National Toxicology Program
U.S. Department of Health and Human Services

Draft Report on Carcinogens Monograph on *Helicobacter pylori* (Chronic Infection)
Public Draft

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Foreword

The National Toxicology Program (NTP) is an interagency program within the Public Health Service (PHS) of the Department of Health and Human Services (HHS) and is headquartered at the National Institute of Environmental Health Sciences, of the National Institutes of Health (NIEHS/NIH). Three agencies contribute resources to the program: NIEHS/NIH, the National Institute for Occupational Safety and Health, of the Centers for Disease Control and Prevention (NIOSH/CDC), and the National Center for Toxicological Research, of the Food and Drug Administration (NCTR/FDA). Established in 1978, NTP is charged with coordinating toxicological testing activities, strengthening the science base in toxicology, developing and validating improved testing methods, and providing information about potentially toxic substances to health regulatory and research agencies, scientific and medical communities, and the public.

The Report on Carcinogens (RoC) is prepared in response to Section 301 of the Public Health Service Act as amended. The RoC contains a list of identified substances (i) that either are *known to be human carcinogens* or are *reasonably anticipated to be human carcinogens* and (ii) to which a significant number of persons residing in the United States are exposed. NTP, with assistance from other federal health and regulatory agencies and nongovernmental institutions, prepares the report for the Secretary, Department of HHS. The most recent RoC, the 14th Edition (2016), is available at http://ntp.niehs.nih.gov/go/roc.

Nominations for (1) listing a new substance, (2) reclassifying the listing status for a substance already listed, or (3) removing a substance already listed in the RoC are evaluated in a scientific review process (http://ntp.niehs.nih.gov/go/rocprocess) with multiple opportunities for scientific and public input and using established listing criteria (http://ntp.niehs.nih.gov/go/15209). A list of substances under consideration for listing in (or delisting from) the RoC can be obtained by accessing http://ntp.niehs.nih.gov/go/37893.

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1 Objective and Methods

1.1 Objective

Helicobacter pylori is a gram-negative, multi-flagellated bacterium that colonizes the luminal mucosal surface of the body (corpus) and lower portion (antrum) of the stomach; if untreated, the infection usually lasts for the individual's lifetime. Chronic infection can cause gastritis and peptic ulcers.

The objective of this monograph is to present NTP's preliminary conclusions regarding the level of evidence for carcinogenicity from studies in humans and experimental animals and its preliminary Report on Carcinogens (RoC) listing recommendation. These conclusions were reached by applying the RoC listing criteria to the cancer assessment.

The rationale for selecting *H. pylori* for review for the RoC and the approach to preparing the monograph were outlined in the draft concept document, "*Helicobacter pylori:* Chronic Infection" (NTP 2016). The draft concept document was released for public comment and presented to the NTP Board of Scientific Counselors at its meeting on April 11, 2016, which provided opportunity for written and oral public comments. After the meeting, the concept document was finalized, and *Helicobacter pylori* (Chronic Infection) was approved by the NTP Director as a candidate substance for review. The concept document is available on the RoC website (NTP 2016).

1.2 Monograph development and contents

In developing the monograph, NTP relied on the International Agency for Research on Cancer assessment (IARC 2012) and peer review of the cancer studies in humans and experimental animals and mechanistic and other relevant data. The rationale for relying primarily upon the IARC monograph is that the role of *H. pylori* as the major risk factor for stomach cancer is well established in the scientific community (see the concept document, NTP 2016).

H. pylori infection is responsible for approximately 780,000 cancer cases annually worldwide (Plummer *et al.* 2015). The current question for the health community is not about causation, but whether *H. pylori* screening and eradication programs should be implemented and, if so, how these prevention strategies should be carried out. Therefore, this monograph also reports on the status of activities for preventing *H. pylori*–induced stomach cancer. Providing information on activities to reduce exposure is consistent with the spirit of the congressional mandate for the RoC (as the report is expected to discuss Federal agency regulations to limit exposure) and should facilitate hazard communication efforts when the RoC monograph is published.

The monograph consists of the following sections:

- Objective and methods (Section 1), including methods for conducting the cancer hazard evaluation (Section 1.3)
- Substance profile: Science supporting the preliminary listing recommendation (Section 2)
- Status and summary of cancer prevention strategies (Section 3)

- Appendices: Literature search strategies and a summary of human studies of *H. pylori* infection and pancreatic and colorectal cancer

The substance profile includes a description of the substance, discussion of exposure-related data, a summary of the scientific information considered key to its listing, and applicable current federal regulations and guidelines to limit exposure. If *H. pylori* is listed in the 15th RoC, then the substance profile (but not the other sections of the monograph) will become part of the RoC. The profile is written for a broad audience.

1.3 Methods for conducting the cancer hazard evaluation

As outlined in the concept document, NTP conducted several problem-formulating activities. These included searching the peer-reviewed literature (1) to determine the extent of U.S. exposure to *H. pylori* and (2) to identify any potential controversies concerning IARC's assessment or any reports of cancer studies published since the IARC review whose findings were not consistent with findings from the earlier studies. Based on these literature searches, no information was identified that would argue against using the IARC assessment as the scientific basis for applying the RoC listing criteria and reaching a listing recommendation. NTP did not conduct its own systematic review of the primary cancer studies in humans and experimental animals.

The scientific information in the substance profile and cancer prevention strategies sections underwent scientific review and quality assurance review by a separate reviewer. The information in the profile was checked against the cited reference (e.g., IARC monograph, primary reference, review, or meta-analysis). Any discrepancies were resolved between the writer and the reviewer through discussion and reference to the original data source.

1.3.1 Selection of the literature

NTP supplemented the IARC assessment and peer review of the cancer studies in humans and experimental animals and mechanistic studies (IARC 2012) with recent reviews or meta-analyses on cancer and mechanistic studies and exposure information. NTP also reviewed individual studies (cited in reviews, the IARC monograph, or other publications) when information in the IARC monograph was not clear or was related to a specific scientific issue.

Details on the literature search procedures and search terms are available in Appendix A.

1.3.2 Evaluation of human cancer studies

NTP applied the RoC listing criteria (shown at the end of Section 1.3) to the body of literature to reach a decision on the level of evidence (sufficient, limited, or inadequate) for carcinogenicity based on cancer studies in humans. Human cancer studies on *H. pylori* infection were reported in the most recent IARC monograph on *H. pylori* (IARC 2012). NTP supplemented this information with a few more-recent studies that addressed key issues, such as information regarding chronic infection.

NTP focused on the two cancer outcomes for which IARC concluded there was sufficient evidence of carcinogenicity from studies in humans: stomach cancer and gastric mucosa-associated lymphoid tissue (MALT) lymphoma (IARC 2012, Tables 2.1 to 2.7). Evidence was considered to be lacking for *H. pylori* as a cause of esophageal cancer (adenocarcinoma). In evaluating the human cancer data, NTP considered (1) IARC working-group comments on the strengths and limitations of the studies, (2) the consistency of a positive association across studies, (3) patterns such as exposure-response or latency relationships, (4) effect modifiers or co-factors, and (5) whether the association across studies could be explained by chance, bias, or confounding. The science supporting the NTP level-of-evidence conclusions is captured in the substance profile (Section 2).

With respect to other types of cancer, the IARC working group expressed concerns about the quality of the studies or the small numbers of studies available (IARC 2012). NTP also reviewed recent meta-analyses, systematic reviews, and other reviews evaluating the association of *H. pylori* infection with other types of cancer, primarily pancreatic and colorectal cancer. In general, primary studies on these two types of cancer were identified from the meta-analyses or cited references. Based on the review of recent studies and of the IARC monograph, NTP concluded that no formal cancer hazard evaluation of pancreatic or colorectal cancer was warranted. A short summary of the updated findings on pancreatic and colorectal cancer is provided in Appendix B.

1.3.3 Evaluation of cancer studies in experimental animals

NTP applied the RoC listing criteria to the body of literature to reach a decision on the level of evidence (sufficient or not sufficient) from cancer studies in experimental animals. NTP accepted IARC’s conclusions concerning the association between *H. pylori* infection and specific types of tumors (e.g., gastric adenocarcinoma and gastric lymphoma) in various animal models to determine whether the increases in tumors occurred at multiple tissue sites or in multiple species, or whether tumors occurred to an unusual degree with respect to incidence, site, type of tumor, or age at onset. In evaluating the data on cancer in experimental animals, NTP considered sources of heterogeneity across studies, such as differences in *H. pylori* strain, animal strain, or experimental methods, such as study duration.

1.3.4 Evaluation of mechanistic and other relevant data

The objective of the section on mechanistic and other relevant data is to provide a concise overview of the pathogenesis of *H. pylori* chronic infection and potential mechanisms of *H. pylori* carcinogenicity. As mentioned above, the substance profile is written for a broad audience, and its purpose is to provide an overview of the information that was key to the listing recommendation. Therefore, this section does not provide a detailed, comprehensive assessment of the mechanistic data or develop proposed modes of action. However, the section does evaluate whether the available mechanistic data provide biological plausibility for the findings observed in humans.

1.3.5 Overall evaluation and preliminary listing recommendation

The evidence from the cancer studies in humans and experimental animals was integrated with the assessment of the mechanistic and other relevant data. The RoC listing criteria were then applied to the body of knowledge to reach a listing recommendation regarding chronic infection with *H. pylori*.

RoC Listing Criteria

Known To Be Human Carcinogen:

There is sufficient evidence of carcinogenicity from studies in humans*, which indicates a causal relationship between exposure to the agent, substance, or mixture, and human cancer.

Reasonably Anticipated To Be Human Carcinogen:

There is limited evidence of carcinogenicity from studies in humans*, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded,

OR

there is sufficient evidence of carcinogenicity from studies in experimental animals, which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site, or type of tumor, or age at onset,

OR

there is less than sufficient evidence of carcinogenicity in humans or laboratory animals; however, the agent, substance, or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Report on Carcinogens as either known to be a human carcinogen or reasonably anticipated to be a human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to, dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub-populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals, but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

*This evidence can include traditional cancer epidemiology studies, data from clinical studies, and/or data derived from the study of tissues or cells from humans exposed to the substance in question that can be useful for evaluating whether a relevant cancer mechanism is operating in people.

1.4 Method for developing the section on prevention of *H. pylori*–associated cancer

The purpose of the section is to provide information and summarize studies and expert working group recommendations related to the prevention of *H. pylori*–associated gastric cancers. The IARC Working Group report, “*Helicobacter pylori* Eradication as a Strategy for Preventing Gastric Cancer,” served as the basis for Section 3 of the monograph (IARC 2014). The information was supplemented with new studies that evaluated the effectiveness of screening and eradication, cost-benefit analysis, and expert or government recommendations or guidelines. NTP did not make an assessment of the studies or provide its own recommendations or policies. The scientific information in the cancer prevention strategies sections underwent scientific review and quality assurance review by a separate reviewer, in a process similar to that described for the substance profile.

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2 *Helicobacter pylori* (Chronic Infection) Substance Profile

The substance profile provides a summary of the carcinogenicity information supporting NTP's preliminary listing recommendation for *Helicobacter pylori*, together with information on biological properties, detection methods, human exposure, and regulations to limit exposure. The exposure information includes data on transmission and risk factors, non-cancer diseases, treatment, and prevention.

2.1 Biological properties

H. pylori is a gram-negative, spiral- (or helical-) shaped, multi-flagellated 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). Some gastric *Helicobacter* species from animals that can also infect humans include *H. bizzozeroni, H. salomonis, H. felis, H. candidates,* and *H. suis* (IARC 2012). Some *Helicobacter* species that cause non-gastric diseases (primarily liver diseases) in humans include *H. hepaticus, H. pullorum,* and *H. bilis* (Mateos-Muñoz *et al.* 2013).

H. pylori colonizes the mucosal surface of the body (corpus) and 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. The major *H. pylori* protein involved in colonization is blood group antigen binding adhesin (BabA), which 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, the infection usually lasts for the individual's lifetime (Logan and Walker 2001, Testerman and Morris 2014).

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. A neutral pH environment thus is created in the mucosal layer adjacent to the surface epithelium of the stomach, allowing the bacterium to grow (Testerman and Morris 2014). Other properties of the bacterium also facilitate a persistent infection. Its helical shape and flagella help it to propel itself through the viscous mucosa, and a chemotaxis system (by which an organism moves in response to a chemical stimulus) helps the bacterium 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 reduce the infected individual's inflammatory response to the infection.

The *H. pylori* genome codes for several virulence factors, including cytotoxin-associated gene A product (CagA) and vacuolating cytotoxin A (VacA), which vary geographically and across strains (IARC 2012, Yamaoka and Graham 2014). Humans can be infected with several *H. pylori* strains, which may then exchange DNA, promoting the spread of virulence factors and antibiotic resistance (IARC 2012).

2.2 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, Testerman and Morris 2014, Diaconu *et al.* 2017). These methods are summarized in the table below. Biopsy samples can also be evaluated for gastric pathology. All of these tests have moderate to high sensitivity (74% to 100%) and specificity (75% to 100%); however, sensitivity and specificity may vary depending on the condition of the patient, and some methods require several samples. The method of detection used depends in part on the purpose of the testing (e.g., selection of treatment method or population studies), cost and technical skills, and patient considerations, such as age.

Table 2-1. Methods for detection of *H. pylori* infection

Test	Agent	Type of sample	Comment
Histology: staining (e.g., Diff-QuiK, Giemsa, hematoxylin and eosin)	*H. pylori* organism	Stomach tissue biopsy	Sensitivity: 93%–96% Specificity: 98%–99% Several samples needed; high cost; should be performed only on selected samples, such as from patients with gastritis or using certain types of antibiotics
Culture	*H. pylori* organism	Stomach tissue biopsy	Sensitivity: 80%–98% Specificity: ~100% Used for antimicrobial sensitivity testing; high cost
Rapid urease testing	*H. pylori* activity (active organisms)	Stomach tissue biopsy	Sensitivity: 88%–95% Specificity: 95%–~100%
Molecular methods (e.g., polymerase chain reaction)	*H. pylori* DNA or RNA	Stomach tissue biopsy; stool, saliva, or oral-cavity specimens	Sensitivity and specificity > 95%
Serology testing using *H. pylori* antigens: enzyme-linked immuno-sorbent assay (ELISA), immunoblot	*H. pylori* antibodies (mainly immunoglobulin G [IgG])	Serum or plasma	Sensitivity: 85%–96% Specificity: 75%–95% False-negative results can occur with underlying atrophic gastritis or gastric cancer or lifelong infections
Urea breath test	*H. pylori* urease activity (active infection) by measuring carbon dioxide (CO_2)	Expired air	Sensitivity: 90%–99% Specificity: 88%–98%
Stool antigen test (e.g., ELISA, immunocards)	*H. pylori* antigens (active infection)	Stool	Sensitivity: 94% Specificity: 92% Recommended for children

Sources: Reynders *et al.* 2012, Testerman and Morris 2014, Diaconu *et al.* 2017.

Serological tests (such as ELISA or immunoblot) 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). Antibodies to *H. pylori* persist for up to half a year, so these tests thus detect both past and current infections. An advantage of serological tests is that they are not affected by recent antibiotic use or acid-suppression therapy (Testerman and Morris 2014); however, they are not useful for measuring antibiotic treatment efficacy (Diaconu *et al.* 2017), as antibody titers are slow to fall. The sensitivity and specificity of serological tests depends on the antigens used in the assay, the type of assay (e.g., ELISA vs. immunoblot), the immunoglobulin class tested (mainly IgG, but also IgA), 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 immunoblot 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). A urine-based ELISA has also been developed to detect antibodies to *H. pylori*, which in a study of over 800 children had sensitivity (~85%) and specificity (~96%) similar to that of the serum-based test (Kato *et al.* 2001).

2.3 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. Prevalence rates in most of the world (e.g., especially the United States, Korea, and Japan) have decreased with each successive generation (referred to as the “birth cohort effect”) but have remained stable in many lower-income countries (such as in Latin 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).

In the United States, approximately 36% of people are infected with *H. pylori,* the highest prevalence being found among minority groups (e.g., the Alaskan indigenous population, Hispanics, and African Americans) and individuals born outside the United States, especially recent Asian immigrants (Khalifa *et al.* 2010, Siao and Somsouk 2014, Krueger *et al.* 2015, Hooi *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 African-Americans than whites (Epplein *et al.* 2011).

The prevalence of *H. pylori* infection increases with increasing age (Krueger *et al.* 2015), and geographic differences in *H. pylori* infection are related to the rate of acquisition early in life (Khalifa *et al.* 2010). In low-income countries, initial infection often occurs in early childhood, and prevalence rates peak by 50 years of age. In high-income countries, infection is more common in adulthood, with peak prevalence among those over the age of 60 (Malnick *et al.* 2014). However, in a study in Colombia, two populations with different risks of stomach cancer (high and low) had similar prevalence patterns of *H. pylori* infection at an early age, suggesting that age of acquisition of infection may not play a major role in explaining gastric cancer risk (Camargo *et al.* 2004).

2.3.1 Transmission

Data from the U.S. National Health and Nutrition Examination Survey (NHANES) suggest that risk factors for *H. pylori* infection include age, race or ethnicity (minority), socioeconomic status (low family income and lower 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 by person-to-person contact, especially among family members. This occurs primarily via oral-to-oral transmission and possibly via gastro-oral transmission mediated by refluxed gastric juice or fecal-oral transmission. *H. pylori* has been isolated from the oral cavity, gastric juices, and fecal samples (Khalifa *et al.* 2010). A meta-analysis of 22 studies found that *H. pylori* infection in the oral cavity was significantly more common among subjects with gastric *H. pylori* infection than among subjects without gastric *H. pylori* infection (Zou and Li 2011).

H. pylori can also be transmitted indirectly by 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). The bacterium has been detected in surface, ground, and well water in the United States and in treated municipal, tap, well, and bottled water in other countries (such as Peru and Sweden), and *H. pylori* can remain viable in chlorinated water (reviewed by IARC 2012, Aziz *et al.* 2015). 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). Some epidemiological studies, including a study using NHANES data (for people aged 3 to 19) found that using well water or other unpurified water is a risk factor for *H. pylori* infection (Khalifa *et al.* 2010, Aziz *et al.* 2015, Krueger *et al.* 2015). In Japan, *H. pylori* prevalence was substantially lower in a cohort of individuals born between the 1960s and 1980s (14%) than in cohorts born between 1927 (54%) and 1949 (42%), which could be the result of improvements in sanitary conditions, such as the introduction of municipal water supply in the 1950s to 1970s (Leja *et al.* 2016). NHANES data also indicated that soil-related occupations among adults are a risk factor for *H. pylori* infection, which suggests an environmental route of transmission (Krueger *et al.* 2015).

2.3.2 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 non-ulcer dyspepsia (indigestion) and 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) (Testerman and Morris 2014).

Many different therapies are used in the United States, but the American College of Gastroenterology Clinical Guideline for Treatment of *H. pylori* Infection update in 2017 (Chey *et al.* 2017) indicates that first-line regimens approved by the U.S. Food and Drug Administration (FDA) are either (1) clarithromycin triple therapy, with that antibiotic in combination with a proton-pump inhibitor (PPI) and a second antibiotic for 14 days, or (2) bismuth quadruple therapy, with a bismuth salt, a PPI, and two antibiotics for 10 to 14 days. 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 metabolism of PPIs, and past antibiotic use) and (2) *H. pylori*–related factors. The susceptibility of *H. pylori* to specific antibiotics is the most important determinant of successful *H. pylori* treatment, and patterns of resistance to specific antibiotics can vary geographically (Chey *et al.* 2017, Malfertheiner *et al.* 2017). If first-line treatment fails, second-line or salvage therapy generally is based on local antibiotic resistance rates (where known) and an individual's previous antibiotic use. Globally, *H. pylori* eradication rates have declined as antibiotic resistance rates have increased (Thung *et al.* 2016). Currently, no *H. pylori* vaccine is commercially available (CDC 2016, FDA 2017); however, vaccine development efforts are ongoing (Zeng *et al.* 2015, Moss 2017).

