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# *Helicobacter pylori* in health and disease

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## Abstract

*Helicobacter pylori* is highly adapted for colonization of the human stomach and is present in about half of the human population. When present, *H. pylori* is usually the numerically dominant gastric microorganism. *H. pylori* typically does not cause any adverse effects, but is associated with an increased risk of non-cardia gastric adenocarcinoma, gastric lymphoma and peptic ulcer. Disorders such as esophageal diseases and childhood-onset asthma have been recently reported to occur more frequently in individuals who lack *H. pylori*, compared with *H. pylori*-positive persons. In this review, we discuss biologic factors that allow *H. pylori* to colonize the human stomach, mechanisms by which *H. pylori* increases the risk for peptic ulcer disease and non-cardia gastric adenocarcinoma, and potential benefits that *H. pylori* might confer to humans.

## *H. pylori* as a member of the normal human microbiota

From birth to death, humans are in contact with microbes, either transiently or persistently. Virtually every mucosal and cutaneous surface in the human body is colonized by persistent residential microbes [1–5] (Figure 1). In most niches of the human body, including the oral cavity, esophagus, colon and skin, many bacterial species are present and no single species predominates. The distribution of the microbes is not accidental; each niche is colonized by microbes that are either conserved among most humans or host-specific. It has been presumed that the conserved microbiota have specific adaptations that permit persistence at particular locales.

What is known about bacterial colonization of the human stomach? Most studies of this topic have focused on *Helicobacter pylori*. Several points can be summarized:

- **Natural colonization by *H. pylori* is restricted to humans and possibly several other primates** (although the latter is not certain).
- **The stomach is the major habitat of *H. pylori***. There may be extension of the *H. pylori* habitat into the proximal duodenum or distal esophagus, usually in the presence of gastric metaplasia in those sites [6, 7]. *H. pylori* also has been found overlying ectopic gastric epithelium in Meckel's diverticulum, but this is an



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Conflict of interest disclosure: The authors are potential recipients of royalties for licensed products involving CagA or VacA. At present, there are no licensed commercial products involving CagA or VacA. This article does not discuss any commercial products.

uncommon circumstance [8]. *H. pylori* genetic sequences have been identified in oral and colonic contents, but it is not clear whether these organisms are transient or residential.

- ***H. pylori* gastric colonization is acquired early in life (almost always before the age of 10 years), and in the absence of antibiotic therapy, generally persists for life** [9, 10].
- **When present, *H. pylori* usually is the numerically dominant gastric microorganism**. Studies of the bacterial flora of the human stomach, based on PCR amplification of 16S rRNA sequences, show that *H. pylori* represents a high proportion (70%–95%) of the clones identified [11, 12]. The human stomach is occasionally colonized by "Candidatus *Helicobacter heilmannii*" [13], which is closely related to *H. pylori*, but such colonization is relatively uncommon. Colonization of the human stomach by a single dominant species is similar to the bacterial colonization pattern sometimes observed in the human vagina [14]. However, in the vagina, the dominant organism may be one of several *Lactobacillus* species, whereas in the stomach, only a single species (*H. pylori*) is typically present. Thus, *H. pylori* can be considered as the dominant microbiota of the human stomach.

## *H. pylori* in human populations

*H. pylori* is present in human populations throughout the world. Phylogeographic studies indicate that humans have been colonized by *H. pylori* for at least 58,000 years, since before the most recent (but pre-historic) out-of-Africa migration [15]. As humans traveled around the world populating new geographic regions, they carried their ancestral *H. pylori* with them [16]. Based on the presence of gastric *Helicobacter* species (but not *H. pylori*) in other mammals (reviewed in [17]), it is possible that gastric helicobacters are ancestral in mammals, and we may have carried the ancestors of present-day *H. pylori* before we evolved into humans. Unlike most other residential microbiota of which we are aware, *H. pylori* is becoming less common in human populations with socioeconomic development; this clearly has been happening over the course of the 20$^{th}$ century in Western countries [18, 19]. Since humans are the only natural host for *H. pylori*, the decreasing prevalence can be attributed to diminished transmission among humans and perhaps a decreased duration of gastric colonization. Contributing factors include improved sanitation, smaller family sizes, and the frequent use of antibiotics during childhood. Thus, *H. pylori* is a major human residential organism that is becoming increasingly less common.

