THE GEOGRAPHIC VARIANCE OF *HELICOBACTER PYLORI* INFECTION IN EUROPE AND ITS IMPACT ON THE INCIDENCE OF GASTRIC CANCER

***Ayse Nilüfer Özaydın**

Department of Public Health, Medical Faculty, Marmara University, Istanbul, Turkey
**Correspondence to nozaydin@gmail.com*

Disclosure: No potential conflict of interest.
Received: 04.05.14 **Accepted:** 12.08.14
Citation: EMJ Gastroenterol. 2014;3:94-102.

ABSTRACT

The discovery of *Helicobacter pylori* was hopeful as this agent was included in the list of 'preventable-infectious carcinogens', and many non-treatable gastroduodenal disorders with uncertain causes became treatable infectious diseases. Nevertheless, nowadays frequent antibiotic resistance is observed among *H. pylori* infections, sometimes as high as 95%. *H. pylori* is a bacteria that existed for a very long time, which was only recognised in the last 30 years. It can cause a variety of symptoms leading to gastroduodenal disorders from chronic inflammation in the gastrointestinal system to non-cardia gastric cancer. It is acquired in the early years of life and infection is commonly lifelong. The accepted primary route of transmission is person-to-person contact because humans are the only known significant reservoir of *H. pylori.* The target cell of *H. pylori* is the gastric mucus secreting cell. The prevalence in Europe shows a huge variety with almost all studies showing a decreasing trend. During childhood the highest prevalence was from Turkey (56.6%) and the lowest was from Czech Republic (4.8%). Among adults, the overall prevalence was found to be between 18.3% (Denmark) and 82.5% (Turkey), with substantial country-to-country variations. The prevalence rate differs by socioeconomic lifestyle characteristics and also genomic structure; it is also higher in less developed countries/populations. While the more commonly used test to determine *H. pylori* infection is serology, immunoglobulin G by enzyme-linked immunosorbent assay, the urea breath test (UBT), and stool antigen testing are non-invasive tests which are also recommended.

Keywords: Prevalence, childhood, adulthood, European countries, gender, alcohol consumption.

INTRODUCTION

At the beginning of the 1990s *Helicobacter pylori* was placed in the potential human carcinogen list by International Agency for Research on Cancer because of a causal link showing it to cause non-cardia gastric carcinoma.[1] It is estimated that the cancer cases caused by infectious agents amount to 20% in total. Among these agents, the highest proportion belongs to *H. pylori* with 37% of the causes (Figure 1).[2] The cancer frequency is consistently increasing throughout the world. The ratio of cancers caused by infectious agents is estimated to be around 23% in developing countries, whereas this ratio is close to 7% in developed countries. If these cancer-causing infectious agents can be controlled or treated, 26% of cancer cases in developing countries and 8% in developed countries can be prevented.[1,3]

H. pylori was described by Barry Marshall and Robin Warren with the successful isolation and culture.[4,5] *H. pylori* can colonise the human stomach and induce inflammation of the gastric mucosa.[6] It is accepted that *H. pylori* can cause chronic gastritis, peptic ulcer disease, gastric mucosa-associated lymphoid tissue lymphoma, and gastric cancer.[7] *H. pylori* as an infectious agent has been claimed to be acquired during childhood, stay in latency for long periods of time, and cause gastric diseases in advanced adult ages. Where the morbidity rate of *H. pylori* is high, the mortality rate is low.[8] *H. pylori*

infections can be diagnosed by a variety of tests and usually treated with antibiotic use.[9] However, recent increase in antibiotic resistance among *H. pylori* is starting to affect the successful treatment, and preventive vaccinations still do not exist.[6] Even with the increasing attention to *H. pylori*, the transmission route, acquisition, and loss of *H. pylori* are not understood completely.[8,10] The prevalence of *H. pylori* in the developing world is widespread even though a decreasing trend is observed in developed Western countries. This review is going to focus on the prevalence of *H. pylori* infection in childhood and adulthood periods in Europe, with the aim of aiding the understanding of infection and related risk factors, through the basic information available to the writer and with the main interest on large scale, population-based studies since 2000.

