Helicobacter pylori (Chronic Infection)

CAS No.: none assigned

Known to be a human carcinogen

First listed in the *Fifteenth Report on Carcinogens*

Also known as *H. pylori*

Carcinogenicity

Helicobacter pylori (chronic infection) is known to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in humans. Epidemiological studies provide evidence that *H. pylori* infection causes stomach cancer (especially non-cardia gastric cancer) and a specific type of lymphoma in the stomach (gastric mucosa-associated lymphoid tissue [MALT] lymphoma). Mechanistic studies indicate that chronic infection of the stomach with *H. pylori* can lead to cancer by biological pathways that are plausible in humans. In experimental animals, *H. pylori* infection induces types of tumors similar to those it causes in humans: adenocarcinoma and lymphoma of the stomach.

H. pylori is linked to almost all cases of non-cardia gastric cancer (89%) and gastric MALT lymphoma (92% to 98%). It is responsible for approximately 780,000 cancer cases (primarily stomach cancer) worldwide each year, accounting for 6.2% of all cancer cases (Testerman and Morris 2014, Plummer *et al.* 2015).

Cancer Studies in Humans

Worldwide, stomach cancer is the fifth most common type of cancer and the third leading cause of death from cancer. It disproportionally affects people living in poverty and members of certain racial and ethnic groups. Most cases and deaths occur in low- and middle-income countries and among people living in poverty, people of color, and indigenous and immigrant populations in higher-income countries, including the United States, Australia, New Zealand, and the nations of western Europe (Epplein *et al.* 2011, Taylor *et al.* 2014, Balakrishnan *et al.* 2017, SEER 2018). In contrast, gastric MALT lymphoma is very rare, with a worldwide incidence of 1 to 1.5 cases per 100,000 people (Pereira and Medeiros 2014). Adenocarcinoma accounts for over 90% to 95% of all stomach cancer and can be broadly classified by the location in the stomach where the cancer develops: (1) cardia gastric cancer develops in the first portion of the stomach, closest to the esophagus, and (2) non-cardia gastric cancer develops in more distal parts of the stomach, closer to the small intestine (Balakrishnan *et al.* 2017). Gastric MALT lymphoma is a slow-growing type of stomach tumor that arises outside of the lymph nodes or other lymphoid tissue (specifically, in extranodal B lymphocytes) (Pereira and Medeiros 2014). Gastric lymphoma accounts for approximately 2% to 8% of all stomach tumors (Zullo *et al.* 2010b, Park and Koo 2014).

Stomach Cancer

A large body of epidemiological studies, including a pooled analysis and a meta-analysis, conducted in different geographical locations, found a credible association between *H. pylori* infection and an increased risk of stomach (non-cardia gastric) cancer in humans. Several of these studies controlled for other risk factors for stomach cancer. The risk of stomach cancer was highest in the studies that followed infected subjects for the longest time and in the studies that used the most sensitive methods for detecting *H. pylori* infection. The body of evidence indicates that the association between *H. pylori* infection and stomach cancer is causal and is unlikely to be explained by bias, chance, or confounding.

Several cohort studies found that *H. pylori*–infected individuals were more likely than uninfected individuals to develop stomach cancer (of unspecified types of stomach cancer) after 4 to 10 years of follow-up (IARC 2012). Evidence that the increased risk was specifically for non-cardia gastric cancer comes from numerous nested case-control studies (case-control analyses conducted within cohorts of subjects) that followed *H. pylori*–infected individuals for up to 15 years (IARC 2012). A pooled analysis of individual participant data from 12 nested case-control studies, which included 762 case subjects and 2,250 control subjects, found that *H. pylori* infection increased the risk of non-cardia gastric cancer by a factor of about 3 (odds ratio [OR] = 2.97, 95% confidence interval [CI] = 2.34 to 3.77) (*Helicobacter* Cancer Collaborative Group 2001). These findings are supported by a meta-analysis of risk estimates for non-cardia gastric cancer from eight studies (Huang *et al.* 2003). Nested case-control studies that either were published after the 2001 pooled analysis or had accrued more cases since that analysis also found significantly elevated risks for non-cardia gastric cancer, confirming the association with *H. pylori* infection (IARC 2012). In the pooled analysis, the risk of stomach cancer was highest in studies that followed the infected subjects for at least 10 years (in whom the risk was increased by a factor of nearly 6) (*Helicobacter* Cancer Collaborative Group 2001). In other studies, the risk was also highest (increased by over tenfold) in the studies that used the most sensitive methods to detect *H. pylori* infection (Simán *et al.* 2007, Mitchell *et al.* 2008, González *et al.* 2012).

