

Helicobacter pylori Public Health Implications

Paul Moayyedi and Richard H. Hunt

Department of Medicine, Gastroenterology Division, McMaster University, Hamilton, Ontario, Canada

ABSTRACT

Population *Helicobacter pylori* screening and treatment has the potential to dramatically reduce global gastric cancer mortality. There is overwhelming evidence that the infection is a major cause of distal gastric adenocarcinoma. There is also randomized controlled trial evidence that *H. pylori* eradication reverses or ameliorates histological changes in the gastric mucosa that are important in carcinogenesis. Preliminary randomized controlled trial data suggest that screening and treatment may reduce the risk of gastric cancer although the number of cancer cases was small. Population *H. pylori* screening and treatment will also reduce mortality from peptic ulcer complications and reduce the burden of dyspepsia in the community. The reduction in health service dyspepsia costs

means that this could be the first programme to pay for itself.

From a scientific perspective, we still have insufficient evidence to conclude the benefits of population *H. pylori* screening are greater than the possible harms and we need more randomized controlled trial data. From a public health perspective however, sometimes screening programmes are developed with imperfect information. The medical community should be consistent and if we are instituting other population screening programmes without randomized controlled trial evidence then *H. pylori* testing and treatment should also be considered.

Keywords. *Helicobacter pylori*, screening, eradication therapy, gastric adenocarcinoma, prevention.

Screening is an important tool in the fight against cancer mortality. Many developed countries offer breast and cervical cancer screening and are considering similar programmes for prostate and colorectal cancer. These strategies aim to detect neoplasia early, at a stage where the lesion is more amenable to treatment. However, one problem of this approach is that it can be difficult to decide whether someone has early cancer. This can lead to unnecessary operations in some patients and in other cases the possibility that early detection is not achieved. Breast cancer is supported by the most comprehensive body of evidence for the efficacy of screening, yet after 30 years of randomized trials in hundreds of thousands of subjects we are unclear whether screening improves mortality despite a 20% increase in the number of mastectomies [1,2].

From a public health perspective it is better to prevent cancer than detect it early. There is overwhelming evidence that *Helicobacter pylori* is a major cause of distal gastric cancer [3] and it is

likely that early treatment of the infection will prevent neoplasia developing [4]. *H. pylori* testing and treatment is increasingly used in the management of dyspepsia [5,6] but this must be offered to a much broader section of the community if there is to be a major impact on gastric cancer at the population level. Recent data have provided more evidence on the effects of population *H. pylori* screening and treatment on gastric cancer as well as other benefits and risks of such a programme.

Gastric cancer and preneoplastic gastric lesions

A meta-analysis of 12 nested case control studies [7] has suggested that *H. pylori* infection is associated with a six-fold increase in the risk of developing noncardia gastric cancer if the sample was taken at least 10 years previously. These data may underestimate the association between *H. pylori* and gastric cancer in high risk populations. The infection is common in populations at highest risk and it can be difficult to demonstrate the magnitude of the problem in areas where most people are infected with *H. pylori* anyway. For example, in Japan the odds ratio for *H. pylori* and gastric cancer is approximately 6

Correspondence: Paul Moayyedi, Department of Medicine, Gastroenterology Division, McMaster University, 1200 Main Street West, HSC-3 N51, Hamilton, Ontario, L8N 3Z5, Canada. Tel.: + 905 525 9140 (Ext. 26688); Fax: + 905 522 3454; E-mail: moayyep@mcmaster.ca

but this increases to 15 in cancer cases less than 40 years of age where the prevalence of infection in the general population is much lower [8]. There is therefore little doubt that *H. pylori* is a major gastric carcinogen but it is less certain whether eradication of the infection will reduce this risk and if so over what age range is therapy effective.

H. pylori infection is associated with both diffuse and intestinal type gastric cancer. Diffuse gastric cancer is thought arise from a background of chronic gastritis and randomized controlled trials suggest that *H. pylori* eradication returns the gastric mucosa to almost normal within 1 year [9–11]. *H. pylori* eradication is therefore very likely to prevent diffuse gastric cancer even if given to older subjects.

