

***Helicobacter pylori*: Epidemiology and Routes of Transmission**

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INTRODUCTION

Helicobacter pylori, a spiral-shaped pathogenic bacterium found on the human gastric mucosa, was first isolated by Warren and Marshall (1) in 1982 and soon after was linked with chronic antral gastritis and peptic ulceration (2). Initially, this bacterium was classified as *Campylobacter pylori* but in 1989 was included in a new genus, *Helicobacter*, and renamed *Helicobacter pylori* (3). Although it was "discovered" less than 20 years ago, thousands of articles have been written about *H. pylori*, one of the most common bacterial infections in the world (4). Since a complete summary of the *H. pylori* literature is beyond the scope of this review, it briefly discusses the microbiologic characteristics of *H. pylori*, the diagnostic tests used in epidemiologic studies, and the association of *H. pylori* with gastric cancer and other diseases. The primary focus is on the epidemiology and transmission of *H. pylori* infection in adults, including reviews of the prevalence of *H. pylori* in various countries, risk factors for *H. pylori* infection, and hypothesized modes of transmission. Findings from studies of children have been added where appropriate to supplement the adult literature. The major emphasis is on scientific articles selected from the recent literature, but important scientific papers published in peer-reviewed journals prior to 1995 have also been included.

MICROBIOLOGIC CHARACTERISTICS

H. pylori is an S-shaped or curved gram-negative rod. It has from two to six flagella that give it the mobility to withstand rhythmic gastric contractions and penetrate the gastric mucosa. It is 2.4–4.0 μm long and 0.5–1.0 μm wide. The principal reservoir for *H. pylori* infection appears to be the human stomach, especially the antrum. However, it does not colonize areas of the stomach in which intestinal metaplasia or dysplasia is present (5). *H. pylori* contains a large urease enzyme protein that produces urease, which enables the

organism to survive in the acidic stomach by creating an alkaline environment. *H. pylori* produces a number of virulence factors, including vacuolating cytotoxin (*vacA*), that may have different disease associations (6). Approximately 10–20 percent of the population will never become chronically infected with *H. pylori* (7). Establishment of chronic infection may be influenced by host genetic factors such as ABO blood group and Lewis blood-group antigen (8) and by differences in susceptibility to particular strains of *H. pylori* (9).

DIAGNOSTIC TESTS

Because acute infection with *H. pylori* is generally asymptomatic, it is not possible to ascertain when infection occurs on the basis of symptoms or clinical findings (10). Most epidemiologic studies of the prevalence of *H. pylori* infection usually use serologic tests or ^{13}C urea breath tests. Biopsy-based methods are often used in hospital or clinic settings.

Biopsy-based tests

Originally, the diagnosis of *H. pylori* infection was based on either isolating bacteria from gastric biopsy specimens obtained from endoscopy or identifying the bacteria on stained biopsy sections (2, 11). Today, a positive culture obtained from endoscopy and usually augmented with a biopsy urease test and/or histology is often used as a "gold standard" to detect patients with active *H. pylori* infection, to differentiate among the various strains of *H. pylori*, and to study the effects of multiple strains of *H. pylori* (12, 13). While biopsy/culture is 100 percent specific, it is not 100 percent sensitive; the method can evaluate only a relatively small portion of the stomach, and it is highly invasive and expensive.

Serology test

A nonquantitative enzyme-linked immunosorbent assay detects *H. pylori* antibodies in serum. A major advantage of this serologic test is that it enables large numbers of subjects to be screened quickly and relatively inexpensively; thus, it is a good test to use in epidemiologic studies (14). The prevalence of *H. pylori* (in either fresh or stored serum) is usually found by using serologic tests that detect immunoglobulin (Ig)G antibodies to *H. pylori* infection, although IgA and IgM antibodies have also been used (15).

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Abbreviations: CI, confidence interval; Ig, immunoglobulin; OR, odds ratio; PCR, polymerase chain reaction; SES, socioeconomic status.

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There are, however, several limitations to the use of serologic tests. First, since no single antigen is recognized by sera from all subjects, antigen reagent preparations should contain multiple strains of *H. pylori* (16, 17). It has also been suggested that assays based on indigenous strains may perform better (18). In fact, a study in Henan Province, China, found a much higher prevalence of *H. pylori* by using a biopsy-based technique (85.6 percent) than by using serology (56.2 percent) (19). The authors of this study noted that one explanation for the large discrepancy may be that the antigen used for serology was derived from a single *H. pylori* strain isolated in Germany. However, other studies have found little difference in outcome between local and referent strains (20, 21). Second, it is difficult to define the cutoff value that divides positive from negative subjects. One approach to improve both sensitivity and specificity, although it biases both values upward, is to include a gray or indeterminate zone for subjects whose values cannot be considered truly positive or truly negative. In an epidemiologic study comparing the characteristics of positive and negative subjects, such an approach would help to minimize misclassification by not including those subjects for whom results are equivocal. A receiver operating characteristic is often used to determine the effect on the test of varying the cutoff value or to compare the performance of different tests (13).

Third, the test is sensitive to changes in reagents and laboratory conditions; thus, sera collected at different times (e.g., before and after treatment or longitudinally at yearly intervals) should be run together in the same enzyme-linked immunosorbent assay plate. Also, depending on the sensitivity and specificity of the serologic test in the study population, variation in seroconversion and seroreversion rates may be due to imperfectly repeated measures. Fourth, serology is not an appropriate test to use immediately following treatment for *H. pylori*, since it takes several months for elevated antibody titers to fall. Because these titers may never fall low enough to be considered "negative," some researchers suggest considering IgG values that have fallen by 50 percent or more 6 months after treatment as an indication of successful *H. pylori* eradication (16, 22).

Breath test

The urea breath test in which either ^{13}C or ^{14}C is used is noninvasive, is nonquantitative, and determines current *H. pylori* status by detecting urease activity produced by the bacteria. This test has recently been approved by the US Food and Drug Administration for routine use. Although it is not universal, several researchers now consider the breath test a noninvasive gold standard (13, 16). Generally, this test is useful following antibiotic treatment, since gastric urease is present in the stomach only when the bacteria that make the urease are present. However, false negatives can result in treated subjects if there are too few bacteria to produce detectable urease. For a small percentage of people infected by other bacteria that also produce urease (generally less than 5 percent in most populations), false positives can result. The urea breath test is generally more expensive than serology, but its use in epidemiologic

studies, especially those in which children are the study subjects, is increasing.

