

Quantifying the population impact of a prophylactic *Helicobacter pylori* vaccine

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Abstract

Background: *Helicobacter pylori* vaccines, which have been suggested as promising interventions to control infection, are under development. We sought to quantify the potential population impact of a prophylactic *H. pylori* vaccine. **Methods:** We developed a mathematical model that compartmentalized the population according to age, infection status and clinical state. A proportion of individuals was assumed to acquire infection and develop gastritis, duodenal ulcer (DU), chronic atrophic gastritis and gastric cancer (GC). We first simulated the model without vaccine intervention, to obtain estimates of *H. pylori* prevalence, and GC and DU incidences based on intrinsic dynamics. We then incorporated a prophylactic vaccine (80% efficacy, lifetime protection, 80% coverage) targeting all infants. We tested vaccination programs over unlimited as well as limited time spans. Analyses were performed for the US, Japan and a prototypical developing country. **Results:** In the US, our model predicted a decrease in *H. pylori* prevalence from 12.0% in 2010 to 4.2% in 2100 without intervention. With 10 years of vaccination beginning in 2010, prevalence would decrease to 0.7% by year 2100. In the same period, incidence of *H. pylori*-attributable GC would decrease from 4.5 to 0.4 per 100,000 with vaccine (compared to 1.3 per 100,000 without vaccine). Incidence of *H. pylori*-attributable DU would decrease from 33.3 to 2.5 per 100,000 with vaccine (compared to 12.2 per 100,000 without vaccine). In Japan, incidence of *H. pylori*-attributable GC would decrease from 17.6 to 1.0 per 100,000 after 10 years of vaccination (compared to 3.0 per 100,000 without vaccine). In a prototypical developing country, after 10 years of vaccination, *H. pylori*-attributable GC would decrease from 31.8 to 22.5 per 100,000 by 2090, returning to the original level by mid-2100s. Under continuous vaccination, it would decrease to 5.8 per 100,000 by 2100. **Interpretation:** In the US and Japan, a 10-year vaccination program would confer almost the same reduction in *H. pylori* and associated diseases as a vaccination effort that extends beyond 10 years. In developing countries, a continuous vaccination effort would be required to eliminate the pathogen and its associated diseases. © 2001 Elsevier Science Ltd. All rights reserved.

Keywords: *H. pylori*; Vaccination; Gastric cancer

1. Introduction

Helicobacter pylori, one of the most common human bacterial pathogens [1], is a cause of duodenal and gastric ulcers (DU and GU), gastric cancer (GC), and gastric mucosa-associated lymphoid tissue (MALT) lymphoma. Studies showing cure of ulcers after *H. pylori* eradication have led the National Institute of Health to recommend antimicrobial treatment of *H. pylori* in ulcer patients [2]. Indications for *H. pylori* eradication in patients with non-ulcer dyspepsia and precancerous conditions are still controver-

sial. Concerns particularly with drug resistance limit the use of antibiotics, and a vaccine has been suggested as a better strategy to control *H. pylori* infection.

Incidence of an infectious pathogen can be lowered by: (1) decreasing the number of susceptible individuals through vaccination; (2) decreasing the number of infected individuals through antimicrobial treatment; and (3) increasing barriers to transmissibility of the pathogen (β) through, for instance, improvement in hygiene or sanitation. In a previous study, we estimated the future trends of *H. pylori* and associated diseases based on its natural history [3]. Because *H. pylori* incidence has been decreasing over time in the absence of a vaccine or widespread use of antibiotics, the historic decrease must have been due to decrease in β . We estimated β and its change over time since mid-1800s, extrapolated β for the future, and simulated the future trends of *H. pylori* and

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Nomenclature

a, a'	age index
$AG(a, t)$	number of infected individuals of age a with antrum-predominant gastritis, at time t
$CAG(a, t)$	number of individuals of age a with chronic atrophic gastritis, at time t
$CG(a, t)$	number of infected individuals of age a with corpus-predominant gastritis, at time t
$DU(a, t)$	number of individuals of age a with duodenal ulcer, at time t
$GC(a, t)$	number of individuals of age a with gastric cancer, at time t
$I(a, t)$	number of isolated (non-susceptible) individuals of age a , at time t
$p(a)$	proportion of newly infected individuals of age a developing antrum (vs. corpus) predominant gastritis
p_I	proportion of population that is non-susceptible at birth
$S(a, t)$	number of susceptible individuals of age a , at time t
t	time index
$Z(t)$	number of vaccinated infants at time t

