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SYSTEMATIC REVIEWS

Epidemiology of *Helicobacter pylori* infection among the healthy population in Iran and countries of the Eastern Mediterranean Region: A systematic review of prevalence and risk factors

Ahad Eshraghian

Ahad Eshraghian, Department of Internal Medicine, Namazi Hospital, Shiraz University of Medical Sciences, Shiraz 71345-1744, Iran
Author contributions: Eshraghian A sorely contributed to this paper.
Correspondence to: Ahad Eshraghian, MD, Department of Internal Medicine, Namazi Hospital, Shiraz University of Medical Sciences, Fars, Shiraz 71345-1744, Iran. eshraghiana@yahoo.com
Telephone: +98-711-6125600 Fax: +98-711-6276212
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Abstract

AIM: To investigate the epidemiology of *Helicobacter pylori* (*H. pylori*) infection among the healthy asymptomatic population in Iran and countries of the Eastern Mediterranean Region.

METHODS: A computerized English language literature search of PubMed, ISI Web of Science, Scopus, and Google Scholar was performed in September 2013. The terms, "Eastern Mediterranean Regional Office (EMRO)" and "*Helicobacter pylori*", "*H. pylori*" and "prevalence" were used as key words in titles and/or abstracts. A complementary literature search was also performed in the following countries: Afghanistan, Bahrain, Djibouti, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Pakistan, Palestine, Qatar, Saudi Arabia, Somalia, Sudan, Syria, Tunisia, The United Arab Emirates, and Yemen.

RESULTS: In the electronic search, a total of 308 articles were initially identified. Of these articles, 26 relevant articles were identified and included in the study. There were 10 studies from Iran, 5 studies from the Kingdom of Saudi Arabia, 4 studies from Egypt, 2 from the United Arab Emirates, and one study from Libya, Oman, Tunisia, and Lebanon, respectively. The overall prevalence of *H. pylori* infection in Iran, irrespective of time and age group, ranged from 30.6% to 82%. The overall prevalence of *H. pylori* infection, irrespective of time and age group, in other EMRO countries ranged from 22% to 87.6%.

CONCLUSION: The prevalence of *H. pylori* in EMRO countries is still high in the healthy asymptomatic population. Strategies to improve sanitary facilities, educational status, and socioeconomic status should be implemented to minimize *H. pylori* infection.

Key words: *Helicobacter pylori*; Prevalence; Epidemiology; Iran; Eastern Mediterranean Region Office

Core tip: Countries in the World Health Organization, Eastern Mediterranean Regional Office include a group of developing countries located in the southwest and west of Asia as well as North Africa. Understanding the epidemiological aspects of *Helicobacter pylori* (*H. pylori*) infection is important and helpful in clarifying the consequences and complications of infection. There are no systematic reviews on the prevalence and epidemiology of *H. pylori* in this geographically important region of the world. The aim of this study was to perform a comprehensive review of the epidemiology of *H. pylori* infection in this area.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a gram negative, non-spore forming spiral bacterium which colonizes the human stomach and is prevalent worldwide[1]. It has been associated with peptic ulcer disease, gastric adenocarcinoma, and type B low-grade mucosal-associated lymphoma[2]. Furthermore, the organism is also thought to be involved in other human illnesses such as hematologic and autoimmune disorders, insulin resistance and the metabolic syndrome[3-5]. Although nearly 50% of the population is infected with *H. pylori* worldwide, the prevalence, incidence, age distribution and sequels of infection are significantly different in developed and developing countries[6]. The prevalence of *H. pylori* infection is decreasing in both developed and developing countries; however, the prevalence is still high in developing countries[6]. In Argentina, the prevalence of a positive urea breath test (UBT) declined from 41.2% during 2002-2004 to 26% during 2007-2009 among children[7]. Furthermore, the age of developing the infection is lower in developing countries compared with industrialized nations[6]. It has been estimated that more than 50% of the population aged 5 years is infected and this rate may exceed 90% during adulthood[8]. In a cohort of Brazilian children, the prevalence of *H. pylori* was 53.4% at baseline and 64.7% 8 years later[9].

