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Cost-effectiveness of screening and treating H. Pylori for gastric cancer prevention

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Abstract

Gastric cancer is second leading cause of cancer-related death worldwide. A meta-analysis of seven randomized controlled trials concluded that H. Pylori eradication reduces gastric cancer incidence by 35%. Current consensus is that H. Pylori screening and treatment is cost-effective only in high-risk populations. This paper provides an up-to-date overview of the evidence for cost-effectiveness of H. Pylori screening and treatment in different population settings and risk levels for H. Pylori infection. Ten unique cost-effectiveness or cost-utility analyses were identified. All found that screening for H. Pylori to prevent gastric cancer in the general population costs less than $50,000 per LYG. This finding was robust for differences in H. Pylori prevalence, gender and ethnicity. Based on limited evidence, re-treatment (for treatment failure), repeated screening, limiting screening and treatment to those with the CagA phenotype, or universal treatment, does not appear to be cost-effective. However, most included studies failed to consider both the broader benefits as well as the adverse effects of widespread use of antibiotics for H. Pylori.

Keywords

Cost-benefit analysis; Helicobacter pylori; stomach neoplasms; early detection of cancer

Introduction

Gastric cancer is the fourth most common cancer and second leading cause of cancer-related death worldwide [1]. Almost 1 million people are newly diagnosed with stomach cancer each year and more than 700,000 people die of the disease. Stomach cancer accounts for 8% of the total cancer cases and 10% of total cancer deaths. Over 70% of new cases and deaths occur in developing countries (Figure 1) [2]. Eastern Asia, Eastern Europe, and South America have the highest incidence of stomach cancer, whereas in North America and most parts of Africa the lowest rates can be found. Generally, stomach cancer rates are about twice as high in males as in females.

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Conflict of interest
None

The majority of gastric malignancies are intestinal type adenocarcinomas [3]. Intestinal gastric carcinomas are assumed to develop according to a multistep process of carcinogenesis, which is strongly associated with Helicobacter Pylori (H. Pylori) infection. In this process, H. pylori causes chronic inflammation of the gastric mucosa, which slowly progresses through the premalignant stages of atrophic gastritis, intestinal metaplasia and dysplasia to gastric adenocarcinoma [4]. In 1994, H. Pylori was designated a necessary (but not sufficient) cause of cancers of the distal stomach by the International Agency for Research on Cancer [5]. The average duration of premalignant gastric lesions to gastric cancer is unobserved but is believed to takes decades [3]. This long latent phase provides an excellent window of opportunity for early detection and treatment of gastric carcinomas, and furthermore potentially for cancer prevention by early intervention, such as H. pylori eradication. In addition, re-infection with H. Pylori in adulthood is relatively uncommon (although the rate is higher in high-risk populations [6]). Therefore, unlike other cancer screening programmes, which require attendance for a series of screening tests – theoretically – H. pylori screening need only be performed once during adult life [7].

While there is evidence from observational studies in humans that H. pylori eradication might plausibly reduce the risk of gastric cancer [8], individual randomized controlled trials comparing eradication treatment with no treatment in H. Pylori-positive patients have not found a significant effect of H. Pylori eradication treatment on gastric lesions [9–13]. One randomized controlled trial did find a significant protective effect from H. Pylori eradication, but only for H. Pylori patients without premalignant gastric lesions [14]. This finding led authors to suggest that H. Pylori eradication may only be effective in the early phases of carcinogenesis, before preneoplastic lesions have developed. However, a meta-analysis of seven randomized controlled trials concluded that H. Pylori eradication also is effective after gastric atrophy or intestinal metaplasia have developed, reducing gastric cancer incidence by 35% [15].

Based on the available evidence, the Gastric Cancer Consensus Conference recommended H. Pylori screening and treatment in asymptomatic persons from high-risk populations to prevent gastric cancer [16]. High-risk populations were defined as populations with incidence of gastric cancer of more than 20/100,000 population. The group suggested that screening for H. Pylori should commence 10–20 years before the initial incidence of gastric cancers begins to rapidly rise in these populations. Population-based screening was not recommended for lower-risk populations [17], because data on H. pylori eradication and gastric cancer prevention were from high-risk populations. In terms of potential screening tests, a variety of H. pylori tests are available with heterogeneous performance characteristics [18–20]. The recent Maastricht IV/ Florence Consensus Report recommended non-invasive tests for application within a “test and treat” strategy noting that both the ^{13}C-Urea Breath Test (UBT) and stool antigen testing (SAT), based on monoclonal antibodies and with laboratory-based analysis (rather than in-office immunochromatic techniques) could be considered acceptable in this setting [8]. However, serological testing, which is not affected by local changes in the stomach which could lead to low bacterial load and false-negative results using other tests, was recommended by the Gastric Cancer Consensus Conference as the best option for population-based screening [16].

Rather than screening for H. pylori in the asymptomatic general population, an alternative approach to prevention could be to focus on sub-groups of the population at higher-risk of gastric cancer. The Maastricht IV/ Florence Consensus Report recommended that H. pylori eradication to prevent gastric cancer should be considered in: first-degree relatives of family members with gastric cancer; patients with a risk of gastritis; patients with chronic gastric acid inhibition for more than one year; and individuals with strong environmental risk factors for gastric cancer, such as heavy smoking, or particular occupational exposures [16].

