Low prevalence of *Helicobacter pylori* infection in Canadian children: A cross-sectional analysis

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BACKGROUND: The incidence and prevalence rates of childhood *Helicobacter pylori* infection vary greatly by nation, with infection rates of 8.9% to 72.8% reported in developed and developing countries, respectively. To date, few studies have assessed the prevalence of *H pylori* in Canadian children, with studies limited to Aboriginal communities and single tertiary care centres from Ontario and Quebec.

OBJECTIVES: To determine the prevalence of *H pylori* in consecutive children referred to three Canadian tertiary care academic centres for upper gastrointestinal (GI) endoscopy due to upper GI symptoms, and to determine the sensitivity and specificity of the carbon-13-labelled urea breath test, the rapid urease test and the *H pylori* stool monoclonal antigen test.

RESULTS: Two hundred four patients were recruited. The prevalence of *H pylori* was 7.1%. Of the *H pylori*-positive patients, 41.7% were male, with a mean age of 10.3 years. Ethnic minorities accounted for 42% of the *H pylori*-positive patients. Consistent with previous observations, the sensitivity and specificity of the carbon-13-labelled urea breath test were 1.0 and 0.98, respectively. The sensitivity and specificity of the rapid urease test were 1.0 and 0.99, respectively. Stool samples were collected from 34 patients from one centre, with a sensitivity and specificity of 1.0 and 0.68, respectively. No defining symptoms of *H pylori* infection were evident and no peptic ulcer disease was demonstrated.

CONCLUSION: *H pylori* infection rates in Canadian children with upper GI symptoms are low, and are lower than those reported for other developed countries. Further studies are required in Canada to determine the prevalence in the general population and specifically in the populations at risk.

Key Words: Helicobacter pylori; *Pediatrics; Prevalence; UBT*

Faible prévalence de l'infection à *Helicobacter pylori* chez les enfants canadiens : Analyse transversale

HISTORIQUE : L'incidence et la prévalence de l'infection à *Helicobacter pylori* chez les enfants varient beaucoup d'un pays à l'autre et des taux d'infection de 8,9 % à 72,8 % sont signalés respectivement dans les pays industrialisés et en développement. À ce jour, peu d'études ont mesuré la prévalence d'*H. pylori* chez les enfants canadiens, ces études s'étant limitées aux communautés autochtones et à des centres de soins tertiaires de l'Ontario et du Québec.

OBJECTIFS : Mesurer la prévalence d'*H. pylori* chez des enfants adressés consécutivement dans trois centres hospitaliers universitaires canadiens pour endoscopie des voies digestives hautes en raison de symptômes GI et déterminer la sensibilité et la spécificité du test respiratoire à l'urée marquée au ^{13}carbone, du test d'uréase rapide et du dépistage de l'antigène monoclonal fécal d'*H. pylori*.

RÉSULTATS : Deux cent quatre patients ont été recrutés. La prévalence d'*H. pylori* a été de 7,1 %. Parmi les patients *H. pylori*-positifs, 41,7 % étaient de sexe masculin et l'âge moyen était de 10,3 ans. Les minorités ethniques représentaient 42 % des patients *H. pylori*-positifs. Conformément aux observations antérieures, la sensibilité et la spécificité du test respiratoire à l'urée marquée au ^{13}carbone était de 1,0 et 0,98, respectivement. La sensibilité et la spécificité du test d'uréase rapide étaient de 1,0 et 0,98, respectivement. Les échantillons de selles recueillis chez 34 patients d'un centre présentaient une sensibilité et une spécificité de 1,0 et 0,67, respectivement. Aucun signe définitoire de l'infection à *H. pylori* ne s'est manifesté et on n'a observé aucun cas d'ulcère gastroduodénal.

CONCLUSIONS : Les taux d'infection à *H. pylori* chez les enfants canadiens qui présentent des symptômes GI sont faibles, et inférieurs aux taux rapportés dans d'autres pays industrialisés. Des études plus approfondies sont nécessaires au Canada pour déterminer la prévalence des infections dans la population générale et plus spécifiquement dans les populations à risque.

