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Exploring the cost-effectiveness of *Helicobacter pylori* screening to prevent gastric cancer in China in anticipation of clinical trial results

Jennifer M. Yeh[1,*], **Karen M. Kuntz**[2], **Majid Ezzati**[3], and **Sue J. Goldie**[1]

1*Program in Health Decision Science, Department of Health Policy and Management, Harvard School of Public Health, Boston, MA*

2*Division of Health Policy and Management, School of Public Health, University of Minnesota, Minneapolis, MN*

3*Department of Population and International Health and Department of Environmental Health, Harvard School of Public Health, Boston, MA*

Abstract

Gastric cancer is the second leading cause of cancer-related deaths worldwide. Treatment for *Helicobacter pylori* infection, the leading causal risk factor, can reduce disease progression, but the long-term impact on cancer incidence is uncertain. Using the best available data, we estimated the potential health benefits and economic consequences associated with *H. pylori* screening in a high-risk region of China. An empirically calibrated model of gastric cancer was used to project reduction in lifetime cancer risk, life-expectancy and costs associated with (*i*) single lifetime screening (age 20, 30 or 40); (*ii*) single lifetime screening followed by rescreening individuals with negative results and (*iii*) universal treatment for *H. pylori* (age 20, 30 or 40). Data were from the published literature and national and international databases. Screening and treatment for *H. pylori* at age 20 reduced the mean lifetime cancer risk by 14.5% (men) to 26.6% (women) and cost less than $1,500 per year of life saved (YLS) compared to no screening. Rescreening individuals with negative results and targeting older ages was less cost-effective. Universal treatment prevented an additional 1.5% to 2.3% of risk reduction, but incremental cost-effectiveness ratios exceeded $2,500 per YLS. Screening young adults for *H. pylori* could prevent one in every 4 to 6 cases of gastric cancer in China and would be considered cost-effective using the GDP per capita threshold. These results illustrate the potential promise of a gastric cancer screening program and provide rationale for urgent clinical studies to move the prevention agenda forward.

Keywords

simulation model; cost-effectiveness; Helicobacter pylori; gastric cancer

Helicobacter pylori (*H. pylori*) infection is classified as a human carcinogen by the International Agency for Research on Cancer (IARC) and is associated with an estimated 65–80% of gastric cancer.[1-3] Gastric cancer is the second leading cause of cancer-related deaths worldwide and a major public health problem with over 40% of all cases occurring in China.

*Correspondence to: Program in Health Decision Science, Department of Health Policy and Management, Harvard School of Public Health, 718 Huntington Avenue, 2nd Floor, Boston, MA 02115, USA. Fax: 617-432-0190. E-mail: jyeh@hsph.harvard.edu.

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On the basis of current age-specific rates of gastric cancer and projected demographic changes, the annual number of expected cases in the country alone will increase from 393,000 in 2002 to 795,700 in 2030.[4]

Over the past 30 years, the understanding of gastric carcinogenesis has advanced. Specifically, the role of *H. pylori* and the development of gastric cancer through a series of precancerous lesions have shifted the focus of gastric cancer research from palliative strategies to the development of preventive strategies, including screening for *H. pylori*, especially in China where nearly 60% are infected, the majority of whom are asymptomatic.[5,6] Although the infection is relatively easy to detect and treat with a non-invasive diagnostic test and course of antibiotics, the effectiveness of treatment to prevent gastric cancer is uncertain and screening thus far has not been recommended. Ideally, the strongest evidence would come from randomized controlled trials that use gastric cancer incidence as the primary outcome. Several clinical trials are underway[7] and results from the first of such studies showed that after 7.5 years, treatment for *H. pylori* reduces cancer incidence among individuals without preexisting precancerous lesions, defined as atrophy, intestinal metaplasia and dysplasia, at time of treatment.[8] Studies measuring intermediate outcomes also provide indirect support for a benefit on cancer risk *via* reduced progression of precancerous lesions to cancer.

To estimate the public health benefits of a *H. pylori* screening program, several factors must be considered: the underlying natural history of *H. pylori*-associated disease; the heterogeneity of risk conferred by gender, age and country; the effectiveness of treatment for *H. pylori* in interrupting the pathway to cancer; and the feasibility of implementing a secondary prevention program at the population level. As no single empirical study can evaluate all possible *H. pylori* screening and treatment strategies, by integrating the best biologic, epidemiologic and economic data, mathematical simulation models can assist in decision making by leveraging available data on intermediate outcomes to estimate the avertable burden of disease expected with different strategies, identify influential factors for which better empirical data would be most valuable, and provide insight into the potential cost-effectiveness of different strategies.[9]

The feasibility of introducing a new public health intervention in any country, especially one that is resource-constrained, is complex given competing health priorities. Cost-effectiveness analysis when used in conjunction with other equally important information on affordability, political will and cultural preferences and distributional and equity considerations can provide useful information to decision makers considering alternative public health interventions and policies. By quantifying the relative health and economic consequences of one investment compared with another, cost-effectiveness analyses provide information on the investment's "value for money." To inform the dialogue and debate about the potential value of gastric cancer prevention programs, we explored the health benefits and economic consequences associated with screening for *H. pylori* in China.

Material and methods

Analytical overview

We used an empirically calibrated natural history model of noncardia intestinal gastric adenocarcinoma to estimate the benefits, costs and cost-effectiveness of multiple *H. pylori* screening strategies to prevent gastric cancer.[10] The model was calibrated using a likelihood-based approach that ensures multiple model outputs are consistent with epidemiologic data on the prevalence of precancerous lesions and incidence of gastric cancer. We used a randomly-selected subset of good-fitting parameter sets identified in our model calibration to project the mean (and range) of lifetime risk of cancer, life expectancy and lifetime costs associated with different screening strategies. To assess the comparative performance of various screening

strategies, we calculated incremental cost-effectiveness ratios, defined as the additional cost of a specific strategy divided by its additional clinical benefit, compared to the next least expensive strategy. We adopted a modified societal perspective in that we did not include patient time costs, and discounted all costs and clinical consequences at a rate of 3% per year as recommended by the U.S. Panel on Cost-Effectiveness in Health and Medicine and other guidelines.[11-13] Costs are expressed in US 2005 dollars (US$ 1 = 8.18 Yuan).