Randomized controlled trials (clinical studies with control groups that receive placebos) 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 that *H. pylori* eradiation is 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 (GERD). Numerous international and national working groups have recommended that planned programs should consider objective assessments of feasibility, effectiveness, program acceptance, cost-effectiveness, and adverse consequences relevant to the local area before implementation. (See Section 3 for more information on prevention strategies.)

2.4 Carcinogenicity

This section reviews the evidence for carcinogenicity in humans (Section 2.4.1) and experimental animals (Section 2.4.2) and mechanistic data (Section 2.4.3) that are key to NTP's preliminary listing recommendation (Section 2.4.4).

2.4.1 Cancer studies in humans

Worldwide, stomach cancer is the fifth most common type of cancer and third leading cause of death from cancer, with most cases occurring in low- and middle-income countries. Adenocarcinoma accounts for over 90% to 95% of all stomach cancer (Balakrishnan *et al.* 2017), which 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. Gastric lymphoma, which consists primarily of gastric mucosa-associated lymphoid tissue (MALT) lymphoma and diffuse large B-cell lymphoma, accounts for approximately 2% to

8% of all stomach tumors (Zullo *et al.* 2010b, Park and Koo 2014). Gastric MALT lymphoma is a type of extranodal B-cell lymphoma (i.e., not arising in lymph nodes or other lymphoid tissue) that is low-grade, slow growing, and very rare (with a worldwide incidence of 1 to 1.5 cases per 100,000 people) (Pereira and Medeiros 2014).

Stomach cancer

Evidence that *H. pylori* causes stomach (non-cardia gastric) cancer in humans is based on (1) consistent evidence from numerous epidemiological studies on stomach cancer, (2) a pooled analysis of 12 epidemiological studies, and (3) several meta-analyses (combined statistical analyses of the data from several different studies).

Cohort studies found that *H. pylori*–infected individuals were more likely to develop stomach cancer than were uninfected individuals (IARC 2012). These studies followed subjects with and without *H. pylori* infection for 4 to 10 years. Depending on the study, the subjects were either asymptomatic or had various types of stomach disease and were enrolled in various types of screening programs. Numerous nested case-control studies (case-control analyses conducted within cohorts of subjects) provided evidence that the increased risk was specifically for non-cardia gastric cancer (IARC 2012). A pooled analysis of 12 of these nested case-control studies, which included 762 case subjects and 2,250 control subjects, matched to the case subjects by age, sex, and date of sample collection for *H. pylori* testing, found a risk factor of 2.97 (95% confidence interval [CI] = 2.34 to 3.77) for non-cardia gastric cancer and *H. pylori* infection (*Helicobacter* Cancer Collaborative Group 2001). The highest risk was for subjects followed for a longer time after enrollment (odds ratio [OR] = 5.93, 95% CI = 3.41 to 10.30 for ≥ 10 years of follow-up, compared with OR = 2.39, 95% CI = 1.82 to 3.12 for < 10 years of follow-up).

Similar findings of an excess risk of non-cardia gastric cancer were reported in a meta-analysis of data 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 the 2001 pooled analysis also found significantly elevated risks for non-cardia gastric cancer, confirming the association with *H. pylori* infection.

Most epidemiological studies measured *H. pylori* infection status by the presence of antibodies to *H. pylori* (i.e., seropositivity). Higher risks for non-cardia gastric cancer (increased by over tenfold) were found when *H. pylori* seropositivity was measured by a more sensitive assay (immunoblot, rather than the ELISA typically used) (Simán *et al.* 2007, Mitchell *et al.* 2008, González *et al.* 2012). In most studies that looked at infection with various strains of *H. pylori*, higher risks were found for infection with strains that produced CagA than for infection with CagA-negative strains. A meta-analysis of data on *H. pylori*–positive cases from nine studies found that CagA seropositivity approximately doubled the risk of non-cardia gastric cancer over that due to *H. pylori* infection alone (Huang *et al.* 2003).

Some studies found a higher risk of stomach cancer among *H. pylori*–infected individuals who smoked or who consumed salted, smoked, processed foods, or red meat, and a lower risk among those with diets high in vegetables or intake of vitamins, suggesting that these exposures (diet or types of food) may be co-factors for *H. pylori*–induced stomach cancer (IARC 2012, Epplein *et al.* 2014). Several studies controlled for known risk factors for stomach cancer, and increased risks were found in studies in various geographical locations, which increases confidence that the elevated risks observed in these studies are not explained by bias, chance, or confounding.

Evidence for a role of *H. pylori* in cardia gastric cancer is less clear and may be restricted to specific subtypes 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 and *H. pylori* infection. However, a meta-analysis of all type of studies (primarily case-control studies) found that *H. pylori* infection increased the risk of cardia gastric cancer in high-risk countries (adjusted 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 different subtypes of cardia gastric cancer or inclusion of esophageal adenocarcinoma or the gastroesophageal junction with cardia gastric cancer; however, few studies have addressed these anatomical distinctions (Malfertheiner *et al.* 2017).

Gastric MALT lymphoma

Evidence that *H. pylori* causes gastric MALT lymphoma comes primarily from 16 intervention (non-controlled) studies (as reviewed by IARC 2012), which found that 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 approximately 78% of the patients who were cured of *H. pylori* infection (Zullo *et al.* 2010a). Because of the rarity of this cancer, the number of observations is limited. Two small case-control analyses (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, which provides additional support for a causal relationship (Parsonnet *et al.* 1994 and de Sanjose *et al.* 2004, as cited by IARC 2012).

2.4.2 Cancer studies in experimental animals

H. pylori infection (orally administered by gavage) caused malignant tumors in two different types of stomach tissue in rodents. Importantly, the types of cancer observed in animals infected with *H. pylori* — gastric tumors and gastric lymphoma — are 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) (1) in Mongolian gerbils in some, but not all, studies and (2) in transgenic (genetically altered) mice. 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, Franco *et al.* 2008, Romero-Gallo *et al.* 2008, as cited by IARC 2012). 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 in INS-GAS transgenic mice, which have been genetically modified to produced more gastrin (a peptide that increases the secretion of gastric acid). In studies of other types of transgenic mice (TGF-β- or p27-deficient mice, which have increased susceptibility to carcinogens), *H. pylori* infection increased the incidence of combined gastric dysplasia (a precancerous lesion) and carcinoma (IARC 2012). Two studies, one in Mongolian gerbils (Romero-Gallo *et al.* 2008, as cited by IARC 2012) and the other in transgenic mice (Lee *et al.* 2008, as cited by IARC 2012), 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.

There is strong evidence that *H. pylori* given in combination with other carcinogens (*N*-methyl-*N*-nitrosourea [MNU], *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine, or ethylnitronitrosoguanidine) increased the incidences of stomach tumors over those in rodents (IARC 2012) and non-human primates (Liu *et al.* 2009) exposed only to the other carcinogens. Early *H. pylori* eradication therapy reduced the incidence of stomach tumors (adenocarcinoma) induced by combined administration of *H. pylori* and MNU (Nozaki *et al.* 2002, as cited by IARC 2012). The addition of a high-salt diet also increased the incidence of stomach tumors in *H. pylori*–infected gerbils.

H. pylori infection caused gastric lymphoma in two different strains of inbred mice (Wang *et al.* 2003, as cited by IARC 2012) and in neonatal mice that had had their thymus glands removed (Fukui *et al.* 2004). In the latter study, all of the mice developed gastric MALT lymphoma by the age of 12 months.

2.4.3 Mechanisms of carcinogenesis and other relevant data

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, 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 is usually 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 increased pH (reduced acidity) in the stomach, oxidative stress, and changes in the types of tissues and cells in the stomach. Increased pH can favor further colonization and proliferation of *H. pylori*, allowing the bacterium to adapt to the conditions of the stomach, which would otherwise be too acidic for its survival.

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 relative to that in uninfected men 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 that having chronic atrophic gastritis was associated with a fivefold increase in the risk of non-cardia gastric cancer (Chen *et al.* 2016b). 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).

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.* 2016b) 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. These biological effects (chronic inflammation, changes in gene expression, mutations, genomic instability, and cellular proliferation) are associated with carcinogenesis.

2.4.4 NTP's Preliminary listing recommendation

Helicobacter pylori (chronic infection) is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans. This conclusion is based on epidemiological studies showing that *H. pylori* infection causes stomach cancer (especially non-cardia gastric cancer) and a specific type of lymphoma in the stomach (gastric MALT lymphoma).

H. pylori is estimated to cause 89% of non-cardia gastric cancer and 92% to 98% of all gastric MALT lymphoma cases. It is responsible for approximately 780,000 cancer cases (primarily gastric cancer) worldwide each year, accounting for 6.2% of all cancer cases (Testerman and Morris 2014, Plummer *et al.* 2015). Mechanistic and toxicological data indicate that chronic infection of the stomach with *H. pylori* is required for carcinogenicity, and they demonstrate the biological plausibility of its carcinogenicity. Studies in experimental animals indicate that *H. pylori* induces types of tumors similar to those found in humans: adenocarcinoma and lymphoma of the stomach.

2.5 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.

3 Prevention of *H. pylori*–Associated Cancer

Stomach cancer is the fifth most common cancer worldwide, with around 1.3 million new cases occurring annually, and the third most common cause of death from cancer — it is estimated that over 800,000 people died of stomach cancer worldwide in 2015 (Fitzmaurice *et al.* 2017). An estimated 73% of all stomach-cancer cases are non-cardia gastric cancer (Colquhoun *et al.* 2015). Worldwide, 70% of all stomach-cancer cases occur in low-income countries. In low-risk areas, such as the United States, Europe, Australia, and New Zealand, the incidence of and mortality from stomach cancer show disparities, with minority, indigenous, and immigrant populations at higher risk (Epplein *et al.* 2011, Taylor *et al.* 2014, Balakrishnan *et al.* 2017, SEER 2018). In the United States, stomach cancer accounts for 1.7% of all new cancer cases, but some minority populations have a 40% to 50% higher risk (Bjorkman 2017, SEER 2018). In addition to disparities by geography and race, stomach-cancer incidence and mortality are higher in men than women; worldwide, the estimated age-standardized incidence rate in men is twice that in women (Forman and Sierra 2014, Herrero *et al.* 2014). Overall stomach-cancer incidence has decreased in recent years, by approximately 2% per year; however, recent evidence suggests it may be increasing in younger populations (Anderson *et al.* 2018). The estimated global burden of the disease is expected to increase in the next 10 to 15 years, primarily as a result of population growth and aging (Ferlay *et al.* 2013, as cited by IARC 2014).

H. pylori infection has been established as a cause for non-cardia gastric cancer and gastric MALT lymphoma (IARC 2012; see Section 2) and may account for up to 6.2% of all cancer deaths worldwide (Plummer *et al.* 2015). Calculated population attributable fractions range from 75% to 89%, indicating that a large majority of these cancer cases could be avoided if *H. pylori* exposure were eliminated (de Martel *et al.* 2012, Plummer *et al.* 2015, Song and Zhou 2015).

This section provides an overview of the state of science for prevention of *H. pylori*–induced cancer, the cost-effectiveness of this prevention, issues and concerns for large-scale prevention programs, and current national and regional policies for stomach cancer prevention.

3.1 Prevention of *H. pylori*–induced cancers: State of the science

Screening and treatment of *H. pylori*–infected individuals shows promise as a method for the prevention of stomach cancer. Over the past 20 years, numerous studies have been conducted on the effectiveness of screening and treatment methods. Three screening methods and two types of treatment have been evaluated (see Section 3.1.1). The benefits of *H. pylori* eradication have been evaluated in 10 randomized controlled trials and at least 16 cohorts. These studies support eradication of *H. pylori* for the prevention of stomach cancer, and recent meta-analyses have confirmed these findings (see Section 3.1.2). Moreover, several economic analyses have determined that screening and treatment of *H. pylori* is cost-effective as a prevention method (see Section 3.1.3). Several issues and concerns relevant to the implementation of large-scale eradication efforts must be taken into account. These include antibiotic resistance, the likelihood of *H. pylori* reinfection, the possible inverse relationship between *H. pylori* infection and some other gastric illnesses, the presence of atrophic damage at the time of eradication, and the need to tailor treatment programs to specific geographic regions (see Section 3.1.4).

3.1.1 Screening for and treatment of *H. pylori* infection

H. pylori screening and treatment have been identified as candidates for population-level intervention programs in high-prevalence areas, supported by several cost-benefit analyses; however, additional data are needed. Several methods exist for *H. pylori* population screening, including serology tests for *H. pylori* antibodies, a stool antigen test, and a urea breath test. Stool antigen and urea breath tests offer greater sensitivities and specificities than the antibody tests, but these options are more expensive and may be harder to implement at a population level. *H. pylori* serological tests (for antibodies) detect past and present infections, and therefore are not useful for determining the efficacy of *H. pylori* treatment (Moayyedi 2014) (see Section 2 for more details on detection methods).

Treatment of *H. pylori* infection often can achieve a high rate of eradication. The most common treatment is a standard triple therapy, which includes a PPI, clarithromycin, and either amoxicillin or metronidazole antibiotics given for one to two weeks. This PPI triple therapy is relatively low-cost and widely available. Early reports suggested that this treatment resulted in eradication rates of over 90%; however, rates more recently have fallen well below 80%. In some locations in Europe, the eradication rate for the standard PPI triple therapy is as low as 25% to 60%. This variability in effectiveness is likely due to the rise in antibiotic resistance, specifically to clarithromycin. In many parts of the world, clarithromycin resistance is so high that the clarithromycin-based PPI triple therapy is not recommended as the first-line treatment. Methods to improve the effectiveness of the PPI triple therapy have been proposed, such as increasing the dose by increasing the frequency of treatment, using second-generation PPIs, or increasing treatment duration (reviewed by Gisbert and Greenberg 2014). Another treatment currently recommended as a first-line therapy (concomitant therapy) adds metronidazole or nitroimidazole to the standard PPI treatment (Chey *et al.* 2017).

Another low-cost therapy (bismuth-containing quadruple therapy) combines bismuth salts, tetracycline, a PPI, and metronidazole for 14 days, with a reported eradication rate of over 80% to 90%. Bismuth-containing quadruple therapy is now recommended as the first-line treatment in areas of high clarithromycin resistance, while standard PPI triple therapy may be used in areas of low resistance. Although metronidazole resistance is high worldwide, the clinical impact of this resistance is low, and the quadruple therapy is effective when dose and duration are increased. Additional studies are needed on the effectiveness of bismuth-containing quadruple therapy as a first-line treatment. The unavailability of bismuth and tetracycline in many areas also must be considered for any population-level intervention programs. Because antibiotic resistance varies within populations, programs should use treatment regimens that have proven reliably effective in the target population and area, or methods based on the observed pattern of resistance (reviewed by Gisbert and Greenberg 2014, Herrero *et al.* 2014).

In addition to *H. pylori* prevention through the use of antibiotics, a recent study of an oral vaccination showed promising results, indicating a possible future direction for *H. pylori* eradication (Moss 2017).

3.1.2 Efficacy and effectiveness of *H. pylori* eradication in preventing stomach cancer

Gastric cancer

Since 1997, a number of cohort studies and randomized controlled trials have been conducted to determine the efficacy and effectiveness of *H. pylori* eradication therapy in preventing gastric cancer. These studies looked at the effectiveness of eradication among individuals who had never had stomach cancer (primary prevention) and among patients with previous endoscopic resection of early gastric cancer (secondary prevention, sometimes referred to as tertiary prevention). The cohort studies were generally conducted in Japan and Korea, with one study each in Taiwan and Finland, and enrolled between 50 and 8,000 participants, with follow-up times ranging from 2 to 10 years.

Since 2000, six randomized controlled trials have investigated the primary prevention of gastric cancer following *H. pylori* eradication therapy. These trials have been primarily in China, with one each in Colombia (Correa *et al.* 2000) and Japan (Saito *et al.* 2005); follow-up times ranged from 3 to 14.7 years. An additional three trials, one in Japan (Fukase *et al.* 2008) and two in South Korea (Choi *et al.* 2014b, Choi *et al.* 2018), looked at the efficacy of *H. pylori* eradication for the secondary prevention of gastric cancer, with follow-up times of approximately 3 to 6 years.

Taken together, the nine trials demonstrated the partial effectiveness of *H. pylori* eradication therapy in reducing the incidence of gastric cancer. These studies generally had adequate sample sizes, but many had small numbers of cases in both study arms. Only two of the nine studies had follow-up times exceeding 10 years, which may explain the lack of significant findings in several studies. Furthermore, all of these trials used the standard PPI triple therapy for eradication, and not the bismuth-containing quadruple therapy, which may be more effective in areas with high levels of clarithromycin resistance. Finally, all but one trial took place in eastern Asia, which may limit the generalizability of the results to other populations. The results of the randomized controlled trials are summarized in Table 3-1. Additional data will be provided by several ongoing trials, as well as long-term follow-up of the current studies. Additional data on prevention efficacy may provide additional support for large-scale eradication programs.

Table 3-1. Randomized controlled trials of *H. pylori* eradication and the incidence of gastric cancer

Reference Geographic location Related references	Study population No. of subjects: treatment/placebo Follow-up duration	End points	RR, HR, or OR (95% CI); No. of cases treatment/placebo
Individuals without gastric cancer			
Correa *et al.* 2000 Colombia[a]	Asymptomatic men and women aged 29–69 with advanced gastric lesions (CAG, IM, and DYS); enrolled 1991 491/485 6 yr	Gastric cancer	[1.48 (0.25–8.83); 3/2 cases][b]
		IM regression	3.1 (1.0–9.3)
		IM progression	0.4 (0.2–0.9)

Reference **Geographic location** **Related references**	**Study population** **No. of subjects: treatment/placebo** **Follow-up duration**	**End points**	**RR, HR, or OR (95% CI); No. of cases treatment/placebo**
Wong *et al.* 2004 China	Asymptomatic men and women aged 35–65 with mixed gastric lesions; enrolled 1994 817/813 7.5 yr	Gastric cancer	
		All subjects	0.63 (0.24–1.62); 7/11
		Baseline precancerous lesions	
		No (62%)	*P* = 0.02; 0/6
		Yes (CAG, IM, DYS)	*P* = 0.67; 7/5
Saito *et al.* 2005 Japan	Asymptomatic men and women aged 20–59 379/313 4 yr	Gastric cancer	0.55 (0.09–3.27); 2/3
Zhou *et al.* 2014 China Leung *et al.* 2004	Asymptomatic men and women aged 35–75 with mixed gastric lesions; enrolled 1996 276/276 (2014); 295/292 (2004) 10 yr (2014) 5 yr (2004)	Gastric cancer	
		2014 (all)	[0.29 0.06–1.36)][c];2/7
		2014 (no CAG)	0.00 (0.00–0.81); 0/6
		2004 study	0.66 (0.18–2.36)]; 4/6
		IM progression	
		2014	0.85 (0.78–0.92); NR
		2004	0.63 (0.43–0.93); 104/126
Ma *et al.* 2012 China You *et al.* 2006 (7-yr follow up) Li *et al.* 2014 (sub group analyses)	Asymptomatic men and women aged 35–64 with mixed gastric lesions; enrolled 1994–1995 (Shandong Intervention Trial) 1130/1128 14.7 yr	All subjects	
		Incidence	0.61 (0.39–0.96); 34/52
		Mortality	0.68 (0.36–1.29); 16/23
		Age ≥ 55	
		Incidence	0.36 (0.17–0.79); 10/24
		Mortality	0.26 (0.09–0.79); 4/15
		Baseline lesions	
		Less severe	1.08 (0.31–3.81); 5/5
		(includes CAG)	(0.56 (0.34–0.91); 28/46
		IM, and DYS	
Wong *et al.* 2012 China	Asymptomatic men and women aged 35–64 with advanced gastric lesions (CAG or greater) enrolled 2002 255/285 4 yr	Gastric cancer	[3.04 (0.32–28.99)][d]; 3/1
		Regression	2.19 (1.32–3.64); 96/82
		Progression	1.08 (0.58–2.02); 30/50
Gastric cancer patients[e]			
Fukase *et al.* 2008 Japan	Men and women aged 20–79 with early gastric cancer resection; enrolled 2001–2003 (secondary prevention) 272/272 3 yr	Secondary gastric cancer	0.35 (0.16–0.78); 9/24

Reference **Geographic location** **Related references**	**Study population** **No. of subjects: treatment/placebo** **Follow-up duration**	**End points**	**RR, HR, or OR (95% CI); No. of cases treatment/placebo**
Choi *et al.* 2014b South Korea	Men and women aged 20–75 with early gastric cancer resection; enrolled 2005–2011 (secondary prevention) 444/457 2.6–93.3 mo (median = 38 mo)	Secondary gastric cancer	[0.61 (0.28–1.31)][c]; 10/17 (*P* = 0.15 by log rank)
Choi *et al.* 2018 South Korea	Men and women aged 18–75 with early gastric cancer resection; enrolled 2003–2013 (secondary prevention) 194/202 Median = 5.9 yr, Maximum = 12.9 yr	Secondary gastric cancer	0.50 (0.26–0.94); 14/27 *P* = 0.03

CAG = chronic atrophic gastritis, DYS = dysplasia, HR = hazard ratio, IM = intestinal metaplasia, IRQ = interquartile range, OR = odds ratio, RR = relative risk.

