Journal of
Agriculture and Biology
ISSN: 3007-1763 (Online), 3007-1755 (Print)

Research Article

Epidemiology and Pathogenesis of *H. pylori* Infection

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ABSTRACT

Helicobacter pylori infection is very common in Pakistan and other nations all over the world. It induces chronic gastritis, the strongest known risk factor for peptic ulcer disease, distal gastric cancer and a number of extra gastric related morbidity. Increased incidence may be caused by worse hygienic conditions and lower socioeconomic level. Age, smoking, crowded housing, poor-quality food (such as fast food or restaurant cuisine), and unclean water may also exacerbate the problem. Clinical consequences depend on the genetic diversity of the host and the virulence factors of the bacterium, especially in relation to immune response genes. The organism develops many strategies that help it accomplish sustained colonization, allowing it to avoid the hostile acidic environment of the stomach mucosa and the human immune response. By routinely monitoring the risk factor system, as well as by raising the socioeconomic position and hygienic circumstances of the populace, it is possible to reduce the spread of *H. pylori* infection in Pakistan.

Keywords: *Helicobacter pylori*, Epidemiology, Virulence factors, Pathogenicity, Pakistan.

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Article History
Received: April 27, 2023
Accepted: July 25, 2023
Published: September 22, 2023

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INTRODUCTION

Helicobacter pylori is a type of bacteria a gram-negative which have spiral or rod like shape. It can measure 2-4 micrometers in length and 0.5 to 1 micrometer in width. You can find it on the surface of gastric epithelium. Marshall and Warren discovered *H. pylori* back in 1983 (Warren and Marshall, 1983). The bacterium can cause long term inflammation of mucosa if left untreated. The infection can persist over time (Kim et al., 2018). Increases in the prevalence of infection in older age as compared to younger age due to lower socioeconomic status and poorer hygienic conditions in early age and *H. pylori* vary a lot depending on where you are in the world t. It tends to be more in old age people dye to cohort effect to very poor or bad living circumstances in backward times. More than half of the world population has had contact with *H. pylori* infection (Kim et al., 2018). *H. pylori* is a tough bacterium that can survive in acidic stomach environments. It has urease activity which converts urea into ammonia and carbon dioxide which help it to thrive in gastric juice (Marshall et al., 1990). *H. pylori* Infection plays a significant role in the development of several upper GIT diseases. This includes duodenal or gastric ulcer which can occur 0.5 to 10% of patients. There is also a risk of gastric cancer which affects about 0.1-3% of infected patients. Additionally, it is also related with gastric mucosa-associated lymphoid-tissue (MALT) lymphoma. The risk of developing this disease can vary among different populations. Most people with *H. pylori* infection won't have major complications. Peptic ulcer disease which is caused by *H. pylori* infection can be cured by eliminating bacteria.

We have made huge progress in understanding how this infection works while there is no specific treatment available, but we do have antimicrobial therapy available. The indications of therapy are continuously evolving as we learn more. This review is a great resource for clinicians providing important information about *H. pylori*. It focuses on characteristics, effects, prevalence of infection that are relevant to doctors. *H. pylori* has been found in the stomach of all people around the world. In developing countries, a high percentage ranging from 70-90% of the population carries the infection. In developing countries, the rate of *H. pylori* is lower as compared to developing countries. The human stomach is the main source for this bacterium, and it can be transmitted through saliva, medical procedures and contaminated food and water. Once in the stomach *H. pylori* can colonize and survive due to its urease activity. The activity is not only important for bacterial pathogenesis but also for it's survival. Now a days there are many different tests available to diagnose *H. pylori* infection. These tests are divided into two categories endoscopic test and non-endoscopic tests. Endoscopic test like culture, rapid urease testing, DNA probe involve examining gastric tissue during endoscopy. On the other hand, non-invasive tests like breath test, serology and gastric juice PCR don't require endoscopy are more convenient to patients (Khorshid et al., 2017).

