

Helicobacter pylori infection and mode of transmission in a population at high risk of stomach cancer

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Background	<i>Helicobacter pylori</i> (<i>H. pylori</i>) is a recognized cause of chronic gastritis and peptic ulcer disease, and is strongly suspected to play a role in the aetiology of stomach cancer but little is known about the mode of transmission.
Aim	To determine the prevalence of <i>H. pylori</i> infection in children and investigate potential modes of transmission in rural China.
Subjects and setting	We examined 98 children aged 3-12 years and 289 adults aged 35-64 years in a village in Linqu County, China, which has one of the highest rates of stomach cancer in the world.
Method	<i>H. pylori</i> infection was determined by ¹³ C-urea breath test in children and by an enzyme-linked immunosorbent assay in adults.
Results	Among 98 tested children, 68 (69%) were <i>H. pylori</i> positive, but the prevalence rates varied as a function of age, rising from about 50% at ages 3-4 to 85% at ages 9-10 before falling to 67% at ages 11-12. Boys had a higher infection rate than girls (77.8% versus 59.1%, $P < 0.05$). Among 289 adults, 195 (68%) were <i>H. pylori</i> positive, with a somewhat higher rate of positivity in younger compared to older age groups. The prevalence of <i>H. pylori</i> infection clustered within families. In families with at least one infected parent, 85% of children were <i>H. pylori</i> positive, while in families with both parents uninfected, only 22% of children were <i>H. pylori</i> positive (odds ratio [OR] = 30.4, 95% CI : 4.0-232).
Conclusions	These findings demonstrate the acquisition of <i>H. pylori</i> infection during early childhood in a population at high risk of stomach cancer, in a manner consistent with a person-to-person mode of transmission between parents and children.
Keywords	<i>Helicobacter pylori</i> , children, transmission, stomach cancer
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Helicobacter pylori (*H. pylori*) is a recognized cause of chronic gastritis and peptic ulcer disease, and is strongly suspected to play a role in the aetiology of stomach cancer.¹⁻³ The prevalence of *H. pylori* infection may reach 70% or more in certain

developing countries, but tends to average about 30% or less in developed countries.²⁻⁴ *H. pylori* infection appears to occur in early childhood, particularly in developing countries,⁵⁻⁷ although little is known about the mode of transmission.⁶ We previously reported that the prevalence of *H. pylori* infection in Linqu County, China (a rural area in northeast China with one of the highest rates of stomach cancer in the world and an exceptionally high prevalence of precancerous gastric lesions) exceeds 70% at ages 35-39 and appears to contribute to gastric carcinogenesis.⁴ To investigate the epidemiology of *H. pylori* infection in this high-risk area and the pattern of transmission in early life, we studied 98 children aged 3-12 years and 289 adults in one village of Linqu County, and examined the intra-familial patterns of *H. pylori* infection among 49 of these children and their parents.

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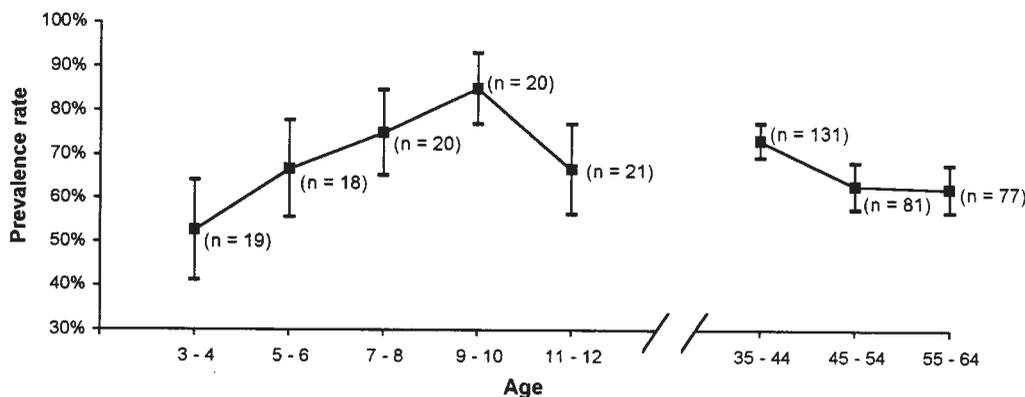


Figure 1 Prevalence rate of *H. pylori* infection in Linqu

Materials and Methods

In the spring of 1994, one village was selected at random from 14 villages in Linqu County where an endoscopic screening survey had been conducted.⁸ The names of all residents aged 3–12 and 35–64 years were transcribed from the village roster. All adults and 10 randomly selected children in each of the 10 single year categories aged 3–12 were invited to participate in a test to detect *H. pylori* infection. *H. pylori* status was determined by the ¹³C-urea breath test (¹³C-UBT) in children and by an enzyme-linked immunosorbent assay (ELISA) in adults.