DISEASE ASSOCIATIONS

H. pylori is thought to be indigenous to the human population and is well adapted to existing in the human stomach for the lifetime of its host (23). Spontaneous eradication of *H. pylori* from the gastric mucosa, as measured by seroreversion, is a relatively rare event—0.1–1.1 percent annually (24). Infection with *H. pylori* can result in chronic gastritis, a cellular infiltrate of immunocompetent lymphocytes and of IgA-, IgG-, and IgM-secreting plasma cells in the gastric mucosa (25). Infection is generally asymptomatic, with the majority of those persons infected not developing clinical disease (26). However, because *H. pylori* has been recognized as a major cause of gastritis and is associated with duodenal ulcer disease, gastric ulcer disease, gastric lymphoma, and gastric cancer in humans (27, 28), it is a public health problem in both developed and developing countries.

Environmental and genetic factors appear to be important in the progression of *H. pylori*-initiated gastritis to more serious outcomes. Additionally, variation in age at acquisition of *H. pylori* has been proposed as a possible factor to explain the observation that the same organism, *H. pylori*, apparently produces different effects on the gastric mucosa that result in different clinical outcomes (28). Early age at acquisition of *H. pylori* infection may result in more intense inflammation and the early development of atrophic gastritis and subsequent risk of gastric ulcer, gastric cancer, or both. Later acquisition of infection would induce a different series of gastric changes that would favor the development of duodenal ulcer. High rates of gastric cancer in areas in which infection is common in early childhood support this hypothesis. Other host and environmental factors such as hygiene practices and diet may also play a role in the acquisition of infection and the expression of clinical disease (7).

In 1994, an International Agency for Research on Cancer Working Group found sufficient evidence to classify *H. pylori* as a human carcinogen for gastric cancer (29). However, some researchers now believe that the epidemiologic evidence is contradictory and that this agency was premature in its group 1 designation, because *H. pylori* seems to play a role in only the initial steps that result in chronic inflammation (a common occurrence in much of the world) but not in the later steps that lead to carcinogenesis (30–32). Intervention studies that include treatment for *H. pylori* for subjects at different stages in the progression toward cancer (33) will be informative in clarifying the "*H. pylori* = gastric cancer" controversy.

On the other hand, some *H. pylori* strains, particularly *cagA+*, appear to protect against adenocarcinomas of the esophagus and gastric cardia (34–36). Also, the prevalence of *H. pylori* infection appears to be lower in persons with gastroesophageal reflux disease (the major risk factor for Barrett's esophagus, which is strongly associated with adenocarcinoma of the esophagus) than in controls (37, 38).

The relation between *H. pylori* infection and nonulcer dyspepsia is controversial. For example, while a recent

meta-analysis reported an improvement in dyspeptic symptoms among subjects receiving antibiotics treatment (39), two recent randomized controlled trials did not (40, 41).

There is now some concern that *H. pylori* infection may be associated with an increased risk of coronary heart disease possibly because of a low-grade systemic inflammatory response or an increase in concentrations of circulating coagulation factors (42–44). However, the results from several prospective studies (42, 45, 46) and a meta-analysis of more than 20 epidemiologic studies (47) suggest that *H. pylori* is probably not an important contributor to coronary heart disease.

EPIDEMIOLOGY

Descriptive studies and prevalence

The prevalence of *H. pylori* infection varies widely by geographic area, age, race, and socioeconomic status (SES). Because it is not possible to ascertain when infection occurs clinically (10), most of the information on the rates of *H. pylori* in geographically and demographically diverse populations comes from seroprevalence studies. This has major disadvantages for epidemiologists, since it is generally not possible to distinguish between factors associated with acquiring versus maintaining *H. pylori* infection (48).

The acquisition rate of *H. pylori* appears to be more rapid in developing than developed countries (49, 50). In a rural village of Linqu County, Shandong Province, China, a study of 98 children found that nearly 70 percent of those aged 5–6 years were infected with *H. pylori* (51), a rate similar to that reported for adults in that area (52), suggesting that most infection takes place early in childhood. The annual rate of seroconversion in adult populations in developed countries appears to be small, about 0.2–1.0 percent (24). However, two recent studies of young adults, one of Israeli backpackers to southeast Asia, South America, and Africa (53) and the other of military personnel deployed to the Persian Gulf during Desert Storm (54), found much higher annual rates of seroconversion, 6.4 and 7.3 percent, respectively, suggesting that adults can seroconvert at higher rates than normal under unusual circumstances.

Studies of *H. pylori* prevalence among adults have generally been cross-sectional in design and have included random surveys of the general population, groups of healthy volunteers, military personnel, students, employed workers, groups of institutionalized patients, or patients attending hospitals or outpatient clinics. Included in table 1 is the prevalence of *H. pylori* in adult populations from various geographic areas of the world. While it is difficult to compare the rates from these studies directly because they vary by age and type of population, the table does illustrate the large range in prevalence rates reported worldwide. *H. pylori* prevalence in developing countries may reach 70 percent or more compared with 40 percent or less in developed countries. Comparison of prevalence rates by age (55) suggests that acquisition of *H. pylori* is decreasing in recent cohorts. This finding is most apparent in developed countries and may be linked to improvements in hygiene practices.

In the United States, differences by race are evident, with Whites having a substantially lower seroprevalence of *H. pylori* than either Blacks or Hispanics (43, 56–59). In the study by Replogle et al. in California (43), the odds ratios for being *H. pylori* seropositive given African-American and Hispanic ethnicity were 4.1 (95 percent confidence interval (CI): 2.2, 7.4) and 3.1 (95 percent CI: 1.6, 6.2), respectively. Similar risk estimates for Blacks (odds ratio (OR) = 4.4, 95 percent CI: 3.0, 6.3) and Hispanics (OR = 4.2, 95 percent CI: 2.1, 8.6) were found in a study of US Army recruits (58) and a study of US Navy and Marine Corps personnel (59) (OR = 4.2, 95 percent CI: 2.9, 6.0 for Blacks; OR = 3.9, 95 percent CI: 2.4, 6.3 for Hispanics). Ethnic differences were also evident in New Zealand (60), where *H. pylori* infection was most prevalent in Pacific Islanders, intermediate in Maori, and least prevalent in Europeans. After adjusting for age and SES, the relative risks for Maori and Pacific Island subjects compared with European subjects were 1.4 (95 percent CI: 1.1, 1.8) and 1.8 (95 percent CI: 1.4, 2.2), respectively. These differences in *H. pylori* prevalence by race/ethnicity and nationality may reflect differences in social and/or hygiene factors or the widespread use of antimicrobials for treatment of other common infections, especially during childhood (61). This variability may also be explained by differences in ethnic or genetic predisposition to infections.

