

Research

Impact of *Helicobacter pylori* eradication on dyspepsia, health resource use, and quality of life in the Bristol helicobacter project: randomised controlled trial

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Abstract

Objective To determine the impact of a community based *Helicobacter pylori* screening and eradication programme on the incidence of dyspepsia, resource use, and quality of life, including a cost consequences analysis.

Design *H pylori* screening programme followed by randomised placebo controlled trial of eradication.

Setting Seven general practices in southwest England.

Participants 10 537 unselected people aged 20-59 years were screened for *H pylori* infection (¹³C urea breath test); 1558 of the 1636 participants who tested positive were randomised to *H pylori* eradication treatment or placebo, and 1539 (99%) were followed up for two years.

Intervention Ranitidine bismuth citrate 400 mg and clarithromycin 500 mg twice daily for two weeks or placebo.

Main outcome measures Primary care consultation rates for dyspepsia (defined as epigastric pain) two years after randomisation, with secondary outcomes of dyspepsia symptoms, resource use, NHS costs, and quality of life.

Results In the eradication group, 35% fewer participants consulted for dyspepsia over two years compared with the placebo group (55/787 *v* 78/771; odds ratio 0.65, 95% confidence interval 0.46 to 0.94; *P* = 0.021; number needed to treat 30) and 29% fewer participants had regular symptoms (odds ratio 0.71, 0.56 to 0.90; *P* = 0.05). NHS costs were £84.70 (£74.90 to £93.91) greater per participant in the eradication group over two years, of which £83.40 (\$146; €121) was the cost of eradication treatment. No difference in quality of life existed between the two groups.

Conclusions Community screening and eradication of *H pylori* is feasible in the general population and led to significant reductions in the number of people who consulted for dyspepsia and had symptoms two years after treatment. These benefits have to be balanced against the costs of eradication treatment, so a targeted eradication strategy in dyspeptic patients may be preferable.

Introduction

Dyspepsia is a common recurrent condition that causes "pain or discomfort centered on the upper abdomen"¹ and affects up to 40% of the UK population.² Dyspepsia accounts for about 4% of all consultations in primary care,³ with annual costs to the NHS of around £1.1 billion (\$1.9bn; €1.6bn).⁴ Most dyspeptic patients are managed in primary care (uninvestigated dyspepsia); a

minority of patients, particularly those with "alarm" symptoms such as dysphagia or weight loss, are referred for an endoscopy. Common causes of dyspepsia diagnosed at endoscopy are peptic ulcer disease (mostly due to *Helicobacter pylori* infection), gastro-oesophageal reflux disease, and "functional" dyspepsia (that is, no identifiable underlying cause).¹

Two previous trials of community screening and *H pylori* eradication in Leeds and in Odense, Denmark, showed modest reductions in self reported dyspepsia symptoms.^{5 6} However, the Danish study included many uninfected people, thus diluting any effects of the eradication treatment, and the Leeds study included only people aged 40-49 years and eradication therapy failed in a quarter of those assigned to active treatment. A Cochrane review of management of dyspepsia in primary care concluded that *H pylori* eradication may benefit some dyspeptic patients,⁷ and the CADET-Hp trial of "test and treat" in uninvestigated dyspeptic patients in Canada showed clinical and economic benefits.⁸ Two meta-analyses have, however, differed as to whether endoscopically diagnosed functional dyspepsia improves after *H pylori* eradication,^{9 10} in part as a result of different studies being included in the reviews.¹¹

The Bristol helicobacter project was established as a large community based randomised controlled trial to assess the impact of *H pylori* eradication on the outcomes of dyspepsia, quality of life, health resource use, and NHS costs over two years of follow-up among patients detected through screening. The study randomised *H pylori* positive patients, used a well tolerated and highly effective *H pylori* eradication regimen, and assessed consultation rates for dyspepsia in primary care. An economic evaluation was done alongside the randomised trial.

