Screening for *Helicobacter pylori*

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ABSTRACT

Introduction: *The aim of this review is to assess whether a screening programme for Helicobacter pylori will be both successful and cost-effective.*

Method: *We searched the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and the NHS Database of Abstracts of Reviews of Effectiveness; MEDLINE; EMBASE; SilverPlatter, Biological Abstracts and Science Citation Index-Expanded. We used the search terms Helicobacter pylori and (diagnos$ or identif$ or find$) and (systematic review$ or meta-anal$), and searched for articles in all languages and limited the search to humans.*

Evaluation of the Level of Evidence: *We used the rating system of the American Family Physician journal: Level A (randomized controlled trial/meta-analysis); Level B (other evidence); and C (consensus/expert opinion).*

Results: *Serological tests: Antibody levels persist in serum for many years and do not permit us to distinguish between past and present infection or to identify treatment failures.*

Saliva and urine tests: A saliva test had sensitivity of 81% and specificity of 73%. A urine test had sensitivity of 86-89% and specificity of 69-91%.

Breath urea tests: The tests have a high sensitivity and specificity but require expensive equipment.

Stool tests: showed a high sensitivity and specificity. The European Helicobacter study group recommends either the breath urea or stool antibody tests in the initial diagnosis of H. pylori.

Tests for specific gene sequences showed a high sensitivity and specificity.

Endoscopy: is invasive, uncomfortable for patients, and expensive.

The cost-effectiveness of tests for H. pylori: The better accuracy of the stool and breath tests, despite their greater cost, make them more cost-effective than the serology or near-patient tests.

Conclusions: *Tests with good sensitivity and specificity are available. The costs of non-invasive diagnostic tests acceptable to patients have been worked out, and the cost-effective dominance of stool and particularly urea breath tests over serological tests has been determined in a systematic review. What remains is to implement and test further the cost-effectiveness of national testing strategies.*

Key-words (from MeSH): *Helicobacter Pylori; Diagnosis; Mass Screening; Screening.mp; Cost-benefit Aanalysis; Cost-effectiveness.mp; Meta-analysis; Systematic Review.mp.*

INTRODUCTION

Gastric cancer is the second most important cancer worldwide. It has a long pre-cancerous latent period during which it can be identified. The pathological process has been carefully established by which *H. pylori* causes either duodenal ulcers and a reduced risk of gastric cancer or a pre-cancerous cascade ending in atrophic gastritis then gastric cancer. Once the patient has been host to *H. pylori* for three or four decades severe gastric atrophy occurs and is difficult to reverse.

Whether a screening programme for *Helicobacter pylori* will be both successful and cost-effective depends on several factors: the perceptions of patients and physicians of the importance of the condition; the pre-test probability of infection; the perceived reduction in the risk of gastric carcinoma by identification

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and treatment of *H. pylori* and precancerous conditions; the ease and comfort of the diagnostic tests; the sensitivity and specificity of the tests; the costs of diagnosis and treatment; the effectiveness of treatment; the relief from associated symptoms of dyspepsia; and the overall cost-effectiveness of treatment from the viewpoint of society.

OBJECTIVE

The aim of this review is to assess whether a screening programme for *Helicobacter pylori* will be both successful and cost-effective.

METHOD

Searches: We searched the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews and the NHS Database of Abstracts of Reviews of Effectiveness (DARE) (all to Cochrane Library Issue 1, 2006); MEDLINE (OVID, January 1966 to April 2006 week 1); EMBASE (Dialog 1974 to 1979; SilverPlatter 1980 to April 2006 week 1), Biological Abstracts (SilverPlatter 1969 to April 2006) and Science Citation Index-Expanded (Web of Science 1974 to April 2006). We used the search terms *Helicobacter pylori* and (diagnos$ or identif$ or find$) and (systematic review$ or meta-anal$), and searched for articles in all languages and limited the search to humans. The Science Citation Index-Expanded was used to identify articles that cite the relevant studies. The relevant studies were also keyed into PubMed and the Related Articles feature used. We selected for review all those articles which, from their abstract or title, appeared to be relevant, and obtained full-text versions of the abstract or title to assess them fully. We then reviewed all the relevant articles in full text.

