Is there a rationale for eradication of Helicobacter pylori?
Cost–benefit: the case for

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Screening and treating the community for Helicobacter pylori would have seemed inconceivable 5 years ago. This has now become a real possibility given that H. pylori is a major risk factor for gastric carcinoma. Screening should not be introduced, however, before the costs and benefits of the programme are established. It has been estimated that 1:30–1:60 of the UK population die from an H. pylori related disease. If treating H. pylori were to reduce premature mortality, then this would be a persuasive argument for a screening strategy. The financial costs of screening and treating H. pylori are significant but this would be partially offset by savings that would accrue from reducing dyspepsia in the community. Indeed, decision analysis models suggest H. pylori screening is cost-effective. The potential benefits are enormous and prospective randomised trials are urgently required to establish whether such a programme is worthwhile.

The availability of simple, non-invasive tests for Helicobacter pylori and the development of safe, effective treatments for this infection has encouraged a debate as to which patients should be treated. There is now overwhelming evidence that patients with peptic ulcer disease should be tested for H. pylori and offered antibiotic therapy. Decision analysis suggests that the diagnosis and treatment of H. pylori in young dyspeptic patients could also be cost-effective, although it may take many years for savings to be realised. It is tempting to extend this philosophy further and screen entire populations for H. pylori with the intention of treating all those who are infected. What is the evidence that the benefits of this strategy would outweigh the costs?

Financial benefits of H. pylori eradication

There is no definitive evidence concerning the cost of dyspepsia to the community, but it undoubtedly represents a considerable burden to health services. Anti-secretory medication is the most expensive category
in the NHS drug budget costing £389.4 million in England\(^7\). Approximately 8% of the UK population visit their general practitioner each year with dyspeptic symptoms\(^8,9\) and this group represents 50% of gastroenterology referrals\(^9\). Patients often undergo further investigation. An estimated 8.6 per 1000 of the population have an endoscopy each year whilst 4.8 per 1000 have a barium meal\(^10\). A conservative crude calculation suggests that the cost of dyspepsia to the NHS is over half a billion pounds each year in England alone (Table 1) excluding in-patient costs. \textit{H. pylori} eradication should prevent most peptic ulcer disease which accounts for approximately 10% of dyspepsia expenditure\(^8\). A screening and eradication programme would be expensive but this would be partially offset by over £50 million each year saved by \textit{H. pylori} eradication. These savings will be even more impressive if studies demonstrate that \textit{H. pylori} therapy is beneficial in a proportion of patients with non-ulcer dyspepsia.

**Medical benefits of \textit{H. pylori} eradication**

\textit{H. pylori} is the most important factor in the aetiology of uncomplicated peptic ulcers and eradication therapy dramatically reduces recurrence rates\(^11,12\). \textit{H. pylori} infection is less prevalent in complicated peptic ulcer disease where non-steroidal inflammatory drugs play a more prominent role\(^13\). Nevertheless, \textit{H. pylori} was present in 71% of patients with bleeding duodenal ulcers\(^14\), 65–79% of bleeding gastric ulcers\(^14,15\) and 83% of perforated peptic ulcers\(^16\). Furthermore, preliminary studies suggest that treatment of \textit{H. pylori} reduces peptic ulcer rebleeding rates. In an analysis of four randomised studies\(^17\), rebleeding occurred in 2/147 (1.4%) of patients given eradication therapy compared with 8/66 (12.1%) prescribed maintenance \(\text{H}_2\) receptor antagonist and 11/37 (29.7%) cases receiving only a healing course of anti-secretory therapy.
This is persuasive evidence that *H. pylori* eradication also alters the natural history of complicated ulcer disease.

Three nested case control studies have shown that infection with *H. pylori* increases the risk of gastric cancer. A combined analysis of these studies has estimated that 73% of gastric cancers are attributable to *H. pylori* in those that have been infected for over 14 years. Evidence such as this persuaded the International Agency for Research on Cancer (IARC) to categorised *H. pylori* as a class 1 carcinogen. The IARC did not make any public health recommendations concerning the eradication of *H. pylori* as there is no direct evidence that treatment of the infection will reduce the gastric cancer risk. Indirect evidence, however, does support this hypothesis. *H. pylori* infection reduces gastric juice vitamin C levels and increases cell proliferation which are thought to be important in the carcinogenic process and eradication therapy reverses these effects. Moreover, patients who received treatment for *H. pylori* after early gastric cancer had been locally resected were less likely to develop recurrent gastric cancer than those that did not receive eradication therapy.

There are over 4000 deaths from peptic ulcer complications and 7500 deaths from gastric cancer annually in England and Wales. Assuming that *H. pylori* is associated with 73% of gastric cancer and 65% of peptic ulcer deaths then this infection causes over 8000 deaths each year. It has been estimated that, in the England and Wales, 1 in 35 men and 1 in 60 women will die from a complication of *H. pylori* infection. No other infection causes as high a mortality as this in the developed world and these figures emphasise the importance of establishing whether *H. pylori* screening and eradication will reduce mortality in randomised controlled trials. Such trials would be expensive if performed in Western Europe but are perhaps more feasible in countries with a high incidence of gastric carcinoma, such as China or Japan.

*H. pylori* infection is becoming less common in developed countries and this is reflected in the declining incidence of age standardised gastric cancer mortality. It may be argued, therefore, that intervention is unnecessary, as gastric cancer deaths will fall anyway. In global terms, however, the population is expanding and people are living longer. These demographic changes will increase the absolute number of gastric cancer deaths even if age standardised mortality continues to decline.

