Population screening and treatment of *Helicobacter pylori* infection

Anthony O'Connor[1,2], Colm A. O'Morain[2] and Alexander C. Ford[1,3]

Abstract | *Helicobacter pylori* is an important human pathogen, associated with a substantial burden from both malignant and non-malignant diseases. The bacterium is classed as a human carcinogen, being strongly linked with gastric cancer, the third most common cause of cancer death worldwide and is also associated with common conditions such as dyspepsia and peptic ulcer. Eradication of *H. pylori* reduces the incidence of gastric cancer and peptic ulcer, as well as the prevalence and costs of managing dyspepsia. Economic analyses suggest that eradication of *H. pylori* as a means of controlling gastric cancer is cost-effective in high-risk populations. Even in populations at low risk of gastric cancer, there might be other benefits arising from screening and treatment, owing to the effects on non-malignant upper gastrointestinal diseases. However, public health authorities have been slow to consider the benefits of population-based screening and treatment as a means of reducing the morbidity and mortality associated with the infection. There are also concerns about widespread use of eradication therapy, including antimicrobial resistance and a rise in the prevalence of diseases that are negatively associated with *H. pylori*, such as GERD, Barrett oesophagus, asthma and obesity. This Review summarizes these issues.

[1]*Leeds Gastroenterology Institute, Level 4, Bexley Wing, St James's University Hospital, Beckett Street Leeds, LS9 7TF, UK.*
[2]*Tallaght Hospital/Trinity College Dublin, Belgard Road, Dublin 24, Dublin, Ireland.*
[3]*Leeds Institute of Biomedical and Clinical Sciences, University of Leeds, Leeds, LS2 9JT, UK.*

Correspondence to A.O.
jpoconno@tcd.ie

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Helicobacter pylori is probably the most successful of human pathogens, colonizing the stomach of ~50% of the world's population[1]. Prevalence in many parts of the world are higher still, for example 80% or more in parts of China, and some Eastern European and South American countries, although in the USA and Western European countries the prevalence is falling[2,3]. Rates of infection are linked to socioeconomic factors, such as level of education and living standards, with less-well-developed areas (as measured by the human development index) more likely to have high *H. pylori* prevalence and increased levels of recurrence of infection post-treatment[4]. Some of the latest epidemiological data on *H. pylori* prevalence are summarized in TABLE 1 (REFS 5–20). Notably, variability occurs not only between diverse global areas, but also between distinct populations within the same continental region.

Gastric cancer, despite a declining incidence, was the fifth most common cancer, and the third most common cause of cancer death worldwide in 2012 (REF. 21) (FIG. 1), responsible for almost three-quarters of a million deaths annually. The current accepted model for gastric carcinogenesis is an expansion of that first published by Correa *et al.*[22] in 1975. This model proposes that gastric cancer is the end result of a number of mutations that begin with an unknown environmental trigger in early life, now known to be infection with *H. pylori*, leading to a superficial gastritis, then chronic non-atrophic gastritis, followed by gastric atrophy and achlorhydria[23]. Gastric intestinal metaplasia then ensues, assuming progressively more primitive forms before, finally, cell transformation occurs with the development of dysplasia and ultimately carcinoma (FIG. 2). This model is supported by evidence from a study of individuals from communities with differing risks of gastric cancer, in which <25% of individuals from the highest risk region had an entirely normal gastric mucosa by the age of 25 years[24].

This Review will focus on the epidemiological association between *H. pylori* and gastric cancer, and the probable role of the bacterium as the environmental trigger in its development. The association of *H. pylori* with other relevant diseases will also be reported. In addition, we will evaluate the feasibility and timing of population screening and treatment for *H. pylori*, as well as appraising the available evidence that supports this approach as a means of preventing gastric cancer. Finally, possible additional benefits that might arise from such a strategy, as well as potentially deleterious effects, will be discussed.

H. pylori and gastric cancer

The incidence of gastric cancer is highest in the Far East, in countries such as China, Japan and Korea, and in South American countries, such as Colombia and Chile, which are also regions where *H. pylori* infection

Key points

- *Helicobacter pylori* is an important cause of gastric cancer, as well as benign diseases such as peptic ulcer and dyspepsia
- The eradication of *H. pylori* leads to a reduced risk of gastric cancer and can cure peptic ulcer and dyspepsia
- *H. pylori* is negatively associated with conditions such as GERD, obesity and asthma; concerns have been raised about the effect of a mass treatment programme on burden of these diseases, as well as antimicrobial resistance and microbiota
- Population screening and treatment of *H. pylori* as a means of preventing gastric cancer fulfils the Wilson and Jungner criteria for a successful screening programme
- Serological testing for *H. pylori* seems to be the most cost-effective means of delivering such a screening programme
- Population screening and treatment of *H. pylori* infection to control gastric cancer is cost-effective in high-risk populations; in countries with a lower incidence, cost-effectiveness might depend on reduction of burden of non-malignant diseases (e.g. peptic ulcer and dyspepsia)

is endemic. The first epidemiological studies to establish an association between the bacterium and gastric cancer were geographical correlation surveys of the prevalence of *H. pylori* in populations at differing risks of the disease[25,26]. In a prospective study of 17 populations worldwide, a 10% increase in the prevalence of *H. pylori* was estimated to increase the incidence of gastric cancer by ~25%, and mortality from the disease by 18%[27]. A subsequent meta-analysis of nested case–control studies confirmed that *H. pylori*-positive individuals were between three and six times more likely to develop gastric cancer, compared with uninfected controls in the general population[28]. However, this relationship is not seen in all geographical regions, including Africa and South Asia, for reasons that remain unclear[29].

