



HAL
open science

Clinical Trial: Prolonged beneficial effect of Helicobacter pylori eradication on dyspepsia consultations - the Bristol Helicobacter Project

Richard F Harvey, Athene Lane, Prakash Nair, Matthias Egger, Ian Harvey,
Jenny Donovan, Liam Murray

► **To cite this version:**

Richard F Harvey, Athene Lane, Prakash Nair, Matthias Egger, Ian Harvey, et al.. Clinical Trial: Prolonged beneficial effect of Helicobacter pylori eradication on dyspepsia consultations - the Bristol Helicobacter Project. *Alimentary Pharmacology and Therapeutics*, 2010, 32 (3), pp.394. 10.1111/j.1365-2036.2010.04363.x . hal-00552576

HAL Id: hal-00552576

<https://hal.science/hal-00552576>

Submitted on 6 Jan 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Clinical Trial: Prolonged beneficial effect of Helicobacter pylori eradication on dyspepsia consultations - the Bristol Helicobacter Project

Journal:	<i>Alimentary Pharmacology & Therapeutics</i>
Manuscript ID:	APT-0271-2010.R1
Manuscript Type:	Original Scientific Paper
Date Submitted by the Author:	13-May-2010
Complete List of Authors:	Harvey, Richard; Frenchay Hospital, Medicine Lane, Athene; University of Bristol, Social Medicine Nair, Prakash; Frenchay Hospital,, Medicine Egger, Matthias; University of Bristol, Social Medicine Harvey, Ian; University of Bristol, Social Medicine Donovan, Jenny; University of Bristol, Social Medicine Murray, Liam; University of Bristol, Social Medicine
Keywords:	Gastric cancer < Disease-based, Peptic ulcer disease < Disease-based, Abdominal pain < Topics, Epidemiology < Topics, H. pylori < Topics, Screening < Topics, Stomach and duodenum < Organ-based

1
2
3 | **Clinical trial: prolonged beneficial effect of *Helicobacter pylori***
4 **eradication on dyspepsia consultations - the Bristol Helicobacter Project**
5
6

7 Richard F Harvey¹, J Athene Lane², Prakash Nair¹, Matthias Egger², Ian Harvey², Jenny
8 Donovan², Liam Murray²
9

10 ¹Frenchay Hospital, North Bristol Healthcare Trust, Bristol BS16 1LE, United Kingdom
11

12 ²Department of Social Medicine, University of Bristol, Canynge Hall, Whiteladies Road,
13 Bristol, BS8 2PR, United Kingdom
14

15 Correspondence to:

16
17 Dr Richard F Harvey
18 richard.harvey1@virgin.net
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For Peer Review

Summary

Background Chronic infection of the stomach with *Helicobacter pylori* is widespread throughout the world, and is the major cause of peptic ulcer disease and gastric cancer. Short-term benefit results from community programmes to eradicate the infection, but **there is little information on** cumulative long-term benefit.

Aim To determine whether a community programme of screening for and eradication of *Helicobacter pylori* infection produces further benefit after an initial two-year period, as judged by a reduction in GP consultations for dyspepsia.

Methods 1,517 people aged 20-59 years, who were registered with seven general practices in Frenchay Health District, Bristol, had a positive ^{13}C -urea breath test for *H. pylori* infection and were entered into a randomised double-blind trial of *H. pylori* eradication therapy. After two years, we found a 35% reduction in GP consultations for dyspepsia (previously reported). In this extension to the study, we analysed dyspepsia consultations between two and seven years after treatment.

Results Between two and seven years after treatment, 81/764 (10.6%) of participants randomised to receive active treatment consulted for dyspepsia, compared with 106/753 (14.1%) of those who received placebo, a 25% reduction, odds ratio 0.84 (0.71, 1.00), $p = 0.042$.

Conclusions Eradication of *H. pylori* infection in the community gives cumulative long-term benefit, with a continued reduction in the development of dyspepsia severe enough to require a consultation with a general practitioner up to at least seven years. The cost savings resulting from this aspect of a community *H. pylori* eradication programme, in addition to the other theoretical benefits, make such programmes worthy of serious consideration, particularly in populations with a high prevalence of *H. pylori* infection.

[ISCTRN44816925](#)

Key words: *Helicobacter*; dyspepsia; peptic ulcer; randomised controlled trial; ^{13}C -urea breath test; community; cost-effectiveness.

Introduction

Chronic infection of the stomach with *Helicobacter pylori* is widespread throughout the world, affecting more than half of the global population. It is a serious and costly public health problem (1), being the major cause of peptic ulcer disease and gastric cancer.