Natural history model

We developed a state-transition simulation model of the natural history of noncardia intestinal gastric adenocarcinoma in which disease progression of a cohort entering the model is characterized as a sequence of monthly transitions between health states (Fig. 1).[10] At the start of the simulation, a cohort representative of 20-year olds in the high-risk region of Linqu, China enters the model and is distributed among the health states defined by the precancerous process based on *H. pylori* seroprevalence, age-specific prevalence of precancerous lesions and the proportion of gastric cancers that are *H. pylori*-positive (Fig. 1). Although some *H. pylori*-negative individuals have normal gastric mucosa, all individuals infected with *H. pylori* have gastritis or more advanced precancerous lesions. Movement through the health states occurs in monthly increments according to probabilities that are dependent on sex and *H. pylori* status. Individuals are followed throughout their lifetime and the model is run separately for men and women.

Model assumptions

We convened an expert panel to review our model assumptions and identify reasonable estimates for model parameters for which direct clinical data are unavailable. The following assumptions were made based on the expert consultation: (*i*) individuals acquire *H. pylori* infection during childhood and unless treated with antibiotics, remain infected;[14] (*ii*) new infections and reinfection in adulthood are rare;[15,16] (*iii*) all infected individuals develop gastritis and face a higher risk of developing atrophy;[17] (*iv*) precancerous lesions may regress to less advanced lesions;[18-20] (*v*) in the absence of other causes of death, all gastric cancers become clinically symptomatic within 2 years;[21] and (*vi*) 95% of all gastric cancers are adenocarcinomas, 95% of adenocarcinomas are distal to the cardia and 40, 50 and 60% of noncardia adenocarcinomas are intestinal type for individuals younger than 44, between 45 and 65, and older than 65 years of age.[22]

Model parameterization and calibration

Details of model parameterization, including the calibration methods, have been described previously.[10] Briefly, we first identified a plausible range for each parameter by conducting a literature review and selecting the highest and lowest values among all available studies. We then established targets for calibration using epidemiologic data on: (*i*) age-specific prevalence of gastritis, atrophy, intestinal metaplasia and dysplasia for 5-year age groups between the ages of 35 and 64 and (*ii*) age-specific incidence of gastric cancer for 5-year age groups between the ages of 25 and 84. Likelihood-based methods were used to identify good-fitting parameter sets, defined as those with goodness-of-fit scores statistically indistinguishable from the score of the best-fitting parameter set (α level = 0.05), which produced output consistent with these data. To explicitly incorporate the effect of parameter uncertainty, analyses were conducted with a random subset of 50 such good-fitting parameter sets, and results were reported as a mean and range of outcomes, whereas incremental cost-effectiveness ratios were reported as the ratio of the mean-costs divided by the mean-effects of all 50 parameter sets.

Screening strategies

For a cohort of 20-year olds, we assessed the health and economic outcomes associated with the baseline strategy of no screening or treatment for *H. pylori* and the following 3 strategies at ages 20, 30, 40, 50 and 60: (*i*) *H. pylori* screening once with a serology test and antibiotic treatment for positive test results, (*ii*) *H. pylori* screening once followed by rescreening individuals with negative results and (*iii*) universal treatment for *H. pylori* with antibiotics. We also evaluated the strategies for older cohorts between the ages of 30 and 60. For the screening strategy with rescreening, we varied the number of opportunities to repeat screening in individuals who originally tested negative (1 or 2 opportunities for rescreening) and assumed the next screening opportunity would occur during the subsequent 5-year interval. Although screening for *H. pylori* among asymptomatic individuals has been debated, proposals for universal treatment to our knowledge are not currently being considered.[23] Because of the high prevalence of *H. pylori* in China and limited consequences associated with treatment, we evaluated this strategy to illustrate the relative benefits and costs associated with avoiding all screening costs and allocating resources to simply providing treatment.

We assumed that (*i*) all individuals without symptomatic gastric cancer are eligible for screening; (*ii*) diagnostic test characteristics do not vary by precancerous lesion; (*iii*) once screened, all test positive individuals receive treatment; (*iv*) treatment takes effect after 1 month;[24] (*v*) *H. pylori*-positive individuals who are screened, test positive and treated will face a lower risk of progression to atrophy and a higher likelihood of regressing to gastritis than untreated *H. pylori*-positive individuals;[25] (*vi*) all other individuals will face transition probabilities that reflect disease progression for their *H. pylori* status and (*vii*) individuals who progress to symptomatic gastric cancer during the month of screening will still receive *H. pylori* treatment.

Clinical data

Table I shows selected model variables and their plausible ranges.[8,18,26-46] For *H. pylori* treatment, based on 3 epidemiologic studies which evaluated the effect on precancerous lesions or gastric cancer incidence after 5–7.5 years,[8,18,36] we assumed that effectiveness depended on the absence of advanced precancerous lesions and reduced the probabilities of disease progression for individuals with gastritis and atrophy as described above. To estimate the magnitude of effect, we calibrated the transition probabilities between gastritis and atrophy to fit intention-to-treat post-treatment data on the prevalence of gastritis and atrophy from a clinical study in Linqu, China (see Supplementary Appendix for additional details).[36] In sensitivity analysis, as the clinical evidence for atrophy regression after treatment is less conclusive,[25] we limited treatment effect to individuals with gastritis. Because the estimate of treatment effectiveness was specific to the amoxicillin and omeprazole regimen used in the Linqu clinical study, we varied the relative risk of progression to atrophy over a wide range uniformly across all parameter sets to provide insight on other treatments for which no empirical data are available.

Other clinical data, including test characteristics of *H. pylori* diagnostic tests,[33-35] 5-year gastric cancer survival rate,[29-31] all-cause mortality rates[32] and health-related quality of life associated with symptomatic cancer[46] were obtained from the published literature. Quality-adjusted life years (QALYs) were age- and sex-specific to China.[45]

Cost data

Direct medical costs were based on the treatment protocol of the clinical study in Linqu, China[36] and estimated from a comprehensive review of published cost-effectiveness studies, cost studies and national and international databases (Table I). We utilized a quantity-and-price approach for costing, in which quantities of each input and cost per input were estimated and

total cost was then computed by multiplying price per unit and number of units per service to calculate price per service. Direct medical costs included costs for outpatient visits,[37] *H. pylori* diagnostic tests,[33,37-40] anti-*H. pylori* antibiotic treatment[8,36,41,42] and gastric cancer treatment.[33,37,43,44] Costs were based on World Health Organization (WHO) regional estimates for outpatient visits,[37] published estimates for diagnosis test and gastric cancer treatment costs,[33] and an international drug price indicator guide,[41] adjusted upwards to reflect transportation costs associated with tradable goods,[42] for antibiotic costs.

