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## ***Helicobacter pylori* Infection causes both protective and deleterious effects in human health and disease**

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### **Abstract**

Infection with *Helicobacter pylori* (*H. pylori*) is necessary but not sufficient for the development of gastric cancer, the third leading cause of cancer death globally. *H. pylori* infection affects over half of people globally; however, it does not affect populations uniformly. *H. pylori* infection rates are declining in Western industrialized countries but are plateauing in developing and newly industrialized countries where gastric cancer is most prevalent. Despite *H. pylori* infection being the primary causative agent for gastric cancer, *H. pylori* infection can also cause other effects, detrimental or beneficial, throughout an individual's life, with the beneficial effects often being seen in childhood and the deleterious effects in adulthood. *H. pylori* is an ancient bacterium and its likelihood of affecting disease or health is dependent on both human and bacterial genetics that have co-evolved over millennia. In this review, we focus on the impact of infection and its genetic bases in different populations and diseases throughout an individual's lifespan, highlighting the benefits of individualized treatment and argue that universal eradication of *H. pylori* in its host may cause more harm than good for those infected with *H. pylori*.

### **Keywords**

*H. pylori* ; Human; Genetics; Gastric cancer; Precision medicine

## **INTRODUCTION**

Gastric cancer is the fifth most frequently diagnosed cancer and the third leading cause of cancer death globally, accounting for 1 000 000 new cases and approximately 783 000 deaths in 2018 (1). It is most prevalent in low-income countries, but incidence of gastric cancer has been increasing in high-income countries (1, 2). *Helicobacter pylori* (*H. pylori*) is the principal cause and strongest known risk factor for gastric cancer. It infects over half

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Competing Interests

The authors declare that they have no competing interests.

of the world's population, more than 4.4 billion individuals, and in developing countries, up to 80% of middle-aged adults may be infected (3–5). *H. pylori* infection rates vary widely between regions with prevalence being highest in Africa (79.1%), Latin America and the Caribbean (63.4%), and Asia (54.7%) and lowest in Northern America (37.1%) and Oceania (24.4%) (Figure 1). However, the infection rate does not necessarily correlate with gastric cancer prevalence. For example, despite *H. pylori* infection declining in highly industrialized countries of the West, prevalence has been increasing, and in many low- and middle-income countries, disease is rare despite high infection rates countries (5, 6). Therefore, not only is there variability in prevalence of *H. pylori* infection, but there can also be a disconnect between infection rate and disease.

*H. pylori* infection is most often thought to associate with gastric cancer and ulcers. However, *H. pylori* infection is not sufficient to cause either disease, as only a small percentage of *H. pylori*-infected develop ulcers or progress on the gastric disease cascade to gastric cancer. Therefore, dissecting both genetic and environmental factors that drive or prevent these diseases, is important for developing preventative strategies (4, 7). There is a disparity in gastric cancer in the US and globally (8). In the US, nonwhites, including Latinxs, have twice the incidence rate of whites (9). The disconnect between infection rates and disease has led to the designation of three paradoxes: the “African enigma”, the “Asian enigma”, and the “Altitude enigma” that represent inconsistencies between infection rate and gastric cancer prevalence (Figure 1). Studies have indicated that factors beyond geographical location, such as the compatibility of the genomes of the host and pathogen, can be determinants of gastric disease prevalence and severity, thereby redefining the possible causes of these enigmas (8).

*H. pylori* is a Gram negative spiral-shaped bacterium and one of the most diverse bacterial species (10, 11). To initiate colonization of the stomach, *H. pylori* neutralizes the acidic conditions, moves towards the host gastric epithelium, and binds to the host cell receptors (Figure 2) (12). The *H. pylori* genome is highly plastic, and a study of 1 531 genes showed that as many as 25% of the genes were absent from at least one of the 56 studied strains (13). It is thought that the plasticity and high rates of intraspecific recombination improves *H. pylori*'s ability to colonize the stomach (10, 11, 13).

*H. pylori* is usually acquired in childhood via fecal-oral or oral-oral transmission (14). There is considerable evidence that *H. pylori* is an ancient bacterium as it colonized humans at least 100 000 years ago (15, 16). Therefore, it can be used to trace human migration as a commensal bacterium and, similar to infectious agents such as *Mycobacterium tuberculosis* and human papillomavirus, *H. pylori* has presumably co-evolved with humans (17–21). *H. pylori* is considered a dominant member of the human gastric microbiota (22, 23). Further, *H. pylori* is an amphibiont bacterium, as some cases of infection promote pathological conditions and others protect from pathology. These different effects of *H. pylori* infection may vary by life stage with protection against diseases acquired in early life but promotion of disease later in life (Table 1) (24, 25). In this review, we will describe the deleterious and protective effects of *H. pylori* infection and argue that treatment of *H. pylori* infection should vary, using a precision-medicine based approach, that incorporates a number of factors, including patient age.