The relationship between *H. pylori* infection and gastric cancer meets most of the Bradford Hill criteria for causation (BOX 1). In 1994, the International Agency for Research on Cancer (IARC) concluded that *H. pylori* was a class I human carcinogen[30]. The bacterium has been postulated to spread via the gastro–oral route mainly during childhood[31], with high numbers of transcriptionally active *H. pylori* detected in vomitus[32]. However, as the exact mode of transmission still remains unknown, the opportunity to develop effective primary interventions is limited. As a result, approaches to reduce the prevalence of *H. pylori*, and the burden of infection, centre on the opportunistic detection of the bacterium in at-risk groups of symptomatic patients, such as those with peptic ulcer disease or functional dyspepsia. Infected patients are offered a course of eradication therapy, which usually consists of an acid-suppressant drug, such as a PPI, in combination with two antibiotics administered for 2 weeks.

Interventions such as eradication therapy, together with improvements in living conditions over the past 50 years, have led to a decline in the prevalence of *H. pylori* infection in both the East and the West[33,34]. Despite this finding, modelling studies predict that the total number of cases of gastric cancer will continue to rise, with a doubling in incidence estimated by 2050, due to changing population demographics globally[35]. These data suggest that although the prevalence of *H. pylori* infection is falling, even in regions at high-risk of gastric cancer, prevention strategies are still required in the medium to long-term to reduce the number of future cases.

As a public health measure, a policy of searching for and eradicating *H. pylori* infection among healthy asymptomatic individuals in populations at high risk

Table 1 | **Recent global prevalence data for *H. pylori* infection**

Region	Country	Year	Population studied (number of included individuals)	Method of assessment of *H. pylori* infection	Prevalence (%)	Refs
Sub-Saharan Africa	Uganda	2014	Pregnant women (447)	Stool antigen	45.2	5
	Ethiopia	2013	Patients with dyspepsia (1,388)	Serology	65.7	6
Far East	China	2014	Randomized cluster sampling of older adults (2,006)	Serology	83.4	7
	Japan	2014	Cross-section of seven Japanese areas (14,716)	Serology, stool antigen or urea breath test	39.9	8
South America	Chile	2014	Pregnant women (274)	Serology	68.6	9
	Bolivia	2014	Cross-section of two rural villages (1,065)	Urea breath test	80.0	10
Eastern Europe	Poland	2014	National survey (3,307)	Serology	84.2	11
	Turkey	2013	General population (4,622)	Urea breath test	82.5	12
Western Europe	Netherlands	2013	Blood donors (1,550)	Serology	31.7	13
	Portugal	2013	General population (2,067)	Serology	84.2	14
North America	Canada	2013	Aboriginal population (203)	Histological examination of gastric biopsies	37.9	15
	USA	2013	Elderly patients in care facilities (281)	Serology	17.7	16
North Africa	Morocco	2013	Patients with dyspepsia (429)	Histological examination of gastric biopsies	75.5	17
Oceania	Australia	2011	Healthy individuals (1,355)	Serology	15.5	18
Middle East	Saudi Arabia	2013	Healthy individuals (456)	Serology	28.3	19
	Israel	2011	General population (1,466)	Serology	45.2	20

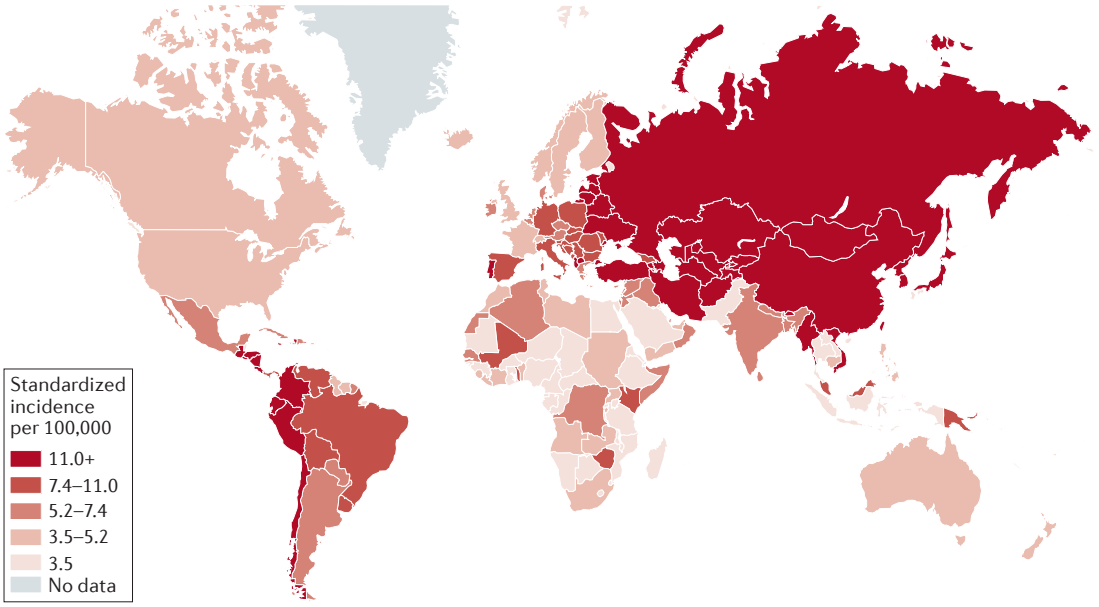

Figure 1 | **Global incidence of gastric cancer in 2012.** Incidence of gastric cancer in 2012 globally, using age-standardized rates, in both men and women[21]. Reproduced with permission from Ferlay J. *et al.* GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 08/12/2016.

of gastric cancer could therefore, theoretically, lead to a reduction in incidence of the disease. However, despite knowledge of the carcinogenic effect of *H. pylori* in the human stomach for >20 years, to date, no country has adopted such an approach[36]. Health-care providers are unlikely to consider this policy seriously until the long-term consequences of population screening and treatment are known. To further complicate matters, *H. pylori* is associated with a wide array of other gastrointestinal and non-gastrointestinal diseases, and eradication of the infection might therefore have other beneficial, or even potentially deleterious, effects. These outcomes could have additional implications for adopting this strategy as a means of gastric cancer prevention.

