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

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

Anan Raghunath, A Pali S Hungin, David Wooff, Susan Childs

**Abstract**

**Objectives** To ascertain the prevalence of *Helicobacter pylori* infection 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 is a common condition affecting 25-40% of the population. It is managed mainly in primary care and is associated with the largest prescribing cost in the NHS. Although there is good evidence that infection with *H pylori* is the principal cause of peptic ulcer disease, there is uncertainty about the organism’s role in gastro-oesophageal reflux disease. Treating *H pylori* infection is effective in healing duodenal ulcers. The effect of eradication of the organism in patients with gastro-oesophageal reflux disease is less clear, with some reports suggesting that this might be counterproductive and that *H pylori* infection might protect against the disease. 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. This is because profound acid suppression may accelerate the progression of *H pylori* induced atrophic gastritis, increasing the potential risk of cancer.

The evidence for an association between *H pylori* and gastro-oesophageal reflux disease remains mixed and largely uncertain. 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. Fundamentally it is not certain whether there are differences in the prevalence of *H pylori* between patients with and without gastro-oesophageal reflux disease. 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 increasing potential risk of cancer.

**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 of retrieved studies were reviewed, experts in six countries and pharmaceutical companies contacted (see bmj.com), and general medical and major gastroenterology journals searched over the previous year.

**Assessment of eligibility and trial quality**

Gastro-oesophageal reflux disease was defined according to published definitions. 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 according to the predefined criteria (see box). Abstracts were included only if they met the eligibility criteria. Disagreements were resolved by consensus with a third reviewer. Quality assessments focused on whether the methods for obtaining cases and controls, data collection, and H pylori testing were stated.

Data extraction
AR collated data from eligible studies on standardised forms, which were checked by SC. Data on the prevalence of H pylori in various grades of oesophagitis and the absence of visible reflux disease on endoscopy were recorded as reported, but for analysis the overall prevalence of H pylori in gastro-oesophageal reflux disease was used.

Data synthesis
Each of the 20 included studies was summarised according to its odds ratio, with an odds ratio of less than one indicating a higher prevalence of H pylori among controls than among patients with gastro-oesophageal reflux disease. Results were pooled with a fixed effect (Mantel-Haenszel) model, which was assessed with a test of homogeneity and a funnel plot.6 Odds ratios were pooled with a random effects model in cases of substantial heterogeneity.20 The statistical analysis was performed with the free package R, and the rmeta subpackage contributed by Thomas Lumley (University of Washington).20

Results
Our initial search identified 654 articles, but only 45 evaluated the prevalence of H pylori in patients with gastro-oesophageal reflux disease. Thirty seven of these met the eligibility criteria; 16 were excluded after further scrutiny (see table A on bmj.com).13 14 20–35 and one was excluded because of overlap with a study by the same lead author (the proportions between the two studies were so close that there was virtually no difference in results; see table A on bmj.com).14 30 This left 20 studies for review, totalling 4134 patients, of whom 58.5% (n=2418) were in control groups (table).

Prevalence of H pylori infection
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 (fig 1 and table B on bmj.com).20 30 40 47 The remaining studies showed a lower prevalence among patients with gastro-oesophageal reflux disease, significantly so in six studies.13 14 22 23 25 37 The pooled odds ratio was 0.58 (95% confidence interval 0.51 to 0.66), indicating a lower prevalence of H pylori infection among patients with gastro-oesophageal reflux disease (heterogeneity test: $\chi^2=83.01, df=19, P<0.001$).

