Trends and Predictors of *Clostridium difficile* Infection among Children: A Canadian Population-Based Study

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Objective To assess time trends in *Clostridium difficile* infection (CDI) rates, and predictors of CDIs, including recurrent CDIs, in children.

Study design Data were extracted from Manitoba Health Provider Claims, and other population registry datasets from 2005 to 2015. CDI was identified from the Manitoba Health Public Health Branch Epidemiology and Surveillance population-based laboratory-confirmed CDI dataset. Children aged 2-17 years with CDI were matched by age, sex, area of residence, and duration of residence in Manitoba with children without CDI. The rates and time trends of CDIs using previously recommended definitions were determined. Predictors of CDI subtypes were determined using multivariable logistic regression models. Cox regression analysis was used to assess for the potential predictors of recurrent CDI.

Results Children with and without CDI were followed for 828 and 2753 persons-years, respectively. The overall CDI rate during the study period was 7.8 per 100 000 person-years. There was no significant change in CDI rates over the observation period. Comorbid conditions, more prevalent among children with CDI than matched controls, included Hirschsprung disease ($P < .001$) and inflammatory bowel disease ($P < .0001$). Recurrent CDIs (>2 occurrences) were responsible for 10% of CDI episodes (range, 2-6 infections). Predictors of recurrence included malignancy (hazard ratio, 3.0, 95% CI, 1.1-8.8), diabetes (hazard ratio, 4.8; 95% CI, 1.1-21.4), and neurodegenerative diseases (hazard ratio, 8.4; 95% CI, 1.9-37.5).

Conclusions The incidence of CDI is stable among children in Manitoba. Children with Hirschsprung disease and inflammatory bowel disease are more susceptible to CDI, and those with malignancy, diabetes. and neurodegenerative disorders are more likely to develop recurrent CDI. *(J Pediatr 2019;206:20-5).*

Clostridium difficile causes a wide spectrum of clinical illness, from asymptomatic colonization and mild diarrhea to pseudomembranous colitis and toxic megacolon. Infants acquire *C difficile* in the first few months of life, with the prevalence of colonization without symptoms reported to be as high as 73% by 6 months of age.[1] Detection of both toxigenic and nontoxigenic *C difficile* strains decreases rapidly during the second and third years, and by the time children reach 2-3 years of age, *C difficile* is detected in 0%-3% of children without diarrhea, which is similar to that in adults.[1,2]

There has been a steady increase in the incidence of *C difficile* infection (CDI) reported over the last few decades.[3-5] Moreover, the reported severity of CDI also has increased, with higher case-fatality and increased colectomy rates.[3-5] The rate of CDI-related hospitalizations in children nearly doubled in the US between 1997 and 2006, from 7.24 to 12.8 per 10 000 hospitalizations.[3] However, most prior studies on the incidence of CDI in children were hospital based, and used single institution databases or *International Classification of Diseases* (ICD) codes in administrative health/hospital discharge databases. We have recently reported limited accuracy of the ICD codes in the hospital discharge databases to identify CDI cases: We reported that 30% of laboratory detected cases of CDI in hospitals may not be identified by using an ICD-10 CDI code in hospital discharge abstracts.[6]

In a study from Manitoba, Canada, Lambert et al identified 1006 incident laboratory-confirmed CDI cases over 1 year with >51% of cases associated with healthcare facilities and 27% acquired in the community. The provincial rate of community-associated CDI was 23.4 per 100 000 person years. For those who were

CDI	*C difficile* infection
HCF	Healthcare facility
IBD	Inflammatory bowel disease
ICD	*International Classification of Diseases*
MH	Manitoba Health, Seniors, and Active Living
SEFI	Socioeconomic Factor Index

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younger than the age of 19 years, community-associated CDI was more common that healthcare facility (HCF)-associated CDI.[7] However, this study did not clearly characterize CDI in the pediatric age group because cases of CDI were examined over a period of only 1 year. In addition, the study included children <2 years of age, who may have asymptomatic colonization. Consequently, in a population-based study of laboratory confirmed CDI cases, we aimed to examine the time trends of rates of CDIs in children 2-17 years of age in the province of Manitoba from 2005 to 2015, and the predictors of CDI and recurrent CDI.