H. pylori infection and disease

Positive disease associations of H. pylori. Gastric mucosa-associated lymphoid tissue (MALT) lymphoma is a rare type of non-Hodgkin lymphoma (NHL) that represents ~12–18% of extra-nodal NHL, with an annual incidence of 1 per 100,000 population[37]. Nearly all patients with gastric MALT lymphoma have confirmed *H. pylori* infection, and the disease can be cured by eradicating the bacterium[38,39]. *H. pylori* is also implicated in the majority of cases of peptic ulcer disease[40], particularly duodenal ulcer. Eradication therapy is both effective in healing peptic ulcer disease and in preventing relapse, and is cost-effective[41]. In a large UK cohort, it was estimated that ~5% of dyspepsia in the community, most of which is functional in origin, was attributable to infection with *H. pylori*[42]. Eradication therapy has a modest, but statistically significant, benefit over placebo in terms of its effect on the natural history of functional dyspepsia, and again is cost-effective[43,44]. *H. pylori* infection has also been associated with weight loss and failure to thrive among older adults[45]. With respect to non-gastrointestinal diseases, clear associations between *H. pylori* and iron deficiency anaemia and idiopathic thrombocytopaenic purpura have been demonstrated[46,47], although proposed associations with a multitude of other conditions, including atherosclerotic vascular disease and neurological syndromes remain contentious.

Negative disease associations of H. pylori. An increase in the prevalence of symptoms of GERD has mirrored the decline in prevalence of *H. pylori* and peptic ulcer[34,48]. The precise relationship between *H. pylori* infection and GERD is probably complex, but one theory that has been proposed is that, due to induction of gastric atrophy by the bacterium and the resultant achlorhydria that ensues, infected individuals are less likely to develop GERD, which is a potential risk factor for both Barrett oesophagus and oesophageal adenocarcinoma[49,50]. The concern, therefore, is that injudicious eradication of *H. pylori* could lead to an increase in prevalence of symptoms of GERD, which might explain the increasing incidence of oesophageal adenocarcinoma worldwide[51].

Indirect evidence to support this hypothesis includes a meta-analysis reporting that the prevalence of *H. pylori* infection was 40% lower among patients with GERD compared with patients without GERD at endoscopy[52], although the strength of this relationship varied according to geographical location of the study, suggesting that other confounding factors influenced this association. Another study demonstrated a twofold risk of developing erosive oesophagitis 3 years after successful eradication of *H. pylori* in a cohort of infected patients with duodenal ulcer[53]. However, randomized controlled trials (RCTs) of eradication therapy in *H. pylori*-positive patients with GERD have shown no definite evidence of

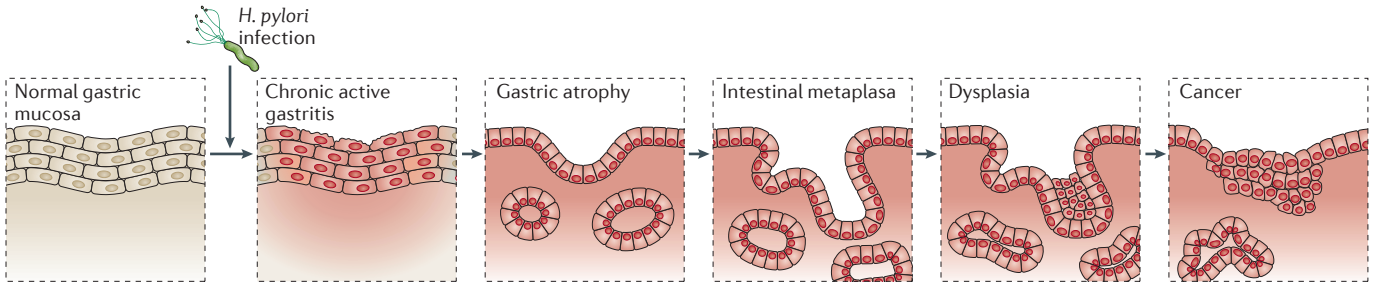

Figure 2 | **A model for the development of gastric cancer.** Stepwise progression from normal gastric mucosa to gastric cancer after infection with *Helicobacter pylori*, as proposed by Correa *et al.*[22] In some individuals, infection with the bacterium induces chronic active gastritis, which progresses on to pan-gastric atrophy, followed by intestinal metaplasia, dysplasia and, ultimately, cancer.

harm associated with treatment of the infection[54,55], and a meta-analysis of 10 studies that recruited >4,400 patients also failed to demonstrate an increased incidence of GERD after *H. pylori* eradication[56]. Reports have noted a markedly reduced odds (50–70%) of *H. pylori* infection in both individuals with Barrett oesophagus and oesophageal adenocarcinoma, compared with healthy individuals[57,58], and this statistically significant association was confirmed in a meta-analysis[59].

