Implications of *Helicobacter pylori* infection for stomach cancer prevention

Implicações da infecção por *Helicobacter pylori* na prevenção do câncer de estômago

Karen J. Goodman

School of Public Health, University of Texas Health Science Center. P. O. Box 20816, Houston, TX 77225, USA.

Abstract *Accumulating evidence has implicated* Helicobacter pylori*, an established cause of chronic gastritis and peptic ulcer, in the etiology of gastric cancer. Control of this infection would reduce the occurrence of chronic gastritis and peptic ulcer and might substantially lower the risk of stomach cancer as well. The public health impact of this infectious agent warrants efforts to identify preventive measures. This paper reviews the evidence linking* H. pylori *infection to gastric cancer and evaluates the potential for control in high-risk populations. Current obstacles to* H. pylori *control are discussed, including the link to poor socioeconomic conditions, difficulty in identifying incident cases, lack of natural immunity to reinfection, limited effectiveness of antibiotic therapy in high-prevalence populations, and incomplete knowledge regarding the reservoir of infection, mode of transmission, host susceptibility factors, and the potential for developing an effective vaccine. Worthwhile avenues of research include studies designed to identify modifiable risk factors for acquisition of the infection, modifiable host factors that may increase resistance to chronic infection, more effective antibiotic therapies, and effective vaccines.*
Key words Helicobacter pylori*; Prevention; Stomach; Cancer; Epidemiology*

Resumo *Um acúmulo de evidências aponta para* Helicobacter pylori*, uma causa comprovada de gastrite e úlcera péptica, na etiologia do câncer gástrico. O controle dessa infecção poderia reduzir a ocorrência de gastrite crônica e úlcera péptica, além de diminuir o risco de câncer de estômago. O impacto desse agente infeccioso em nível de saúde pública justifica os esforços no sentido de identificar medidas preventivas. Este artigo revê as evidências ligando o* H. pylori *ao câncer de estômago e avalia o potencial para controle em populações de alto risco. A autora discute os obstáculos atuais ao controle do* H. pylori*, inclusive sua associação com condições suir o risco de câncer de estômago. O impacto desse agente infecciodentes, a falta de imunidade natural à reinfecção, a eficácia limitada da antibioticoterapia em populações com alta prevalência e o conhecimento incompleto sobre o reservatão com condições suir o risco de câncer de estômago. O impacto desse agente infecciopedeiro e possibilidade de desenvolver uma vacina eficaz. Linhas de pesquisa prioritárias incluem estudos projetados para identificar fatores de risco modificáveis para a aquisição da infecção, fatores modificáveis no hospedeiro que possam aumentar a resistência à infecção, antibioticoterapias e vacinas mais eficazes.*
Palavras-chave Helicobacter pylori*; Prevenção; Câncer; Estômago; Epidemiologia*

Accumulating evidence has implicated *Helicobacter pylori*, now an established cause of chronic gastritis and peptic ulcer (Marshall, 1986; Korman & Tytgat, 1995), in the etiology of gastric cancer (Forman, 1995; Parsonnet, 1993; Parsonnet et al., 1994). Successful control of this chronic infection would reduce the occurrence of gastritis and peptic ulcer and might substantially lower the risk of one of the world's deadliest neoplasms. The public health impact of this infectious agent justifies efforts to identify and implement preventive measures. Currently, however, limited knowledge regarding the natural history of *H. pylori* infection in asymptomatic carriers, susceptibility factors, and the precise mode of transmission present obstacles to prevention (Goodman & Correa, 1995). Furthermore, it is unclear how to treat this infection in patients from populations of low socioeconomic status who are most at risk of gastric cancer; eradication trials conducted in such populations have encountered limited success, and the risk of reinfection appears high. This paper reviews the evidence linking *H. pylori* infection to cancer of the stomach and evaluates the potential for control in high-risk populations.

Background

H. pylori is a helical or curved bacillus that colonizes the gastric mucosa. It transforms to a nonculturable coccoid form under adverse environmental conditions, notably in the presence of antibiotics (Bode et al., 1992). Detection of *H. pylori* has been problematic; special microbiological techniques are required for successful growth from gastric biopsy specimens (Goodwin & Worsley, 1993). Attempts to isolate *H. pylori* from bodily secretions or environmental sources have been unsuccessful in general. This problematic detection has presented obstacles to pinpointing portals of entry and exit as well as implicating or ruling out environmental reservoirs. Innovations in laboratory procedures have been gradually improving the sensitivity of detection techniques.

