MAJOR ARTICLE

Risk Factors Associated with *Helicobacter pylori* Infection among Children in a Defined Geographic Area

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Factors influencing the pattern of *Helicobacter pylori* infection among children living in adjacent urban and rural areas of northern Sardinia, Italy, were compared. The seroprevalence of *H. pylori* infection was 22% (625 of 2810 children) in the study population and was significantly higher among children in rural areas (37%) than in urban areas (13%) (odds ratio [OR], 3.8; 95% confidence interval [CI], 3.2–4.7; *P* < .005). This difference was consistent within each age group. In rural areas, children who had dogs were at greatest risk for *H. pylori* infection (OR, 1.8; 95% CI, 1.3–2.6; *P* < .05). No association was seen between *H. pylori* seropositivity and a history of breast-feeding. Urban children attending day care centers had a higher prevalence of infection (17%) than did those who never attended (12%) (OR, 1.5; 95% CI, 1.1–2.0; *P* < .05). The epidemiology of *H. pylori* infection is complex; even within the same geographic area, different factors influence acquisition of *H. pylori* infection.

It is now recognized that *Helicobacter pylori* infection is commonly acquired during childhood [1–5] and, therefore, that differences in prevalence of the infection within or among populations likely result from factors that were in effect during childhood. The rate of acquisition of infection is generally higher in underdeveloped countries than in industrialized countries [6–9]. Even within developed countries, there are marked differences in prevalence in different strata of the population. For example, in the United States, the prevalence of *H. pylori* infection is approximately twice as high among blacks and Hispanics as it is among age-matched whites [10, 11].

Attempts to understand why rates of *H. pylori* infection differ among groups have focused on household hygiene practices and on socioeconomic status, as defined by occupation, family income level, and living conditions [10, 11]. That genetic factors have a role in susceptibility to *H. pylori* infection and the outcome of infection has also been reported, but these appear to be less important than environmental factors [12]. Variation in the rate of acquisition of infection among ethnic and social groups is likely related to differences in exposure, which, in turn, may be influenced by cultural background and social, dietary, or other environmental factors [13]. Sardinia has a strong agropastoral tradition, and the population is in contact with large numbers of sheep and sheepdogs [14]. Sardinian shepherds are a very homogeneous population with respect to childhood, sociocultural factors, hygiene conditions, and lifestyle [15]. It has been shown elsewhere that the prevalence of *H. pylori* infection among shepherds who reside in northern Sardinia is one of the highest in the world (98%) and is associated with direct contact with sheep and sheepdogs [16]. The prevalence of the infection was also found to be higher among members

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of shepherds' families who did not have daily contact with sheep (73%, vs. 43% among matched blood donors) (OR, 3.5; 95% CI, 1.5–8; $P = .0026$) [16]. Sardinian shepherds primarily reside in rural areas. This study evaluated the seroepidemiology of *H. pylori* infection among Italian children who had the same genetic background but resided in different environments (urban vs. rural) within the same geographic area of northern Sardinia.

METHODS

Design. A cross-sectional study of *H. pylori* prevalence was conducted among elementary and middle school children who lived in the same region but in different settings (rural vs. urban). Informed consent was obtained from children's parents for participation in the study, and the study protocol was approved by the Ethics Committee of the Faculty of Medicine at the University of Sassari (Sassari, Italy). The study was performed in northern Sardinia, Italy, and included residents of an urban area (Porto Torres) characterized by the presence of several petrochemical industries and of 7 villages (Alà dei Sardi, Bono, Padria, Buddusò, Sedini, Laerru, and Nughedu) located in nearby rural areas where the economy is based on agriculture and sheep rearing [14, 15]. Porto Torres has 21,450 inhabitants and a population density of 205 persons/m^2, with 5 elementary and 4 middle schools. The total population in the 7 rural villages is 14,238 inhabitants, with a population density of 32 persons/m^2. All elementary and middle schools located in the villages and in the urban area were included. High schools are not present in the urban area or in the 7 villages studied. The school population is estimated to account for ~7%–8% of the total population in each region and is slightly higher in urban areas than in rural areas.