Finally, an association has been suggested between declining rates of *H. pylori* infection in communities with higher living standards and the increase in prevalence of both atopic diseases and obesity. With respect to atopic disease, it has been hypothesized that any protective effect of the bacterium arises via infection leading to stimulation of a type 1 T-helper-mediated immune response[60]. In the absence of such a stimulus, there might be over-activity of a type 2 T-helper-type response, which is associated with allergy and atopy[60]. Some investigators have shown lower rates of *H. pylori* infection in individuals with eosinophilic oesophagitis, eczema, allergic rhinitis or asthma than in healthy individuals[61–63]. The proposed association between eradication of *H. pylori* infection and the development of obesity is thought to be mediated via ghrelin[64], a hormone that regulates appetite and which is secreted from the oxyntic glands of the stomach. The numbers of these glands are diminished by the gastric mucosal atrophy induced by *H. pylori* infection[65]. RCT data have suggested a link between *H. pylori* eradication and weight gain[66], but the differences were small and difficult to interpret.

Population screening and eradication

Feasibility and means of population screening and eradication of H. pylori infection. An IARC working group report published in 2014 called for the commitment of more public health resources towards gastric cancer control, and recommended that countries explore the possibility of introducing population-based *H. pylori* screening and treatment programmes[67]. However, any decision as to whether or not to adopt these proposals needs to be made based on the availability of a safe, valid, accurate, acceptable and affordable method of screening for the bacterium, as well as effective treatments to eradicate the infection.

Upper gastrointestinal endoscopy and biopsy with rapid urease test has the advantage of being safe, valid and accurate, with sensitivity for the detection of *H. pylori* approaching 90% and specificity in the range of 95–100%[68,69]. If biopsy specimens are also obtained for histological examination, this approach will facilitate the accurate diagnosis and triage of malignant and pre-malignant conditions (using operative links for gastritis and intestinal metaplasia assessment[70]) that might require further treatment or follow-up. Drawbacks, however, include the invasive nature of the procedure, and the cost and inconvenience accrued to patients and providers at a time when endoscopy services in many countries are struggling to meet demands. Noninvasive means of detecting infection with the bacterium are therefore preferable for population screening purposes.

Serological methods of detecting *H. pylori* using ELISAs to human IgG have been in existence for >30 years[71], and have a number of advantages. Certain clinical circumstances might lead to a low bacterial load in the stomach, which decreases the sensitivity of other diagnostic methods, except serology. These circumstances include PPI or antibiotic use and atrophic gastritis[72]. In addition, serological testing for *H. pylori* can be performed concurrently with serum pepsinogen testing, which enables noninvasive detection of pre-malignant lesions of the stomach, such as gastric atrophy and intestinal metaplasia[73,74]. This approach could help select individuals most likely to benefit from future upper gastrointestinal endoscopy and surveillance, although sensitivity and specificity for gastric atrophy were only modest in a study including patients with dyspepsia in Europe[75]. Numerous serology tests are available commercially, some with a sensitivity and specificity >90%[76]. However, a major limitation is that serology only confirms prior exposure to *H. pylori*, so it cannot be used to assess for current infection, nor can it be used to determine whether eradication of the bacterium has been successful.

The ^{13}C-urea breath test is also a noninvasive approach to the diagnosis of *H. pylori* infection, which is very widely used and has a high sensitivity (96%) and specificity (93%)[77,78]. Monoclonal stool antigen testing is another option, again with high levels of specificity (94%) and sensitivity (97%), as noted in a

meta-analysis[79]. Both the urea breath test and the stool antigen test are inexpensive and, unlike serological testing, can be used to confirm successful eradication of *H. pylori*[80,81], but are disadvantaged somewhat by the fact that patients need to discontinue PPI therapy for at least 2 weeks before testing[82]. In addition, as a population screening method, stool antigen testing might be less acceptable due to patient reluctance to handle stool[83].

Above any other consideration, efficacious therapies must be available to eradicate infection with the bacterium to justify an attempt at population screening and treatment of *H. pylori*. Previously, the gold-standard treatment was considered to be a 1-week course of PPI triple therapy, consisting of a PPI in combination with clarithromycin and either amoxicillin or metronidazole[84]. However, in the past 5–10 years, eradication rates with 1 week of PPI triple therapy have declined to unacceptable levels[85], with cure rates as low as 70%, largely due to the burgeoning problem of antibiotic resistance[86,87], particularly to clarithromycin.

As a result, current recommendations to improve eradication rates require knowledge of local clarithromycin resistance rates. If these are <20%, PPI triple therapy can still be used, although treatment should be extended to 2 weeks. However, in regions where they are 20% or greater, quadruple therapy should be preferred[82], which consists of bismuth in combination with a PPI and two antibiotics (usually metronidazole and tetracycline). The efficacy of eradication therapy is partly dependent upon effective acid suppression, and with the advent of a new class of potent acid-inhibiting drugs, the potassium-competitive acid blockers (PCABs), eradication rates seem to be improving once again. An RCT published in 2016 of the PCAB vonoprazan, in combination with amoxicillin and clarithromycin, reported eradication rates >90%[88].

Vaccination has also been proposed as a means of reducing the prevalence of *H. pylori* and the morbidity associated with the infection. A model to evaluate vaccine candidates, by challenging healthy human volunteers with the bacterium, was first reported in 2004 (REF. 89). Subsequently, an oral recombinant vaccine has been developed, progressing on to phase III clinical trials. In a large randomized, placebo-controlled study it was shown to be effective, safe and immunogenic in *H. pylori*-naive children in China, and was reported to have an efficacy of 71.8%[90].

Timing of population screening and treatment of H. pylori infection. Another key consideration of any proposal for population screening and treatment of *H. pylori* should be at what stage of life this step ought to be undertaken. The vast majority of *H. pylori* infection is acquired in childhood[91], probably between the ages of 6 and 15 years[92,93]. To interrupt progression of the cascade through the various pre-malignant states towards gastric cancer, it would therefore seem intuitive that screening for, and eradication of, *H. pylori* infection should occur at an early point in life, either in adolescence or young adulthood. This approach would also circumvent some problems associated with the detection of *H. pylori* in older people, in whom both the more widespread use of acid-suppressant drugs and the increasing likelihood of pre-malignant conditions of the stomach having become established mean there is an increased risk of false-negative tests.