## Tropism of *H. pylori* for the human stomach

*H. pylori* is highly adapted to colonize the human stomach, whereas most other bacteria cannot persistently colonize this niche. The major factors that limit bacterial colonization of the human stomach are: (i) acidity, (ii) peristalsis, (iii) nutrient availability, (iv) host innate and adaptive immunity, and (v) competing microbes. Specific features of *H. pylori* allow it to resist each of these stresses (Table 1). *H. pylori* resists acid by hydrolyzing urea to yield ammonia, and by regulating gene expression to respond to changes in pH [20–22]. *H. pylori* expresses multiple paralogous outer membrane proteins, many of which are phase-variable; several of these appear to bind to receptors on the surface of gastric epithelial cells and could diminish the rate of bacterial wash-out due to peristalsis [23, 24]. *H. pylori* has numerous mechanisms to obtain nutrients, including the induction of tissue inflammation and the presence of systems that facilitate transport and uptake of nutrients. Innate and adapative host immune responses are limited by several secreted *H. pylori* proteins (discussed in the next section) and multiple systems counteract the actions of reactive oxygen and nitrogen

species [25, 26]. *H. pylori* produces anti-bacterial peptides [27] that might reduce competition from other microbes.

Studies in rodent models have provided further insight into the *H. pylori* constituents required for gastric colonization. Approaches such as signature-tagged mutagenesis and microarray tracking of transposon mutants have led to the identification of more than 100 bacterial genes required for gastric colonization [28–30]. The expression of several of these genes is upregulated during growth of *H. pylori* in the gastric environment [31].

*H. pylori* exclusively colonizes gastrointestinal sites overlying gastric mucosa [6–8]. The development of atrophic gastritis late in life (characterized by thinning of the gastric mucosa and loss of gastric acidity) diminishes or eliminates *H. pylori* colonization [32]. Potential reasons for the specific association of *H. pylori* with normal gastric mucosal epithelium include a low pH requirement for metabolic processes; dependence on specific nutrients, mucins or cell-surface components that are specific features of gastric epithelium; or the inability to compete in environments where other microbes are more abundant. The reasons that *H. pylori* variants have not arisen that can breech the requirement for gastric epithelium are not known, but we speculate that the biologic cost of the necessary adaptations to increase the host tissue niche exceeds the benefit to the organism, in terms of transmission to new hosts, consistent with a Nash equilibrium [33]. At least in the past, when *H. pylori* was so successful at colonizing humans, niche expansion was not necessary, and possibly deleterious. In the future, with an increasingly narrow bottleneck for *H. pylori* transmission, there could be selection for variants that colonize a broader range of epithelial surfaces; such variants might be more readily transmitted to new hosts.

## Biologic factors that promote the co-existence of *H. pylori* and humans

Most *H. pylori* localize within the gastric mucus layer and do not directly interact with host cells. However, some organisms adhere to gastric epithelial cells and occasionally are internalized by these cells [34]. Adherence of *H. pylori* to gastric epithelial cells stimulates numerous signaling pathways [35], and many *H. pylori* strains secrete toxins or other effector molecules [36, 37]. *H. pylori* elicits a humoral immune response [38], and tissue infiltration by mononuclear and polymorphonuclear leukocytes occurs in all humans who are persistently colonized [39]. The host inflammatory response to *H. pylori* is relatively weak in comparison to the response to many transient bacterial pathogens, but the host response to *H. pylori* is more substantial and complex than that which occurs in response to other intestinal luminal bacteria. Despite causing numerous alterations in the gastric environment and eliciting a host immune response, *H. pylori* persistently colonizes the human stomach for long time periods and usually does not have adverse effects [40, 41].

What factors contribute to the stability of the *H. pylori*-host equilibrium? One salient factor is the localization of *H. pylori* within the gastric mucus layer, without any substantial invasion of host tissue [42]. Another factor is the synthesis of *H. pylori* components that are highly adapted to reduce the intensity of the host immune response. *H. pylori* lipopolysaccharide (LPS) is characterized by modifications of the lipid A component that make it less proinflammatory than LPSs from other gram-negative bacterial species [43]. *H. pylori* flagella are poorly recognized by TLR5 (a component of the innate immune recognition system), due to modifications in the TLR5 recognition site [44]. Many *H. pylori* strains express LPS O antigens that are structurally related to Lewis blood group antigens found on human cells [45]. This molecular mimicry could permit *H. pylori* LPS to be recognized as a self antigen. Incorporation of a modified form of cholesterol into *H. pylori* membranes and the coating of *H. pylori* with host molecules such as plasminogen might represent additional types of antigenic disguise [46, 47].