Serology has been the most extensively used diagnostic procedure for examining the distribution of *H. pylori* infection in humans. The presence of *H. pylori* antibodies indicates current infection with reasonable accuracy, except in individuals recently cleared of the infection, due to the persistence of elevated antibody levels for some months after clearance (Kosunen et al., 1992; Veenendaal et al., 1991). Infants born to *H. pylori*-infected mothers appear to have passively acquired *H. pylori* IgG antibodies that disappear within the first months of life (Blecker et al., 1994). The urea breath test, a noninvasive procedure based on *H. pylori* urease activity, has been developed in two versions, using either 13C-labeled (Graham et al., 1987; Graham & Klein, 1991) or 14C-labeled (Marshall & Surveyor, 1988; Surveyor et al., 1989) urea as an alternative to serology; the breath tests detect active infection exclusively and can be used for short-term follow-up of anti-*H. pylori* therapy. In validation studies the urea breath tests yield an accuracy that is comparable to the gold standard biopsy-based microbiological and histological diagnoses (Vandenplas et al., 1992; Logan et al., 1991; Dill et al., 1990; Raju et al., 1994; Marshall et al., 1991; Veldhuyzen van Zanten et al., 1990). Little validation of the urea breath tests has been conducted in Latin American populations; Coelho and colleagues (1990) reported a sensitivity of 97 percent and a specificity of 100 percent for the 14C-urea breath test validated against culture in 41 gastroscopy patients in Brazil. The radioactive exposure of the 14C-urea breath test, although minimal, makes this test inappropriate for studies involving children, pregnant women, or follow-up screening at frequent intervals, whereas the higher cost of the 13C-urea breath test limits its usefulness in population-based research. Serum pepsinogens have been proposed as markers of response to anti-*H. pylori* therapy (Hunter et al., 1993).

The prevalence of *H. pylori* infection ranges from 20% to over 90% in adult populations around the world (Pounder & Ng, 1995). The prevalence is highest in developing regions, including the countries of Latin America (Table 1). A birth cohort effect noted in several developed countries, where the prevalence is relatively low in children and young adults but commonly exceeds 50% in adults over 50 years of age (Pounder & Ng, 1995), has prompted speculation that transmission has decreased as sanitation has improved (Banatvala et al., 1993; Asaka et al., 1992; Gasbarrini et al., 1994). Within countries, *H. pylori* infection is linked to low socioeconomic status, residential overcrowding and migration from high prevalence regions (Eurogast Study Group, 1993; Smoak et al., 1994; Blecker & Vandenplas, 1993; Malaty et al., 1992; Sitas et al., 1991; Graham et al., 1991; Fiedorek et al., 1991).

Several lines of evidence suggest that individuals become infected with *H. pylori* primarily during childhood (Goodman & Correa, 1995). It is commonly believed that the infection persists indefinitely, spontaneous elimination oc-

Table 1

Prevalence of *Helicobacter pylori* in Latin American populations.

Population (Reference)		**Age**	**n**	**% HP+***
BRAZIL				
Belo Horizonte	abattoir workers	18 – 64	160	66
(Rocha et al., 1992)	blood donors	18 – 64	160	62
(Oliveira et al., 1994)	low SES,† laboratory outpatients‡	3 – 8	104	34
		9 – 14	64	47
		15 – 18	14	64
CHILE**				
Santiago & Punta Arenas	high SES, household cluster sample	5 – 9	216	30
(Hopkins et al., 1993)		10 – 14	86	35
		15 – 19	69	58
		20 – 34	295	62
	low SES, household cluster sample	5 – 9	118	45
		10 – 14	69	55
		15 – 19	57	62
		20 – 34	121	69
Iquique	middle class vaccine trial volunteers	1 – 5	229	23
(Russell et al., 1993)		6 – 8	47	45
		10 – 16	112	70
COLOMBIA, ANDEAN REGION††				
Aldana	rural, low SES census sample	2 – 9	685	69
(Goodman et al., in press)				
Ipiales‡‡	health professionals' children	2 – 9	57	54
COSTA RICA				
Turrubares & Hojancha	rural low SES schools, census sample	7 – 10	97	60
(Sierra et al., 1992)		11 – 13	106	73
		14 – 20	76	75
EL SALVADOR				
refugees in Australia	routine entry examinations	20 – 59	63	41
(Dwyer et al., 1988)				
PERU				
Lima††	high SES community volunteers	2 – 12	141	32
(Klein et al., 1991)	low SES health post patients	2 – 12	266	56

