Eradication of *Helicobacter pylori* to prevent gastroduodenal diseases: Hitting more than one bird with the same stone

Therapeutic Advances in Gastroenterology
(2008) 1(2) 111–120
DOI: 10.1177/1756283X08094880

Yi-Chia Lee, Jyh-Ming Liou, Ming-Shiang Wu, Chun-Ying Wu and Jaw-Town Lin

***Abstract*:** *Helicobacter pylori* (*H. pylori*) are gram-negative bacteria that selectively colonizes the gastric mucosa. The prevalence of *H. pylori* infection varies from 20 to 50% in industrialized countries to over 80% in developing countries. The infection may persist lifelong without specific treatment. Prolonged infection and inflammation due to bacterial virulence and host genetic factors will lead to chronic gastritis. A certain portion of infected patients then develop more severe pathologies such as peptic ulcer (10–15%), gastric cancer (1%), and mucosa-associated lymphoid tissue lymphoma (<0.01%). Although the majority of infected patients remain asymptomatic, much of the evidence has shown that eradication of *H. pylori* infection can reduce the recurrence of peptic ulcer and benefit a substantial portion of patients with nonulcer dyspepsia. Though controversial in population-based clinical trials, several cost-effectiveness analyses also reveal that *H. pylori* eradication is cost effective in the primary prevention of gastric cancer. Therefore, the discovery of *H. pylori* offers the chance to prevent several gastroduodenal diseases by means of their eradication. In other words, gastroenterologists could hit more than one bird with one stone. However, there are concerns regarding application of a 'test and treat' strategy in the general population. In this review, we will focus on current evidence of *H. pylori* eradication in the primary and secondary prophylaxis of gastric cancer and peptic ulcer disease.

***Keywords*:** Helicobacter pylori, eradication, gastric cancer, peptic ulcer, nonulcer dyspepsia, prevention

Correspondence to:
Prof Jaw-Town Lin MD, Phd
Department of Internal Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan and Department of Internal Medicine, E-DA Hospital/Kaohsiung County I-Shou University No. 7, Chung-Shan South Road, Taipei, Taiwan
jawtown@ntu.edu.tw

Yi-Chia Lee
Departments of Internal Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan and Division of Biostatistics, Graduate Institute of Epidemiology, College of Public Health, National Taiwan University, Taipei, Taiwan

Jyh-Ming Liou
Ming-Shiang Wu
Departments of Internal Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan

Chun-Ying Wu
Department of Internal Medicine, Veteran General Hospital, Taichung, Taiwan

Introduction

Helicobacter pylori are gram-negative bacteria that selectively colonize the gastric mucosa, and have been shown to be an important risk factor for several gastroduodenal diseases, including gastric malignancy and peptic ulcer diseases [Wu *et al.* 2005; Peek and Blaser, 2002; Suerbaum and Michetti, 2002]. This infection is usually acquired in childhood and may persist lifelong without specific treatment [Feldman, 2001; Rowland *et al.* 1999]. The prevalence of *H. pylori* infection varies from 20 to 50% in industrialized countries to over 80% in developing countries [Suerbaum and Michetti, 2002; Feldman, 2001; Rowland *et al.* 1999]. Prolonged infection and inflammation due to bacterial virulence and host genetic factors will lead to one of the three phenotypes of gastritis: (1) mild pan-gastritis, (2) corpus-predominant gastritis, and (3) antrum-predominant gastritis [Suerbaum and Michetti, 2002; Dixon, 2001]. Patients with mild pan-gastritis usually do not have alterations in gastric physiology and do not have clinically significant diseases. Patients with corpus-predominant gastritis usually have gastric atrophy and hypochlorhydria and have an increased risk of gastric cancer [Suerbaum and Michetti, 2002; Dixon, 2001]. Patients with antrum-predominant gastritis usually have higher secretion of gastric acid and have an increased risk of duodenal ulcer disease [Lochhead and El-Omar, 2007; Suerbaum and Michetti, 2002; Dixon, 2001]. Notably, these three phenotypes of gastritis are not separate entities as there may be a progression from antral predominant to corpus predominant

or to pan-gastritis. Although, the majority of *H. pylori* infected patients will remain asymptomatic throughout their life, about 10–15% patients will have peptic ulcer disease and 1% of patients will have gastric cancer or mucosa-associated lymphoid tissue lymphoma (MALToma) [Suerbaum and Michetti, 2002; Feldman, 2001; Wotherspoon, 1998; Schlemper *et al*. 1996; Parsonnet *et al*. 1994]. Besides, a certain portion of patients with nonulcer dyspepsia (NUD) are associated with *H. pylori* infection and may benefit from eradication therapy [Moayyedi *et al*. 2006].

Eradication of *H. pylori* has been shown to reduce the recurrence of gastric cancer in patients who received endoscopic mucosal resection (EMR) for early gastric cancer and the recurrence of peptic ulcer in patients with peptic ulcer disease [Ford *et al*. 2006; Uemura *et al*. 1997; Van der Hulst *et al*. 1997; Hopkins *et al*. 1996]. Therefore, eradication of *H. pylori* as a secondary prophylaxis to prevent recurrence of peptic ulcer disease and gastric cancer has become the standard treatment in clinical practice. However, whether eradication of *H. pylori* eradication could be further extended as a method for the primary prophylaxis of peptic ulcer or gastric cancer remains controversial. Hypothetically, elimination of *H. pylori* could greatly reduce the occurrence of noncardia gastric cancer because several observational studies have indicated that 60–90% of noncardia gastric cancer is attributable to *H. pylori* [Uemura *et al*. 2001; Lin *et al*. 1995; Forman *et al*. 1991; Nomura *et al*. 1991; Parsonnet *et al*. 1991]. Similarly, it is also expected that eradication of *H. pylori* could reduce the occurrence of peptic ulcer disease because 10–15% of *H. pylori* infected patients will have peptic ulcer disease throughout their life [Suerbaum and Michetti, 2002]. However, there are several issues to be resolved before such kind of prophylactic treatment could be advocated to the general population. In this review, we will focus on current evidence about whether eradication of *H. pylori* can prevent gastric cancer, peptic ulcers and several other gastroduodenal diseases, and in other words, can we hit more than one bird with one stone?