H. pylori infection is usually acquired in early life, and then persists long-term unless it is eradicated. Infected individuals may develop peptic ulcers at any age and they remain at risk of this throughout their lives. In contrast, gastric cancer develops generally in older age groups. Peptic ulcer disease is common, with a prevalence of 2-3% in developed countries such as the United States and Australia (2,3). Management is expensive, for example costing about six billion dollars each year in the USA (4). Gastric cancer is also common, being the second most frequent cause of cancer deaths worldwide, and accounting for approximately 800,000 deaths each year (5). This considerable morbidity might be prevented by a programme of screening for and eradication of *H pylori* infection, because in adults re-infection following eradication is uncommon.

Eradication of *H. pylori* infection from a community should in theory be quite straightforward. The population would be screened for the infection and all infected subjects would then be given a course of *H. pylori* eradication therapy. The costs of carrying out such a programme would be offset by the potential future savings resulting from the reduced requirement to treat peptic ulcer disease and gastric cancer over subsequent years. The clinical and financial benefits of preventing gastric cancer would usually be delayed for many years after *H. pylori* eradication, making such a programme aimed at cancer prevention less immediately attractive financially (6). In contrast, dyspepsia due to peptic ulcer disease, although only one of several causes of dyspepsia, is much commoner and can occur at any age. Cost savings due to prevention of *H. pylori*-related dyspepsia by a community *H. pylori* eradication programme should be apparent within a much shorter time. The rationale of such a programme differs from that of the "test and treat" management of dyspepsia, since as many as possible of the population are included, irrespective of any symptoms. Some participants may benefit immediately, by being cured of previously untreated *H. pylori*-related dyspepsia, but the main effect of a community *H. pylori* eradication programme is to prevent the future development of any *H. pylori*-related peptic ulcers. If the benefits continue to accumulate over many years, the long-term savings in health costs could make a community *H. pylori* eradication programme an economically realistic possibility (7).

We have carried out a large double-blind community-based trial of the effects of *H. pylori* infection and its eradication on the symptoms, treatment and costs of dyspepsia in the community, the Bristol Helicobacter Project (8). This has shown that screening for

1
2 and eradication of *H. pylori* infection in a community is feasible and effective. Beneficial
3 effects were seen within two years, with a 35% reduction in general practitioner (GP)
4 consultations for dyspepsia in the group receiving active treatment (9). Cost-effectiveness
5 calculations showed a slightly greater cost in the group given active treatment, the
6 difference being approximately equivalent to the cost of the eradication therapy.
7 However, if further benefit continued to accumulate over subsequent years, cost-
8 effectiveness would most probably be substantially increased.
9

Deleted: 8

10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60

This study extended the original Bristol Helicobacter Project (8,9). All people aged 20-59
years who were registered with 7 general practices in North East Bristol (total 26,203)
were invited to participate in a community-based prospective randomised controlled trial
of the effects of *H. pylori* eradication on dyspepsia, quality of life and health resource
utilisation. 10,537 individuals (40.2%) gave informed consent to take part in the study,
and had a ¹³C-urea breath test for active *H. pylori* infection, using a standard orange juice
and citric acid test meal, with a cut-off of δ 3.5 per ml (10).

Deleted: 7,8

Deleted: 9

1558 of 1634 participants whose ¹³C-urea breath test showed that they had *H. pylori*
infection (95.2%) were randomised in equal numbers to receive clarithromycin, 500mg
twice daily and ranitidine bismuth citrate 400mg twice daily for two weeks or matching
placebo (8). The unit of randomisation was the individual. Randomisation was stratified
by age into four bands of 10 years (20-29 to 50-59) and by sex. Staff independent of the
study prepared the randomisation schedule by computer with a block size of ten.
Pharmacists who prepared the study medication had no contact with study participants
and knew only their age stratum, sex and study number. Sealed opaque envelopes
containing individual randomisation codes were held by the study coordinator (JA Lane).
These envelopes were only opened after two years, unless a participant was being
withdrawn from the study (e.g., following a suspected adverse reaction to the treatment or
at the request of their physician). We asked participating primary care physicians not to
prescribe *H. pylori* eradication therapy during the first two years of follow-up.