Some evidence suggests that *H. pylori*–associated stomach-cancer risk depends on the characteristics of the bacterial strain. Higher risks were found for infection with *H. pylori* strains that produced cytotoxin-associated gene A product (CagA, a virulence factor) than for infection with CagA-negative strains. A meta-analysis of nine studies found that infection with CagA-positive *H. pylori* strains approximately doubled the risk of non-cardia gastric cancer over the risk due to *H. pylori* infection alone (Huang *et al.* 2003). Some studies suggest that risk patterns for specific CagA variants (differing in types and numbers of EPIYA motifs; see Properties) may vary geographically. For example, stomach cancer risk was associated with a different CagA variant in Asia (single EPIYA-D motif) than in Europe and the United States (multiple EPIYA-C motifs) (Li *et al.* 2017).

Some evidence also suggests that diet and lifestyle exposures may be co-factors that modify *H. pylori*–induced stomach cancer risk. *H. pylori*–infected individuals who smoked or who consumed salted, smoked, or processed foods or red meat had a higher risk of stomach cancer, whereas infected individuals with diets high in vegetables or intake of vitamins had a lower risk (IARC 2012, Epplein *et al.* 2014).

It is unclear whether *H. pylori* infection increases the risk of cardia gastric cancer. Neither the *Helicobacter* Cancer Collaborative Group pooled analysis of nested case-control studies (274 cases and 827 controls) nor the meta-analysis by Huang *et al.* (2003) of 16 published studies found an excess risk of cardia gastric cancer with *H. pylori* infection. However, a meta-analysis of primarily case-control studies found that *H. pylori* infection increased the risk of cardia gastric cancer in studies conducted in countries where the overall risk of stomach cancer was high (adjusted relative risk [RR] = 1.59, 95% CI = 1.03 to 1.45; 11 studies) but not in low-risk countries (RR = 0.80, 95% CI = 0.63 to 1.02; 14 studies) (Cavaleiro-Pinto *et al.* 2011). The differences in the risk patterns might be due to the occurrence of different subtypes of cardia gastric cancer or to the inclusion of other types of cancer in anatomical proximity to the cardia (e.g., esophageal cancer); however, few studies have addressed these anatomical distinctions (Malfertheiner *et al.* 2017).

Gastric MALT Lymphoma

Evidence that *H. pylori* infection causes gastric MALT lymphoma comes primarily from intervention studies (i.e., *H. pylori* eradication studies) in cancer patients and is supported by observational studies (as reviewed in IARC 2012). In 16 intervention studies (noncontrolled), eradication of *H. pylori* infection in gastric MALT lymphoma patients resulted in high rates (62% to 100%) of complete remission of the cancer. A pooled analysis of patients with gastric MALT lymphoma from 32 studies found that remission occurred in 78% of the patients who were cured of *H. pylori* infection (Zullo *et al.* 2010a). The number of observational studies is limited by the rarity of this cancer. Two small studies (a prospective nested case-control study and a hospital-based case-control study) found a positive association between *H. pylori* infection and gastric MALT lymphoma (Parsonnet *et al.* 1994, de Sanjose *et al.* 2004).