Characteristics of *H. pylori*

H. pylori is a highly heterogeneous bacterium showing a large genomic diversity.[1] Humans with multiple strains have been observed, and during colonisation of a single host, the bacterium can genotypically and phenotypically change.[11] *H. pylori* genotypes were found to be diverse in different geographic areas, especially cagA and vacA. Strains from Western countries predominantly possessed cagA Type 2a, vacA s1a or s1b/m1a, or vacA m2a genotypes, whereas strains from East Asia possessed cagA Type 1a, vacA s1c/m1b, or vacA m2b genotypes. Studies from Turkey, which has the highest *H. pylori* prevalence, showed that Turkish strains predominantly possessed cagA Type 2a, vacA s1a/m1a, or vacA m2a genotypes, which were typical genotypes in strains from Western countries.[12] The presence of duodenal ulcer and gastric cancer were found significantly related with *H. pylori* vacA s1a, cagA, and cagE genotypes. On the other hand, cagE and vacA s1a genotypes are independent predictors of duodenal ulcer, and babA2 and cagE genotypes are independent predictors of gastric cancer.[13] Production of immunoglobulin A (IgA) antibodies has also been associated with a CagA-positive infection, which is associated, in turn, with an increased risk of severe complications, such as gastric cancer. In a study of Finnish adults, maturation of the IgA response in *H. pylori* infection in adulthood (both as an increased number of IgA responders and in rising antibody titres) was presented, whereas the IgG titres in children have disappeared in adulthood.[14]

H. PYLORI PREVALENCE AND GEOGRAPHIC DISTRIBUTION

Predominantly, the recent population-based and large scale studies were taken into consideration for this review. This was not an easy task, mainly because they cannot be compared in reality as they are so different from each other; for example study types, study populations, selection methods of sampling, and also tests used to define the *H. pylori* status. Several non-invasive *H. pylori* tests are established in clinical routine.[9] The Maastricht IV/Florence Consensus report declared that the urea breath test (UBT) using 13C urea remains the best test to diagnose *H. pylori* infection, has a high accuracy, and is easy to perform. Stool antigen test is regarded as an equivalent to the UBT and, from a diagnostic accuracy standpoint, a monoclonal test from a validated laboratory is used.

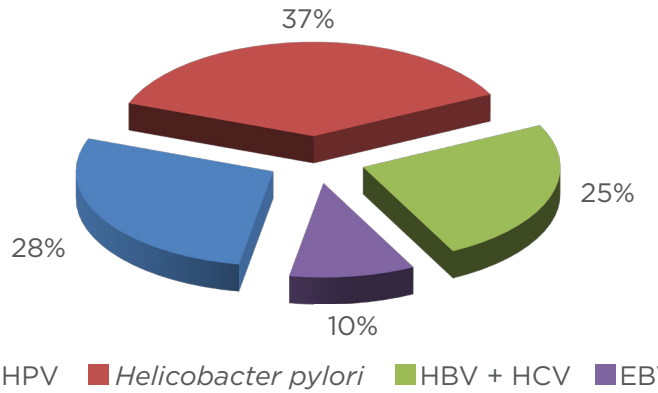

Figure 1: Cancers due to five infectious agents (correspond to 18.6% of total cancer incidence).[2]
HPV: human papilloma virus; HBV: hepatitis B virus; HCV: hepatitis C virus; EBV: Epstein–Barr virus.

Table 1: The prevalence of *Helicobacter pylori* in childhood, in various countries, after 2000.

H. pylori (+)%	n	Average age/ Age groups (years)	Diagnostic Test	Study population	Country	Reference
31.6	844	0-15	Stool test	Asymptomatic children	Portugal	Oleastro et al.[16]
15.8	284	1-14	Stool test	Descriptive	Spain	Leandro Liberato et al.[17]
9: 2005/2006 9: 1993 19: 1978	545	7-9 6-8	Serology	Birth cohort study	Netherlands	Den Hoed et al.[18]
1.2 0.5 (Dutch parents) 2.6 (non-Dutch parents)	1,258	2-4	Serology	A serum bank of 6,127 children who attended the community child healthcare centres in the Dutch province of Zuid-Holland.	Netherlands	Mourad-Baas et al.[19]
6.5: 2006 5.7: 2000 6.1: 1998	1,905	School children School starters-8th Grade students	UBT	Long-term, follow-up study	Germany (Leipzig)	Bauer et al.[20]
27	137	1-4	Stool assay	1 year follow-up of asymptomatic Turkish children on whom participating pediatricians had performed routine health screening Sept. 1997-Oct. 1998	Germany	Rothenbacher et al.[21]
4.8 (≤15 years)	1,837	5-98	UBT*	General population (22 cities)	Czech Republic	Bures et al.[22]
7.1	1,545	0-15	Stool test	Cross-sectional	Czech Republic	Sykora et al.[23]
56.6: 2004 49.5: 1998 14%: incidence rate 5.5%: loss rate	327	3-12 13.5 mean age	UBT	Cohort of healthy school children	Turkey	Özen et al.[24]
66.3: 2000 78.5: 1990	219 184	7-14	Serology	Cohort of primary school, healthy children	Turkey (Ankara)	Ozden et al.[25]
43.9 Father: 76.3 Mother: 85.4	346	Children	Serology	Descriptive healthy children	Turkey (Eastern Turkey)	Yılmaz et al.[26]
13: 2005 44: 1995	370 307	2-19	Serology	Cross-sectional	Russia (St Petersburg)	Tkachenko et al.[27]
28.1 42.2	296: 2002 425: 1991	Children	Serology	Hospital based	Estonia	Oona et al.[28]

