Helicobacter pylori Prevalences and Risk Factors among School Beginners in a German Urban Center and Its Rural County

Olf Herbarth,[1] Peter Krumbiegel,[1] Gisela J. Fritz,[2] Matthias Richter,[1] Uwe Schlink,[1] Detlef M. Müller,[3] and Thomas Richter[3]

[1]Department of Human Exposure Research and Epidemiology, UFZ-Centre for Environmental Research Leipzig-Halle, Leipzig, Germany; [2]Environmental Hygiene and Epidemiology; and [3]Children´s Hospital, University of Leipzig, Leipzig, Germany

In 1998, the *Helicobacter pylori* [^{13}C]urea breath test was offered to all school beginners (birth cohort 1991/1992) in the city of Leipzig and in Leipzig County, Germany, to determine the colonization prevalence and potential transmission pathways of the bacterium. A total of 3,347 school beginners participated in the test, and 2,888 parents completed the detailed, self-administered questionnaire. The *H. pylori* prevalence was 6.5% [95% confidence interval (CI), 5.3–7.6] in the city and 5.7% (CI, 4.2–7.0) in the county. Using cluster analysis (WARD's method, Euclidean distances), we identified different sets of variables (confirmed by multivariate logistic regression analyses [odds ratios (ORs)] that are signficantly associated with *H. pylori* positivity. Among city children, the risk is significantly increased with contact to a pet hamster (OR = 2.4; 95% CI, 1.2–4.7; $p < 0.015$) and travels to Asian countries (OR = 3.7; 95% CI, 1.6–8.7; $p < 0.002$). Among county children, *H. pylori* positivity increased significantly with drinking of water from nonmunicipal sources (OR = 16.4; 95% CI, 3.1–88.5; $p < 0.001$), more than 3 children living in a household (OR = 4.2; 95% CI, 1.2–14.6; $p < 0.02$), and contact with pet hamsters (OR = 2.4; 95% CI, 1.0–5.7; $p < 0.04$). These data suggest that, in a general population sample, indirect fecal–oral transmission and living conditions are important risk factors in the spread of *H. pylori* infection. However, clinical symptoms do not necessarily indicate *H. pylori* positivity. *Key words*: ^{13}C breath test, Germany, *Helicobacter pylori*, prevalences, risk factors, rural county, school beginners, urban center. *Environ Health Perspect* 109:573–577 (2001). [Online 21 May 2001]
http://ehpnet1.niehs.nih.gov/docs/2001/109p573-577herbarth/abstract.html

Helicobacter pylori is one of the most common pathogens. Since the observations of Warren and Marshall in 1983/1984 (*1*), its significance as a causal agent for peptic ulcers and public health problems is evident. Numerous papers have been published discussing potential risk factors of transmission and infection.

In a recent review of *H. pylori* epidemiologic studies, the European *Helicobacter pylori* Study Group (*2*) concluded that "The route of transmission still remains unclear." The authors observed problems in the interpretation of some past studies in relation to study design, selection and size of the study population, and the statistical methods applied. The recommendation was that future epidemiologic studies take these aspects into consideration.

The large number of cases and the high cost of medical treatment have now turned the focus of epidemiologic research toward certain risk populations. Preschool children are thought to be the main risk population (*3*). Generally accepted risk factors for the aquisition of *H. pylori* infection are socioeconomic status, childhood living conditions (*4*), and large family size (*5*). In a recent German study, family history of gastric disease correlated with aquisition of the bacterium (*6*), whereas pets have not been considered a risk factor (*7*). As far as the routes of transmission are concerned, the results have been contradictory (*2*). There is no doubt that the bacterium gains entry to the stomach via the mouth. Oral–oral, fecal–oral, and iatrogenic spread, as well as several vectors such as domestic cats, nonhuman primates, and the domestic housefly, have all been discussed as possible routes of transmission; however, a major route has not been identified (*8*).