We found no clear evidence of publication bias (fig 2); nor would any be expected in this context. Because of the presence of substantial heterogeneity, the studies were pooled with the DerSimonian-Laird 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 year of study (no effect) and by location. Five studies were of patients from the Far East,13 14 22 23 25 seven of patients from North America,13 20 30 40 41 44 45 50–52 and seven of patients from western Europe.13 14 20 42 44 45 47 48 One further study originated from Chile.53 Some similarities were found in results for studies from particular geographical locations (fig 1). When the three main groups were analysed separately, the results for western Europe gave an odds ratio of 0.76 (0.61 to 0.96) and a test for heterogeneity of $\chi^2=14.01, df=6, P=0.030$. One study seemed to dominate the analysis, but repeating the analysis after excluding this study gave an odds ratio of

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
Studies included in systematic review

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of study</th>
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<th>Outcome</th>
<th>Comments or conclusions</th>
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</thead>
<tbody>
<tr>
<td>Werdelin and Loffeld 1997</td>
<td>Descriptive, prospective</td>
<td>Consecutive patients undergoing endoscopy of upper gastrointestinal tract for upper abdominal symptoms or reflux symptoms. Cases (n=340, of which 116 patients proved gastro-oesophageal reflux disease included), Retest with hiatus hernia and no reflux oesophagitis or with Barrett’s oesophagus excluded. Controls (n=399): normal endoscopy and presumed absence of typical reflux symptoms.</td>
<td>Endoscopy of upper gastrointestinal tract. H pylori testing by histology, rapid urease test, and serology (not all tests in every patient)</td>
<td>H pylori prevalence in patients with gastro-oesophageal reflux disease (29%) and reference group (51%)</td>
<td>We assumed from details that patients in reference group do not have reflux disease</td>
</tr>
<tr>
<td>Koike et al 1999</td>
<td>Case–control</td>
<td>Patients were self referred and referred by doctor. Cases (n=175): patients with reflux oesophagitis. Controls: age-sex matched, randomly selected, who visited hospital, were asymptomatic, and had normal endoscopy results.</td>
<td>Endoscopy of upper gastrointestinal tract, H pylori testing by histology, rapid urease test, and serology.</td>
<td>H pylori prevalence in patients with reflux oesophagitis, reflux disease negative on endoscopy. Barrett’s oesophagus, and controls. No significant difference in H pylori prevalence between patients with reflux oesophagitis (32%), reflux disease negative on endoscopy (29%), and controls (29%). Also no difference in age and socio-demographic variables between reflux patients and controls</td>
<td>Exclusion of peptic ulcer not clearly stated</td>
</tr>
<tr>
<td>Csendes et al 1997</td>
<td>Case–control, prospective, prevalence study</td>
<td>Cases (n=140): patients with chronic gastro-oesophageal reflux disease (reflux oesophagitis, negative reflux disease on endoscopy) symptoms of at least three years duration. Controls (n=190): patients needing endoscopy; of whom had symptoms of gastro-oesophageal reflux disease</td>
<td>Endoscopy of upper gastrointestinal tract in cases and controls, H pylori testing by histology, pH-metry in all cases of gastro-oesophageal reflux disease, no pH-metry in controls</td>
<td>H pylori prevalence in patients with reflux oesophagitis, reflux disease negative on endoscopy. Different methods of H pylori testing in cases and controls. No endoscopy in controls</td>
<td>This study looked at protective effect of corpus gastritis against reflux oesophagitis. We excluded Barrett’s oesophagus from our analysis</td>