*The cut-off point was 3.5 for urea breath test (UBT) test.

Table 2: *Helicobacter pylori* prevalence in adults according to various European countries after 2000.

H. pylori (+)%	n	Average age/ Age groups (years)	Test	Study population	Country	Reference
71.3	430	Adults	Serology	Hospital based controls	Spain	Sanjose et al.[29]
40.0	407	49-51	Serology	The birth cohort	UK	Pearce et al.[30]
2	3,928	50-59	UBT	Cross-sectional	UK	Ford et al.[31]
15.5	10,537	20-59	UBT	Cross-sectional	UK	Lane et al.[32,33]
14	10,118	1-84	Serology	Cross-sectional	UK	Vyse et al.[34]
27.5	8,455	40-49	UBT	Randomised clinical trial	UK	Moavyedi et al.[35]
37.7	22,612	All age group	Gastric biopsy	In medical centre	Belgium	Miendje[36]
15.2: 2007 36.2: 1988	11,238	Adults	Gastric biopsy	Western European patients		
40.0: 2007 71.7: 1988	3,200	Adults	Gastric biopsy	North African patients		
18.3: 2009 20.1: 2003	36,629	42 median age 26-56	UBT	Primary health care level	Denmark	Dahlerup et al.[37]
17.5 (Eradication rate 95%)	20,000	40-65	Serology + UBT	Randomised clinical trial	Denmark	Christensen et al.[38]
24.7	2,527	Adults	Serology	Population based study	Denmark	Rosenstock et al.[39]
35.0	117	16-40 30.9	Serology	Nested case control	Sweden	Persson et al.[40]
40.0	499	51-79 69	Serology	Case-control	Sweden	Yee et al.[41]
25	1,030	17-79 50.5	Serology	Cross-sectional	Sweden	Sörberg et al.[42]
79.2	3,564	17-99 54 median age	Serology	Cross-sectional, General population	Latvia	Leja et al.[43]
51.9	9,953	63 '50-74'	Serology	Population based	Germany	Schöttker et al.[44]
44.4	2,318	0-30	Serology	Hospital based, Patients	Germany	Wex et al.[45]
40.7	6,545	18-79	Serology	Cross-sectional	Germany	Kuepper-Nybelen et al.[46]
23.5 39.8: ≥55 years	1,837	5-98	UBT*	General population (22 cities)	Czech Republic	Bures et al.[47]
41.7	2,509	5-100	UBT	Cross-sectional, 19 GP centre	Czech Republic	Bures et al.[48]
35	1,838	≥18	UBT*	Workplace	Slovak Republic	Kuzela et al.[49]
63.8 M:73.5/ FM:63.8	960	18-60 36.8	Serology	Employees in a company	Romania	Sporea et al.[50]
82.5	4,622	≥18	UBT	Cross-sectional	Turkey	Ozaydin et al.[15]
63	200	21.4	Stool test	Descriptive	Turkey	Yucel T et al.[51]

UBT: urea breath test; GP: general practitioner.

