HELICOBACTER PYLORI SEROSTATUS IN BACKPACKERS FOLLOWING TRAVEL TO TROPICAL COUNTRIES

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Abstract. The mode of transmission of Helicobacter pylori is unknown. The seroprevalence of H. pylori and the rate of transmission of feco-oral pathogens in developing countries are both high. Long-term travelers to these regions, who come from developed countries are thus potentially at increased risk of an infection with this bacterium. We studied the H. pylori serology status before and after travel of 104 backpackers who traveled to tropical countries; 76 medical students who did not leave Israel served as controls. Southeast Asia (70%) and South America (24%) were the major destinations, but the area of travel had no effect on the seroconversion rate. The total time spent abroad was 53 person-years. Thirty-six of the travelers and 30 controls were positive at the outset. Seropositivity at entry was significantly associated with being a Sepharadic Jew or having a parent with a peptic ulcer disease. The majority of travelers (86.5%) and controls (92.1%) did not change their serostatus. Four travelers seroconverted, but 10 seroreverted, while three controls seroconverted, and three others seroreverted. No significant association with gastroenteritis was found. Serostatus may have been affected by mefloquine use because none of the four seroconverters, but eight of 10 seroreverters used it as malaria prophylaxis. In vitro studies demonstrated that mefloquine has anti-H. pylori activity. Feco-oral transmission is apparently not an important route of transmission of this organism among travelers.

Helicobacter pylori infection is one of most common bacterial infections worldwide. Infection with this ubiquitous bacterium increases with age, the prevalence of antibodies to H. pylori is higher, and the seroconversion occurs earlier in developing countries. Despite an immense body of knowledge about H. pylori, its mode of transmission is still unclear. Direct interpersonal or indirect common source transmission could occur by either the oro-oral or feco-oral routes. There is indeed evidence for both modes. Helicobacter pylori has been detected by the polymerase chain reaction in both stool and saliva. The prevalence of hepatitis A virus, a fecally transmitted agent, was found to be directly correlated with the prevalence of H. pylori in India, but not in China. In Peru, H. pylori seropositivity was linked to a water source and in Chile to consumption of uncooked vegetables. Supporting oro-oral transmission is the finding that maternal premastication of food was a risk factor for acquisition of H. pylori infection in children in Burkina-Faso. Also, there is evidence for intrafamilial and intranstitutional clustering of specific strains of H. pylori.

Back-packers traveling from developed to developing countries are potentially at increased risk for acquisition of feco-oral transmitted organisms; if feco-oral transmission is the principal mode by which H. pylori spreads, then these travelers are at increased risk for contracting H. pylori. In contrast, seropositive people may, at times, serorevert. As yet, there have been no prospective, controlled studies addressing the association between travel and acquisition or loss of H. pylori. Our main objective was to study in a prospective, controlled trial the rate of acquisition or loss of H. pylori by travelers, and its association with lifestyle and drug consumption.

SUBJECTS AND METHODS
The study was approved by the Ethical Review Board (Helsinki Committee) of the Bnai Zion Medical Center. The purpose of the study was explained to the travelers, and informed consent was obtained upon enrollment.

Serum was drawn from a cohort of 216 travelers to Southeast Asia, South America, and Africa who attended the travel clinic at the Bnai Zion university hospital in Haifa. We included travelers younger than 32 years of age, with a length of travel greater than three months, and those who gave a post-travel serum sample. After returning to Israel all 216 travelers were contacted by telephone and invited to give a second serum sample. One hundred four (48%) gave a second sample and filled out a questionnaire. The control group consisted of 80 medical students who did not leave the country during the study period. Seventy-six of them (95%) gave a second sample, filled out the questionnaire, and were thus included in the study.

The questionnaires covered demographic data, destinations, lengths of stay, health problems during the trip, with special emphasis on gastrointestinal problems, medications taken during the trip, and strictness of following food and water hygiene recommendations.

