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BRIEF ARTICLE

Significant decrease in prevalence of *Helicobacter pylori* in the Czech Republic

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Abstract

AIM: To study possible decrease in prevalence of *Helicobacter pylori* (*H. pylori*) infection in the Czech Republic within a 10-year period.

METHODS: A total of 22 centres entered the study. The catchment areas of these centres covered cities and towns with more than 20 000 inhabitants, smaller towns (≤ 20 000 inhabitants) with surrounding villages and rural areas, and were spread over the whole country, corresponding well to the geographical distribution of the Czech population. A total of 1 837 subjects (aged 5-98 years) took part in the study, randomly selected out of 38 147 people from the general population. *H. pylori* infection was investigated by means of a ^{13}C-urea breath test. Breath samples in duplicates were analysed using isotope ratio mass spectrometry. The cut-off point was 3.5. Social and demographic characteristics were based on data from self-completed questionnaires.

RESULTS: The overall prevalence of *H. pylori* infection was 23.5% (430/1826), and 4.8% (20/420) in children aged 15 or less. There was no statistically significant difference in prevalence between males (24.3%; 208/857) and females (22.9%, 222/969, P = 0.494). *H. pylori* infection was strongly associated with higher age, among subjects aged 55+ years, prevalence of *H. pylori* infection was 39.8% (252/633, P < 0.001). The highest prevalence of *H. pylori* infection was found among persons aged 55-64 years (43.9%, 97/221) and 75+ years (37.9%, 58/153). Among study subjects aged 15+ years, prevalence of *H. pylori* infection was significantly increased in those with lowest education (odds risk 3.19, 95% CI 1.87-5.47). Compared to never married (14.1%), the prevalence of *H. pylori* infection was statistically significantly higher among married (35.4%, 246/694, P < 0.001), divorced (36.8%, 49/133, P < 0.001) and widowed study subjects (40.2%, 45/112, P < 0.001), both in minimally and fully adjusted analysis. There was no significant difference in the prevalence of *H. pylori* infection between married and widowed subjects (35.4%, 246/694 *vs* 40.2%, 45/112, P = 0.389). There was little variation in smoking prevalence across categories of smoking and there was no evidence of an increased risk of *H. pylori* infection among current or past smokers in our data (odds risk 1.04 with 95% CI 0.78-1.40 for current smokers; odds ratio 0.83 with 95% CI 0.60-1.16 for former smokers). The current prevalence of *H. pylori*

in 2011 was significantly lower compared to the prevalence reported from identical geographical areas in 2001 (23.5% *vs* 41.7%, $P < 0.001$).

CONCLUSION: The overall prevalence of *H. pylori* infection in the general population has fallen substantially in the Czech Republic over the past 10 years.

Key words: Epidemiology; *Helicobacter pylori*; Czech Republic; ^{13}C-urea breath test; Decline of prevalence

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INTRODUCTION

Helicobacter pylori (*H. pylori*) infection is still the most common human infection worldwide. It is estimated that 50%-80% of the population is infected[1-3]. The prevalence in developed countries of Europe is 10%-30% (with an increase of 1%-3% for each age decade). Up to 95% of the adult population is infected in developing countries[4-8].

Our group accomplished a large multi-centre epidemiologic study on the prevalence of *H. pylori* and dyspepsia in the Czech Republic, a Central European country, in 2001[9-11]. The Project was executed on a total of 2509 persons aged 5-100 years, randomly selected out of 30 012 subjects from the general population. *H. pylori* infection was investigated by means of ^{13}C-urea breath test. The overall prevalence of *H. pylori* was 41.7% in 2001[9]. Meanwhile, several concerns have been raised about the possible decrease of *H. pylori* prevalence in developed countries. The aim of our current multi-centre prospective study was to evaluate the prevalence of *H. pylori* infection in the Czech Republic using the same methods in a representative sample of general unselected population from the same geographical areas 10 years later.

MATERIALS AND METHODS

Study population

A total of 22 centres entered the study. They included 15 centres of general practitioners for adults and 7 for children and adolescents. These centres covered cities and towns with more than 20 000 inhabitants (10 centres), smaller towns (≤ 20 000 inhabitants) with surrounding villages (9 centres) and rural areas (3 centres), and were spread over the whole country, corresponding well to the geographical distribution of the Czech population. A total of 1837 subjects (aged 5-98 years) took part in the study, randomly selected out of 38 147 registered males and females in this age range.

