

# Controlled, Household-Randomized, Open-Label Trial of the Effect of Treatment of *Helicobacter pylori* Infection on Iron Deficiency among Children in Rural Alaska: Results at 40 Months

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**Background.** *Helicobacter pylori* infection treatment was found not to reduce the prevalence of iron deficiency or anemia among Alaska Native children at 14 months after treatment initiation. We hypothesized that 14 months was too early to resolve *H. pylori*-induced gastric damage. Consequently, we conducted a 40-month follow-up.

**Methods.** We enrolled 219 children 7–11 years old who had *H. pylori* infection (as diagnosed by <sup>13</sup>C-labeled urea breath test) and iron deficiency (serum ferritin level, <22.47 pmol/L) in a controlled, household-randomized trial of the effect of treatment of *H. pylori* on iron deficiency and anemia (hemoglobin level, <115 g/L). At 40 months, 176 children were evaluated.

**Results.** Forty-four (52%) of 85 children in the intervention group and 53 (58%) of 91 in the control group had iron deficiency (adjusted relative risk [ARR], 0.92 [95% confidence interval {CI}, 0.68–1.26]), versus 4 (5%) and 17 (19%), respectively, with both iron deficiency and anemia (ARR, 0.25 [95% CI, 0.09–0.73]). Reinfection occurred among 33 (52%) of 64 children who had cleared their infection. *H. pylori*-negative children had lower prevalences of iron deficiency (ARR, 0.62 [95% CI, 0.38–1.01]) and iron deficiency and anemia (ARR, 0.22 [95% CI, 0.03–1.50]), compared with *H. pylori*-positive children.

**Conclusions.** The resolution of *H. pylori* infection for >14 months modestly reduced the prevalence of iron deficiency and substantially reduced the prevalence of iron deficiency and anemia. *H. pylori* likely plays a causal role in hematological outcomes for some children.

Iron deficiency is one of the most common and widespread nutritional disorders in the world [1]. Anemia affects up to 50% of children worldwide, and the disease burden is heavily concentrated among economically disadvantaged populations [1, 2]. Studies in diverse geographic areas, including western Alaska, have identified an association between *Helicobacter pylori* infection and pediatric iron deficiency [3–7]. Also, multiple reports describe refractory or unexplained anemia among chil-

dren that resolved only after successful treatment of *H. pylori* infection [8–14]. Limited sample sizes and lack of control groups have limited the ability to generalize the results of these studies. Nevertheless, these data raise the possibility that a substantial proportion of global pediatric iron deficiency is attributable to *H. pylori* infection and that treatment or prevention of *H. pylori* infection might be an important intervention for reducing the iron deficiency disease burden worldwide.

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The findings and conclusions in this report are those of the author(s) and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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Previously, we reported the results of a controlled, household-randomized, open-label trial of treatment of *H. pylori* infection among Alaska Native children with iron deficiency [15]. Treatment of *H. pylori* infection did not reduce the prevalence of iron deficiency or anemia at 14 months after treatment initiation. In a follow-up letter, we proposed that the negative findings at 14 months might have resulted from *H. pylori*-associated gastrointestinal changes that were not reversible within 14 months [16]. We conducted an additional follow-up evaluation at 40 months after treatment initiation.

## SUBJECTS, MATERIALS, AND METHODS

**Study location.** A full description of our methods has been presented previously [15]. We conducted the study in 10 villages in the Yukon-Kuskokwim Delta and Bristol Bay regions of western Alaska, because previous work demonstrated high prevalences of pediatric anemia, iron deficiency, and *H. pylori* infection in these areas [3, 17–19]. Each village had populations of 471–1014 persons in 2000 [20]. The villages were not accessible by road, and 3 of them did not have public water or sewage systems connected to residences.

**Initial screening and study participants.** We screened 690 (68%) of the 1011 members of the population aged 7–11 years in the study villages [6]. Of 690 children screened, 237 were eligible for the study (i.e., they were iron deficient and *H. pylori* positive), and 219 enrolled in the treatment phase of the study. Approximately 685 (99%) of the screened children and 100% of enrolled children were Alaska Native.

**Intervention.** Children in the treatment phase were randomized to receive iron sulfate alone (6 week course) or iron sulfate (6 week course) plus *H. pylori* treatment [15]. The latter consisted of a 2-week course of amoxicillin, clarithromycin, and lansoprazole; children allergic to amoxicillin received metronidazole [21, 22]. Children in the intervention group who were still *H. pylori* positive 2 months after the initiation of treatment received another 2-week course of antibiotic treatment in which metronidazole replaced clarithromycin and to which bismuth subsalicylate was added; children with amoxicillin allergy received clarithromycin. A review of treatment compliance has been published [23].

