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One health approach on zoonotic helicobacter pylori in animals and man

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ABSTRACT

Zoonotic disease-causing microbes are those naturally spread from animals to people, either directly or indirectly, with a serious hazard on the public health. Emerging zoonoses are mostly caused by travel, animal transhumance, population increase, and migration from rural to urban regions. Regarding the principal transmission route of *Helicobacter pylori (H. pylori)*, one of the most global prevalent anthroponotic illnesses, not a lot of information is currently known. In the 20th century, *H. pylori* contribute to individuals stomach problems and cancer. Subsequently, an extensive amount of study has been conducted on the epidemiology of this intestinal infection, revealing that the likelihood of illness varies throughout individuals. This is a concise overview of the several epidemiological factors connected to zoonotic *H. pylori* infection. There are notable differences in the epidemiology of *H. pylori* in human and animal populations between developing and developed nations. Moreover, a multiplicity of consistent lines of evidence suggests that demographic data, different individual habits, socioeconomic position and living conditions are the main risk factors influencing the acquisition rate of *H. pylori* pathogen. These results are troubling since they are expected to change global demography and increase the number of people susceptible to *H. pylori* and its emergence. To reduce the danger to public health and the associated economic effects, stakeholders in the *H. pylori* management plan need to start merging technological, social, political, policy, and regulatory problems and working together. An active mitigation program offers the chance to address global health concerns and halt the development of zoonoses.

Contribution/Originality: The current study provides an overall view on the zoonotic impact of H. pylori in different animals and humans as an aid in health education of the public about the danger of the disease, sources, reservoirs transmission modes, epidemiology, different diagnostic tools, methods of prevention and control.

1. INTRODUCTION

Naturally, microorganisms that cause zoonotic illnesses can spread from animals to people. Human health is seriously threatened by the present zoonotic disease epidemic, especially for those with close contact with domestic or wild animals and reside in underdeveloped areas [1-13]. The main way for different illnesses transmission is spread, either directly or indirectly, from animals to humans. The main causes of the emergence of new zoonotic illnesses are changing patterns between rural and urban areas, animal transhumance, international travel, and climate change [1-13]. Two species of *Campylobacter* belong in the genus *Helicobacter*, according to Parija [14]. These are Campylobacter mustelae, also known as *Helicobacter mustelae*, and *Campylobacter pylori*, now known as *Helicobacter pylori*. There are currently 47 species recognized in the genus *Helicobacter*, a considerable increase from earlier estimates [15]. Based on ecological settings and phylogenetic analyses, this genus of bacteria are roughly classified into: stomach (GH) and enterohepatic (EHH) *Helicobacter* species [16].

H. pylori, often known as *Helicobacter pylori*, is the species that has attracted the most attention from researchers. Up to 50% of people worldwide suffer from some of the most severe human illnesses, which are caused by *H. pylori*. But in recent years, new illnesses and perhaps zoonotic infections have increased the significance of the remaining GH. Reviews [17-19] have already addressed the evolution of these gastrointestinal species' taxonomy, epidemiology, and clinical significance.

That being said, not much research has been done on EHH. But, there has been evidence linking EHH members to a range of human ailments, including acute gastroenteritis, inflammatory bowel disease, and problems related to the liver, gallbladder, and bile duct [19]. Since the most recent research on EHH has piqued interest, more investigation is required to ascertain the possible significance of these recently discovered ailments. Given this, the present review offers a brief of the current understanding of taxonomy, clinical relevance, and epidemiology of EHH with respect to animal hosts.

2. ETIOLOGY

Employing *Helicobacter pylori* as a model organism. Every single individual from the *Helicobacter* genus possesses the following physical traits: Fusiform bacteria do not create spores and have a size range of 0.2 to 1.2 to 1.5 to 10 µm. They also generate cytochrome oxidase. In addition to having a helical, curved, microaerophilic, spiral, or rod-shaped structure where cells can become coccoid when exposed to air or become old cultures, they can also be gram-negative and feature periplasmic fibers. One or more sheathed or unsheathed flagella are what allow them to move. The majority of them grow well at 37 °C and are carbohydrate-free [20, 21].

2.1. TAXONOMY

Table 1. Taxonomy of *Helicobacter pylori* according to Polaka, et al. [21].

Phylum:	**Campylobacterota**
Class:	Campylobacteria
Order:	Campylobacterales
Group:	Proteobacteria
Subgroup:	Epsilon subgroup of Proteobacteria
Family:	*Helicobacteraceae*
Genus:	*Helicobacter*
Most known Pathogenic species:	*Helicobacter winghamensis*, *Helicobacter pullorum*, *Helicobacter canadensis*, *Helicobacter apodemus*, *Helicobacter hepaticus*, *Helicobacter cinaedi*, *Helicobacter equorum*, *Helicobacter trogontum*, and *Helicobacter mustelae* are among the species of Helicobacter that are commonly found in the stomach.