[a] Subjects were followed after the intervention, and patients in the placebo group were offered treatment (Mera *et al.* 2005, Mera *et al.* 2017).

[b] Effect estimate calculated by Ford *et al.* 2014 meta-analysis.

[c] Effect estimate calculated by Lee *et al.* 2016 meta-analysis.

[d] Effect estimate calculated by Ford *et al.* 2014 meta-analysis. The authors did not evaluate gastric cancer, because 7 of the 9 cancer cases across several treatment groups occurred during the treatment period.

[e] Patients with previous endoscopic resection of early gastric cancer.

The most informative studies were two large trials in China that evaluated primary prevention of gastric cancer. The Shandong Intervention Trial (You *et al.* 2006, Ma *et al.* 2012, Li *et al.* 2014) enrolled and randomized 2,258 *H. pylori*–seropositive subjects who were followed for 14.7 years, resulting in 34 cancer cases in the intervention group and 52 in the placebo group (OR = 0.61, 95% CI = 0.38 to 0.96). The next-largest trial, also conducted in China, enrolled 1,630 *H. pylori*–seropositive participants who were followed for 7.5 years. A total of 7 cancer cases were seen in the intervention group and 11 in the placebo group (HR = 0.63, 95% CI = 0.24 to 1.52) (Wong *et al.* 2004). These studies stratified by the type of gastric lesion at baseline, but defined the lesion categories differently. The Shandong Intervention Trial grouped chronic atrophic gastritis with less severe lesions and found that *H. pylori* eradication was effective in preventing gastric cancer among participants with precancerous lesions (intestinal metaplasia and dysplasia) at baseline, but not among patients with less severe lesions; however, few cases of gastric cancer were seen in either treatment arm (intervention or placebo) among the patients with less severe lesions. In contrast, Wong *et al.* (2004) grouped chronic atrophic gastritis with the precancerous lesions and found that *H. pylori* eradication was effective only among patients with less severe lesions (see Table 3-1).

The additional four trials of primary prevention, two in China (Wong *et al.* 2012, Zhou *et al.* 2014) and one each in Columbia (Correa *et al.* 2000) and Japan (Saito *et al.* 2005), had a combined total of 10 gastric cancer cases in the intervention groups and 13 in the placebo groups. Two smaller studies lacked sufficient statistical power to evaluate gastric cancer incidence, but reported that *H. pylori* treatment was effective in promoting the regression of histological gastric lesions (Correa *et al.* 2000, Zhou *et al.* 2014). Wong *et al.* (2012) did not evaluate the effect of treatment on gastric cancer incidence, because 7 of the 9 cancer cases (across several treatment options, such as COX 2 inhibitor treatment) occurred during the treatment period.

When all six randomized controlled trials of primary prevention were included in a meta-analysis, the risk ratio was 0.66 (95% CI = 0.46 to 0.95), indicating a beneficial effect of *H. pylori* eradication therapy (Ford *et al.* 2014). It should be noted that these results were heavily weighted by the results in the Shandong Intervention Trial. Ford *et al.* (2014) also conducted a meta-analysis evaluating cancer mortality and found a non-statistically-significant decrease in mortality in the intervention group (RR = 0.67, 95% CI = 0.40 to 1.11); the analysis included 24 deaths in the intervention groups and 36 in the placebo groups (Ford *et al.* 2014).

Three trials evaluating secondary prevention of gastric cancer (in Japan and South Korea) found a lower risk of new cancer in the *H. pylori* intervention group than in the control group (Fukase *et al.* 2008, Choi *et al.* 2014b, Choi *et al.* 2018). The findings were statistically significant in the Japanese study and in the Choi *et al.* (2018) study (see Table 3-1); additionally, when the results of the two earliest studies (Fukase *et al.* 2008, Choi *et al.* 2014b) were combined in a meta-analysis, a protective effect of eradication therapy was seen (RR = 0.47, 95% CI = 0.28 to 0.80) (Wald 2014).

Meta-analyses that pooled the results of cohort studies or of cohort studies and randomized controlled trials combined found results similar to those of the meta-analyses of the trials. An analysis of eight primary-prevention cohort studies reported a relative risk of 0.46 (95% CI = 0.32 to 0.66) (Doorakkers *et al.* 2016). A meta-analysis of both trials and cohort studies found relative risks of 0.62 (95% CI = 0.49 to 0.79) for primary prevention (6 trials and 8 cohorts) and 0.46 (95% CI = 0.35 to 0.60) for secondary prevention of gastric cancer (2 trials and 8 cohorts) (Lee *et al.* 2016). Another secondary-prevention meta-analysis (Yoon *et al.* 2014) found a relative risk of 0.42 (95% CI = 0.32 to 0.56) in a pooled analysis of 13 trials or cohort studies. Additional meta-analyses that combined both primary- and secondary-prevention studies (Hernández *et al.* 2014, Chen *et al.* 2016a, Lee *et al.* 2016) were considered to be less informative. The results of these meta-analyses are summarized in Table 3-2. Other meta-analysis publications were identified but are not included in Table 3-2 because they included multiple publications of the same study in the analysis or included studies that did not evaluate efficacy or effectiveness in cancer prevention.

Table 3-2. Meta-analyses of randomized controlled trials and cohort studies investigating the effectiveness of *H. pylori* eradication in reducing gastric cancer incidence

Reference	Type of study (no. of studies)	Exposure group (no. of studies)	Risk estimate	Heterogeneity
Studies on individuals without gastric cancer				
Ford *et al.* 2014	Trial (6)	Type of outcome		
		Incidence (6)	0.66 (0.46–0.95)	I^2 = 0%; *P* = 0.60
		Mortality (3)	0.67 (0.40–1.11)	I^2 = 0%; *P* = 0.90
		Pre-neoplastic lesions present		
		No (2)	0.42 (0.02–7.69)	
		Yes (4)	0.86 (0.47–1.59)	
		Mixed (2)	0.38 (0.12–1.23)	
Doorakkers *et al.* 2016	Cohort (8)	Overall analysis	0.46 (0.32–0.66)	I^2 = 32.3%; *P* = 0.17
		Adjusted for follow-up and confounding (4)	0.46 (0.29–0.72)	I^2 = 44.4%; *P* = 0.15
Studies on gastric cancer patients[a]				
Yoon *et al.* 2014[b]	Trial (2) Cohort (8) Other observational (2)	Trial and prospective cohort (3)	0.39 (0.20–0.75)	I^2 = 24.7 %; *P* = 0.27 Outcome is metachronous gastric cancer
Combined studies of cancer and cancer-free patients				
Chen *et al.* 2016a	Trial (8)	All studies	0.64 (0.48–0.85)	I^2 = 32.3%; *P* = 0.93
		Baseline diagnosis		
		Non-atrophic gastritis/gastritis	0.25 (0.08–0.81)	
		IM/DYS	0.88 (0.59–1.31)	
Hernández *et al.* 2014	Trial (7)	Overall five studies	0.57 (0.42–0.79)	I^2 = 0%; *P* = 0.48 Does not include Wong *et al.* 2012, Saito *et al.* 2005, or Choi *et al.* 2014
Lee *et al.* 2016	Trial (8) Cohort (16)	All studies	0.54 (0.46–0.65)	I^2 = 0.0%; *P* = 0.67
		Trial	0.60 (0.44–0.81)	
		Cohort	0.52 (0.41–0.64)	
		Primary intervention	0.62 (0.49–0.79)	
		Secondary intervention	0.46 (0.35–0.60)	
		Baseline incidence of gastric cancer (tertiles)		
		Lowest	0.80 (0.56–1.15)	
		Middle	0.49 (0.38–0.64)	
		Highest	0.45 (0.32–0.64)	

CAG = chronic atrophic gastritis; DYS = dysplasia; IM = intestinal metaplasia.

[a] Patients with previous endoscopic resection of early gastric cancer.

[b] Because the meta-analysis of all studies included those that were not analytic studies, the results of that analysis are not included in the table.

Several additional planned or ongoing studies will investigate the efficacy of *H. pylori* eradication in reducing the incidence of gastric cancer. A large-scale study in Baltic and Eastern European countries (the GISTAR study), which has recently begun recruitment, aims to recruit 30,000 men and women aged 40 to 64 and follow them for 15 years (Leja *et al.* 2014, Leja *et al.* 2017). A study in South Korea that has also recently begun recruitment plans to recruit 11,000 men and women aged 40 to 65 who are invited to participate in the national gastric cancer screening program. Those found to be infected with *H. pylori* will be randomized into the eradication study and followed for at least 10 years (Choi *et al.* 2014a, Park *et al.* 2017). A third ongoing study in the United Kingdom (the *H. pylori* Screening Study) recruited participants between 1997 and 2006. Although this is not an eradication study, those screened for *H. pylori* who tested positive were treated. All participants will be followed for 15 to 20 years (Wald 2014). Although not a placebo-controlled trial, a large study in China will compare a high-dose treatment with a low-dose treatment in 180,000 participants followed for at least 7 years. Initial eradication rates in the high-dose group were approximately 73% (Pan *et al.* 2016).

Gastric MALT lymphoma

Because MALT lymphoma is a rare cancer, no randomized controlled trials have assessed the efficacy of *H. pylori* eradication therapy for its prevention and treatment; however, efficacy has been assessed in numerous observational studies. In a meta-analysis of 32 observational studies with 1,408 gastric MALT lymphoma patients, Zullo *et al.* (2009) found that *H. pylori* eradication treatment resulted in an overall remission rate of 77.5% (95% CI = 75.3% to 79.7%). Remission rates were higher for Stage 1 than Stage 2 lymphoma (75.3% vs. 55.6%), but treatment was effective at both cancer stages. Median follow-up times for these studies ranged from one to five years. Recently, long-term follow-up studies of gastric MALT lymphoma patients receiving *H. pylori* eradication therapy have shown remission in up to 80% of cases, with 80% of these individuals remaining disease-free after ten years (Wündisch *et al.* 2012, Fischbach 2014).

3.1.3 Cost-benefit analyses studies

Numerous economic models in numerous geographic locations, including both low- and high-prevalence countries, have been published that evaluated whether *H. pylori* screening and treatment are cost-effective measures for the prevention of stomach cancer in a variety of populations. Two systematic reviews published in 2013 (Areia *et al.* 2013, Lansdorp-Vogelaar and Sharp 2013) reviewed twelve cost-effectiveness studies on *H. pylori* screening and treatment in the general population, including four studies each from North America, Europe, and Asia. Areia *et al.* (2013) also reviewed one South Korean cost-effectiveness study on *H. pylori* eradication after endoscopic removal of gastric cancer. The IARC working group on *H. pylori* eradication reviewed nine economic studies (Moayyedi 2014). Several new cost-effectiveness studies of screening and treatment have been published since these 2013 reviews. These newer studies were conducted in the United States (Schulz *et al.* 2014, Yeh *et al.* 2016), New Zealand (Teng *et al.* 2017), Taiwan (Cheng *et al.* 2015), and Hong Kong (Wong *et al.* 2014). All studies found *H. pylori* screening and treatment to be effective based on a threshold of $50,000 per life-year saved; importantly, the findings were robust to differences in *H. pylori* prevalence and patient gender and ethnicity (Lansdorp-Vogelaar and Sharp 2013). Most studies assumed 30% effectiveness of *H. pylori* eradication in reducing gastric cancer incidence; however, sensitivity analyses found that *H. pylori* eradication would still be cost-effective if the effectiveness of *H.*

pylori eradication in reducing stomach cancer incidence were as low as 15% (Lansdorp-Vogelaar and Sharp 2013).

Factors that may influence the cost-effectiveness of *H. pylori* screening and treatment include screening methods, type of *H. pylori* therapy, and population characteristics such as age, race or ethnicity, migrant status, and geographic region. Most general-population studies in both high- and low-prevalence countries evaluated serology screening (the most available test) and found it to be cost-effective (reviewed by Areia *et al.* 2013, Lansdorp-Vogelaar and Sharp 2013, Wong *et al.* 2014, Cheng *et al.* 2015, Yeh *et al.* 2016, Teng *et al.* 2017). However, some studies reported that the stool antigen screening method, which has greater sensitivity and specificity, was more cost-effective than either serology or urea breath test screening (Xie *et al.* 2009, as cited by Areia *et al.* 2013, Schulz *et al.* 2014). Most cost-effectiveness studies considered only the standard PPI triple therapy; however, one study evaluated the bismuth-containing quadruple therapy and found it to be cost-effective as well (Xie *et al.* 2009, as cited by Moayyedi 2014).

Population characteristics were also considered in the economic models. The overall conclusion of Areia *et al.* (2013) was that screening at or above age 50 was the most cost-effective; however, several Asian studies concluded that screening beginning at age 30 would be the most cost-effective (Lee *et al.* 2007, Cheng *et al.* 2015, and Yeh *et al.* 2009, as cited by Areia *et al.* 2013). The effect of age may depend on the population; for example, Teng *et al.* (2017) found that cost-effectiveness was highest for Māori participants aged 45 to 49 and non-Māori participants aged 60 to 64. A study in Australia (Schulz *et al.* 2014) found screening and treatment of immigrants and refugees from high-prevalence countries to be cost-effective, and concluded that it may be an effective strategy for reducing stomach cancer in these populations.

All cost-effectiveness studies found *H. pylori* screening and treatment to be cost-effective, coming in well below the threshold of $50,000 per life-year saved (Lansdorp-Vogelaar and Sharp 2013, Yeh *et al.* 2016, Teng *et al.* 2017). In high-prevalence countries, estimated costs ranged from $200 to $17,000 per life-year saved. The studies with the lowest assumed *H. pylori* prevalence had the highest cost per life-year saved, but eradication was still cost-effective. Likewise, studies reporting cost-effectiveness in low-prevalence countries also found screening and treatment to be cost-effective, ranging from $10,000 to $35,000 per life-year saved. While the cost-effectiveness estimates were, on average, higher in low-prevalence countries, they were still well below the threshold estimates.

In many of these studies, the cost-effectiveness threshold analyses considered only stomach cancer, and did not take into account the additional potential savings from *H. pylori* screening and treatment that could result from decreases in dyspepsia, ulcers, and other *H. pylori*–related disorders. The analyses also did not take into account the potential detrimental effects of increased antibiotic resistance or the potential reinfection rates, which have not been well studied (Lansdorp-Vogelaar and Sharp 2013). The IARC working group (IARC 2014) recommended that further studies should evaluate benefits using quality-adjusted life-years rather than life-years saved (Lansdorp-Vogelaar and Sharp 2013, Moayyedi 2014). Additional economic cost-benefit analyses are needed from randomized controlled trials, especially in areas where the eradication programs are most likely to be implemented first.

3.1.4 Issues and concerns

Although the potential for *H. pylori* eradication to prevent 30% to 40% of new cases of non-cardia gastric cancer has been demonstrated, no large-scale *H. pylori* eradication programs have been implemented; however, a few smaller, targeted eradication programs have been implemented regionally (see Section 3.2.2). This caution is partially due to concern about unintended consequences of such programs. Three major concerns about *H. pylori* eradication are the potential for increased bacterial resistance to antibiotics, a negative impact on the normal gastrointestinal flora found in the body, and the likelihood of reinfection with *H. pylori* after treatment. These concerns are compounded by the fact that many of the antibiotics used to treat *H. pylori* infection are commonly used to treat other serious infections. A recent European consensus report cautioned that use of commonly used antibiotics could create additional resistance selection on pathogens other than *H. pylori* (Malfertheiner *et al.* 2017). In addition, some evidence suggests an inverse relationship between *H. pylori* infection and GERD and its complications, including Barrett's esophagus and esophageal adenocarcinoma (reviewed by Parsonnet 2014). However, eradication does not appear to worsen pre-existing GERD (Zagari *et al.* 2015).

Reinfection with *H. pylori* has been observed to occur in more than 10% of those who were successfully treated, and reinfection rates increased as time since treatment increased (Morgan *et al.* 2013). Reinfection rates ranged from 3.4% in high-income countries to 18% in low-income countries. Factors associated with reinfection included treatment adherence and study site, which was likely associated with regional antibiotic resistance, which suggests that recrudescence is a component of one-year recurrence rates in many populations (Morgan *et al.* 2013).

Any eradication efforts should be tailored to the specific geographic area and target population, to guide the selection of appropriate antibiotic therapy and to develop better methods of treatment (Thung *et al.* 2016). All randomized controlled trials of eradication published to date were conducted in high-prevalence countries. However, both the short- and long-term effects of treatment programs will differ between regions with differing prevalence levels. Factors to consider in *H. pylori* eradication include the prevalence of *H. pylori* in the population, identification of the most appropriate population for screening (the general population or those showing symptoms of disease), the best age at which to begin screening, and the stage of disease at which eradication would be most effective. In high-prevalence regions, screening and treatment of the general population may be indicated, whereas in lower-prevalence countries with low-to-moderate risk of gastric cancer, integration of screening into existing prevention methods (such as colonoscopy screening) or screening those who show symptoms may be more effective (Lee *et al.* 2007). The optimal age for general screening and treatment programs may vary based on the prevalence of *H. pylori* in the population, and age should be taken into account (as discussed in Section 3.1.2).

The effectiveness of *H. pylori* eradication therapy in the prevention of stomach cancer may depend on the presence and severity of atrophic damage at the time of eradication (Sugano *et al.* 2015). *H. pylori* eradication therapy abolishes the inflammatory response and, in those with no symptoms, can prevent the appearance of preneoplastic lesions. The optimal timing for stomach-cancer prevention may be before these preneoplastic conditions appear (Malfertheiner *et al.* 2017); however, *H. pylori* eradication may offer some benefits by reducing risk in the presence of preneoplastic conditions (Coelho *et al.* 2013, Malfertheiner *et al.* 2017). As mentioned in

Section 3.1.1, the largest randomized controlled trial found that *H. pylori* eradication was effective in reducing cancer incidence among participants with precancerous lesions at baseline (Li *et al.* 2014).