On the basis of evidence from observational studies [21–24] and a randomised controlled trial [25], this Consensus Report also recommended H. pylori eradication in patients with gastric neoplasia already treated by endoscopic or subtotal gastric resection [16].

In this paper, we provide an up-to-date overview of the evidence for cost-effectiveness of H. Pylori screening and treatment, with a specific focus on the population settings and risk levels for which H. Pylori screening and treatment may be cost-effective.

Review Methods

Medline, Embase and PubMed were searched for cost-effectiveness or cost-utility analyses of H. pylori screening for the prevention of gastic cancer in either (1) asymptomatic individuals in the general population or (2) high-risk subgroups of the population. Databases were searched using combinations of disease, infection and economic search strings based on both MeSH headings and text words. MeSH terms used included, but were not limited to, “stomach neoplasms”, “helicobacter pylori”, “mass screening”, “costs and cost analysis” and “economic evaluation”. Text terms searched included “gastric tumour”, “cost-effectiveness” and “cost-benefit”. Studies published in English as peer-reviewed journal articles between January 1993 and July 2013 were considered eligible for inclusion in this overview.

Ten unique cost-effectiveness or cost-utility analyses in the asymptomatic general population were identified [6, 26–39]. One economic evaluation of eradication in high-risk subgroups was identified and this is discussed separately below [40].

Cost-effectiveness of screening for H. Pylori in the general population

Of the ten evaluations in the asymptomatic general population, three studies were conducted in North America and two in the UK, two reported results for Finland and one each reported results for Colombia, Thailand, Taiwan, Singapore, China and Japan (Table 1). In the main, these studies evaluated once-only screening followed by eradication treatment of all those who tested positive for H. pylori, although some variants on this were also considered (e.g. repeat screening, repeat treatment in the event of treatment failure) in a few studies. The comparator was no screening or treatment. Seven studies evaluated the cost-effectiveness of screening based on serology testing [26–33, 36, 37, 39], one study considered screening using C-UBT [6], and two studies compared both methodologies (one of which also considered SAT)[34, 35, 38]. Seven studies considered screening in both sexes (with some reporting results for males and females separately), two evaluated screening in men only, and one assessed screening of both sexes in one ethnic group and in males only in other ethnic groups. The screening age varied between 20 and 60; the base-case age was generally younger in studies in countries with higher H. pylori prevalence.

Two studies did not express results explicitly in terms of costs per life-years gained (LYG), or per quality-adjusted life years (QALY) gained. All eight studies which reported costs per LYG (or per QALY gained) of screening for H. Pylori compared to no screening found them to be well below the commonly-used threshold for cost-effectiveness in developed countries of US$50,000 per life-year gained (Table 2). However, the range in costs per life-year gained between studies was considerable, varying from cost-saving to around $30,000 per life-year gained.

The variety in costs per life-year gained between studies is mostly likely explained by differences in the population under investigation. The studies were performed in different countries with different gastric cancer risks, H. pylori prevalence, and costs of screening and eradication therapy (Table 2). Screening was assumed to take place at a range of different ages in different studies. The assumptions on the screening test sensitivity and specificity, as

well as the effectiveness of H. pylori eradication therapy were quite consistent between studies. Sensitivity of serology testing varied between studies from 85% to 98%, with a majority of studies using an estimate of 90%. Specificity varied between 79% and 97%, again with a majority of studies using a 90% estimate. H. pylori eradication efficacy varied between 80–92%. The resulting gastric cancer reduction from eradication therapy was clustered around 30% (in those studies reporting it), which is surprisingly consistent given the lack of evidence on the long-term benefits or H. pylori eradication therapy.

Low-prevalence countries

Six studies reported findings for low H. pylori prevalence countries – the USA, UK, Canada and Finland [26–33, 38]. Prevalence of H. pylori infection was generally assumed to be 27–40% with Leivo et al [33], in their study in Finland, assuming considerably lower prevalence (13%). Interestingly, two studies with the lowest assumed prevalence [29, 33], were also the studies that found H. pylori screening might be cost-saving. However, both of these studies considered additional health care cost savings besides cost savings from gastric cancer prevention, such as costs savings of preventing peptic ulcers. The one additional study which considered other health outcomes [32], also reported a relatively low cost per life year gained of screening compared to no screening (GBP 5,860). For the remaining studies costs per life-years gained ranged from $10,000 to $35,000 [26–28, 38]. Even when comparing studies within one country cost-effectiveness estimates of H. pylori screening were quite different [26, 28, 29, 32].

High-prevalence countries

Results were reported from five studies for six high-prevalence countries: Singapore [34], Thailand [39], China [36], Colombia [27], Japan [27] and Taiwan [6]. Three studies reported assumptions on H. pylori prevalence. Yeh et a [36] assumed a prevalence rate of 70% for China, Harris et al [27] assumed rates of 93% for Colombia and 73% for Japan, and Xie et al [34] assumed a prevalence rate up to 43% for Chinese men in Singapore depending on age. Interestingly, this latter estimate is only slightly higher than the estimate for low-prevalence countries. The costs per life-year gained of H. pylori screening in high-prevalence countries varied from $200 to $17,000 per life-year gained. The study with the relatively low assumed prevalence [34] was at the upper end of this range.