The incidence and prevalence rates of childhood infection with *Helicobacter pylori* vary greatly by nation. Infection rates of 8.9% to 72.8% are reported in developed and developing countries, respectively. Infection rates are affected by socioeconomic status, crowded conditions and poor hygiene, and the rates increase with age (1-4). However, the determination of *H pylori* prevalence in study populations has been affected by detection method and cohort selection.

Within developed nations, prevalence rates of *H pylori* infection among children have been shown to range from 5.4% to 40% (3-6). To date, few studies have assessed the prevalence of *H pylori* in Canadian children, with studies limited to Aboriginal communities and single tertiary care centres from Ontario and Quebec (7-13).

The lack of data from large-scale prospective studies has hampered the development of evidence-based guidelines regarding the diagnostic criteria and investigations for the detection of *H pylori* infection in Canadian children and adolescents. Small-scale studies indicate that the carbon-13-labelled urea breath test (^{13}C-UBT) – a noninvasive investigation – has

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a high sensitivity and specificity in adults and children (10,14-16). However, these results are dependent on the method of test administration and diagnostic threshold values. Similarly, data on the association among clinical presentation, endoscopy referral patterns and the presence of *H pylori* are inconsistent (17-20).

Current guidelines on the approach to *H pylori* detection and treatment published by the Canadian *H pylori* Study Group (16) state that when the investigation of children with persistent or severe upper abdominal symptoms is indicated, upper endoscopy with biopsy is the investigation of choice and the ^{13}C-UBT is the best noninvasive diagnostic test. Although the ^{13}C-UBT is reliable for the detection of *H pylori* in children older than six years, upper endoscopy with biopsy remains the current gold standard choice, which has the added advantage of being able to detect complications associated with *H pylori* infection, and to rule out non-*H pylori*-associated pathology (16,21). On the other hand, *H pylori* stool antigen testing appears to be accurate and easy to perform (22-24). However, acceptability of this noninvasive test for diagnosis of infection remains limited due to the use of various antigen tests, studies restricted to specialized referral centres and insufficient data on children in areas with a low *H pylori* prevalence (16,25,26).

The primary objectives of the present study were to determine the prevalence of *H pylori* in consecutive children referred to three Canadian tertiary care academic centres for upper gastrointestinal (GI) endoscopy due to upper GI symptoms, and to determine the sensitivities and specificities of the ^{13}C-UBT, the rapid urease test (RUT) and the *H pylori* stool monoclonal antigen test (*Hp*SA), using *H pylori* positivity on histology as the gold standard for diagnosis. The secondary goal was to evaluate the clinical determinants that prompted an upper GI endoscopy in children presenting with unexplained upper GI symptoms.

PATIENTS AND METHODS

Patients

Three tertiary pediatric care academic centres participated in the current prospective study: McMaster University Medical Centre (Hamilton, Ontario), IWK Grace Health Centre (Halifax, Nova Scotia) and the BC Children's Hospital (Vancouver, British Columbia). All children aged five to 18 years who were referred for upper GI endoscopy during the study period (January 2001 to June 2003) were evaluated. Neurologically impaired children or adolescents unable to blow into a tube for the ^{13}C-UBT were excluded from the study. The indications for endoscopy, symptoms, previous treatment, and endoscopic and histological findings were recorded. All patients had to have stopped acid-suppressing medications and/or antibiotics two weeks before testing.

Investigations

Biopsy-based methods: At upper GI endoscopy, two biopsies each from the gastric antrum and body were taken for histological examination, fixed in 10% formalin, and stained with hematoxylin-eosin and Giemsa staining to detect *H pylori* infection by light microscopy. One additional antral biopsy was obtained for the RUT (Pantozol *Hp* Test, Cambridge Life Sciences Ltd, United Kingdom). The RUT result was considered to be positive if a colour change occurred within 8 h of incubation at room temperature.

