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REVIEW

Clinical Practice: *Helicobacter pylori* infection in childhood

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Abstract *Helicobacter pylori* infection is recognised as a cause of gastritis and peptic ulcer disease (PUD) and usually acquired during the first years of life. While there is a decline in the prevalence of *H. pylori* infection in northern and western European countries, the infection is still common in southern and eastern parts of Europe and Asia. Symptoms of *H. pylori*-related PUD are nonspecific in children and may include epigastric pain, nausea and/or vomiting, anorexia, iron deficiency anaemia and hematemesis. Besides, only a small proportion of children develop symptoms and clinically relevant gastrointestinal disease. *H. pylori* infection can be diagnosed either by invasive tests requiring endoscopy and biopsy or non-invasive tests including the ^{13}C-urea breath test, detection of *H. pylori* antigen in stool and detection of antibodies in serum, urine and saliva. The aim of treatment is at least 90 % eradication rate of the bacteria, and a combination of two antibiotics plus a proton pump inhibitor has been recommended as first-line treatment. However, frequent use of antibiotics during childhood is associated with a decline in eradication rates and the search for new treatment strategies as well. This is an overview of the latest knowledge and evidence-based guidelines regarding clinical presentation, diagnosis and treatment of *H. pylori* infection in childhood.

Keywords *Helicobacter pylori* · Prevalence · Abdominal pain · Peptic ulcer disease · Diagnosis · Treatment

Abbreviations

H. pylori	*Helicobacter pylori*
^{13}C-UBT	^{13}C-Urea breath test
MALT	Mucosa-associated lymphoid tissue
IDA	Iron deficiency anaemia
RAP	Recurrent abdominal pain
EIA	Enzyme immunoassay
RUT	Rapid urease test
FISH	Fluorescence in situ hybridization
PUD	Peptic ulcer disease
PPI	Proton pump inhibitor

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Introduction

Helicobacter pylori is a gram-negative bacterium which naturally colonises gastric mucosa and causes chronic active and chronic persistent gastritis in both adults and children. Almost half of the world's population is estimated to be infected with *H. pylori*, and it is a major risk factor for several gastroduodenal diseases, including gastric ulcer, duodenal ulcer, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, and distal gastric cancer [10, 31, 47]. There are epidemiological data linking chronic *H. pylori* infection, probably beginning in childhood, with the development of gastric cancer and MALT lymphoma [30]. Infection is usually acquired during early childhood particularly in developing countries, and the prevalence of *H. pylori* gastritis in children increases with age [42]. Factors determining the subset of infected individuals developing the disease compared with *H. pylori* carriers remain unclear. Both host and bacterial factors may contribute to differences in *H. pylori* pathogenicity. Relative infrequency of clinical disease from *H. pylori* infection among children may suggest that the host response to the bacteria differs between adults and children. Lesser inflammatory response to *H. pylori* by a developing immune system may alleviate the risk of disruption to the mucosa of gastric epithelium and

may modify associated physiological changes which favour survival of *H. pylori* [9].

Epidemiology and risk factors

At adolescence, approximately 65 % of children in developing countries are infected with *H. pylori* [48, 49]. The human host remains the principal reservoir. Transmission occurs via person-to-person transmission, and unclean water sources have also been implicated [6, 14]. Several studies have suggested that children acquire *H. pylori* most frequently from their mothers; hence, infected mothers are the main independent source of *H. pylori* infection for children [36, 61]. While there is a decline in the prevalence of *H. pylori* infection in Europe, the high prevalence in Asia and developing countries still persists [48, 56, 59]. A literature search regarding the prevalence of *H. pylori* among healthy subjects by using different screening methods is presented in Table 1. Since different screening methods such as stool antigen test, serology and ^{13}C-urea breath test (^{13}C-UBT) were used in those studies, the prevalence rates varied according not only to the different geographical areas but also to the sensitivity of the test used to detect *H. pylori* infection. The rate of infection in developed countries has fallen dramatically over recent decades, with a more precipitous decline in transmission found in children compared to adults [16, 56].

Most of the published studies regarding risk factors focused on socioeconomic indicators, and family income, household crowding, number of children sharing the same room, parents' education and sharing a bed with children were identified as major risk factors associated with *H. pylori* infection [12, 13, 32, 44, 48, 58]. Cultural factors determine the child-rearing practices in different populations. It has been shown that peculiar eating habits such as sharing plates, glasses, and spoons, and tasting the food before feeding the child might be associated with *H. pylori* infection particularly in countries with higher prevalence of the infection [16, 44].

Clinical presentation in *H. pylori* infection

In children, symptoms of *H. pylori*-related peptic ulcer disease are nonspecific and may include epigastric pain especially after meals, night-time waking, unexplained nausea and/or vomiting, anorexia, hematemesis and iron deficiency anaemia.