Serology. Sera were frozen at -20°C. After thawing, each pair of pre- and post-travel samples was evaluated in parallel for the presence of anti-H. pylori IgG antibodies by enzyme immunoassay (EIA) (Cobas core anti-H. pylori EIA; Roche SA, Basel, Switzerland). Only a qualitative determination was obtained. A cut-off value was calculated as follows: the mean absorbency value of the negative controls + 0.07. A gray zone was calculated as the cutoff +/- 10%. Values above it were considered positive and those below it negative. The method showed a high level of sensitivity (93%) and specificity (95%) when compared with reference methods. Seroconversion refers to a negative first sample and a positive second sample. Seroreversion refers to a positive first sample and a negative second sample. In none of the subjects were both samples in the gray zone, and only two controls and two travelers had one sample in the gray zone. We therefore considered all subjects who did not clearly seroconvert or serorevert to be either positive or negative in both samples.

Mefloquine sensitivity testing. Mefloquine sensitivity testing was done by Dr. M. Tabak (Faculty of Food Engi-
neering and Biotechnology, Technion, Haifa). Basically, three strains of \textit{H. pylori} were obtained from the regional Health Maintenance Organization microbiology laboratory (not from study participants) and tested by the Kirby-Bauer method.\textsuperscript{11} Mefloquine was tested at concentrations of 12.5 mg and 6.25 mg, and ampicillin (10 µg/disk) served as control.

### RESULTS

The mean ± SD age of the study subjects was 22.5 ± 2.2 years, and the mean ± SD age of the control group was 25.5 ± 2.5 years (\( P < 0.001 \)). The average length of stay abroad was 6.1 months (range = 3–16 months), and the total time abroad for all 104 travelers was 53 person-years. The average time interval between the serum samples was 11.1 months (range = 4–24 months), and 8.4 months (range = 7–12 months) for the study and control groups, respectively. The destinations in decreasing order were Southeast Asia (70%), South America (24%), Africa (4%), and both Southeast Asia and South America (2%).

Among the travelers, 36 (35%) were seropositive before travel, but only 30 (29%) after repatriation. In all, four seroconverted, but 10 seroreverted (Table 1). Neither the rate of seropositivity within each group in the first and second examinations nor the difference between the control and the study groups were statistically significant (\( \chi^2 \) test). Seropositivity to \textit{H. pylori} at the outset was higher among older travelers versus younger travelers (38% versus 29%), as well as among older versus younger controls (48% versus 31%); however, these differences were not statistically significant. \textit{Helicobacter pylori} seropositivity before travel was significantly associated with having a parent with peptic ulcer disease (\( P = 0.007 \)), and being a Sepharadic Jew rather than Ashkenazi (\( P = 0.007 \)). Ninety-four of the travelers compared with 60 of the controls (43% seropositivity) were Israeli born. Twelve of the controls (33% seropositivity) and one of the travelers were born in east European countries. None of the four controls born in North America were seropositive at the outset. Country of birth data were missing for eight travelers. The differences among these subsets were not statistically significant. We did find a significant difference in the serostatus between those who traveled to Southeast Asia, South America, or Africa (Table 2).

Fifty-eight percent of the travelers strictly followed our recommendations concerning food and water hygiene. Only 23% of these travelers were seropositive after travel in comparison with 40% of those who were less strict (\( P = 0.077 \)). An episode of gastroenteritis during travel was reported by 56% of the study group, with no difference between those who strictly followed the above recommendations and those who did not. There was no significant difference in seroprevalence after travel between those who had or did not have gastroenteritis. A history of peptic ulcer disease was elicited in one traveler who was \textit{H. pylori} negative and in two controls (one treated for \textit{H. pylori}), of whom one remained negative and the other seroconverted.

Since the serostatus may have been affected by the use of drugs, this parameter was examined by checking mefloquine and antibiotic consumption. Mefloquine was used as antimalarial prophylaxis by 56% of the travelers (Table 3). None of the four seroconverters used mefloquine, in comparison with eight of the 10 seroreverters who did use it. There was no significant difference in seroprevalence after travel between those who used mefloquine and those who did not. Only 39% of the travelers knew the brand name of the antibiotic they used; in total 24% of them used a penicillin (mostly amoxicillin).