^{13}C-UBT: The ^{13}C-UBT (PyloriTest, Glaxo Wellcome Inc, Canada and Helikit, Isotechnica Diagnostics, Canada) was administered within one week of the endoscopy, in accordance with test guidelines. Briefly, after a fasting period of at least 4 h, a baseline breath sample was obtained using a collection tube. The children then drank 75 mL of a citrus-flavoured liquid preparation (75 mg of ^{13}C-labelled urea). Fifteen minutes, 30 min and 45 min later, breath samples were stored in collection tubes. The breath samples were stored at room temperature, batched and then transferred to the Division of Gastroenterology at the McMaster University Medical Centre for analysis. The breath samples were analyzed by isotopic ratio mass spectrometry (BreathMAT, Finnigan MAT Gmbh, Germany). The test was defined as positive when delta over baseline (DOB) values calculated after 15 min and/or 30 min were 3.5 δ‰ or more (27).

***Hp*SA:** Stool samples were collected in sterile containers from patients at the BC Children's Hospital on the day of endoscopy and stored at –20°C for later analysis. The *Hp*SA Plus enzyme immunoassay test (Meridian Diagnostics, USA) was performed by ELISA to detect the *H pylori* antigen using monoclonal antibodies, without prior knowledge of *H pylori* status. The test was performed at the British Columbia Centre for Disease Control in accordance with manufacturer's instructions (28). Based on manufacturer's guidelines, an optical density (OD 450 nm/650 nm) of less than 0.100 was defined as a negative test result, an optical density greater than 0.120 was defined as a positive test result and an optical density of 0.100 to 0.120 was defined as an equivocal test result.

Statistics

Descriptive statistics such as percentages, means and SDs were calculated for demographic and upper GI endoscopy characterization. Sensitivity, specificity, positive predictive value (PPV) and their corresponding 95% CIs were determined for the ^{13}C-UBT, the RUT and the *Hp*SA as predictors, compared with a positive histological finding serving as the gold standard. Statistical analysis was performed using SPSS version 15.0 (SPSS Inc, USA).

The study protocol was approved by the ethics committees of each participating hospital. Informed consent for participation of each child was given by a parent, legal guardian or child, where applicable.

RESULTS

During the study period, 214 patients who met the inclusion criteria underwent an upper GI endoscopy in the three participating centres. Sufficient data for evaluation were collected from 204 patients. The mean age of all children undergoing the procedure was 11.7 years (range five to 17.6 years), and 46% were male. Of the patients recruited, 20%, 43.3% and 36.7% were from the Halifax, Hamilton and Vancouver centres, respectively. Of the patients recruited, 79%, 83% and 100% from Vancouver, Hamilton and Halifax, respectively were Caucasian. Ethnic minorities, including East Asian, South Asian, First Nations, Middle Eastern and mixed nationalities accounted for the remainder of the patients. Seven of the 12 *H pylori*-positive patients (58%) were Caucasian, two were First Nations and the remaining three were of East Indian, African and Middle Eastern descent.

The primary indications for referral for an upper endoscopy at all centres included epigastric pain (45%), periumbilical or

TABLE 1
Symptoms of *Helicobacter pylori*-positive and *H pylori*-negative patients referred for upper gastrointestinal endoscopy

Symptom	*H pylori*-negative, n (%)	*H pylori*-positive, n (%)
Epigastric pain	87 (45.3)	8 (66)
Periumbilical pain	62 (32.2)	3 (25)
Lower abdominal pain	41 (21.3)	1 (8.3)
Retrosternal/chest pain	36 (18.7)	–
Heartburn	41 (21.3)	–
Nausea/vomiting	6 (3.1)	–
Anemia	4 (2)	–
Failure to thrive/weight loss	3 (1.5)	–
Halitosis	2 (1.04)	–

Percentages do not add up to 100% because some patients reported more than one symptom

