Cost-Effectiveness of a Potential Prophylactic Helicobacter pylori Vaccine in the United States

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Background. Helicobacter pylori vaccines are under development to prevent infection. We quantified the cost-effectiveness of such a vaccine in the United States, using a dynamic transmission model.

Methods. We compartmentalized the population by age, infection status, and clinical disease state and measured effectiveness in quality-adjusted life years (QALYs). We simulated no intervention, vaccination of infants, and vaccination of school-age children. Variables included costs of vaccine, vaccine administration, and gastric cancer treatment (in 2007 US dollars), vaccine efficacy, quality adjustment due to gastric cancer, and discount rate. We evaluated possible outcomes for periods of 10–75 years.

Results. H. pylori vaccination of infants would cost $2.9 billion over 10 years; savings from cancer prevention would be realized decades later. Over a long time horizon (75 years), incremental costs of H. pylori vaccination would be $1.8 billion, and incremental QALYs would be 0.5 million, yielding a cost-effectiveness ratio of $3871/QALY. With school-age vaccination, the cost-effectiveness ratio would be $22,137/QALY. With time limited to <40 years, the cost-effectiveness ratio exceeded $50,000/QALY.

Conclusion. When evaluated with a time horizon beyond 40 years, the use of a prophylactic H. pylori vaccine was cost-effective in the United States, especially with infant vaccination.

Helicobacter pylori, one of the most common human bacterial pathogens, causes duodenal and gastric ulcers, gastric cancer, and gastric mucosa–associated lymphoid tissue (MALT) lymphoma [1]. There is strong evidence to support antimicrobial treatment of H. pylori in patients who have ulcer disease, uninvestigated dyspepsia in populations with a high prevalence of ulcer disease, or gastric MALT lymphoma and in those who have undergone resection of early gastric cancer [1–3]. Treatment of H. pylori to prevent gastric cancer, however, remains controversial. Today, numerous antimicrobial therapies against H. pylori are available, some with success rates of >90% [4]. Current antimicrobial therapies, however, are complicated and demanding, causing serious side effects in a subset of patients, thereby reducing patient compliance and the overall efficacy of treatment [5, 6]. Moreover, increasing antibiotic resistance may ultimately limit the use of antibiotics [7, 8]. Because of these issues, as well as the lack of evidence that cure of established infections prevents cancer [1, 9], screening and treatment at a population level have not, to our knowledge, been instituted anywhere in the world. A prophylactic vaccine, on the other hand, would obviate many treatment concerns and could be an attractive strategy to control H. pylori infections.

In previous studies, we estimated the future trends of H. pylori and associated gastric cancer and ulcer disease based on natural history with or without prophylactic H. pylori vaccination of infants [10, 11]. These predictions were based on a dynamic transmission model that simulated the infection and disease progression process in the population. We concluded that in the United States, H. pylori and associated diseases would continue to decrease in the 21st century without mass intervention. If infants received prophylactic vaccine, the decrease would be accelerated enough to eradicate the organism by the next century. Because
of the decreasing incidence of *H. pylori* infection in developed
countries, a 10-year vaccination program would achieve almost
the same benefit as a vaccination effort extending beyond 10
years.

In 2000, the Institute of Medicine evaluated numerous vac-
cine candidates for cost-effectiveness (CE) by using a static
model. It concluded that *H. pylori* was a good candidate for
vaccine development [12]. In our present analysis, we added
to the static Institute of Medicine model by estimating the CE
of a prophylactic *H. pylori* vaccine with a dynamic transmission
model that reflects changing epidemiology of the pathogen over
time.