**Hypotheses.** For this evaluation, our primary hypothesis was that children in the intervention group would have a lower prevalence of iron deficiency at 40 months after treatment initiation than would those who received only iron supplementation. We also hypothesized that children in the intervention group would have a lower prevalence of anemia, greater changes from baseline values in serum ferritin and hemoglobin levels, and higher serum ferritin and hemoglobin levels at study completion.

**Outcomes and definitions.** At screening and ~2, 8, 14, and 40 months after treatment initiation, participants were assessed for *H. pylori* infection, serum ferritin level, hemoglobin level,

serum iron level, iron saturation level, and antibiotic receipt during the preceding 30 days. The <sup>13</sup>C-labeled urea breath test (BreathTek; Meretek Diagnostics) was selected to determine *H. pylori* infection status because it has high sensitivity and specificity among pediatric populations [24, 25] and among adult Alaska Natives [26]. *H. pylori* infection was defined as a change in the calculated urea hydrolysis rate of >10 µg/min from the baseline level for CO<sub>2</sub> production after adjusting for weight, height, and sex on the basis of the manufacturer's recommendations [27]. The primary outcome was iron deficiency (serum ferritin level <22.47 pmol/L [<10 µg/L]). We repeated analyses using higher or lower ferritin cutoff levels for iron deficiency.

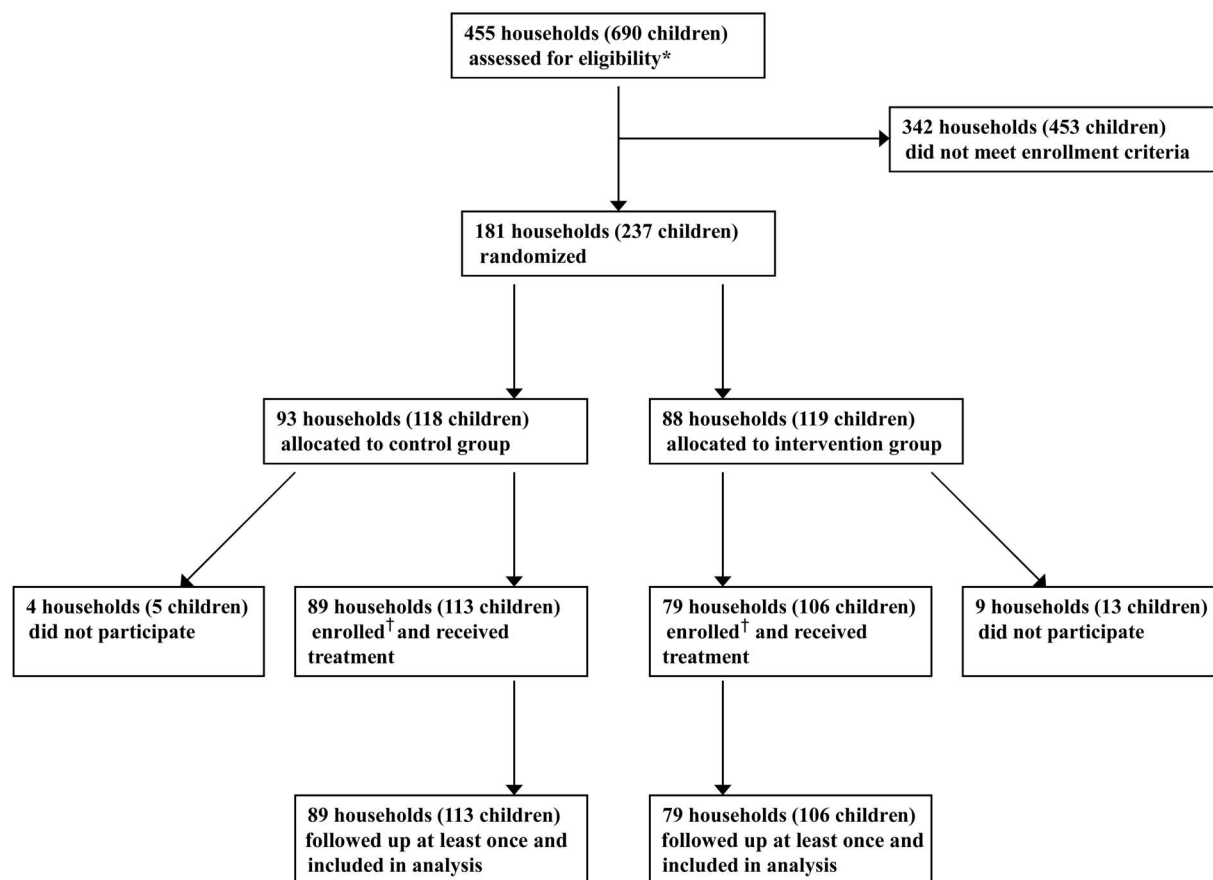
Secondary outcomes included anemia (hemoglobin level <115 g/L), which was defined on the basis of portable blood hemoglobin photometer results (HemoCue B-Hemoglobin system, HemoCue AB); serum iron level <4.5 µmol/L (<25 µg/dL); iron-binding capacity, total (TIBC) >80.6 µmol/L (>450 µg/dL); and iron saturation <15%.

