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REVIEW: EPIDEMIOLOGY OF *HELICOBACTER PYLORI* INFECTION

R.I. Alfaray[1,2], B. Saruuljavkhlan[1], S. Ansari[1,3], K.A. Fauzia[1,2,4], Y. Yamaoka[1,2,5]

[1]Department of Environmental and Preventive Medicine, Oita University Faculty of Medicine, Yufu, Oita, Japan
[2]Institute of Tropical Disease, Universitas Airlangga, Surabaya, Indonesia
[3]Karnali Academy of Health Sciences, Jumla, Nepal
[4]Department of Public Health and Preventive Medicine, Universitas Airlangga, Surabaya, Indonesia
[5]Department of Medicine, Gastroenterology and Hepatology Section, Baylor College of Medicine, Houston, TX, USA

Ricky Indra Alfaray, Batsaikhan Saruuljavkhlan and Shamshul Ansari contributed equally

Corresponding Author: Yoshio Yamaoka, MD, Ph.D; email: yyamaoka@oita-u.ac.jp

Abstract – This review presents a summary of recent publications regarding the epidemiology of *Helicobacter pylori* infection. We initially discuss the prevalence of *H. pylori* in several countries in Asia and Africa. African countries generally have a prevalence of more than 50%, while Asian countries show a high prevalence in countries such as Korea (43.9%) and China (44.2%), and a low prevalence in countries such as Indonesia (10.4%) and Sri Lanka (2.5%). The prevalence of *H. pylori* in children, the geriatric population, military personnel, and disease-related studies was described by several meta-analyses. We highlight the current knowledge of risk factors of *H. pylori* infection. In 2021, various studies were published regarding age, sex, eating habits, crowding and annual income, drinking water sources, washing hand habits, smoking, and periodontitis. These risk factors could affect *H. pylori* transmission, which are divided into family-based transmission, zoonotic-based transmission, and habit-based transmission. These three transmissions can be considered as environmental factors that should be managed to prevent further transmission and reinfection. Finally, we briefly summarise the current knowledge of *H. pylori* co-infection with Epstein–Barr virus, hepatitis C virus, and severe acute respiratory syndrome coronavirus 2, which affect the clinical outcome of *H. pylori*-infected patients.

Keywords: *Helicobacter pylori*, Epidemiology, Prevalence, Risk factor, Transmission, Reinfection, Co-infection.

INTRODUCTION

Helicobacter pylori causes persistent infection that leads to the development of gastroduodenal complications, including peptic ulcer disease, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue lymphoma[1,2]. In this review, we summarise the recent findings of *H. pylori* infection published from April 2021 to March 2022.

PREVALENCE OF *H. PYLORI* INFECTION

Africa

The prevalence of *H. pylori* infection in Africa varies between countries, but it is relatively high[3]. The highest prevalence (93.1%) is in the Republic of the Congo. The prevalence is 70.8% in Burundi, 75% in Rwanda, 70.41% in Togo, 89.0% in the Democratic Republic of Congo (Bukavu City), 63.8% in Morocco, 88% in Ghana, 66.12% in Egypt, 71.5% in the Republic of Benin, 73.2% in Cameroon, 71.43% in Algeria, 88.9% and 82.8% for men and women in Ethiopia, respectively, and 54.5% in South Africa[3-5]. These prevalence data were reported using several methods, and histology was generally the main standard3. Because different methods can provide different results, future studies using the same standard detection method are warranted to determine the general prevalence of *H. pylori* in Africa[6]. Additionally, some countries have a different prevalence within their area. An example of this difference is in Nigeria, where the prevalence of *H. pylori* is 87.8% in the north, but 51.4% in the south and 34.2% in the southeast[3].

Asia

Studies on the prevalence of *H. pylori* were reported from China, Korea, Iran, Lebanon, Indonesia, and Sri Lanka. Among these countries, the first four had a similar prevalence (approximately 40%), while Indonesia and Sri Lanka had a lower prevalence[7-11]. A meta-analysis[7] concerning 1.3 million subjects in China showed that the overall prevalence of *H. pylori* in the mainland was 44.2%, with the highest prevalence (66.4%) in Xizang and the lowest (35.4%) in Chongqing. A meta-analysis[8] conducted on the Korean population showed that the current prevalence of *H. pylori* infection was 43.9%. Fortunately, this prevalence was decreased compared with that in previous years, ranging from 74.3% in 1990, 66.9% in 1998, 58.6% in 2005, 54.5% in 2011, and 43.9% in 2016[8]. This prevalence is similar to that in Iran where the prevalence was 46.8% among 233 patients[12]. A lower prevalence was observed in Lebanon where the prevalence was 39% among 300 individuals[9].