Cancer Studies in Experimental Animals

H. pylori infection (with bacteria orally administered by gavage) caused malignant tumors in two different types of stomach tissue in rodents, providing sufficient evidence of carcinogenicity. Importantly, the types of cancer observed in animals infected with *H. pylori* — gastric tumors and gastric lymphoma — were similar to those linked with *H. pylori* infection in humans. Some of these animal models are thought to mimic tumor progression in humans, as they also show similar types of *H. pylori*–induced gastric lesions.

H. pylori infection increased the incidences of malignant stomach tumors (mainly adenocarcinoma and some carcinoid) in Mongolian gerbils in some (but not all) studies and in transgenic (genetically altered) mice (IARC 2012). Differences in the findings in gerbils may be due to differences in the *H. pylori* strain, gerbil strain, dose, and/or duration of exposure. A gerbil-adapted strain of *H. pylori* (derived from a human gastric ulcer strain) increased the incidence of malignant stomach tumors in Mongolian gerbils as early as 8 to 12 weeks after infection (Franco *et al.* 2005, 2008, Romero-Gallo *et al.* 2008). In general, findings in gerbils infected with other *H. pylori* strains were mixed; positive findings were more common in studies of longer duration, conducted in Asia, or using higher doses. IARC (2012) noted that the genetic background of the Mongolian gerbils may have evolved differently among colonies established in different geographic locations and that the pathology grading varied among studies. *H. pylori* infection caused gastric carcinoma in several studies of different types of transgenic mice that had been genetically modified to increase their susceptibility to cancer (IARC 2012). Two studies, one in Mongolian gerbils (Romero-Gallo *et al.* 2008) and the other in transgenic mice (Lee *et al.* 2008), found that *H. pylori* eradication therapy, when given early, inhibited the development of malignant stomach tumors (adenocarcinoma), which increases confidence that *H. pylori* causes stomach cancer in experimental animals. The addition of a high-salt diet also increased the incidence of stomach tumors in *H. pylori*–infected gerbils (Kato *et al.* 2006), which is consistent with studies in humans suggesting that diet may be a co-factor in *H. pylori* carcinogenicity.

H. pylori infection caused gastric lymphoma in two different strains of inbred mice (Wang *et al.* 2003) and in neonatal mice whose thymus glands had been removed (Fukui *et al.* 2004). In the latter study, all of the mice developed gastric MALT lymphoma by the age of 12 months.

Studies on Mechanisms of Carcinogenesis

The mechanisms by which *H. pylori* causes stomach cancer are complex and involve many different factors. They involve interactions between (1) direct effects of the toxic action of *H. pylori* virulence factors (e.g., the effects of CagA, vacuolating cytotoxin A [VacA], and outer inflammatory protein), (2) indirect effects due to modification of the infected individual's inflammatory responses to chronic *H. pylori* infection, which can be influenced by the genes regulating immune processes and by lifestyle and dietary habits, and (3) changes in acid secretion in the stomach. Collectively, this information may help to explain why only a small fraction of *H. pylori*–infected individuals (10% in high-risk countries and 1% to 3% in other countries) develop stomach cancer (IARC 2012, Servetas *et al.* 2016, Balakrishnan *et al.* 2017).

H. pylori infection usually is acquired in childhood and can cause inflammation or irritation of the lining (mucosa) of the stomach (chronic infection, or gastritis). This gastritis is associated with recruitment of various types of immune cells (e.g., neutrophils and lymphocytes). Progression to more serious stomach diseases, such as ulcers, MALT lymphoma, and non-cardia gastric cancer, occurs as the infected individual grows older, and it depends on factors specific to the infected individual and to the bacterium, as well as on the acidity of the stomach environment. Chronic inflammation of the stomach mucosa (chronic atrophic gastritis, occurring mainly in the corpus of the stomach) is associated with changes in the types of tissues and cells in the stomach (IARC 2012).

