Helicobacter pylori

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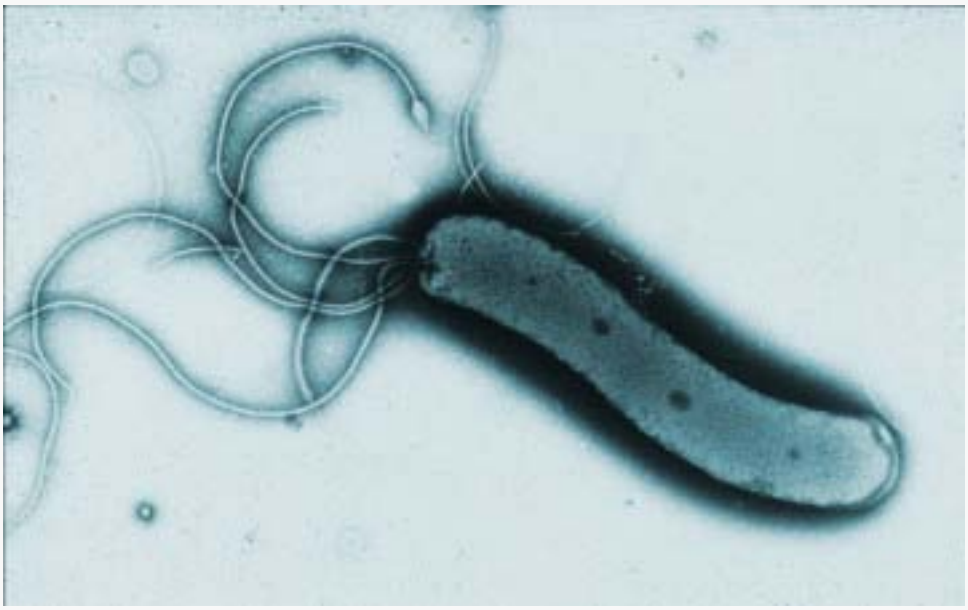

Scientific classification
Kingdom: Bacteria
Phylum: Proteobacteria
Class: Epsilonproteobacteria
Order: Campylobacterales
Family: Helicobacteraceae
Genus: *Helicobacter*
Species: ***H. pylori***
Binomial name
Helicobacter pylori (Marshall et al. 1985) Goodwin et al., 1989

Contents

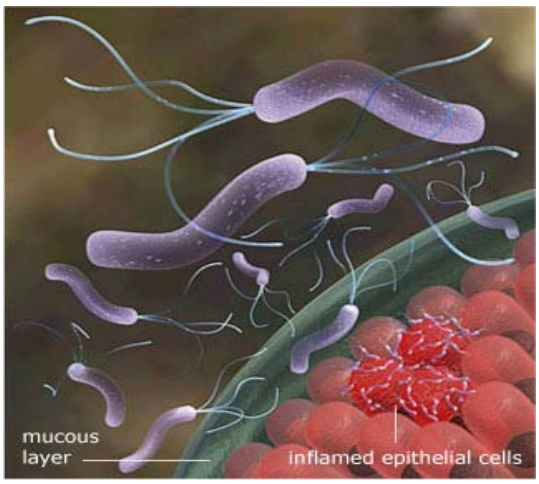
Helicobacter pylori (English pronunciation: /ˌhɛlɨkəˈbæktər pɪˈlɔraɪ/) is a Gram-negative, microaerophilic bacterium that can inhabit various areas of the stomach, particularly the antrum. It causes a chronic low-level inflammation of the stomach lining and is strongly linked to the development of duodenal and gastric ulcers, stomach cancer. Over 80 percent of individuals infected with the bacterium are asymptomatic.[1]

The bacterium was initially named *Campylobacter pyloridis*, then renamed *C. pylori* (pylori being the genitive of pylorus) to correct a Latin grammar error. When 16S ribosomal RNA gene sequencing and other research showed in 1989 that the bacterium did not belong in the genus *Campylobacter*, it was placed in its own genus, *Helicobacter*. The genus derived from the ancient Greek *hĕlix*/ἕλιξ "spiral" or "coil".[2] The specific epithet *pylōri* means "of the pylorus" or pyloric valve (the circular opening leading from the stomach into the duodenum), from the Ancient Greek word *πυλωρός*, which means gatekeeper.[2]