Evaluation of the Level of Evidence: We used the rating system of the American Family Physician: Level A (randomized controlled trial/ /meta-analysis); Level B (other evidence); and C (consensus/expert opinion).[1]

The operational qualities of tests for *H. pylori*

Non-invasive tests are either direct (bacterial antigens in stool) or indirect (labelled CO_2 in breath; IgG antibodies to *H. pylori* in serum)[2] [Evidence Level B, non-quantitative review]

Serological tests: Antibody levels persist in serum for many years and do not permit us to distinguish between past and present infection or to identify treatment failures. However, if the patient has never received any antibiotic therapy the presence of antibodies likely indicates persistent infection. A meta-analysis of 21 studies of ELISA serology found an average sensitivity of 85% and specificity of 79%.[3] [Evidence Level A, meta-analysis]. The UK Department of Health evaluated sixteen ELISA kits and found an average 78% accuracy (range 68-82%).[4] [Evidence Level A, meta-analysis].

Near-patient ELISA tests in an analysis in 1999-2000 had an average sensitivity of 71% and specificity of 88%.[5] [Evidence Level A, meta-analysis].

Saliva and urine tests: A saliva test had sensitivity of 81% and specificity of 73%.[6] [Evidence Level B, clinical cohort study]. A urine test in an initial trial with 132 patients had sensitivity of 86% and specificity of 91%; and in a large multicentre trial the sensitivity was 89% and the specificity 69%.[7] [Evidence Level B, clinical cohort study].

Breath urea tests: *H. pylori* produces urease which splits urea into ammonia and CO^2. The urea breath tests measure the CO^2 produced by *H. pylori*. The test which uses ^{14}C has a sensitivity of 97% and a specificity of 95%[5] [Evidence Level A, meta-analysis], requires a scintillation counter and has many disadvantages compared to the ^{13}C non-radioactive test. The ^{13}C test requires an initial expense of buying a mass spectrophotometer but, because it is not radioactive, has the additional advantage that it can be used with children and pregnant females. It has a sensitivity of 95% and specificity of 96%.[5] [Evidence Level A, meta-analysis]. The ^{13}C test which uses urea in a tablet form permits sampling ten minutes after ingestion with the same accuracy as after 30 minutes.[8, 9] [Evidence Level B, clinical cohort studies]. The excellent review by Gisbert and Pajares[10] discusses the factors that affect the accuracy of the test and notes that the original cut-off point of 5% for a positive test needs to be modified for the dose of urea used and whether the test is the screening or post-treatment test. Sensitivity and specificity were 100% for a urea dose of 125mg and a cut-off point as low as 2.4% but the best sensitivity and specificity for a dose of urea of 250 mg was at a cut-off point of 4.4%. For the screening test the sensitivity of 97.5% and specificity of 96.7% were achieved with a cut-off point of 4.0% but for the follow-up test after treatment the sensitivity and specificity were only 80% and 97.6% with the same cut-off of 4.0%, while sensitivity improved to 82.8% at a cut-off of 3.5%, 88.6% at 3.0%, and 94.3% at 2.5% whilst specificity remained at 95.2% for each of these

cut-off points. [Evidence Level A, meta-analysis].

Stool tests: Polyclonal antibody tests used on stool specimens showed a sensitivity of 93% and specificity of 93%.[5] [Evidence Level A, meta-analysis]. A systematic review of 89 studies with 10,858 patients found that the stool test, compared to two other tests or the urea breath test, had a sensitivity of 91%, a specificity of 93%, a positive predictive value of 92%, and a negative predictive value of 87%. For 39 studies with 3,147 patients in whom eradication was tested four or more weeks after completion of therapy, the sensitivity was 96%, the specificity 97%, the positive predictive value 96% and the negative predictive value 97%. The monoclonal is more accurate than the polyclonal test in both the pre- and post-treatment setting.[11] [Evidence Level A, meta-analysis]. Yee assessed the accuracy for 187 patients of stool tests on samples frozen at –70 ºC for an average of 120 days and found that sensitivity was 84%, specificity 98%, the positive predictive value 97% and the negative predictive value 89%.[12] [Evidence Level B, clinical cohort study]. The European Helicobacter study group recommends either the breath urea or stool antibody tests in the initial diagnosis of *H. pylori*.[13] [Evidence Level A, Consensus conference based on meta-analyses].