Eradication of *H. pylori* in the prevention of gastric cancer

Gastric cancer is the second most common cause of cancer-related death. Unless detected early, it is associated with high mortality rate and poor prognosis. Early detection of gastric cancer through a nationwide screening program has been conducted in Japan since 1970s. This program leads to early detection of gastric cancer and improved survival of gastric cancer, but this kind of secondary prevention program does not reduce the incidence of gastric cancer. Therefore, primary prevention by identification of risk factors for gastric cancer and elimination of these factors might be more ideal in reducing the incidence of gastric cancer.

Since the successful culture of *H. pylori* in 1983, several nested case control studies and meta-analysis have shown the strong and consistent association of *H. pylori* and gastric cancer [Lin *et al*. 1995; Forman *et al*. 1991; Nomura *et al*. 1991; Parsonnet *et al*. 1991]. *H. pylori* infected patients have 2–7 fold increased risk of gastric cancer than those without this infection [Lin *et al*. 1995; Forman *et al*. 1991; Nomura *et al*. 1991; Parsonnet *et al*. 1991]. The association was even stronger (OR 5.9) when blood samples used for *H. pylori* serology were obtained 10 years or longer before cancer diagnosis [Lin *et al*. 1995; Parsonnet *et al*. 1991; Nomura *et al*. 1991; Forman *et al*. 1991]. In animal models, Watanabe *et al*. reported that 37% of Mongolian gerbils developed gastric cancer 62 weeks after oral inoculation of *H. pylori* [Watanabe *et al*. 1998]. These animal studies have solidified the causal relationship between *H. pylori* infection and gastric cancer [Watanabe *et al*. 1998]. A prospective observational study in Japan further showed that gastric cancer developed in 2.9% of 1246 patients with *H. pylori* infection over 7.8 years, whereas none of the 280 uninfected subjects developed gastric cancer [Uemura *et al*. 2001]. These epidemiological studies indicate that *H. pylori* is a necessary but not sufficient cause of gastric cancer and that elimination of this bacterium has the potential to prevent the occurrence of gastric cancer [Uemura *et al*. 2001; Lin *et al*. 1995; Forman *et al*. 1991; Nomura *et al*. 1991; Parsonnet *et al*. 1991].

The goal of *H. pylori* eradication in the prevention of gastric cancer can be divided into two parts. The first part is secondary prophylaxis: eradication of *H. pylori* in patients with gastric cancer after curative resection to prevent the recurrence of gastric cancer. The second part is primary prophylaxis: eradication of

H. pylori-infected noncancer patients to prevent the occurrence of gastric cancer.

Secondary prophylaxis: prevention of gastric cancer recurrence

Uemura and colleagues performed a nonrandomized trial in patients with early gastric cancer removed by EMR to evaluate the efficacy of eradication therapy in the prevention of recurrent gastric cancer [Uemura *et al*. 1997]. They found that none of the 65 patients who received eradication therapy had recurrent gastric cancer after three years of follow-up, whereas 6 (9%) of the 67 patients without eradication therapy experienced recurrent gastric cancer. A large-scale multicenter randomized trial comparing the recurrence rate of gastric cancer after EMR with and without eradication of *H. pylori* is ongoing in Japan and the result will be analyzed in 2008 [Kato *et al*. 2007]. The forthcoming results will provide further evidence about the effect of *H. pylori* eradication in the secondary prophylaxis of gastric cancer recurrence after curative resection.

Primary prophylaxis: prevention of gastric cancer occurrence

Ideally, randomized controlled studies could provide the strongest evidence about whether *H. pylori* eradication reduces the incidence of gastric cancer. However, such kinds of studies are difficult to conduct for the following reasons. First, if we choose cancer as the endpoint, a large number of subjects (~18,000) has to be recruited and it will take one to two decades to observe the difference because the incidence of gastric cancer is low [Graham and Shiotani, 2005]. Second, it is difficult and relatively unethical to randomize an *H. pylori*-infected patient into an untreated arm because this bacterium has been classified as a type I carcinogen since 1994. Therefore, only one randomized trial conducted in China before 1994 has demonstrated a 37% reduced risk after 7.5 years in the *H. pylori* eradication group [Wong *et al*. 2004]. Although this result was not statistically significant, subgroup analysis showed that the incidence of gastric cancer for subjects without premalignant lesions (e.g., atrophic gastritis, intestinal metaplasia, and dysplasia) was substantially reduced [Wong *et al*. 2004]. The results suggested that the benefits of *H. pylori* eradication might diminish in the presence of premalignant lesions in which many types of molecular damage have become irreversible [Wong *et al*. 2004]. This hypothesis was supported in two recent animal models [Lee *et al*. 2008; Romero-Gallo *et al*. 2008]. In an *H. pylori*-infected transgenic INS-GAS mice model, Lee and collogues found that *H. pylori* eradication at 8, 12, and 22 weeks postinfection (WPI) significantly reduced the severity of dysplasia [Lee *et al*. 2008]. However, the development of GIN was completely prevented only in mice that received *H. pylori* eradication at eight WPI. In a Mongolian gerbils model, Romero-Gallo *et al*. also found that none of the animals treated with antibiotics at four weeks of infection developed gastric cancer, whereas eradication of *H. pylori* eight weeks after infection resulted in an attenuation, but not complete prevention, of premalignant and malignant lesions [Romero-Gallo *et al*. 2008].

Instead of using the occurrence of gastric cancer as an endpoint, several randomized controlled studies used surrogate outcomes of histological regression (atrophic gastritis and intestinal metaplasia) as the endpoint of *H. pylori* eradication [Sung *et al*. 2000]. The limitation of such kind of studies is that the annual incidence of gastric cancer is as low as 0.1% for patients with atrophic gastritis and 0.25% for patients with intestinal metaplasia [de Vries *et al*. 2008]. Alternatively, several cost effectiveness analyses with computer simulation to predict the late benefits of *H. pylori* eradication have been conducted [Lee *et al*. 2007; Roderick *et al*. 2003; Wang *et al*. 2003; Fendrick *et al*. 1999; Harris *et al*. 1999; Parsonnet *et al*. 1996]. Most of these cost-effectiveness analyses have found that eradication of *H. pylori* is cost-effective in terms of primary prevention of gastric cancer. In the United States where the prevalence of gastric cancer is low, Parsonnet *et al*. found that the benefit would be optimized if chemoprevention were implemented in patients aged 50–70 years and if it targeted high-risk populations (e.g., Japanese Americans) [Parsonnet *et al*. 1996]. In contrast, Fendrick *et al*. reported that testing and treating at an initial age of 40 years was most cost effective [Fendrick *et al*. 1999]. In the United Kingdom, Roderick *et al*. also confirmed the cost effectiveness of population screening for *H. pylori* [Roderick *et al*. 2003]. Harris *et al*. found that screening for CagA-positive strains alone did not improve cost effectiveness compared with screening for all *H. pylori* strains [Harris *et al*. 1999]. In areas

where gastric cancer is highly prevalent, Wang *et al*. suggested that testing and treating for *H. pylori* infection would be feasible in China if eradication could prevent 50% of gastric cancers [Wang *et al*. 2003]. In Taiwan, a recent cost-effectiveness analysis comparing primary and secondary preventive strategies for gastric cancer showed that early *H. pylori* eradication once in lifetime seems more cost effective than the surveillance strategy [Lee *et al*. 2007].