Methods

Protocol

The Bristol helicobacter project was a community based screening study followed by a randomised controlled trial of *H pylori* eradication. The study design and methods have been published elsewhere.^{12 13} Briefly, unselected patients aged 20-59 years and registered at seven general practices in southwest England were invited by letter to attend for screening. Research nurses used the ¹³C urea breath test to screen attendees for *H pylori* infection, and infected participants were randomised to *H pylori* eradication treatment or placebo.¹² Participants gave written informed consent.

Assignment and masking

H pylori infected participants were randomised to receive either ranitidine bismuth citrate (400 mg) and clarithromycin (500 mg) twice daily for 14 days or matching placebo. Staff independent of the study prepared the randomisation sequence with a block size of 10. Randomisation was stratified by sex and age into four 10 year age bands (20-9 to 50-9). Pharmacists who had no contact with participants prepared drug packs, and research nurses who were blind to the treatment allocation dispensed them. Eradication was assessed by a ¹³C urea breath test six months later, and the results were withheld from participants and the staff conducting follow-up. At two years participants reported what sort of tablets they thought they had received or that they were unsure. General practitioners were requested not to prescribe *H pylori* eradication treatment during follow-up, except in patients with endoscopically confirmed peptic ulcer disease.

Outcomes and follow-up

The primary outcome was the consultation rate for dyspepsia (epigastric pain) in primary care over two years. Trained research nurses blinded to the treatment allocation examined the primary care records two years after randomisation. They recorded consultations related to dyspepsia (epigastric pain) or to heartburn, reflux, or dysmotility-type symptoms, as well as prescribed dyspepsia treatments and referrals to secondary care for dyspepsia. A gastroenterologist (RFH) who was blind to the treatment allocation verified a sample of the reviews carried out by the nurses against primary care records for accuracy and completeness.

Secondary outcomes were the frequency and type of symptoms, impact on quality of life, resource use, and costs to the NHS two years after randomisation. We measured frequency of symptoms within a three month period with five point Likert-type scales in participant completed questionnaires.^{14 15} Participants rated the frequency of dyspepsia (epigastric pain) symptoms, as well as heartburn and reflux, belching (wind), nausea, and bloating, from 1 (none) to 5 (daily). We defined regular or frequent symptoms as occurring on two or more occasions over each of the previous three months (as defined by the developers of the questionnaire).¹⁴ We used the SF-36 questionnaire to assess generic health status (quality of life)—0 indicated poor health and 100 indicated good health.¹⁶

We did the economic evaluation from the NHS viewpoint. The most appropriate form of economic evaluation was a cost consequences analysis to ensure the inclusion of multiple important secondary outcomes alongside the cost data, rather than a cost effectiveness analysis.¹⁷ Resource use for each participant for the two years after randomisation came from the note reviews. We analysed dyspepsia (epigastric pain) related general practitioner consultations, secondary care referrals, and drugs from the *British National Formulary* gastrointestinal systems (section 1.1-1.3 anti-secretory medication).¹⁸ We applied unit costs at 2002 prices (including value added tax) from UK sources and discounted costs in the second year at the UK Treasury discount rate of 3.5%.

Sample size calculations and statistical analyses

Before the study started, we predicted *H pylori* prevalence to be 15%. We assumed conservatively that the successful eradication of *H pylori* would reduce dyspepsia only in those participants with undiagnosed peptic ulcer disease. Survey results from southern England and elsewhere suggested that in a six month period 8.6% of 20-59 year olds would consult their general practitioner because of dyspepsia, that 20-25% of these patients would have peptic ulcers, and that at least 80% of peptic ulcers

would occur in those with *H pylori* infection.^{2 19} A sample size of 1550 participants could detect a reduction in the consultation rate from 8.5% to 4.25% in the eradication group, with 90% power at a two sided significance level of 5%.¹²

We used Stata version 7 to do intention to treat analyses of all randomised participants with note review for the primary analysis and all participants with completed follow-up questionnaires for the self reported secondary outcomes. We used logistic regression with adjustment for the stratification variables for all the parametric analyses; results are presented as odds ratios with 95% confidence intervals. We used Mann-Whitney U tests to analyse quality of life data, because of the non-Gaussian distribution.