One study directly compared cost-effectiveness of H. pylori screening in both low-and high-prevalence countries [27]. The authors concluded that screening in countries where gastric cancer incidence is higher is more cost-effective than screening in the United States which has lower gastric cancer incidence. They considered population screening worth further consideration.

Ethnicity

Two studies from the USA evaluated cost-effectiveness in different ethnic groups [26, 28]. Parsonnet et al [26] estimated that the cost per life year saved of screening at age 50 in all ethnic groups was $25,000, but found that this varied between ethnic groups. The cost per life year saved increased as gastric cancer risk decreased, from $4,500 among Japanese-Americans (high-risk) to $13,700 in African-Americans (moderate risk) to $34,900 in whites (low-risk). Similarly, Fendrick et al [28] modelled screening and treatment at age 40 in White men, White women, African-American and Hispanic men and Japanese-American men. Assuming a slightly greater than 30% reduction in gastric cancer risk, for all groups the ICER was below $50,000 per life year gained; it was highest in Whites and lowest in Japanese-Americans.

Screening age

Six studies [6, 26, 32–34, 36] investigated the optimal age of a single screen for H. pylori infection. Two studies concluded that it was optimal to screen at a young age (20 or 30 years), because H. pylori screening in older cohorts was both less effective and less cost-effective [6, 36]. The other studies also found a higher effectiveness of H. pylori screening at younger ages, but this effectiveness was accompanied by higher costs per life-year gained. They therefore suggested older ages for H. pylori screening, mostly centred around 40–50 years. The two studies with better cost-effectiveness at younger ages were both studies in high-prevalence countries, whereas all others, except Xie et al [34] were based in low-prevalence countries. As noted earlier, the prevalence of H. pylori assumed by Xie et al [34] was only slightly higher than that in low-prevalence countries.

Gender

Three studies reported cost-effectiveness of gastric cancer prevention separately in men and women, two in low-risk settings (USA)[26, 28] and one in a high-risk population (China) [36]. Parsonnet et al [26] reported that, in the base-case model, cost-effectiveness of screening and treatment at age 50 was considerably more favourable in men ($19,900 per life year saved) than women ($35,700 per life year saved), a finding attributed to the fact that gastric cancer incidence and mortality rates in men were more than double those in women. Similarly, in the study by Fendrick et al [28], across a range of different levels of gastric cancer risk reduction, the cost per life years gained was around double for White women compared to White men. In contrast, in the study from China, screening and treatment at age 20 had a similar cost-effectiveness profile in both sexes: $1,560 (men) and $1,500 (women) per QALY gained versus no screening [36].

Type of test

Two studies, by the same group of authors, compared cost-effectiveness of different tests applied the same population [34, 38]. The first study compared screening by serology or C-UBT in Singapore Chinese males aged 35–44 years [34]. The serology-based screening cost considerably less ($9.8 million vs $23.0 million) but resulted in only slightly fewer gastric cancers prevented (272 vs 281) Compared to no screening the ICER for serology was lower than that for C-UBT ($13,571 and $32,525 per QALY gained). When compared to serology screening, the ICER for C-UBT was $390,337 per QALY gained, clearly indicating that screening using serology would be preferable in this population.

The second study compared screening by serology, C-UBT, or SAT among Canadian men aged 35 [38]. There was little difference between the tests in numbers of cancers detected, although the UBT-based strategy was considerably more costly. Compared to no screening, the ICER was lowest for SAT ($29,850 per QALY gained), followed by the serology test ($33,115) and the UBT ($33,115). The SAT dominated the serology test yielding more QALYs at less cost.

Strategies involving repeat treatment

In terms of strategies to accommodate treatment failure, Fendrick et al [28] explicitly compared two scenarios with no screening: the first involved serological testing and treatment of those who tested positive; the second also included confirmatory testing 6 weeks after eradication therapy and the offer of a second eradication regimen to those who tested positive. In 40-year old white men, assuming 80% effectiveness of initial eradication therapy, the scenario with the confirmatory test resulted in more life years gained than the serology-only strategy, but was substantially more costly, thus the ICER comparing these two strategies was $37,870 per LYG. The scenario with the confirmatory test only became

cost-effective compared to serology alone when the excess cancer risk reduction associated with H. pylori testing was assumed to be more than 80%.

Strategies involving repeat screening

Two studies considered the cost-effectiveness of repeated screening strategies [6, 36]. In a study in China, a once-only screening at ages 20, 30, 40, 50 or 60 was compared with single screening at the same ages followed by rescreening individuals with negative results either after 5 years ("rescreen once") or after both 5 and 10 years ("rescreen twice") and universal treatment (which is discussed further below) [36]. In both men and women, in those aged 20, the strategies involving repeat screening resulted in slightly greater life expectancy than once-only screening, but were more costly. They were also dominated by universal treatment. The authors concluded that strategies including rescreening did not provide substantial additional benefit provided the false-negative rate of screening was less than 15%. In the study in Taiwan, the authors considered once-off and annual, biennial, triennial, four-yearly and five-yearly screening options initiated at age 30 [6]. The strategy of once-only screening resulted in slightly fewer LYG than annual screening but somewhat lower costs, leading the authors to prefer once-only screening. Biennial, triennial, four-yearly and five-yearly screening were internal to the efficiency frontier between once-only screening and annual screening and were ruled out by extended dominance.

