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Original Article

Epidemiology and Healthcare Resource Utilization of Rett Syndrome in Canada: The Ontario Experience

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ABSTRACT: ***Background:*** Rett Syndrome (RTT) is an X-linked neurodevelopmental disorder, characterized by the gradual loss of motor, verbal and social skills. This study describes the epidemiology and healthcare resource utilization (HCRU) of RTT in Ontario, Canada. ***Methods:*** Rett Syndrome (RTT) cases (≥ one ICD-10-CA code F84.2) were identified utilizing the Institute for Clinical Evaluative Sciences (ICES) data. Incident cases were identified between September 2017 and August 2023, while prevalent cases were captured from April 2002 to August 2023. Prevalent cases identified before September 2017 were indexed on that date. Demographic and clinical characteristics were collected and analyzed descriptively. Prevalence and incidence were calculated. Healthcare resource utilization (HCRU) was analyzed as the number of cases with at least one touchpoint and the number of touchpoints. ***Results:*** In total, 246 RTT cases were indexed; 40% from central Ontario, 95% female, median age 21 years. From September 2017 to August 2023, 57 incident cases and 257 prevalent cases were reported in Ontario. Common comorbidities included developmental disability (85.4%), epilepsy (49.6%) and gastrointestinal symptoms (42.3 %). Most patients had at least one outpatient visit (primary care 96.7%, specialist 86.6%), emergency department visit (76.8%) and inpatient hospitalization (54.5%). During the 5-year follow-up period, most cases (95.1%) had at least one public claim for all-cause medication. Disease-specific medication claims included antibiotics (69.1%) and anti-seizure medications (73.6%). ***Conclusion:*** This study provides population-based estimates of RTT in Ontario. Findings highlight the high burden of illness in RTT in terms of comorbidity prevalence and HCRU. Further research may identify opportunities to improve healthcare outcomes in this population.

RÉSUMÉ: **Le syndrome de Rett au Canada : l'épidémiologie de la maladie et l'utilisation des soins de santé en Ontario**. ***Contexte :*** Le syndrome de Rett (SR) est un trouble neurodéveloppemental, lié au chromosome X, qui se caractérise par une perte progressive des habiletés motrices ainsi que des aptitudes verbales et sociales. L'étude avait pour but de décrire la situation épidémiologique de la maladie ainsi que l'utilisation des soins de santé (USS), en Ontario, au Canada. ***Méthode :*** Le nombre de cas de SR (≥ 1 code F84.2, CIM10CA) a été calculé à l'aide des données de l'Institut de recherche en services de santé (IRSS). Les cas incidents ont été relevés entre septembre 2017 et août 2023, et les cas prévalents, d'avril 2002 à août 2023. Les cas prévalents répertoriés avant septembre 2017 ont été ramenés à la date retenue ce mois-là. Les caractéristiques démographiques et cliniques ont été recueillies, puis ont fait l'objet d'une analyse descriptive. Ont ensuite été calculées la prévalence et l'incidence de la maladie. Quant à l'analyse de l'USS, elle reposait sur le nombre de cas comptant au moins un point de contact et sur le nombre total de ces points de contact. ***Résultats :*** Au total, 246 cas de SR ont été indexés : 40 % provenaient du centre de l'Ontario; il y avait 95 % de personnes de sexe féminin, et l'âge médian s'élevait à 21 ans. De septembre 2017 à août 2023, 57 cas incidents et 257 cas prévalents ont été déclarés en Ontario. Figuraient parmi les affections comorbides courantes la déficience développementale (85,4 %), l'épilepsie (49,6 %) et des symptômes gastro-intestinaux (42,3 %). La plupart des patients comptaient au moins une consultation externe (soins primaires : 96,7 %; soins spécialisés : 86,6 %), une consultation au service des urgences (76,8 %) et une hospitalisation (54,5 %). Au cours de la période de suivi d'une durée de 5 ans, on a relevé, dans la plupart des cas (95,1 %), au moins une demande de remboursement de médicaments, toutes causes confondues, au régime public d'assurance maladie. Quant aux médicaments propres au traitement de la maladie, il y avait des antibiotiques (69,1 %) et des antiépileptiques (73,6 %). ***Conclusion :*** L'étude dresse un tableau estimatif du syndrome de Rett en Ontario, fondé sur la population. D'après les résultats obtenus, le SR impose un lourd tribut en ce qui concerne la prévalence des affections comorbides et l'USS. La poursuite de la recherche pourrait donner lieu à l'amélioration des résultats cliniques dans la population touchée.