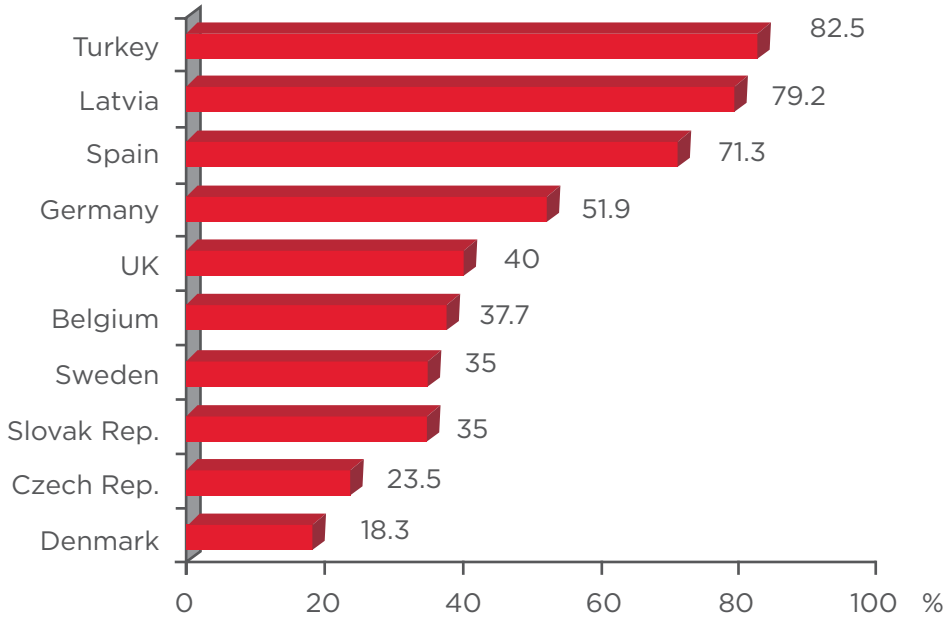

Figure 2: The prevalence of *Helicobacter pylori* in adults in Europe after 2000 according to various countries (the latest results from published literature were presented in the graph).

The third commonly used method to diagnose *H. pylori* infection is serology and, given the chronic status of the infection, IgG detection by enzyme-linked immunosorbent assay is favoured. Another problem that must be mentioned is the relative lack of large scale, population-based, representative, cross-sectional studies. One of the population-based, representative studies was done by Ozaydin et al.,[15] where the sample was selected throughout the country. All related studies listed in this review, in Tables 1 and 2 were published about European countries after 2000, considering the frequency of *H. pylori* infection in childhood and adulthood.[15-51]

European Prevalence of *H. pylori* in Childhood

In Europe, after 2000, as far as the author can reach, there were few large scale studies about *H. pylori* prevalence in childhood (Table 1). Among the present studies, according to the latest one from each country, the highest prevalence was found in Turkey[24] (56.6% among 3-12 years), the lowest seroprevalence rate was from Czech Republic[22] with 4.8% ≤15 years. However, there was a huge range between the prevalence of countries in Europe, with almost all of them showing a decreasing trend.[16-28]

European Prevalence of *H. pylori* in Adulthood

A great diversity of *H. pylori* infection prevalence among adults in Europe has been recorded since 2000, with an overall prevalence for adulthood being between 18.3-82.5%, with substantial country-to-country variations (according to the latest literature from each country; Table 2, Figure 2).[15,21-51] The highest prevalence of 82.5%, for adults aged ≥18 years was measured by the UBT test in Turkey, by a population-based, nationally representative, cross-sectional study (n=4,622),[15] whereas the lowest prevalence of *H. pylori* was found in Denmark, by UBT test, as 18.3%, at the primary healthcare level.[33]

The Role of Family Members in the Acquisition of *H. pylori* Infection

H. pylori infection is acquired usually after the first year of life and persists, at least, for decades.[1,8,42] Under the conditions of poor hygiene, gastrointestinal microbes have been easily transmitted. Still, such enteric transmission occurs in some developing countries as *H. pylori* are ubiquitous, and their presence is possibly nearly universal. Oral-oral, faecal-oral, waterborne, and iatrogenic routes are usually accepted ways of transmission of *H. pylori*. Because humans are the only known significant reservoir, intra-familiar clustering, person-to-person transmission, appears to be the predominant mode of transmission.[1,4] Risk factors for *H. pylori* transmission can be listed such as crowded family, parents (especially mothers) with *H. pylori*, *H. pylori*-positive older siblings, and household crowding during childhood. In Sweden,