More than 50% of the world's population harbor *H. pylori* in their upper gastrointestinal tract. Infection is more prevalent in developing countries, and incidence is decreasing in Western countries. *H. pylori*'s helix shape (from which the generic name is derived) is thought to have evolved to penetrate the mucoid lining of the stomach.[3][4]

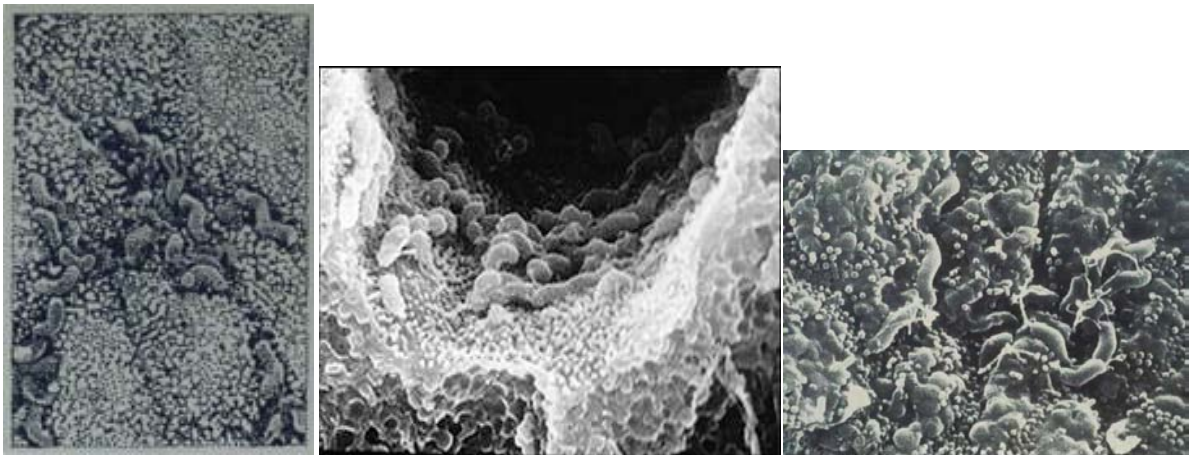
Signs and symptoms

Although over 80% of individuals infected with the bacterium are asymptomatic,[1] symptoms associated with *H. pylori* can be vague or vary over time. They may be nonspecific, or caused by other conditions. Inflammation of, or damage to the stomach lining (gastritis) by *H. pylori* may cause mild or serious reactions to the stomach's contents—stomach ache or abdominal pain, acid reflux, regurgitation, vomiting, belching, flatulence, and nausea.



If untreated for a long time, *H. pylori* infections may be related to several serious illnesses: gastroesophageal reflux disease (GERD), peptic ulcers (duodenal or gastric ulcers), and cancers of the esophagus and stomach.

Microbiology



Scanning electron micrograph of *H. pylori*

H. pylori is a helix-shaped (classified as a curved rod, not spirochaete) Gram-negative bacterium, about 3 micrometres long with a diameter of about 0.5 micrometres. It is microaerophilic; that is, it requires oxygen, but at lower concentration than is found in the atmosphere. It contains a hydrogenase which can be used to obtain energy by oxidizing molecular hydrogen (H_2) that is produced by intestinal bacteria.[5] It produces oxidase, catalase, and urease. It is capable of forming biofilms[6] and can convert from spiral to a possibly viable but nonculturable coccoid form,[7] both likely to favor its survival and be factors in the epidemiology of the bacterium. The coccoid form can adhere to gastric epithelial cells *in vitro*.[8]

H. pylori possesses five major outer membrane protein (OMP) families.[9] The largest family includes known and putative adhesins. The other four families include porins, iron transporters, flagellum-associated proteins and proteins of unknown function. Like other typical Gram-negative bacteria, the outer membrane of *H. pylori* consists of phospholipids and lipopolysaccharide (LPS). The O antigen of LPS may be fucosylated and mimic Lewis

blood group antigens found on the gastric epithelium.[9] The outer membrane also contains cholesterol glucosides, which are found in few other bacteria.[9] *H. pylori* has 4-6 lophotrichous flagella; all gastric and enterohepatic *Helicobacter* species are highly motile due to flagella.[10] The characteristic sheathed flagellar filaments of *Helicobacter* are composed of two copolymerized flagellins, FlaA and FlaB.[11]