The lowest prevalence of *H. pylori* was found in Indonesia and Sri Lanka. A review described that the overall prevalence in Indonesia was only 10.4% among 1,053 patients, which was different from its neighbouring countries, although the prevalence was different between areas within Indonesia[10]. Sri Lanka also showed an extremely low prevalence (2.5%) among 353 patients[11]. These results suggest that poor hygiene and low socioeconomic status are not the only predictors of the prevalence of *H. pylori* infection.

Prevalence of *H. pylori* in Children and the Geriatric Population

A worldwide meta-analysis of 152,650 children showed that the overall prevalence of *H. pylori* was 32.3%[13]. Different diagnostic methods provided different results, ranging from 28.6% for serology-based methods to 35.9% for the urea breath test (UBT) or stool antigen test (SAT)[13]. A meta-analysis[14] showed that the prevalence of *H. pylori* was 23.6% in Poland, 56.0% in South Korea, 44.3% in Uganda, 72.4% in Egypt, 28.7% in Brazil, and 59.7% in Italy. This prevalence could vary between areas even within one country. In Japan, the prevalence ranged from 3.8% to 9.5% depending on the prefecture[14]. The prevalence of *H. pylori* is low (6.0%) in children from North-Central Nigeria, whereas it is relatively high (28%) in the Southwest part of the country[3].

Studies that focused on the prevalence of *H. pylori* in geriatric patients were rare in 2021. One study stated that developing countries were still facing the challenge of a high prevalence of *H. pylori* infection in geriatric group. For example, the prevalence in Chinese geriatric patients reached 46.5%[15]. Further studies need to be conducted to clearly determine the prevalence among geriatric patients in other countries because these patients have a high risk of developing gastric cancer[16], and *H. pylori* eradication in these patients can considerably reduce the probability for the development of gastric cancer[17].

Relation of the Prevalence of *H. pylori* Infection with Occupation and Disease

A unique meta-analysis[18] that highlighted the prevalence of *H. pylori* infection among military personnel was published in March 2022. Among the studies included, six were performed in Asia, seven in Europe, and three in North America. The prevalence of *H. pylori* was 32% overall and varied depending on the region, with the highest prevalence (50.2%) in Asia[18]. Further epidemiological studies that analysed the prevalence of *H. pylori* related to a particular occupation need to be conducted because different jobs might have different risk factors for *H. pylori* infection[19].

Two meta-analyses[20,21] that determined the prevalence of *H. pylori* in disease-specific patients were published. One meta-analysis was based on patients with non-alcoholic fatty liver disease, and the other on patients with non-cardiac gastric cancer[20,21]. The proportion of patients with non-alcoholic fatty liver disease was higher among *H. pylori*-infected patients than uninfected patients; therefore *H. pylori*-infected patients showed a higher risk of developing this disease[20]. With regard to patients with non-cardia gastric cancer, the meta-analysis performed in China showed that the prevalence of *H. pylori* infection in patients with cancer was 66.5%. This prevalence varied between areas with the highest prevalence (78.9%) in Northwest China and the lowest (53.1%) in North China[21].

RISK FACTORS FOR INFECTION

Age

A community-based survey of 2,232 subjects was performed in Wuwei City, Gansu Province, China[22]. This area had a high prevalence of gastric cancer, and *H. pylori* infection was found already in newborns (12%), and its prevalence increased with age each 10 years, with an odds ratio (OR) of 1.28. The overall prevalence of *H. pylori* in children (age: 3-11 years) was 22.9% and kept increasing up to 56.3% (adults: 30-39 years)[22]. A community-based study in Hanoi, Vietnam, involving 1,272 subjects showed a prevalence of 92.2% in children aged <12 years, which decreased to 79.8% at >45 years[23]. This finding could be due to a higher exposure to infection by feeding and chewing habits from caretakers[23].

Age can be used to determine not only the risk of infection, but also the progression to intestinal metaplasia (IM) after *H. pylori* infection. Older *H. pylori*-infected individuals were found to have a higher persistent IM, with an OR of 2.47, compared to younger patients[24]. Furthermore, persistently infected individuals had a much higher progression rate of IM to dysplasia than patients without persistent infection. An age older than 65 years together with persistent *H. pylori* infection and diabetes mellitus may be a significant predictor for persistent IM and its progression to dysplasia[24].