Kivi et al.[52] studied *Helicobacter* status in family members as risk factors for infection in children, and showed that *H. pylori* infections in mothers and siblings in high prevalence countries stand out as strong factors for infection risk, although birth in high prevalence countries was an independent risk factor. The role of infected parents with *H. pylori* infection was also studied; an infected mother is shown to be a much stronger risk factor for childhood infection than an infected father.[21,53] The evidence about infected parents showed that mothers especially may play a key role in the transmission of *H. pylori* to the children.[21,53] It was found that sibling number in the household was independently associated with prevalence of *H. pylori* infection; whereas prevalence of infection in those with no siblings was 20%, it was 63% with eight or more siblings.[31]

Reasons behind the Inter-Country Variation

Different *H. pylori* subtypes in different countries

It is known that a clear phylogeographic differentiation exists between *H. pylori* strains from different geographic areas to an extent that it is possible to use these strains as a marker of the origins of various ethnic populations.[12,13,54] The virulence gene cagA, and vacA genotypes in particular, differ in different geographic areas, and are commonly used as markers. However, the difference between strains is not sufficient to explain the difference of prevalence between the countries in Europe.

Significant sociodemographic differences

Low prevalence rates in developed countries, high prevalence rates in developing countries, and even prevalence rate differences between regions in the same countries, are reported based on the different sociodemographic and socioeconomic levels (Tables 1 and 2, and Figure 2).

The effect of birth cohorts

The prevalence rate is decreasing with each new year, but this decrease is not parallel in different countries. Highly organised population-based screening projects were implemented in a small number of European countries, and antibiotic treatment was administered to the small number of positives in these screening projects.[32,33,35,38] This was not advised by their researchers, even with the indication number being too high, as the dyspepsia treatment and overall life quality improvement was negligible. However, during these screening projects, positives were administered antibiotics and 95% of the *H. pylori* infections were eradicated. If the fact that the only host of *H. pylori* is humans is taken into account, this might be accounted for as a very important intervention to the chain of infection.

Antibiotic resistance

After identification by Warren and Marshal, *H. pylori* was supposed to be eradicated by antibiotics easily. However, until the present time, the prevalence of *H. pylori* gradually decreased, yet infection is still common in some countries.[15] Two antibiotics (amoxicillin and clarithromycin) plus a proton pump inhibitor, given for 1 or 2 weeks, has been recommended as the treatment of *H. pylori*.[6,9,55] However, failure of this treatment was reported due to antibiotic resistance. Clarithromycin, metronidazole, tetracycline, fluoroquinolones, and rifampicin resistance has recently become an emerging issue. Although the prevalence of antimicrobial resistance shows variation even among regions per antibiotic, antibiotic resistance in *H. pylori* is widespread, and it can be as high as 95% in some cases. For example, metronidazole resistance is around 35% in developed countries, yet it varies between 20-95% in developing countries. For example, *H. pylori* prevalence is very high in Turkey, and 27.5-40.5% resistance to clarithromycin and up to 85% resistance to metronidazole has been reported.[56,57]

The causes of resistance are not known exactly, but widespread consumption of antibiotics could be one of the reasons. Also, there might be some factors related with antibiotics unknowingly consumed with food. Antibiotics are widely used in pasture animals and recently about 80% of antibiotics produced in the US are given to farm animals for enhanced growth.[58] In addition, usage of recombinant bovine growth hormone is a known side-cause of mastitis, and widespread antibiotic treatment for mastitis is known in milk production.[59] It is hypothesised that this side consumption of antibiotics may contribute to emerging antibiotic resistance.

Alcohol consumption variations

In a study done in the UK by Murray et al.[60] in 2002, higher wine consumption was found to lower *H. pylori* risk by 11%, and a similar effect was confirmed for beer consumption. In 2005, Kuepper-Nybelen

et al.[61] reported that alcohol consumption may facilitate elimination of *H. pylori* infection among adults, and a similar trend is reported by Ozaydin et al.[15] in 2013, in Turkey. Alcohol consumption was reported to be 7.4% in male Turkish adults, and subsequently *H. pylori* risk is found to be 2.18-times higher in adult males who never drink alcohol. However, alcohol and tobacco use for women are not found to be related to *H. pylori* infection risk, maybe because alcohol and tobacco use were so low in Turkish women (1%).[15] Interestingly, in countries with high *H. pylori* infection, the consumed alcohol amounts are low, whereas in communities with low and decreasing *H. pylori* prevalence rates, alcohol consumption is high and increasing. This might have contributed to the decrease in *H. pylori* prevalence.