Genome

H. pylori consists of a large diversity of strains, and the genomes of three have been completely sequenced.[12][13][14][15][16] The genome of the strain "26695" consists of about 1.7 million base pairs, with some 1,550 genes. The two sequenced strains show large genetic differences, with up to 6% of the nucleotides differing.[14]

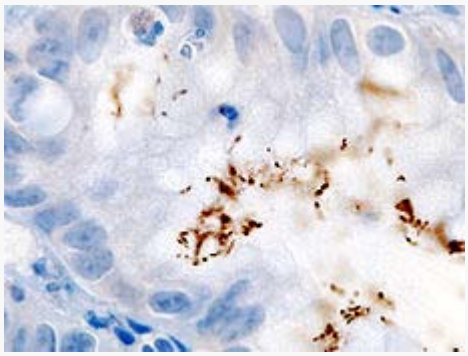
Study of the *H. pylori* genome is centered on attempts to understand pathogenesis, the ability of this organism to cause disease. Approximately 29% of the loci are in the "pathogenesis" category of the genome database. Two of sequenced strains have an approximately 40 kb-long Cag pathogenicity island (a common gene sequence believed responsible for pathogenesis) that contains over 40 genes. This pathogenicity island is usually absent from *H. pylori* strains isolated from humans who are carriers of *H. pylori*, but remain asymptomatic.[17]

The *cagA* gene codes for one of the major *H. pylori* virulence proteins. Bacterial strains that have the *cagA* gene are associated with an ability to cause ulcers.[18] The *cagA* gene codes for a relatively long (1186 amino acid) protein. The *cag* pathogenicity island (PAI) has about 30 genes, part of which code for a complex type IV secretion system. The low GC-content of the *cag* PAI relative to the rest of the *Helicobacter* genome suggests the island was acquired by horizontal transfer from another bacterial species.[12]

Pathophysiology

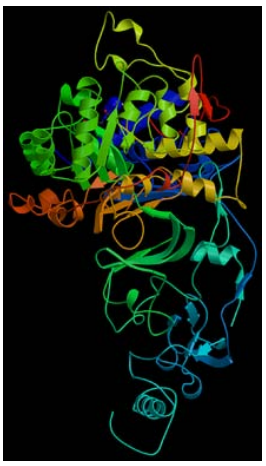
Helicobacter pylori infection

Classification and external resources



Immunohistochemical staining of *H. pylori* from a gastric biopsy

ICD-9	041.86
DiseasesDB	5702
MedlinePlus	000229
eMedicine	med/962
MeSH	D016481



Molecular model of *H. pylori* urease enzyme

To colonize the stomach, *H. pylori* must survive the acidic pH of the lumen and burrow into the mucus to reach its niche, close to the stomach's epithelial cell layer. The bacterium has flagella and moves through the stomach lumen and drills into the mucoid lining of the stomach.[19] Many bacteria can be found deep in the mucus, which is continuously secreted by mucus-secreting cells and removed on the luminal side. To avoid being carried into the lumen, *H. pylori* senses the pH gradient within the mucus layer by chemotaxis and swims away from the acidic contents of the lumen towards the more neutral pH environment of the epithelial cell surface.[20] *H. pylori* is also found on the inner surface of the stomach epithelial cells and occasionally inside epithelial cells.[21] It produces adhesins which bind to membrane-associated lipids and carbohydrates and help it adhere to epithelial cells. For example, the adhesin BabA binds to the Lewis b antigen displayed on the surface of stomach epithelial cells.[22] *H. pylori* produces large amounts of the enzyme urease, molecules of which are localized inside and outside of the bacterium. Urease breaks down urea (which is normally secreted into the stomach) to carbon dioxide and ammonia. The ammonia is converted to ammonium by taking a proton (H^+) from water, which leaves only a hydroxyl ion. Hydroxyl ions then react with carbon dioxide, producing bicarbonate, which neutralizes gastric acid. The survival of *H. pylori* in the acidic stomach is dependent on urease. The ammonia produced is toxic to the epithelial cells, and, along with the other products of *H. pylori*—including proteases, vacuolating cytotoxin A (VacA), and certain phospholipases—damages those cells.[23]