Greek letters

α	reduction factor in transmissibility due to reduced <i>H. pylori</i> density in CAG
$\beta(a, a')$	transmission parameter; probability that an infective of age a' will infect a susceptible of age a
$\chi(t)$	proportion of target population receiving <i>H. pylori</i> vaccine
$\delta_1(a)$	transition rate from antrum- to corpus-predominant gastritis in age group a
$\delta_2(a)$	progression rate from antrum-predominant gastritis to duodenal ulcer in age group a
$\delta_3(a)$	transition rate from duodenal ulcer to chronic atrophic gastritis in age group a
$\delta_4(a)$	progression rate from corpus-predominant gastritis to chronic atrophic gastritis in age group a
$\delta_5(a)$	progression rate from chronic atrophic gastritis to gastric cancer in age group a
ϕ	efficacy of vaccine
$\lambda_1(a, t)$	rate at which one susceptible of age a acquire infection and develop antrum-predominant gastritis
$\lambda_2(a, t)$	rate at which one susceptible of age a acquire infection and develop corpus-predominant gastritis
$\mu(a)$	age-specific background mortality rate due to all cases
μ_{DU}	mortality rate due to duodenal ulcer

μ_{GC}	mortality rate due to gastric cancer
μ_{GU}	mortality rate due to gastric ulcer
Π	birth rate per unit time

associated DU and GC. We concluded that *H. pylori* and associated diseases would continue to decrease in the 21st century without mass intervention, but it would take more than a century for *H. pylori* to disappear from the US population.

In the present analysis, we quantify the impact — in terms of reduction in the prevalence of *H. pylori*, and incidence of GC and DU — of a prophylactic *H. pylori* vaccine administered to infants, compared to the findings in our previous study. Vaccination has been suggested as a promising mass intervention strategy to control *H. pylori*. In light that *H. pylori* is disappearing on its own, we sought to evaluate the incremental benefit of using *H. pylori* vaccine to prevent infection and subsequent development of clinical conditions.

2. Methods**2.1. Model description and input assumptions**

We previously developed a dynamic compartmental model that captures the age-dependence of *H. pylori* infection and disease progression in infected persons [3]. In this model, the population is divided according to three characteristics: age, infection state, and clinical state. DU and GC states corresponded to individuals in whom *H. pylori* was a necessary condition to develop the disease. In other words, our model tracked down the *H. pylori*-attributable DU and GC cases only.

Mathematical equations governing the transition from one compartment to the other are described in the Appendix A. Computer simulation was used to numerically solve the system of equations and calculate the flow of individuals, determining the number of people in each compartment at each time. The structure of the model and epidemiological assumptions were discussed in detail elsewhere [3].

Fig. 1 incorporates one additional element to the previously published model: vaccination of individuals at birth. A prophylactic vaccination administered early in infancy would prevent *H. pylori* infection by conferring immunity to newborns before exposure to the organism, thereby stopping the process of clinical progression. In the present analysis, we assumed that protection by the vaccine would last for lifetime; thus, we did not incorporate the flow of vaccinated individuals from non-susceptible to susceptible state.

The model assumed that 20% of the population is not susceptible to *H. pylori* infection at all, based on data from developing countries where *H. pylori* is endemic, that a small percentage of individuals do not seem to get infected despite probable exposures to the organism [4,5]. However, since we cannot distinguish susceptible from non-susceptible persons

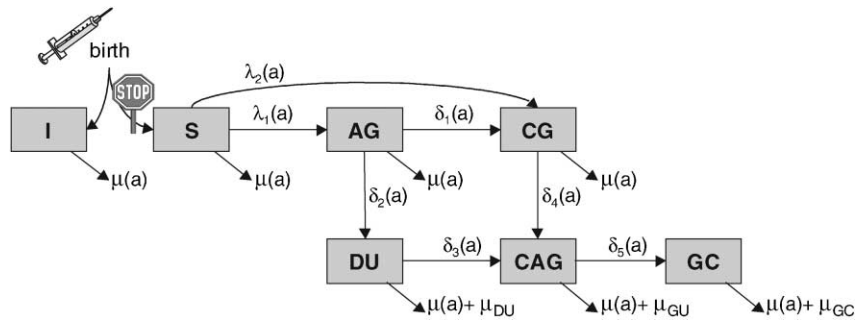


Fig. 1. Simplified diagram of the model of *H. pylori* transmission and disease progression. In this model, the population is divided into compartments according to infection status and clinical state. The arrows represent transitions between compartments, as well as into and out of the population (birth and death). Prophylactic *H. pylori* vaccine is administered to newborns, with the objective of stopping the process of infection with *H. pylori* and subsequent development of clinical conditions.

at birth, we set the target population to be all infants. To obtain estimates for vaccine efficacy, we interviewed experts affiliated with companies developing *H. pylori* vaccine. In addition, we considered the efficacy assumptions of *H. pylori* and other potential vaccines analyzed in the Institute of Medicine study [6]. To address the uncertainty around vaccine efficacy, we performed a sensitivity analysis to investigate how results may change depending on the efficacy.