## GENE VARIANTS AND EPIGENETIC EFFECTS DRIVE GASTRIC CANCER

### H. pylori Genetic Variation

Once *H. pylori* binds to host cell receptors, it releases effector proteins and toxins including cytotoxin-associated gene A (*cagA*) and vacuolating cytotoxin A (*vacA*) (Figure 2) (12). The *cagA* gene is prevalent in high gastric cancer incidence areas and presence of *cagA* associates with increased gastric cancer risk.(26, 27) The CagA protein sequence is variable and can be divided into Western-type CagA and East Asian-type CagA, using the repeated Glu-Pro-Ile-Tyr-Ala (EPIYA) motifs at the N-terminus of CagA. Once the translocated CagA protein is injected into the host cell cytoplasm, it can alter host cell signaling in both phosphorylation-dependent and phosphorylation-independent manners (12). VacA can disrupt the balance of cell proliferation and death by affecting cell cycle genes, can induce acute inflammatory responses through the host cell release of IL-8, and can induce the release of cytochrome C, ER stress, and apoptosis. All *H. pylori* strains carry the *vacA* gene, but the gene varies in its signal sequence (s1a, s1b, s1c, and s2), mid-region (m1, m1T, and m2), and the intermediate region (i1, i2, and i3). Thus, there is a variable genotype dependent response as *vacA s1* and *m1* strains are associated with high levels of inflammation in the gastric mucosa and increased risk of carcinoma in comparison to less virulent *vacA s2* and *m2* strains (12). Both *cagA* and gastric cancer associated *vacA* genotypes are not present in all strains of *H. pylori*, but they are important cancer risk factors, and are independent of host genotype (26, 27). With the general global decline of *H. pylori* infection, the variation of gastric cancer incidence may be tied not only to infection prevalence but to strain characteristics. For example, prevalence of high-risk CagA positive *H. pylori* strains may more accurately describe a population's gastric cancer risk (28). Nonetheless, they alone are not sufficient to predict who will develop gastric diseases (26, 27).

With the availability of more *H. pylori* genomes and new bioinformatics methods, there is a greater understanding of *H. pylori* genetic diversity and evolution, virulence, and putative new targets for treatments. Recent studies have described genes associated with functions in the adaptability and pathogenicity of *H. pylori* to the human host including *cag* pathogenicity island (*cagPAI*), *babA*, *babB*, and *sabB*.(29–32) The *cagPAI* consists of approximately 30 genes that can deliver CagA and a bacterial cell wall component into host cells (33). Blood group antigen binding adhesin (BabA) binds to Lewis b (Leb) blood group antigen or sialic acid-binding adhesion (SabA) as the primary mode of *H. pylori* adhesion to the human gastric epithelium. BabA expression is regulated by phase variation and recombination between *babA* and *babB* or *babC*(30, 31). Thus, there is a wide variety of *H. pylori* genes that affect gastric disease risk and severity.

Genetic diversity of *H. pylori* can be substantial within a host population and can associate with differential gastric disease risk. This has been demonstrated in African, Middle East, and American populations, using multilocus sequence typing (MLST) lineages determined from sequences of seven housekeeping genes (17, 29). In one or more MLST lineages, pan-genome analyses have identified over-expressed or under-expressed genes among MLST lineages or associated with the *cag* pathogenicity island (34). Thus, *H. pylori* MLST genome

sequence can be used to detect varying genetic diversity between populations and possibly disease risk.

A study using MLST genome sequence of *H. pylori* in North, Central, and South America found evidence of admixture between ancestries that created new *H. pylori* subpopulations that spread and adapted rapidly during times of demographic flux. Admixture was seen in high prevalence regions, e.g., Colombia and Nicaragua, where bottlenecks and rampant genetic exchange between *H. pylori* isolates has led to chimeric gene pools unique to the local population and correlated with national boundaries. This indicates that adaption of bacteria genetics to particular human ethnic groups may be indicative of interaction with the host immune system (35–37).

### Host Genetic Variation

Polymorphisms in the host that modulate levels of cytokines *IL-10*, *IL-1 $\beta$* , and *TNF- $\alpha$*  have been associated with elevated risk of non-cardia gastric cancer.(38, 39) Genome-wide associations studies (GWAS) in Asian populations have identified other variant associations with gastric cancer including variants in *PSCA* and *MUC1* (40–42), variants near *PRKAA1* and *PTGER4*(40, 43, 44), a nonsynonymous SNP located in *PLCE1*(41), and variants in *CUX2* and *ABO* (45). A recent gastric cancer GWAS in European populations also showed association with *MUC1*. Haplotype analysis of two previously reported *MUC1* variants further verifies the association of *MUC1* variants with gastric cancer and is indicative of a pathogenic role for a tandem repeat in exon 2 of MUC1 that causes alternative splicing (46). Additionally, associations of SNPs in *PRKAA1* and *PSCA* with gastric cancer have been replicated (46). Variation in *PRKAA1* associated with gastric cancer in both Asian and European populations, but the specific SNPs differed between the populations. Gastric cancer in the Han Chinese populations associated with rs13361707[C] and 33 proxy variants and in the European population association with rs10036575 was more significant when adjusting for rs13361707. In a study of another European sample, two independent loss-of-function mutations in *ATM*, a gene with a key role in the DNA damage response, were identified (46). Therefore, associations between gastric cancer and multiple human gene variants have been found with some replicating across populations while others have not to date.