Methods

Manitoba is a central Canadian province with a relatively stable population (1.3 million in 2016). Manitoba Health, Seniors, and Active Living (MH) is a publicly funded department within the Government of Manitoba that provides a comprehensive universal health insurance to all residents of Manitoba. There is minimal nonparticipation because residents do not pay premiums to register for insured benefits. MH maintains several electronic administrative databases to monitor the services provided and to reimburse healthcare providers. The accuracy and comprehensiveness of these databases have been established previously.[8] The MH hospitalization discharge database records all admissions and discharges from Manitoba hospitals. The MH provider claims database records all visits with healthcare providers and services provided by private laboratories. The Drug Programs Information Network database records the dispensation of outpatient prescription drugs from 1995. The Population Registry includes demographic, vital status, and migration status data of all residents in the province. Individual records in these administrative databases can be reliably linked from 1984 onward using a unique personal health identification number assigned to every Manitoba resident.

In this study, CDI was identified from a population-based laboratory confirmed CDI dataset, namely, the Manitoba Health Public Health Branch Epidemiology and Surveillance Unit CDI database, which records all cases of CDI in the province since 2005. Provincial legislation mandates reporting of all confirmed CDI cases to this surveillance unit from the 6 provincial laboratories that perform tests for CDI. All CDI cases were diagnosed on the basis of positive laboratory test results for *C difficile* toxin. A diagnosis of CDI was made if either the enzyme immunoassay Triage test yielded a positive result for the enzyme glutamate dehydrogenase, and then toxin A was detected in the Triage test, or there was a positive result for glutamate dehydrogenase but not toxin A, and then in vitro cytopathic effect of sterile stool filtrate was detected, with neutralization by specific antitoxin.[7] Since May 2013, a polymerase chain reaction assay has been used to confirm the presence of toxin-producing *C difficile*.[6] Importantly, to avoid detecting asymptomatic carriers, stool samples must be watery/loose to be accepted for *C difficile* examination by any of the laboratories in Manitoba.

In this study, children aged 2-17 years with CDI were matched (≤5 matches per CDI case) to children without CDI, based on age (±5 years), sex, 3-digit postal code of residence, and duration of public health insurance coverage before the index date (defined as date of CDI diagnosis based on the stool sample collection date). All study participants were residents of Manitoba for ≤1 year before the index date, to allow determination of medical conditions, drug dispensation history, and prior CDIs from the datasets used.

The study protocol was approved by the local Health Research Ethics Board. All authors had access to the study data and had reviewed and approved the final manuscript.

Study Measures and Definitions

Rates and time trends of CDIs (including HCF [hospital-onset]-associated CDI, community-associated CDI, community-onset HCF-associated CDI, incident CDI, recurrent CDI, and indeterminate CDIs, all defined using previously recommended definitions) were determined.[6] These definitions were consistent throughout the study period. HCF-associated CDI was ascertained based on toxin-positive specimen collected >48 hours after admission to a HCF and before discharge. An individual with community-onset, HCF-associated CDI was defined as one who had a toxin-positive specimen collected while in the community or within 48 hours after admission to a HCF, provided the individual had been discharged from a HCF <4 weeks prior. An individual with community-associated CDI was defined as one who had a toxin-positive specimen collected while in the community or within 48 hours after admission to a HCF, provided the individual either had never been in a HCF or was discharged from a HCF >12 weeks before CDI onset. Indeterminate CDIs were defined as those that did not fit in any of the previous classifications.

An incident case of CDI was defined by a positive specimen result >8 weeks after a previous positive result or by the absence of a previous positive result. A recurrent case of CDI was characterized by a positive specimen result 2 to <8 weeks from the last positive result. A toxin-positive result within 2 weeks of the previous positive result was considered a confirmation of the initial positive result[7] and was not included in the study.