The economic evaluation included all participants with complete resource use information. We used *t* tests to assess cost differences. We used multiple ordinary least squares regression to adjust for the stratification variables. We also estimated bias corrected confidence intervals by bootstrap methods to investigate the underlying data distribution (the confidence intervals were almost identical by the two methods).²⁰

Results

Study population flow, *H pylori* prevalence, and eradication

The figure shows the flow of the 27 536 study population. Of the 26 203 people who received an invitation letter, 10 714 (41%) attended (a further 507 were deemed ineligible by their general practitioner, and the letter was returned undelivered for 826). In all, 10 537 participants entered the study (127 people were ineligible, and 50 declined to participate); 1636 (15.5%) participants were infected with *H pylori*, and 1558 (95%) of these agreed to be randomised. Eradication of *H pylori* was 91%. Proton pump inhibitors (which can cause false negative urea breath test results) were being taken by only 3.4% of eradication group participants at the second breath test, so any potential impact on the eradication rate was small. Table 1 shows the baseline characteristics of randomised participants. Recruitment took place between 1996 and 1999 and follow-up between 1998 and 2001. We saw two serious unexpected adverse events in the intervention group—one participant had rectal bleeding, and a second had severe vomiting. Two hundred and sixty six participants in the eradication group guessed that they had received active treatment at two years compared with 241 expected by chance ($\chi^2=1.90$, $P=0.1683$). Follow-up was 99% (1539) for the primary outcome and 92% (1438) for the secondary outcomes, based on questionnaire data.

Health resource use and costs of dyspepsia

The number of people consulting for dyspepsia (epigastric pain) in primary care was reduced by 35% (55 *v* 78) over two years in the eradication group compared with the placebo group (odds ratio 0.65, 95% confidence interval 0.46 to 0.94; $P=0.021$). Thirty people with *H pylori* would have to be treated to prevent one person consulting their doctor for dyspepsia. We found no difference in the numbers consulting for dyspepsia by sex (odds ratio for men 0.69, 0.39 to 1.19; for women 0.63, 0.63 to 1.01; interaction test $\chi^2=0.07$, $P=0.79$).

The total number of general practice consultations for dyspepsia over two years was also reduced in the eradication group, but all other resource use was very similar (table 2). No significant differences existed between the two groups in the costs of general practice consultations, prescription drugs, or secondary care procedures, including endoscopies for dyspepsia (table 3). However, the cost of the *H pylori* eradication treatment (£83.40 (\$146; €121)) resulted in significantly greater NHS costs

per participant in the eradication group (difference = £84.70, 95% confidence interval £74.90 to £93.91).

Cost consequences: dyspepsia symptoms and quality of life

Regular symptoms of dyspepsia (epigastric pain) were reported by 29% fewer participants two years after *H pylori* eradication treatment than after placebo (odds ratio 0.71, 0.56 to 0.90). In a subgroup analysis, we found no difference in the effect of *H pylori* eradication on dyspepsia symptoms by sex (odds ratio for men 0.70, 0.49 to 0.98; for women 0.72, 0.52 to 1.01; interaction test $\chi^2=0.01$, $P=0.90$). No differences existed between the two groups in any of the quality of life dimensions at two years (table 4). All participants reported good health “most of the time” except for the vitality dimension, which was equivalent to reduced vitality “a good bit of the time.”

