Acute Helicobacter pylori Infection Is Followed by an Increase in Diarrheal Disease Among Peruvian Children

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ABSTRACT. Background. Cohort and case-crossover studies were conducted to evaluate whether new Helicobacter pylori infections are followed by increased diarrhea.

Methods. Participants were 6-month-old to 12-year-old shantytown residents living near Lima, Peru. Baseline data were collected from community households. Health interviews were completed daily, and sera, drawn every 4 months, were tested for H pylori immunoglobulin G. Diarrhea rates among newly H pylori-infected (seroconverting) children were compared with rates among persistently uninfected and infected children using cohort and case-crossover analyses.

Results. Sera were obtained from 345 children from January 1, 1995, through September 1, 1997. H pylori incidence was 12% per year (36 H pylori infections in 109 866 seronegative days). In adjusted cohort analyses, seroconverters had more diarrhea days (rate ratio: 2.0; 95% confidence interval: 1.6–2.4), episodes, and sick days than did persistently uninfected and infected children using cohort and case-crossover analyses.

Conclusion. Preventing H pylori infection may help reduce pediatric diarrheal disease. Pediatrics 2001;108(5).

METHODS

Participants

This study was conducted in Pampas de San Juan de Miraflores (Pampas), a community 10 km north of Lima. Of its 36 000 inhabitants, 45% are ≤18 years old. Most residences are huts with sheet metal roofing; indoor plumbing is rare.31 The cohort was comprised of 3 population-based samplings of Pampas children: 1) a random sample of children aged 0–24 months that comprised 36% of final cohort; 2) a random sample of children aged 0 to 30 months that comprised 28% of the final cohort; and 3) a random sample of children 0 to 12 years old that comprised 28% of the final cohort; and 3) a random sample of children 0 to 12 years old that comprised 36% of the final cohort. Enrolling 1 child per consenting household yielded a
H pylori Antibody Testing

Sera were tested for H pylori-specific immunoglobulin G (IgG) using an in-house enzyme-linked immunosorbant assay (ELISA) modified for use in Peru. High-binding microwell plates were coated with antigen (1:428 dilution) derived from 5 Peruvian H pylori strains. Serum (1:150) and goat anti-human IgG (1:2000) were added. The assay was standardized using sera from 19 seronegative and 16 biopsy-confirmed seropositive Peruvian adult and child controls. An optical density (OD) twice the mean of the negative controls indicated H pylori infection; using this cutoff, positive and negative controls showed complete separation. Serial samples from each child were run on the same plate; ODs were adjusted using at least three calibrated controls per plate. Analyses were performed using the mean adjusted OD of triplicate runs. Infants <6 months old were excluded to avoid interference from maternal IgG antibody. Children were categorized as uninfected (all samples negative), persistently infected (all samples positive), transiently infected [earlier sample(s) positive and later sample(s) negative] or newly infected (change between 2 consecutive samples from negative to positive with a 50% or greater increase in OD). Newly infected children could also be considered transiently infected if they later lost H pylori antibody. Children in whom consecutive sera changed from negative to positive with a <50% increase in OD were excluded from analysis.

An assessment of the time required to develop H pylori-specific IgG antibody has been published in 3 adults and 1 child who developed acute infection. Seroconversion in the 3 adults occurred, respectively, between 3 and 14 weeks, between 2 and 11 weeks, and >7 weeks after the probable date of infection. Seroconversion in the child probably occurred between 5 and 10 weeks after infection. We therefore estimated that H pylori infection occurred at the midpoint between each child’s last negative and first positive serum minus 7 weeks.

Measures of illness included:

1. Diarrhea day: a 24-hour period in which the child was reported to have abnormally loose or frequent stools.
2. Diarrhea episode: a period of 1 or more diarrhea days that first positive serum minus 7 weeks.
3. Diarrhea sick day: a diarrhea day when the child was also reported to have abnormally loose or frequent stools.

Bivariate Analysis

Bivariate analyses were performed using the Mantel-Haenszel χ² test for categorical variables and the Student t test or the Kruskal-Wallis 2-sample test for integer and continuous variables. All comparisons were 2-tailed. Confidence intervals for proportions were calculated using a normal approximation of the binomial distribution. Seasonality was assessed using a modification of the Peto-Wilson test.