In a Colombian study population, *GATA-5* genotype and promoter methylation as well as the interaction between these two factors associated with the development of gastric disease (47). Recent *in vitro* and *in vivo* studies indicate that the upregulation of *GATA-5* and *TFF1* correlate with a protective effect of the gastric mucosa in response to *H. pylori* infection (48). *GATA-5* and *TFF1* were upregulated in *H. pylori* infected human cells 48 hours post infection, and in mice with long-term (6 and 12 months) *H. pylori* infections. Additionally, biopsies from infected pediatric, chronic gastritis, and gastric cancer patients had epigenetic inactivation of *GATA-5*, indicating that methylation occurs as an early event following *H. pylori* infection (48). Furthermore, the *GATA-5* methylation signature was suggested to be a valuable marker for past exposure to *H. pylori* and to assess gastric cancer risk (48). Epigenetic inactivation of *GATA-5* is further seen in human gastric mucosa samples where methylation of CpG islands correlates with *H. pylori* infection and occurs frequently in

early gastric carcinogenesis (49). Therefore, multiple lines of evidence support the role of *GATA-5* in gastric disease risk.

Variation in host gene expression has also been associated with *H. pylori* infection in model organisms. In mice infected with *H. pylori* for 6 months, gastric and pulmonary tissues had increased expression of multiple immune response genes, including those for T cell activation and pro-inflammatory molecules. The expression of multiple immune response genes was increased, conserved across all mice and over time in the stomach and lungs (50). Therefore, *H. pylori* infection affects local histologic, physiologic, immune, and microbiologic features in both the stomach and distal organs (50). Indeed, *H. pylori* infection influences the microbiota and host immune responses that drive gastric disease progression in the stomach as well as distal sites, and therefore *H. pylori*'s widespread effects should be considered in understanding not the development of future treatments but their total impacts.

## OTHER EFFECTS OF *H. PYLORI* INFECTION

Although *H. pylori* is generally thought of as the causative agent for gastric disease, it has the potential to cause other deleterious effects as well as some beneficial effects in those who are infected (Table 1) (51). The other diseases associated with *H. pylori* infection with the most supporting data are described below. The association with other diseases is less clear and require further studies (i.e., malaria incidence (52) and lung cancer(53)).

## OTHER DELETERIOUS EFFECTS OF *H. PYLORI* INFECTION

**PEPTIC ULCERS**—*H. pylori* was first discovered in patients with ulcers and is the primary etiological agent for peptic ulcer disease (5, 54). CagA-positive *H. pylori* strains are known to associate with higher risk of several diseases including peptic ulcer disease, atrophic gastritis, and gastric cancer (6). With eradication methods for *H. pylori* in Western Europe, the United States, and Japan, peptic ulcer incidence has decreased (5). The decrease of *H. pylori* prevalence and, as a result, peptic ulcer incidence in more developed countries further demonstrates the deleterious impact of reduced sanitation, decreased access to clean water, and lower socioeconomic status in less developed countries on peptic ulcer incidence (5). An 18-year cohort study in Taiwan revealed a significant decrease in *H. pylori* infection, duodenal ulcer prevalence, and gastric ulcer prevalence, following reductions in infection prevalence. Interestingly, over the 18 years of the study, despite the decrease in duodenal ulcer prevalence, gastric ulcer prevalence remained the same. This may be related to human genetic variation. Genetic analysis of the urease gene of *H. pylori* positive individuals showed that gastric ulcer patients were more likely to have an MboI-restriction fragment length polymorphism-defined genotype 3 for the gene encoding Urease subunit alpha, *UreC* (55). The *UreC* genotype was significantly correlated with only gastric ulcers but not duodenal ulcers. Therefore, this genotype may be a target for a precision based method for predicting and treating gastric ulcers, particularly in endemic areas (55).

Peptic ulcers are more common in children, and children with peptic ulcers are at a higher risk for developing celiac disease, an immune-related, gluten sensitivity of the small intestine that induces both gastrointestinal and non-gastrointestinal symptoms (56). However, even though *H. pylori* prevalence is associated with peptic ulcers, it does not

associate with an increase in cases of celiac disease. Therefore, the mechanism of peptic ulcer disease and *H. pylori* and how it may interact with celiac disease needs to be further studied (57).