Because this organism appears to be ubiquitous and may be picked up anywhere, we hypothesized that indirect fecal–oral transmission could possibly be a dominant pathway in its acquisition. Thus, we conducted this study to determine potential sources of *H. pylori* in the environment of young children. The data are based on a detailed parent-completed questionnaire designed to explore a wide range of possible risk factors and an *H. pylori* colonization screening test administered to the entire 1998 school entry population in Leipzig, Germany, as well as its rural region, the County of Leipzig.

Materials and Methods

The Leipzig *Helicobacter pylori* study was a joint project of the UFZ (Centre for Environmental Research Leipzig-Halle, GmbH), the University Children's Hospital Leipzig, and the Departments of Public Health, City and County of Leipzig, conducted in the fall and winter of 1997/1998. The investigation included all children eligible to enter grade one in the fall of 1998. Participation was voluntary, and the test was scheduled to be administered during the mandatory medical examinations carried out by the Departments of Public Health. The study involved the administration of the gastric *H. pylori* colonization test using the stable-isotope–aided *in vivo* [^{13}C]urea breath test and a detailed, parent-completed questionnaire. The [^{13}C]urea breath test involved two breath samples, one taken before and another 30 min after drinking 75 mL orange juice with 75 mg [^{13}C]urea (99.3 atom% ^{13}C; chemical purity according to U.S. Pharmacopeia assay: 99.8%; Chemotrade Leipzig, portioned out by the Children's Hospital pharmacy). A child was considered infected with *H. pylori* (positive) when the ^{13}C values of the two exhaled carbon dioxide test samples (measured by a ^{13}C isotope analyzer, FANci; Dr. Fischer Analysen, Leipzig, Germany) differed significantly. The underlying biochemical principle is that [^{13}C]urea is split in the stomach only in the presence of *H. pylori*.

We used the epidemiologic questionnaire to elicit information on education, employment, and medical history of the proband's parents and siblings, past and present home address, living conditions, water supply, leisure-time garden plots, and a detailed medical history of the child. Information was sought on the family's nationality and travels to foreign countries. Further questions focused on the child's past and present contacts to various pets and different sources of

Address correspondence to O. Herbarth, Department of Human Exposure Research and Epidemiology, UFZ Leipzig-Halle, Permoserstrasse 15, 04318 Leipzig, Germany. Telephone: +49-341-235-2365. Fax: +49-341-235-2288. E-mail: herbarth@expo.ufz.de

We thank W. Braun and W. Kiess, University Children's Hospital, B. Gronemann, Public Health Department, Leipzig; and F.-J. Gutsmuths and R. Remane, Public Health Services, City and County of Leipzig. We are grateful to all of the participating doctors and technical staff of the Public Health Services, Division of Children and Adolescents, City and County of Leipzig, for incorporating our study into their work schedule and the medical students, S. Jedwilayties, J. Donaubauer, T. Richter, S. List, D. Boeckler, J. Nounia, B. Düring, P. Mehlhorn, J. Üri, and H. Pawlowski, for carrying out the tests. We especially thank all of the children and their parents for their interest and participation in the study.

This study was funded by the UFZ-Centre for Environmental Research Leipzig-Halle, GmbH.

Received 28 June 2000; accepted 4 January 2001.

drinking water. Further details regarding the study's methodology have been described elsewhere (*9*).

The criterion for a child's participation in the study was the parents' written, informed consent. Only children with a consent form signed by at least one parent could take the *H. pylori* breath test. A total of 3,347 of the 3,919 eligible school beginners undergoing the medical examination participated in the voluntary *H. pylori* [^{13}C]urea breath test (response rate 85.4%) (*9*). Mean age of the children was 6.1 years (range 5.2–7.0 years).

The life-time prevalences and potential risk factors in the transmission of the infection, and thus in association with an *H. pylori* positive test, were analyzed using STATISTICA for Windows (*10*). Because more children participated in the *H. pylori* test than parents completed questionnaires, this assessment is based on the data of only those children with an *H. pylori* test and a completed questionnaire (responses to all variables under investigation). Thus, this analysis includes the data of 1,844 (73.8%) of the 2,498 city children and 1,044 (73.5%) of the 1,421 county children.

