Community-driven research on environmental sources of *H. pylori* infection in arctic Canada

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The role of environmental reservoirs in *H. pylori* transmission remains uncertain due to technical difficulties in detecting living organisms in sources outside the stomach. Residents of some Canadian Arctic communities worry that contamination of the natural environment is responsible for the high prevalence of *H. pylori* infection in the region. This analysis aims to estimate associations between exposure to potential environmental sources of biological contamination and prevalence of *H. pylori* infection in Arctic Canada.

Using data from 3 community-driven *H. pylori* projects in the Northwest and Yukon Territories, we estimated effects of environmental exposures on *H. pylori* prevalence, using odds ratios (OR) and 95% confidence intervals (CI) from multilevel logistic regression models to adjust for household and community effects. Investigated exposures include: untreated drinking water; livestock; dogs; cats; mice or mouse droppings in the home; cleaning fish or game.

Our analysis did not identify environmental exposures associated clearly with increased *H. pylori* prevalence, except any exposure to mice or mouse droppings (OR = 4.6, CI = 1.2–18), reported by 11% of participants. Our multilevel models showed *H. pylori* clustering within households, but environmental exposures accounted for little of this clustering; instead, much of it was accounted for by household composition (especially: having infected household members; number of children).

Like the scientific literature on this topic, our results do not clearly implicate or rule out environmental reservoirs of *H. pylori*; thus, the topic remains a priority for future research. Meanwhile, *H. pylori* prevention research should seek strategies for reducing direct transmission from person to person.

In prevalence studies of adults aged 18 to 86 y in various locations across southern Canada, prevalence of *H. pylori* infection ranged from 30–38%.¹⁵ Some studies have reported increasing prevalence with age; for example, in a 1997 study of healthy individuals from Manitoba, including 469 aged 20 to 34 y and 265 aged 35 to 64 years, the prevalence of *H. pylori* infection was 35% and 46%, respectively.¹⁴ Very low prevalence in southern Canadian children of 5% was shown in a 2005 study of 246 pediatric endoscopy patients aged 5 to 18 y from 4 academic centers.⁷ Because the acquisition of chronic *H. pylori* infection is known to occur most frequently in childhood,²,¹⁶,¹⁷ the trend of increasing prevalence with age suggests that transmission levels have decreased over several decades.

Conversely, the literature has shown that Indigenous communities in the circumpolar region have a disproportionately high prevalence of *H. pylori* infection and associated health consequences. *H. pylori* prevalence estimates from community-based studies of Indigenous populations in Canada, Alaska, Greenland and Russia range from 51–95%.⁹,¹⁴,¹⁸ In a study of a 306 adults from a Wasagamack Cree community in Northern Manitoba, 95% were...
found to be \textit{H. pylori}-positive.\textsuperscript{11} A study investigating \textit{H. pylori} infection in 163 children aged 0 to 12 y from the same community revealed that 56\% were positive.\textsuperscript{15} An investigation of \textit{H. pylori} infection in the Inuit communities of Chesterfield Inlet and Repulse Bay, Nunavut found that of 256 individuals of all ages, 51\% in this age group were positive for \textit{H. pylori} infection.\textsuperscript{18}

In response to questions raised by community leaders and health care providers, the Canadian North \textit{Helicobacter pylori} (CANHelp) Working Group (http://canhelpworkinggroup.ca) formed to link Arctic communities, territorial health agencies and investigators from a variety of disciplines based at the University of Alberta. In the conduct of collaborative research aimed to: obtain representative data from diverse settings in northern Canada for informing regional public health strategies for reducing risks from \textit{H. pylori}; conduct policy analysis to identify cost-effective \textit{H. pylori} management strategies that are ethically, economically and culturally appropriate for northern communities; and develop knowledge exchange strategies that help community members understand \textit{H. pylori} health risks as well as available solutions and unsolved challenges for reducing these risks.

The science surrounding the transmission of \textit{H. pylori} remains unclear. Transmission has only been documented in 3 circumstances: patients undergoing endoscopic procedures; accidental infection through gastric pH electrodes; and voluntary oral ingestion of the bacteria.\textsuperscript{2,29} Because it typically colonizes the stomach, the predominantly hypothesized routes involve the mouth as the portal of entry to the stomach. Abundant evidence suggests that the infection is usually transmitted directly from person to person and investigated pathways include fecal-oral, oral-oral, and gastro-oral (ingestion of another person’s regurgitated stomach contents)\textsuperscript{10}; however the relative frequency of transmission through each route is unknown. The human stomach is the only known source of \textit{H. pylori} and evidence from extra-gastric sources has been inconclusive,\textsuperscript{19} leaving the question of how the natural environment impacts transmission unanswered to date. Using data from CANHelp Working Group community projects, this analysis investigates the hypothesis that environmental sources of biological contamination are involved in transmission of \textit{H. pylori} infection.