A questionnaire was completed by the investigators with the cooperation of the parents of each child to obtain demographic information, including the age and sex of the child, place of residence, occupation of the head of household, living and hygiene conditions (the number of persons living in the household, the size of the home, whether the child shared a bed, and the presence or absence of hot running water, a refrigerator, and a toilet inside the home), and exposure to animals (dogs and other animals, e.g., cats, parrots, pigs, goats, horses, ducks, donkeys, and chickens). Whether the child had a history of breast-feeding or attendance at day care centers was also recorded. The main reason for an eligible child not to participate in the study was absence from school because of sickness, such as cold or influenza, during the day on which blood samples were collected.

After consent was obtained from the head of each school, 5–7 physicians visited the schools. The screening phase took place during regular school hours. Blood samples were obtained in the 7 villages between October 1996 and May 1998. The staff was composed of the same physicians and nurses throughout the study period. Serum was frozen at −20°C until assays were performed.

Serologic testing. *H. pylori* serostatus was evaluated by use of a commercial ELISA for anti–*H. pylori* IgG, according to the manufacturer's directions (HM-CAP; Enteric Products). The antigens used were high–molecular-weight cell-associated antigens of *H. pylori,* as described elsewhere [17]. The HM-CAP ELISA has been shown to have specificity and positive predictive value of 100%, sensitivity of 98.7%, and negative predictive value of 98.6% [17]. There is no cross-reactivity with *Campylobacter jejuni.* The test has been validated in a pediatric context [18] and for the same geographic area (northern Sardinia) [19].

Statistical analysis. "*H. pylori* infection" was defined as a positive ELISA result. Categorization of socioeconomic status was based on the occupation of the head of the household [19]. Four categories were identified: I, major professionals (persons who had graduated from university); II, minor professionals and administrators (persons who had not graduated from university); III, clerks and sales technicians; and IV, semiskilled and unskilled workers, uneducated farmers, and shepherds.

The Mantel-Haenszel χ^2 test was used to assess associations between each independent factor included in the study and the prevalence of *H. pylori* infection. Univariate and multivariate analyses were performed, and age-adjusted ORs and 95% CIs were calculated for the association between *H. pylori* status and the study variables. Differences with a P value of $<.05$ were considered to be statistically significant. Factors found to be significant risk factors in the univariate analysis were used in the multiple logistic regression model. Children were divided into 2 groups, according to area of residence (urban vs. rural), and each group was analyzed independently. Data were analyzed using SAS software (SAS Institute) [20].

RESULTS

Population. Ninety-five percent of eligible schoolchildren participated in the study. There were 2810 healthy school-age children enrolled: 1741 from the urban area (Porto Torres), and 1069 from the 7 rural villages. These children represented 8.1% of the total population of the urban area and 7.5% of total population of the rural villages.

H. pylori *seropositivity in urban and rural cohorts.* Table 1 shows the distribution of age-specific *H. pylori* status for the total sample of children and for each cohort. The overall seroprevalence of *H. pylori* was 22% (625 of 2810 children) and was higher among children aged 14–16 (26%; 110 of 423 children) than among children 5–7 years old (20%; 68 of 344 children) ($P = .051$). However, *H. pylori* seroprevalence was

Table 1. Comparison of rates of age-specific seropositivity for *Helicobacter pylori* infection among children included in a study of risk factors associated with *H. pylori* infection in urban and rural areas.