*H. pylori* produces several factors that target host immune cells. For example, many *H. pylori* strains secrete a protein (VacA) that targets human $CD4^+$ T cells, inhibiting the transcription factor NFAT and inhibiting T cell proliferation [48–51]. VacA targets not only $CD4^+$ T cells, but also inhibits antigen presentation by B cells [52] and disrupts the normal functions of $CD8^+$ T cells, macrophages and mast cells [53–56]. Two other *H. pylori* proteins (arginase and gamma-glutamyl transferase (GGT)) are also reported to cause alterations in T cells [57, 58], and *H. pylori* arginase downregulates production of inducible nitric oxide synthase by macrophages [59]. In addition to the targeting of immune cells by the *H. pylori* proteins described above, *H. pylori* causes numerous additional effects on immune cells via mechanisms that have not yet been elucidated [41]. By targeting host immune cells, *H. pylori* can potentially downregulate host responses and thereby maximize its persistence.

## Heterogeneity among *H. pylori*

*H. pylori* strains isolated from unrelated individuals exhibit a high level of genetic diversity (reviewed in [60, 61]). Nucleotide sequences of conserved genes are 92%–99% identical among different *H. pylori* strains, but several *H. pylori* genes are more highly diverse in sequence [62–64]. In addition to variation in the sequences of individual genes among *H. pylori* strains, there is considerable variation in gene content. One study analyzed genomic DNA from 56 different *H. pylori* strains using array hybridization methods and identified 1150 genes that were present in all of the strains tested (thus representing a “core” genome) [65]. In contrast, 25% of the 1531 genes analyzed were absent from at least one of the 56 strains, indicating the extensive plasticity of the *H. pylori* genome.

*H. pylori* has evolved highly effective systems for generating diversity [61, 66]. Mechanisms include lack of mismatch DNA repair to maximize variation [67], use of repetitive DNA for intragenomic recombination to change phenotypes, and natural competence for DNA uptake to facilitate acquisition of new genetic sequences. Gastric colonization with more than one distinct *H. pylori* strain is common; this multiplicity of infection provides substrate for acquisition of new genetic sequences and recombination events, which occur commonly [68]. Efficient systems for generating genetic diversity allow *H. pylori* to adapt to changing conditions within individual human stomachs and also permit bacterial adaptation to the gastric environments of new hosts [69, 70]. The simultaneous presence in the stomach of multiple *H. pylori* strains that can recombine could permit the emergence of the most flexible and robust bacterial populations; conversely, a decrease in the multiplicity of strains in the stomach, associated with socioeconomic advancement, might accelerate the loss of *H. pylori* [61, 66].

One of the most striking differences among *H. pylori* strains is the presence or absence of a 40-kb region of chromosomal DNA known as the *cag* pathogenicity island (PAI) [71]. One gene in the *H. pylori cag* PAI encodes an effector protein (CagA) whereas others encode proteins that assemble into a type IV secretion apparatus that translocates CagA into gastric epithelial cells [37, 72]. Within gastric epithelial cells, CagA is phosphorylated by host cell kinases [73]. Both phosphorylated CagA and non-phosphorylated CagA cause numerous alterations in gastric epithelial cells, including activation of the phosphatase SHP-2 and dephosphorylation of cellular proteins [74], alterations in cell morphology and cell motility [75, 76], alterations of tight junctions [77], alterations in cell scattering and proliferation [78], activation of β-catenin [79], and perturbation of epithelial cell differentiation and polarity [80, 81]. In addition to the effects on gastric epithelial cells that result from actions of CagA, products of the *cag* PAI contribute to CagA-independent alterations in gastric epithelial cells, including stimulation of the synthesis of interleukin (IL)-8, a proinflammatory cytokine [82, 83].

Most *H. pylori* strains secrete a protein known as VacA via an autotransporter mechanism (reviewed in [84]). The VacA protein was originally identified based on its capacity to cause vacuolation in cultured human epithelial cells [36], but multiple other activities of this protein have subsequently been identified [84]. All *H. pylori* strains contain a *vacA* gene, but there is marked variation among strains in *vacA* nucleotide sequences. *vacA* alleles have been classified into separate families based on diversity at several loci (designed s, i, m); variations in sequence are associated with variations in VacA functional activity in cell culture assays [62, 85–87]. Active forms of VacA cause detectable alterations in gastric epithelial cells and immune cells whereas inactive forms of VacA (predominantly type s2) lack activity in most *in vitro* cell culture assays[62, 88, 89]. Effects of active VacA on gastric epithelial cells include alterations of late endocytic compartments [90], increased plasma membrane permeability [91], increased mitochondrial membrane permeability [92, 93] and apoptosis [94] (reviewed in [84]). Most VacA-induced alterations are attributable to insertion of VacA into cell membranes, oligomerization, and formation of anion-selective channels [91, 95–97]. Since the inactive s2 form of VacA is well-conserved, it is likely to have a functional role that it not yet understood.

