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Details of the searches and tables of the excluded studies and prevalence appear on [bmj.com](http://bmj.com)

# Prevalence of *Helicobacter pylori* in patients with gastro-oesophageal reflux disease: systematic review

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## Abstract

**Objectives** To ascertain the prevalence of *Helicobacter pylori* in patients with gastro-oesophageal reflux disease and its association with the disease.

**Design** Systematic review of studies reporting the prevalence of *H pylori* in patients with and without gastro-oesophageal reflux disease.

**Data sources** Four electronic databases, searched to November 2001, experts, pharmaceutical companies, and journals.

**Main outcome measure** Odds ratio for prevalence of *H pylori* in patients with gastro-oesophageal reflux disease.

**Results** 20 studies were included. The pooled estimate of the odds ratio for prevalence of *H pylori* was 0.60 (95% confidence interval 0.47 to 0.78), indicating a lower prevalence in patients with gastro-oesophageal reflux disease. Substantial heterogeneity was observed between studies. Location seemed to be an important factor, with a much lower prevalence of *H pylori* in patients with gastro-oesophageal reflux disease in studies from the Far East, despite a higher overall prevalence of infection than western Europe and North America. Year of study was not a source of heterogeneity.

**Conclusion** The prevalence of *H pylori* infection was significantly lower in patients with than without gastro-oesophageal reflux, with geographical location being a strong contributor to the heterogeneity between studies. Patients from the Far East with reflux disease had a lower prevalence of *H pylori* infection than patients from western Europe and North America, despite a higher prevalence in the general population.

## Introduction

Gastro-oesophageal reflux disease affects 25-40% of the population, is managed mainly in primary care, and accounts for the largest prescribing cost in the NHS.<sup>1,2</sup> Treating *H pylori* infection is effective in healing duodenal ulcers, but the effect of eradication of the organism in patients with gastro-oesophageal reflux disease is less clear, with some reports suggesting that *H pylori* infection might protect against the disease.<sup>3-5</sup> However, the recent Maastricht 2 guidelines on the management of patients with *H pylori* infection recommend eradication in those with gastro-oesophageal reflux disease who are likely to require long term proton pump inhibitor therapy.<sup>6</sup> This is because profound acid suppression may accelerate the progression of *H pylori* induced atrophic gastritis, increasing the potential risk of cancer.

Studies evaluating the presence or absence of *H pylori* on gastro-oesophageal reflux disease have often had drawbacks in design and have given conflicting results.<sup>7,8</sup> Fundamentally it is not certain whether there are differences in the prevalence of *H pylori* between

patients with and without gastro-oesophageal reflux disease.<sup>9-13</sup>

We conducted a systematic review to establish the overall prevalence of *H pylori* in patients with gastro-oesophageal reflux disease and to determine if this is significantly different from patients without the disease. This is important for determining if patients with the disease differ and to quantify the extent of infection. This topic is also of relevance because of the large numbers of patients in the community taking long term proton pump inhibitors, mostly for reflux. The determination of *H pylori* status in these patients has so far not been a clinical issue; gastro-oesophageal reflux disease is commonly diagnosed and treated in primary care on the basis of a clinical history alone.

## Methods

We included studies to November 2001 fulfilling certain eligibility criteria (box) by searching Medline, Embase, Cinahl, and Cochrane using subject terms and text words. Bibliographies were reviewed, experts in six countries and pharmaceutical companies contacted (see [bmj.com](http://bmj.com)), and general medical and major gastroenterology journals searched over the previous year.

Gastro-oesophageal reflux disease was defined according to published definitions.<sup>14-17</sup> These comprised two categories, both in patients who had heartburn or reflux as the predominant symptoms. The first was the presence of endoscopically defined oesophagitis and the second, when endoscopy did not show oesophagitis, a positive result for pH monitoring with or without oesophagitis on histology. Two investigators independently reviewed the papers. Disagreements were resolved by consensus with a third reviewer.

Each of the 20 included studies was summarised according to its odds ratio. Study results were pooled with a fixed effect model (assessed with a test of homogeneity) and the odds ratios were pooled with a random effects model in cases of substantial heterogeneity.

## Results

Our initial search identified 654 articles. Thirty seven of these met the eligibility criteria; 16 were excluded after further scrutiny (see table A on [bmj.com](http://bmj.com)). This left 20 studies, totalling 4134 patients, of whom 58.5% (n=2418) were in control groups.