Helicobacter pylori eradication in the prevention of peptic ulcer

Secondary prophylaxis – prevention of ulcer recurrence

Peptic ulcer disease is a common disease worldwide and the lifetime prevalence in the adult population is ~10% [Dobrilla *et al*. 1993]. Patients with peptic ulcer diseases can be troubled by recurrent bouts of pain and severe complications. Before the era of *H. pylori* eradication, ~20–25% of patients with peptic ulcer disease would develop complications such as bleeding, perforation, or obstruction [Penston, 1993]. The expenditures attributed to recent ulcers were reported to be as high as $5.65 billion per year in the United States [Sonnenberg and Everhart, 1997]. *H. pylori* infection is present in 90–100% of duodenal ulcer patients and in 60–90% of gastric ulcer patients [Tytgat, 1998]. Several studies have shown that *H. pylori* infection is associated with at least 3–4 fold increased risk of peptic ulcer diseases and that 10–15% of *H. pylori*-infected individuals will have peptic ulcer disease in their lifetime [Kuipers *et al*. 1995]. It was estimated that approximately one-third of patients who present with a bleeding ulcer will develop recurrent bleeding in the following 1–2 years without testing for, and eradication of, *H. pylori* [Laine, 1996].

After successful eradication of *H. pylori* with antibiotics, the risk of ulcer recurrence is reduced dramatically to 5–20% at 1 year [Ford *et al*. 2006; Van der Hulst *et al*. 1997; Hopkins *et al*. 1996; Imperiale *et al*. 1995]. A prospective long-term follow-up study in patients without aspirin or NSAIDs use also showed that none of the *H. pylori*-eradicated patients with duodenal ulcers (141 patients) and gastric ulcers (45 patients) had an ulcer relapse after a mean follow-up for 9.8 years [Van der Hulst *et al*. 1997]. In a meta-analysis, Hopkins *et al*. found that ulcer recurrence was significantly less common among *H. pylori*-cured patients as compared to noncured patients (6% vs. 67% for patients with duodenal ulcers; 4% vs. 59% for patients with gastric ulcers) [Hopkins *et al*. 1996]. In a recent meta-analysis, Ford *et al*. also revealed that *H. pylori* eradication therapy was superior to no treatment in preventing duodenal ulcer recurrence (relative risk (RR) = 0.19; 95% Confidence Interval (CI) = 0.15 to 0.26) and gastric ulcer recurrence (RR = 0.31; 95% CI = 0.19 to 0.48) [Ford *et al*. 2006]. Eradication of *H. pylori* also promotes duodenal ulcer healing, as compared to ulcer healing drug (RR = 0.66; 95% CI = 0.58 to 0.76) and no treatment (RR = 0.37; 95% CI 0.26 to 0.53) [Ford *et al*. 2006]. Several health economic models also suggest that *H. pylori* eradication is cost-effective in reducing the recurrence of peptic ulcer disease [Ford *et al*. 2004; Ofman *et al*. 2002; Leodolter *et al*. 2001; Imperiale *et al*. 1995]. Imperiale *et al*. showed that initial *H. pylori* eradication provides the lowest costs per symptomatic cure and was associated with lower recurrence rates than initial treatment with an H2-receptor antagonist [Imperiale *et al*. 1995]. Leodolter *et al*. compared the eradication, healing, and relapse rates in patients with *H. pylori*-associated gastric or duodenal ulcer and concluded that the cure rates are similar for both gastric and duodenal ulcer [Leodolter *et al*. 2001]. In a Markov model, Ford *et al*. found *H. pylori* eradication is cost-effective for duodenal ulcer over one year and gastric ulcer over two years [Ford *et al*. 2004]. Ofman *et al*. reported that test/retest strategies for *H. pylori* can result in fewer recurrent hemorrhages and fewer patients requiring antisecretory therapy and are cost-effective for the prevention of recurrent ulcer-related hemorrhage [Ofman *et al*. 2002]. Therefore, eradication of *H. pylori* in infected patients with peptic ulcer has become the standard treatment in clinical practice.

Primary prophylaxis – prevention of ulcer occurrence

As previous observational studies have indicated that 10–15% of *H. pylori* infected patients will have peptic ulcer disease throughout their life, eradication of *H. pylori* can theoretically reduce and prevent the occurrence of peptic ulcer diseases [Tytgat, 1998; Kuipers *et al*. 1995]. However, a randomized controlled study on this