</tr>
<tr>
<td>Haruma et al 2000</td>
<td>Descriptive, prospective</td>
<td>Patients referred for elective endoscopy of upper gastrointestinal tract. Cases (n=154, of which 116 patients were included, 38 excluded because of Barrett’s oesophagus): all patients with erosive oesophagitis. Controls (n=148): Patients with normal endoscopy result and absence of symptoms of gastro-oesophageal reflux disease</td>
<td>Endoscopy of upper gastrointestinal tract in cases and controls, H pylori testing by haematoxylin and eosin stain</td>
<td>H pylori prevalence in patients with gastro-oesophageal reflux disease (31%) and controls (43%)</td>
<td>Some patients with reflux disease negative on endoscopy but reflux not proved may have been included in our prevalence data. This study concluded that gastro-oesophageal reflux disease was associated with a lower rate of vacA S1 genotypes than in controls</td>
</tr>
<tr>
<td>Follone et al 2000</td>
<td>Descriptive, prospective</td>
<td>Patients scheduled for endoscopy of upper gastrointestinal tract. Cases (n=167, of which 81 patients with gastro-oesophageal reflux disease included). Retest were classified into non-ulcer disease, duodenal ulcer, gastric ulcer, and therefore excluded. Patients with gastro-oesophageal reflux disease who had reflux oesophagitis or negative reflux disease on endoscopy. Comparator group (n=78): patients in whom there were no symptoms of gastro-oesophageal reflux disease and in whom indications for endoscopy were multiple. All had normal endoscopy results.</td>
<td>Endoscopy of upper gastrointestinal tract, H pylori testing by histology and culture; detection of specific genes or sequence within H pylori and detection of CagA antibodies</td>
<td>H pylori prevalence in patients with gastro-oesophageal reflux disease (33%) and comparator group (48%)</td>
<td>This study concluded that H pylori infection and cardia intestinal metaplasia are associated with H pylori infection</td>
</tr>
<tr>
<td>Gisbert et al 2000</td>
<td>Descriptive, prospective, prevalence</td>
<td>Consecutive patients undergoing 24 hour oesophageal pH monitoring in most of cases and controls because of symptoms suggestive of gastro-oesophageal reflux disease. Cases (n=86), typical symptoms of gastro-oesophageal reflux disease and positive pH findings. Controls (n=44): symptoms of gastro-oesophageal reflux disease but negative pH findings</td>
<td>Endoscopy of upper gastrointestinal tract, 24 hour oesophageal pH monitoring and H pylori testing by histology and rapid urease test</td>
<td>H pylori prevalence in patients with gastro-oesophageal reflux disease (57%) and controls (52%)</td>
<td>Comparator group may represent patients with non-ulcer dyspepsia</td>
</tr>
<tr>
<td>Goldblum et al 1997</td>
<td>Case–control, prospective</td>
<td>Cases (n=58): patients with classic symptoms of gastro-oesophageal reflux disease enrolled into study. Controls (n=57): patients undergoing endoscopy for reasons other than symptoms of gastro-oesophageal reflux disease. Barrett’s oesophagus, peptic ulcer disease, or dysphagia.</td>
<td>Endoscopy of upper gastrointestinal tract in cases and controls, H pylori testing by histology and rapid urease test in cases, 13-carbon urea breath test</td>
<td>H pylori prevalence in patients with gastro-oesophageal reflux disease (38%) and controls (39%)</td>
<td>This study also concluded that H pylori testing by histology and rapid urease test in cases, 13-carbon urea breath test</td>
</tr>
<tr>
<td>Hackeberger et al 1997</td>
<td>Case–control, prospective</td>
<td>Cases (n=130 of 171 included, remaining 41 had associated peptic ulcer disease): consecutive Caucasian patients undergoing elective endoscopy. Controls (n=227): asymptomatic volunteers or patients attending for other reasons and without any symptoms of gastro-oesophageal reflux disease</td>