The average prevalence of *H pylori* infection in patients with gastro-oesophageal reflux disease was 38.2% (range 20.0-82.0%) compared with 49.5% (29.0-75.6%) in the comparator group. Four studies showed a higher prevalence of *H pylori* infection among patients with gastro-oesophageal reflux disease, but not significantly so (figure and table B on [bmj.com](http://bmj.com)). The remaining studies showed a lower prevalence among patients with gastro-oesophageal reflux disease, significantly so in six studies. The pooled odds ratio was 0.58 (95%

**Eligibility and quality criteria for inclusion in systematic review**

**Studies with a comparator, control, or reference group**

Patients with gastro-oesophageal reflux disease should have undergone gastroscopy.

- Included:
- Patients with endoscopically proved oesophagitis
- Patients with normal appearance of oesophagus on endoscopy and with confirmation of gastro-oesophageal reflux disease either by pH studies or histology
- Excluded:
- Patients with non-ulcer dyspepsia in whom other confirmation of gastro-oesophageal reflux disease by pH studies or histology of the oesophagus was not available
- Patients with normal endoscopy result and typical reflux symptoms but confirmation by pH studies or histology not available or confirmed
- Patients known or discovered to have Barrett's oesophagus
- Patients with confirmed peptic ulcer disease
- Patients who had received proton pump inhibitors within the previous two weeks or undergone eradication of *H pylori*

**Comparator group (one or more of the following)**

- Normal endoscopy result and absence of symptoms of gastro-oesophageal reflux disease
- Healthy asymptomatic volunteers
- Absence of pathological reflux on pH monitoring—that is, oesophageal pH is < 4 for more than 3.5% of total recorded time, or as defined by author of the study
- Normal endoscopy result and absence of oesophagitis on histology

**Quality criteria**

- Documentation of how cases were obtained
- Appropriateness of comparator
- Similar data collection for cases and comparator group
- Similar *H pylori* testing for cases and comparator group
- Basic data adequately described
- Statistical methods described and significance levels assessed

confidence interval 0.51 to 0.66), indicating a lower prevalence of *H pylori* infection among patients with gastro-oesophageal reflux disease (heterogeneity test:  $\chi^2=83.01$ ,  $df=19$ ,  $P<0.001$ ).

Because of the presence of substantial heterogeneity, studies were also pooled with a random effects model (summary odds ratio 0.60, 0.47 to 0.78), which showed weaker but still strong evidence of a lower prevalence of *H pylori* infection among patients with gastro-oesophageal reflux disease.

Statistical heterogeneity was investigated by location. Five studies were from the Far East, seven from North America, and seven from western Europe. One study originated from Chile. Some similarities were found for studies from particular geographical locations (fig 1). When the three main groups were analysed separately, the odds ratio for western Europe was 0.76 (0.61 to 0.96)

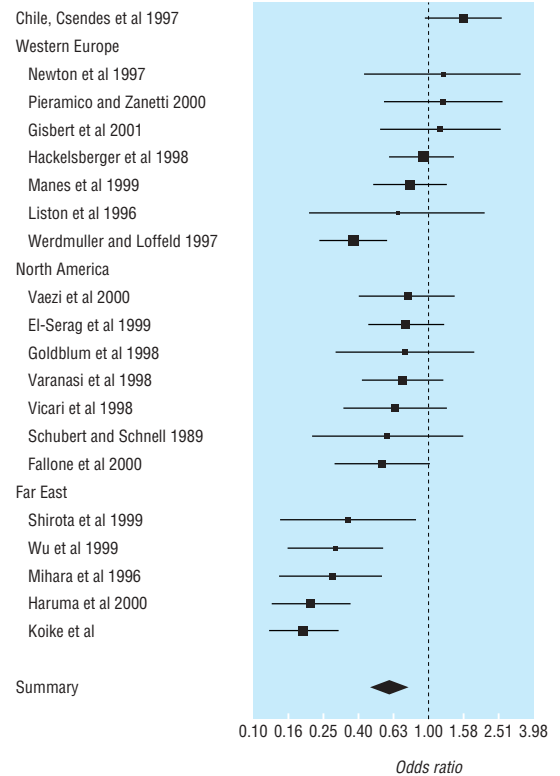
and test for heterogeneity  $\chi^2=14.01$ ,  $df=6$ ,  $P=0.030$ . One study dominated the analysis, but after its exclusion the odds ratio was 0.97 (0.75 to 1.27) and test for heterogeneity  $\chi^2=1.8$ ,  $df=5$ ,  $P=0.88$ .<sup>10</sup> The evidence for western Europe is therefore equivocal.