Gender

In a community-based study on the Navajo Nation in northern Arizona, USA, male gender was a factor for *H. pylori* infection[25]. This indigenous population has a higher gastric cancer rate than that in other regions of the USA. A similar result was observed in a household survey in Bangladesh, which showed a higher prevalence of organic/structural dyspepsia in male subjects than in female subjects[26]. Female subjects also showed a tendency to have functional dyspepsia rather than organic dyspepsia.

Another study[27] showed that women (58.22%) possessed significantly higher average knowledge scores regarding *H. pylori* infection than men (56.25%). In this study, the prevalence of *H. pylori*-induced gastric ulcers in female patients was significantly lower than that in male patients[27]. This clearly suggests that a lack of general knowledge in men is a predictor for *H. pylori*-associated gastric ulcers.

Eating Habits

In a survey in Wuwei City, China, children > 3 years who frequently consumed yogurt had a lower prevalence of *H. pylori* infection (OR: 0.8) than those who never consumed yogurt[22]. In the kindergarten age group (4-6 years), fruit consumption was associated with a lower prevalence of *H. pylori* infection[22]. At the junior-senior high school age (13-18 years), eating at the school cafeteria more than six times each week increased the risk of *H. pylori* infection by 1.86 times, compared with the reference. This phenomenon indicates transmission through meals. Therefore, improving hygiene during meal preparation in the school cafeteria might be necessary[22].

Crowding and Annual Income

The prevalence of *H. pylori* infection was found to be higher in people who lived in overcrowded areas[9]. In a study including an adolescent population, the prevalence of *H. pylori* was significantly higher in the military group than in the civilian group[28]. Additionally, the incidence of peptic ulcers and/or gastric cancers was higher in the military group than in the civilian group[28]. Certain housing conditions such as their source of drinking water and washing hand habit inside family, are also a main risk factor of transmission in children aged 3-11 years[22]. In adult cases in Vietnam and Korea, subjects whose family members were infected with *H. pylori* had a higher risk of *H. pylori* infection[23,29]. This overcrowding was also affected by income; a lower income was associated with a higher prevalence of *H. pylori* (p=0.02)[22]. A higher income is related to more living space and better living conditions.

Drinking Water Source and Washing Hands

H. pylori can be a water-borne pathogen. Therefore, the drinking water source and washing hands are significant risk factors for infection[22]. Drinking from running water and frequent hand washing are negatively associated with *H. pylori* infection. Adults older than 18 years in rural areas also have a higher prevalence (OR: 1.44) than those living in urban areas[22]. The soil-water is still used as the main drinking water source in rural areas instead of the sterilised water found in urban areas. The drinking water source was also significantly associated with a higher prevalence of *H. pylori* infection in a study of the Navajo Nation in northern Arizona[25].

Smoking

Smoking is a well-known factor contributing to *H. pylori* positivity[30]. A hospital-based study of 445 dyspeptic outpatients in Turkey reported that a higher rate of waterpipe tobacco smoking was an independent predictor for *H. pylori* infection (OR: 5.51, 95% CI: 3.158-9.617)[31]. This result is also supported by a study from Cyprus, which included 445 adult subjects[31]. The waterpipe system has several parts, but only the mouthpiece is changed, thus enabling the transmission of *H. pylori.* Moreover, in Vietnam, the tobacco heating system, which requires charcoal, increases toxic inhalation and this combined with *H. pylori* infection increases the risk of gastric cancer[32].

Periodontitis

Periodontitis is a chronic inflammation in the tissues supporting the teeth and is accompanied by the growth of microorganisms[33]. Therefore, the oral cavity is a potential reservoir for bacteria. A retrospective study of periodontitis in Taiwan involving 134,747 participants showed that periodontitis increased the risk of *H. pylori* infection[34]. This risk was higher at >50 years old, in male participants, and with the presence of comorbidities, such as hypertension, hyperlipidaemia, chronic obstructive pulmonary disease, and chronic kidney disease.

BACTERIAL TRANSMISSION

Documented epidemiological evidence suggests the transmission of *H. pylori* directly from person to person or indirectly from the environment to people[35]. The most common route of its transmission may be oral–oral or fecal-oral from person to person (intrapersonal) among family members (intrafamilial) or through sexual intercourse. Typically, the bacterium is contracted during childhood when an infant starts to eat. Although person-to-person transmission is considered as the primary mode of transmission in developing countries, food and waterborne transmission may also be more likely in developing countries with poor hygienic conditions.