Discussion

Study validity and generalisability

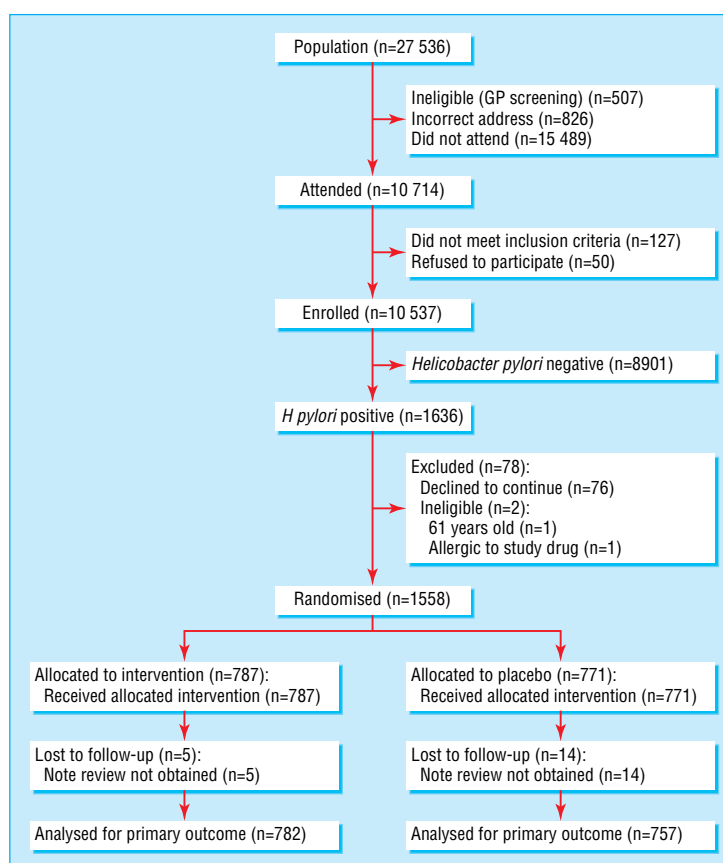
The number of people who consulted for dyspepsia (epigastric pain) in primary care and had symptoms was reduced by about 30% two years after *H pylori* eradication. Large numbers of participants across a wide age range were recruited, with few exclusions, thus increasing the study’s generalisability. The high rates of *H pylori* eradication and follow-up, with blinded assessment of the primary outcome, enhanced the internal validity of the study, and the breath test (the non-invasive “gold standard” detection method) minimised misclassification biases compared with serology (as initially used in the Danish screening study)⁶ and probably facilitated recruitment, as no blood test was necessary. The clinically important primary outcome of dyspepsia

consultations in primary care contrasts with the use of self reported dyspepsia symptoms as the primary outcome in the two other community based *H pylori* studies.^{5 6}

Forty one per cent of the target population participated in this study, which was more than in the other UK based *H pylori* eradication study (25%) but less than in the Danish study (63%).^{5 6} Data protection regulations (UK Data Protection Act 1998) prevented access to the primary care notes of non-responders to ascertain if the population recruited was representative of the dyspepsia burden in primary care, but both previous trials found lower healthcare resource use for dyspepsia in non-responders.^{5 6} Previously reported analyses from this study showed that non-responders were more likely to be male, younger, and from the lower socioeconomic groups, findings consistent with other population based studies.¹² Few non-white patients participated in our trial, so the results of the screening component may not be generalisable to more ethnically diverse populations. *H pylori* prevalence at 15% was comparable to the Danish study (17.5%) but was lower than in the Leeds study (28%), and prevalence is decreasing to less than 15% in the Western world.¹ We chose an efficacious (but relatively expensive) *H pylori* eradication regimen to achieve a high eradication rate, achieving similar results to another community based trial.²¹ This regimen does not affect the study’s generalisability, however, as the objective was to examine the impact of *H pylori* eradication on dyspepsia.

Comparison with other studies

Similar reductions in dyspepsia symptoms were observed in all three population based *H pylori* eradication trials.^{5 6} Results after one year showed a 4% absolute reduction in dyspepsia



Trial profile

Table 1 Characteristics of randomised participants. Values are numbers (percentages) unless stated otherwise

Characteristic	Eradication group (n=787)	Placebo group (n=771)
Sex		
Men	385 (49.0)	378 (49.0)
Women	402 (51.1)	393 (51.0)
Mean (SD) age (years)	48.4 (8.0)	48.6 (7.9)
Socioeconomic group*		
I and II	233 (30.0)	233 (30.7)
III	387 (50.0)	363 (47.8)
IV and V	155 (20.0)	164 (21.5)
Ethnic origin		
White	758 (97.1)	748 (97.9)
Non-white†	23 (2.9)	16 (2.1)
Smoking status		
Never smoked	405 (52.8)	389 (50.9)
Past smoker	179 (23.3)	190 (24.9)
Current smoker	183 (23.9)	185 (24.2)
Alcohol consumption		
None	145 (19.5)	123 (17.0)
Low alcohol intake	541 (72.8)	534 (74.0)
High alcohol intake‡	57 (7.7)	65 (9.0)
NSAID usage		
None	558 (76.5)	526 (72.7)
Less than daily	132 (18.1)	154 (21.3)
Daily	39 (6.0)	43 (6.0)
Dyspepsia symptoms§	185 (24.3)	194 (26.6)