Consistent evidence was found for a lower prevalence of *H pylori* infection among both North American patients with gastro-oesophageal reflux disease (odds ratio 0.70, 0.55 to 0.9; test for heterogeneity  $\chi^2=0.92$ ,  $df=6$ ,  $P=0.99$ ) and patients from the Far East with gastro-oesophageal reflux disease (0.24, 0.19 to 0.32 and  $\chi^2=2.36$ ,  $df=4$ ,  $P=0.670$ ). The study from South America found a higher prevalence. Differences in location may explain much of the heterogeneity among the studies. Some of the remaining heterogeneity may be a product of clinical heterogeneity—for example, differences in methods of *H pylori* testing, pH measurements, and endoscopic classification of oesophagitis.<sup>18</sup>

**Discussion**

Our systematic review found a significantly lower prevalence of *H pylori* infection among patients with gastro-oesophageal reflux disease than among those without the disease, geographical location being an important determinant. Although the results we found were based on studies with a comparator group, there were significant differences between study design, study population, identification of cases and controls,

Study Reference



Odds ratios (95% confidence intervals) for prevalence of *H pylori* infection, grouped by geographical location. Large boxes indicate studies with small standard errors (essentially larger sample sizes) and vertical dotted line indicates no difference between groups

### What is already known on this topic

The relation between *H pylori* infection and gastro-oesophageal reflux disease is controversial

Studies on the prevalence of *H pylori* in patients with gastro-oesophageal reflux disease have given conflicting results

Recent guidelines recommend eradication of *H pylori* in patients requiring long term proton pump inhibitors, essentially for reflux disease

### What this study adds

Despite heterogeneity between studies, the prevalence of *H pylori* was significantly lower in patients with than in those without gastro-oesophageal reflux disease

Further well designed studies are required to establish the clinical relevance of the findings, particularly in relation to eradication therapy

inclusion and exclusion criteria, matching of cases and controls, and methods of testing for *H pylori*. Results therefore need to be interpreted with caution.

Most of the participants underwent endoscopy for clinical reasons and thus did not constitute a population group, although we discovered three community based studies. Ascertaining the prevalence of *H pylori* thus depended on a proportion of patients who were being investigated for suspected lesions. This is unlikely to have substantially compromised our results because of the exclusion of patients with symptoms of gastro-oesophageal reflux disease who had negative results for endoscopy or pH testing.

A possible difference was found between the Far East and North America or western Europe in prevalence of *H pylori* infection in patients with gastro-oesophageal reflux disease; the study from South America gave a higher prevalence. This seems to indicate that the prevalence of *H pylori* in patients with gastro-oesophageal reflux disease is lower in countries where the prevalence of *H pylori* in the general population is high. Reasons are unclear and may be related to dietary or genetic factors. Four studies reported a higher prevalence among patients with gastro-oesophageal reflux disease, but in only one was the difference significant. The reasons are uncertain but may partly be related to factors such as study design, selection of cases and controls, and method of testing for *H pylori*.

The clinical relevance of a lower prevalence of *H pylori* in patients with gastro-oesophageal reflux disease is unclear. Some studies have shown that *H pylori* may protect against gastro-oesophageal reflux disease and that infected patients may have a less severe form of the disease.<sup>4,5</sup> Evidence is also conflicting on the effect of *H pylori* infection on the efficacy of proton pump inhibitors. One study found that patients with gastro-oesophageal reflux disease and *H pylori* infection responded significantly better to proton pump inhibitors than those without the infection.<sup>8</sup> Another trial found that patients not infected with *H pylori* did not need higher doses of acid suppression with proton pump inhibitors to stay in remission.<sup>7</sup>