Although some studies have reported an excess of *H. pylori* in one gender versus the other (43, 58), no noteworthy gender differences exist in *H. pylori* prevalence overall. Differences in *H. pylori* prevalence by SES factors can be striking and are presented in detail in the section that follows. The high rates evident in institutionalized populations are discussed in relation to *H. pylori* transmission.

Risk factors

In addition to determining the prevalence of *H. pylori* in various geographic areas, a number of studies included a questionnaire component designed to investigate risk factors for *H. pylori* positivity. The quality of these studies was variable, and, in many cases, the statistical procedures used were not well described. Also, it was not always clear whether prevalence rates for the various groups compared were standardized either directly or indirectly to adjust for differences in their age structures. The most common tests used to determine statistical significance were the chi-square test (for independence and homogeneity), Fisher's exact test, and Student's *t* test. Crude and adjusted relative risks and odds ratios were calculated by using the Mantel-Haenszel procedure and unconditional logistic regression, respectively. Odds ratios were the most common measure of association presented.

While the odds ratio is a legitimate measure of association in its own right, it can be used as an estimate of the relative risk only when the incidence of disease in the population studied is rare. In addition, the cases and noncases included in the study should be representative of the cases and noncases in the population from which the study subjects were recruited. Because this "rare disease assumption"

TABLE 1. Prevalence of *Helicobacter pylori* in selected adult populations of the world

Author(s), year (reference no.)	Country or US state	No. in study	Population	Age range (years)	Diagnostic test	% Positive			
Wong et al., 1999 (199)	China		Healthy volunteers	36-65	Serology	80			
	Hong Kong	397				58			
	Fujian Province	1,456							
Kawasaki et al., 1998 (200)	Nepal	1,142	General population	4-93	Serology	57			
Kikuchi et al., 1999 (69)	Japan	4,361	Public service workers	19-69	Serology	30			
Lin et al., 1998 (62)	Australia	273	General population	20-80	Serology	38			
Senra-Varela et al., 1998 (201)	Spain	332	General population	Adult	Serology	43			
Souto et al., 1998 (107)	Brazil	164	General population	20-90	Serology	85			
Strachan et al., 1998 (42)	South Wales	1,796	General population	45-59	Serology	70			
Torres et al., 1998 (109)	Mexico	5,997	General population	20-90	Serology	81			
Ahmad et al., 1997 (202)	Bangladesh	181	Outpatients	20-44	Serology	92			
Bohmer et al., 1997 (81)	Netherlands	338	Institutionalized	11-89	Serology	83			
		254	Healthy employees	18-50		27			
		4,742	General population	12-64		50			
Murray et al., 1997 (64)	Ireland	4,742	General population	12-64	Serology	50			
Andersen et al., 1996 (15)	Denmark	3,589	General population	30-60	Serology	26			
Fraser et al., 1996 (60)	New Zealand	579	Workers	40-64	Serology	56			
		190	European			36			
		195	Maori			57			
		194	Pacific Islander			73			
Malaty et al., 1996 (110)	Korea	161	Healthy volunteers	20-75	Serology	75			
Malaty et al., 1996 (108)	Russia	213	Outpatients	20-75	Serology	88			
Gilboa et al., 1995 (203)	Rural Israel	377	General population	30-90	Serology	72			
Harris et al., 1995 (114)	United Kingdom	424	Institutionalized	18-106	Serology	87			
		267	Healthy controls	18-80+		41			
Hyams et al., 1995 (59)	United States	1,000	Navy and Marine Corps personnel	17-50	Serology	25			
		730	White			18			
		168	Black			46			
		76	Hispanic			45			
		24	Other race			29			
Lambert et al., 1995 (113)	Australia	122	Institutionalized	19-47	Serology	75			
		273	Population controls			23			
Repogle et al., 1995 (43)	California	556	Outpatients	20-39	Serology	27			
Smoak et al., 1994 (58)	United States	938	Army recruits	17-26	Serology	26			
		536	White			14			
		324	Black			44			
		47	Hispanic			38			
Teh et al., 1994 (95)	Taiwan	823	General population	1-40+	Serology	54			
Webb et al., 1994 (106) EUROGAST Study Group, 1993 (55)	United Kingdom	471	Male volunteers	18-64	Serology	37			
				Japan		386	General population	25-34	61
								55-64	89
	Poland	171		25-34	69				
				55-64	89				
	Denmark	157		25-34	15				
				55-64	30				
	Minnesota	198		25-34	15				
				55-64	34				
	Malaty et al., 1992 (56)	Texas		Healthy volunteers	20-75	Serology			
				89	Hispanic			65	
				89	Black			66	
				89	White			26	
Graham et al., 1991 (57)	Texas		Healthy volunteers	15-80	Serology				
			246	Blacks			70		
			239	Whites			34		

does not hold for *H. pylori* infection in any of the populations studied, the odds ratio should not be considered an approximation of the relative risk in studies of *H. pylori*. In addition, since these are cross-sectional studies, the outcome

measure is prevalence of *H. pylori* infection at the time blood was drawn for serology, biopsy and culture were performed, or the breath test samples were obtained. Thus, the measure of association in a logistic regression analysis is the

prevalence odds ratio, which compares the odds of being infected with *H. pylori* in the exposed group with the odds of being infected with *H. pylori* in the unexposed/referent group.

Described in subsequent portions of this review are the major factors investigated for their possible association with *H. pylori* positivity. The following topics are included: smoking, alcohol consumption, diet, occupational exposures, waterborne exposures, hygiene practices, density/crowding, social factors, and family history of gastric disease.

Smoking. Studies have assessed the possible association between *H. pylori* infection and smoking. Whereas some found that *H. pylori*-seropositive subjects were overall more likely than -seronegative subjects to be current smokers (62–65), results were often not consistent by race or gender. For example, Hamajima et al. (63) found an odds ratio of 7.8 for *H. pylori* infection for current male smokers but an odds ratio of only 1.2 for current female smokers. Conversely, Lin et al. (62) found a significant association with current smoking for females (OR = 2.8) but not for males. The positive finding (OR = 1.7) reported by Fontham et al. (65) held for Blacks (OR = 3.1) but not for Whites (OR = 0.6), and Lin et al. (62) found no association with intensity or age at which smoking began. Most of the recent studies found no significant association with current smoking or any other measure of tobacco use (52, 55, 60, 66–68), and one recent study from Japan (69) reported a significant negative association with current smoking. Some authors have suggested that these contradictory results may be due to uncontrolled confounding by social class (64, 69) or to differential antibiotic use, since smoking appears to affect treatment success (63). While one cannot rule out that an association between smoking and *H. pylori* infection may exist, such a hypothesis is not strongly supported by the current literature.