We used the ambulatory care and hospital admission diagnoses within the year before the index date to determine the Charlson Comorbidity Index score.[9] Socioeconomic status was assigned based on the neighborhood of residence on the index date using the Socioeconomic Factor Index (SEFI), a previously validated residential area-level measure based on Statistics Canada Census data.[10] A lower SEFI score indicates a more favorable socioeconomic status. Diabetes cases were ascertained using a previously validated administrative data definition (1 hospital discharge abstract or 2 physician claims for ambulatory care within a 3-year period with a diagnosis of diabetes ICD-9-CM code 250 or *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*, Canada (codes E10-E14).[11]

Statistical Analyses

Joinpoint analysis (Joinpoint 4.2, Statistical Methodology and Applications Branch, National Cancer Institute, Bethesda,

Maryland) was used to test time trends for rates of different forms of CDIs between 2005 and 2015 as well as change in CDI with age. Time trends were expressed as annual percent change in rates with 95% CI. Change with age was expressed as year percent change with 95% CI.

Patients with and without CDI were described and compared using the Fisher exact test for dichotomous measures, the χ^2 test of independence for multicategorical measures and the Wilcoxon rank-sum test for continuous variables. These 2 groups were also compared using stratified logistic analyses. Cox proportional hazards regression models with single predictors were used to examine recurrence risk within the CDI group; covariates included age, sex, SEFI, overall comorbidity burden, as determined from the average number of healthcare visits in the year before incident CDI and Charlson Comorbidity Index score (and in a separate model specific comorbid medical conditions (such as inflammatory bowel disease [IBD]) and medications used in the 12 months before the index date.

Results

Over the observation period, 277 CDIs in children and young adults were identified and matched with 1314 controls without CDI. After excluding those who had CDI before the age of 2 years, 193 incident CDIs from 162 children (age 2-17 years, 47% males) were identified. Children with and without CDI were followed for 828 and 2753 persons-years, respectively. The median age for children with CDI was 10 years. CDIs were community acquired in 51%, and 18.7% were HCF associated, and 15% were community-onset, HCF-associated CDI.

Time Trends of Rates and Predictors of CDIs

There was no significant change in CDI rates over the observation time period. The overall infection rate over the study period was 7 per 100 000 person-years (95% CI, 6-8) with relatively stable rates over the 10-year period (**Figure 1**). CDI rates among boys and girls were not significantly different at 6 and 7 per 100 000 person-years, respectively ($P = .32$) (**Figure 1**).

The annual percentage change in CDI incidence was 1% (95% CI, 5-9; $P = .64$), which was not statistically significant.

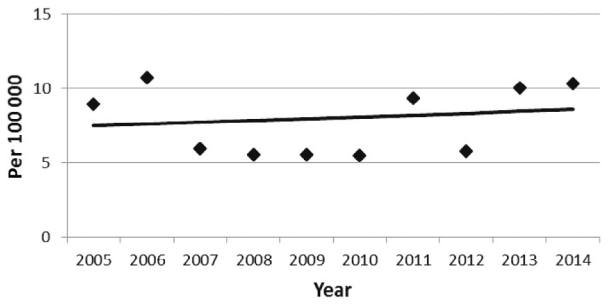

Figure 1. CDI rate among children 2-17 years of age between 2005 and 2015.

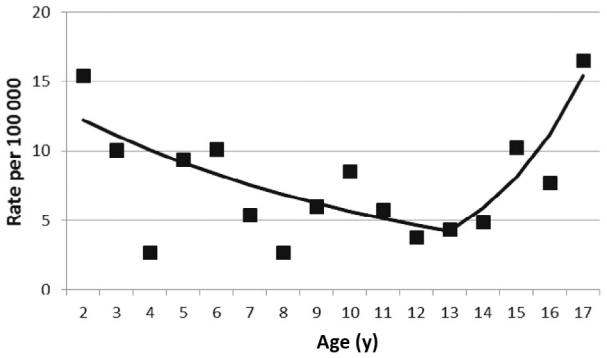

Figure 2. CDI rate among different age groups (2-17 years).