Strategies involving targeted screening and treatment

The CagA protein is expressed in 30–80% of H. pylori isolates [27]. CagA is a marker for virulence [41] and individuals who are seropositive for CagA strains of H. pylori are at an especially increased risk for developing noncardia gastric cancer [42]. This raises the possibility that it might be preferable to selectively screening and treat only those individuals with CagA-positive strains of infection, thereby targeting therapy to those at highest gastric cancer risk and reducing costs and the potential burden of adverse effects. Harris et al [27] evaluated the cost-effectiveness of screening and treating either all H. pylori strains or CagA-positive strains only. Screening and treating only CagA-positive infection reduced the number treated, the number of cases of anaphylaxis and overall costs of screening and treatment, but it also reduced the number of cancers prevented and life years gained. Compared to no screening, the ICER for the two options were similar (CagA-positive only: $23,900 per LYG; treating all H. pylori: $24,300 per LYG), and when the two strategies were compared directly, the ICER for screen and treat all H. pylori versus CagA-positive only was $25,100 per life year gained. The authors repeated the analysis for Colombia, Finland and Japan and, in all countries, the ICER for screening for all H. pylori compared to CagA-positive strains only was less than $4,500 per life-year gained. These results suggested that screening only for CagA-positive infection is not substantially better than screening for all H. pylori, a finding due to the fact that CagA-negative individuals have increased cancer risk compared to H, pylori negative patients.

Universal treatment

In countries with high prevalence of H. pylori, it is possible that, instead of screening the population and selectively treating infected individuals, it might be more cost-effective to simply treat everyone. Parsonnet et al. [26] estimated that universal treatment would cost $33,000 per life year gained compared to no screening, in a US population aged 50 in whom H. pylori prevalence was estimated to be 40%. Yeh et al. [36] evaluated cost-effectiveness of universal treatment for a region of China where H. pylori seroprevalence was assumed to be 70% among those aged 20. Compared to no screening, universal treatment was considered highly cost-effective among both men and women (ICERs of $3,250 per QALY gained for men and $3,060 per QALY gained for women). However, screening plus selective treatment (the most usual strategy) would also be considered highly cost-effective

and, in fact, the ICERs for this option were lower ($1,560 per QALY gained for men; $1,500 per QALY gained for women), due to the higher cost of universal treatment. Age-groups from 20 to 50 were considered and, at all ages, universal treatment was less cost-effective compared to no screening or treatment than screening and selective treatment.

Cost-effectiveness of screening and treating H. pylori for gastric cancer prevention in specific high-risk groups

One study, based in Korea, evaluated the cost-effectiveness of eradication in gastric cancer survivors comparing eradication at age 60 in people who had had complete resection of early gastric cancer by endoscopy, with no eradication [40]. In the base-case, eradication cost less than no eradication ($29,780 vs $30,594) and resulted in longer life expectancy (13.60 years vs 13.55 years). H. pylori eradication remained the dominant strategy across a range of one-way sensitivity analyses in which risk of developing metachronous gastric cancer in the no eradication group, relative risk of metachronous cancer in the intervention group, cost of eradication, cost of gastric cancer treatment, and the discount rate were varied. Even in the most extreme scenarios considered (e.g. very low risk of metachronous gastric cancer) the ICER for eradication remained less than $4000 per life year gained.

Discussion

All studies of cost-effectiveness included in this overview found that screening for H. pylori to prevent gastric cancer in the general population costs less than $50,000 per LYG, a commonly used threshold for cost-effectiveness in literature. This finding was robust for differences in H. pylori prevalence, gender and ethnicity in and between studies. When using 3 times the gross domestic product (GDP) per capita as the threshold for cost-effectiveness (as recommended by the WHO), H. pylori screening would still be considered cost-effective in all studies. Based on relatively limited evidence there do not appear to be benefits of cost-effectiveness of repeated screening or re-treatment, or limiting treatment to those with the CagA phenotype. However, whether studies have considered realistic estimates of the treatment effectiveness, success and compliance is debatable.

All studies place an important caveat concerning their conclusion that H. pylori screening and treatment appears to be cost-effective in the prevention of gastric cancer, namely concerning the effectiveness of H. pylori eradication to prevent future gastric cancer risk. So far, no individual randomized controlled trial has been able to show a significant preventive effect of H. Pylori eradication treatment on gastric cancer incidence [9–13]. A meta-analysis of seven randomized controlled trials concluded that H. Pylori eradication is effective, reducing gastric cancer incidence by 35% [15]. Most cost-effectiveness studies in this overview assumed an effectiveness of 30% of H. pylori eradication in reducing gastric cancer incidence, which is slightly more conservative than the estimated 35% reduction from the meta-analysis. H. pylori screening may therefore be even more cost-effective than currently estimated.

Because of the uncertainty in the effectiveness of H. pylori eradication, most studies performed a sensitivity or threshold analysis on the effectiveness of H. pylori eradication. The results proved quite robust for the effectiveness H. pylori eradication: five studies specifically evaluated the required effectiveness of H. pylori eradication in the reduction of gastric cancer incidence [26–29, 34]. These studies all found that even with a preventive effect of H. pylori eradication on gastric cancer incidence as low as 15%, H. pylori screening would still be cost-effective.

