Burden of disease from *Helicobacter pylori* infection in western Canadian Arctic communities

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**Abstract**

**Background:** Indigenous communities across the circumpolar north have elevated *H. pylori* (*Hp*) prevalence and stomach cancer incidence. We aimed to describe the *Hp*-associated disease burden among western Canadian Arctic participants in community-driven projects that address concerns about health risks from *Hp* infection.

**Methods:** During 2008–2013, participants underwent *Hp* screening by urea breath test and gastroscopy with gastric biopsies. We estimated *Hp* prevalence and prevalence by *Hp* status of endoscopic and histopathologic diagnoses.

**Results:** Among 878 participants with *Hp* status data, *Hp* prevalence was: 62% overall; 66% in 740 Indigenous participants; 22% in 77 non-Indigenous participants (61 participants did not disclose ethnicity); 45% at 0–14 years old, 69% at 15–34 years old, and 61% at 35–96 years old. Among 309 participants examined endoscopically, visible mucosal lesions were more frequent in the stomach than the duodenum: the gastric to duodenal ratio was 2 for inflammation, 8 for erosions, and 3 for ulcers. Pathological examination in 308 participants with gastric biopsies revealed normal gastric mucosa in 1 of 224 *Hp*-positive participants and 77% (65/84) of *Hp*-negative participants with sharp contrasts in the prevalence of abnormalities between *Hp*-positive and *Hp*-negative participants, respectively: moderate-severe active gastritis in 50 and 0%; moderate-severe chronic gastritis in 91 and 1%; atrophic gastritis in 43 and 0%; intestinal metaplasia in 17 and 5%.

**Conclusions:** The observed pattern of disease is consistent with increased risk of stomach cancer and reflects substantial inequity in the *Hp*-associated disease burden in western Arctic Canadian hamlets relative to most North American settings. This research adds to evidence that demonstrates the need for interventions aimed at reducing health risks from *Hp* infection in Indigenous Arctic communities.

**Keywords:** *Helicobacter pylori*, Arctic, Canada, Indigenous health, Prevalence, Gastritis, Gastric cancer, Peptic ulcer disease

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Background

Indigenous Peoples residing in northern Canada have an elevated prevalence of Helicobacter pylori (Hp) infection relative to southern Canadians [1]. This bacterial infection can persist lifelong, causing chronic inflammation of the stomach lining; in a small proportion of cases (5–15%), it causes peptic ulcer disease and, more rarely, stomach cancer [2]. Elevated Hp prevalence and stomach cancer rates have been observed in Indigenous communities across the circumpolar north relative to the average occurrence in the respective countries [1].

Systematic reviews of population-based studies report Hp prevalence estimates over 50% across most of Africa, Asia and Latin America, with lower and declining prevalence in Australia-New Zealand, Europe and North America [3, 4]. While Hp prevalence varies substantially within countries by ethnicity and socioeconomic status, and many region-specific prevalence estimates come from unrepresentative samples [5], rough regional estimates range from 24% for Australia-New Zealand to 79% for Africa, with prevalence in Canada and the United States estimated at 36 and 38%, respectively, in a 2017 systematic review [3]. Evidence from the late twentieth century showed Hp prevalence inversely associated with socioeconomic status within Europe and the United States [6, 7]. Because the infection typically is acquired in childhood, observed increases in Hp prevalence with age result from a cohort effect reflecting transmission levels within the first years after birth. Decreases in Hp prevalence observed in younger age groups in affluent countries suggests that transmission is decreasing in such countries, though it remains high in socioeconomically disadvantaged groups. In Canada, for example, the prevalence in pediatric patients residing in major urban centers was estimated in 2005 at just 5%, while 56% (92/163) of Wasagamack Cree children in northern Manitoba screened positive for Hp in 2002 [2, 8].

The Canadian North Helicobacter pylori (CANHelp) Working Group, a collaboration of academic scientists with Indigenous community leaders and their health care providers [9], conducts community-driven investigations focused on Hp infection in the Northwest Territories (NT) and Yukon (YT) [10–16]. Incorporating the perspective of those who bear the burden, results from these projects will be used to develop Hp control strategies that are cost-effective and culturally appropriate for Arctic Indigenous communities. Previous reports describe details of CANHelp projects and their community-driven approaches [10, 12–15, 17]. This paper describes the burden of disease from Hp infection among participants in CANHelp community projects.

Methods

Research sought by communities

The CANHelp research program arose from the confluence of three constituencies: residents of western Canadian Arctic communities worried about Hp infection and its link to stomach cancer; health care practitioners frustrated by poor effectiveness of available clinical management strategies for this frequently encountered infection; and public health officials seeking evidence to inform infection control strategies. In the early 2000s, NT health care officials sought input from University of Alberta researchers to respond to concerns voiced by community leaders. In 2006, a meeting between academic scientists and NT medical directors generated support for community-driven research aimed at describing the burden of disease from Hp infection in concerned communities. NT health care partners recommended the Hamlet of Aklavik for the initial project because Aklavik community leaders had advocated for research to reduce health risks from Hp infection. The Aklavik H. pylori Project launched in 2007. Word of its success generated interest in neighboring communities. Invited by community leaders, the research team launched community H. pylori Projects in Old Crow YT in 2010, Tuktoyaktuk NT in 2011 and Fort McPherson NT in 2012. Projects launched in 2016–2017 are not included in this report. The University of Alberta Health Research Ethics Board approved this research, and as required by law, we obtained annual research licenses in both NT and YT before collecting data.