Some reports suggest *H. pylori* is associated with ischaemic heart disease. This is controversial and there is no evidence that treatment of *H. pylori* will reduce mortality from this condition. Nevertheless, if such an effect was established, this would considerably increase the medical benefits of a screening programme.
Financial costs of *H. pylori* eradication

Screening for *H. pylori* requires a simple, accurate, non-invasive test for the infection. The [13C]-urea breath test ([13C]-UBT) is accurate even in non-fasting subjects. This test takes at least 20 min to complete, however, and is probably too expensive for general use in populations. Serology is simpler, quick and an in-house ELISA kit can cost as little as £5.00 (M Wilcox, personal communication). Initially, serology was not as accurate as the [13C]-UBT, but second generation commercial kits and in-house ELISA assays have recently been reported to have sensitivities and specificities in excess of 95%. The results of serology have to be processed and the subjects informed of the outcome. This will increase the expense of the screening programme, but could be avoided by the use of near patient *H. pylori* tests although, at present, there is considerable variation in the accuracy of these.

An *H. pylori* screening programme also requires a simple, cheap, safe and effective eradication therapy. Proton pump inhibitor based triple therapies seem to fulfil these criteria although some are expensive. Perhaps the most appropriate triple therapy is the Bazzoli regimen replacing tinidazole with metronidazole. This has the advantage that it employs low doses of antibiotics and can be used in those allergic to penicillin.

Testing and treating *H. pylori* in the community is, therefore, feasible.

An *H. pylori* screening programme aimed at 50–59 year-olds would cost the UK at least £170 million. This figure assumes that 50% are infected, serology costs £5, treatment costs £20 and organisation costs £2 per person. Such a large scale project is clearly expensive and, even if efficacy can be proved, a programme of this magnitude should only be undertaken if it is cost-effective. One decision analysis model (based on American data) suggested that, using conservative estimates of the prevalence of *H. pylori* and efficacy, a screening programme would cost $25,000 per year of life saved. If *H. pylori* eradication prevented as little as 5% of gastric cancers, the programme would only cost $50,000 per year of life saved in high risk populations. These figures compare favourably with cost-effectiveness of breast and cervical screening programmes and are likely to be underestimates as the model did not take into account deaths due to peptic ulcers or the savings that would accrue from preventing dyspepsia. If *H. pylori* eradication has an effect on ischaemic heart disease, the programme would be even more cost-effective.

Medical costs of *H. pylori* eradication

An *H. pylori* screening programme would involve giving a large proportion of the population a 1 week course of antibiotics. Approximately
one-third of those given treatment might experience an adverse event and, in 1%, this might be severe enough to interfere with daily activities\textsuperscript{38}. There have been case reports of fatalities related to eradication therapy, although the doses of antibiotics used in these regimens were high\textsuperscript{43}. Community \textit{H. pylori} eradication trials that are currently being completed will give more information on the magnitude of the risk of giving antibiotics to the population. Most screening programmes are associated with some risk to participants but, provided trials show that the benefits far exceed these risks, this is generally regarded as acceptable.

There is concern that widespread use of antibiotics will increase the prevalence of antibiotic resistant bacteria. The effect of \textit{H. pylori} treatment on community resistance patterns is likely to be small compared to the effect of the 50 million courses of antibiotic that are prescribed each year in the UK\textsuperscript{44}. Development of antibiotic resistance is not a problem for vaccines and some advances have been made in the search for a \textit{H. pylori} vaccine over the last few years\textsuperscript{45}. Even if \textit{H. pylori} eradication proved beneficial, it could be argued that it is better to wait until these have been developed. Unfortunately, this will take at least 8 years\textsuperscript{46} and, in the mean time, an estimated third of a million deaths in the world will be caused by \textit{H. pylori} each year\textsuperscript{47}. It is important to establish, as soon as possible, whether \textit{H. pylori} eradication will reduce mortality rather than wait for possible future technologies.

Re-testing to assess efficacy of treatment would be expensive if undertaken as part of a community screening programme and is probably impracticable: however, it is inevitable that some individuals will wish to have their status re-checked to assess persistent dyspeptic symptoms. \textit{H. pylori} eradication fails in 10% of cases and, although other regimens may be successful\textsuperscript{48}, there will be a group of subjects with persistent infection. These individuals will know that they harbour a carcinogen that cannot be treated and will be understandably concerned. Other screening programmes have also generated anxiety in previously healthy individuals\textsuperscript{49}, but this has not prevented the development of programmes that substantially reduce mortality.

Finally it has been suggested that \textit{H. pylori} infection may be ecologically beneficial\textsuperscript{50}. Reflux symptoms may increase after eradication therapy\textsuperscript{51}, although it is possible that gastro-oesophageal reflux was unmasked as a consequence of stopping long-term anti-secretory medication or induced by weight increase after improvement of ulcer symptoms. Large randomised trials of \textit{H. pylori} screening and eradication would provide information on the benefits of \textit{H. pylori} infection as well as the risks.
Helicobacter infection

Conclusion

Substantial evidence indicates that *H. pylori* is a significant cause of mortality and morbidity and that a screening and treatment programme would be cost-effective. Trials are needed to establish whether such a programme will reduce mortality and, in England and Wales alone, possibly save the lives of over 8000 people a year.

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