Vaccination of infants in our model was assumed to start in year 2010. This was based on experience in development of other vaccines and an expert assessment that it would take at least another eight years for the vaccine to become commercially available [7]. We assumed a vaccine efficacy of 80% under base scenario. In addition, we assumed that a new vaccine would not get full coverage upon its introduction, but that coverage of *H. pylori* vaccine in the population would increase from 20% in the second year of introduction to 65% in the fourth year, gradually increasing to a maximum of 80%, following the Gompertz diffusion model [8]. The maximum of 80% was based on coverage achieved by other vaccines [9].

We first tested the scenario in which vaccination would start in year 2010 and would extend for an unlimited time. We then modified the model to simulate a vaccination program that extended for a limited time span. In this model, vaccination is interrupted after a relatively short time from its introduction to the market (we used 10 years for the base case scenario). Besides vaccine efficacy, we performed univariate sensitivity analyses on vaccine coverage, as well as years of vaccination.

2.2. Analysis of vaccine impact in other countries

We used the modeling framework described above to compute the impact of a prophylactic *H. pylori* vaccine in a developed country with continued high GC rates (e.g. Japan) and in a prototypical developing country (e.g. China). We adopted the same disease progression rates, mortality rates, and vaccine parameters as the US model. The difference

among these countries in our model was the year in which childhood infection incidence of *H. pylori* began to decrease. In the US, Sonnenberg has estimated that GC risk has decreased steadily in all cohorts born after 1850 [10]. In the US, we therefore simulated a decrease in *H. pylori* acquisition in childhood starting in year 1850, by decreasing the transmission parameters from high levels to low values consistent with incidence and prevalence of *H. pylori* observed in present days [3].

In Japan, on the other hand, the declining trend of GC was observed in cohorts born after 1913 [11], which represented a delay of about six decades compared to the US. To simulate this scenario, we kept the transmission parameters at high levels until 1910, and decreased the values in subsequent years following a similar decreasing trend as of that estimated for the US (presented in detail elsewhere [3]).

In a prototypical developing country, *H. pylori* is still hyper-endemic currently, and incidence of GC has not decreased significantly over time. We simulated this scenario by keeping the transmission parameters at high levels. In estimating the benefits of an *H. pylori* vaccine, we further assumed that *H. pylori* infection would remain endemic in the next century.

For Japan and developing countries, we did not include results on DU incidence because available data on DU statistics are very limited and therefore, there is very little basis for comparison and validation.

3. Results

3.1. Effect of a prophylactic vaccine for infants in the US

We have previously estimated that without any intervention, *H. pylori* prevalence in the overall US population would decrease from 12.0% in 2010 to 4.2% by year 2100. In comparison, continuing administration of a prophylactic *H. pylori* vaccine starting in year 2010 would reduce *H. pylori* prevalence to 0.3% by the end of the 21st century; a

