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Endemic Iron Deficiency Associated With *Helicobacter pylori* Infection Among School-Aged Children in Alaska

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ABSTRACT

OBJECTIVES. Rural Alaska Natives have a high prevalence of iron deficiency and *Helicobacter pylori* infection. The objective of this study was to estimate the prevalence of iron deficiency, iron-deficiency anemia, and active *H pylori* infection among school-aged children in rural Alaska.

METHODS. We enrolled 68% (688) of the 7- to 11-year-old children from 10 predominantly Alaska Native villages in southwestern Alaska. We collected venous blood samples to assess iron deficiency and anemia. Each child was tested for active *H pylori* infection by ^{13}C-urea breath test (UBT). Evaluated risk factors included age, gender, village of residence, number of household members, number of household members who were younger than 5 years, recent antibiotic use, and household water source.

RESULTS. Of 688 enrolled children, iron deficiency was present in 38%, iron-deficiency anemia was present in 7.8%, and *H pylori* infection by UBT was present in 86%. Iron deficiency was independently associated with living in a household with >6 people and village of residence. *H pylori* infection by UBT was independently associated with child's age ≥10 years and village of residence. Ninety-one percent of children with iron deficiency had *H pylori* infection by UBT, and children with active *H pylori* infection were more likely to be iron deficient than uninfected children. Children with *H pylori* infection by UBT were also more likely to have iron-deficiency anemia than uninfected children.

CONCLUSIONS. In this study of nearly 700 children in 10 different villages in Alaska, we confirmed that the high prevalence of iron deficiency persists among school-aged children. We found that active *H pylori* infection was independently associated with iron deficiency and iron-deficiency anemia among children in this region. *H pylori* infection may account for a portion of the iron deficiency and iron-deficiency anemia in rural Alaska and other areas with high prevalences of both conditions. Innovative approaches are critically needed to address the iron deficiency in high prevalence areas such as rural Alaska and most of the developing world.

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Key Words
Helicobacter pylori, children, iron deficiency, infection, Alaska

Abbreviations
CI— confidence interval
PR—prevalence ratio
OR— odds ratio

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IRON DEFICIENCY ADVERSELY affects cognitive development and behavior in infants and children[1] and is the most common micronutrient deficiency among children worldwide.[2] The prevalence of iron deficiency among children in developing countries exceeds 50% and is usually attributed to inadequate nutrition.[2] Although the iron deficiency prevalence among school-aged children in the United States is only 4%,[3] the prevalence among Alaska Native children approaches 30%,[4–6] similar to that seen in developing nations and other arctic populations.[7,8]

Iron deficiency among children in most high-prevalence areas has been attributed primarily to poor nutritional intake or parasitosis.[2,9] In Alaska, however, evidence has not supported a substantial role for either of these common causes of iron deficiency. Three separate studies found that the average daily iron intake among Alaska Natives in rural Alaska was very near or above the US recommended dietary allowance.[5,10,11] Excessive parasitosis among this population has not been reported by the Alaska Division of Public Health, and a prevalence study in Alaska found the incidence of hookworm infection, an important cause of anemia in developing countries, to be well below the US average.[12]

Many areas of the world with high iron deficiency prevalences also have high *Helicobacter pylori* prevalences,[13–15] including western Alaska, where seroprevalence among adults exceeds 80%.[6] Recent investigations among Alaska Natives[5,6,11] and other populations worldwide[16–21] found an association between iron deficiency and *H pylori* infection. Previous studies were limited by small sample sizes or the use of anti–*H pylori* immunoglobulin G antibody positivity as a surrogate marker of infection. Serologic testing in children often leads to false-positive and -negative results and does not distinguish between past and current infection.[22] These data raise the possibility that *H pylori* infection may contribute to global iron deficiency, but no large or population-based studies have been conducted to evaluate the association between iron deficiency and active *H pylori* infection (ie, infection documented by breath and/or stool testing) among children.