Tests for specific gene sequences: The HeloriCTX anti-Cag ELISA test showed a sensitivity of 100% and specificity of 75% and the Eurospital It test showed 90% and 94% for the cag gene sequence which makes the *H. pylori* strains which possess it more likely to be associated with severe atrophic gastritis and gastric cancer.[14]

[Evidence Level B, clinical cohort study]

Endoscopy: Endoscopy is invasive, uncomfortable for patients, and expensive. For 708 dyspeptic patients, McColl found that, for those under 55 years with uncomplicated dyspepsia, the "test and treat" strategy was as safe and as effective as endoscopy.[15] [Evidence Level A, RCT]. Arents found that the "test and treat" strategy and prompt endoscopy had similar outcomes for dyspeptic symptoms, quality of life and satisfaction and that the "test and treat" strategy resulted in 62% fewer endoscopies.[16] [Evidence Level A, RCT]. The "test and treat" strategy in a UK study had an average cost of £205.67 (approximately 302,46 €)* and endoscopy was £404.31 (594,57 €).[17] [Evidence Level A, RCT].

The American Gastroenterological Association (1998), The Maastricht 2 Consensus Report and the European Society for Primary care Gastroenterology [18, 19] have all recommended a test and treat strategy without endoscopy for those under 45 or 55 and with no alarm symptoms (weight loss, anemia, dysphagia, palpable mass, or malabsorption). [Evidence Level C, consensus conference].

The cost-effectiveness of tests for *H. pylori*

The better accuracy of the stool and breath tests, despite their greater cost, make them more cost-effective than the serology or near-patient tests.[20] [Evidence Level A, decision analysis].

The sensitivity and specificity of a test do not change with the prevalence of *H. pylori*, but the predictive probability changes with the pre-test probability for groups of individuals (e.g those with a duodenal ulcer are more likely to have *H. pylori*) or populations with higher prevalences. A decision analysis was undertaken using US Medicare fees for 2000 and estimates of test performance from studies of the highest methodological quality. It identified 15 testing strategies as dominant on grounds of both cost and effectiveness. The averaged costs used for ELISA tests were US$76 (approximately 42 €)†, for stool tests $118 (65.56 €), and for breath tests $176 (97.78 €).[20] [Evidence Level A, decision analysis].

- At low *H. pylori* prevalence (30%) the preferred test was the stool test with 93% accuracy and cost per correct diagnosis of $95 (52.78 €). The ELISA serological test was 80% accurate and the cost per correct diagnosis was $95 (52.78 €).
- At intermediate prevalence (60%) the preferred test was again the stool test with 93% accuracy and cost per correct diagnosis of $126 (70 €). The ELISA test was 82% accurate and the cost per correct diagnosis was $92 (51.1 €).
- At high prevalence (90%) the preferred test was the ELISA followed by a urea breath test for the negatives, which provided 96% accuracy and the cost per correct diagnosis was $117 (65 €).
- At low and intermediate prevalence, if the cost of the urea breath test could be lowered below $50 (36.1€), it became preferable to the stool test; and if the stool test cost more than $82 (45.56 €), then the stool test became preferable.
- Fingerstick whole blood tests are not cost-effective because of their low sensitivity and specificity.

Watabe followed 6,983 of the

*The average exchange rate in the 1st trimester of 2006 of £0.68 for 1€ has been used.
†The average exchange rate in the 1st trimester of 2006 of US$1,8 for 1€ has been used.

9,293 participants in a health-screening programme in Tokyo.[21] The ELISA test in this Japanese population had a sensitivity of 95% and specificity of 83%, while the pepsinogen test had 70% sensitivity and 97% specificity for atrophic gastritis compared to histology. They were able to identify groups at high risk of gastric cancer: those who had "atrophic" levels of pepsinogen I and were *H. pylori* negative (in severe atrophic gastritis *H. pylori* tends to disappear) had an annual risk of gastric cancer of 0.6%; those with "atrophic" pepsinogen levels and *H pylori* positive 0.35%; and those with normal pepsinogen levels had rates of 0.04-0.06%. [Evidence Level B, clinical cohort study].

A systematic review concluded that for healing duodenal ulcers *H. pylori* eradication therapy was superior to medications for healing ulcers (RR [relative risk] of ulcer persisting = 0.66; 95% CI = 0.58 to 0.76) and superior to no treatment (RR = 0.37; 95% CI = 0.26 to 0.53). For healing gastric ulcers *H. pylori* eradication therapy was not statistically superior to medications for healing ulcers (RR = 1.32; 95% CI = 0.92 to 1.90). The Markov model suggested that *H. pylori* eradication is cost-effective for duodenal ulcers at one year and for gastric ulcers at two years with more than 95% confidence.[22] [Evidence Level A, meta-analysis].