3.2 Policies and recommendations

Even though *H. pylori* is a treatable infection, and stomach cancer is one of the leading causes of cancer death worldwide, few national efforts at screening and prevention have been made (Section 3.3.2). There have been, however, numerous national and regional consensus statements on *H. pylori* screening and treatment in the prevention of *H. pylori*–induced cancer (Section 3.2.1).

3.2.1 National consensus recommendations for the prevention of *H. pylori*–induced cancer

Over the last five years, numerous publications have reported on national and regional consensus statements on *H. pylori* management. Typically, these statements are the result of a workshop of international, national, or regional experts who are charged with (1) reviewing the clinical and other relevant studies related to *H. pylori* management (e.g., diagnosis, treatment, and prevention) and (2) voting on the level of evidence (a grade reached according to specific guidelines) and the strength of recommendations for specific statements. Recommendations relevant to the prevention and treatment of *H. pylori*–induced cancer are summarized in Table 3-3. (Not included in the table are other recommendations, such as those for diagnosis and type of treatment.)

Table 3-3. Recommendations for prevention of *H. pylori*–induced cancer

Type of recommendation	Population	Strength of the association/region	References
Screen and treat	General population	*Strong:* Should be considered for those under 35: Brazil (Third Brazilian Consensus)	Coelho *et al.* 2013
		Insufficient: Chile (Chilean Society of Gastroenterology)	Torres *et al.* 2016
		Weak: Asia (10 ASEAN countries); Bangkok Report) (Community screening)	Mahachai *et al.* 2018
Screen and treat	Communities or individuals with a high risk of gastric cancer	*Strong*[a]:	
		Europe (Maastricht V/Florence Consensus Report 20)	Malfertheiner *et al.* 2017
		Italy (II Working Group Consensus Report)[c]	Zagari *et al.* 2015
		Moderate[b]: Taiwan (Convened by the Steering Committee)	Sheu *et al.* 2017
		Need more research: Chile	Torres *et al.* 2016
Screen and treat	Populations with low and/or intermediate gastric cancer risk	*Moderate*[b]: Taiwan (intermediate risk only)	Sheu *et al.* 2017
		Weak recommendation: Europe	Malfertheiner *et al.* 2017

Type of recommendation	Population	Strength of the association/region	References
Screen and treat	Individuals with family history of gastric cancer (e.g., first-degree relatives of gastric cancer patients)	*Strong or recommended:* 10 ASEAN countries, Italy[c], Brazil, China (Chinese Society of Gastroenterology), South Korea (Korean College of *Helicobacter* and Upper Gastrointestinal Research Guideline Steering Committee)	Coelho *et al.* 2013, Lee 2014a, Zagari *et al.* 2015, Mahachai *et al.* 2018
		Insufficient: United States	Bjorkman and Steenblik 2017
Screen and treat	Immigrants from high-risk regions	*Recommended*: Canada (Canadian Helicobacter Study Group and Canadian Cancer Society)	Taylor *et al.* 2014 (cites Canadian Cancer Society 2014)
Screen and treat	Patients with symptoms of gastric diseases	*Strong or recommended*: Italy, China, South Korea	Lee 2014a, Zagari *et al.* 2015
		Moderate: Brazil	Coelho *et al.* 2013
		Insufficient: United States	Bjorkman and Steenblik 2017
Screen and treat	Patients with precancerous gastric lesions	*Strong*: 10 ASEAN countries	Mahachai *et al.* 2018
		Moderate: Brazil	Coelho *et al.* 2013
		"Favors": Chile	Torres *et al.* 2016
		Weak: South Korea	Choi 2013
Treatment of cancer	Patients with gastric MALT lymphoma	*Strong or recommended*: 10 ASEAN countries, Taiwan, China, South Korea, Japan, United States	Lee 2014a, Bjorkman and Steenblik 2017, Sheu *et al.* 2017, Mahachai *et al.* 2018
Secondary prevention and/or treatment of cancer	Patients with gastric cancer	*Strong or recommended*: Italy, Chile, China, South Korea, Japan, United States	Lee 2014a, Zagari *et al.* 2015, Torres *et al.* 2016, Bjorkman and Steenblik 2017

[a] Some reports referred to this as Group A recommendation.
[b] Some reports referred to this as Group B recommendation.
[c] Statement was "that the recommendation should be considered."
ASEAN = Association of Southern Asian Nations. The 10 members are Brunei Darussalam, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam.

Overall, there was consensus across the working groups that *H. pylori* eradication could reduce but not completely eliminate *H. pylori*–induced cancer, and that endoscopic or histological surveillance may be needed after treatment (Lee *et al.* 2007, Sheu *et al.* 2017). Most, but not all, working groups recommended screening and treatment programs for individuals with a high risk of non-cardia gastric cancer (including those with a family history of non-cardia gastric cancer or immigrants from high-risk regions); however, working groups from some countries (such as the United States and Chile) thought more research was needed. Some working groups recommended that screening and treatment programs include patients without advanced gastric lesions, and other groups (e.g., South Korea) recommended treatment of patients with intestinal metaplasia. Most groups recommended that the cancer-treatment program treat patients with gastric MALT lymphoma as well as non-cardia gastric cancer.

3.2.2 Screening and treatment programs

Worldwide, only a few countries have instituted gastric cancer prevention programs, either regionally or nationwide, and only some of these include *H. pylori* screening and treatment. The majority of these programs are in Asia. In Japan, which has high rates of stomach cancer, but also one of the highest five-year survival rates, at 90% (Asaka 2014), an early stomach-cancer detection screening program has been in place for many years, although participation rates have been low. In 2013, after a successful trial showed that eradicating *H. pylori* reduced the incidence of secondary non-cardia gastric cancer, Japan approved national health insurance coverage of *H. pylori* eradication therapy for all patients with gastric MALT lymphoma, early non-cardia gastric cancer, idiopathic thrombocytopenia purpura, gastric and duodenal ulcers, and chronic gastritis. In Taiwan, a general-population stomach-cancer prevention program was pilot-tested on Matsu Island, a high-risk population, with promising results (Lee *et al.* 2013, Lee and Lin 2017). Based on these results, two additional regions of Taiwan have implemented a similar program combining a test for *H. pylori* and screening for stomach cancer among those aged 50 to 69 (Lee 2014b). Another region in Taiwan is conducting a large-scale randomized controlled trial that combines colon-cancer screening with *H. pylori* screening, with treatment for those who test positive (Lee and Lin 2017). In South Korea, a national program was begun in the early 2000s to provide stomach-cancer screening every two years for all residents aged 40 and over. Participation rates have increased each year; in 2011, about half of those eligible were screened (Suh *et al.* 2013).

In 2006, Chile became the first Latin American country to institute a program that provides stomach-cancer screening to symptomatic people aged 40 and over. The program provides endoscopic examination for *H. pylori* detection, biopsy, and treatment (Ferreccio 2014). This program has had limited success, as population coverage has been small (Torres *et al.* 2016). The program is currently under review, and other strategies are being considered, including general-population screening and eradication in high-risk populations, accompanied by more efficient early-detection methods.

3.3 Summary of the recommendations of international expert working groups (including the IARC working group)

Given the strong link between *H. pylori* and non-cardia gastric cancer, as well as the high global burden of disease, international expert working groups have recommended that countries worldwide should devote additional public health resources to this disease. This global burden and the feasibility of treating the main cause of disease make *H. pylori* a possible target for intervention. Recent randomized trials have provided support for *H. pylori* eradication in the prevention of stomach cancer, while economic analyses have shown it to be cost-effective. Several additional large randomized trials currently under way may add to the evidence. As well as preventing non-cardia gastric cancer (and gastric MALT lymphoma), *H. pylori* eradication may also prevent diseases such as dyspepsia and peptic ulcers, increasing its cost-effectiveness.

Although evidence for the effectiveness of screening and treatment in reducing stomach-cancer incidence is increasing, caution should be exercised in any planned intervention program. Local antibiotic resistance patterns should be taken into account in the choice of treatment method, as well as in targeting of the appropriate populations for intervention. Other potential consequences of eradication therapy must be also considered in any program, including increases in antibiotic resistance, changes in the natural gastrointestinal flora, and increases in diseases on which *H. pylori* may have a beneficial effect, such as GERD and esophageal cancer. Before implementation, any planned programs should consider objective assessments of feasibility, effectiveness, program acceptance, cost-effectiveness, and adverse consequences relevant to the local area.

References

1. Anderson WF, Rabkin CS, Turner N, Fraumeni JF, Jr., Rosenberg PS, Camargo MC. 2018. The changing face of noncardia gastric cancer incidence among US non-Hispanic whites. *J Natl Cancer Inst* 110(6): 1-8. (Supported by NIH and NCI. Authors affiliated with NCI, MD.)

2. Areia M, Carvalho R, Cadime AT, Rocha Goncalves F, Dinis-Ribeiro M. 2013. Screening for gastric cancer and surveillance of premalignant lesions: a systematic review of cost-effectiveness studies. *Helicobacter* 18(5): 325-337. (No funding received. Authors affiliated with Porto University, Portugal; Portuguese Oncology Institute – Coimbra, Portugal.)

3. Asaka M. 2014. Chapter 1.2 Strategy to eliminate gastric cancer deaths in Japan. In *Helicobacter pylori Eradication as a Strategy for Preventing Gastric Cancer*. IARC Working Group Report, vol. 8. Lyon, France: International Agency for Research on Cancer. p. 21-27.

4. Aziz RK, Khalifa MM, Sharaf RR. 2015. Contaminated water as a source of *Helicobacter pylori* infection: A review. *J Adv Res* 6(4): 539-547. (Support not reported. Authors affiliated with Cairo University, Egypt; Community Pharmacist, Al-Baharyia Oasis, Egypt; Charité Medical School, Germany.)

5. Balakrishnan M, George R, Sharma A, Graham DY. 2017. Changing trends in stomach cancer throughout the world. *Curr Gastroenterol Rep* 19(8): 36. (Supported by the Office of Research and Development Medical Research Service Department of Veterans Affairs, Public Health Service, the Cancer Prevention and Research Institute of Texas–CPRIT, and the Texas Medical Center Digestive Diseases Center. Authors affiliated with Baylor College of Medicine and Michael E. DeBakey VA Medical Center, TX; Michael E. DeBakey Veterans Affairs Medical Center, TX.)

6. Bjorkman DJ. 2017. *Racial and Ethnic Disparities in Gastric Cancer Risk*. NEJM Journal Watch. https://production.jwatch.org/na43129/2017/01/17/racial-and-ethnic-disparities-gastric-cancer-risk. Accessed on 3/14/18.

7. Bjorkman DJ, Steenblik M. 2017. Best practice recommendations for diagnosis and management of *Helicobacter pylori*-synthesizing the guidelines. *Curr Treat Options Gastroenterol* 15(4): 648-659. (Support not reported. Authors affiliated with University of Utah School of Medicine, UT.)

8. Blase JL, Campbell PT, Gapstur SM, Pawlita M, Michel A, Waterboer T, Teras LR. 2016. Prediagnostic *Helicobacter pylori* antibodies and colorectal cancer risk in an elderly, caucasian population. *Helicobacter* 21(6): 488-492. (Supported by the Centers for Disease Control and Prevention National Program of Cancer Registries, and the National Cancer Institute Surveillance, Epidemiology, and End Results program. Authors affiliated with American Cancer Society, GA; German Cancer Research Center, Germany.)

9. Bui D, Brown HE, Harris RB, Oren E. 2016. Serologic evidence for fecal-oral transmission of *Helicobacter pylori*. *Am J Trop Med Hyg* 94(1): 82-88. (Support not reported. Authors affiliated with University of Arizona, AZ.)

10. Camargo MC, Yepez MC, Ceron C, Guerrero N, Bravo LE, Correa P, Fontham ET. 2004. Age at acquisition of *Helicobacter pylori* infection: comparison of two areas with contrasting risk of gastric cancer. *Helicobacter* 9(3): 262-270. (Supported by the Louisiana Board of Regents Health Excellence Fund and by 2POI CA 28842, Authors affiliated with Louisiana State University Health Science Center, LA; Universidad de Nariño, Columbia; Universidad del Valle, Colombia.)

11. Canadian Cancer Society. 2014. *Helicobacter pylori (H. pylori).* www.cancer.ca/en/cancer-information. Retrieved on July 30, 2014. (as cited in Taylor *et al.* 2014)

12. Cavaleiro-Pinto M, Peleteiro B, Lunet N, Barros H. 2011. *Helicobacter pylori* infection and gastric cardia cancer: systematic review and meta-analysis. *Cancer Causes Control* 22(3): 375-387. (Supported by the Fundação para a Ciência e Tecnologia. Authors affiliated with University of Porto Medical School, Portugal.)

13. CDC. 2016. *List of Vaccines Used in United States*. Centers for Disease Control and Prevention. Updated on 11/22/16. https://www.cdc.gov/vaccines/vpd/vaccines-list.html. Accessed on 12/7/17.

14. Chen HN, Wang Z, Li X, Zhou ZG. 2016a. *Helicobacter pylori* eradication cannot reduce the risk of gastric cancer in patients with intestinal metaplasia and dysplasia: evidence from a meta-analysis. *Gastric Cancer* 19(1): 166-175. (Support not reported. Authors affiliated with Sichuan University, China.)

15. Chen XZ, Schöttker B, Castro FA, Chen H, Zhang Y, Holleczek B, Brenner H. 2016b. Association of *Helicobacter pylori* infection and chronic atrophic gastritis with risk of colonic, pancreatic and gastric cancer: A ten-year follow-up of the ESTHER cohort study. *Oncotarget* 7(13): 17182-17193. (Supported by the Baden-Württemberg State Ministry of Science, Research and Arts, and the National Natural Science Foundation of China. Authors affiliated with Sichuan University, China; German Cancer Research Center, Germany; Saarland Cancer Registry, Germany; German Cancer Consortium, Germany.)

16. Cheng HC, Wang JD, Chen WY, Chen CW, Chang SC, Sheu BS. 2015. *Helicobacter pylori* test-and-treat program can be cost-effective to prevent gastric cancer in Taiwanese adults: referred to the nationwide reimbursement database. *Helicobacter* 20(2): 114-124. (Supported by the National Science Council, the Ministry of Health and Welfare, and the Ministry of Education, Taiwan, R.O.C., the Aim for the Top University Project to the National Cheng Kung University. Authors affiliated with National Cheng Kung University, Taiwan; National Taiwan University, Taiwan; National Taiwan University of Science and Technology, Taiwan.)

17. Chey WD, Leontiadis GI, Howden CW, Moss SF. 2017. ACG Clinical Guideline: Treatment of *Helicobacter pylori* infection. *Am J Gastroenterol* 112(2): 212-239.

(Supported by the American College of Gastroenterology. Authors affiliated with University of Michigan Health System, MI; McMaster University, Canada; University of Tennessee Health Science Center, TN; Brown University, RI.)

18. Choi IJ. 2013. Current evidence of effects of *Helicobacter pylori* eradication on prevention of gastric cancer. *Korean J Intern Med* 28(5): 525-537. (Supported by the National Cancer Center, Korea. Author affiliated with National Cancer Center, Korea.)

19. Choi IJ, Park JY, Herrero R. 2014a. Chapter 4.3. Effect of *Helicobacter pylori* eradication on gastric cancer prevention in the Republic of Korea: a randomized controlled clinical trial. In *Helicobacter pylori Eradication as a Strategy for Preventing Gastric Cancer*. IARC Working Group Report, vol. 8. Lyon, France: International Agency for Research on Cancer. p. 154-160.

20. Choi IJ, Kook MC, Kim YI, Cho SJ, Lee JY, Kim CG, Park B, Nam BH. 2018. *Helicobacter pylori* therapy for the prevention of metachronous gastric cancer. *N Engl J Med* 378(12): 1085-1095. (Supported by the National Cancer Center, South Korea. Authors affiliated with National Cancer Center, South Korea.)

21. Choi J, Kim SG, Yoon H, Im JP, Kim JS, Kim WH, Jung HC. 2014b. Eradication of *Helicobacter pylori* after endoscopic resection of gastric tumors does not reduce incidence of metachronous gastric carcinoma. *Clin Gastroenterol Hepatol* 12(5): 793-800. (Supported by the Liver Research Institute, Seoul National University College of Medicine. Authors affiliated with Seoul National University College of Medicine, Korea.)

22. Coelho LG, Maguinilk I, Zaterka S, Parente JM, Passos MCF, Moraes-Filho JPP. 2013. 3rd Brazilian consensus on *Helicobacter pylori*. *Arq Gastroenterol* 50(2): 1-17. (Supported by Medley and Ache. Authors affiliated with Universidade Federal de Minas Gerais, Brazil; Universidade Federal do Rio Grande do Sul, Brazil; Brazil Universidade Federal do Piauí, Brazil; Universidade de São Paulo, Brazil.)

23. Colquhoun A, Arnold M, Ferlay J, Goodman KJ, Forman D, Soerjomataram I. 2015. Global patterns of cardia and non-cardia gastric cancer incidence in 2012. *Gut* 64(12): 1881-1888. (Supported by a Vanier Canada Graduate Scholarship, a Michael Smith Foreign Study Supplement, and Alberta Innovates Health Solutions. Authors affiliated with University of Alberta, Canada; IARC, France.)

24. Conteduca V, Sansonno D, Lauletta G, Russi S, Ingravallo G, Dammacco F. 2013. *H. pylori* infection and gastric cancer: state of the art (review). *Int J Oncol* 42(1): 5-18. (Supported by the Italian Association for Cancer Research, the Italian Foundation ‘Cassa di Risparmio di Puglia’, and the strategic project ‘Biotecnoter’ of the Apulia Region. Authors affiliated with University of Bari ‘Aldo Moro’ Medical School, Italy.)

25. Correa P, Fontham ET, Bravo JC, Bravo LE, Ruiz B, Zarama G, Realpe JL, Malcom GT, Li D, Johnson WD, Mera R. 2000. Chemoprevention of gastric dysplasia: randomized trial of antioxidant supplements and anti-*Helicobacter pylori* therapy. *J Natl Cancer Inst* 92(23): 1881-1888. (Supported by the National Cancer Institute, National Institutes of

Health, Department of Health and Human Services. Authors affiliated with Louisiana State University Health Sciences Center, LA; Universidad del Valle, Colombia; Hospital Departamental, Colombia.)

26. de Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D, Plummer M. 2012. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. *Lancet Oncol* 13(6): 607-615. (Supported by the Fondation Innovations en Infectiologie (FINOVI) and the Bill & Melinda Gates Foundation (BMGF). Authors affiliated with IARC, France.)

27. de Sanjose S, Dickie A, Alvaro T, Romagosa V, Garcia Villanueva M, Domingo-Domenech E, Fernandez de Sevilla A, El-Omar E. 2004. Helicobacter pylori and malignant lymphoma in Spain. *Cancer Epidemiol Biomarkers Prev* 13(6): 944-948. (as cited in IARC 2012)

28. Diaconu S, Predescu A, Moldoveanu A, Pop CS, Fierbinteanu-Braticevici C. 2017. *Helicobacter pylori* infection: old and new. *J Med Life* 10(2): 112-117. (Support not reported. Authors affiliated with University Emergency Hospital, Romania.)

29. Doorakkers E, Lagergren J, Engstrand L, Brusselaers N. 2016. Eradication of *Helicobacter pylori* and gastric cancer: A systematic review and meta-analysis of cohort studies. *J Natl Cancer Inst* 108(9). (Supported by the Swedish Research Council (SIMSAM), Swedish Cancer Society, and Strategic Research Area (SFO). Authors affiliated with Karolinska Institutet, Sweden; King’s College London, UK.)

30. EPA. 2016. *Contaminant Information Sheets (CISs) for the Final Fourth Contaminant Candidate List (CCL 4)* EPA 815-R-16-003. U.S. Environmental Protection Agency. 337 pp.