Keywords: epidemiology; neurodevelopmental disorders; pediatric neurology; Rett syndrome

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Highlights

- This study describes for the first time the incidence and prevalence of Rett syndrome in Ontario, Canada.
- A substantial disease burden was evidenced by the high prevalence of chronic comorbidities and high rates of healthcare resource utilization.
- The high rates of medication use suggest an urgent need for treatment options.

Introduction

Rett syndrome (RTT) is a rare neurodevelopmental disorder primarily affecting females due to de novo variants in the MECP2 gene located on the X chromosome.[1] The estimated global incidence of RTT is 1 in 10,000 to 15,000 live female births,[1,2] with a prevalence of 1 in 20,000 to 40,000 people.[3] In Canada, limited epidemiological data are available, but a recent study estimated that approximately 600 to 900 people are affected by RTT in Canada.[4]

Following an apparent normal early development, clinical manifestations of RTT such as the development of unique stereotypical hand movements appear during the first 6 to 18 months of age, with an average age at diagnosis of 2.5 years.[3] Initially, there is a period of regression in acquired developmental skills – including the gradual decline and loss of spoken language, social communication, and motor skills – and appearance of other multisystem symptoms, such as seizures/epilepsy, sleep disturbances and impairments in musculoskeletal, cardiac, endocrine and/or gastrointestinal functions.[5,1] Following the disorder onset, a stabilization of clinical symptoms occurs to finally progress into motor and function disability.[6] Despite early onset, the estimated survival rate in over 70% of RTT patients is 45 years of age.[7] Until recently, treatment options for RTT were limited to managing comorbidities and symptoms based on pharmacotherapy (e.g., anti-seizure medications, antibiotics) and rehabilitative therapies (e.g., physical, speech–language, and occupational therapy).[8] Currently, trofinetide has been approved for the treatment of RTT, showing promise for the management of RTT patients.[9–11]

Given that RTT has a progressive nature, patients require lifelong healthcare services, including frequent specialist visits, hospitalizations, home care and long-term care.[2,8] The high healthcare resource utilization (HCRU) incurred by patients with RTT may represent substantial costs to the healthcare system.[2,8] Studies have identified higher HCRU among patients with RTT in specific situations. A survey conducted in Australia identified higher RTT-associated hospitalizations due to respiratory infections,[12,13] whereas retrospective cohort studies identified that surgical correction of scoliosis, seizures/epilepsy, sepsis and gastrointestinal or nutritional problems such as gastrostomy malfunction and constipation were major contributors to hospitalizations and emergency department visits.[14,15] These observations highlight the frequent lifelong comorbidities and medical complications that patients with RTT often experience. A US real-world study found RTT-associated total costs per pediatric female patient to exceed $40,000 USD per year.[8] These costs are reportedly higher than costs for other common neurologic diseases, such as cerebral palsy (CP) ($25,844 USD) and fragile X syndrome ($17,878 USD).[8,16,17] Despite the increased care burden of RTT, there exists limited information on the epidemiology and HCRU of RTT in Canada. This study aims to describe the epidemiology of RTT and the HCRU incurred by patients with RTT in Ontario, Canada, thereby assisting in filling the literature gaps and supporting the future research in this area to improve patient outcomes.