We assumed that (*i*) screening entailed an initial outpatient visit and *H. pylori* serology test, anti-*H. pylori* antibiotic treatment for test positive results, a follow-up visit to evaluate treatment success with a C^{13} urea breath test, and re-treatment for test positive results; (*ii*) universal treatment included an initial outpatient visit and anti-*H. pylori* antibiotic treatment, a follow-up visit with a C^{13} urea breath test to confirm treatment success, and retreatment for test positive results and (*iii*) gastric cancer treatment consisted of an initial surgery with hospitalization and 2 years of outpatient care. On the basis of expert opinion, we assumed program-related costs for each strategy were equivalent to 25% of initial outpatient visit and serology test costs. Details on the plausible range used for each cost in sensitivity analyses are described in the Supplementary Appendix. Sensitivity analyses also explored the impact of alternative discount rates and inclusion of indirect patient time costs.

Because our analysis is intended to inform decision making within China and to primarily compare different strategic approaches to screening (as opposed to broad international comparison of the cost-effectiveness of gastric cancer prevention between countries), we do not express results in international dollars. Costs in Chinese Yuan were adjusted to 2005 for inflation using the country-specific consumer price index (CPI) and then converted to US dollars.[47] Results in international dollars are available from the authors upon request.

Results

Calibration results

The majority of model output for men from the random subset of 50 good-fitting parameter sets fell within the 95% confidence intervals of the epidemiological data on age-specific prevalence of precancerous lesions and incidence of gastric cancer (Fig. 2). Overall results for women were similar although showed lower rates of dysplasia (see Supplementary Appendix).

Reduction in lifetime risk of gastric cancer

Among a cohort of 20-year-old men with a *H. pylori* seroprevalence of 70%, a single screening at age 20 was estimated to reduce the lifetime risk for intestinal type gastric cancer by a mean of 14.5% (Table II). Strategies which employed 1 and 2 opportunities for rescreening individuals who tested negative during their initial screen provided little incremental benefit. Universal *H. pylori* treatment at age 20 reduced lifetime risk by 16.1%. Results for women were similar although the mean reduction was greater (26.6–29.5%), reflecting the higher proportion who had gastritis or atrophy and benefited from treatment.

Cost-effectiveness of *H. pylori* screening and treatment

Cost-effectiveness results are shown in Table II for a 20-year-old cohort. In the absence of *H. pylori* screening or treatment, the discounted per-person average lifetime cost was $19 and the discounted average life expectancy was 25.8015 years. Screening once at age 20 provided a mean reduction of 14.5% in the lifetime risk of gastric cancer, providing an average increase in life expectancy of 3.2 days and an increase in lifetime costs of $12. The incremental cost-effectiveness ratio (ICER) was $1,340/YLS compared to no screening. Universal treatment dominated strategies that included rescreening in that they were less costly and less cost-

effective (extended dominance), or more costly and less effective (strong dominance). Results in which life expectancy was quality-adjusted were similar, with an ICER of $1,560 per QALY for screening once and $3,250 per QALY for universal treatment. The ranking of strategies, incremental costs and ICERs (screening once = $1,230/LYS; universal treatment = $2,510/LYS) were comparable for women. There is no universal criterion that defines a threshold about which an intervention would be considered cost-effective (or good value for money). One heuristic that has evolved from the Commission on Macroeconomics and Health suggests that interventions with ICERs less than 3-times the GDP per capita ($5,400 in China) are "cost-effective" and less than 1-times GDP per capita ($1,700) to be cost-effective.[48] At the 1-times GDP per capita threshold, screening 20-year olds for *H. pylori*, and treating those who test positive, would be considered very cost-effective for both men and women. (Of note, cost-effectiveness analysis does not provide insight into affordability. There are many interventions that would be considered good value for money but are not affordable).

Sensitivity analyses

Univariate sensitivity analyses showed that results were stable despite varying in the base case values for *H. pylori* serology test characteristics, medical costs for outpatient visits and gastric cancer treatment and program costs (Fig. 3). Results were most sensitive to *H. pylori* diagnostic test costs, antibiotic costs, *H. pylori* seroprevalence and treatment effectiveness. Rank ordering of strategies and general results were robust despite discount rates of 6% and inclusion of patient time costs. *H. pylori* screening was less effective and cost-effective for older cohorts ranging from 30 to 60 years of age (Table III). For all cohorts, screening or treatment at the youngest age was more cost-effective than all other strategies. When new infection and reinfection rates after treatment of 1% per year were included, results were similar for screening once ($1,540–1,600/LYS), although universal treatment was dominated by strategies that included rescreening.

We also found results were insensitive to assumptions about the proportion of gastric cancers related to *H. pylori*, screening participation rates and alternative *H. pylori* treatment and detecting protocols. For example, if a lower cost, lower specificity *H. pylori* stool test was used to confirm post treatment eradication, ICERs for screening once ($950–1,040/LYS) and universal treatment remained similar ($1,240–1,350/LYS). Results varied by time interval between rescreening opportunities and *H. pylori* diagnostic test characteristics. Shorter 1-year intervals increased the incremental cancer incidence reduction compared with screening once by 20%. Although our base case false negative rate (FNR) of 10% resulted in only a 10.3% increase in cancer reduction compared to a single screen, at a FNR of 30%, strategies that included rescreening increased the cancer reduction by 37.5%. Despite this greater benefit, these strategies were still more costly and less effective or less costly and less cost-effective than universal treatment, and the ICER associated with the preemptive strategy became more attractive ($1,480/YLS).

To reflect the geographical variation in *H. pylori* seroprevalence in China, we identified the optimal strategy for a given seroprevalence and cost-effectiveness threshold (Fig. 4). Given the 1-times the GDP per capita cost-effectiveness threshold, *H. pylori* screening or universal treatment was the preferred strategy for seroprevalence levels greater than 40%.