EPIDEMIOLOGY

H. Pylori Infection happens globally, but the occurrence differs widely among countries and within different population groups within a country (Feldman, 2001). Most people, around 70-90 percent of the population, are carriers of *H. pylori* in developing nations. On the other hand, the prevalence of infection is minimum in developed nations. The overall *H. pylori* bacterial infection prevalence is strongly linked to socioeconomic factors and living conditions (Malaty and Graham, 1994). In many less economically developed countries, the prevalence among people with age approximately 45-65 years old is over 80 percent, as compared with developed countries. 20 to 50 percent of *H. pylori* infection prevalence in elevated income countries. Factors such as lower financial position, poorer hygienic conditions in the early years of life and also increases in older age which are noticeable on a global scale (Woodward et al., 2000). Elevated rates in the older population are due to reflect a cohort-specific impact related to lower socioeconomic status or very poor or bad living circumstances of children in past generations. The frequency of acquisition of *H. pylori* in industrialized countries has significantly dropped in the past few decades. Therefore, the occurrence of *H. pylori* with age is because of cohort impact, reflecting the transmission of *H. pylori* is more pronounced during that period when kids from earlier birth cohorts were ones who were more intensely affected by transmission (Banatvala et al., 1993). The high rate of H pylori infection rated have been recorded in Russia, Jordania, Iranistan, China, and Latin American countries as well as in Arctic populations in Canada. The Arctic original people were found to have significant infection rates (Mezmale et al., 2020). In China, a country with significant occurrence of *H. pylori* infection and gastric cancer around 55 percent of population carries *H. pylori* (Nagy et al., 2016). The total occurrence of *H. pylori in* Linqu County which is a Chinese county-level city was 57.6% (Pan et al., 2016). Japan has actively screened for *H. pylori* infection. In 2008, a study in Japan tested 21,144 healthy individuals for *H. pylori* out of those tested 5,815 (27.5%) were found *H. pylori*-positive, so the overall occurrence of *H. pylori* infection in Japan is 35.1% in the 2010s (Naito et al., 2008; Hirayama et al., 2014). In 2011, Korea had a significant occurrence of *H. pylori* infection is often associated with significant occurrence of stomach cancer. The study revealed that occurrence of it was approximately 54.4% indicating substantial prevalence (Lim et al., 2013). Among kids the total occurrence of *H. pylori* infection was 7.4 with minimal rates has been seen in younger age kids experiencing chronic stomachache. In Thailand, a nation with a comparatively small likelihood the prevalence of *H. pylori* infection was 45.9% (Uchida et al., 2015). The frequency of infection in the rest of the Asia-Pacific region can range from 15.5% to 94.3% because of variation in territories (Goh et al., 2012). In the USA, the overall average occurrence of *H. pylori* infection was 35%, which was lower than that in China. The occurrence of infection persisted relatively stable without any significant increase or decrease in the USA due to developed country (Nagy et al., 2016). Even though financial and hygienic conditions have been enhanced currently in American children. Out of 176 American kids were checked for infection using the 13C–urea breath test (UBT), 48 tested were positive with infection. The researcher conducted a study in 6 Latin American nations to determine prevalence of infection the results showed 79.4% prevalence (Elitsur et al., 2009; Porras et al., 2013). In their investigation of anti-*H. pylori* IgG antibody levels in 1,104 Brazilian children, it was found *H. pylori* positive cases were 28.7% (Dattoli et al., 2010). *H. pylori* occurrence concerning stomach cancer was conducted in 35 European countries and four European regions, which revealed that the *H. pylori* prevalence infection rate varied 17% in Aarhus Denmark to 88% in St. Petersburg, Russia (Robert et al). In northern or western Europe, the occurrence of h pylori is lower as compared to southern or eastern Europe (Roberts et al., 2016). In Poland, the prevalence of *H. pylori infection* is

16.05% in children (Biernat et al., 2016). The *H. pylori* occurrence was lower in the year 2010 (8.90%) as compared with the 2000 year (23.06%). In Africa, there is high prevalence of *H. pylori* in both adults and children despite the low incidence of gastric cancer. That could be possible explanation of high h pylori rates in Africa as poor hygienic conditions and socioeconomic circumstances contribute to its spread (Tadesse et al., 2014). However, there has been turn down in prevalence of infection in Ghana that gastrointestinal cases were 69.7% in 1999 decreased to 45.2% in 2012 (Darko et al., 2015). So, when we look at all finding rates of infection have been going down in different countries like Japan and Korea this could be due to better socioeconomic and hygiene circumstances (Figure 1).