31. Epplein M, Signorello LB, Zheng W, Peek RM, Jr., Michel A, Williams SM, Pawlita M, Correa P, Cai Q, Blot WJ. 2011. Race, African ancestry, and *Helicobacter pylori* infection in a low-income United States population. *Cancer Epidemiol Biomarkers Prev* 20(5): 826-834. (Supported by NCI, the Joint Initiative for Innovation and Research of the German Helmholtz Association, the American Cancer Society, the Komen for the Cure Foundation, and the Vanderbilt-Ingram Cancer Center. Authors affiliated with Vanderbilt University School of Medicine, TN; International Epidemiology Institute. MD; German Cancer Research Center, Germany.)

32. Epplein M, Pawlita M, Michel A, Peek RM, Jr., Cai Q, Blot WJ. 2013. *Helicobacter pylori* protein-specific antibodies and risk of colorectal cancer. *Cancer Epidemiol Biomarkers Prev* 22(11): 1964-1974. (Supported by NCI, the Joint Initiative for Innovation and Research of the German Helmholtz Association, CTSA, and the Vanderbilt-Ingram Cancer Center. Authors affiliated with Vanderbilt University School of Medicine, TN; German Cancer Research Center, Germany; International Epidemiology Institute, MD.)

33. Epplein M, Zheng W, Li H, Peek RM, Jr., Correa P, Gao J, Michel A, Pawlita M, Cai Q, Xiang YB, Shu XO. 2014. Diet, *Helicobacter pylori* strain-specific infection, and gastric cancer risk among Chinese men. *Nutr Cancer* 66(4): 550-557. (Supported by NIH and

NCI. Authors affiliated with Vanderbilt University School of Medicine, TN; Shanghai Jiaoting University School of Medicine, China; German Cancer Research Center, Germany.)

34. FDA. 2017. *Vaccines Licensed for Use in the United States*. U.S. Food and Drug Administration. https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm093833.htm. Accessed on 12/7/17.

35. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. 2013. *GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]*. International Agency for Research on Cancer. http://globocan.iarc.fr. (As cited in IARC 2014)

36. Fernández de Larrea-Baz N, Michel A, Romero B, Pérez-Gómez B, Moreno V, Martín V, Dierssen-Sotos T, Jiménez-Moleón JJ, Castilla J, Tardón A, Ruiz I, Peiró R, Tejada A, Chirlaque MD, Butt JA, Olmedo-Requena R, Gómez-Acebo I, Linares P, Boldo E, Castells A, Pawlita M, Castaño-Vinyals G, Kogevinas M, de Sanjosé S, Pollán M, del Campo R, Waterboer T, Aragonés N. 2017. *Helicobacter pylori* antibody reactivities and colorectal cancer risk in a case-control study in Spain. *Front Microbiol* 8: 888. (Supported by the "Acción Transversal del Cáncer," approved on the Spanish Ministry Council on the 11th October 2007, by the Consortium for Biomedical Research in Epidemiology and Public Health (CIBERESP), by the Instituto de Salud Carlos III grants, co-funded by FEDER funds, by the Fundación Marqués de Valdecilla, by Catalan Government DURSI, by the Junta de Castilla y León, by the Consejería de Salud of the Junta de Andalucía, by the Regional Government of the Basque Country, and by the Conselleria de Sanitat of the Generalitat Valenciana. Authors affiliated with Instituto de Salud Carlos III, Spain; CIBERESP, Spain; German Cancer Research Center, Germany; Ramón y Cajal University Hospital, Spain; Puerta de Hierro Health Research Institute, Spain; Hospitalet de Llobregat, Spain; University of Barcelona, Spain; University of León, Spain; University of Cantabria-IDIVAL, Spain; Instituto de Investigación Biosanitaria de Granada, Spain; University of Granada, Spain; IdiSNA-Navarra Institute for Health Research, Spain; University of Oviedo, Spain; Donostia University Hospital, Spain; FISABIO, Spain; Huelva University Hospital Complex, Spain; IMIB-Arrixaca, Spain; University of Murcia, Spain; Complejo Asistencial Universitario de León, Spain; Hospital Clínic, Spain; IDIBAPS, Spain; CIBEREHD, Spain; CREAL, Spain; IMIM, Spain; Universitat Pompeu Fabra, Spain; Spanish Network for Research in Infectious Diseases, Spain.)

37. Ferreccio C. 2014. Chapter 1.4 The regional status of current or planned gastric cancer prevention strategies in Latin America. In *Helicobacter pylori Eradication as a Strategy for Preventing Gastric Cancer*. IARC Working Group Report, vol. 8. Lyon, France: International Agency for Research on Cancer. p. 37-43.

38. Figura N, Marano L, Moretti E, Ponzetto A. 2016. *Helicobacter pylori* infection and gastric carcinoma: Not all the strains and patients are alike. *World J Gastrointest Oncol* 8(1): 40-54. (Support not reported. Authors affiliated with University of Siena and

Policlinico S. Maria alle Scotte,, Italy; Hospital San Matteo degli Infermi, Italy; University of Siena, Italy; University of Torino, Italy.)

39. Fischbach W. 2014. Gastric MALT lymphoma - update on diagnosis and treatment. *Best Pract Res Clin Gastroenterol* 28(6): 1069-1077. (Supported by the Deutsche Krebshilfe. Author affiliated with Academic Teaching Hospital of the University of Würzburg, Germany.)

40. Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, Brenner H, Dicker DJ, Chimed-Orchir O, Dandona R, Dandona L, Fleming T, Forouzanfar MH, Hancock J, Hay RJ, Hunter-Merrill R, Huynh C, Hosgood HD, Johnson CO, Jonas JB, Khubchandani J, Kumar GA, Kutz M, Lan Q, Larson HJ, Liang X, Lim SS, Lopez AD, MacIntyre MF, Marczak L, Marquez N, Mokdad AH, Pinho C, Pourmalek F, Salomon JA, Sanabria JR, Sandar L, Sartorius B, Schwartz SM, Shackelford KA, Shibuya K, Stanaway J, Steiner C, Sun J, Takahashi K, Vollset SE, Vos T, Wagner JA, Wang H, Westerman R, Zeeb H, Zoeckler L, Abd-Allah F, Ahmed MB, Alabed S, Alam NK, Aldhahri SF, Alem G, Alemayohu MA, Ali R, Al-Raddadi R, Amare A, Amoako Y, Artaman A, Asayesh H, Atnafu N, Awasthi A, Saleem HB, Barac A, Bedi N, Bensenor I, Berhane A, Bernabe E, Betsu B, Binagwaho A, Boneya D, Campos-Nonato I, Castaneda-Orjuela C, Catala-Lopez F, Chiang P, Chibueze C, Chitheer A, Choi JY, Cowie B, Damtew S, das Neves J, Dey S, Dharmaratne S, Dhillon P, Ding E, Driscoll T, Ekwueme D, Endries AY, Farvid M, Farzadfar F, Fernandes J, Fischer F, TT GH, Gebru A, Gopalani S, Hailu A, Horino M, Horita N, Husseini A, Huybrechts I, Inoue M, Islami F, Jakovljevic M, James S, Javanbakht M, Jee SH, Kasaeian A, Kedir MS, Khader YS, Khang YH, Kim D, Leigh J, Linn S, Lunevicius R, El Razek HMA, Malekzadeh R, Malta DC, Marcenes W, Markos D, Melaku YA, Meles KG, Mendoza W, Mengiste DT, Meretoja TJ, Miller TR, Mohammad KA, Mohammadi A, Mohammed S, Moradi-Lakeh M, Nagel G, Nand D, Le Nguyen Q, Nolte S, Ogbo FA, Oladimeji KE, Oren E, Pa M, Park EK, Pereira DM, Plass D, Qorbani M, Radfar A, Rafay A, Rahman M, Rana SM, Soreide K, Satpathy M, Sawhney M, Sepanlou SG, Shaikh MA, She J, Shiue I, Shore HR, Shrime MG, So S, Soneji S, Stathopoulou V, Stroumpoulis K, Sufiyan MB, Sykes BL, Tabares-Seisdedos R, Tadese F, Tedla BA, Tessema GA, Thakur JS, Tran BX, Ukwaja KN, Uzochukwu BSC, Vlassov VV, Weiderpass E, Wubshet Terefe M, Yebyo HG, Yimam HH, Yonemoto N, Younis MZ, Yu C, Zaidi Z, Zaki MES, Zenebe ZM, Murray CJL, Naghavi M. 2017. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: A systematic analysis for the Global Burden of Disease Study. *JAMA Oncol* 3(4): 524-548. (Supported by the Bill and Melinda Gates Foundation and NIH. Authors affiliated with the Global Burden of Disease Cancer Collaboration.)

41. Ford AC, Forman D, Hunt RH, Yuan Y, Moayyedi P. 2014. *Helicobacter pylori* eradication therapy to prevent gastric cancer in healthy asymptomatic infected individuals: systematic review and meta-analysis of randomised controlled trials. *BMJ* 348: g3174. (No funding received. Authors affiliated with St James's University Hospital, UK; University of Leeds, UK; IARC, France; McMaster University, Canada.)

42. Forman D, Sierra M. 2014. Introduction. The current and projected global burden of gastric cancer. In *Helicobacter pylori Eradication as a Strategy for Preventing Gastric Cancer*. IARC Working Group Report, vol. 8. Lyon, France: International Agency for Research on Cancer. p. 5 - 15.

43. Franco AT, Israel DA, Washington MK, Krishna U, Fox JG, Rogers AB, Neish AS, Collier-Hyams L, Perez-Perez GI, Hatakeyama M, Whitehead R, Gaus K, O'Brien DP, Romero-Gallo J, Peek RM, Jr. 2005. Activation of beta-catenin by carcinogenic *Helicobacter pylori*. *Proc Natl Acad Sci U S A* 102(30): 10646-10651. (as cited in IARC 2012)

44. Franco AT, Johnston E, Krishna U, Yamaoka Y, Israel DA, Nagy TA, Wroblewski LE, Piazuelo MB, Correa P, Peek RM, Jr. 2008. Regulation of gastric carcinogenesis by *Helicobacter pylori* virulence factors. *Cancer Res* 68(2): 379-387. (as cited in IARC 2012)

45. Fukase K, Kato M, Kikuchi S, Inoue K, Uemura N, Okamoto S, Terao S, Amagai K, Hayashi S, Asaka M, Japan Gast Study Group. 2008. Effect of eradication of *Helicobacter pylori* on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. *Lancet* 372(9636): 392-397. (Supported by the Hiroshima Cancer Seminar Foundation. Authors affiliated with Yamagata Prefectural Central Hospital, Japan; Hokkaido University Hospital, Japan; Aichi Medical University School of Medicine, Japan; Matsue Red Cross Hospital, Japan; International Medical Center of Japan, Japan; Kure Kyosai Hospital, Japan; Kyoto Min-I-Ren Chuoh Hospital, Japan; Ibaraki Prefectural Central Hospital, Japan; Jichi Medical University, Japan; Hokkaido University Graduate School of Medicine, Japan.)

46. Fukui T, Okazaki K, Tamaki H, Kawasaki K, Matsuura M, Asada M, Nishi T, Uchida K, Iwano M, Ohana M, Hiai H, Chiba T. 2004. Immunogenetic analysis of gastric MALT lymphoma-like lesions induced by *Helicobacter pylori* infection in neonatally thymectomized mice. *Lab Invest* 84(4): 485-492. (Supported by the Ministry of Culture and Science of Japan, The Japan Society for the Promotion of Science, The Japanese Foundation for Research and Promotion of Endoscopy, and the Shimidzu Immunology Foundation. Authors affiliated with Kyoto University, Japan; Kansai Medical University, Japan.)

47. Gawin A, Wex T, Lawniczak M, Malfertheiner P, Starzynska T. 2012. [Helicobacter pylori infection in pancreatic cancer]. *Pol Merkur Lekarski* 32(188): 103-107. (Support unknown due to foreign language. Authors affiliated with Pomeranian Medical University, Poland.)

48. Gisbert JP, Greenberg ER. 2014. Chapter 3.2. Potential regimens for the mass eradication of *Helicobacter pylori* infection. In *Helicobacter pylori Eradication as a Strategy for Preventing Gastric Cancer*. IARC Working Group Report, vol. 8. Lyon, France: International Agency for Research on Cancer. p. 95 - 110.

49. González CA, Megraud F, Buissonniere A, Lujan Barroso L, Agudo A, Duell EJ, Boutron-Ruault MC, Clavel-Chapelon F, Palli D, Krogh V, Mattiello A, Tumino R, Sacerdote C, Quirós JR, Sanchez-Cantalejo E, Navarro C, Barricarte A, Dorronsoro M, Khaw KT, Wareham N, Allen NE, Tsilidis KK, Bas Bueno-de-Mesquita H, Jeurnink SM, Numans ME, Peeters PH, Lagiou P, Valanou E, Trichopoulou A, Kaaks R, Lukanova-McGregor A, Bergman MM, Boeing H, Manjer J, Lindkvist B, Stenling R, Hallmans G, Mortensen LM, Overvad K, Olsen A, Tjonneland A, Bakken K, Dumeaux V, Lund E, Jenab M, Romieu I, Michaud D, Mouw T, Carneiro F, Fenge C, Riboli E. 2012. *Helicobacter pylori* infection assessed by ELISA and by immunoblot and noncardia gastric cancer risk in a prospective study: the Eurgast-EPIC project. *Ann Oncol* 23(5): 1320-1324. (Supported by the Health Research Fund of the Spanish Ministry of Health, La Caixa, Red Temática de Investigación Cooperativa en Cáncer, the European Commission, IARC, Regional Governments of Andalucía, Asturias, Catalunya, Basque Country, Murcia and Navarra (Spain), the Danish Cancer Society (Denmark), the Liguecontre le Cancer, 3M, Mutuelle Générale de l'Education Nationale, Institut National de la Santéet de la Recherche Medicale (France), the Deutsche Krebshilfe, Deutsches Krebsforschungszentrum and Federal Ministry of Education and Research (Germany), the Ministry of Health and Social Solidarity, Stavros Niarchos Foundation and Hellenic Health Foundation (Greece), the Italian Association for Research on Cancer (AIRC) and National Research Council (Italy), the Dutch Ministry of Public Health, Welfare and Sports (VWS), Netherlands Cancer Registry (NKR), LK Research Funds, Dutch Prevention Funds, Dutch ZON (Zorg Onderzoek Nederland), World Cancer Research Fund (WCRF), and Statistics Netherlands (The Netherlands), the Norwegian Cancer Society (Norway), the Swedish Cancer Society, Swedish Scientific Council and Regional Government of Skåne and Västerbotten (Sweden), the Cancer Research UK, Medical Research Council, Stroke Association, British Heart Foundation, Department of Health, Food Standards Agency, and Wellcome Trust (UK). Authors affiliated with IDIBELL, Spain; INSERM, France; Institut Gustave Roussy, France; Paris South University, France; ISPO, Italy; Fondazione IRCCS Istituto Nazionale dei TumoriMilan, Italy; Federico Ii University, Italy; ‘‘Civile M.P. Arezzo’’ Hospital, Italy; Centre for Cancer Epidemiology and Prevention, Italy; Health and Health Care Services Council. Italy; CIBERESP, Spain; Basque Regional Health Department, Spain; University of Cambridge, UK; University of Oxford, UK; National Institute for Public Health and the Environment, Denmark; University Medical Centre Utrecht, Netherlands; University of Athens Medical School, Greece; Hellenic Health Foundation, Greece; German Cancer Research Center, Germany; German Institute of Human Nutrition Potsdam-Rehbrücke, Germany; Lund University, Sweden; Sahlgrenska University Hospital, Sweden; Umea University, Sweden; Aarhus University, Denmark; Danish Cancer Society, Denmark; University of Tromsø, Norway; IARC, France; Imperial College London, UK; University of Porto (IPATIMUP) and Medical Faculty/HS João, Portugal; Odense University Hospital, Denmark.)

50. Graham DY. 2015. *Helicobacter pylori* update: gastric cancer, reliable therapy, and possible benefits. *Gastroenterology* 148(4): 719-731. (Supported by the Office of Research and Development, Medical Research Service, Department of Veterans Affairs,

Public Health Service. Authors affiliated with Michael E. DeBakey VA Medical Center, TX; Baylor College of Medicine, TX.)

51. Helicobacter Cancer Collaborative Group. 2001. Gastric cancer and *Helicobacter pylori:* a combined analysis of 12 case control studies nested within prospective cohorts. *Gut* 49(3): 347-353. (Supported by the Digestive Disorders Foundation, UK (previously the British Digestive Foundation). Authors affiliated with Helicobacter And Cancer Collaborative Group.)

52. Hernández DBP, Sabogal IAR, Arenas JDT. 2014. Efficacy of eradicating *Helicobacter pylori* for prevention of gastric cancer: Systematic review and meta-analysis. *Rev Colomb Gastroenterol* 29(3): 262-269. (Support not reported. Authors affiliated with Hospital Santa Clara, Colombia; Universidad El Bosque in Bogotá, Columbia.)

53. Herrero R, Park JY, Forman D. 2014. The fight against gastric cancer - the IARC Working Group report. *Best Pract Res Clin Gastroenterol* 28(6): 1107-1114. (Support not reported. Authors affiliated with IARC, France.)

54. Hooi JKY, Lai WY, Ng WK, Suen MMY, Underwood FE, Tanyingoh D, Malfertheiner P, Graham DY, Wong VWS, Wu JCY, Chan FKL, Sung JJY, Kaplan GG, Ng SC. 2017. Global prevalence of *Helicobacter pylori* infection: Systematic review and meta-analysis. *Gastroenterology* 153(2): 420-429. (Support not reported. Authors affiliated with Chinese University of Hong Kong, China; Tan Tock Seng Hospital, Singapore; University of Calgary, Canada; Otto-von-Guericke University of Magdeburg, Germany; Baylor College of Medicine, TX.)

55. Hsu WY, Lin CH, Lin CC, Sung FC, Hsu CP, Kao CH. 2014. The relationship between *Helicobacter pylori* and cancer risk. *Eur J Intern Med* 25(3): 235-240. (Supported by the Taiwan Ministry of Health and Welfare Clinical Trial and Research Center for Excellence, the Taiwan Ministry of Health and Welfare Cancer Research Center for Excellence, and the International Research-Intensive Centers of Excellence in Taiwan. Authors affiliated with Taichung Veterans General Hospital, Taiwan; China Medical University Hospital, Taiwan; National Yang Ming University, Taiwan.)

56. Huang J, Zagai U, Hallmans G, Nyrén O, Engstrand L, Stolzenberg-Solomon R, Duell EJ, Overvad K, Katzke VA, Kaaks R, Jenab M, Park JY, Murillo R, Trichopoulou A, Lagiou P, Bamia C, Bradbury KE, Riboli E, Aune D, Tsilidis KK, Capellá G, Agudo A, Krogh V, Palli D, Panico S, Weiderpass E, Tjonneland A, Olsen A, Martinez B, Redondo-Sanchez D, Chirlaque MD, Hm Peeters P, Regner S, Lindkvist B, Naccarati A, Ardanaz E, Larrañaga N, Boutron-Ruault MC, Rebours V, Barré A, Bueno-de-Mesquita HB, Ye W. 2017. *Helicobacter pylori* infection, chronic corpus atrophic gastritis and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort: A nested case-control study. *Int J Cancer* 140(8): 1727-1735. (Supported by the Cancerfonden, the Karolinska Institutet, the European Commission, IARC, the Danish Cancer Society, the Ligue Contre le Cancer, Institut Gustave Roussy, Mutuelle Generale de l'Education Nationale, Institut National de la Sante et de la Recherche Medicale (INSERM; France), the German Cancer Aid, Deutsches German

Cancer Research Center (DKFZ) and Federal Ministry of Education and Research (Germany), the Hellenic Health Foundation (Greece), the Associazione Italiana per la Ricerca sul Cancro-AIRC-Italy and National Research Council (Italy), the Dutch Ministry of Public Health, Welfare and Sports (VWS), Netherlands Cancer Registry (NKR), LK Research Funds, Dutch Prevention Funds, Dutch ZON (Zorg Onderzoek Nederland), World Cancer Research Fund (WCRF), Statistics Netherlands (The Netherlands), the Nordic Centre of Excellence programme on Food, Nutrition and Health (Norway), the Health Research Fund, Regional Governments of Andalucıa, Asturias, Basque Country, Murcia and Navarra, ISCIII RETIC, the Swedish Cancer Society, Swedish Scientific Council and County Councils of Skåne and V€asterbotten (Sweden), Cancer Research UK, the Medical Research Council. Authors affiliated with Karolinska Institutet, Sweden; Umeå University, Sweden; NIH, MD; ICO-IDIBELL, Spain; Aarhus University, Denmark; German Cancer Research Center, Germany; IARC, France; Hellenic Health Foundation, Greece; WHO Collaborating Center for Nutrition and Health, Greece; Harvard T. H. Chan School of Public Health, MA; University of Oxford, UK; Imperial College London, UK; Fondazione IRCCS Istituto Nazionale dei Tumori, Italy; Cancer Research and Prevention Institute – ISPO, Italy; Dipartimento di medicina clinica e chirurgia Federico II, Italy.)