However, there was a significant difference in CDI incidence between age groups (ie, age distribution was U-shaped) with declining rates between ages of 2 and 12 years and increasing infection rates between the ages of 13 and 17 years (**Figure 2**). The overall yearly percent changes between the ages of 2 to <13 years and 13-17 years were -9% ($P = .02$) and 37% ($P = .06$), respectively.

Overall case fatality was significantly higher in children with CDI (10%) compared with controls (no fatalities) ($P < .0001$). No colectomy was recorded in CDI cases or controls during the study period. Children with CDI had significantly greater number of outpatient clinic visits (18% vs 2% in controls; $P < .001$) and hospitalizations (39% vs 1% in controls; $P < .0001$) in the year before CDI diagnosis. Comorbid conditions that were significantly more prevalent among those with CDI compared with controls included chronic neurodegenerative disease ($P < .001$), cardiovascular disease ($P = .02$), liver disease ($P < .0001$), kidney disease ($P < .0001$), diabetes ($P < .0001$), malignancy ($P < .0001$), Hirschsprung disease ($P < .001$), and IBD ($P < .0001$), but not pulmonary disease or HIV infection. There was no significant difference in SEFI between patients and controls (**Table I**).

Recurrent CDI

Recurrent CDIs (range, 2-6 infections) were responsible for 10.4% of CDI episodes. There was no difference in the proportion of CDI episodes that were recurrent in the earlier versus later part of the study time period (ie, recurrence rate between 2005 and 2009 was 9% and between 2010 and 2015, was 11%; $P = .8$). Of the CDI cases, 15% were recurrent among those aged 13-17, compared with 7% in children aged 2-12 years, but the difference was not statistically significant ($P = .14$).

Independent predictors of recurrence (**Table II**) included malignancy (hazard ratio [HR], 3; 95% CI, 1-8), diabetes (HR, 4; 95% CI, 1-21), chronic liver disease (HR, 7; 95% CI, 2-27), chronic kidney disease (HR, 5; 95% CI, 1-17), neurodegenerative diseases (HR, 8; 95% CI, 2-37), and exposure to antibiotics in the previous 3 months before CDI. Recurrent CDI was more likely to occur following CDI in HCF than community (HR, 7; 95% CI, 2-26).

Table I. Factors associated with CDI among children of Manitoba between 2005 and 2015

	Case	Control	*P* value
n	193	615	
Age at CDI diagnosis			.45
Median (IQR)	10 (5-15)	9	
Q1	5	6	
Q3	15	13	
SEFI			.88
n	192	612	
Median	0.01	−0.004	
Q1	−0.52	−0.54	
Q3	0.52	0.58	
Number of ambulatory care visits in the previous year			<.0001
Median	13	2	
Q1	6	1	
Q3	46	5	
Males (%)	47.7	48.6	.87
IBD (%)	3.1	0	.0002
Type of CDIs (%)			
1. HCF	18.7		
2. Community, HCF-associated	15.5		
3. Community	51.8		
4. Indeterminate	14		
Recurrent CDI (%)	10.4		

Discussion

Using a laboratory-based CDI dataset and a well-characterized, heterogeneous population, we determined that there has been no change in the incidence of CDI between 2005 and 2015. We also found that community-acquired CDI is responsible for a greater proportion of Canadian pediatric CDI cases than has been reported previously.

Table II. Cox proportional regression analysis for factors associated with recurrent CDIs among children of Manitoba 2005-2015

Predictor	*P* value	Hazard ratio	95% CI limit
Age (<13 years vs >13 years)	.17	0.5	0.2-1.4
Male vs female	.6	0.7	0.3-2.1
SEFI	.9	1.0	0.6-1.6
Ambulatory care > median vs less	.02	4.3	1.2-15.3
Comorbid conditions (components of Charlson Index)			
Neurodegenerative	.005	8.4	1.9-37.5
Chronic pulmonary	.68	1.4	0.3-6.1
Renal disease	.003	5.6	1.8-17.8
Liver disease	.002	7.6	2.1-27.1
Cancer	.04	3.0	1.0-8.8
Diabetes	.04	4.8	1.1-21.4
Type of CDI			
HCF associated	.002	7.4	2.1-26.4
Indeterminant	.60	1.9	0.2-17.7
Community		Reference	
Corticosteroids use in the year before initial CDI	.5	1.6	0.5-5.6
Antibiotics dispensations in 90 days before initial CDIs	<.0001	6.5	2.0-22.6