TABLE 2
Histological findings in *Helicobacter pylori*-negative patients

Histological finding	n
No abnormality	81
Nonspecific gastritis	35
Lymphocytic gastritis	6
Reflux esophagitis	30
Celiac disease	11
Chronic duodenitis	5
Eosinophilic esophagitis/gastroenteritis	13
Granulomatous gastritis	3
Chemical/nonsteroidal anti-inflammatory drug gastritis	8
Total	192

lower abdominal pain (20.5%), retrosternal or chest pain, other symptoms suggestive of reflux (heartburn, vomiting, regurgitation, and cough and asthma) (19.6%), positive anti-tissue transglutaminase/antiendomysial antibody results (1.9%), positive *H pylori* serology (6.3%) or other indications (follow-up, failure to thrive, diarrhea) (6.3%).

The symptoms described by patients undergoing endoscopy are outlined in Table 1.

Of the patients undergoing endoscopy, 29 of 204 (14.2%) carried a previous gastrointestinal diagnosis: six (2.9%) had inflammatory bowel disease, 13 (6.3%) had gastroesophageal reflux disease and 10 (4.9%) had other diagnoses including eosinophilic esophagitis/gastroenteritis, vasculitis, *H pylori*-associated duodenal ulcer, non-*H pylori*-associated duodenal ulcer or asthma. Histological findings and diagnoses in all *H pylori*-negative patients are shown in Table 2.

The prevalence of *H pylori* in all patients referred for upper GI endoscopy was 12 of 204 (5.8%). When evaluating patients undergoing their first upper GI endoscopy, the prevalence of *H pylori* was 12 of 167 (7.1%). Of the *H pylori*-positive patients, 41.7% were male, with a mean age of 10.3 years (range 5.1 to 14.1 years). The prevalence varied among sites, with an *H pylori* prevalence of 6.8% in Hamilton and 8.1% in Vancouver; no *H pylori*-positive cases were identified in Halifax. In *H pylori*-positive patients, symptoms that led to upper GI endoscopy referral were epigastric pain (66%), periumbilical pain (25%) and lower abdominal pain (8.3%) (Table 1).

Histological findings in the *H pylori*-positive patients ranged from mild to severe chronic active gastritis/antral gastritis. No cases of gastric metaplasia were recorded. In all cases, *H pylori* organisms were identified and confirmed by the study centre. The ^{13}C-UBT was performed in 159 of 204 (77.9%) patients undergoing an upper GI endoscopy, and in nine of 12 *H pylori*-positive patients. All noninfected patients had DOB values of less than 2.5 δ‰, except for two patients, who had DOB values between 2.5 δ‰ and 5 δ‰. In contrast, *H pylori*-positive patients had DOB values greater than 5 δ‰. All *H pylori*-positive patients had DOB values above 5 δ‰ at 15 min and/or 30 min. The ^{13}C-UBT was in agreement with the biopsy-based *H pylori* status in the nine infected and 121 of 124 noninfected patients, giving a sensitivity and specificity of 1.0 (95% CI 0.63 to 1.0) and 0.98 (95% CI 0.94 to 1), respectively, and a PPV of 0.75 (Table 3). The RUT was performed on 186 patients, with a sensitivity and specificity of 1 (95% CI 0.63 to 1) and 0.99 (95% CI 0.95 to 1), respectively, and a PPV of 0.82 (Table 3). Stool samples were collected from 34 patients, with a sensitivity and specificity of 1 (95% 0.31 to 1) and 0.68 (95% CI 0.49 to 0.83), respectively, and a PPV of 0.23 (Table 3).