57. Huang JQ, Zheng GF, Sumanac K, Irvine EJ, Hunt RH. 2003. Meta-analysis of the relationship between cagA seropositivity and gastric cancer. *Gastroenterology* 125(6): 1636-1644. (Support not reported. Authors affiliated with McMaster University Medical Center, Canada; Queen Mary Hospital, China.)

58. IARC. 2012. Helicobacter pylori. In *Biological Agents*. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 100B. Lyon, France: International Agency for Research on Cancer. pp. 365-435.

59. IARC. 2014. *Helicobacter pylori Eradication as a Strategy for Preventing Gastric Cancer*. IARC Working Group, vol. 8. Lyon, France: International Agency for Research on Cancer. 190 pp.

60. Ishaq S, Nunn L. 2015. *Helicobacter pylori* and gastric cancer: a state of the art review. *Gastroenterol Hepatol Bed Bench* 8(Suppl 1): S6-s14. (Support not reported. Authors affiliated with Birmingham City University, UK; SGU Grenada, West Indies.)

61. Kato S, Tachikawa T, Ozawa K, Konno M, Okuda M, Fujisawa T, Nakazato Y, Tajiri H, Iinuma K. 2001. Urine-based enzyme-linked immunosorbent assay for the detection of *Helicobacter pylori* infection in children. *Pediatrics* 107(6): E87. (Support not reported. Authors affiliated with Tohoku University School of Medicine, Japan; Sapporo Kousei General Hospital, Japan; Wakayama Rosai Hospital, Japan; Kurume University School of Medicine, Japan; Social Insurance Ohmiya General Hospital, Japan; Osaka University School of Medicine, Japan.)

62. Khalifa MM, Sharaf RR, Aziz RK. 2010. *Helicobacter pylori*: a poor man's gut pathogen? *Gut Pathog* 2(1): 2. (Support not reported. Authors affiliated with Cairo University, Egypt; San Diego State University, CA.)

63. Krueger WS, Hilborn ED, Converse RR, Wade TJ. 2015. Environmental risk factors associated with *Helicobacter pylori* seroprevalence in the United States: a cross-sectional analysis of NHANES data. *Epidemiol Infect* 143(12): 2520-2531. (Supported by the USEPA. Authors affiliated with Oak Ridge Institute for Science and Education, TN; USEPA, NC.)

64. Lansdorp-Vogelaar I, Sharp L. 2013. Cost-effectiveness of screening and treating *Helicobacter pylori* for gastric cancer prevention. *Best Pract Res Clin Gastroenterol* 27(6): 933-947. (Supported by the National Cancer Institute at the National Institutes of Health and the Centers for Disease Control, and the National Cancer Registry Ireland. Authors affiliated with Erasmus Medical Centre, Netherlands; National Cancer Registry, Ireland.)

65. Lee CW, Rickman B, Rogers AB, Ge Z, Wang TC, Fox JG. 2008. *Helicobacter pylori* eradication prevents progression of gastric cancer in hypergastrinemic INS-GAS mice. *Cancer Res* 68(9): 3540-3548. (as cited in IARC 2012)

66. Lee SY. 2014a. Current progress toward eradicating *Helicobacter pylori* in East Asian countries: differences in the 2013 revised guidelines between China, Japan, and South Korea. *World J Gastroenterol* 20(6): 1493-1502. (Supported by Konkuk University. Authors affiliated with Konkuk University School of Medicine, South Korea.)

67. Lee Y-C. 2014b. Chapter 1.3 The regional status of current or planned gastric cancer prevention strategies in Taiwan, China. In *Helicobacter pylori Eradication as a Strategy for Preventing Gastric Cancer*. IARC Working Group Report, vol. 8. Lyon, France: International Agency for Research on Cancer. p. 28-36.

68. Lee YC, Lin JT, Wu HM, Liu TY, Yen MF, Chiu HM, Wang HP, Wu MS, Hsiu-Hsi Chen T. 2007. Cost-effectiveness analysis between primary and secondary preventive strategies for gastric cancer. *Cancer Epidemiol Biomarkers Prev* 16(5): 875-885. (Supported by the Bureau of Health Promotion, Department of Health, Taiwan, and the Taipei Institute of Pathology. Authors affiliated with National Taiwan University, Taiwan; Health Bureau of Lienchiang County, Taiwan,)

69. Lee YC, Chen TH, Chiu HM, Shun CT, Chiang H, Liu TY, Wu MS, Lin JT. 2013. The benefit of mass eradication of *Helicobacter pylori* infection: a community-based study of gastric cancer prevention. *Gut* 62(5): 676-682. (Supported by the Bureau of Health Promotion, Department of Health, Taiwan, the National Science Council, and the National Taiwan University Hospital. Authors affiliated with National Taiwan University, Taiwan; Institute of Pathology, Taiwan; Health Bureau of Lienchiang County, Taiwan.)

70. Lee YC, Chiang TH, Chou CK, Tu YK, Liao WC, Wu MS, Graham DY. 2016. Association between *Helicobacter pylori* eradication and gastric cancer incidence: A systematic review and meta-analysis. *Gastroenterology* 150(5): 1113-1124. (Supported by the Health Promotion Administration, Ministry of Health and Welfare, National Taiwan University Hospital, and National Research Program for Biopharmaceuticals. Authors affiliated with National Taiwan University College of Medicine, Taiwan;

National Taiwan University, Taiwan; National Taiwan University Hospital, Taiwan; Chia-Yi Christian Hospital, Taiwan; Baylor College of Medicine Houston, TX.)

71. Lee YC, Lin JT. 2017. Screening and treating *Helicobacter pylori* infection for gastric cancer prevention on the population level. *J Gastroenterol Hepatol* 32(6): 1160-1169. (Supported by the Ministry of Health and Welfare, Taiwan (R.O.C.), the Minister of Science and Technology, Taiwan (R.O.C.), National Taiwan University Hospital, and the Taipei Institute of Pathology. Authors affiliated with National Taiwan University, Taiwan; Fu Jen Catholic University, Taiwan.)

72. Leja M, Park YY, Plummer M, Herrero R. 2014. Chapter 4.2 Multicentre randomized study of *Helicobacter pylori* eradication and pepsinogen testing for prevention of gastric cancer mortality (Gastric cancer prevention study by predicting atrophic gastritis; GISTAR). In *Helicobacter pylori Eradication as a Strategy for Preventing Gastric Cancer*. IARC Working Group Report, vol. 8. Lyon, France: International Agency for Research on Cancer. p. 147-153.

73. Leja M, Axon A, Brenner H. 2016. Epidemiology of *Helicobacter pylori* infection. *Helicobacter* 21 Suppl 1: 3-7. (Supported by the National Research Program in Latvia BIOMEDICINE 2014-2017. Authors affiliated with University of Latvia, Latvia; Riga East University Hospital, Latvia; Digestive Diseases Centre GASTRO, Latvia; University of Leeds, UK; German Cancer Research Center, Germany; National Center for Tumor Diseases, Germany.)

74. Leja M, Park JY, Murillo R, Liepniece-Karele I, Isajevs S, Kikuste I, Rudzite D, Krike P, Parshutin S, Polaka I, Kirsners A, Santare D, Folkmanis V, Daugule I, Plummer M, Herrero R. 2017. Multicentric randomised study of *Helicobacter pylori* eradication and pepsinogen testing for prevention of gastric cancer mortality: the GISTAR study. *BMJ Open* 7(8): e016999. (Supported by the European Regional Development Fund (ERDF), the National Program for Research in Latvia: Biomedicine 2014–2017, and the European Social Fund No. 009/0220/1DP/1.1.1.2.0/09/APIA/VIAA/016 ‘Multidisciplinary research group for early cancer detection and cancer prevention’. Authors affiliated with University of Latvia, Latvia; Riga East University Hospital, Latvia; Digestive Diseases Centre GASTRO, Latvia; IARC, France; Academic Histology Laboratory, Latvia; Riga Technical University, Latvia.)

75. Leung WK, Lin SR, Ching JY, To KF, Ng EK, Chan FK, Lau JY, Sung JJ. 2004. Factors predicting progression of gastric intestinal metaplasia: results of a randomised trial on *Helicobacter pylori* eradication. *Gut* 53(9): 1244-1249. (Supported by the Hong Kong Society of Digestive Endoscopy. Authors affiliated with Chinese University of Hong Kong, China; Third Hospital of Peking University, China.)

76. Li WQ, Ma JL, Zhang L, Brown LM, Li JY, Shen L, Pan KF, Liu WD, Hu Y, Han ZX, Crystal-Mansour S, Pee D, Blot WJ, Fraumeni JF, Jr., You WC, Gail MH. 2014. Effects of *Helicobacter pylori* treatment on gastric cancer incidence and mortality in subgroups. *J Natl Cancer Inst* 106(7). (Supported by NIH, NCI, and the National Basic Research Program of China. Authors affiliated with NCI, MD; Peking University Cancer Hospital and Institute, China; RTI International, MD; Linqu County Public Health Bureau, China;

Westat,, MD; Information Management Services, MD; nternational Epidemiology Institute,, MD; Vanderbilt University, TN.)

77. Limburg PJ, Stolzenberg-Solomon RZ, Colbert LH, Perez-Perez GI, Blaser MJ, Taylor PR, Virtamo J, Albanes D. 2002. *Helicobacter pylori* seropositivity and colorectal cancer risk: a prospective study of male smokers. *Cancer Epidemiol Biomarkers Prev* 11(10 Pt 1): 1095-1099. (Supported by NCI, NIH, the Department of Health and Human Services and the Medical Research Service of the Department of Veterans Affairs. Authors affiliated with Mayo Clinic, MN; NCI, MD; New York University School of Medicine and Veterans Affairs Medical Center, NY; National Public Health Institute, Finland.)

78. Liu H, Merrell DS, Semino-Mora C, Goldman M, Rahman A, Mog S, Dubois A. 2009. Diet synergistically affects *Helicobacter pylori*-induced gastric carcinogenesis in nonhuman primates. *Gastroenterology* 137(4): 1367-1379.e1361-1366. (Supported by NIH and USUHS. Authors affiliated with Uniformed Services University of the Health Sciences, MD.)

79. Logan RP, Walker MM. 2001. ABC of the upper gastrointestinal tract: Epidemiology and diagnosis of *Helicobacter pylori* infection. *BMJ* 323(7318): 920-922. (Support not reported. Authors affiliated with University Hospital, UK; Imperial College, UK.)

80. Ma JL, Zhang L, Brown LM, Li JY, Shen L, Pan KF, Liu WD, Hu Y, Han ZX, Crystal-Mansour S, Pee D, Blot WJ, Fraumeni JF, Jr., You WC, Gail MH. 2012. Fifteen-year effects of *Helicobacter pylori*, garlic, and vitamin treatments on gastric cancer incidence and mortality. *J Natl Cancer Inst* 104(6): 488-492. (Supported by the NIH, NCI, and the National Basic Research Program of China. Authors affiliated with NCI, MD; Peking University School of Oncology, China; Linqu County Public Health Bureau, China; Westat, MD; Information Management Services, MD; RTI International, MD; International Epidemiology Institute, Ltd, MD; Vanderbilt University Medical Center, TN.)

81. Machida-Montani A, Sasazuki S, Inoue M, Natsukawa S, Shaura K, Koizumi Y, Kasuga Y, Hanaoka T, Tsugane S. 2007. Atrophic gastritis, *Helicobacter pylori,* and colorectal cancer risk: a case-control study. *Helicobacter* 12(4): 328-332. (Supported by the Agricultural Technology Institute of the Nagano Farmers' Federation, the Grant-in-Aid for Cancer Research, the Third Term Comprehensive 10-year Strategy for Cancer Control from the Ministry of Health and Welfare of Japan, and the Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan. Authors affiliated with National Cancer Center, Japan; Osaka City University, Japan; Saku General Hospital, Japan; Hokushin General Hospital, Japan; Shinonoi General Hospital, Japan; Nagano Matsushiro General Hospital, Japan.)

82. Maeda M, Moro H, Ushijima T. 2017. Mechanisms for the induction of gastric cancer by *Helicobacter pylori* infection: aberrant DNA methylation pathway. *Gastric Cancer* 20(Suppl 1): 8-15. (Support not reported. Authors affiliated with National Cancer Center Research Institute, Japan; Kyoto University Graduate School of Medicine, Japan; National Cancer Center Hospital, Japan.)

83. Mahachai V, Vilaichone RK, Pittayanon R, Rojborwonwitaya J, Leelakusolvong S, Maneerattanaporn M, Chotivitayatarakorn P, Treeprasertsuk S, Kositchaiwat C, Pisespongsa P, Mairiang P, Rani A, Leow A, Mya SM, Lee YC, Vannarath S, Rasachak B, Chakravuth O, Aung MM, Ang TL, Sollano JD, Trong Quach D, Sansak I, Wiwattanachang O, Harnsomburana P, Syam AF, Yamaoka Y, Fock KM, Goh KL, Sugano K, Graham D. 2018. *Helicobacter pylori* management in ASEAN: The Bangkok consensus report. *J Gastroenterol Hepatol* 33(1): 37-56. (Supported by the Asian Pacific Association of Gastroenterology (APAGE), Ministry of Public Health (Thailand), and Gastroenterology association of Thailand (GAT). Authors affiliated with Chulalongkorn University and King Chulalongkorn Memorial Hospital, Thailand; National Gastric Cancer and Gastrointestinal Diseases Research Center, Thailand; Thammasat University Hospital, Thailand; Thonburi Hospital, Thailand; Mahidol University, Thailand; Bumrungrad Hospital, Thailand; KhonKaen University, Thailand; University of Jakarta, Indonesia; University of Malaya, Malaysia; Yangon General Hospital, Myanmar; National Taiwan University Hospital, Taiwan; Mahosot Hospital, Laos; University of Health Science, Cambodia; Changi General Hospital, Singapore; University of Santo Tomas Hospital, Phillipines; University of Medicine and Pharmacy, Vietnam; Udonthani Hospital, Thailand; Rajavithi Hospital, Thailand; University of Indonesia, Indonesia; Oita University, Japan; National University of Singapore, Singapore; Jichi Medical University, Japan; Baylor College of Medicine and Michael E. DeBakey VA Medicine Center, TX.)

84. Malfertheiner P, Megraud F, O'Morain CA, Gisbert JP, Kuipers EJ, Axon AT, Bazzoli F, Gasbarrini A, Atherton J, Graham DY, Hunt R, Moayyedi P, Rokkas T, Rugge M, Selgrad M, Suerbaum S, Sugano K, El-Omar EM, European Helicobacter Microbiota Study Group Consensus panel. 2017. Management of *Helicobacter pylori* infection-the Maastricht V/Florence Consensus Report. *Gut* 66(1): 6-30. (Supported by the Malesci/Menarini Foundation. Authors affiliated with Otto-von Guericke University Magdeburg, Germany; Université de Bordeaux, France; Trinity College, Ireland; Instituto de Investigación Sanitaria Princesa (IP), Spain; CIBEREHD, France; Erasmus University Medical Center, Netherlands; General Infirmary Leeds, UK; University of Bologna, Italy; Gastroenterology, and Liver Unit, Italy; Michael E. DeBakey Veterans Affairs Medical Center, TX; McMaster University, Canada; Hillcroft, UK; Henry Dunant Hospital, Greece; University of Padova, Italy; Institut für Medizinische Mikrobiologie, Germany; Jichi Medical School, Japan; University of New South Wales, Australia.)

85. Malnick SD, Melzer E, Attali M, Duek G, Yahav J. 2014. *Helicobacter pylori*: friend or foe? *World J Gastroenterol* 20(27): 8979-8985. (Support not reported. Authors affiliated with Kaplan Medical Center, Israel; Hebrew University, Israel.)

86. Mateos-Muñoz B, Pérez-de-la-Serna J, Ruiz-de-León A, Serrano-Falcón B, Casabona-Francés S, Velasco-Cerrudo A, Rey-Diaz-Rubio E. 2013. Enterohepatic *Helicobacter* other than *Helicobacter pylori*. *Rev Esp Enferm Dig* 105(8): 477-484. (Support not reported. Authors affiliated with Hospital Clínico San Carlos, Spain.)

87. Mera R, Fontham ET, Bravo LE, Bravo JC, Piazuelo MB, Camargo MC, Correa P. 2005. Long term follow up of patients treated for *Helicobacter pylori* infection. *Gut* 54(11):

1536-1540. (Supported by NCI, the Health Excellence Fund of the Board of Regents of the State of Louisiana, and the Instituto Colombiano para el Desarrollo de las Ciencias y Tecnología ‘‘Francisco José de Caldas.’’ Authors affiliated with Louisiana State University Health Sciences Center, LA; Universidad del Valle, Colombia.)

88. Mera RM, Bravo LE, Camargo MC, Bravo JC, Delgado AG, Romero-Gallo J, Yepez MC, Realpe JL, Schneider BG, Morgan DR, Peek RM, Jr., Correa P, Wilson KT, Piazuelo MB. 2017. Dynamics of *Helicobacter pylori* infection as a determinant of progression of gastric precancerous lesions: 16-year follow-up of an eradication trial. *Gut*. (Supported by NIEHS, Vanderbilt Digestive Disease Research Center, the Office of Medical Research, Department of Veterans Affairs, the the Pasto Cancer Registry of the Centro de Estudios en Salud, Universidad de Nariño, Colombia, NCI and NIH. Authors affiliated with Vanderbilt University Medical Center, TN; Universidad del Valle School of Medicine, Colombia; NCI, MD; Universidad de Nariño, Colombia; Veterans Affairs Tennessee Valley Healthcare System, TN.)

89. Mitchell H, English DR, Elliott F, Gengos M, Barrett JH, Giles GG, Forman D. 2008. Immunoblotting using multiple antigens is essential to demonstrate the true risk of *Helicobacter pylori* infection for gastric cancer. *Aliment Pharmacol Ther* 28(7): 903-910. (Supported by Cancer Research UK, the Australian National Health and Medical Research Council, the Cancer Council Victoria and VicHealth. Authors affiliated with University of New South Wales, Australia; University of Melbourne, Australia; University of Leeds, UK; St James University Hospital, UK.)

90. Moayyedi P. 2014. Chapter 3.3. Feasibility and cost–effectiveness of population-based *Helicobacter pylori* eradication. In *Helicobacter pylori Eradication as a Strategy for Preventing Gastric Cancer*. IARC Working Group Report, vol. 8. Lyon, France: International Agency for Research on Cancer. p. 111-121.