\section*{Results}

\subsection*{Participant characteristics}

The combined number of participants from the 3 communities was 670: 564 participants provided health history data; 580 individuals provided data on their own socio-environmental exposures; 279 households provided information on socio-environmental household exposures for 650 individual household members; 652 participants were screened for \textit{H. pylori} infection by 13C-urea breath test (UBT) and 645 had classifiable results; 265 participants consented to endoscopy and biopsies were obtained and analyzed from 257 (194 from Aklavik and 63 from Old Crow). The total number of participants with complete data on all environmental exposures and \textit{H. pylori} status was 368 (227 from Aklavik, 89 from Old Crow and 52 from Tuktoyaktuk).

\subsection*{Classification of \textit{H. pylori} status}

Of the 368 individuals included in the analysis, 4\% (n = 16) did not have a UBT result and 51\% (n = 188) did not have histopathology or culture results. Among those with results from all 3 tests used to classify \textit{H. pylori} infection status, 81\% (n = 145) were concordant on all tests. Of those with results on just 2 tests, 93\% (14/15) were concordant on the 2 tests. Of 35 participants with 3 test results that were not concordant, 40\% were positive on 2 of the 3 tests and 60\% were negative on 2 of the 3 tests. These participants were classified based on the results of the 2 tests that agreed (40\% positive, 60\% negative). Of these 35 participants, 74\% (n = 26) had a culture result that disagreed with the other 2 tests. A high level of agreement was observed between the UBT and histopathology; of those with results on both tests (n = 165), 95\% were concordant.

\subsection*{Prevalence of \textit{H. pylori} infection}

\textit{H. pylori} prevalence was 63\% (408/645) in the total study population: 61\% (217/354) in Aklavik; 69\% (132/190) in Old Crow; 58\% (59/101) in Tuktoyaktuk. In those with complete data on all variables, \textit{H. pylori} prevalence was 62\% (227/368).

\subsection*{Socio-demographic effects}

Results of purposeful selection procedures for regression modeling indicated the most important adjustment variables were age, sex, household income, highest educational attainment of each individual, ethnicity and community. Considerable variation across households was observed (standard deviation (SD): 1.3; 95\%CI: 0.69, 2.6). The distribution of socio-demographic characteristics and the estimated ORs and 95\% CIs for their effects on the prevalence odds of \textit{H. pylori} infection in individuals with complete data on all variables (n = 368) are presented in Table 1. In order to more accurately adjust for the non-linear effect of age, a cubic spline with 4 knots was fitted; for this reason, an OR for age is not reported.

\subsection*{Pathways for zoonotic transmission}

The distribution of zoonotic exposures and exposure-specific prevalence of \textit{H. pylori} infection is shown by community in Table 2. The most common zoonotic exposure was contact with animal innards (76\%; 279/368), followed by caring for animals (75\%; 277/368) and, more specifically, caring for dogs (73\%; 269/368). The prevalence of \textit{H. pylori} infection ranged widely from 42–75\% across categories of zoonotic exposures. Observed prevalence was lowest in individuals who reported caring for cats (42\%; 15/36) and highest in those who reported evidence of mice in their homes (78\%; 31/40).

Results of logistic regression analysis for zoonotic exposures appear in Table 3, with unadjusted ORs presented along with ORs from 2 multivariable models: the first including age as a cubic spline, sex, ethnicity, income, education, community as a fixed effect, and household as a random effect; and the second adding to that set of variables all water and zoonotic exposures. The largest effect observed was for the comparison of individuals who reported having seen mice or mouse droppings in their homes compared to those who reported that they had not. The
most fully adjusted OR for the effect of exposure to mice compared to no exposure to mice on prevalent *H. pylori* infection was 4.6 (95%CI: 1.2, 18). It should be noted, however, that only 14.4% of participants reported exposure to mice. Remaining effects were modest, with the exception of the crude OR for the effect of cat ownership compared to not owning cats. However, this effect became weak and highly imprecise following adjustment for socio-demographic and other environmental variables (OR: 1.4; 95%CI: 0.34, 5.4).

### Pathways for waterborne transmission

The distribution of exposure to pathways for waterborne transmission and associated prevalence of *H. pylori* infection in each community is shown in Table 4. Having ever consumed untreated water was the most commonly reported exposure to water potentially contaminated with human pathogens (77%; 282/368). Prevalence of *H. pylori* infection in different exposure categories ranged from 59–61%. The combined prevalence among those included in the analysis fell just outside of this range (62%). Further, this range is much narrower than that of the community-specific estimates of prevalence. *H. pylori*-positivity was highest in those who reported ever consuming untreated water (61%; 172/282) and doing so in the past year (61%; 75/123). It should be noted that *H. pylori* prevalence among participants reporting consumption of untreated water was much lower in Tuktoyaktuk than the other 2 communities.