Methods

Study design

This retrospective, observational cohort study was designed to identify RTT cases in Ontario, Canada's largest province by population (approximately 14 million). The study utilized the Institute for Clinical Evaluative Sciences (ICES) administrative datasets, which capture publicly funded healthcare touchpoints and medications for Ontario residents. Encrypted identifier numbers (Ontario Health Insurance Plan [OHIP] numbers) were used by ICES to link patient-level data across multiple healthcare databases to execute longitudinal analyses of cases.

Study population

RTT cases (incident and prevalent) were identified based on the 10th International Classification of Diseases Canadian Version (ICD-10-CA). Cases were included if they had at least one hospitalization record (from the Discharge Abstract Database, DAD) with a diagnosis code of RTT (ICD-10-CA code F84.2). Cases were excluded if (1) they had an invalid OHIP number, (2) were ineligible for OHIP, (3) had missing demographics such as birth date, sex or postal code or (4) died before the index date. The earliest date of diagnosis code record was considered the index date.

Incident cases were identified during the selection period from September 1, 2017, to August 30, 2022. Prevalent cases were identified from April 1, 2002, to August 30, 2022. Prevalent cases identified from April 1, 2002, to August 31, 2017, were accrued and included in the study cohort if they were still alive as of September 1, 2017. For these cases, the index date was assigned as September 1, 2017. The follow-up period was considered from the index date until the first instance of any of the following events: date of death, loss to follow-up in the ICES datasets (including loss of OHIP eligibility), most recent data availability or end of the study period (i.e., August 30, 2023). Study time periods are illustrated in Figure 1.

Variables

Demographic information was analyzed at index date from different data sources. Sex and age groups were collected from the Registered Persons Database (RPDB). Neighborhood Level Income Quintile, Local Health Integration Network of residence and rurality were estimated based on residential address using the Postal Code Conversion File Plus.[18] Comorbidities of interest, as listed in Table 2 were captured either through ICD-10-CA codes or established ICES cohorts at any time prior to the index and during the follow-up period. All-cause mortality during the study period was estimated from the RPDB.

Healthcare resource utilization (HCRU) was captured during the follow-up period from different data sources. Hospital admissions were retrieved from the DAD, and emergency department visits from the National Ambulatory Care Reporting System. Patient claims for physician services, including visits to outpatient specialists such as neurologists, were collected from the OHIP database. Prescription drug claims, including all-cause and disease-specific drugs, dispensed under the Ontario provincial public drug program, came from the Ontario Drug Benefit

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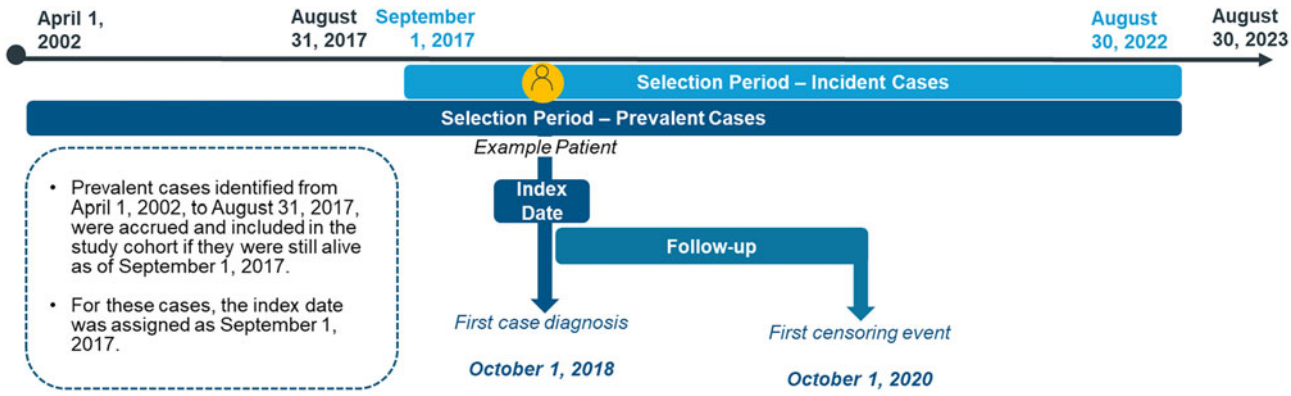


Figure 1. Study time periods.