Individual *H. pylori* strains differ considerably in the expression and binding properties of outer membrane proteins (OMP) that function as adhesins. In particular, there are differences among strains in the expression and binding properties of BabA (an OMP that binds the fucosylated Lewis b receptor on gastric epithelial cells) and SabA (an OMP that binds to sialyl Lewis X receptors) [23, 24]. These differences among strains in adhesin expression result in strain-specific variations in binding of *H. pylori* to gastric epithelial cells. There also are differences among strains in the expression of the outer membrane OipA (HopH) due to phase variation, which could result in strain-specific variations in *H. pylori*-induced signaling in gastric epithelial cells [98].

*H. pylori* strains can be broadly categorized into 2 groups: strains that express multiple factors that interact with host tissue (including proteins encoded by the *cag* PAI, active forms of VacA, and outer membrane proteins such as BabA) and strains that lack these factors [62, 99, 100]. Strains with intermediate properties have been identified, although less frequently than expected than if the distribution of *H. pylori* virulence factors were completely random. Recent studies indicate that CagA and active forms of VacA have reciprocal or antagonistic actions; consequently, there may be selection for strains that encode both of these factors or strains that lack both factors [101–103].

*H. pylori* strains that express multiple 'interaction factors' ($CagA^+$, s1-$VacA^+$, $BabA^+$ strains) are predicted to be highly interactive with the host, whereas strains that lack these factors would be relatively non-interactive (Figure 2). Concordant with these predictions, $CagA^+$, s1-$VacA^+$, $BabA^+$ strains are associated with increased gastric mucosal inflammatory cell infiltration and increased gastric epithelial injury, compared to strains that do not express these factors [99, 104]. In addition, the colonization density of $CagA^+$, s1-$VacA^+$, $BabA^+$ strains is typically higher than that of strains that do not express these factors [105].

*H. pylori* strains expressing multiple interaction factors and strains that lack these factors might occupy different niches in the gastric environment or each could have selective advantages at different times during prolonged colonization. Currently, people in developing countries are predominantly colonized by $cagA^+$ strains, whereas those in many developed countries are colonized by an almost equal proportion of $cagA^+$ and $cagA^-$ strains [100, 106]. This suggests that there is an accelerated loss of $cagA^+$ strains from some populations [18]. $cagA^+$ strains induce the production of beta-defensin 2 and other antimicrobial effectors to a greater extent than *cagA*strains [107], which might render $cagA^+$ strains more susceptible to

eradication from the host. In addition, *cagA*$^+$ strains seem to be more efficiently eradicated by antibiotics than are *cagA*strains [108].

## *H. pylori* and gastroduodenal disease

Although *H. pylori* typically colonizes the human stomach for many decades without adverse consequences, the presence of *H. pylori* is associated with an increased risk for several diseases, including peptic ulcers, non-cardia gastric adenocarinoma, and gastric MALT lymphoma (reviewed in [109, 110]). What factors account for the development of these diseases in subsets of people who harbor *H. pylori*?

The risks of peptic ulcer disease and non-cardia gastric adenocarcinoma are determined in part by characteristics of the *H. pylori* strain with which an individual is colonized. Most of the *H. pylori* polymorphisms associated with varying disease risk are found in genes that encode bacterial products that interact with host tissue. Numerous studies, particularly in Western countries, have shown that *cag* PAI-positive *H. pylori* strains are associated with an increased risk of peptic ulcer disease, premalignant gastric lesions and gastric cancer, compared to strains that lack the *cag* PAI [100, 111–114]. Moreover, the number of tyrosine phosphorylation (EPIYA) motifs in CagA proteins correlates with gastric cancer risk [115, 116]. Strains that express forms of VacA that are active *in vitro* (for example, s1/i1/m1) are associated with a higher risk of disease than those that express inactive forms of VacA [62, 85, 112, 117]. Similarly, strains that express BabA and OipA (HopH) outer membrane proteins are also associated with a higher risk of disease than strains that lack these factors [99, 118]. Based on data from human epidemiologic studies, it is difficult to determine which of these bacterial factors is most closely linked to adverse disease outcomes, since these interaction factors tend to cluster together in *H. pylori* strains [62, 99, 117].