**METHODS**

**Model description and input assumptions.** The CE analysis
was based on a dynamic compartmental model that captures
the age dependence of *H. pylori* infection and disease progres-
sion in infected individuals (Figure 1). The dynamic compart-
mental model simulates the movement of population across
different health states based on transition probabilities. In this
model, the population is divided according to 3 characteristics:
(1) age, including children (0–4 years old), youth (5–14 years
old), and adults (>=15 years old); (2) infection state, including
uninfected (susceptible and nonsusceptible) and infected (gas-
tritis and subsequent clinical conditions); and (3) disease state,
including normal stomach, antrum-predominant gastritis (AG),
corpus-predominant gastritis (CG), duodenal ulcer (DU), chronic
atrophic gastritis (CAG), and gastric cancer. We excluded from
the model DU and gastric cancer not related to *H. pylori*. Math-
ematical equations governing the transition from one compart-
ment to the other are described in the Appendix. Computer
simulation was used to solve the system of equations and calculate
the flow of individuals numerically, and thus determined the
number of persons in each compartment at each time point.

The structure of the model and epidemiological assumptions
are discussed in detail elsewhere [10, 11]. The incidence of *H.
pylori* infection was calculated as a function of the number of
susceptible and infected persons in the population. The model
assumed that 20% of the population would not be susceptible
to infection. This assumption was based on data from *H. pylori–*
endemic countries showing that some individuals do not be-
come infected at all, despite probable exposure [13, 14]. We
assumed that vaccination would offer lifetime protection.

Transmission of *H. pylori* was modeled using 9 transmission

![Figure 1. Compartemental model of *Helicobacter pylori* transmission and disease progression.](image)
parameters, according to the age groups of infected and susceptible persons. We assumed that *H. pylori* acquisition would be most rapid for younger persons (age, <5 years) and that transmission among children would be 5–10 times higher than among adults. We assumed that transmission between age groups would be negligible compared with transmission within an age group and that patients with gastric cancer were a negligible source of *H. pylori* infection.

In the model, a susceptible person could become infected with *H. pylori* at any age and develop either AG or CG. We assumed that earlier acquisition of *H. pylori* is associated with development of CG, gastric ulcer (GU), and gastric cancer and that acquisition at older ages is more likely to lead to AG and subsequent DU. The rates of clinical progression from gastritis to cancer were derived from published information, as follows: 14% progression from AG to DU in 32 years [15], 2% progression from DU to CAG in 10 years [16], 30% progression from CG to CAG in 32 years [15], and 3% progression from CAG to gastric cancer in 10 years [17].

Table 1 lists the costs and vaccine inputs and ranges used in the model. Costs of treatment of gastric cancer were derived from published studies. For the base-case analysis, we adopted $122 for the cost of a course of vaccine; this estimate was based on assessment by experts involved in vaccine development (A. Lee and T. Monath, personal communication). We used $61 for vaccine administration, which was based on the cost of a primary care physician visit. We assumed that costs from vaccine side effects would be negligible, based on costs incurred by other vaccines in use in the United States; the highest cost from side effects is <$1 million per 1 million vaccinees (therefore, <$1 per vaccinee) [22]. We used the inflation rate based on the gross domestic product deflator to express all costs in 2007 US dollars. Furthermore, we discounted all future costs and benefits to the reference year of 2007 and used a 3% annual rate.

The efficacy of a prophylactic vaccine is unknown. In our base-case analyses, we assumed that vaccination efficacy was 80% on the basis of input from vaccine developers. Because these estimates are uncertain, we used a wide range of values for the sensitivity analyses. Furthermore, we assumed that the coverage of a new vaccine would ramp up according to the Gompertz diffusion model, from 20% in the second year to 65% in the fourth year, increasing to a maximum of 80% [11].

In the present study, we considered only the cost of gastric cancer, because it has a high case-fatality rate. DUs, on the other hand, can be cured successfully with relatively inexpensive antibiotic therapies; for DU alone, it is unlikely that mass vaccination would be less expensive than treatment of ulcers. However, if our results indicated that *H. pylori* vaccination was cost-effective for preventing gastric cancer, they could be assumed to underestimate the true CE, because benefits would also be realized from the prevention of DUs, dyspepsia, and MALT lymphoma, without additional costs. If, on the other hand, we found that prophylactic *H. pylori* vaccine was not cost-effective for gastric cancer prevention, further investigation and analysis of the costs and benefits of vaccine for peptic ulcer disease would be required. Specifically, we would need to know whether there was an added benefit to vaccinating the entire population in lieu of using antibiotics to treat the small subset with ulcer disease. We analyzed vaccination programs for 2 target populations in the United States: (1) infants and (2) school-age children. Because our disease incidence model [11] indicated that incident cases of *H. pylori* were reduced to very low levels with 10 years of vaccination, we assumed in both cases that the vaccination program would start in year 2010 and would be halted after 10 years.