The explanation that H. pylori screening is so cost-effective probably is a result of the relatively low cost of the screening test (the serology test was estimated to cost less than $40 in all studies) and H. pylori treatment (less than $200 in all studies, and often considerably less than $100) - and the fact that screening need be conducted once - especially compared to the high treatment savings that can be obtained from preventing gastric cancer incidence. Estimates for H. pylori screening and treatment costs were less than 1% of gastric cancer treatment costs in all studies and often considerably less than that. As a consequence, H. pylori screening is a cheap intervention with considerable potential for cost-savings. When also considering the additional potential of H. pylori screening and treatment to prevent dyspepsia and/or peptic ulcers, cost-effectiveness of H. pylori screening becomes even more favorable and two of the three studies including this potential [32, 33, 36] found that H. pylori screening may even be cost-saving.

While serology as a H. pylori screening test has good performance characteristics, and is relatively cheap, this is also true of the other available tests, C-UBT and SAT. The Gastric Cancer Consensus Conference recommended screening using a serological test [16], and this is what has been considered in most of the available studies. Only two studies have, so far, compared different screening tests and these provided little clarity on the issue of which is most cost-effective across settings: in the high-prevalence population serology dominated C-UBT, whereas in the lower-prevalence population, SAT dominated the other two options [34, 38]. However, cost-effectiveness is not the only issue worth considering as regards choice of screening test. For example, the breath test offers the advantage of being non-invasive, so might prove more acceptable if screening was to be implemented in the general population resulting in higher uptake. Acceptability of the test is one of the pre-requisites for the introduction of population-based screening [43]. Moreover, although cost-effectiveness results may be relatively insensitive to variations in assumed uptake (because increasing uptake usually increases both costs and benefits), high uptake is essential if screening is to be effective in terms of cancer prevention at the population-level. Further investigation is required of both cost-effectiveness and likely acceptability of screening based on different tests.

As regards limitations, these are several issues which could mean that the potential cost-effectiveness of screening and treatment may have been over-estimated. Only three studies expressed benefits in terms of quality-adjusted life years [34, 36, 38]. There appears to be limited evidence on utility in patients with gastric cancer, but it seems likely that, as for other cancers, a diagnosis of gastric cancer results in decrements in health-related quality-of-life and hence disutility. Expressing benefits of screening in terms of life years gained means that this disutility has not been taken into account. It is also possible that other aspects of screening and treatment could impact adversely on health-related quality-of-life or psychological wellbeing, but this is less certain. Most of the cost-effectiveness studies adopted a healthcare payer perspective and considered only direct costs. One study in Taiwan took a societal perspective and included a range of indirect costs, including patient time associated with screening, confirmatory testing, in-patient hospitalizations, outpatient visits and lost productivity costs [6]. It was noteworthy that the ICER for screening and treatment versus no screening in this study was not as low as in some other studies ($17,044).

In terms of other issues of potential note, those studies which reported the H. pylori re-infection rate tended to assume it is around 1%. A recent cohort study from Latin America, which followed almost 1500 individuals who had undergone apparently successful eradication therapy, reported that 11.5% tested H. pylori positive at one year [44]. Other studies suggest that the annual recurrence risk is between 3% and 9% [45]. While the recurrence rate does fall over time [44], the apparent difference between the recurrence rates

in these studies and the re-infection rates in the cost-effectiveness analyses is important. Firstly the assumption that the rate of re-infection is low is one of the main arguments for once-only screening. Secondly, it appears that the rate of re-infection may strongly influence cost-effectiveness. In the study in Taiwan, increasing the reinfection rate from 1% to 2.5% increased the cost per life year gained for screening and treatment versus no screening by 76% [6].

A related issue concerns treatment effectiveness. For some people, therapy fails to eradicate infection and others fail to comply with therapy. In the cost-effectiveness analyses, the estimate of H. pylori eradication efficacy varied between 80% and 92%. However, a 2010 meta-analyses of 9 randomised controlled trials estimated that the eradication rate for triple therapy was somewhat lower than this (77%)[46]. Moreover, effectiveness in a screening programme in the real-world may be even lower than in trials. In addition, it has been noted that some of the economic models failed to accommodate treatment failures explicitly as a health state [35]. Only a few studies reported explicitly allowing for treatment failure and second (or third)-line therapy (see, for example, [28, 33]). As would be expected, to the limited extent to which this has been investigated, strategies which allow for repeat treatment result in greater benefits, but are more costly than a strategy based on once-only screening and treatment [28].

The extent to which models adequately incorporated complications of screening and treatment for individuals is uncertain; failure to do this may also mean that costs of screening and treatment are under-estimated and benefits over-estimated. Finally, a major limitation of the evidence-base generally is the lack of consideration of the adverse effects of widespread use of antibiotics in the population, most notably antimicrobial resistance [47]. The implications of this are important albeit difficult to quantify. They are also difficult to accommodate within economic models which tend to be focussed on a single outcome (i.e. gastric cancer). This issue, however, deserves greater consideration.