Results of logistic regression analysis for exposure to sources of water potentially contaminated with human pathogens are presented in Table 5. The largest effect was for the comparison of individuals who had consumed untreated water at some point in their life compared to those who had not. The OR estimated a strong inverse association following adjustment for socio-

### Table 1: Effects of socio-demographic characteristics on *H. pylori* prevalence odds among 368 community *H. pylori* project participants, Northwest and Yukon Territories, 2008–2011.

| Variable             | N    | OR   | 95%CI |
|----------------------|------|------|-------|
| Sex                  |      |      |       |
| Male                 | 177  | 1.0  |       |
| Female               | 191  | 1.0  | (0.57, 1.8) |
| Ethnicity            |      |      |       |
| Inuvialuit           | 173  | 1.0  |       |
| Gwich’in             | 134  | 0.58 | (0.24, 1.3) |
| Other Aboriginal     | 16   | 2.0  | (0.36, 11) |
| Non-Aboriginal       | 45   | 0.058| (0.013, 0.26) |
| Household Size       |      |      |       |
| 5+ people            | 114  | 1.0  |       |
| 2–4 people           | 193  | 0.49 | (0.22, 1.1) |
| 1 person             | 61   | 0.34 | (0.11, 1.0) |
| Household Income     |      |      |       |
| <$25,000             | 104  | 1.0  |       |
| $25,000–34,999       | 41   | 0.66 | (0.24, 1.8) |
| $35,000–49,999       | 35   | 1.3  | (0.41, 3.9) |
| $50,000–74,999       | 80   | 0.49 | (0.22, 1.2) |
| ≥ $75,000            | 108  | 0.41 | (0.18, 0.95) |
| Education            |      |      |       |
| Less than High School| 193  | 1.0  |       |
| High School          | 57   | 1.0  | (0.46, 2.4) |
| Trades Certificate   | 53   | 0.68 | (0.28, 1.7) |
| College or University| 65   | 1.2  | (0.46, 2.9) |
| Community            |      |      |       |
| Aklavik              | 227  | 1.0  |       |
| Old Crow             | 89   | 3.1  | (1.2, 8.0) |
| Tuktoyaktuk          | 52   | 0.84 | (0.33, 2.1) |

Adjusted for age as a cubic spline, sex, ethnicity, income, education, all waterborne and zoonotic exposures, community as a fixed effect, and household as a random effect.

### Table 2: Pathways for zoonotic transmission: Exposure prevalence and exposure-specific *H. pylori* prevalence by community among 368 community *H. pylori* project participants, Northwest and Yukon Territories, 2008–2011.

| Variable                          | Aklavik, NT | H. pylori prevalence in category n (%) | Old Crow, YT | H. pylori prevalence in category n (%) | Tuktoyaktuk, NT | H. pylori prevalence in category n (%) |
|-----------------------------------|-------------|----------------------------------------|-------------|----------------------------------------|-----------------|----------------------------------------|
| Evidence of Mice                  |             |                                        |             |                                        |                 |                                        |
| No                                | 195 (86)    | 116 (60)                               | 84 (94)     | 56 (67)                                | 49 (94)         | 24 (49)                               |
| Yes                               | 32 (14)     | 23 (72)                                | 5 (6)       | 5 (100)                                | 3 (6)           | 3 (100)                               |
| Cared for Any Animals/Livestock   |             |                                        |             |                                        |                 |                                        |
| No                                | 53 (23)     | 36 (68)                                | 14 (16)     | 9 (64)                                 | 24 (46)         | 14 (58)                               |
| Yes                               | 174 (77)    | 102 (59)                               | 75 (84)     | 52 (69)                                | 28 (54)         | 13 (46)                               |
| Cared for Dogs                    |             |                                        |             |                                        |                 |                                        |
| No                                | 55 (24)     | 37 (67)                                | 15 (17)     | 10 (67)                                | 29 (56)         | 15 (52)                               |
| Yes                               | 172 (76)    | 102 (59)                               | 74 (83)     | 51 (69)                                | 23 (44)         | 12 (52)                               |
| Cared for Cats                    |             |                                        |             |                                        |                 |                                        |
| No                                | 207 (91)    | 130 (63)                               | 86 (97)     | 59 (69)                                | 39 (75)         | 23 (59)                               |
| Yes                               | 20 (9)      | 9 (45)                                 | 3 (3.4)     | 2 (67)                                 | 13 (25)         | 4 (31)                                |
| Contact with Animal Innards       |             |                                        |             |                                        |                 |                                        |
| No                                | 64 (28)     | 42 (66)                                | 14 (16)     | 7 (50)                                 | 11 (21)         | 3 (27)                                |
| Yes                               | 163 (72)    | 97 (60)                                | 75 (84)     | 54 (72)                                | 41 (79)         | 24 (59)                               |
demographic variables (OR: 0.44; 95%CI: 0.20, 0.96) and other environmental exposures (OR: 0.36; 95%CI: 0.14, 0.94), consistent with a protective effect of having ever consumed untreated water on *H. pylori* infection prevalence odds. Given the large difference between Tuktoyaktuk and the other communities, this effect was also estimated among participants from Aklavik and Old Crow alone (OR: 0.62; 95%CI: 0.29, 1.4).