**Model implementation.** The implementation of models for

<table>
<thead>
<tr>
<th>Variable (symbol)</th>
<th>Base</th>
<th>Range</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cost parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per-person cost of a course of vaccine, $</td>
<td>122</td>
<td>25–367</td>
<td>Assumption&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Per-person cost of administration of vaccine, $</td>
<td>61</td>
<td>18–98</td>
<td>[18–21]&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Per-person average cost of vaccine side effects, $</td>
<td>0</td>
<td>0–12</td>
<td>[22]&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Per-patient average annual cost of gastric cancer, $1000</td>
<td>70</td>
<td>12–98</td>
<td>[18]</td>
</tr>
<tr>
<td><strong>Vaccine and other parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy of vaccine, %</td>
<td>80</td>
<td>20–100</td>
<td>Assumption</td>
</tr>
<tr>
<td>Quality adjustment due to chronic atrophic gastritis</td>
<td>0.95</td>
<td>0.8–1</td>
<td>Assumption</td>
</tr>
<tr>
<td>Quality adjustment due to gastric cancer</td>
<td>0.3</td>
<td>0.3–0.8</td>
<td>[23, 24]</td>
</tr>
<tr>
<td>Inflation rate, %</td>
<td>3</td>
<td>0–7</td>
<td>[25, 26]</td>
</tr>
<tr>
<td>Discount rate, %</td>
<td>3</td>
<td>0–7</td>
<td>[25, 26]</td>
</tr>
</tbody>
</table>

<sup>a</sup> A. Lee and T. Monath, personal communication.

<sup>b</sup> Primary care physician visit.

<sup>c</sup> Based on studies of other vaccines.
CE analysis consisted of adding costs and effectiveness parameters to the basic transmission dynamics models, both with and without the vaccination program. Simulations were performed in Powersim models (Powersim Constructor, version 2.5; Powersim Corporation), and data (total costs and quality-adjusted life years [QALYs]) were transferred to an Excel 97 spreadsheet (Microsoft). The spreadsheet stored the results for different simulation scenarios (sensitivity analyses) and facilitated the generation of base-case CE graphs, as well as several 2-way sensitivity graphs.

RESULTS

Effect of a prophylactic vaccine for infants in the United States.

The total annual cost of population-wide infant vaccination in the United States would follow a curve similar to that of vaccine coverage. Cost would be <$200 million (in absolute terms) in the first 3 years because coverage would be low. As more and more infants receive the vaccine, cost would increase to $652 million. The total cost of a 10-year vaccination program, when annual costs were discounted at a rate of 3%, amounted to $3.7 billion.

There were considerable but deferred savings from the vaccination program. By decreasing overall H. pylori prevalence, a vaccination program targeting infants would also prevent H. pylori infection in other age groups through herd immunity and decreased transmission. Savings from gastric cancer treatment averted at the population level increased gradually after 12 years from the start of the infant vaccination program, peaked at 74 years, and decreased thereafter. The latter decrease was due to diminishing difference in gastric incidence between the scenarios with vaccine and those without vaccine, in addition to the discounting of future outcomes.

Figure 2 shows the CE ratio of an infant H. pylori vaccination program according to the time horizon of analysis. When the time horizon was limited to <40 years, the CE ratio exceeded $50,000/QALY. When we extended the time horizon to 50 years, the CE ratio dropped to $17,684/QALY. Over the long time horizon of 75 years, the CE ratio was estimated at $3871/QALY.