On the other hand, younger individuals are less likely to present with dyspepsia or peptic ulcer disease[34,94], and are therefore less likely to derive any symptomatic benefit from cure of the infection, which would be expected from screening and treatment in older individuals. In addition, prescribing eradication therapy in younger people could promote antibiotic resistance and lead to substantial alterations of the gut microbiota[95], although the long-term consequences of this dysbiosis are unknown. However, even though several meta-analyses have shown that gastric atrophy can reverse in both antrum and corpus after *H. pylori* eradication[96–98], it has been suggested that intestinal metaplasia is the 'point of no return' (REFS 99,100), beyond which eradication of the bacterium cannot reverse the changes in the gastric mucosa, although further progression might be halted in some individuals[101]. The diminished benefit from eradication when metaplasia has become established is probably due to reduced levels of *H. pylori* colonization by that time[102], and implies that earlier intervention before these mucosal changes take place is preferable.

For population screening and treatment

The scientific rationale for *H. pylori* eradication as a means of gastric cancer prevention is supported by rodent studies[103,104], including one demonstrating that the risk of cancer increased with time to administration of eradication therapy in *H. pylori*-positive Mongolian gerbils in which gastric carcinogenesis had been initiated

Box 1 | **Bradford Hill criteria for assessment of causation between *H. pylori* and gastric cancer**

- Strength: odds ratio for association strong (3–6-fold increased risk)[28]
- Consistency: relationship between *H. pylori* infection and gastric cancer observed worldwide[27]
- Specificity: no other likely explanation for the association; for example, excessive gastric acid[48]
- Temporality: *H. pylori* infection predates the occurrence of gastric cancer[28]
- Biological gradient: decreasing prevalence of *H. pylori* is linked to a lower incidence of gastric cancer[100]
- Plausibility: mechanism between cause and effect described[22]
- Coherence: *H. pylori* infection induces corpus gastritis, gastric atrophy and achlorhydria[22]; Mongolian gerbils develop gastric cancer following *H. pylori* infection[103,104]
- Experiment: eradication of *H. pylori* infection leads to resolution of gastric atrophy and a reduction in incidence of gastric cancer[100,109,113,117]

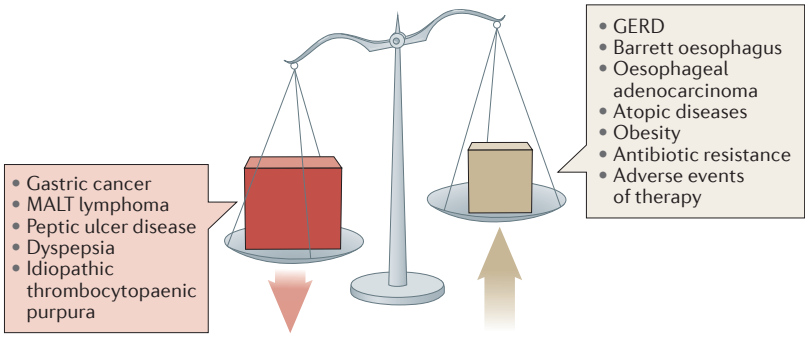

Figure 3 | **Potential beneficial and deleterious effects of population screening and treatment of *H. pylori* infection.** The schematic represents the dynamic interplay between infection with *Helicobacter pylori*, and eradication of the infection. Treatment of the infection with eradication therapy reduces the subsequent incidence of gastric cancer, cures mucosa-associated lymphoid tissue (MALT) lymphoma, both heals and prevents relapse of peptic ulcer, reduces the prevalence and costs of dyspepsia in the community and might increase platelet counts in idiopathic thrombocytopaenic purpura. Conversely, persistent infection might protect against GERD, Barrett oesophagus, oesophageal adenocarcinoma, atopic disease and obesity, and adverse consequences of eradication of the bacterium include antibiotic resistance and adverse effects of therapy.

chemically[104]. In this cohort of gerbils, in which eradication therapy was performed at 15, 35, or 55 weeks, gastric cancer occurred in 6.7% in those given eradication therapy at 5 weeks, compared with 38.2% in those given eradication therapy at 55 weeks, and 56.3% among animals who did not receive eradication therapy at all. The study authors concluded that the duration of chronic inflammation induced by *H. pylori* infection influenced incidence of cancer.

RCTs conducted in patients with early gastric cancer infected with *H. pylori* who were undergoing endoscopic mucosal resection have shown a reduction in the incidence of metachronous gastric cancer after eradication therapy compared with no treatment[105–107]. However, clinical arguments in favour of population screening and treatment are centred on the benefits of reducing disease incidence, mortality and morbidity, and also costs of managing the various malignant and non-malignant diseases, associated with *H. pylori* infection in healthy individuals, rather than in those who have already developed gastric cancer (FIG. 3).

Effects on gastric cancer: evidence from RCTs. Six RCTs to date have examined the effect of population screening and treatment of *H. pylori* on gastric cancer in healthy asymptomatic infected individuals, with data reported at multiple intervals after screening, and published as numerous separate articles[108–116] (summarized in TABLE 2). All were conducted in China or Japan, with the exception of one RCT conducted in Colombia[110], and used varying methods to detect infection with *H. pylori*, as well as different eradication therapy regimens. In one Chinese RCT, with follow-up for 7 years, seven (0.9%) of 817 individuals from the eradication group developed gastric cancer, compared with 11 (1.4%) of 813 in the placebo group ($P=0.33$)[113]. In a *post-hoc* analysis of those without gastric atrophy, intestinal metaplasia or dysplasia at baseline, none of the treated individuals developed cancer, compared with six in the placebo arm ($P=0.02$), supporting the so-called point of no return theory. In the RCT with the longest duration of follow-up to date, there was a statistically significant effect of eradication therapy on future incidence of gastric cancer at 14.7 years, with an odds ratio (OR) of 0.61 (95% CI 0.38–0.96, $P=0.03$)[109]. Other trials have probably been underpowered to detect any statistically significant effect of eradication therapy, or have not followed up participants for a sufficient length of time.

