Effect of population screening and treatment for *Helicobacter pylori* on dyspepsia and quality of life in the community: a randomised controlled trial

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### Summary

**Background** Infection with *Helicobacter pylori* is the main cause of peptic-ulcer disease. Treatment of this infection might lower the prevalence of dyspepsia in the community and improve quality of life. We investigated this possibility in a double-blind randomised controlled trial.

**Methods** Individuals aged 40–49 years were randomly selected from the lists of 36 primary-care centres. A researcher interviewed participants with a validated dyspepsia questionnaire and the psychological general wellbeing index (PGWB). *H pylori* status was assessed by the carbon-13-labelled urea breath test. Infected participants were randomly assigned active treatment (omeprazole 20 mg, clarithromycin 250 mg, and tinidazole 500 mg, each twice daily for 7 days) or identical placebo. Participants were followed up at 6 months and 2 years.

**Findings** Of 32 929 individuals invited, 8455 attended and were eligible; 2324 were positive for *H pylori* and were assigned active treatment (1161) or placebo (1163). 1773 (76%) returned at 2 years. Dyspepsia or symptoms of gastro-oesophageal reflux were reported in 247 (28%) of 880 in the treatment group and 291 (33%) of 871 in the placebo group (absolute-risk reduction 5% [95% CI 1–10]). *H pylori* treatment had no significant effect on quality of life (mean difference in PGWB score between groups 0.86 [−0.33 to 2.05]).

**Interpretation** Community screening and treatment for *H pylori* produced only a 5% reduction in dyspepsia. This small benefit had no impact on quality of life.

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### Introduction

Dyspepsia is common and imposes a substantial clinical and financial burden on health services, yet the causes of dyspeptic symptoms are poorly characterised. Lifestyle factors such as smoking and alcohol consumption are believed to be important, but their overall effect on dyspeptic symptoms is likely to be small. *Helicobacter pylori* is the major cause of peptic-ulcer disease and may have a role in non-ulcer dyspepsia. Cross-sectional population surveys have suggested that 0–23% of dyspepsia in the community is attributable to *H pylori* infection. The uncertainty is related to the bias and confounding to which cross-sectional studies are predisposed. A randomised placebo-controlled trial of eradication of *H pylori* in the community would reliably show what effect this infection has on population dyspepsia symptoms. Population screening and treatment for *H pylori* are being advocated as a method of preventing gastric cancer, and trials to assess the efficacy of this policy are under way. Evidence that screening and treatment for *H pylori* substantially decrease the amount of dyspepsia in the community would support the introduction of such programmes.

Some studies have suggested that *H pylori* infection is less common in patients with oesophagitis than in those with a normal endoscopy result, but this finding is not universal. In a study of patients with peptic ulcer, 25% of those whose *H pylori* infection was eradicated had oesophagitis after 3 years, a significantly higher rate than in infected controls. These findings raised concern that widespread *H pylori* treatment may increase symptoms of gastro-oesophageal reflux in the community. The overall effect of *H pylori* on upper gastrointestinal symptoms is therefore unclear. We have investigated this effect in a placebo-controlled randomised trial of *H pylori* screening and eradication treatment in the community.

### Methods

**Study population**

The study was carried out in the Leeds and Bradford area (combined population 1 200 000), a predominantly urban community in the north of England. Individuals aged 40–49 years were randomly selected from the lists of 36 general practices and invited by letter to attend their local surgery. Reasons for exclusion were treatment with antibiotics, proton-pump inhibitors, or bismuth salts within the previous 2 weeks; refusal to abstain from alcohol for 1 week; allergy to macrolides, proton-pump inhibitors, or 5-nitroimidazoles; and current treatment with warfarin, digoxin, disopyramide, antiarrhythmics, or theophyllines. Informed written consent was obtained from all participants, and the relevant local research ethics committees...
approved the study. To assess whether trial participants were representative of the population sampled, we reviewed the primary-care notes from a random selection of those who did not attend. The numbers of visits to the general practitioner for dyspepsia or to obtain a prescription for an H₂-receptor antagonist or proton-pump inhibitor were compared between the trial participants and non-participants.