Table 1 presents that the taxonomic categorization of *Helicobacter* has been hampered by the limited function of the 16S rRNA gene, which is recognized as the "gold standard" gene for bacterial phylogeny. It is true to say that

16S rDNA is insufficient for identification of variant *Helicobacteraceae* species because of the potential for misidentification [22]. This is in line with the creation of mosaic molecules lacking phylogenetic information and the horizontal transport of 16S rRNA gene segments [23].

A greater number of identified pertinent phylogenetic markers have been examined to provide a more precise taxonomic evaluation of *Helicobacter* species. A few of these markers are *gyr*A, *gyr*B, *cpn*60, and *atp*A [23-26].

2.2. Virulence Factors

Thanks to the identification and examination of more relevant phylogenetic markers, the taxonomic identity of *Helicobacter* species may now be ascertained with greater certainty. Several of these markers include *gyr*A and *gyr*B [23] *cpn*60 [24] and *atp*A [25].

This gave information on the progression of the disease and assisted in identifying several virulence factors. Since then, efforts have been made to determine the genes responsible for the virulence mechanisms of enterohepatic species. The orthologues of *Peb*1 *Campylobacter coli* and *Campylobacter jejuni*, which are present in *Helicobacter apodemus* and *Helicobacter hepaticus*, have been shown to have an effect on adhesion [27].

Additionally, it was shown that five EHH species—*Helicobacter hepaticus*, *Helicobacter cinaedi*, *Helicobacter equorum*, *Helicobacter trogontum*, and *Helicobacter mustelae*—carry *H. pylori* homologs, such as *hor*, *hom*, *hop*, and maybe *hor*D and *hor*G. They are referred to as "Hof-like outer membrane proteins" (OMPs). The bulk of OMPs, which are Hop proteins, have a porin or sticky quality that aids in the pathogens' adhesion to the mucosal surface [28].

The existence of homologous genes is also established. These include virulent adhesin/OMPs *flp*A (fibronectin-like protein A), enables adherence of EHH species to the extracellular intestinal fibronectin, and *irg*A (a virulence protein, is iron-regulated outer membrane protein), which appears in the enteric bacteria as *Campylobacter* spp., *Escherichia coli*, and *Salmonella enterica* [29].

The urease gene cluster in *Helicobacter mustelae* (*ure*ABIEFGH; *ure*A2B2), cell-binding factor 2, gamma-glutamyl transpeptidase, orthologs of systemic factor protein A (*Sfp*A) and lipid A deacylase (*Lpx*R), "immune evasion" genes (*fut*A, *fut*C, *rfa*J), and the outer membrane protein phospholipase A (OMPLA) are additional factors linked to EHH. Additionally noted are genes associated with "secretion systems" (*vir*B2, *vir*B3, *vir*B4, *vir*B5, *vir*B6, *vir*B8, *vir*B9, *vir*B11, *vir*D4, *cag*) and the HHGI1 type VI secretion system (*icm*F, *hpc*, *vrg*G). Additionally, it was found that the cag-PAI type IV secretion system (T4SS) is linked to the genes "*Helicobacter apodemus*" and "*Helicobacter typhlonius*". This route promotes cell division and proliferation, which in turn helps the bacterial gene *cag*A enter stomach and aid in *H. pylori* pathogenesis. The latter species' DNA was found to lack *cag*A, and its relationship to T4SS is still unclear [30]. The only known cytotoxin of this bacterial family, cytolethal distending toxin (CDT), is translated by a collection of genes named *cdt*A, *cdt*B, and *cdt*C, which occur in some species of EHH and other Gram-negative bacteria [31]. This toxin, which is made up of the three subunits *Cdt*A, *Cdt*B, and *Cdt*C, is a heterotrimeric AB2 toxin [32].

The active "A" component of the AB2 toxin, *Cdt*B, is transported into cells by the combination of the two binding "B" subunits, *Cdt*A and *CdtC*. *Cdt*B is taken up from the host cell surface by the endoplasmic reticulum, the Golgi apparatus, and the nucleus in a clathrin-dependent manner after adhering to the cell surface [16]. *Cdt*B is structurally and functionally similar to mammalian DNase I. In a cell, it could result in chromosomal DNA double strand breaks (DSBs). Moreover, *Cdt*B has been shown to have phosphatase activity, which speeds up T-cell death [33].