A systematic review and meta-analysis of all six available RCTs published in 2014 included data from 6,497 healthy *H. pylori*-positive individuals who were randomly assigned to eradication therapy, or to placebo or no treatment[117]. In total, there were 51 (1.6%) gastric cancers seen among 3,294 individuals in the eradication therapy arms, compared with 76 (2.4%) of 3,203 in the placebo or no treatment arms. The relative risk (RR) of developing gastric cancer with eradication therapy, compared with placebo or no treatment, was 0.66 (95% CI 0.46–0.95), with a number needed to treat (NNT) of 124. However, there was no effect on either all-cause mortality or mortality from gastric cancer. The use of sex-specific lifetime risks of developing gastric cancer from individual countries to calculate NNT revealed marked variability in the magnitude of the effect of treatment among different populations. The NNT was as low as 15 for Chinese men, and as high as 245 for women in the USA.

Effects on gastric cancer: evidence from the real world. Real-world evidence for the effects of population screening and treatment originate from an observational study conducted in the Matsu Island region of Taiwan[100]. Before 1995, the annual death rate from gastric cancer on the island was threefold that of the rest of the country. As a result, a population-based eradication programme began in 2004, with 4,121 adults >30 years of age screened for *H. pylori* infection via urea breath testing. In total, 2,598 (63.0%) individuals tested positive, underwent upper gastrointestinal endoscopy, and were given a 1-week course of PPI triple therapy, consisting of esomeprazole, amoxicillin and clarithromycin. A second urea breath test and endoscopy was performed in those followed up successfully in 2008. By this time, the prevalence of *H. pylori* in the population had fallen to 13.4%, based on breath test results.

Among the 841 individuals who underwent repeat endoscopy, the prevalence of gastric atrophy fell from 59.9% in 2004 to 13.7% in 2008, although intestinal metaplasia increased from 31.7% to 38.9%, again supporting the 'point of no return' theory. During the 4 years before the screening programme commenced, the incidence of gastric cancer per 100,000 person-years on Matsu Island was 40.3, compared with 30.4 for the years 2004 to 2008, corresponding to a 25% reduction in incidence. A reduction in the prevalence of peptic ulcer disease at endoscopy was also observed, from 11.0% in 2004 to 3.6% in 2008. Despite these findings, mortality from gastric cancer increased from 20.1 per 100,000 person-years between 1999 and 2003

to 26.3 between 2004 and 2008. This finding might relate to the increased prevalence of intestinal metaplasia during the study period, which is probably irreversible, and the study authors suggested that longer follow-up would be required to shed light on whether population screening and treatment could reduce mortality from gastric cancer.

Cost-effectiveness. If the principle that the commitment of more public health resources to gastric cancer control is accepted, the question arises as to how this health programme can be delivered in the most cost-effective and efficacious manner possible. Population screening to detect early gastric cancer in high-risk countries such as Japan, via upper gastrointestinal endoscopy, is feasible[118]. However, the costs of adopting such a strategy in countries at lower risk of gastric cancer are likely to be prohibitive, as thousands of asymptomatic people would need to undergo upper gastrointestinal endoscopy to detect one case of early gastric cancer. Even if only those with symptoms that might be indicative of an occult gastric cancer, such as dyspepsia, were screened by endoscopy the cost of detecting one malignant lesion has been estimated to be as high as US$83,000 (REF. 119).

Population screening and treatment of *H. pylori* to prevent gastric cancer fulfils the Wilson and Jungner criteria for a successful screening programme[120,121] (BOX 2). However, ideally, screening programmes should also be cost-effective. The first economic model to examine this issue was based on screening and treating people for *H. pylori* infection at the age of 50 years, and estimated a cost-effectiveness of $25,000 per life-year saved[122]. A number of other similar studies modelling various populations and methods of screening have been published, all of which demonstrate cost-effectiveness using a cut-off of $50,000 per life-year saved[123–129]. Direct comparisons between urea breath test and serology suggest the latter is probably markedly more cost-effective[128,129].

However, in many populations, including much of the Western Hemisphere[2], the incidence of gastric cancer is declining, so there needs to be other benefits to society from adopting a strategy of screening for, and eradicating, *H. pylori*. In addition, estimates from available decision models are probably conservative, as many do not consider economic benefits that could accrue as a result of other potential effects of adopting such a programme, including a reduction in the prevalence of peptic ulcer disease or the incidence of dyspepsia in the community[100,130].

Other beneficial effects. Two population-based screening studies conducted in the UK provide valuable insight into these issues. The Leeds HELP study, a double-blind placebo-controlled trial conducted in the Leeds–Bradford area of England, screened 8,407 randomly selected healthy individuals aged 40–49 years for *H. pylori* using urea breath testing[130]. In total, 2,324 (27.6%) people were *H. pylori*-positive, and were randomly assigned to 1 week of PPI triple therapy, consisting of omeprazole, clarithromycin and tinidazole, or placebo. Follow-up was at 2 years, when 247 (28.1%) of 880 participants assigned to eradication therapy reported dyspepsia, compared with 291 (33.4%) of 871 allocated to placebo (RR 0.84; 95% CI 0.73–0.97, $P = 0.015$). During the 2 years of follow-up, there were 17 new cases of peptic ulcer, 13 of which occurred in the placebo arm ($P = 0.04$). However, there was no effect of eradication therapy on quality of life.