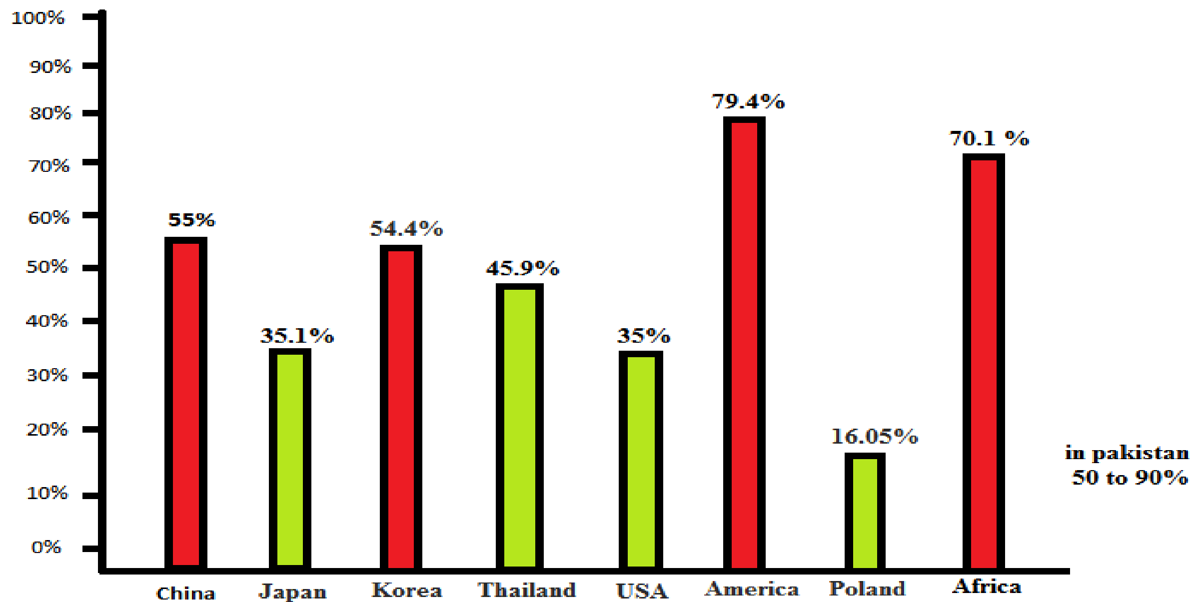

Figure 1. Prevalence of *H. pylori* infection.

H. PYLORI STATUS IN PAKISTAN

High range of *H. pylori* prevalence reported within Pakistan. The range of prevalence is 50–90%. The wide range in prevalence of *H. pylori* due to different way of diagnostic tests and inconsistent use of antibiotics (Mehmood et al., 2014). In Pakistan, the occurrence of peptic ulcer is unknown, but the age-adjusted rate of gastric ulcer patients is 0.7 in man and 0.3 in women of ten thousand population of Karachi may be going through gastric ulcers. Some conditions are contributed to or lead to *H. pylori* infection like Poor personal hygiene, sanitary conditions, and people with below-average income (Kotilea et al., 2019). Some risk factors also raised the rate of *H. pylori infection and* gastrointestinal diseases. Factors that contribute to the increase in prevalence of *H. pylori* include age, smoking, crowded living conditions, poor quality food such as junk food and unfiltered drinking water. According to age, *H. pylori* tends to have higher impact on children and people above 50 ages compared to younger children. Smoking is indeed a major risk factor for cancer. It can have different impacts on the body but in the case of *H. pylori* it contributes to the development of infection and increases the risk of cancer. Smoking making it harder to get rid of h pylori. Smoking affects metabolic activity in humans and causes stomach cancer. Monitoring risk factors for control of the disease (Nadeem et al., 2022).

TRANSMISSION OF INFECTION

The infection is acquired through saliva from one individual to another, iatrogenic, fecal contamination of water and food (fecal-oral route), and oral intake of that microbe and is specifically spread in families during young age (Rowland et al., 1999). In industrialized countries *H. pylori* can be spread directly from one-to-one individual by vomiting, saliva, or by fecal contamination of water and food; additional routes, such as water and food may be significant in developing nations (Goodman et al., 1996; Parsonnet et al., 1999). Now there is no proof of *H. pylori* being transmitted from animals to human, but it has been found in non-human primates (Handt et al., 1994; Dore et al., 2001). Mostly chronic *H. pylori* infection develops in elderly people, and it required specific and effective therapy for recovery; on the other hand, it is possible that bacteria is normally cleared in kids (Tindberg et al., 1999). In other studies, drinking water and food along with socioeconomic factors can play a big role in how the infection spreads (Mezmale et al., 2020).

