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

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3 | **Clinical trial: prolonged beneficial effect of *Helicobacter pylori***  
4 **eradication on dyspepsia consultations - the Bristol Helicobacter Project**  
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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  $^{13}\text{C}$ -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;  $^{13}\text{C}$ -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.  
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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 <sup>13</sup>C-urea breath test for active *H. pylori* infection, using a standard orange juice  
and citric acid test meal, with a cut-off of  $\delta$ 3.5 per ml (10).

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1558 of 1634 participants whose <sup>13</sup>C-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.

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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%.

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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).  
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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.  
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## 37 Results

### 38 Study population

39 Of the 10,537 participants who had a <sup>13</sup>C-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.  
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### 46 Completeness of *H. pylori* eradication and of follow-up

47 Six months after treatment, the second <sup>13</sup>C-urea breath test showed that *H. pylori*  
48 infection was no longer present in 714/787 (90.7%) of those receiving active treatment.  
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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).  
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#### 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),  $p = 0.879$ .  
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#### 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).  
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### 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  
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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.

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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

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

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12 Our finding of an apparently greater benefit from *H. pylori* eradication in men than in  
13 women is unexplained. However, very similar findings were reported from the Leeds  
14 community *H. pylori* eradication study (19), where dyspepsia at two years was reduced in  
15 the eradication group from 36% to 27% in men but only from 31% to 30% in women.  
16 One possible explanation is that peptic ulcer disease is more frequent among men than  
17 women infected with *H. pylori*. Thus in the mid-20<sup>th</sup> century, when most of the UK  
18 population had *H. pylori* infection, approximately 80% of peptic ulcers in the UK were  
19 seen in men (25). The biological explanation for these gender differences remains  
20 unknown.  
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23 Consultation rates for heartburn and gastro-oesophageal reflux over the period from two  
24 to seven years after randomisation were not affected by *H. pylori* eradication, confirming  
25 the findings after two years of follow-up (26).  
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28 The strengths of this study are that large numbers of participants across a wide age range  
29 were recruited, with few exclusions, thus increasing generalisability. The high rates of *H*  
30 *pylori* eradication and follow-up enhance the internal validity of the study, whilst the  
31 breath test (the noninvasive 'gold standard' detection method) minimised  
32 misclassification biases and probably facilitated recruitment compared with serology, as  
33 no blood test was necessary. The clinically important primary outcome of dyspepsia  
34 consultations in primary care allowed objective reporting from the medical notes without  
35 further patient contact, giving a very high rate of follow-up, even after seven years. All  
36 participants were followed up for seven years, even if they had consulted their general  
37 practitioners after a shorter interval. [Potential unblinding after 2 years did not seem to  
38 have been a significant problem, as very few requests for unblinding were received from  
39 the GPs. Prescribing information was obtained for all participants. Only 41 \(2.6%\) had  
40 been given \*H. pylori\* eradication therapy by their GPs. 35 of these had received placebo  
41 and were \*H. pylori\* positive and 6 had received \*H. pylori\* eradication therapy and were \*H.\*  
42 \*pylori\* negative.](#)

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44 In a community testing and eradication programme for *H. pylori* infection, Ford and his  
45 colleagues showed that participants who were negative for the infection and were  
46 informed of this fact were less likely to seek general practice consultations than those  
47 who were not informed (27). This response to knowledge of *H. pylori* status suggests that  
48 there would be further cost savings in any community programme, as there would be  
49 fewer consultations by uninfected subjects as well as by those in whom the infection had  
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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 <sup>13</sup>C-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.