Urea breath test

Urea breath tests were performed in the morning after overnight fasting by means of ^{13}C-urea breath test[12]. Citric acid solution (3 g dissolved in 150 mL of still water) was given initially as a test drink. Five min later two baseline exhaled breath samples were collected into 20-mL vacutainers using a straw. Thereafter all persons ingested 75 mg ^{13}C-urea (*Helicobacter* Test INFAI, INFAI GmbH, Köln, Germany) dissolved in 50 mL of still water with 1 g citric acid (at time 0). Breath samples were collected in duplicates using a straw into 20-mL vacutainers after 30 min. Tubes with breath samples were sent to a single analytical centre by post and measured within a one-week period. Breath samples in duplicates were analysed using isotope ratio mass spectrometry (AP 2003, Analytical Precision Products, Cambridge, United Kingdom). The cut-off point was 3.5. Results of 13C-urea breath test for *H. pylori* status were obtained for 99.4% (1826/1837) of subjects.

Questionnaires

Data were collected by self-completed questionnaires distributed to adults and parents of children aged 5-15 years. The questionnaire included information on place of residence in childhood, mother's and father's education, access to running warm water in childhood, crowding in childhood and number of siblings. Information on the study subjects' current place of residence, education, marital status, self-reported socio-economic group and smoking habits was also collected in the questionnaire and was used in the analysis of determinants of *H. pylori* positivity in subjects aged above 15 years.

Ethical approval

The study was approved by the University Ethics Committee. All participants received detailed written information about the Project in advance and signed written consent (parents on behalf of their children). For all data obtained, all personal identification information was deleted in compliance with the laws for the protection of confidentiality of the Czech Republic.

Statistical analysis

The data was analysed using STATA statistical software (StataCorp. 2011. Stata Statistical Software: Release 12, College Station, TX). Education was analysed in six categories (university, secondary, vocational higher and lower, elementary and students) and marital status in five categories (single, first time married, re-married, divorced and widowed). In the analysis, we used three categories

Table 1 Prevalence of *Helicobacter pylori* by age and gender in a representative sample of Czech population *n* (%)

	Males	Females	Total
Age (yr)			
5-14	188 (4.8)	197 (5.1)	385 (4.9)
15-24	124 (10.5)	151 (7.9)	275 (9.1)
25-34	97 (16.5)	107 (13.1)	204 (14.7)
35-44	84 (30.9)	79 (19.0)	163 (25.1)
45-54	73 (42.5)	93 (34.4)	166 (37.9)
55-64	94 (42.5)	127 (44.9)	221 (43.9)
65-74	122 (38.5)	137 (36.5)	259 (37.4)
⩾ 75	75 (34.7)	78 (41.0)	153 (37.9)

Czech population examined in 2011 (n = 1826).

of smoking (never smoker, past smoker and current smoker). Proportions were compared using Chi-square test and the relative risk of *H. pylori* infection was studied in logistic regression with adjustment for age, gender and other social variables. Multivariable analyses were restricted to subjects with non-missing data on the variables studied.

RESULTS

The overall prevalence of *H. pylori* infection was 23.5% (430/1826), and 4.8% (20/420) in children aged 15 or less. There was no statistically significant difference in prevalence between males (24.3%, 208/857) and females (22.9%, 222/969, P = 0.494). *H. pylori* infection was strongly associated with higher age (Table 1).

Among study subjects aged above 15 years, prevalence of *H. pylori* infection was significantly increased in those with lowest education (Table 2). Compared to never married, the prevalence of *H. pylori* infection was statistically significantly higher among married and divorced study subjects, both in minimally and fully adjusted analyses (Table 2). There was little variation in smoking prevalence across categories of smoking and there was no evidence of an increased risk of *H. pylori* infection among current or past smokers in our data (Table 2).

The current prevalence of *H. pylori* in 2011 was significantly lower compared to the prevalence reported from identical geographical areas in 2001 (23.5% *vs* 41.7%, P < 0.001).