Most individuals infected with *H. pylori* do not develop symptoms; however, in some people, atrophic gastritis can progress to stomach ulcers or precancerous lesions (e.g., intestinal metaplasia and dysplasia), which can progress to stomach cancer (adenocarcinoma). Several studies provided evidence that progression of gastric lesions increased the risk of *H. pylori*–induced gastric cancer. A cohort study of middle-aged Japanese men found that the risk of *H. pylori*–induced gastric cancer increased with increasing severity of *H. pylori* lesions (i.e., from non-chronic atrophic gastritis to chronic atrophic gastritis to metaplastic gastritis; Ohata *et al.* 2004, Yoshida *et al.* 2014). A German cohort study found chronic atrophic gastritis to be associated with a fivefold increase in the risk of non-cardia gastric cancer (Chen *et al.* 2016). In this study, serological biomarkers were used to assess the stages of gastritis.

In infected individuals with higher acid secretion, gastritis is more likely to develop in the lower part of the stomach (antrum-predominant gastritis) and can progress to ulcers in the small intestine (duodenal ulcers). Gastric MALT lymphoma can develop from gastritis in any part of the stomach (pangastritis) (IARC 2012, Conteduca *et al.* 2013, Testerman and Morris 2014, Ishaq and Nunn 2015).

H. pylori–induced chronic inflammation can lead to oxidative stress, aberrant expression of genes (e.g., suppression of the expression of some genes and enhancement of the expression of others, primarily via the process of aberrant DNA methylation), and disruption of enzymes involved in repairing DNA damage. This results in increased DNA damage in cells of the stomach lining (epithelial cells) and can result in mutation and genetic instability (Graham 2015, Servetas *et al.* 2016, Maeda *et al.* 2017). In addition, *H. pylori* either directly or indirectly (e.g., via inflammation) targets biological pathways involved in cell turnover, survival, and proliferation (e.g., by inhibiting tumor-suppressor genes). *H. pylori* also initiates changes in the characteristics of stomach epithelial cells (known as the "epithelial to mesenchymal transition") that enable the cells to proliferate as cancer cells do (Servetas *et al.* 2016). These biological effects (chronic inflammation, changes in gene expression, mutations, genomic instability, and cellular proliferation) are associated with carcinogenesis.

Some of these biological effects vary depending on virulence factors, the production of which can differ among *H. pylori* strains. For example, some *H. pylori* strains (such as CagA-positive strains) can

induce a high degree of chronic inflammation (Figura *et al.* 2016). Moreover, studies in animals and cells have shown that CagA is an oncoprotein (i.e., when the gene is transferred into cells or animals, it causes gastric cells to proliferate and develop into tumors) (Wang *et al.* 2015). Virulence factors in *H. pylori* strains vary geographically, which may help to explain geographical patterns of stomach-cancer risk (Yamaoka and Graham 2014, Wang *et al.* 2015). As discussed above, cancer risks are higher for CagA-positive *H. pylori* infection than for CagA-negative infection. A German cohort study (Chen *et al.* 2016) found that people with *H. pylori* CagA-positive infection who had markers in their blood for chronic atrophic gastritis had a much higher risk of developing non-cardia gastric cancer (hazard ratio [HR] = 32.4, 95% CI = 7.6 to 137.6) than did people without these two risk factors.

Biological Properties

H. pylori is a gram-negative, spiral- (or helical-) shaped, multiflagellated bacterium that has infected humans for more than 58,000 years. It is a member of the family Helicobacteraceae, which includes over 24 *Helicobacter* species that colonize gastric or enterohepatic tissues (i.e., intestinal tract, biliary tree, and liver) (Mateos-Muñoz *et al.* 2013).

H. pylori colonizes the mucosal surface of the body (corpus) and the lower portion (antrum) of the stomach. Colonization involves an interaction between the proteins of the bacterium's outer membrane and the epithelial cells of the stomach lining. One of the major *H. pylori* proteins involved in colonization is blood group antigen-binding adhesin that binds to blood group antigen A (IARC 2012). Although *H. pylori* triggers an immune response, the infected individual usually is unable to clear the infection; without treatment, an established infection usually lasts for the individual's lifetime (Logan and Walker 2001, Testerman and Morris 2014).