Intestinal type gastric cancer is thought to develop from a sequence of chronic gastritis, intestinal metaplasia (IM), gastric atrophy and dysplasia. The impact of *H. pylori* eradication on IM and atrophy is less clear. One large randomized controlled study of Colombian patients with gastric atrophy and/or intestinal metaplasia suggested that *H. pylori* eradication caused regression of both atrophy and IM [12]. A recent RCT has confirmed that *H. pylori* eradication causes regression of gastric atrophy in European esophagitis patients [10]. A further RCT in Chinese patients suggests that *H. pylori* eradication prevents progression [9] rather than causing regression whilst there was no statistically significant change between treatment and placebo after 1 year in an RCT in healthy Mexican volunteers with preneoplastic gastric lesions [13]. The balance of evidence suggests *H. pylori* eradication has a favourable impact on gastric atrophy.

There is now emerging evidence from a randomized controlled trial in 1630 healthy Chinese *H. pylori* positive subjects, from an area with a high incidence of gastric cancer, that eradication may reduce the risk of gastric malignancy [14]. Subjects were randomized to *H. pylori* eradication or placebo and were followed up over 7.5 years. Seven gastric cancers developed in the treatment arm compared with 11 in the control group ($p = .33$). In a *post hoc* analysis of the 988 subjects that did not have precancerous lesions at baseline, gastric cancer developed in none of those receiving *H. pylori* eradication compared with six of the control group ($p = .02$). These data suggest that population *H. pylori* screening and treatment may reduce the risk of gastric cancer particularly when given before precancerous

lesions have developed. Sceptics might argue, however, that the main results of the trial were negative and more information is required before instituting population *H. pylori* screening and treatment [15]. More randomized trials are being conducted and may provide a definitive answer although some are underpowered and having recruitment difficulties [16].

Overall the weight of evidence suggests that *H. pylori* eradication will prevent the majority of gastric cancers that are caused by gastric inflammation and many that are associated with gastric atrophy. There is little evidence that *H. pylori* eradication has any impact on intestinal metaplasia and dysplasia and at this stage therapy may be ineffective [17].

NSAIDs and complicated peptic ulcer disease

Peptic ulcer complications are a significant cause of mortality in developed countries with over 4000 patients dying each year in England and Wales [18]. *H. pylori* infection is the main cause of uncomplicated peptic ulcer disease (PUD) [19] but the proportion of complicated PUD that is attributable to the infection is unclear. It is likely however, that *H. pylori* is the causative agent in most patients not taking NSAIDs. A Cochrane systematic review [20] of randomized controlled trials reported that eradication therapy was superior to no intervention or maintenance antisecretory therapy in preventing recurrent ulceration in *H. pylori* positive patients who were not taking NSAIDs but had a peptic ulcer bleed. The number needed to treat to prevent one ulcer recurrence in patients taking no therapy was five (95% CI = 4–8) and 20 (95% CI = 12–100) in patients taking maintenance antisecretory drugs [20]. These data apply to the efficacy of eradication therapy in secondary prevention of complicated ulcer recurrence. The relative effect of *H. pylori* eradication in primary prevention of complicated peptic ulcer is likely to be similar although the number needed to treat will be much higher as the event rate will be lower in the general population.

H. pylori may also have a role in peptic ulcer complications in patients taking NSAIDs [21]. A meta-analysis of observational data [22] reported that the risk of PUD without complications was increased over three-fold in patients infected with *H. pylori* whilst the risk of a bleeding ulcer was approximately doubled. These data are supported by a recent case-control study where

H. pylori infection almost doubled the risk of upper gastrointestinal bleeding in patients taking NSAIDs [23]. Randomized controlled trials indicate that *H. pylori* eradication reduces the risk of peptic ulcer, with or without complications in patients starting NSAID therapy [24–26]. This includes patients starting low-dose aspirin as *H. pylori* increases the risk of upper GI bleeding [27] and eradication therapy has a similar efficacy to maintenance proton pump inhibitors in preventing ulcer complications [25]. In contrast to NSAID naïve patients, *H. pylori* eradication does not appear to reduce ulcer disease in those already taking NSAID therapy [28]. *H. pylori* eradication alone is insufficient for individual patients that have had an NSAID related peptic ulcer bleed. Nevertheless at a population level screening and treating for *H. pylori* may reduce the burden of NSAID bleeding in the community.