	All children		Children residing in a rural area		Children residing in an urban area				
Age group, years	No. tested	Percentage seropositive for *H. pylori*	No. tested	Percentage seropositive for *H. pylori*	No. tested	Percentage seropositive for *H. pylori*	Difference in no. of seropositive children, rural vs. urban, %	OR (95% CI)	*P*
5–7	344	20	132	25	212	16.5	8.5	1.7 (1.0–2.9)	.05
8–10	926	22	347	42	579	10	32	6.7 (4.7–9.4)	.001
11–13	1117	22	434	36	683	13	23	3.6 (2.7–5.0)	.001
14–16	423	26	156	40	267	18	22	3.1 (2.0–4.8)	.001
Total	2810	22	1069	37	1741	13	24	3.8 (3.2–4.7)	.001

significantly higher among children residing in the rural areas (396 [37%] of 1069 children) than among those living in the urban area (229 [13%] of 1741 children) ($P < .005$). This difference extended to each birth cohort (i.e., the prevalence of infection was consistently higher among children living in rural areas than among children living in the urban area [OR, 3.8; 95% CI, 3.2–4.7; $P < .001$]) (table 1). In the rural areas, the *H. pylori* seroprevalence was higher among children 8–10 years old (42%; 145 of 347 children) than among children 5–7 years old (25%; 33 of 132 children) ($P < .005$). In contrast, among children living in the urban area, the seroprevalence was lower among children 8–10 years old (10%) than among those 5–7 years old (16.5%) (OR, 0.5; 95% CI, 0.3–0.9; $P < .005$) but was higher among those 14–16 years old (18%) than in any of the younger groups. There was no statistically significant difference between the *H. pylori* prevalences for boys and for girls overall or within different areas. The prevalence was 35% (201 of 567 boys) among boys and 39% (195 of 502 girls) among girls living in rural areas ($P = .25$) and 13% (117 of 928 boys) among boys and 14% (112 of 813 girls) among girls living in the urban area ($P = .52$). The absence of a statistically significant difference between boys and girls remained after the analysis was adjusted for other confounding factors.

H. pylori *seropositivity and demographic, socioeconomic, and environmental variables.* Adjusted ORs were calculated for *H. pylori* seropositivity in relation to age, sex, occupation of the head of the household, contact with dogs and other animals, and whether the child was breast-fed (table 2). In the rural areas, the prevalence of *H. pylori* infection was higher among children with dogs (50%; 75 of 150 children) than among children whose families did not own a dog (35%; 321 of 919 children) (adjusted OR, 1.8; 95% CI, 1.3–2.6; $P < .05$). This difference was not observed among children who lived in the urban area: for that group, the *H. pylori* prevalence was 15% (66 of 437 children) for children with dogs and 13% (170 of 1304 children) for children whose families did not own dogs (OR, 1.2; 95% CI, 0.9–1.6; $P = .2$). Interestingly, the presence of animals other than dogs had no significant effect on *H. pylori* prevalence in either rural or urban areas.

In the rural area, no association was seen between *H. pylori* infection and the occupation of the head of the household; the prevalence of infection was almost identical among the 4 occupation categories (table 2). In contrast, in the urban areas, the seroprevalence of *H. pylori* was inversely related to the occupation category of the head of the household (5% [2 of 40 children] among children in category I vs. 18% [10 of 55 children] among children in category IV) (OR, 8.7; 95% CI, 1.1–71.0; $P < .05$). The only statistically significant variable related to *H. pylori* seropositivity among children who lived in the urban area was attendance at a day care center before the child started school. Children who attended day care centers or nurseries were at greater risk for *H. pylori* acquisition (17%; 57 of 339 children) than were children who had never attended a day care center (12%; 168 of 1402 children) (OR, 1.5; 95% CI, 1.1–2.0; $P < .05$). Because day care centers and nurseries generally are not present in rural areas, this information was not collected for that group.

Whether the child was breast-fed did not have a statistically significant effect on *H. pylori* seropositivity, either among children who lived in the rural areas (38% [312 of 819 children] for those who were breast-fed vs. 33% [83 of 249 children] for those who were not; OR, 0.8; 95% CI, 0.6–1.1; $P = .2$) or among children who lived in the urban area (14% [181 of 1267 children] for those who were breast-fed vs. 10% [48 of 474 children] for those who were not; OR, 0.6; 95% CI, 0.4–1.1; $P = .4$). However, 70%–75% of the children in the study had been breast-fed. No child's home was reported to be lacking in hot running water, a refrigerator, or inside toilet facilities.