Multivariate Analysis

Cohort Analysis

Adjusted incidence rate (incidence density) ratios for diarrhea days among the entire cohort were determined using 2 Poisson regression models. Covariates initially included in model 1 included: age (using its square root, as it significantly improved the fit of the model), season, household crowding, sleeping density, birth order (firstborn versus other) and the presence of stunting. Household socioeconomic variables included: type of household flooring, presence of electricity or running water, ownership of a television or farm animals, and educational attainment of the head of household (whether or not completed eighth grade). Model 2, developed for children <4 years old, also included whether the child had been breastfed or bottle-fed at least once in the previous day. Stepwise backward elimination was used to remove covariates not associated with diarrhea days (P < .2) in at least 1 model.

We first developed adjusted baseline rates of illness (diarrhea days, diarrhea episodes, diarrhea sick days, and cough days) for persistently H pylori-infected and uninfected children throughout the study period. We then compared adjusted baseline rates of illness in persistently uninfected or persistently infected children with rates among newly infected children at several time periods beginning after the estimated dates of infection. The periods analyzed were: from 12 through 3 months before; 2 months before; month 1 after (ie, the first month after); month 2 after; months 3 and 4 after; months 5 through 8 after; and months 9 through 12 after the estimated onset of infection. The population-attributable risk (PAR) of diarrhea sick days from acute H pylori infection was calculated using the formula:

\[
PAR = \frac{Pr \times (RR - 1)}{(Pr \times (RR - 1)) + 1}
\]

where Pr represents the prevalence of new H pylori infection and RR represents the rate ratio of diarrhea sick days among children with new infection. The value of Pr for children <48 months old was approximated by assuming a constant incidence of H pylori infection and then calculating prevalence among children at the midpoint of this age range (ie, 24 months old). This approximation provides a more reliable estimate of the population prevalence at this age than the sample prevalence based on the small number of children who were exactly 24 months old at the time of the study.

Case-Crossover Analysis

To assess unrecognized sources of confounding, a case-crossover analysis compared newly infected children to themselves at earlier and later periods. Crude rates of diarrheal illness for these children in the first 3 months after acquisition of infection were compared with the pooled rates during the same 3 months 1 year earlier and 1 year later, using the rank-sum test. This analysis was performed using only the subset of children who had sero-converted and who had complete follow-up for the case period and 1 or more months in the crossover periods.

Definitions

Breastfed means that the child was breastfed at least once in the preceding 24-hour period, irrespective of other feeding methods. Bottled means that the child was bottle-fed at least once in the preceding 24-hour period, irrespective of other feeding methods. Sleeping density is the number of people who stayed overnight in the bedroom at the study area at least twice weekly divided by the number of bedrooms. Crowding is the number of people who stayed overnight at least twice weekly divided by the number of rooms. Stunting means height-for-age >2 standard deviations below World Health Organization norms.

RESULTS

H pylori Status of Participants

Of 412 enrolled children, 345 (84%) provided baseline and ≥1 follow-up serum sample (mean: 3.8 samples per child). The 67 children who did not provide follow-up sera were of similar age and socioeconomic status as children who provided follow-up serum. Children who provided follow-up sera were a median of 17.5 months (interquartile range: 13–50 months) of age during the study period and were followed for a median of 424 days, contributing 109 866 days of follow-up. Of these 345 children, 259
(75%) were persistently uninfected, 39 (11%) were persistently infected, 2 (1%) were initially seropositive but were subsequently seronegative (transiently infected) and 32 (9%) developed a new *H pylori* infection. Thirteen children (4%) became seropositive during the study period and had small (<50%) increases in OD between consecutive sera and were not included in subsequent analyses. Of the 32 newly infected children, 7 (22%) later lost *H pylori* antibodies; 4 of these 7 again became seropositive during the study period. Children who lost antibodies (and the subset who regained them) had similar rates of antibiotic use as other seroconverting children. Assuming all seroconversions were detected, the incidence of *H pylori* infection was 12% per person-year (36 *H pylori* infections in 109,866 seronegative days-at-risk; 95% confidence interval [CI]: 8%–17%); if the 13 borderline seroconversions were considered to represent real infections, then the incidence of *H pylori* infection was 14% (45 new *H pylori* infections in 115,398 seronegative days-at-risk; 95% CI: 10%–19%). Eighteen girls and 14 boys seroconverted (Fig 1). Although more seroconversions occurred in January than in any other month, no seasonal clustering was evident.

