

RISK OF *HELICOBACTER PYLORI* INFECTION AMONG LONG-TERM RESIDENTS IN DEVELOPING COUNTRIES

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Abstract. The seroprevalence and incidence of *Helicobacter pylori* infection were determined among 312 North American missionaries who were serving in developing countries between 1967 and 1984. The majority (81%) resided in sub-Saharan Africa. When initially evaluated, the missionaries had a mean age of 40 years, 65% were female, and all were of white race/ethnicity. An ELISA showed that the initial prevalence of IgG antibody to *H. pylori* was 17%. After a mean of 7.4 years of service (1917 person-years of exposure), 37 (14%) of 259 initially seronegative subjects seroconverted to anti-*H. pylori*, giving an annual incidence of 1.9%. These data indicate a relatively higher risk of *H. pylori* infection among missionaries compared with an annual incidence of seroconversion of 0.3–1.0% in industrialized nations. Long-term residents in developing countries should be evaluated for *H. pylori* infection when gastrointestinal symptoms develop.

Helicobacter pylori has been determined to be a gastrointestinal pathogen in humans.¹ Voluntary ingestion of this bacteria results in dyspeptic symptoms and histological findings of type B gastritis;² antimicrobial treatment that effectively eliminates the bacteria also reverses the gastritis.³ Importantly, *H. pylori* has been isolated in most individuals with duodenal ulcers⁴ and in 69% of individuals with active chronic gastritis not associated with the use of nonsteroidal anti-inflammatory agents.⁵ Type B gastritis caused by *H. pylori* infection may also progress to atrophic gastritis or intestinal metaplasia,^{6,7} which are known histologic precursors of gastric cancer.

The incidence of *H. pylori* infection in industrialized countries has been found to be 0.3–1.0% per year.^{8–10} Epidemiologic studies have shown that low socioeconomic status,^{11–16} African-American race/ethnicity,^{7,15–18} unsanitary conditions,^{14,19,20} and foreign birth²¹ are significant independent risk factors for infection. Also, populations living in developing countries have been found to have a higher risk and earlier age of infection compared with populations in industrialized regions.^{22–24} For example, in the Ivory Coast and Algeria, 50% of the tested population was infected by 10 years of age, with the prevalence of infection increasing to 80–90% by the third decade of life.²² In France, very few children were infected and the prevalence of infection rose to only 25% by the age of 30 years.²²

These data indicate that unsanitary water and possibly food supplies may play an important role in the transmission of *H. pylori*. Although *H. pylori* has not been successfully isolated from water sources, it has been isolated from fecal specimens in the Gambia.²⁵ In a study conducted in London, the absence of a fixed hot water supply during childhood was a strong independent risk factor for infection.²⁰ Children of high socioeconomic status in Lima, Peru were 12 times more likely to be infected if their homes were connected with municipal water supplies compared with community wells.¹⁹ Lastly, in Chile it was shown that seropositivity was correlated with consumption of uncooked vegetables that was independent of other risks attributed to low socioeconomic status.¹⁴

Long-term travelers to developing countries may also be

at increased risk of *H. pylori* infection due to unsanitary conditions.²⁶ United States military personnel on foreign deployments have been found to have an increased risk of acquiring *H. pylori* infection, with an annual infection rate of between 1.9% and 7.3%.^{18,27} Like other travelers, missionaries from the United States are likely to be exposed to presumptive modes of *H. pylori* transmission, including locally grown vegetables and fecally contaminated water supplies.²⁸

Serologic testing has been shown to be an accurate tool for the identification of *H. pylori* infection. The presence of serum IgG antibodies is closely associated with infection found by microbiological and histological methods.^{29–31} In this study, *H. pylori* seroconversion rates among North American missionaries residing in developing countries were examined. The objective of this study was to evaluate the risk of *H. pylori* infection among individuals from industrialized countries following extended residence in developing regions.

MATERIALS AND METHODS

The study was conducted using previously banked (anonymous) sera obtained between 1967 and 1984 during routine medical care examinations of missionaries by Dr. John D. Frame. The subjects had blood drawn during examinations prior to assignment and again upon return. Approximately 5% of these examinations were conducted on missionaries who returned home due to illness. Personal identifications and clinical data of the subjects has been purged, and only sex, age, dates of service, and country of service were available for analysis.

Approximately 50% of the samples were either depleted or damaged during the years of storage; therefore, only subjects for whom at least two samples were available could be included in the study, for a total of 312 subjects. The risk factors for seroconversion examined in this study included age, gender, length of time spent abroad, and country of service.