Studies involving gerbil and transgenic mouse models suggest that products of the *cag* PAI (including CagA) have an important role in contributing to adverse disease outcome [119–122]. Some studies in rodents suggest that products of the *cag* PAI and VacA enhance the ability of *H. pylori* contribute to colonize the stomach [123, 124], but other studies have not reached the same conclusions [125]. Notably, there are limitations of various animal models in replicating the human host environment. For example, some *H. pylori* factors (such as those encoded by the *cag* PAI) are present on genetically metastable elements that are commonly deleted during colonization of mice [126, 127]. Furthermore, human T cells are susceptible to VacA, whereas mouse T cells are not [51, 128].

Host and environmental factors also are important determinants of *H. pylori*-associated disease risk. For example, male gender, specific IL-1β haplotypes, and various other proinflammatory gene polymorphisms are associated with an increased risk of non-cardia adenocarcinoma [129, 130]. There might be synergy between bacterial and host polymorphisms in determining disease risk [112]. Environmental factors that may influence the risk of gastric cancer include the level of dietary salt intake, intake of fresh fruit and vegetables, and the presence of various parasitic infections [131–133].

The use of antibiotics to eradicate *H. pylori* has dramatically altered the incidence and natural history of peptic ulcer disease [134]. *H. pylori* resistance to macrolides, fluoroquinolones, and nitroimidzaoles is gradually increasing due to the widespread use of these antibiotics in the community for multiple indications. Increasing antibiotic resistance decreases the efficacy of current triple-drug treatment regimens for *H. pylori* and may portend future difficulties in our ability to treat peptic ulceration with antibiotics.

## Potential benefits of *H. pylori*

*H. pylori* colonization is associated with many biological costs to the host; conversely, a growing body of literature suggests that the absence of *H. pylori* might also be associated with an increased risk of various diseases. An absence of *H. pylori* could indicate that an individual was never colonized, or that the organism was present earlier in life and subsequently eradicated. The idea that *H. pylori* might actually confer benefits to humans has engendered considerably controversy among investigators, but we review here the current data and discuss the potential importance of health benefits that might be afforded by *H. pylori*. Not surprisingly, most of the potential benefits (as with the costs) come from *cagA*$^+$ strains, which are the most interactive with their human hosts. In 1998, one of us used the term *acagia* to describe the absence of *cagA*$^+$ *H. pylori*, a condition associated with disease risks that differ from those associated with the presence of *cagA*$^+$ *H. pylori* [135].

### Esophageal diseases

There are inverse associations between the presence of *H. pylori* (especially *cagA*$^+$ strains) and disorders such as gastroesophageal reflux disease, Barrett's esophagus and esophageal adenocarcinoma [136–140], suggesting a protective role of *H. pylori*. Depending on the study, the odds ratios for the presence of esophageal disorders in persons with cagA$^+$ strains range as low as 0.2 (the inverse of an odds ratio of 5.0). One potential mechanism for this effect could be that *H. pylori* colonization diminishes gastric acidity; therefore, during reflux episodes, the acidic refluxate might be more damaging to the esophageal epithelium of *H. pylori*-negative than of *H. pylori*-positive persons. Another hypothesis is that *H. pylori* alters the expression of multi-functional gastric hormones that have effects on esophageal tissue [141, 142]. The presence or absence of *H. pylori* might also affect other microbiota of the stomach [11, 12] and/or the distal esophagus [5, 143], which may have an effect on esophageal mucosal integrity. Better understanding of the mechanisms that underlie the inverse relationships between *H. pylori* and esophageal disorders will permit improved assessment of risk and could lead to new approaches for prevention of these diseases.

### Asthma and allergic disorders

As *H. pylori* prevalence has declined, the incidence of asthma and related disorders, especially those that appear during childhood, has risen [144]. Asthma is part of an allergy syndrome that can include rhinitis and cutaneous atopy (also called eczema) and is generally considered to arise from dysfunctional immune responses to common allergens. The absence of *H. pylori* is associated with an increased risk for allergies [145–147]; this inverse association is specific for childhood-onset, but not later-onset, asthma, and is most pronounced for *cagA*$^+$ *H. pylori* strains. The reduced incidence of colonization with *cagA*$^+$ strains [18] (increased incidence of *acagia*) is consistent with increased incidences of asthma and allergic disorders [135]. It is possible that the presence of *cagA*$^+$ *H. pylori* in the stomach leads to gastric recruitment of T-cell populations, including regulatory T cells, that ultimately affect the activities of T-cells present in other mucosal and cutaneous sites [148, 149]. Another hypothesis is that *H. pylori*-induced alterations in gastric hormone expression contribute to the pathogenesis of asthma and allergic disorders.