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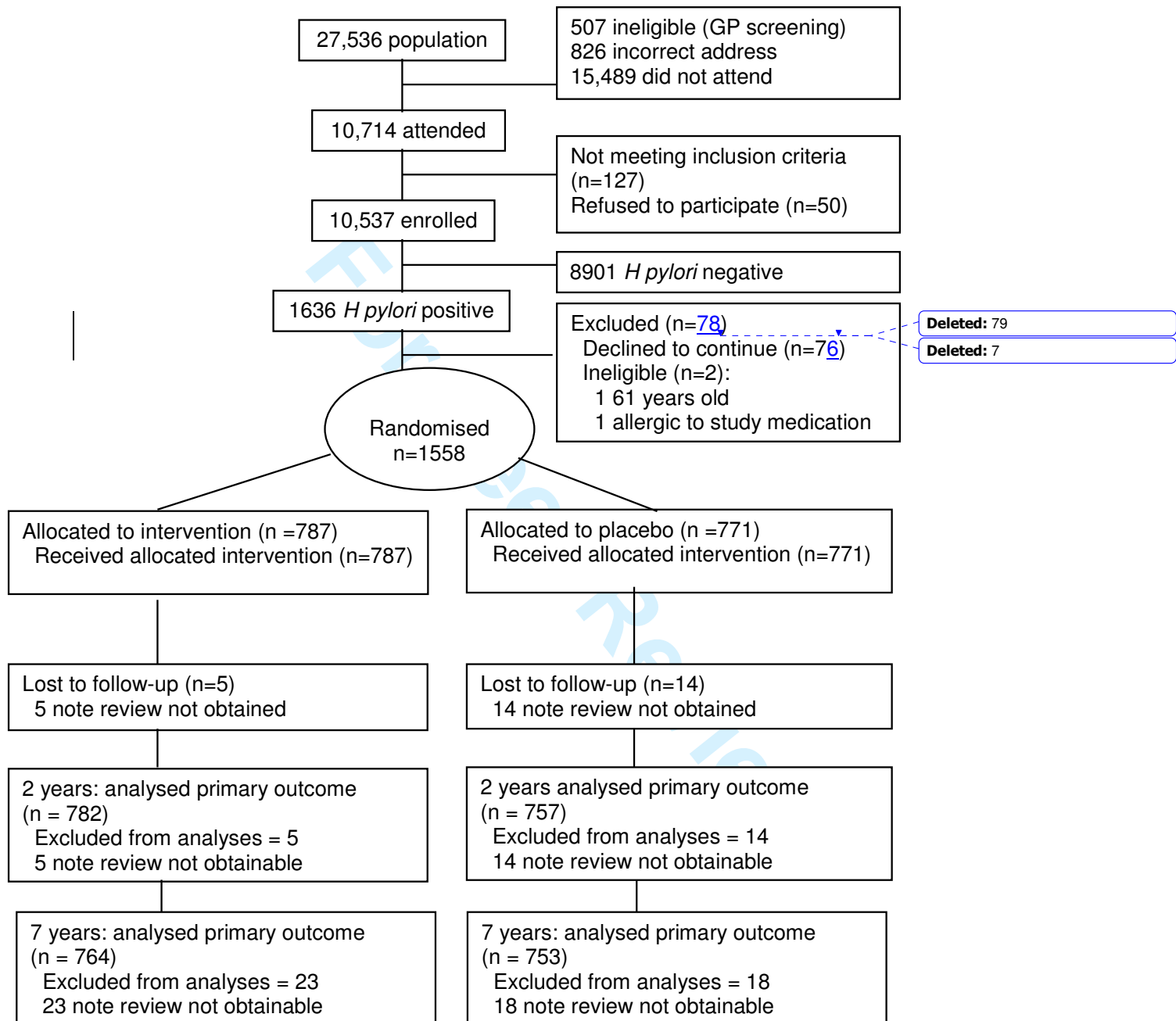
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Figure 1: Trial profile





**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)
<b>Age (years) at time of recruitment:</b>		
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%)
<b>Sex:</b>		
Male	385 (48.9%)	378 (49.0%)
Female	402 (51.1%)	393 (51.0%)
<b>Lifestyle:</b>		
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**

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

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

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