Initially, we selected for the analysis 47 variables assumed to be possible risk factors for acquiring the *H. pylori* bacterium. Thirty of these were tentative sources of infection, such as domestic crowding, water and food, pets, hygienic and sanitary living conditions of residence, weekend cottage, travels to foreign countries. The other 17 variables were clinically potential diagnostic indicators. To identify the most important variables in terms of risk associated with the outcome variable (*H. pylori* positivity), we performed a cluster analysis [Ward's method (*11*), Euclidean distances]. The cluster analysis was carried out using a subset of all cases to avoid overestimation of the cluster variables entering the multivariate logistic regression. We used the Ward's method to derive small clusters. This process was repeated with differing case data sets and continued until stable clusters were obtained. All variables identified in this way were entered into the logistic regression. We began the multivariate logistic regression calculations with an initial model. The model was varied by adding and eliminating variables until we reached a stable model (assessment based on *p*-value). We calculated all stepwise logistic regressions with identical, complete sets of variables in order to be able to compare the results. To avoid an overestimation in the regression analysis, the cluster analysis was carried out on successive, arbitrary 75% subsamples of the available population data. The model was defined as stable when the calculated odds ratio value of the significant variables no longer changed during the process.

Authorities of the city of Leipzig granted permission for participation of preschool children in the study, and the study was approved by the Ethics Committee of the University of Leipzig.

Results

Table 1 summarizes the demographics of the study population and the study areas. A total of 3,347 (85.4%) of the school beginners in 1998 (city and county of Leipzig) took part

Table 1. Demographics and prevalences of the study population and study area.

	City	County	Total
Population	445,846	211,032	656,878
Medical examinations (*n*)	2,498	1,421	3,919
Questionnaires completed (*n*)	1,881	1,069	2,950
H. pylori tests (*n*)	2,228	1,119	3,347
Children with questionnaire and test (*n*)	1,844	1,044	2,888
Positive tests (*n*)	120	59	179
H. pylori prevalence[a]	6.5%	5.7%	6.2%
95% CI	5.3–7.6	4.2–7.0	5.3–7.1

[a]Based on data set of children with a completed questionnaire and *H. pylori* test.

Table 2. Potential risk factors for *H. pylori* transmission entered into cluster analysis and their occurrence.

		Percent[a]			*p*-Value
Transmission factors	Acronyms	City	County	Total	(city vs. county)
Domestic crowding					
Persons per apartment (*n*)					
1–2	P1–2	12.8	6.1	10.4	< 0.0000
3–4	P3–4	72.8	76.1	73.9	0.0620
5	P5	9.1	12.8	10.4	0.0024
6–10	P6–10	5.0	4.8	4.9	0.8173
Living space per person					
< 16 m^2	R16	13.5	14.2	13.7	0.6215
16–25 m^2	R25	57.2	50.5	54.9	0.0011
25–50 m^2	R50	28.2	34.1	30.2	0.0018
> 50 m^2	R > 50	1.1	1.2	1.1	0.8186
Siblings in family (*n*)					
0	S0	38.9	31.1	36.0	< 0.0000
1	S1	42.5	48.3	44.6	0.0030
2	S2	11.5	14.7	12.7	0.0142
3	S3	4.2	2.8	3.7	0.0588
4	S4	1.9	1.8	1.8	0.8505
5	S5	0.6	0.4	0.5	0.4820
> 5	S > 5	0.4	0.6	0.5	0.4568
Water- and foodborne factors					
Residence with public water supply	RpW	98.4	98.2	98.4	0.6916
Garden with public water supply	GpW	17.7	22.9	19.6	0.0006
Garden with well water	GwW	4.5	4.9	4.6	0.6200
Drinking well water (in the garden)	GdwW	1.3	0.7	1.1	0.1311
Use of human excrement as garden fertilizer	GhFert	4.6	3.1	4.1	0.0488
Contact with pets					
Dog	AD	35.6	45.1	39.0	< 0.0000
Cat	AC	32.1	48.0	37.9	< 0.0000
Fish	AF	15.3	16.4	15.7	0.4209
Rabbit	AR	18.1	27.9	21.7	< 0.0000
Bird	AB	22.1	25.5	23.4	0.325
Guinea pig	AGP	26.5	25.9	26.3	0.7240
Hamster	AHA	4.6	6.0	5.1	0.0997
Horse	AHO	3.0	8.8	5.1	< 0.0000
Sanitary standards (residence and personal hygiene)					
Toilet inside apartment	HWC	98.3	98.1	98.2	0.6946
Washbasin in washroom	HWB	89.9	92.0	90.6	0.0614
Washing of hands after use of toilet	HWHT	88.9	90.9	89.6	0.0885
Washing of hands before meals	HWHE	89.1	92.6	90.4	0.0021
Toilet-training (dry and bowel-trained)	TTU + TTB	7.8	5.3	6.9	0.0176
Travels to foreign countries					
Northern Europe	TNEU	12.9	13.5	13.1	0.6447
Southern Europe	TSEU	34.4	34.7	34.5	0.8700
Eastern Europe	TEEU	0.0	10.1	3.7	< 0.0000
Turkey and North Africa	TTNA	15.0	13.3	14.3	0.2084
Africa	TAFR	2.8	1.9	2.4	< 0.0000
Asia	TASI	2.2	1.9	2.1	0.5861
South America	TSAM	0.9	0.5	0.7	0.2298
Carribean Islands	TCAR	1.6	2.5	1.9	0.0895