### Infectious diseases

There has recently been interest in the hypothesis that *H. pylori* colonization might confer protection against various other infectious diseases. In support of this concept, a recent study demonstrated that another chronic infection (latent herpesvirus) conferred resistance to infection with two bacterial pathogens in a mouse model [150]. Several studies have suggested that *H. pylori* protects against diarrheal diseases [151, 152], although this relationship has not been consistently observed [153]. Mechanisms for protection might include production of

antibacterial peptides by *H. pylori* or the host [27, 107], activating the immune system as an adjuvant [154], competition for niche, or hypergastrinemia leading to maintainence of gastric acidity throughout childhood. Recent studies in West Africa, where tuberculosis is endemic, have indicated that *H. pylori*-positive persons are less likely to reactivate latent tubercular infections [155]. By providing partial protection against infectious diseases common in childhood, there would be strong selection for the presence of *H. pylori*. If *H. pylori* increased morbidity or mortality due to other infectious diseases, then there would have been a very powerful selection against its presence. As the incidence of childhood infectious diseases declines, so too would the positive selective pressure for maintenance of *H. pylori* in human populations. The introduction of clean water supplies, improved sanitation, and less crowding into human populations have resulted in a decreased incidence of lethal diarrheal diseases; these changes would be expected to result in reduced *H. pylori* transmission and reduced selection for maintenance of *H. pylori*.

### Effects on metabolism

The mammalian stomach produces about 5%–10% of the body's leptin and 60%–80% of ghrelin. Leptin and ghrelin are multi-functional hormones that help to regulate body weight [156]. Is *H. pylori* involved in the physiologic regulation of these hormones? Multiple studies have shown that *H. pylori*-positive persons produce lower amounts of ghrelin than do *H. pylori*-negative persons [157, 158] and *H. pylori* eradication is associated with a subsequent increase in ghrelin production [159, 160]. Since ghrelin has effects throughout the body, it is likely that the presence or absence of *H. pylori* will have substantial long-term metabolic consequences [161]. The effects on leptin are less clear-cut, with apparently conflicting results [142, 162, 163] that could reflect many variables, such as a subject's age, medications, and extent of gastric inflammation. Regardless of the specific findings, a generation of children is currently growing and developing without the contribution of *H. pylori* to gastric physiology; the consequent alterations in ghrelin and leptin production may affect overall energy homeostasis.

### *H. pylori* as an indicator of changes in human microbiota

Are the apparent benefits associated with *H. pylori* colonization directly attributable to the presence of *H. pylori*, or is *H. pylori* simply a marker or "indicator organism" for exposure to other bacteria or foreign antigens that stimulate the immune system? Just as *H. pylori* is disappearing as a consequence of modern lifestyles (e.g. improved sanitation and exposure to antibiotics), other organisms (including those that are currently unknown or unappreciated by medical science) might be disappearing in parallel. *H. pylori* might be a marker or indicator organism for a more widespread change in human microecology [164]. Some of the disease consequences associated with the lack of *H. pylori* (and specifically *acagia*) might reflect this phenomenon. At the very least, *H. pylori* is a marker for our changing (or disappearing) microbiota; at the most, its disappearance is central to these diseases. As our understanding of the broad effects associated with *acagia* continue to increase, it is likely that we will discover examples of phenotypes that are directly attributable to the absence of *H. pylori*, as well as phenotypes for which *H. pylori* is an indicator organism.

## Conclusions

The rediscovery of gastric microbiota and the first sucessful culture of *H. pylori* in 1982 by Marshall and Warren opened a new chapter in human medicine [165]. Early work, demonstrating a relationship between *H. pylori* and peptic ulcer disease, changed medical practice [134]. The finding that *H. pylori* also increased the risk of gastric adenocarcinoma bolstered the view that *H. pylori* is a human pathogen. However, it is now becoming clear that the progressive disappearance of *H. pylori* in the 20$^{th}$ and 21$^{st}$ centuries, abetted by

modern medical practices (including overuse of antibiotics in childhood), may have consequences. These may include an increased risk of gastroesophageal reflux disease and its sequelae, childhood asthma, and metabolic disorders. If continued studies confirm the findings reported thus far, then our medical approaches to *H. pylori* will need to change. These next years will be an exciting period in which the relationship between *H. pylori* and humans becomes more thoroughly understood.