Alcohol consumption. None of several recent epidemiologic studies of the relation between alcohol consumption and *H. pylori* infection found a positive association, but many noted a nonstatistically significant reduction in risk (55, 60, 62, 65, 66, 68–71). Brenner et al. (66, 70, 71), who incorporated a quantitative measure of alcohol consumption while controlling for potential confounding factors, found a significant negative association with alcohol consumption, especially at moderate to high levels. In two of these studies (70, 71), the association was stronger for wine than for beer. Several studies did not adequately control for potential confounding variables or did not present the actual risk estimate or prevalence; thus, it is difficult to evaluate whether alcohol consumption has a “protective” effect on the prevalence of *H. pylori*. *H. pylori* is better able to survive in the acid environment of the stomach than other bacteria are because of its production of urease. Therefore, it is not surprising that the reduction in pH that may accompany alcohol consumption would have little effect on the prevalence of *H. pylori* (72). However, alcohol is known to have direct antimicrobial effects that appear to be more pronounced for wine than for other types of alcoholic beverages (73). The differing results may be due to the different methodologies used or to real differences in either the type or amount of alcohol consumed and its effect on *H. pylori* in different populations.

Diet. Studies have also looked at dietary associations with *H. pylori*. Although the studies cover many different types of populations and include both adults and children, some consistent associations suggest that nutritional status may be related to *H. pylori* infection. Goodman et al. (74, 75) and Fontham et al. (65) found significantly reduced odds ratios and negative gradients in risk of *H. pylori* infection with increased consumption of fruits and/or vegetables. An intervention study by Jarosz et al. (76) found that *H. pylori* infection was apparently eradicated in 30 percent of patients with chronic gastritis who were treated with vitamin C for 4 weeks compared with 0 percent in the control group. Trends of decreasing risk with increasing consumption of vitamin C were observed in studies by Goodman et al. (74) and Fontham et al. (65); however, Malaty et al. (77) found high levels of vitamin C to be associated with *H. pylori* infection in twins reared apart. Goodman et al. (74) also reported high levels of beta-carotene to be protective. In contrast, in studies by Goodman et al. (75) and Hopkins et al. (78), consumption of raw or uncooked vegetables was related to the risk of *H. pylori* infection (OR = 2.0 for three or more servings per day and OR = 3.2, respectively). The cause of this increased risk has not been determined but may have been due to contaminated water or soil (78) or contamination by a vector such as the fly (79). The role of food prepared under less than ideal sanitary conditions as a possible mechanism of *H. pylori* transmission was suggested by Begue et al. (80), who found elevated risks for consumption of food obtained from street vendors in Peru.

Occupational exposures. Occupational exposures have been studied by several researchers to determine whether people working in certain occupations with potentially greater exposure to *H. pylori* had an increased prevalence of infection. Bohmer et al. (81), in a study of inhabitants of institutes for the intellectually disabled in the Netherlands, found most of the intellectually disabled to be seropositive (83 percent). They also reported a higher rate of seropositivity (32 percent) among employees such as the nursing staff, who had intensive contact with institutionalized inhabitants, than among employees such as medical staff, speech trainers, secretarial staff, and drivers, who had little or no direct contact (14.1 percent). Risk of infection from potential exposure to these bacteria in wastewater was investigated by Friis et al. (82) in a study of Swedish sewage workers. They found that seroprevalence rates did not differ between sewage workers and other municipal workers matched on age, SES, and location. In studies conducted in Australia and Wales, dentists, dental nurses, and dental students were not at increased risk for *H. pylori* infection (83, 84). When Lin et al. (83) compared the prevalence of *H. pylori* in dentists and dental nurses with that in endoscopists and endoscopy nurses, they found endoscopists (80 percent) to have significantly higher rates of *H. pylori* than dentists did (21 percent), but the rates for the two types of nurses were not significantly different.

There has been conflicting data regarding the prevalence of *H. pylori* in endoscopy staff. Studies in China and Taiwan found that medical staff who performed endoscopies had a higher prevalence of *H. pylori* than medical staff who did

not perform these procedures (85, 86), and two studies in Australia reported the prevalence of *H. pylori* to be significantly higher in endoscopists compared with population controls (87, 88). In Germany, Braden et al. (89) found no increased risk of *H. pylori* infection in endoscopy staff (physicians and nurses) compared with the general medical staff (physicians and nurses) but did find a risk for all medical staff compared with controls. On the other hand, Rudi et al. (90) reported that exposure to neither patients in an acute care hospital nor endoscopic procedures increased the rate of *H. pylori* infection. In a study by Nishikawa et al. in Japan (91), *H. pylori* seroprevalence among endoscopists and endoscopy nurses did not differ significantly from that among healthy controls, although the prevalence among younger (less than age 40 years) endoscopy staff was significantly higher than among younger controls (24 vs. 12 percent, $p < 0.05$). It is possible that differences in medical practices, including the use of gloves and other protective equipment, may be responsible for these discrepancies. To obtain a more definitive answer, a large prospective study of endoscopists but not dentists suggests that gastric mucous may be a better medium than saliva for transmission of *H. pylori* (93).

Waterborne exposures. Water has been suggested as a possible source of *H. pylori* infection. Studies in Colombia, rural China, and Lima, Peru (52, 75, 94) found that water source may be related to risk of *H. pylori* infection. Three waterborne factors were linked to higher risks of *H. pylori* infection in Colombian children: drinking water from a stream, swimming in a stream, and swimming in a swimming pool (75). Klein et al. (94) found that the water supply in Lima, Peru, may be vulnerable to bacterial contamination, especially if it is stored in a cistern or obtained through central community water taps. Although their findings were not significantly different because of the small percentage of subjects reporting use of a pond or ditch as a source of drinking water, Zhang et al. (52) found a substantially higher seroprevalence of *H. pylori* (88 percent) among those obtaining their water from a surface-water source compared with subjects obtaining their water from a well (73 percent). However, studies by Teh et al. in Taiwan (95) and Hopkins et al. in Chile (78) found no excess risk of *H. pylori* for subjects who obtained their water from the river and for either swimming near contaminated beaches or bathing in local rivers, irrigation ditches, or lakes, respectively.