Peptic ulcer bleeding is a significant problem in the developed world with 70 per 100,000 of the general population being admitted to hospital each year [29] at an average cost of €2000 per patient [30] with a 5–15% mortality rate [31]. Randomized controlled trials suggest population *H. pylori* screening and treatment could significantly reduce mortality from ulcer bleeding [20] and this will reduce the cost of associated hospital admissions.

Other benefits of population *H. pylori* screening and treatment

H. pylori infection is the main cause of peptic ulcer disease and may be associated with a small proportion of nonulcer dyspepsia [32]. Population *H. pylori* screening and treatment should therefore reduce the burden of dyspepsia in the community and this has been confirmed by three population based randomized trials [33–35]. The reduction in dyspepsia is only 5–6% but this is expected given the multifactorial nature of upper gastrointestinal symptoms. The first trial randomized 2329 *H. pylori* positive 40–49 years olds from Leeds and Bradford in the UK to eradication therapy or placebo [33]. There was a 5% absolute reduction (95% CI = 1–10%) in the proportion of subjects with dyspepsia in the intervention group at 2 years. This was confirmed by a randomized trial of 1634 *H. pylori* positive 20–59 years olds from Bristol, UK with a 6% reduction in dyspepsia (95% CI = 2–10%) in the *H. pylori* eradication group compared with controls

at 2 years [34]. In these two studies all subjects received *H. pylori* screening with positive participants being randomized to eradication or placebo. A Danish study took a different approach by randomizing over 12,000 subjects aged 40–65 years to *H. pylori* screening or no intervention [33]. Participants randomized to screening all received open label eradication therapy if infected with *H. pylori*. This design assessed the effect of the overall strategy on the population rather than the specific impact of *H. pylori* eradication in positive individuals. Interestingly, this study found a 5% reduction in dyspepsia in both *H. pylori* positive and negative subjects suggesting that those not infected may have been reassured by this knowledge [35]. None of these trials showed any influence on quality of life as the impact on dyspepsia was modest [33,35]. Nevertheless, these data show that a population *H. pylori* screening and treatment programme can have other benefits in addition to a reduction in mortality from distal gastric cancer and complicated PUD. Health economic models have consistently reported that population *H. pylori* screen and treat is likely to be cost-effective and when additional benefits of reduction in dyspepsia are included, the programme will be either very inexpensive [36] or cost saving [37].

Possible harms of population *H. pylori* screening and treatment

The ethics of screening is intensely debated [38]. Subjects are asked to undergo a test which may lead to interventions that harm as well as benefit. There is therefore the possibility that well individuals who have not sought health care will be labelled as ‘sick’ and may come to harm from the programme [39].

All screening programmes can cause anxiety in participants [40] but there are other concerns that are more specific to population screening and treatment for *H. pylori* infection. The more widespread use of antibiotics in the community is likely to increase bacterial resistance [41]. This has been demonstrated in a small number of patients prescribed *H. pylori* eradication therapy [42]. The impact of population screening and treatment for *H. pylori* infection on resistance is likely to be small in proportion to the antibiotic prescribing already occurring in the community.

A systematic review of observational studies suggested that *H. pylori* is associated with a reduced prevalence of GERD [43]. The same

authors, however, found no evidence that *H. pylori* eradication induces GERD in PUD patients in a meta-analysis of observational and randomized controlled studies [44]. There was also no evidence from randomized trials that *H. pylori* eradication worsens symptoms in patient with GERD [44,45]. This is supported by data from two community studies where there has been no increase in reflux symptoms in almost 3000 patients randomized to eradication therapy [46,47]. This emphasizes the caveat for all epidemiological studies that association does not mean causation and that any 'protective' effect could be due to one or more confounding factors. In this case, it is possible that those with a higher acid output will be relatively protected from acquiring *H. pylori* infection but will be more susceptible to GERD [48].