**Risk Factors for Diarrhea**

Of 345 children, 262 (76%) had diarrhea at some point during the study period. Diarrhea was reported on 2.2% of follow-up days, ranging from 3.9% in children 6 to 12 months old to 0.7% in children 10 to 12 years old. Children <4 years old had 4.0 reported diarrheal episodes per year. Diarrheal illness was seasonal; diarrhea days were more frequent in all months from February through June than in other months (Hewitt’s *P* = .02). In multivariate analysis (model 1), the following factors were associated with an increased risk of diarrhea days: younger age, calendar years 1996 and 1997, calendar quarter April through June, female sex, having older siblings in the household, and having farm animals in the household. Higher educational attainment by the head of household and the presence of a television, electricity, or running water were associated with a decreased risk of diarrhea days. In model 2 (the adjusted model restricted to children 4 years old or younger), running water in the house and breastfeeding or bottle-feeding (as opposed to eating only solid food) were also associated with a decreased risk of diarrhea days (Table 1).

**Cohort Analyses**

The rate of diarrheal illness among children who developed a new *H pylori* infection was compared with rates in persistently uninfected and infected children. The rate of diarrheal illness among children who developed a new *H pylori* infection was compared separately against rates in persistently uninfected and in persistently infected children. Crude rates of diarrheal illness and coughing (unadjusted for age or other covariates) were lowest for persistently infected children, highest for persistently uninfected children, and intermediate for newly infected children in the year after onset of infection (Table 2). However, in the adjusted analysis (model 1), newly infected children had more diarrheal illness than persistently uninfected children during the first 2, 8 and 12 months after the estimated onset of *H pylori* infection (Table 3). In the year after infection, these children had more diarrhea days (rate ratio [RR]: 2.0; 95% CI: 1.6–2.4), more diarrhea episodes (RR: 1.9; 95% CI: 1.4–2.5), and more diarrhea sick days (RR: 2.0; 95% CI: 1.4–2.9) than did uninfected children. The rate of cough (the comparison symptom) decreased during this time (RR: 0.8; 95% CI: 0.7–0.9). These effects were unchanged when analyzing only children 4 years old or younger (model 2; Table 3). Assuming a *H pylori* incidence of 12% in this community, 10.6% of 24-month-old children would be expected to have an *H pylori* infection that had occurred in the previous year. Therefore, 11.5% of diarrhea sick days among Pampas children <4 years old could be attributed to new *H pylori* infection.

The influence of new *H pylori* infection on rates of diarrheal illness was strongest in the first 2 months after infection. Rate ratios for all measures of diarrhea among newly infected children showed a clear rise and fall during the year after infection; no similar
Rates for newly infected children were calculated for the year after estimated date of infection onset. To evaluate the effects of acute versus chronic *H. pylori* infection, we compared the rates of illness in newly infected children with rates in persistently infected children. When compared with persistently infected children, newly infected children had an increase in diarrhea days (RR: 1.7; 95% CI: 1.3–2.4), episodes (RR: 1.6; 95% CI: 1.0–2.5; *P* = .065), and sick days (RR: 3.2; 95% CI: 1.6–6.7) in the year after infection. Analyses adjusting for breastfeeding or bottle-feeding (model 2) could not be performed because of small numbers.