Citrus fruit consumption

An interesting result was found in Turkey; people in the South of Turkey have the least *H. pylori* prevalence, whereas the Western region is more developed, have better housing conditions, and smaller family size. In the Southern region of Turkey, oranges, lemons, tangerines, and bitter oranges are produced. People eat them or drink their fresh juices all year round because they are cheap and plentiful. *H. pylori* may not survive in acidic gastric conditions produced by the acidic citrus fruits.[15,62,63]

CONCLUSION

H. pylori are unique bacteria that are known to cause cancer, yet our knowledge and understanding of this organism is far from complete, or even satisfactory. Modes of transmission are all studied extensively, but the evidence remains rare and uncertain. According to the present evidence, the prevalence of *H. pylori* infection in Europe shows a huge variety, with almost all studies showing a decreasing trend. The genomic structure of *H. pylori* has been reported from different geographic regions; strains from Western countries, which have lower incidences of gastric cancer, predominantly possessed cagA Type 2a, vacA s1a or s1b/m1a, or vacA m2a genotypes, whereas strains from East Asia, which has a higher incidence of gastric cancer, possessed cagA Type 1a, vacA s1c/m1b, or vacA m2b genotypes. As is the case with many gastrointestinal system infectious agents, many choices exist for treatment, yet most of these treatment approaches for *H. pylori* have a 20% failure rate, as well as emerging antibiotic resistance. Under the light of these points, research on knowing this organism from a better standpoint, the roots of transmission, and even on the survival of this bacteria is elemental, as this new understanding may be employed to explain and comprehend the differences in prevalence of infection and incidence of gastric cancer between different regions and communities.

REFERENCES

1. Tomatis L (ed.), A Review of Human Carcinogens. IARC Monographs on the evaluation of carcinogenic risks to humans, Biological Agents (2012), Volume 100B, Lyon: International Agency for Research on Cancer, pp. 1017-606.
2. Zur Hausen H. The search for infectious causes of human cancers: where and why? Virology. 2009;392(1):1-10.
3. de Martel C et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. Lancet Oncol. 2012;13(6):607-15.
4. Egan BJ, O'Morain CA. A historical perspective of Helicobacter gastroduodenitis and its complications. Best Pract Res Clin Gastroenterol. 2007;21(2):335-46.
5. Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet. 1984;1(8390):1311-5.
6. Gerritis MM et al. Helicobacter pylori and antimicrobial resistance: molecular mechanisms and clinical implications. Lancet Infect Dis. 2006;6(11):669-709.
7. Flora SD, Bonanni P. The prevention of infection-associated cancers. Carcinogenesis. 2011;32(6):787-95.
8. Malaty HM. Epidemiology of Helicobacter pylori infection. Best Pract Res Clin Gastroenterol. 2007;21(2):205-14.
9. Malfertheiner P et al. Management of Helicobacter pylori infection—the Maastricht IV/ Florence Consensus Report. Gut. 2012;61(5):646-64.
10. Kusters JG et al. Pathogenesis of Helicobacter pylori infection. Clin Microbiol Rev. 2006;19(3):449-90.
11. Suerbaum S, Josenhans C. Helicobacter pylori evolution and phenotypic diversification in a changing host. Nat Rev Microbiol. 2007;5(6):441–52.
12. Saribasak H et al. Genotypes and correlation with clinical outcome in Turkey. J Clin Microbiol. 2004;42(4):1648–51.
13. Erzin Y et al. Prevalence of Helicobacter pylori vacA, cagA, cagE, iceA, babA2 genotypes and correlation with clinical outcome in Turkish patients with dyspepsia. Helicobacter. 2006;11:574–80.
14. Salomaa-Räsänen A et al. IgA antibodies in persisting Helicobacter pylori infection in Finnish adults. Clin Microbiol Infect. 2006;12(3):236-40.
15. Ozaydin N et al. Prevalence and risk factors of helicobacter pylori in Turkey: a nationally-representative, cross-sectional, screening with the C-Urea breath test. BMC. 2013;13:1215.
16. Oleastro M et al. Prevalence and incidence of Helicobacter pylori infection in a healthy pediatric population in the Lisbon area. Helicobacter. 2011;16(5): 363-72.
17. Leandro Liberato SV et al. Helicobacter pylori infection in the child population in Spain: prevalence, related factors and

influence on growth. An Pediatr (Barc). 2005;63(6):489-94.