Understanding the epidemiological aspects of *H. pylori* infection is important and helpful in clarifying the consequences and complications of the infection, and is fundamental for eradication, treatment, and the pattern of antibiotic resistance. Countries in the World Health Organization, Eastern Mediterranean Regional Office (EMRO) include a group of developing countries located in southwest and western Asia as well as North Africa[10]. Economically heterogenous nations ranging from rich oil producing countries to poor countries are included in this group of countries. The ancient land of Iran is also located in this region. There are no systematic reviews on the prevalence and epidemiology of *H. pylori* in this geographically important region of the world. The aim of this study was to perform a comprehensive review of the epidemiology of *H. pylori* infection in this area.

MATERIALS AND METHODS

The study was conducted according to the PRISMA (Preferred reporting items for systematic review and meta-analyses) guidelines, flow diagram and checklist[11]. A computerized English language literature search of PubMed, ISI Web of Science, Scopus, and Google Scholar was performed in September 2013. No time limitation was applied and studies on animal models were excluded. After a preliminary search of the MeSH database, search terms were selected. The terms, "EMRO" and "*Helicobacter pylori*", "*H. pylori*" and "prevalence" were used as key words in titles and/or abstracts. A complementary literature search was also performed in the following countries: Afghanistan, Bahrain, Djibouti, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Pakistan, Palestine, Qatar, Saudi Arabia, Somalia, Sudan, Syria, Tunisia, The United Arab Emirates (UAE), and Yemen.

Eligibility and critical appraisal of the studies

All the studies were reviewed and carefully appraised for inclusion in the study. All descriptive/analytical cross-sectional, case-control, and epidemiological studies, as well as cohort studies with appropriate methods were included. *H. pylori* was detected using anti-IgG *H. pylori*, the UBT, stool antigen, saliva anti-IgG *H. pylori* or endoscopy. Editorials, case reports, letters to the editor, hypotheses, studies on animals or cell lines, abstracts from conferences and unpublished reports were excluded. Studies were eligible for review if they reported *H. pylori* epidemiology in asymptomatic healthy individuals. Therefore, studies reporting the prevalence of *H. pylori* in patients with dyspepsia, gastroesophageal reflux disease, gastric or duodenal ulcer, gastritis, esophagitis, and gastric and esophageal cancer were excluded (Figure 1). Studies on pediatric subjects (age < 18 years) were also included.

Data extraction

Data were abstracted from the full texts of relevant articles. Relevant data from articles reporting the prevalence of *H. pylori* and its epidemiology in Iran and other countries of the EMRO were extracted. Data on the number and sex of participants in each eligible study, study country (including city for Iran), prevalence of *H. pylori* infection, method of *H. pylori* detection, population age group, year of study, and risk factors were collected and classified in separate tables.

RESULTS

In the electronic search, a total of 308 articles were initially identified. After a review of titles/ abstracts and assessment of the relevance and validity of papers, studies with other determinants, those not related to our aims, case reports, animal studies, editorials, papers from other regions, and overlapping studies, 270 articles in total, were excluded. Based on the full text review of 38 papers, another 12 papers were excluded. Thus, 26 relevant articles were included in the review and data were abstracted and categorized into subsections. The detailed search strategy and results of the search for eligible studies are outlined in Figure 1. There were 10 relevant studies from Iran and 16 other studies from Saudi Arabia, Egypt, Lebanon, Jordan, United Arab Emirates, Tunisia and Libya. Unfortunately, there were no relevant studies from Afghanistan, Bahrain, Djibouti, Iraq, Kuwait, Morocco, Pakistan, Pal-