Apoptosis and distention are the outcomes of the host cell cycle arrest that these two *Cdt*B activities induce at the G2/M phase [33]. The existence of the toxin, its effects in vivo and in vitro, and the genes that encode it have all been reported by many EHH. Furthermore, a putative cytotoxin homologs that were resembled the *vac*A gene were found to be present in "*Helicobacter winghamensis*", "*Helicobacter pullorum*", "*Helicobacter canadensis*", and "

Helicobacter apodemus" [34]. Further investigation is required to ascertain the role this putative cytotoxin plays in virulence.

Additional factors that have been linked to the pathogenicity of bacteria include the N-linked protein glycosyltransferase, similar to the general protein glycosylation (pgl) genes in *Campylobacter jejuni*. These genes facilitate attachment and entry into the epithelial cells of the host, even in vitro or in vivo. Additionally, the Campylobacter major protein (cmp), *Helicobacter pullorum* ortholog, is responsible for both activity and adhesion to the cultured cells, according to EHH. Pro-inflammatory cytokine release, the ability to resist complement protein degradation in vitro, and the durability of colonization in vivo are all linked to this [34].

2.3. ANTIBIOTIC RESISTANCE

The global enormous issue of increasing antibiotic resistance among bacterial pathogens [8, 9] researchers began to study the mechanism of antibiotic resistance of different bacteria in a trial to evolve novel medications against them [8, 9]. However, the techniques of determining one's susceptibility to an EHH infection and managing the infection are not standardized. It is true that the Clinical and Laboratory Standards Institute (CLSI) does not currently have any guidelines available for evaluating the antibiotic susceptibility of *Helicobacteria* that are not *Helicobacter pylori* (NHPH).

This is because *Helicobacter* is a species that has particular growth requirements, which makes it challenging to develop precise techniques for determining the Minimal Inhibitory Concentration (MIC) [22]. EHH species have also been compared to conventional antibiotics (b-lactams, tetracyclines, aminoglycosides, fluoroquinolones, phenicols, diaminopyrimidines, carbapenems, glycopeptides, and sulphonamides) used to treat *Campylobacter* sp. Infections [35, 36].

Amoxicillin is commonly used in mixed therapy to treat EHH infections because it works by getting rid of *H. pylori* [37]. Despite the fact that other *Helicobacter* species benefit from this treatment, the scant information now available raises concerns over the antibiotic sensitivity of these species [38].

3. RESERVOIRS OF THE INFECTION

3.1. Pet Animals

In terms of carrying EHH, dogs are the companion animal that are exposed to the various examinations. However, it is hitherto how EHH reservoirs could affect the future zoonotic transmission. A limited culture-based studies presented *Helicobacter cinaedi*, *Helicobacter bilis*, and *Helicobacter canis* in feces of both healthy and diarrheal dogs offer most of the available EHH data in dogs [39]. The high incidence of these organisms in dogs implies that EHH might be a part of the canine microbiota, despite the lack of evidence demonstrating any beneficial or health-promoting effects on their hosts [40].

Abundant research of bacteraemia due to *Helicobacter canis* in the immunosupressed individuals have been linked to close contact with infected dogs [41]. In addition, contact with infected cats also might be linked with *Helicobacter canis* [38].

3.2. Livestock (Farm Animals)

Research on the connection between EHH and farm animals has been less extensive than that on *Campylobacteria*. Sheep are reservoirs for most zoonotic diseases, as evidenced by the recent isolation of *Helicobacter canis* from their manure [42]. Moreover, Egypt has provided phylogenetic evidence in favor of the theory that humans acquired *Helicobacter canis* from sheep [43]. In fact, a transmission dynamic might be linked to *H. pylori*, that fact is also showed in individuals with direct or indirect contact with sheep [44].

3.3. Wildlife

Initially, a significant quantity of EHH was found in the waste products of wild animals including rats and birds. Since EHH often affects numerous organs, it is unclear if these wild animals are true reservoirs for the sickness [45].

Both wild rats and laboratory animals harbor these infections [46]. Furthermore, several species of Helicobacter have been found in wild birds [47]. Research on the toxicity, clinical relevance, and zoonotic potential of most of these freshly found species remains necessary.

4. TRANSMISSION OF H. PYLORI INFECTION

Table 2 explains both the direct and indirect routes of *H. pylori* transmission in animals and man, where the direct (main) route is oral route while the indirect (secondary) route is via contact.

Table 2. explains the transmission routes of *H. pylori*.

Direct transmission route	Indirect transmission route
Mainly through ingestion of the pathogen (Oral transmission) via vomitus, feces, chopsticks, oral microbiota [48, 49]	It is not a primary route. Occurs through contact with food, water, and animals have all been reported to contain *H. pylori* or its DNA [48].