**MALT LYMPHOMA**—Inflammation caused by chronic *H. pylori* infection is also associated with a rare form of lymphoma, gastric lymphoma of mucosa-associated lymphoid tissue (MALT). In a study of 110 patients with gastric MALT lymphoma, 92% were infected by *H. pylori*. (58, 59) *H. pylori* eradication caused regression of low-grade B-cell gastric MALT lymphoma with tumor size decreasing in approximately 75% of patients. Therefore, eradication treatment has been indicated for this lymphoma (59, 60). As regression of MALT lymphoma by *H. pylori* eradication is most successful in the early stages of disease, early treatment is recommended (61). Additionally, patients with MALT lymphomas are more likely to have the HLA-DQA1\*0103, HLA-DQB1\*0601 alleles and R702W mutation in the NOD2/CARD15 gene. Therefore, individuals with *H. pylori* infection can be genetically screened for early eradication treatment in a precision medicine approach for treating MALT lymphoma.

**CORONARY ARTERY DISEASE**—Coronary Artery Disease (CAD) is a leading cause of death world-wide and the most prevalent cause of myocardial infarction. Current research has shown an involvement of microbes, including *H. pylori*, with the development of vascular and atherosclerotic disease, heart abnormalities, and the development and progression of CAD (62). In several studies, how other CAD risk factors associate with *H. pylori* to affect risk are unclear but new molecular studies should elucidate the relationship (62).

**IRON DEFICIENCY ANEMIA**—Colonization by *H. pylori* leads to iron deficiency anemia (IDA), especially in children and adolescents (63, 64). Several studies have shown that *H. pylori* eradication therapy can improve IDA. In a meta-analysis of observational epidemiological studies and randomized controlled trials, individuals had increased hemoglobin levels and serum ferritin concentrations after eradication (64). The soluble transferrin receptor (sTFR), a significantly elevated receptor in *H. pylori*-infected children, may be a means for assessing iron status (64). In addition, a study examining IDA in children and adolescents examined patterns of *H. pylori* gene expression and showed increased expression of SabA in those with IDA (63). However, the mechanism leading to IDA via this gene is unclear, although there was some indication that there is a synergistic relationship with VacA, which is also upregulated in IDA (63).

## PROTECTIVE EFFECTS OF H. PYLORI INFECTION

**ESOPHAGEAL DISEASES**—The absence of *H. pylori*, predominantly in individuals after eradication, has been linked to some esophageal diseases including Gastro-esophageal Reflux Disease (GERD), Barrett's Esophagus, and adenocarcinoma of the esophagus and the adjacent gastroesophageal junction (65–67). Similarly, epidemiological studies have shown that over the past 50 years, the incidence of the cardia-subtype of gastric cancer has increased several fold, especially in the developed world, while non-cardia gastric cancer has declined. The timing of decreased infection and changes in disease frequency of cancer

do not necessarily follow the same trend (68). This link between absence of *H. pylori* and esophageal disease may be due to *H. pylori* colonization diminishing gastric acidity and protecting against damage to the esophageal epithelium during reflux episodes. It has also been proposed that *H. pylori* modifies the expression of gastric hormones that effect the esophageal tissue (13).

A generalized link between the absence of *H. pylori* infection and esophageal disease may be overly broad. A protective *H. pylori* effect has been proposed for Eosinophilic esophagitis, a relatively new, allergen/immune-mediated disease in the esophagus, but this conclusion is controversial (69). Overall, the mechanism(s) by which *H. pylori* protects against esophageal diseases is incomplete and further mechanistic studies are required to confirm potential associations, particularly for eosinophilic esophagitis (69).

**ASTHMA AND ALLERGY**—A potential inverse relationship between *H. pylori* and asthma and allergy has been widely reported but also remains controversial (67, 70–76). The presence of *H. pylori* has been linked in multiple large, blinded epidemiological studies with decreased risk of childhood-onset asthma, hay fever, and cutaneous allergies. These studies support the hypothesis that the rise in asthma is in part due to lower prevalence of *H. pylori* and several accompanying protective immunological functions, including TLR2/NLRP3/CASP1/IL-18 axis (13, 23, 77). As part of this axis, *H. pylori* activates CASP1 and induces IL-1 $\beta$  and IL-18 secretion by dendritic cells in the Toll-like receptor 2 (TLR2), a caspase recruitment domain (ASC), and the NLR family pyrin domain containing 3 (NLRP3) (77). These proteins are critical to the *H. pylori* specific immune response in humans.