**Sample size calculation.** The study had a within-household intraclass correlation coefficient of 0.15 for iron deficiency and an average of 1.3 participants/household. We had 80% power to detect a 30% lower prevalence of iron deficiency among the intervention group, compared with the control group, by using a 2-tailed  $\alpha$  level of .05 and allowing for a 20% dropout rate in the originally randomized 181 households.

**Randomization.** We randomized children by household to limit treatment crossover within families, and we stratified the randomization by village so that each village had an equal number of households in the intervention and control groups. Computer-generated random numbers were used to assign each family to the control or intervention group. Participants and investigators were not blinded to treatment assignments.

**Statistical methods.** Enrollment was defined as receipt of  $\geq 1$  dose of any study medication. Primary intention-to-treat analyses compared outcomes among enrolled children according to assigned treatment group. Secondary analyses compared children by their *H. pylori* infection status at 40 months. We also compared children who were always *H. pylori* negative with children who were always *H. pylori* positive at 8, 14, and 40 months. Children were categorized according to the total number of abnormal indicators of iron status (serum ferritin level, serum iron level, and TIBC) and analyzed by treatment group and *H. pylori* infection status, but results of these analyses did not alter the study conclusions and are not presented.

Children with missing data were not included in relevant analyses. We computed adjusted relative risks (ARRs) of iron deficiency and anemia through use of a binomial regression model with a log-link function. We used generalized estimating equations to account for correlations between participants in the same household with an exchangeable correlation structure. Mann-Whitney tests were used to compare levels of hemoglobin and ferritin, as well as ancillary measures of iron status among



**Figure 1.** Flow diagram of a trial of treatment of *Helicobacter pylori* infection and iron deficiency among Alaska Native children, 2002–2007. Asterisk (\*) indicates children who were infected with *H. pylori* and had iron deficiency who were eligible for enrollment in the treatment phase. Dagger (†) indicates children who received  $\geq 1$  dose of any study-assigned medication and who were considered to be enrolled in the treatment phase.

groups. All statistical tests were 2-sided, and  $P \leq .05$  was considered statistically significant. Analyses were conducted by using SPSS (version 13.0; SPSS) and SAS (version 9.1; SAS Institute) statistical software.

**Study approval and informed consent.** We obtained approval from the institutional review boards of the Centers for Disease Control and Prevention and the Alaska Area Health Research Board, the Human Subjects Committee of the Yukon-Kuskokwim Regional Health Corporation, and the village or tribal councils of the 10 study villages. Data forms were amended for the 40-month visit to gather data regarding females' menstrual history. At enrollment and again at 40 months, children gave written assent for participation, and their guardians gave written, informed consent. Guardians were given \$25 at each visit to compensate them for their time.