topic for the general population is lacking except for patients with ulcer-like functional dyspepsia and naïve nonsteroidal anti-inflammatory drug (NSAID) users [Vergara *et al*. 2005; Huang *et al*. 2002; Hsu *et al*. 2001]. In patients with 'ulcer-like' functional dyspepsia, Hsu *et al*. reported that eradication of *H. pylori* can prevent the subsequent development of peptic ulcers in a double-blind, placebo-controlled trial followed for one year in Taiwan [Hsu *et al*. 2001]. *H. pylori* infection and aspirin/NSAID use were reported to have synergistic effects in the development of peptic ulcer and ulcer bleeding in a meta-analysis [Huang *et al*. 2002]. Huang *et al*. reported that *H. pylori* infection increased the risk of peptic-ulcer disease in NSAID takers 3.53-fold in addition to the risk associated with NSAID use [Huang *et al*. 2002]. Eradication of *H. pylori* was reported to reduce the incidence of peptic ulcer in the patients receiving NSAID in some randomized clinical trials [Vergara *et al*. 2005]. In a meta-analysis that included five studies and 939 patients, Vergara *et al*. found that 7.4% (34/459) patients developed a peptic ulcer in the eradicated group, as compared to 13.3% (64/480) in the control group. Subanalyses further showed a significant reduction of risk for NSAIDs-naïve [Odds Ratio (OR) = 0.26] but not for previously treated patients [Vergara *et al*. 2005]. Yet, eradication seems less effective than maintenance proton pump inhibitor (PPI) therapy for preventing ulcers [Vergara *et al*. 2005]. Peptic ulcer developed in 2.6% (5/196) patients in the *H. pylori* eradication group, as compared to 0% (0/189) in the maintenance PPI group (OR = 7.43) [Vergara *et al*. 2005]. Based on this evidence, it has been recommended that naïve NSAID users be tested and treated for *H. pylori* infection before initiation of NSAID [Malfertheiner *et al*. 2007]. A similar strategy is also suggested for naïve aspirin users, although the efficacy of such an approach has not been evaluated yet [Papatheodoridis and Archimandritis, 2005]. In summary, *H. pylori* eradication may prevent peptic ulcer and/or bleeding in naïve users of NSAIDs. *H. pylori* eradication is also of value in chronic NSAID users but it is insufficient to prevent NSAID-related ulcer disease completely. PPI maintenance therapy is better than *H. pylori* eradication alone in the prevention of ulcer recurrence for chronic NSAID users who have already experienced peptic ulcer and/or ulcer bleeding [Malfertheiner *et al*. 2007].

Helicobacter pylori eradication in the treatment of NUD

Dyspepsia is a common problem worldwide, with an annual prevalence of 25–30% in Western countries and 10–20% in Asia-Pacific regions [Lam and Talley, 1998; Talley *et al*. 1998]. Due to the large burden of this problem, it has been recommended that endoscopy be reserved for patients at higher risk for malignancy, including those with older age, having alarm features, and a positive family history of gastroesophageal malignancy [Ikenberry *et al*. 2007; Talley *et al*. 2005; Tytgat, 2002; Wai *et al*. 2002]. A 'test and treat' strategy has been recommended in younger patients and the age cut-off point may vary between countries, depending on the local prevalence of gastric cancer [Ikenberry *et al*. 2007; Liou *et al*. 2005; Tytgat, 2002; Wai *et al*. 2002]. However, around 60% of the patients with dyspepsia do not have obvious organic lesions after thorough investigation and were referred to as having NUD [Williams *et al*. 1988]. NUD is a complex disease entity with respect to its pathophysiology and can be categorized into three groups: ulcer-like, dysmotility-like, and reflux-like dyspepsia according to their predominant symptoms [Tack *et al*. 2006]. As a result, there is no clear evidence on the best treatment for this disease. As patients with typical reflux symptoms usually respond well to empirical PPIs, the discussion in this article is limited on functional dyspepsia which exclude 'reflux-type' of dyspepsia [Tack *et al*. 2006].

The role of *H. pylori* in the pathogenesis of NUD has been debated for years. The prevalence of *H. pylori*-associated gastritis in patients with NUD has ranged from 39% to 87% [Tytgat *et al*. 1993; Loffeld *et al*. 1989]. Although, some studies have shown that patients infected with *H. pylori* are more likely to have ulcer-like dyspepsia rather than dysmotility-like dyspepsia, other studies failed to find such kind of association [Andersson *et al*. 1994; Trespi *et al*. 1994; Wyatt *et al*. 1990]. Previous randomized controlled trials evaluating the effect of *H. pylori* eradication on NUD also met with conflicting results, probably related to the lack of a validated dyspepsia questionnaire in the outcome assessment, short follow-up period, and inadequate *H. pylori* eradication regimens [Jaakkimainen *et al*. 1999; Laheij *et al*. 1996]. In a recent meta-analysis including well-designed randomized controlled trials comparing the efficacy of *H. pylori* eradication for patients with NUD,

Moayyedi *et al*. found that there was a 10% RR reduction in the *H. pylori* eradication group (95% CI = 6% to 14%) compared to placebo [Moayyedi *et al*. 2006]. The number needed to treat to cure one case with NUD is 14 (95% CI = 10 to 25). It was concluded that *H. pylori* eradication therapy has a small but statistically significant effect in *H. pylori*-positive NUD [Moayyedi *et al*. 2006].

In contrast to developing countries where the prevalence of gastric cancer is high, the focus of cost-effectiveness analyses of population *H. pylori* eradication in developed countries is usually on saving costs related to managing dyspepsia. In the United Kingdom, Moayyedi *et al*. found that dyspepsia-related expenditures declined after *H. pylori* was eradicated and that the savings were greater than the initial cost of a 'test and treat' strategy [Moayyedi *et al*. 2000]. Lane *et al*. also confirmed that the 'test and treat' strategy could reduce the costs associated with dyspepsia by 30% at two years after eradication [Lane *et al*. 2006]. However, in areas of low *H. pylori* prevalence (< 20%), PPI empirical treatment is the preferred treatment of choice than the 'test and treat' strategy [Malfertheiner *et al*. 2007; Spiegel *et al*. 2002].