Participating communities

Population estimates (from census nearest project launch) were 594 (2006) for Aklavik, 245 (2011) for Old Crow, 854 (2011) for Tuktoyaktuk, and 792 (2011) for Fort McPherson (Fig. 1) [18–21]. Most residents of participating communities identify as Indigenous: by census counts, in Aklavik, 92% were Indigenous (mainly Inuvialuit (western Canadian Inuit) or Gwich’In (Athabaskan) First Nation); in Old Crow, 90% were Vuntut Gwitchin (Athabaskan) First Nation; in Tuktoyaktuk, 92% were Inuvialuit; and in Fort McPherson, 94% were Indigenous (mainly Gwich’in) [18, 22]. Aklavik, 113 km south of the Arctic Coast, is accessible by air, ice road in winter and water in summer [23]. Old Crow, north of the Arctic Circle on the Porcupine River, is accessible only by air [24]. Tuktoyaktuk, on the Arctic Ocean coast, is accessible by air, highway year-round since November 2017 (before that by ice road in winter). Fort McPherson, on the Peel River, is accessible by highway year-round [23].

Community-driven approach

Each project launch required the formation of a planning committee of community residents; the process for recruiting committee members was devised by community
partners. An exception was the Tuktoyaktuk project, launched at the request of the Inuvialuit Regional Corporation [25], with planning occurring in partnership with regional Inuvialuit leadership and a Tuktoyaktuk community health representative. Planning committees and other community partners provided input on design and implementation of all research activities to ensure they adhered to community priorities and cultural values. Planning committees and other community partners reviewed all research reports before they were made public.

**Study population and design**

Project recruitment activities in each community encouraged all residents to participate in baseline research activities: interviewer-administered questionnaires; *Hp* screening; and endoscopy with gastric biopsies for culture and pathological examination. After endoscopy activities concluded, randomized trials offered treatment to eliminate *Hp* infection to those testing positive. Participants gave written informed consent for overall project participation with additional consents for endoscopy and treatment. Participants < 17 years old required written parental consent, with children deemed sufficiently mature providing written assent. Details can be found on the CANHelp Working Group website [9].

**Hp screening**

Beginning in January 2008, we offered screening for *Hp* infection using the 13C-urea breath test (UBT), the most accurate non-invasive test for detecting *Hp* infection in children and adults [26]; most well-designed validation studies estimate both sensitivity and specificity greater than 95% against biopsy-based diagnosis [27], though it should be noted that biopsy-based diagnosis is not an optimal gold standard because tissue sampling can miss *Hp* in the stomach due to its patchy distribution and diagnostic accuracy also depends on tissue preparation techniques and observer expertise [26, 28, 29]. The UBT avoids these limitations, but its accuracy depends on optimal breath sample collection [30]. We used nondispersive isotope-selective infrared spectroscopy to measure the 13C/12C ratio in breath samples collected before and after consumption of 13C-labeled urea [31, 32]; a positive result reflects presence of urease in the stomach, a highly specific marker for *Hp* infection. We asked participants to avoid acid-suppressing medications for 24 h before the test and to fast except for water for 4 h before the test. We obtained a baseline breath sample, asked participants to swallow 50–75 mg of 13C-labeled urea dissolved in citric acid, and collected a second breath sample 30 min after the urea solution was swallowed [17].
Upper gastrointestinal endoscopy, histopathology, and microbiological culture

Using ultra-slim Olympus gastroscopes, gastroenterologists performed unsedated upper gastrointestinal endoscopy for consenting participants, regardless of Hp status, in temporary endoscopy clinics organized in community health centers (2008 in Aklavik, 2012 in Old Crow, 2013 in Fort McPherson and at the Inuvik Regional Hospital for Tuktoyaktuk participants) [33]. The regional planning approach used for the Tuktoyaktuk project created logistic constraints that reduced time periods, relative to the other community projects, for recruiting participants and carrying out project activities; as a result, participation was not sufficient to warrant resources required for an endoscopy team to visit this community. Instead, we offered to pay travel expenses for Tuktoyaktuk residents willing to undergo endoscopy in Inuvik (a 2-h drive). Gastric biopsies collected during endoscopy were transported to the University of Alberta for histopathologic examination (2–3 from antrum, 2–3 from corpus) and tissue culture (1 from antrum, 1 from corpus) [14]. A single pathologist (SG) evaluated antral and corpus biopsies separately, grading Hp density, active and chronic gastritis, gastric atrophy, and other neoplastic lesions using the updated Sydney system [34]. We differentiate active gastritis, characterized by polymorphonuclear neutrophil infiltration occurring in the context of chronic inflammation, from chronic gastritis, characterized by the presence of mononuclear cells, chiefly lymphocytes, plasma cells and macrophages [34]. For culture, antral and corpus biopsies were pooled and mechanically homogenized; resulting suspensions were plated on brain heart infusion/yeast extract/5% horse serum agar plates and incubated at 37 °C in microaerophilic conditions. Cultures were checked for growth every 48 h, for up to a month. Colonies consistent with Hp growth were subplated and expanded for generation of glycerol stocks. Hp classification was confirmed by urease, catalase, oxidase and 16S ribosomal RNA PCR testing.