We conducted a population-based, cross-sectional study to estimate the prevalence of iron deficiency, iron-deficiency anemia, and active *H pylori* infection among school-aged children in rural Alaska. We evaluated risk factors for each of these conditions and hypothesized that iron deficiency was independently associated with active *H pylori* infection.

METHODS

Setting

The current study was the preliminary screening phase of a randomized clinical trial to evaluate the effect of *H pylori* therapy on iron deficiency and was conducted in the Bristol Bay and Yukon-Kuskokwim regions of southwestern Alaska. These regions have a combined population of ~30 000, which is 85% Alaska Native (Yup'ik Eskimo) and which lives predominantly in isolated and small villages (outside of the 2 main regional centers, the population per village ranges from 75 to 1014 people). At the time of the study, most village residents had a subsistence lifestyle, and 20% to 30% of household incomes fell below the federal poverty level.[23] Seven of the 10 study villages had piped water and sewer services to most households.[23] The remaining villages had running water available for public use only at a central location, such as a washeteria. Primary health care delivery occurred at village health clinics staffed by community health aides, who provided basic acute and preventive care services. None of the villages was accessible by road.

Participants

We selected the 8 most-populous villages in the Yukon-Kuskokwim region and the 2 most populous in the Bristol Bay region, not including the 2 regional centers (population range per village: 471–1014; median: 734). During November and December 2002, we invited all resident children who were 7 to 11 years of age to participate in this investigation. We actively sought participation by contacting all families with eligible children by mail and telephone using lists that were generated by local assistants. Children were excluded when they were receiving iron therapy.

We conducted in-person interviews with the child or the parent using a standard questionnaire to collect information on the number and ages of people in the household and the household water source. Each child's medical chart was reviewed to determine whether he or she had been prescribed antibiotics in the 30 days before enrollment. A venous blood sample was collected in a serum separator tube from each participant.

Iron Deficiency and Iron-Deficiency Anemia

Immediately after blood collection, a drop of blood was drawn into a microcuvette for hemoglobin measurement using a portable hemoglobinometer (HemoCue AB; HemoCue, Ängelholm, Sweden). The remaining blood was stored at room temperature for 30 to 60 minutes, centrifuged, and poured into a separate plastic tube. The serum was refrigerated for 1 to 4 days and transported in a cold box to the Centers for Disease Control and Prevention, Arctic Investigations Program laboratory (Anchorage, AK). Serum samples then were frozen at −30°C until processed for testing.

Serum ferritin concentrations were determined by using a radioimmunometric assay (ICN Pharmaceuticals Diagnostic Division, Orangeburg, NY). Iron deficiency was defined as a serum ferritin concentration of <10 μg/L and iron-deficiency anemia as a ferritin level of <10 μg/L and a hemoglobin concentration <115 g/L.[24]

Transferrin saturation was determined as a secondary measure of iron stores using standard methods at a local hospital laboratory, and a value of <15% was considered abnormal. All participants with iron deficiency (ferritin < 10 μg/L) were offered iron replacement therapy. Those with anemia but without iron deficiency were referred to their local provider for treatment.

Detection of *H pylori*

We assessed active *H pylori* infection using the urea breath test (UBT) (BreathTek; Meretek Diagnostics Inc, Lafayette, CO), a sensitive (>95%) and specific (>95%) measure of infection.[25–27] After the children fasted for ≥1 hour, a baseline breath sample was collected in the manufacturer's breath collection bag. The participant then ingested 3 g of Pranactin-Citric (75 mg of ^{13}C-urea, citric acid, aspartame, and mannitol) reconstituted in 100 mL of bottled water. A second breath sample was collected 15 minutes later. This method has not been shown to cause false-positive results in pediatric populations as a result of urease-producing oral flora.[27,28] Breath samples were stored at room temperature for 1 to 4 days before being transported to Anchorage for analysis. The urea hydrolysis rate was determined using the UbiT-IR300 mass spectrophotometer (Otsuka Pharmaceutical Co, Ltd, Tokyo, Japan). Infection was defined as a calculated urea hydrolysis rate of >10 from the suggested δ over baseline for $^{13}CO_2$ cutoff of 2.4 after adjustment for weight, height, and gender on the basis of the manufacturer's recommendation for pediatric patients.[28] Using an unadjusted cutoff value of 2.4 for δ over baseline did not change results for any participants, whereas using an unadjusted cutoff value of 4.5 resulted in a change in infection status from positive to negative for only 2 of 578 children. We conducted serologic testing for *H pylori*–specific antibodies using the HM-CAP enzyme immunoassay (E-Z-EM, Lake Success, NY) to detect immunoglobulin G antibodies against high molecular weight cell-associated proteins of *H pylori*.[29]