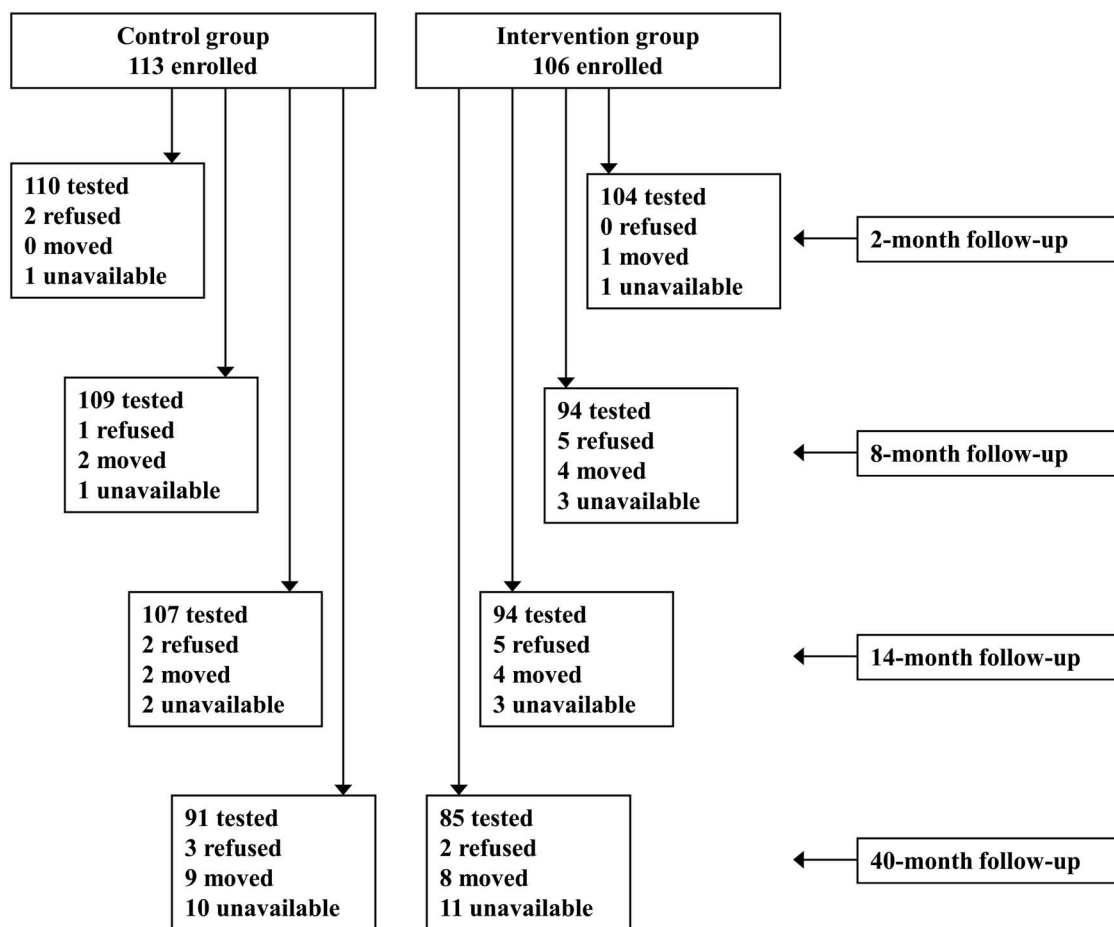
## RESULTS

**Study flow.** Of children in the control and intervention groups, 85 (81%) of 106 and 91 (80%) of 113, respectively, received follow-up at 40 months (figures 1 and 2). The characteristics of these children did not differ according to assigned treat-

ment group (table 1). Baseline household and individual characteristics of children lost to follow-up were similar to those of children evaluated at 40 months.

***H. pylori* infection status across time, according to treatment group.** At  $\sim 2, 8, 14,$  and 40 months after treatment initiation, respectively, 35 (34%) of 104, 71 (75%) of 95, 63 (68%) of 93, and 32 (38%) of 85 children in the intervention group and 1 (1%) of 111, 3 (3%) of 110, 4 (4%) of 107, and 1 (1%) of 91 children in the control group were *H. pylori* negative. Of the 78 children in the intervention group who were *H. pylori* negative after receiving their first or second treatment course for *H. pylori* infection, 13 (18%) of 74 were *H. pylori* positive at 14 months, and 33 (52%) of 64 were positive at 40 months.

**Iron and hemoglobin status at enrollment and 40 months.** Among the 219 study participants, the median ferritin level at enrollment was 13.8 pmol/L (6.2  $\mu\text{g/L}$  [range, 3.0–22.5 pmol/L {1.3–10.0  $\mu\text{g/L}$ ]}), and the median hemoglobin level at enrollment was 121 g/L (range, 82–143 g/L). Anemia was present at enrollment in 49 (22%) of 219 children, including 1 child who had severe anemia (hemoglobin < 90 g/L). At 40 months, the median ferritin level among all study participants was 22.5



**Figure 2.** Enrollment of children in control and intervention groups, according to time of follow-up visit.

pmol/L (10.0  $\mu\text{g/L}$  [range, 2.3–89.9 pmol/L {1.0–40.0  $\mu\text{g/L}$ ]]) and the median hemoglobin level was 125 g/L (range, 54–177 g/L). At 40 months, 29 (16%) of 176 study participants had anemia, including 2 children who had severe anemia.

**Effect of treatment and *H. pylori* infection status on iron deficiency and anemia.** At 40 months, children in the intervention and control groups had similar prevalences of iron deficiency (table 2). A 46% lower prevalence of anemia was observed among children in the intervention group (anemia prevalence, 12%), compared with the control group (anemia prevalence, 21%), and a 75% lower prevalence of iron deficiency anemia was observed among children in the intervention group (iron deficiency anemia prevalence, 5%), compared with the control group (iron deficiency anemia prevalence, 19%). When children were compared by *H. pylori* infection status at 40 months, reductions in the prevalence of iron deficiency, anemia, and iron deficiency anemia among *H. pylori*-negative children were substantial, but not statistically significant.