Concerns about *H. pylori* eradication in the general population

Although, eradication of *H. pylori* has the opportunity to prevent the occurrence and recurrence of gastric cancer and peptic ulcer disease, several potential risks should be taken into consideration before population 'test and treat' programs are started [Malfertheiner *et al*. 2005]. First, does the use of antibiotics increase the antibiotic resistance rate of *H. pylori* and other bacterial flora of gastrointestinal tract in the population? Several ecological studies have shown a positive correlation between the resistance rate of *H. pylori* to macrolides and the consumption of these drugs [Perez Aldana *et al*. 2002; Cars *et al*. 2001; Glupczynski *et al*. 2001; Granizo *et al*. 2000; Ena *et al*. 1998]. Several hospital-based studies also showed a similar association [Harthug *et al*. 2002; Lepper *et al*. 2002; Gulbinovic *et al*. 2001]. However, whether the results from ecological studies can also be observed at an individual level and in the community remains unknown. Besides, whether the antimicrobial resistance rate for bacteria other than *H. pylori* would also increase after eradication therapy for *H. pylori* also deserves our attention, but only few data are available at this time [Sjolund *et al*. 2003; Adamsson *et al*. 1999]. Two studies have showed that the MICs against *Streptococcus* species and *Enterococcus* species have increased after administration of amoxycillin and clarithromycin. However, whether the induction of resistant strains of bacteria is transient or persistent remains controversial [Sjolund *et al*. 2003; Adamsson *et al*. 1999]. Therefore, further community-based randomized controlled trials with larger sample size and longer follow-up periods are warranted to clarify the risk. Second, reinfection after successful *H. pylori* eradication could counterbalance the merit of eradication therapy. Although, the reported annual reinfection rate seems to be relatively low (~3%) in developed countries, the annual reinfection rate could be greater than 10% in some developing countries where local sanitary conditions are poor [Gisbert 2005]. Thirdly, whether eradication of *H. pylori* will increase the severity of preexisting gastroesophageal reflux disease (GERD) or increase the risk of newly onset GERD is another concern. A meta-analysis including 20 case control studies evaluating the prevalence of *H. pylori* in patients with GERD showed that patients from the Far East with reflux disease had a lower prevalence of *H. pylori* infection than patients from western countries [Raghunath *et al*. 2003]. Some epidemiological studies also showed a reverse association between *H. pylori* CagA seropositivity and the risk of esophageal adenocarcinoma, but this observation remains controversial [Ye *et al*. 2004; Wu *et al*. 2003; Chow *et al*. 1998]. However, the 6–20 folds increased risk of gastric adenocarcinoma associated with *H. pylori* infection should outweigh the uncertain and weak protective role of *H. pylori* infection for esophageal adenocarcinoma [Malfertheiner *et al*. 2005]. Therefore, it is generally agreed that the decision to eradicate *H. pylori* should not be withheld due to concerns about the risk of developing GERD and esophageal cancer [Malfertheiner *et al*. 2007; Malfertheiner *et al*. 2005]. Finally, some studies have reported an inverse association of *H. pylori* infection and childhood asthma, allergic rhinitis and atopy [Blaser *et al*. 2008]. Although, this inverse relationship remains controversial, *H. pylori* might be beneficial in childhood and becomes more deleterious later in life. Together with the higher reinfection rate after *H. pylori* eradication in childhood, primary prophylaxis of gastroduodenal disorders by means of *H. pylori*

eradication cannot be recommended in childhood based on current evidence.

Conclusion

H. pylori eradication is the treatment of choice for patients with peptic ulcer and low grade gastric MALToma. Current evidence also supports *H. pylori* eradication to prevent the recurrence of peptic ulcer and gastric cancer (secondary prophylaxis). 'Test and treat' for *H. pylori* infection is also recommended for naïve NSAID users to prevent peptic ulcer disease (primary prophylaxis) and for patients with NUD. Several economic models and some clinical trails suggest that *H. pylori* eradication is cost effective in the primary prevention of gastric cancer, especially in high-risk populations. However, concerns regarding the increased antibiotic resistance rate of *H. pylori* and other bacteria exist and should be clarified before implementation of a 'test and treat' strategy at a population level. Besides, evidence to support primary prevention of peptic ulcer by means of *H. pylori* eradication is lacking. Therefore, although primary prophylaxis of peptic ulcer and gastric cancer through *H. pylori* eradication is theoretically plausible, more data are needed before we can apply such kind of chemoprevention to the general population. Alternatively, identifying subpopulations at higher risk for developing significant *H. pylori*-associated gastroduodenal disease might be a more ideal alternative strategy to the strategy of eradication of *H. pylori* in the whole population. Future studies are warranted to improve techniques in the identification of high-risk subpopulations (e.g., genetic polymorphisms in proinflammatory cytokines and strain characteristics of *H.* pylori) and to evaluate the cost effectiveness of a tailored 'test and treat' strategy.

Acknowledgment

All authors contributed equally to the preparation of this manuscript.

Conflict of interest statement

None declared.

References

Adamsson, I., Nord, C.E., Lundquist, P., Sjöstedt, S. and Edlund, C. (1999) Comparative effects of omeprazole, amoxycillin plus metronidazole versus omeprazole, clarithromycin plus metronidazole on the oral, gastric and intestinal microflora in *Helicobacter pylori*-infected patients. *J Antimicrob Chemother* 44: 629–640.

Andersson, S.I., Hovelius, B., Molstad, S. and Wadstrom, T. (1994) Dyspepsia in general practice: psychological findings in relation to *Helicobacter pylori* serum antibodies. *Journal of Psychosomatic Research* 38: 241–247.

Blaser, M.J., Chen, Y. and Reibman, J. (2008) Does *Helicobacter pylori* protect against asthma and allergy? *Gut* 57: 561–567.

Cars, O., Mölstad, S. and Melander, A. (2001) Variation in antibiotic use in the European Union. *Lancet* 357: 1851–1853.

Chow, W.H., Blaser, M.J., Blot, W.J., Gammon, M.D., Vaughan, T.L., Risch, H.A. *et al.* (1998) An inverse relation between CagA+ strains of *Helicobacter pylori* infection and risk of esophageal gastric cardia adenocarcinoma. *Cancer Res* 58: 588–590.

de Vries, A.C., van Grieken, N.C., Looman, C.W., Casparie, M.K., de Vries, E., Meijer, G.A. *et al.* (2008) Gastric cancer risk in patients with premalignant gastric lesions: a nationwide cohort study in the Netherlands. *Gastroenterology* 134: 945–952.

Dobrilla, G., Zancanella, L. and Amplatz, S. (1993) The need for long-term treatment of peptic ulcer. *Alimentary Pharmacology and Therapeutics* 7(Suppl 2): 3–15.

Dixon, M.F. (2001) Pathology of gastritis and peptic ulceration. In Mobley, H.L.T., Mendz, G.L. and Hazell, S.L. (eds) *Helicobacter pylori: physiology and genetics*. Washington, D.C.ASM Press, 459–469.

Ena, J., Lopez-Perezagua, M.M., Martinez-Peinado, C., Cia-Barrio, M.A., Ruíz-López, I. *et al.* (1998) Emergence of ciprofloxacin resistance in *Escherichia coli* isolates after widespread use of fluoroquinolones. *Diagn Microbiol Infect Dis* 30: 103–107.

Feldman, R.A. (2001) Epidemiologic observations and open questions about disease and infection caused by *Helicobacter pylori*. In Achtman, M and Suerbaum, S. (eds) *Helicobacter pylori: molecular and cellular biology*. Wymondham, United Kingdom, Horizon Scientific Press, 29–51.

Fendrick, A.M., Chernew, M.E., Hirth, R.A., Bloom, B.S., Bandekar, R.R. and Scheiman, J.M. (1999) Clinical and economic effects of population-based *Helicobacter pylori* screening to prevent gastric cancer. *Arch Intern Med* 159: 142–148.