Statistical Analysis

Analysis was performed by using Stata 8.0 (Stata Corp, College Station, TX). We estimated the prevalence of iron deficiency, iron-deficiency anemia, and *H pylori* infection as the proportion of tested children with the given condition; 95% confidence intervals (CIs) were calculated adjusting for the cluster sampling by village. Binary exposures were compared by using the χ^2 test. Age and household size (number of people living in the home) were dichotomized for analysis at the median value for all participants. Potential risk factors for iron deficiency, iron-deficiency anemia, and *H pylori* infection were evaluated in univariate analysis, and prevalence ratios (PRs) and 95% CIs were calculated.

We used multiple logistic regression to evaluate the independent effect of risk factors for iron deficiency, iron-deficiency anemia, and *H pylori* infection by calculating adjusted odds ratios (OR). We evaluated all exposure variables that were associated with the outcome of interest at a level of $P \leq .1$ in univariate analysis. Exposure variables were tested individually using a forward addition approach and kept in the model when they were associated with the outcome of interest with a 2-sided $P \leq .1$. In a separate analysis, we specifically tested the a priori hypothesis that *H pylori* infection was an independent risk factor for iron-deficiency and iron-deficiency anemia. In this analysis, we kept potentially confounding variables in the final model when they changed the OR describing the association between iron deficiency and *H pylori* infection by ≥10%. We included demographic variables (village of residence, gender, and a categorical age variable [7, 8, 9, and ≥10 years]) in all logistic-regression models as potential confounders. A 2-sided $P < .05$ was considered statistically significant.

Ethical Approval

This study was approved by the Institutional Review Boards of the Centers for Disease Control and Prevention and the Alaska Area Research and Publications Committee, the Human Subjects Committee at the Yukon-Kuskokwim Regional Health Corporation, and the village or tribal councils in each of the 10 study villages. Written assent was obtained from all participants, and written consent was obtained from their guardians.

RESULTS

Participants

We enrolled 688 children (range: 40–110 per village), which represented 68% of all age-eligible children in the study villages based on the 2000 census (range: 45–92% by village). No children were excluded for taking iron replacement therapy at the time of testing. Participants had a mean age of 9.5 years, 51% were male, and 99.6% were Alaska Native (Table 1).

Prevalence of Iron Deficiency and Iron-Deficiency Anemia

Of 686 tested children, 263 (38.3%) were iron deficient as defined by a ferritin level of <10 μg/L (95% CI: 30.5–46.1%; Table 2), and the median serum ferritin level was 11.8 μg/L. Iron deficiency prevalence differed by village, from 19.7% to 56.1% ($P < .001$). Transferrin saturation was low in 332 (48.4%) of 686 children tested (95% CI: 42.5–54.3%), and the median was 15.2%. Serum ferritin and transferrin saturation both were low in 145 (21.1%) children (95% CI: 15.4–26.9%). Anemia was present in 104 (15.2%) of 683 tested children (95% CI: 10.0–0.4%), and the median hemoglobin level was 123 g/L. Iron-deficiency anemia was present in 53 (7.77%) children (95% CI: 4.20–11.3%).

