Helicobacter pylori in childhood : aspects of prevalence, diagnosis and treatment

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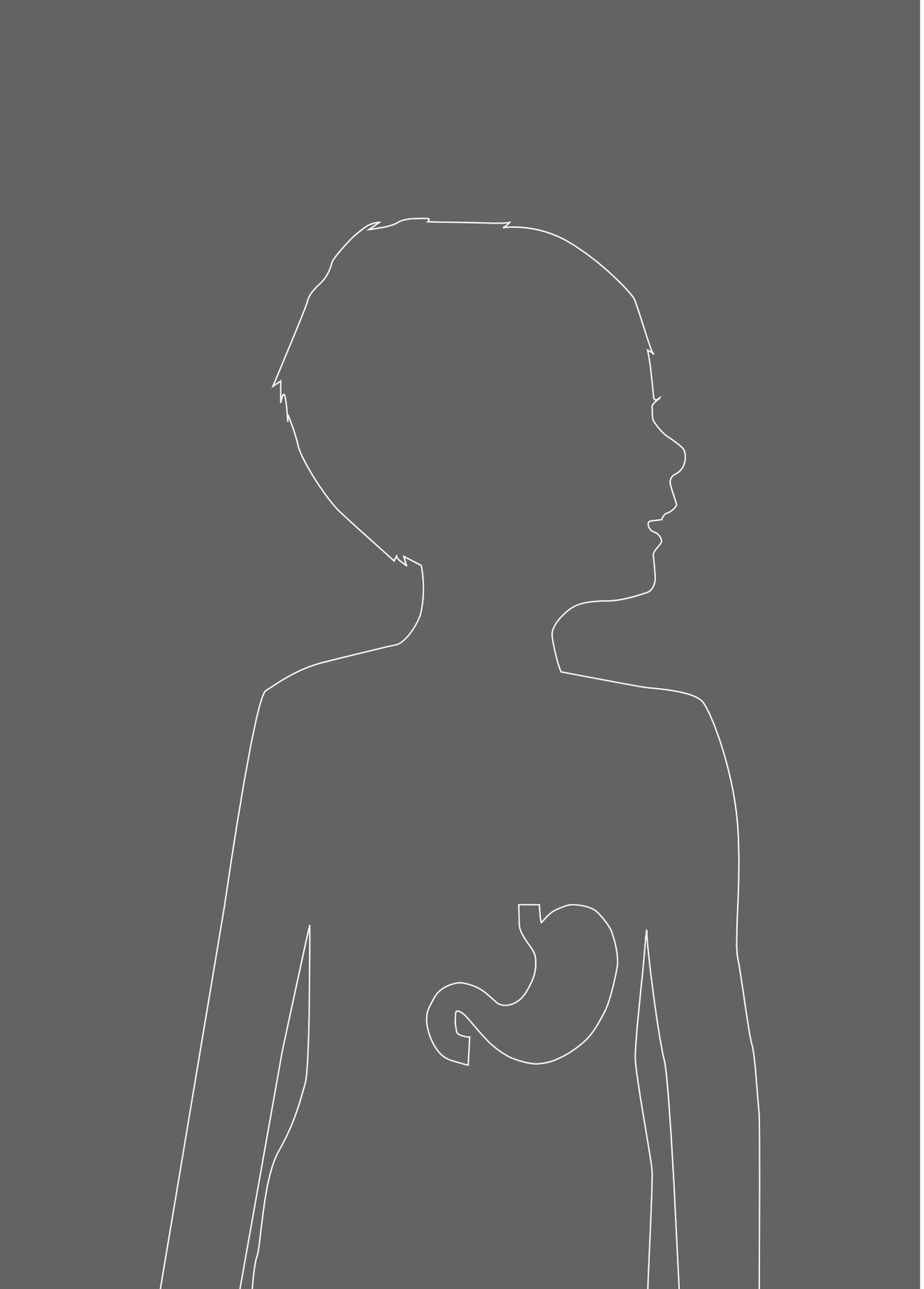

CHAPTER 3

Helicobacter pylori infection and childhood 2009-2010

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ABSTRACT

Pediatric-based *Helicobacter pylori* research continues to contribute significantly to our understanding of both clinical and pathophysiological aspects of this infection. Here, we review the published pediatric *H. pylori* literature from April 2009–March 2010.

Analysis of pediatric *H. pylori* strains continues to suggest that CagA$^+$ and CagPAI competent strains are less prevalent than in adult isolates. Studies from the Middle East report a high *H. pylori* prevalence and intrafamilial transmission. Data continue to show a lack of association between *H. pylori* and recurrent abdominal pain of childhood, gastroesophageal reflux disease, and growth retardation.