Hygiene practices. Studies also have assessed the relation between *H. pylori* infection and various hygiene practice indicators in a number of countries. Overall, poor hygiene practices, especially during childhood, appear to be related to a higher seroprevalence of *H. pylori*. Some of these practices include having no water closet or bathroom or no hot water supply in the house when the subject was a child, sharing cups as children, having mothers who did not use soap when they washed their hands, having mothers prechew the food for their young children, using chopsticks, not usually washing one's hands after going to the toilet, and living in a relatively small area with extremely limited sanitary facilities (e.g., submarine crews) (68, 75, 96–100).

Other hygiene practices during adulthood, such as sharing a toothbrush or cup and the type of toilet/bathroom facility, were not strongly related to *H. pylori* infection (68, 96).

Density/crowding. In all recent studies that have evaluated various density measures during both childhood and adulthood (68, 69, 75, 96, 97, 100–103), some measure of overcrowding, such as living in a crowded environment, sibship size, number of persons or children in the home, number of persons per room, crowding index, having to share a room or bed with a parent, or living in an overcrowded space in a submarine, was consistently related to *H. pylori* positivity. The positive association of *H. pylori* with high-density environments, especially during childhood, suggests that crowded household quarters may facilitate transmission of infection among siblings and other family members. This finding is consistent with the data on intrafamilial clustering of *H. pylori* (discussed in the Familial Exposures section of this review).

Social factors. In a variety of studies throughout the world, social factors have been independently associated with *H. pylori* status. The most commonly used measures were SES-based occupation (usually based on the Registrar General's *Classification of Occupations* (104) I–V that separated jobs into professional, managerial, skilled, semiskilled, and unskilled occupations), education, and income. Occupation-based SES was associated with *H. pylori* seroprevalence in studies in Ireland (64, 105) and South Wales (42) and in a United Kingdom study by Webb et al. (106) but not in a study by Mendall et al. (97). Income was related to *H. pylori* infection in Australia and Brazil (62, 107) and in Russia (in children but not adults) (108) but not in Taiwan (95). Low educational level was significantly related to a higher risk of *H. pylori* in several studies (43, 55, 56, 68, 99, 101, 109). Low SES, as defined differently by various investigators, also was associated with a higher seroprevalence of *H. pylori* in most studies in which it was evaluated (78, 103, 110).

Family history of gastric disease. Studies have also evaluated the relation between *H. pylori* infection and family history of gastric disease. In a recent study by Brenner et al. (111), the risk of being infected with *H. pylori* was significantly greater for adults with a parental history of stomach cancer than for those without such a history. The results for ulcer are somewhat inconsistent. Whereas the study in Germany by Brenner et al. (112) found a significantly elevated risk for children whose mothers, but not fathers, had ulcer disease, the study by Kikuchi et al. in Japan (69) reported a significantly elevated risk in public service workers whose fathers, but not mothers, had a history of ulcer disease. The study by Gasbarrini et al. in San Marino (67) found significantly elevated risks of *H. pylori* infection for subjects whose siblings, but not parents, had a history of ulcer disease.

POSSIBLE ROUTES OF TRANSMISSION

Person-to-person transmission

Institutionalized populations. Several studies have assessed the relation between *H. pylori* infection and institutionalized populations. The study by Lambert et al. (113)

of institutionalized young mentally and physically handicapped adults in Austria was one of the first to investigate the prevalence of *H. pylori* infection in institutionalized patients as a way to evaluate the possibility of person-to-person transmission. These authors found a much higher prevalence of *H. pylori* among residents in 1989 (75 percent) compared with age- and sex-matched controls (23 percent) and to stored serum taken from the same subjects in 1977 (34 percent). In 1977 but not in 1989, the prevalence of infection was related to length of stay. Fifty-one *H. pylori*-negative subjects in 1977 were positive in 1989, for an annual seroconversion rate of 7.4 percent, much higher than the rate of 0.2–1 percent common in most developed countries.

Significantly higher rates of *H. pylori* infection also were found in other institutionalized populations. In a study in England by Harris et al. (114), *H. pylori* seroprevalence was higher in adult residents of a hospital for people with severe learning difficulties (87 percent) than in controls from the local community (41 percent). However, there were no differences among the residents in *H. pylori* seroprevalence by age or duration of stay. Bohmer et al. (81) found a strong association between *H. pylori* positivity and length of institutionalization among adult inhabitants of two large institutes for the intellectually disabled in the Netherlands. Risks were elevated for subjects with IQs of less than 50 and for those who regurgitated their food, suggesting that these factors may increase the spread of *H. pylori* because of less than adequate sanitary practices among these residents. In a study of Japanese patients institutionalized with neurologic impairments, Kimura et al. (115) found *H. pylori* to be significantly more prevalent among institutionalized patients (81 percent) than among patients living at home (20 percent) or among healthy Japanese. The percentage positive was found to increase with both age and duration of institutionalization. In addition, 18 of 38 seronegative patients (47 percent) seroconverted after 1 year. For this population of patients, possible routes of transmission include salivary secretions or fecal-oral contamination. Among institutionalized schizophrenic patients in Belgium, the risk of *H. pylori* infection was elevated (OR = 3.0, 95 percent CI: 1.4, 7.3) compared with volunteer blood donor controls (116). Again, prevalence increased with length of stay in the institution.

Lewindon et al. (117) found that institutionalized children in Hong Kong with profound neurodevelopmental disabilities had significantly higher rates of *H. pylori* infection (55 percent) than age-matched controls did (8 percent). In a group of normal children in Russia, Malaty et al. (108) found the prevalence of *H. pylori* infection to be greater in children from orphanages and communal apartments (64 percent) than in children with families (40 percent). Although a common source of exposure cannot be ruled out in several of these studies, they do support the hypothesis that most *H. pylori* infection is transmitted from person to person.

Familial exposures. Most of the selected studies that looked at the relation between *H. pylori* infection and intrafamilial clustering of *H. pylori* did not use DNA fingerprinting to confirm that relatives had the same strain of *H.*

pylori. Studies in Austria and Canada (118, 119) noted an increased prevalence of *H. pylori* infection in family members of *H. pylori*-positive children compared with family members of *H. pylori*-negative children, age-matched control groups, or both. Excess risks were found for both parents and siblings of infected children, with no consistent differences apparent according to the gender of the parent. Similarly, a higher prevalence of *H. pylori* infection in children who lived in households with *H. pylori*-positive relatives was reported in studies conducted in the Colombian Andes, Italy, Germany, and China (51, 112, 120–122). The study of children in rural Colombia suggested that a major mode of transmission of *H. pylori* infection might be from older to younger siblings, especially in populations in which large families are common (120).