Hp infection status

We classified Hp infection status using all available results (UBT, histopathologic examination, and/or bacterial culture) for each participant. When results were discordant, we used an algorithm based on the probability that the status was negative or positive (for example, UBT positive + histopathology positive + culture negative was classified as positive; UBT negative + histopathology positive + culture negative was classified as negative). Among 254 participants with classifiable Hp status from 3 tests, 216 (85%) were concordant on all 3 tests; among 53 participants with classifiable Hp status from just 2 tests, 47 (89%) had concordant status. Of the 3 tests, UBT and histopathology agreed most frequently, for 263 of 272 (97%) participants with results from both, while the results of culture diverged more frequently, agreeing with UBT for 218 of 254 (86%) participants with both of these tests and with histopathology for 252 of 289 (87%) participants with both of these tests. The more frequent discordance of culture is not surprising given the technical challenges inherent in tissue culture of Hp in the laboratory [30, 35]. The high agreement of UBT and histopathology indicates comparable and excellent accuracy of these 2 diagnostic tests. Comparing UBT against histopathology as the gold standard, estimated sensitivity is 96% (95% confidence interval (CI), 94–99%) and estimated specificity is 97% (95% CI, 94–100%). Conversely, comparing histopathology against UBT as the gold standard, estimated sensitivity is 99% (95% CI, 98–100%) and estimated specificity is 91% (95% CI, 85–97%).

Statistical analysis

The cross-sectional design is appropriate for investigations of the burden of disease from Hp in a community setting, given that the infection onset generally goes undetected, the infection often persists indefinitely without symptoms, and gastric disease caused by the infection is often asymptomatic. Screening for prevalent cases is, therefore, the starting point for describing the occurrence of Hp infection and related disease in a population. To describe the burden of infection in participating communities, we present the estimated prevalence of Hp infection and 95% confidence intervals by age, sex, ethnicity and community. To describe the burden of gastric disease related to Hp infection and demonstrate relatedness of specific conditions to Hp infection, we present the estimated prevalence of endoscopic diagnoses (esophagitis/esophageal erosions, Barrett's esophagus, gastritis, gastric erosions, gastric ulcer, duodenitis, duodenal erosions, duodenal ulcer) and histopathologic diagnoses (active gastritis, chronic gastritis, gastric atrophy, benign MALT hyperplasia or lymphoid aggregates, lymphoepithelial lesions, intestinal metaplasia, dysplasia, carcinoma) and 95% CIs by Hp status. In analyses of endoscopy or histopathology results, we excluded the small number of participants who underwent treatment to eliminate Hp after the screening UBT and before endoscopy.

Results

Participation and data availability

The four community projects enrolled 934 participants, representing 38% of the combined populations of these communities (Table 1). The first two community projects had the highest participation, with 64 and 85% of residents of Aklavik and Old Crow, respectively. Hp status was available for 878 (94%) of the 934 participants. Table 2 shows participation in UBT screening and endoscopy by community, with UBT results available for 90% (841/934) and histopathology results available for 33% (308/934). Due to the logistic challenges, only 5 Tuktoyaktuk residents had
eligible histopathology results: each fell in a different age group; 4 were women; 5 were Indigenous (4 were Inuvialuit, the dominant ethnicity in Tuktoyaktuk); and 4 were \( H_p \)-positive with a distribution of endoscopic and histopathologic outcomes reflective of the larger study population.

Table 3 shows the distribution of age, sex, community and ethnicity in all 934 participants and in two study population subsets: the 878 with \( H_p \) status and the 308 with histopathology results. Aside from the exclusion of young children from endoscopy, the age distribution of the two subpopulations approximates that of the total study population. The sex distribution is similar across study population subsets, with women accounting for 54–56% of each. The proportion identifying as Indigenous is 90–92% across study subpopulations. The representation of communities is nearly identical in the total study population and among those with \( H_p \) status, but among those with histopathology results Aklavik is overrepresented due to a much higher proportion of participants undergoing endoscopy in the first project, and Tuktoyaktuk is underrepresented due to only 13 participants traveling to Inuvik for endoscopy. Just 56 (6%) participants lacked data on \( H_p \) status; these participants were disproportionately younger and male.