Recent probiotic trials have not shown a benefit on *H. pylori* eradication in children, while sequential therapy remains an attractive therapeutic eradication strategy in children, which requires validation in different geographic regions.

Keywords: Review, recurrent abdominal pain, resistance, sequential therapy.

PATHOPHYSIOLOGY

The relationship between apoptosis and *Helicobacter pylori* remains an important aspect of *H. pylori* pathogenesis research. In a Polish cohort of children with symptomatic *H. pylori* infection and gastritis, Fas receptor expression was increased in the CD4$^+$ T cell population in the lamina propria at diagnosis and Fas antigen expression was significantly decreased in both epithelial cells and mucosal lymphocytes following successful eradication[1]. The authors speculate that apoptosis of CD4$^+$ T cells could contribute to bacterial persistence in the mucosa.

Studies of the spectrum of *H. pylori* genetic variability between childhood and adult isolates may help to elucidate age-specific microbial genetic factors involved in pathogenesis. Rick *et al* suggested that in situ hybridization techniques, which reflect in vivo gene transcription, may be superior to testing isolates for CagA in vitro and used this method to confirm the association between gastric mucosal *H. pylori* CagA expression and pediatric gastro-duodenal ulcer disease [2]. While children had a higher prevalence of CagA$^+$ strains compared to adults in one study from China, CagA was not shown to influence their disease phenotype [3]. *H. pylori* strains from symptomatic children in the USA and Greece were more likely to be CagA- and lack a functional CagPAI, although the USA isolates were more likely to retain outer membrane protein (OMP) and adherence gene expression than adult strains, a possible microbial advantage for early life infection and colonization [4,5]. The adherence properties and expression profile of OMP genes of *H. pylori* isolates from 200 symptomatic patients were characterized by Odenbreit *et al* [6]. Apart from AlpA and AlpB, the expression of other OMPs was variable. In vitro interleukin (IL)-8 expression was again shown to be increased by CagA$^+$ strains, while co-expression of OipA, but not OipA alone, further enhanced IL-8 secretion. The presence of the putative virulence factor gene IceA, while common, was not predictive of the extent of inflammation on histology in Slovenian children; CagA and VacA s1 genotypes were associated with more severe gastritis and greater bacterial density [7].

Autophagy, an evolutionary conserved process in eukaryotic cells, is an integral component of our innate immune system and is implicated in the pathogenesis of a number of gastrointestinal diseases [8]. *H. pylori* VacA toxin has recently been shown to induce autophagy in gastric cells in vitro, a potential host defense strategy to limit toxin damage, but auto-phagosome formation may also facilitate bacterial replication and survival [9]. *H. pylori* has also been shown to multiply in autophagosomes in macrophages, suggesting that it may be subverting autophagy for its own benefit [10].

EPIDEMIOLOGY AND TRANSMISSION

The estimated 7.1% prevalence of *H. pylori* infection in asymptomatic children in the Czech Republic is among the lowest reported in Europe [11]. Sykora *et al* found a positive association with increasing age, the number of children in the household (OR 4.26,CI 1.91–9.80), lack of formal education of the father (OR 0.23; CI0.18–0.64), and institutionalization (OR 6.33; CI 2.25–26.50). Their findings are consistent with improving trends in living and housing conditions in recent years and with decreasing family size.

While the prevalence in Western countries and America is decreasing, the high prevalence in Asia remains. Malekzadeh *et al* using stool antigen and serology testing, reported a high prevalence of *H. pylori* infection in 592 Iranian children from Shiraz and 386 children from Rafsanjan (82% and 47%, respectively,) [12]. Iran and Iraq have a high prevalence of CagA$^+$ *H. pylori* [13]. In a study from Pakistan, a seroprevalence of 47% among 1976 children (1–15 years) was reported. The father's educational status, crowding, and increasing age, were the main factors influencing sero-positivity [14].

Understanding the intrafamilial spread of *H. pylori* is an important aspect of transmission research. A study of 100 children with abdominal symptoms (44 *H. pylori*+) found a higher percentage of *H. pylori* infected siblings, mothers, and fathers, tested by urea breath test (UBT), among *H. pylori*+ than *H. pylori*- index cases ($p < .001$, $p < .001$ and $p < .035$, respectively) [15]. Each *H. pylori*+ child had at least one infected family member, implicating the family as the source of *H. pylori* infection in children. Nahar *et al* found evidence of intrafamilial transmission of *H. pylori* by characterizing *H. pylori* in 35 families, including 138 family members, using DNA fingerprinting [16]. Forty-six percent of strains from the mothers shared related genotype with strains from their children. Only 6% of parents shared a related genotype, suggesting mother– child transmission as the most probable transmission route.