Several properties of the bacterium facilitate its ability to maintain a persistent infection. All *H. pylori* strains produce the enzyme urease, which converts urea to ammonia and carbon dioxide, raising the pH (decreasing the acidity) of the surrounding area, thus allowing the bacterium to grow (Testerman and Morris 2014). The bacterium's helical shape and flagella help it to propel itself through the viscous mucus covering the inside lining of the stomach, and a chemotaxis system (by which an organism moves in response to a chemical stimulus) helps it to avoid the acidic stomach environment and stay closer to the surface epithelium. A non-toxic lipopolysaccharide component of the bacterium's outer membrane may help to reduce the infected individual's inflammatory response to the infection (Sachs *et al.* 2011).

The *H. pylori* genome codes for several virulence factors, including CagA and VacA, which vary geographically and across strains (IARC 2012, Yamaoka and Graham 2014). Moreover, variants of CagA-producing *H. pylori* strains differ in types or numbers of EPIYA phosphorylation motifs (which are involved in binding of CagA to host proteins), and these variant strains have different geographical distributions (Cover 2016). Humans can be infected simultaneously with several *H. pylori* strains, which may then exchange DNA, promoting the spread of virulence factors and antibiotic resistance (IARC 2012).

Detection

Numerous methods for diagnosing and screening for *H. pylori* infection are available, including assays to detect the bacterium itself, its DNA, antigens, antibodies, and urease activity. The types of samples used in these tests range in invasiveness from biopsy samples taken during endoscopy, to blood samples, to collection of saliva, stool, urine, and expired air (Kato *et al.* 2001, Reynders *et al.* 2012, Testerman and Morris 2014, Diaconu *et al.* 2017). Biopsy samples can also be evaluated for gastric pathology. All of these tests have moderate to high sensitivity (80% to 100%) and specificity (75% to 100%). Sensitivity and specificity may vary depending on the condition of the patient and population under study (Biranjia-Hurdoyal and Seetulsingh-Goorah 2016). (See NTP 2018 for more information on methods of detection for *H. pylori*.)

The method of detection used depends in part on the purpose of the testing (e.g., selection of treatment method vs. population studies), the cost and technical skills required, and patient considerations, such as age. Serological tests (such as enzyme-linked immunosorbent assay [ELISA] or immunoblotting) to detect *H. pylori* antibodies are widely available and relatively inexpensive. They are used in epidemiological and prevalence studies and are recommended for screening and treatment programs to prevent chronic disease (Areia *et al.* 2013). Serological tests are not recommended for low-prevalence areas, because of their low specificity (Chey *et al.* 2017). Antibodies to *H. pylori* can persist for life, so these tests thus detect both past and current infections. The sensitivity and specificity of serological tests depend on the antigens used in the assay, the type of assay (e.g., ELISA vs. immunoblot), the immunoglobulin class tested (mainly G, but also A), and factors that vary among infected individuals (González *et al.* 2012, Reynders *et al.* 2012). False-negative results can occur in individuals with advanced stomach diseases (e.g., atrophic gastritis) or cancer, because the bacteria are cleared from the mucosa of the stomach as the disease progresses. Case-control studies using ELISA may therefore underestimate the risk associated with *H. pylori* infection, because they will underestimate the prevalence in case but not control subjects (González *et al.* 2012, IARC 2012). Studies using immunoblotting with multiple antigens have high sensitivity (95% to 96%) and specificity (93% to 96%) for detecting *H. pylori* infection (Simán *et al.* 2007, Mitchell *et al.* 2008).

Exposure

More than half of the world's population, approximately 4.4 billion in 2015, are infected with *H. pylori* (Hooi *et al.* 2017). However, infection rates vary substantially within and among countries. In general, infection rates are related to socioeconomic status and levels of hygiene and are highest in low-income countries. Age-adjusted prevalence rates are particularly high (70% to 87%) in some countries in Africa, Latin America, the Caribbean, and Asia.