The association between *H. pylori* infection and iron deficiency anaemia (IDA) has been the focus of attention for more than one decade [4, 5, 43, 50, 53]. However, it is often difficult to distinguish between IDA due to *H. pylori* infection and to the other confounding factors such as poor nutritional status or another underlying disease. Hence, endoscopic examination may be indicated in children with refractory IDA in order to rule out not only the presence of *H. pylori* but also other causes of IDA such as malabsorption syndromes. Recently published guidelines regarding *H. pylori* infection in children have recommended that children with unexplained IDA should be tested for *H. pylori* infection [35].

Table 1 Most recent studies reporting prevalence of *H. pylori* infection in children

Authors	Country, study population	Methods of sampling	Diagnostic test	Age range (years)	Number of subjects	*H. pylori* (+) (%)
Chi et al. 2009 [12]	Children, Taiwan, healthy high-school students	Not stated	^{13}C-UBT	Mean, 14.3	106	55
Dube et al. 2009 [13]	South Africa, healthy children and adults	Not stated	Stool antigen testing	0–60	356	87
Jafri et al. 2010 [31]	Pakistan, children	Cluster	Serum IgG antibodies	1–15	1,976	47
Santos et al. 2009 [52]	Bolivia, healthy school children	Random	^{13}C-UBT	5–8	424	74
	Cuba, healthy school children	Random intention	^{13}C-UBT	6–14	996	48
	Venezuela, school children	sampling of schools	^{13}C-UBT	4–13	418	78
Sykora et al. 2009 [55]	Czech Republic, healthy children	Random	Stool antigen	0–15	1,545	7
Yucel et al. 2008 [64]	Turkey, healthy children	Volunteered by parents	Stool antigen	2–12	165	31
Ozen et al. 2006 [48]	Turkey, healthy school children	Random	^{13}C-UBT	3–12	327	49.5
Tam et al. 2008 [57]	Chinese healthy children	Random	^{13}C-UBT	6–19	2,480	13.1

H. pylori infection is the most important cause of primary duodenal ulcers in children. Since duodenal ulcer and use of nonsteroidal antiinflammatory drugs are the most common aetiologies of upper gastrointestinal bleeding during childhood, *H. pylori* infection should be sought in children with acute upper gastrointestinal bleeding [28].

There are several studies investigating the association between recurrent abdominal pain (RAP) and *H. pylori* infection, but no association has been identified [7, 42]. Hence, children with RAP should not undergo non-invasive or endoscopy-based tests in order to seek evidence of *H. pylori* infection in primary care [35]. Several consensus statements and guidelines have suggested that children with recurrent abdominal pain should be investigated for *H. pylori* only when upper gastrointestinal endoscopy is required to look for an organic disease such as peptic ulcer or esophagitis [9, 35, 39]. In the revised guidelines regarding the management of *H. pylori* infection, recurrent abdominal pain is not an indication for a "test and treat" strategy for *H. pylori* infection in children [35, 39]. Whether *H. pylori* gastritis *per se* causes abdominal pain in the absence of peptic ulcer disease is still debatable.

There is insufficient evidence regarding the causative association between *H. pylori* infection and otitis media, upper respiratory tract infections, periodontal disease, food allergy, sudden infant death syndrome, idiopathic thrombocytopenic purpura and short stature [35].

Epidemiological evidence has indicated that there is a link between gastric cancer and *H. pylori* infection; however, no study has yet shown that *H. pylori* eradication during childhood prevents the development of gastric malignancies. The significance of *H. pylori* infection in children in terms of the risk of gastric cancer occurring in adult life requires further studies, because it is likely to be a critical issue in determining whether widespread screening and treatment strategies are implemented among children [26, 30, 54]. The World Health Organisation's statement classifying *H. pylori* as a group 1 carcinogen could result in significant parental pressure for screening of children and treatment if *H. pylori* is found to be present [31]. Screening of children with a family history of gastric cancer is recommended if they are symptomatic [35].

Diagnosis: non-invasive and invasive tests

H. pylori infection can be diagnosed by several methods. Non-invasive techniques include the ^{13}C-UBT, detection of *H. pylori* antigen in stool and detection of antibodies against *H. pylori* in serum, urine and saliva.

Invasive techniques require endoscopy and biopsy (histological examination, rapid urease test, culture, polymerase chain reaction and fluorescence in situ hybridization, FISH) (Table 2). At least two tests are needed to diagnose the *H. pylori* infection, and a biopsy-based test (such as culture or histology or rapid urease test) should be the reference for non-invasive tests.

In a large number of paediatric studies of high quality, the ^{13}C-UBT has been evaluated against biopsy-based tests, showing high accuracy, sensitivity and specificity [15, 41]. However a positive ^{13}C-UBT does not confirm or exclude the presence of an ulcer, gastritis or esophageal pathologies. Detection of *H. pylori* antigen in stool is a reliable and cost-effective non-invasive method that seems suitable for both clinical use and epidemiological studies. Several methods are available for the detection of *H. pylori* antigen in stool, such as enzyme immunoassay (EIA) based on polyclonal or monoclonal antibodies and immunochromatographic tests (so-called rapid or quick tests) [51, 56, 62]. So far, only the EIA based on monoclonal antibodies has achieved the accuracy of the ^{13}C-UBT.