### TABLE 1. Covariates of Diarrhea Days in a Cohort of 345 Peruvian Children: Final Multivariable Models

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Rate Ratio (95% CI), All Ages†</th>
<th>P-value</th>
<th>Rate Ratio (95% CI), ≤4 Years Only‡</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (d)‡</td>
<td>0.97 (0.97–0.98)</td>
<td>&lt;.001</td>
<td>0.97 (0.97–0.97)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Quarter of year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>January–March</td>
<td>0.97 (0.84–1.13)</td>
<td>.73</td>
<td>1.03 (0.89–1.21)</td>
<td>.66</td>
</tr>
<tr>
<td>April–June</td>
<td>1.43 (1.26–1.64)</td>
<td>&lt;.001</td>
<td>1.48 (1.28–1.71)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>July–September</td>
<td>1.93 (0.82–1.06)</td>
<td>.29</td>
<td>0.92 (0.79–1.06)</td>
<td>.23</td>
</tr>
<tr>
<td>October–December</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calendar year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1995</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1996</td>
<td>1.73 (1.54–1.95)</td>
<td>&lt;.001</td>
<td>1.74 (1.53–1.98)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>1997 (through September)</td>
<td>2.11 (1.64–2.73)</td>
<td>&lt;.001</td>
<td>1.78 (1.34–2.38)</td>
<td>.09</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.24 (1.14–1.35)</td>
<td>&lt;.001</td>
<td>1.15 (1.15–1.19)</td>
<td>.05</td>
</tr>
<tr>
<td>Stunting (growth retardation)</td>
<td>1.22 (1.10–1.36)</td>
<td>&lt;.001</td>
<td>1.17 (1.05–1.32)</td>
<td>.006</td>
</tr>
<tr>
<td>Head of household completed grade 8</td>
<td>0.89 (0.81–0.97)</td>
<td>.009</td>
<td>0.83 (0.76–0.91)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Older siblings in house</td>
<td>1.08 (0.95–1.23)</td>
<td>.22</td>
<td>1.30 (1.11–1.51)</td>
<td>.001</td>
</tr>
<tr>
<td>Electricity in house</td>
<td>0.60 (0.58–0.73)</td>
<td>.14</td>
<td>0.22 (0.05–0.88)</td>
<td>.03</td>
</tr>
<tr>
<td>Television in house</td>
<td>0.65 (0.58–0.73)</td>
<td>&lt;.001</td>
<td>0.69 (0.61–0.78)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Running water in house</td>
<td>0.90 (0.82–1.00)</td>
<td>.04</td>
<td>0.83 (0.75–0.91)</td>
<td>.001</td>
</tr>
<tr>
<td>Farm animals in yard</td>
<td>1.29 (1.19–1.42)</td>
<td>&lt;.001</td>
<td>1.16 (1.05–1.27)</td>
<td>.003</td>
</tr>
<tr>
<td>House has false floor</td>
<td>1.07 (0.98–1.17)</td>
<td>.15</td>
<td>1.16 (1.05–1.28)</td>
<td>.002</td>
</tr>
<tr>
<td>Child was breastfed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child was bottle-fed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* † Square root of age was substituted for age in the model as it significantly improved goodness-of-fit.
  ‡ Variable was not included in all ages model because it does not pertain to older children.

### TABLE 2. Crude Rates of Diarrheal Illness, by *H. pylori* Infection Status, in a Cohort of Peruvian Children

<table>
<thead>
<tr>
<th>Categories of Illness</th>
<th>Events</th>
<th>Days at Risk</th>
<th>Events per Child-Year*</th>
<th>Crude RR (95% CI) Versus Persistently Persistently Uninfected Children Infected Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistently uninfected children</td>
<td>2082</td>
<td>87 195</td>
<td>8.7</td>
<td>0.5 (0.4–0.6)</td>
</tr>
<tr>
<td>Persistently infected</td>
<td>127</td>
<td>10 745</td>
<td>4.3</td>
<td>0.8 (0.7–1.0)</td>
</tr>
<tr>
<td>Newly infected children</td>
<td>128</td>
<td>6382</td>
<td>7.3</td>
<td></td>
</tr>
<tr>
<td>Diarrhea episodes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistently uninfected</td>
<td>797</td>
<td>87 195</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>Persistently infected</td>
<td>60</td>
<td>10 745</td>
<td>2.0</td>
<td>0.6 (0.5–0.8)</td>
</tr>
<tr>
<td>Newly infected children</td>
<td>57</td>
<td>6382</td>
<td>3.3</td>
<td>1.0 (0.7–1.3)</td>
</tr>
<tr>
<td>Diarrhea sick days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistently uninfected</td>
<td>676</td>
<td>82 744</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>Persistently infected</td>
<td>34</td>
<td>10 393</td>
<td>1.2</td>
<td>0.4 (0.3–0.6)</td>
</tr>
<tr>
<td>Newly infected children</td>
<td>33</td>
<td>6153</td>
<td>2.0</td>
<td>0.7 (0.5–0.9)</td>
</tr>
</tbody>
</table>