All children fasted overnight, and baseline samples of exhaled CO₂ were collected. Each subject consumed 150 ml of a sweet starch paste to delay gastric emptying and then drank 10 ml of cold water containing 100 mg ¹³C-urea (>99%) (Baylor Medical College, USA). Expired gas was collected with the sampling bags at 15, 25, and 50 minutes. Around 20 ml of expired gas was then purified into CO₂ via a vacuum system for ¹³C analysis on gas-isotope-ratio mass spectrometry (MAT 250, Germany).⁹ Excess delta ¹³CO₂ >6 (by subtraction of the baseline pre-¹³C-urea breath sample) was regarded as positive.

Details of the serologic assay are described elsewhere.⁴ Briefly, approximately 5 ml of blood were collected from each fasting adult. *H. pylori* strains cultured from gastric biopsies of two patients in Linqu County were used to provide an antigenic preparation for serology. Serum *H. pylori* IgG antibody concentrations were measured using an ELISA procedure.¹⁰ An individual was considered positive if the ELISA optical density reading was above 1.0, a cutoff based on examination of the distribution of such readings in relation to a group of uninfected people and reference sera. Both the ¹³C-UBT and the ELISA were run in duplicate.

The χ^2 test was used to evaluate the significance of differences in the prevalence of *H. pylori* positivity among several subgroups. Odds ratios (OR) were computed as a measure of association between the risk of childhood infection and parental *H. pylori* status. OR adjusted for sex and age were obtained by logistic regression techniques.¹¹

Results

Ninety-eight of the 100 eligible children (54 boys and 44 girls) were tested. Among those tested, 68 (69.4%) were *H. pylori* positive, with a significantly higher infection rate in boys than

girls (77.8% versus 59.1%, $P < 0.05$). Of the 318 eligible adults, 289 (151 men and 138 women) were tested. Among those tested, 195 (67.5%) were *H. pylori* positive with a slightly higher rate in women than men (71.7% versus 63.4%, $P = 0.1$). As shown in Figure 1, the prevalence rates of *H. pylori* infection among children rose significantly from 52.6% at 3–4 years to 66.7% at 5–6 years, 75.0% at 7–8 years, and 85.0% at 9–10 years (one-tailed trend test $P = 0.012$) and then dropped to 66.7% at 11–12 years. Among adults, the rates declined from 73.3% at age 35–44 to 63.0% at age 45–54 and 62.3% above age 54 (one-tailed trend test $P = 0.047$).

Of the 98 children tested, 49 came from 41 (one child in 34 families, 2 children in 6 families and 3 children in one family) families for whom *H. pylori* status was measured in both parents ($n = 28$), in fathers only ($n = 16$) and in mothers only ($n = 5$). The median age of the parents was 42 years (range 35–58). Of the 28 children with both parents tested, 13 had both parents positive, 5 had both negative, 2 had father positive and mother negative, while 8 had mother positive and father negative. Where data were available on only one parent, 13 of 16 fathers were positive and 4 of 5 mothers were positive. Among the children in these 41 families, 15 were siblings, all of whom came from 7 families with at least one infected parent; 14 of 15 siblings were *H. pylori* positive.

Table 1 shows the per cent of *H. pylori* positivity in children according to the infection status of parents. The infection rate was 85.0% in families with at least one infected parent compared with 22.2% in families with no known infected parent (OR = 30.4). When infection occurred in mothers, the odds of *H. pylori* positivity in children was 30 times that seen when mothers were not infected (OR = 30.1). The corresponding OR associated with infection in fathers was 10.1. Despite the higher OR seen among children with maternal versus paternal infection, a formal test of the hypothesis that mothers carried greater risk than fathers was not statistically significant (one-sided $P = 0.20$), possibly because the study included only 49 children. This test was based on bootstrap resampling from the entire set of 41 families to account for correlations that arise when two or more children come from the same family.

Only a slight non-significant excess risk was seen for *H. pylori* infection among husbands with infected wives (OR = 1.5, 95% CI: 0.6–3.7) and among wives with infected husbands (OR = 1.5, 95% CI: 0.6–3.7).

Table 1 *H. pylori* prevalence rates and odds ratios among children in Linqu according to their parents' *H. pylori* status

Parents' <i>H. pylori</i> status	Children's <i>H. pylori</i> status			Odds ratio ^a	95% CI
	- (-%)	+ (+%)			
At least one parent positive					
no	7 (77.8)	2 (22.2)		1.0	
yes	6 (15.0)	34 (85.0)		30.4	4.0–232.2
Father					
no	7 (43.7)	9 (56.3)		1.0	
yes	3 (10.7)	25 (89.3)		10.1	1.6–63.2
Mother					
no	6 (75.0)	2 (25.0)		1.0	
yes	4 (16.0)	21 (84.0)		30.1	2.8–325.2

^a Odds ratio estimated from logistic regression with adjustment for age (<7 or ≥7 years) and child's gender as main effects.