Moreover, the presence of *H. pylori* in dental plaque and saliva of infected individuals suggests more frequent bacterial spread than expected between family members. A recent systematic review and meta-analysis of 12 eligible articles published up to September 2021 showed the presence of *H. pylori* in the oral cavity[36]. The prevalence of *H. pylori* infection in the oral cavity ranges from 5.4% to 83.3%. *H. pylori* colonisation in the oral cavity or periodontal pockets is hypothetically listed as a cause of reinfection and recolonisation in the *H. pylori* infection cycle. However, this topic has huge gaps in its comprehension and there is confusion in the mechanisms of *H. pylori* infection, especially concerning the role of the oral cavity in transmission. We shall summarise the most recently published transmission modes and divide them into three types below.

Family-Based Transmission

A Chinese group published a consensus report on family-based *H. pylori* infection and its control and management, including 23 statements to prevent intrafamily transmission of *H. pylori* and the complications of its related diseases[37]. In most developing countries, intrafamilial transmission of *H. pylori* is still the most common route of *H. pylori* infection, particularly in children. The infection is primarily transmitted to children by their parents (particularly by mothers). This theory was supported by a study in Vietnam that also stated above in the risk factor of age[23]. This study showed that children aged <12 years had more *H. pylori* infection (92.2%) than adults aged >18 to <45 years (83.5%), and mothers, sons, and girls had a higher prevalence of *H. pylori* infection than fathers[23]. Intrafamilial transmission is influenced by factors such as lifestyle (*e.g.*, eating type, gathering), home conditions (*e.g.*, animals, hygiene), and socioeconomic status. Infected family members are a possible source of infection and have the potential for continuous transmission to other members. Again, the Vietnam study supported this theory by reporting that they found a treatment failure rate of 22.6% because of the infection status of other family members, beside of eradication treatment regimens[23]. In patients with related diseases (gastric cancer or gastric mucosal precancerous lesions), *H. pylori* infection should be screened using the urea breath test and family members living in the same household should be treated. In children and older people, *H. pylori* infection should be managed according to a risk-benefit assessment and the individual disease status or condition. Taken together, these findings suggest that family-based *H. pylori* infection control and management are essential to prevent new infections or reinfections. This, in turn, can reduce the risk of gastric cancer, as well as medical expenses for future complications in *H. pylori*-infected patients.

Zoonotic-Based Transmission

H. pylori can also be acquired from domestic animals[38]. Non-*Helicobacter pylori* Helicobacters are frequently detected in domestic animals. One case reported in Japan showed the *H. pylori*-specific gene *ure*AB in biopsy samples from dogs and their owners. Interestingly, even though both dogs and their owners were positive for *H. pylori*, both were negative for other Helicobacters (*Helicobacter felis, Helicobacter bizzozeronii*, and *Helicobacter heilmannii*)[38]. The theory of zoonotic-based transmission is also supported by another study, which showed that non-*Helicobacter pylori* Helicobacters, such as *Helicobacter heilmannii,* cause dyspeptic symptoms together with erosive disease of the gastric mucosa in humans. These species should be considered to cause acute peptic ulcer disease, especially in patients who have pets, such as cats or dogs[39].

Habit-Based Transmission

Habits have been considered as probable risks of *H. pylori* infection in humans. As mentioned above in discussing the risk factors for infection, a recent study[40] also reported that habits such as smoking could help *H. pylori* transmission. However, more research is required to determine whether waterpipe tobacco is a source of *H. pylori*.

REINFECTION

One of the questionable topics in *H. pylori* infection is the recurrence of infection. A recurrence can occur *via* either recrudescence or reinfection[41]. The difference between recrudescence or reinfection is that recrudescence has a shorter time window, and it occurs following *H. pylori*-related diseases[41]. The other difference is that reinfection is considered if a patient is infected with a new *H. pylori* strain due to several factors, such as intrafamilial transmission, poor hygiene conditions, and health status[41]. In this review, we shall focus on reinfection because recent studies have been based on this topic. In a pilot non-blinded trial study from Chile that included 61 children, the reinfection rate of *H. pylori* was 13% during the follow-up[42]. This reinfection suggested that *H. pylori* eradication among children should be supported by further eradication for their families or environments.

A study on *H. pylori* infection using 16S rRNA amplicon sequences showed *H. pylori* DNA in a gastric biopsy whereas a rapid urease test, culture, and immunohistochemical staining were all negative[43]. The authors concluded that environmental contamination of *H. pylori* (*e.g.*, water, ground, and surrounding contaminations) could be the reason for reinfection in countries with a high prevalence of *H. pylori* infection. These studies suggest that environmental factors should be managed well to prevent the transmission of *H. pylori* infection, including a reinfection event.