Inflammatory processes of *H. pylori* infections are also mediated by highly disulfide-bridged proteins. Hcp (Helibacter cysteine-rich proteins), particularly HcpA (hp0211), triggers an immune response through the differentiation of human myeloid Thp1 monocytes into macrophages. In analogy to eucaryotic cytokines, they interfer with host cell functions and change the morphology of monocytes inducing the expression of the surface marker protein CD11b, phagocytic activity as well as cell adherence, which are indicative of monocyte differentiation into macrophages.[24]

Colonization of the stomach by *H. pylori* results in chronic gastritis, an inflammation of the stomach lining. The severity of the inflammation is likely to underlie *H. pylori*-related diseases.[25] Duodenal and stomach ulcers result when the consequences of inflammation allow the acid and pepsin in the stomach lumen to overwhelm the mechanisms that protect the stomach and duodenal mucosa from these caustic substances. The type of ulcer that develops depends on the location of chronic gastritis, which occurs at the site of *H. pylori* colonization.[26] The acidity within the stomach lumen affects the colonization pattern of *H. pylori* and therefore ultimately determines whether a duodenal or gastric ulcer will form. In people producing large amounts of acid, *H. pylori* colonizes the antrum of the stomach to

avoid the acid-secreting parietal cells located in the corpus (main body) of the stomach.[9] The inflammatory response to the bacteria induces G cells in the antrum to secrete the hormone gastrin, which travels through the bloodstream to the corpus.[27] Gastrin stimulates the parietal cells in the corpus to secrete even more acid into the stomach lumen. Chronically increased gastrin levels eventually cause the number of parietal cells to also increase, further escalating the amount of acid secreted.[28] The increased acid load damages the duodenum, and ulceration may eventually result. In contrast, gastric ulcers are often associated with normal or reduced gastric acid production, suggesting that the mechanisms that protect the gastric mucosa are defective.[28] In these patients, *H. pylori* can also colonize the corpus of the stomach, where the acid-secreting parietal cells are located. However chronic inflammation induced by the bacteria causes further reduction of acid production and, eventually, atrophy of the stomach lining, which may lead to gastric ulcer and increases the risk for stomach cancer.[29]

About 50-70% of *H. pylori* strains in Western countries carry the *cag* pathogenicity island (*cag* PAI).[30] Western patients infected with strains carrying the *cag* PAI have a stronger inflammatory response in the stomach and are at a greater risk of developing peptic ulcers or stomach cancer than those infected with strains lacking the island.[9] Following attachment of *H. pylori* to stomach epithelial cells, the type IV secretion system expressed by the *cag* PAI "injects" the inflammation-inducing agent, peptidoglycan, from their own cell wall into the epithelial cells. The injected peptidoglycan is recognized by the cytoplasmic pattern recognition receptor (immune sensor) Nod1, which then stimulates expression of cytokines that promote inflammation.[31]

The type IV secretion apparatus also injects the *cag* PAI-encoded protein CagA into the stomach's epithelial cells, where it disrupts the cytoskeleton, adherence to adjacent cells, intracellular signaling, cell polarity, and other cellular activities.[32] Once inside the cell, the CagA protein is phosphorylated on tyrosine residues by a host cell membrane-associated tyrosine kinase (TK). CagA then allosterically activates protein tyrosine phosphatase/protooncogene Shp2.[33] Pathogenic strains of *H. pylori* have been shown to activate the epidermal growth factor receptor (EGFR), a membrane protein with a tyrosine kinase domain. Activation of the EGFR by *H. pylori* is associated with altered signal transduction and gene expression in host epithelial cells that may contribute to pathogenesis. It has also been suggested that a C-terminal region of the CagA protein (amino acids 873–1002) can regulate host cell gene transcription, independent of protein tyrosine phosphorylation.[17][18] There is a great deal of diversity between strains of *H. pylori*, and the strain with which one is infected is predictive of the outcome.