The prevalence of *H. pylori* infection was reported to be lower in patients with esophageal adenocarcinoma [49] but data are conflicting [50]. This debate is fuelled by a further well-designed case control study that suggested the risk of esophageal adenocarcinoma was reduced in those infected with *H. pylori* (OR = 0.3; 95% CI = 0.2–0.6) [51]. Neither gastric atrophy or Cag A positive *H. pylori* strains were associated with an additional increased risk of esophageal adenocarcinoma. Interestingly, the risk of esophageal squamous carcinoma was increased in those infected with *H. pylori* (OR = 2.1; 95% CI = 1.1–4.0) and this effect was associated with gastric atrophy [51]. The balance of evidence therefore suggests that *H. pylori* infection is less common in patients with esophageal adenocarcinoma but whether this association is causal or due to confounding factors needs to be evaluated by randomized controlled trials.

In view of the possible harm of population screening and treatment for *H. pylori* infection a more conservative approach of 'search and treat' has been recommended [52]. In this strategy, *H. pylori* screening is offered to those with any upper GI symptom, those with first degree relatives with gastric cancer and patients commencing long-term NSAID therapy. This avoids some of the ethical problems of population screening and improves the risk–benefit ratio of screening but will have a negligible impact on community mortality from *H. pylori* related diseases. An alternative approach is to limit screening to patients at high risk of developing gastric cancer [53] or offer treatment only to patients infected with Cag A positive *H. pylori* strains as

a recent meta-analysis suggests these strains are particularly associated with gastric cancer [54].

Conclusions

Population screening and treatment for *H. pylori* infection is an appealing strategy [55] as the aim is to prevent disease rather than early detection. The evidence that this should be introduced is persuasive but not conclusive as screening programmes can result in unforeseen harm as well as benefit [56]. As scientists, we should therefore wait for the results of ongoing randomized trials although it is likely that more trials will be needed before a definite conclusion can be reached. It is interesting however, that some countries are instituting colonoscopy screening to detect early colorectal cancer with no randomized controlled trials and virtually no case control evidence [57]. Decisions to institute screening programmes are sometimes made with imperfect evidence but it is difficult for countries to justify conducting widespread colonoscopy screening and not consider population *H. pylori* test and treat.

References

- 1 Gotzsche PC, Olsen O. Is screening for breast cancer with mammography justifiable? *Lancet* 2000;355:129–34.
- 2 Horton R. Screening mammography – an overview revisited. *Lancet* 2001;358:1284–5.
- 3 Moayyedi P, Dixon MF. Significance of *Helicobacter pylori* infection and gastric cancer: implications for screening. *Gastrointest Endosc Clin N Am* 1997;7:47–64.
- 4 Uemura N, Mukai T, Okamoto S, et al. Effect of *Helicobacter pylori* eradication on subsequent development of cancer after endoscopic resection of early gastric cancer. *Cancer Epidemiol Biomarkers Prev* 1997;6:639–42.
- 5 Arents NL, Thijs JC, van Zwet AA, Oudkerk PM, Gotz JM, van de Werf GT, et al. Approach to treatment of dyspepsia in primary care: a randomized trial comparing 'test-and-treat' with prompt endoscopy. *Arch Intern Med*, 2003;163:1606–12.
- 6 Delaney BC, Moayyedi P, Forman D. Initial management strategies for dyspepsia. (Update of *Cochrane Database Syst Rev* 2001 (3): CD001961; PMID: 11687004). *Cochrane Database Syst Rev* 2003: CD001961.
- 7 Helicobacter and Cancer Collaborative Group. Gastric cancer and *Helicobacter pylori*: a combined analysis of 12 case control studies nested within prospective cohorts. *Gut* 2001;49:347–53.