There are no previous studies on the epidemiology of CDIs among Canadian children. Our results are different from those reported in the studies from the US that documented increasing CDI rates among hospitalized children. Nonetheless, the majority of those studies were hospital based rather than population based, with high risk of referral and hospitalization bias. In a population-based study of CDI in pediatric residents (aged 0-18 years) of Olmsted County, Minnesota, from 1991 through 2009, the overall CDI incidence was 13 per 100 000 persons with a significant increase in CDI incidence over the observation period. However, the study was limited by the smaller sample size, because only 92 children with CDI were identified. In addition, the initial search for cases was conducted based on ICD-9 code for CDI.[12] In a retrospective, hospital-based cohort study of children at 22 freestanding children's hospitals in US from 2001 to 2006, cases of *C difficile*-associated disease were defined as a hospitalized child with a discharge code for CDI, a laboratory billing charge for a *C difficile* toxin assay, or receipt of antimicrobial therapy for *C difficile*-associated disease. The annual incidence of *C difficile*-associated hospital admissions significantly increased from 2.4 to 4.0 per 10 000 admissions.[4] Twenty-six percent of those patients were <1 year of age.[4] Another retrospective cohort study using the triennial Healthcare Cost and Utilization Project KID's Inpatient Database in the US reported an increase in the number of CDIs, from 3565 cases in 1997 to 7779 cases in 2006 among hospitalized children.[5] Dubberke et al compared incidence rates of CDI in adults during a 6-year period, from 2000 to 2006, among 5 geographically diverse academic medical centers across the US.[13] Over the study period, there were significant increases in the overall incidence of hospital-onset, HCF-associated CDI (from 7.0 to 8.5 cases/10 000 patient-days; $P < .001$); community-onset, HCF-associated study hospital CDI (from 1.1 to 1.3 cases/10 000 patient-days; $P = .003$); and community-onset, HCF-associated other HCF CDI (from 0.8 to 1.5 cases/10 000 admissions overall; $P < .001$). For each CDI surveillance definition, there were significant differences in total incidence rates between institutions.[13] In contrast, reports from other parts of the world suggested a decrease in the incidence of CDI. In an administrative database-driven study from England, Jen et al estimated the rate of national CDI hospital admissions among adults.[14] The investigators demonstrated an increase in CDI rates per admission and per bed-days over the 9-year period between 1997/1998 and 2006/2007, followed by significant decrease from 2008/2009 to 2009/2010.[14] One possible explanation for the discrepancy between our study and US studies may be that we evaluated changes in incidence over a more recent timeframe, and it is possible that the incidence of CDI has stabilized more recently. A more likely explanation is that the US studies used different case-finding definitions that did not include results of stool testing to confirm the presence of CDI.[15] Moreover, we excluded children before their second birthday because testing this age group for CDI is not recommended because the interpretation of results is difficult. Young children (<2 years of age) have the highest rate of colonization without symptoms.[1,2,16] Recent data have shown that 26% of hospitalized children with CDI are younger than

<1 year of age. However, it is not clear whether this infection represents true disease.[17]

We showed that 51% of CDI is community acquired. This finding may be related to ease of transmission and inconsistent adherence to proper hand hygiene and environmental cleaning and disinfection. Community implementation of antibiotic stewardship program may help in reducing community-acquired CDIs.

Concordant with our results, known risk factors for CDI include underlying gastrointestinal disease such as IBD, gastrointestinal surgery, renal insufficiency, and malignancy.[1,14,18-20] In a retrospective cohort study that described the epidemiologic features of *C difficile*-associated disease in hospitalized children, 67% had underlying chronic medical conditions.[4] Concordant with other reports,[21] antibiotics in the preceding 3-month period before CDI were significantly associated with CDI.

