Acquisition versus Loss of *Helicobacter pylori* Infection in Japan: Results from an 8-Year Birth Cohort Study

Toshiko Kumagai, Hoda M. Malaty, David Y. Graham, Sigemi Hosogaya, Keiko Misawa, Kenichi Furihata, Hiroyoshi Ota, Chizu Sei, Eiji Tanaka, Taiji Akamatsu, Toshiki Shimizu, Kendo Kiyosawa, and Tsutomu Katsuyama

Studies of the pattern of change in the epidemiology of *Helicobacter pylori* infection are scarce. A longitudinal cohort study consisted of 644 children and adults, and two independent cross-sectional surveys were conducted in rural Japan between 1986 and 1994. The anti-*H. pylori* IgG seroconversion rates were 1.1% and 1% per year for children and adults, respectively. The seroreversion rate per year was 1.8% for children and 1.5% for adults. The cohort study was confirmed by the two cross-sectional studies. *H. pylori* prevalence fell in all age groups in both children (odds ratio [OR] = 0.5, 95% confidence interval [CI] = 0.2–1.0, P = .05) and adults (OR = 0.4, 95% CI = 0.3–0.6, P = .001). The rate of loss of *H. pylori* infection was greater than the acquisition. Data regarding acquisition and loss of *H. pylori* infection are critical to understanding the epidemiology of the infection and to developing treatment and vaccination strategies.

*Helicobacter pylori* infection is causally related to chronic gastritis and peptic ulcer disease and indirectly related to gastric adenocarcinoma and primary gastric B cell lymphoma [1–5]. The prevalence of *H. pylori* infection varies both between and within populations, with the rate of acquisition being generally higher in underdeveloped than in industrialized countries [6–16]. Cross-sectional studies have consistently shown a gradual increase in *H. pylori* seroprevalence with age, which has been interpreted as a birth cohort effect reflecting the fall in the rate of acquisition in successive generations of children as sanitation improved and standards of living increased [17–19].

In Japan, the prevalence and the mortality rates of peptic ulcer disease among Japanese men and women decreased dramatically between 1955 and 1985 [20] such that by 1980, the rate was similar to that in the United States and Europe [20, 21]. The decrease in the frequency of a disease in successive generations (i.e., birth cohorts) is most likely due to changes in an environmental factor(s) [22]. Since *H. pylori* infection is a critical factor in the etiology of peptic ulcer, the prevalence of the infection is a strong candidate for the changing environmental factor.

We studied *H. pylori* seroepidemiology in Japanese children and adults from a typical mountain village in the district of Nagano Prefecture, Japan. We report a cohort study and compare the results with the age-specific seroprevalence from two independent cross-sectional surveys conducted in the same population during 1986 and 1994.

Material and Methods

**Study area.** The study was done in a small district of South Kiso town in central Japan. This district is surrounded by mountains and consists of 19 small communities that have a total population of 1117 inhabitants. The current water supply system was introduced in 1959 and utilizes spring water from two locations. Prior to 1959, the river, wells, and springs were the source of drinking water. There is a central sewage system.

**Serum collection.** Sera were obtained from adults and children. Participants had been monitored from June 1986 to September 1994 with repeated blood samples and questionnaires within the framework of a study of hepatitis C transmission [23]. Each person completed questionnaires. Thereafter, 20 mL of blood was obtained from each patient, and the serum was separated. Blood samples were collected each year in a 2-day survey during the month of June, July, August, or September. Each serum sample was divided into three parts, of which one-third was stored at −80°C until the current study was begun. Subjects were eligible for this study if they had available at least 2 serum samples in ≥2 successive years.

Additional serum samples from other adults and children were obtained from two cross-sectional surveys conducted in the same region (641 samples in 1986 and 549 samples in 1994). *H. pylori* “eradication therapy” was not used during the period of study.

**Sero logic methods.** *H. pylori* status was determined by the presence of anti-*H. pylori* IgG antibodies by ELISA, using the GAP-IgG Kit (Biomerica, Newport Beach, CA). A standard curve was drawn by measuring the absorbance of the reference serum included in the kit. The reference serum was diluted serially 1:2–1:16 with PBS (pH 7.2), and the amount of anti-*H. pylori* IgG corresponding to 1:8 was expressed as 1.0 arbitrary index. The cross-reactivity of the antibody in a patient’s serum against 2 closely related bacteria (4 strains of *Campylobacter jejuni*, 1 strain of *Campylobacter ralidis*, and 1 strain of *Escherichia coli*) was examined as described previously [24–25]. In brief, sera from 10 adults and 10 children who had anti--*H. pylori* IgG were incubated...
for 30 min at 37°C with the sonicated cell extracts of the bacterial strains, and the unabsorbed anti–H. pylori IgG was measured. A control test employing an authentic H. pylori strain (ATCC 43504) was run in parallel.