In a study from Iran, Amini *et al* described the association between *H. pylori* infection and eating habits (sharing plates, glasses, and spoons) and found a significantly higher prevalence of *H. pylori* infection in families where common dishes were used[17].

Travis *et al* used UBT at 6-month intervals from birth to 24 months to describe possible water-borne transmission of *H. pylori* in a cohort study of 472 children from Mexico and Texas [18]. Their results provide some support for water-borne transmission. On the other hand, Vale and Vitor reviewed water- and food-borne transmission of *H. pylori* and concluded that the principal transmission route remains to be clearly defined [19].

SYMPTOMS

Recurrent Abdominal Pain

The discussion about the association between recurrent abdominal pain (RAP), epigastric pain, unspecified abdominal pain, and *H. pylori* infection in children continues. Thakkar *et al* published a retrospective study on upper digestive endoscopy in 1191 children with abdominal pain; 55 children (5%) were diagnosed with *H. pylori* infection, the second most common diagnosis after reflux esophagitis (23%) [20]. They agreed that earlier studies did not show a causal relation between *H. pylori* infection and abdominal pain in absence of ulcer disease, but conceded that there is a trend to offer eradication therapy once the *H. pylori* infection has been diagnosed. In a meta-analysis, Spee *et al* found no association between RAP and *H. pylori* infection in children and limited evidence for an association between unspecified abdominal pain and *H. pylori* in referred, but not in primary care patients [21]. Although current evidence does not support infection as a significant cause of common symptoms in children, guidelines on *H. pylori* screening in children are contradictory [22,23]. For example, discrepancies exist between the earlier European Pediatric Task Force on *H. pylori* report and the more recent Maastricht III statement, which suggests that although RAP is not an indication for a test-and-treat strategy in children, those with upper gastrointestinal symptoms should be tested after exclusion of other causes of symptoms [23,24].

Peptic Ulcer

H. pylori infection is the most important cause of primary duodenal ulcers in children. A retrospective study of differences between *H. pylori*+ and *H. pylori*- primary ulcers in 43 Chinese children diagnosed >8 years showed that boys vs. girls (91.3 vs. 50%) and older children (12 vs. 10 years) were more likely to have *H. pylori*+ ulcers (53.5%) [25]. In the *H. pylori*- group, ulcer recurrence was more common. In an editorial comment, Oderda *et al* noted the emergence of 'a new disease': *H. pylori*-negative gastric or duodenal ulcer, occurring more frequently in younger children, without gender preference and tending to have a higher recurrence rate [26]. Rick *et al* investigated 51 children, of whom six had gastric ulcers (all *H. pylori*+) and 11 had duodenal ulcers (10 *H. pylori*+), and found *H. pylori* by 16S rDNA and CagA PCR significantly higher in children with ulcer compared with normal children [2].

Gastroesophageal Reflux Disease (GERD)

The role of *H. pylori* in GERD remains controversial, limited by sufficient published data in children. Both a positive and negative association between *H. pylori* and GERD was reported recently [27,28]. Moon *et al* found reflux esophagitis in 13 of 16

H. pylori-positive patients, but in only 38.1% of 404 *H. pylori*-negative children and concluded a positive association. However, the prevalence of *H. pylori* in the study was low, and they did not address CagA status in *H. pylori*-positive patients in the study. On the other hand, researchers in Turkey did not found a positive association between *H. pylori* infection and the severity of esophagitis [28].

DIAGNOSIS

Guarner *et al* published a ten-year review on diagnostic tests in children between 1999 and 2009, concluding that most commercial noninvasive tests now have adequate sensitivity and specificity for detecting the presence of *H. pylori*. They again emphasized that endoscopy with histopathology is the only method that can diagnose and confirm *H. pylori* infection, its lesions and other causes of symptoms; UBT test and monoclonal stool antigen test being good tests for post-treatment control [29].

The same rapid office-based stool test using an immunoassay with monoclonal antibodies was tested in young children in Germany and in France. Prell *et al* compared it to biopsy tests considered as reference in the setting of pre-and post eradication of *H. pylori* and found a sensitivity of 85.5–90.8% and a specificity of 91.0–97.6% [30]. Results of Kalach *et al*. were similar, showing a sensitivity of 87.5% and a specificity of 97.8% [31]. She *et al* confirmed the lack of clinical utility of serology testing in children and adults, including an unacceptably low IgM sensitivity of just 6.8% [32].