To further access the uncertainty around treatment effectiveness among men, we conducted a series of scenario analyses in which *H. pylori* treatment affected disease progression for gastritis only (*i.e*. no effect on atrophy). Under this assumption, the mean reduction in gastric cancer incidence was 29% lower, and the ICER moderately increased to $1,990/LYS. When we varied the relative risk of progressing to atrophy uniformly for all parameter sets, the mean reduction in gastric cancer incidence ranged from 3% to 42% depending on whether treatment reduced the risk of progressing to atrophy by 20% (relative risk = 0.8) or halted progression

entirely (relative risk = 0; Fig. 5). Figure 6 shows that if treatment reduced disease progression rate by 60–70% (relative risk = 0.3–0.4), screening once would be considered cost-effective given the 1-times GDP per capita threshold, even if antibiotic costs increased by 3-fold from $4 to $13.

Discussion

Currently, clinical guidelines do not recommend screening for *H. pylori* in asymptomatic individuals.[49-53] Our results suggest that *H. pylori* screening and treatment has the potential to significantly reduce gastric cancer incidence among both men and women, and there appear to be strategies that would be considered cost-effective in China. Reductions were greatest when screening occurred at age 20, suggesting that *H. pylori* prevention efforts should target younger age groups. This policy-relevant result presents an interesting contrast to the older age groups who are the focus of on-going *H. pylori* clinical trials and from which results are awaited.[7] We also found that opportunities for rescreening did not provide substantial additional benefit provided the false-negative rate of serological screening was less than 15%. The reduction in gastric cancer risk was greater among women than men, reflecting the higher proportion with gastritis or atrophy who benefited from treatment.

Using a cost-effectiveness threshold of the GDP per capita ($1,700 in China), we found screening for *H. pylori* at age 20 would be considered very cost-effective for both men and women. For cohorts of all ages, screening or treatment at the youngest age was more cost-effective than all other strategies. For example, for a cohort of 20-year olds, delaying screening for 10 or 20 years *versus* beginning screening at age 20 was not only less effective, but more costly, as at older ages, a greater proportion of the cohort had progressed to more advanced precancerous lesions and did not benefit from *H. pylori* treatment as a result.

Given a specific cost-effectiveness threshold, we found that the optimal strategy was influenced by the underlying seroprevalence of *H. pylori* infection. This could be particularly important for establishing regional priorities within China because there is geographical variation of *H. pylori* seroprevalence.[54,55] At the GDP per capita threshold, *H. pylori* screening once would be optimal in regions where *H. pylori* seroprevalence was between 40 and 80%; in regions where more than 80% were infected, universal treatment would be the preferred strategy. Because we did not include the consequences of antibiotic resistance and treatment side-effects, the threshold for universal treatment may be higher, although studies have consistently found rates of amoxicillin-resistant *H. pylori* equal to less than 1%[56] and our results did not significantly change when we assumed treatment for side-effects increased antibiotic costs by 50%. As the emergence of resistant strains would adversely impact the efficacy of *H. pylori* treatment regimens, as well as antibiotic efficacy against other infections, efforts to minimize noncompliance should accompany all screening strategies.

From a public health perspective, screening for *H. pylori* is particularly attractive. Because reinfection in adulthood is rare, once treated, individuals do not need to be rescreened or retreated. This differs with prevention programs for other cancers such as breast, colon and cervical, which rely on routine screening to detect precancerous or cancerous growths or lifestyle changes that require continual modification of diet, exercise or smoking habits to achieve significant reductions in cancer risk. For example, *H. pylori* screening once would result in an average life expectancy gain of 17.0 days which is 2 to 4 times greater than the estimated 4.3–9.4 days achieved with biennial mammography screening to prevent breast cancer among Hong Kong Chinese women.[57] In addition, *H. pylori* screening is appealing because of the low false-negative risk associated with the high sensitivity of serology tests available to detect the infection. Although test specificity may be lower, the consequences of false-positives are small given the low cost of antibiotic treatment and occurrence of adverse

side-effects. For example, even at a 30% false positive rate, the ICER of *H. pylori* screening increased only to $1,440/YLS.

Adherence to the 14-day antibiotic regimen is critical to the effectiveness of an *H. pylori* screening program. More convenient and tolerable, shorter duration regimens with comparable eradication rates may improve patient adherence and minimize the emergence of antibiotic resistance from incomplete treatment. Although we reflected compliance rates of the clinical trial, real world rates are likely to be lower. By lowering treatment effectiveness by 25% to estimate the impact of lower compliance and adherence rates, we found that the cost-effectiveness of a single *H. pylori* screening would still be considered good value for resources given the GDP per capita threshold. However, if real world screening participation rates are lower than 70% or the per-person cost of *H. pylori* screening is $2 to $3 higher, universal treatment would be a strategy to seriously consider, even in medium-prevalence regions, although these thresholds are likely conservative as costs associated with consequences of treatment (*i.e*., antibiotic resistance and side-effects) were not included in our analyses.

Our findings are consistent with previous cost-effectiveness analyses that suggest *H. pylori* screening is cost-effective in both relatively low-risk populations in the US and UK ($10,000–$40,000/YLS)[58-62] and high-risk populations in China or Taiwan ($200–$17,000/YLS).[33, 63] In contrast to previous models, we based treatment effectiveness on empirical data from an ongoing randomized clinical trial which showed *H. pylori* treatment reduced the prevalence precancerous gastric lesions.[36] In addition, because we modeled gastric cancer development through a series of precancerous lesions, we were able to evaluate alternative assumptions on treatment impact. Although the ability of *H. pylori* treatment to heal gastritis and halt progression to precancerous lesions is well-supported by clinical evidence, the impact on regression is still debated.[25] If treatment only reduced disease progression among individuals with gastritis, we found that screening once for *H. pylori* could still reduce the risk of gastric cancer among young adults by more than 10%. Specific to a low-efficacy dual therapy regimen no longer considered a choice of treatment,[64] our estimate likely provides a lower bound estimate upon which higher-efficacy triple therapies can improve upon.