Contributors: See bmj.com

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- 1 Jones R. Gastro-oesophageal reflux disease in general practice. *Scand J Gastroenterol Suppl* 1995;211:35-8.
- 2 Office of Health Economics. *Health expenditures in the UK*. London: Stationery Office, 1996.
- 3 Hosking SW, Ling TK, Chung SC, Yung MY, Cheng AF, Sung AF, et al. Duodenal ulcer healing by eradication of *Helicobacter pylori* without anti-acid treatment: randomised controlled trial. *Lancet* 1994;343:508-10.
- 4 Graham DY, Yamaoka Y. *H pylori* and cagA. Relationships with gastric cancer, duodenal ulcer, and reflux esophagitis and its complications. *Helicobacter* 1998;3:145-51.
- 5 Richter JE, Falk GW, Vaezi MF. *Helicobacter pylori* and gastroesophageal reflux disease: the bug may not be all bad. *Am J Gastroenterol* 1998;93:1800-2.
- 6 Malfertheiner P, Magraud F, O'Morain C, Hungin APS, Jones R, Axon A, et al. Current concepts in the management of *Helicobacter pylori* infection. The Maastricht 2-2000 consensus report. *Aliment Pharm Ther* 2002;6:167-80.
- 7 Schenk BE, Kuipers EJ, Klinkenberg-Knol EC, Eskes SA, Meuwissen SG. *Helicobacter pylori* and the efficacy of omeprazole therapy for gastroesophageal reflux disease. *Am J Gastroenterol* 1999;94:884-7.
- 8 Holtmann G, Cain C, Malfertheiner P. Gastric *Helicobacter pylori* infection accelerates healing of reflux esophagitis during treatment with the proton pump inhibitor pantoprazole. *Gastroenterology* 1999;117:11-6.
- 9 Cheng EH, Bermanski P, Silversmith M, Valenstein P, Kawanishi H. Prevalence of *Campylobacter pylori* in esophagitis, gastritis, and duodenal disease. *Arch Intern Med* 1989;149:1373-5.
- 10 Werdmuller BF, Loffeld RJ. *Helicobacter pylori* infection has no role in the pathogenesis of reflux esophagitis. *Dig Dis Sci* 1997;42:103-5.
- 11 De Koster E, Ferhat M, Deprez C, Deltenre SM. *H pylori*, gastric histology and gastro-oesophageal reflux disease. *Gastroenterology* 1995;108(suppl):A81.
- 12 Boixeda D, Gisbert JP, Canton R, Alvarez BI, Gil GL, Martin de AC. Is there any association between *Helicobacter pylori* infection and peptic esophagitis? *Med Clin (Barc)* 1995;105:774-7.
- 13 McCallum RW, De Luca V, Marshall BJ, Prakash C. Prevalence of campylobacter-like organisms in patients with gastro-oesophageal reflux disease versus normals. *Gastroenterology* 1987;92:A1524.
- 14 Anonymous-French-Belgian consensus conference on adult gastro-oesophageal reflux disease "diagnosis and treatment": report of a meeting held in Paris, France, on 21-22 January 1999. The jury of the consensus conference. *Eur J Gastroenterol Hepatol* 2000;12:129-37.
- 15 Dent J, Jones R, Kahrilas P, Talley NJ. Management of gastro-oesophageal reflux disease in general practice. *BMJ* 2001;322:344-7.
- 16 DeVault KR, Castell DO. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. The Practice Parameters Committee of the American College of Gastroenterology. *Am J Gastroenterol* 1999;94:1434-42.
- 17 Kroes RM, Numans ME, Jones RH, de Wit NJ, Verheij TJM. Gastro-oesophageal reflux disease in primary care. Comparison and evaluation of existing national guidelines and development of uniform guidelines. *Eur J Gen Pract* 1999;88-97.
- 18 Thompson SG. Why sources of heterogeneity in meta-analysis should be investigated. In: Chalmers I and Altman DG. *Systematic reviews*. London: BMJ Publishing Group, 1995.

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### Endpiece

#### Evidence based practice

Do not believe in anything simply because you've heard it. Do not believe in traditions because they have been handed down for many generations. Do not believe in anything because it is spoken and rumoured by many. Do not believe in anything simply because it is found written in your religious books. Do not believe in anything merely on the authority of your teachers and elders. But after observation and analysis, when you find anything agrees with reason and is conducive to the good and benefit of one and all then accept it and live up to it.

Buddha, *Anguttara Nikaya* III, 65

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