The recurrence rate in our cohort was 10%, a rate that was within that reported in other pediatric studies (4.5%-14.0%)[22,23] but lower than that reported in adult studies (20%-30%).[24,25] Predictors of recurrence in adult studies included older age group, initial CDI disease severity, and hospitalization at time of CDI diagnosis.[22] Older age is a consistent strong predictor of recurrent CDI that may explain the higher recurrence rate in adult studies compared with that of pediatric literature.

Our study has several strengths. We excluded infection in the first 2 years of life because testing this age group for CDI is not recommended. The results of our study show a stable incidence of CDI in recent years, in contrast with studies from the US that were mainly based on the use of hospital discharge ICD codes for definitions of CDI. We have previously demonstrated that different patterns of CDI emerge when using hospital discharge ICD code definition versus laboratory-confirmed cases and that the hospital discharge code has limited diagnostic accuracy for determining occurrence of CDI in hospitals.[6]

Our study has limitations. We identified a small number of cases, especially those with severe outcome (death), which did not permit investigation of predictors of death among children with CDI. We could not report on certain characteristics such as type of IBD owing to Manitoba Health rule of "no descriptive" for <6 people to protect confidentiality. We used the Charlson Comorbidity Index score for comorbidities, which has not been validated in pediatrics, but we are not aware of any validated pediatric comorbidity index for the administrative datasets. Other populations may be different from Canadian population, which may limit generalizability of our study. Future studies will be important to identify potential sources of *C difficile* acquisition among children in the community. ■

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50 Years Ago in *The Journal of Pediatrics*

A Chromosome Survey of 2400 Normal Newborn Infants

Waltzer S, Breau G, Gerald PS. J Pediatr 1969;74:438-48

Although performing chromosome microarray to identify pathogenic copy number variants is medically indicated among children with a single or multiple congenital anomalies and/or dysmorphic features in the newborn period, there is limited information regarding the presence of pathogenic copy number variants among newborn infants who are eumorphic in appearance and who do not present with birth defects. Fifty years ago, Waltzer, Breau, and Gerald in a pioneering study funded by the National Institutes of Health identified 13 major nonmosaic chromosome abnormalities in a chromosome survey of 2400 "normal" newborn infants in which 2 metaphase figures were microscopically examined. The purposes of this study were to obtain population-level data regarding the frequency of chromosome abnormalities in otherwise normal individuals and to follow-up infants with sex chromosome abnormalities. Infants with Turner syndrome, Down syndrome, or significant birth defect were excluded from study. Identified chromosome abnormalities included infants with Klinefelter syndrome (47,XXY) and various structural chromosome rearrangements. This study was performed during a time period where there was concern regarding possible violent behavior among males with 47,XXY and 47,XYY chromosome aneuploidies. Owing to controversies regarding the ethical implications of these studies, Dr Gerald (cytogeneticist and senior author of this paper) terminated this study.[1]

During the following 50 years, cytogenetics technology has undergone a series of changes including high-resolution banding, fluorescence in situ hybridization, subtelomeric fluorescence in situ hybridization, comparative genomic hybridization, and single nucleotide polymorphism chromosome microarray. Routine banding at the- 400 to 450-band level will provide a 5- to 15-million base pair level of resolution. High-resolution chromosome banding provides a level of 1- to 3-million base pair level of resolution. Comparative genomic hybridization, fluorescence in situ hybridization, and chromosome microarrays provide a 50- to 250 000-base pair level of resolution. It is now apparent that pathogenic copy number variants are associated with autism and intellectual disability and may be present in individuals without major birth defects or dysmorphic facial features. Examples of this include 15q and 22q11.2 duplication syndromes. The 15q duplication syndrome, which includes autism susceptibility as a feature, is associated with minor dysmorphism in infancy, which may not be detected. There is no characteristic pattern of facial features associated with 22q11.2 duplication syndrome. Individuals with this duplication may have delayed psychomotor development, intellectual disability, growth retardation, and muscular hypotonia or be unaffected.

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