Laboratory methods. Sera were stored at a continuous temperature of -20°C to -30°C since 1967, although two brief freezer malfunctions occurred in 1987 and 1992. The

TABLE 1
Incidence of seroconversion by region of service among 312 North American Missionaries

Geographic region	Total no. of subjects (%)	Person-years of exposure*	Seroconversion rates per 100 person-years*
Africa	251 (80.4)	1,539	2.1
Ethiopia	78 (25.0)	428	2.6
Nigeria	63 (20.2)	430	2.6
Liberia	20 (6.4)	148	2.7
Benin	17 (5.4)	58	1.7
Zaire	13 (4.2)	83	1.2
Ivory Coast	11 (3.5)	67	0.0
Niger	11 (3.5)	70	2.9
Other areas of Africa	38 (12.2)	255	0.8
Pacific	26 (8.3)	135	1.5
Asia	21 (6.7)	160	1.3
Americas	14 (4.5)	83	1.2
Total	312 (100)	1,917	1.9

* Person-years of exposure and seroconversion rates based on 259 initially seronegative subjects.

sera from the 312 subjects were tested for *H. pylori* IgG antibody with a commercial ELISA that uses a partially purified *H. pylori* antigen (Pylori Stat Test Kit; BioWhittaker, Inc., Walkersville, MD).^{32,33} In comparison with gastric biopsy findings, the Pylori Stat Test Kit has a sensitivity of 96%, a specificity of 94%, a positive predictive value of 90%, and a negative predictive value of 98%.³⁰ Reactivity was defined as an absorbance index of greater than 1, according to the manufacturer's guidelines, and was based on negative, low-positive, and high-positive serum standards provided with each test kit.

Post-assignment serum from each of the subjects was analyzed first; if post-serum testing was positive, pre-serum from the same subject was analyzed. Seroconversion was defined as a change from a non-reactive *H. pylori* IgG result during the pre-assignment examination to a reactive *H. pylori* IgG result at the return examination. Sera from the 312 subjects were also tested for IgG antibody to hepatitis A virus (anti-HAV) by ELISA, as described previously.³⁴

Analysis. The prevalence of *H. pylori* infection was defined as the percentage of subjects with reactive pre-assignment sera. Incidence was defined as the percentage of seroconversions among subjects initially seronegative divided by the number of person-years of exposure. In univariate analysis, the chi-square test with Yates' correction or Fisher's exact test were used to compare proportions; the Student's *t*-test was used to compare mean values. Multiple logistic regression analysis was performed using the SPSS/PC software package (SPSS, Inc., Chicago, IL). Odds ratios (ORs) were reported with 95% confidence intervals (95% CIs).

RESULTS

Study population. There were 312 missionaries evaluated. Their mean age was 40 years, 65% were female, and all were of white race/ethnicity. Evaluated subjects had a mean of 7.4 person years of service between sequential serum samples (range = 1–21 years). Sub-Saharan Africa was the most common location of overseas service among 80.4% of missionaries; 8.3% served in the Pacific (including Papua

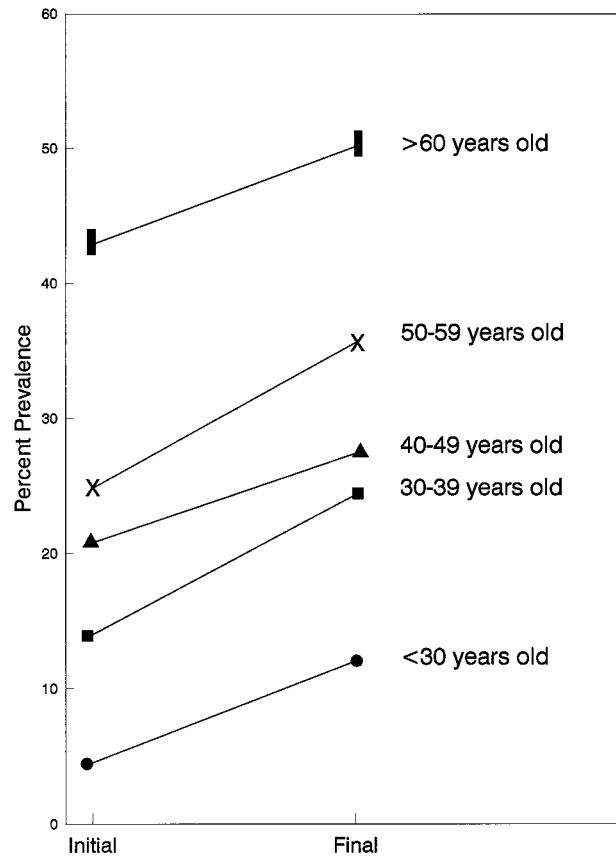


FIGURE 1. Percentage of 312 North American missionaries with antibody to *Helicobacter pylori* before and after overseas service by age group (for > 60 years old, n = 22; 50–59 years old, n = 56; 40–49 years old, n = 91; 30–39 years old, n = 78; and < 30 years old, n = 65).