DISCUSSION

Our multi-centre prospective study proved that the current prevalence of *H. pylori* in 2011 is significantly lower compared to the prevalence of identical geographical areas in 2001. Both our studies were based on a representative sample of the general population, covering large and small urban population as well as rural areas and using ^{13}C-urea breath test as a gold standard for *H. pylori* diagnostics. Thus our results are reliable and trustworthy. The decline of *H. pylori* was found not only in overall prevalence but also in particular age decades. Explanation of this phenomenon is not easy and unequivocal. Although

Table 2 Prevalence of *Helicobacter pylori* by social characteristics and smoking in a representative sample of Czech population

	n	*H. pylori* (%)	OR[1] (95% CI)	OR[2] (95% CI)
Education				
University	351	25.6	1.0	1.0
Secondary	435	26.9	0.99 (0.71,1.38)	1.02 (0.73,1.43)
Vocational (higher)	66	31.8	1.31 (0.73,2.33)	1.33 (0.74,2.39)
Vocational (lower)	307	40.1	1.63 (1.16,2.29)	1.68 (1.18,2.37)
Elementary	80	53.7	2.84 (1.69,4.75)	3.19 (1.87,5.47)
Studying	188	8.0	0.51 (0.27,0.96)	0.60 (0.31,1.16)
Marital status				
Never married	488	14.1	1.0	1.0
First time married	566	34.8	1.75 (1.18,2.59)	1.55 (1.03,2.33)
Re-married	128	38.3	1.91 (1.15,3.20)	1.77 (1.05,2.99)
Divorced	133	36.8	1.88 (1.13,3.13)	1.74 (1.03,2.92)
Widowed	112	40.2	1.60 (0.88,2.92)	1.20 (0.65,2.20)
Smoking				
Never smoker	871	28.5	1.0	1.0
Former smoker	232	30.6	0.83 (0.60,1.16)	0.78 (0.55,1.09)
Current smoker	324	27.8	1.04 (0.78,1.40)	0.84 (0.61,1.15)

Czech population aged above 15 years and examined in 2011 (n = 1427). [1]Adjusted for age and gender; [2]Adjusted for age, gender and mutually adjusted for other variables. OR: Odds ratio; *H. pylori*: *Helicobacter pylori*.

there are no strictly unimpeachable epidemiologic data available, the decrease of *H. pylori* prevalence probably already started in the Czech Republic in the late 1990's[9]. It could be explained mostly by the relatively favourable and improving socio-economic conditions and standards of living together with falling fertility rates. In the same period, the age-standardised death rate from stomach cancer in the Czech Republic fell from 17.3/100 000 (in 1992) to 11.9/100 000 (2001) followed by further current decline to 8.7/100 000 (in 2010)[13]. Two large Czech seroprevalence studies found decreased *H. pylori* prevalence in the mid 2000's among subjects screened for thyroid disease[14] and in patients with peptic ulcer disease, functional dyspepsia and gastro-oesophageal reflux disease[15].

Decrease in the prevalence of *H. pylori* infection was also reported in other former communist countries such as Estonia (in children from 42% in 1991 to 28% in 2002)[16], Slovakia (in adults from 52% in 1992 and 41% in 2002 to 35% in 2007)[17,18] and Russia (in children from 44% in 1995 to 13% in 2005)[19]. This decline in *H. pylori* prevalence was explained by the profound socio-economic changes after the fall of communist regimes.

However, significant decrease of the prevalence of *H. pylori* infection was also found in stable developed European countries like the Netherlands[20-22], Finland[23,24], the United Kingdom[25,26], Germany[27], Norway[28] and Denmark[29]. This decrease could not be explained only by the birth-cohort phenomenon either. In developed countries, spontaneous subsequent clearance of *H. pylori* infection seems to be common[30]. In Finland, decrease of prevalence of *H. pylori* infection is believed to be due to the "screen and treat" project[31,32]. The main explanation for the decrease in *H. pylori* prevalence cannot merely be wide use of antibiotics for various indications.

The prevalence of *H. pylori* infection is significantly lower in patients with inflammatory bowel disease but not in those with chronic obstructive pulmonary disease (despite of extensive antibiotic use)[33]. There was no difference in *H. pylori* prevalence in Crohn's disease with or without previous treatment with sulfasalazine or antibiotics[34].

In our previous study, we did not find a birth-cohort phenomenon of *H. pylori* infection after the Second World War[35], in contrast to developed countries[8,36-41]. This could be explained by the great migration of population in former Czechoslovakia after the Second World War, forced unnatural collectivisation (in fact expropriation) of agriculture, equalisation of society and mostly low socio-economic status under the communist government[35]. den Hoed *et al*[42] found a new birth-cohort phenomenon of *H. pylori* infection in the Netherlands. They observed a decline in *H. pylori* prevalence in 6- to 8-year-old Dutch children from 19% in 1978 to 9% in 1993. The further prevalence of *H. pylori* in childhood has remained stable in the Netherlands from 1993 to 2005, suggesting a stabilisation of the previously decreasing trend in subsequent birth cohorts. This finding may reflect stabilisation in determinants such as family size, housing, and hygienic conditions (or offset by day care)[42].