Several studies evaluated intraspousal transmission of *H. pylori* infection. In studies conducted among couples from the general population and among employees of a health insurance company and their partners, Singh et al. in India (123) and Brenner et al. in Germany (124), respectively, found a strong relation between the infection status of partners. In the Indian study, 60 percent of *H. pylori*-positive spouses had seroconverted at the 1-year follow-up (123). The German study reported an increase in risk with the amount of time that a spouse had lived with an infected partner (124). Georgopoulous et al. in Greece (125) and Parente et al. in Italy (126) found higher rates among spouses in *H. pylori*-positive than in *H. pylori*-negative patients, matched controls, or both. However, in the Italian study (126), rates of positivity differed substantially for spouses and controls (73 and 33 percent, respectively) aged 20–34 years but were the same for spouses and controls (75 percent and 74 percent, respectively) older than age 50 years. This finding is similar to the study by Ma et al. in an area of China in which the overall prevalence rate of *H. pylori* in adults was high (68 percent) and differed little by age; these authors found no significant difference in the seroprevalence of *H. pylori* in spouses of *H. pylori*-positive and *H. pylori*-negative subjects (51). Several studies performed DNA fingerprinting to determine the specific strains of *H. pylori* harbored by family members (125, 127–129). They found the same strain of *H. pylori* to be present in a small percentage of spouses and siblings (125, 127–129).

These studies, taken as a whole, lend support to the concept of intrafamilial clustering of *H. pylori* infection. They suggest that person-to-person transmission occurred in these families possibly because of close interpersonal contact, that family members shared a genetic predisposition to *H. pylori* infection, that family members were exposed to a common source of infection, or that spouses' childhood socioeconomic class was similar.

Oral-oral route. Many scientists have hypothesized that the oral-oral route of *H. pylori* transmission is the most likely, especially in developed countries. An elevated prevalence of *H. pylori* within families and institutionalized populations provides support for this route of transmission. However, it is not clear whether *H. pylori* is a constant or an intermittent inhabitant of the oral cavity (130, 131). Because numerous bacteria in the oral cavity show urease activity,

the specificity of urease-based tests may be too low to be useful in detecting oral *H. pylori* infection (132, 133). Polymerase chain reaction (PCR) is a very sensitive assay technique, but positive results cannot confirm the viability of the bacteria and whether it is able to transmit disease (133). Microbiologic culture of *H. pylori* is the recognized gold standard for diagnosis of infection (134). The most likely routes of oral infection include saliva, dental plaque, and refluxed gastric contents or vomit.

Recent studies by several investigators have detected *H. pylori* DNA in saliva in *H. pylori*-positive subjects by using PCR assays (135–140). Ferguson et al. (141), Pytko-Polonczyk et al. (133), and Parsonnet et al. (142) have successfully isolated *H. pylori* from saliva. However, several other researchers were not successful (138, 143–145). Evidence that *H. pylori* might be transmitted by saliva comes from a study by Megraud (98), who found a higher risk of *H. pylori* associated with pre-mastication of food to feed their infants by mothers in western Africa (OR = 2.9, 95 percent CI: 0.9, 9.0). In addition, a study by Chow et al. (99) reported that Chinese immigrants in Australia who used chopsticks to eat from communal dishes had a significantly higher prevalence of *H. pylori* infection (64.8 percent) than those who did not (42.3 percent). However, Leung et al. (135) were able to detect *H. pylori* DNA in both saliva and chopstick washings in only 1 of 15 subjects with *H. pylori* DNA in saliva and in only 1 of 45 subjects with *H. pylori* documented by the urea breath test, suggesting that this mode of transmission is probably not common. The low quantities of *H. pylori* detected in the saliva of *H. pylori*-infected subjects participating in a clinical study by Parsonnet et al. further suggest that oral-oral transmission through saliva is uncommon (142). A study by Luzzza et al. in rural Italy (146) found no evidence to suggest that *H. pylori* and Epstein-Barr virus (the etiologic agent of infectious mononucleosis, a common infection transmitted by the oral-oral route) share a common mode of transmission.

Several investigators have been successful in isolating *H. pylori* from the dental plaque of infected subjects, but the percentage positive has varied from 1 to 88 percent (132, 133, 145, 147, 148). Other investigators have not been able to culture *H. pylori* from dental plaque (149–151) or to detect its presence by using an indirect immunoperoxidase technique (152). The inability of some researchers to culture *H. pylori* could be due to the presence of too few organisms to detect or the presence of too many other types of bacteria in the mouth that inhibit the growth of *H. pylori* (131). Peach et al. (68), in a study of Australian adults selected from electoral rolls, found that positive *H. pylori* status was associated with a high plaque score (OR = 1.7, 95 percent CI: 1.1, 2.7) and with visiting the dentist less than once a year (OR = 4.4, 95 percent CI: 0.8, 23.0). Hardo et al. (149), in a study of dyspeptic patients in the United Kingdom, found no association between *H. pylori* infection and time between visits to the dentist, number of times per week that patients brushed their teeth, oral hygiene index, and periodontal status scale. In a study of patients with duodenal ulcer and of hospital employees with and without occupational exposure to *H. pylori*, Doré-Davin et al. (153) found

no correlation between *H. pylori* status as determined by PCR on saliva and dental plaque and status as determined by the urea breath test.

It has been suggested that *H. pylori* is transmitted gastro-orally by gastroesophageal reflux or regurgitation of stomach contents (131, 142, 145, 154, 155). Support for transmission of *H. pylori* via stomach contents comes from a recent clinical study by Parsonnet et al. (142) that cultured *H. pylori* (often in large numbers) from all 80 vomitus samples collected from 16 seropositive, asymptomatic subjects. *H. pylori* also was cultured from air sampled during vomiting for 38 percent of these subjects (142). Additional support for the gastro-oral route comes from a case report of possible transmission of *H. pylori* infection between adults by ingestion of vomit during mouth-to-mouth resuscitation (156) and from a study by Bohmer et al. (81) that found a higher prevalence of *H. pylori* among institutionalized, intellectually disabled adults who regurgitated their food (OR = 2.0, 95 percent CI: 1.1, 3.6).