There are several commercially available, easy to perform and inexpensive tests based on detection of antibodies (IgG and IgA) against *H. pylori* in blood and body secretions. Despite the advantages, the lower sensitivity and a wide test-to-test variability of these IgG-based tests prevent the use of serological tests in the clinical setting [35, 37]. Therefore, tests detecting antibodies against *H. pylori* in serum, whole blood, urine and saliva are not reliable for use in children of any age group [35].

Recently, Guarner et al. published a study regarding the diagnostic tests for *H. pylori* infection in children by reviewing literature from 1999 to 2009 and concluded that most of the commercially available non-invasive tests such as the ^{13}C-UBT, monoclonal stool antigen test have adequate sensitivity and specificity for detecting the presence of *H. pylori*. They emphasized that endoscopy with histopathology is the only method which can diagnose and confirm *H. pylori* infection, its associated lesions (atrophy, intestinal metaplasia) and other causes of gastrointestinal symptoms as well [22]. In symptomatic children with suspected *H. pylori* infection, gastric biopsies should be obtained not only

Table 2 Tests for investigating *H. pylori* infection

I.	Invasive tests requiring endoscopy
	Biopsies and histology
	Rapid urease testing
	Bacterial culture
	Polymerase chain reaction of bacterial DNA
II.	Non-invasive tests
	Serum and whole blood antibody
	Saliva antibody
	Urine antibody
	Stool antigen
	Urea breath testing

for histopathology but also for rapid urease test and, if available, for culture. Rapid urease test can be performed in endoscopic biopsy specimens by using commercially available reagents [38].

FISH or PCR techniques can be applied to the frozen or paraffin-embedded gastric tissues for the diagnosis of *H. pylori* infection [35]. The major advantage of these methods is the ability to study antibiotic resistance in biopsy specimens. Culture is the only method that consistently has 100 % specificity, but sensitivity varies depending on the experience of the laboratory [22]. At present, culture procedures have not been standardized, and relatively few clinical laboratories offer this service routinely in several countries.

In summary, upper gastrointestinal endoscopy with biopsies is the preferred method of investigation in children with upper digestive symptoms suggestive of organic disease and is the gold standard for diagnosing pathologies related to *H. pylori.* Therefore, it has been recommended that the initial diagnosis of *H. pylori* infection should be based on either positive histopathology plus a positive rapid urease test or a positive culture [35]. That is, the diagnosis of *H. pylori* infection in children requires an esophagogastroduodenoscopy and obtaining gastric biopsies.

Who should be tested and treated?

Children with a suspicion of organic upper gastrointestinal disease should be tested for *H. pylori* infection and should be treated if they are infected [35, 39]. In adults, eradication of *H. pylori* in patients with peptic ulcer disease (PUD) significantly reduces the relapse rate of ulcer disease and the recurrence of bleeding. Although the data regarding children with PUD were not as convincing as in adult studies, eradication of *H. pylori* is recommended in children with *H. pylori*-associated PUD [35]. Unexplained and refractory iron deficiency anaemia is another indication for testing for *H. pylori* infection in children and for eradication if the patient is found to be positive. *H. pylori* infection is the most consistent risk factor for gastric cancer; hence, its elimination has been regarded as the most promising strategy to reduce the incidence of gastric cancer in adulthood [40]. Therefore, endoscopy and treatment should be considered in children who are found to be infected with *H. pylori* and having a first-degree relative with gastric cancer (Table 3).

Treatment options for *H. pylori* infection in children

The goal of treatment is at least a 90 % eradication rate of *H. pylori* at the first attempt so that a high initial eradication rate will prevent the development of antibiotic resistance and spread of resistant *H. pylori* strains in the population. Since the initial guidelines, first-line treatment options include triple therapy, i.e. a proton pump inhibitor (PPI) plus two antibiotics. In the last guidelines, several alternative first-line therapies have been recommended (Table 4) [21, 35, 55]. Although there are no well-designed randomised studies comparing bismuth-based triple therapy with the alternate recommended first-line therapies, bismuth salts are included in the latest guidelines as an alternative first-line therapy in countries where bismuth salts are available commercially [35, 46]. The period of triple therapy should be 10–14 days, taking the cost, compliance and side effects into consideration. Tetracycline should not be used to treat *H. pylori* infection in children younger than 12 years of age with incomplete teeth development.