NSAID=non-steroidal anti-inflammatory drug.
 *I and II=professional; III=skilled occupation; IV and V=partly skilled or unskilled occupations.
 †Non-white participants grouped owing to low numbers enrolled.
 ‡Greater than 20 units/week for men and 13 units/week for women.
 §Epigastric pain symptoms on two or more occasions in each of previous three months.

symptoms in the intervention arm of the Danish study, which included participants uninfected with *H pylori* and infected participants who had received eradication treatment. However, participants could have ascribed changes in dyspepsia symptoms to their knowledge of *H pylori* eradication, as the Danish study was not a placebo controlled trial. The Leeds study reported an overall reduction in dyspepsia symptoms of 5% in people aged 40-49 years, with a 74% *H pylori* eradication rate and 76% follow-up at two years. The lack of response to treatment in women observed

Table 2 Health resource use for dyspepsia over two years and unit costs

Resource use related to dyspepsia	Resource use events; mean (SD) per participant*		Unit cost or range (£) and source
	Eradication group (n=775)	Placebo group (n=750)	
General practitioner consultations	88; 0.11 (0.50)	120; 0.16 (0.52)	20†
General practitioner home visits	10; 0.001 (0.04)	10; 0.001 (0.04)	61†
Drug prescriptions	139; 0.18 (0.65)	127; 0.17 (0.56)	Variable‡
Endoscopies	25; 0.03 (0.20)	19; 0.03 (0.16)	65§
Secondary care procedures¶	21; 0.03 (0.20)	25; 0.03 (0.20)	65-226§

*Rounded to two decimal places.
 †Netten and Curtis.²⁸
 ‡BNF (gastrointestinal systems section 1.1-1.3).¹⁸
 §North Bristol NHS Trust, Bristol.
 ¶Non-endoscopic secondary care procedures such as imaging combined as few occurred, and no inpatient stays occurred.

Table 3 Health service costs for dyspepsia over two years

Costs related to dyspepsia	Health service cost (£); mean (SD) per participant*		Difference† (95% CI) in mean adjusted costs (£)
	Eradication group (n=775)	Placebo group (n=750)	
General practitioner consultations	1 785; 2.30 (10.06)	2 417; 3.22 (10.47)	-0.93 (-1.87 to 0.18)
Drug prescriptions	14 363; 18.53 (82.63)	12 362; 16.48 (97.74)	2.16 (-7.08 to 10.52)
<i>Helicobacter pylori</i> eradication drugs	64 636; 83.40 (0)	0	83.40 (83.40 to 83.40)
Endoscopies	1 596; 2.06 (12.62)	1 204; 1.61 (9.97)	0.47 (-0.71 to 1.53)
Secondary care procedures‡	1 878; 2.42 (18.73)	2 119; 2.83 (16.95)	-0.40 (-2.11 to 1.43)
Total healthcare costs§	84 259; 108.72 (95.14)	18 101; 24.13 (101.39)	84.70 (74.90 to 93.91)

*Rounded to two decimal places.
 †Eradication group minus placebo group, adjusted for the stratification variables.
 ‡Non-endoscopic secondary care procedures such as imaging combined, as few occurred and no inpatient stays occurred.
 §Totals not exact due to rounding up by £0.01.

in the Leeds study was not replicated in either this or the Danish study.^{5 6} Heartburn or acid reflux symptoms were similarly prevalent (28%) to dyspepsia symptoms (25%) in our study, but they were unaltered after *H pylori* eradication in our study and the Leeds study, whereas the Danish study observed a small reduction after eradication.^{5 6 13}

Economic analyses

Reductions in the numbers of people consulting for dyspepsia were reported in all three *H pylori* eradication population based trials. None, however, observed significant reductions in endoscopies or prescribed dyspepsia drugs after eradication, and no change in dyspepsia prescriptions was observed after *H pylori* eradication treatment in a general practice record review of 470 000 people in Denmark.²²