We also reflected in our model the impact of disease natural history uncertainty on outcomes by using an array of natural history parameters that provide a good fit to observed epidemiologic data. Although we estimated that screening once for *H. pylori* could significantly reduce cancer risk, we found that estimates of the absolute magnitude of benefit varied considerably when we explicitly considered the underlying uncertainty around disease progression and regression, highlighting the need for more data. As ongoing clinical trials are focused on older age groups, future clinical trials on younger adults are needed, with specific attention to the presence of precancerous lesions at time of treatment and high-efficacy, well-tolerated regimens that can achieve high compliance rates and minimize the emergence of antibiotic resistance. Given the need to follow large numbers of individuals for several years or decades, these trials will take many years to complete. In the short term, clinical trials with intermediate outcomes as their primary endpoints, such as the progression to atrophy or intestinal metaplasia, can provide valuable information on the effectiveness of *H. pylori* treatment. Our model suggests that if treatment reduces the risk of progression to atrophy by more than 40%, *H. pylori* screening once could be an effective and cost-effective gastric cancer prevention policy. Empirical data, especially on gastritis, from large, well-designed, randomized controlled trials should be high-priority. In addition, studies providing better estimates of disease progression rates for all precancerous lesions can reduce the uncertainty around disease natural history and provide insight into the management of advanced precancerous lesions, such as intestinal metaplasia, for which *H. pylori* treatment is unlikely to benefit and surveillance guidelines are currently unavailable.

Our analysis has several limitations. Data were combined from multiple sources with varied study designs, and many variables are uncertain. On the basis of the data from prospective cohort studies, we assumed that all lesions are reversible, though at some point in the precancerous process, this may no longer be biologically possible.[20,65] Although a proportion of the regression observed in the prospective cohort studies may stem from low biopsy sensitivity for advanced lesions and histological misclassification, data on the precise proportion attributable are unavailable. Similarly, although some clinical studies suggest that *H. pylori* treatment may reduce disease progression among individuals with intestinal metaplasia, we conservatively assumed that lesions beyond atrophy do not benefit from treatment. As China-specific data on the proportion of intestinal type gastric cancers were unavailable, we also relied on data from Sweden. Because the incidence of intestinal type gastric cancers has declined more rapidly in developed countries, we may have therefore underestimated the proportion.[66] All of these assumptions bias our results against treatment effect.

In addition, we included only the benefit of treatment on intestinal type gastric cancer reduction. *H. pylori* treatment may also reduce the risk of MALT lymphomas,[67] duodenal ulcers,[68] and dyspepsia-related illness,[69] and thus, our analysis does not reflect these health gains or treatment cost reductions that may result from the reduction of these diseases. Although *H. pylori* infection may protect against cardia or esophageal adenocarcinomas, the causal link is still uncertain and was not incorporated into our model.[70] Finally, our results are based on data from one specific region in China and may not be generalized to other regions where disease progression may differ given the prevalence of other risk factors. Nonetheless, *H. pylori* is the leading risk factor for gastric cancer and the relative risk associated with the infection (5.9)[2] is three- to four-fold higher than other important risk factors, including smoking (1.5-2.2).[71] As such, our results likely provide reasonable estimates of the comparative benefits and economic consequences of *H. pylori* screening in other regions of China, as well as other countries, that share similar risk factor profiles to Linqu.

Screening young adults for *H. pylori*, followed by treatment in those who test positive, has the potential to prevent 1 in every 4 to 6 cases of gastric cancer in China, and would be considered cost-effective using the GDP per capita threshold. Although additional criteria such as affordability, capacity to deliver and equity are equally influential and important to consider, these results clearly illustrate the potential promise of gastric cancer prevention. Given the ease of detecting and treating *H. pylori* infection and the poor prognosis and limited treatment options for gastric cancer, better data on the effectiveness of treatment to reduce disease progression are needed while results from ongoing clinical trials are eagerly awaited.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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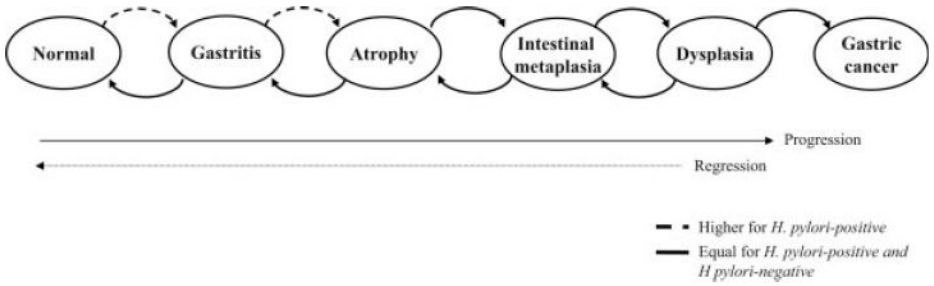

Figure 1.

Model structure of gastric cancer natural history. The model simulates the natural history of gastric carcinogenesis through a series of health states (normal gastric mucosa, chronic nonatrophic gastritis, gastric atrophy, intestinal metaplasia, dysplasia and gastric cancer). Each month, individuals can progress and regress among the health states and face age-dependent risks of dying from other causes. *H. pylori*-infected individuals face higher probabilities of progressing to gastritis and atrophy. Not shown are unique health states, which were defined to distinguish individuals with *H. pylori* infection and gastric cancer detected through symptoms, and the dead state.