18. Den Hoed CM et al. Helicobacter pylori and the birth cohort effect: evidence for stabilized colonization rates in childhood. Helicobacter. 2011;16(5):405–9.

19. Mourad-Baas PE et al. Low prevalence of Helicobacter pylori infection in young children in the Netherlands. Eur J Gastroenterol Hepatol. 2007;19(3):213-6.

20. Bauer S et al. Influence of sociodemographic factors on Helicobacter pylori prevalence variability among schoolchildren in Liebzig, Germany. A long term follow-up study. Cent Eur J Public Health. 2011;19(1):42-5.

21. Rothenbacher D et al. Dynamics of Helicobacter pylori infection in early childhood in a high-risk group living in Germany: loss of infection higher than acquisition. Aliment Pharmacol Ther. 2002;16(9):1663-8.

22. Bures J et al. Significant decrease in prevalence of Helicobacter pylori in the Czech Republic. World J Gastroenterol. 2012;18(32):4412-8.

23. Sykora J et al. Epidemiology of Helicobacter pylori infection in asymtomatic children: a prospective population based study from the Czech Republic. Application of a monoclonal-based antigen in stool enzyme immunoassay. Helicobacter. 2009;14(4):286-97.

24. Özen A et al. Natural history and symptomatology of Helicobacter pylori in childhood and factors determining the epidemiology of infection. J.Pediatr Gastroenterol Nutr. 2006;42(4):398-404.

25. Ozden A et al. Changes in the seroepidemiological pattern of Helicobacter pylori infection over the last 10 years. Turk J Gastroenterol. 2004;15(3):156-8.

26. Yılmaz E et al. Seroprevalence of Helicobacter pylori infection among children and their parents in eastern Turkey. J Pediatr Child Health. 2002;38(2):183-6.

27. Tkachenko MA et al. Dramatic changes in the prevalence of Helicobacter pylori infection during childhood: a 10-year follow-up study in Russia. J Pediatr Gastroenterol Nutr. 2007;45(4): 428-32.

28. Oona M et al. Helicobacter pylori infection in children in Estonia: decreasing seroprevalence during the 11 year period of profound socioeconomic changes. Helicobacter. 2004;9(3):233-41.

29. Sanjose S et al. Helicobacter pylori and malignant lymphoma in Spain. Cancer Epidemiol Biomarkers Prev. 2004;13: 944-8.

30. Pearce MS et al. Deprivation, timing of preschool infections and H. pylori seropositivity at age 49-51 years: the Newcastle thousand families birth cohort. BMC Infect Dis. 2013;13:422.

31. Ford AC et al. Effect of sibling number in the household and birth order on prevalence of Helicobacter pylori: a cross-sectional study. Int J Epidemiol. 2007;36(6):1327-33.

32. Lane JA et al. A placebo-controlled randomised trial of eradication of Helicobacter pylori in the general population: study design and response rates in the Bristol helicobacter project. Control Clin Trials. 2002;23:321–32.

33. Lane JA et al. Impact of Helicobacter pylori eradication on dyspepsia, health resource use, and quality of life in the Bristol helicobacter project: randomised controlled trial. BMJ. 2006;332:199.

34. Vyse A.J et al. The burden of Helicobacter pylori infection in England and Wales. Epidemiol Infect. 2002;128(3):411-7.

35. Moayyedi P et al. Effect of population screening and treatment for Helicobacter pylori on dyspepsia and quality of life in the community: a randomised controlled trial. Lancet. 2000;355(9216):1665-9.

36. Miendje Deyi VY. Marching cohort of Helicobacter pylori infection over two decades (1988-2007): combined effects of secular trend and population migration. Epidemiol and Infect. 2011;139(4):572-80.

37. Dahlerup S et al. First time Urea breath tests performed at home by 36,629 patients: a study of Helicobacter pylori prevalence in primary care. Helicobacter. 2011;16(6):468-74.

38. Winder-Christensen M et al. Rates of dyspepsia one year after Helicobacter pylori screening and eradication in a Danish population. Gastroenterology. 2003;125(2):372-9.

39. Rosenstock S et al. Seroconversion and seroreversion in IgG antibodies to Helicobacter pylori: a serology based prospective cohort study. J Epidemiol Community Health. 2000;54:444-50.