We performed univariate sensitivity analysis on discount rate and bivariate sensitivity analysis for all other inputs listed in Table 1. H. pylori vaccine was most sensitive to the assumption of discount rate, which was 3% in our base-case analyses. If the discount rate was <1%, infant vaccination would save costs over the long time horizon of 75 years. When we assumed a higher discount rate of 5%, the CE ratio at 75 years was <$15,000/QALY. Even when we assumed the discount rate of 7% (upper limit of the recommended range of 0%–7% [26]), the CE ratio at 75 years was <$50,000/QALY. The efficacy and cost of the vaccine also affected CE outcome. However, even under the least favorable assumptions—use of a vaccine efficacy of 20% and the highest values of cost parameters for vaccine, administration, and side effects (see ranges in Table 1)—the CE ratio was <$50,000/QALY.

Vaccination of school-age children in the United States.

If the target population was school-age children, health and economic gains from gastric cancers prevented would be smaller than in an infant vaccination program, because some children would acquire infection before vaccination and eventually progress to gastric cancer. The CE ratio at 75 years for vaccination at school age was found to be $22,137/QALY, >5-fold higher than for infant vaccination, as shown in Figure 3. The CE ratio would drop to <$50,000/QALY only if the time horizon of analysis exceeded 50 years. In sensitivity analyses of the input parameters listed in Table 1, discount rate, efficacy, and vaccine cost were, again, the most sensitive variables. Although in most scenarios the CE ratio was <$50,000/QALY, in some cases, particularly with low efficacy, the CE ratio exceeded $50,000/QALY.

DISCUSSION

In this study, we found that H. pylori vaccine would be cost-effective in the United States, even though H. pylori is disappearing without any intervention. In the United States, the most cost-effective strategy would be to administer the vaccine to infants. Newborns should receive the vaccine in their first year of life unless it could not be made safe for infants or could not be delivered in conjunction with other vaccines currently recommended for infants. Because the prevalence of H. pylori and incidence of H. pylori-associated gastric cancer are already low and the natural decreasing trend (ie, without intervention) will most likely continue in the next century, a vaccination for 10 years would be enough to achieve the same health benefits as a continuous vaccination program [10]. This result is encouraging from a societal perspective: an intervention strategy limited to a relatively short time frame lowers the economic burden of “investment” in future health. The vaccination strat-
Cost-effectiveness (CE) of a prophylactic *Helicobacter pylori* vaccine administered to school-age children. When the time horizon of analysis was restricted to <50 years, the CE ratio exceeded $50,000 per quality-adjusted life year (QALY); under the base-case assumption, the CE ratio was $22,137/QALY. *H. pylori* vaccine was therefore cost-effective under a wide range of assumptions.

...gery would be different in less developed regions of the world, however, where rates of ongoing transmission of *H. pylori* are high; in these settings, long-term vaccination would be required to prevent malignancy (data not shown).

Nonetheless, a nationwide *H. pylori* vaccination program would be burdensome to the US health care budget unless the vaccine is made available at a lower price. Under the assumption of $122 per course of vaccine, the likely total costs of a vaccination program targeting all infants would be on the order of $3.7 billion distributed over 10 years. To put this in perspective, the US national health expenditure was $2.105 billion in 2006 [27]. Whether $3.7 billion is too much depends on the health priorities and the national budget that the country faces when a vaccine becomes available. In industrialized nations such as Japan, however, where gastric cancer rates are higher, it is likely that a national vaccination program would be even more warranted (data not shown).

Gastric cancer prevention would be difficult to assess in clinical trials of *H. pylori* vaccination. However, surrogate outcomes could be measured in feasible, short-term studies (1–5 years) to support the implementation of a nationwide vaccination program. For example, the incidence and prevalence of *H. pylori* infection could be measured in a sample population that receives the vaccine. Alternatively, serological markers of CAG, such as the ratio of pepsinogen I to pepsinogen II [28, 29], could be examined within 5 years of vaccination. These approaches would not evaluate the ultimate outcome of interest—development of gastric cancer—but would provide useful information about vaccine performance in a real population.