Several interesting data came from other studies outside Europe. Decreased prevalence of *H. pylori* was also found for instance in the United States[43,44], China[45,46], Japan[47], South Korea[48] and Singapore[49]. After fifteen years, the prevalence of *H. pylori* infection among both children and adults in China remained significantly higher in areas with a high incidence of gastric cancer compared with that in areas with a low incidence of gastric cancer. *H. pylori* infection rates have decreased in the general Chinese population during recent years[50].

Poor standard of living, low socio-economic status, overcrowded families, low education of parents and smoking (in adults) are still major risk factors of *H. pylori* infection. Acquisition, chronic infection and possible spontaneous clearance of *H. pylori* are influenced by several other factors like ethnicity and genetic factors. Extensive broad use of antibiotics for different indications might be less important[9].

It is necessary to revive the so-called hygiene hypothesis[51]. It was suggested that with the higher hygiene standards in developed countries, people (especially raising children) are less exposed to helminths and this fact modulates development of the immune system (Th1/Th2 shift of CD4+ T-lymphocytes) and thereby increases the risk of several diseases like inflammatory bowel disease, bronchial asthma, food allergy and many others. The high prevalence of *H. pylori* and low rate of gastric cancer in Africa and some parts of Asia were called the "African or Asian (Indian) Enigma" and explained merely by the high prevalence of helminth infections[52]. Subsequent prospective studies found that no such dissociation existed[53]. Nowadays the "African Enigma" is considered to be a myth[54]. Nevertheless, hygiene theories should be considered in explanation of the gradual decline of *H. pylori* infection. Blaser and his group pointed out an inverse association between *H. pylori* infection and bronchial asthma[55-57], even though not confirmed by some others[58]. Sonnenberg *et al*[59] found low prevalence of *H. pylori* infection in inflammatory bowel disease.

Sýkora *et al*[60] published an excellent study on *H. pylori* among children in the Western Bohemian region (based on *H. pylori* stool antigen testing). The overall prevalence was 7.1% among 1545 children (aged 0-15 years; in the period 2003-2005). Breast-feeding was an important protective factor, *H. pylori* was found in 12.4% children that were not breast-fed. The prevalence of *H. pylori* was 80.8% among subjects living in children's homes in this study[60].

Smoking is another independent risk factor for *H. pylori* infection in adults[61,62]. The lower number of current smokers in Europe might also influence the decline of *H. pylori* infection. In our previous study in 2001, smoking habits were strongly related to risk of *H. pylori* positivity in adults, men and women with lowest education and heavy smokers being at the highest risk of *H. pylori* infection[9]. Surprisingly, there was no evidence of an increased risk of *H. pylori* infection among current or past smokers in our present study. It is necessary to mention another interesting phenomenon: the decreased prevalence of *H. pylori* represents a prominent decline of CagA positive *H. pylori* strains[42]. Explanation for this finding still remains unclear.

However, several studies recently showed that the prevalence of *H. pylori* is also declining among children in developing countries like Uganda, Brazil and the Middle East region despite persisting poor hygiene, standard of living and low socio-economic conditions[5,6,63-65].

On top of all those aspects mentioned above, it is necessary to admit that the reasons for decline of *H. pylori* infection have not been fully clarified yet[66,67]. It is necessary to also consider the fundamental determinants of "modern times" that could cause gradual disappearance of *H. pylori* from the human microbiome[68-72].

In summary, the overall prevalence of *H. pylori* infection in the general population has fallen substantially in the Czech Republic over the past 10 years. This decrease can be explained mostly by the relatively favourable and improving socio-economic status and high standard of living conditions. However, it is necessary to also consider that both environmental factors and the human host create an unfavourable milieu responsible for the decline of *H. pylori* infection.

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COMMENTS

Background

Helicobacter pylori (*H. pylori*) infection is still the most common human infection worldwide. It is estimated that 50%-80% of the population is infected. The prevalence in developed countries of Europe is 10%-30%. Up to 95% of the adult population is infected in developing countries.

Research frontiers

The authors accomplished a large multi-centre epidemiologic study on the prevalence of *H. pylori* and dyspepsia in the Czech Republic, a Central European country, in 2001. *H. pylori* infection was investigated by means of ^{13}C-urea breath test. The overall prevalence of *H. pylori* was 41.7% in 2001. The aim of the current multi-centre prospective study was to evaluate the prevalence of *H. pylori* infection in the Czech Republic using the same methods in a representative sample of general unselected population from the same geographical areas 10 years later.

