthcare databases.[20] Forty-nine incident cases of pediatric-onset SMA were identified, representing a five-year incidence of 1.03 (95% CI: 0.77–1.36) per 100,000 person-years. When stratified by age, those < 6 months of age had the highest five-year incidence at 7.44 (95% CI: 3.57–13.68) per 100,000 person-years. The five-year prevalence of pediatric-onset SMA was 9.97 per 100,000 persons.[20] An Ontario-based study using provincial data from 2003 to 2014 by Rose and colleagues reported lower incidence for SMA in 2014 as 0.03 per 100,000 persons for adults (18–105 years) and < 0.2 per 100,000 children aged 0– < 18 years of age.[22] As well, their prevalence for SMA in 2014 was < 0.2 per 100,000 persons for adults and 0.8 per 100,000 children.[22] Results from these Alberta and Ontario studies differed from those found in this study likely due to their reliance on retrospective province-based administrative health records, whereas our study used prospective data from across Canada. This study also included only genetically confirmed 5q SMA to estimate minimum incidence, which is not possible to confirm when using administrative data; accordingly, estimates derived in the Alberta and Ontario studies may include cases of non-5q SMA or other motor neuron diseases. A recent 20-year (2000–2020) retrospective study by McKee-Muir and colleagues observed an overall SMA incidence of 1 in 11,900 (95% CI: 8,336–17,638) in Maritime Canada, with province-specific estimates of 1 in 22,657 for Nova Scotia, 1 in 8,662 for New Brunswick, and 1 in 5,699 for Prince Edward Island.[23] Results from the Maritime study were similar to incidence estimates found in this study, in part due to their reliance on genomics laboratory data and inclusion of only genetically confirmed cases of SMA.[23]

Several other studies have reported on the incidence and prevalence of pediatric SMA outside of Canada. Similar to the approach employed for this study, Verhaart and colleagues[24] combined data from multiple sources (including genetics laboratories and patient registries) between 2011 and 2015 to estimate the median incidence of genetically confirmed SMA in 18 European countries. They observed an incidence of 11.9 cases (range 6.3–26.7) per 100,000 live births, or approximately 1 in 3,900–16,000 live births.[24] The same study provided a prevalence estimate of SMA ranging from 0.00 to 4.11 cases per 100,000 across SMA subtypes I-III based on data from SMA registries.[24] In another study by Verhaart and colleagues based on review of publications up through December 2016, they found an estimated incidence of approximately 8 in 100,000 (or 1 in 12,000) live births and a prevalence of 1–2 per 100,000 persons for SMA.[9] Notably, most of the studies included in this literature review were conducted prior to 1995 when the *SMN1* gene was identified; thus, many cases were based on clinical diagnosis without genetic confirmation.

SMA newborn screening has recently been implemented in many provinces and territories across Canada, which will help to provide more accurate incidence estimates of SMA by geographic location.[21,25] One recent study by Kernohan and colleagues included data from the first year of SMA newborn screening in Ontario; 139,900 newborns were tested and five were confirmed with SMA, which represented a birth prevalence of 1 in 27,960 live births during 2020–2021.[26] This birth prevalence is in line with the combined rates from CPSP and CNDR observed in the current study of 1 in 25,951. However, monitoring these rates over a longer period of follow-up will be important to accurately assess the birth incidence of SMA in Canada. According to a recent global survey by Dangouloff and colleagues, the overall incidence SMA was estimated to be 1 in 12,757 (range 5,000–28,137) or 7.8 per 100,000 based on 288 cases out of 3,674,277 newborns identified from SMA newborn screening programs in 9 countries.[27]

The variability in incidence and prevalence estimates across studies both within and outside of Canada may be due to differences in period of reporting, data sources used, geographic location, ethnicity/race with variable carrier frequencies, age groups assessed, and estimation methodologies employed.[9,24] Moreover, on March 11, 2020, the World Health Organization declared COVID-19 a global pandemic. Disease screening and surveillance activities were

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known to be impacted by the COVID-19 pandemic.[28,29] Our study was conducted during the height of the COVID-19 pandemic. Despite the potential impact, the minimum incidence rates and prevalence estimates observed in this study are in line with recent publications.

With respect to clinical features and treatment approaches for patients with SMA, the differences observed between the CPSP and CNDR datasets are likely related to the age and composition of the cohort. Specifically, the CPSP can be considered as a young cohort of pediatric patients who were recently diagnosed, with early stages of SMA; the majority (52.6%) had type I disease, with 2 (42.1%) or 3 (36.8%) copies of *SMN2* (see Fig. 1). The CNDR, on the other hand, includes a broader 5q SMA patient population who were identified and diagnosed over a longer period, thus capturing the natural history of the disease. The majority had type II (42.1%) or type III (34.4%) disease; only 19.7% of patients in the CNDR had type I SMA, likely due to reduced life expectancy of these patients before the availability of DMTs and SMA newborn screening.