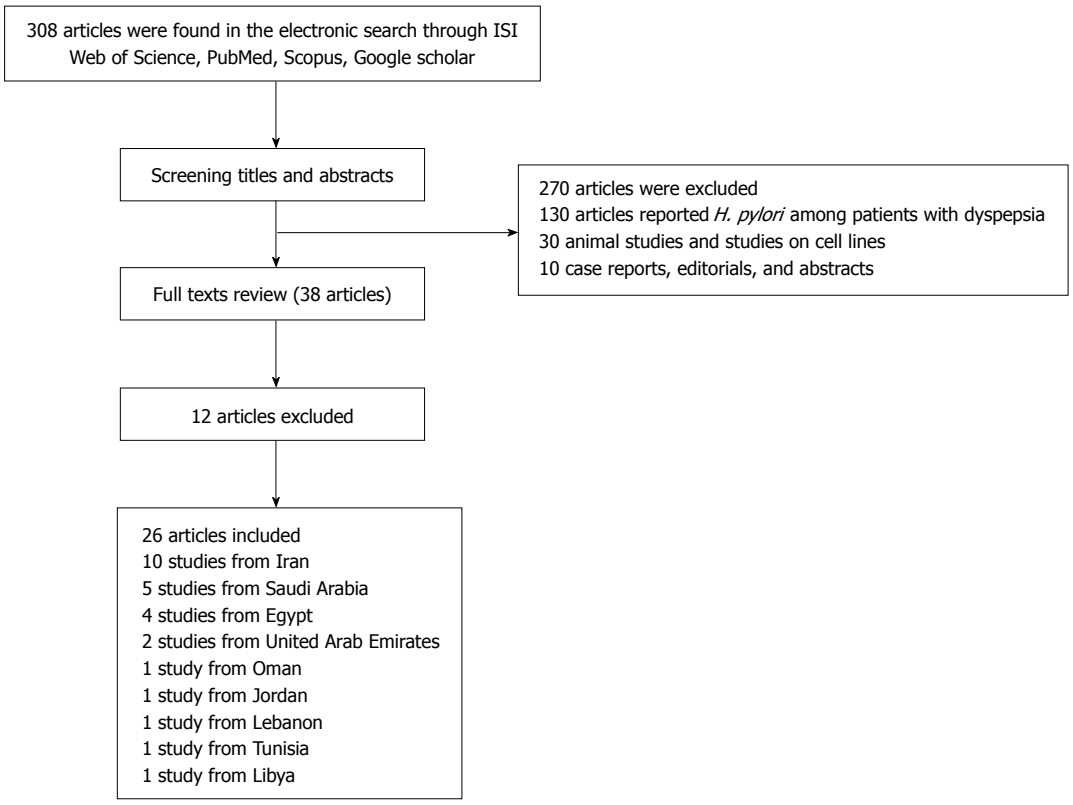

Figure 1 Flow diagram of the study. *H. pylori*: *Helicobacter pylori*.

estine, Qatar, Somalia, Sudan, Syria, and Yemen on the prevalence of *H. pylori* in healthy populations.

Prevalence and risk factors of H. pylori infection in Iran

In total, 10 relevant articles from different geographical areas in Iran were included. Seven studies used enzyme-linked immunosorbent assay IgG-Ab for detection of *H. pylori* and 3 studies used stool antigen. There were 8459 participants in these 10 studies (3575 males and 4172 females; one study did not report gender). The age of the patients ranged from 4 mo to 83 years. These studies were conducted from 1997 to 2010. The overall prevalence of *H. pylori* infection, irrespective of time and age group, ranged from 30.6% to 82%. The prevalence of Anti-Cag A positivity was reported in 3 studies, and ranged from 57.7% to 72.8% (Table 1). The results regarding risk factors were conflicting; however, higher age, female sex, larger family size, source of water supply, level of education and hygiene practice were associated with *H. pylori* infection in different populations. Interestingly, residing in urban or rural areas was not among the independent risk factors for *H. pylori* infection, while anti-Cag A positivity was reported to increase with increasing age and in male gender, and this was higher in subjects aged < 30 years in one study (Table 2).

Prevalence and risk factors of H. pylori infection in other countries of the Eastern Mediterranean region

There were 16 studies from other countries in the eastern Mediterranean region: Saudi Arabia (5 studies), Egypt (4 studies), Jordan (1 study), Libya (1 study), UAE (2 studies), Tunisia (1 study), Lebanon (1 study) and Oman (1 study). Of these, (ELISA) IgG-Ab was used for the detection of *H. pylori* in 13 studies. One study from Lebanon used stool antigen and one study form Saudi Arabia used saliva IgG-Ab for the detection of *H. pylori* infection. In total, 5233 participants were included in these 16 studies. These studies were conducted between 1989 and 2013 among individuals aged 1 mo to 97 years. The overall prevalence of *H. pylori* infection, irrespective of time and age group, ranged from 22% to 87.6%. Living in rural areas, poor sanitation, overcrowding, lower educational level, and low socioeconomic status were independent risk factors for *H. pylori* infection in different countries of the EMRO (Table 3).