Using alternative ferritin cutoff values did not affect differences in the prevalence of iron deficiency between treatment groups, and using lower cutoffs (20.22 pmol/L [9  $\mu\text{g/L}$ ] or 17.98 pmol/L [8  $\mu\text{g/L}$ ]) did not affect differences between the

*H. pylori*-negative and -positive groups. Using a higher ferritin cutoff (24.72 pmol/L [11  $\mu\text{g/L}$ ]) led to a modestly larger difference in the prevalence of iron deficiency between the *H. pylori*-negative and -positive groups (ARR, .56 [95% CI, 0.34–0.90], compared with 0.62, for a cutoff of <22.47 pmol/L [10  $\mu\text{g/L}$ ]).

**Effect of treatment and *H. pylori* infection status on median ferritin and hemoglobin levels.** At 40 months, children in the intervention and control groups had similar median ferritin and hemoglobin levels, and similar median changes from baseline in ferritin and hemoglobin levels (table 3). When children were compared by *H. pylori* infection status at 40 months, *H. pylori*-negative children had statistically significant improvements in median ferritin level and median change in ferritin level from baseline. Median hemoglobin level and median change in hemoglobin level were similar among children who tested *H. pylori* negative and those who were *H. pylori* positive.

**Prevalences of iron deficiency and anemia across time.** Control and intervention groups demonstrated similar temporal trends regarding iron deficiency, anemia, and iron deficiency anemia (figure 3A). However, when groups were compared by *H. pylori* infection status at 40 months, children without *H. pylori* infection demonstrated better resolution of all outcomes

**Table 1. Household and individual characteristics for Alaska Native children in rural Alaska who participated in 40-month follow-up in 2007, according to assigned treatment group.**

Characteristic	Intervention group	Control group
<b>Household</b>		
Households per group, no.	64	72
Participants per household, no.		
1	46 (72)	54 (75)
2	15 (23)	17 (24)
3	3 (5)	1 (1)
Persons residing in household, no.		
2–5	17 (27)	16 (22)
6–9	38 (59)	49 (68)
10–13	9 (14)	7 (10)
Households by geographic region, no.		
Yukon-Kuskokwim Delta area	52 (81)	61 (85)
Bristol Bay area	12 (19)	11 (15)
<b>Individual</b>		
Individuals per group, no.	85	91
Female sex	39 (46)	45 (50)
Menstruating females	26 (68)	26 (60)
Mean height, in	60.5	60.3
Mean weight, lbs	115	113
Mean age, years	13.5	13.6
Baseline serum ferritin level		
Median (range), pmol/L	13.56 (2.97–22.46)	14.84 (4.20–22.38)
Median (range), $\mu\text{g/L}$	6.04 (1.32–10.00)	6.60 (1.87–9.96)
<6.7 pmol/L or <3 $\mu\text{g/L}$	6 (7)	5 (5)
<11.2 pmol/L or <5 $\mu\text{g/L}$	33 (39)	35 (38)
Baseline hemoglobin level		
Median (range), g/L	120 (82–138)	121 (107–143)
<100 g/dL	1 (1)	0 (0)
<115 g/dL	25 (29)	18 (20)
Initial treatment doses completed, mean no. received/total no.	19/28	19/28

**NOTE.** Data are no. (%) of subjects, unless otherwise indicated.

(figure 3B). Iron deficiency prevalence remained similar through 14 months and then diverged at 40 months. In contrast, the prevalence of anemia diverged at 8 months and then further at 14 months, followed by no further change at 40 months. The prevalence of iron deficiency anemia in the *H. pylori*-negative group declined below that seen among the *H. pylori*-positive group at 2 months and remained lower through study completion.

**Effect of treatment and *H. pylori* infection status on ancillary iron measurements.** The median change from baseline in TIBC was a decrease of 2.06  $\mu\text{mol/L}$  among intervention group children and an increase of 2.33  $\mu\text{mol/L}$  among control group children ( $P = .04$ ). When groups were compared according to *H. pylori* infection status, the median change from baseline was a decrease of 4.39  $\mu\text{mol/L}$  among the *H. pylori*-negative group and an increase of 1.61  $\mu\text{mol/L}$  among the *H. pylori*-positive

group ( $P < .01$ ). No differences were noted in median TIBC levels by treatment group or *H. pylori* infection status. Neither serum iron levels nor percentage of iron saturation was associated with treatment group or *H. pylori* infection status.