91. Morgan DR, Torres J, Sexton R, Herrero R, Salazar-Martínez E, Greenberg ER, Bravo LE, Dominguez RL, Ferreccio C, Lazcano-Ponce EC, Meza-Montenegro MM, Peña EM, Peña R, Correa P, Martínez ME, Chey WD, Valdivieso M, Anderson GL, Goodman GE, Crowley JJ, Baker LH. 2013. Risk of recurrent *Helicobacter pylori* infection 1 year after initial eradication therapy in 7 Latin American communities. *JAMA* 309(6): 578-586. (Supported by the Bill & Melinda Gates Foundation, NIH, and SWOG. Authors affiliated with Vanderbilt Medical Center, TN; University of North Carolina, NC; Instituto Mexicano del Seguro Social, Mexico; SWOG Statistical Center, WA; IARC, France; Fundación INCIENSA, Costa Rica; Instituto Nacional de Salud Pública, Mexico; Fred Hutchinson Cancer Research Center, WA; Universidad del Valle, Colombia; Hospital Regional de Occidente, Honduras; Pontificia Universidad Católica de Chile, Chile; Instituto Tecnológico de Sonora, Mexico; Universidad Nacional de Nicaragua, Nicaragua; University of California San Diego, CA; University of Michigan Medical School, MI; Swedish Medical Center Cancer Insitute, WA.)

92. Moss SF. 2017. The clinical evidence linking *Helicobacter pylori* to gastric cancer. *Cell Mol Gastroent Hepatol* 3(2): 183-191. (Support not reported. Author affiliated with Brown University, RI.)

93. Nobel Prize. 2005. *Press Release: Nobel Proze in Physiology or Medicine for 2005 Awarded to Barry J. Marshall and J. Robin Warren*. Nobel Media AB. Updated on 10/3/05. https://www.nobelprize.org/nobel_prizes/medicine/laureates/2005/press.html. Accessed on 1/5/18.

94. Nozaki K, Shimizu N, Inada K, Tsukamoto T, Inoue M, Kumagai T, Sugiyama A, Mizoshita T, Kaminishi M, Tatematsu M. 2002. Synergistic promoting effects of *Helicobacter pylori* infection and high-salt diet on gastric carcinogenesis in Mongolian gerbils. *Jpn J Cancer Res* 93(10): 1083-1089. (as cited in IARC 2012)

95. NTP. 2016. *Draft Report on Carcinogens Concept. Helicobacter pylori: Chronic Infection*. Research Triangle Park, NC: National Toxicology Program. 9 pp.

96. Ohata H, Kitauchi S, Yoshimura N, Mugitani K, Iwane M, Nakamura H, Yoshikawa A, Yanaoka K, Arii K, Tamai H, Shimizu Y, Takeshita T, Mohara O, Ichinose M. 2004. Progression of chronic atrophic gastritis associated with Helicobacter pylori infection increases risk of gastric cancer. *Int J Cancer* 109(1): 138-143.

97. Pan KF, Zhang L, Gerhard M, Ma JL, Liu WD, Ulm K, Wang JX, Zhang L, Zhang Y, Bajbouj M, Zhang LF, Li M, Vieth M, Liu RY, Quante M, Wang LH, Suchanek S, Zhou T, Guan WX, Schmid R, Classen M, You WC. 2016. A large randomised controlled intervention trial to prevent gastric cancer by eradication of Helicobacter pylori in Linqu County, China: baseline results and factors affecting the eradication. *Gut* 65(1): 9-18.

98. Park JB, Koo JS. 2014. *Helicobacter pylori* infection in gastric mucosa-associated lymphoid tissue lymphoma. *World J Gastroenterol* 20(11): 2751-2759. (Support not reported. Authors affiliated with Dongguk University, South Korea; Korea University Ansan Hospital, South Korea.)

99. Park JY, Forman D, Greenberg ER, Herrero R. 2013. *Helicobacter pylori* eradication in the prevention of gastric cancer: are more trials needed? *Curr Oncol Rep* 15(6): 517-525. (Support not reported. Authors affiliated with IARC, France; Fred Hutchinson Cancer Research Center, WA.)

100. Park JY, Nam B-H, Herrero R, Choi IJ. 2017. Effect of *Helicobacter pylori* eradication on gastric cancer prevention in Korea: A randomized controlled clinical trial. In *Frontiers of Biostatistical Methods and Applications in Clinical Oncology*. Matsui S, Crowley J, eds. Singapore: Springer. pp. 315-330.

101. Parsonnet J, Hansen S, Rodriguez L, Gelb AB, Warnke RA, Jellum E, Orentreich N, Vogelman JH, Friedman GD. 1994. *Helicobacter pylori* infection and gastric lymphoma. *N Engl J Med* 330(18): 1267-1271. (as cited in IARC 2012)

102. Parsonnet J. 2014. Chapter 2.2. Are there benefits of Helicobacter pylori infection? In *Helicobacter pylori Eradication as a Strategy for Preventing Gastric Cancer*. IARC Working Group Report, vol. 8. Lyon, France: International Agency for Research on Cancer. p. 72-79.

103. Pereira MI, Medeiros JA. 2014. Role of *Helicobacter pylori* in gastric mucosa-associated lymphoid tissue lymphomas. *World J Gastroenterol* 20(3): 684-698. (Support not reported. Authors affiliated with Coimbra University Hospital Center, Portugal; University of Coimbra, Portugal.)

104. Plummer M, Franceschi S, Vignat J, Forman D, de Martel C. 2015. Global burden of gastric cancer attributable to *Helicobacter pylori*. *Int J Cancer* 136(2): 487-490. (Supported by the Fondation de France. Authors affiliated with IARC, France.)

105. Raderer M, Wrba F, Kornek G, Maca T, Koller DY, Weinlaender G, Hejna M, Scheithauer W. 1998. Association between *Helicobacter pylori* infection and pancreatic cancer. *Oncology* 55(1): 16-19. (Support not reported. Authors affiliated with Vienna University Medical School, Austria.)

106. Reynders MB, Miendje Deyi VY, Dahma H, Scheper T, Hanke M, Decolvenaer M, Dediste A. 2012. Performance of individual *Helicobacter pylori* antigens in the immunoblot-based detection of *H. pylori* infection. *FEMS Immunol Med Microbiol* 64(3): 352-363. (Support not reported. Authors affiliated with AZ Sint-Jan,Belgium; Brugmann University Hospital, Belgium; Sint-Pieter University Hospital, Belgium; EUROIMMUN AG, Germany.)

107. Risch HA, Yu H, Lu L, Kidd MS. 2010. ABO blood group, *Helicobacter pylori* seropositivity, and risk of pancreatic cancer: a case-control study. *J Natl Cancer Inst* 102(7): 502-505. (Supported by NCI and NIH. Authors affiliated with Yale University School of Medicine, CT.)

108. Risch HA, Lu L, Kidd MS, Wang J, Zhang W, Ni Q, Gao YT, Yu H. 2014. *Helicobacter pylori* seropositivities and risk of pancreatic carcinoma. *Cancer Epidemiol Biomarkers Prev* 23(1): 172-178. (Supported by NCI, the Science and Technology Commission of Shanghai Municipality, and the Shanghai Cancer Institute. Authors affiliated with Yale School of Medicine, CT; Shanghai Cancer Institute, China; Jiao Tong University, China; Fudan University, China; University of Hawaii Cancer Center. HI.)

109. Rokkas T, Sechopoulos P, Pistiolas D, Kothonas F, Margantinis G, Koukoulis G. 2013. The relationship of *Helicobacter pylori* infection and colon neoplasia, on the basis of meta-analysis. *Eur J Gastroenterol Hepatol* 25(11): 1286-1294. (Support not reported. Authors affiliated with 'Henry Dunant Hospital,' Greece.)

110. Romero-Gallo J, Harris EJ, Krishna U, Washington MK, Perez-Perez GI, Peek RM, Jr. 2008. Effect of *Helicobacter pylori* eradication on gastric carcinogenesis. *Lab Invest* 88(3): 328-336. (Supported by NIH. Authors affiliated with Vanderbilt University, TN; New York University, NY; Department of Veterans Affairs Medical Center, TN.)

111. Saito D, Boku N, Fujioka T, Fukuda Y, Matsushima Y, Sakaki N, Sato K, Sugiyama T, Takahashi S, Sato T, Emura F, Gotoda T, Wakabayashi K, Kakizoe T. 2005. Impact of *H. pylori* eradication on gastric cancer prevention: Endoscopic results of the Japanese intervention trial (JITHP-Study): A randomized multi-center trial. *Gastroenterology* 128(Suppl 2): A4. (Support and author affiliations not reported.)

112. Schulte A, Pandeya N, Fawcett J, Fritschi L, Risch HA, Webb PM, Whiteman DC, Neale RE. 2015. Association between *Helicobacter pylori* and pancreatic cancer risk: a meta-analysis. *Cancer Causes Control* 26(7): 1027-1035. (Supported by the National Health and Medical Research Council Australia and the Australian Research Council. Authors affiliated with QIMR Berghofer Medical Research Institute, Australia; University of Queensland, Australia; Curtin University, Australia; Yale School of Public Health, CT.)

113. Schulz TR, McBryde ES, Leder K, Biggs BA. 2014. Using stool antigen to screen for *Helicobacter pylori* in immigrants and refugees from high prevalence countries is relatively cost effective in reducing the burden of gastric cancer and peptic ulceration. *PLoS One* 9(9): e108610. (No funding received. Authors affiliated with Royal Melbourne Hospital. Australia; University of Melbourne, Australia; Monash University, Australia; Burnet Institute Prahran, Australia.)

114. SEER. 2018. *Cancer Stat Facts: Stomach Cancer*. National Cancer Institute. https://seer.cancer.gov/statfacts/html/stomach.html. Accessed on 2/5/18.

115. Servetas SL, Bridge DR, Merrell DS. 2016. Molecular mechanisms of gastric cancer initiation and progression by *Helicobacter pylori*. *Curr Opin Infect Dis* 29(3): 304-310. (Supported by NIH, the Uniformed Services University of the Health Sciences, and the Henry M. Jackson Foundation for the Advancement of Science. Authors affiliated with Uniformed Services University of the Health Sciences, MD.)

116. Sheu BS, Wu MS, Chiu CT, Lo JC, Wu DC, Liou JM, Wu CY, Cheng HC, Lee YC, Hsu PI, Chang CC, Chang WL, Lin JT. 2017. Consensus on the clinical management, screening-to-treat, and surveillance of *Helicobacter pylori* infection to improve gastric cancer control on a nationwide scale. *Helicobacter* 22(3). (Supported by the Gastroenterological Society of Taiwan, and the Ministry of Health and Welfare, Taiwan. Authors affiliated with National Cheng Kung University, Taiwan; Ministry of Health and Welfare, Taiwan; National Taiwan University Hospital, Taiwan; Chang Gung Memorial Hospital, Taiwan; Taipei Veterans General Hospital, Taiwan; Private Kaohsiung Medical University Hospital, Taiwan; Taichung Veterans General Hospital, Taiwan; Kaohsiung Veterans General Hospital, Taiwan; Private

117. Taipei Medical University Hospital, Taiwan; Fu Jen Catholic

118. University, Taiwan.)

119. Shimoyama T, Takahashi R, Abe D, Mizuki I, Endo T, Fukuda S. 2010. Serological analysis of *Helicobacter hepaticus* infection in patients with biliary and pancreatic diseases. *J Gastroenterol Hepatol* 25(Suppl 1): S86-89. (Supported by the Ministry of Education, Culture, Sports, Science and Technology, Japan. Authors affiliated with Hirosaki University Graduate School of Medicine, Japan; Wakamoto Pharmaceutical Co., Ltd., Japan; Fuyoukai Murakami Hospital, Japan.)

120. Siao D, Somsouk M. 2014. *Helicobacter pylori*: evidence-based review with a focus on immigrant populations. *J Gen Intern Med* 29(3): 520-528. (Supported by NIH. Authors affiliated with University of California San Francisco, CA.)

121. Simán JH, Engstrand L, Berglund G, Forsgren A, Florén CH. 2007. *Helicobacter pylori* and CagA seropositivity and its association with gastric and oesophageal carcinoma. *Scand J Gastroenterol* 42(8): 933-940. (Supported by the Swedish Cancer Society, the General Hospital in Malmö Foundation for Control of Cancer and the Ernhold Lundström Foundation. Authors affiliated with Lund University, Sweden; Karolinska Institutet, Sweden.)

122. Song ZQ, Zhou LY. 2015. *Helicobacter pylori* and gastric cancer: Clinical aspects. *Chin Med J* 128(22): 3101-3105. (Supported by the National Science and Technology Pillar Program during the Twelfth Five-year Plan Period, the Capital Health Research and Development of Special, and Key Laboratory for *Helicobacter pylori* Infection and Upper Gastrointestinal Diseases in Beijing. Authors affiliated with Peking University Third Hospital, China.)

123. Stolzenberg-Solomon RZ, Blaser MJ, Limburg PJ, Perez-Perez G, Taylor PR, Virtamo J, Albanes D. 2001. *Helicobacter pylori* seropositivity as a risk factor for pancreatic cancer. *J Natl Cancer Inst* 93(12): 937-941. (Supported by NCI, the National Institute of Diabetes and Digestive and Kidney Diseases, and NIH. Authors affiliated with NCI, MD; New York University, NY; Department of Veterans Affairs Medical Center, NY; National Public Health Institute, Finland.)

124. Sugano K, Tack J, Kuipers EJ, Graham DY, El-Omar EM, Miura S, Haruma K, Asaka M, Uemura N, Malfertheiner P, on behalf of the faculty members of Kyoto Global Consenus Conference. 2015. Kyoto global consensus report on *Helicobacter pylori* gastritis. *Gut* 64(9): 1353-1367. (Supported by the Japanese Society of Gastroenterology. Authors affiliated with Jichi Medical University, Japan; University of Leuven, Belgium; Erasmus MC University Medical Center, Netherlands; Baylor College of Medicine, TX; Aberdeen University, UK; National Defense Medical College, Japan; Kawasaki Medical School, Japan; Hokkaido University, Japan; National Center for Global Health and Medicine, Japan; University of Magdeburg, Germany.)

125. Suh M, Choi KS, Lee YY, Jun JK. 2013. Trends in cancer screening rates among Korean men and women: Results from the Korean National Cancer Screening Survey, 2004-2012. *Cancer Res Treat* 45(2): 86-94. (Supported by the National Cancer Center of Korea. Authors affiliated with National Cancer Center, Korea.)

126. Taylor VM, Ko LK, Hwang JH, Sin MK, Inadomi JM. 2014. Gastric cancer in Asian American populations: A neglected health disparity. *Asian Pac J Cancer Prev* 15(24): 10565-10571. (Supported by the CDC and NCI. Authors affiliated with Fred Hutchinson Cancer Research Center, WA; University of Washington, WA; Seattle University, WA.)

127. Teng AM, Kvizhinadze G, Nair N, McLeod M, Wilson N, Blakely T. 2017. A screening program to test and treat for *Helicobacter pylori* infection: Cost-utility analysis by age, sex and ethnicity. *BMC Infect Dis* 17(1): 156. (Supported by the Health Research Council of New Zealand. Authors affiliated with University of Otago, New Zealand.)

128. Testerman TL, Morris J. 2014. Beyond the stomach: an updated view of *Helicobacter pylori* pathogenesis, diagnosis, and treatment. *World J Gastroenterol* 20(36): 12781-

12808. (Support not reported. Authors affiliated with Uniformed Services University of the Health Sciences, MD; Louisiana State University Health Sciences Center-Shreveport, LA.)

129. Thung I, Aramin H, Vavinskaya V, Gupta S, Park JY, Crowe SE, Valasek MA. 2016. Review article: The global emergence of *Helicobacter pylori* antibiotic resistance. *Aliment Pharmacol Ther* 43(4): 514-533. (No funding received. Authors affiliated with University of California San Diego Medical Center, CA; University of Texas Southwestern Medical Center and Children's Medical Center, TX.)

130. Torres J, Correa P, Herrero R, Piazuelo MB, Ferreccio C. 2016. Population-based strategies for *Helicobacter pylori*-associated disease management: Latin American perspective. In *Helicobacter pylori Research: From Bench to Bedside*. Backert S, Yamaoka Y, eds.: Springer Japan. p. 503-518. (Support not reported. Authors affiliated with Unidad de Investigación en Enfermedades Infecciosas, Mexico; Vanderbilt University Medical Center, TN; IARC, France; Universidad Pontificia Católica de Chile, Chile.)

131. Wald NJ. 2014. Chapter 4.5. The treatment of *Helicobacter pylori* infection of the stomach in relation to the possible prevention of gastric cancer. In *Helicobacter pylori Eradication as a Strategy for Preventing Gastric Cancer*. IARC Working Group Report, vol. 8. Lyon, France: International Agency for Research on Cancer. p. 174-181.

132. Wang F, Sun MY, Shi SL, Lv ZS. 2014. *Helicobacter pylori* infection and normal colorectal mucosa-adenomatous polyp-adenocarcinoma sequence: A meta-analysis of 27 case-control studies. *Colorectal Dis* 16(4): 246-252. (Support not reported. Authors affiliated with Tianjin Union Medicine Center & Tianjin People's Hospital, China; General Hospital of Tianjin Medical University, China.)

133. Wang MY, Liu XF, Gao XZ. 2015. *Helicobacter pylori* virulence factors in development of gastric carcinoma. *Future Microbiol* 10(9): 1505-1516. (Supported by the Shandong Provincial Natural Science Foundation, China, the National Natural Science Foundation of China, and the 2013 Technology Development Project of Shandong Medicine and Health Science. Authors affiliated with Dalian Medical University, China; General Hospital of Ji'nan Military Region of PLA, China.)

134. Wang X, Willén R, Svensson M, Ljungh A, Wadström T. 2003. Two-year follow-up of *Helicobacter pylori* infection in C57BL/6 and Balb/cA mice. *APMIS* 111(4): 514-522. (Supported by the Swedish Medical Research Council, Lund University Hospital (ALF), Kungliga Fysiografiska sällskapet in Lund, John and Augusta Perssons Foundation in Lund, the Medical Faculty, Lund University, Lund, Sweden, the Medical Faculty, Gothenburg University, Gothenburg, Sweden and Anna-Lisa and Bror Björnssons Foundation. Authors affiliated with University of Lund, Sweden; Sahlgrenska University Hospital, Sweden.)

135. Wong BC, Lam SK, Wong WM, Chen JS, Zheng TT, Feng RE, Lai KC, Hu WH, Yuen ST, Leung SY, Fong DY, Ho J, Ching CK, Chen JS, China Gastric Cancer Study G. 2004. *Helicobacter pylori* eradication to prevent gastric cancer in a high-risk region of

China: a randomized controlled trial. *JAMA* 291(2): 187-194. (Supported by Research Grant Council Earmarked Research Grants of the University Grant Council, Hong Kong Special Administration Region, the Peptic Ulcer Research Fund, the Simon K. Y. Lee Gastroenterology Research Fund of the University of Hong Kong, and the Henry Fok Foundation, Hong Kong. Authors affiliated with University of Hong Kong, China; Changle Institute for Cancer Research, China; Chinese Academy of Preventive Medicine, China.)

136. Wong BC, Zhang L, Ma JL, Pan KF, Li JY, Shen L, Liu WD, Feng GS, Zhang XD, Li J, Lu AP, Xia HH, Lam S, You WC. 2012. Effects of selective COX-2 inhibitor and *Helicobacter pylori* eradication on precancerous gastric lesions. *Gut* 61(6): 812-818. (Supported by the National High Technology R&D Program, National Basic Research Program of China, National Natural Science Foundation, a grant from Peking University and the Earmarked Research Grant from the Research Grant Council, Hong Kong. Authors affiliated with University of Hong Kong, China; Peking University Cancer Hospital & Institute, China; Health Bureau of Linqu County, China.)