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## Biographies

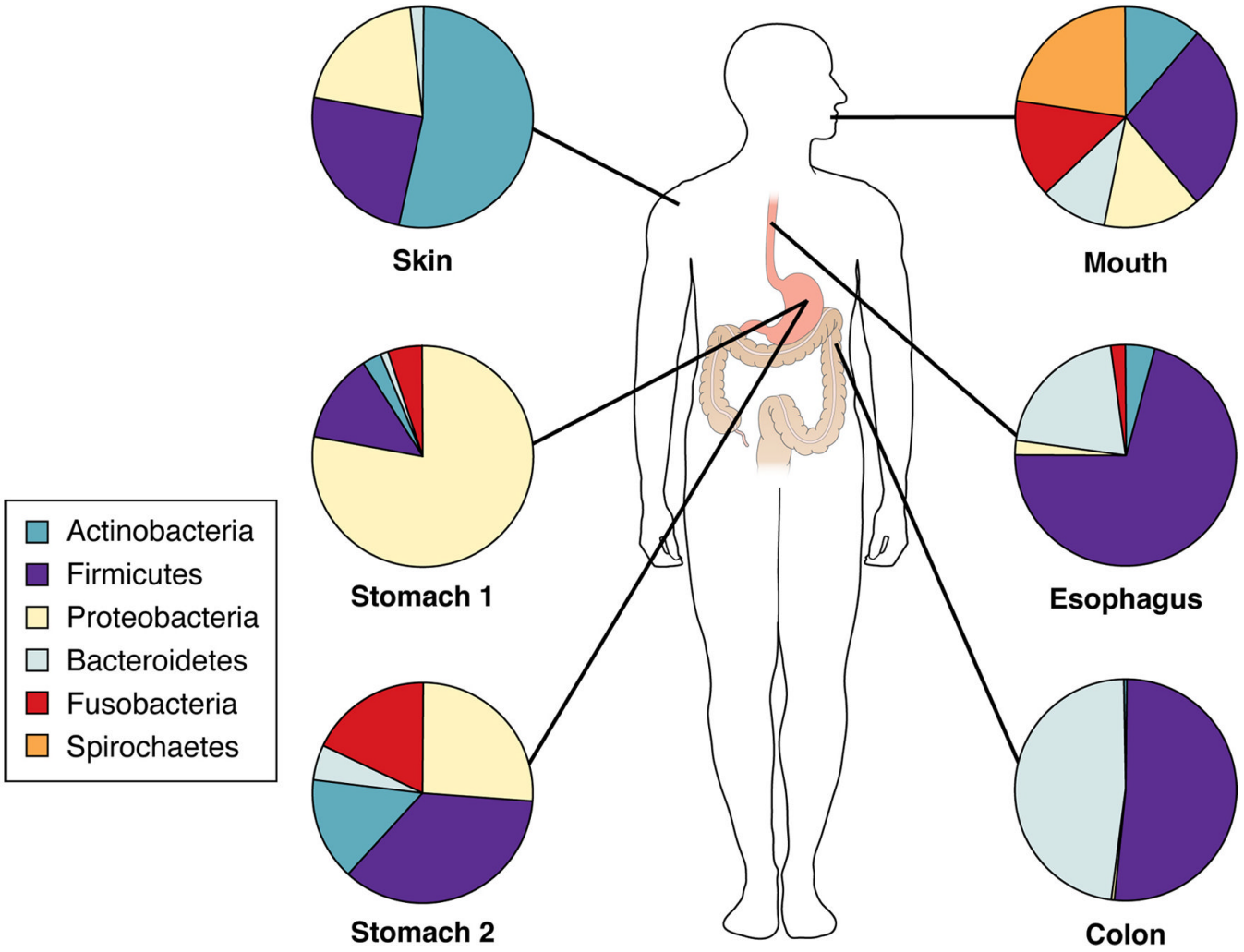


**Figure 1.**
Major bacterial phyla in the stomach and at diverse anatomical sites [1, 2, 4, 5, 11]. Stomach 1 depicts a stomach in which *H. pylori* is detected by conventional methods and Stomach 2 depicts a stomach in which *H. pylori* is not detected.