Interestingly, the effect of *H. pylori* factors vary due to ethnicity as reported in an multi-ethnic study of children where 6 year old European children with CagA-negative *H. pylori* were associated with an increased prevalence of asthma, but children of a non-European background were not (78). Additionally, only *H. pylori* positive children with a *H. pylori* negative mother had an increased risk of asthma; thus, the mother's infection may protect against asthma in *H. pylori* positive children (78).

*H. pylori* infection and obesity may interact to affect risk of asthma and allergy, but the causal pathway linking these is unclear (66, 79, 80). In a case-control study using the second Nord-Trøndelag Health Study (HUNT), abdominal obesity and *H. pylori* infection were associated with reduced risk of asthma and allergy (70). Additionally, *H. pylori* eradication has been shown to change BMI. This has been hypothesized as being due to the regulation of appetite and energy expenditure by leptin and ghrelin, energy related hormones produced in the gastric mucosa (81). This reveals a likely causal pathway that increases risk of asthma and allergy from reduced *H. pylori* infections through obesity as well as a possible protective effect of *H. pylori* infection in the development of asthma and allergy.

Studies in model organisms also support an inverse relationship between *H. pylori* and allergy. Studies in mice reported that *H. pylori* protects against allergic asthma by regulating factors seen in human studies, including effector T-cell and T regulatory cells and inhibiting dendritic cells and HSP70 (23, 82). In a study of mice sensitized and challenged with house

dust mite (HDM), extract of *H. pylori* was an effective treatment to reduce mucus production and various features of inflammation in mice rechallenged with HDMs after 1 to 3.5 months of rest (83). Thus, these *in vivo* studies support the protective role of *H. pylori* infection on asthma and allergy.

**INFLAMMATORY BOWEL DISEASE**—Inflammatory bowel disease (IBD) is a chronic relapsing and remitting inflammation of the gastrointestinal tract that results from genetic, environmental, and microbial factors. IBD includes the subtypes Crohn’s disease (CD) and ulcerative colitis (UC) (84, 85). Ecological studies show that IBD is more prevalent in areas with lower rates of *H. pylori* infection and multiple meta-analyses have shown a significant negative association between *H. pylori* infection and IBD. This supports a possible protective effect of *H. pylori* infection against the development of IBD (23, 84–86). In a meta-analysis of 32 studies, a significant negative association was identified between *H. pylori* infection and IBD that varies by IBD subtype (CD and UC) and by geographic region. *H. pylori* infection provides more protection against UC than CD, and the protection is more apparent in East Asian populations than Mediterranean ones. However, there is no evidence for an interaction between IBD subtype and region in risk (85). A systemic review of electronic databases including 63 clinical studies also proposed that *Helicobacter* suppresses proinflammatory products and pathways or prevent or mitigate underlying dysbiosis (84).

An inverse relationship between *H. pylori* and IBD may be due to the co-evolution of *H. pylori* strain-specific constituents, such as CagA (84). Nonetheless, heterogeneity among studies and the possibility of publication bias limits the veracity of concluding a negative association. Functional studies are warranted to investigate the effect of *H. pylori* eradication on the development of IBD with mechanistic studies in *H. pylori* mouse models defining the mechanism of the negative association, if it exists (87).

**OTHER PUTATIVE PROTECTIONS**—*H. pylori* colonization has also been proposed to provide protection against various other infectious diseases. For example, *H. pylori* infection may protect against gastrointestinal infections and exogenous intestinal pathogens that cause diarrhea, but this relationship has not been consistently observed and may be due to recent changes in other factors (13, 88, 89). Specifically, as *H. pylori* prevalence has decreased with industrialization, other factors such as the introduction of clean water, improved sanitation, and less crowding also occurred and both therefore associate with the incidence of lethal diarrheal disease decreasing. Reduced *H. pylori* transmission is expected as a result of these environmental changes, making it impossible to infer a causal protective relationship between *H. pylori* infection and diarrheal disease (13).

Individuals infected by *H. pylori* also show a negative association with tuberculosis. In endemic areas of West Africa, individuals infected by *H. pylori* are less likely to reactivate latent tubercular infections (13). It has been suggested that *H. pylori* infection may induce bystander effects with continuous inflammation and T-cell signaling to enhance the host’s innate response and modify the risk of active tuberculosis in humans and non-human primates (13, 90). Ergo, functional studies are needed to elucidate the mechanism to improve protection against tuberculosis.



In summary, while the association of the absence of *H. pylori* with increased prevalence of chronic diseases have been observed several times as noted above, the statistical association may be due to confounding of other factors that are causative. Further studies will be needed for all disease associations described above to conclude causation.