In other cancers, prevention strategies focussed on high-risk subgroups of the population have undergone economic evaluation (e.g. screening and/or surveillance for women at high genetic risk of breast cancer [48]). Although the Maastricht IV/ Florence Consensus Report recommended H. pylori eradication to prevent gastric cancer should be considered in various high-risk sub-groups [8], this issue has received very little attention in terms of cost-effectiveness. The single study of patients who had undergone complete resection of early gastric cancer suggested that eradication for the purposes of preventing had a favourable cost-effectiveness profile and appeared to be robust to changes in various parameters [40], but whether this holds in other countries, with lower gastric cancer incidence, requires investigation. Moreover, the major limitation of this analysis was that the model assumed that all of the patient group were H. pylori positive initially, effectively disregarding any costs associated with the identification of positive individuals. This assumption is in conflict with recommendations that economic evaluations of interventions in high-risk groups should explicitly consider the costs and outcomes of the method of targeting (i.e. the method of identifying the high-risk group), since these are likely to have a significant impact on cost-effectiveness [49].

Conclusion

In conclusion, once-only screening for H. pylori with eradication therapy in those who test positive appears to be cost-effective in the asymptomatic general population. Based on limited evidence there do not appear to be benefits of re-treatment of those in whom treatment fails, repeated screening, targeting screening and treatment to those with the CagA phenotype, or universal treatment. These conclusions are against a background where most

studies have failed to consider the other broader benefits that could accrue from screening and treatment, in terms of impacts on dyspepsia and/or ulcers, which would be expected to improve cost-effectiveness. However, most studies also failed to adequately address the potential negative effects of eradication therapy. In addition, whether studies have considered realistic estimates of the treatment effectiveness, success and compliance is debatable, given the lack of evidence for these parameters.

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Summary

Gastric cancer is the second leading cause of cancer-related death worldwide. Gastric cancer development is strongly associated with Helicobacter Pylori (H. Pylori) infection. A meta-analysis of seven randomized controlled trials concluded that H. Pylori eradication reduces gastric cancer incidence by 35%. Ten unique studies evaluated the cost-effectiveness of H. Pylori screening and treatment in different population settings and risk levels for H. Pylori infection. All studies found that screening for H Pylori to prevent gastric cancer in the general population costs less than $50,000 per LYG. Although screening was generally found to be more cost-effective in higher-risk populations than in lower-risk populations (i.e. Asian and South-American countries vs European countries and the US; men vs. women; Japanese-American vs. African-American vs whites), H Pylori screening remained cost-effective also in the lower-risk populations. Serology testing and stool antigen testing were found to be more cost-effective than the currently most recommended C-Urea breath test. Repeated screening, re-treatment, or limiting treatment to those with the CagA phenotype does not appear to be cost-effective. There is tentative evidence that eradication is worthwhile in gastric cancer survivors. To date, the cost-effectiveness of targeted H Pylori screening and eradication-based strategies has not been addressed. In future cost-effectiveness analyses, the broader benefits that could accrue from H Pylori screening and treatment, in terms of impacts on dyspepsia and/or ulcers, as well as the adverse effects of widespread use of antibiotics in the population need to be addressed.

Practice Points

- Gastric cancer is second leading cause of cancer-related death worldwide.
- A meta-analysis of seven randomized controlled trials concluded that H. Pylori eradication reduces gastric cancer incidence by 35%.
- Current consensus is that H. Pylori screening and treatment is cost-effective only in high-risk populations.

Research agenda

- Long-term evidence concerning the H. pylori re-infection rate and gastric cancer incidence reduction of H. Pylori screening is needed
- Cost-effectiveness analysis including both the broader benefits as well as the adverse effects of widespread use of antibiotics for H Pylori needs to be performed
- Economic evaluations of targeted H pylori eradication-based strategies for gastric cancer prevention are required
- More studies on the cost/effectiveness of H Pylori eradication in gastric cancer survivors are required.

