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REVIEW – EPIDEMIOLOGY OF *HELICOBACTER PYLORI* INFECTION

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Abstract: We encompassed recent data related to *Helicobacter pylori* epidemiology. Infection prevalence was low (<20%) in countries, such as Canada, Sweden, Korea and Taiwan, but still high (>50%) in other countries, such as Cameroon, Chile and Bangladesh. Among positive subjects, CagA frequency ranged from ≤33.3% in Japan and Italy to >90% in Chile. In Bulgaria, the infection was frequent (>76%) in children with anemia and weight loss. Huge racial differences in infection prevalence were observed. In the USA, African Americans were 2- and 3-fold more likely to be *H. pylori*- and CagA-positive than the Caucasians, respectively. Canadian endoscopy patients of Asian/South American origin were 3.8-fold more often infected than the Caucasians. Overall, the infection affected ≥62.0% of diabetics in studies from Europe and Africa and was also more frequent in patients with autoimmune thyroid diseases, arteriosclerosis, glaucoma, osteoporosis and various neurological and skin diseases than in controls. Recent data concerning infection transmission, including *H. pylori* DNA in oral samples, food, animals, and yeasts were added. *H. pylori* DNA was found in one-half of vaginal yeasts and one-third of oral yeasts. In addition to the well-known risk factors for the infection, contact with dogs and sheep was reported. Annual recurrence rate of the infection was 0.2-4.8%, although the rate was higher (>18%) in Chinese children. Preservation and variegation of *H. pylori* genes in numerous American countries were revealed by whole genome sequencing. Briefly, *H. pylori* infection remains a concern in several countries and in certain subpopulations, as well as in patient groups with some non-gastric diseases.

Keywords: *H. pylori*, Epidemiology, Prevalence, Recurrence, Risk factors, Transmission.

INTRODUCTION

Helicobacter pylori is a recognized strong (class I) carcinogen associated with development of gastric cancer and mucosa-associated lymphoid tissue (MALT) lymphoma, as well as with chronic gastritis and duodenal and gastric ulcers in humans[1]. The infection is one of the most common chronic bacterial infections worldwide, affecting approximately 30% of the population in many Western countries with oscillation among studies but much higher prevalence in some developing countries[2]. The infection is usually acquired during childhood and can be transmitted by oral-oral, gastro-oral and fecal-oral routes[3,4]. Although most risk factors for the infection have been linked to socioeconomic characteristics of the country or subpopulation, assessing specific risk factors and parameters of the infection, as well as the most affect-

ed subpopulations, can help with predicting future morbidity and mortality of the associated diseases in the region, thus improving both diagnosis and therapeutic approaches.

In this review, we present recent data on the epidemiology of *H. pylori* infection published since March 2020, concerning prevalence and evolution of both *H. pylori* infection and its virulence factors, transmission and recurrence of the infection, as well as infection rates in patients with different racial origin or different non-gastric disorders. For this purpose, publications in PubMed and Google Scholar were searched with the following keywords and word combinations in either the title or the abstract: "*Helicobacter pylori*", "*H. pylori*", "prevalence", "rate", "recurrence", "reinfection", "relapse", "transmission", "virulence genes", "CagA", "oral *H. pylori*", "microbiome-gut-brain axis", "microbiome-gut-skin axis" and "whole genome sequencing". The publications included were mostly in English language and two articles in French and Spanish were also considered.

PREVALENCE OF *HELICOBACTER PYLORI* INFECTION

H. pylori infection is usually acquired in early childhood. Furthermore, the overall decrease in the infection can be observed most clearly in children. A decline in *H. pylori* infection was found in a number of studies. Only 14.6% of Jordanian asymptomatic children aged 4-17 years attending pediatric clinics were *H. pylori* positive by urea breath test versus 55% as detected 13 years earlier[3]. Living in an urban versus a rural area, family history of the infection and the lack of some personal hygienic factors, such as hand washing and the use of school toilets were detected as risk factors for the infection[3]. The decline of infection frequency in Jordanian children was linked to the improvement in sanitation and access to safe drinking water for 99% of the population, as well as the frequent use of both prescribed and unprescribed antibiotics in the country[3]. In Korean asymptomatic children and adolescents, seropositivity rate decreased 3.4-fold from 1988 (62.2%) to 2015 (18.2%)[5]. Some details concerning the studies are presented in Table 1.