Table 1. Disease-specific drug claims definition

Category	Examples of drug claims
Centrally acting medication	Clonidine, guanfacine
Anti-seizure medication	Carbamazepine, phenobarbital, diazepam, lorazepam, clonazepam, phenytoin, ethosuximide, lamotrigine, gabapentin
Anti-psychotics	Chlorpromazine, perphenazine, haloperidol, risperidone
Anti-spastic agents	Baclofen, botulinum toxin, cyclobenzaprine, methocarbamol, dantrolene
Corticosteroids	Prednisone, hydrocortisone, dexamethasone
H2 Antagonists	Cimetidine, famotidine, nizatidine
PPI	Omeprazole, lansoprazole, pantoprazole
Anti-depressants	Fluoxetine, fluvoxamine, paroxetine, sertraline
Anti-asthma and bronchodilators	Mometasone, budesonide, beclomethasone, fluticasone, montelukast, albuterol
Antibiotics	Cephalosporines, nitrofurantoin, lyncomycine, penicillin, glycopeptides.

Abbreviations: H2 = Histamine-2 Receptor; PPI = proton pump inhibitors.

database. Disease-specific drug categories further included centrally acting medications, anti-seizure medications, anti-psychotics, anti-spasticity medications, corticosteroids, histamine 2-receptor antagonists, proton pump inhibitors, anti-depressants, anti-asthma/bronchodilators and antibiotics. Drug categories are further detailed in Table 1.

Analysis

Demographics, clinical characteristics, prevalence of comorbidities and all-cause mortality were analyzed using numbers and percentages for categorical variables and mean (SD) and median (IQR) for continuous variables.

Incidence and prevalence of RTT in Ontario were analyzed as the annual new number and annual number of RTT cases identified in the study cohort and reported per 10,000 births and people, respectively, using population estimates for each corresponding year from Statistics Canada.[19,20] Incidence and prevalence of RTT were assessed for different 2-year follow-up periods, including 2017–2019, 2019–2021 and 2021–2023.

Healthcare resource utilization (HCRU), including prescription drug claims, was analyzed as the number and proportion of cases with at least one touchpoint per HCRU category, and as the total number of touchpoints observed during the follow-up period. Average visit length was calculated in days and reported as the mean (SD), median (IQR), minimum and maximum.

Results based on less than six cases were masked as "1–5" for privacy reasons based on standard ICES policies. All analyses were conducted using SAS version 9.3 or higher (SAS Institute, Cary, NC). Missing data were reported as their own category. This study was approved by Advarra IRB Services (IRB approval Pro00076448). Analyses were conducted by an ICES analyst using the analysis plan developed by the study authors. Study authors received only aggregate data.

Results

A total of 246 RTT cases met the study inclusion criteria. The included RTT cases were predominantly female (95.1%), had a median (IQR) age of 21 years (11–33) and a majority (40%) resided in central Ontario (which includes Toronto where one of the specialized Rett clinics is located). The most common comorbidities among RTT cases included developmental disabilities (85.4%), epilepsy (49.6%) and gastrointestinal comorbidities (42.3%). Participant characteristics are summarized in Table 2.

From September 2017 to August 2023, in Ontario there were a total of 57 incident RTT cases with annual rates ranging from 1.13–1.69 cases per 10,000 births (1.69 cases per 10,000 births from September 2017 to August 2019, 1.13 cases per 10,000 births from September 2019 to August 2021 and 1.22 cases per 10,000 births from September 2021 to August 2023). The number of prevalent RTT cases in Ontario, accrued from 2002, was 257 (0.15 cases per 10,000 people from September 2017 to August 2019, 0.15 cases per 10,000 people from September 2019 to August 2021 and 0.16 per 10,000 people from September 2021 to August 2023). Death from all causes during the study period was 11.8% (29 RTT cases). Incident and prevalent cases are summarized in Figure 2.