DISCUSSION

This study investigated the seroepidemiology of *H. pylori* infection among Italian children who resided in different environments within the same geographic area. The study had the advantage of large sample size and included almost all of the children in the area, thus allowing comparisons to be made within and among birth cohorts and areas with potentially different risk factor(s) for *H. pylori* infection. Variation in ac-

Table 2. Adjusted ORs and 95% CIs for *Helicobacter pylori* seropositivity among children included in a study of risk factors associated with *H. pylori* infection in urban and rural areas.

Variable	All children				Children residing in a rural area				Children residing in an urban area			
	No. tested	Percentage seropositive for *H. pylori*	OR (95% CI)	*P*	No. tested	Percentage seropositive for *H. pylori*	OR (95% CI)	*P*	No. tested	Percentage seropositive for *H. pylori*	OR (95% CI)	*P*
Age, years												
5–7	344	20	Reference	—	132	25	Reference	—	212	17	Reference	—
8–10	926	22	1.1 (0.8–2)	.5	347	42	2.1 (1.4–3.4)	.007	579	10	0.5 (0.3–0.9)	.008
11–13	1117	22	1.1 (0.9–2)	.4	434	36	1.7 (1.1–2.6)	.02	683	13	0.8 (0.5–1.2)	.2
14–16	423	26	1.4 (1.0–2.0)	.05	156	40	2.0 (1.2–3.3)	.008	267	18	1.1 (0.7–2)	.8
Sex												
Female	1315	23	Reference	—	502	39	Reference	—	813	14	Reference	—
Male	1495	21	0.9 (0.7–1)	.2	567	35	0.9 (0.6–1.1)	.25	928	13	0.9 (0.6–1.1)	.2
Occupational category for head of household												
I	66	18	Reference	—	26	38	Reference	—	40	5	Reference	—
II	1398	20	1.2 (0.6–2)	.6	466	36	0.9 (0.4–2.0)	.8	932	13	3 (0.7–12)	.2
III	1254	24	1.5 (1–2)	.001	546	37	0.9 (0.4–2.0)	.9	708	14	3 (0.7–13)	.2
IV	80	24	1.4 (0.8–3)	.2	25	36	0.9 (0.3–3)	.9	55	18	4 (0.9–20)	.06
Data missing	12	—	—	—	6	—	—	—	6	—	—	—
Ownership of animals												
No	2213	21	Reference	—	807	35	Reference	—	1406	13	Reference	—
Yes	597	27	1.4 (1–2)	.002	262	42	1.3 (1.0–1.8)	.06	335	15	1.2 (0.9–2)	.3
History of breast-feeding												
Yes	2086	24	Reference	—	819	38	Reference	—	1267	14	Reference	—
No	723	18	1.4 (1–2)	.02	249	33	0.8 (0.6–1.1)	.2	474	10	0.6 (0.4–1.1)	.4
Data missing	1	—	—	—	1	—	—	—	0	—	—	—
Day care center attendance[a]												
No	—	—	—	—	NA	—	—	—	1402	12	Reference	—
Yes	—	—	—	—	—	—	—	—	339	17	1.5 (1.1–2.0)	.05

NOTE. Occupation categories are described in the section "Statistical analysis" in Methods. NA, not applicable.

[a] Before attending school.

quisition of the infection among ethnic and social groups is thought to be primarily related to differences in exposure, which in turn may be influenced by cultural background and social, dietary, or environmental factors [13]. Despite the fact that the study population was drawn from a single ethnic group, children from rural villages had a significantly higher prevalence of *H. pylori* infection than did children who lived in the adjoining urban area. In the rural area, the study variable that most influenced the prevalence of *H. pylori* infection was the presence of dogs in the home. In the urban area, the occupation of the head of the household, which measures a major component of socioeconomic status, was the main factor associated with *H. pylori* prevalence.