## DISCUSSION

Treatment followed by sustained resolution of *H. pylori* infection modestly improved iron status among rural Alaska Native school-age children with both iron deficiency and *H. pylori* infection. This was true whether prevalences of iron deficiency, absolute ferritin levels, or changes in ferritin levels were compared temporally. Differences in the prevalence of iron deficiency among *H. pylori*-negative or -positive children became statistically significant at higher ferritin cutoff values, but differences between groups were otherwise stable across changes in



**Table 2. Presence of iron deficiency and anemia after treatment initiation among Alaska Native children in rural Alaska in 2007, according to treatment group or *Helicobacter pylori* infection status.**

Characteristic, risk group	Iron deficiency <sup>a</sup> at 40 months		Anemia <sup>b</sup> at 40 months		Iron deficiency and anemia at 40 months	
	Subjects, no. (%)	ARR (95% CI)	Subjects, no. (%)	ARR (95% CI)	Subjects, no. (%)	ARR (95% CI)
<b>Treatment assignment</b>						
Intervention ( <i>n</i> = 85)	44 (52)	0.92 (0.68–1.26)	10 (12)	0.54 (0.26–1.15)	4 (5)	0.25 (0.09–0.73)
Control ( <i>n</i> = 91)	53 (58)	Reference	19 (21)	Reference	17 (19)	Reference
<b><i>H. pylori</i> infection status at 40 months</b>						
Negative ( <i>n</i> = 33)	11 (33)	0.62 (0.38–1.01)	3 (9)	0.48 (0.16–1.43)	1 (3)	0.22 (0.03–1.50)
Positive ( <i>n</i> = 143)	75 (52)	Reference	26 (18)	Reference	20 (14)	Reference
<b><i>H. pylori</i> infection status at 8, 14, and 40 months</b>						
Always negative ( <i>n</i> = 31)	11 (35)	0.67 (0.39–1.13)	2 (6)	0.31 (0.08–1.20)	1 (3)	0.21 (0.03–1.39)
Always positive ( <i>n</i> = 99)	51 (52)	Reference	20 (20)	Reference	16 (16)	Reference

**NOTE.** ARR, relative risk adjusted for household clustering; CI, confidence interval.

<sup>a</sup> Iron deficiency was defined as a serum ferritin level <22.47 pmol/L (<10 μg/L).

<sup>b</sup> Anemia was defined as a hemoglobin level <115 g/L.

cutoff values. *H. pylori* infection treatment and resolution led to dramatic differences in the prevalence of anemia and particularly in the prevalence of iron deficiency anemia. Remarkably, only 1 *H. pylori*-negative child had iron deficiency anemia at 40 months. However, over 50% of the children with no active infection at the 8-month visit had been reinfected 32 months later, and iron deficiency did not resolve among one-third of children who remained *H. pylori*-negative at 40 months. Additionally, iron deficiency improved with time, even among children who remained *H. pylori*-positive at 40 months.