DISCUSSION

As *H. pylori* is known to be the responsible pathogen in several gastrointestinal disorders, especially gastric cancer, understanding the epidemiology of *H. pylori* in different regions is of great importance. More than 60% of gastric cancers occur in developing countries with great variations in different geographical areas[38]. Geographical variations in the prevalence of *H. pylori* have been established not only in different countries from different regions of the world, but also within regions of a single country. In Ardabil, which has the highest incidence of gastric cancer in Iran, the prevalence of *H. pylori* among adults aged 40 years and over was estimated to be as high as 90% using

Table 1 Prevalence of *Helicobacter pylori* infection in the Iranian population

Ref.	Year	Location	Age group	Number (M/F)	Prevalence	Prevalence (%) (M/F)	Method of detection
Alborzi *et al*[12]	2005	Shiraz (Southern Iran)	8 mo-15 yr	593 (308/284)	82.0%	81/83	Stool antigen
Nouraie *et al*[13]	2009	Tehran	18-65 yr	2326 (968/1358)	69.0%	67.6/70.0	ELISA IgG-Ab
Jafarzadeh *et al*[14]	2005	Rafsanjan (Southeast Iran)	1-15 yr	386 (187/199)	46.6%	51.9/41.7	ELISA IgG-Ab
Jafarzadeh *et al*[15]	2005	Rafsanjan (Southeast Iran)	20-60 yr	200 (114/86)	67.5%	71.9/61.6	ELISA IgG-Ab
Alizadeh *et al*[16]	2003	Nahavand (Western Iran)	≥ 6 yr	1518 (653/865)	70.6%	66.6/73.4	ELISA IgG-Ab
Ghasemi Kebria *et al*[17]	2010	Golestan province (Northeast Iran)	1-83 yr	1028 (489/539)	66.4%	66.3/66.6	ELISA IgG-Ab
Jafar *et al*[18]	2007	Sanandaj (Western Iran)	4 mo-15 yr	458 (231/227)	64.2%	65/63	Stool antigen
Mikaeli *et al*[19]	1997	Ardebil and Yazd (Northwest and Central Iran)	< 20 yr	711 (NA)	47.5% (Ardebil) 30.6% (Yazd)	NA	ELISA IgG-Ab
Mansour-Ghanaei *et al*[20]	2007	Rasht (Northern Iran)	7-11 yr	961 (475/486)	40.0%	49.7/50.3	Stool antigen
Mahram *et al*[21]	2004	Zanjan (Western Iran)	7-9 yr	278 (150/128)	52.8%	56.0/50.7	ELISA IgG-Ab

M: Male; F: Female; ELISA: Enzyme- linked immunosorbent assay; Ab: Antibody; NA: Not available.

Table 2 Risk factors for *Helicobacter pylori* infection and prevalence of Anti-Cag A seropositivity in the Iranian population

Ref.	Prevalence of Anti-Cag A	Main findings and risk factors
Alborzi *et al*[12]	NA	The prevalence of *H. pylori* was significantly lower in the 15-yr-old age group compared to the < 14-yr-old age group Sex was not a risk factor for prevalence
Nouraie *et al*[13]	NA	Higher maternal education was protective against *H. pylori* infection Low education, increasing age and overcrowding were risk factors for *H. pylori* infection
Jafarzadeh *et al*[14]	72.8%	Prevalence of Anti-Hp IgG and Anti-Cag A Ab were increased with age
Jafarzadeh *et al*[15]	67.4%	Prevalence of Anti-Cag A Ab was higher in males than females Prevalence of Anti-Cag A Ab was higher in those < 30 yr
Alizadeh *et al*[16]	NA	Female sex and age (median 37 yr) were risk factors for *H. pylori* infection Hygienic practice and crowding were not risk factors for *H. pylori* infection
Ghasemi Kebria *et al*[17]	57.7%	No significant difference between rural and urban areas regarding prevalence Seroprevalence increased with increasing age
Jafar *et al*[18]	NA	Larger family size was associated with higher prevalence Increasing age was associated with *H. pylori* infection
Mikaeli *et al*[19]	NA	Increasing age was the only predictor of *H. pylori* infection
Mansour-Ghanaei *et al*[20]	NA	Water supply was a predictor of *H. pylori* infection
Mahram *et al*[21]	NA	Age and sex were not risk factors for *H. pylori* infection

NA: Not available; *H. pylori*: *Helicobacter pylori*.

the rapid urease test and histopathology[39,40]. This study confirmed a parallel increase in the rate of gastric cancer with increased incidence of *H. pylori*.