## THE CO-EVOLUTION HYPOTHESIS

*H. pylori* infection, human and *H. pylori* genetics, and the environment alone do not predict gastric cancer incidence. Therefore, the interaction of human and *H. pylori* genetics may play a role in disease severity. Recent work indicated that humans and *H. pylori* coevolved to reciprocally impact each other and that gastric cancer risk is higher in host-pathogen genomic pairs that did not co-evolve together (91). There is strong evidence for human and *H. pylori* co-evolution as the migration of humans and their cohabiting *H. pylori* dates to the original human exodus from Africa, allowing for the coordinated evolution of the two species (92). This relationship has been observed in Latin America's "Altitude enigma" where human populations living in the mountains have gastric cancer incidence rates up to 25 times higher than the coast with nearly identical and universal *H. pylori* prevalence (91). When comparing two Colombian sites, gastric disease severity was less severe in *H. pylori*-human pairs that had similar ancestries; patients with a high proportion of African *H. pylori* ancestry with primarily Amerindian host ancestry had more severe disease. Contrastingly, those with primarily African *H. pylori* ancestry and African human ancestry had less severe disease (91, 93). In the discussion of Latin America coevolution, it is important to note that that ancestral Amerindian *H. pylori* strains have been mostly displaced by ones of European origin (93, 94); this may provide additional disruption. Although the role of co-evolution is difficult to definitively prove, multiple studies have shown patterns of parallel host-pathogen genetic variation that have correlated with functional and molecular changes that increase severity of disease (8).

Another hallmark of co-evolution is the adaptive microevolution in humans seen in the adhesion protein encoding *H. pylori* gene variant, *babA2*, that exhibits host-specific effects. *H. pylori* blood group antigen binding adhesin (BabA) is involved in the binding with receptors and can be modulated at the molecular and functional level to adapt to stress in the gastro-intestinal tract. Amerindians, who almost all carry the O blood group, harbor *BabA* variant strains that have up to 1500-fold greater O blood group binding affinity (93, 95). Therefore, a human and *H. pylori* pair with disrupted coevolution may be in part responsible for triggering more severe gastric disease.

## H. PYLORI TREATMENTS AND EVOLVING DRUG RESISTANCE

In addition to the potential beneficial effects of *H. pylori* infection, there is also another reason to limit eradication as a strategy of dealing with it. *H. pylori* eradication treatments rely on aggressive and regular antibiotic treatment. This has resulted in widespread resistance against commonly used antibiotics (5). In Nigeria, an epidemiological study detected high frequency of bacterial resistance for metronidazole (99.1%) followed by commonly used treatments amoxicillin (33.3%), clarithromycin (14.4%) and tetracycline (4.5%) (96). In contrast, North-East Indian strains are highly resistant to levofloxacin, but

highly sensitive to clarithromycin (97). Thus, antibiotic sensitivity varies regionally due to the predominant local antibiotic treatment options but may also be in part due to the underlying genetics of the different populations. In patients in southern Mexico with chronic gastritis, the prevalence of clarithromycin resistance is within internationally accepted ranges (17.8%), but patients with clarithromycin resistant strains (*vacA s1m1/cagA<sup>+</sup>* and *vacA s1m1/cagA<sup>+</sup>/babA2<sup>+</sup>*) are likely at an increased risk of progression to more severe gastric disease due to failure of eradication treatment (98). Therefore, treatment methods will need to vary by region, as well as human and *H. pylori* genetics.

While there are varying infection rates and gastric cancer incidences, only 1.87% of males and 0.79% of females will develop gastric cancer in their lifetime (68). The majority of people who are infected with *H. pylori* will never progress to severe gastric disease and may benefit from a precision medicine-based treatment approach. Central America is a prime location for the implementation of precision medicine-based treatments as the infection rate is high and the gastric cancer incidence varies regionally. In a large population-based study in the high gastric cancer incidence region of Central America, using 94 hypothesis-driven variants in 54 genes, an association with gastric cancer models including covariates age, sex, and the *H. pylori* virulence genotype *cagA* was detected for three genes, one being ornithine decarboxylase (*ODC*) (99). *ODC* has been associated with colorectal cancer and is a possible target for chemoprevention with the *ODC* inhibitor, eflornithine (100). Therefore, the association of the *ODC1* SNP (rs230615) with gastric cancer supports chemoprevention trials using the available agents, such as difluoromethylornithine (DFMO) as seen in colorectal cancer, that interact with the *ODC*-related polyamine pathway. The *ODC1* SNP association with gastric cancer was also significant when stratified by one of the other detected SNPs, toll-like receptor-4 (*TLR4*), rs1927914 genotype TT. Thus, DMFO treatment may be most effective in persons harboring the TT *TLR4* genotype and *ODC1* CC genotype at rs230615 (99).