137. Wong IO, Schooling CM, Cowling BJ. 2014. Cost-effectiveness of *Helicobacter pylori* screening and treatment for gastric cancer in Hong Kong: a decision analytic approach. *Hong Kong Med J* 20(Suppl 7): 13-15. (Supported by the Health and Health Services Research Fund, Food and Health Bureau, Hong Kong SAR Government. Authors affiliated with University of Hong Kong, China.)

138. Wu Q, Yang ZP, Xu P, Gao LC, Fan DM. 2013. Association between *Helicobacter pylori* infection and the risk of colorectal neoplasia: a systematic review and meta-analysis. *Colorectal Dis* 15(7): e352-364. (Supported by the National Natural Science Foundation of China. Authors affiliated with Fourth Military Medical University, China; Second Military Medical University, China.)

139. Wündisch T, Dieckhoff P, Greene B, Thiede C, Wilhelm C, Stolte M, Neubauer A. 2012. Second cancers and residual disease in patients treated for gastric mucosa-associated lymphoid tissue lymphoma by *Helicobacter pylori* eradication and followed for 10 years. *Gastroenterology* 143(4): 936-942; quiz e913-934. (Supported by Deutsche Krebshilfe. Authors affiliated with Heinrich-Heine-Universität, Germany; Philipps-Universität, Germany; Universitätsklinikum Carl Gustav Carus, Germany; Klinikum Kulmbach, Germany.)

140. Xie F, O'Reilly D, Ferrusi IL, Blackhouse G, Bowen JM, Tarride JE, Goeree R. 2009. Illustrating economic evaluation of diagnostic technologies: comparing *Helicobacter pylori* screening strategies in prevention of gastric cancer in Canada. *J Am Coll Radiol* 6(5): 317-323. (Support not reported. Authors affiliated with St Joseph’s Healthcare Hamilton, Canada; McMaster University, Canada.)

141. Yamaoka Y, Graham DY. 2014. *Helicobacter pylori* virulence and cancer pathogenesis. *Future Oncol* 10(8): 1487-1500. (Supported by NIH and the Ministry of Education, Culture, Sports, Science, and Technology of Japan. Authors affiliated with Oita

University Faculty of Medicine, Japan; Michael E DeBakey Veterans Affairs Medical Center & Baylor College of Medicine, TX.)

142. Yeh JM, Kuntz KM, Ezzati M, Goldie SJ. 2009. Exploring the cost-effectiveness of *Helicobacter pylori* screening to prevent gastric cancer in China in anticipation of clinical trial results. *Int J Cancer* 124(1): 157-166. (Supported by NCI. Authors affiliated with Harvard School of Public Health, MA; University of Minnesota, MN.)

143. Yeh JM, Hur C, Ward Z, Schrag D, Goldie SJ. 2016. Gastric adenocarcinoma screening and prevention in the era of new biomarker and endoscopic technologies: a cost-effectiveness analysis. *Gut* 65(4): 563-574. (Supported by NCI. Authors affiliated with Harvard T. H. Chan School of Public, MA; Massachusetts General Hospital Institute for Technology Assessment, MA; Harvard Medical School, MA.)

144. Yoon SB, Park JM, Lim CH, Cho YK, Choi MG. 2014. Effect of *Helicobacter pylori* eradication on metachronous gastric cancer after endoscopic resection of gastric tumors: a meta-analysis. *Helicobacter* 19(4): 243-248. (Support not reported. Authors affiliated with Catholic University of Korea, Korea.)

145. Yoshida T, Kato J, Inoue I, Yoshimura N, Deguchi H, Mukoubayashi C, Oka M, Watanabe M, Enomoto S, Niwa T, Maekita T, Iguchi M, Tamai H, Utsunomiya H, Yamamichi N, Fujishiro M, Iwane M, Takeshita T, Ushijima T, Ichinose M. 2014. Cancer development based on chronic active gastritis and resulting gastric atrophy as assessed by serum levels of pepsinogen and Helicobacter pylori antibody titer. *Int J Cancer* 134(6): 1445-1457.

146. You WC, Brown LM, Zhang L, Li JY, Jin ML, Chang YS, Ma JL, Pan KF, Liu WD, Hu Y, Crystal-Mansour S, Pee D, Blot WJ, Fraumeni JF, Jr., Xu GW, Gail MH. 2006. Randomized double-blind factorial trial of three treatments to reduce the prevalence of precancerous gastric lesions. *J Natl Cancer Inst* 98(14): 974-983. (Supported by NIH and NCI. Authors affiliated with Beijing Cancer Hospital, China; Beijing Institute for Cancer Research, China; NCI, MD; Linqu County Public Health Bureau, China; Westat, MD; Information Management Services, MD; International Epidemiology Institute, Ltd., MD; Vanderbilt University, TN.)

147. Yu G, Murphy G, Michel A, Weinstein SJ, Männistö S, Albanes D, Pawlita M, Stolzenberg-Solomon RZ. 2013. Seropositivity to *Helicobacter pylori* and risk of pancreatic cancer. *Cancer Epidemiol Biomarkers Prev* 22(12): 2416-2419. (Supported by NIH and NCI. Authors affiliated with National Institutes of Health, MD; German Cancer Research Center, Germany; National Institute for Health and Welfare, Finland.)

148. Zagari RM, Romano M, Ojetti V, Stockbrugger R, Gullini S, Annibale B, Farinati F, Ierardi E, Maconi G, Rugge M, Calabrese C, Di Mario F, Luzza F, Pretolani S, Savio A, Gasbarrini G, Caselli M. 2015. Guidelines for the management of *Helicobacter pylori* infection in Italy: The III Working Group Consensus Report 2015. *Dig Liver Dis* 47(11): 903-912. (Support not reported. Authors affiliated with University of Bologna, Italy; Second University of Naples, Italy; Catholic University, Italy; University of Ferrara, Italy; University Sapienza, Italy; University of Padua, Italy; University of Bari, Italy; L.

Sacco University Hospital, Italy; University of Parma, Italy; University of Catanzaro “Magna Graecia”, Italy; Maggiore Hospital, Italy; Fondazione Poliambulanza, Italy.)

149. Zeng M, Mao XH, Li JX, Tong WD, Wang B, Zhang YJ, Guo G, Zhao ZJ, Li L, Wu DL, Lu DS, Tan ZM, Liang HY, Wu C, Li DH, Luo P, Zeng H, Zhang WJ, Zhang JY, Guo BT, Zhu FC, Zou QM. 2015. Efficacy, safety, and immunogenicity of an oral recombinant *Helicobacter pylori* vaccine in children in China: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 386(10002): 1457-1464. (Supported by Chongqing Kangwei Biological Technology. Authors affiliated with Jiangsu Provincial Center for Disease Control and Prevention, China; National Institute for Food and Drug Control, China; Third Military Medical University, China; Kangwei Biological Technology, China; Ganyu County Center for Disease Control and Prevention, China.)

150. Zhang Y, Hoffmeister M, Weck MN, Chang-Claude J, Brenner H. 2012. *Helicobacter pylori* infection and colorectal cancer risk: evidence from a large population-based case-control study in Germany. *Am J Epidemiol* 175(5): 441-450. (Supported by the German Research Council and the German Federal Ministry of Education and Research. Authors affiliated with German Cancer Research Center, Germany.)

151. Zhou L, Lin S, Ding S, Huang X, Jin Z, Cui R, Meng L, Li Y, Zhang L, Guo C, Xue Y, Yan X, Zhang J. 2014. Relationship of *Helicobacter pylori* eradication with gastric cancer and gastric mucosal histological changes: a 10-year follow-up study. *Chin Med J (Engl)* 127(8): 1454-1458. (Support not reported. Authors affiliated with Third Hospital of Peking University, China.)

152. Zou QH, Li RQ. 2011. *Helicobacter pylori* in the oral cavity and gastric mucosa: a meta-analysis. *J Oral Pathol Med* 40(4): 317-324. (Supported by Research Funds for the Central Universities of Peking University. Authors affiliated with Peking University Health Science Center, China; Beijing Center for Disease Control and Prevention, China.)

153. Zullo A, Hassan C, Andriani A, Cristofari F, De Francesco V, Ierardi E, Tomao S, Morini S, Vaira D. 2009. Eradication therapy for *Helicobacter pylori* in patients with gastric MALT lymphoma: a pooled data analysis. *Am J Gastroenterol* 104(8): 1932-1937; quiz 1938. (No financial support recieved. Authors affiliated with “Nuovo Regina Margherita” Hospital, Italy; “San Giacomo” Hospital, Italy; University of Foggia, Italy; “La Sapienza” University, Italy; University of Bologna, Italy.)

154. Zullo A, Hassan C, Cristofari F, Andriani A, De Francesco V, Ierardi E, Tomao S, Stolte M, Morini S, Vaira D. 2010a. Effects of *Helicobacter pylori* eradication on early stage gastric mucosa-associated lymphoid tissue lymphoma. *Clin Gastroenterol Hepatol* 8(2): 105-110. (Support not reported. Authors affiliated with “Nuovo Regina Margherita” Hospital, Italy; University of Foggia, Italy; “La Sapienza” University, Italy; Klinikum Kulmbach, Germany; University of Bologna, Italy.)

155. Zullo A, Hassan C, Cristofari F, Perri F, Morini S. 2010b. Gastric low-grade mucosal-associated lymphoid tissue-lymphoma: *Helicobacter pylori* and beyond. *World J*

Gastrointest Oncol 2(4): 181-186. (Support not reported. Authors affiliated with “Nuovo Regina Margherita” Hospital, Italy; “Casa Sollievo della Sofferenza” Hospital, Italy.)

156. Zumkeller N, Brenner H, Chang-Claude J, Hoffmeister M, Nieters A, Rothenbacher D. 2007. *Helicobacter pylori* infection, interleukin-1 gene polymorphisms and the risk of colorectal cancer: evidence from a case-control study in Germany. *Eur J Cancer* 43(8): 1283-1289. (Supported by the German Research Foundation. Authors affiliated with German Cancer Research Centre, Germany.)

Appendix A: Literature Search Strategy

The objective of the literature-search approach was to identify published literature relevant for evaluating the potential carcinogenicity of the *Helicobacter pylori* (*H. pylori*) bacterium. As discussed in the *Helicobacter pylori* Concept Document (NTP 2016), this monograph relies on the 2012 IARC monograph and key studies published since the monograph. Two literature searches were conducted: (1) to identify key reviews or meta-analyses for updating exposure and mechanistic data and for determining whether a formal review of other cancer sites was merited and (2) to identify intervention and prevention studies published since the 2014 publication of the IARC working group report on *H. pylori* eradication.

Identification of intervention studies

General approach

Database searching encompasses selecting databases and search terms, as well as conducting the searches. Searches of several citation databases generally use search terms for the individual topic of interest, along with search terms for cancer and/or specific topics, including epidemiological and mechanistic studies. A critical step in the process involves consultation with an information specialist to develop relevant search terms, which are used to search bibliographic databases. The IARC working group report on *H. pylori* eradication was published in 2014, so PubMed, Web of Science, and Scopus were searched for new information about *H. pylori* from 2013 through 2017. Table A-1 highlights the general concepts searched, with selected example terms.

Table A-1. Major topics searched

Topics	Example terms
H. pylori	H-pylori, Helicobacter pylori, Helicobacter-pylori
Intervention/prevention	Controlled before-after studies, Interrupted time series analysis, Early medical intervention, Treatment, Intervention, Therapy, Prevention
Study type and topics	Meta-Analysis, Clinical Trial, Public Health Surveillance, Medical Economics, Markov Chains, Statistical Models, Health Care Costs, Cost-Benefit Analysis, Review, Treatment Outcome
Cancer	Neoplasms, Carcinogenicity tests, Carcinogens

The large and complex body of literature for *H. pylori* was searched through the use of narrowing terms for the relevant major topics within the bibliographic databases. The results were then processed in EndNote to remove duplicates, before being transferred to Health Assessment Workspace Collaboration (HAWC), a computational content management system, for screening.

The bibliographic database search results (1,198 references) were processed in EndNote and then imported into HAWC for first- and second-tier screening. Relevant studies found through the citations in review articles and other secondary searches were also included. Tagging in HAWC categorized the useful articles into categories such as Health Assessment (66 references), Antibiotic intervention (31 references), Other Intervention (19 references), and so on.

Search strings for H. pylori searches

Each search detailed below was limited to publication year from 2013 to 2017 and combined with the RoC Cancer Filter.

Table A-2. The full search strings for *H. pylori* searches

Database	Search terms
PubMed	(("Meta-Analysis"[pt] OR meta-analysis[tiab] OR Meta-Analyses[tiab] OR MetaAnalysis[tiab] OR metaanalyses[tiab]) OR ("Clinical Trial"[pt] OR Clinical-Trial*[tiab]) OR ("Public Health Surveillance"[mh] OR "Economics, Medical"[mh]) OR ("Markov Chains"[Mh] AND "Models, Statistical"[Mh] OR Markov-chain*[tiab]) OR ("Health Care Costs"[mh] OR "Cost-Benefit Analysis"[mh] OR cost-benefit[tiab]) OR "Review"[pt] OR "Treatment Outcome"[mh])) AND (("Controlled Before-After Studies"[Mh] OR "Interrupted Time Series Analysis"[Mh] OR "Early Medical Intervention"[Mh] OR Treatment*[tiab] OR intervention*[tiab] OR therapies[tiab] OR Therapy[tiab] OR prevent*[tiab])) AND (H-pylori[tiab] OR "*Helicobacter pylori*"[mh] OR Helicobacter-pylori[tiab])
Web of Science	(TS=("Meta-Analysis" OR "Meta-Analyses" OR "Metaanalysis" OR "metaanalyses" OR "Review" OR "Clinical Trial*" OR "Public Health Surveillance" OR "Medical Economics" OR "Markov Chain*" OR "Health Care Costs" OR "Cost-Benefit Analysis" OR cost-benefit OR "Review" OR "Treatment Outcome")) AND (TS=("Controlled Before-After Studies" OR "Interrupted Time Series Analysis" OR "Early Medical Intervention" OR Treatment* OR intervention* OR therapies OR Therapy OR prevent*)) AND (TS=(H-pylori OR "*Helicobacter pylori*"))
Scopus	(TITLE-ABS-KEY ("Meta-Analysis" OR "Meta-Analyses" OR "Metaanalysis" OR "metaanalyses" OR "Review" OR "Clinical Trial*" OR "Public Health Surveillance" OR "Medical Economics" OR "Markov Chain*" OR "Health Care Costs" OR "Cost-Benefit Analysis" OR cost-benefit OR "Review" OR "Treatment Outcome")) AND (TITLE-ABS-KEY ("Controlled Before-After Studies" OR "Interrupted Time Series Analysis" OR "Early Medical Intervention" OR Treatment* OR intervention* OR therapies OR Therapy OR prevent*)) AND (TITLE-ABS-KEY (H-pylori OR "*Helicobacter pylori*"))

Identification of cancer and exposure studies, reviews, and meta-analyses

Literature on cancer and exposure studies, reviews, and meta-analyses related to *H. pylori* infection were identified through the use of narrowing terms for the relevant major topics within PubMed, and the resulting citations were saved directly into HAWC. HAWC was used to screen results and eliminate out-of-scope or duplicate references.

1. *Prevalence* searches in PubMed combined the MeSH term for *H. pylori* with the MeSH term for prevalence, limited to reviews published in the past five years, and 69 references were added to HAWC for evaluation.
2. *Diagnosis* searches used the *H. pylori* MeSH term and the diagnosis MeSH term, limited to review articles published since 01/01/2017, and 19 references were added to HAWC.
3. Finally, 368 recent reviews and meta-analyses for *H. pylori* were identified and added to HAWC for evaluation.

Appendix B: Summary of Human Studies of Pancreatic and Colorectal Cancer

As mentioned in the Objective and Methods, NTP also reviewed recent meta-analyses, systematic reviews, and other reviews evaluating the association of *H. pylori* infection and other types of cancer, primarily pancreatic and colorectal cancer. A short summary of the updated findings on pancreatic and colorectal cancer is provided below.

Pancreatic cancer

The 2009 IARC evaluation of *H. pylori* included four nested case-control studies (see IARC 2012, Table 2.21) and one case-control study of pancreatic cancer (Raderer *et al.* 1998). Since that time, five case-control studies (Risch *et al.* 2010, Shimoyama *et al.* 2010, Gawin *et al.* 2012, Risch *et al.* 2014, Schulte *et al.* 2015), one nested case-control study (Huang *et al.* 2017), two cohort studies (Hsu *et al.* 2014, Chen *et al.* 2016b), and an update of a nested case-control study (Yu *et al.* 2013, which updated Stolzenberg-Solomon *et al.* 2001) were identified. In addition, several recent meta-analyses were identified, of which the analysis by Schulte *et al.* (2015), which included eleven studies, was considered to be the most informative. This analysis reported meta ORs of 1.13 (95% CI = 0.86 to 1.50; 11 studies) for *H. pylori* infection and pancreatic cancer, 0.78 (95% CI = 0.67 to 0.91; 6 studies) for cytotoxin-associated gene A– (CagA-) positive strains, and 1.30 (1.02 to 1.65; 4 studies) for CagA-negative strains. The meta-analysis did not include the recent large nested case-control study, which did not find an association with *H. pylori* infection, or sub-analyses for Cag-negative or -positive strains (Huang *et al.* 2017), nor the ESTHER cohort study, which found non-significant elevated risks for *H. pylori* infection with CagA-negative strains (Chen *et al.* 2016b). NTP considered the database of studies inadequate to evaluate the association between *H. pylori* infection and pancreatic cancer and did not conduct a formal evaluation.

Colorectal cancer

The 2009 IARC working group evaluation of *H. pylori* included twelve case-control studies (IARC 2012, Table 2.19) and two nested case-control studies of colorectal cancer (IARC 2012, Table 2.18). Since that time, several meta-analyses and at least ten studies on colorectal cancer have been published. Recent meta-analyses that were specific for colorectal cancer (i.e., did not include colon adenoma) reported modestly increased colorectal cancer risks (~20% to 40%) with *H. pylori* infection (e.g., Rokkas *et al.* 2013, Wu *et al.* 2013, Wang *et al.* 2014); however, heterogeneity was observed, and many studies included in the analyses were small, cross-sectional, hospital-based case-control studies, or did not adjust for potential confounding factors. The most informative studies were four large population-based case-control studies (Machida-Montani *et al.* 2007, Zumkeller *et al.* 2007, Zhang *et al.* 2012, Fernández de Larrea-Baz *et al.* 2017), three nested case-control studies (Limburg *et al.* 2002, Epplein *et al.* 2013, Blase *et al.* 2016), and a cohort study (Chen *et al.* 2016b) that reported adjusted risk estimates. Findings among these studies were inconsistent. Two population-based case-control studies in Germany (Zumkeller *et al.* 2007, Zhang *et al.* 2012) found positive associations with *H. pylori* infection. In addition, two nested case-control studies, an analysis within the U.S. Southern Community Cohort Study (Epplein *et al.* 2013), and an analysis of elderly Caucasians in the CPS-II Nutrition

Cohort (Blase *et al.* 2016) reported positive associations with some specific *H. pylori* antigens but not *H. pylori* infection in general. Few studies have looked at specific antigens, and the results were inconsistent across studies. The other informative studies did not find an association with *H. pylori* infection or specific antigens (Limburg *et al.* 2002, Machida-Montani *et al.* 2007, Chen *et al.* 2016b, Fernández de Larrea-Baz *et al.* 2017). The evidence for an association between *H. pylori* infection and colon adenoma or polyps may be stronger, but adenoma is outside the scope of a cancer hazard evaluation. Based on this initial review, NTP did not conduct a formal evaluation of colorectal cancer.