[a]Based on data set of children with a completed questionnaire and *H. pylori* test shown in Table 1. Acronyms are used in Figure 1.

in the *H. pylori* survey. Nonresponders could not be analyzed in detail because parents could not be questioned about the reasons for not letting their children participate in the study. Our data are based on an approximately 73% subsample comprised of city and rural children who participated in the test and returned the parent-completed questionnaire with responses to all questions. Among this preschool population, a total of 179 children (119 city and 60 county) were found to be infected with *H. pylori*. The prevalences of *H. pylori* colonization are presented in Table 1.

The risk factors assumed to play a role in the transmission of *H. pylori* infection and their frequency of occurrence among these probands are summarized in Tables 2 and 3.

Results of the cluster analysis of the total population (city and county) are presented in Figure 1. The main cluster, the variables close to the target HP test (*H. pylori* positivity), includes the varibles with the least geometric distance from the target. These variables were entered into the multivariate logistic regression analysis to determine odds ratios and significance levels. When applied separately to the data sets (Leipzig city and Leipzig County), cluster analyses of the same 47 selected variables showed that the distance of some cluster variables to the target, *H. pylori* positivity, varied for the city and county, indicating differences in their importance in the association. The variable "contact with pet hamsters" was associated more closely with *H. pylori* positivity in the city children than in the county children. In contrast, the variables "use of human excrement as garden fertilizer" and the "drinking of water from nonmunicipal sources" appear closer linked to the target variable in the county. The odds ratios (Table 4) show that not all variables clustering close to the target are significant.

Table 3. Clinical predictors of *H. pylori* infection among probands and their family members and their occurrence in percent.

Diagnostic predictors	Acronyms	Percent[a] City	Percent[a] County	Percent[a] Total	*p*-Value (city vs.county)
Illness/symptoms in family members					
Gastric/duodenal ulceration					
Mother	IFUM	1.9	1.9	1.9	1.0000
Father	IFUF	1.5	1.9	1.6	0.4204
Gastric/duodenal cancer					
Mother	IFCM	0.2	0.6	0.3	0.0767
Father	IFCF	0.2	0.1	0.1	0.5276
Endoscopy (lifetime)	IFENDO	17.9	20.1	18.7	0.1429
Recurrrent abdominal pain	IFRAP	7.1	9.6	8.0	0.0175
Recurrent belching	IFRBELCH	3.6	4.4	4.0	0.2853
Recurrent bloating	IFBLOAT	3.5	4.5	3.8	0.1804
Recurrent heartburn	IFHB	7.1	10.0	8.1	0.0062
Illness/symptoms in child					
Colicky baby	ICCOLIB	4.3	4.2	4.3	0.8975
Recurrent vomiting as a baby	ICRVOMB	2.3	1.9	2.1	0.4736
Recurrent abdominal pain	ICRAP	16.0	16.0	16.0	1.0000
Recurrent belching	ICRBELCH	1.1	1.1	1.1	1.0000
Recurrent bloating	ICBLOAT	0.5	0.5	0.5	1.0000
Recurrent heartburn	ICHB	0.2	0.0	0.1	0.1458
Medication (heartburn)	ICMEDS	12.8	12.8	12.8	1.0000

[a]Based on data set of children with a completed questionnaire and *H. pylori* test shown in Table 1.