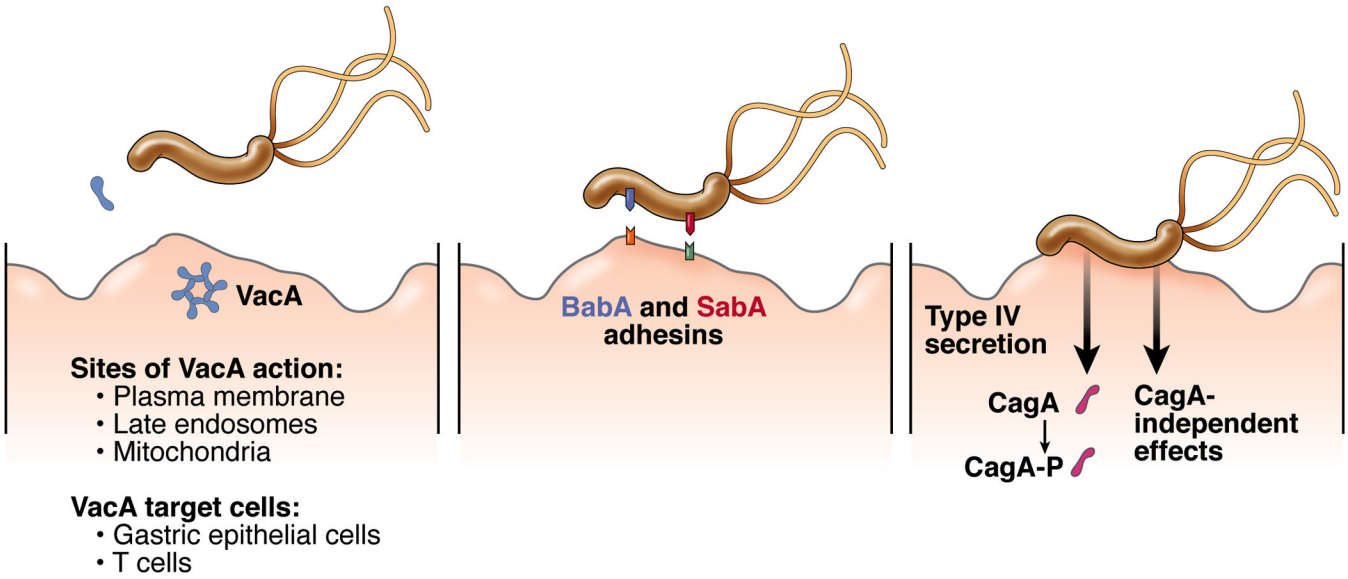


**Figure 2.**

Interactions of *H. pylori* with human gastric mucosa. Within the gastric mucosa, most *H. pylori* localize within the gastric mucus layer and do not directly adhere to gastric epithelial cells. VacA, secreted by non-adherent bacteria, can cause alterations in several cell types, including gastric epithelial cells and T cells [84]. Binding of *H. pylori* to gastric epithelial cells is mediated by several bacterial adhesins, including BabA and SabA[23, 24]. Adherent *H. pylori* assemble a type IV secretion apparatus (comprised of proteins encoded by genes in the *cag* pathogenicity island), which translocates the CagA protein into gastric epithelial cells [37, 72]. Within gastric epithelial cells, CagA is phosphorylated by host cell kinases; both phosphorylated and non-phosphorylated CagA can cause numerous cellular alterations. Strain-specific variations in the expression of these bacterial factors are an important determinant of interactions between *H. pylori* and the human host.

**Table 1**

Examples of *H. pylori* adaptations that facilitate gastric colonization

| Adaptation | Function | Reference |
|---|---|---|
| Spiral shape | Hydrodynamic movement | 42 |
| Polar flagella | Motility in the gastric niche | 42 |
| Flagellin structure | Modification of TLR5 recognition site | 44 |
| Urease | Resistance to gastric acidity | 20 |
| LPS structure | Lipid A with low bioactivity | 43 |
| LPS Lewis antigens | Mimicry of host cell molecules | 45 |
| Natural competence | Ability to adapt to changing gastric conditions | 69 |
| Multiple adhesins | Attachment to epithelium resists peristalsis | 23, 24 |
| VacA | Inhibition of T cell activities | 48–50, 53 |
| Products of *cag* PAI | Signaling within gastric epithelium | 35, 37, 83 |