Eradication rates of *H. pylori* infection following standard triple therapies are largely decreasing all over the world, and this phenomenon has been related to an increasing prevalence of bacterial resistance which varies in different regions [45, 46]. Today, the overall eradication rate of *H. pylori* is around

Table 3 Indications for *H. pylori* investigation in children

Who should be tested for *H. pylori* infection?
The primary goal of clinical investigation of gastrointestinal symptoms should be to determine the underlying cause of the symptoms and not solely the presence of *H. pylori* infection.
1. Children with unexplained, refractory iron deficiency anaemia
2. Children with first-degree relatives with gastric cancer

Table 4 First-line treatment recommendations for *H. pylori* eradication in children

Triple therapies	Dose
I. PPI	1–2 mg/kg/day
Amoxicillin	50 mg/kg/day (max, 2 g/day)
Clarithromycin	20 mg/kg/day (max, 1 g/day)
Given twice daily for 10–14 days	
II. PPI	1–2 mg/kg/day
Amoxicillin	50 mg/kg/day (max, 2 g/day)
Metronidazole	20 mg/kg/day (max, 1 g/day)
Given twice daily for 10–14 days	
III. Bismuth salts	8 mg/kg/day
Amoxicillin	50 mg/kg/day (max, 2 g/day)
Metronidazole	20 mg/kg/day (max, 1 g/day)
Given twice daily for 10–14 days	
Sequential therapy	Dose
PPI	1–2 mg/kg/day
Amoxicillin for 5 days	50 mg/kg/day (max, 2 g/day)
PPI	1–2 mg/kg/day
Amoxicillin	50 mg/kg/day (max, 2 g/day)
Metronidazole for 5 days	20 mg/kg/day (max, 1 g/day)

PPI proton pump inhibitor

65 % which is lower than the ratios reported previously [38], and the major reason for this eradication failure is antibiotic resistance, particularly clarithromycin resistance [1–3, 11, 18, 27]. A multicenter antibiotic resistance study which included children from 14 European countries revealed a resistance rate of 25 % to metronidazole, 24 % to clarithromycin and double resistance rate of 6.9 % [34]. In this study, resistance to amoxicillin was exceptional as expected.

There are limited data regarding the susceptibility testing to target initial therapy in children; nevertheless, susceptibility test-guided treatments demonstrated higher eradication rates in children [1]. Antibiotic susceptibility testing for clarithromycin is recommended before initial clarithromycin-based triple therapy in areas with a known high resistance rate (>15–20 %) of *H. pylori* to clarithromycin. The combination of PPI–amoxicillin–metronidazole is preferable in areas where the metronidazole resistance is lower than 40 % [27, 35, 40].

Declining eradication rates with the triple regimens have led to the development of alternate first-line treatment options [17, 20]. Sequential therapy involves 5 days of therapy with a PPI and amoxicillin followed sequentially by 5 days of PPI–clarithromycin–imidazole. The sequential treatment, which is now widely used in adults, yielded a superior eradication rate compared to the conventional 7- or 10-day triple regimens [17]. However, eradication failure secondary to clarithromycin resistance is still a problem for the sequential therapy as well. In the most recently published paediatric guidelines, the sequential therapy is recommended as an initial therapy in eradication of childhood *H. pylori* infection [35].

Primary antibiotic resistance adversely affects the success of *H. pylori* eradication; however, development of secondary antibiotic resistance seems to be more common in children [8, 33]. When the initial treatment with one of the first-line alternatives fails in a child infected with *H. pylori*, primary culture with antibiotic sensitivity testing should be performed along with endoscopy to guide second-line therapy. Another option may be FISH on previously obtained paraffin-embedded biopsies to test clarithromycin resistance. If culture or susceptibility tests are not available, trying second-line treatment options or increasing the dose of PPIs (2 mg/kg/day) and/or duration of treatment (14 instead of 10 days) may be recommended.

The choice of second-line therapy should take the initial therapy into account, and the physician should avoid using an antibiotic that was previously prescribed. Second-line treatment options and doses are listed in Table 5. Fluoroquinolone resistance is an emerging problem in the adult population; thus, fluoroquinolones should be cautiously used in children who were previously exposed to this drug [29]. Supplementation of *Saccharomyces boulardii* to *H. pylori* eradication regimens emerged as an alternative at the beginning of the 2000s [60]. However, rather than being an additional therapeutic effect, probiotics significantly reduced the incidence of side effects [57, 60]. To date, the most reasonable policy to adopt is to treat a child according to the result of the antibiotic susceptibility test whenever possible, or at least according to what is known about the antibiotic susceptibility of *H. pylori* strains cultured in this geographical area [35].

Regardless of being asymptomatic after the treatment, it is recommended that the success of eradication therapy should be evaluated in children with *H. pylori* infection [35]. Persistence of infection, particularly in children who had PUD, would warrant additional treatment. The ^{13}C-UBT is recommended as a reliable non-invasive test for evaluation of the eradication success. Today, it is considered the reference standard of the non-invasive tests for assessment of the eradication success [15, 41, 63]. Since collecting breath samples is not easy in small children, stool samples can be used for follow-up of eradication success in small children. A laboratory-based validated monoclonal stool test can be used in children who cannot supply a breath sample as well. Factors that can lead to false-positive or false-negative results should be considered before interpreting the test results. Data extrapolated from the adult studies show that antibiotics and acid-suppressive drugs, particularly PPIs, should be discontinued before testing for at least 4 and 2 weeks, respectively [35, 40]. Tests based on the detection of antibodies (IgG, IgA) against *H. pylori* in serum, whole blood, urine and saliva are not reliable for evaluation of the eradication success [35, 40].