- 8 Kikuchi S, Crabtree JE, Forman D, Kurosawa M. Association between infections with CagA-positive or -negative strains of *Helicobacter pylori* and risk for gastric cancer in young adults. Research Group on Prevention of Gastric Carcinoma Among Young Adults. *Am J Gastroenterol* 1999;94:3455–9.
- 9 Sung JJ, Lin SR, Ching JY, et al. Atrophy and intestinal metaplasia one year after cure of *H. pylori* infection: a prospective, randomized study. *Gastroenterology* 2000;119:7–14.
- 10 Kuipers EJ, Nelis GF, Klinkenberg-Knol EC, et al. Cure of *Helicobacter pylori* infection in patients with reflux oesophagitis treated with long-term omeprazole reverses gastritis without exacerbation of reflux disease: results of a randomised controlled trial. *Gut* 2004;53:12–20.
- 11 Moayyedi P, Wason C, Peacock R, et al. Changing patterns of *Helicobacter pylori* gastritis in long-standing acid suppression. *Helicobacter* 2000;5:206–14.
- 12 Correa P, Fontham ET, Bravo JC, et al. Chemoprevention of gastric dysplasia: randomized trial of antioxidant supplements and anti-*Helicobacter pylori* therapy. *J Natl Cancer Inst* 2000;92:1881–8.
- 13 Ley C, Mohar A, Guarner J, et al. *Helicobacter pylori* eradication and gastric preneoplastic conditions: a randomized, double-blind, placebo-controlled trial. *Cancer Epidemiol Biomarkers Prev* 2004;13:4–10.
- 14 Wong BC, Lam SK, Wong WM, et al. *Helicobacter pylori* eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. *JAMA* 2004;291:187–94.
- 15 Parsonnet J, Forman D. *Helicobacter pylori* infection and gastric cancer – for want of more outcomes. *JAMA* 2004;291:244–5.
- 16 Forman D. Lessons from ongoing intervention studies. In: Hunt RH, Tytgat GNJ, eds. *Helicobacter pylori: Basic Mechanisms to Clinical Cure*. Dordrecht, the Netherlands: Kluwer Academic Publishers, 1998;354–61.
- 17 Hunt RH. Will eradication of *Helicobacter pylori* infection influence the risk of gastric cancer? *Aliment Pharmacol Ther* 2004;20: in press.
- 18 Office of National Statistics. *Causes of Death, England and Wales 2001*. London, UK: Department of Health, 2004.
- 19 Ford AC, Delaney BC, Forman D, Moayyedi P. Eradication therapy in *Helicobacter pylori* positive peptic ulcer disease: systematic review and economic analysis. *Am J Gastroenterol* 2004; in press.
- 20 Gisbert JP, Khorrami S, Carballo F, Calvet X, Gene E, Dominguez-Munoz JE. *H. pylori* eradication therapy vs. antisecretory non-eradication therapy (with or without long-term maintenance antisecretory therapy) for the prevention of recurrent bleeding from peptic ulcer. *Cochrane Database Syst Rev* 2003: CD004062.
