Helicobacter pylori and gastric cancer: what are the benefits of screening only for the CagA phenotype of H. pylori?

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Screening and consequent treatment for CagA phenotype of H. pylori.

Type of intervention
Screening and treatment.

Economic study type
Cost-effectiveness analysis.

Study population
A hypothetical population of asymptomatic 50-year-old individuals.

Setting
The study setting was the community. The economic study was carried out in the United States, although the analysis was extended to Colombia, Finland and Japan.

Dates to which data relate
Effectiveness data were derived from studies published between 1989 and 1997. Screening costs and the costs of antibiotic therapy were taken from studies published between 1995 and 1996. The marginal cost of treating gastric cancer was from a source published in 1989.

Source of effectiveness data
Effectiveness data were mostly taken from previously completed studies, with one estimate based on expert opinion.

Modelling
A decision analysis model was employed to trace the path of patients being screened, with a 4-state Markov model at the right terminus of each branch following annual transitions until death.

Outcomes assessed in the review
The outcomes assessed from reviewed studies were the prevalence of H. pylori infection at age 50, the proportion of H. pylori infections expressing the CagA phenotype, the relative risk of cancer from both CagA-negative and CagA-positive H. pylori infections, sensitivity and specificity of both H. pylori and CagA screening, the efficacy of antibiotics, and the annual risk of re-infection.
Study designs and other criteria for inclusion in the review
All studies included in the review were grade II-2 (cohort or case-control trials), except for the efficacy of antibiotics, which was grade II-1 (non-randomised controlled trial). Inclusion and exclusion criteria for studies used in the review were published elsewhere.

Sources searched to identify primary studies
No details were provided.

Criteria used to ensure the validity of primary studies
No details were provided.

Methods used to judge relevance and validity, and for extracting data
No details were provided.

Number of primary studies included
Twelve studies were included in the review.

Methods of combining primary studies
Most effectiveness figures were sourced from one study. Where more than one study was used to generate an estimate, details of combination methods were not reported.

Investigation of differences between primary studies
No details were given.

Results of the review
The prevalence of H. pylori infection at age 50 was 40%, of which 60% exhibited the CagA phenotype. The relative risk of cancer from CagA-negative H. pylori was 2.2, and from CagA-positive, 5.8. Estimates of sensitivity and specificity of screening for H. pylori and CagA were all set at 90%. The efficacy of antibiotics was 90%, and the annual risk of re-infection, 1.2%.

Methods used to derive estimates of effectiveness
Expert opinion was also used to supply an estimate of effectiveness.

Estimates of effectiveness and key assumptions
The authors estimated the baseline reduction in risk of cancer by curing H. pylori infection to be 30%. The authors stated that this was a conservative estimate.

Measure of benefits used in the economic analysis
The outcome measure was life-years gained. There was no measure of quality of life.

Direct costs
Unit costs for screening (H. pylori and CagA), antibiotic therapy and cancer treatment were included. These costs were consistent with the perspective of a national health care system. Costs for screening and antibiotics were taken from Medicare reimbursement sources for 1995, and costs for gastric cancer treatment were from 1984 Medicare charges.
Costs were discounted at 3%.

The costs of screening and antibiotic therapy were one-off costs. The cost of gastric cancer was a marginal (annual) cost, although this was reported as incremental.

All costs were expressed in 1995 US dollars, with cancer costs inflated from 1984 figures.

**Indirect Costs**
No indirect costs were included in the study.

**Currency**
US dollars ($). International comparisons were reported in US dollars.

**Sensitivity analysis**
A one-way sensitivity analysis was performed on all input variables, costs and the discount rate. The ranges, with the exception of the estimate of reduction in risk of cancer which was based on expert opinion, were based on 95% confidence intervals, for which a threshold analysis was performed.

**Estimated benefits used in the economic analysis**
The expected years of life remaining for a patient screened and treated for H. pylori were 18.039, for CagA-positive H. pylori only were 18.038, for an unscreened patient were 18.035. No discount rate was reported.

Thus the incremental benefit of screening for H. pylori over CagA was 0.001 years of life gained, and between CagA screening and no screening was 0.003 years of life gained.

The authors stated that antibiotic side-effects were considered (anaphylaxis, Clostridium difficile, vaginitis and others), and acknowledged their impact on quality of life. However, it was unclear how they were incorporated into the analysis. The number of deaths from anaphylaxis was reported, but it is unclear whether this was taken into account in the 'life-years saved from cancers prevented' sum.

**Cost results**
The total lifetime expected costs for a patient screened and treated for H. pylori infection were $71,538, for a patient screened and treated for CagA-positive H. pylori were $71,522 and for unscreened patients were $71,453. All costs were discounted at 3%. Undiscounted figures were not reported.

The incremental cost of all H. pylori screening versus CagA screening was $16, and CagA versus no screening was $59.

It was unclear whether and how the cost of adverse events was incorporated in the analysis.

**Synthesis of costs and benefits**
An incremental cost per life-year gained was calculated. Costs were discounted at 3%. It was not stated whether life-years were discounted.