<td>Endoscopy of upper gastrointestinal tract in cases only. H pylori testing by histology and rapid urease test in cases, 13-carbon urea breath test</td>
<td>H pylori prevalence in patients with gastro-oesophageal reflux disease (45%) and controls (48%)</td>
<td>Different methods of H pylori testing in cases and controls. No endoscopy in controls</td>
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<tr>
<td>Haruna et al 2000</td>
<td>Retrospective case–control</td>
<td>Of 8285 patients undergoing endoscopy of upper gastrointestinal tract between defined periods, 229 were defined as having reflux oesophagitis. Of these, 95 met authors’ inclusion criteria. Controls (n=190), healthy, asymptomatic; age-sex matched selected from among 608 healthy individuals who had undergone routine healthcare check for gastric cancer</td>
<td>Endoscopy of upper gastrointestinal tract. H pylori testing by histology and rapid urease test, tetracycline, and 13-carbon urea breath test</td>
<td>H pylori prevalence in patients with reflux oesophagitis (41%) and comparator group (76%)</td>
<td>The authors found significant low prevalence of H pylori in patients over 60 but not under 59 with reflux oesophagitis, when compared with age-sex matched controls</td>
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<tr>
<td>Liston et al 1995</td>
<td>Descriptive, prospective, prevalence</td>
<td>Consecutive patients admitted for gastroscopy; included regardless of reasons for procedure. Main reasons were anaemia, reflux symptoms, and epigastric pains. Cases (n=37): reflux oesophagitis (macroscopic or microscopic). Comparator group (n=33): normal endoscopy result and no evidence of histological oesophagitis</td>
<td>Endoscopy of upper gastrointestinal tract. H pylori testing by histology and rapid urease test, tetracycline, and 13-carbon urea breath test</td>
<td>H pylori prevalence in patients with reflux oesophagitis (42%) and comparator group (42%). Patterns of gastritis described in the two groups were similar</td>
<td>Although exclusion of patients with peptic ulcer disease had not been clearly stated, on reading the paper, we assumed this to be the case</td>
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<tr>
<td>Reference</td>
<td>Type of study</td>
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<td>Intervention</td>
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<tr>
<td>Mones et al 1999[^52^]</td>
<td>Case-control, prospective, prevalence</td>
<td>Cases (159 of 302, of which 105 patients with proved gastro-oesophageal reflux disease included): consecutive patients with typical symptoms of gastro-oesophageal reflux disease lasting more than six months, Peptic ulcer cases excluded. Controls (n=200): healthy asymptomatic blood donors and patients with functional non-specific abdominal problems with normal endoscopy result except for signs of chronic gastritis</td>
<td>Endoscopy of upper gastrointestinal tract in cases only. Pylor testing by histology and rapid urease test in cases and serology in controls</td>
<td>H pylori prevalence in patients with erosive reflux oesophagitis (32%), non-ulcer disease negative on endoscopy (42%), and control group (48%). Also patterns of gastritis, H pylori colonization, and dyspepsia symptoms in patients with reflux disease negative on endoscopy and reflux oesophagitis compared.</td>
<td>We excluded patients with Barrett's oesophagus (as stated in our protocol) and also reflux disease negative on endoscopy (proved to have gastro-oesophageal reflux disease) from our analysis. Different methods of Pylor testing in cases and controls, no endoscopy in controls</td>
</tr>
<tr>
<td>Mihara et al 1996[^45^]</td>
<td>Case-control, prospective, prevalence</td>