**Design and procedures**

The study was a double-blind randomised placebo-controlled trial. A trained researcher interviewed eligible individuals at baseline using the Leeds dyspepsia questionnaire. This instrument has been validated in hospital and primary-care settings; it evaluates the presence and severity of dyspepsia. The questionnaire assesses epigastric pain, heartburn, acid reflux, nausea, vomiting, early satiety, excessive belching, and dysphagia over the previous 6 months. The questionnaire has possible scores from 0 to 40, and it also records the most troublesome dyspeptic symptom. Participants completed the psychological general wellbeing index (PGWB), which evaluates six domains of quality of life (wellbeing, anxiety, depression, vitality, health, and self-control) and generates an overall quality-of-life score. The overall score has a possible range of 22–132 with a higher value representing a better quality of life.

We sought *H. pylori* infection by use of a non-fasting carbon-13-labelled urea breath test. Participants were permitted to have had a cup of coffee or tea with two slices of toast within the 4 h before the test. The participant was given 4 g citric acid, and a baseline breath sample was obtained in a 10 mL exetainer. 100 mg C-labelled urea (99% pure, Boston Isotopes, Boston MA, USA) was ingested, and a further breath sample was collected 30 min later. Samples were analysed by mass spectrometry (ABCA-NT, Europa Scientific, UK). A positive result was defined as an excess ¹³CO₂ value of more than 5 per mL. This protocol has been previously validated in our population and has 98% sensitivity and 96% specificity.

Participants found to be positive for *H. pylori* infection were randomly assigned active treatment (omeprazole 20 mg twice daily, clarithromycin 250 mg twice daily, and tinidazole 500 mg twice daily for 7 days) or placebos of identical appearance. The allocation schedule was generated by computer in random permuted blocks stratified by general practice so that similar allocation schedule was generated by computer in random permuted blocks stratified by general practice so that similar patients nor the investigators were aware of the *H. pylori* status and were not randomised. An equivalent number of uninfected cases were assigned placebo so neither the participants nor the investigators were aware of the *H. pylori* status of those selected for follow-up. The remaining *H. pylori* negative cases were informed of their *H. pylori* status and were withdrawn from the trial.

Participants returned at 6 months and 2 years to repeat the baseline tests. Those who did not attend their appointments were contacted, by telephone and letter, at least three times. Participants were classified as lost to follow-up if they had not been assessed 3 months after their 2-year appointment. We reviewed the primary-care notes of all individuals selected for follow-up and compared the numbers of peptic ulcers diagnosed among those positive for *H. pylori* who had been randomly assigned eradication treatment or placebo. At this review of primary-care notes, we also acquired information on baseline use of non-steroidal anti-inflammatory drugs and dyspepsia-related visits to the general practitioner.

**Statistical analysis**

On the assumptions that 40% of the participants with *H. pylori* infection had dyspepsia at baseline and that the overall drop-out rate would be 20%, a sample size of 2400 (1200 in each group) could detect a 7% difference in the primary endpoint (the frequency of dyspepsia) between the groups with 90% power at 5% significance. For the PGWB endpoint, if we assume that the scale has an SD of 15, a sample size of 2400 could also detect a 3-point difference in PGWB score between the two groups with 90% power at 5% significance. The presence of dyspepsia at 2 years was evaluated by use of the χ² test.

Severe of dyspepsia, type of dyspepsia symptom, and PGWB score at 2 years were secondary endpoints. Severity of dyspepsia and PGWB scores were compared by use of Student’s t test and the Mann-Whitney U test because the data were positively skewed. Scores were adjusted for baseline value and compared by ANCOVA with ranked data. The parametric, non-parametric, adjusted, and unadjusted tests gave similar results; therefore, for ease of interpretation we give only the unadjusted parametric results. Symptoms were classified into three groups: epigastric pain; heartburn/reflux; and other (nausea, vomiting, early satiety, excessive belching, and dysphagia). The presence of these symptoms at 2 years and the most predominant symptom were compared between the groups by use of the χ² test. A p value <0·01 was taken as statistically significant for secondary endpoints because multiple comparisons were made. The data were also analysed for men and women separately because baseline results suggested that *H. pylori* was associated with an increase in dyspepsia costs in men only.