5. DETERMINANTS OF H. PYLORI EPIDEMIOLOGY (RISK FACTORS)

All the associated risk factors of acquisition of H. pylori concerning host factors, environmental factors and even pathogenic factors, are already shown in Figure 1.

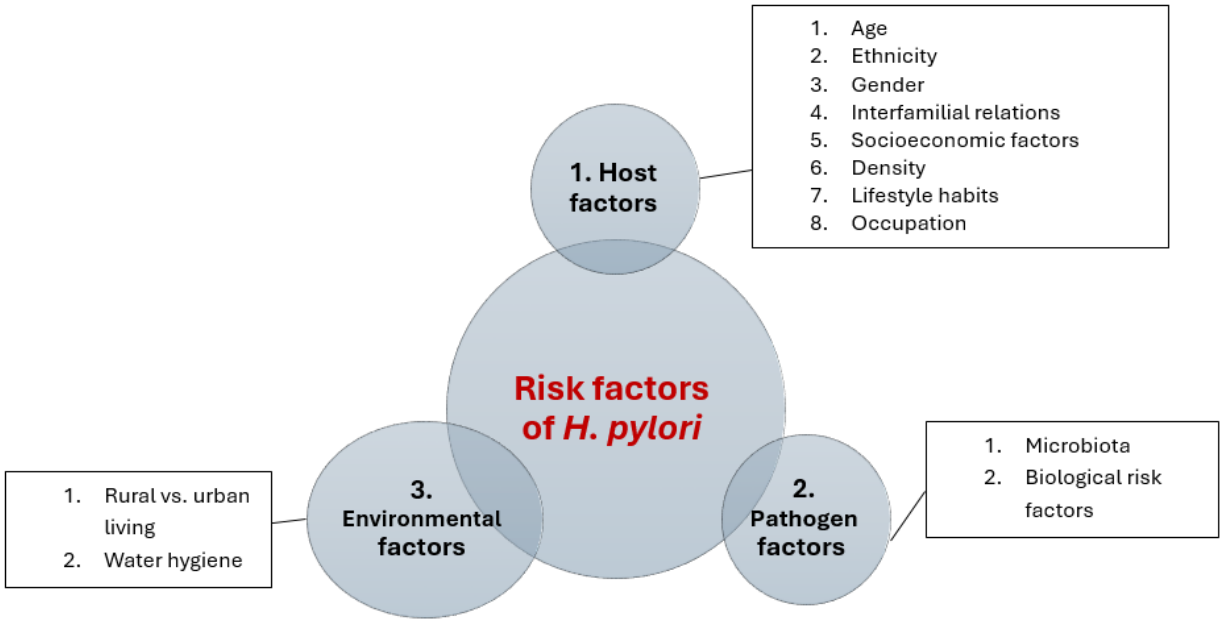

Figure 1. shows the schematic draw on risk factors of *H. pylori*.

6.1. Host Factors

6.1.1. Age

One of the most well-established and rarely contested features of the infection's epidemiology is the impact of age on the frequency of *H. pylori* infection. Age and prevalence have been found to be strongly correlated in both developed and developing nations [50].

The trend of adults having a higher frequency of infection than children has been partially explained by the birth cohort phenomenon, which was brought on by a greater prevalence in the past as a result of unsanitary living circumstances and inadequate sanitation [51].

6.1.2. Ethnic and Genetic Predisposition

Helicobacter pylori seroprevalence has been observed to differ significantly among people of different racial and cultural backgrounds [52]. According to certain theories, Malaysian Chinese and Indian communities are more likely to contract *H. pylori* infection due to genetic predispositions [53]. Ethnicity has been identified by a number of New Zealand demographic groupings as a risk factor. Maori had an intermediate prevalence of *H. pylori* infection, while Europeans had the lowest prevalence. Ethnicity was a significant covariate even after consideration of other variables like age and even socioeconomic levels [54].

However, an American study discovered that while the prevalence of *H. pylori* infection was somewhat greater in Caucasians, it was almost the same in African Americans and Hispanic Americans. However, socioeconomic circumstances were blamed for the observed variance and ethnicity was rejected as a relevant component [55]. In conclusion, studies on monozygotic and dizygotic twins revealed a possible genetic component to the frequency of *H. pylori* infection [56].

6.1.3. Gender

Studies evidenced that one sex/gender is more susceptible to infection than the other [2, 3, 9]. For example, it was shown that *H. pylori* infection was more among men than among women [57]. Additional investigation shows that the incidence of *H. pylori* illness is not gender-specific [58].