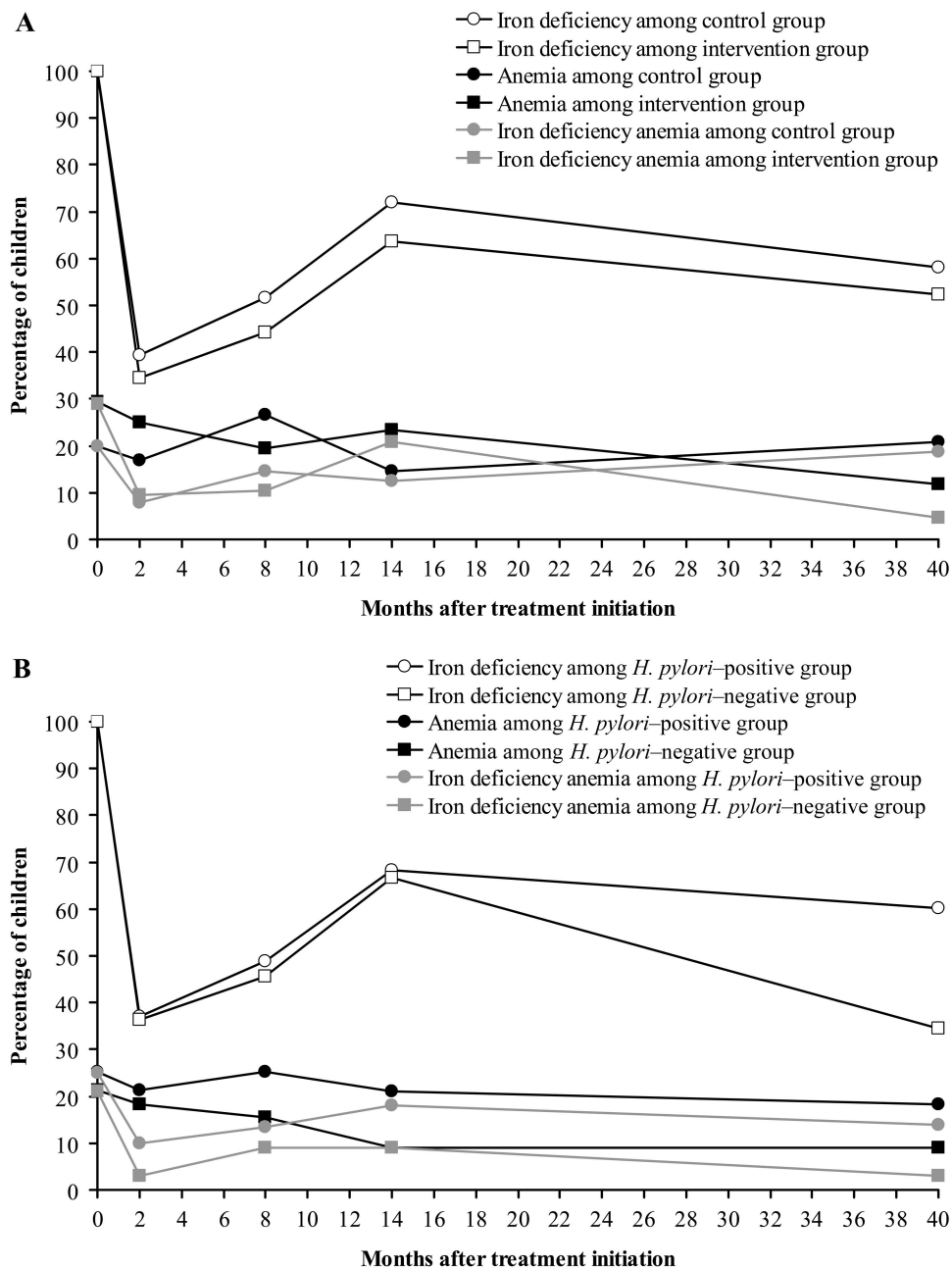
These findings provide evidence that *H. pylori* infection is a causal factor in the chain of events leading to iron deficiency and anemia among some Western Alaska Native children. But our

results also indicate that *H. pylori* infection alone likely does not explain the high prevalence of iron deficiency that exists in the study population. Additionally, the overall benefits of *H. pylori* treatment are likely to be modest, in part because of the high rate of infection recurrence experienced by this population residing in a highly *H. pylori*-endemic area. For these reasons, and because we did not observe a statistical difference between the intervention and control groups with respect to the prevalence of iron deficiency at 40 months, we do not recommend a strategy of population-based screening and treatment for *H. pylori* infection for school-aged Alaska Native children in western Alaska. More targeted screening and treatment, for example among children with iron deficiency and anemia, may have a role.

**Table 3. Median values and median increases in baseline values for serum ferritin and blood hemoglobin among Alaska Native children in rural Alaska in 2007, according to treatment assignment or *Helicobacter pylori* infection status.**

Characteristic, group	Median value at 40 months				Median increase in value from baseline to 40 months			
	Serum ferritin level, pmol/L (μg/L)	<i>P</i>	Blood hemoglobin level, g/L	<i>P</i>	Serum ferritin level, pmol/L (μg/L)	<i>P</i>	Blood hemoglobin level, g/L	<i>P</i>
<b>Treatment assignment</b>								
Intervention ( <i>n</i> = 85)	22.5 (10.0)	.210	125	.681	9.6 (4.3)	.218	4.0	.244
Control ( <i>n</i> = 91)	20.2 (9.0)	...	124	...	6.5 (2.9)	...	3.0	...
<b><i>H. pylori</i> status at 40 months</b>								
Negative ( <i>n</i> = 33)	29.2 (13)	.005	126	.268	14.8 (6.6)	.005	4.0	.381
Positive ( <i>n</i> = 143)	20.2 (9.0)	...	124	...	6.6 (3.0)	...	3.0	...
<b><i>H. pylori</i> status at 8, 14, and 40 months</b>								
Always negative ( <i>n</i> = 31)	29.2 (13.0)	.015	126	.221	14.7 (6.5)	.018	4.0	.307
Always positive ( <i>n</i> = 99)	20.2 (9.0)	...	124	...	6.6 (3.0)	...	3.0	...