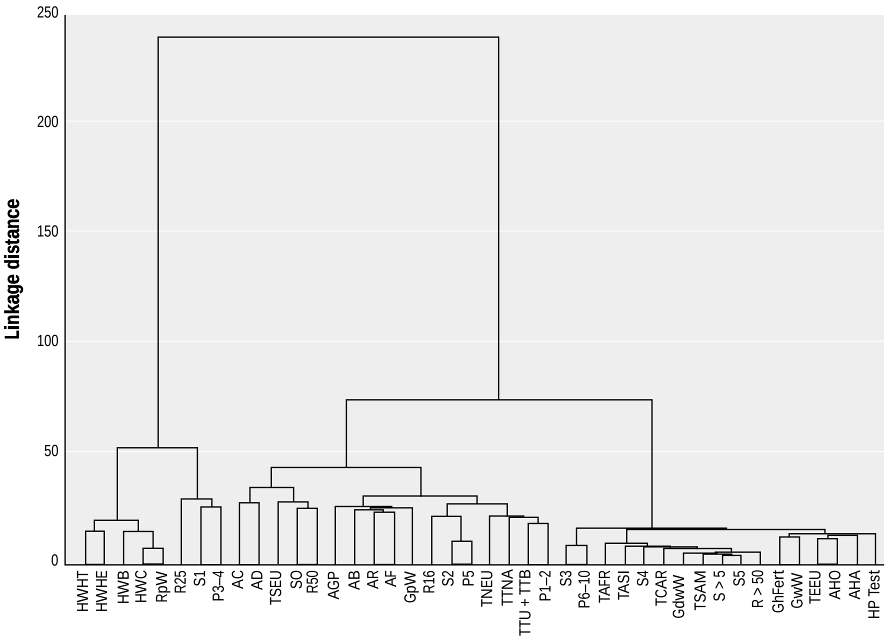

Figure 1. Cluster analysis of 47 selected variables related to possible routes of transmission of *H. pylori* infection using data sets of the total study population (Ward's method, Euclidean distances). Acronyms are defined in Table 2. The shorter the distance between a variable and the target HP test (positive *H. pylori* test), the closer the association and, thus, the more important as a risk factor.

Among city children, the models with significant associations with *H. pylori* positivity are "contact with pet hamsters" (OR = 2.4; 95% CI, 1.2–4.7; $p < 0.015$) and "travels to Asian countries" (OR = 3.7; 95% CI, 1.6–8.7; $p < 0.002$); among county children, there are significant associations for "drinking of water from nonmunicipal sources" (OR = 16.4; 95% CI, 3.1–88.5; $p < 0.001$), "more than 3 children in the household" (OR = 4.2; 95% CI, 1.2–14.6; $p < 0.02$) and "contact with pet hamsters" (OR = 2.4; 95% CI, 1.0–5.7; $p < 0.04$). The model for the entire sample population, based on 2,727 data sets, is highly significant ($p = 0.0008$). The variables included are "contact with pet hamsters" (OR = 2.1; 95% CI, 1.2–3.8; $p < 0.009$), "travels to Asian countries" (OR=3.1; 95% CI, 1.4–6.6; $p < 0.005$), "drinking of water from nonmunicipal sources" (OR = 2.8; 95% CI, 1.0–8.2; $p < 0.05$) and "more than 3 children in the household" (OR = 2.6; 95% CI, 1.1–5.9; $p < 0.024$).