Deleted: 7

Sample size calculations were based on the primary end point. *H. pylori* prevalence was
projected to be 15%. It was assumed that the eradication of *H. pylori* infection would
only reduce dyspepsia in those participants who suffered from undiagnosed peptic ulcer
disease. Based on the findings from a survey done in the same region as this study (11),
and other evidence (12), we assumed that in a six month period 8.5% of 20-59 year olds
would consult their general practitioner because of dyspepsia, and that 20-25% of these
would have peptic ulcers, with at least 80% of these ulcers being caused by *H. pylori*
infection. A total sample size of 1500 participants would detect a reduction in the
consultation rate from 8.5% to 4.25% in the eradication group, with 90% power at a
significance level of 5%.

Deleted: 10

Deleted: 11

1
2
3 The main outcome measure was a consultation with the general practitioner between two
4 and seven years after randomisation and treatment, which had been recorded in the
5 participants' primary care notes as being for upper abdominal pain or discomfort (13,14).
6 Consultations for heartburn or reflux, were also noted. During the trial, the randomisation
7 codes for each participant were held in opaque sealed envelopes, the participants being
8 identified only by trial number. After two years and again after seven years the research
9 nurse (who was blind to the treatment allocation) visited the relevant general practice
10 surgery during the outcome assessment. The nurse retrieved the medical records of each
11 participant and reviewed all entries made over the period of the study, recording the dates
12 and details of any consultations for any of the above upper alimentary symptoms,
13 together with any medications prescribed and any related hospital referrals. The primary
14 outcome measure was any consultation for dyspepsia, defined as pain or discomfort
15 centred in the upper abdomen, as described in the Rome criteria for functional dyspepsia
16 (13). A secondary outcome was a consultation for heartburn or reflux. The reliability of
17 the data extraction from the medical records by the nurse was validated by a consultant
18 gastroenterologist in a random sample of 20 successive participants and found to be
19 accurate and complete. Details of the numbers in each category are shown in the Consort
20 flow chart (Fig 1).
21
22

Deleted: 12,13

23 The study was approved by Frenchay Healthcare NHS Trust Research Ethics Committee
24 for Bristol and District Health Authority. All prospective participants were sent an
25 information sheet with full details of the project, and written informed consent was
26 obtained by a research nurse when they attended for their first breath test.
27

28 Statistical analysis of the data was carried out using SPSS version 10 (14). The
29 significance of differences was assessed by Pearson's chi-square test. Analyses of
30 consultation rates between two and seven years after treatment were performed using
31 odds ratios on an intention to treat basis. In addition, the influence of age and gender
32 were analysed by randomisation groups, also using Pearson's chi-square test and odds
33 ratios.
34
35
36

Deleted: 14

37 Results

38 Study population

39 Of the 10,537 participants who had a ¹³C-urea breath test, 1,634 (15.5%) were positive
40 for *H. pylori* infection and were eligible for inclusion in the randomised controlled trial of
41 *H. pylori* eradication therapy. 1558 (95.2% of those testing positive) were randomised to
42 receive either active treatment (n=787) or placebo (n=771). The characteristics of the two
43 groups were similar, and are shown in Table 1.
44
45

46 Completeness of *H. pylori* eradication and of follow-up

47 Six months after treatment, the second ¹³C-urea breath test showed that *H. pylori*
48 infection was no longer present in 714/787 (90.7%) of those receiving active treatment.
49
50
51
52
53
54
55
56
57
58
59
60

1
2 Follow-up seven years after treatment was complete in 1517 of the 1558 participants
3 (97.4%), the remaining 41 having either died (11) or moved away (30).
4

5 Participants consulting for dyspepsia

6 In the period between two and seven years after treatment, 81/764 (10.6%) of participants
7 given active therapy consulted their general practitioner for symptoms of dyspepsia,
8 compared with 106/753 (14.1%) of those who had placebo, odds ratio (OR) 0.84
9 (0.71,1.00), $p = 0.042$. Of these, 47/764 (6.2%) of the participants given active therapy
10 and 61/753 (8.1%) of those who received placebo consulted for dyspepsia for the first
11 time more than two years after randomisation, having not consulted previously OR 0.85
12 (0.69,1.06), $p = 0.084$ (Table 2). Over the whole 7-year period, 102/782 participants
13 given active treatment consulted for dyspepsia, compared with 139/757 given placebo,
14 OR 0.69 (0.51,0.88), $p = 0.041$.
15

16 Influence of gender on consultations for dyspepsia

17 The benefit of receiving active *H. pylori* eradication therapy appeared to be greater in
18 men than in women. In the period between two and seven years after treatment, 41/366
19 (11.2%) of men given active therapy consulted for dyspepsia, compared with 64/348
20 (18.4%) of those who had placebo, (OR 0.73 (0.57,0.94), $p = 0.008$). In the same period,
21 40/398 (10.1%) of women given active therapy consulted for dyspepsia, compared with
22 42/405 (10.4%) of those who had placebo, OR 0.98 (0.78,1.24),
23 $p = 0.908$.
24