In correlating symptoms and histological findings, no specific symptom was most likely to be associated with abnormal histological findings (P=0.33). Of the patients who reported epigastric pain, 65% had normal gastric, esophageal and duodenal histology. In contrast, 13.7% of these patients had reflux esophagitis, and the remainder had *H pylori*-associated gastritis (6.8%), chronic active gastritis (6.8%), celiac disease (5%) and eosinophilic esophagitis (1%). In patients with lower abdominal pain, normal histological results were reported in 44.4% of cases, whereas 22.2% had eosinophilic gastroenteritis, and the remainder had celiac disease (16.6%), granulomatous gastritis (5.5%), lymphocytic gastritis (5.5%) and *H pylori*-associated gastritis (5.5%). Of the patients with periumbilical pain, 54% had normal histology, 14.2% had celiac disease, 11.4% had reflux esophagitis, 8.5% had eosinophilic esophagitis and the remainder had granulomatous gastritis, *H pylori*-associated gastritis and nonspecific duodenitis. In patients complaining of retrosternal pain and heartburn, 71.5% had normal histological findings, and 28.5% had evidence of reflux esophagitis.

DISCUSSION

The present study of children from three Canadian medical centres is the largest published study to estimate the national prevalence rates of *H pylori* in symptomatic children in Canada. The study demonstrated a low prevalence rate of *H pylori* infection in patients referred for upper endoscopy because of upper GI symptoms and a high sensitivity and specificity of the ^{13}C-UBT.

We observed an *H pylori* infection rate of 7.1%, in contrast to other studies in Canadian children, which have demonstrated rates ranging from 15.2% to 100% (9-13). The present study was limited to outpatients; a factor that may have led to an underestimation of the true prevalence of *H pylori* infection due to exclusion of children with complicated

TABLE 3
Diagnostic tests performed in all patients referred for upper gastrointestinal endoscopy

Test	Tests performed, n	Positive results, n	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
^{13}C-UBT	159	12	1 (0.63 to 1)	0.98 (0.94 to 1)	0.75 (0.42 to 0.93)	1 (0.96 to 1)
*Hp*SA*	34	13	1 (0.31 to 1)	0.68 (0.49 to 0.83)	0.23 (0.06 to 0.54)	1 (0.8 to 1)
RUT	164	11	1 (0.63 to 1)	0.98 (0.95 to 1)	0.82 (0.47 to 0.96)	1 (0.96 to 1)

**Performed at a single centre (BC Children's Hospital, Vancouver, British Columbia). ^{13}C -UBT Carbon-13-labelled urea breath test;* Hp*SA* Helicobacter pylori *stool monoclonal antigen test; RUT Rapid urease test*

H pylori-associated peptic ulcer disease. Moreover, a limited number of Aboriginals and immigrant children were included in the study.

In the previous Canadian studies, variability in prevalence rates depended on the community tested, method of detection and association with symptomatology. Studies conducted in tertiary care centres on symptomatic Canadian children undergoing upper GI endoscopy demonstrated histologically positive prevalence rates of 15.2% in Quebec (10) and 25.8% to 43% in Ontario (7,12). Several factors are likely responsible for the differences in prevalence rates observed between studies. Age differences might be a factor, because the prevalence of *H pylori* acquisition increases with age (1-3,29). However, no significant differences in the mean age of enrolled subjects were evident among studies (Quebec, 12.4 years; Ontario, 12.6 years; and the present study, 11.7 years). Differences in referral base, including variations in ethnicity and populations at risk, could also explain the differences in *H pylori* infection rates. Many immigrants originate from countries with high prevalence rates of *H pylori* infection (2,30). Fifty-six per cent of the pediatric immigrant population resides in Ontario, in contrast to 18%, 13% and 1% in British Columbia, Quebec and Nova Scotia, respectively (adapted from Statistics Canada, Census of population 2001 for Visible Minorities, http://www40.statcan.ca/l01/ind01/l3_30000_30007.htm?hili_none). Consistent with these data, no *H pylori*-positive patients were observed in the present study's Halifax cohort.