In the United States, approximately 30% to 36% of people are infected with *H. pylori,* and infection disproportionately affects racial and ethnic minority groups (e.g., the black, Hispanic, and Alaskan indigenous populations and individuals born outside the United States, especially recent Asian immigrants); in these populations, seroprevalence ranges from 42% to 77% (Khalifa *et al.* 2010, Siao and Somsouk 2014, Krueger *et al.* 2015, Hooi *et al.* 2017). Prevalence is lowest among non-Hispanic white people, who account for 17% of people infected, according to U.S. National Health and Nutrition Examination Survey (NHANES) data (Krueger *et al.* 2015). A smaller, more recent study reported an infection rate as low as 9% among non-Hispanic white male Texans (Long Parma *et al.* 2017). Moreover, the prevalence of more virulent strains may be higher among minorities; for example, in a study of mostly low-income individuals in the southeastern United States, the risk of CagA-positive infection was higher among black than white people (Epplein *et al.* 2011).

The prevalence of *H. pylori* infection increases with increasing age (Krueger *et al.* 2015). However, the age of peak prevalence varies geographically, occurring at a younger age in lower-income countries than in higher-income countries (50 vs. over 60). Geographical

differences in *H. pylori* prevalence may be related in part to differences in the rate of infection early in life (Khalifa *et al.* 2010, Malnick *et al.* 2014). In low-income countries, initial infection often occurs in early childhood, and chronic infection continues through adulthood, whereas in high-income countries, infection rates are low among young children and adolescents. However, in a study in Colombia, two populations with different risks of stomach cancer (high and low) showed similar patterns of *H. pylori* prevalence at an early age, suggesting that age of acquisition of infection may not play a major role in explaining stomach-cancer risk (Camargo *et al.* 2004).

The lower rate of infection among children may be due to the decrease in prevalence rates in most of the world (especially in the United States, Korea, and Japan) with each successive generation (referred to as the "birth cohort effect"); in contrast, prevalence has remained stable in many lower-income countries (e.g., in Central and South America). The decline in *H. pylori* prevalence is related to access to clean water, improvements in sanitation, and improved household hygiene (Balakrishnan *et al.* 2017). Although *H. pylori* infection has decreased in many countries, its prevalence remains high in adults.

Areas of high prevalence of *H. pylori* do not always directly correspond to areas of high risk for stomach cancer; for example, *H. pylori* prevalence is high in Africa, but not stomach-cancer incidence (Hooi *et al.* 2017). Geographical differences in gastric cancer incidence may be explained in part by geographical variation in *H. pylori* genotypes, co-exposures (such as diet), and patients' characteristics (see Carcinogenicity, above).

Transmission

Data from NHANES indicate that the most important risk factors for *H. pylori* infection include age, minority race or ethnicity, low socioeconomic status (family income and education level), and crowded housing (Krueger *et al.* 2015). Studies in other countries have also identified age, socioeconomic status, crowding, and poor sanitation as major risk factors and have suggested that gender and genetic predisposition also may influence *H. pylori* prevalence rates (Khalifa *et al.* 2010).

The bacterium is spread predominantly by person-to-person contact, especially among family members. This occurs primarily via oral-to-oral transmission and possibly via gastro-oral or fecal-to-oral transmission. *H. pylori* has been isolated from the oral cavity, gastric juices, and fecal samples (Khalifa *et al.* 2010, Zou and Li 2011). *H. pylori* can also be transmitted from the environment indirectly through drinking of contaminated water or possibly in food or from animal reservoirs (Khalifa *et al.* 2010, IARC 2012, Aziz *et al.* 2015, Bui *et al.* 2016); transmission via contaminated water likely plays a minor role in the United States. The bacterium has been detected in surface, ground, and well water in the United States. Some epidemiological studies, including a study using NHANES data (for people aged 3 to 19), found that using well water or other unpurified water was a risk factor for *H. pylori* infection (Khalifa *et al.* 2010, Aziz *et al.* 2015, Krueger *et al.* 2015). However, *H. pylori* can remain viable even in chlorinated water, and the U.S. Environmental Protection Agency considers *H. pylori* a drinking-water contaminant and a candidate for possible regulatory action under the Safe Drinking Water Act (Krueger *et al.* 2015, EPA 2016). (See NTP 2018 for more information on transmission of *H. pylori*.)