25 Influence of age on consultations for dyspepsia

26 The benefits of active treatment were more obvious in older participants; in those aged 45
27 years and above who were given active therapy, 57/543 (10.5%) consulted, compared
28 with 82/545 (15.0%) of those given placebo, OR 0.80 (0.65, 0.99), $p = 0.029$. In contrast,
29 of those aged 44 or less who were given active therapy 24/221 (10.9%) consulted,
30 compared with 24/208 (11.5%) of those given placebo, OR 0.97 (0.72, 1.30), $p = 0.879$.
31
32

33 Participants consulting for heartburn or reflux

34 There was no difference in the rate of consultation for new heartburn and/or reflux (i.e.,
35 developing for the first time more than two years after randomisation) (OR 0.99
36 (0.83,1.15), $p = 0.81$ (Table 3).
37
38

39 **Discussion**

40 The Bristol Helicobacter Project was set up to assess the feasibility and costs of a
41 programme aimed at the complete eradication of *H. pylori* infection from a community.
42 This would have obvious health benefits, abolishing dyspepsia due to *H. pylori*-related
43 peptic ulcer disease (as well as the serious complications of bleeding and perforation) and
44 reducing the risk of gastric cancer. After two years we found that detection and
45 eradication of *H. pylori* infection was straightforward and effective. Consultations with
46 the general practitioner for dyspepsia were reduced by 35% within two years (9). The
47 costs per individual were dominated by the cost of the *H. pylori* eradication therapy that
48
49
50
51
52
53
54
55
56
57
58
59
60

Deleted: 8

we used. This was a non-standard regime designed specifically for this trial, with the aim of achieving as high an eradication rate as possible, by using a two-week course of acid suppressant, antibiotic and bismuth. The *H. pylori* eradication rate achieved (90.7%) was the best ever recorded in any community-based study, but the treatment cost at that time (£83.40 (\$146, €121)) was more than three times greater than the cost of currently available regimes. We concluded then that the cost-effectiveness of a community *H. pylori* eradication programme in a population such as ours, with a relatively low prevalence of *H. pylori* infection, was inferior to that of a targeted *H. pylori* test and treat strategy focusing on uninvestigated dyspeptic patients. There is still debate as to whether a test and treat strategy is more or less appropriate than initial management of dyspeptic patients with acid suppressant medication (in a UK population the cost-effectiveness is similar) (15-17), but the result of such comparisons depends to a great extent on the population concerned, in particular the local prevalence of *H. pylori* infection. In most developed countries, the prevalence of *H. pylori* infection has been falling in recent years, particularly in younger age groups, with a closely related decrease in the incidence of peptic ulcer disease (18). This relatively rapid decrease has not been due to the use of *H. pylori* eradication, but probably mostly to improvements in public health reducing the transmission of *H. pylori* infection. This process seems to be very variable, so that even within a single country such as the UK the prevalence of *H. pylori* infection varies greatly. Thus in 50-year-old men the prevalence of *H. pylori* infection is 15% in Bristol (8), 30% in Leeds (19), and 60% in Glasgow (20). The cost-effectiveness of a community *H. pylori* eradication programme would clearly be very different in these three areas, and it could be argued that such a programme would in any case not be worth considering in a particular area if the spontaneous rate of decline in *H. pylori* infection in that area was rapid. Before considering any community *H. pylori* eradication programme, the local prevalence of the infection would therefore need to be ascertained. Thus, in Leeds, where the prevalence of *H. pylori* infection is approximately twice that in Bristol, a 40% follow-up of a community screening and *H. pylori* eradication programme in 40-49-year olds suggested that the savings in healthcare costs were greater than the costs of carrying out the programme (7). In areas where *H. pylori* infection is becoming less common, the proportion of non-*H. pylori*-related peptic ulcers is increasing. Most of these are related to treatment with NSAIDs, but a few seem not to have any known cause.