The patterns of prevalence for children from rural areas and for children from the urban area also differed. For example, there was a steady increase in seroprevalence after the age of 7 years among children in rural areas, whereas there was a transient decrease in seroprevalence among children living in the urban area. This transient decrease in prevalence has been repeatedly demonstrated in other populations and as yet remains unexplained [21–23]. Spontaneous elimination of *H. pylori* infection (i.e., seroreversion) has also been described in children from developed and developing countries [22, 24–26], which suggests that the epidemiology of *H. pylori* infection in childhood is complicated by both acquisition and loss of infection in different ethnic groups. A reduction in the prevalence of infection might be followed by exposure to new or different sources of infection during puberty, with an increase of prevalence of infection at this age, so that a cohort effect by itself cannot explain the epidemiology of *H. pylori* infection or predict the prevalence in a specific population [27].

H. pylori infection was very common (37%) among children residing in rural northern Sardinia. There are a number of differences between the rural and urban areas, especially with regard to the activities, diets, and habits of the children. For example, the diet in rural areas is more likely to contain homemade foods, such as cheese, yogurt, salami, bread, cookies, pasta, and ravioli, than is the diet in the urban area, where foods are typically purchased in groceries. The use of spring water is also more common among children residing in the rural areas [15, 22, 28–30]. Drinking raw sheep milk is also more common among inhabitants of villages than among individuals who live in an urban environment. Such variables were not evaluated in the present study and will be the focus of subsequent studies of these populations. In rural villages, children play more frequently outside the house, which allows more opportunity to interact with animals, especially sheepdogs, which are allowed in the family home. The prevalence of *H. pylori* infection among asymptomatic Sardinian shepherds was closely associated with direct contact with sheep and sheepdogs. Such results are consistent with the results of a study from Colombia that reported an association between *H. pylori* infection and contact with dogs and sheep among children living in rural villages in the Andes [31]. Additionally, *H. pylori* was recently isolated from raw sheep milk and from sheep stomach [32, 33].

Although our study provides strong epidemiological evidence of the importance of the environment in *H. pylori* transmission, some limitations must be considered. Classification of the socioeconomic classes in our study was based on a single factor, the occupation of the head of the household, rather than a scale of combined factors, such as years of schooling, income, and ownership of property. However, in this region of Italy, the occupation of the head of the household represents the major lifestyle indicator of the family. For example, income may not be an ideal measure of socioeconomic status among shepherds, because they generally have high incomes and live in larger homes; however, the lifestyle is much poorer in terms of hygiene conditions and cultural background. Another limitation of the current study is the reduced sensitivity of serologic testing for *H. pylori* among young children. However, the test used has been examined in the Italian population [19] and other Westernized populations (e.g., the United States) [18, 34] and has shown excellent results. The serologic test used for our study has consistently shown a positive predictive value >90% when used in children [18, 34].

Our study found no association between *H. pylori* prevalence and the number of people in the home, size of the home, or whether the child shared a bed. The finding of a high prevalence of *H. pylori* infection among children who lived in rural areas, despite the fact that they lived in larger homes, highlights the importance of factors outside the home in the transmission of *H. pylori* infection.

It is of interest that *H. pylori* seropositivity among boys was similar to that among girls, whereas in prior studies in this population, shepherds, who predominantly are men, appear to be at very high risk of having *H. pylori* infection. This suggests that being a shepherd has an additional risk over and above that experienced by the families or siblings of shepherds. At this time, it is unknown whether this increased risk is associated with a particular practice (e.g., drinking raw sheep milk), association with sheepdogs, or some other factor, but it does suggest that there are periods or occupational exposures other than childhood that may be associated with an increased risk of *H. pylori* acquisition.

In conclusion, our study showed that the epidemiology of *H. pylori* infection in childhood is influenced by environmental factors both inside and outside the home. In addition, the differences in the pattern of the age-related distribution of *H. pylori* infection provide important clues for further studies to define the practices related to transmission, such as drinking raw sheep milk, that could be avoided to prevent or reduce *H. pylori* transmission.

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