* *H. pylori* prevalence, determined by serology except as noted
† socioeconomic status
‡ excludes immunocompromised patients or those having taken antimicrobial drugs in the three preceding months
** prevalence approximated from graph
†† *H. pylori* status determined by 13C-urea breath test
‡‡ city on the Colombia-Ecuador border, author's unpublished data

curring rarely. However, this impression is based primarily on follow-up of prevalent cases, that is, cases with unknown time of onset. Follow-up of newly occurring cases has been extremely limited (Parsonnet, 1995); therefore, the proportion of acute infections that become chronic is not known. Recent longitudinal observation of Peruvian infants suggests that spontaneous elimination of *H. pylori* infection may not be uncommon in young children (Klein et al., 1994).

Helicobacter pylori and gastric cancer

According to Correa's (1995) model of gastric carcinogenesis, continuous exposure to irritants of the gastric mucosa produces repeated episodes of superficial gastritis; when this occurs in concert with specific nutritional deficits, a degenerative sequential process yields atrophic gastritis, intestinal metaplasia, dysplasia and, ultimately, carcinoma. Although the

precise role of *H. pylori* in this sequence is not understood, the organism fits into the model as an irritant that causes chronic inflammation of the gastric mucosa (Correa, 1991).

Correa's model of gastric carcinogenesis evolved largely from longitudinal observations of a community-based cohort recruited between 1973 and 1983 from three small towns in the Andean region of Nariño in southern Colombia (Correa et al., 1990b, a). In previous studies, natives of this region displayed the highest stomach cancer rates in Colombia (Correa et al., 1970). The Nariño cohort revealed an extremely high prevalence of chronic gastritis and more advanced degenerative lesions as well as a high incidence of progression of these lesions and of gastric carcinoma itself. The prevalence of *H. pylori* infection in a random sample of this cohort was over 90 percent (Correa et al., 1989).

While the evidence establishing *H. pylori* as a cause of chronic gastritis accumulated, investigators began to study the occurrence of this infection in association with cancer of the stomach. Ecological studies contrasting regions of high and low gastric cancer risk conducted in Colombia and China revealed correlations between gastric cancer rates and *H. pylori* seroprevalence, as did a 13-country comparison (IARC, 1994). Similar studies conducted in Costa Rica, Italy, and Japan did not reveal such associations, the observed range of *H. pylori* seroprevalence being quite narrow in each of these countries (IARC, 1994). The observation of distinct gastric cancer rates in populations of similar *H. pylori* prevalence does not constitute evidence against a role for *H. pylori* in the etiology of cancer of the stomach, but rather, suggests that *H. pylori* itself is not a sufficient cause of this cancer; the contrasting gastric cancer rates in these populations could reflect different distributions of cofactors that interact with *H. pylori* in the carcinogenic process.

Case-control studies conducted in nine countries comparing *H. pylori* seroprevalence status in gastric cancer patients to controls matched on age and sex, show inconsistencies but overall suggest a positive association (IARC, 1994). It has been argued that this design results in an underestimate of the relative risk, however, because *H. pylori* colonization tends to diminish with increasing degeneration of the gastric mucosa and antibodies titers decline following clearance of the infection (Forman, 1995). Gastric cancer cases would have increasingly less normal mucosa relative to controls and would be more likely to lose their infection over time. To address this problem, nested case-control studies determining *H. pylori* status from stored sera collected prior to cancer diagnosis were conducted in England and Wales (odds ratio (OR)=2.8, 95% confidence interval (CI)=1.0-8.0) (Forman et al., 1991), California (OR=3.6, CI=1.8-7.3) (Parsonnet et al., 1991), and Hawaii (OR=6.0, CI=2.1-17.0) (Nomura et al., 1991). In order to assess the potential misclassification of infection status in cancer cases when the follow-up is brief, Forman and colleagues (1994) pooled the data from these three studies and stratified the observations by time interval between collection of serum and cancer diagnosis, observing a monotonic increase in the odds ratio (2.3 for 5-9 years; 4.4 for 10-14 years; 8.7 for >14 years) as the follow-up interval lengthens.