Deleted: 15-17

Deleted: 7

Deleted: 18

Deleted: 19

Our choice of a consultation with a general practitioner for dyspepsia as our main outcome measure was based on the hypothesis that *H. pylori* eradication would reduce dyspepsia by preventing the later development of peptic (mainly duodenal) ulcers. The commonest symptom of such ulcers is pain in the upper abdomen, "dyspepsia" (13). Minor dyspepsia is extremely common in the community (21), which would create considerable background "noise" against which any changes due to *H. pylori* eradication might appear to be relatively small. Dyspepsia due to peptic ulcer disease is usually marked, so would be more likely to result in the sufferer seeking a medical consultation. This hypothesis is supported by the findings of an unblinded but otherwise similar study to ours (22), in which a screening and *H. pylori* eradication programme in Denmark showed after five years no significant effect on dyspepsia prevalence, but a significantly reduced consultation rate for dyspepsia (23). A consultation would also represent objective "hard" evidence, which would always be recorded in the medical notes and

Deleted: 12,13

Deleted: 21

Deleted: 22

Deleted: 23

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

would thus be available for assessment over many later years, ensuring a maximal follow-up rate. [Factors influencing the frequency and reasons for consultation for dyspeptic symptoms have been reviewed recently \(24\). Independently of any *H. pylori* infection, dyspepsia consultations are influenced by age and gender, so adequate randomisation is essential, as achieved in this study.](#)

Our finding of an apparently greater benefit from *H. pylori* eradication in men than in women is unexplained. However, very similar findings were reported from the Leeds community *H. pylori* eradication study (19), where dyspepsia at two years was reduced in the eradication group from 36% to 27% in men but only from 31% to 30% in women. One possible explanation is that peptic ulcer disease is more frequent among men than women infected with *H. pylori*. Thus in the mid-20th century, when most of the UK population had *H. pylori* infection, approximately 80% of peptic ulcers in the UK were seen in men (25). The biological explanation for these gender differences remains unknown.

Deleted: 19

Deleted: 24

Consultation rates for heartburn and gastro-oesophageal reflux over the period from two to seven years after randomisation were not affected by *H. pylori* eradication, confirming the findings after two years of follow-up (26).

Deleted: 25

The strengths of this study are that large numbers of participants across a wide age range were recruited, with few exclusions, thus increasing generalisability. The high rates of *H. pylori* eradication and follow-up enhance the internal validity of the study, whilst the breath test (the noninvasive 'gold standard' detection method) minimised misclassification biases and probably facilitated recruitment compared with serology, as no blood test was necessary. The clinically important primary outcome of dyspepsia consultations in primary care allowed objective reporting from the medical notes without further patient contact, giving a very high rate of follow-up, even after seven years. All participants were followed up for seven years, even if they had consulted their general practitioners after a shorter interval. [Potential unblinding after 2 years did not seem to have been a significant problem, as very few requests for unblinding were received from the GPs. Prescribing information was obtained for all participants. Only 41 \(2.6%\) had been given *H. pylori* eradication therapy by their GPs. 35 of these had received placebo and were *H. pylori* positive and 6 had received *H. pylori* eradication therapy and were *H. pylori* negative.](#)

In a community testing and eradication programme for *H. pylori* infection, Ford and his colleagues showed that participants who were negative for the infection and were informed of this fact were less likely to seek general practice consultations than those who were not informed (27). This response to knowledge of *H. pylori* status suggests that there would be further cost savings in any community programme, as there would be fewer consultations by uninfected subjects as well as by those in whom the infection had

Deleted: 26

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

been eradicated. [A further potential benefit might result from a reduction in the incidence of functional \(non-ulcer\) dyspepsia, some of which could be attributable to *H. pylori* infection \(28\).](#)

This present study indicates that *H. pylori* eradication has a prolonged beneficial legacy, by ~~reducing the development of dyspepsia~~ in individuals infected by *H. pylori*, so that treated individuals will benefit over many subsequent years, producing significant further cost savings. The costs of the community *H. pylori* eradication programme that we started in the Bristol Helicobacter Project more than ten years ago would now be substantially lower, since both ¹³C-urea breath tests and *H. pylori* eradication therapy have become much cheaper. The cost-effectiveness of such programmes could in the future be further increased by concentrating on populations with a high prevalence of *H. pylori* infection, and perhaps particularly on men. Further benefits would result from a reduction in healthcare use by individuals who know that they do not have *H. pylori* infection, and in the longer term from the anticipated reduction in gastric cancer. All of these factors together suggest that a combination of improvements in public health with targeted and affordable community *H. pylori* eradication programmes would speed up the eventual eradication of *H. pylori* infection from mankind.