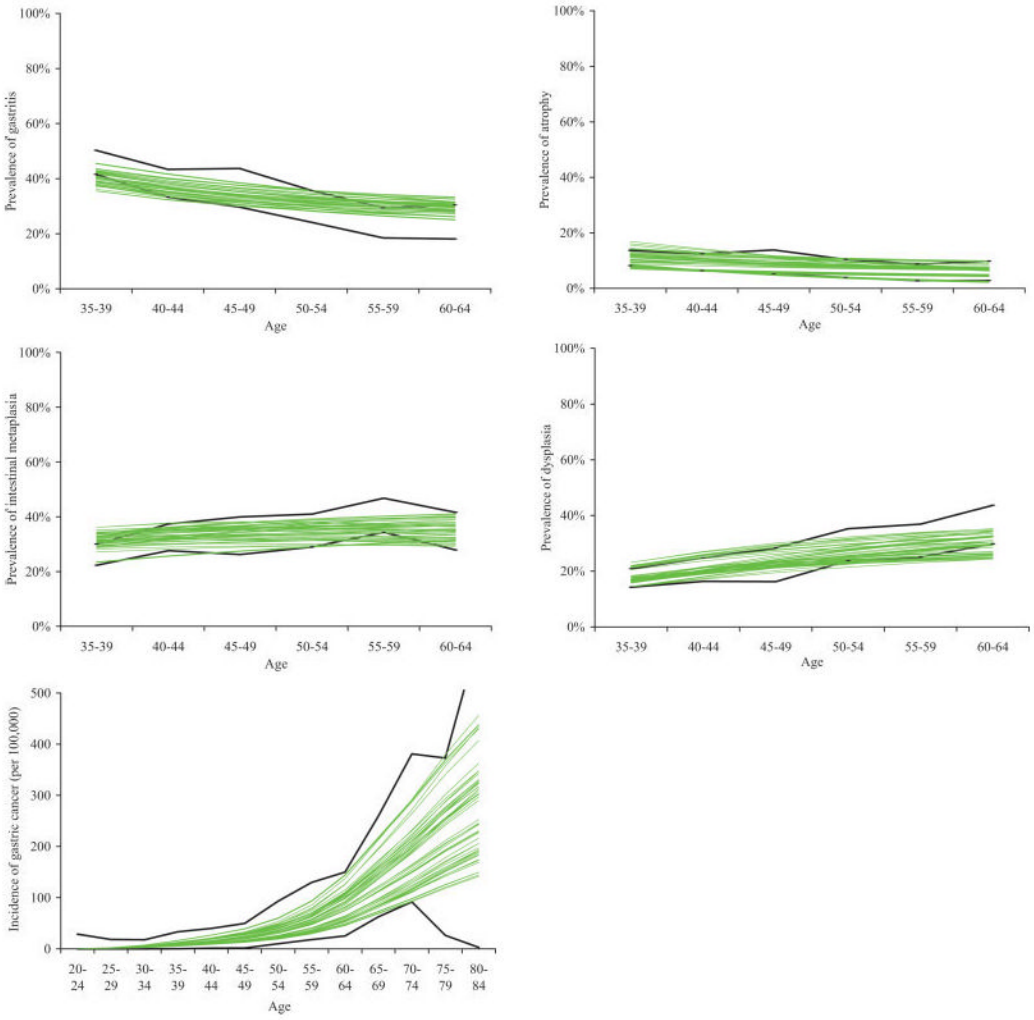

Figure 2.

Comparison of model output to epidemiologic data on prevalence of precancerous lesions and gastric cancer incidence for 50 good-fitting parameter sets for men. Model output for precancerous lesions prevalence are depicted in the top rows and for gastric cancer incidence in the bottom row. Bold lines indicate 95% confidence intervals of age-specific prevalence or incidence data. Non-bold lines depict model output for 50 randomly-selected good-fitting parameter sets. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

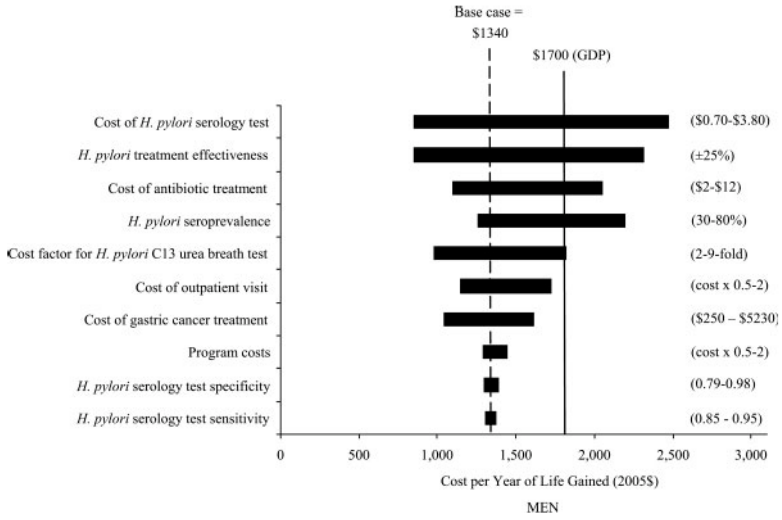

Figure 3.

Sensitivity analysis on select variables for men. The *X*-axis shows the effect of changes in selected variables on the incremental cost-effectiveness ratio ($/YLS) for *H. pylori* screening once among men. The *Y*-axis shows the selected model variables. Values in parentheses are the upper and lower bounds used in the sensitivity analysis; the shaded bars indicate the variation in the cost-effectiveness ratio caused by changes in the value of the indicated variable while all other variables were held constant. The vertical dashed line indicates the incremental cost-effectiveness ratio for the base case. The solid line indicates an implied cost-effectiveness threshold using the gross domestic product (GDP) per capita in China.

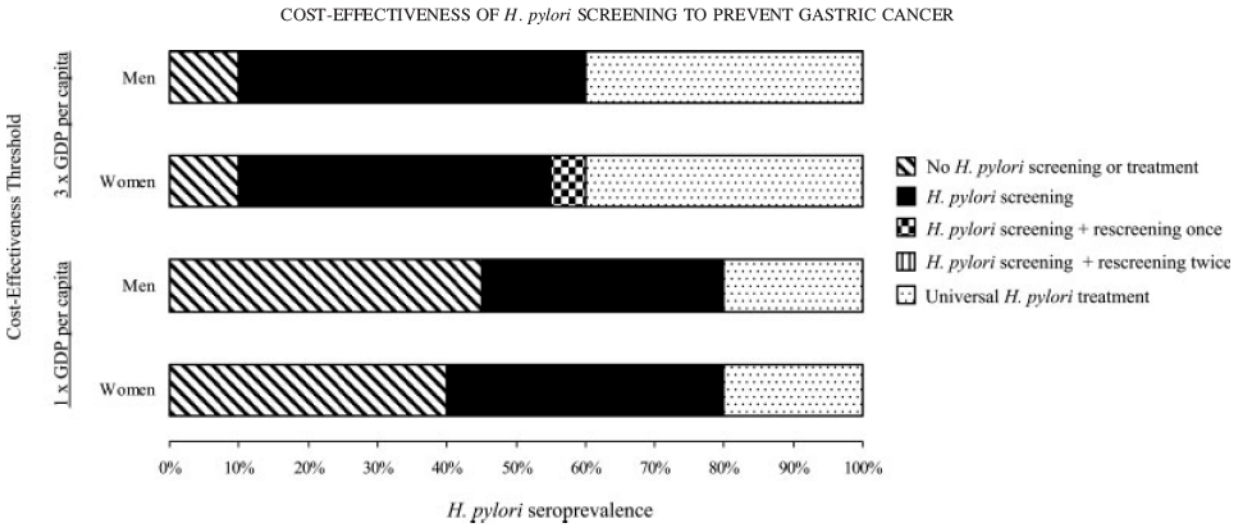

Figure 4.