Particularly strong and consistent evidence has linked *H. pylori* infection to gastric lymphoma, a relatively rare form of stomach cancer. A high *H. pylori* prevalence has been observed in cases of gastric lymphoma (Forman, 1995). A nested case-control study using two large cohorts in the U.S. and Norway matched 33 gastric lymphoma cases, primarily of the diffuse large-cell type, to each of four controls on cohort, date of birth, sex, and date and site of serum collection, observing a relative risk of 6.3 (CI=2.0-19.9) for *H. pylori* seropositivity and subsequent development of gastric non-Hodgkin's lymphoma, while nongastric non-Hodgkin's lymphoma did not appear related to previous *H. pylori* infection (Parsonnet et al., 1994). The median interval between serum collection and cancer diagnosis was 14 years and the relative risk increased to 12.3 (CI=1.5-103.9) among those whose serum had been collected 14 years or more prior to diagnosis. The strongest suggestion that *H. pylori* causes gastric lymphoma comes from the follow-up of several series of *H. pylori*-infected patients with primary low-grade gastric lymphoma of the mucosa-associated lymphoid tissue type after anti-*H. pylori* therapy; tumor regression occurred in most patients whose infection was successfully eradicated (Wotherspoon et al., 1993; Roggero et al., 1995; Bayerdorffer et al., 1995).

Based on the above evidence, a Working Group on the Evaluation of Carcinogenic Risks to Humans convened by the International Agency for Research on Cancer in June 1994 concluded that infection with *Helicobacter pylori* is carcinogenic to humans (IARC, 1994). It must be noted, however, that no published study to date has produced estimates of the effect of *H. pylori* infection on the subsequent in-

cidence of gastric cancer adjusted for known dietary risk factors including high intake of salt and nitrates and deficient intake of vitamin C and beta-carotene (Correa, 1991). There is reason to suspect that these dietary factors, being more common among populations of low socioeconomic status, may confound observed associations between *H. pylori* infection and gastric cancer, given the clear link between the infection and low socioeconomic status.

Perspectives for control

Little progress has been made towards identifying preventive measures for *H. pylori* infection, primarily due to obstacles presented by the natural history of this infection, its epidemiology, resistance to eradication, and limitations of our current state of knowledge.

Obstacles to *H. pylori* Control

- **Natural history**

H. pylori infection is frequently asymptomatic and when symptoms do occur these represent nonspecific forms of stomach discomfort (Rauws & Tytgat, 1989); incident cases, therefore, are not generally detected at the time of onset. Given that antibody levels decline following clearance of infection (Kuipers et al., 1993), natural immunity does not appear to provide lasting protection against reinfection. Coinfection with multiple strains is not uncommon (Costas et al., 1991), suggesting the possibility of continual reinfection.

- **Epidemiology**

H. pylori occurs commonly throughout the world, implying a vast reservoir of infection. Given that the infection is linked to poor socioeconomic conditions, control may require broad socioeconomic changes.

- **Eradication of infection**

Due to the protection afforded to *H. pylori* by its ecological niche under the mucus layer of the gastric mucosa, effective antibiotic treatment requires costly and burdensome multidrug regimens that have shown limited effectiveness in populations where the infection is most prevalent (Buiatti et al., 1994; Glupczynski & Burette, 1990). Factors that may contribute to this reduced effectiveness include high bacterial loads in individuals from such populations due to continual exposure to the agent, the high prevalence of drug resistant strains, and lifestyle factors including deficient diet, limited education, economic constraints, and alcoholism that do not favor compliance and/or drug tolerance. Furthermore, even when treatment is successful in high prevalence populations, the risk of reinfection appears high. Although few follow-up studies have been conducted in developing countries, Brazilian investigators observed the reinfection rate in the first year after standard triple therapy among 269 patients who had been successfully cleared of *H. pylori* infection as confirmed by negative urea breath tests at a median time of 83 days following treatment (Coelho et al., 1995). The proportion of patients who became reinfected by approximately one year after treatment was 31 percent among 223 participants of low socioeconomic status in contrast to nine percent among 46 participants of high socioeconomic status. The reinfection rate among Brazilians of high socioeconomic status approximates rates observed in developed countries; reported reinfection rates following confirmed eradication in adults from the U.S., Australia, Finland, Austria, Belgium, France and the UK range from 0-5 percent per year (Parsonnet, 1995). Aside from socioeconomic status, another risk factor for reinfection detected in the Brazilian study was receiving endoscopy at the initial post-treatment follow-up visit. This finding is consistent with previous reports implicating gastroscopes disinfected by manual washing as potential vehicles of *H. pylori* transmission (Goodman & Correa, 1995).