In adult residents of Taiwan, *H. pylori* infection rates gradually decreased from 63.0% among 4,121 participants evaluated in 2004 to 15.5% among 2,907 residents evaluated in 2018[6]. Although *H. pylori* infection prevalence has been decreasing in many countries, in some of them, the decrease can be slow. In a meta-analysis in mainland China performed on 670,572 adult inhabitants of 26 provinces, *H. pylori* positivity was 63.8% in 1983-1994, dropping to 46.7% in 2006-2018[7]. The decline of the infection rate was only by 0.9% yearly over 35 years, and the year of the study and the living place (in rural areas) were important risk factors for the infection[7].

In rural Bangladeshi residents, *H. pylori* seroprevalence among adults was 54.5%[8]. By multivariate analysis, underweight and marital status (married) were risk factors for the seropositivity[8]. In Cuba, the seroprevalence of 92 old subjects aged from 60 to 89 years was evaluated by ELISA and showed a positivity rate of 57.1% in those aged 60-69 years and 7.9% in those aged 80-89 years[9]. The decline in the oldest group is possibly due to atrophic gastritis.

Importantly, the prevalence of *H. pylori* infection may differ greatly not only among countries but also among regions of the same country. In Bhutan, among 1,178 dyspeptic patients from six regions, the total infection prevalence was 66.2%, however, huge differences (from 57.7 to 85.6%) were found between the different regions[10]. Additionally, the infection was more prevalent (73.5%) in urban areas compared to rural districts (63.3%)[10]. Likewise, in the meta-analysis performed by Li et al[7], in some of the Chinese provinces evaluated, the prevalence of the infection ranged from <21% to >81%. In Ethiopia and Thailand, 43-44% of the dyspeptic patients were *H. pylori* positive[11,12].

Racial differences in the infection prevalence are an important concern. Low *H. pylori* prevalence (13.0%) was observed among adult patients in an endoscopy clinic in Canada, however, the positivity rates were significantly higher in subjects of Asian (30.8%), South American (34.9%) and African (25.0%) origin compared with those of the Caucasian population (8.0%)[2]. Swedish authors, evaluating *H. pylori* infection prevalence in patients with acute myocardial infarction, found a link between smoking and *H. pylori* infection[13]. In this group of patients, the infection was 1.4-fold more frequent in smokers (36%) than in non-smokers (21%)[13].

TABLE 1. PREVALENCE OF HELICOBACTER PYLORI INFECTION AND CAGA POSITIVITY ACCORDING TO RECENT PUBLICATIONS.

Country	Group	Years	No of subjects or patients	Method	*H. pylori* prevalence (%)	CagA prevalence (%)	Reference
Bangladesh	Adults, rural residents	2014-15	767	Serology	54.5	NA	8
Bulgaria	Pediatric patients	2010-18	150	RUT, Gram stain and culture	76.6 (anemia) vs. 21.3 (controls), 82.2 (weight loss) vs. 17.8 (controls)	NA	20
Bhutan	Dyspeptic patients	2010-15	1,178	RUT, histology and culture	66.2 (from 57.7 to 85.6 in some regions)	NA	10
Cameroon	Type 2 dyspeptic diabetic patients and controls	2014	205	RCI	73.1 (diabetic), 58.0% (non-diabetic)	NA	15
Canada	Adult patients in an endoscopy clinic	2011	500	Histology	13.0 (8.0 in Caucasian group, >30% in Asian and South	NA	2
Chile	General population	2014-15	1,395	Serology	63.0-67.0	>90 of the positive cases	18
China	Adults, general population	1983-2018	670,572	Different	63.8 (in 1983-1994), 46.7 (in 2006-2018)	NA	7
China	Dentists and volunteers	2016	200	Nested PCR	16.7 (dentists), 7.3 (nondentists)	NA	29
Cuba	Old adults, general population	2018-19	92	Serology	68.4	NA	9
Ethiopia	Dyspeptic adults	2018	208	Serology	42.8	NA	11
France	General population	NA	NA	NA	15-30% (<20% in people aged <30 yrs; 50% in those aged 50-60 yrs)	NA	18
Italy	Adults, general population	11 year follow up	1,149	Serology	49.3	30 (osteroporosis) vs. 21 in controls	25

CONTINUED

TABLE 1 *CONTINUED*. PREVALENCE OF HELICOBACTER PYLORI INFECTION AND CAGA POSITIVITY ACCORDING TO RECENT PUBLICATIONS.