Innovations and breakthroughs

The current prevalence of *H. pylori* in 2011 was significantly lower compared to the prevalence of identical geographical areas in 2001 (23.5% *vs* 41.7%, $P < 0.001$).

Applications

This decrease can be explained mostly by the relatively favourable and improving socio-economic status and high standard of living conditions. However, it is necessary to also consider that both environmental factors and the human host create an unfavourable milieu responsible for the decline of *H. pylori* infection.

Peer review

The paper aims at assessing the prevalence of *H. pylori* infection based on ^{13}C urea-breath test in a large random sample of Czech population. The study results show that the prevalence is declining in comparison with a similar previous study from the same group. Potential reasons for this fall are considered in the discussion. The paper is interesting, scientifically sound and well written.

REFERENCES

1 **Mahadeva S**, Goh KL. Epidemiology of functional dyspepsia: a global perspective. *World J Gastroenterol* 2006; **12**: 2661-2666
2 **Malaty HM**. Epidemiology of Helicobacter pylori infection. *Best Pract Res Clin Gastroenterol* 2007; **21**: 205-214
3 **Bruce MG**, Maaroos HI. Epidemiology of Helicobacter pylori infection. *Helicobacter* 2008; **13** Suppl 1: 1-6
4 **Azevedo NF**, Huntington J, Goodman KJ. The epidemiology of Helicobacter pylori and public health implications. *Helicobacter* 2009; **14** Suppl 1: 1-7
5 **Ford AC**, Axon AT. Epidemiology of Helicobacter pylori infection and public health implications. *Helicobacter* 2010; **15** Suppl 1: 1-6
6 **Goh KL**, Chan WK, Shiota S, Yamaoka Y. Epidemiology of Helicobacter pylori infection and public health implications. *Helicobacter* 2011; **16** Suppl 1: 1-9
7 **Mandeville KL**, Krabshuis J, Ladep NG, Mulder CJ, Quigley EM, Khan SA. Gastroenterology in developing countries: issues and advances. *World J Gastroenterol* 2009; **15**: 2839-2854
8 **Crowe SE.** Bacteriology and epidemiology of Helicobacter pylori infection. Feldman M, Grover S, editors. 2012. Available from: URL: http://www.uptodate.com/contents/bacteriology-and-epidemiology-of-helicobacter-pylori-infection
9 **Bures J**, Kopácová M, Koupil I, Vorísek V, Rejchrt S, Beránek M, Seifert B, Pozler O, Zivný P, Douda T, Kolesárová M, Pintér M, Palicka V, Holcík J. Epidemiology of Helicobacter pylori infection in the Czech Republic. *Helicobacter* 2006; **11**: 56-65
10 **Kopácová M**, Bures J, Koupil I, Rejchrt S, Vorísek V, Seifert B, Pozler O, Zivný P, Douda T, Palicka V, Holcík J. Body indices and basic vital signs in Helicobacter pylori positive and negative persons. *Eur J Epidemiol* 2007; **22**: 67-75
11 **Rejchrt S**, Koupil I, Kopácová M, Vorísek V, Seifert B, Pozler O, Zivný P, Douda T, Palicka V, Holcík J, Bures J. Prevalence and sociodemographic determinants of uninvestigated dyspepsia in the Czech Republic. *Eur J Gastroenterol Hepatol* 2008; **20**: 898-905
12 **Kopácová M**, Bures J, Vorísek V, Konstacký M, Rejchrt S, Zivný P, Douda T, Palicka V. Comparison of different protocols for 13C-urea breath test for the diagnosis of Helicobacter pylori infection in healthy volunteers. *Scand J Clin Lab Invest* 2005; **65**: 491-498
13 **World Health Organisation Regional Office for Europe**. European Mortality database (MDB).
14 **Sterzl I**, Hrdá P, Matucha P, Cerovská J, Zamrazil V. Anti-Helicobacter Pylori, anti-thyroid peroxidase, anti-thyroglobulin and anti-gastric parietal cells antibodies in Czech population. *Physiol Res* 2008; **57** Suppl 1: S135-S141
15 **Fixa B**, Komárková O, Nozicka Z. Changing prevalence of some selected gastrointestinal diseases vis-à-vis H. pylori infection. *Hepatogastroenterology* 2011; **58**: 1062-1066
16 **Oona M**, Utt M, Nilsson I, Uibo O, Vorobjova T, Maaroos HI. Helicobacter pylori infection in children in Estonia: decreasing seroprevalence during the 11-year period of profound socioeconomic changes. *Helicobacter* 2004; **9**: 233-241
17 **Jurgos L.** Infekce baktérií Helicobacter pylori a funkční dyspepsie - argumenty pro a proti. *Postgrad Med* (Prague) 2003; **5:** 530-534
18 **Kuzela L**, Oltman M, Sutka J, Zacharova B, Nagy M. Epidemiology of Helicobacter pylori infection in the Slovak Republic. *Hepatogastroenterology* 2012; **59**: 754-756
19 **Tkachenko MA**, Zhannat NZ, Erman LV, Blashenkova EL, Isachenko SV, Isachenko OB, Graham DY, Malaty HM. 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**: 428-432
20 **Roosendaal R**, Kuipers EJ, Buitenwerf J, van Uffelen C, Meuwissen SG, van Kamp GJ, Vandenbroucke-Grauls CM. Helicobacter pylori and the birth cohort effect: evidence of a continuous decrease of infection rates in childhood. *Am J Gastroenterol* 1997; **92**: 1480-1482
21 **Loffeld RJ**, van der Putten AB. Changes in prevalence of Helicobacter pylori infection in two groups of patients undergoing endoscopy and living in the same region in the Netherlands. *Scand J Gastroenterol* 2003; **38**: 938-941
22 **Arents NL**, Thijs JC, van Zwet AA, Kleibeuker JH. Does the declining prevalence of Helicobacter pylori unmask patients with idiopathic peptic ulcer disease? Trends over an 8 year period. *Eur J Gastroenterol Hepatol* 2004; **16**: 779-783
23 **Kosunen TU**, Aromaa A, Knekt P, Salomaa A, Rautelin H, Lohi P, Heinonen OP. Helicobacter antibodies in 1973 and 1994 in the adult population of Vammala, Finland. *Epidemiol Infect* 1997; **119**: 29-34
24 **Rehnberg-Laiho L**, Salomaa A, Rautelin H, Koskela P, Sarna S, Kosunen TU. Accelerated decline in Helicobacter pylori seroprevalence rate during the screen and treat project in Vammala, Finland, as demonstrated in 29- to 45-year-old pregnant women. *APMIS* 2004; **112**: 34-38
25 **Harvey RF**, Spence RW, Lane JA, Nair P, Murray LJ, Harvey IM, Donovan J. Relationship between the birth cohort pattern of Helicobacter pylori infection and the epidemiology of duodenal ulcer. *QJM* 2002; **95**: 519-525