The presence of dyspepsia in the individuals without *H. pylori* infection was recorded but was not formally compared with the infected groups, because any differences could be due to confounding factors such as age or social class.

All analyses were by intention to treat on participants who completed a dyspepsia questionnaire at 2 years. The robustness of the conclusions relating to dyspepsia was tested by analyses that assumed all those not followed up at 2 years either did or did not have dyspeptic symptoms. Statistical analyses used STATA (version 5.0).
Results

Study sample

32,929 individuals were invited to participate, but only 8,445 (25.6%) attended and were eligible (figure). To ensure that the sample was representative of the population, we sought permission from 8,477 randomly selected non-responders to review their primary-care notes. 624 gave consent. These non-responders had a similar age distribution to participants (mean age 45.8 years [SD 2.9] vs 45.5 years [2.9] for participants), a similar frequency of prescriptions for H₂-receptor antagonists (3.8% vs 4.0%), and no significant difference in the frequency of prescriptions for proton-pump inhibitors (2.0% vs 3.4%). Non-respondents were, however, less likely than were participants to have visited their general practitioner for dyspepsia during the previous 2 years (8.2% vs 13.0%; p=0.005).

Effect of eradication on dyspepsia

2,329 participants were positive for *H pylori*. 2,324 were randomly assigned eradication therapy or placebo (figure; five people withdrew from the trial before randomisation). There were no significant differences in baseline characteristics between the randomised groups (table 1).

1,773 (76%) participants returned at 2 years. *H pylori* eradication had been achieved in 659 (74%) of the treatment group compared with 41 (5%) of the placebo group at 2 years. The result of the ¹³C urea breath test was borderline or missing in four cases, and dyspepsia questionnaire data were incomplete in a further 18 cases (ten in the treatment group, eight in the placebo group). There was no significant difference in use of non-steroidal anti-inflammatory drugs between the two groups during the 2-year follow-up as shown by the review of primary-care notes (174/889 [19.6%] in the eradication group vs 154/879 [17.5%] in the placebo group; p=0.27). Dyspepsia was significantly less frequent in the eradication group than in the placebo group (relative risk 0.84 [95% CI 0.73–0.97], p=0.015; table 2). This association remained significant whether all participants lost to follow-up were presumed to have had dyspepsia or not to have had dyspepsia. There was a 16% relative-risk reduction and a 5% (95% CI 1–10) absolute-risk reduction of dyspepsia in the eradication group compared with the control group. 20 (95% CI 15–25) people with *H pylori* infection would have to be given eradication therapy for one case of dyspepsia to be cured.

Dyspepsia scores were significantly lower in the eradication group than in the control group (baseline 4.03 vs 4.24; 2 years 2.50 vs 3.09; adjusted mean difference in dyspepsia score 0.5 [95% CI 0.1–0.8]). In the group of 1,101 individuals without *H pylori* infection who were followed up for 2 years, 332 (29%) had dyspepsia at the end of the trial.

From the primary-care note review, we found that 17 (0.8%) of 2,122 participants positive for *H pylori* at baseline (nine men and eight women) were diagnosed as having peptic-ulcer disease during the 2-year follow-up. 13 of the 17 events were in participants assigned placebo (p=0.04) and these included two cases of bleeding peptic ulcers. Of the four participants assigned eradication treatment who had peptic ulcers, two had a negative ¹³C-urea breath test at 2 years. There were no cases of bleeding peptic ulcers in this group.