During the 5-year follow-up period, in terms of HCRU, most RTT cases had at least one outpatient primary care visit (96.7%) and outpatient specialist visit (86.6%), which were either in-office (97.2%) or by phone (88.6%). The most frequently visited specialists included neurologists (56.1%), followed by orthopedic surgeons (31.7%) and anesthesiologists (30.5%). Most cases also had at least one emergency department visit (76.8%) and inpatient

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Table 2. RTT cases characteristics

Patient characteristics	Study Cohort ($n = 246$)
Age at index (years)	
Mean (SD)	22.9 (14.9)
Median (IQR)	21 (11, 33)
Age Group at Index (years), *n* (%)	
0–4	21 (8.5%)
5–10	35 (14.2%)
11–15	25 (10.2%)
16–20	85 (34.6%)
21–40	40 (16.3%)
41+	40 (16.3%)
Sex, *n* (%)	
Female	234 (95.1%)
Neighborhood Income Quintile, *n* (%)	
Q1, Lowest	39 (15.9%)
Q2	54 (22.0%)
Q3	47 (19.1%)
Q4	43 (17.5%)
Q5, Highest	63 (25.6%)
LHIN, *n* (%)	
Central	33 (13.4%)
Central East	33 (13.4%)
Central West	16 (6.5%)
Champlain†	24 (9.8%)
Erie St Clair	15 (6.1%)
Hamilton Niagara Haldimand Brant	24 (9.8%)
Mississauga Halton	13 (5.3%)
North East	13 (5.3%)
North Simcoe Muskoka	*1–5
North West	*1–5
South East	16 (6.5%)
South West†	29 (11.8%)
Toronto Central†	18 (7.3%)
Waterloo Wellington	6 (2.4%)
Comorbidity, *n* (%)‡	
Autism	15 (6.1%)
Breathing Disorder (any)	58 (23.6%)
Asthma	53 (21.5%)
Chronic Obstruction Pulmonary Disease	6 (2.4%)
Cardiac/Vascular/Blood Problem (any)	12 (4.9%)
Atrial Fibrillation	0 (0.0%)
Congestive Heart Failure	*1–5
Hypertension	*6–10
Ischemic Heart Disease	0 (0.0%)
Transient Ischemic Attack History	0 (0.0%)
Sickle Cell Anemia	*1–5
Cerebral Palsy	26 (10.6%)
Developmental Disability	210 (85.4%)
Epilepsy	122 (49.6%)
Scoliosis	45 (18.3%)
Children with medical complexity - neurologic and neuromuscular	235 (95.5%)
Children with medical complexity - metabolic	36 (14.6%)
Children with medical complexity - other congenital or genetic defect	76 (30.9%)
Children with medical complexity - gastrointestinal	104 (42.3%)
Children with medical complexity - renal and urologic	22 (8.9%)

Abbreviations: RTT = Rett syndrome; SD = standard deviation; IQR = Interquartile; LHIN = Local Health Integration Network.
*1–5: N values < 6 have been masked.
†LHINs were a specialized Rett clinic is located.
‡Comorbidity categories are not mutually exclusive and may not add to 100%.

hospitalization (54.5%). The mean length of stay of inpatient hospitalizations was 7.9 ± 18.09 days, with a maximum stay of 294 days. In the same follow-up period, most cases (95.1%) had at least one public claim for all-cause medication. In the entire cohort, there was a total of 80,424 all-cause drug claims, representing a median of 114 claims per patient (median of 2 claims per patient per day). Similarly, many cases (90.7%) claimed at least one disease-specific medication, with a total of 50,581 disease-specific drug claims. Disease-specific drug claims were predominantly for antibiotics (69.1%) and anti-seizure medications (73.6%). Healthcare resource utilization (HCRU) is summarized in Table 3.