Despite these differences, there are several key findings that were concordant between these 2 cohorts, including those reporting a family history of SMA, age of symptom onset and diagnosis, median length of diagnostic delay, proportions of patients experiencing dysphagia or respiratory insufficiency, and accessing multidisciplinary clinics for management of SMA as part of standard of care. These multidisciplinary clinics represent a snapshot of the broader network of healthcare resource utilization by patients. As the findings from this study demonstrate, 5q SMA is a severe neuromuscular disease with variable symptom onset and age at presentation. It commonly requires nutritional and/or ventilatory support, scoliosis surgery, multidisciplinary assessments, substantial healthcare resources, and burden of care over time.[30,31] In both CPSP and CNDR data, we observed a significant delay from the time of symptom onset to the time of diagnosis (Fig. 2), which is consistent with the published literature.[32–34] During the start of the study, only Ontario had a pilot SMA newborn screening program, thus the diagnosis of SMA remained delayed for the majority of reported cases during 2020-2021. In addition to causing significant distress for caregivers,[35] the diagnostic delay represents a missed opportunity to maximize the benefits of early treatment.[36,37]

Most affected children in the CPSP received nusinersen as the initial treatment, as negotiations with the pan-Canadian Therapeutic Alliance (pCTA) for public funding of onasemnogene abeparvovec and risdiplam were not concluded until late 2021 and early 2022, respectively.[38,39] We observed that at least 11.7% of SMA patients enrolled in CNDR were not accessing any DMTs; this proportion may be even higher among adult patients. Currently, access to DMTs for 5q SMA remains nonuniform across Canada.[40–45] In addition to regulatory approval by Health Canada, negotiations and coverage decisions depend on health technology assessment (HTA)-based reimbursement recommendations by the Institut National d'Excellence en Santé et en Services Sociaux (INESSS, for the province of Quebec) or by the Canadian Agency for Drugs & Technologies in Health (CADTH, for the rest of Canada), followed by reimbursement decisions by each federal, provincial, and territorial drug plans based on patients' characteristics such as age, ambulatory status, SMA type, *SMN2* copy number, disease duration and severity.[46,47] For instance, apart from Quebec, public funding for nusinersen is recommended for pediatric patients under 18 years of age, but not for adults with SMA.[40,41] As well, *SMN1* gene replacement therapy (onasemnogene abeparvovec) is recommended for pediatric patients 180 days old or younger with SMA; those with 4 copies of *SMN2* (up to 15.7% and 12.0% of patients in the CPSP and CNDR respectively) are not eligible for this treatment based on current Canadian guidelines.[42,43] Future studies should consider examining long-term outcomes based on variable coverage of DMTs for SMA patients across Canada and the associated impact on the natural history of their disease.[48]

The results of this study should be interpreted with consideration of the following limitations. First, the data sources are based on voluntary reporting; this may have led to an underestimation of pediatric 5q SMA cases over the study period, including those living in rural or remote areas and youth transitioning to adult care. Due to Quebec legislation, detailed case information from CPSP could not be collected, and these cases were excluded from detailed data analysis. Additionally, nearly half of the cases reported to the CPSP did not have a corresponding detailed questionnaire completed by the participating physicians; the reason for this missing information is unfortunately unknown despite follow-up efforts by CPSP staff. Furthermore, some of the new pediatric cases of SMA with early onset or severe disease might not be seen by a community pediatrician affiliated with CPSP, or in a CNDR-affiliated clinic, until they were well enough to be discharged from hospital, leading to potential delay in the reporting as well as discrepancy in case numbers when compared with available molecular genetics laboratories' data. Additionally, information bias is possible since surveillance data required extraction from patients' charts and some items were either not available or not collected as part of routine care, and thus may be absent from the surveillance results. There is also a possibility of selection bias in the CNDR due to the process of obtaining informed consent for recruitment; patients who did not provide consent were excluded from the registry. Variability in the number of cases and response rates across the multiple sources in this study could not be verified by data linkage to protect patients' privacy and confidentiality. Finally, only four molecular genetics laboratories from three provinces responded to the online survey request; the results could not be generalized for the rest of Canada and likely led to an underestimation of SMA cases over the study period.

Despite these limitations, this is the first surveillance study to report on the incidence and prevalence of 5q SMA using three independent sources of Canadian data. The CPSP has an extensive network and is a reliable tool for identification and surveillance of children with rare diseases. Similarly, the CNDR continues to expand its reach and has been able to successfully recruit and enroll individuals across Canada based on a close working network of clinicians, affiliated sites, and partnerships with patient organizations. The CNDR also provides in-depth real-world data and longitudinal outcomes for individuals with a variety of neuromuscular diseases, including SMA. Molecular genetics laboratories remain a reliable source of disease estimates; they help to inform trends and changes in disease frequency, especially when combined with newborn screening and genetic counselling. The discrepancies in SMA reporting across the CPSP, CNDR, and molecular genetics laboratories datasets underscore the complexities inherent in studying rare diseases across diverse datasets. Findings from our study further highlight the critical importance for multiple data sources to work collaboratively to gain greater insights into the epidemiology of 5q SMA in Canada.

Conclusions

This study provides estimates on the annual minimum incidence of pediatric 5q SMA using three Canadian-based data sources, as

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well as information on the prevalence, the clinical features, and current therapies for patients with SMA. Newborn screening will become increasingly important in providing population estimates on the incidence of 5q SMA across Canada. As well, access to DMTs will likely impact the prevalence of 5q SMA and ultimately have implications on healthcare planning, resource utilization, quality of life, and the natural history of the disease.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/cjn.2024.1.

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