**\( H_p \) prevalence**

Among 878 participants with \( H_p \) status, 62% were \( H_p \)-positive (Table 4). The prevalence was 45% (95% CI, 36–55%) in children under 15, 69% (95% CI, 63–74%) in the 15–34-year age group, and 61% (95% CI, 57–66%) in the 35–96-year age group. The prevalence was somewhat higher in men (65%; 95% CI, 60–70%) than women (59%; 95% CI, 55–63%). Across communities, the prevalence ranged from 57% in Tuktoyaktuk to 68% in Old Crow. The largest variation in prevalence was by ethnicity, with non-Indigenous participants having a much lower prevalence (22%; 95% CI, 13–31%) than Indigenous participants (66%; 95% CI, 62–69%).

**Endoscopic assessment**

Table 5 shows the prevalence of abnormalities observed during endoscopy by \( H_p \) status. Of note, 79% of \( H_p \)-positive participants had gastric mucosa that appeared normal. Visible esophagitis and Barrett’s esophagus were more prevalent in \( H_p \)-negative participants (11 and 7%, respectively) than \( H_p \)-positive participants (8 and 4%, respectively). Paradoxically, the prevalence of visible gastritis, gastric erosions and gastric ulcers was not markedly different in groups defined by \( H_p \) status: 12–15% had visible gastritis, 8–11% had gastric erosions, and 3–4% had gastric ulcers. The prevalence of visible duodenal lesions was lower: duodenal lesions were observed in 9% of \( H_p \)-positive participants and 4% of \( H_p \)-negative participants. No \( H_p \)-negative participants had visible duodenal erosions or ulcers and 4% had duodenitis, while 1% of \( H_p \)-positive participants had duodenal erosions, 1% had duodenal ulcers, and 7% had duodenitis. In all 308 participants with complete endoscopic assessment, the gastric to duodenal ratio was 2 for inflammation, 8 for erosions, and 3 for ulcers. In 271 Indigenous participants, the gastric to duodenal ratio was 2 for inflammation, 6 for erosions, and 8 for ulcers.

**Table 1** Participation in CANHelp projects and availability of \( H_p \) status data, western Arctic Canadian communities, 2007–2013

| Community   | Launch Year | Census-estimated Population | Enrolled Participants (signed consent) | Participants with Data on \( H_p \) Status |
|-------------|-------------|------------------------------|----------------------------------------|----------------------------------------|
|             |             | n                            | % of Census                            | n                                      | % of Participants |
| Aklavik     | 2007        | 594                          | 383                                    | 352                                    | 92 |
| Old Crow    | 2010        | 245                          | 208                                    | 200                                    | 96 |
| Tuktoyaktuk | 2011        | 854                          | 107                                    | 102                                    | 95 |
| Fort McPherson | 2012   | 792                          | 236                                    | 224                                    | 95 |
| Total       |             | 2485                         | 934                                    | 878                                    | 94 |

*From 2006 census for Aklavik [18]; from 2011 census for other communities [19–21]

**Table 2** Participation in CANHelp project diagnostic testing and availability of results, western Arctic Canadian communities, 2008–2013

| Community   | Enrolled Participants | UBT Completed | Classifiable Result | Endoscopy Completed | Histopathology Results |
|-------------|-----------------------|---------------|---------------------|---------------------|------------------------|
|             | n                     | n %           | n %                 | n %                 | n %                    |
| Aklavik     | 383                   | 334           | 87                  | 333                 | 87                     | 194 51 194 51 |
| Old Crow    | 208                   | 199           | 96                  | 192                 | 92                     | 59 28 59 28 |
| Tuktoyaktuk | 107                   | 104           | 97                  | 102                 | 95                     | 5 5 5 5 |
| Fort McPherson | 236           | 228           | 97                  | 214                 | 91                     | 50 21 50 21 |
| Total       | 934                   | 865           | 93                  | 841                 | 90                     | 310 33 308 33 |
We examined whether the similar frequencies of endoscopically observed gastric abnormalities in groups defined by Hp status were due to previous Hp infection eliminated by antimicrobial therapy among Hp-negatives or recent use of proton pump inhibitors (PPI) or H2-receptor antagonists (H2RA), which decrease the density of Hp organisms, thereby reducing the sensitivity of diagnostic tests. In the 84 Hp-negative participants with treatment history data, 30 (36%) had previous treatment; the proportion classified as having normal gastric mucosa was 80% among those treated previously and 77% among those not treated previously (for duodenal mucosa, these proportions were 97 and 96%, respectively). Among 302 participants with medication data, recent PPI/H2RA use was reported by 11% of Hp-positives and 27% of Hp-negatives. To assess the hypothesis that Hp-negatives with abnormal gastric mucosa were false negatives due to medication use, we compared the proportion classified as having normal gastric mucosa by PPI/H2RA use: in 85 Hp-negatives, 74% among users and 79% among non-users (for duodenal mucosa, 91 and 96%, respectively); in 218 Hp-positives, 68% among users and 80% among non-users (for duodenal mucosa, 91 and 96%, respectively). Thus, this paradox does not appear to be due to previously treated Hp infection or medication use among current Hp-negatives.