VIRAL CO-INFECTION

Recently, research regarding *H. pylori*-viral co-infection has focused mainly on Epstein–Barr virus (EBV), hepatitis C virus (HCV), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). EBV virus may increase the risk of developing gastric cancer by 3.3 times[44]. A study[45] showed EBV DNA in 40% of gastric cancer cases, and co-infection with *H. pylori* was detected in 16% of gastric cancer cases. Moreover, the incidence of *H. pylori* and EBV co-infection has been frequently reported in the diffuse type of gastric cancer[45]. EBV infection enhances the expression of the oncogenic protein gankyrin in *H. pylori*-infected individuals. Gankyrin causes dysregulation of cancer-associated genes, such as cell migratory, tumour suppressor, DNA damage response, and pro-apoptotic genes[46]. In fact, infection with two oncogenic agents (*H. pylori* and EBV) leads to enhanced carcinogenic activity in gastric epithelial cells through enhanced expression of gankyrin[46].

The fact that only 1-3% of *H. pylori*-infected individuals develop gastric cancer suggests the involvement of other factors. HCV infection in individuals with *H. pylori* infection inhibits lymphatic metastasis[47]. *H. pylori* infection increases tumour aggressiveness by promoting lymphatic metastasis, whereas HCV infection in *H. pylori*-infected individuals inhibits lymphatic metastasis[47]. However, this possibility needs to be verified by more research on the inhibitory effect of HCV in metastatic development of gastric cancer.

With regard to co-infection with SARS-CoV-2, Gonzalez et al[48] suggested that this virus together with *H. pylori* infection could affect the emergence of the global coronavirus disease 2019 (COVID-19) pandemic because their co-infection could affect the patients' pathogenesis. Chronic infection of *H. pylori* in the stomach may have systemic consequences and lead to cell damage in various organs, including the lungs. This process could be facilitated by a molecular mimicry mechanism. Gonzalez et al[48] also stated that the successful eradication of *H. pylori* infection may help to improve dysfunction and the inflammatory process of the lungs in patients with SARS-CoV-2 infection. A study from Turkey[49] showed that the rates of abdominal pain and diarrhoea were significantly higher in patients with SARS-CoV-2 and *H. pylori* than in those without *H. pylori* infection. This study also showed that the presence of *H. pylori* did not affect the duration of hospitalisation or severity of the outcome of SARS-CoV-2-infected patients.

The patient's clinical profile is also correlated with the management of *H. pylori* infection therapy. This correlation was shown by a study on the clinical outcome of COVID-19-associated proton pump inhibitors (PPIs) in Korea[50]. This nationwide cohort study included 111,911 non-users, 14,163 current PPI users, and 6,242 past PPI users. The main finding of this study was that current PPI use increased the risk of severe clinical outcomes of COVID-19 by 79% and, in particular, current PPI use (previous 30 days) was increased by 90%.

Together, these studies suggested that viral co-infection in *H. pylori*-infected patients should be carefully assessed because it could affect the pathogenesis and clinical outcomes of patients. While the effects of EBV, HCV, and SARS-CoV-2 have been examined, further studies on viral co-infection are required because each virus could have a different effect on the development of disease.

CONCLUSIONS

Recent studies have shown that African countries and some Asian countries have a high prevalence of *H. pylori* infection, while other countries, such as Indonesia and Sri Lanka, have a low prevalence. Studies have highlighted the importance of age, gender, eating habits, crowding and annual income, drinking water source, washing hands, smoking, and periodontitis as risk factors for *H. pylori* infection. *H. pylori* infection can be transmitted by family-based transmission, zoonotic-based transmission, and habit-based transmission. These transmissions indicate the importance of managing environmental factors to prevent *H. pylori* transmission and reinfection. Furthermore, several studies have shown the importance of viral co-infection in *H. pylori*-infected patients. Although viral co-infection affects the clinical outcome, the exact mechanism is still unknown. Further studies will be needed on several issues related to *H. pylori* infection, such as prevalence, risk factors, transmission, reinfection, and co-infection.

Conflict of Interest

The authors declare no conflict of interest.

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Authors' Contribution

Manuscript preparation: RIA, BS, SA, KAF, YY. Leading of manuscript writing: RIA, BS. Essential Revision: RIA, YY. Supervision and funding acquisition: YY.

ORCID ID

RIA https://orcid.org/0000-0001-7721-9455; BS https://orcid.org/0000-0003-3258-4453; SA https://orcid.org/0000-0003-1846-1377; KAF https://orcid.org/0000-0001-6901-3270; YY https://orcid.org/0000-0002-1222-5819.

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