Although we included reported clinical symptoms in a child or a family history of recurrent abdominal pain, dyspepsia, gastric/peptic ulceration, etc. in the model to test their general and specific importance as risk factors, this analysis indicated that these host factors did not significantly contribute to the prediction of *H. pylori* positivity. For example, inclusion of the symptoms "recurrent abdominal pain" and "recurrent belching" into the regression model for the total population (Table 5) only weakened the association. The *p*-value of the model, in spite of remaining significant, increased from 0.0008 (without the clinical indicators) to 0.0028.

Discussion

Compared to similar studies (*4–7*), this investigation is, to our knowledge, the largest study of a homogeneous cohort population at risk for *H. pylori* (Table 1). Moreover, this study allowed the comparison of an almost complete birth cohort of urban and rural children (city and its surrounding county).

Table 4. Significant odds ratios of risk factors for city and county children and for the total population.

Transmission routes	OR	95% CI	*p*-Value
Contact with pet hamsters			
City	2.4	1.2–4.7	0.015
County	2.4	1.0–5.7	0.04
City + County	2.1	1.2–3.7	0.009
Travels to Asian countries			
City	3.7	1.6–8.7	0.002
Total	3.1	1.4–6.8	0.005
Drinking water in garden			
County	16.4	3.1–88.5	0.001
Total	2.8	1.0–8.3	0.05
> 3 children in household			
County	4.2	1.2–14.6	0.02
Total	2.6	1.1–6.6	0.024

City odds ratios are based on 1,785 complete data sets; $p = 0.003$. County odds ratios are based on 976 complete data sets; $p = 0.0005$. City + County odds ratios are based on 2,727 complete data sets; $p = 0.0008$.

Table 5. Clinical symptoms as diagnostic predictors of *H. pylori* positivity for the total population.

Diagnostic predictors	OR	95% CI	*p*-Value
Recurrrent abdominal pain	1.1	0.7–1.6	0.792
Recurrent belching	1.6	0.5–5.6	0.429

Odds ratios based on 2,715 complete data sets; $p = 0.003$.

Also, 95.8% of the children were white, which further indicates the homogeneity of the cohort.

We found no significant difference in the prevalence of *H. pylori* colonization between city (6.5%) and county (5.7%) children (a total of 6.2%; Table 1). The prevalences are within the norm expected for a developed country, where an acquisition of the bacterium among children is estimated to be less than 1% per year (*12*). In a recent study of preschool children in a southern German city with a high proportion of foreigners, the total mean prevalence was 11.3%, with 4.9% among German children, and thus comparable to our findings (*13*).

The risk factor analysis showed some unexpected results. The analyses, cluster analysis, and odds ratio calculations indicated four significant risk factors suggestive of being routes for the acquisition of *H. pylori* bacteria (Table 4, Figure 1):

- "Travels to Asian countries" as a possible source of infection; the prevalence of *H. pylori* is much higher in Asian countries than in Central Europe (*14–16*)
- "Large family size," also a known risk factor (*16*)
- "Contact with pet hamsters"
- "Drinking water from nonmunicipal sources."

The latter two are less known risk factors and require further discussion.

In a recent paper, Bode et al. (*7*) found no significant association with cats, guinea pigs, birds, and rabbits. Our results for these types of pets support their findings. However, the multivariate logistic regression analysis in our study population confirmed the cluster analysis, and indicated that "contact with pet hamsters" significantly increased the odds (OR = 2.1) of infection with *H. pylori* (Table 4). Furthermore, among rural children the risk of being infected with *H. pylori* increased with the "drinking of water from nonmunicipal sources" (OR = 16.4; Table 4). This may occur at allotment gardens, where well water may be used for human consumption. The result of the cluster variable analysis of "use of human excrement as fertilizer" (top-dressing) on vegetation in gardens was closely associated with the target *H. pylori* positivity among county children, even though the regression analysis showed a nonsignificant association. These findings point to the possibility that handling and/or eating vegetables (as well as grass and flowers), which may be contaminated with (human) feces, could be a route of acquiring the infection. *H. pylori* has been isolated from human feces (*17*) and has been found to be associated with the consumption of uncooked vegetables (*18*). Furthermore, consuming water from sources other than public supplies or drinking contaminated water is a risk factor in developing countries (*19*), and Carballo et al. (*20*) reported that untreated water is a possible source of *H. pylori* infection. Early results of an epidemiologic and microbiologic investigation now being carried out by our team suggest that, even in Central Europe, well water could be a source of *H. pylori* infection (*21*). The *H. pylori* bacterium appears to survive in water in a coccoid form, even in very cold water (*22*). All of these studies lend support to the hypothesis that indirect fecal–oral transmission may be an important pathway by which the bacterium gains entrance into the human body, with children being especially at risk.