* † Rate = (number of events × 365.24) ÷ days at risk.
  † Rates for newly infected children were calculated for the year after estimated date of infection onset.

### Case-Crossover Analyses

Data for crossover periods were available for only 11 of the 36 seroconversions that were followed in the in the cohort study. Among these children, crude rates of diarrhea were higher in the 3 months after *H. pylori* infection than in either the 3 months of the year before or after this period (Table 4). In the pooled case-crossover analysis, diarrhea days (RR: 2.84; 95% CI: 0.15 – ∞), episodes (RR: 2.77; 95% CI: 0.34 – ∞), and sick days (RR: ∞; 95% CI: 0 – ∞), but not cough days (RR: 0.95; 95% CI: 0.0 – 14.9), tended to be more frequent in the 3 months immediately after *H. pylori* infection than in the 3 corresponding months of the years before and after.

### DISCUSSION

In this study, we found that new *H. pylori* infection in children is followed by a period—several months
to a year—of increased diarrhea. This increase occurred among children who, at baseline, did not have more diarrhea than other children (Fig 2). Moreover, because diarrhea rates in the setting of acute \( H\) \( pylori\) infection were greater than those seen in chronically infected children, we cannot attribute the increased diarrhea simply to the presence of \( H\) \( pylori\), or to spurious effects associated with \( H\) \( pylori\) serostatus. Instead, it appears to result from some, as yet unclear, factor related to acute infection.

Loss of the gastric acid barrier permits ingested pathogens to more readily cause diarrheal disease.\(^46\)–\(^48\) Postmarketing surveillance of the histamine-blocker cimetidine revealed a 4.3-fold increase in diarrhea among persons taking the drug compared with controls.\(^49\)

\section*{TABLE 3. RRs for Diarrheal Illness in Children Newly Infected with \textit{H pylori} During the First 2, 8, and 12 Months After Infection versus Persistently Uninfected and versus Persistently Infected Children in a Cohort of Peruvian Children}

<table>
<thead>
<tr>
<th>Category of Illness</th>
<th>RR (95% CI), All Ages* Newly Infected Versus Uninfected Children</th>
<th>RR (95% CI), ( \leq ) 4 Years Only† Newly Infected Versus Uninfected Children</th>
<th>RR (95% CI), All Ages* Newly Infected Versus Persistently Infected Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First 2 mo after onset‡</td>
<td>2.41 (1.74–3.34)§</td>
<td>2.17 (1.48–3.20)§</td>
<td>1.99 (1.26–3.13)§</td>
</tr>
<tr>
<td>First 8 mo after onset</td>
<td>2.06 (1.69–2.50)§</td>
<td>1.99 (1.58–2.51)§</td>
<td>1.74 (1.26–2.40)§</td>
</tr>
<tr>
<td>First 12 mo after onset</td>
<td>1.98 (1.64–2.40)§</td>
<td>1.94 (1.54–2.45)§</td>
<td>1.72 (1.25–2.38)§</td>
</tr>
<tr>
<td>Diarrhea episodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First 2 mo after onset</td>
<td>2.33 (1.43–3.79)§</td>
<td>2.46 (1.44–4.22)§</td>
<td>2.04 (1.06–3.90)§</td>
</tr>
<tr>
<td>First 8 mo after onset</td>
<td>1.90 (1.40–2.58)§</td>
<td>2.00 (1.41–2.83)§</td>
<td>1.51 (0.94–2.43)§</td>
</tr>
<tr>
<td>First 12 mo after onset</td>
<td>1.87 (1.40–2.53)§</td>
<td>1.94 (1.38–2.75)§</td>
<td>1.56 (0.97–2.49)§</td>
</tr>
<tr>
<td>Diarrhea sick days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First 2 mo after onset</td>
<td>2.96 (1.69–5.17)§</td>
<td>2.40 (1.18–4.90)§</td>
<td>5.39 (2.21–13.19)§</td>
</tr>
<tr>
<td>First 8 mo after onset</td>
<td>2.07 (1.42–3.02)§</td>
<td>2.26 (1.46–3.49)§</td>
<td>3.21 (1.53–6.72)§</td>
</tr>
<tr>
<td>First 12 mo after onset</td>
<td>2.01 (1.39–2.93)§</td>
<td>2.23 (1.45–3.45)§</td>
<td>3.22 (1.55–6.72)§</td>
</tr>
</tbody>
</table>