26 **Vyse AJ**, Gay NJ, Hesketh LM, Andrews NJ, Marshall B, Thomas HI, Morgan-Capner P, Miller E. The burden of Helicobacter pylori infection in England and Wales. *Epidemiol Infect* 2002; **128**: 411-417

27 **Rothenbacher D**, Schultze V, Jähnig P, Scharschmidt B, Brenner H. Evidence of a rapid decrease in prevalence of Helicobacter pylori infection in children of a high risk group living in Germany. *Eur J Pediatr* 2004; **163**: 339-340

28 **Asfeldt AM**, Steigen SE, Løchen ML, Straume B, Johnsen R, Bernersen B, Florholmen J, Paulssen EJ. The natural course of Helicobacter pylori infection on endoscopic findings in a population during 17 years of follow-up: the Sørreisa gastrointestinal disorder study. *Eur J Epidemiol* 2009; **24**: 649-658

29 **Dahlerup S**, Andersen RC, Nielsen BS, Schjødt I, Christensen LA, Gerdes LU, Dahlerup JF. First-time urea breath tests performed at home by 36,629 patients: a study of Helicobacter pylori prevalence in primary care. *Helicobacter* 2011; **16**: 468-474

30 **Granström M**, Tindberg Y, Blennow M. Seroepidemiology of Helicobacter pylori infection in a cohort of children monitored from 6 months to 11 years of age. *J Clin Microbiol* 1997; **35**: 468-470

31 **Rautelin H**, Kosunen TU. Helicobacter pylori infection in Finland. *Ann Med* 2004; **36**: 82-88

32 **Salomaa-Räsänen A**, Kosunen TU, Aromaa AR, Knekt P, Sarna S, Rautelin H. A "screen-and-treat" approach for Helicobacter pylori infection: a population-based study in Vammala, Finland. *Helicobacter* 2010; **15**: 28-37

33 **Prónai L**, Schandl L, Orosz Z, Magyar P, Tulassay Z. Lower prevalence of Helicobacter pylori infection in patients with inflammatory bowel disease but not with chronic obstructive pulmonary disease - antibiotic use in the history does not play a significant role. *Helicobacter* 2004; **9**: 278-283