Recurrence of Ulcers After Treatment, and Resistance to Antibiotics

In a study of 4,930 patients with peptic ulcer the total recurrence rate after treatment was 3%, with 2.3% of gastric, 1.6% of gastroduodenal and 1.6% of duodenal ulcers recurring.[23] [Evidence Level B, clinical cohort study].

Hiyama studied sixty patients with *H. pylori* in Hiroshima in 2000, and using gene analysis, found resistance to clarithromycin in 20%, to metronidazole in 15% and to both in 8%.[24] [Evidence Level B, clinical cohort study].

For preventing recurrence of duodenal ulcers, a systematic review found that *H. pylori* eradication therapy was not statistically superior to maintenance therapy with ulcer healing medications (RR ulcer recurring = 0.73; 95% CI = 0.42 to 1.25) but was superior to no treatment (RR 0.19; 95% CI = 0.15 to 0.26). For preventing gastric ulcer recurrence, *H. pylori* eradication therapy was superior to no treatment (RR= 0.31; 95%CI = 0.19 to 0.48).[22] [Evidence Level A, meta-analysis].

Conclusions

Tests with good sensitivity and specificity are available. The costs of non-invasive diagnostic tests acceptable to patients have been worked out and the cost-effective dominance of stool and, particularly, urea breath tests over serological tests has been determined in a systematic review. Post-treatment serological tests may remain positive for months whereas urea and stool tests will be promptly negative if eradication therapy was successful. What remains is to implement and test further the cost effectiveness of national testing strategies. These need to begin with local pilot schemes in specific areas to test the willingness of health personnel to undertake regular and complete screening of the identified target population and to measure the costs of each link of the testing strategy in specific countries.

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RESUMO

***Introdução: O objectivo desta revisão é avaliar a segurança e custo-efectividade de um programa de rastreio de* Helicobacter pylori.**

Metodologia: Pesquisámos o* Cochrane Central Register of Controlled Trials, *o* Cochrane Database of Systematic Reviews *e o* NHS Database of Abstracts of Reviews of Effectiveness; MEDLINE; EMBASE; SilverPlatter, Biological Abstracts and Science Citation Index-Expanded. *Usámos os termos de pesquisa* Helicobacter pylori *e* (diagnos$ or identif$ or find$) *e* (systematic review$ or meta-anal$), *e pesquisámos artigos de todas as línguas limitando a pesquisa a humanos.

Avaliação do Nível de Evidência: usámos o sistema de classificação da revista* American Family Physician: *Nível A (ensaios clínicos aleatorizados/meta-análises). Nível B (outras fontes de evidência). Nível C (consensos/opinião de peritos).

Resultados: Testes serológicos: os níveis de anticorpos persistem no soro durante vários anos e não nos permitem distinguir entre infecção presente e passada ou identificar o insucesso do tratamento.

Testes de saliva e urina: um teste de saliva tinha sensibilidade de 81% e especificidade de 73%; um teste de urina tinha sensibilidade de 86-89% e especificidade de 69-91%.

Testes respiratórios com ureia: os testes têm uma sensibilidade e especificidade altas mas requerem equipamento caro.

Teste fecal: demonstrou uma alta sensibilidade e especificidade. O* European Helicobacter study group *recomenda a utilização do teste respiratório com ureia ou o teste fecal no diagnóstico inicial de* H. Pylori. *Os testes de sequenciação genética demonstraram elevada sensibilidade e especificidade.

Endoscopia: é invasiva, desconfortável e cara.

O custo-efectividade dos testes para o* H. Pylori: *a maior precisão dos testes fecal e respiratório, apesar do seu custo, fazem com que sejam mais custo-efectivos do que a serologia ou outros testes.

Conclusões: Existem testes com boa sensibilidade e especificidade. Foram examinados os custos dos testes não-invasivos aceitáveis para os pacientes: um maior custo-efectividade do teste fecal e, particularmente, do teste respiratório da ureia em relação aos testes serológicos foi determinado numa revisão sistemática. Seria necessário implementar e testar o custo-efectividade de estratégias nacionais de rastreio.

Palavras-chave: Helicobacter Pylori; *Diagnóstico; Rastreio Populacional; Análise de Custo-benefício; Meta-análise; Revisão Sistemática.*