Discussion

This retrospective real-world study utilizing administrative claims data is the first study in Canada to provide population-based estimates of RTT and its associated burden of illness. Findings from this study showed that the annual incidence rates of RTT from 2017 to 2023 were relatively low (1.13–1.69 cases per 10,000 births per year). Meanwhile, as expected, the annual prevalence rates (0.15–0.16 cases per 10,000 people) remained stable over time. Additionally, these study findings suggest a substantial disease burden in RTT cases in Ontario, Canada, as evidenced by the high prevalence of chronic serious comorbidities and high rates of HCRU. Most cases claimed at least one outpatient primary care visit (96.7%), specialist visit (86.6%), emergency visit (76.8%) and/or inpatient hospitalization (54.5%). Likewise, this study found high rates of medication claims, with 95.1% of RTT cases claiming at least one medication.

The baseline population demographics and prevalence of comorbidities in the current study are aligned with previously published data from North America. A recent study from the US using similar real-world settings data reported that RTT predominantly affects females with a mean age of 20 years. Incident and prevalent RTT cases found in Ontario were low and are comparable to previous non-Canadian epidemiological estimates. For example, a

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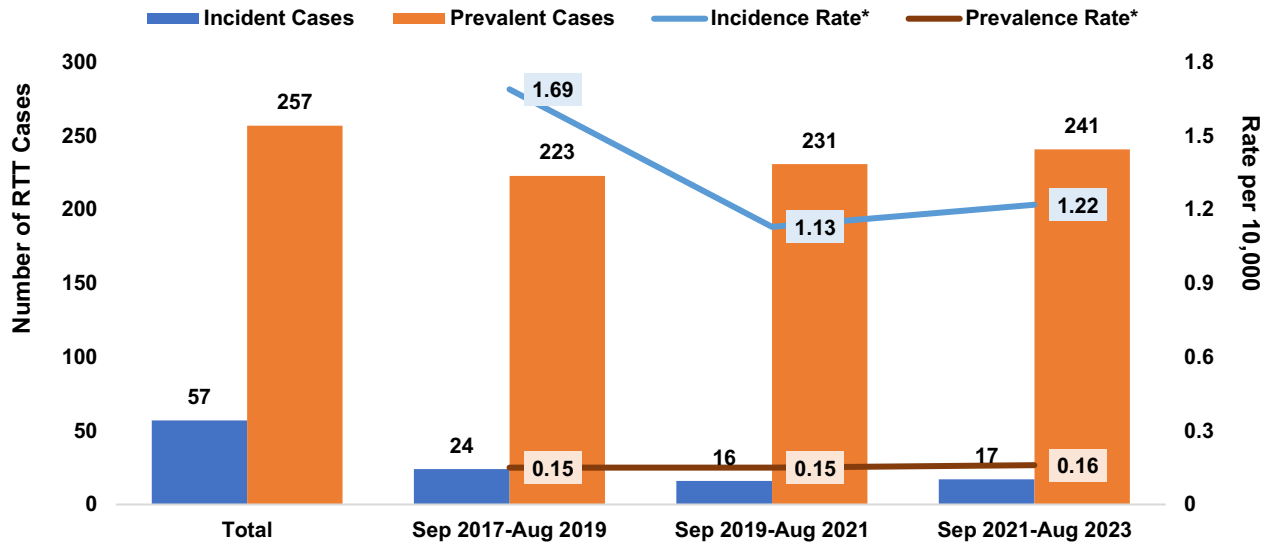


Figure 2. Incidence and prevalence of RTT in Ontario, Canada. Abbreviations: RTT = Rett syndrome. *Incidence rate per 10,000 births, using Statistics Canada Birth Rates; Prevalence rate per 10,000 people, using Statistics Canada Population Rates.