Deleted: prevent

Deleted: peptic ulcers

Acknowledgements

We thank the participants in the Bristol Helicobacter Project and the general practitioners and Health Centre staff; the nursing team of Lynne Bradshaw, Julie Watson, Tina Critchley, Jo Lee, Carol Everson-Coombe, Penny Nettlefield and Joanne Smith; Judy Millward, Helen Davies, Amy Hawkins and Sarah Pike for secretarial support and Erwin Brown, Paul Thomas, Nick Pope and Phil Hedges of the Microbiology Department and Peter Spurr, Martin Bullock and Fiona Greenwood of the Pharmacy Department, Frenchay Hospital, for help with the 10,537 breath tests. This study was funded jointly by the NHS South and West Regional Research and Development Directorate and GlaxoSmithKline UK.

References

1. Axon A, Forman D. Helicobacter gastroduodenitis: a serious infectious disease. *BMJ* 1997;314:1430-1431.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

2. Everhart JE, Ed. Digestive Diseases in the United States: Epidemiology and Impact. NIH Publication No 94-1447. 1994.

3. National Health Survey 2001: Australia's Health. Australian Bureau of Statistics. 2004
AIHW

4. Sandler R, Everhart J, Donowitz M, Adams E, Cronin K, Goodman C, Gemmen E, Shah S, Advic A, Rubin R. The burden of selected digestive diseases in the United States. *Gastroenterology* 2002;122:1500-1509.

5. Cancer. Fact Sheet No 297, 2009. World Health Organisation.

6. Parsonnet J, Harris RA, Hack HM, Owens DK, Modelling cost-effectiveness of *Helicobacter pylori* screening to prevent gastric cancer: a mandate for clinical trials. *Lancet* 1996;348:150-154.

[7. Ford AC, Forman D, Bailey AG, Axon ATR, Moayyedi P. A community screening Program for *Helicobacter pylori* saves money: 10-year follow-up of a randomised controlled trial. *Gastroenterology* 2005;129:1910-1917.](#)

8. Lane JA, Harvey RF, Murray L, Harvey IM, Nair P, Egger M, Donovan J
A placebo-controlled randomized trial of eradication of *Helicobacter pylori* in the general population: Study design and response rates of the Bristol Helicobacter Project. *Controlled Clinical Trials* 2002; 23: 321-332.

9. Lane, JA, Murray LJ, Noble S, Egger M, Harvey IM, Donovan JL, Nair P, Harvey RF. Impact of *Helicobacter pylori* eradication on dyspepsia, health resource use and quality of life in the Bristol Helicobacter project: randomised controlled trial. *BMJ* 2006;332:199-202.

10. Dominguez-Munoz JE, Leodolter A, Sauerbruch T, Malfertheiner P.
A citric acid solution is an optimal test drink in the ¹³C-urea breath test for *Helicobacter pylori* infection. *Gut* 1997; 40:459-462.

1
2
3
4 11. Jones R, Lydeard S. Prevalence of symptoms of dyspepsia in the community. *BMJ*
5 1989;298:30-32.
6

7
8
9 12. Heatley RV, Rathbone BJ. Dyspepsia: a dilemma for doctors? *Lancet* 1987;2:778-
10 782.
11

12
13
14 13. [Talley NJ, Silverstein MD, Agrus L, Nyren O, Sonnenberg A, Holtmann G. AGA](#)
15 [Technical Review: Evaluation of dyspepsia. *Gastroenterology* 1998;114:582-595.](#)
16

17
18
19 14. Argyrous G. *Statistics for Research: with a guide to SPSS, Second Edition* 2005.
20 SAGE UK London. ISBN 1412919487.
21

22
23 15. Chiba N, van Zanten SJOV, Sinclair P, Ferguson RA, Escobido S, Grace E. Treating
24 *Helicobacter pylori* infection in primary care patients with uninvestigated dyspepsia: the
25 Canadian adult dyspepsia empiric treatment-*Helicobacter pylori* positive (CADET-*Hp*)
26 randomised controlled trial. *BMJ* 2002;324:1012-1016.
27

28
29 16. Spiegel BMR, Vakil NB, OfmanJJ. Dyspepsia management in primary care: a
30 decision analysis of competing strategies. *Gastroenterology* 2002;122:1270-1285.
31

32
33 17. Delaney BC, Qume M, Moayyedi P, Logan RFA, Ford AC, Elliott C, McNulty C,
34 Wilson S, Hobbs FDR. *Helicobacter pylori* test and treat versus proton pump inhibitor in
35 initial management of dyspepsia in primary care: multicentre randomised controlled trial
36 (MRC-CUBE trial). *BMJ* 2008;336:651-654.
37