Optimal strategy by cost-effectiveness threshold and *H. pylori* seroprevalence. Top 2 graphs depict optimal strategy for men and women given the 3-times the GDP per capita cost-effectiveness threshold ($5,400). Lower 2 graphs depict optimal strategy given the 1-times GDP per capita threshold ($1,700).

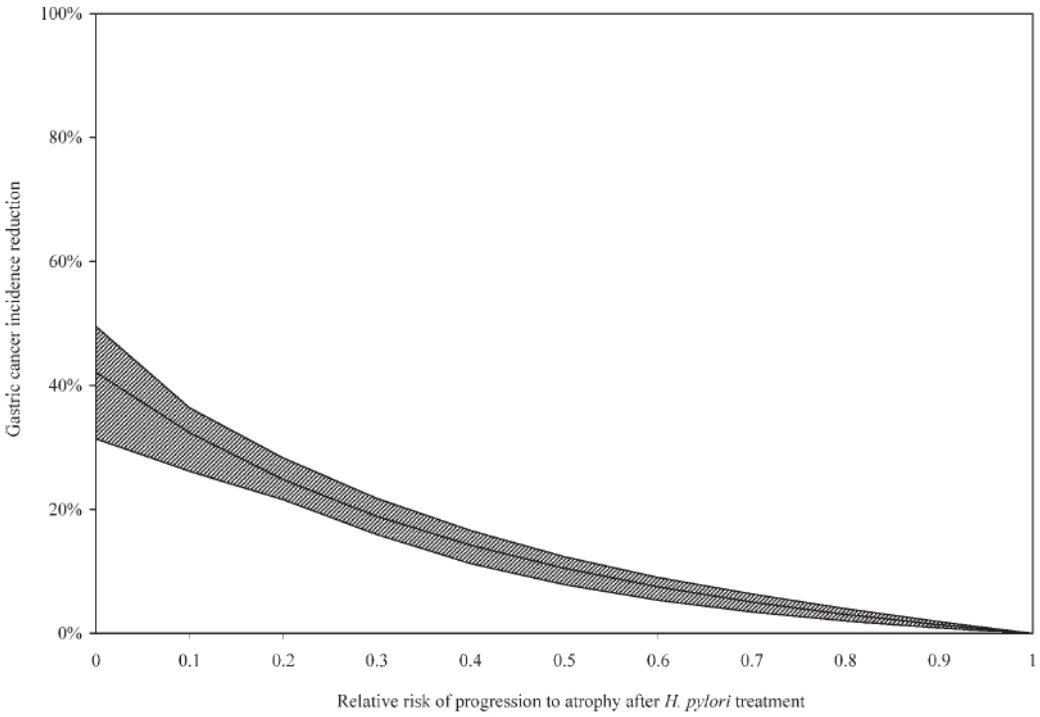

Figure 5.

Sensitivity analysis on treatment effectiveness for gastritis. If treatment for *H. pylori* reduced disease progression for gastritis only (*i.e*. no effect on atrophy), the mean reduction in gastric cancer incidence ranged from 0% (RR = 1; no effect) to 42% (RR = 0; halt progression entirely). Solid line indicates the mean reduction among 50 good-fitting parameter sets. Shaded area indicates the range.

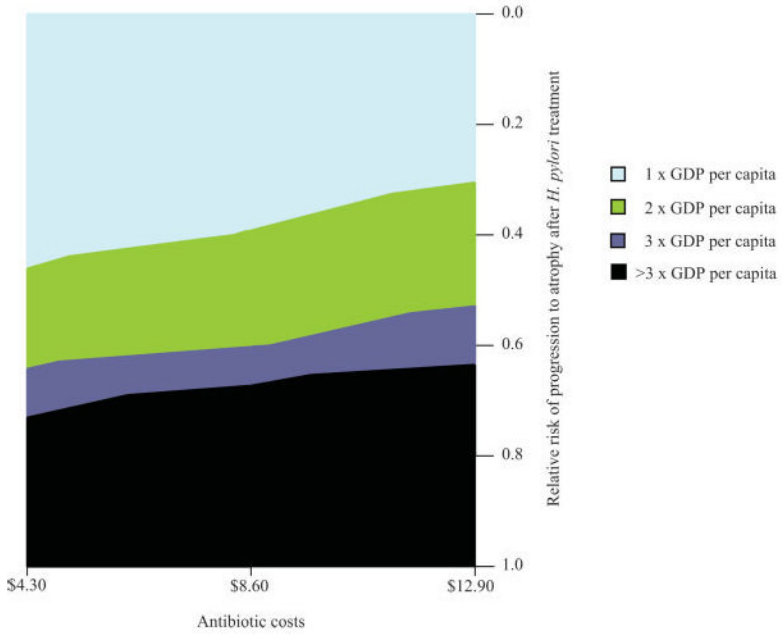

Figure 6.