PATHOGENESIS

The stomach mucosa has a defense mechanism for protection if a bacterial infects stomach. *H. pylori* has a unique characteristic that it has abilities that help it enter the mucus, move around and stick to stomach lining, adhesion to epithelial cells, evading the immunogenic response.

There are 1500 proteins coded in *H. pylori* genome (1.65 million bp) (Weeks et al., 2000; Achtman and Suerbaum, 2001). Two significant discoveries of *H. pylori* genome sequencing were extensive group of 32 related proteins found in outer membrane protein known as hop gene which aid in adhesion and identification of genes that can be controlled through DNA replication error induced mutagenesis. The phase variable genes encode protein that have various functions such as modifying surface molecule's antigenic structure, regulating invasion of foreign DNA and disrupt bacterial ability to move. During chronic colonization the *H. pylori* genome undergoes Continuous change as small fragments of foreign DNA from other *H. pylori* strains enter the host during persistent mixed infection (Gerhard et al., 2001; Josenhans and Suerbaum, 2001). Once consumed, the bacteria enter the mucous layer by evading the ability of gastric fluid to kill bacteria. In the first step of infection, Urease production and motility play crucial rule in facilitating infection and promoting spread of pylori. Urease produced by *H. pylori* helps it survive in the low pH environment of gastric line by converting $CO(NH_2)_2$ into carbon dioxide and NH_3. This allows bacteria to thrive and establish infection (Tomb et al., 1997). The catalytic capability depends on pH, which is defined by urel protein acts as specialized urea channel that respond to pH change, which is open or enzyme active at pH below 6 shutting down influx of urea in neutral pH conditions (Weeks et al., 2000). Mobility plays a critical role in colonization of *H. pylori* in gastric niche and flagella of *H. pylori* have specifically adapted to thrive in environment (Falush et al., 2001). *H. pylori* in the gastric niche forms tight bond through various bacterial-surface components (Gerhard et al., 2001). The outer membrane protein called blood group antigenic binding adhesin (BabA) is best characterized adhesin in *H. pylori*. It's a 78-kd protein specifically bind to fucosylated Lewis B blood group antigen (Ilver et al., 1998). There are other members of the hop protein family in *H. pylori* that also adhere to epithalamiums. Growing evidence from animal models indicates that the ability to bind by BaBA plays a significant role in *H. pylori* associated disease (Guruge et al., 1998). and may affect disease intensity. Many strains of *H. pylori* make a toxin called VacA which is about 95-KD in size. This toxin is produced by bacteria and causes vacuolation in cells. (Montecucco et al., 2001). The toxin creates a channel in epithelial cell surface forming a six-subunit anion channel activated by Voltage (Gerhard et al., 2001), which released HCO_3 and organic molecule with charge particles (Szabo, 1999) that possibly provide bacterial growth. VacA has the ability to specifically target mitochondrial membrane once it disrupts the normal functioning of mitochondria leading to release of cytochrome and ultimately triggering apoptosis of cell membrane (Galmiche, 2000). Scientists are still investigating and discussing exact role of toxin they have found some strains without an active VacA gene can still colonize animals and patients suggesting VacA might not be necessary for colonization. The disease-causing role of the toxin is still under investigation or debated. VacA-negative mutants can colonize in animal models, and strains have inactive VacA genes which are isolated from patients, indicating that VacA is not essential for colonization. The exact role of toxin is being studied and debated scientist have observed some strains of pylori can still colonize animal models without this toxin. They have also found some patients with inactive VacA genes in patients suggesting it may not require for colonization (Salama et al., 2001). The role of VacA in disease is complex due to the wide range of VacA genes. In Western nations, specific variants of VacA gene have been linked to more severe disease (Atherton et al., 1997). It interesting to note that in Asia they haven't found the Same association between specific VacA gene variants and disease severity however most of *H. pylori* do have the cag pathogenicity island which contains gene like cag that are linked to vac a gene expression (Galmiche, 2000). Those genes in cag pathogenicity island actually encodes component of type 4 secretion apparatus, this apparatus helps to transport the cag protein into host cell (Segal et al., 1999; Odenbreit et al., 2000). Once inside CagA gets phosphorylated it attaches to SHP-2 tyrosine phosphatase enzyme, triggering cellular response similar to growth factors and causing host cell to produce cytokine (Higashi et al., 2002) (Figure 2).