34 **Guslandi M**, Fanti L, Testoni PA. Helicobacter pylori seroprevalence in Crohn's disease: lack of influence by pharmacological treatment. *Hepatogastroenterology* 2002; **49**: 1296-1297

35 **Kopacova M**, Bures J, Koupilova I, Vorisek V, Seifert B, Pozler O, Rejchrt S, Jancova E, Hanka V, Ponizil M, Janik K, Koudelka T, Holdsvendova I, Appelt J, Balatkova R, Srutkova J, Charvatova M, Koudelkova G, Sircova M, Bumbova I, Herber O, Charvatova E, Cermakova S, Klikova O, Seifertova J, Douda T, Zivny P, Palicka V. Prevalence of Helicobacter pylori infection in non-selected general population in Czech republic. No birth-cohort phenomenon found in multicentre prospective study. *Gut* 2002; **51** Suppl 3: A108

36 **Bardhan PK**. Epidemiological features of Helicobacter pylori infection in developing countries. *Clin Infect Dis* 1997; **25**: 973-978

37 **Brown LM**. Helicobacter pylori: epidemiology and routes of transmission. *Epidemiol Rev* 2000; **22**: 283-297

38 **Graham DY**, Malaty HM, Evans DG, Evans DJ, Klein PD, Adam E. Epidemiology of Helicobacter pylori in an asymptomatic population in the United States. Effect of age, race, and socioeconomic status. *Gastroenterology* 1991; **100**: 1495-1501

39 **Malaty HM**, Graham DY. Importance of childhood socioeconomic status on the current prevalence of Helicobacter pylori infection. *Gut* 1994; **35**: 742-745

40 **O'Connor H**, Sebastian S. The burden of Helicobacter pylori infection in Europe. *Aliment Pharmacol Ther* 2003; **18** Suppl 3: 38-44

41 **Sipponen P**. Helicobacter pylori: a cohort phenomenon. *Am J Surg Pathol* 1995; **19** Suppl 1: S30-S36

42 **den Hoed CM**, Vila AJ, Holster IL, Perez-Perez GI, Blaser MJ, de Jongste JC, Kuipers EJ. Helicobacter pylori and the birth cohort effect: evidence for stabilized colonization rates in childhood. *Helicobacter* 2011; **16**: 405-409

43 **Manuel D**, Cutler A, Goldstein J, Fennerty MB, Brown K. Decreasing prevalence combined with increasing eradication of Helicobacter pylori infection in the United States has not resulted in fewer hospital admissions for peptic ulcer disease-related complications. *Aliment Pharmacol Ther* 2007; **25**: 1423-1427

44 **McJunkin B**, Sissoko M, Levien J, Upchurch J, Ahmed A. Dramatic decline in prevalence of Helicobacter pylori and peptic ulcer disease in an endoscopy-referral population. *Am J Med* 2011; **124**: 260-264

45 **Xia B**, Xia HH, Ma CW, Wong KW, Fung FM, Hui CK, Chan CK, Chan AO, Lai KC, Yuen MF, Wong BC. Trends in the prevalence of peptic ulcer disease and Helicobacter pylori infection in family physician-referred uninvestigated dyspeptic patients in Hong Kong. *Aliment Pharmacol Ther* 2005; **22**: 243-249

46 **Chen J**, Bu XL, Wang QY, Hu PJ, Chen MH. Decreasing seroprevalence of Helicobacter pylori infection during 1993-2003 in Guangzhou, southern China. *Helicobacter* 2007; **12**: 164-169

47 **Nakajima S**, Nishiyama Y, Yamaoka M, Yasuoka T, Cho E. Changes in the prevalence of Helicobacter pylori infection and gastrointestinal diseases in the past 17 years. *J Gastroenterol Hepatol* 2010; **25** Suppl 1: S99-S110

48 **Lee SY**, Park HS, Yu SK, Sung IK, Jin CJ, Choe WH, Kwon SY, Lee CH, Choi KW. Decreasing prevalence of Helicobacter pylori infection: a 9-year observational study. *Hepatogastroenterology* 2007; **54**: 630-633

49 **Ho KY**, Chan YH, Kang JY. Increasing trend of reflux esophagitis and decreasing trend of Helicobacter pylori infection in patients from a multiethnic Asian country. *Am J Gastroenterol* 2005; **100**: 1923-1928