A post-hoc analysis suggested that the reduction in dyspepsia in the eradication group was greater in men than in women (table 2). The relative-risk reduction in men was 25%, with a 9% absolute-risk reduction for dyspepsia in the eradication group. An interaction test showed that this finding was of borderline significance (p=0.09).

Effect of eradication on individual symptoms

Participants were classified as having epigastric pain, heartburn/acid reflux, or other dyspepsia if this symptom was reported at a frequency of more than once a month for 6 months. Each of these symptom types was less frequent in the eradication group than in the placebo group (table 3), but none of the differences was significant at the prespecified p<0.01 value. Participants were also classified into subgroups on the basis of the most troublesome symptoms. Those assigned eradication did not report heartburn/acid reflux as a predominant symptom more frequently than did placebo controls (137/885 [15%] vs 118/879 [13%], p=0.22) at 2 years.

Effect of eradication on quality of life

At baseline, the overall PGWB score was similar in the placebo and treatment groups (table 1). Among participants with *H pylori* infection, baseline PGWB score was significantly lower in those with dyspepsia than in those without (mean difference 6.9 [95% CI 1.02–12.8]).

<table>
<thead>
<tr>
<th>Sex</th>
<th>Eradication group (n=1,161)</th>
<th>Placebo group (n=1,163)</th>
</tr>
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<tbody>
<tr>
<td>M</td>
<td>587 (51%)</td>
<td>558 (48%)</td>
</tr>
<tr>
<td>F</td>
<td>573 (49%)</td>
<td>604 (52%)</td>
</tr>
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<table>
<thead>
<tr>
<th>Lifestyle</th>
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<th>Placebo group (n=1,163)</th>
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<tbody>
<tr>
<td>Smoker</td>
<td>356 (31%)</td>
<td>396 (34%)</td>
</tr>
<tr>
<td>Alcohol abstainer</td>
<td>144 (12%)</td>
<td>161 (14%)</td>
</tr>
<tr>
<td>NSAI user</td>
<td>137 (12%)</td>
<td>136 (12%)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Social class*</th>
<th>Eradication group (n=1,161)</th>
<th>Placebo group (n=1,163)</th>
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<tbody>
<tr>
<td>I and II</td>
<td>347 (30%)</td>
<td>317 (27%)</td>
</tr>
<tr>
<td>III</td>
<td>524 (45%)</td>
<td>531 (46%)</td>
</tr>
<tr>
<td>IV and V</td>
<td>158 (14%)</td>
<td>184 (16%)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Dyspepsia</th>
<th>Eradication group (n=1,161)</th>
<th>Placebo group (n=1,163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) overall PGWB score</td>
<td>103 (15)</td>
<td>103 (15)</td>
</tr>
<tr>
<td>Mean (SD) age (years)</td>
<td>45.4 (2.9)</td>
<td>45.5 (2.9)</td>
</tr>
</tbody>
</table>

| NSAI = non-steroidal anti-inflammatory drug. |

*Social class III (housewives, members of armed forces, &c) omitted.

Table 1: Baseline characteristics of randomised groups of participants positive for *H pylori*

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Number with symptom/total</th>
<th>Relative risk (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Eradication group</td>
<td>Placebo group</td>
<td></td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>133/884 (15%)</td>
<td>154/875 (18%)</td>
<td>0.85 (0.69–1.06)</td>
</tr>
<tr>
<td>Heartburn/acid reflux</td>
<td>200/895 (23%)</td>
<td>247/878 (27%)</td>
<td>0.82 (0.73–0.97)</td>
</tr>
<tr>
<td>Regurgitation</td>
<td>192/985 (22%)</td>
<td>227/878 (26%)</td>
<td>0.84 (0.71–0.99)</td>
</tr>
</tbody>
</table>

Table 3: Dyspepsia symptom types at 2 years according to treatment group

Table 2: Presence of dyspepsia at 2 years according to treatment group

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Dyspepsia was associated with a reduction in the PGWB score of 6.9 according to baseline data. The overall prevalence of dyspepsia at 2 years was 30.7% and *H. pylori* eradication was associated with a 15% relative-risk reduction in dyspepsia. If the association between dyspepsia and quality of life is causal and the relation is linear, eradication of *H. pylori* should increase the PGWB score by 0.3. The sample size in this study had power to detect a 3-point difference in PGWB score; to identify a 0.3-point difference between groups would require 39,000 people in each group.