<td>Cases (n=75): patients with reflux oesophagitis. Controls (n=70): age-sex matched, no symptoms of gastro-oesophageal reflux disease and normal endoscopy result</td>
<td>Endoscopy of upper gastrointestinal tract. Pylor testing by Giemsa stain and serology, gastritis and atrophy scores, and serum pepsinogen levels</td>
<td>H pylori prevalence in patients with gastro-oesophageal reflux disease (42%) and controls (36%). H pylori colonization and dyspepsia symptoms in patients with reflux disease were determined.</td>
<td>Abstract</td>
</tr>
<tr>
<td>Newton et al 1997[^46^]</td>
<td>Case-control, prospective, prevalence</td>
<td>Cases (83, of which 25 patients with proved gastro-oesophageal reflux disease included): patients referred for endoscopy divided into four groups. Reflux oesophagitis, duodenal ulcer, or both, and Barrett's oesophagus. Controls (n=20): asymptomatic patients with anaemia referred for endoscopy</td>
<td>Endoscopy of upper gastrointestinal tract in cases and controls. Pylor testing by histology and CLO test</td>
<td>H pylori prevalence in patients with gastro-oesophageal reflux disease (42%) and controls (36%).</td>
<td>We excluded patients with Barrett's oesophagus, duodenal ulcer, and duodenal ulcer with reflux oesophagitis from our analysis.</td>
</tr>
<tr>
<td>Peramsi and Zenetti 2000[^48^]</td>
<td>Case-control, prospective</td>
<td>Cases (122, of which 54 patients with proved gastro-oesophageal reflux disease included. 68 patients with negative reflux disease on endoscopy excluded because reflux not proved): consecutive patients referred for gastro-oesophageal reflux disease symptoms to endoscopy unit. Controls (n=49): patients who underwent endoscopy in same period as cases for reasons other than symptoms of gastro-oesophageal reflux disease, Barrett's oesophagus, active or previous peptic ulcer disease, gastritis or oesophageal neoplasias, or dyspepsia</td>
<td>Endoscopy of upper gastrointestinal tract in cases and controls. Pylor testing by Giemsa stain before endoscopy and no symptoms of gastro-oesophageal reflux disease</td>
<td>H pylori prevalence in patients with gastro-oesophageal reflux disease (44%) and controls (38%).</td>
<td>Grade G (reflux disease negative on endoscopy, 68 patients) were not proved to have gastro-oesophageal reflux disease, hence we excluded them from our analysis.</td>
</tr>
<tr>
<td>Schutzer and Schnell 1989[^40^]</td>
<td>Descriptive, prospective, retrospective</td>
<td>All consenting patients referred for endoscopy between defined periods. Cases (310, of which 31 patients with proved gastro-oesophageal reflux disease included). Rest were classified into several diagnostic groups (duodenal ulcer, gastric ulcer, non-ulcer dyspepsia, gastritis, duodenitis) and therefore excluded. Control or comparator group (n=42): patients with absence of symptoms of gastro-oesophageal reflux disease and normal endoscopy result</td>
<td>Endoscopy of upper gastrointestinal tract. Pylor testing by histology, rapid urease test, and culture</td>
<td>H pylori prevalence in patients with gastro-oesophageal reflux disease (28%) and comparator group (40%).</td>
<td>Some patients with reflux disease negative on endoscopy but reflux not proved may have been included in our prevalence data</td>
</tr>
<tr>
<td>Shirai et al 1999[^42^]</td>
<td>Descriptive, prospective, retrospective</td>
<td>Random selection of cases and controls: patients who underwent endoscopy of upper gastrointestinal tract between defined periods. Cases (n=72): reflux oesophagitis (mild, severe). Controls (n=28): normal endoscopy result and presumed absence of symptoms of gastro-oesophageal reflux disease</td>
<td>Endoscopy of upper gastrointestinal tract. Pylor testing by histology, rapid urease test, and serology, serum pepsinogen levels, and oesophageal manometry</td>