In the current study, the epidemiology of *H. pylori* infection among the asymptomatic healthy population of Iran and other countries in the EMRO region was reviewed. In Iran, 2 studies reported the prevalence of *H. pylori* infection among healthy asymptomatic adults (> 18 years). The prevalence of *H. pylori* infection among asymptomatic healthy adults in Tehran, the capital of Iran, was estimated to be 69% using ELISA[13]. In this study, low education, increasing age, and overcrowding were risk factors for *H. pylori* infection[13]. In another study conducted in Kerman province (southern Iran), the seroprevalence of *H. pylori* infection among healthy adults was 67.5% which is comparable to the prevalence in a previous report[15]. Based on the results of the present review, the prevalence of *H. pylori* in the pediatric age group in Iran seems to be more diverse than in adults. This may be secondary to the different methods of *H. pylori* detection or different inclusion criteria regarding the age of the study population. However, it should be noted that different sanitary, cultural and educational levels in different Iranian provinces may have an important role in this pattern. This important point should be interpreted cautiously. For instance, Alborzi *et al*[12] reported a *H. pylori* prevalence of 82% using stool antigen in Shiraz, a municipal city in southern Iran which is a medical referral center with good sanitary facilities. On the other hand, the prevalence was much lower in other areas with fewer sanitary facilities than Shiraz. The prevalence of *H. pylori* in the asymptomatic pediatric age group in Rafsanjan, southern Iran, was reported to be 46.6%[14]. In four other studies on healthy pediatric age groups, the prevalence of *H. pylori* was reported to range from 40% to 65%[18-21].

In other countries of the EMRO, Egypt had the highest prevalence of *H. pylori* in the healthy asymptomatic population both in adults and the pediatric age group[28,29,31]. Low socioeconomic status, low body weight and height, living in rural areas and lower educational

Table 3 Prevalence and risk factors of *Helicobacter pylori* infection in the healthy population of Eastern Mediterranean Regional Office countries

Ref.	Year	Country	Age group	Number	Prevalence	Method of detection	Risk factors
Bani-Hani *et al*[22]	2006	Jordan	1-9 yr	200	55.5%	ELISA IgG-Ab	Living in rural areas, poor sanitation, overcrowding, low maternal educational level, low socioeconomic status
Naous *et al*[23]	2007	Lebanon	1 mo-17 yr	414	21.0%	Stool antigen	Low socioeconomic status, overcrowded houses, lower family income and poor parental education
Bakka *et al*[24]	2002	Libya	1- > 70 yr	360	76.0%	ELISA IgG-Ab	Low socioeconomic status, low educational level
Mansour *et al*[25]	2010	Tunisia	Any age	250	64.0%	ELISA IgG-Ab	NA
Bener *et al*[26]	2000	UAE	Any age	223	78.4%	ELISA IgG-Ab	NA
Bener *et al*[27]	2006	UAE	Any age	151	74.1%	ELISA IgG-Ab	Unavailable drinking water, low educational level, long working duration, BMI > 25, housing conditions
Salem *et al*[28]	1993	Egypt	< 30 yr	89	87.6%	ELISA IgG-Ab	NA
Mohammad *et al*[29]	2007	Egypt	6-15 yr	286	72.38%	UBT	Low socioeconomic status, low body weight and height, living in rural areas
Naficy *et al*[30]	1997	Egypt	< 36 mo	187	10.0%	ELISA IgG-Ab	Only age (6-17 mo)
Bassily *et al*[31]	1992	Egypt	17-42 yr	169	88.0%	ELISA IgG-Ab	Lower level of education
Al Faleh *et al*[32]	2007	KSA	16-18 yr	1200	47.0%	ELISA IgG-Ab	Being female Residing in Medina region
Hanafi *et al*[33]	2012	KSA	Any age	456	28.3%	ELISA IgG-Ab	Rural residence, crowded housing, low socioeconomic status, use of tanks for drinking water supply, active smoking, alcohol drinking, eating raw vegetables, eating spicy food, presence of asthmatic/atopic symptoms
Khan *et al*[34]	2003	KSA	15-50 yr	396	51.0%	ELISA IgG-Ab	Higher age
Al-Moagel *et al*[35]	1989	KSA	5-90 yr	364	66.0%	ELISA IgG-Ab	Higher age
Al-knawy *et al*[36]	1999	KSA	2-97 yr	355	67% Mother 64% Father 23% Children	Saliva IgG-Ab	The infection was higher in infants when both parents were positive
Al-Balushi *et al*[37]	2013	Oman	15-50 yr	133	69.5%	ELISA IgG-Ab	Increasing age Being male

ELISA: Enzyme-linked immunosorbent assay; Ab: Antibody; NA: Not available; UAE: United Arab Emirates; KSA: Kingdom of Saudi Arabia; UBT: Urea breath test.