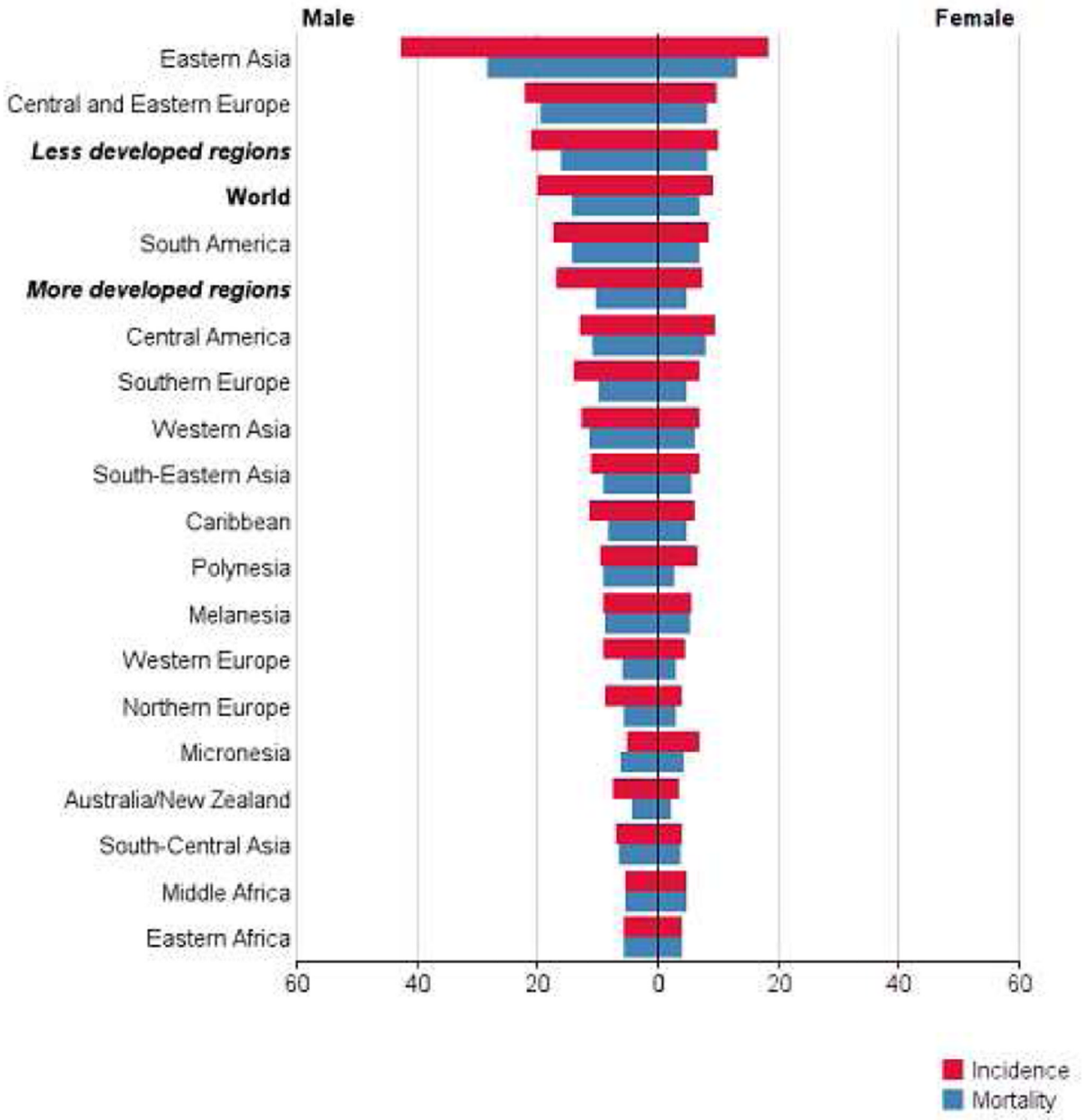

Figure 1.
World age-standardised incidence and mortality rates of gastric cancer, per 100,000 population, 2008, by sex1
1 From Ferlay et al., 2010

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Table 1

Summary of characteristics of studies of cost-effectiveness of *H pylori* eradication in the asymptomatic general population – countries, scenarios modelled, disease outcomes, ethnic groups and gender, age group and test

Reference(s)	Year of publication	Country(ies)	Scenarios modelled	Disease outcome(s)	Ethnic groups and gender	Age group	Test
[26,27]	1996,1999	USA [Harris: USA, Colombia, Finland, Japan]	Parsonnet (1) Screen and treat those positive (2) Universal treatment [Harris (3) Screen and treat all those positive; (4) Screen and treat those with CagA-positive strains]	Gastric cancer	General US population (both sexes combined); general US population of males; general US population of females; Whites (both sexes combined), African-Americans (both sexes combined); Japanese-Americans (both sexes combined) [Harris: General population in each country]	50–54 years [with SA for 10, 20, 30, 40, 60 and 70 years]	Serology
[28]	1999	USA	(1) Screen and treat those positive; (2) Screen, treat those positive, test to confirm success and re-treat those positive	Gastric cancer	White men; White women; African-American/Hispanic men; Japanese-American men	40 year olds	Serology
[29]	2002	England	Screen and treat those positive	Distal gastric cancer; peptic ulcer disease	General population; both sexes combined for gastric cancer; males and females separately for peptic ulcer disease	45 year olds	Serology
[30–32]	2002, 2003	England & Wales	Screen and treat those positive [and assuming degree of opportunistic testing of patient with dyspepsia]	Gastric cancer; peptic ulcer disease	General population (both sexes combined)	40 year olds [with SA for 20, 30 and 50 years]	Serology
[33]	2004	Finland	Screen and treat those positive [with second and third eradication therapy, if required, for treatment failures]	Gastric cancer; premalignant lesions; duodenal ulcer; gastric ulcer	General population (both sexes combined)	15, 30 or 45 years	Serology
[6]	2007	Taiwan	Screen and treat those positive [with annual, biennial, triennial, 4-yearly and 5-yearly screening in SA]	Gastric cancer	General population (both sexes combined)	30 year-olds [with SA for 35, 40, 45, 50, 55, 60 and 65 years]	C-UBT
[34,35]	2008	Singapore	Screen and treat those positive	Gastric cancer	Chinese males	35–44 year olds	Serology; C-UBT
[36,37]	2008, 2009	China	(1) Screen and treat those positive; (2) Screen and treat those positive, with one re-screen of those negative; (3) Screen and treat those positive, with two opportunities to re-screen those negative; (4) Universal treatment. [Treatment in all scenarios included follow-up visit	Gastric cancer	General population; males and females separately	20 year-olds [with SA for 30, 40, 50 and 60 years]	Serology