**Discussion**

Cross-sectional studies have shown an association between *H. pylori* infection and dyspepsia.6–7 This association could be due to residual confounding and does not necessarily mean that *H. pylori* eradication will cure dyspepsia in the population. This trial of screening and treatment for *H. pylori* in the community showed that 15% of dyspepsia in infected individuals could be cured by eradication therapy. Overall, 20 people with the infection need to take eradication therapy for one case of dyspepsia to be successfully treated in the community. This clinical effect is small, and the cause of dyspepsia in the majority of individuals remains uncertain.

This trial did not address the underlying cause of the dyspepsia. The commonest cause of upper gastrointestinal symptoms is non-ulcer dyspepsia, and a randomised placebo-controlled trial suggested that eradication therapy successfully treats a subset of these cases.16 A further trial, of similar design, did not confirm these findings,17 suggesting that there is no association between *H. pylori* and non-ulcer dyspepsia or that the relation is very weak. Studies report that 5–20% of people with *H. pylori* infection have peptic-ulcer disease, although it is symptomless in many cases.18,19 *H. pylori* cures most peptic ulcers.20 This effect is likely to be the main reason for the reduction in dyspepsia in this community trial. Only 0.8% of the population were formally diagnosed as having peptic ulcer during the 2-year follow-up, but the disorder is likely to be present in a larger pool of uninvestigated individuals with dyspepsia.

Peptic-ulcer disease is more common in men than in women, which suggests that the outcome of *H. pylori* infection depends on the sex of the patient.21 We found a greater benefit of *H. pylori* eradication in men, which might be explained by the difference in peptic-ulcer disease, but this may be a chance finding because it was a post-hoc analysis. The interaction between *H. pylori* dyspepsia and sex needs further investigation in prospective trials.

The association between *H. pylori* and symptoms of gastro-oesophageal reflux is controversial.22 We found a lower, but not significantly so, rate of retrosternal burning and acid reflux in the eradication group than in the placebo group. Heartburn and acid reflux can be non-specific symptoms of gastro-oesophageal reflux, but the diagnosis is more accurate if these are the predominant complaints.23 There was no association between *H. pylori* eradication therapy and symptoms of gastro-oesophageal reflux when participants were classified according to their most troublesome symptom. There is no gold-standard method of diagnosing symptoms of gastro-oesophageal reflux, however, and some individuals are likely to be misclassified. This uncertainty will reduce the ability of the trial to detect any association between *H. pylori* and symptoms of gastro-oesophageal reflux. Any association is likely to be small and, given that there was a trend for symptoms of gastro-oesophageal reflux to be less frequent in the eradication group, these data do not support the hypothesis that treatment of *H. pylori* increases symptoms of gastro-oesophageal reflux in the community. Labenz and colleagues31 reported a higher rate of oesophagitis in patients with peptic ulcers successfully treated by eradication therapy than in controls, but the control group in that study was not ideal. Our data are consistent with reports that *H. pylori* eradication therapy does not increase reflux symptoms in randomised trials of non-ulcer dyspepsia.24

Dyspepsia is associated with a poor quality of life in patients attending secondary care.25 *H. pylori* eradication therapy, however, was not associated with an improved quality of life in the infected population in our study. This finding is expected because *H. pylori* eradication therapy caused only a small reduction in population dyspepsia, and a study to detect the consequent impact on quality of life would have to be very large. Whether this small change in quality of life is clinically relevant at a health policy level is doubtful.