Country	Group	Years	No of subjects or patients	Method	*H. pylori* prevalence (%)	CagA prevalence (%)	Reference
Japan	Adults, general population	2017-19	90	Stool PCR	20.0	33.3 of the positive cases	16
Japan	Adults, general population	2020	88	Nested PCR	30.7 (supragingival biofilms)	NA	4
Jordan	Asymptomatic children in pediatric clinics	2019	328	UBT	14.6	NA	3
Jordan	Symptomatic children	2008-16	98	Histology	54.0	NA	19
Korea	General population	1994-95 to 2014-15	1,305	Immunoblot	NA	63.2% (in 1994-95), 42.5% (in 2014-15)	23
Korea	Asymptomatic pediatric patients	1988, 1915	NA	Immunoblot	62.2% (in 1988), 18.2% (in 2015)	NA	5
Sweden	Patients with acute myocardial infarction	2019-20	310	UBT	20.0 (36.0 in smokers, 21 in non-smokers)	NA	13
Taiwan	Adult residents	2004-2018	16,119	Histology, culture	63 (in 2004), 15.5 (in 2018)	NA	6
Thailand	Upper gastrointestinal endoscopy patients	2018-19	1,370	Histology	43.8	NA	12
USA	Colorectal cancer patients and controls	1985-2009	4,476	Multiplex serology	33 (whites subjects), 71 (African Americans)	59 (whites), 87 (African Americans) of the positive cases	24
Meta-analysis of 13 studies	Diabetic patients	1990- 2019	1,934	Different	54.0 (15.0 in the USA, 53.0 in Asia, 62.0 in Europe, 66.0 in Africa)	NA	14

ISAT- immunochromatographic stool antigen test; RCI rapid chromatographic immunoassay; RUT-rapid urease test, UBT- urea breath test; NA-not available.

Other recently reported factors associated with infection were diabetes[14,15], the presence of domestic animals (in Ethiopia)[11] and contact with animals, such as dogs[16,17] and sheep[17] (see below).

Cohort phenomenon is characteristic for *H. pylori* infection. In Chile, the ENIGMA Chile study group performed a large epidemiologic study in two areas with distinct gastric cancer incidence[18]. Samples from residents in various age groups were set by design. The cohort phenomenon was observed, showing the lowest (20%) infection prevalence in children <10 years old, increasing to 40% in older children and adolescents, to 60% in the subjects aged 20-29 years and to ≥80% in the older residents[18].

It is important to note *H. pylori* prevalence in groups with specific conditions or diseases. In a Jordanian study, no association between the infection and anemia was found[19], however, in Bulgaria, *H. pylori* infection was found in 76.6% of pediatric patients with anemia *vs.* 21.3% in controls and in 82.2% of children with weight loss *vs.* 17.8% in controls[20].

H. pylori infection was more prevalent in diabetic than in non-diabetic people. Despite some controversy in previous studies, in a meta-analysis[14], the infection prevalence in diabetics was 54%, ranging from 15% in the USA to 53% in Asia, and ≥62% in Europe and Africa, regardless the subjects' age, type of diabetes, duration of the disease and glycated hemoglobin (HbA1C) values. Likewise, the infection was more frequent (73.1%) in diabetic adults compared with controls (58.0%) in Cameroon[15]. The results were explained by inflammatory markers, insulin resistance, delayed gastric emptying and gastric mucosal changes[14]. *H. pylori* association with autoimmune thyroid diseases such as Grave's disease and Hashimoto's thyroiditis was also evaluated and attributed to molecular mimicry and cross-reactivity[21].

In a meta-analysis, an association between glaucoma and histologically detected *H. pylori* infection was revealed and the infection was more prevalent in subjects with glaucoma (odds ratio, OR: 5.4) than in controls[22]. The association might be a result of diffusion of reactive nitrogen species as a consequence of the chronic inflammation[22].

PREVALENCE OF *H. PYLORI* VIRULENCE FACTORS

Cytotoxin-associated gene A (*cag*A) and vacuolating cytotoxin (*vac*A) gene alleles are important *H. pylori* virulence factors and are associated with more severe diseases. In Japan, *H. pylori glm*M gene was found in 20% of fecal specimens from 90 adults, of which one-third were *cag*A positive as well[16]. The ENIGMA study performed in two Chilean regions revealed that *H. pylori* seroprevalence was similar (63-67%) in both regions and most (>90%) positive subjects had anti-CagA and anti-VacA antibodies[18]. However, despite the common infection and high proportion of virulent infections in both Chilean regions, additional factors, such as chili consumption in the region of higher risk, and consumption of non-green vegetables in the region of lower risk appear important for the disease outcome[18].