- **Limitations in knowledge**

Currently it is not known if a reservoir exists outside of humans and the precise mode of transmission has not been identified. Modifiable risk factors for infection have not been clearly identified, with the exception of clinical procedures that transfer gastric secretions from one patient to another. Furthermore, vaccine research is at a preliminary stage. The knowledge required for proposing preventive measures, aside from precautions against iatrogenic transmission, is lacking.

Current state of knowledge relevant to prevention

- **Transmission of *H. Pylori***

Table 2 summarizes the evidence supporting hypothesized modes of transmission, while Table 3 presents factors that have been associ-

Table 2

Evidence for *Helicobacter pylori* transmission pathways*.

Person-to-person transmission
clustering in families and groups residences
association with residential crowding
childhood acquisition suggests transmission related to personal hygiene
isolation from human feces and dental plaque (though most attempts unsuccessful)
detection in human feces, saliva, and dental plaque by polymerase chain reaction
Waterborne transmission
survival in laboratory aquatic environments
detection by polymerase chain reaction in water samples from Colombia† and Peru‡
association with drinking water source in Andean countries**
association with raw vegetable consumption in Andean countries**
association with swimming in rivers and swimming pools in Colombia**
Zoonotic transmission
successful experimental infection of monkeys, mice, cats, germ-free pigs, germ-free dogs
observation of natural infection in research monkeys and cats
observation of human infection by animal *Helicobacter* species
Iatrogenic transmission
outbreaks of acute gastritis among gastroscopy patients and research subjects exposed to gastric pH electrodes
detection of viable *H. pylori* in manually disinfected gastrofiberscopes

* referenced in (Goodman & Correa, 1995) except as noted
† (Schauer et al., 1995)
‡ (Hulten et al., 1995)
** see also (Goodman et al., 1996)

ated with *H. pylori* infection in Latin American studies. At present there is no evidence of sexual transmission or of foodborne transmission, other than by means of raw vegetables contaminated by unpurified water (Goodman & Correa, 1995). It is of interest to note that the evidence supporting waterborne transmission has come primarily from Andean countries of South America. Contrary evidence was observed in southern China where *H. pylori* prevalence was not associated with drinking water source (Mitchell et al., 1992). It is possible that different hygienic practices regarding drinking water and/or climatic differences relevant to the survival of *H. pylori* in water account for this discrepancy.

Acute outbreaks of *H. pylori*-induced gastritis in clinical settings have been attributed to endoscopic procedures and exposure of research subjects to gastric pH electrodes (Goodman & Correa, 1995). *H. pylori* DNA has been detected in gastrointestinal equipment disinfected according to standard procedures (Katoh et al., 1993; Roosendaal et al., 1993). Viable *H. pylori* was recovered by bacterial culture from 19% of wash-out samples from the gastrofiberscope biopsy-suction channel after manual Hyamine washing; however, no *H. pylori* was recovered after mechanical washing (Katoh et al., 1993). These observations along with the previously cited evidence that endoscopy may increase the risk of reinfection in patients undergoing anti-*H. pylori* therapy points to the urgency of adopting stringent precautions aimed at preventing infection in the clinical setting.

- **Cofactors for infection**

A small number of studies have attempted to identify cofactors linked to *H. pylori* infection that are not indicators of specific transmission pathways, but may reflect host susceptibility. Very few studies have examined cofactors associated with the risk of acquiring infection. In a cohort of U.S. epidemiologists, frequent consumption of caffeinated beverages was linked to an increased risk of seroconversion, while frequent consumption of milk appeared protective (Parsonnet et al., 1992). In a follow-up study of Peruvian infants, males were more likely than females to become infected and to remain infected (Klein et al., 1994). Most studies linking potential cofactors to *H. pylori* infection have been cross-sectional. For exposures that change over time, it may not be clear whether cross-sectionally identified covariates are causes or consequences of infection. Furthermore, if spontaneous elimination of *H. pylori* occurs to an important degree, it cannot be determined whether such covariates influence the acquisition of the infection or its chronicity. Indicators of deficient nutritional status have been linked to increased *H. pylori* prevalence in both developed and developing countries (Goodman et al., 1996; Klein et al., 1991; Raymond et al., 1994; Patel et al., 1994; Mendall et al., 1994; Eurogast Study Group, 1993), although the importance of specific indicators varies across studies. A study of 249 children, 0-18 years of age, sampled from an outpatient clinic serving patients of low socioeconomic status in Belo Horizonte, Brazil reported no statistically significant associations between *H. pylori* serostatus and nutritional status (Oliveira et al., 1994), although it must be noted that the study sample was not

Table 3

Factors associated with *Helicobacter pylori* infection in Latin American populations.