TABLE 1 **Demographic and Household Characteristics of all Children Enrolled in the Investigation ($N = 688$)**

Mean age (SD), y	9.5 (1.4)
Male, *n* (%)	354 (51)
Alaska Native, *n* (%)	685 (99.6)
Village of residence, *n* (%)	
A	80 (12)
B	83 (12)
C	93 (14)
D	110 (16)
E	40 (6)
F	41 (6)
G	52 (8)
H	61 (9)
I	53 (8)
J	75 (11)
No. of people in household, mean (SD)	6.6 (2)
Child aged <5 y in household, *n* (%)	426 (62)
Other child aged 7–11 y in household, *n* (%)	443 (64)
Village of residence with piped water services, *n* (%)	435 (63)
Household water primarily from community or private well, *n* (%)[a]	495 (72)
Received antibiotics within 30 d before testing, *n* (%)	87 (13)

[a] Compared with collection from rain, snow, or pond/lake.

TABLE 2 **Estimated Prevalence of Iron Deficiency, Anemia, and *H pylori* Infection Among Children Aged 7 to 11 Years: Southwestern Alaska, 2001**

	n/N	Prevalence, % (95% CI)[a]
Iron deficiency		
Ferritin <10 μg/L	263/686	38.3 (30.5–46.1)
Transferrin saturation <15%	332/677	48.4 (42.5–54.3)
Ferritin <10 μg/L and transferrin saturation <15%	145/686	21.1 (15.4–26.9)
Anemia (hemoglobin <115 g/L)	104/683	15.2 (10.0–20.4)
Iron-deficiency anemia[b]	53/682	7.8 (4.2–11.3)
H pylori infection		
UBT-positive	578/668	86.5 (78.4–94.7)
Serology-positive	446/664	67.2 (60.6–73.8)
UBT- and serology-positive	419/644	65.1 (57.4–72.7)

[a] The 95% CI was adjusted for cluster sampling by village.
[b] Ferritin < 10 μg/L and hemoglobin < 115 g/L.

Risk Factors for Iron Deficiency and Iron-Deficiency Anemia

During univariate analysis, iron deficiency, as measured by low ferritin, was associated with residing in a household of at least 6 people or with a child age <5 years and residence in the Yukon-Kuskokwim region (Table 3). Results were similar when the measure of iron deficiency was low transferrin saturation, except that the association with household size was not statistically significant ($P = .39$, data not shown). During multivariate logistic-regression analysis, children who were living in homes with ≥6 people were more likely to be iron deficient than those in homes with <6 people (OR: 1.5; 95% CI: 1.1–2.2). Iron deficiency prevalence also differed by village of residence ($P = .0017$) but was no longer significantly associated with residence in the Yukon-Kuskokwim region.

Of evaluated risk factors, iron-deficiency anemia was associated only with residence in the Yukon-Kuskokwim region in univariate analysis (Table 3). However, the association was not statistically significant in multiple logistic-regression modeling; only village of residence remained significantly associated with iron-deficiency anemia ($P = .04$).

Prevalence of *H pylori* Infection

UBTs were completed successfully for 668 (97%) of the 688 participants; samples from the remaining 20 children were inadequate for testing. *H pylori* infection prevalence was 86.5% (95% CI: 78.4–94.7%; Table 2). Serologic evidence of *H pylori* infection was present in 446 (67.2%) of 664 children with interpretable results (95% CI: 60.6–73.8%). Among children with positive UBTs, 65.1% (419 of 644) also had a positive *H pylori* serology (95% CI: 57.4–72.7%).

Risk Factors for *H pylori* Infection

During univariate analysis, *H pylori* infection based on UBT results was associated with older age, residing in a household of at least 6 people or in a household with a child aged <5 years, residence in the Yukon-Kuskokwim region, household water source, and living in a village without piped water services (Table 3). During multivariate analysis, age ≥10 years (OR: 2.0; 95% CI: 1.2–3.4) and village of residence ($P < .001$) remained significantly associated with *H pylori* infection. After controlling for village of residence, we could not evaluate effectively the risk for *H pylori* associated with living in a village without piped water services, because these services did not vary within villages.