US study found annual incidence proportion estimates of 0.34 and 0.23 per 10,000 people in 2018 and 2019, respectively,[8] while prevalence estimates ranged from 0.30 to 0.32 per 10,000 people.[8] However, a global systematic review showed higher prevalence trends, with a pooled prevalence estimate of 0.71 per 10,000 females. The higher prevalence trends observed in the systematic review were mainly driven by the varying ascertainment methods of each study.[5] Overall, prevalence estimates are influenced by disease incidence and disease chronicity and survival. Studies have found that deaths among RTT cases usually occur before age 45.[7] Given the known low incidence of RTT, its progressive nature and that most of the RTT cases were identified in the second decade of life, it is expected that prevalence estimates were low and stable over the study period.

Aligned with our findings, RTT has been associated with high rates of comorbid conditions, including epilepsy (52.1%), gastrointestinal and nutritional disorders (41.9%) and orthopedic conditions (34.6%), which are known for being major contributors to HCRU, particularly to hospital admissions, emergency department visits and surgical procedures such as gastrostomies and orthopedic surgeries.[14,15,12,8] When compared to the general population in Canada, RTT cases lived proportionally with more frequent quality-of-life-impacting comorbidities, such as developmental disability (85.4%) and epilepsy (49.6%). As of 2022, 13% of Canadians aged 1–19 years lived with epilepsy from different causes,[21] and only 1.5% of the total Canadian population (youth aged 15–24 years - 20.1%) lived with a developmental disability.[22] These findings suggest that RTT cases experience more lifelong comorbidities that impact quality of life and result in multiple clinical complications and disabilities (e.g., reduced mobility, poor oromotor control), requiring increased and prolonged HCRU.

Few studies have explored the HCRU incurred by patients with RTT. A US study found an all-cause HCRU of 3.01 visits per person-month, mainly driven by outpatient services (0.7 ± 2.4),[8] similar to the findings in this study. Moreover, HCRU incurred by patients with other neurological diseases appears similar to our results. A US study on HCRU found that the occurrence of outpatient visits in patients with CP was similarly high (96.7–97.2% RTT; 97.5% CP).[17] However, when compared to CP HCRU, emergency department visits (76.8% RTT; 38.4% CP) and inpatient visits (54.5% RTT; 23.7% CP) were descriptively higher in patients with RTT.[17] Although the differences between diseases and study designs make comparisons challenging, these findings may suggest a high disease burden among RTT cases. RTT is associated with multisystem symptoms and comorbidities such as seizures/epilepsy and gastrointestinal affections that often require acute HCRU due to common medical complications (e.g., infections, aspiration). Nonetheless, multisystemic comorbidities often require long-term supportive therapy such as feeding assistance or orthopedic surgery for scoliosis correction.[8] Moreover, a Canadian study showed that the mean per capita total costs of CP patients were higher when compared with their counterparts who do not live with the condition, with the greater differences in costs observed in those cases < 15 years old.[23] The high rates of medication claims found in this study may correspond to an increased frequency of dispensing medications due to regional or institutional practicing and dispensing requirements for certain medications. Examples of these include weekly dispensing policies in long-term and group care homes, or daily drug dispensing under government programs for specific categories of medications (e.g., anti-seizure medication, anti-depressants) often used in patients with neurological conditions, including RTT.[1,8] The high rates of antibiotics and anti-seizure medication used in this study align with the high clinical burden of illness observed in RTT cases as reflected by the increased comorbidity prevalence. Given that the current treatment options for RTT are limited to the management of symptoms or associated complications (e.g., infections, seizures, gastrointestinal symptoms), findings from this study suggest an urgent need for treatment options for RTT.[8]

Some limitations should be considered when interpreting the results of this study. First, the administrative claims data used for this study were generated from financial transactions for services and drugs received by patients. As such, only cases accessing healthcare services were captured and incidence and prevalence estimates may potentially be underestimated. This may be especially true among pediatric and adolescent populations (in early disease stages), as illustrated by the low number of cases in these age groups. Second, the use of claims data may lead to measurement errors common to administrative databases, such as possible inaccuracy of diagnostic

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Table 3. Healthcare resource utilization (HCRU) among RTT cases during the follow-up period