Like the infection prevalence, that of CagA-positive strains was also variable. A long-term (20-year) evolution of CagA positive infections was serologically evaluated in Jinju, Korea[23]. This study revealed that anti-CagA IgG antibody positivity dropped significantly from 63.2% in 1994-1995 to 42.5% in 2014-2015, showing a sharp decline in children and young adults aged ≤30 years, most probably due to the cohort phenomenon[23]. A high rate (>63%) of anti-CagA IgG in neonates was detected over the whole study period due to transplacental IgG antibody transmission[23].

Significant racial differences in the prevalence of *H. pylori* virulence factors were reported as well. Among 4,476 US adult participants evaluated by multiplex serology, the prevalence of the infection was 33% in the Caucasian subpopulation *vs.* 71% in the African Americans[24]. Overall CagA seropositivity rate was also higher in the African Americans (62%) compared to that of the Caucasian participants (19%). Therefore, whereas both the infection and CagA prevalence are declining in the Caucasian subpopulation, they remain high in the African Americans, with a 2-fold higher risk of the infection and a 3-fold higher risk of CagA seropositivity compared to white US residents[24].

CagA positivity can also be high in some patients with non-gastric diseases. In the study led by Gennari et al[25] in Italy, 1,149 adult patients aged 50 to 80 years were evaluated over 11 years and 49.3% of them were *H. pylori* positive. Interestingly, the CagA positivity rate was

higher in subjects with osteoporosis (30%) compared to controls (21%), and it was assessed that *H. pylori* infections with virulent strains may raise the risk of nonvertebral fractures 2-fold and the risk of vertebral fractures 5-fold[25]. This association may be due to chronic inflammation and changes in the levels of estrogen, ghrelin and serotonin[25].

Prevalence of virulent *H. pylori* strains was also evaluated in patients with autoimmune diseases. In these patients, *H. pylori* positivity was 43% and presence of CagA positivity was 35.7%, however, no significant associations were detected[26]. A review article focused on *H. pylori,* CagA and arteriosclerosis[27].

TRANSMISSION OF THE INFECTION

Oral-oral and fecal-oral transmission are considered to be the main *H. pylori* transmission routes. Among 88 asymptomatic Japanese adults, oral *H. pylori* was PCR detected in 30.7% of supragingival biofilms and less frequently in saliva (4.5%) and tongue specimens (2.3%), and the most common was on incisor teeth[4]. PCR detection rate of the *cag*A gene in oral samples varied from 8.7% to 26.1% in patients with gastric *H. pylori*[28].

Professional exposure to saliva was evaluated in China, revealing that 17.6% of the 90 dentists evaluated had *H. pylori* DNA in their saliva vs. 7.3% of the 110 non-dentist volunteers[29].

A meta-analysis[30] summarized data about fecal-oral transmission of the infection in Iran. *H. pylori* was found in 11.4% of food and water samples and, notably, most (69.3%) positive samples were *vac*As1a positive[30]. In a North-Eastern part of Brazil, drinking untreated water was linked to the frequency of *cag*A+ genotype[31]. Multivariate analysis revealed that Brazilian dyspeptic patients drinking untreated water were more likely (OR 2.89) to harbor *cag*A positive *H. pylori*[31].

Dore et al[17] evaluated specimens from 44 sheep and 6 sheep-dogs in Northern Sardinia using ELISA for anti-*H. pylori* IgG, HpSA stool antigen test for fecal samples and PCR. In this study, *H. pylori* antigens were found in most (82%) stool samples from sheep and in all stool samples from the dogs, and anti-*H. pylori* IgG were present in >95% of sheep sera and in all six sera from the dogs, suggesting a possible infection transmission from contaminated animals or food[17]. However, all attempts to culture *H. pylori* were negative.

In a Japanese study[16], daily contact with dogs was also linked (OR 3.89) to *H. pylori* positivity. In another study, identical strains were detected in two dogs and their owner[32].