Household effect

A random effects parameter for household was required for the multivariable logistic regression models because the odds of *H. pylori* infection among participants residing in the same household cannot be assumed to be independent. This parameter captures the degree to which *H. pylori* infection clusters by household among participants and yields information about any residual effect of household membership on *H. pylori* prevalence odds that cannot be explained by variables included in the model. The size of the standard deviation (SD) of the random effects parameter reflects the degree of residual household effect, with the SD shrinking as the random effect diminishes. Fig. 1 shows the random household effect relative to the effect of independent variables from logistic regression models with different subsets of independent variables. Comparison of these models shows a strong effect of household membership on *H. pylori* prevalence beyond that captured by the investigated environmental exposures. Adding cohabitation with another research participant...

### Table 3: Pathways for zoonotic transmission

| Variable                      | Unadjusted Estimates | Model 1 | Model 2 |
|-------------------------------|----------------------|---------|---------|
|                               | OR 95%CI             | OR 95%CI| OR 95%CI|
| Evidence of Mice              |                      |         |         |
| No                            | 1.0                  | 1.0     | 1.0     |
| Yes                           | 2.3 (1.1, 5.0)       | 4.1 (1.2, 14) | 4.6 (1.2, 18) |
| Cared for Any Animals/Livestock|                     |         |         |
| No                            | 1.0                  | 1.0     | 1.0     |
| Yes                           | 0.84 (0.51, 1.4)     | 0.78 (0.39, 1.6) | 0.82 (0.38, 1.8) |
| Cared for Dogs                |                      |         |         |
| No                            | 1.0                  | 1.0     | 1.0     |
| Yes                           | 0.94 (0.59, 1.5)     | 0.76 (0.38, 1.5) | 0.72 (0.33, 1.6) |
| Cared for Cats                |                      |         |         |
| No                            | 1.0                  | 1.0     | 1.0     |
| Yes                           | 0.40 (0.20, 0.81)    | 1.26 (0.37, 4.3) | 1.4 (0.34, 5.4) |
| Contact with Animal Innards   |                      |         |         |
| No                            | 1.0                  | 1.0     | 1.0     |
| Yes                           | 1.2 (0.74, 1.9)      | 1.19 (0.57, 2.5) | 1.6 (0.70, 3.6) |

*Adjusted for age as a cubic spline, sex, ethnicity, income, education, community and household as a random effect. Model 1 plus all waterborne and zoonotic exposures.*

### Table 4: Pathways for waterborne transmission

| Variable                | Aklavik, NT | Old Crow, YT | Tuktoyaktuk, NT |
|-------------------------|-------------|--------------|-----------------|
| Proportion of 227       |             |              |                 |
| participants in         |             |              |                 |
| category n (%)          |             |              |                 |
| Ever Consumed Untreated |             |              |                 |
| Water                  |             |              |                 |
| No                      | 75 (33)     | 46 (61)      | 8 (9)           |
| Yes                     | 152 (67)    | 93 (61)      | 81 (91)         |
| Contaminated Water      |             |              |                 |
| (Sewage)                |             |              |                 |
| No                      | 180 (79)    | 111 (62)     | 44 (49)         |
| Yes                     | 47 (21)     | 28 (60)      | 45 (51)         |
| Proportion of 89        |             |              |                 |
| participants in         |             |              |                 |
| category n (%)          |             |              |                 |
| Ever Consumed Untreated |             |              |                 |
| Water                  |             |              |                 |
| No                      | 169 (74)    | 103 (61)     | 58 (65)         |
| Yes                     | 58 (26)     | 36 (62)      | 31 (35)         |
| Contaminated Water      |             |              |                 |
| (Sewage)                |             |              |                 |
| No                      | 132 (59)    | 101 (53)     | 62 (33)         |
| Yes                     | 47 (21)     | 28 (60)      | 31 (35)         |
who was \textit{H. pylori} -positive considerably reduced the residual household effect (SD: 0.62; 95%CI: 0.96, 4.04), as did the number of children in the home (SD: 43; 95%CI: 0.016, 11.3).

Table 6 shows estimated ORs for the effects of the household composition variables on prevalent \textit{H. pylori} infection. Though estimated somewhat imprecisely, the estimated ORs show a strong positive association with increasing household size and an even stronger one with an increasing number of children in the home. The weak effect estimated for living with an \textit{H. pylori}-positive household member may be due to many households including members who did not participate in the community projects.

Sensitivity analysis

Table 7 shows results from models that repeat the analysis using different approaches to classifying participants with discordant results on \textit{H. pylori} tests: classifying them in one model based on the culture result, in another model based on the histopathology result and in another model based on the UBT result. While the largest changes are noted for the model that bases the classification on culture, the degree of change across the models does not substantially alter the interpretations of the estimated effects. Of note, none of the estimates in any of the 3 models fall outside of the originally estimated 95% CIs.