At £83.40 per participant, *H pylori* eradication treatment dominated costs in the economic evaluation using trial data; however, current treatment (Heliclear) costs £37.65, so halving the costs of screening and eradication to the NHS.¹⁸ The Leeds study reported non-significantly lower NHS costs (£11.42) over two years in the eradication group, although perhaps the *H pylori* eradication treatment costs were not included, which would have reversed the difference between the two groups.²³ Leeds data were incorporated into a Markov model that explored the impact of *H pylori* screening and eradication on future peptic ulcer disease and gastric cancer in 45 year olds, with effectiveness measured in life years saved. The model indicated that *H pylori* screening and treatment would cost less than a non-intervention strategy and save more lives, provided that savings of at least £2.16 a year in men were made after eradication. Our study does not support that conclusion because we found no cost savings after eradication. In contrast, a “test and treat” strategy in

Table 4 Health related quality of life at two years. Values are mean (SD) scores unless stated otherwise

Dimension	Eradication group (n=787)	Placebo group (n=771)	P value*
Physical functioning	87 (19.8)	87 (19.5)	0.64
Social functioning	86 (18.4)	85 (19.0)	0.37
Role limitation—physical	85 (31.0)	83 (32.5)	0.20
Role limitation—emotional	86 (29.1)	86 (30.8)	0.95
Pain	76 (23.8)	75 (24.7)	0.34
Mental health	75 (16.7)	74 (17.7)	0.53
Vitality	67 (18.8)	67 (20.4)	0.72
General health perception	71 (20.6)	71 (20.5)	0.64

*Eradication group minus placebo group.

What is already known on this topic

Dyspepsia is common and is usually managed in primary care

Helicobacter pylori infection is a major cause of peptic ulcer disease, but its role in dyspepsia is less certain

Dyspepsia symptoms were reduced after *H pylori* eradication in people aged 40-49 years in a community based trial

What this study adds

In the general practice population, the number of people who consulted for dyspepsia (epigastric pain) and who had symptoms decreased by 30% after *H pylori* screening and eradication

H pylori eradication in patients with dyspepsia offers long term relief from symptoms but with increased cost due to the eradication treatment

uninvestigated dyspeptic patients in Canada showed a cost effectiveness ratio of \$C387 (≈£188) in favour of *H pylori* eradication, showing that a targeted approach was a more cost effective policy.^{8, 24}

A recent systematic review of the effects of *H pylori* eradication on quality of life in patients with functional dyspepsia noted that most evidence was drawn from secondary care patients.²⁵ No major changes in quality of life were found after *H pylori* eradication in any of the three eradication trials based in the community.^{5, 6} The scores for the individual dimensions of the quality of life obtained in our study were comparable to normative UK data.¹⁶

Policy implications and conclusions

The reduction in the numbers of people consulting for dyspepsia and reporting symptoms—alongside the potential future prevention of peptic ulcers and gastric cancer²⁶—has to be balanced against the lack of benefit to people with heartburn or reflux symptoms after eradication previously reported by this study¹³ and the NHS costs. Concerns also exist about the widespread use of antibiotics in healthy people as part of the *H pylori* eradication regimen.²⁷ A targeted *H pylori* test and treat strategy focusing on uninvestigated dyspeptic patients was highly effective,⁸ and our study potentially supports that approach, as many participants gained long term relief from dyspepsia symptoms after eradication. Nevertheless, both test and treat and population screening strategies are likely to be more cost effective in areas of higher *H pylori* prevalence, as fewer people have to be tested for one to gain benefit from treatment.

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Contributors: JAL ran the project from day to day and did most of the analyses for the paper with advice from ME, LJM, IMH, JLD, and RFH initiated, planned, and obtained funding for the project. PN helped to set up the project. SN did the economic analysis and was responsible for this aspect of the paper. JAL wrote the initial draft of the paper, and all authors contributed to the final version. JAL is the guarantor.

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Competing interests: JAL and RFH were funded by GlaxoSmithKline to attend the AGA meeting in 2000.

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