Population	Outcome measure	Associated factor
BRAZIL, Belo Horizonte		
249 outpatients, 0 – 18 years old (Oliveira et al., 1994)	seroprevalence	age
269 duodenal ulcer patients after successful anti-*H. pylori* therapy,* 18 – 79 years old (Coelho et al., 1995)	reinfection rate by 14C-UBT†	low socioeconomic status gastroscopy at the first postreatment visit
CHILE, Santiago & Punta Arenas‡	seroprevalence	age
1,815 community members, household cluster sample, 0 – 34 years old (Hopkins et al., 1993)		male sex low socioeconomic status consumes uncooked vegetables resides in Santiago v. Punta Arenas consumes uncooked shellfish
COLOMBIA, Aldana‡	prevalence	age
684 rural residents, census sample, 2 – 9 years old (Goodman et al., 1996)	by 13C-UBT†	male sex more than 1 child resides in home consumes <2 fruits/vegetable servings/day consumes <2 cups of milk/day low height/age nonagricultural parental occupation mother not gainfully employed home has no toilet/latrine drinking water obtained from river swims in river/swimming pool cares for or plays with sheep recent history of amebiasis (protective)
COLOMBIA, Ipiales (border city)‡	prevalence	age
69 children of health professionals census sample, 2 – 12 years old (author's unpublished data)	by 13C-UBT†	infrequent consumption of fruits and vegetables household has pet(s) (protective) recent history of parasitic infection (protective)
PERU, peri-urban Lima	incidence	male sex
56 infants, 6 – 30 months old (Klein et al., 1994)	by 13C-UBT†	
PERU, Lima‡		
407 community members, 0 – 12 years old (Klein et al., 1991)	prevalence by 13C-UBT†	age low socioeconomic status municipal v. well drinking water source external v. internal drinking water source low height/age low weight/height

* five day treatment with amoxicillin, furazolidone, and metronidazole followed by a negative 14C-urea breath test at a median of 83 days following treatment
† multivariate analysis including all factors listed
‡ urea breath test

population-based and reflected a high degree of homogeneity on relevant exposures. In a large study conducted in Southern China, frequent use of antibiotics was linked to decreased *H. pylori* seroprevalence (Mitchell et al., 1992).

- **Vaccine prospects**

The mouse has been established as an animal model that can be infected with *H. pylori* for the purpose of vaccine research; recently, oral immunization with purified *H. pylori* antigens has been reported to protect mice against *H. pylori* infection (Marchetti et al., 1995). Previous reports document successful protection against infection by *Helicobacter felis* in mice, using the following orally administered combinations: *H. felis* antigen plus adjuvant cholera toxin as well as the nontoxic cholera toxin B subunit (Lee, A. & Chen, 1994); recombinant *H. pylori* GroES-like heat shock proteins in combination with the B subunit of *H. pylori* urease (Ferrero et al., 1995); and recombinant *H. pylori* urease with adjuvant E. coli toxin (Lee, C. K. et al., 1995). Currently it is not known whether a similar protection against *H. pylori* infection of adequate duration can be achieved in humans.

Conclusions

Current obstacles to the control of *H. pylori* infection include its widespread distribution linked to poor socioeconomic conditions, difficulty in identifying incident cases, lack of natural immunity to reinfection, limited effectiveness of antibiotic therapy in populations where transmission is most frequent, difficulty in detecting the organism outside the stomach, and incomplete knowledge regarding the reservoir of infection, mode of transmission, host susceptibility factors and the potential for developing a successful vaccine. These obstacles not only represent a challenge to those concerned with prevention of the infection itself, they also impede research designed to observe the potential for anti-*H. pylori* therapy to prevent the progression of precancerous lesions of the stomach. Worthwhile avenues of research include studies designed to identify risk factors for acquisition of the infection that may be modified in order to interrupt transmission, modifiable host factors that may make individuals resistant to chronic infection, antibiotic therapies that are effective in high prevalence populations of low socioeconomic status and effective vaccines.

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