Diseases (Non-Cancer), Treatment, and Prevention

In 2005, the Nobel Prize in Physiology or Medicine was awarded to Barry Marshall and Robin Warren for their discovery that an infectious agent, *H. pylori*, causes gastritis and peptic ulcers (up to 80% of gastric ulcers and over 90% of duodenal ulcers) (Nobel Prize 2005). *H. pylori* infection is also associated with some non-stomach diseases, such as iron-deficiency anemia and immune thrombocytopenia purpura (a tendency to bleed easily because of reduced numbers of blood platelets), and may be associated with non-ulcer dyspepsia (indigestion), although this association is not clear (AlMalki 2008, Testerman and Morris 2014, Dore *et al.* 2016).

The American College of Gastroenterology recommends *H. pylori* testing of individuals with peptic ulcers and treatment of those who test positive; current treatment recommendations are available in their guidelines for treatment of *H. pylori* infection as updated in 2017 (Chey *et al.* 2017, Randel 2018). Eradication of *H. pylori* infection in an individual can be affected by (1) patient-related factors (e.g., adherence to the treatment regimen, smoking, diabetes, genetic factors influencing antibiotic metabolism, and past antibiotic use) and (2) *H. pylori*–related factors. Globally, *H. pylori* eradication rates have declined as antibiotic resistance rates have increased (Thung *et al.* 2016). No *H. pylori* vaccine is currently available (CDC 2018, FDA 2020). Vaccine development efforts are ongoing, but no large-scale efforts are known to be under way (Zeng *et al.* 2015, Sutton and Boag 2019).

Randomized controlled trials (clinical studies with control groups that receive a placebo) have shown that screening and treatment of *H. pylori* reduces stomach-cancer risk by approximately 35% (Park *et al.* 2013, Herrero *et al.* 2014). Moreover, economic modeling studies, in both low- and high-prevalence countries, have shown *H. pylori* eradication to be cost-effective. However, effectiveness in reducing cancer risk depends on several factors, such as patient characteristics, screening methods, efficacy of *H. pylori* eradication, and the stage of *H. pylori*–associated gastric disease. *H. pylori* eradication may increase bacterial resistance to antibiotics, alter the normal gastrointestinal flora found in the body, and possibly increase the incidence of diseases for which *H. pylori* infection may offer protection, such as esophageal cancer and gastro-esophageal reflux disease. Numerous international and national working groups have recommended that prevention programs consider objective assessments of feasibility, effectiveness, program acceptance, cost-effectiveness, and adverse consequences relevant to the local area before implementation. Most working groups have recommended that patients with gastric MALT lymphoma and non-cardia gastric cancer be treated for *H. pylori* infection. Population-based screening and treatment programs generally have been recommended only for people at high risk for gastric cancer, and have not been recommended for the United States or other countries with a low risk of gastric cancer. (See NTP 2018 for more information on treatment and prevention strategies.)

Regulations

Department of Transportation (DOT)

Infectious substances are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

Food and Drug Administration (FDA, an agency of Health and Human Services)

Helicobacter pylori is listed as a qualifying pathogen having the potential to pose a serious threat to public health under the Generating Antibiotic Incentives Now (GAIN) title of the Food and Drug Administration Safety and Innovation Act (FDASIA). GAIN is intended to encourage development of new antibacterial and antifungal drugs for the treatment of serious or life-threatening infections.

Occupational Safety and Health Administration (OSHA)

First-aid training program trainees must have adequate instruction in the value of universal precautions for minimizing exposure to blood and other potentially infectious material.

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