<td>H pylori prevalence in patients with gastro-oesophageal reflux disease (36%) and controls (61%). Pepsinogen 1 to pepsinogen 2 ratios determined to assess severity of atrophic gastritis</td>
<td>We assumed from details that patients in control group did not have symptoms of gastro-oesophageal reflux disease. Authors concluded that low prevalence of H pylori might result in milder grade of atrophic gastritis and consequently exacerbate reflux oesophagitis</td>
</tr>
<tr>
<td>Vaz et al 2000[^41^]</td>
<td>Descriptive, prospective, retrospective</td>
<td>Patients undergoing endoscopy of upper gastrointestinal tract. Based on questionnaire before endoscopy and endoscopy findings, patients were grouped into cases: gastro-oesophageal reflux disease (n=108), short and long-segment Barrett's oesophagus, and controls (n=65). Controls had normal endoscopy and no symptoms of gastro-oesophageal reflux disease</td>
<td>Endoscopy of upper gastrointestinal tract. Pylor testing by Giemsa stain, serology to determine IgG response to H pylori whole cell antigen and to CagA using enzyme linked immunosorbent assay</td>
<td>H pylori and CagA prevalence in cases gastro-oesophageal reflux disease (short segment and long segment Barrett's oesophagus) and controls. H pylori prevalence in patients with gastro-oesophageal reflux disease (38%) and controls (42%).</td>
<td>Authors concluded that CagA positive H pylori strains might protect against Barrett's oesophagus. We excluded patients with Barrett's oesophagus from our analysis</td>
</tr>
<tr>
<td>Varanasi et al 1998[^50^]</td>
<td>Descriptive, retrospective</td>
<td>Review of records of all patients (n=18 years) who had endoscopy of upper gastrointestinal tract and rapid urease testing. Cases (n=54): gastro-oesophageal reflux disease (reflux oesophagitis or proved negative reflux disease on endoscopy), typical symptoms of gastro-oesophageal reflux disease, normal endoscopy, and histological oesophagitis and Barrett's oesophagus. Comparator (n=257): normal endoscopy and presumed absence of symptoms of gastro-oesophageal reflux disease</td>
<td>Endoscopy of upper gastrointestinal tract. Pylor testing by rapid urease test in all. Histopathology and serology in some</td>
<td>H pylori prevalence in patients with gastro-oesophageal reflux disease as well as stratifying for presence or absence of peptic ulcer disease in each group. H pylori prevalence in patients with gastro-oesophageal reflux disease (50%) and controls (44%).</td>
<td>We excluded patients with Barrett's oesophagus and cases of reflux oesophagitis associated with peptic ulcer disease from our analysis. Authors found no variability of H pylori between different groups of patients with reflux oesophagitis.</td>
</tr>
<tr>
<td>Vitani et al 1998[^51^]</td>
<td>Prospective, case-control</td>
<td>Cases: patients with classic symptoms of gastro-oesophageal reflux disease (123, of which 84 patients included and 59 with Barrett's oesophagus excluded) enrolled into study. Controls: patients undergoing endoscopy for reasons other than symptoms of gastro-oesophageal reflux disease, Barrett's oesophagus, peptic ulcer disease, or dyspepsia</td>
<td>Endoscopy of upper gastrointestinal tract in cases and controls. Pylor testing by histology (haematoxylin and eosin and Giemsa stain) and serology</td>
<td>H pylori prevalence in patients with gastro-oesophageal reflux disease (42%) and controls (44%). CagA positivity status also determined in cases and controls.</td>
<td>Some patients with reflux disease negative on endoscopy but reflux not proved may have been included in our prevalence data. We excluded patients with Barrett's oesophagus from our analysis</td>
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</table>
of patients with gastrosophageal reflux disease; a single study