Another population at risk for *H pylori* acquisition is the Canadian First Nations community. Population-based screening studies in Canadian First Nations children have demonstrated high *H pylori* prevalence rates. In the Wasagamack community in Northeastern Manitoba, prevalence rates of 56% were observed in children up to 12 years of age based on stool antigen tests (11). In an additional study (13), all children up to 15 years of age were serologically positive. Another study (8) in First Nations children from Arctic communities in Nunavut detected *H pylori* seropositivity in 32% of children up to 15 years of age. The high prevalence rates within these communities reflect well-demonstrated risk factors for acquisition of the bacterium: poor living conditions (such as primitive toileting), overcrowding and low socioeconomic status. This information was not collected in our study. One limitation of these studies could be related to the method of detection, because serology does not necessarily represent present infection status. Moreover, the common inadvertent use of antibiotics in pediatric patients may further confound the relevance of seroprevalence.

The high rates of *H pylori* positivity in the First Nations communities may have contributed to the differences in *H pylori* prevalence observed between the studies in tertiary care centres. Although a similar number of Aboriginals live in Ontario and British Columbia (17% to 19% of the total pediatric aboriginal population, respectively [from Statistics Canada, Census of population 2005], with smaller numbers in Quebec [8%] and Nova Scotia [2%]), this is not reflected in the distribution of the *H pylori* prevalence in various studies. Concerns regarding referral practices, accessibility of consulting services and utilization of health care may be raised for some of these remote communities.

Another important confounding factor to explain the variability in prevalence rates between tertiary care centres is the timeframe difference between studies. The Toronto studies (7,12) were conducted more than a decade ago, and prevalence rates may have shifted over time.

A North American study in children by Chong et al (17) demonstrated a seroprevalence rate of 22.5% in children with upper GI symptoms. This significantly higher number could be explained by the method of testing (serology), which is considered to be unreliable according to the current North American Society for Pediatric Gastroenterology, Hepatology and Nutrition guidelines for the diagnosis of *H pylori* infection in children (25). Other possible explanations are differences in ethnicity and socioeconomic status. The study by Chong et al compared symptomatic and nonsymptomatic children, and found that nonsymptomatic children had a significantly lower infection rate (14.1%) than symptomatic children from the same centres (22.5%). Extrapolating these data to the Canadian pediatric population would imply lower prevalence rates in the whole population. Further studies are required to assess population-based prevalence rates.

The limited number of *H pylori*-positive patients precluded statistical analysis. However, 92% of *H pylori*-positive patients complained of epigastric or periumbilical pain, in contrast to 78% in the *H pylori*-negative group. Moreover, the remainder of noninfected patients presented with lower abdominal pain or symptoms suggestive of reflux. In keeping with this observation, previous studies have not been able to show differences in symptoms between groups of *H pylori*-positive and *H pylori*-negative patients, and no specific symptoms have been associated with *H pylori* infection (17-20,31). Moreover, our study demonstrated a poor correlation between symptoms and significant histological findings on upper GI endoscopy. This observation requires validation, together with more detailed symptom analysis.

In the present study, we assessed the accuracy of the common invasive and noninvasive tests to detect the presence of *H pylori*, comparing them with the histological findings.

The sensitivity and specificity of the ^{13}C-UBT were comparable with those recorded in previous pediatric studies (14,15). Compliance with collecting stool samples in our study was exceptionally low, unlike other large studies, which used this modality as part of the study protocol (22-26); this may

have affected the detection rates. Although stool samples were limited, stool antigen testing had a high sensitivity and low specificity, as previously found in another study (23). However, one study (22) in symptomatic patients demonstrated a lower sensitivity (88.9%), but higher specificity of the polyclonal enzyme immunoassay.

CONCLUSIONS

H pylori infection rates in Canadian children with upper GI symptoms are low, and are lower than those reported for other developed countries. We contemplate that the actual total pediatric population rate of infection is lower than the 7.1% reported here, although specific populations (eg, immigrants from endemic countries and Aboriginals) should be considered to be at a high risk for carriage of *H pylori* infection. Further studies should be conducted in specific populations (eg, immigrants and Aboriginals) to estimate the true prevalence of *H pylori* in these high-risk groups.

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