- 21 Hunt RH, Bazzoli F. Review article: should NSAID/low-dose aspirin takers be tested routinely for *H. pylori* infection and treated if positive? Implications for primary risk of ulcer and ulcer relapse after initial healing. *Aliment Pharmacol Ther* 2004;19:9–16.
- 22 Huang JQ, Sridhar S, Hunt RH. Role of *Helicobacter pylori* infection and non-steroidal anti-inflammatory drugs in peptic-ulcer disease: a meta-analysis. *Lancet* 2002;359:14–22.
- 23 Papatheodoridis GV, Papadelli D, Cholongitas E, Vassilopoulos D, Mentis A, Hadziyannis SJ. Effect of *Helicobacter pylori* infection on risk of upper gastrointestinal bleeding in users of nonsteroidal anti-inflammatory drugs. *Am J Med* 2004;116:601–5.
- 24 Chan FK, Sung JJ, Chung SC, et al. Randomised trial of eradication of *Helicobacter pylori* before non-steroidal anti-inflammatory drug therapy to prevent peptic ulcers. *Lancet* 1997;350:975–9.
- 25 Chan FK, Chung SC, Suen BY, et al. Preventing recurrent upper gastrointestinal bleeding in patients with *Helicobacter pylori* infection who are taking low-dose aspirin or naproxen. *N Engl J Med* 2001;344:967–73.
- 26 Labenz J, Blum AL, Bolten WW, et al. Primary prevention of diclofenac associated ulcers and dyspepsia by omeprazole or triple therapy in *Helicobacter pylori* positive patients: a randomised, double blind, placebo controlled, clinical trial. *Gut* 2002;51:329–35.
- 27 Lanas A, Fuentes J, Benito R, Serrano P, Bajador E, Sainz R. *Helicobacter pylori* increases the risk of upper gastrointestinal bleeding in patients taking low-dose aspirin. *Aliment Pharmacol Ther* 2002;16:779–86.
- 28 Hawkey CJ, Tulassay Z, Szczepanski L, et al. Randomised controlled trial of *Helicobacter pylori* eradication in patients on non-steroidal anti-inflammatory drugs: HELP NSAIDs study. *Helicobacter Eradication for Lesion Prevention*. *Lancet* 1998;352:1016–21.
- 29 Paimela H, Paimela L, Myllykangas-Luosujarvi R, Kivilaakso E. Current features of peptic ulcer disease in Finland: incidence of surgery, hospital admissions and mortality for the disease during the past twenty-five years. *Scand J Gastroenterol* 2002;37:399–403.
- 30 Marshall JK, Collins SM, Gafni A. Demographic predictors of resource utilization for bleeding peptic ulcer disease: the Ontario GI Bleed Study. *J Clin Gastroenterol* 1999;29:165–70.
- 31 Rockall TA, Logan RF, Devlin HB, Northfield TC. Risk assessment after acute upper gastrointestinal haemorrhage. *Gut* 1996;38:316–21.
- 32 Moayyedi P, Deeks J, Talley NJ, Delaney B, Forman D. An update of the Cochrane systematic