Ford, A.C., Delaney, B.C., Forman, D. and Moayyedi, P. (2004) Eradication therapy in *Helicobacter pylori* positive peptic ulcer disease: systematic review and economic analysis. *Am J Gastroenterol* 99: 1833–1855.

Ford, A.C., Delaney, B.C., Forman, D. and Moayyedi, P. (2006) Eradication therapy for peptic ulcer disease in *Helicobacter pylori* positive patients. *Cochrane Database Syst Rev* 2: CD 003840.

Forman, D., Newell, D.G., Fullerton, F., Yarnell, J.W., Stacey, A.R., Wald, N. *et al.* (1991) Association between infection with *Helicobacter pylori* and risk of gastric cancer: evidence from a prospective investigation. *BMJ* 302: 1302–1305.

Gisbert, J.P. (2005) The recurrence of *Helicobacter pylori* infection: incidence and variables influencing it. A critical review. *Am J Gastroenterol* 100: 2083–2099.

Glupczynski, Y., Mégraud, F., Lopez-Brea, M. and Andersen, L.P. (2001) European multicentre survey of *in vitro* antimicrobial resistance in *Helicobacter pylori*. *Eur J Clin Microbiol Infect Dis* 20: 820–823.

Graham, D.Y. and Shiotani, A. (2005) The time to eradicate gastric cancer is now. *Gut* 54: 735–738.

Granizo, J.J., Aguilar, L., Casal, J., García-Rey, C., Dal-Ré, R. and Baquero, F. (2000) *Streptococcus pneumoniae* resistance to erythromycin and penicillin in relation to macrolide and beta-lactam consumption in Spain (1979–1997). *J Antimicrob Chemother* 46: 767–773.

Gulbinovic, J., Myrback, K.E., Bytautiene, J., Wettermark, B., Struwe, J. and Bergman, U. (2001) Marked differences in antibiotic use and resistance between university hospitals in Vilnius, Lithuania, and Huddinge, Sweden. *Microb Drug Resist* 7: 383–389.

Harris, R.A., Owens, D.K., Witherell, H. and Parsonnet, J. (1999) *Helicobacter pylori* and gastric cancer: what are the benefits of screening only for the CagA phenotype of *H. pylori*?. *Helicobacter* 4: 69–76.

Harthug, S., Jureen, R., Mohn, S.C., Högel, J. and Trautmann, M. (2002) Norwegian enterococcal study group. The prevalence of faecal carriage of ampicillin-resistant and high-level gentamicin-resistant enterococci among inpatients at 10 major Norwegian hospitals. *J Hosp Infect* 50: 145–154.

Hopkins, R.J., Girardi, L.S. and Turney, E.A. (1996) Relationship between *Helicobacter pylori* eradication and reduced duodenal and gastric ulcer recurrence: a review. *Gastroenterology* 1996; 110: 1244–1252.

Hsu, PI., Lai, K.H., Tseng, H.H., Lo, G.H., Lo, C.C., Lin, C.K. *et al.* (2001) Eradication of *Helicobacter pylori* prevents ulcer development in patients with ulcer-like functional dyspepsia. *Aliment Pharmacol Ther* 15: 195–201.

Huang, J.Q., Sridhar, S. and Hunt, R.H. (2002) Role of *Helicobacter pylori* infection and non-steroidal anti-inflammatory drugs in peptic-ulcer disease: a meta-analysis. *Lancet* 359: 14–22.

Ikenberry, S.O., Harrison, M.E., Lichtenstein, D., Dominitz, J.A., Anderson, M.A., Jagannath, S.B. *et al.* (2007) The role of endoscopy in dyspepsia. *Gastrointest Endosc* 66: 1071–1075.

Imperiale, T.F., Speroff, T., Cebul, R.D. and McCullough, A.J. (1995) A cost analysis of alternative treatments for duodenal ulcer. *Ann Int Med* 123: 665–672.

Jaakkimainen, R.L., Boyle, E. and Tudiver, F. (1999) Is *Helicobacter* associated with non-ulcer dyspepsia and will eradication improve symptoms? A meta-analysis. *British Medical Journal* 319: 1040–1044.

Kato, M., Asaka, M., Ono, S., Nakagawa, M., Nakagawa, S., Shimizu, Y. *et al.* (2007) Eradication of *Helicobacter pylori* for primary gastric cancer and secondary gastric cancer after endoscopic mucosal resection. *J Gastroenterol* 42(Suppl 17): 16–20.

Kuipers, E.J., Thijs, J.C. and Festen, H.P. (1995) The prevalence of *Helicobacter pylori* in peptic ulcer disease. *Aliment Pharmacol Ther* 9 (Suppl 2): 59–69.

Laheij, R.J., Jansen, J.B., van de Lisdonk, E.H., Severens, J.L. and Verbeek, A.L. (1996) Review article: symptom improvement through eradication of *Helicobacter pylori* in patients with non-ulcer dyspepsia. *Alimentary Pharmacology and Therapeutics* 10: 843–850.

Laine, L.A. (1996) *Helicobacter pylori* and complicated ulcer disease. *Am J Med* 100(5A): 52S–57S.

Lam, S.K. and Talley, N.J. (1998) Report of the 1997 Asia Pacific Consensus Conference on the management of *Helicobacter pylori* infection. *J Gastroenterol Hepatol* 13: 1–12.

Lane, J.A., Murray, L.J., Noble, S., Egger, M., Harvey, I.M., Donovan, J.L. *et al.* (2006) Impact of *Helicobacter pylori* eradication on dyspepsia, health resource use, and quality of life in the Bristol *Helicobacter* project: randomized controlled trial. *BMJ* 332: 199–204.

Lee, C.W., Rickman, B., Rogers, A.B., Ge, Z., Wang, T.C. and Fox, J.G. (2008) *Helicobacter pylori* eradication prevents progression of gastric cancer in hypergastrinemic INS-GAS mice. *Cancer Res* 68: 3540–3548.

Lee, Y.C., Lin, J.T., Wu, H.M., Liu, T.Y., Yen, M.F., Chiu, H.M. *et al.* (2007) Cost-effectiveness analysis between primary and secondary preventive strategies for gastric cancer. *Cancer Epidemiol Biomarkers Prev* 16: 875–885.