Health service costs for dyspepsia were obtained from primary care records during the 2 years of the study, with a mean saving of UK£11.42 per person in the eradication therapy arm, which was not statistically significant[124]. There seemed to be a reduction in dyspepsia-related costs of a similar magnitude among non-infected individuals who were informed of their infection status, perhaps due to the reassurance value of a negative test result[131]. After 10 years of follow-up,

Table 2 | **Characteristics of completed RCTs of *H. pylori* eradication therapy in the prevention of gastric cancer**

Study and location	Method used to confirm presence of *H. pylori*	No. in treatment arm		*H. pylori* eradication therapy regimen used	Duration of follow-up (years)	No. of gastric cancer cases	
		Eradication therapy	Placebo or no treatment			With eradication therapy	With placebo or no treatment
Correa *et al.* (2000)[110] Narino Province, Colombia	Histology	437	415	2 weeks of bismuth, amoxicillin, and metronidazole	6 years	3	2
Zhou *et al.* (2008)[111,112,116] Shandong Province, China	Histology and rapid urease testing	276	276	1 week of omeprazole, amoxicillin, and clarithromycin	10 years	2	7
Wong *et al.* (2004)[113] Fujian Province, China	Histology and rapid urease testing	817	813	2 weeks of omeprazole, co-amoxiclav and metronidazole	7.5 years	7	11
Saito *et al.* (2005)[115] Japan	Not reported	379	313	1 week of lansoprazole, amoxicillin and clarithromycin	≥4 years	2	3
Ma *et al.* (2012)[109] Shandong Province, China	Serology	1,130	1,128	2 weeks of omeprazole and amoxicillin	14.7 years	34	52
Wong *et al.* (2012)[114] Shandong Province, China	Urea breath test	255	258	1 week of omeprazole, amoxicillin, and clarithromycin	5 years	3	1

RCT, randomized controlled trial.

Box 2 | **Wilson and Jungner principles of early disease detection**[120]

- The condition sought should be an important health problem
- There should be an accepted treatment for people with recognized disease
- Facilities for diagnosis and treatment should be available
- There should be a recognizable latent or early symptomatic stage
- There should be a suitable test or examination
- The test should be acceptable to the population
- The natural history of the condition, including development from latent to declared disease, should be adequately understood
- There should be an agreed policy on whom to treat as patients
- The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole
- Case-finding should be a continuing process and not a 'once and for all' project

there was a significant reduction in dyspepsia-related health services costs in those receiving eradication therapy, with a mean cost saving of £65 per person (95% CI £6–122, $P = 0.03$)[132]. The authors concluded that the magnitude of the cost savings observed at 10 years were sufficient to cover the initial cost of screening and treating individuals positive for *H. pylori*. The majority of these savings arose from a reduction in dyspepsia-related prescribing (mean difference £81; 95% CI £19–141, $P = 0.01$). The prevalence of dyspepsia was lower among all individuals assigned to eradication therapy than those assigned to placebo (40.4% versus 43.6%), and also among those with dyspepsia at baseline who received eradication therapy (58.7% versus 65.7%), but neither of these differences were statistically significant.

A study of similar design, the Bristol *Helicobacter* project, was conducted in the south-west of England[133]. This study recruited 10,537 randomly selected healthy individuals, aged between 20 and 59 years, who underwent urea breath testing. The 1,636 (15.4%) participants who tested positive for *H. pylori* entered a double-blind, placebo-controlled trial of 2 weeks of eradication therapy, consisting of ranitidine bismuth citrate and clarithromycin. After 2 years of follow-up, the odds of both frequent dyspeptic symptoms (OR 0.71; 95% CI 0.56–0.90, $P = 0.05$), and dyspepsia-related consultations in primary care (OR 0.65; 95% CI 0.46–0.94, $P = 0.02$), were significantly reduced among those receiving eradication therapy. Again, there were no differences in quality of life reported between the two arms of the trial. Costs were much higher in the eradication therapy arm, with a mean difference of £85 (95% CI £75–94), but this increased cost was driven by the expense of eradication therapy, which cost £83 per person. The substantial reduction in dyspepsia-related consultations in primary care with eradication therapy was still evident at 7 years[134].

Against population screening and treatment

Various arguments have been made against the concept of population screening and treatment of *H. pylori* infection (FIG. 3). For example, resistance to antibiotics is considered as one of the biggest challenges that medicine faces globally, and concerted efforts are underway to limit antimicrobial usage[135]. More widespread use of *H. pylori* eradication therapies could therefore have profound effects at both a population and an individual level. In population terms, as *H. pylori* eradication regimens contain broad-spectrum antibiotics (such as amoxicillin, clarithromycin and fluoroquinolones), there could be implications for efforts to control antimicrobial use. This issue is of particular concern for those agents used to treat serious or life-threatening infections. For example, increased utilization of drugs such as rifabutin, which are useful as rescue therapies for resistant strains of *H. pylori* infection[136], could compromise efforts to treat multidrug resistant tuberculosis, as the drug is also used for this indication[137]. At the individual level, treatment for *H. pylori* infection could select for microorganisms that are resistant to the antibiotics contained in the regimen used[138]. Resistance rates are increasing and, with eradication rates seen to fall from almost 90% when strains are clarithromycin-sensitive to <20% when clarithromycin-resistant, this phenomenon is thought to be the single biggest reason for failure of first-line eradication therapy[139]. More widespread use of agents such as clarithromycin and metronidazole could therefore add to the burden of *H. pylori*-related disease by fostering the development of more resistant strains. When the indication for eradication therapy in an individual patient is a MALT lymphoma or a serious complication of an *H. pylori*-positive peptic ulcer there could be substantial implications.