- review of *Helicobacter pylori* eradication therapy in nonulcer dyspepsia: resolving the discrepancy between systematic reviews. *Am J Gastroenterol* 2003;98:2621–6.
- 33 Moayyedi P, Feltbower R, Brown J, et al. Effect of population screening and treatment for *Helicobacter pylori* on dyspepsia and quality of life in the community: a randomised controlled trial. Leeds HELP Study Group. *Lancet* 2000;355:1665–9.
 - 34 Lane JA, Murray L, Egger M, et al. Effect of eradication of *Helicobacter pylori* infection in the community on the incidence of dyspepsia: The Bristol *Helicobacter* project. *Gastroenterology* 2002;122:A475.
 - 35 Wildner-Christensen M, Moller HJ, Schaffalitzky De Muckadell OB. Rates of dyspepsia one year after *Helicobacter pylori* screening and eradication in a Danish population. *Gastroenterology* 2003;125:372–9.
 - 36 Roderick P, Davies R, Raftery J, et al. The cost-effectiveness of screening for *Helicobacter pylori* to reduce mortality and morbidity from gastric cancer and peptic ulcer disease: a discrete-event simulation model. *Health Technol Assess* 2003;7:1–86.
 - 37 Mason J, Axon AT, Forman D, et al. The cost-effectiveness of population *Helicobacter pylori* screening and treatment: a Markov model using economic data from a randomized controlled trial. *Aliment Pharmacol Ther* 2002;16:559–68.
 - 38 Axon A. Ethical issues in the management of *Helicobacter pylori* infection. *Can J Gastroenterol* 2003;17:62B–64B.
 - 39 Edwards PJ, Hall DM. Screening, ethics, and the law. *BMJ* 1992;305:267–8.
 - 40 Meystre-Agostoni G, Paccaud F, Jeannin A, Dubois-Arber F. Anxiety in a cohort of Swiss women participating in a mammographic screening programme. *J Med Screen* 2001;8:213–9.
 - 41 Seppala H, Klaukka T, Vuopio-Varkila J, et al. The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A streptococci in Finland. Finnish Study Group for Antimicrobial Resistance. *N Engl J Medical* 1997;337:441–6.
 - 42 Sjolund M, Wreiber K, Andersson DI, Blaser MJ, Engstrand L. Long-term persistence of resistant *Enterococcus* species after antibiotics to eradicate *Helicobacter pylori*. *Ann Intern Med* 2003;139:483–7.
 - 43 Raghunath A, Hungin AP, Wooff D, Childs S. Prevalence of *Helicobacter pylori* in patients with gastro-oesophageal reflux disease: systematic review. *BMJ* 2003;326:737.
 - 44 Raghunath A, Hungin AP, Wooff D, Childs S. The effect of *Helicobacter pylori* and its eradication on gastro-oesophageal reflux disease in patients with duodenal ulcers or reflux oesophagitis – a systematic review. *Aliment Pharmacol Ther* 2004;20: in press.
 - 45 Moayyedi P, Bardhan C, Young L, Dixon MF, Brown L, Axon AT. *Helicobacter pylori* eradication does not exacerbate reflux symptoms in gastroesophageal reflux disease. *Gastroenterology* 2001;121:1120–6.
 - 46 Harvey RF, Lane JA, Murray LJ, Harvey IM, Donovan JL, Nair P. Randomised controlled trial of the effects of *Helicobacter pylori* infection and its eradication on heartburn and gastro-oesophageal reflux: the Bristol *Helicobacter* Project. *BMJ* 2004;328:1417–9.
 - 47 Delaney BC, Moayyedi P. Eradicating *Helicobacter pylori* does not increase symptoms of gastro-oesophageal reflux disease. *BMJ* 2004;328:1388–9.
 - 48 Axon AT. Personal view: to treat or not to treat? *Helicobacter pylori* and gastro-oesophageal reflux disease – an alternative hypothesis. *Aliment Pharmacol Ther* 2004;19:253–61.
 - 49 Chow WH, Blaser MJ, Blot WJ, et al. Inverse relation between *cagA*+ strains of *Helicobacter pylori* infection and risk of esophageal and gastric cardia adenocarcinoma. *Cancer Res* 1998;58:588–90.
 - 50 Wu AH, Crabtree JE, Bernstein L, et al. Role of *Helicobacter pylori* CagA+ strains and risk of adenocarcinoma of the stomach and esophagus. *Int J Cancer* 2003;103:815–21.
 - 51 Ye W, Held M, Lagergren J, et al. *Helicobacter pylori* infection and gastric atrophy: risk of adenocarcinoma and squamous-cell carcinoma of the esophagus and adenocarcinoma of the gastric cardia. *J Natl Cancer Inst* 2004;96:388–96.
 - 52 Forman D, Graham DY. Review article: impact of *Helicobacter pylori* on society-role for a strategy of 'search and eradicate'. *Aliment Pharmacol Ther* 2004;19:17–21.
 - 53 Ley C, Mohar A, Guarner J, et al. Screening markers for chronic atrophic gastritis in Chiapas, Mexico. *Cancer Epidemiol Biomark Prev* 2001;10:107–12.
 - 54 Huang JQ, Zheng GF, Sumanac K, Irvine EJ, Hunt RH. Meta-analysis of the relationship between *cagA* seropositivity and gastric cancer. *Gastroenterology* 2003;125:1636–44.
 - 55 Sullivan T, Ashbury FD, Fallone CA, et al. *Helicobacter pylori* and the prevention of gastric cancer. *Can J Gastroenterol* 2004;18:295–302.
 - 56 Aaby P, Samb B, Simondon F, et al. Divergent mortality for male and female recipients of low-titer and high-titer measles vaccines in rural Senegal. *Am J Epidemiol* 1993;138:746–55.
 - 57 Winawer S, Fletcher R, Rex D, et al. Colorectal cancer screening and surveillance: clinical guidelines and rationale-Update based on new evidence. *Gastroenterology* 2003;124:544–60.