## CONCLUSION AND FUTURE DIRECTIONS

Gastric cancer is a complex disease driven by *H. pylori* infection. Yet, the overwhelming majority of people infected with *H. pylori* suffer no consequences related to their infection. Prevalence and severity of gastric cancer varies by population and by distinct genetic factors in both host and *H. pylori* that may have resulted from a complex evolutionary interaction between the two species that involves both deleterious disease and beneficial health effects. Additionally, *H. pylori* infection's multiple effects, both protective and deleterious ones, vary throughout an individual's lifetime, and according to host and *H. pylori* genetic factors. Therefore, universal eradication for early stage gastric disease that is unlikely to proceed to gastric cancer and other deleterious effects may cause more harm than good. Treatment should vary by the individual and should target host and *H. pylori* genetic factors as a safer, more realistic method to reduce deleterious effects.

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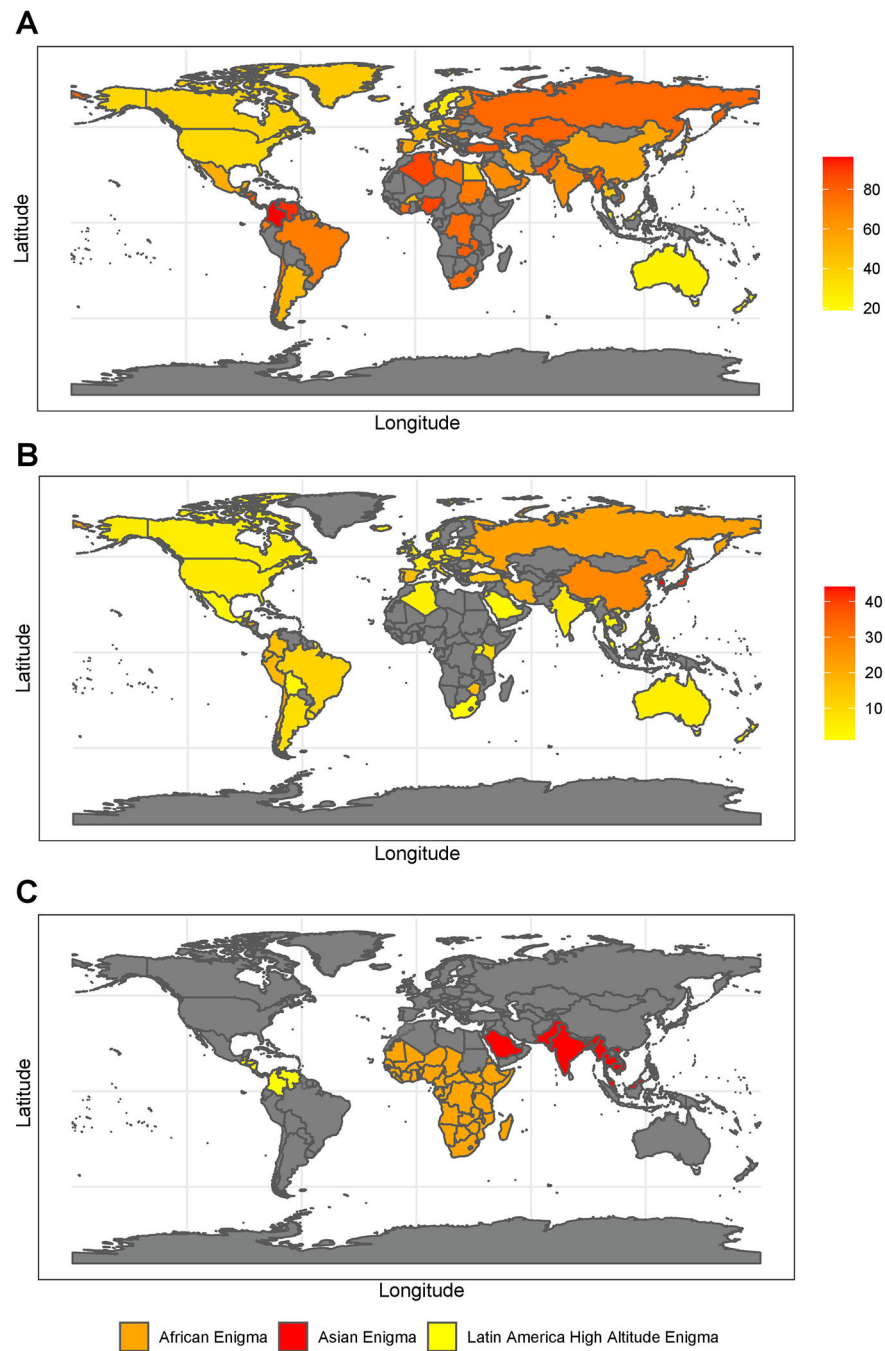
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**Figure 1: Global distribution of *H. pylori* and Gastric Cancer.**