Two related mechanisms by which *H. pylori* could promote cancer are under investigation. One mechanism involves the enhanced production of free radicals near *H. pylori* and an increased rate of host cell mutation. The other proposed mechanism has been called a "perigenetic pathway"[34] and involves enhancement of the transformed host cell phenotype by means of alterations in cell proteins, such as adhesion proteins. It has been proposed that *H. pylori* induces inflammation and locally high levels of TNF-α and/or interleukin 6 (IL-6). According to the proposed perigenetic mechanism, inflammation-associated signaling molecules, such as TNF-α, can alter gastric epithelial cell adhesion and lead to the dispersion and migration of mutated epithelial cells without the need for additional mutations in tumor suppressor genes, such as genes that code for cell adhesion proteins.[35]

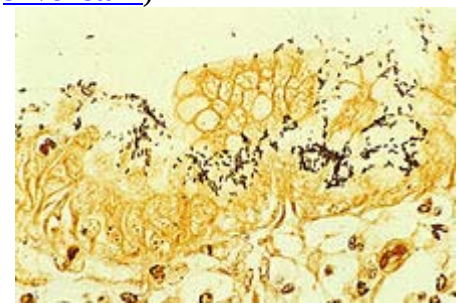
Diagnosis

Petri dish with* Helicobacter pylori *growth at 48 ours on

Trypticase Soy Agar (TSA) + 5% sheep blood. The bacteria

was isolated from a gastric biopsy

H. pylori colonized on the surface of regenerative epithelium (image from Warthin-Starry's silver stain)



Diagnosis of infection is usually made by checking for dyspeptic symptoms and by tests which can indicate *H. pylori* infection. One can test noninvasively for *H. pylori* infection with a **blood antibody test**, **stool antigen test**, or with the carbon urea breath test (in which the patient drinks ^{14}C- or ^{13}C-labelled urea, which the bacterium metabolizes, producing labelled carbon dioxide that can be detected in the breath).[36] However, the most reliable method for detecting *H. pylori* infection is a biopsy check during endoscopy with a rapid urease test, histological examination, and microbial culture. There is also a urine ELISA test with a 96% sensitivity and 79% specificity. None of the test methods are completely failsafe. Even biopsy is dependent on the location of the biopsy. Blood antibody tests, for example, range from 76% to 84% sensitivity. Some drugs can affect *H. pylori* urease activity and give false negatives with the urea-based tests.[37]

Prevention

H. pylori is a major cause of diseases of the upper gastrointestinal tract. Eradication of the infection in individuals will improve symptoms including dyspepsia, gastritis and peptic ulcers, and may prevent gastric cancer. Rising antibiotic resistance increases the need for a prevention strategy for the bacteria.[38] Extensive vaccine studies in mouse models have shown promising results.[39] Researchers are studying different adjuvants, antigens, and routes of immunization to ascertain the most appropriate system of immune protection, with most of the research only recently moving from animal to human trials.[40]

An intramuscular vaccine against *H. pylori* infection is undergoing Phase I clinical trials, and has shown an antibody response against the bacterium. Its clinical usefulness requires further study.[41]

Studies have recently been published suggesting *H. pylori* activity could be suppressed via dietary methods. A 2009 Japanese study in *Cancer Prevention Research* found eating as little as 70 g (2.5 ounces) of broccoli sprouts daily for two months reduces the number of colonies of *H. pylori* bacteria in the stomach by 40% in humans. This treatment also seems to help by enhancing the protection of the gastric mucosa against *H. pylori*, but is relatively ineffective on related gastric cancers. The previous infection returned within two months after broccoli sprouts were removed from the diet, so an ongoing inclusion in the diet is best for continued protection from *H. pylori*.[42]

A 2008 study published in *Korean Journal of Microbiology and Biotechnology* found *kimchi* (fermented cabbage) contains a bacterial strain "showing strong antagonistic activity against *H. pylori*." The bacterium strain isolated from *kimchi*, designated *Lb. plantarum NO1*, was found to reduce the urease activity of *H. pylori* by 40-60% and suppress its binding to a human gastric cancer cell line by more than 33%.[43]

A 2009 study has found green tea can prevent *Helicobacter*-related inflammation.[44][45]

Vaccines

An effective vaccine is needed to improve the success of anti-*H. pylori* therapy. Cooperative action of cell-mediated, humoral and molecular responses is necessary for effective protection against it. Vaccines against *H. pylori* can be used as prophylactic vaccines to prevent the infection or as therapeutic vaccines to cure the infection, to improve the eradication success of standard regimens or to reduce the bacterial density in the gastric mucosa and the risk for emergence of antibiotic resistant strains. In recent years, many attempts, using various *H. pylori* antigens such as urease, CagA, HP-NAP, HspA or combinations, many adjuvants and different routes of immunisation have been made to create vaccines against *H. pylori* infection. Although some attempts are promising, no effective and safe vaccine against *H. pylori* is currently available for humans. New directions for immunisation with the use of DNA, living vectors, microspheres etc. are currently under evaluation. The vaccination plan and the groups who should receive vaccination are still to be determined, but the vaccination will be useful, especially in developing countries.[1]