6.1.4. Interfamilial Relations

The effect of interfamilial interactions on the *H. pylori* pathogen's transmission from adult to kid, particularly mother-to-child transmission, was the subject of earlier research [59]. Moreover, it was suggested that parents or siblings could contract the virus from sick children [60]. *H. pylori* disease has also been represented to be favorably influenced by family size; the likelihood of infection in a home rises with the number of children residing there [61]. Records of transfers between spouses were also kept [62].

6.1.5. Socioeconomic Factors

The likelihood that an *H. pylori* infection will spread is apparently significantly influenced by socioeconomic position [63]. On the other hand, higher socioeconomic status of inhabitants may be linked with *H. pylori* lower prevalences in developed countries [53]. The linkage between increasing age and increased frequency of *H. pylori* in underdeveloped countries would be directly related to low socioeconomic position. It should go without saying that socioeconomic standing includes elements like living standards, sanitization, urbanization, and educational attainment in addition to social class and money [64]. When taken as a whole, these variables may raise the chance of contracting infectious diseases generally.

6.1.6. Crowding Index (Density of Living)

Living in close quarters, sharing a bed, and having more household contact have all been related to an increased risk of *H. pylori* infection [65]. One's current *H. pylori* status is influenced by their upbringing in close quarters, and having more children in the house increases an adult's risk of infection [66].

6.1.7. Lifestyle Habits

6.1.7.1. Breast-Feeding

According to Dore, et al. [36] no statistical difference was shown in *H. pylori* seropositivity among children residing either urban or rural districts according to the infants' breastfeeding status. Nevertheless, a prospective population-based investigation on asymptomatic neonates in the Czech Republic found that children who had never been nursed had a higher incidence of *H. pylori* [61]. However, children from low socioeconomic families in Lagos, Nigeria did not show any correlation or duration of *H. pylori* infection with exclusive nursing [62].

It has been suggested that breastfeeding serves as a natural antibiotic, shielding infants from illness. So, if mothers' breath milk included more anti-*H. pylori* IgA than if it contained less, children were less likely to contract the virus [63].

6.1.7.2. Food

Studies have shown that dairy products, particularly raw milk, contain *H. pylori* DNA, which is thought to be the primary food transmission mechanism [53]. Traditional cheese and ovine milk were shown to be the most often contaminated items by Dore, et al. [36] suggesting that milk consumed by humans may be affected. Similar outcomes were also represented for raw cow milk specimens from farms in America [53] Greece [64] and Japan [60].

Significantly, it was discovered by Talaat Al Sherief and Thabet [65] that milk and dairy products were often the source of *H. pylori* strains that were resistant to antibiotics. Another notion about the potential reservoir of *H. pylori* is meat. It has been suggested that shepherds and their families may contract *H. pylori* from sheep [66]. Direct interaction with sheep and sheepdogs may be connected to it.

Eating raw veggies can put a person at risk for *H. pylori* [53]. Because of tainted washing water, raw veggies may have included *H. pylori*. Thus, insufficient or nonexistent wastewater disinfection may enhance *H. pylori* persistence and is most likely a significant contributing factor to the chain of events that leads from people to bacteria. However, given the link between the condition and a lower socioeconomic standing, individuals with poor nutritional status may be more vulnerable to *H. pylori* infection [67].

6.1.7.3. Habits of Tobacco Smoking and Even Alcohol Drinking

Research on the relationship between alcohol and tobacco use and *H. pylori* infection has produced a variety of results. Despite the fact that Gunathilake, et al. [68] showed no connection between alcohol or tobacco use and the development of *H. pylori* infection, smoking tobacco was found to be substantially linked to *H. pylori* seropositivity in adult Japanese persons [69]. Research conducted in Northern Ireland has revealed a favorable link between smoking and *H. pylori* infection. However, no significant correlation has been observed between alcohol use and smoking [70]. The higher stomach acidity caused by smoking may account for the unfavorable correlation between tobacco usage and illness. Moreover, it has been proposed recently that nonsmokers and heavy alcohol users may be less susceptible to *H. pylori* infection than the general population [71].

6.1.7.4. Close Contact with Animals

Numerous research investigations looked at the processes by which various zoonotic bacteria could infect people as well as the toxicity of the bacteria in animals [1-13, 72]. EHH, however, has been given a considerable degree of zoonotic significance because it has been demonstrated that frequent and intimate human-animal contact is harmful [34].

6.1.8. Occupation

The risk of *H. pylori* in healthcare workers who work with patients has been the subject of numerous research. Hospital work with a direct patient contact has been found to be a substantial risk for infection in comparison with other jobs without such contact [73]. As a result, research revealed that nursing staff was more likely than technical and administrative professionals to have an *H. pylori* infection [74].