The prevalence of *H. pylori* infection as percent of total adult population (A), gastric cancer incidence presented as number per 100,000 (B) mapped with the most recent *H. pylori* prevalence data(5) and gastric cancer incidence rates from the WHO except where WHO did not have data, in which case data was supplemented from recent publications or presented as no data available (in gray) (101–103). As gastric cancer incidence is generally presented for male and females separately we took average of the two for the figures. The average for each country is presented. The locales of the three gastric cancer enigmas, the African

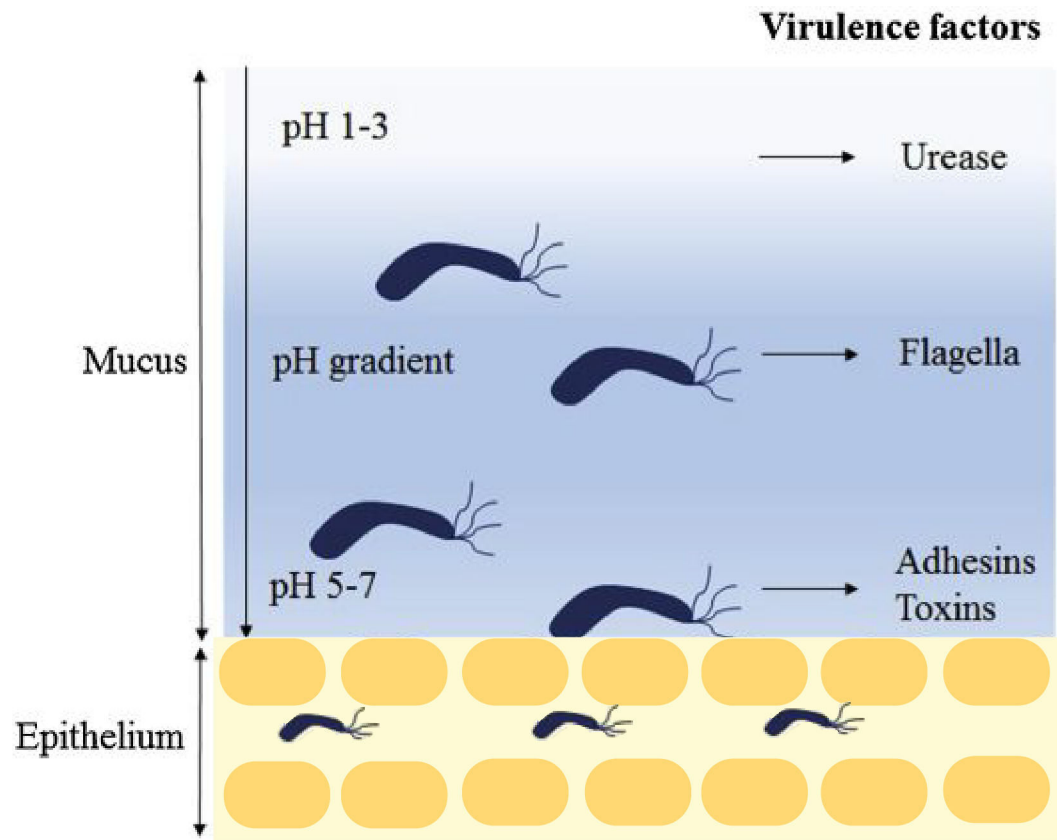
Enigma, the Asian Enigma, and the Latin America High Altitude Enigma (C), highlighting the contrast of *H. pylori* infection incidence and gastric cancer prevalence.

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**Figure 2: *H. pylori* colonization.**

*H. pylori* enters the stomach, and the urease activity reduces the acidity of the local environment. The *H. pylori* flagella-mediated motility facilitate its movement towards the lower mucosa, and it enters the epithelium with assistance from several adhesins including *babA* and *sabA*. Once the epithelium is successfully colonized, *H. pylori* release toxins including *cagA* and *vacA*. The figure modified from Kao et al (12).

**Table 1:**Deleterious and Protective effects of *H. pylori* Infection

<b>Deleterious</b>	<b>Protective</b>
Gastric Adenocarcinoma and Gastritis(3, 4)	Esophageal Diseases(65–67)
Peptic ulcers(5, 6)	Asthma and Allergy(67, 70–76)
MALT lymphoma(58–61)	Inflammatory Bowel Disease(23, 84–86)
Chronic Obstructive Pulmonary Disease (COPD) (104)	Diarrheal disease(13, 88, 89)
Atherosclerosis/coronary artery disease(105, 106)	Tuberculosis(13, 81)
Iron deficiency anemia(63, 64)	Metabolism and Obesity(13, 81)
Preeclampsia (PE)/Small for Gestational Age (SGA)/Spontaneous Preterm Birth (SPB) (107)	Food Allergy(23)
Metabolic Syndrome (MetS) in pregnancy(108)	Celiac Disease(109)
Idiopathic thrombocytic purpura(64)	Graves's Disease(110)
Impaired Glucose Intolerance(111)	

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