Relationship Between *H pylori* Infection and Iron Deficiency

Ninety-one percent (235 of 257) of children with iron deficiency had *H pylori* infection. Children with *H pylori* infection based on the UBT were more likely to be iron deficient than uninfected children (Table 4); however, iron deficiency prevalences were similar among *H pylori*–seropositive (39%) and –seronegative (36%) children. The association between breath test positivity and iron deficiency differed by age and was present only for children who were at least 9 years of age (Table 5). During multivariate analysis, iron deficiency remained associated with *H pylori* infection after adjustment for age, gender, village of residence, and household size; this relationship was modified by age and was statistically significant only for children who were ages 9 and ≥10 years.

Results were similar when iron deficiency was defined as having a serum ferritin level of <12 μg/L or as a combination of a ferritin level of <10 μg/L and transferrin saturation of <15% (Table 4). When iron deficiency was defined as a low ferritin and low transferrin saturation, prevalence ratios were higher for children

TABLE 3 **Characteristics of Children With Iron Deficiency (Ferritin <10 μg/L), Iron-Deficiency Anemia (Ferritin <10 μg/L and Hemoglobin <115 g/L), and *H pylori* Infection by UBT: Southwestern Alaska, 2001**

	Iron Deficiency		Iron-Deficiency Anemia		*H pylori* Infection[a]	
	n (%)	PR (95% CI)	*n* (%)	PR (95% CI)	*n* (%)	PR (95% CI)
Age, y						
≥10	116 (41)	1.1 (0.9–1.4)	20 (7.1)	0.86 (0.51–1.5)	250 (90)	1.1 (1.0–1.1)[b]
<10	146 (36)		33 (8.2)		328 (84)	
Gender						
Male	134 (38)	1.0 (0.8–1.2)	29 (8.3)	1.2 (0.69–1.9)	294 (84)	0.95 (0.9–1.0)[c]
Female	128 (38)		24 (7.2)		284 (89)	
Household size						
≥6 people	207 (41)	1.4 (1.1–1.8)[b]	44 (8.8)	1.8 (0.90–3.6)[c]	431 (88)	1.1 (1.0–1.2)[b]
<6 people	55 (30)		9 (4.9)		147 (82)	
Household member aged <5 y						
Yes	178 (42)	1.3 (1.0–1.6)[b]	33 (7.8)	1.0 (0.59–1.7)	367 (89)	1.1 (1.0–1.1)[c]
No	85 (33)		20 (7.8)		211 (84)	
Home village region						
Bristol Bay Area	39 (30)	0.8 (0.6–1.0)[b]	4 (3.1)	0.3 (0.1–1.0)[b]	86 (77)	0.9 (0.8–1.0)[b]
Yukon-Kuskokwim	224 (40)		49 (8.9)		492 (88)	
Village of residence with piped water services						
Yes	166 (38)	1.0 (0.8–1.2)	32 (7.4)	0.9 (0.5–1.5)	348 (83)	0.9 (0.8–0.9)[b]
No	97 (38)		21 (8.4)		230 (93)	
Household water primarily from community or private well[d]						
Yes	191 (39)	1.0 (0.8–1.3)	35 (7.1)	0.8 (0.4–1.3)	403 (85)	0.9 (0.9–1.0)[c]
No	72 (37)		18 (9.4)		175 (91)	
Antibiotic use in previous 30 d						
Yes	27 (31)	0.8 (0.57–1.1)[c]	9 (10)	1.4 (0.7–2.8)	70 (81)	0.9 (0.8–1.0)[c]
No	39 (236)		44 (7.4)		508 (87)	

[a] $N = 668$. Excludes 20 children with indeterminate test results.
[b] $P < .05$
[c] $P \leq .1$
[d] Compared with collection from rain, snow, or pond/lake.