Clinical outcomes of Pylori infection

Infected individuals who have duodenal and gastric ulcers have inflammation of the gastral mucous membrane, which is triggered by an infection that is most pronounced in the antral region of stomach, which does not secrete acid, and an increase in gastrin release (El-Omar et al., 1995). The increase in gastrin levels stimulates the more proximal fundic mucosa, which secretes acid and is often devoid of inflammation, to secrete more acid than usual (El-Omar et al., 1995; Gillen et al., 1998). The duodenal mucosa damage caused by an increase in the duodenal acid load results in ulcer and gastral metaplasia. The presence of *H. pylori* in the metaplastic mucosa promotes the growth of ulcers.

https://doi.org/10.55627/agribiol.001.02.0649

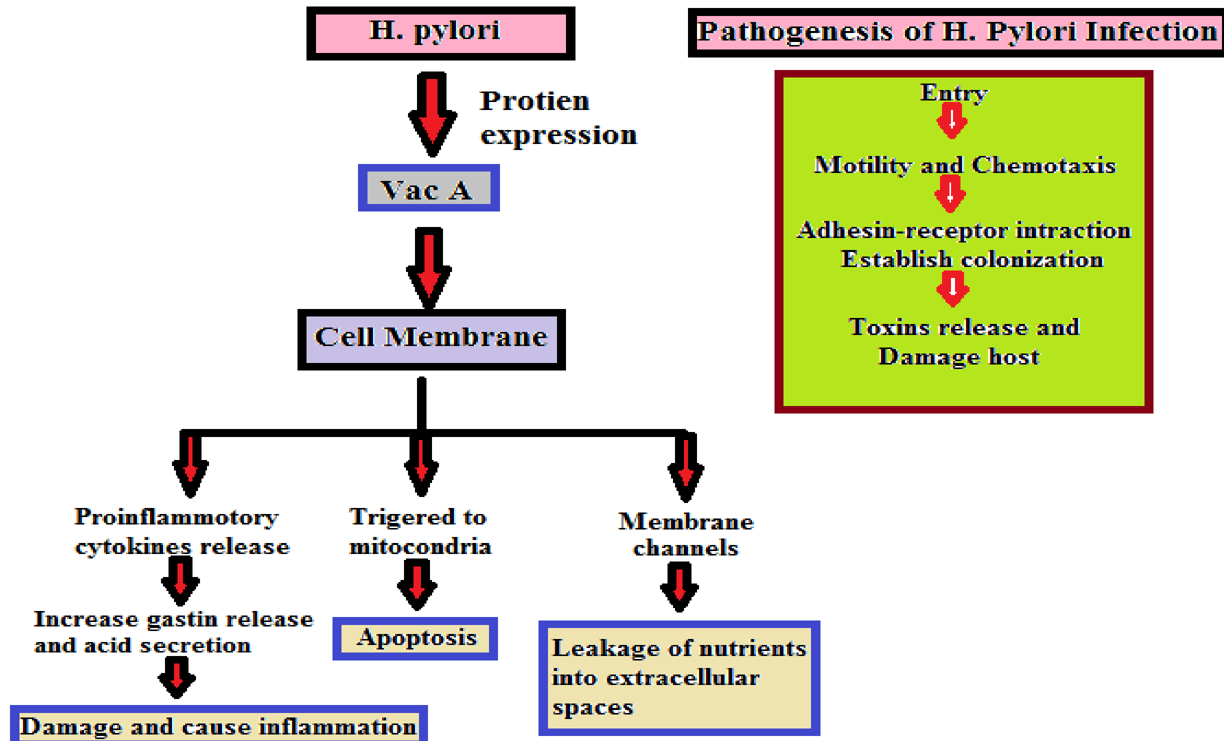

Figure 2. Pathogenesis of *H. pylori* infection.