6.2. Pathogen Factors

6.2.1. Microbiota

The makeup of the gut microbiota may be influenced by a wide range of factors, such as lifestyle choices, infections, diseases, and environmental pollutants [75]. In stomach cancer dysbiosis, helicobacter abundance and microbial diversity are both reduced [76]. Disease states have been associated with reduced microbial diversity; reports of this have been presented for inflammatory and malignant disorders [77]. According to Zhang [75] *H. pylori* affects the intestinal microbiota indirectly in addition to influencing the makeup of the stomach microbiota in the animal model. Moreover, the age-dependent immune responses of *H. pylori*-infected mice may influence the host's vulnerability to illness and infection [78]. An infant's microbiome may be significantly influenced by the shared microbiota of parents and children.

6.2.2. Biological Risk Factors

There are set of biological risk factors linked to increase the incidence of cancer among individuals. For example, viruses in humans account for 10% to 20% of cancer incidence globally. Numerous experimental and epidemiological investigations have verified the link between anal cancer and the papillomavirus of humans. Likewise, cancer of the upper and lower gastrointestinal tracts is probably caused by the Epstein-Barr virus (EBV) and the John Cunningham virus (JCV) [79]. In a similar vein, human carcinogenicity has been linked to parasite illnesses such as schistosomiasis, opisthorchiasis, and clonorchiasis [80].

Numerous bacteria have been connected to different neoplasms, such as *Chlamydia pneumoniae*, *Salmonella typhi*, and *Streptococcus bovis*; however, it is unclear how these bacteria may aid in the development of cancer [81]. Although *H. pylori*, *Prevotella copri*, and *Propionibacterium acnes* are critical factors for stomach cancer, a previously published case-control research [82] found that Lactococcus lactis acts as a protective factor against stomach cancer. The main biological agent for stomach cancer is *H. pylori* pathogen. Numerous studies that have looked at the various facets of this correlation have found a link between stomach cancer and *H. pylori* infection [83].

6.3. Environmental Context

6.3.1. Rural vs. Urban Living Conditions

One of the variables increasing the acquisition of *H. pylori* in people in the world is the variation in living conditions between urban and rural areas. There were more children living in rural regions than in urban areas [68]. Socializing with dogs appears to have benefits, particularly in rural settings. In urban areas, the infection rate of *H. pylori* was substantially correlated with the parents' socioeconomic status, whereas in rural areas, there was no association between the head of the household's employment status and the incidence of infection [77].

6.3.2. Water Hygiene

Water may be a significant source of *H. pylori* contamination, according to a number of epidemiologic studies [78]. Due to the unsanitary distribution of water among the populace, waterborne infections—especially in poor nations—are the primary cause of *H. pylori* infections. In Japan, well water containing *H. pylori* DNA was tested positive for the infection by customers [79]. Accordingly, two studies—one from Portugal and the other from

Germany—found a favorable correlation between *H. pylori* infection and well water intake [43, 84]. Furthermore, it has been proposed that *H. pylori* contamination may exist in Japanese river water [82].

Public health is concerned about the possibility of live *H. pylori* infecting cells in water samples [83]. These results provide credence to the theory that water tainted with excrement could serve as a reservoir for the propagation of *H. pylori*. According to some theories, *H. pylori*'s capacity to produce biofilm allows it to proliferate in natural water sources and water distribution networks [54]. When the temperature is over 20 °C, the optimal temperature range for *H. pylori* cultivability in water is fewer than ten hours [85]. The morphological transformation of bacteria into a rod shape, which is connected to the turnover of peptidoglycan (PG), is linked to the development of a culturable phenotype in water [54].

Consequently, *H. pylori* undergoes a morphological transformation from a spiral form to a coccoid form and becomes a viable but not culturable (VBNC) pathogen few days after being injected into water [85].

7. EPIDEMIOLOGY OF H. PYLORI (GLOBAL DISTRIBUTION)

In the past year, a lot of study has been done on the frequency of mutations associated with *H. pylori* and antibiotic resistance in patients with oncological illnesses (pancreatic cancer, colorectal cancer, gastric carcinoma, etc.). Alaridah, et al. [86] study Ma, et al. [87] examined 933 Jordanians' general population's awareness and information regarding *H. pylori*. Stomach cancer is highly prevalent among neoplasms in terms of occurrence in the country.