\textbf{Figure 1.} Random effect of household (SD) relative to the effect of independent variables in the model. Model 1. Household Random Effect (SD): 1.26; 95%CI: 0.70, 2.3 Model 2. Household Random Effect (SD): 1.16; 95%CI: 0.59, 2.3 Model 3. Household Random Effect (SD): 1.11; 95%CI: 0.54, 2.3 Model 4. Household Random Effect (SD): 0.62; 95%CI: 0.96, 4.04 Model 5. Household Random Effect (SD): 0.43; 95%CI: 0.016, 11.3.
Discussion

The prevalence of *H. pylori* infection observed in the CANHelp Working Group community projects in the Northwest and Yukon Territories of 62% falls within the expected range for Indigenous communities in the circumpolar north, based on reports from the eastern Canadian Arctic and other Arctic countries. In contrast to evidence from major urban centers across Canada that suggests decreasing *H. pylori* transmission over time and an average prevalence of approximately 20–30%, the much higher *H. pylori* prevalence observed in these western Canadian Arctic communities shows it to be a health inequity and justifies the concerns expressed by leaders of these communities and their health care providers. Among the major research goals of interest in these community-driven projects is finding out if there are local environmental reservoirs of *H. pylori* infection that can be eliminated or reduced. The present analysis does not clearly identify indicators of exposure to waterborne or zoonotic pathways as exposures of concern in the participating communities.

While this analysis showed participants who reported evidence of mice in their homes to have a relatively high prevalence of *H. pylori* infection compared to others, only 40 of 368 (11%) participants reported this exposure, thus it is unlikely that mice play a major role in transmission, unless the exposure generally goes unnoticed, is otherwise underreported, or occurs more frequently outside the home. A review of the literature pertaining to mice and *H. pylori* transmission revealed the pervasive use of mice in animal models and repeated demonstration of the ability to inoculate mice with *H. pylori*, supporting the plausibility of mice playing a role in transmission. However, the literature lacks epidemiologic investigations of the effect of exposure to mice on the risk of *H. pylori* infection. Thus, conclusions about this observation cannot be drawn without further research to determine whether this association is observed in other settings, and if so, if it reflects a role in transmission or is confounded by

| Variable                                      | n  | OR  | 95%CI |
|-----------------------------------------------|----|-----|-------|
| Number of Household Members (per person increase) | 368| 1.2 | 0.98, 1.5 |
| Positive Family Member                        |    | 1.0 |       |
| No                                            | 201| 1.0 |       |
| Yes                                           | 167| 1.2 | 0.5, 3.0 |
| Number of Children in Home (per person increase) | 368| 1.4 | 0.96, 2.2 |

Table 7: Sensitivity analysis showing estimates based on different methods for classifying *H. pylori* infection status of participants with discordant results (n = 368)

| ta | Model 1 | Model 2 | Model 3 | Model 4 |
|----|---------|---------|---------|---------|
| Evidence of Mice | 1.0 | 1.0 | 1.0 | 1.0 |
| Yes | 4.6 (1.2, 18) | 6.1 (1.5, 25) | 4.7 (1.3, 17) | 4.1 (1.2, 15) |
| Cared for Any Animals/Livestock | 1.0 | 1.0 | 1.0 | 1.0 |
| No | 0.82 (0.38, 1.8) | 1.2 (0.57, 2.6) | 0.95 (0.47, 1.9) | 0.92 (0.46, 1.9) |
| Yes | 0.72 (0.33, 1.6) | 1.2 (0.56, 2.5) | 0.88 (0.44, 1.8) | 0.85 (0.42, 1.7) |
| Cared for Cats | 1.0 | 1.0 | 1.0 | 1.0 |
| No | 1.4 (0.34, 5.4) | 0.81 (0.23, 2.9) | 0.98 (0.29, 3.3) | 1.02 (0.3, 3.5) |
| Yes | 1.6 (0.70, 3.6) | 1.2 (0.53, 2.7) | 1.84 (0.74, 3.2) | 1.5 (0.71, 3.2) |
| Contact with Animal Innards | 1.0 | 1.0 | 1.0 | 1.0 |
| No | 1.0 (0.36, 0.94) | 0.45 (0.19, 1.1) | 0.47 (0.21, 1.1) | 0.45 (0.2, 1) |
| Yes | 0.85 (0.40, 1.8) | 0.87 (0.44, 1.7) | 0.73 (0.38, 1.4) | 0.76 (0.40, 1.5) |
| Ever Consumed Untreated Water | 1.0 | 1.0 | 1.0 | 1.0 |
| No | 1.0 (0.22, 1.1) | 0.46 (0.21, 1) | 0.49 (0.24, 0.98) | 0.55 (0.27, 1.1) |
| Yes | 0.49 | 1.0 | 1.0 | 1.0 |

Discordant results adjusted based on the developed algorithm.
Discordant results re-classified based on culture result.
Discordant results re-classified based on histopathology result.
Discordant results re-classified based on 13C-UBT result.
All models adjusted for age as a cubic spline, sex, ethnicity, income, education, community, all waterborne and zoonotic exposures and household as a random effect.
other risk factors. The estimated effects of regular contact with dogs or cats on *H. pylori* prevalence were modest and imprecise. The estimate for regular care of dogs was slightly more precise, with a 95% CI indicating the data are compatible with effect estimates ranging from a large protective effect to a small detrimental effect. The imprecision around the effect estimate for cat ownership on *H. pylori* prevalence is likely due to the very small number of participants who reported owning a cat.