Vaccination

H. pylori infection is usually acquired during childhood and tends to persist unless treated. It is highly prevalent all over the world and an important cause of gastritis, peptic ulcer

Table 5 Second-line treatment for *H. pylori* in children who failed the initial therapy

Quadruple therapy	Dose
PPI	1–2 mg/kg/day
Amoxicillin	50 mg/kg/day (max, 2 g/day)
Metronidazole	20 mg/kg/day (max, 1 g/day)
Bismuth	8 mg/kg/day
For 14 days	
Triple therapy	Dose
PPI	1–2 mg/kg/day
Levofloxacin	10 mg/kg/day (max, 500 mg/day)
Amoxicillin	50 mg/kg/day (max, 2 g/day)
For 14 days	

PPI proton pump inhibitor

disease, MALT lymphoma and gastric adenocarcinoma [40]. Treatment of *H. pylori* requires multidrug regimens because of the barrier function of the gastric mucus layer, and resistance is also an important issue with the antibiotics commonly used for eradication of the bacteria. Hence, a vaccine, administered during infancy would obviate many treatment concerns and could be an attractive strategy to control *H. pylori* infection [25, 52].

Since the initial studies have demonstrated that it was possible to reduce gastric *H. pylori* colonisation by vaccination with *H. pylori* antigen and adjuvant, various approaches including whole cell vaccines, recombinant antigens (e.g. urease A/B subunits, CagA, VacA, NapA, catalase or heat shock proteins) in combination with bacterial toxins or other adjuvants have been successfully tested in animals [23, 24]. However, similar vaccine trials in humans have shown adjuvant-related adverse effects and only moderate effectiveness [25, 52]. It is obvious that infections caused by microorganisms which gain access to the body via the mucosal membranes are best prevented by mucosal vaccination. Further, vaccination at mucosal surfaces may stimulate both systemic and mucosal immunity not only at the site of vaccination, but also at distant mucosal epithelia [19, 25]. Transcutaneous immunization may be effective as a route for inducing protection against *H. pylori* colonisation and warrants further studies.