To examine the possibility of a suppressive effect of mefloquine on \textit{H. pylori}, in vitro studies were carried out. Mefloquine showed some activity against all three strains of \textit{H. pylori}, albeit at concentrations 1,000 times higher than ampicillin (Table 4).

### DISCUSSION

We investigated a cohort of young travelers to Southeast Asia, South America, and Africa for the presence of newly acquired infection with \textit{H. pylori}.
acquired \textit{H. pylori} infection. This cohort had been exposed to feco-oral infection, as indicated by the high rate (56\%) of gastroenteritis episodes during the trip. Thus, if the feco-oral route of transmission of \textit{H. pylori} is a significant one, we would have expected that the study population, which had a relatively low seroprevalence of \textit{H. pylori}, and traveled to areas highly endemic for \textit{H. pylori}, would demonstrate a higher seroconversion rate in comparison with a control group. Nevertheless, the rate of infection not only did not increase, but even decreased from 35\% to 29\% (not statistically significant), while in the control group no change in seroprevalence for the time interval under investigation was found.

Our results concur with those of Lindkvist and others,\textsuperscript{14} who failed to find even one seroconverter among 133 Swedish travelers. Although our group was somewhat smaller, the combined exposure time was longer, 53 person-years (including 35 person-years of primarily seronegative travelers) versus 16.4 person-years. Yet, the seroconversion rate was higher than the seroconversion rate. How can this enigma be settled?

We postulated that the use of medications during travel may explain this decrease. The most consistently used medication during travel is malaria prophylaxis. Mefloquine was used by 56\% of the travelers, and 42\% used other antibiotics. A significant correlation between drug use and \textit{H. pylori} serology could not be established despite the fact that eight of the 10 seroconverters used mefloquine, while all the four seroconverters did not. To corroborate this postulate, which had never been examined before, we tested whether mefloquine had any activity against three random strains of \textit{H. pylori} in vitro. Inhibition zones of 18–36 mm were demonstrated, although at concentrations 3 logs higher than ampicillin. Is this inhibition meaningful? No one drug had been shown to be capable of eradicating \textit{H. pylori} alone. However, mefloquine, which has a long half life (7–33 days), and is taken by travelers for prolonged periods may act locally in the stomach, as well as systemically, against \textit{H. pylori}. It may further be speculated that mefloquine had not only suppressed \textit{H. pylori} in the seroconverters, but also prevented infection among the seronegative travelers. Although we presume that mefloquine had an anti-\textit{H. pylori} effect, 44\% did not use it, and if a strong tendency for acquiring the infection did exist, similar to the 20\% per year reinfection rate after eradication observed in Brazil,\textsuperscript{15} we would have expected a higher seroconversion rate in those who did not use mefloquine.

Several other studies examined the seroprevalence of \textit{H. pylori} before and after a long-term stay in a developing country.\textsuperscript{14,16,17} Two of them involved soldiers deployed abroad, a less suitable population for study than travelers, since soldiers are presumably exercising a tighter control over the food they consume, and their hygiene in general than do travelers. Lindkvist and others\textsuperscript{14} studied travelers, but lacked a control group, and included only seronegative subjects. That study was thus unable to detect seroreversion as demonstrated in the present study. Significant seroconversion was not detected in any of those studies: the results, in comparison with ours are summarized in Table 5.

The seroconversion rate in the originally seronegative subjects mounted to a calculated risk of 6.4\% annually. This rate is higher than in other studies, and much higher than the spontaneous seroconversion rate in developed countries of 0.1–1\%.\textsuperscript{18} In conclusion, regarding the decreasing overall seropositivity after the travel, and the combined observations in other studies, our results do not support, or at least leave in doubt the possibility of feco-oral spread of \textit{H. pylori}.

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**REFERENCES**