These findings were consistent with a body of literature that examined the prevalence of non-*pylori* Helicobacter organisms in a variety of animals, with reported prevalence of 67 to 100% in some species.23-28 While the prevalence of these other Helicobacter species is quite high in some animal species, it is estimated that no more than 1% of humans are infected with these other species, indicating they are not readily transmitted between animals kept as pets or livestock and humans.16,29 The present analysis is inconclusive about a moderate effect of exposure to animal innards in the transmission of *H. pylori* in the participating communities.

The estimated effects of sources of potential exposure to contaminated water on *H. pylori* prevalence show inverse associations, with widely varied effects across communities. Based on the reviewed literature, inverse associations were not expected. While the scientific community has been unable to demonstrate conclusively whether *H. pylori* organisms are able to retain infectivity in water, epidemiologic investigations of exposure to sources of untreated water suggest the potential for waterborne transmission of *H. pylori*.34-45 However, a large proportion of the estimates reported in the literature have 95% CIs that indicate the association may actually be closer to the null.34,36,40,41,43,45 While some authors have reported null associations between untreated water consumption and prevalence of *H. pylori* infection,16,36,46 null findings were not commonly reported in the literature. This may be due, in part, to a tendency for papers presenting positive results to be favored for publication over those presenting null associations. It may be that our analysis failed to identify factors that confound the association between untreated water consumption and prevalent *H. pylori* infection among our community project participants, or perhaps was affected by differential recall of water consumption.

An important limitation of this analysis is misclassification of exposure and confounding variables caused by errors in questionnaire data, which likely occurred to some degree due to the respondents’ imperfect recall. Additionally, some of the exposures of interest had a low prevalence among participants, and this led to poor statistical precision for some of the estimated effects. Selection bias due to differential participation rates in relevant project components is also possible. At the same time, major strengths of this analysis include the population-based dataset and the high level of engagement of community members who seek solutions for this health problem and their health care providers.

The observations reported here likely apply more broadly to understanding *H. pylori* transmission in northern Canadian communities and similar populations. Clear identification of *H. pylori* transmission pathways is needed for the development of meaningful public health policy aimed at preventing the spread of the bacteria. While the science surrounding transmission remains unclear, evidence suggests that *H. pylori* often spreads directly from person to person through contact with digestive fluids containing the organism. The prospect of contamination of the local environment with *H. pylori* is a commonly expressed concern among CANHelp Working Group community project participants. Because the available evidence does not clearly rule out waterborne or zoonotic transmission of *H. pylori* infection, it remains important to investigate potential environmental reservoirs. Additional data from other Arctic communities will permit more precise estimation of the effects of exposure to environmental sources of biological contamination on prevalent *H. pylori* infection. At the same time, *H. pylori* control efforts should help communities focus on strategies for reducing the frequency of communicable diseases that spread directly from person to person.

### Materials and Methods

#### Study populations

Health officials in the Northwest Territories (NT) sought this research on behalf of communities like the Hamlet of Aklavik, where leaders expressed concern about the role of *H. pylori* in gastric cancer, perceived as afflicting an excessive number of community members. Thus, the CANHelp Working Group selected Aklavik NT as the target community for beginning its research in 2007, as described elsewhere.47 According to the 2006 census, Aklavik had 590 residents with 92% identifying with either Gwitch’in (Athabascan First Nations) or Inuvialuit (western Canadian Inuit) cultures.48 In 2010, the second community project began in Old Crow, Yukon Territory (YT), at the request of community leaders. According to the 2011 census, the population of Old Crow was 245, with 86% identifying as Gwitch’in.49 The third community project began in Tuktoyaktuk, NT in 2011. According to the 2011 census, the population of Tuktoyaktuk was 854, with 85% identifying as Inuvialuit, First Nations or Métis (officially recognized by the Canadian government as an Aboriginal group with mixed European and Indigenous ancestry).50 Many residents of these communities follow a traditional lifestyle of hunting, trapping and fishing, incorporating modern technologies such as computers and snowmobiles. Aklavik and Tuktoyaktuk are accessible by water or air in the summer and ice road in the winter. Old Crow is accessible only by air.48-52

#### Study design and community projects

This analysis used data collected in cross-sectional studies of *H. pylori* infection as part of the CANHelp Working Group community projects in Aklavik, Old Crow and Tuktoyaktuk. The cross-sectional design is appropriate for initial investigations of the burden of disease from *H. pylori* in a community setting, given that the onset of this infection generally goes undetected and often persists indefinitely without symptoms. Thus, the starting point for describing the frequency of *H. pylori* infection in a community is screening to detect prevalent cases. Projects were
established independently in each community, with the guidance of a local planning committee. Each participating community chose to follow a similar design to previous projects, to allow for comparability. Community projects included 5 components: questionnaire-based interviews to collect information on relevant personal and household characteristics, non-invasive screening for H. pylori infection, endoscopy of the stomach with gastric biopsy for endoscopic and histopathological assessment of gastro-duodenal disease and isolation of H. pylori to investigate characteristics of bacterial strains, treatment to eliminate H. pylori, and knowledge exchange. Planning committees comprised community representatives and University of Alberta project staff. The planning committees guided the design and conduct of the projects to ensure that the research addressed local priorities in a culturally appropriate manner. Community planning committees were given the opportunity to review this report and provided feedback prior to publication.