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References

1. Ahmad N, Zakaria WR, Abdullah SA, Mohamed R (2009) Characterization of clarithromycin resistance in Malaysian isolates of *Helicobacter pylori*. World J Gastroenterol 15:3161
2. Alvarez A, Moncayo JI, Santacruz JJ, Santacoloma M, Corredor LF, Reinosa E (2009) Antimicrobial susceptibility and mutations involved in clarithromycin resistance in *Helicobacter pylori* isolates from patients in the western central region of Colombia. Antimicrob Agents Chemother 53:4022–4024
3. Bakir Ozbey S, Ozakin C, Keskin M (2009) Antibiotic resistance rates of *Helicobacter pylori* isolates and the comparison of E-test and fluorescent in situ hybridization methods for the detection of clarithromycin resistant strains. Mikrobiyol Bul 43:227–234
4. Barabino A, Dufour C, Marino CE, Claudiani F, De Alessandri A (1999) Unexplained refractory iron- deficiency anemia associated with *Helicobacter pylori* gastric infection in children: further clinical evidence. J Pediatr Gastroenterol Nutr 28:116–119
5. Baysoy G, Ertem D, Ademoglu E, Kotiloglu E, Keskin S, Pehlivanoglu E (2004) Gastric histopathology, iron status and iron deficiency anemia in children with *Helicobacter pylori* infection. J Pediatr Gastroenterol Nutr 38:146–151
6. Bellack NR, Koehoorn MW, MacNab YC, Morshed MG (2006) A conceptual model of water's role as a reservoir in *Helicobacter pylori* transmission: a review of the evidence. Epidemiol Infect 134:439–449
7. Berger MY, Spee LA, Madderom MB, Pijpers M, van Leeuwen Y (2010) Association between *Helicobacter pylori* and gastrointestinal symptoms in children. Pediatrics 125:e651–e669
8. Bontems P, Devaster JM, Corvaglia L, Dezsöfi A, Van Den Borre C, Goutier S, Butzler JP, Cadranel S (2001) Twelve year observation of primary and secondary antibiotic-resistant *Helicobacter pylori* strains in children. Pediatr Infect Dis J 20:1033–1038
9. Bourke B, Ceponis P, Chiba N, Czinn S, Ferraro R, Fischbach L, Gold B, Hyunh H, Jacobson K, Jones NL, Koletzko S, Lebel S, Moayyedi P, Ridell R, Sherman P, van Zanten S, Beck I, Best L, Boland M, Bursey F, Chaun H, Cooper G, Craig B, Creuzenet C, Critch J, Govender K, Hassall E, Kaplan A, Keelan M, Noad G, Robertson M, Smith L, Stein M, Taylor D, Walters T, Persaud R, Whitaker S, Woodland R, Canadian Helicobacter Study Group (2005) Canadian *Helicobacter* Study Group Consensus Conference: update on the approach to *Helicobacter pylori* infection in children and adolescents—an evidence-based evaluation. Can J Gastroenterol 9:399–408
10. Brenner H, Arndt V, Stegmaier C, Ziegler H, Rothenbacher D (2004) Is *Helicobacter pylori* infection a necessary condition for noncardiac gastric cancer? Am J Epidemiol 159:252–258
11. Chang WL, Sheu BS, Cheng HC, Yang YJ, Yang HB, Wu JJ (2009) Resistance to metronidazole, clarithromycin and levofloxacin of *Helicobacter pylori* before and after clarithromycin-based therapy in Taiwan. J Gastroenterol Hepatol 24:1230–1235
12. Chi H, Bair M-J, Wu M-S, Chiu NC, Hsiao YC, Chang KY (2009) Prevalence of *Helicobacter pylori* infection in high-school students on Lanyu Island, Taiwan: risk factor analysis and effect on growth. J Formos Med Assoc 108:929–936
13. Dube C, Nkosi TC, Clarke AM, Mkwetshana N, Green E, Ndip RN (2009) *Helicobacter pylori* antigenemia in an asymptomatic population of Eastern Cape Province, South Africa: public health implications. Rev Environ Health 24:249–255
14. Dube C, Tanih NF, Ndip RN (2009) *Helicobacter pylori* in water sources: a global environmental health concern. Rev Environ Health 24:1–14
15. Elitsur Y, Tolia V, Gilger MA, Reeves-Garcia J, Schmidt-Sommerfeld E, Opekun AR, El-Zimaity H, Graham DY, Enmei K (2009) Urea breath test in children: the United States prospective, multicenter study. Helicobacter 14:134–140
16. Ford AC, Axon AT (2010) Epidemiology of *Helicobacter pylori* infection and public health implications. Helicobacter 15(Suppl 1):1–6
17. Francavilla R, Lionetti E, Castellaneta SP, Magistà AM, Boscarelli G, Piscitelli D, Amoruso A, Di Leo A, Miniello VL, Francavilla A, Cavallo L, Ierardi E (2005) Improved efficacy of 10-day sequential treatment for *Helicobacter pylori* eradication in children: a randomized trial. Gastroenterology 129:1414–1419
18. Francavilla R, Lionetti E, Castellaneta S, Margiotta M, Piscitelli D, Lorenzo L, Cavallo L, Ierardi E (2010) Clarithromycin resistant genotypes and eradication of *H. pylori*. Pediatrics 157:228–232
19. Fujihashi K, Koga T, van Ginkel FW, Hagiwara Y, McGhee JR (2002) A dilemma for mucosal vaccination: efficacy versus toxicity using enterotoxin-based adjuvants. Vaccine 20:2431–2438
20. Gatta L, Vakil N, Leandro G, Di Mario F, Vaira D (2009) Sequential therapy or triple therapy for *Helicobacter pylori* infection: systematic review and meta-analysis of randomized controlled trials in adults and children. Am J Gastroenterol 104:3069–3079
21. Gold B, Colletti RB, Abbott M, Czinn SJ, Elitsur Y, Hassall E, Macarthur C, Snyder J, Sherman PM (2000) *Helicobacter pylori* infection in children: recommendations for diagnosis and treatment. J Pediatr Gastroenterol Nutr 31:490–497