Fecal-oral route. Another possible method of *H. pylori* transmission is the fecal-oral route. *H. pylori* DNA has been detected in feces of infected subjects by some researchers (138, 139, 157) but not others (158). Recently, Gramley et al. (157) found detectable *H. pylori* DNA in the feces of 73 percent of infected subjects. Isolation of *H. pylori* by fecal culture has been performed by a number of investigators from around the world (138, 159, 160). However, isolation of *H. pylori* from feces has been problematic for some researchers, especially for those unable to obtain fresh feces. Delay in processing could have resulted in the small number of *H. pylori* organisms present being overgrown by other fecal bacteria. Recently, Parsonnet et al. were able to culture *H. pylori* from cathartic-induced diarrheal stools in 7 of 14 *H. pylori*-infected subjects but not from normal stools (142). Studies by Hazell et al. in China (161) and Webb et al. in the United Kingdom (162) noted serum antibodies to *H. pylori* and hepatitis A, a sensitive marker of fecal-oral exposure, but did not find strong evidence supporting community-wide fecal-oral spread of *H. pylori* via food or water.

Waterborne transmission

It has been demonstrated that *H. pylori* can live for several days in milk and tap water in its infectious bacillary form (163, 164) and in river water for several months in a coccoid form (165). However, the idea of coccoid forms is very controversial. While experimental tests have shown that, under physical or chemical stress, *H. pylori* is able to convert to a viable but nonculturable coccoid form (166), researchers have failed to convert a coccoid to a bacillary form in culture (167). In addition, it has not yet been determined whether *H. pylori* can revert from its coccoid to its infectious form in humans (168). Support for waterborne transmission comes from epidemiologic studies conducted in Colombia, rural China, and Lima, Peru, that found that water source may be related to risk of *H. pylori* infection (52, 75, 94). The finding of *H. pylori*-positive drinking and sewage water samples by PCR assays in Peru and Japan (161, 169, 170) provides additional evidence that waterborne transmission may be impor-

tant, especially in areas of the world that have high rates of *H. pylori* infection and less than adequate water quality. The possible role of waterborne transmission of *H. pylori* is further supported by a study by Baker and Hegarty in Pennsylvania. (K. H. Baker and J. P. Hegarty, Environmental Engineering Program, Environmental Microbiology Research Laboratory, Pennsylvania State University Harrisburg, unpublished manuscript). They reported a strong association ($p < 0.02$) between consumption of well water contaminated by *H. pylori* and *H. pylori* infection in those persons consuming the water. In addition, an analysis of surface water and groundwater samples in Pennsylvania and Ohio, in which a microscopic technique that detected actively respiring microorganisms bound to monoclonal anti-*H. pylori* antibody was used, found 61 percent of the samples to be contaminated with *H. pylori* (171).

Zoonotic or vectorborne transmission

Although the principal reservoir for *H. pylori* infection appears to be people, *H. pylori* has been isolated from non-human primates and domestic cats (9, 172, 173). Under controlled laboratory conditions, human *H. pylori* has been shown to infect monkeys (172). However, even if *H. pylori* occurs naturally in monkeys, they are unlikely to represent a major route of transmission to humans, since close contact between nonhuman primates and humans is limited in most of the world (172).

Handt et al. were the first to report isolation of *H. pylori* from domestic cats (173, 174). Their laboratory was able to experimentally infect naive cats with *H. pylori* (175), to culture *H. pylori* from feline salivary and gastric sections, and to find *H. pylori* DNA in feline feces and dental plaque (176). These studies raised the possibility that *H. pylori* could be transmitted from cats to humans via saliva, vomit, or feces. Recently, El-Zaatari et al. found no evidence of *H. pylori* infection when they examined 25 stray cats (177). Instead, they reported that *H. helmanni* was the organism responsible for the chronic gastritis in these cats. The epidemiologic evidence is also inconsistent. A study in Germany by Rothenbacher et al. (101) found that adults who owned a cat as a child had a significantly higher prevalence of *H. pylori* infection. Other studies, however, found no association with having a cat or other pet during either childhood or adulthood (80, 101, 102, 106, 146, 178), and two studies in the United States found pet owners to have significantly lower rates of *H. pylori* infection (57, 179). Although it is possible that lower rates among pet owners may be due to confounding by social class, one large population-based study in Canada (180) that adjusted for social class found no association between pet ownership and a history of peptic ulcer disease. These results suggest that *H. pylori* infection is probably uncommon in cats and should not be a public health problem for cat owners.

Gnotobiotic pigs have been successfully infected with *H. pylori*. However, there is currently no convincing evidence that swine are a reservoir for *H. pylori*, even though the monogastric pig stomach is anatomically and physiologically similar to human and nonhuman primate stomachs (172).

Exposure to sheep was implicated in two recent epidemiologic studies. In a study of children from the Colombian Andes, Goodman et al. (75) reported that children who "played with sheep" had a higher risk of *H. pylori* infection (OR = 4.5). A study by Dore et al. (181) revealed that the prevalence of *H. pylori* was significantly higher among Sardinian shepherds occupationally exposed to sheep than among their nonexposed family members or among Sardinian blood donors. In addition, in Sardinia, 32 of 32 sheep were seropositive for *H. pylori*, *H. pylori* DNA was detected in the mucosal strips from the stomachs of 3 of 10 sheep or lambs, and *H. pylori* DNA was present in raw sheep milk (181, 182). In light of the interesting findings regarding sheep, further investigation of exposure to other domestic animals is warranted.

The most recent reservoir suggested for *H. pylori* transmission is the housefly. In controlled experimental studies, Grubel et al. found that houseflies infected with *H. pylori* in the laboratory could harbor viable *H. pylori* bacteria in their intestines as well as on their body hairs (183). In further investigations, these researchers captured wild flies from rural, agricultural, and metropolitan areas of the United States, Japan, Poland, and Egypt (79) and found high levels of *H. pylori*-contaminated flies in Egypt (33 percent) and Poland (57 percent), areas in which there is a high seroprevalence of *H. pylori* in children. However, the investigators also uncovered high levels in California (38 percent), where seroprevalence of *H. pylori* is not very high. The possibility that flies could transmit *H. pylori* from contaminated feces to food or mucosal surfaces is indirectly supported by a number of epidemiologic studies in which subjects without indoor bathroom facilities, especially during childhood, had a higher seroprevalence of *H. pylori* than did subjects with indoor facilities (75, 96, 106, 146). However, evidence is lacking that *H. pylori* can be isolated from flies that have been in contact with *H. pylori*-infected feces and that *H. pylori* can be transmitted from contaminated flies to food in a quantity sufficient to infect humans (184). In a recent experimental study by Osato et al. (185), researchers were unable to recover *H. pylori* from houseflies that were fed human feces infected with *H. pylori*. Therefore, it seems less likely that the domestic housefly serves as a vector for *H. pylori* transmission.