Treatment

Once *H. pylori* is detected in patients with a peptic ulcer, the normal procedure is to eradicate it and allow the ulcer to heal. The standard first-line therapy is a one week "triple therapy" consisting of proton pump inhibitors such as omeprazole, lansoprazole and the antibiotics clarithromycin and amoxicillin.[46] Variations of the triple therapy have been developed over the years, such as using a different proton pump inhibitor, as with pantoprazole or rabeprazole, or replacing amoxicillin with metronidazole for people who are allergic to penicillin.[47] Such a therapy has revolutionized the treatment of peptic ulcers, and has made a cure to the disease possible; previously, the only option was symptom control using antacids, H_2-antagonists or proton pump inhibitors alone.[48][49]

An increasing number of infected individuals are found to harbour antibiotic-resistant bacteria. This results in initial treatment failure and requires additional rounds of antibiotic therapy or alternative strategies, such as a quadruple therapy, which adds a bismuth colloid, such as bismuth subsalicylate.[36][50][51] For the treatment of clarithromycin-resistant strains of *H. pylori*, the use of levofloxacin as part of the therapy has been suggested.[52][53]

An article in the *American Journal of Clinical Nutrition* found evidence that "ingesting lactic acid bacteria exerts a suppressive effect on *Helicobacter pylori* infection in both animals and humans," noting that "supplementing with Lactobacillus- and Bifidobacterium-containing yogurt (AB-yogurt) was shown to improve the rates of eradication of *H. pylori* in humans."[54]

Prognosis

H. pylori colonizes the stomach and induces chronic gastritis, a long-lasting inflammation of the stomach. The bacterium persists in the stomach for decades in most people. Most individuals infected by *H. pylori* will never experience clinical symptoms despite having chronic gastritis. Approximately 10-20% of those colonized by *H. pylori* will ultimately develop gastric and duodenal ulcers.[9] *H. pylori* infection is also associated with a 1-2% lifetime risk of stomach cancer and a less than 1% risk of gastric MALT lymphoma.[9]

In the absence of treatment, *H. pylori* infection—once established in its gastric niche—is widely believed to persist for life.[4] In the elderly, however, it is likely infection can disappear as the stomach's mucosa becomes increasingly atrophic and inhospitable to colonization. The proportion of acute infections that persist is not known, but several studies that followed the natural history in populations have reported apparent spontaneous elimination.[55][56]

The incidence of acid reflux disease, Barrett's esophagus, and esophageal cancer have been rising dramatically.[57] In 1996, Martin J. Blaser advanced the hypothesis that *H. pylori* has a beneficial effect: by regulating the acidity of the stomach contents.[27][57] The hypothesis is not universally accepted as several randomized controlled trials failed to demonstrate worsening of acid reflux disease symptoms following eradication of *H. pylori*.[58][59] Nevertheless, Blaser has refined his view to assert that *H. pylori* is a member of the normal flora of the stomach.[60] He postulates that the changes in gastric physiology caused by the loss of *H. pylori* account for the recent increase in incidence of several diseases, including type 2 diabetes, obesity, and asthma.[60][61] His group has recently shown that *H. pylori* colonization is associated with a lower incidence of childhood asthma.[62]

Epidemiology

At least half the world's population are infected by the bacterium, making it the most widespread infection in the world.[63] Actual infection rates vary from nation to nation; the developing world has much higher infection rates than the West (Western Europe, North America, Australasia), where rates are estimated to be around 25%.[63] Infections are usually acquired in early childhood in all countries.[9] However, the infection rate of children in developing nations is higher than in industrialized nations, probably due to poor sanitary conditions. In developed nations it is currently uncommon to find infected children, but the percentage of infected people increases with age, with about 50% infected for those over the age of 60 compared with around 10% between 18 and 30 years.[63] The higher prevalence among the elderly reflects higher infection rates when they were children rather than infection at later ages.[9] Prevalence appears to be higher in African-American and Hispanic populations, most likely due to socioeconomic factors.[64][65] The lower rate of infection in the West is largely attributed to higher hygiene standards and widespread use of antibiotics. Despite high rates of infection in certain areas of the world, the overall frequency of *H. pylori* infection is declining.[66] However, antibiotic resistance is appearing in *H. pylori*; there are already many metronidazole- and clarithromycin-resistant strains in most parts of the world.[67]