**NOTE.** *P* values determined by Mann-Whitney *U* test.



**Figure 3.** Prevalences of iron deficiency (serum ferritin level  $<22.47$  pmol/L [ $<10$   $\mu\text{g/L}$ ]) and anemia (hemoglobin level  $<115$  g/L) across time, according to assigned treatment group (A) and *Helicobacter pylori* infection status at 40 months (B).

The resolution of *H. pylori* infection did not reduce the prevalence of iron deficiency or improve ferritin levels in our study until after 14 months. We hypothesized that negative findings at 14 months resulted from *H. pylori*-associated gastrointestinal changes, particularly atrophic gastritis. Gastric atrophy has been documented among children with *H. pylori* infection [28–30], and in adults it might take years to resolve after eradication of infection [31–33]. However, of 20 gastric biopsy samples obtained from *H. pylori*-positive Alaska Native children from western Alaska aged 7–15 years during 2002–2007, none exhibited atrophy (C. Allan Pratt, MD; verbal communication, March

2008), indicating that atrophic gastritis is unlikely to explain our results. Inadequate initial iron supplementation is also unlikely to explain the negative findings at 14 months, because previous studies have reported that resolution of *H. pylori* infection led to the resolution of iron deficiency even in the absence of iron supplementation [13, 34, 35]. Additionally, multiple studies have documented adequate dietary iron intake among Alaska Natives living in Western Alaska [18, 19, 36].

Our study was not placebo-controlled for 2 reasons. Scientifically, the most relevant question was the marginal benefit provided by eradication of *H. pylori* infection beyond the accepted

standard of care. Additionally, withholding iron from children with known iron deficiency would have been unethical. The lack of a true placebo group could have caused us to underestimate the effect of *H. pylori* infection eradication as an isolated intervention on ferritin levels and ancillary iron measurements. However, 3 other randomized trials of the effect of *H. pylori* infection treatment on iron deficiency anemia also lacked true placebo groups but reported improved hemoglobin [34, 37, 38] and ferritin levels [37, 38] among patients who received *H. pylori* treatment and iron, compared with persons who received iron therapy alone. Unlike our study, these trials studied older patients (aged  $\geq 10$  years), compared smaller groups (range, 7–43 patients), and had shorter maximum follow-up times (range, 2–3 months). Most importantly, these studies enrolled only patients with severe anemia, that is, mean or median hemoglobin levels  $\leq 81$  g/L. In contrast, anemia was present in just 22% of the children enrolled in our study, and most of it was mild. For statistical reasons, the mild level of anemia may have caused us to miss a true impact of *H. pylori* treatment. Also, proteomic and genomic variations in *H. pylori* strains may be associated with different effects on host iron metabolism [39–43]; if strains circulating in our study population differed in this respect from those in other studies, this could also explain the relatively small effect size we observed. We could not evaluate this possibility because we did not collect *H. pylori* isolates.

Although our study was not blinded, this limitation is usually associated with an erroneous rejection of the null hypothesis (i.e., a type I error) [44]. To our knowledge, our study had the longest follow-up period and was the largest conducted on the hypothesis of interest, and only our study addressed the usefulness of *H. pylori* screening and treatment as a population-based intervention for school-aged children with endemic iron deficiency and mild anemia. Nevertheless, our study was not powered to detect differences in outcomes between subgroups or small effects, and the paucity of children with anemia—particularly severe anemia—make it difficult to draw firm conclusions for this outcome. We did not define dietary intake of iron or foods that enhance iron absorption in our study. The randomized study design should have controlled for dietary differences between study groups, and previous data indicate that Alaska Natives in Western Alaska consume levels of dietary iron higher than the US norms [18, 19, 36]. Nevertheless, inadequate nutrition among certain participants may have blunted the overall effect of *H. pylori* infection resolution and might explain the initial reductions in the prevalence of anemia among children in the control group, who received iron supplementation but not *H. pylori* treatment.

Among children living in an area with high prevalences of *H. pylori* infection and iron deficiency, sustained resolution of *H. pylori* infection modestly improved iron status and substantially reduced the prevalence of mild iron deficiency anemia. Intention-to-treat analyses identified smaller differences be-

tween groups, probably largely because of the high *H. pylori* re-infection rate. Because populations in developing countries worldwide have prevalences of iron deficiency, anemia, and *H. pylori* infection that are similar to those among Alaska Natives, and because anemia and iron deficiency have substantial health effects, future work in this area is needed. For example, the usefulness of population-based primary prevention will depend on further documentation of the extent to which early infection and subsequent gastrointestinal changes lead to inadequately reversible hematologic changes. Additional studies should also evaluate the effect of treatment among other populations with iron deficiency, such as those with low prevalences of *H. pylori* infection, more severe anemia, or concurrent gastrointestinal symptoms.

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