Leodolter, A., Kulig, M., Brasch, H., Meyer-Sabellek, W., Willich, S.N. and Malfertheiner, P. (2001) A meta-analysis comparing eradication, healing and relapse rates in patients with *Helicobacter pylori*-associated gastric or duodenal ulcer. *Aliment Pharm Ther* 15: 1949–1958.

Lepper, P.M., Grusa, E., Reichl, H., Högel, J. and Trautmann, M. (2002) Consumption of imipenem correlates with beta-lactam resistance in *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* 46: 2920–2925.

Lin, J.T., Wang, L.Y., Wang, J.T., Wang, T.H., Yang, C.S. and Chen, C.J. (1995) A nested case-control study on the association between *Helicobacter pylori* infection and gastric cancer risk in a cohort of 9775 men in Taiwan. *Anticancer Res* 15: 603–606.

Liou, J.M., Lin, J.T., Wang, H.P., Huang, S.P., Lee, Y.C., Shun, C.T. *et al.* (2005) The optimal age threshold for screening upper endoscopy for uninvestigated dyspepsia in Taiwan, an area with a higher prevalence of gastric cancer in young adults. *Gastrointest Endosc* 61: 819–825.

Lochhead, P. and El-Omar, E.M. (2007) *Helicobacter pylori* infection and gastric cancer. *Best Pract Res Clin Gastroenterol* 21: 281–297.

Loffeld, R.J., Potters, H.V., Stobberingh, E., Flendrig, J.A., van Spreeuwel, J.P. and Arends, J.W. (1989) *Campylobacter* associated gastritis in patients with non-ulcer dyspepsia: a double blind placebo controlled trial with colloidal bismuth subcitrate. *Gut* 30: 1206–1212.

Malfertheiner, P., Sipponen, P., Naumann, M., Moayyedi, P., Mégraud, F., Xiao, S.D. *et al.* (2005) *H. pylori*-Gastric Cancer Task Force. *Helicobacter pylori* eradication has the potential to prevent

gastric cancer: a state-of-the-art critique. *Am J Gastroenterol* 100: 2100–2115.

Malfertheiner, P., Megraud, F., O'Morain, C., Bazzoli, F., El-Omar, E., Graham, D. *et al.* (2007) Current concepts in the management of *Helicobacter pylori* infection: the Maastricht III Consensus Report. *Gut* 56: 772–781.

Moayyedi, P., Feltbower, R., Brown, J., Mason, S., Mason, J., Nathan, J. *et al.* (2000) Effect of population screening and treatment for *Helicobacter pylori* on dyspepsia and quality of life in the community: a randomized controlled trial. Leeds HELP Study Group. *Lancet* 355: 1665–1669.

Moayyedi, P., Soo, S., Deeks, J., Delaney, B., Harris, A., Innes, M. *et al.* (2006) Eradication of *Helicobacter pylori* for non-ulcer dyspepsia. *Cochrane Database Syst Rev* 19: CD002096.

Nomura, A., Stemmermann, G.N., Chyou, P.H., Kato, I., Perez-Perez, G.I. and Blaser, M.J. (1991) *Helicobacter pylori* infection and gastric carcinoma among Japanese Americans in Hawaii. *N Engl J Med* 325: 1132–1136.

Ofman, J., Wallace, J., Badamgarav, E., Chiou, C.F., Henning, J. and Laine, L. (2002) The cost-effectiveness of competing strategies for the prevention of recurrent peptic ulcer hemorrhage. *Am J Gastroenterol* 97: 1941–1950.

Papatheodoridis, G.V. and Archimandritis, A.J. (2005) Role of *Helicobacter pylori* eradication in aspirin or non-steroidal anti-inflammatory drug users. *World J Gastroenterol* 11: 3811–3816.

Parsonnet, J., Friedman, G.D., Vandersteen, D.P., Chang, Y., Vogelman, J.H., Orentreich, N. *et al.* (1991) *Helicobacter pylori* infection and the risk of gastric carcinoma. *N Engl J Med* 325: 1127–1131.

Parsonnet, J., Hansen, S., Rodriguez, L., Gelb, A.B., Warnke, R.A., Jellum, E. *et al.* (1994) *Helicobacter pylori* infection and gastric lymphoma. *N Engl J Med* 330: 1267–1271.

Parsonnet, J., Harris, R.A., Hack, H.M. and Owens, D.K. (1996) Modelling cost-effectiveness of *Helicobacter pylori* screening to prevent gastric cancer: a mandate for clinical trials. *Lancet* 348: 150–154.

Peek, R.M. and Blaser, M.J. (2002) *Helicobacter pylori* and gastrointestinal adenocarcinoma. *Nat Rev Cancer* 2: 28–37.

Penston, J.G. (1993) A decade of experience with long-term continuous treatment of peptic ulcers with H2-receptor antagonists. *Alimentary Pharmacology and Therapeutics* 7(Suppl 2): 27–33.

Perez Aldana, L., Kato, M., Nakagawa, S., Kawarasaki, M., Nagasako, T., Mizushima, T. *et al.* (2002) The relationship between consumption of antimicrobial agents and the prevalence of primary *Helicobacter pylori* resistance. *Helicobacter* 7: 306–309.

Raghunath, A., Hungin, A.P., Wooff, D. and Childs, S. (2003) Prevalence of *Helicobacter pylori* in patients with gastro-oesophageal reflux disease: systematic review. *BMJ* 326: 737.

Roderick, P., Davies, R., Raftery, J., Crabbe, D., Pearce, R., Patel, P. *et al.* (2003) Cost-effectiveness of population screening for *Helicobacter pylori* in preventing gastric cancer and peptic ulcer disease, using simulation. *J Med Screen* 10: 148–156.

Romero-Gallo, J., Harris, E.J., Krishna, U., Washington, M.K., Perez-Perez, G.I., Peek and R.M.Jr. (2008) Effect of *Helicobacter pylori* eradication on gastric carcinogenesis. *Lab Invest* 88: 328–336.

Rowland, M., Kumar, D., Daly, L., O'Connor, P., Vaughan, D. and Drumm, B. (1999) Low rates of *Helicobacter pylori* reinfection in children. *Gastroenterology* 117: 336–341.

Sonnenberg, A. and Everhart, J.E. (1997) Health impact of peptic ulcer in the United States. *Am J Gastroenterol* 92: 614–620.

Suerbaum, S. and Michetti, P. (2002) *Helicobacter pylori* infection. *N Engl J Med* 347: 1175–1186.