Table 3 Characteristics of CANHelp project participants by data availability, 2007–2013

|                      | All 934 Participants | 878 Participants with Hp Status | 308 Participants with Histopathology | 56 Participants without Hp Status |
|----------------------|----------------------|---------------------------------|--------------------------------------|-----------------------------------|
| **Age**              |                      |                                 |                                      |                                   |
| 0–9.75               | 76  8                | 65  7                           | 0  0                                 | 11 20                             |
| 9.8–14<sup>c</sup>   | 45  5                | 41  5                           | 8  3                                 | 4  7                              |
| 15–24                | 136 15               | 124 14                          | 46 15                                | 12 22                             |
| 25–34                | 142 15               | 135 15                          | 45 15                                | 7 13                              |
| 35–44                | 121 13               | 118 13                          | 41 13                                | 3 6                               |
| 45–54                | 170 18               | 165 19                          | 75 24                                | 5 9                               |
| 55–64                | 133 14               | 128 15                          | 57 18                                | 5 9                               |
| 65–96                | 109 12               | 102 12                          | 36 12                                | 7 13                              |
| missing              | 2 0                   | 0 0                             | 0 0                                  | 2                                 |
| **Sex**              |                      |                                 |                                      |                                   |
| Male                 | 430 46               | 398 45                          | 137 44                               | 32 57                             |
| Female               | 504 54               | 480 55                          | 171 56                               | 24 43                             |
| missing              | 0 0                   | 0 0                             | 0 0                                  | 0                                 |
| **Community**        |                      |                                 |                                      |                                   |
| Aklavik              | 383 41               | 352 40                          | 194 63                               | 31 55                             |
| Old Crow             | 208 22               | 200 23                          | 59 19                                | 8 14                              |
| Tuktoyaktuk          | 107 11               | 102 12                          | 5 2                                  | 5 9                               |
| Fort McPherson       | 236 25               | 224 26                          | 50 16                                | 12 21                             |
| missing              | 0 0                   | 0 0                             | 0 0                                  | 0                                 |
| **Ethnicity**        |                      |                                 |                                      |                                   |
| Non-Indigenous       | 82 10                | 77 9                            | 22 8                                 | 5 13                              |
| Indigenous           | 775 90               | 740 91                          | 271 92                               | 35 88                             |
| Inuvialuit (Inuit)   | 305 36               | 289 35                          | 121 41                               | 16 40                             |
| Gwich’in (First Nations) | 424 49          | 405 50                          | 133 45                               | 19 48                             |
| Other/mixed<sup>d</sup> | 46 5              | 46 6                            | 17 6                                 | 0 0                               |
| missing              | 77 61                 | 61                              | 15                                   | 16                                |

Hp H. pylori
<sup>a</sup>% of column total minus missing; distributions do not all sum 100% due to rounding
<sup>b</sup>For the comparison of the distribution in participant groups with and without Hp status
<sup>c</sup>The 9.8–14 category includes two participants < 10: one who was 9 years and 10 months at the time of UBT and 9 years and 11 months at endoscopy, and one who was 9 years and 11 months at the time of UBT with no endoscopy
<sup>d</sup>Includes: Métis; mixed Indigenous ethnicities; unspecified Indigenous ethnicity; Indigenous mixed with non-Indigenous ethnicities

Among 302 participants with medication data, recent PPI/H2RA use was reported by 11% of Hp-positives and 27% of Hp-negatives. To assess the hypothesis that Hp-negatives with abnormal gastric mucosa were false negatives due to medication use, we compared the proportion classified as having normal gastric mucosa by PPI/H2RA use: in 85 Hp-negatives, 74% among users and 79% among non-users (for duodenal mucosa, 91 and 98%, respectively); in 218 Hp-positives, 68% among users and 80% among non-users (for duodenal mucosa, 96 and 91%, respectively). Thus, this paradox does not appear to be due to previously treated Hp infection or medication use among current Hp-negatives.
Table 4  *Hp* prevalence by demographic characteristics, 878 CANHelp project participants with * Hp* status, 2008–2013

| Category          | n | Hp Prevalence | n | % | 95% CI |
|-------------------|---|---------------|---|---|--------|
| Total             | 878 | 541 | 62 | 58, 65 |
| Age               |    |               |   |    |        |
| 0–9.75            | 65  | 30 | 46 | 34, 58 |
| 9.8–14a           | 41  | 18 | 44 | 29, 59 |
| 15–24             | 124 | 85 | 69 | 60, 77 |
| 25–34             | 135 | 93 | 69 | 61, 77 |
| 35–44             | 118 | 70 | 59 | 50, 68 |
| 45–54             | 165 | 103 | 62 | 55, 70 |
| 55–64             | 128 | 78 | 61 | 52, 69 |
| 65–96             | 102 | 64 | 63 | 53, 72 |
| Sex               |    |               |   |    |        |
| Male              | 398 | 258 | 65 | 60, 70 |
| Female            | 480 | 283 | 59 | 55, 63 |
| Community         |    |               |   |    |        |
| Aklavik           | 352 | 213 | 61 | 55, 66 |
| Old Crow          | 200 | 136 | 68 | 62, 74 |
| Tuktoyaktuk       | 102 | 58 | 57 | 47, 66 |
| Fort McPherson    | 224 | 134 | 60 | 53, 66 |
| Ethnicity         |    |               |   |    |        |
| Non-Indigenous    | 77  | 17 | 22 | 13, 31 |
| Indigenous        | 740 | 486 | 66 | 62, 69 |
| Inuvialuit (Inuit)| 289 | 193 | 67 | 61, 72 |
| Gwich’in (First Nations) | 405 | 260 | 64 | 60, 69 |
| Other/mixedb      | 46  | 33 | 72 | 59, 85 |
| missing           | 61  |               |   |    |        |