68.7% of participants are ignorant as possible considerations for stomach cancer, despite this and the fact that 63% of participants had a higher education degree [88]. In a different study, researchers looked at patients from over 360 US hospitals (18–65 years old, or 47,714,750 overall) to find out how much of a risk *H. pylori* infection had for colorectal cancer. Based on a large population-based analysis, the correlation between occurrence of colorectal cancer and *H. pylori* illness (OR 1.89, 95%CI: 1.69-2.10) has not been demonstrated before [88]. A different case-control study carried out in the USA looked at five prospective cohorts to see if there was a connection between pancreatic cancer and *H. pylori* illness.

Investigators declared that no significant relation was found between pancreatic cancer risk and *H. pylori* infection (OR 0.83, 95% CI: 0.65-1.06) [89]. The frequency of evolutions related to clarithromycin resistance and the connection between virulence factors and *H. pylori* infection were the subjects of a study carried out in Mexico. To get rid of H. pylori, a treatment strategy based on clarithromycin is required. The researchers discovered a greater than 15% frequency of mutations connected to clarithromycin resistance in addition to a linkage between 23S rRNA gene alterations and *cag*A and *vac*A genotypes. A2143G (56%) and A2142C (25%) were the most prevalent alterations, according to Husnik, et al. [90].

There are several challenges associated with *H. pylori* infection. For more than 40 years, a large number of studies on risk factors, vaccination prophylaxis, effective eradication therapy, and interruption of transmission pathways have been carried out. The World Gastroenterology Organization (WGO) updated its *H. pylori* guidelines by using the "cascade" technique, which distills the management basics on regional resources and expertise [91]. With a total population of 2,163, Alaridah, et al. [86] looked at 22 studies from 9 African countries to calculate the rate of *H. pylori* eradication in that continent, showing a pooled elemination rate of 79% (95% CI: 75%-82%), associated with a heterogeneity rate of 93.02%.

An increased percentage of eradication (85%) was found in observational research as compared to randomized control trials (77%). Ivory Coast had the lowest eradication rate (22.3%) while Ethiopia had the highest (90%). The occurrence of *H. pylori* infection in Africa will be impacted by long-term eradication initiatives. Of the 1,160 cases included in a Pakistanian study conducted by Boustany, et al. [92] 48% were *H. pylori* positive. That research was carried out to reveal the frequency and various features of *H. pylori*. Higher incidence rates were seen among men between the ages of 20 and 40, the illiterate, diners at restaurants, users of municipal water systems, owners of pets,

and people who had interacted with animals. Additionally, a linkage was discovered between *H. pylori* prevalence and sociodemographic characteristics [94].

8. CLINICAL IMPORTANCE

Different clinical signs can be recorded in cases infected with *H. pylori* either in animals or even humans as explained in Table 3.

Table 3. Clinical manifestations of Helicobacteriosis in animals and man according to Lee, et al. [93] and Alarcón-Millán, et al. [94].

In humans	In animals
Can induce:	**May be asymptomatic or may include:**
- Diarrhoea	- Inflammatory bowel disease (IBD)
- Bacteraemia	- Biliary and liver diseases
- Systemic disease	- Gastric, breast, colon, and liver cancers
- Development of neoplasia	- Rectal prolapse
- Gastroenteritis	- Ovine abortion
- Proctocolitis	- Vibrionic hepatitis in laying hens
- Cellulitis	- Episodic diarrhoea in cats
- Arthritis	
- Septicaemia	
- Inflammatory bowel disease (IBD)	
- Crohn's disease (CD)	
- Ulcerative colitis (UC)	
- Hepatobiliar disease	

9. DIAGNOSIS OF H. PYLORI INFECTION

There are many available direct and indirect diagnostic tools of zoonotic *H. pylori* available in both human and animals' fields as shown in Figure 2.