Schlemper, R.J., van der Werf, S.D., Biemond, I. and Lamers, C.B. (1996) Seroepidemiology of gastritis in Japanese and Dutch male employees with and without ulcer disease. *Eur J Gastroenterol Hepatol* 8: 33–39.

Sjolund, M., Wreiber, K., Andersson, D.I., Blaser, M.J. and Engstrand, L. (2003) Long-term persistence of resistant Enterococcus species after antibiotics to eradicate *Helicobacter pylori*. *Ann Intern Med* 139: 483–487.

Spiegel, B.M., Vakil, N.B. and Ofman, J.J. (2002) Dyspepsia management in primary care: a decision analysis of competing strategies. *Gastroenterology* 122: 1270–1285.

Sung, J.J., Lin, S.R., Ching, J.Y., Zhou, L.Y., To, K.F., Wang, R.T. *et al.* (2000) Atrophy and intestinal metaplasia one year after cure of *H. pylori* infection: a prospective, randomized study. *Gastroenterology* 119: 7.

Tack, J., Talley, N.J., Camilleri, M., Holtmann, G., Hu, P., Malagelada, J.R. *et al.* (2006) Functional gastroduodenal disorders. *Gastroenterology* 130: 1466–1479.

Talley, N.J., Silverstein, M.D., Agreus, L., Nyren, O., Sonnenberg, A., Holtmann, G. *et al.* (1998) AGA technical review: evaluation of dyspepsia. American Gastro-enterological Association. *Gastroenterology* 114: 582–595.

Talley, N.J., Vakil, N.B. and Moayyedi, P. (2005) American gastroenterological association technical review on the evaluation of dyspepsia. *Gastroenterology* 129: 1756–1780.

Trespi, E., Broglia, F., Villani, L., Luinetti, O., Fiocca, R. and Solcia, E. (1994) Distinct profiles of gastritis in dyspepsia subgroups. Their different clinical responses to gastritis healing after *Helicobacter pylori* eradication. *Scandinavian Journal of Gastroenterology* 29: 884–888.

Tytgat, G.N., Lee, A., Graham, D.Y., Dixon, M.F. and Rokkas, T. (1993) The role of infectious agents in peptic ulcer disease. *Gastroenterology International* 6: 76–89.

Tytgat, G.N. (1998) Treatment of peptic ulcer. *Digestion* 59: 446–452.

Tytgat, G.N. (2002) Role of endoscopy and biopsy in the work up of dyspepsia. *Gut* 50 (Suppl 4): 13–16.

Uemura, N., Mukai, T., Okamoto, S., Yamaguchi, S., Mashiba, H., Taniyama, K. *et al.* (1997) Effect of

Helicobacter pylori eradication on subsequent development of cancer after endoscopic resection of early gastric cancer. *Cancer Epidemiol Biomarkers Prev* 6: 639–642.

Uemura, N. and Okamoto, S. (2000) Effect of *Helicobacter pylori* eradication on subsequent development of cancer after endoscopic resection of early gastric cancer in Japan. *Gastroenterol Clin North Am* 29: 819–827.

Uemura, N., Okamoto, S., Yamamoto, S., Matsumura, N., Yamaguchi, S., Yamakido, M. *et al.* (2001) *Helicobacter pylori* infection and the development of gastric cancer. *N Engl J Med* 345: 784–789.

Van der Hulst, R.W., Rauws, E.A., Köycü, B., Keller, J.J., Bruno, M.J., Tijssen, J.G. *et al.* (1997) Prevention of ulcer recurrence after eradication of *Helicobacter pylori*: a prospective long-term follow-up study. *Gastroenterology* 113: 1082–1086.

Vergara, M., Catalán, M., Gisbert, J.P. and Calvet, X. (2005) Meta-analysis: role of *Helicobacter pylori* eradication in the prevention of peptic ulcer in NSAID users. *Aliment Pharmacol Ther* 21: 1411–1418.

Wai, C.T., Yeoh, K.G., Ho, K.Y., Kang, J.Y. and Lim, S.G. (2002) Diagnostic yield of upper endoscopy in Asian patients presenting with dyspepsia. *Gastrointest Endosc* 56: 548–551.

Wang, Q., Jin, P.H., Lin, G.W., Xu, S.R. and Chen, J. (2003) Cost-effectiveness of *Helicobacter pylori* screening to prevent gastric cancer: Markov decision analysis. *Zhonghua Liu Xing Bing Xue Za Zhi* 24: 135–139.

Watanabe, T., Tada, M., Nagai, H., Sasaki, S. and Nakao, M. (1998) *Helicobacter pylori* infection induces gastric cancer in mongolian gerbils. *Gastroenterology* 115: 642–648.

Williams, B., Luckas, M., Ellingham, J.H., Dain, A. and Wicks, A.C. (1988) Do young patients with dyspepsia need investigation? *Lancet* 2: 1349–1351.

Wong, B.C., Lam, S.K., Wong, W.M., Chen, J.S., Zheng, T.T., Feng, R.E. *et al.* (2004) *Helicobacter pylori* eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. *JAMA* 291: 187–194.

Wotherspoon, A.C. (1998) *Helicobacter pylori* infection and gastric lymphoma. *Br Med Bull* 54: 79–85.

Wu, A.H., Crabtree, J.E., Bernstein, L., Hawtin, P., Cockburn, M., Tseng, C.C. *et al.* (2003) Role of *Helicobacter pylori* Cag A+ strains and risk of adenocarcinoma of the stomach and esophagus. *Int J Cancer* 103: 815–821.

Wu, M.S., Chen, C.J. and Lin, J.T. (2005) Host-environment interactions: their impact on progression from gastric inflammation to carcinogenesis and on development of new approaches to prevent and treat gastric cancer. *Cancer Epidemiol Biomarkers Prev* 14: 1878–1882.

Wyatt, J.I., Rathbone, B.J., Sobala, G.M., Shallcross, T., Heatley, R.V., Axon, A.T. *et al.* (1990) Gastric epithelium in the duodenum: its association with *Helicobacter pylori* and inflammation. *Journal of Clinical Pathology* 43: 981–986.

Ye, W., Held, M., Lagergren, J., Engstrand, L., Blot, W.J., McLaughlin, J.K. *et al.* (2004) *Helicobacter pylori* infection and gastric atrophy: risk of adenocarcinoma and squamous cell carcinoma of the esophagus and adenocarcinoma of the gastric cardia. *J Natl Cancer Inst* 96: 396–402.