New Guinea, Manus Island, and the Philippines), 6.7% served in Asia (including Indonesia), and 4.5% served in the Americas (Table 1).

Univariate analysis. Among all 312 subjects, the prevalence of *H. pylori* infection was 17.0% (53 missionaries with reactive sera). There was no difference in prevalence between men and women, but the prevalence of infection was higher among older age groups (Figure 1). The mean age of the 53 subjects with infection before service overseas was 46.3 years compared with 38.9 years for subjects who were initially seronegative ($P = 0.0001$).

Among 259 initially seronegative subjects, 37 (14.3%) seroconverted during a mean of 7.4 person-years of exposure (total of 1,917 person-years), giving a rate of 1.9/100 person-years of service. Seroconverters were older (mean age = 42.5 years) than those who remained seronegative (mean age of 38.3 = years; $P = 0.05$). Seroconverters were found to have completed a mean of 8.2 years of service compared with 7.3 years among subjects who remained negative ($P = 0.2$). There was no statistically significant difference in seroconversion rate by gender or region of service.

There was an association between the initial seroprevalence of anti-*H. pylori* and anti-HAV: among 53 subjects with anti-*H. pylori*, 66% had anti-HAV compared with 49% of subjects negative for anti-*H. pylori* ($P = 0.03$). However, no relationship was found between the 37 subjects who sero-

converted to anti-*H. pylori* and the 18 subjects who seroconverted to anti-HAV.

Multivariate analysis. After controlling for gender, age was found to be significantly associated with initial *H. pylori* seroprevalence: OR = 1.7, 95% CI = 1.3–2.3 per 10 years of age, $P = 0.0001$. Also, only age was associated with risk of seroconversion in a logistic regression model that included gender, years of service, and region of service: OR = 1.4, 95% CI = 1.01–1.9 per 10 years of age, $P = 0.046$.

In contrast to univariate analysis, the initial prevalence of anti-HAV and anti-*H. pylori* were not significantly associated after controlling for age and gender. Also, after controlling for age and gender, there was no relationship between anti-*H. pylori* and anti-HAV seroconversion during service in a developing country.

DISCUSSION

The findings of this serosurvey suggest that North American missionaries residing in the developing world are at relatively increased risk of *H. pylori* infection. The study found a 1.9% seroconversion rate per year, compared with rates of 0.3–1.0% per year previously reported in studies of populations living in industrialized countries.^{8–10} These findings support earlier studies that have shown an increased risk of infection among individuals residing, or previously residing, in the developing world.^{16,21–24} Also, the risk of seroconversion among missionaries was comparable with that of a study of deployed U.S. military personnel.¹⁸

The initial seroprevalence of *H. pylori* infection among missionaries (17%) was somewhat lower than described previously in U.S. populations of this age group.³⁵ However, a similar prevalence was reported in a study of epidemiologists in 1992.⁹ The initially low prevalence among the subjects of this study may therefore reflect relatively higher socioeconomic background.

The slightly increased risk of seroconversion among older subjects is a potentially important finding that may be explained by changes in the gastric mucosa, such as decreased hydrochloride production, that accompany aging. However, this hypothesis requires further investigation. The lack of association between seroconversion to anti-*H. pylori* and anti-HAV could indicate that the risk of exposure is different for these two pathogens, their transmissibility is not the same, or their mode of transmission differs.

The increased risk of *H. pylori* infection among those residing in developing countries has implications for the diagnosis and treatment of gastrointestinal complaints. In the study of Parsonett and others,⁹ subjects with recent seroconversion experienced a greater frequency of upper gastrointestinal symptoms compared with persistent nonreactors or persistent reactors. In the self-inoculation studies,^{2,36} subjects experienced gastrointestinal symptoms, including epigastric fullness and pain, nausea, and vomiting, beginning 3–7 days following ingestion of *H. pylori*. Consequently, acute *H. pylori* infection should be included in the differential diagnosis of travelers to the developing world with upper gastrointestinal complaints.

Importantly, individuals infected with *H. pylori* are also at increased risk of developing peptic ulcer disease. Although many individuals infected with *H. pylori* remained

asymptomatic, it is estimated that there is a 10% risk of developing peptic ulcer disease within 10 years of infection.³⁷ Individuals with chronic gastritis due to *H. pylori* may also be at increased risk of developing duodenal ulcers.^{4,38}

In summary, the incidence data obtained in this study suggest that long-term residents in developing countries have a relatively higher risk of *H. pylori* infection than in their native industrialized countries. These findings support previous studies that have shown an increased risk of infection in developing countries. Infection with *H. pylori* should be considered in the evaluation of upper gastrointestinal complaints among long-term travelers to developing countries.

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