40. Persson C et al. H. pylori seropositivity before age 40 and subsequent risk of stomach cancer: a glimpse of the true relationship? PLoS One. 2011;6(3):17404.

41. Ye W et al. Helicobacter pylori infection and gastric atrophy: risk of adenocarcinoma and squamous-cell carcinoma of the esophagus and adenocarcinoma of the gastric cardia. J Natl Cancer Inst. 2004;96(5):388-96.

42. Sörberg M et al. Unexpected decrease with age of Helicobacter pylori seroprevalence among Swedish blood donors. J Clin Microbiol. 2003;41(9): 4038-42.

43. Leja M et al. Prevalence of Helicobacter pylori infection and atrophic gastritis in Latvia. Eur J Gastroenterol Hepatol. 2013;24(12):1410-7.

44. Schöttker B et al. Helicobacter pylori infection, chronic atrophic gastritis and major cardiovascular events: a population based cohort study. Atherosclerosis. 2012;220(2):569-74.

45. Wex T et al. Serological prevalence of Helicobacter pylori infection in Saxony-Anhalt, Germany, in 2010. Clin Vaccine Immunol. 2011;18(12):2109-12.

46. Kuepper-NybelenJ et al. Pattern of alcohol consumption and Helicobacter pylori infection: results of a population based study from Germany among 6545 adults. Aliment Pharmacol Ther. 2005;21:57-64.

47. Bureš J et al. Significant decrease in prevalence of Helicobacter pylori in the Czech Republic. World J Gastroenterol. 2012;18(32):4412-8.

48. Bureš J et al. Epidemiology of Helicobacter pylori infection in the Czech Republic. Helicobacter. 2006;11(1):56-65.

49. Kuzela L et al. Epidemiology of Helicobacter pylori infection in the Slovak Republic. Hepatogastroenterology. 2012;59(115):754-6.

50. Sporea I et al. The prevalence of Helicobacter pylori infection in Western Romania. Rom J Gastroenterol. 2003;12(1):15-8.

51. Yucel T et al. The prevalence of Helicobacter pylori and related factors among university students in Turkey. Jpn J Infect Dis. 2008;61(3):179–83.

52. Kivi M et al. Helicobacter pylori status in family members as risk factors for infection in children. Epidemiol Infect. 2005;133(4):645-52.

53. Weyermann M et al. The mother as source of Helicobacter pylori infection. Epidemiology. 2006;17(3):332-4.

54. Yamaoka Y et al. Geographic differences in gastric cancer incidence can be explained by differences between Helicobacter pylori strains. Intern Med. 2008;47(12):1077-83.

55. Mégraud F et al. H. pylori antibiotic resistance: prevalence, importance, and advances in testing. Gut. 2004;53(9): 1374-84.

56. Tüzün Y et al. The prevalence of primary and secondary Helicobacter pylori resistance to clarithromycin and probable contributing cofactors: data from Southeastern Anatolia. Hepatogastroenterology. 2008;55(81):289-93.

57. Sezgin O et al. Detection of point mutations on 23S rRNA of Helicobacter pylori and resistance to clarithromycin with PCR-RFLP in gastric biopy specimens in Mersin, Turkey. Turk J Gastroenterol. 2008;19(3):163-7.

58. Untreatable: report by CDC details today's drug-resistant health threats.

2013. Available at: http://www.cdc.gov/media/releases/2013/p0916-untreatable.html.

59. Hansen M et al. Potential public health impacts of the use of recombinant bovine somatotropin in dairy production. Toxicology evaluation of certain veterinary drug residues in food. WHO Food Additives Series 41. 1998. Available at: http://www.inchem.org/documents/jecfa/jecmono/v041je11.htm.

60. Murray LJ et al. Inverse relationship between alcohol consumption and active Helicobacter pylori infection: the Bristol Helicobacter project. Am J Gastroenterol. 2002;(11):2750-5.

61. Kuepper-Nybelen J et al. Relationship between lifetime alcohol consumption and Helicobacter pylori infection. Ann Epidemiol. 2005;15(8):607–13.

62. Rokkas T et al. Relationship of Helicobacter pylori CagA(+) status to gastric juice vitamin C levels. Eur J of Clin İnvest. 1999;29(1):56–62.

63. Kato I et al. Environmental factors in Helicobacter pylori related gastric precancerous lesions in Venezuela. Cancer Epidemiol Biomarkers Prev. 2004;13(3):468–76.