Two-way sensitivity analysis on treatment effectiveness and cost. *H. pylori* screening once would be considered cost-effective given commonly-used thresholds if treatment reduced disease progression to atrophy by more than 40% (RR = 0.6), even if antibiotic costs were 3-fold higher than base case estimates. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

TABLE I

MODEL VARIABLES: BASELINE VALUES AND RANGES USED IN SENSITIVITY ANALYSIS

Variable	Base case	Range	Reference
H. pylori and precancerous lesions prevalence			
H. pylori seroprevalence (%)	70	30–80	26, 27
Baseline prevalence at age 20 (%)			
Gastritis	65	—	28
Atrophy	18	—	28
Intestinal metaplasia	12	—	28
Dysplasia	5	—	28
Clinical			
Invasive cancer to symptomatic cancer[1]	0.25	0.2–0.3	[2]
Five-year gastric cancer survival rate (%)	20	18–23	29–31
Monthly all-cause mortality rate	0.0001–0.0469[3]	—	32
Screening and treatment			
H. pylori diagnostic test characteristics (%)			
Serology test			
Sensitivity	90	85–95	33–35
Specificity	90	79–98	33–35
C^{13} urea breath test			
Sensitivity	95	92–98	35
Specificity	95	94–99	35
Treatment effectiveness[4]			
Relative risk of progression to atrophy	0.1–0.7	[5]	8, 18, 36
Relative risk of regression to gastritis	2.0–2.4	[5]	8, 18, 36
Direct medical costs, US $ (2005)[6]			
Outpatient visit	1.8	0.9–3.5	37
H. pylori serology test	1.6	0.7–3.8	33, 37–40
H. pylori C^{13} urea breath test	8.0	3.2–14.5	37, 39
Antibiotic treatment for *H. pylori*	4.3	2.0–12.0	8, 36, 41, 42
Gastric cancer treatment	2615	250–5230	33, 37, 43, 44
Program costs (%)[7]	25.0	12.5–50.0	[2]
Quality of life, weights			
Normal gastric mucosa	0.566–0.945	[3]	45
Gastritis	0.566–0.945	[3]	45
Atrophy	0.566–0.945	[3]	45
Intestinal metaplasia	0.566–0.945	[3]	45
Dysplasia	0.566–0.945	[3]	45
Symptomatic gastric cancer	0.49	0.17–0.79	46

[1] Monthly probability.

[2] Based on expert opinion.

[3] Values are age- and sex-specific.

[4] Values are sex-specific and vary by natural history parameter set.

[5] For sensitivity analysis, base case estimate was varied ±25%.

[6] Unit costs, except where noted. See Supplementary Appendix for details on upper and lower bound estimations.

[7] Percent of initial outpatient visit and serology test costs.

TABLE II

THE COSTS, LIFE EXPECTANCY, AND INCREMENTAL COST-EFFECTIVENESS OF *H. pylori* SCREENING STRATEGIES FOR A 20-YEAR-OLD COHORT

Sex	Strategy	Mean for 50 good-fitting parameter sets (range)				ICERs[1]	
		Gastric cancer incidence reduction, %	Additional undiscounted life expectancy *vs.* no screen or treat, days	Additional discounted life expectancy *vs.* no screen or treat, days	Discounted lifetime costs, $	$ per YLS	$ per QALY
Men	No screen or treatment[2]	—	—	—	18.50 (10.00–31.30)	—	—
	Screen	14.5 (6.5–30.2)	14.1 (11.1–25.0)	3.2 (2.5–5.8)	30.30 (22.40–41.20)	$1,340	$1,560
	Screen + rescreen once	15.6 (7.0–32.5)	15.1 (11.9–26.6)	3.4 (2.7–6.2)	32.50 (24.60–43.30)	Dominated[3]	Dominated[3]
	Universal treatment	16.1 (7.2–33.6)	15.6 (12.3–27.5)	3.6 (2.8–6.4)	32.90 (25.10–43.70)	$2,720	$3,250
	Screen + rescreen twice	15.7 (7.0–32.7)	15.2 (12.0–26.8)	3.4 (2.7–6.2)	33.60 (25.70–44.30)	Dominated	Dominated
Women	No screen or treatment[2]	—	—	—	10.70 (5.50–20.00)	—	—
	Screen	26.6 (12.9–40.0)	17.0 (10.2–33.5)	3.4 (2.0-6.8)	22.30 (18.20–28.90)	$1,230	$1,500
	Screen + rescreen once	28.8 (13.9–43.3)	18.3 (11.0–36.0)	3.7 (2.2–7.2)	24.50 (20.50–30.90)	Dominated[3]	Dominated[3]
	Universal treatment	29.5 (14.3–44.5)	18.9 (11.4–37.2)	3.8 (2.3–7.5)	25.00 (20.90–31.30)	$2,510	$3,060
	Screen+ rescreen twice	28.9 (14.0–43.6)	18.4 (11.1–36.2)	3.7 (2.2–7.3)	25.60 (21.50–32.00)	Dominated	Dominated

[1] Calculated as the ratio of the mean-costs divided by the mean-effects of the 50 good-fitting parameter sets for each strategy compared with the next-best strategy. ICER denotes incremental cost-effectiveness ratio. YLS denotes year of life saved. QALY denotes quality-adjusted life year.

[2] Assumes no screening and cases identified only via symptoms.

[3] Eliminated because of extended dominance: strategies with a higher incremental cost-effectiveness ratio than a more effective alternative strategy.

TABLE III

REDUCTION IN LIFETIME RISK OF GASTRIC CANCER AND COST-EFFECTIVENESS OF *H. pylori* SCREENING STRATEGIES FOR OLDER COHORTS

Cohort age	Gastric cancer incidence reduction, %[1]	Men–ICER ($/YLS)[2]				Gastric cancer incidence reduction, %[1]	Women–ICER ($/YLS)[2]			
		Screen	Screen + rescreen once	Screen + rescreen twice	Universal treatment		Screen	Screen + rescreen once	Screen + rescreen twice	Universal treatment
20	14–16	$1,340	Dominated[3]	Dominated	$2,720	27–30	$1,230	Dominated[3]	Dominated	$2,510
30	9–10	$2,050	Dominated[3]	Dominated	$4,030	18–20	$1,710	Dominated[3]	Dominated	$3,420
40	5–6	$3,940	Dominated[3]	Dominated	$7,530	11–12	$2,790	Dominated[3]	Dominated	$5,460
50	2–3	$9,420	Dominated[3]	Dominated	$19,020	6–7	$5,430	Dominated[3]	Dominated	$10,560
60	1	$30,030	Dominated[3]	Dominated	$60,360	3	$13,680	Dominated[3]	Dominated	$24,290

[1] Range of mean reductions calculated using all 50 good-fitting parameter sets among all *H. pylori* screening strategies.

[2] Calculated as the ratio of the mean-costs divided by the mean-effects of the 50 good-fitting parameter sets for each strategy compared with the next-best strategy. ICER denotes incremental cost-effectiveness ratio. YLS denotes year of life saved.

[3] Eliminated because of extended dominance: strategies with a higher incremental cost-effectiveness ratio than a more effective alternative strategy.