The ELISA was validated in this population using a receiver operating characteristic curve to determine the cut-off value (0.51 arbitrary index). The results were compared with those obtained by bacteriologic or histologic examinations (or both); the specificity and sensitivity were 93% and 96.7%, respectively [26–27].

Statistical analyses. H. pylori infection was defined as a positive ELISA result. The objective of the statistical analyses was to examine the seroconversion and seroreversion rates in order to calculate the incidence and the loss rate of H. pylori infection, respectively. Subjects who were seronegative at study entry and seropositive at follow-up were considered seroconverters. Those who were seropositive at entry and became seronegative at follow-up were considered seroreverters. The cohort was grouped according to age when the first blood sample was obtained.

Mantel-Haenszel χ² test was used to measure the difference between the prevalence of H. pylori infection during 1986 and 1994 within each age group. The data were analyzed by use of SAS software (SAS Institute, Cary, NC) [28].

Results

The study consisted of 112 children between the ages of 6 and 19 and 552 adults between the ages of 20 and 80 who participated from 1986 to 1994. The distribution of H. pylori status of the study population at their initial visit is presented in Table 1. The mean follow-up interval for children and adults was 5.3 and 7.5 years, respectively. For children and adults, seroreverters and seroconverters consistently remained seronegative and seropositive, respectively, in subsequent samples.

Of the 86 children, 5 (5.8%) who were seronegative at their first visit converted to seropositive during follow-up, and 2 of the 22 (9.1%) seropositive children became seronegative (Table 2). The incidence and loss rates for H. pylori infection were calculated using the assumption that the seroconversion and seroreversion rates were equally distributed throughout the mean observation periods (5.4 and 5 years for seroconverters and seroreverters, respectively). The incidence and loss rates of H. pylori infection were 1% and 1.5% per year for adults. Adults who were seroconverters were significantly younger than seroreverters (mean age 44.8 vs. 54, respectively; P = .001).

In the two cross-sectional studies, seropositivity increased with age (Table 3). The overall prevalence in children declined from 32% in 1986 to 17% in 1994, and in adults, the prevalence decreased from 87% in 1986 to 74% in 1994. The odds ratio (OR) in declining H. pylori seropositivity between 1986 and 1994 was similar for both children (OR = 0.5, 95% confidence interval [CI] = 0.2–1.0) and adults (OR = 0.4, 95% CI = 0.3–0.6).

Discussion

It is well established that the prevalence of H. pylori infection increases with age [6–16]. It is now generally assumed that the higher prevalence rate in older age groups is due to a birth cohort effect that reflects the decrease in the incidence of infection due to improvement in standards of living and sanitation practices [17–19]. These conclusions are consistent with the falling prevalence of infection in different age groups when measured at a single time point. Longitudinal studies permit the calculation of the seroconversion and the seroreversion rates within a single population.

The results from the cohort study confirmed that H. pylori acquisition continues throughout life; however, the rate of disappearance was greater than the rate of acquisition. The results in the cohort study were confirmed in the two cross-sectional studies showing that the prevalence of H. pylori infection fell during the observation period. Of particular interest was the observation that there was a decrease in prevalence in every age group (figure 1). The fact that the same population was examined in two cross-sectional studies allowed us to look at the prevalence of infection within each age group in 1986 and again when the population had increased in age by 8 years (figure 1). The fall in prevalence that occurred during the observation period does not reflect changes in the rate of acquisition of H. pylori in childhood but rather the higher rate of loss of the infection.

There was a rapid change in sanitary conditions and the standard of living in Japan after World War II, and clean public

### Table 1. H. pylori status among study participants at their initial visit.

<table>
<thead>
<tr>
<th>Age range, years</th>
<th>Children (%)</th>
<th>Adults (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6–19</td>
<td>112 (100.0)</td>
<td>552 (100.0)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>22 (19.6)</td>
<td>464 (84.1)</td>
</tr>
<tr>
<td>Negative</td>
<td>86 (76.8)</td>
<td>73 (13.2)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>4 (3.6)</td>
<td>15 (2.7)</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of subjects.
water systems were introduced in Japan in the 1950s. A previous cross-sectional study from Japan reported a significant difference in the seroprevalence of *H. pylori* infection among people >40 years old and those ≤40, and this change was related to the standard of living and, thus, to differences in the risk of acquiring the infection [29]. The continuing change in the epidemiology of *H. pylori* infection reflects greater loss than acquisition of the infection and is thus unlikely to be related to changes in the standard of living, being instead likely related to changes in medical practices. Since eradication therapy was not used during our study period, the disappearance of *H. pylori* antibodies is thought to possibly be due to the use of antimicrobials for other common infections.