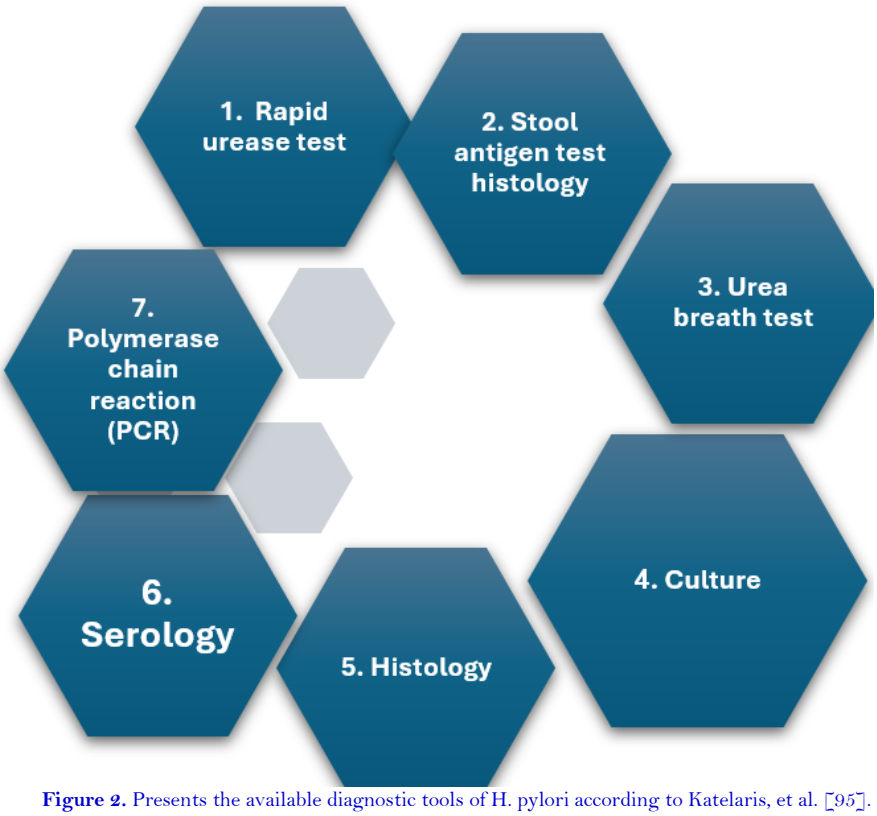

Figure 2. Presents the available diagnostic tools of H. pylori according to Katelaris, et al. [95].

10. TREATMENT OF H. PYLORI INFECTION

There are many treatment lines concerning the treatment of *H. pylori* in animals and man as shown in Table 4.

Table 4. Presents ideal conventional lines of medications used for *H. pylori* infection.

Line of medication	Drugs used	References
First and second line	Clarithromycin, amoxicillin, clarithromycin, and proton pump inhibitor (PPI) bismuth-containing triple therapy	Fekadu, et al. [96]
Third line	bismuth-based quadruple treatment amoxicillin, metronidazole, and PPI quinidine levofloxacin amoxicillin with high-dose PPI - Research suggest that eliminating H. pylori as soon as possible may help prevent stomach cancer.	Awan, et al. [97] Awan, et al. [97]

11. FUTURE ASPECTS

In the purpose of shedding more light on the precise sources of infection and the part that animals play in the spread of disease, further case report studies are necessary. Given the significant risk that *H. pylori* poses to the public, we advise public health authorities to give priority to developing preventive interventions against *H. pylori* infection.

12. CONCLUSION

GH is more better understood than EHH, despite the fact that a substantial amount of data has just been gathered. To understand the role of EHH in human and animal sickness, a great deal of unresolved questions remain to be explored. The microbiological identification of EHH is one of the most crucial areas for advancement; there wouldn't be many clinical reports without better isolation and detection techniques.

A thorough understanding of the range of species that act as EHH reservoirs is also essential. This will enable us to ascertain their epidemiology, pinpoint potential channels of transmission, and maybe initiate preventive measures to avert human infection. Similar opacity covers the specific pathologic pathways connected to EHH. Therefore, it is necessary to investigate animal models' infection in order to screen the different pathogenicity determinants. Moreover, future research should take these and other relevant factors into account in order to fully comprehend the risk that EHH actually poses to public health. There is hope that with all of the attention this class of bacteria has recently received, our knowledge of these freshly discovered microbes will advance dramatically in the years to come.

13. ABBREVIATIONS

°C, degree Celsius; µm, micrometer; CD, Crohn's disease; CDT, cytolethal distending toxin; CLSI, Clinical and Laboratory Standards Institute; cmp, Campylobacter major protein; DNA, deoxyribonucleic acid; DsBs, double strand breaks; EBV, Epstein-Barr virus; EHH, enterohepatic Helicobacter species; GH, gastric Helicobacter species; H. pylori, Helicobacter pylori; IBD, inflammatory bowel disease; IgA, immunoglobulin type A; irgA, iron-regulated outer membrane virulence protein; JCV, John Cunningham virus; LpxR, Lipid A deacylase; MIC, minimal inhibitory concentration; NHPH, non-Helicobacter pylori species; OMPLA, outer membrane protein phospholipase A; OMPs, outer membrane proteins; PCR, Polymerase Chain Reaction; PG, Peptidoglycan, Pgl, protein glycosylation; PPI,

Proton Pump inhibitor; rDNA, ribodeoxyribonucleic acid; rRNA, ribosomal ribonucleic acid; SfpA, systemic factor protein A; UC, Ulcerative colitis; VBNC, viable but not culturable bacteria.

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