*Hp* H. pylori, CI binomial Wald confidence interval

aThe 9.8–14 category includes two participants < 10: one who was 9 years and 10 months at the time of UBT and 9 years and 11 months at endoscopy, and one who was 9 years and 11 months at the time of UBT with no endoscopy

bCategory includes: Métis; mixed Indigenous ethnicities; unspecified Indigenous ethnicity; mixed Indigenous and non-Indigenous ethnicities

**Histopathologic assessment**

Groups defined by * Hp* status had strikingly different frequencies of abnormal histopathology (Table 6). The proportion with normal gastric mucosa was 77% among * Hp*-negative participants evaluated and just 1 of 224 * Hp*-positive participants evaluated. Compared to * Hp*-negative participants, * Hp*-positive participants not only had a much higher prevalence of histologic abnormalities, but they also had a much higher severity gradient, although the frequency of intestinal metaplasia was low in both groups and the difference between groups less striking. Of the 4 * Hp*-negatives with intestinal metaplasia, 2 had a record of previous treatment to eliminate * Hp*.

The results show good statistical precision for describing the severity distributions of the histopathological outcomes and differentiating these distributions in groups defined by * Hp* status. The study population yields even greater precision for differentiating the presence or absence of these outcomes: active gastritis occurred in 96% (95% CI, 92–98%) of positives and 2% (95% CI, 0–8%) of negatives; chronic gastritis occurred in 99% (95% CI, 98–100%) of positives and 13% (95% CI, 6–20%) of negatives; gastric atrophy occurred in 43% (95% CI, 36–49%) of positives and 0% (95% CI, 0–4%) of negatives; intestinal metaplasia occurred in 17% (95% CI, 12–22%) of positives and 5% (95% CI, 1–12%) of negatives; MALT hyperplasia or lymphoid aggregates occurred in 74% (95% CI, 69–80%) of positives and 12% (95% CI, 5–19%) of negatives; lymphoepithelial lesions occurred in 3% (95% CI, 1–6%) of positives and 0% (95% CI, 0–4%) of negatives. Thus, each of these histopathological outcomes was strongly associated with prevalent * Hp* infection in this population.

**Discussion**

This analysis shows a high * Hp*-associated disease burden in four western Canadian Arctic hamlets, with an estimated * Hp* prevalence of 66% among Indigenous residents and 22% among non-Indigenous residents. Among participants examined endoscopically, visible inflammation, erosions and ulcers were more frequent in the stomach relative to the duodenum. Pathological examination revealed a low prevalence of mild abnormalities among * Hp*-negative participants; in contrast, * Hp*-positive participants had a high prevalence of moderate-severe active and chronic gastritis; the prevalence of atrophic gastritis was 43% among * Hp*-positive participants and 0% among * Hp*-negative participants, while the prevalence of intestinal metaplasia was 17% among * Hp*-positive participants and 5% among * Hp*-negative participants.

The pattern of disease observed in this population is consistent with increased risk of stomach cancer. While no cases of dysplasia or carcinoma were detected, none would be expected due to small numbers. During 2008–2016, 3 of the 726 NT participants in this analysis had gastric cancer diagnosed and reported to the NT Cancer Registry (NT Department of Health and Human Services staff, personal communication, July 2018). While small community sizes preclude meaningful estimates of the frequency of gastric dysplasia or carcinoma, the combined community study population yields good statistical precision for estimating the prevalence and severity distributions of less advanced * Hp*-associated pathological outcomes. The elevated ratio of gastric to duodenal lesions is the inverse of the pattern observed in populations where the risk of stomach cancer is low and * Hp* infection frequently leads to duodenal ulcers.
populations at increased risk of stomach cancer [37, 38]. In addition, chronic gastritis and gastric atrophy are initial stages in Correa’s widely accepted model of gastric carcinogenesis [39]; thus, the high prevalence of these conditions are further indications of increased stomach cancer risk in participating communities.