Adverse events relating to *H. pylori* therapy vary from regimen to regimen, but are common and must also be considered when implementing a population screening and treatment programme, in what are likely to be predominantly healthy, asymptomatic individuals. In addition, it has been shown that adverse effects are associated with treatment failure and reduced adherence to therapy, therefore well-tolerated, easy-to-use treatments are key to the success of any such eradication programme[140]. Although adverse events such as diarrhoea, nausea or vomiting and altered taste do occur with standard therapies[41], they are rarely severe enough to warrant discontinuation of therapy. For standard first-line PPI triple therapy the overall rate of adverse events was 53.3% in a multicentre study, but these events were generally mild, with only one patient experiencing pseudomembranous colitis, and no deaths reported[141].

For second-line or third-line therapies, concerns have been expressed about more serious adverse events. Fluoroquinolones have been associated with Achilles tendonitis and hepatotoxicity[142,143]. Myelosuppression and ocular toxicity have been reported in patients taking rifabutin[144,145]. In addition, *H. pylori* eradication therapy will alter the intestinal microbiota[146], although adverse health consequences have not been demonstrated[95]. Unfortunately, adverse event rates with eradication therapy in RCTs in a population-based setting are relatively unknown, as the vast majority of trials conducted to prevent gastric cancer did not report these data[117]. Adverse events were reported in an ongoing study conducted in >88,000 individuals, and led to discontinuation of therapy in 1.5%[147]. The most common adverse events were nausea or vomiting (in 0.9%) and rash (in 0.4%). No serious or life-threatening adverse events were reported.

In terms of other potentially deleterious effects arising from the widespread use of eradication therapy, the prevalence of erosive oesophagitis in the population screening programme conducted on Matsu Island increased from 13.7% to 27.3% during the 4 years of follow-up[100]. However, neither RCT of population screening and treatment conducted in the UK demonstrated any evidence of an increase in gastro-oesophageal reflux symptoms. In the trial by Moayyedi *et al.*[130], reflux symptoms were less frequent at 2 years among those assigned to eradication therapy (22.6% versus 27.4%, $P = 0.02$). In the Bristol *Helicobacter* project, eradication therapy had no effect on the prevalence of heartburn or regurgitation, and did not lead to a reduction in the prevalence of either condition in those who were symptomatic at baseline[148]. An association between eradication of *H. pylori* and the development of obesity has been reported and, in the Bristol study, 19% of individuals randomly assigned to eradication therapy gained 3 kg or more in weight, compared with 13% of individuals allocated to placebo (OR 1.58; 95% CI 1.19–2.10) and the overall difference in mean BMI between the two treatment arms was 0.20 kg/m^2 (95% CI 0.11–0.31 kg/m^2)[66] although it was unclear whether this finding was related to an improvement in dyspepsia symptoms. To date, there are no RCT data providing an insight on the relationship between eradication therapy and the subsequent development of atopic diseases.

Conclusions

The basis of most public health measures to control cancer includes the elimination of carcinogens, and the detection and surveillance of pre-malignant conditions. Despite the fact that gastric cancer is a condition with a recognized and readily treatable carcinogen, in the form of *H. pylori*, and a clear sequence of detectable pre-malignant conditions, it remains a curious anomaly that it has received neither a great deal of investment nor emphasis from most public health authorities. This oversight is partly due to the perception that gastric cancer, in Western countries at least, is a disease that is declining in incidence. However, according to the latest estimates of the worldwide burden of cancer produced by GLOBOCAN for 2012, the disease is the fifth most common cancer in terms of incidence, and is the third most common cause of cancer death worldwide, responsible for almost three-quarters of a million deaths annually[21].

Despite the declining incidence in many countries in the developed world, the total number of deaths from gastric cancer might well continue to increase for the foreseeable future, due to an increase in the average age of the world's population[35], and patterns of migration of people from high to low prevalence regions will ensure it remains a major public health concern in all parts of the world[149]. Population screening and treatment of *H. pylori* seems to be a feasible, efficacious and cost-effective means of reducing the incidence of gastric cancer in those at high-risk. In addition, eradication probably offers other public health benefits in terms of reducing the incidence of peptic ulcer disease and the economic burden of dyspepsia in the community. Despite this potential benefit, no country has adopted population screening and treatment, although in 2013 Japan approved reimbursement of the use of eradication therapy as a treatment for *H. pylori*-induced gastritis[150], and in China the largest trial of population screening and treatment to date, recruiting >180,000 individuals, is ongoing, although the effect on gastric cancer incidence will not be reported until at least 2018 (REF. 147).

Serological testing for *H. pylori* seems to be the most cost-effective means of delivering a screening programme. Effective treatment regimens are available, which should be tailored to local antibiotic resistance rates of the bacterium. Some questions remain about the cost-effectiveness and feasibility of delivering population screening and treatment in different regions, which would depend on factors such as infrastructure, resources, gastric cancer incidence and PPI use. Given declining eradication rates with current regimens, any potential screening programme should give due consideration to re-testing to ensure successful eradication as part of a local validation process. The effect of searching for and eradicating *H. pylori* on the microbiota and attempts at antimicrobial stewardship remain issues of considerable importance that are not fully understood, and there is a need for studies to address these issues. Nonetheless, it is difficult to conclude that the widespread eradication of *H. pylori* is anything other than a worthwhile effort to control the considerable burden of malignant and non-malignant disease associated with this very common pathogen.

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Competing interests statement
The authors declare no competing interests.