* Model 1 (all ages model) is adjusted for: square root of age, stunting (growth retardation), calendar quarter, calendar year, birth order (firstborn versus other), gender, educational attainment of head of household, and the presence of a television, electricity, running water, or a false floor in the household.
† Model 2 (model restricted to children \( \leq \) 4 years old) is adjusted for: breastfeeding or bottle-feeding, square root of age, stunting (growth retardation), calendar quarter, calendar year, birth order (firstborn versus other), gender, educational attainment of head of household, and the presence of a television, electricity, running water, or a false floor in the household. The model could not be used to compare newly infected with persistently infected children because of small numbers.
‡ Months after the estimated onset date of new \( H\) \( pylori\) infection.
§ \( P \leq .001.\)
∥ \( P \leq .005.\)
¶ \( P \leq .05.\)
\(1005\)
\(1005\)
disproportionately infect hypochlorhydric patients. A hospital-based study showed a 3.1-fold increased odds of salmonellosis among persons with atrophic achlorhydria. Similarly, the infectious dose of ingested Campylobacter jejuni was reduced among volunteers who first drank sodium bicarbonate. Although resistance to gastric acid among Escherichia coli is probably strain-specific, the infectious dose of enterotoxigenic E. coli infection is decreased among hypochlorhydric persons. Other acid-sensitive organisms that might preferentially cause diarrhea in people with hypochlorhydria include rotavirus and other enteric viruses. 

Although not proven, it is therefore plausible that temporary loss of the gastric acid barrier could mediate the observed association between H pylori and diarrheal disease, because H pylori-induced hypochlorhydria has been observed after acute infection in adults. This hypochlorhydria may result from neutrophilic inflammation at the neck of parietal cells—which could physically block acid secretion into the stomach—or from the generation of an acute-phase protein that transiently blocks the acid-producing capability of the cells. However, no direct evidence yet links H pylori, hypochlorhydria, and diarrhea. Moreover, these mechanisms are controversial, and there are other potential mechanisms by which H pylori could lead to gastroenteritis-like illness. H pylori infection has been linked to protein-losing enteropathy and to food allergies, which can cause diarrhea. Application of the H pylori cytotoxin VacA to the surface of human intestine-derived cell monolayers promotes apical Cl− and water secretion. Finally, H pylori attachment to gastric epithelial cells could cause a cytokine-mediated diarrhea by promoting, for example, systemic elaboration of IL-8. One or several of these mechanisms could be responsible for an acute infection syndrome which has—so far—been difficult to elucidate. Research to detect other effects of Helicobacter species in the human intestine and to determine if natural H pylori infections are followed by a period of hypochlorhydria is ongoing.