EXTRA-INTESTINAL MANIFESTATIONS

Iron Deficiency and Growth

The link between *H. pylori* infection and anemia or sub-optimal growth remains tenuous. Ferrara *et al* presented retrospective data on a heterogeneous group of 102 Italian children aged between 10 and 12 years with iron deficiency anemia, suggesting that children with both *H. pylori* infection (positive stool antigen test) and iron deficiency anemia were more likely to have a reduced height standard deviation score (SDS) in comparison with children with other causes of anemia [33]. However, the data spanning an 8- year period lacked growth velocity assessments, case-matched controls, and details regarding the etiological work-up. A cross-sectional study of children from a low socio-economic background from Mexico found an association between *H. pylori* infection and reduced height compared to uninfected matched controls and suggested that the risk was cumulative per annum above the age of 7 years [34]. In a contrasting study from Turkey, Gulcan *et al* did not find a significant association between anemia and growth retardation; a subgroup analysis did suggest an association between endoscopic mucosal disease and lower height SDS ($p = .02$) [35]. Chi *et al* did not find an association between *H. pylori* infection and growth failure in their cross-sectional study from Taiwan, albeit of high-school children and based again on height SDS rather than growth velocity [36]. An Australian cross-sectional study of refugee children from Africa also failed to find an association between *H. pylori* infection and subnormal anthropometric measurements [37].

A series of cross-sectional studies from Latin America did not find significant evidence linking *H. pylori* infection and anemia [38]. Children with a positive UBT in Cuba, Argentina, Bolivia, and Venezuela did not have a statistically increased risk of associated anemia in comparison with their UBT negative counterparts. In a study among Arab-Israeli children, a population with a high prevalence of both *H. pylori* infection and anemia, Muhsen *et al* only found a statistically significant association between low ferritin levels and positive *H. pylori* serology in children less than 5 years of age but not among older age groups [39]. Unfortunately, it remains difficult to extrapolate a causal inference from studies of such design.

Idiopathic Thrombocytopenic Purpura (ITP) and Platelet Dysfunction

A multi-center randomized controlled trial of *H. pylori* eradication in children with chronic ITP failed to show an effect of *H. pylori* eradication on platelet recovery [40]. Ferrara *et al* reported a positive effect of *H. pylori* eradication on the outcome of children with chronic ITP with a positive stool antigen test, although their study was not a randomized controlled trial [41]. One translational study described platelet aggregation dysfunction in children with symptomatic *H. pylori* infection, which improved post-eradication [40].

THERAPEUTIC ISSUES

Drug Resistance

Drug resistance is a growing problem in adults as well as in children. Kato and Fujimura studied 61 strains from Japanese children 4–18 years old from 1999–2007 and reported high primary resistance of clarithromycin (36.1%) and metronidazole (14.8%) with consequences for the eradication rate [42]. Double resistance was detected in 6.6% of the strains. In Bulgaria, resistance to clarithromycin and metronidazole was 19% and 16.2%, respectively; multidrug resistance was 1% [43]. Both authors did not find resistance to amoxicillin and recommend susceptibility tests before treatment. Other studies on resistance came from Asia and South America; a low clarithromycin resistance rate was found in Malaysia (2.1%), Taiwan

(10.6%), and Colombia (3.8%), in notable contrast to the high rates of metronidazole resistance in those countries [44–46]. In children from Thailand, clarithromycin resistance was 29.2% [47]. Raymond *et al* determined antimicrobial susceptibility in 530 biopsies between 2004 and 2007 by E-test and molecular methods [48]. Twenty-six percent of strains were resistant to clarithromycin, 61% to metronidazole and 13% to ciprofloxacin in adults; in an earlier study, they reported primary resistance of 22.8% for clarithromycin in children through a one-year period. All authors recommend periodic monitoring of antibiotic susceptibility to tailor treatment and prevent eradication failure.