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 (prospective or retrospective case-control, trial), study population, identification of cases and controls, inclusion and exclusion criteria, matching of cases and controls, and methods of testing for H pylori. Our 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 as such, although we discovered three community based studies.31 32 33 Ascertainment of 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 we excluded patients with symptoms of gastro-oesophageal reflux disease who had negative results for endoscopy or pH testing.

Given that there was substantial heterogeneity between the studies, we acknowledge issues about the appropriateness of reporting a pooled odds ratio. On further exploration we did find a possible difference between the Far East and North America or western Europe in prevalence of H pylori infection in patients with gastro-oesophageal reflux disease; a single study

**Fig 1** 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

**Fig 2** Size and effect of results from eligible studies of prevalence of H pylori infection in patients with and without gastro-oesophageal reflux disease

0.97 (0.75 to 1.27) and a test for heterogeneity of χ² = 1.8, df = 5, P = 0.88. 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, χ² = 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 χ² = 2.36, df = 4, P = 0.670). A single study from South America found a higher prevalence.36 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.34

**Study Reference**

<table>
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<tr>
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<tbody>
<tr>
<td>Wu et al 199535</td>
<td>Case-control, prospective</td>
<td>Cases (196, of which we included 66 and excluded 40 with reflux disease negative on endoscopy in whom diagnosis of reflux disease was not proved); Patients with typical symptoms of gastro-oesophageal reflux disease and reflux oesophagitis. Controls (n = 120); absence of symptoms of gastro-oesophageal reflux disease, absence of dyspepsia, and recruited from general medical clinics and day care centres without any evidence of gastrointestinal disease</td>
<td>Endoscopy of upper gastrointestinal tract in H pylori positive cases</td>
<td>H pylori prevalence in patients with gastro-oesophageal reflux disease (32%) and controls (91%). Histological assessment of gastritis and H pylori colonisation in patients with gastro-oesophageal reflux disease also studied</td>
<td>We excluded patients with reflux disease negative on endoscopy from our analysis</td>
</tr>
<tr>
<td>Liston et al 199646</td>
<td>Case-control, prospective</td>
<td>Cases (106, of which we included 66 and excluded 40 with reflux disease negative on endoscopy in whom diagnosis of reflux disease was not proved); Patients with typical symptoms of gastro-oesophageal reflux disease and reflux oesophagitis. Controls (n = 120); absence of symptoms of gastro-oesophageal reflux disease, absence of dyspepsia, and recruited from general medical clinics and day care centres without any evidence of gastrointestinal disease</td>
<td>Endoscopy of upper gastrointestinal tract in H pylori positive cases</td>
<td>H pylori prevalence in patients with gastro-oesophageal reflux disease (32%) and controls (91%). Histological assessment of gastritis and H pylori colonisation in patients with gastro-oesophageal reflux disease also studied</td>
<td>We excluded patients with reflux disease negative on endoscopy from our analysis</td>
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<th>Reference</th>
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**Table 1** Studies included in systematic review contd
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. 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*. Again, presenting data as pooled estimates of odds ratios for geographical locations may give the impression of post hoc confirmatory analyses, but we strongly believe that there is a location effect evident in these data and that the prevalence has different patterns within locations.

We did not separately analyse the prevalence of *H pylori* infection in males and females. These data were not obtainable in many studies and, when available, there was no reported difference. We excluded patients with Barrett’s oesophagus because we thought that this condition merited a systematic review in its own right.

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 be protective against gastro-oesophageal reflux disease and that infected patients may have a less severe form of the disease. 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. 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. Evidence shows that *H pylori* induces atrophic gastritis in the presence of long term acid suppression with proton pump inhibitors, and recent guidelines have advocated eradication of *H pylori* in patients receiving long term proton pump therapy.

We are unable to definitely comment on the benefit or possible detriment of *H pylori* eradication in patients with gastro-oesophageal reflux disease; a further review of this is in preparation. Our findings add insight into the complex relation between *H pylori* infection and gastro-oesophageal reflux disease. Clearly, more, well designed, prospective, large scale, case-control studies and trials are required to determine the epidemiological relation between *H pylori* and gastro-oesophageal reflux disease and the clinical implications of this association.

Contributors: AR developed the protocol, reviewed the literature, assessed eligibility of trials, checked eligibility assessments, performed data extraction, and cowrote the manuscript. APSh developed the protocol, checked eligibility assessments, and cowrote and reviewed the manuscript. SC reviewed the literature, performed most of the eligibility assessments, and reviewed the manuscript. DW performed the statistical analyses and cowrote and reviewed the manuscript. APSH and AR will act as guarantors for the paper.

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Competing interests: APSH is coauthor of the Maastricht 2 guidelines on the management of *H pylori* infection; he has received research funding from Abbott Pharmaceuticals and conference travel costs and honoraria for advisory groups to several manufacturers of proton pump inhibitors over the past five years. AR has received research funding from Wyeth.

### What is already known about 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 without gastro-oesophageal reflux disease.

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