38
39 18. Harvey RF, Spence RW, Lane JA, Nair P, Murray LJ, Harvey IM, Donovan J.
40 Relationship between the birth cohort pattern of *Helicobacter pylori* infection and the
41 epidemiology of duodenal ulcer
42 *Q J Med* 2002; 95: 519-525.
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

19. [Moayyedi P, Feltbower R, Brown J, Mason S, Mason J, Nathan J, Richards IDG, Dowell AC, Axon ATR. Effect of population screening and treatment for *Helicobacter pylori* on dyspepsia and quality of life in the community: a randomised controlled trial. Lancet 2000; 355:1665-1669.](#)

Deleted: ¶

20. [Woodward M, Morrison C, McColl K. An investigation into factors associated with *Helicobacter pylori* infection. J Clin Epidemiol 2000;53:175-181.](#)

21. Jones R, Lydeard SE, Hobbs FD, Kenkre JE, Williams EI, Jones SJ, Repper JA, Caldwell JL, Dunwoodie WM, Bottomley JM. Dyspepsia in England and Scotland. Gut 1990;31:401-405

22. Wildner-Christensen M, Moller HJ, Schaffalitzky de Muckadell OB. Rates of dyspepsia one year after *Helicobacter pylori* screening and eradication in a Danish population. Gastroenterology 2003;125:372-379.

23. Hansen JM, Wildner-Christensen M, Hallas J, Schaffalitzky de Muckadell OB. Effect of a community screening for *Helicobacter pylori*: a 5-year follow-up study. Amer J Gastroenterol 2008;103:1106-1113.

24. [Hungin APS, Hill C, Raghunath A. Systematic review: frequency and reasons for consultation for gastro-oesophageal reflux disease and dyspepsia. Aliment Pharmacol Ther 2009;30:331-342.](#)

25. Avery Jones F, Gummer JWP, Lennard-Jones JE. Clinical Gastroenterology, Blackwell Scientific, Oxford and Edinburgh 1960; 470-475.

26. Harvey RF, Lane A, Murray LJ, Harvey IM, Donovan JL, Nair P. Randomised controlled trial of the effects of *Helicobacter pylori* infection and its eradication on heartburn and gastro-oesophageal reflux: Bristol *Helicobacter* Project. BMJ 2004;328:1417.

1
2
3 27. Ford AC, Forman D, Nathan J, Crocombe WD, Axon AT, Moayyedi P. Clinical trial:
4 knowledge of negative *Helicobacter pylori* status reduces subsequent dyspepsia-related
5 resource use. *Aliment Pharmacol Ther* 2007; 26:1267-1275
6

7
8 [28. Moayyedi P, Forman D, Braunholtz D, Feltbower R, Crocombe W, Liptrott M, Axon](#)
9 [ATR, The proportion of upper gastrointestinal symptoms in the community associated](#)
10 [with *Helicobacter pylori*, lifestyle factors and non-steroidal anti-inflammatory drugs.](#)
11 [Amer J Gastro 2000;95:1448-1455.](#)
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For Peer Review