Sequential Therapy

Pediatric trials of sequential therapy (ST) for *H. pylori* eradication have previously reported a superior efficacy over conventional therapies (CT) [49,50]. Two recent meta-analyses of sequential therapy trials in adults and children suggested a benefit of a sequential therapy eradication regimen over conventional 7- or 10-day eradication regimens. Tong *et al* included 11 randomized controlled trials published up to February 2008 that compared ST to CT, including three pediatric studies [51]. The reported pooled risk ratios for eradication suggested superiority of ST over CT for both 7 -day and 10 -day regimens (1.23, CI 1.19–1.27 and 1.16, CI 1.1– 1.23, respectively). The frequency of adverse effects of therapy was similar between the groups. Gatta *et al* included studies published up to October 2008 in their meta-analysis and again suggested a benefit of ST over CT, with an odds ratio for eradication of 1.98 (95% CI: 0.96–4.07) in the pediatric trials [52]. While publication bias is an unlikely explanation of the findings, a number of over-riding concerns remain concerning the use of ST based on these analyses to date. The quality of the studies included was variable, and almost all were conducted in Italy. In addition, the number of patients in the individual trials has been relatively small and compliance concerns regarding a regimen that involves changing medications at the mid-point persist. Whether the medications in the ST regimen would be as effective if given 'conventionally' rather than sequentially is also unclear. These questions remain to be answered by well-designed, multi-center, high-quality studies in different geographic regions before ST is adopted as the new 'first line' eradication regimen for children.

Probiotic Therapy

A lack of benefit of probiotic administration on *H. pylori* eradication in children was reported in two studies this year. In a randomized, double-blind placebo-controlled trial, Szajewska *et al* randomized children receiving 7 days of triple eradication therapy to either supplementation with 109 colony-forming units

of Lactobacillus GG (n = 44) or placebo (n = 39) [53]. Subjects were recruited over a 40-month period, and complete data were only available in 34 of 44 children in the probiotic group and 32 of 39 children in the placebo group. No statistically significant benefit of probiotic supplementation over placebo was evident in terms of either eradication (69% versus 68%) or side effects. There was a no significant trend toward less regimen-associated diarrhea in probiotic treated children (6% versus 20%), although the study may have been underpowered to detect such differences with significance. In a study using functional food to deliver probiotics (cheese containing Lactobacillus gasseri OLL2716), Boonyaritichaikij *et al* studied the effects of probiotic supplementation in two groups of asymptomatic kindergarten children in Thailand – with or without *H. pylori* as determined by stool antigen testing (n = 132 and 308, respectively) [54]. The eradication arm of the study was single-blinded and nonrandomized, whereas the prevention arm was randomized and stratified for age and gender. Compliance was evaluated by the children's teachers. No statistically significant difference was detected between placebo and probiotic treatments in either the eradication or prevention arm of the study.

RE-INFECTION AND SPONTANEOUS BACTERIAL CLEARANCE

The extent of spontaneous clearance of *H. pylori* infection in childhood remains unclear. The Pasitos cohort study was established in 1998 to prospectively study *H. pylori* infection in Hispanic children [55]. A recent follow-up report from this study examined the effect of incidental antibiotic exposure on subsequent *H. pylori* clearance, based on ^{13}C-UBT changes and parental documentation of medication exposure [56]. Medication dose and duration were not recorded. A remarkable 78% of 218 children with a previously positive UBT subsequently tested negative, especially those between ages 1–3. Of the 205 children with complete medication exposure data, 36% received at least one antibiotic course following the initial positive UBT, while 68% had a subsequent negative UBT. Notwithstanding the number of significant limitations of this study, incidental antibiotic exposure in this study cohort seemed to account for a relatively limited proportion of 'spontaneous clearance' of *H. pylori* infection.

VACCINATION

A recent editorial questioned the benefit of eliminating *H. pylori*, as only 10–15% of hosts develop ulcerations and only 1% gastric adenocarcinoma. Vaccination can not yet be recommended, as our understanding of the bacterium is too

preliminary to make complete eradication a feasible option [57]. Several studies have suggested the merits of prophylactic immunization [12,58]. Rupnow *et al* quantified the cost-effectiveness of a prophylactic vaccine in the USA, using variables including costs of vaccine, vaccine administration, gastric cancer treatment, efficacy, quality adjustment caused by gastric cancer, and discount rate for periods of 10–75 years. They concluded that with a time horizon beyond 40 years, the use of such a vaccine could be cost-effective in the USA, especially if administered to infants or newborns. However, the problem is that the efficacy is unknown. This strategy would be different in less developed countries, where rates of *H. pylori* prevalence remain high. If prevention of ulcer disease is included in the calculation, vaccination may also have some shorter term cost-benefits [58]. In Australia, Hickey *et al* reported that transcutaneous immunization (TCI) with a lipid-based formulation against *H. pylori* infection in mice partially protected them against challenge with live *H. pylori*; this was not associated with development of gastric inflammation [59]. Successful vaccination strategies in mice have not proven effective in human subjects. However, TCI may be effective as a route for inducing protection against *H. pylori* colonization and warrants further study.

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