22. Guarner J, Kalach N, Elitsur Y, Koletzko S (2010) *Helicobacter pylori* diagnostic tests in children: review of the literature from 1999 to 2009. Eur J Pediatr 169:15–25
23. Guo L, Liu K, Xu G, Li X, Tu J, Tang F, Xing Y, Xi T (2012) Prophylactic and therapeutic efficacy of the epitope vaccine CTB-UA against *Helicobacter pylori* infection in a BALB/c mice model. Appl Microbiol Biotechnol. doi:10.1007/s00253-012-4122-0
24. Guy B, Hessler C, Fourage S, Haensler J, Vialon-Lafay E, Rokbi B, Millet MJ (1998) Systemic immunization with urease protects mice against *Helicobacter pylori* infection. Vaccine 16:850–856
25. Hickey DK, Aldwell FE, Tan ZY, Bao S, Beagley KW (2009) Transcutaneous immunization with novel lipid-based adjuvants induces protection against gastric *Helicobacter pylori* infection. Vaccine 27:6983–6990
26. Hishida A, Matsuo K, Goto Y, Hamajima N (2010) Genetic predisposition to *Helicobacter pylori*-induced gastric precancerous conditions. World J Gastrointest Oncol 15:369–379
27. Hojsak I, Kos T, Dumančić J, Mišak Z, Jadrešin O, Jaklin Kekez A, Lukić Grlić A, Kolaček S (2012) Antibiotic resistance of *Helicobacter pylori* in pediatric patients—10 years' experience. Eur J Pediatr 171:1325–1330
28. Houben CH, Chiu PW, Lau JY, Lee KH, Ng EK, Tam YH, Yeung CK (2008) Duodenal ulcers dominate acute upper gastrointestinal tract bleeding in childhood: a 10-year experience from Hong Kong. J Dig Dis 9:199–203
29. Hung KH, Sheu BS, Chang WL, Wu HM, Liu CC, Wu JJ (2009) Prevalence of primary fluoroquinolone resistance among clinical isolates of *Helicobacter pylori* at a University Hospital in Southern Taiwan. Helicobacter 14:61–65
30. Imrie C (2001) Is *Helicobacter pylori* infection in childhood a risk factor for gastric cancer? Pediatrics 107:373–380
31. International Agency for Research on Cancer, World Health Organization (1994) Infection with *Helicobacter pylori*. In: IARC Working Group on the Evaluation of Carcinogenic Risk to Humans (eds) Schistosomes, liver flukes and *Helicobacter pylori*, vol 60. AI RC, Lyon, Monogr Eval Carcinog Risks Hum, pp. 177–240
32. Jafri W, Yakoob J, Abid S, Siddiqui S, Awan S, Nizami SQ (2010) *Helicobacter pylori* infection in children: population-based age-specific prevalence and risk factors in a developing country. Acta Paediatr 99:279–282
33. Kato S, Fujimura S (2010) Primary antimicrobial resistance of *Helicobacter pylori* in children during the past 9 years. Pediatr Int 52:187–190
34. Koletzko S, Richy F, Bontems P, Crone J, Kalach N, Monteiro ML, Gottrand F, Celinska-Cedro D, Roma-Giannikou E, Orderda G, Kolacek S, Urruzuno P, Martínez-Gómez MJ, Casswall T, Ashorn M, Bodanszky H, Mégraud F (2006) The European Paediatric Task Force on *Helicobacter pylori*. Prospective multicentre study on antibiotic resistance of *Helicobacter pylori* strains obtained from children living in Europe. Gut 55:1711–1716
35. Koletzko S, Jones NL, Goodman KJ, Gold B, Rowland M, Cadranel S, Chong S, Colletti RB, Casswall T, Elitsur Y, Guarner J, Kalach N, Madrazo A, Megraud F, Oderda G, H pylori Working Groups of ESPGHAN and NASPGHAN (2011) Evidence-based guidelines from ESPGHAN and NASPGHAN for *Helicobacter pylori* infection in children. J Pediatr Gastroenterol Nutr 53:230–243
36. Konno M, Yokota S, Suga T, Takahashi M, Sato K, Fujii N (2008) Predominance of mother-to-child transmission of *Helicobacter pylori* infection detected by random amplified polymorphic DNA fingerprinting analysis in Japanese families. Pediatr Infect Dis J 27:999–1003
37. Leal YA, Flores LL, García-Cortés LB, Cedillo-Rivera R, Torres J (2008) Antibody-based detection tests for the diagnosis of *Helicobacter pylori* infection in children: a meta-analysis. PLoS One 3: e3751
38. Madani S, Rabah R, Tolia V (2000) Diagnosis of *Helicobacter pylori* infection from antral biopsies in pediatric patients: is urease test that reliable? Dig Dis Sci 45:1233–1237
39. Malfertheiner P, Megraud F, O'Morain CA, Bazzoli F, El-Omar E, Graham D, Hunt R, Rokkas T, Vakil N, Kuipers EJ (2007) Current concepts in the management of *Helicobacter pylori* infection: the Maastricht III Consensus Report. Gut 56:772–781
40. Malfertheiner P, Megraud F, O'Morain CA, Atherton J, Axon AT, Bazzoli F, Gensini GF, Gisbert JP, Graham DY, Rokkas T, El-Omar EM, Kuipers EJ, European Helicobacter Study Group. (EHSG) (2012) Management of *Helicobacter pylori* infection—the Maastricht IV/Florence Consensus Report. Gut 61:646–664
41. Megraud F (2005) Comparison of non-invasive tests to detect *Helicobacter pylori* infection in children and adolescents: results of a multicenter European study. J Pediatr 146:198–203
42. Mourad-Baars P, Hussey S, Jones NL (2010) *Helicobacter pylori* infection and childhood. Helicobacter 15(Suppl 1):53–59
43. Muhsen K, Cohen D (2008) *Helicobacter pylori* infection and iron stores: a systematic review and meta-analysis. Helicobacter 13:323–340
44. Nouraie M, Latifi-Navid S, Rezvan H, Radmard AR, Maghsudlu M, Zaer-Rezaii H, Radmard AR, Maghsudlu M, Zaer-Rezaii H, Amini S, Siavoshi F, Malekzadeh R (2009) Childhood hygienic practice and family education status determine the prevalence of *Helicobacter pylori* infection in Iran. Helicobacter 14:40–46
45. O'Connor A, Gisbert JP, McNamara D, O'Morain C (2010) Treatment of *Helicobacter pylori* infection 2010. Helicobacter 15(Suppl 1):46–52
46. Oderda G, Shcherbakov P, Bontems P, Urruzuno P, Romano C, Gottrand F, Gómez MJ, Ravelli A, Gandullia P, Roma E, Cadranel S, De Giacomo C, Canani RB, Rutigliano V, Pehlivanoglu E, Kalach N, Roggero P, Celinska-Cedro D, Drumm B, Casswall T, Ashorn M, Arvanitakis SN, European Pediatric Task Force on Helicobacter pylori (2007) Results from the pediatric European register for treatment of *Helicobacter pylori* (PERTH). Helicobacter 12:150–156
47. Ohata H, Kitauchi S, Yoshimura N, Mugitani K, Iwane M, Nakamura H, Yoshikawa A, Yanaoka K, Arii K, Tamai H, Shimizu Y, Takeshita T, Mohara O, Ichinose M (2004) Progression of chronic atrophic gastritis associated with *Helicobacter pylori* infection increases the risk of gastric cancer. Int J Cancer 109:138–143
48. Ozden A, Bozdayi G, Ozkan M, Köse S (2004) Changes in the seroepidemiological pattern of *Helicobacter pylori* infection over the last 10 years. Turk J Gastroenterol 15(3):156–158
49. Ozen A, Ertem D, Pehlivanoglu E (2006) Natural history and symptomatology of *Helicobacter pylori* in childhood and factors determining the epidemiology of infection. J Pediatr Gastroenterol Nutr 42:398–404
50. Qu XH, Huang XL, Xiong P, Zhu CY, Huang YL, Lu LG, Sun X, Rong L, Zhong L, Sun DY, Lin H, Cai MC, Chen ZW, Hu B, Wu LM, Jiang YB, Yan WL (2010) Does *Helicobacter pylori* infection play a role in iron deficiency anemia? A meta-analysis. World J Gastroenterol 16:886–896
51. Raguza D, Machado RS, Ogata SK, Granato CF, Patrício FR, Kawakami E (2010) Validation of a monoclonal stool antigen test for diagnosing *Helicobacter pylori* infection in young children. J Pediatr Gastroenterol Nutr 50:400–403
52. Rupnow MF, Chang AH, Shachter RD, Owens DK, Parsonnet J (2009) Cost-effectiveness of a potential prophylactic *Helicobacter pylori* vaccine in the United States. J Infect Dis 200:1311–1317
53. Santos IS, Boccio J, Davidsson L, Hernandez-Triana M, Huanca-Sardinas E, Janjetic M, Moya-Camarena SY, Paez-Valery MC, Ruiz-Alvarez V, Valencia ME, Valle NC, Vargas-Pinto G, Solano L, Thomas J (2009) *Helicobacter pylori* is not associated with anaemia in Latin America: results from Argentina, Brazil, Bolivia, Cuba, Mexico and Venezuela. Public Health Nutr 12:1862–1870