Our analysis understates the benefits of the vaccine because it does not include the prevention of all *H. pylori*-associated diseases, such as peptic ulcers. Including ulcer disease in the model is difficult because treatment often involves over-the-counter remedies, and rates of disease are poorly defined [30–32]. Moreover, treatment of peptic ulcers with antibiotics is currently less expensive than vaccination. The inclusion of benefits from ulcer disease prevention, however, would accelerate the realization of health benefits to a shorter time horizon. Conversely, we also did not include any potential benefits of *H. pylori* infection. In developed countries, these include protection against gastroesophageal reflux disease [33, 34] and esophageal adenocarcinoma [35, 36]. In developing countries, *H. pylori* may also benefit children by enhancing cell-mediated immunity and preventing a spectrum of childhood diseases [37–39]. These latter benefits of *H. pylori* remain speculative, however, and do not yet warrant inclusion [40, 41].

Several investigators have reported their efforts to develop a therapeutic vaccine for *H. pylori*, that is, one that will enhance protective immunity in individuals already infected with the organism [42–45]. This approach might circumvent the development of peptic ulcers in the sizable population that is currently infected. Whether curing or reducing the density of *H. pylori* infection prevents development of gastric cancer remains controversial, however, and this goal may not be achieved through therapeutic vaccination. It is possible that the vaccine could be administered to infected persons too late in the process of carcinogenesis to abort the development of gastric cancer.

Instead, a CE analysis of a therapeutic vaccine would have to consider the benefits of preventing or curing peptic ulcers for which treatments are more affordable than vaccination.

In conclusion, when evaluated with a 40-year time horizon, the use of a prophylactic *H. pylori* vaccine to prevent gastric cancer was estimated to be cost-effective in the United States, especially when the vaccine is administered during infancy. In contrast, a short time horizon, such as 20 years, would not account for most of the cancer cases that would be prevented by a prophylactic vaccine and diminishes CE when gastric cancer is considered alone. Vaccination could be cost-effective in the short term, however, if prevention of peptic ulcer disease is included in the calculation.

**APPENDIX**

The following partial differential equations govern the rate of transition from one compartment to the other:

\[
\frac{\partial I}{\partial t} + \frac{\partial I}{\partial a} = -\mu(a) \cdot R(a, t),
\]

\[
\frac{\partial S}{\partial t} + \frac{\partial S}{\partial a} = -[\lambda_1(a, t) + \lambda_2(a, t) + \mu(a)] \cdot S(a, t),
\]
\[
\frac{\partial \text{AG}}{\partial t} + \frac{\partial \text{AG}}{\partial a} = \lambda_s(a, t) \cdot S(a, t) + [\delta_s(a) + \delta_g(a) + \mu(a)] \cdot \text{AG}(a, t),
\]

\[
\frac{\partial \text{CG}}{\partial t} + \frac{\partial \text{CG}}{\partial a} = \lambda_s(a, t) \cdot S(a, t) - [\delta_s(a) + \mu(a)] \cdot \text{CG}(a, t),
\]

\[
\frac{\partial \text{DU}}{\partial t} + \frac{\partial \text{DU}}{\partial a} = \delta_s(a) \cdot \text{AG}(a, t) - [\delta_s(a) + \mu_{\text{DU}} + \mu(a)] \cdot \text{DU}(a, t),
\]

\[
\frac{\partial \text{CAG}}{\partial t} + \frac{\partial \text{CAG}}{\partial a} = \delta_s(a) \cdot \text{DU}(a, t) + \delta_g(a) \cdot \text{CG}(a, t) - [\delta_s(a) + \mu_{\text{CAG}} + \mu(a)] \cdot \text{CAG}(a, t),
\]

and

\[
\frac{\partial \text{GC}}{\partial t} + \frac{\partial \text{GC}}{\partial a} = \delta_s(a) \cdot \text{CAG}(a, t) - [\mu_{\text{GC}} + \mu(a)] \cdot \text{GC}(a, t),
\]