Each community project sought to enrol all consenting community members during defined enrolment periods. Recruitment occurred in Aklavik primarily from November 2007 through February 2008, in Old Crow primarily from November 2010 through February 2011 and in Tuktoyaktuk during February-March 2011 and March-May of 2012. With local guidance from planning committees in each community, recruitment activities included community gatherings, flyers, radio announcements, information tables in high traffic locations and door-to-door outreach.

The planning process highlighted the scientific importance of using similar methodological approaches across communities for the purpose of comparability and each planning committee chose to keep the data collection methods as similar as possible to those used in other communities, with only minor differences arising from variations in the local setting. Due to logistic constraints, the community projects were not all carried out simultaneously, but there is no evidence to suggest that the occurrence of H. pylori infection followed any secular trend during the brief time span of these community projects. For these reasons, this analysis combined the data collected from individual projects in order to enhance statistical power for estimating associations that appeared homogeneous across communities and to explore differences across communities to gain a better understanding of the factors that contribute to the burden of disease at the community level.

Classification of H. pylori infection status

The 13C-urea breath test (UBT) was the primary method used for to detect H. pylori infection in community project participants. Participants who had endoscopy were also classified for H. pylori status according to pathological examination of gastric biopsies and culture. The H. pylori status of each participant was classified using all available information, with a systematic algorithm used in cases with discordant results. Given uncertainty regarding the classification of discordant results, a sensitivity analysis was performed to assess the extent to which the estimated effects would change if the classification scheme for discordant results were altered and the test results of participants with discordant results not adjusted based on all available information. This analysis used 3 variations of the fully adjusted model; each classified the infection status of participants with discordant results based solely on one of the 3 tests (culture, histopathology, UBT).

The UBT is considered the most accurate and convenient noninvasive method for detecting active H. pylori infection in children and adults. The sample collection protocol and interpretation of test values was adapted from the IRIS and labeled urea manufacturer (http://www.helikitt.com/en/physician-information) instructions, modified according to the conclusions of the Gisbert and Parajes (2004) systematic review of validation studies. While providing breath samples, participants were asked about factors believed to impair UBT accuracy (recent use of specific medications, when they last ate, height/weight for children aged 5 y and younger). Most participants were screened by UBT upon enrolment while providing study data in response to interviewer-administered questionnaires. The sample bags were packaged loosely in plastic containers to avoid being put under pressure during transport while being shipped to the University of Alberta. All UBTs were analyzed using an infrared breath test analyzer (IRIS by Wagner).

For participants aged 5 y or younger, methods adapted from Klein et al. (1999) were used to correct for the influence of anthropometric differences in CO2 production believed to inflate the test values. A borderline test value was interpreted as meaning the participant might have the infection but another factor may have influenced the result, for example, a proton pump inhibiting medication, or having recently consumed food or drink with a high 13C level. Individuals with a test result classified as borderline were advised to repeat the test for a more accurate result. Individuals were also advised to repeat their test if the CO2 concentration in either sample was too low for accurate analysis or the test value was implausible. For repeat tests, the test with the best CO2 concentration was used.

Endoscopies were offered to individuals aged 15 y or older in Aklavik in February of 2008 and Old Crow in January of 2012, irrespective of infection status. (The endoscopy phase of the project had not yet taken place in Tuktoyaktuk at the time of this analysis.) In each community, an endoscopy unit was set up in the health center and a medical team led by project gastroenterologists performed unsedated upper gastrointestinal endoscopies using thin gastroscopes. For consenting participants, endoscopists examined the stomach for gastric lesions and took 7 biopsies of the gastric mucosa, 2 for microbiological examination and 5 for histopathological examination, from pre-specified locations in the stomach. The biopsy sampling protocol adhered to the updated Sydney protocol. If an endoscopically visible lesion was present, the endoscopist took an extra biopsy of the lesion for pathological examination. Of the biopsies collected for microbiological examination, one was taken from the antrum and one from the body of the stomach. Upon culture of Helicobacter organisms, project microbiologists confirmed that the organisms were H. pylori. A single pathologist examined all biopsies to identify H. pylori, measure its density in the gastric mucosa, and characterize histopathological abnormalities.
Exposure ascertainment

Selection of environmental exposures of interest was based on the scientific literature and relevance to the communities. Environmental exposures were grouped based on their relevance to known modes of transmission of infectious agents: pathways for zoonotic transmission (evidence of mice in the home; caring for animals; caring for dogs; caring for cats; and contact with animal innards) and pathways for waterborne transmission (ever consumed untreated water; consumed untreated water in the past year; exposure to sewage (contaminated water)).

Structured interviews conducted by trained interviewers were used to collect data on health history, demographic characteristics and exposure to relevant socio-environmental factors. The questionnaire instruments included items pertaining to individuals and households as appropriate. Questionnaires that ascertained characteristics and exposures of individuals were administered to each participant. Parents decided if participating children were mature enough to respond for themselves. Additionally, a household questionnaire was administered to one adult member of each household. Questionnaires were adapted from previous research conducted by the principal investigator and were informed by relevant scientific literature. Members on each community planning committee reviewed the questionnaires to assist in tailoring their content to the cultural context of each community. Environmental exposure variables were taken from responses provided in structured interviews (Table 8).