Reference(s)	Year of publication	Country(ies)	Scenarios modelled	Disease outcome(s)	Ethnic groups and gender	Age group	Test
			to evaluate success and retreatment, if required]				
[38]	2009	Canada	Screen and treat those positive	Gastric cancer	General population of males	35 year-olds	Serology; C-UBT; SAT
[39]	2010	Thailand	Screen and treat those positive	Gastric cancer	General population	20 year-olds	Serology

C-UBT, ^{13}C-urea breath test; HP, Helicobacter pylori; SA, sensitivity analyses; SAT, stool antigen test

Table 2

Studies of cost-effectiveness of *H pylori* eradication in the asymptomatic general population – parameter values for H pylori prevalence, screening test characteristics and costs, characteristics of treatment and cost-effectiveness results in base-case analysis

Reference(s)	H pylori prevalence	Screening test characteristics	Screening test cost	Characteristics of HP treatment	Eradication therapy costs	Costs / LYG
[26,27]	40%[1]	Sensitivity: 90% Specificity: 90%	$33	Effect: 90% HP eradication, no excess gastric cancer risk after eradication → 30% gastric cancer reduction	$125	Screen and treat all HP $25,000 Universal treatment $33,000 [Harris: US $23,900 for CagA-positive, $25,100 for all HP[2]; Colombia $150 for CagA-positive, $200 for all HP[2]; Finland $4,300 for CagA-positive, $4,400 for all HP[2]; Japan $1,050 for CagA-positive, $1,100 for all HP[2]]
[28]	40%	Sensitivity: 90% Specificity: 90%	$20	Effect: 80% HP eradication, no excess gastric cancer risk after eradication	$80	Screen and treat: $6,264 in white men[3] Screen, treat and confirmatory test: $11,313 in white men
[29]	28%	Sensitivity: 90% Specificity: 90%	GBP 7 (5 for test + 2 for invitation)	Effect: 50% reduction in gastric cancer and PUD mortality	GBP 23 (21 for drugs + 2 for invite)	Cost-saving
[30–32]	32% in males; 27% in females	Sensitivity: 95% Specificity: 90%	GBP 12.6 (10.1 for test + 2 for invitation + 0.5 for sending result)	Effect: 90% HP eradication, no reinfection, 10 year lag time for reduced gastric cancer risk	GBP 36.39 (7.76 nurse time + 28.63 for drugs)	GBP 5,860
[33]	13%	Sensitivity: 97% Specificity: 93%	$29 ($5 for invitation + $24 for test)	Effect: 81% HP eradication after 1st treatment, another 82% after 2nd treatment, 3rd treatment unknown, no reinfection	$203–$693 depending on number of treatments required	Not reported, only costs considered. Cost-saving if screening at age 45 years
[6]	Not reported	Sensitivity: 97.8% Specificity: 96.8%	$36.3	Effect: 87% HP eradication, 1% reinfection, no excess gastric cancer risk	$42.2	$17,044[4]
[34,35]	20–43%	Serology Sensitivity: 93% Specificity: 79% C-UBT Sensitivity: 97.9% Specificity: 95.8%	Serology $26 C-UBT $83	Effect: 92% HP eradication, 1% reinfection rate → 30% gastric cancer risk reduction	$30	Serology $16,166 ($13,571 per QALY gained) C-UBT $38,792 ($32,525 per QALY gained)

Reference(s)	H pylori prevalence	Screening test characteristics	Screening test cost	Characteristics of HP treatment	Eradication therapy costs	Costs / LYG
[36,37]	70%	Sensitivity: 90% Specificity: 90%	$3.4 ($1.8 visit + $1.6 for test)	Effect: 30–90% lower risk of progression to atrophy and 2–2.4 times higher likelihood of regressing to gastritis	$4.3	Males: screen and treat $1,340 ($1,540 per QALY gained) Females: screen and treat $1,230 ($1,500 per QALY gained) Males: universal treatment $2,720 ($3,250 per QALY gained) Females: universal treatment $2,510 ($3,060 per QALY gained)
[38]	33%	Serology Sensitivity: 85% Specificity: 79% C-UBT Sensitivity: 99% Specificity: 99% SAT Sensitivity: 94% Specificity: 97%	Serology CAD30 C-UBT CAD69 SAT CAD34	Effect: 87% HP eradication, 1% reinfection rate	CAD44	Serology CAD 33,115[5] C-UBT CAD 50,397[5] SAT CAD 29,850[5]
[39]	Not reported	Not reported	Not reported	Effect: based on Yeh (result in reduction from screening of 14.5% for males and 26.6% for females)	$10	Not reported

CAD, Canadian dollars; C-UBT, ^{13}C-urea breath test; GBP, Great Britain pounds; HP, Helicobacter pylori; LYG, life years gained; PUD, peptic ulcer disease; QALY, quality-adjusted life years, SAT, stool antigen test

1 percentage of isolates assumed to express CagA phenotype, 60%

2 costs per LYG for CagA-positive are compared to no screening; costs per LYG for all H. pylori are compared to CagA-positive strains

3 cost per LYS was higher for white females and lower for African-American males and Japanese-American males at all levels of gastric cancer risk reduction

4 indirect costs were included

5 cost per QALY gained versus no screening