TABLE 4 **Association Between *H pylori* Infection by UBT and Various Measures of Iron Status and Anemia: Southwestern Alaska, 2001**

	H pylori–Positive, *n* (%)	*H pylori*–Negative, *n* (%)	PR (95% CI)
Ferritin <10 μg/L	235 (41)	22 (25)	1.6 (1.1–2.4)
Ferritin <12 μg/L	309 (53)	35 (39)	1.4 (1.0–1.8)
Ferritin <10 μg/L and transferrin saturation <15%	130 (23)	14 (16)	1.4 (0.9–2.4)
Transferrin saturation <15%	278 (48)	46 (52)	0.9 (0.7–1.2)
Iron-deficiency anemia[a]	51 (9)	2 (2)	4.0 (1.0–16)
Anemia not attributable to iron deficiency[b]	47 (8.2)	2 (2)	3.7 (0.9–15)

[a] Ferritin <10 μg/L and hemoglobin <115 g/L.
[b] Hemoglobin <115 g/L and ferritin ≥10 μg/L.

aged 9 (PR: 3.8; 95% CI: 0.55–27.0) and ≥10 years (PR: 3.3; 95% CI: 0.87–13.0). Logistic-regression analysis also revealed a stronger association among older children (9 years old: OR: 4.4 [95% CI: 0.56–34.0]; 10 years old: OR: 3.6 [95% CI: 0.78–16.0]), but the 95% CIs included 1. Low transferrin saturation alone did not differ among *H pylori*–infected and –uninfected children.

Children with *H pylori* infection on the basis of the UBT were more likely to have iron-deficiency anemia than uninfected children (Table 4). The association remained after adjustment for age, gender, and village of residence, but the 95% CI included 1 (OR: 4.1; 95% CI: 0.92–8.0; $P = .06$). We could not assess effect modification by age because only 2 uninfected children had iron-deficiency anemia. Iron-deficiency anemia was also more common among *H pylori*–seropositive (9%) versus *H pylori*–seronegative (5%) children (PR: 2.0; 95% CI: 1.0–4.0). We calculated the percentage of iron deficiency in the population that potentially was attributable to *H pylori* infection (population-attributable fraction) as the difference in the prevalence of iron deficiency among 7- to 11-year-old children overall and those without *H pylori* infection divided by the prevalence overall.[30] Up to 36% of iron deficiency was potentially attributable to *H pylori* infection, and among chil-

TABLE 5 **Prevalence of Iron Deficiency Among *H pylori*–Positive and *H pylori*–Negative Children According to Age Group: Southwestern Alaska, 2001**

Age, y	Iron Deficiency, *n* (%)			
	H pylori–Positive	*H pylori*–Negative	PR (95% CI)	Adjusted OR (95% CI)[a]
7	42 (38)	7 (32)	1.2 (0.6–2.3)	1.2 (0.5–3.4)
8	43 (37)	10 (48)	0.78 (0.5–1.3)	0.5 (0.2–1.4)
9	39 (39)	2 (11)	3.7 (1.0–14.0)	5.1 (1.1–23.0)
≥10	111 (44)	3 (11)	4.0 (1.4–12.0)	5.3 (1.5–19.0)
All ages	235 (41)	22 (25)	1.6 (1.1–2.4)	[b]

[a] Adjusted for age, gender, village of residence, and household size.

[b] Effect modification by age precludes calculation of a summary adjusted OR for all age groups.

dren who were aged 9 and ≥10 years, this fraction increased to 70% and 73%, respectively.

DISCUSSION

For almost 5 decades, studies have documented the high prevalence of iron deficiency and iron-deficiency anemia in rural Alaskan communities.[4–6,10,11,31] In this study of nearly 700 children in 10 different villages, we confirmed that the high prevalence of iron deficiency persists among school-aged children, a group that normally is considered to be at very low risk for iron deficiency in the United States. The prevalence in the current study exceeds estimates for similarly aged children in the United States overall by nearly 10 times[3] and is similar to prevalences seen in developing countries and other arctic pediatric populations.[2,7,8] Unlike developing country populations, though, previous data collected from Alaska Natives do not support poor nutritional iron intake[5,10,11] or parasitosis[12] as causes for iron deficiency, suggesting that other causes must exist.