H. pylori is contagious, although the exact route of transmission is not known.[68][69] Person-to-person transmission by either the oral-oral or fecal-oral route is most likely.[4] Consistent with these transmission routes, the bacteria have been isolated from feces, saliva and dental plaque of some infected people.[4] Transmission occurs mainly within families in developed nations yet can also be acquired from the community in developing countries.[70] *H. pylori* may also be transmitted orally by means of fecal matter through the ingestion of waste-tainted water, so a hygienic environment could help decrease the risk of *H. pylori* infection.[4]

History

Helicobacter pylori was first discovered in the stomachs of patients with gastritis and stomach ulcers in 1982 by Dr. Barry Marshall and Dr. Robin Warren of Perth, Western Australia. At the time, the conventional thinking was that no bacterium can live in the human stomach, as the stomach produced extensive amounts of acid of a strength similar to the acid found in a car battery. Marshall and Warren rewrote the textbooks with reference to what causes gastritis and gastric ulcers. In recognition of their discovery, they were awarded the 2005 Nobel Prize in Physiology or Medicine.[71] German scientists found spiral-shaped bacteria in the lining of the human stomach in 1875, but they were unable to culture it, and the results were eventually forgotten.[57] The Italian researcher Giulio Bizzozero described similarly-shaped bacteria living in the acidic environment of the stomach of dogs in 1893.[72] Professor Walery Jaworski of the Jagiellonian University in Kraków investigated sediments of gastric washings obtained from humans in 1899. Among some rod-like bacteria, he also found bacteria with a characteristic spiral shape, which he called *Vibrio rugula*. He was the first to suggest a possible role of this organism in the pathogenesis of gastric diseases. This work was included in the *Handbook of Gastric Diseases*, but it had little impact, as it was written in Polish.[73] Several small studies conducted in the early 20th century demonstrated the presence of curved rods in the stomach of many patients with peptic ulcers and stomach cancer.[74] Interest in the bacteria waned, however, when an American study published in 1954 failed to observe the bacteria in 1180 stomach biopsies.[75]

Interest in understanding the role of bacteria in stomach diseases was rekindled in the 1970s, with the visualization of bacteria in the stomach of gastric ulcer patients.[76] The bacterium

had also been observed in 1979 by Australian pathologist Robin Warren, who did further research on it with Australian physician Barry Marshall beginning in 1981. After numerous unsuccessful attempts at culturing the bacteria from the stomach, they finally succeeded in visualizing colonies in 1982, when they unintentionally left their Petri dishes incubating for 5 days over the Easter weekend. In their original paper, Warren and Marshall contended that most stomach ulcers and gastritis were caused by infection by this bacterium and not by stress or spicy food, as had been assumed before.[77]

Although there was some skepticism initially, within several years numerous research groups verified the association of *H. pylori* with gastritis and, to a lesser extent, ulcers.[78] To demonstrate *H. pylori* caused gastritis and was not merely a bystander, Marshall drank a beaker of *H. pylori* culture. He became ill with nausea and vomiting several days later. An endoscopy ten days after inoculation revealed signs of gastritis and the presence of *H. pylori*. These results suggested *H. pylori* was the causative agent of gastritis. Marshall and Warren went on to demonstrate that antibiotics are effective in the treatment of many cases of gastritis. In 1987, the Sydney gastroenterologist Thomas Borody invented the first triple therapy for the treatment of duodenal ulcers.[79] In 1994, the National Institutes of Health (USA) published an opinion stating most recurrent duodenal and gastric ulcers were caused by *H. pylori*, and recommended antibiotics be included in the treatment regimen.[80]

Recent research states that genetic diversity in *H. pylori* decreases with geographic distance from East Africa, the birthplace of modern humans. Using the genetic diversity data, the researchers have created simulations that indicate the bacteria seem to have spread from East Africa around 58,000 years ago. Their results indicate modern humans were already infected by *H. pylori* before their migrations out of Africa, and it has remained associated with human hosts since that time.[81]