The questionnaire data included other variables of interest as potential confounding factors: family size and structure, educational attainment, occupation, residential crowding and hygienic practices.

Ethics approval

This research was approved by the University of Alberta Health Research Ethics Board, as well as the Aurora Research Institute, which issues licenses for the conduct of research in the Northwest Territories, and the Heritage Resource Unit of the Yukon Department of Tourism and Culture, which issues licenses of the conduct of research in the Yukon Territory.

Statistical analysis

The goal of this analysis was to estimate the effect of specified environmental exposures on the prevalence of *H. pylori* infection in the combined population of the 3 participating communities. To examine the underlying relationships of relevant variables,

| Table 8 Variable definitions and response options for environmental exposures |
| Variable | Question [Household/Individual Level Variable] | Response Options |
|----------|-----------------------------------------------|-----------------|
| Zoonotic Transmission | **Mice / Mouse Droppings** | Do you ever have problems with mice getting into your house / have you seen mice or mouse droppings in your house? [Household Level] |
| Any Animals | **Any Animals** | Have you yourself ever regularly been the caretaker for one or more animals (such as pets or livestock), doing any of the following: feeding, grooming, cleaning up after, petting or playing with? [Individual Level] |
| Dogs | **Dogs** | Have you ever been the regular caretaker of a dog? [Individual Level] |
| Cats | **Cats** | Have you ever been the regular caretaker of a cat? [Individual Level] |
| Animal Innards | **Animal Innards** | Have you ever cleaned fish or game? [Individual Level] |
| Waterborne Transmission | **Untreated water (ever)** | Did you ever, including when you were a child, drink river water that was not treated at the water treatment plant, for example water taken directly from a river, lake or creek? [Individual Level] |
| Untreated water (past year) | **Untreated water (past year)** | According to your best estimate, how often in the past 12 months have you consumed: untreated, unboiled river water; melted river or lake ice; or melted snow? [Individual Level] |
| Sewage / Contaminated water | **Sewage / Contaminated water** | Has your household ever had any problems with sewage? [Household Level] |
H. pylori prevalence was compared across categories of exposure variables by community. Prevalence odds ratios (OR) and 95% confidence intervals (CI) were used to estimate effects, as recommended for prevalence studies by Pearce (2004). In order to account for lack of independence of response probabilities given a contagious outcome and participants clustered in households and communities, a mixed logistic regression model was used, adjusting for clustering in communities as a fixed effect and in households as a random effect. The statistical software package STATA version 10 was used for statistical analyses.

Purposeful selection, as proposed by Hosmer and Lemeshow (2000), was used to select variables to control confounding in multivariable models. Given the large number of factors to consider, each potential confounder was assessed in a logistic regression model that estimated the crude OR for its association with the dependent variable. Variables with unadjusted ORs yielding a P-value ≤ 0.25 were subsequently included in a multivariable logistic regression model. Variables included in the multivariable model were then removed one at a time; if removal changed the coefficient of any independent variable by ≥10%, the removed variable was included as a confounder in the final model. Exposures of interest and scientifically important variables were included regardless of statistical significance.

Lowess plots were used to visually assess whether continuous variables had a linear relationship with the respective outcome variable. If the relationship did not appear linear, appropriate transformations were tested. In order to faithfully adjust for the shape of the continuous data, cubic splines were fitted to the variable. The mathematical function used to create the cubic spline included terms which allowed the line to move up or down with the data, minimizing residual confounding resulting from fitting a straight-line relationship to non-linear data. The number of knots was chosen based on the visual assessment of the data and locations of the knots generated by STATA were checked by visual assessment of the lowess plot to ensure adequate placement. The LR test was used to statistically assess the fit of a model containing the continuous variable modeled as a cubic spline, relative to a model with the continuous variable modeled as having a linear relationship with the outcome. If the resulting P-value was ≤ 0.05, the model containing the cubic spline was deemed a better fit for the data.

To identify factors that accounted for household clustering of the infection, the coefficient for the household random effect was compared across models that included subsets of the study variables. The household random effects parameter coefficient is the standard deviation (SD), which can be interpreted as an estimate of the change in the log-odds of prevalent H. pylori infection by household. To compare the relative contributions to the household effect of environmental exposures and composition of household membership, independent variables measuring aspects of household composition (household size in one-person increments, cohabitation with one or more research participants who tested H. pylori-positive, and number of children ≤ 12 y of age living in the home in one-person increments) were added one at a time to the model including the selected socio-demographic and environmental variables, to observe their influence on the residual household effect. Because random effects follow a normal distribution with a mean of 0, the standard deviations for the random effects parameter from each model were plotted as normal distributions using Excel. The β coefficients for each independent variable and their 95% confidence intervals were plotted along the x-axis of each graph, to show the amount of variation explained by the independent variables relative to the residual household effect.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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