We found that *H pylori* infection was independently associated with iron deficiency and iron-deficiency anemia among children in this region, with high prevalences of all 3 conditions. This association has been observed in previous studies in rural Alaska[5,6,11] and elsewhere,[16–21] but never in a study that was population based, had a relatively large cohort of children, and used a validated measure of active *H pylori* infection. Our findings suggest that *H pylori* infection may be an important risk factor for iron deficiency and iron-deficiency anemia among children in rural Alaska and possibly in other areas of the world where these conditions are highly prevalent. In contrast to previous studies,[5,6] we did not find an association between iron deficiency and *H pylori* seropositivity. Serologic testing for *H pylori* in children lacks sensitivity and specificity[22] and does not distinguish between past and current infection; this may have led to misclassification of *H pylori* status and subsequent attenuation of the association.

In the current investigation, the association between iron deficiency and *H pylori* infection was modified by age, with the strongest association in children who were aged ≥9 years. In this age group, iron deficiency was 3.7 to 4 times more prevalent among *H pylori*–infected than –uninfected children. We did not anticipate this effect modification given the narrow age range of our sample, but the increased risk in older children seems biologically plausible. Older children likely have been infected longer than younger children, allowing more time for iron deficiency to develop. Furthermore, older children may be less likely to have iron deficiency related to other causes, such as insufficient dietary intake, leaving *H pylori* infection to account for a greater proportion of iron deficiency.

Our findings highlight the potential public health impact of *H pylori* infection in this region of Alaska, as up to 70% of the iron deficiency in children who are ≥9 years of age may be attributable to *H pylori* infection. However, measures of excess risk assume a causal relationship between exposure and disease, which cannot be established from a single cross-sectional study. Therefore, our estimates of population-attributable risk must be interpreted with caution.

This study included 1 of the largest cohorts of children who have been evaluated for active *H pylori* infection in the world and demonstrated that >85% of subjects were infected. The epidemiology of *H pylori* in rural Alaska is similar to that in developing country settings, where infection occurs at an early age and prevalence is high.[13–15] Risk factors for *H pylori* acquisition and transmission are poorly understood but may be related to conditions that are associated with low socioeconomic status, such as crowded housing or relatively poor water and septic systems. In the current investigation, *H pylori* infection was associated with living in a village without piped water and sewer services. We could not evaluate this association independent of village of residence because utility services do not vary within villages. Other studies have documented an epidemiologic association between *H pylori* infection and contaminated water and have found evidence of the organism in water sources using molecular laboratory methods (eg, polymerase chain reaction).[14,32–34] However, the laboratory methods

in these investigations are not well validated for testing environmental samples.

We found that 15% of children had a hemoglobin level <115 g/dL, but only 8% also had a low ferritin, suggesting that important causes of anemia beyond iron deficiency exist. Similar trends have been described in population-based studies among young children in the United States,[35] Great Britain,[36] and New Zealand.[37] Hemoglobinopathies are relatively uncommon among Alaska Natives and are unlikely to account for a substantial portion of the anemia seen in this study; routine newborn screening has revealed no substantial difference in the prevalence of overall or specific hemoglobinopathies between Alaska Native and non–Alaska Native subjects (Alaska Division of Public Health, unpublished data). Anemia of chronic disease (also known as anemia of inflammation) is caused by chronic or acute immune activation and is the second most common cause of anemia after iron deficiency.[38,39] Alaska Natives experience a disproportionately high incidence of several infectious diseases and other inflammatory conditions compared with the US population overall, including respiratory syncytial virus bronchiolitis,[40] chronic lung disease,[41] otitis media,[42] and invasive bacterial infections,[43] which may contribute to anemia in some children in this region. Inflammatory processes can also cause elevated serum ferritin levels, which may have led to underestimation of the proportion of anemic children with iron deficiency.[44] Among the 104 children in our study with low hemoglobin, 82 (79%) had at least 1 measure of low iron stores (ferritin or transferrin saturation).