The estimated prevalence of endoscopically and histopathologically diagnosed gastric disease associated with Hp infection in CANHelp community project participants is a rare resource given that very few community-based studies have assessed geographically-defined communities for these diagnoses. A recent clinic-based study of 432 Alaska Natives undergoing endoscopic assessment for digestive symptoms estimated similarly high prevalence of stomach pathology in Hp-positive participants [40]; prevalence estimates for Alaska Native patients and Indigenous CANHelp project participants, respectively, were 78 and 97% for active gastritis, 98 and 99% for chronic gastritis, and 13 and 17% for intestinal metaplasia [40]. Estimated prevalence of stomach pathology in Hp-negative participants was higher in Alaska Native patients than CANHelp project participants, respectively: 18 and 3% for active gastritis; 69 and 14% for chronic gastritis; and 10 and 6% for intestinal metaplasia [40]. The Alaska Native patients had much higher prevalence of endoscopically detectable gastric disease than the CANHelp project participants (for example, 85% of Alaska Native patients had an endoscopic diagnosis of gastritis, in contrast to 14% of CANHelp project participants), which is likely to be due, at least in part, to the clinic-based study design that recruited symptomatic patients who would have more severe disease on average than a community-based population [40]. In addition, the ratio of gastric to duodenal ulcers in the Alaska Native participants was nearly 5 (33:7) [40].

The pattern of gastric disease observed among Hp-positive CANHelp community project participants contrasts sharply with the pattern we reported previously for Hp-positive patients with gastric biopsies evaluated at the University of Alberta Hospital in Edmonton, Alberta (metro area 2016 census population = 1,321,426) between April 2010 and March 2011 [14, 41]. In this patient population (Hp prevalence = 14% in ~3000 patients assessed), of roughly 400 Hp-positive patients evaluated, 11% had active gastritis, 40% had mild chronic gastritis, 55% had moderate chronic gastritis, 5% had severe chronic gastritis, and just 2% had gastric atrophy. Thus, compared to an urban southwestern Canadian population of patients of predominantly European ancestry [41] evaluated for digestive complaints, the community-based study population of residents of predominantly Indigenous western Canadian Arctic hamlets had a prevalence of Hp infection over 4 times higher along with a notably more severe pattern of gastric mucosal injury among those infected. This contrast reveals substantial inequity in the disease burden associated with Hp infection in western Arctic Canadian hamlets relative to a North American metropolis.

In addition to the small study size for estimating rare outcomes, another limitation of this investigation is the possibility that the participants did not accurately represent the participating communities. Within the constraints of available resources, every effort was made to include all residents of participating communities. If

### Table 5

|                        | Hp positive (n = 224) | Hp negative (n = 85) |
|------------------------|----------------------|----------------------|
|                        | n   | %    | 95% CI | n   | %    | 95% CI |
| Normal gastric mucosa  | 177 | 79   | 74, 84 | 65  | 77   | 68, 86 |
| Normal duodenal mucosa | 204 | 91   | 87, 95 | 82  | 96   | 93, 100|
| Normal gastric and duodenal mucosa | 162 | 72   | 66, 78 | 62  | 74   | 64, 83 |
| Esophagitis/esophageal erosions | 19  | 8    | 5, 12  | 9   | 11   | 5, 19  |
| Barrett’s esophagus    | 8   | 4    | 2, 7   | 6   | 7    | 3, 15  |
| Gastric inflammation, erosions, or ulcers | 46  | 21   | 15, 36 | 17  | 20   | 12, 29 |
| Gastritis              | 33  | 15   | 10, 19 | 10  | 12   | 5, 19  |
| Gastric erosions       | 17  | 8    | 4, 11  | 9   | 11   | 5, 19  |
| Gastric ulcer          | 6   | 3    | 1, 6   | 3   | 4    | 1, 10  |
| Duodenal inflammation, erosions, or ulcers | 20  | 9    | 5, 13  | 3   | 4    | 1, 10  |
| Duodenitis             | 16  | 7    | 4, 11  | 3   | 4    | 1, 10  |
| Duodenal erosions      | 3   | 1    | 0, 4   | 0   | 0    | 0, 4   |
| Duodenal ulcer         | 3   | 1    | 0, 4   | 0   | 0    | 0, 4   |

Hp H. pylori, CI binomial Wald confidence interval (binomial exact CI for numerators < 10; one-sided binomial exact 97.5% CI for numerators of 0)

*aOne Hp-negative participant was missing gastric mucosa assessment, so the denominator is 84 for gastric abnormalities among Hp-negatives
Table 6 Severity of gastric pathology by Hp status, 308 CANHelp project participants with histopathology data, 2008–2013

| Pathology                              | Hp positive (n = 224) | Hp negative (n = 84) | χ²-p-value¹   |
|----------------------------------------|-----------------------|----------------------|--------------|
|                                        | n | %⁺ | 95% CI | n | %⁺ | 95% CI |
| Normal histopathology²                 | 223 | 99.6 | 99, 100 | 19 | 23 | 14, 32 | 0.000 |
| Active gastritis³                      | 7 | 3 | 1, 6 | 82 | 98 | 94, 100 | 0.000 |
| Chronic gastritis                      | 2 | 1 | 0, 2 | 73 | 87 | 80, 94 | 0.000 |
| Atrophy                                | 128 | 57 | 51, 64 | 84 | 100 | 96, 100 | 0.000 |
| Intestinal metaplasia                 | 185 | 83 | 78, 88 | 80 | 95 | 91, 100 | 0.002 |
| MALT hyperplasia²                     | 3 | 3 | 1, 9 | 13 | 72 | 52, 93 | 0.000 |
| Lymphoid aggregates³                   | 74 | 58 | 49, 66 | 5 | 8 | 3, 17 | 0.000 |
| Dysplasia or Carcinoma                 | 7 | 3 | 1, 6 | 0 | 0 | 0, 4 | 0.101 |