The main weakness of this study is that only 25% of the people invited attended and were eligible for the trial. The trial sample may not be representative of the general population. Indeed, participants were more likely than were non-participants to have consulted their general practitioners about dyspepsia in the 2 years before the trial. Bias may also explain how 44% of the placebo-group participants had dyspepsia at baseline compared with 33% at 2 years. People with dyspepsia may be more likely to enrol in the trial than those without symptoms, but over the 2-year follow-up the study sample will tend to regress to the mean. The internal validity of the trial is not threatened by this observation, but extrapolation to the general population should be cautious, because dyspepsia is likely to be over-represented in the study sample. The estimates of reduction of dyspepsia in the population by *H. pylori* eradication may therefore be slightly overestimated.

This trial emphasises that population screening and treatment for *H. pylori* will have only a small effect in reducing the rate of dyspepsia in the community, and that this effect is unlikely to have an important impact on quality of life in the general population. The clinical benefits of community *H. pylori* eradication therefore rest

### Table 4: Quality of life at 2 years according to treatment group (5–5–8–3)]. There was an overall improvement in PGWB score during the trial in participants assigned eradication therapy, but it was not significant (table 4). Furthermore, there was no significant difference between the eradication and placebo groups in overall score or in any of the six domains of quality of life at 2 years (table 4).

<table>
<thead>
<tr>
<th>PGWB variable</th>
<th>Mean (SD) score</th>
<th>Mean difference* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall score</td>
<td>105 (15)</td>
<td>104 (15)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>23 (4)</td>
<td>23 (4)</td>
</tr>
<tr>
<td>Depression</td>
<td>16 (2)</td>
<td>16 (2)</td>
</tr>
<tr>
<td>Positivity</td>
<td>17 (3)</td>
<td>17 (3)</td>
</tr>
<tr>
<td>Self care</td>
<td>16 (2)</td>
<td>16 (2)</td>
</tr>
<tr>
<td>General health</td>
<td>15 (3)</td>
<td>15 (3)</td>
</tr>
<tr>
<td>Vitality</td>
<td>17 (4)</td>
<td>16 (4)</td>
</tr>
</tbody>
</table>

*Eradication group – placebo group.*
on any effect this may have on mortality from gastric cancer. Dyspepsia is an expensive problem and the small reduction in dyspepsia rates may be associated with a reduction in health-service dyspepsia costs. We have collected economic data from this trial and these will be reported elsewhere.

Contributors
Paul Moayyedi, Julia Brown, Su Mason, James Mason, Jackie Nathan, Gerald Richards, and Anthony Dowell were involved in design of the protocol; Anthony Axon was the main contributor to the protocol design. Paul Moayyedi was clinical coordinator, Su Mason was trial coordinator, and Anthony Axon provided senior coordination. Richard Felthower did the main statistical analysis. Julia Brown provided senior statistical support. James Mason helped with statistical analysis. Jackie Nathan was the main data collector, with help from Paul Moayyedi. Anthony Dowell provided support to primary care. The paper was written by Paul Moayyedi, with help from all the other investigators.

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Finance—A Starkey (Research School of Medicine, University of Leeds).

Participating general practices—Meanwood Health Centre, Kippax Health Centre, the Croft Surgery, Windmill Health Centre, Woodley Health Centre, Bridge Street, Marsh Street Surgery, High Field Surgery, Lingwell Croft Surgery, Beeston Hill Health Centre, Woodhouse Medical Centre, Leigh View Medical Practice, Fountain Medical Centre, Dib Lane, Hunslet Health Centre, Grange Medical Centre, Crossland Surgery, St Martin’s Practice, Robin Lane Medical Centre, Manor Park Surgery, Carlton Surgery, Burton Croft Surgery, Ridge Medical Practice, West Lodge Surgery, Windmill Health Centre, Yeadon Health Centre, Garforth Medical Centre, Chapeloak Practice, Burley Park Medical Centre, the Street Lane Practice, and Silver Lane Surgery in Leeds; and the Medical Centre Buttershaw Lane, the Health Centre King’s Road, New Wortley Health Centre, Cullingworth Medical Centre, and Westcliffe Medical Centre in Bradford.

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References