The relatively modest overall association between *H pylori* infection and iron deficiency indicates that other causes of iron deficiency must be considered. Previous studies in rural Alaska concluded that insufficient iron intake was an unlikely cause of disease.[5,10,11] However, the last large nutritional survey was conducted in this area during 1988. Since that time, access to commercially prepared foods has increased in rural areas, which may have led to decreased intake of traditional, iron-rich foods, such as red meat and fish. Inherited abnormalities in iron absorption can cause iron deficiency despite sufficient dietary intake.[45] However, data from Alaska's Women, Infants, and Children Program show that Alaska Native children who were aged <5 years and living in the 4 largest cities in Alaska had hemoglobin levels similar to non–Alaska Natives (Alaska Department of Health and Social Services, unpublished data), which suggests that environmental rather than genetic factors play a key role in iron deficiency in rural settings. Iron absorption can also be inhibited by excessive dietary intake of items such as starch and phytates,[45] but there is no evidence that these inhibitors are common in subsistence diets in rural Alaska.[10]

An important strength of this study was the high participation rate (68%). Although we cannot be sure that volunteers were representative of the entire population of 7- to 11-year-old children, nonparticipants were similar to participants in terms of age (mean: 9.4), gender (51% male), and race (99% Alaska Native), and living conditions were relatively homogeneous within study villages. Our study also had several limitations. We defined iron deficiency solely on the basis of ferritin levels, whereas studies that used the National Health and Nutrition Examination Survey defined iron deficiency as low values for 2 of the following: ferritin, transferrin saturation, or free erythrocyte protoporphyrin.[3] However, 21% (145 of 686) of children in the current study had both a low ferritin level (<10 μg/L) and low transferrin saturation, still well above the 4% prevalence of iron deficiency among US children aged 6 to 11 years found in the National Health and Nutrition Examination Survey.[3] We defined iron deficiency using a low cutoff for serum ferritin (10 μg/L) to increase the specificity of our case definition, although this may have led to an underestimation of the iron deficiency prevalence (eg, prevalence = 51% if iron deficiency is defined as a ferritin level of <12 μg/L). The cross-sectional design of this study limits inference about the causal relationship between *H pylori* infection and iron deficiency. In addition, the modest association between iron deficiency and *H pylori* infection (PR: 1.65) raises concern about confounding by unmeasured exposures. For instance, poor nutrition could cause iron deficiency and potentially increase susceptibility to *H pylori* infection. However, the association was much stronger in children who were 9 years or older (PR: 3.7–4.0) and among those with iron-deficiency anemia, and our findings are consistent with previous studies that evaluated the relationship between *H pylori* and iron deficiency in Alaska and in other settings.[5,6,11,16–21] Confounding by unmeasured socioeconomic factors could also have occurred, but there is relatively little variation in socioeconomic status among Alaska Natives from southwestern Alaska, particularly within villages. Finally, our study was conducted in small villages in rural Alaska, which may limit the generalizability of our findings. However, *H pylori* infection and iron deficiency are highly prevalent in other indigenous arctic populations and many areas of the developing world, and similar associations between *H pylori* and iron deficiency have been found in smaller studies in diverse populations.[16–19,21]

CONCLUSIONS

A significant disparity persists in the prevalence of iron deficiency between Alaska Native and other US school-aged children, with Alaska Native children more closely resembling children from developing countries. Our data suggest that *H pylori* infection may be an important contributor to the disparity in this region, where endemic iron deficiency persists despite apparent adequate

nutritional intake and lack of parasitosis. Innovative approaches in rural Alaska and other areas are critically needed to address the high prevalence of iron deficiency, one of the most common causes of disability worldwide.[46] Future strategies may include prevention or treatment of *H pylori* infection. Additional study is needed to determine whether treating *H pylori* infection facilitates resolution of iron deficiency and whether the benefits of therapy outweigh the risks.

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