The incremental cost-effectiveness ratios (reported in Table 3 of the study) were calculated incorrectly, being based only on the costs of screening and antibiotic treatment, and excluding the lifetime costs of treating cancer. The authors reported costs per life-year gained of $25,100 and $23,900 for all H. pylori compared with CagA-positive H. pylori, and CagA-positive compared with no screening, respectively. The figures based on total lifetime costs were $16,000 and $23,000.
The results of the one-way sensitivity analyses revealed that CagA screening was significantly superior to all H. pylori screening only when the incidence of gastric cancer was considerably lower than US levels. This does not reflect the circumstances of most countries. A threshold analysis indicated that the cost per life-year gained would be less than $50,000 where the reduction in risk of cancer from H. pylori eradication was greater than 15%. The results were also sensitive to the age at which screening took place. According to the authors, a younger screening age increased the cost per life-year gained.

Authors' conclusions
The authors concluded that screening for the CagA phenotype of H. pylori is not considerably better than screening for all strains of H. pylori in either the United States or elsewhere. This is due to the significant benefit of treating CagA-negative infections. Screening in countries with a higher incidence of gastric cancer improves the cost-effectiveness ratio.

CRD COMMENTARY - Selection of comparators
The comparator was selected to address the specific research question of whether screening for a particular phenotype of H. pylori was superior to screening for all variants. The authors also included a 'do nothing' option to allow a baseline comparison.

Validity of estimate of measure of effectiveness
The authors did not state that a systematic review of the literature had been undertaken. In most cases, one study was the source of one effectiveness measure. Details of how studies were combined where two or more sources were used were not provided. The authors did not provide justification for their choice of assumptions in determining the reduction in risk of cancer from H. pylori eradication, although all estimates were investigated by sensitivity analysis. The ranges used appear to have been appropriate.

Validity of estimate of measure of benefit
The estimation of benefits was modelled. The Markov model used to derive a measure of health benefit was appropriate, although limited. For example, it did not allow for the possibility (however remote) of curing gastric cancer. In addition, the two states 'infected or un-infected with a H. pylori strain' and 're-infected' were confusing. Restructuring and labelling the states as 'infected' and 'un-infected' would have been clearer. The authors acknowledged that their model did not allow for other benefits of H. pylori eradication, for example the reduction of gastric ulcers and lymphomas. They also stated that inclusion would enhance the cost-effectiveness of screening. Whilst this may be true for lymphomas, where there is a risk of premature death, the authors included no estimate of quality of life in the study, hence a non-fatal, but quality-of-life-diminishing, ulcer would not affect the cost-effectiveness estimate.

Validity of estimate of costs
All categories of cost relevant to the perspective adopted were included in the analysis, although some relevant costs may have been omitted, for example the cost of medical staff time to screen and administer antibiotics. Whilst not stated, it is possible that these may be implicitly included in the unit costs. As these costs occur in both screening arms, these omissions are unlikely to affect the incremental results between those arms. However, there may be scope for error when comparing screening with no screening.

Costs and quantities for screening and antibiotic treatments were reported separately, but costs for cancer treatment were not disaggregated. A sensitivity analysis of prices was undertaken. Costs for screening and antibiotics were in 1995 prices, and Medicare charges for cancer treatment from 1984 were inflated up to 1995 prices. All costs were discounted by 3%.

When applying the model to countries outside the USA, costs were modified by a factor equal to the ratio of per capita spending on health in each of the countries. It would have been preferable to have used actual cost data as the
technology and availability of drugs and treatments may be very different in other countries.

**Other issues**
There are several errors in the results. The incremental cost-effectiveness ratios were calculated based on the cost of only screening and antibiotic treatment, rather than on the lifetime cost (i.e. excluding the cost of cancer care). It is unclear whether this error was carried forward in the sensitivity analysis and international comparisons, and thus the results should be treated with extreme caution. There was also an error in Figure 2 where the ratio was reported as incremental cost per quality-adjusted life-year (QALY): this should be cost per life-year gained.

The authors did not make appropriate comparisons of their findings with those from other studies. The issue of generalisability to other settings was addressed by applying the model to three other countries (Colombia, Finland and Japan). The study population was 50 year olds with no symptoms of gastric illness and this was reflected in the authors' conclusions. The authors reported a number of limitations to their study. Firstly, uncertainty over all the input variables, especially with regard to the reduction in risk of cancer from H. pylori eradication. In addition, they acknowledged that further benefits of H. pylori eradication were not considered (e.g. reduction in gastric ulceration and lymphomae). Finally, the authors reported that they did not include the possibility of the development of antibiotic resistance by H. pylori.

**Implications of the study**
The authors stated that, whether population screening for H. pylori is warranted remains uncertain pending conclusive data about the effectiveness of eradication in preventing gastric cancer. However, it is worthy of further consideration as it appears cost-effective even at very low levels of treatment effectiveness.

**Source of funding**
Dr Owens is supported by a Career Development award from the Health Services Research and Development Service, Department of Veterans Affairs.

**Bibliographic details**

**PubMedID**
10382118

**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Antibodies, Bacterial /blood; Antigens, Bacterial /immunology /isolation & purification; Bacterial Proteins /isolation & purification; Global Health; Helicobacter Infections /diagnosis /drug therapy; Helicobacter pylori /isolation & purification; Humans; Markov Chains; Mass Screening /economics; Models, Statistical; Risk Assessment; Stomach Neoplasms /prevention & control; United States

**AccessionNumber**
21999001065