By treating the infection, non-steroidal anti-inflammatory drug (NSAID)-unrelated duodenal ulcers can be permanently treated (Hentschel et al., 1993). NSAID ulcers are the main cause of negative gastritis of *H. pylori*. Due to *H. pylori*'s injury to the mucosa, ulceration of the gastric mucosa develops (Axon et al., 1997). Strong relationships between *H. pylori* infection and noncardiac gastric malignancies of gastric and ossiphageous junction have been suggested by considerable epidemiologic data (S. Hansen, K. K. Melby, S. Aase, E., 1999). The infection is categorized as a human oncogenic by the WHO (Humans, 1994). Patients who experience antral and fundic mucosal inflammation, which results in atrophy of mucosal and intestinal metaplasia, have the highest chance of developing cancer (Uemura et al., 2001). *H. pylori* infection eradication slows the development of atrophic gastritis (Leung et al., 2004) but it is unclear whether extermination also lowers the risk of gastric malignancy (Malfertheiner et al., 2005). Gastric MALT lymphoma, a low-grade mucosa-associated lymphoid tissue (MALT) lymphoma, is linked to Helicobacter pylori infection. *H. pylori* infection is strongly associated with the prevalence of stomach MALT lymphomas, according to epidemiologic research (Parsonnet et al., 1994). Most localized gastric MALT lymphomas recur after the virus is eradicated (Fischbach et al., 2004).

Other Gastral conditions

In 50% of patients who have an endoscopy for higher gastral symptoms and are diagnosed with non-ulcer or functional dyspepsia, there is no sign of esophagitis, gastric ulceration, or duodenal ulceration. Patients with non-ulcer dyspepsia have showed no significant symptoms in several random trials of treatment for *H. pylori* obliteration; nevertheless, a few have exhibited a marginal benefit, which is explained by the existence of undetected ulceration (McColl, 2000). Thus, in the absence of gastric or duodenal ulcers, there is no evidence that upper gastrointestinal symptoms can develop as a result of persistent *H. pylori* infection. Patients with gastro-esophageal reflux disease (GERD) (Raghunath et al., 2003) and those with esophageal adenocarcinoma (which may develop as a consequence of GERD) have lower rates of *H. pylori* infection than healthy control subjects (de Martel et al., 2005). These illnesses, such as GERD, may be prevented by *H. pylori* linked atrophic gastritis, which also lowers acid secretion (Yaghoobi et al., 2010).

Diagnostic test for *H. pylori* infection

Non-Endoscopic Tests:

Serum Testing: Antibody IgG, which are frequently used to diagnose infection, are found during serologic testing. Only 85% and 79%, respectively, of its overall sensitivity and specificity were reported (Loy et al., 1996). Population-

specific acceptable cutoff values vary, and test findings are frequently classified as positive or negative.

Urea Breath Test: The 95% sensitivity and specificity of the urea breathe test. During the urea breath test, the urease in *H. pylori* transforms C-labeled urea into labeled carbon dioxide. A breath sample is used to measure the labeled gas (Vaira and Vakil, 2001).

Feces Antigen Test: The fecal antigen test or stool antigen test, uses poly or monoclonal antibodies to identify *H. pylori*-specific antigens in a stool sample (Gisbert and Pajares, 2004). Additionally, the monoclonal antibody test has a sensitivity and specificity of 95%.

Endoscopic Tests

Endoscopic biopsies of the stomach lamina can reveal the presence of the H pylori infection.

Urease-based Method: In this technique, we immerse an endoscopic biopsy sample in a urea and pH-sensitive dye solution. If urease enzyme converts urea into ammonia, the pH will rise, and the dye's hue will change. These alterations point to an *H. pylori* infection. Inhibitors of proton-pump, H2 receptor antagonists, and antibiotic medication should be avoided prior to testing due to the possibility of false negative results (Midolo and Marshall, 2000). The urease-based test offers greater than 90% sensitivity and greater than 95% specificity (Vaira and Vakil, 2001). Routine histologic examination of a biopsy specimen and organism culture are two other methods of diagnosis.

Table 1. Diagnostic tests for H. Pylori infection.

Test Name	Sensitivity	Specificity
Non Endoscopic Tests		
Serologic testing	80%	79%
Urea breath test	90%	95%
Fecal antigen test	95%	95%
Endoscopic Tests		
Urease-based method	More than 90%	More than 95%
Histologic testing	95%	98%
Culturing	96% or low	100%

CONCLUSION

According to the review, *H. pylori* infection is very common in Pakistan and other nations all over the world. Increased incidence may be caused by worse hygienic conditions and lower socioeconomic levels. Age, smoking, crowded housing, poor-quality food (such as fast food or restaurant cuisine), and unclean water may also exacerbate the problem. By routinely monitoring the risk factor system, as well as by raising the socioeconomic position and hygienic circumstances of the populace, it is possible to reduce the spread of *H. pylori* infection in Pakistan.

COMPETING OF INTEREST

The authors declare no competing interests.

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