50 **Zhang DH**, Zhou LY, Lin SR, Ding SG, Huang YH, Gu F, Zhang L, Li Y, Cui RL, Meng LM, Yan XE, Zhang J. Recent changes in the prevalence of Helicobacter pylori infection among children and adults in high- or low-incidence regions of gastric cancer in China. *Chin Med J* (Engl) 2009; **122**: 1759-176

51 **Bures J.** Worms - friend or foe? The new "Old friends' hypothesis". *Folia Gastroenterol Hepatol* 2009; **7:** 50-53

52 **Fox JG**, Wang TC, Nagler-Anderson C. The African enigma: the parasite's perspective. *Gut* 2001; **49**: 156-157

53 **Agha A**, Graham DY. Evidence-based examination of the African enigma in relation to Helicobacter pylori infection. *Scand J Gastroenterol* 2005; **40**: 523-529

54 **Graham DY**, Lu H, Yamaoka Y. African, Asian or Indian enigma, the East Asian Helicobacter pylori: facts or medical myths. *J Dig Dis* 2009; **10**: 77-84

55 **Blaser MJ**, Chen Y, Reibman J. Does Helicobacter pylori protect against asthma and allergy? *Gut* 2008; **57**: 561-567

56 **Reibman J**, Marmor M, Filner J, Fernandez-Beros ME, Rogers L, Perez-Perez GI, Blaser MJ. Asthma is inversely associated with Helicobacter pylori status in an urban population. *PLoS One* 2008; **3**: e4060

57 **Blaser MJ**. Equilibria of humans and our indigenous microbiota affecting asthma. *Proc Am Thorac Soc* 2012; **9**: 69-71

58 **Holster IL**, Vila AM, Caudri D, den Hoed CM, Perez-Perez GI, Blaser MJ, de Jongste JC, Kuipers EJ. The impact of Helicobacter pylori on atopic disorders in childhood. *Helicobacter* 2012; **17**: 232-237

59 **Sonnenberg A**, Genta RM. Low prevalence of Helicobacter pylori infection among patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2012; **35**: 469-476

60 **Sýkora J**, Siala K, Varvarovská J, Pazdiora P, Pomahacová R, Huml M. Epidemiology of Helicobacter pylori infection in asymptomatic children: a prospective population-based study from the Czech Republic. Application of a monoclonal-based antigen-in-stool enzyme immunoassay. *Helicobacter* 2009; **14**: 286-297

61 **Bateson MC**. Cigarette smoking and Helicobacter pylori infection. *Postgrad Med J* 1993; **69**: 41-44

62 **Brenner H**, Rothenbacher D, Bode G, Adler G. Relation of smoking and alcohol and coffee consumption to active He-

licobacter pylori infection: cross sectional study. *BMJ* 1997; **315**: 1489-1492
63 **Ozden A**, Bozdayi G, Ozkan M, Köse KS. Changes in the seroepidemiological pattern of Helicobacter pylori infection over the last 10 years. *Turk J Gastroenterol* 2004; **15**: 156-158
64 **Kawakami E**, Machado RS, Ogata SK, Langner M. Decrease in prevalence of Helicobacter pylori infection during a 10-year period in Brazilian children. *Arq Gastroenterol* 2008; **45**: 147-151
65 **Sýkora J**, Rowland M. Helicobacter pylori in pediatrics. *Helicobacter* 2011; **16** Suppl 1: 59-64
66 **Blaser MJ**. Hypothesis: the changing relationships of Helicobacter pylori and humans: implications for health and disease. *J Infect Dis* 1999; **179**: 1523-1530
67 **Blaser MJ**. Who are we? Indigenous microbes and the ecology of human diseases. *EMBO Rep* 2006; **7**: 956-960
68 **Blaser MJ**. Disappearing microbiota: Helicobacter pylori protection against esophageal adenocarcinoma. *Cancer Prev Res* (Phila) 2008; **1**: 308-311
69 **Atherton JC**, Blaser MJ. Coadaptation of Helicobacter pylori and humans: ancient history, modern implications. *J Clin Invest* 2009; **119**: 2475-2487
70 **Cover TL**, Blaser MJ. Helicobacter pylori in health and disease. *Gastroenterology* 2009; **136**: 1863-1873
71 **Blaser MJ**. Helicobacter pylori and esophageal disease: wake-up call? *Gastroenterology* 2010; **139**: 1819-1822
72 **Blaser MJ**. Heterogeneity of Helicobacter pylori. *Eur J Gastroenterol Hepatol* 2012; **9** Suppl 1: S3-6; discussion S6-7

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