54. Selgrad M, Bornschein J, Rokkas T, Malfertheiner P (2010) Clinical aspects of gastric cancer and *Helicobacter pylori*—screening, prevention, and treatment. Helicobacter 15(Suppl 1):40–45
55. Sherman P, Hassall E, Hunt RH, Fallone CA, Veldhuyzen Van Zanten S, Thomson AB (1999) Canadian *Helicobacter* Study Group Consensus Conference on the approach to *Helicobacter pylori* infection in children and adolescents. Can J Gastroenterol 13:553–559
56. Sykora J, Siala K, Varvarovska J, Pazdiora P, Pomahacová R, Huml M (2009) 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 14:286–297
57. Szajewska H, Albrecht P, Topczewska-Cabanek A (2009) Randomized, double-blind, placebo-controlled trial: effect of lactobacillus GG supplementation on *Helicobacter pylori* eradication rates and side effects during treatment in children. J Pediatr Gastroenterol Nutr 48:431–436
58. Tam YH, Yeung CK, Lee KH, Sihoe JD, Chan KW, Cheung ST, Mou JW (2008) A population-based study of *Helicobacter pylori* infection in Chinese children resident in Hong Kong: prevalence and potential risk factors. Helicobacter 13:219–224
59. Tkachenko MA, Zhannat NZ, Erman LV, Blashenkova EL, Isachenko SV, Isachenko OB, Graham DY, Malaty HM (2007) Dramatic changes in the prevalence of *Helicobacter pylori* infection during childhood: a 10-year follow-up study in Russia. J Pediatr Gastroenterol Nutr 45:428–432
60. Vandenplas Y, Brunser O, Szajewska H (2009) *Saccharomyces boulardii* in childhood. Eur J Pediatr 168:253–265
61. Weyermann M, Rothenbacher D, Brenner H (2009) Acquisition of *Helicobacter pylori* infection in early childhood: independent contributions of infected mothers, fathers, and siblings. Am J Gastroenterol 104:182–189
62. Wu DC, Wu IC, Wang SW et al (2006) Comparison of stool enzyme immunoassay and immunochromatographic method for detecting *Helicobacter pylori* antigens before and after eradication. Diagn Microbiol Infect Dis 56:373–378
63. Yang HR, Ko JS, Seo JK (2008) Does the diagnostic accuracy of the 13C-urea breath test vary with age even after the application of urea hydrolysis rate? Helicobacter 13:239–244
64. Yucel T, Aygin D, Sen S, Yucel O (2008) The prevalence of *Helicobacter pylori* and related factors among university students in Turkey. Jpn J Infect Dis 61:179–183