The clinical predictors investigated did not seem to be significant in this population (Tables 3 and 5). No significant associations were found for "gastric/duodenal disease," "recurrent abdominal pain," or "recurrent heartburn" in children or in their families. Measurement errors associated with the low within- and between-population occurrence (Table 3) are balanced by the odds ratio analysis that is based on the total population (city and county) with 2,715 complete data sets. These odds ratios and confidence intervals suggest that the errors were minimized (Table 5). The role of clinical symptoms as indicators of *H. pylori* infection remains controversial (*23*), but similar findings have been reported indicating that "chronic abdominal pain" in childhood (*24,25*) may not necessarily indicate *H. pylori* positivity.

Conclusion

In this study we demonstrated that *H. pylori* colonization in this preschool population is significantly related to risk factors such as "contact with pet hamsters," "travels to Asian countries," and "drinking of water from nonmunicipal sources." This suggests that indirect fecal–oral transmission may play a key role in the spread of this infection. These factors appear to be as important as household density, which was found to increase the risk of *H. pylori* infection when more than three children live in a household. However, relative to these risks, the clinical symptom indicators investigated do not seem to play the same significant role in predicting *H. pylori* colonization.

Although, at present, the recommendations of the European Society for Primary Care Gastroenterology do not support a "test and treat" strategy (*26*), our goal was to show that epidemiologic screenings of population-based, nonsymptomatic children offer information about current prevalences and risk factors, thus, contributing to future recommendations.

References and Notes

1. Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet 1:1311–1315 (1984).
2. Broutet N, Gisbert JP, Pajares JM. Epidemiology. In: The Year in *Helicobacter pylori* 1999 (Malfertheiner P. Megraud F, Michetti P. Price A, eds). Curr Opin Gastroenterol 15(suppl 1):S43–S47 (1999).
3. Guimber D, Chelimsky G, Gottrand F, Czinn S. Paediatrics. In: The Year in *Helicobacter pylori* 1999 (Malfertheiner P. Megraud F, Michetti P. Price A, eds). Curr Opin Gastroenterol 15(Suppl 1):S49–S52 (1999).
4. Torres J, Leal-Herrera Y, Perez-Perez G, Gomez A, Camorlinga-Ponce M, Cedillo-Rivera R, Tapia-Conyer, R, Munoz O. A community-based seroepidemiologic study of *H. pylori* infection in Mexico. J Infect Dis 178:1089–1094 (1998).
5. Elitsur Y, Hill I, Lichtman SN, Rosenberg AJ. Prospective comparison of rapid urease tests (PyloriTek, CLO test) for the diagnosis of *H. pylori* infection in symptomatic children: a pediatric multicenter study. Am J Gastroenterol 93:217–219 (1998).
6. Brenner H, Rothenbacher D, Bode G, Adler G. Parental history of gastric or duodenal ulcer and prevalence of *Helicobacter pylori* infection in preschool children: population-based study. Br Med J 316:665 (1998).
7. Bode G, Rothenbacher D, Brenner H, Adler G. Pets are not a risk factor for *H. pylori* infection in young children:

results of a population-based study in southern Germany. Pediatr Infect Dis J 17:909–912 (1998).
8. Cave DR. Epidemiology and transmission of *Helicobacter pylori* infection. How is *Helicobacter pylori* transmitted? Gatroentrerol 113:S9–S14 (1997).
9. Krumbiegel P, Herbarth O, Fritz G, Schlink U, Gutsmuths F-J, Kindler A, Richter T. *Helicobacter pylori* prevalence in Leipzig's 1998 school entries: methodology and first results. Int J Hyg Environ Health 203:11–16 (2000).
10. StatSoft. STATISTICA for Windows: General Conventions and Statistics. Tulsa, OK:StatSoft, Inc., 1998.
11. Ward JH. Hierarchical grouping to optimize an objective function. J Am Stat Assoc 58:236 (1963).
12. Graham KS, Graham DY. Contemporary Diagnosis and Management of *H. pylori*-Associated Gastrointestinal Diseases. Newton, PA:Handbooks in Health Care, 1998.
13. Rothenbacher D, Bode G, Berg G, Knayer U, Gonser T, Adler G, Brenner H. *Helicobacter pylori* among preschool children and their parents: evidence of parent-child transmission. J Infect Dis 179:398–402 (1999).
14. Ma J-L, You W-C, Gail MH, Zhang L, Blot WJ, Chang YS, Jiang J, Liu WD, Hu YR, Brown LM, et al. *Helicobacter pylori* infection and mode of transmission in a population at high risk of stomach cancer. Int J Epidemiol 27:570–573 (1998).
15. Youn H-S, Baik S-C, Cho Y-K, Woo HO, Ahn Y-O, Kim K, Cho M-J, Lee W-K, Ko G-H, Okada K, et al. Comparison of *Helicobacter pylori* infection between Fukuoka, Japan and Chinju, Korea. Helicobacter 3:9–14 (1998).
16. Kikuchi S, Kurosawa M, Sakiyama T. *Helicobacter pylori* risk associated with sibship size and family history of gastric diseases in Japanese adults. Jpn J Cancer Res 89:1109–1112 (1998).
17. Thomas JE, Gibson GR, Darboe MK, Dale A, Weaver LT. Isolation of *Helicobacter pylori* from human faeces. Lancet 340:1194–1195 (1992).
18. Hopkins RJ, Vial PA, Ferreccio C, Ovalle J, Prado P, Sotomayor V, Russell RG, Wasserman SS, Morris JG Jr. Seroprevalence of *Helicobacter pylori* in Chile: vegetables may serve as one route of transmission. J Infect Dis 168:222–226 (1993).
19. Hulten K, Han SW, Enroth H, Klein PD, Opekun AR, Gilman RH, Evans DG, Engstrand L, Graham DY, El-Zaatari AK. *Helicobacter pylori* in the drinking water in Peru. Gastroenterology 110:1031–1035 (1996).
20. Carballo F, Caballero P, Parra T, Aldeguer M, Pajares JM. Untreated drink water is a source of *H. pylori* infection [Abstract]. Gut 41(suppl 1):A39 (1997).
21. Krumbiegel P, Boeckler D, Lehmann I, Jorks S, Fritz GJ, Babel W, Richter T, Herbarth O. Is water a source of *H. pylori* infection in Central Europe? [Abstract]. Gut 47(suppl 1):A46 (2000).
22. McKeown I, Orr P, MacDonald S, Kabani A, Brown R, Coghlan G, Dawood M, Embil J, Sargent M, Smart G, et al. *Helicobacter pylori* in the Canadian Arctic: seroprevalence and detection in community water samples. Am J Gastroenterol 94:1823–1829 (1999).
23. Wewer V, Christiansen KM, Andersen LP, Henriksen FW, Hansen JP, Tvede M, Krasilnikoff PA. *Helicobacer pylori* infection in children with recurrent abdominal pain. Acta Paediatr 83:1276–1281 (1994).
24. Leicht C, Richter T, Handrick W, Kehrer U, Krumbiegel P. Der [$^{15}N_2$]Harnstoff-Urintest zur Diagnostik von *Helicobacter pylori* bei Kindern mit Bauchschmerzen. Monatsschr Kinderheilkd 144:1167–1168 (1996).
25. Tindberg Y. *H. pylori* and abdominal pain in school children [Abstract]. Gut 47(suppl1):A94 (2000).
26. Rubin GP, Meineche-Schmidt V, Roberts AP, Childs SM, de Wit NJ. The management of *Helicobacter pylori* infection in primary care. Guidelines from the ESPCG. Eur J Gen Pract 5:98–104 (1999).