Figure 1: Trial profile

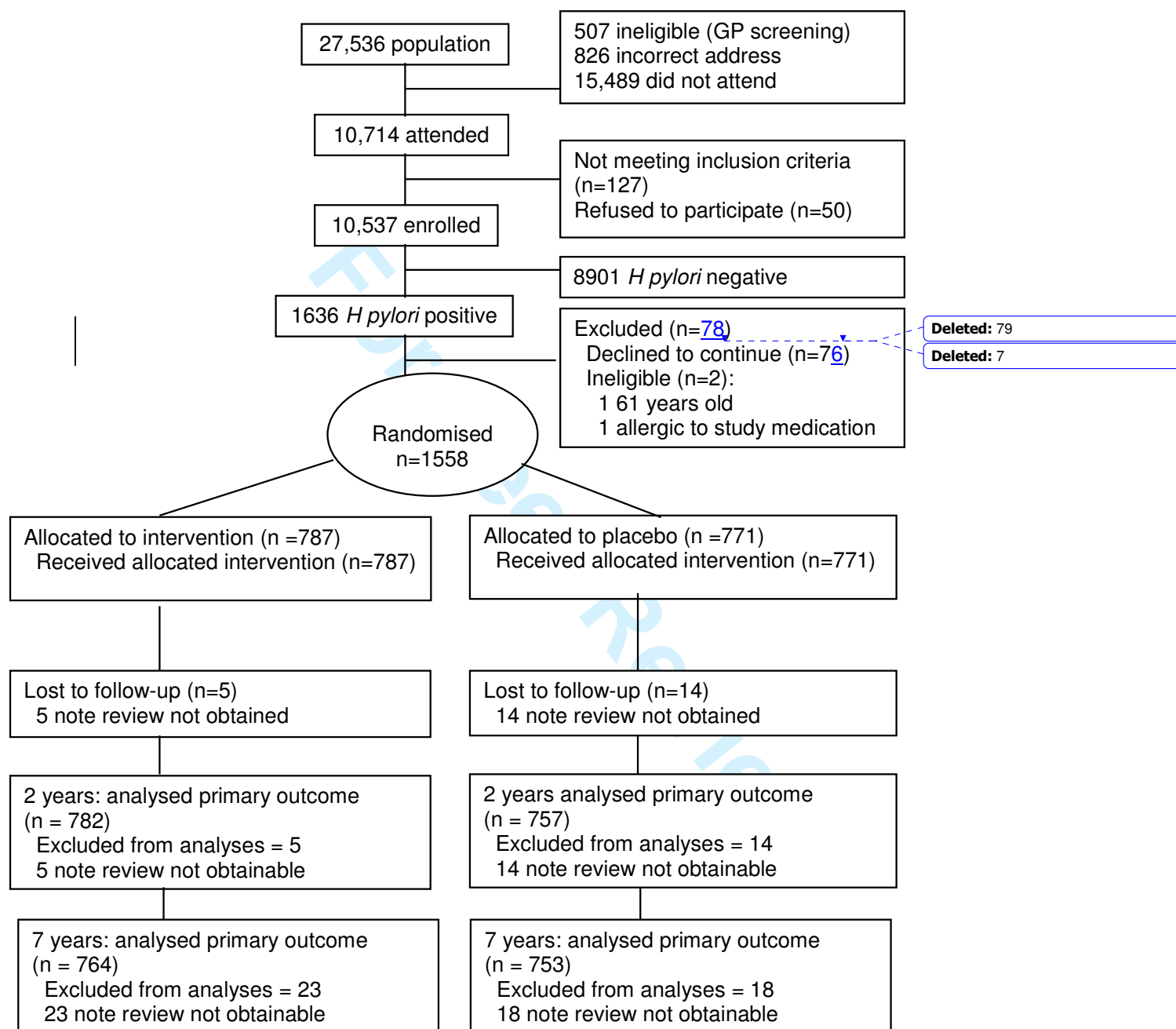


Table 1. Baseline characteristics of the two groups of subjects with *H. pylori* infection who entered the prospective double-blind study

	Active treatment (n=787)	Placebo treatment (n=771)
Age (years) at time of recruitment:		
20-39	120/787 (15.2%)	110/771 (14.3%)
40-54	452/787 (57.5%)	451/771 (58.5%)
55-59	215/787 (27.3%)	210/771 (27.2%)
Sex:		
Male	385 (48.9%)	378 (49.0%)
Female	402 (51.1%)	393 (51.0%)
Lifestyle:		
Smoking - (never)	405/767 (52.8%)	389/764 (50.9%)
(past)	179/767 (23.3%)	190/764 (24.9%)
(current)	183/767 (23.9%)	185/764 (24.2%)
NSAIDs (any in last 3 months)	177/732 (24.2%)	191/720 (26.5%)
BMI 30 or greater	221/787 (28.2%)	195/771 (25.3%)

The slight differences in the figures for total number are due to incomplete or missing data entry by some of the subjects

Table 2. Number of participants consulting for dyspepsia in the seven years after randomisation

Randomisation group	0-2 years	2-7 years			0-7 years
	Participants consulting for dyspepsia	Participants consulting for dyspepsia who had not consulted between 0-2 years	Participants consulting for dyspepsia who consulted in first two years	All participants consulting for dyspepsia after two years	All participants consulting for dyspepsia
Placebo	78/757 (10.3%)	61/753 (8.1%)	45/753 (6.0%)	106/753 (14.1%)	139/757 (18.4%)
Active therapy	55/782 (7.0%)	47/764 (6.2%)	34/764 (4.4%)	81/764 (10.6%)	102/782 (13.0%)

Table 3. Number of participants consulting for heartburn and/or reflux

	0-2 years	2-7 years	0-7 years
Placebo	20/753 (2.7%)	71/753 (9.4%)	86/753 (11.4%)
Active therapy	32/764 (4.2%)	61/764 (8.0%)	84/764 (11.0%)

The slight differences in the total figures are due to incomplete data entry by some of the subjects

For Peer Review

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60