status were risk factors for the acquisition of *H. pylori* in Egyptian studies[29]. In Saudi Arabia, there has been a decline in the prevalence of *H. pylori* in the past ten years according to recent reports[33]. Although this decline may be the result of improvements in sanitary conditions, it may be secondary to different methods of *H. pylori* detection in different studies. Rural residence, crowded housing, low socioeconomic status, the use of tanks for drinking water supply, active smoking, alcohol drinking, eating raw uncooked vegetables, and eating spicy food were risk factors for *H. pylori* infection in Saudi Arabia[33]. In other countries of the Persian Gulf region, a prevalence of 74%-78% was reported from the United Arab Emirates[26,27] and 70% from Oman[37]. In North African countries, data were available for Libya and Tunisia with an estimated prevalence of 76% and 64%, respectively[24,25].

It should be emphasized that these studies are not concordant regarding the time of study, age of the population and methods of *H. pylori* detection. Therefore, comparisons of different countries should be made cautiously. However, it is noteworthy that the prevalence is declining with time even in these developing countries. This is compatible with other reports from other parts of the world[41].

Invasive tests for *H. pylori* detection include histology[42], culture[43], the rapid urease test[44], and molecular studies[45]. These tests have high specificity and sensitivity, but cannot be used for the detection of *H. pylori* in the healthy asymptomatic population. Non-invasive tests including serology[46], stool antigen[47] and the UBT[48] are also available with different sensitivities and specificities. While serology is the most widely available test for *H. pylori* detection, the sensitivity of stool antigen and UBT is higher[49]. Therefore, there is no consensus on the gold standard test for *H. pylori* detection. The studies in this review also used serology or stool antigen testing as non-invasive methods of *H. pylori* detection.

As reflected in the tables, the overall prevalence was lower in children, and childhood is probably the primary period of acquisition of *H. pylori*[50,51]. Transmission occurred during childhood *via* the oral-oral or fecal-oral route[52,53]. Transmission between siblings has also been demonstrated as an important route of transmission[54].

Several treatment regimens have been introduced with different results in different populations[55]. Antibiotic resistance, patient compliance, and environmental factors are among the major factors in eradication failure[56]. Therefore, understanding the epidemiologic burden of *H. pylori* infection is also critical for programming eradication strategies.

EMRO countries are a group of developing countries located in southwest Asia and North Africa. *H. pylori* prevalence in EMRO countries is still high in the healthy asymptomatic population. Strategies to improve sanitary

facilities, educational status, and socioeconomic status should be implemented to minimize *H. pylori* infection.

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COMMENTS

Background

Helicobacter pylori (*H. pylori*) is a gram negative, non-spore forming spiral bacterium which colonizes the human stomach and is prevalent worldwide. It has been associated with peptic ulcer disease, gastric adenocarcinoma, and type B low-grade mucosal-associated lymphoma. Furthermore, the organism is also suspected to be involved in other human illnesses such as hematologic and autoimmune disorders, insulin resistance and the metabolic syndrome.

Research frontiers

Nearly 50% of the population is infected with *H. pylori* worldwide, and the prevalence, incidence, age distribution and sequels of infection are significantly different in developed and developing countries. The prevalence of *H. pylori* infection is decreasing in both developed and developing countries; however, the prevalence is still high in developing countries. In Argentina, the prevalence of a positive urea breath test declined from 41.2% during 2002-2004 to 26% during 2007-2009 among children. Furthermore, the age of infection acquisition is lower in developing countries compared with industrialized nations. It has been estimated that more than 50% of the population aged 5 years is infected and this rate may exceed 90% during adulthood. In a cohort of Brazilian children, the prevalence of *H. pylori* was 53.4% at baseline and 64.7% 8 years later.

Innovations and breakthroughs

There are no systematic reviews on the prevalence and epidemiology of *H. pylori* in this geographically important region of the world. This study is a comprehensive review of the epidemiology of *H. pylori* infection in this area.

Applications

Understanding the epidemiological aspects of *H. pylori* infection is important and helpful in clarifying the consequences and complications of this infection, and is also fundamental for eradication, treatment, and the pattern of antibiotic resistance.

Peer review

This review on prevalence and risk factors of *H. pylori* infection is well written and covered up-to-date information regarding epidemiology among healthy population in Iran and countries of Eastern Mediterranean Region.

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