	Study Cohort ($n = 246$)	
	Cases with at least one visit/claim, *n* (%)	**Total number of visits/claims, *n***
Visit type		
Outpatient primary care	238 (96.7)	5,249
Outpatient specialists	213 (86.6)	3,465
Outpatient neurology	138 (56.1)	927
Outpatient anesthesia	75 (30.5)	497
Outpatient orthopedic surgery	78 (31.7)	348
Outpatient physical medicine	58 (23.6)	270
Outpatient otolaryngology	48 (19.5)	148
Outpatient internal medicine	43 (17.5)	139
Outpatient respiratory disease	29 (11.8)	138
Outpatient ophthalmology	51 (20.7)	119
Allied health	*1–5	40
Emergency department visits	189 (76.8)	1,003
Other ambulatory services	85 (34.6)	181
Inpatient hospitalizations	134 (54.5)	443
Average visit length (days)		
Mean (SD)	–	7.94 (18.09)
Median	–	3 (2–8)
Min–Max	–	1– 294
Days in hospital for the total cohort	–	3,510
Visit location		
Any outpatient visits - Home	37 (15.0)	317
Any outpatient visits - Office	239 (97.2)	4,907
Any outpatient visits - Phone	218 (88.6)	2,877
Any outpatient visits - Long-term Care	12 (4.9)	613
Drug claims		
All-cause drug claims	234 (95.1)	80,424
Disease-specific drug claims	223 (90.7)	50,851
Centrally acting medication	14 (5.7)	226
Anti-seizure medication	181 (73.6)	30,926
Anti-psychotics	36 (14.6)	5,131
Anti-spastic agents	33 (13.4)	1,847
Corticosteroids	62 (25.2)	396
H2 Antagonists	8 (3.3)	143
PPI	76 (30.9)	6,656
Anti-depressants	28 (11.4)	2,899
Anti-asthma and bronchodilators	69 (28.0)	888
Antibiotics	170 (69.1)	1,733

Abbreviations: RTT = Rett syndrome; SD = standard deviation; H2 = Histamine-2 Receptor; PPI = proton pump inhibitors.
*1–5: N values < 6 have been masked.

and procedural codes. As such, the measured comorbidities are not medically confirmed diagnoses. However, given the rare nature of RTT, it is unlikely that any claim with diagnosis codes of interest was inaccurately used. Third, the presence of a record for prescribed or dispensed medication does not indicate that the medication was taken as prescribed. Finally, the data presented in this study are specific to Ontario, and although they may be extrapolated to reflect RTT epidemiology in other Canadian provinces and territories, the significant differences across these populations limit these analyses. Therefore, the generalizability of these results poses a limitation.

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Future research into exploring the epidemiology of RTT in other provinces of Canada will further facilitate the understanding of this complex neurodevelopmental disease within the country. Moreover, future longitudinal studies may assess treatment patterns, specifically the short- and long-term impact of novel pharmacological treatments, in terms of their impact on clinical burden, HCRU and costs, alongside survival.

Conclusion

In conclusion, this study describes for the first time the incidence and prevalence of RTT, comorbidity burden and HCRU incurred by RTT cases in Ontario, Canada. By leveraging a comprehensive set of administrative claims data from the country's most populous province, we provide a robust overview of the RTT disease journey. Although administrative claims data have different considerations, their inclusion of all individuals covered by public health insurance enables a population-based perspective—addressing a key knowledge gap in Canadian literature. Findings from this study highlight the high burden of illness of RTT, particularly in terms of comorbidity prevalence and HCRU, including the reliance on medications for the short-term management of symptoms, when descriptively compared with the general population and other neurological conditions. Together, our findings underscore the urgent need for treatment options that improve clinical management of the multiple multisystem symptoms and comorbidities that affect patients with RTT. Further longitudinal research should explore epidemiological trends, treatment patterns – including the use of novel therapies – and the broader impact of RTT on HCRU and healthcare costs to identify opportunities to improve healthcare outcomes in this population.

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