Hp H. pylori; CI: binomial Wald confidence interval (binomial exact CI for numerators < 10; one-sided binomial exact 97.5% CI for numerators of 0)  
⁺Distributions do not all sum 100% due to rounding  
²Excludes MALT hyperplasia or lymphoid aggregates; includes reactive gastropathy  
³In 2008, presence/absence of lymphoid aggregates was noted without grading MALT hyperplasia; after 2008, MALT hyperplasia was graded instead of noting presence/absence of lymphoid aggregates  
⁴From score test for trend of odds

those who did not participate included a greater proportion of community members who were less eager to engage in health care, then we would likely have underestimated the prevalence of Hp infection and associated pathology. There was also potential for misclassification of Hp status and histopathology outcomes given imperfect diagnostic methods. The accuracy estimates generated by our data for classifying Hp status, however, suggest that our Hp prevalence estimates are roughly accurate for the study population. Also, the comparison of our histopathology results to those of Hp-positive patients evaluated by the University of Alberta Hospital pathology laboratory, where gastric biopsies from our community projects were processed and assessed, enhances the validity of the distinct patterns observed in the Arctic communities.

Conclusions
We have offered an example of the value of community-driven investigations for generating descriptions of the public health burden from diseases identified by affected communities and their healthcare providers to be of high community impact. This research provides evidence of a high burden of disease from Hp infection in Indigenous communities of western Arctic Canada. These results add to a small body of evidence that demonstrates the need for targeted interventions aimed at reducing health risks from Hp infection in Indigenous Arctic communities. In keeping with community-university research agreements, all results have been disseminated within participating communities to address voiced concerns and support community efforts to advocate for relevant resources and policies. In addition, our collaborative team has used these disease burden results, along with results from treatment trials and longitudinal follow-up [17, 42], to create Hp clinical guidelines (not yet published) specific to healthcare practitioners serving Arctic communities in Canada.

Abbreviations
CANHelp: Canadian North Helicobacter pylori; CI: Confidence interval; H2RA: H2-receptor antagonist; Hp: Helicobacter pylori; MALT: Mucosa-associated lymphoid tissue; NT: Northwest Territories; PCR: Polymerase chain reaction; PPI: Proton pump inhibitor; RNA: Ribonucleic acid; UBT: 13C-urea breath test; YT: Yukon

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Authors’ contributions
Each author reviewed the manuscript and gave final approval of the version to be published. Each author takes responsibility for the content that pertains to their area of expertise and agrees to ensure that questions about the accuracy or integrity of any part of the work are investigated and resolved. KFG created databases, cleaned, managed and analyzed data, constructed tables, and drafted the manuscript. JG led community project planning workshops, solicited community input as needed, contributed to the design of participant recruitment and data collection methods, directed...
data collection, created databases, and reviewed the manuscript critically for intellectual content. HJC contributed to the design of participant recruitment and data collection methods and created databases. LM led community project planning workshops, solicited community input as needed, contributed to the design of participant recruitment and data collection methods, and directed data collection. EW led community project planning workshops, solicited community input as needed, directed data collection, and presented results to community planning committees for review. ACol led community project planning workshops, solicited community input as needed, and directed data collection. SVZ directed endoscopy-based inquiry and contributed to planning clinical activities carried out in communities, designing diagnostic testing components, analyzing data and interpreting results. SG designed and directed histopathology-based inquiry and contributed to interpretation of results. BA led the engagement of community members in project planning and contributed to the design of participant recruitment and data collection methods. BH facilitated the input of Yukon health care providers in the research design and contributed to interpretation of results. ACor facilitated the input of Northwest Territories health care providers in the research design and contributed to interpretation of results. JM contributed to the design and implementation of clinical activities. RM facilitated community engagement in research planning and contributed to the design of participant recruitment and data collection methods. KJG led the collaborative team in designing the research, engaging collaborators, as well as analyzing and interpreting the data, and revised the manuscript critically for intellectual content. Other members of the CAN-Help Working Group contributed to the design of research activities and instruments and interpretation of results.

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Availability of data and materials
The datasets used for the current study are available from the corresponding author on reasonable request following community review of proposed data uses.

Ethics approval and consent to participate
This research was approved by the University of Alberta Health Research Ethics Board – Biomedical Panel (study ID Pro00007868). Written informed consent was obtained from all participants or their guardians.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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