This study suggests that H pylori has developed an elegant survival strategy. Our laboratory has shown that H pylori is not normally cultured from the stools of infected adults, but that viable H pylori are routinely excreted when diarrhea is induced. We postulate that H pylori either causes or indirectly promotes gastroenteritis in the months after acute infection as a means of transmission between young children. Because most acute H pylori infections occur in children, and because young children are the most susceptible to diarrheal illness, this is the group most likely to suffer from H pylori-associated diarrhea. After this initial period, H pylori (usually) becomes a quiescent, lifelong infection, thereby maintaining its striking prevalence. In fact, there is evidence from a cross-sectional study in German schoolchildren that chronic infection protects against diarrheal diseases. However, both our study and studies using the 13C-urea breath test to detect H pylori infection among younger Peruvian children have shown that 20% or more of early infections are transient, and may be followed by recurrent acute infection. The deleterious health effects of acute H pylori infection may be most important in areas of the world where infection (and repeat infection) is most common.

One limitation of our study is that seroreversion may not occur for more than a year after H pylori eradication. Because young children spontaneously eradicate H pylori, it is possible that some children classified as persistently seropositive were actually uninfected. This could have diluted the effect of chronic infection on diarrheal disease. However, because we found only 2 seroreverters in this cohort, we suspect that the number of seroreverters misclassified as seropositives was also small. The most critical limitation of this study was our inability to accurately determine infection onset; dates of H pylori seroconversion were crude estimates interpolated from consecutive serum samples. Serology is neither

<table>
<thead>
<tr>
<th>Category of Illness</th>
<th>Events</th>
<th>Days at Risk</th>
<th>Events per Child-Year*</th>
<th>RR (95% CI) Versus</th>
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<tbody>
<tr>
<td>Prevalent diarrhea during</td>
<td></td>
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<td></td>
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<tr>
<td>Months 12-10 before onset</td>
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<td>301</td>
<td>0</td>
<td>—</td>
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<tr>
<td>Months 1-3 after onset</td>
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<td>2493</td>
<td>8.5</td>
<td>1.8 (0.8-13.4)</td>
</tr>
<tr>
<td>Months 13-15 after onset</td>
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<td>2.6</td>
<td>—</td>
</tr>
<tr>
<td>Episodes of diarrhea during:</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Months 12-10 before onset</td>
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<td>301</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Months 1-3 after onset</td>
<td>26</td>
<td>2493</td>
<td>3.8</td>
<td>0.8 (0.6-6.2)</td>
</tr>
<tr>
<td>Months 13-15 after onset</td>
<td>2</td>
<td>282</td>
<td>2.6</td>
<td>—</td>
</tr>
<tr>
<td>Diarrhea sick days during</td>
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<td></td>
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</tr>
<tr>
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<td>298</td>
<td>0</td>
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</tr>
<tr>
<td>Months 1-3 after onset</td>
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<td>2377</td>
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<td>263</td>
<td>0</td>
<td>—</td>
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<td>Cough days during</td>
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<tr>
<td>Months 13-15 after onset</td>
<td>41</td>
<td>282</td>
<td>53.1</td>
<td>—</td>
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</table>

* Events per child-year = (number of events ÷ days at risk) × 365.24.
as sensitive nor as specific as the $^{13}$C-urea breath test for detecting $H. pylori$ colonization\(^73\) in children. However, we used stringent criteria for seroconversion, to maximize the chance that seroconverters truly had been recently infected. Nevertheless, we suspect that trends over time (Fig 2) would have been even more clearly defined had we been able to reduce these sources of misclassification.\(^74\) Our inability to accurately assess infection onset also leaves open the possibility that a period of increased diarrheal disease precedes or facilitates $H. pylori$ infection. However, because diarrheal disease rates were consistently below baseline before seroconversion, this possibility seems unlikely (unless our estimate of the time from infection to IgG formation is grossly incorrect).

This study in a Peruvian community demonstrated that about 12% of susceptible children were infected by $H. pylori$ each year and that these children had twice the risk of diarrheal disease in the year after infection as children who remained uninfected. Complications of diarrheal disease kill 3 million children yearly; most of these complications occur in regions of the world where $H. pylori$ infection is common.\(^75,76\) Prevention of $H. pylori$ infection—for example, by immunization—\(^77,78\) may eventually become part of a broader strategy to reduce the impact of pediatric diarrheal disease as well as to prevent cancer and ulcer disease. Examining the mechanisms underlying $H. pylori$-associated diarrheal disease is an important avenue for future research.

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