Spontaneous elimination of *H. pylori* infection (i.e., seroreversion) was previously reported in adults and children from developed and underdeveloped countries [18, 19, 30–37]. A study from Sweden followed a cohort of 6-month-old infants until age 11. This study reported spontaneous clearance of the infection as a common occurrence in young children [32], and another study from Finland reported the same observation [34]. In addition, a study from Peru examined infants longitudinally using the ^13^C-urea breath test and found that *H. pylori* infection in very young children often appeared to be transient with frequent reinfection, suggesting that there may be a low prevalence rate in children despite a high acquisition rate [33].

Seroreversion among adults has been reported [18, 30, 31, 35–37]. One interpretation has been that the loss of *H. pylori* infection among elderly persons is due to development of gastric atrophy. However, a study from The Netherlands found that 6 of 7 seroreverted patients who were followed for 11.5 years did not have gastric mucosal atrophy as assessed by serum gastrin levels and endoscopy [37]. Moreover, a recent broad-based review study [38] summarized seroconversion and seroreversion rates for all studies conducted between 1986 and 1996 and confirmed a higher spontaneous elimination of *H. pylori* infection (i.e., seroreversion) was previously reported in adults and children from South Kiso town, Japan.

### Table 2. Longitudinal changes in anti-*H. pylori* IgG status among children and adults.

<table>
<thead>
<tr>
<th></th>
<th>Children</th>
<th>Adults</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Converted</td>
<td>Cumulative (%)</td>
<td>Mean years of follow-up</td>
</tr>
<tr>
<td>Total</td>
<td>112</td>
<td>552</td>
<td>9.1</td>
<td>5.0</td>
</tr>
<tr>
<td>Positive</td>
<td>22</td>
<td>2</td>
<td>9.1</td>
<td>5.0</td>
</tr>
<tr>
<td>Negative</td>
<td>86</td>
<td>5</td>
<td>5.8</td>
<td>5.4</td>
</tr>
</tbody>
</table>

NOTE. Data are no. unless otherwise stated. Children ranged in age from 6 to 19 years; adults ranged in age from 20 to 80 years.

### Table 3. Comparison of age-specific seropositivity for *H. pylori* in 1986 and 1994, the percent differences, and the odds ratio (OR) estimates of declining infection rate from 1986 to 1994 in South Kiso town, Japan.

<table>
<thead>
<tr>
<th>Age group, years</th>
<th>1986</th>
<th>1994</th>
<th>% difference 1986–1994</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6–12</td>
<td>56</td>
<td>13</td>
<td>(23.2)</td>
<td></td>
</tr>
<tr>
<td>13–19</td>
<td>29</td>
<td>14</td>
<td>(48.3)</td>
<td>35.8</td>
</tr>
<tr>
<td>20–27</td>
<td>26</td>
<td>17</td>
<td>(65.4)</td>
<td>21.6</td>
</tr>
<tr>
<td>28–35</td>
<td>46</td>
<td>33</td>
<td>(71.7)</td>
<td>26.1</td>
</tr>
<tr>
<td>36–43</td>
<td>62</td>
<td>51</td>
<td>(82.3)</td>
<td>13.8</td>
</tr>
<tr>
<td>44–51</td>
<td>80</td>
<td>71</td>
<td>(88.8)</td>
<td>13.8</td>
</tr>
<tr>
<td>52–59</td>
<td>134</td>
<td>122</td>
<td>(91.0)</td>
<td>16.7</td>
</tr>
<tr>
<td>60–67</td>
<td>102</td>
<td>91</td>
<td>(89.2)</td>
<td>7.2</td>
</tr>
<tr>
<td>68–75</td>
<td>83</td>
<td>77</td>
<td>(92.8)</td>
<td>7.6</td>
</tr>
<tr>
<td>&gt;75</td>
<td>23</td>
<td>21</td>
<td>(91.3)</td>
<td>17.6</td>
</tr>
<tr>
<td>Total</td>
<td>641</td>
<td>510</td>
<td>(79.6)</td>
<td>12.2</td>
</tr>
</tbody>
</table>

NOTE. CI, confidence interval.
In conclusion, our study showed that the assumption that the pattern of the epidemiology of *H. pylori* reflects different rates of acquisition in childhood is inadequate to explain what is actually happening. One cannot use the simple concept of a birth cohort to understand either the epidemiology of *H. pylori* infection or to predict the prevalence in a specific age group in the future. Therefore, longitudinal studies within the same population are critical for measuring the rate of acquisition and loss of infection to provide insights regarding the mode(s) of transmission of infection and to design strategies for the management of *H. pylori*–associated diseases.

**Figure 1.** Seroprevalence of *H. pylori* infection in 2 cross-sectional studies conducted in 1986 and 1994. Each pair of bars represents prevalence of *H. pylori* infection in persons of specific age range (birth cohort) in 1986 and same cohort 8 years later (e.g., 24-year-old age group shows seroprevalence for 20- to 27-year-old age group in 1986 and 28- to 35-year-old age group in 1994). Prevalence of *H. pylori* infection declined overall and in each birth cohort.

**References**