Discussion

In this rural area of China with one of the world's highest rates of stomach cancer, 52% of children aged 3–4 years were infected with *H. pylori*, suggesting that multifocal gastritis begins in early childhood and progresses to chronic atrophic gastritis (CAG) in early adulthood.^{12,13} Although no information is available on the gastric histopathology of the infected children, our previous study showed CAG in more than 90% of the area population aged 35–39, including 28% with both CAG and intestinal metaplasia (IM), and 14% with CAG, IM and dysplasia.⁸ Furthermore, our survey of the prevalence of *H. pylori* antibodies among 2646 adults in Linqu indicated that *H. pylori* infection is a risk factor for progression of early gastric lesions, particularly from mild to severe CAG.⁴ Thus, it seems likely that early infections with *H. pylori* account at least partly for the very high prevalence of CAG and gastric cancer among adults in Linqu. Further evidence linking childhood *H. pylori* infection with development of gastric cancer has been reported in a large prospective study of Japanese-American men.¹⁴

Information on the prevalence of *H. pylori* infection in children elsewhere in China is limited. In Guangdong Province, southern China, an area with lower rates of stomach cancer of 10 per 100 000, the prevalence of *H. pylori* infection was 23% by 5 years of age,⁷ as compared with 65% in Linqu. The high rates of *H. pylori* positivity among children in Linqu are similar to the prevalences reported in Peru and Colombia where stomach cancer is also very common.^{15,16} Thus, our findings provide further evidence linking the high rates of stomach cancer among adults in various populations to the prevalence of *H. pylori* infections acquired in early childhood.

Little is known about the mode of transmission of *H. pylori* in humans, although the presence of *H. pylori* has been reported in saliva, dental plaque and faeces.^{17–19} Several studies in various areas have suggested that crowded living conditions, family size, sharing a bedroom, low socioeconomic status and poor sanitation predispose to *H. pylori* infection.^{6,20–27} The possibility of waterborne transmission has been suggested by studies in Chile and Peru,^{28,29} and by an earlier survey in Linqu suggesting a correlation between prevalence of adult infection and drinking water source.⁴ Since *H. pylori* has been isolated from

faeces,¹⁸ faecal-oral spread could also occur. The key finding of our present study was the intrafamilial clustering of *H. pylori* infection, with elevated risks among children of infected parents. The odds of infection were greatest in offspring of infected mothers, suggesting an important role for mother-to-child transmission of *H. pylori*. This finding is consistent with other studies linking *H. pylori* infection of children to parental^{30–34} or maternal infections.³⁵ It is noteworthy that in rural areas of China, mothers have especially close contact with their young children, often sharing the same bed, eating from the same bowls and using the same chopsticks. Some mothers in Linqu feed infants by pre-chewing their food, a practice that appears to predispose to *H. pylori* infection in West Africa.³⁶ Thus our findings, along with the reported isolation of *H. pylori* from oral secretions,^{17,19} are consistent with a person-to-person route of transmission, although shared environmental exposures may be involved as well.

In Linqu and other populations at high risk of stomach cancer, children appear to be more susceptible to *H. pylori* infection than adults, with peak infection rates in childhood,^{6,7} and little spread of infection between spouses.³⁷ In some high-risk populations transmission may occur horizontally among children in the same household.²⁴ Indeed, our study showed that 14 out of 15 siblings were both *H. pylori* positive, suggesting person-to-person contact in transmission. However, since all of these siblings were in families with at least one infected parent, it is impossible to distinguish between vertical and horizontal transmission. It is unclear why boys in our study had a 20% greater rate of *H. pylori* positivity than girls, although a similar result was reported in Colombia.¹⁶ The findings raise the possibility that high activity levels of boys may increase the potential for infections acquired from other children.

Although based on small numbers, the rising prevalence of *H. pylori* infection in children less than 10 years of age in Linqu resembles the age pattern reported in other studies.^{2,5–7} The prevalence dropped slightly in children aged 11–12 years, possibly due to chance variation. Among adults, infection rates in Linqu were highest at age 35–39 years, and then declined and plateaued at older ages. The lack of a strong age gradient in infection rates has been reported previously in Linqu⁴ and other developing countries.^{1,2,38} The actual decline in the prevalence of infection in Linqu adults is most likely due to the high percentage of subjects developing intestinal metaplasia or dysplasia, which appears to reduce *H. pylori* colonization of the gastric mucosa.^{39–40}

Since it was difficult to draw blood from young children, we used the urea breath test to determine *H. pylori* infection in children. Concerns may be raised about the comparability with serologic assays such as ELISA that was used in classifying *H. pylori* status in adults. However, the sensitivity and specificity of both the ELISA and ¹³C-UBT have previously been reported to surpass 90%.⁴¹ Since the prevalence of *H. pylori* infection in children of infected parents is high (85%), and the association is strong (OR = 30), the difference in infection detection methods is unlikely to substantially influence our findings. Moreover, prevalence trends in children and adults by age are each based on a separate detection method, thus it would not be influenced by variations in sensitivity between the tests.

In summary, our study has demonstrated the early acquisition of *H. pylori* infection among children living in Linqu, and

familial clustering of infection in a manner suggesting person-to-person transmission between parents and children. The high prevalence of *H. pylori* infection among young children in Linqu may help explain the exceptionally high risk of gastric cancer and precancerous lesions in this population. Our findings also suggest that children as well as adults should be included in intervention programmes designed to treat *H. pylori* infection and thus retard the progression of precancerous gastric lesions.

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