where

\[
\lambda_s(a, t) = p(a) \cdot \int_0^\infty \beta(a, a') \cdot [\text{AG}(a', t) + \text{CG}(a', t) + \text{DU}(a', t) + \alpha \cdot \text{CAG}(a', t) + \text{GC}(a', t)] da',
\]

and

\[
\lambda_s(a, t) = [1 - p(a)] \cdot \int_0^\infty \beta(a, a') \cdot [\text{AG}(a', t) + \text{CG}(a', t) + \text{DU}(a', t) + \alpha \cdot \text{CAG}(a', t) + \text{GC}(a', t)] da'.
\]

The boundary conditions without vaccine are

\[
I(0, t) = p_t \cdot \Pi,
\]

\[
S(0, t) = (1 - p_t) \cdot \Pi,
\]

and

\[
\text{AG}(0, t) = \text{CG}(0, t) = \text{DU}(0, t) = \text{CAG}(0, t) = \text{GC}(0, t) = 0.
\]

When vaccine is incorporated in the model, the boundary conditions are modified as follows:

\[
I(0, t) = p_t \cdot \Pi + (1 - p_t) \cdot \Pi \cdot \phi \cdot \chi(t),
\]

\[
S(0, t) = (1 - p_t) \cdot \Pi - (1 - p_t) \cdot \Pi \cdot \phi \cdot \chi(t),
\]

where \(\chi(t)\) corresponds to the Gompertz function that governs the increase in vaccine coverage on introduction:

\[
\chi(t) = 0.8 \cdot \exp[10 \cdot \exp(-t)]^{-1}.
\]

The total number of vaccinated infants per time period, \(Z(t)\), is given by

\[
Z(t) = \Pi \cdot \chi(t).
\]

The terms in the preceding equations are defined as follows: \(\beta(a, a')\), transmission parameter, probability that an infected individual of age \(a'\) will infect a susceptible individual of age \(a\); \(\delta_s(a)\), progression rate from AG to CG in age group \(a\); \(\delta_g(a)\), progression rate from AG to DU in age group \(a\); \(\delta_s(a)\), progression rate from DU to CAG in age group \(a\); \(\delta_g(a)\), progression rate from CAG to CG in age group \(a\); \(\lambda_s(a, t)\), rate at which 1 susceptible individual of age \(a\) acquires infection and develops AG; \(\lambda_s(a, t)\), rate at which 1 susceptible individual of age \(a\) acquires infection and develops CG; \(\mu(a)\), age-specific background mortality rate due to all cases; \(\mu_{\text{CAG}}\), mortality rate due to DU; \(\mu_{\text{GC}}\), mortality rate due to gastric ulcer; \(\mu_{\text{GC}}\), mortality rate due to gastric cancer; \(\Pi\), birth rate per unit time; \(\phi\), efficacy of vaccine; \(\chi(t)\), proportion of target population receiving \(H.\ pylori\) vaccine; \(a', a\) age index; \(\text{AG}(a, t)\), number of infected individuals of age \(a\) with AG, at time \(t\); \(\text{CAG}(a, t)\), number of individuals of age \(a\) with CAG, at time \(t\); \(\text{CG}(a, t)\), number of infected individuals of age \(a\) with CG, at time \(t\); \(\text{DU}(a, t)\), number of individuals of age \(a\) with DU, at time \(t\); \(\text{GC}(a, t)\), number of individuals of age \(a\) with gastric cancer, at time \(t\); \(\text{I}(a, t)\), number of isolated (nonsusceptible) individuals of age \(a\), at time \(t\); \(p_t\), proportion of population that is nonsusceptible at birth; \(p(a)\), proportion of newly infected individuals of age \(a\) developing AG (vs CG); \(\text{S}(a, t)\), number of susceptible individuals of age \(a\), at time \(t\); \(t\), time index; \(Z(t)\), number of vaccinated infants at time \(t\).