Yeasts can be *H. pylori* transmission reservoirs[33-35]. In a Chilean study, 43% of vaginal specimens from 102 term pregnant females had yeasts, most often *Candida albicans*, and half of the vaginal yeast specimens were *H. pylori* 16S rDNA positive, moreover, in approximately one-third of the positive specimens, virulent *cag*A/*vac*A genotypes were detected[33]. In another study[34], one-third of 72 oral samples from Chilean students had oral yeasts and, in most (62.5%) yeasts, *H. pylori* 16S rDNA was also found.

RECURRENCE

Recurrence of an infection can, in fact, be a recrudescence if reactivation of the infection is caused by the same bacterial strain, or a reinfection if the infection is caused by a new strain. The recurrence of *H. pylori* infection is generally associated with infection prevalence and socioeconomic conditions in the given country or region. The reinfection and recrudescence rates of the infection are usually low, ranging from 0.2% to 4.8% per year. Reinfection rate of the infection was evaluated within a year after successful eradication in Chinese patients[36]. The rate was 4.8% and drinking/dining out of home were found as independent risk factors for the recurrence[36].

In a large screening study in the Matsu Islands (Taiwan), reinfection rate remained low over a decade, from <1% per person-year in 2008 to ≤0.74 per person-year in 2012-2018[6]. The authors stated that mass screening and eradication of the infection are important to decrease gastric cancer incidence in countries with high prevalence of *H. pylori* infections[6]. However, following successful eradication of the infection, frequent reinfections (18.8%) were found in the study on 218 Chinese children over a year[37]. Reinfections were more frequent in chil-

dren aged ≤10 years (22.8%) than in the older children (7.1%) and according to multivariable regression analysis, the risk factors were non-urban living places, low family income, infected family members and eating out[37].

Recrudescence of *H. pylori* infection can be due to the presence of persister cells or cells tolerant to the antibiotic treatment that can represent <1% of the microbial population[38]. In Iran, persister cells, exhibiting a high resistance level to antibiotics, were found in 18% of 50 *H. pylori* isolates[38].

MICROBIOME-GUT-BRAIN AND GUT-SKIN AXES

Gorlé et al[39] reviewed data concerning the probable association between *H. pylori* seropositivity rates and neurological diseases, such as dementia, Parkinson's and Alzheimer's disease and the inverse link to multiple sclerosis. The role of release of free radicals, cytokines, neurotransmitters such as acetylcholine and stress hormones, as well as neuropeptides was discussed[39]. In a meta-analysis involving >33,000 patients, *H. pylori* infection was more frequent in patients with Parkinson's disease (OR 1.59) than in controls[40].

Guarneri et al[41] presented data on the infection prevalence in various skin disorders. While a number of studies supported a correlation of *H. pylori* infection with idiopathic thrombocytopenic purpura, rosacea, recurrent aphthous stomatitis and alopecia areata, the association with chronic urticaria, atopic dermatitis, psoriasis, pemphigus vulgaris and vitiligo were unconvincing[41].

H. PYLORI EVOLUTIONARY DYNAMICS

Whole genome investigation of 723 *H. pylori* strains from 14 countries in the Americas and other continents was performed in order to reveal both ancestral background and ongoing differentiation in *H. pylori* genes[42]. The results showed evolutionary changes, mosaics and ongoing admixtures in bacterial genomes from different countries and a strong selection of the main *H. pylori* virulence genes in American strains in association with gastric cancer mortality and high infection prevalence in Latin America. Many American isolates preserved ancestral sources from European or African origin. Other interesting results of this study were the notably high prevalence of admixtures in Mexico and the low admixture prevalence in some indigenous subpopulations, implying a genetic seclusion of these subpopulations[42].

CONCLUSIONS

In conclusion, many known patterns in the epidemiology of *H. pylori* infection were confirmed in recent studies, however, important new data or details were found concerning the racial differences in the prevalence of the infection and virulent strains, the non-gastric disorders associated with frequent *H. pylori* infections, the role of yeasts and animals as a likely transmission tool and the results of whole genome sequencing on preservation and variegation of *H. pylori* genes. Importantly, most of the recently published data are useful for predicting future infection trends in a given country or region, and thus, for controlling the common chronic and potentially oncogenic infection in humans. However, it is highly important to note that, without appropriate diagnostic and eradication, the disappearance of *H. pylori* infection will take a long time, more than 100 years as predicted in a US study[43].

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Conflict of interest

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