Iatrogenic transmission

Endoscopy is a common medical procedure used to diagnose and manage gastrointestinal disease. Because of the complex structure of the endoscope and difficulty in disinfecting it, the possibility of iatrogenic infection in patients following endoscopy is a potential risk factor not only for *H. pylori* but also for other infectious diseases such as hepatitis B, hepatitis C, tuberculosis, and possibly human immunodeficiency virus (186, 187). In fact, nosocomial transmission of *H. pylori* is the only proven mode of transmission (187). According to Tytgat, the rate of iatrogenic infection may approximate four per 1,000 endoscopies (0.4 percent) when the prevalence of *H. pylori* in the endoscoped population is around 60 percent (188). Tytgat suggests that

this rate may reach 1 percent in areas of the world in which improper disinfection techniques are used. The retrospective study by Langenberg et al. in the Netherlands found a rate of 1.1 percent for *H. pylori*-negative patients to develop iatrogenic infection from endoscopy when alcohol instead of glutaraldehyde was used as the disinfectant (189).

Even before the "discovery" of *H. pylori*, Ramsey et al. (190) reported that 17 of 37 (45.9 percent) subjects participating in studies of gastric acid secretion became hypochlorhydric (a condition that occurs during the acute phase of *H. pylori* infection (191)) following gastric biopsy. Iatrogenic infection is also responsible for postendoscopic acute gastric mucosal lesions (subacute *H. pylori* infection) found in Japan that often follow endoscopy as a result of ineffective disinfection methods (155, 189, 191, 192). Proper cleaning requires use of a detergent and brush (and often an enzymatic cleaner) to remove blood, mucous, and tissue from the endoscope channels prior to disinfection (186, 188). In 1990, the working party report to the World Congresses of Gastroenterology recommended that the endoscope be soaked in 2 percent activated glutaraldehyde for at least 5–10 minutes, 10 minutes being sufficient to prepare the instrument for use in any patient about to undergo endoscopy (193).

Rohr et al. investigated the prevalence of *H. pylori* in patients attending hospitals in San Paulo, Brazil (most of which did not follow Centers for Disease Control and Prevention endoscopy cleaning guidelines) (194). They found that *H. pylori*-positive patients had had a greater number of prior endoscopies compared with *H. pylori*-negative patients, although the differences were not statistically significant. Fantry et al., in a study in Baltimore, Maryland, found that endoscopes were frequently contaminated (61 percent of the time) with *H. pylori* following procedures on *H. pylori*-infected patients but that risk of infection was minimal if proper disinfection methods that included soaking in glutaraldehyde were used (187). These results were confirmed by Cronmiller et al. in a controlled study in Rochester, New York, that investigated factors that affect the reprocessing of *H. pylori*-contaminated endoscopes (195). A study of disinfection procedures for endoscopes in 20 Japanese hospitals found that *H. pylori* infection following endoscopy was due to inadequate disinfection procedures rather than to any resistance of *H. pylori* to disinfectants (196). Studies in Japan and Taiwan further suggest that mechanical washing of the endoscope is superior to manual washing in preventing iatrogenic spread of *H. pylori*, especially when recommended disinfection procedures may not be followed routinely (155, 197). Furthermore, because biopsy forceps typically penetrate the gastric mucosa and are difficult to clean, sterilization of the forceps or, preferably, use of disposable forceps is essential (188).

SUMMARY AND CONCLUSIONS

H. pylori is a common bacterium, and approximately 50 percent of the world's population has been estimated to be infected (198). Humans are the principal reservoir. The prevalence of *H. pylori* infection varies widely by geographic area, age, race, ethnicity, and SES. Rates appear to

be higher in developing than in developed countries, with most of the infections occurring during childhood, and they seem to be decreasing with improvements in hygiene practices. *H. pylori* causes chronic gastritis and has been associated with several serious diseases of the gastrointestinal tract, including duodenal ulcer and gastric cancer. Since its "discovery" in 1982 by Warren and Marshall (1), *H. pylori* has been the topic of extensive research.

A number of studies have used questionnaire components to investigate factors possibly related to the etiology of *H. pylori* infection. The majority of recent studies have not found tobacco use or alcohol consumption to be risk factors for *H. pylori* infection. Adequate nutritional status, especially frequent consumption of fruits and vegetables and of vitamin C, appears to protect against infection with *H. pylori*. In contrast, food prepared under less than ideal conditions or exposed to contaminated water or soil may increase the risk. Overall, inadequate sanitation practices, low social class, and crowded or high-density living conditions seem to be related to a higher prevalence of *H. pylori* infection. This finding suggests that poor hygiene and crowded conditions may facilitate transmission of infection among family members and is consistent with data on intrafamilial and institutional clustering of *H. pylori* infection.

Understanding the route of *H. pylori* transmission is important if public health measures to prevent its spread are to be implemented. Iatrogenic transmission of *H. pylori* following endoscopy is the only proven mode. For the general population, the most likely mode of transmission is from person to person, by either the oral-oral route (through vomitus or possibly saliva) or perhaps the fecal-oral route. The person-to-person mode of transmission is supported by the higher incidence of infection among institutionalized children and adults and the clustering of *H. pylori* infection within families. Also lending support to this concept is the detection of *H. pylori* DNA in vomitus, saliva, dental plaque, gastric juice, and feces. Waterborne transmission, probably due to fecal contamination, may be an important source of infection, especially in parts of the world in which untreated water is common. Recent studies in the United States have linked clinical *H. pylori* infection with consumption of *H. pylori*-contaminated well water. This area of research is worthy of further investigation. Although *H. pylori* has been isolated in domestic cats, additional research has suggested that *H. pylori* is probably uncommon in domestic cats and thus is probably not a major concern for cat owners. Several studies have suggested sheep as a possible source of *H. pylori* transmission, a hypothesis that deserves additional investigation. The most recent reservoir suggested for *H. pylori* transmission is the housefly. However, evidence is lacking that *H. pylori* can be transmitted to humans from flies that have been in contact with *H. pylori*-infected feces. Nevertheless, the hypothesis is appealing since flies are known to carry many other infectious diseases. Knowledge of the epidemiology and mode of transmission of *H. pylori* is important to prevent its spread and may be useful in identifying high-risk populations, especially in areas that have high rates of gastric lymphoma, gastric cancer, and gastric ulcer.

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