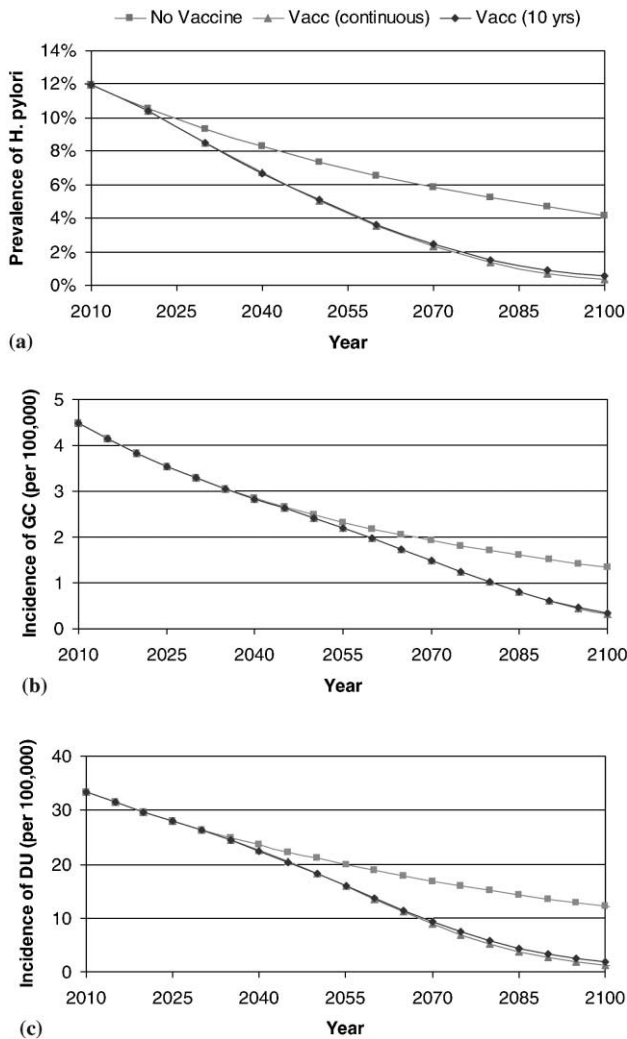


Fig. 2. Effects of a prophylactic *H. pylori* vaccine for infants in the US. (a) Prevalence of *H. pylori*; (b) incidence of *H. pylori*-associated GC; (c) incidence of *H. pylori*-associated DU. Legend applies to all three curves. "No vaccine" represents the situation in which population does not receive any intervention, and the decrease is due solely to the intrinsic dynamics. "Vacc (continuous)" represents a vaccination program that starts in year 2010 and continues into the future. "Vacc (10 years)" represents a vaccination program that starts in year 2010 and phases out in 2020. Because incidence of *H. pylori* is already very low in the US due to low transmissibility, a vaccination program would not have to extend for a long time period: a 10-year program would reach about the same benefits as vaccination effort that extends beyond 10 years.

vaccination program that extends only for 10 years would reduce *H. pylori* prevalence to 0.7% (Fig. 2a). Similarly, incidence of *H. pylori*-attributable GC would decrease from 4.5 per 100,000 US population in year 2010 to 1.3 per 100,000 by the end of the century under no vaccine (Fig. 2b). In comparison, if infants were vaccinated continuously, incidence of *H. pylori*-attributable GC would decrease to 0.3 per 100,000 by year 2100; if vaccination were phased out after 10 years, incidence would decrease to 0.4 per 100,000. For *H. pylori*-attributable DU, the de-

crease would be even more pronounced. Under no vaccine, incidence of *H. pylori*-attributable DU would decrease from 33.3 per 100,000 US population in year 2010 to 12.2 per 100,000 in 2100; if a continuing vaccination were administered to infants, DU incidence would decrease to 1.2 per 100,000 by the end of the century; if vaccination were limited to 10 years, DU incidence would decrease to 2.5 per 100,000 (Fig. 2c).

3.2. Effect of a prophylactic vaccine for infants in other countries

In Japan, without any intervention, *H. pylori* prevalence would decrease from 30.1% in 2010 to 8.6% in 2100 without vaccine; under continuous or a 10-year vaccination, respectively, *H. pylori* prevalence would decrease to 0.7% and 1.6% by the end of the 21st century. The incidence of *H. pylori*-attributable GC would decrease from an estimated 17.6 per 100,000 population in year 2010 to 3 per 100,000 by the end of the 21st century without vaccine; under continuing prophylactic vaccination, the incidence would decrease to 0.8 per 100,000 by year 2100; if vaccine were limited to 10 years, it would decrease to 1.0 per 100,000 by year 2100 (Fig. 3a).

In a prototypical developing country, *H. pylori* prevalence would remain at 73.5% without vaccine; it would decrease to 3.7% by year 2100 under a continuous vaccination effort. If vaccine were limited to 10 years, however, prevalence would decrease to 61.5% by year 2040 and would increase to above 70% by the end of the 21st century. The incidence of *H. pylori*-attributable GC would remain at a constant level of 31.8 per 100,000 if the population did not receive any treatment. If prophylactic vaccine were given to infants continuously, the incidence of GC would decrease from 31.8 per 100,000 in year 2010 to 5.8 per 100,000 by the end of the 21st century, and would continually decrease to 0.1 per 100,000 by year 2150. If vaccination were limited to 10 years, however, the incidence of *H. pylori*-attributable GC would only decrease to 22.5 by year 2090, but would soon start increasing again, returning to the original level by the mid-2100s (Fig. 3b).

3.3. Sensitivity analyses — US

We first tested the sensitivity of our results to efficacy of vaccine. If efficacy were dropped to 50%, prevalence of *H. pylori* would decrease to 0.3% and 1.0% by year 2100, under continuous and 10 years of vaccination, respectively. The incidence of *H. pylori*-attributable GC would decrease to 0.4 per 100,000 by 2100 under continuous vaccination; if vaccination were limited to 10 years, GC incidence would decrease to 0.5 per 100,000. In the same time period, the incidence of *H. pylori*-attributable DU would decrease to 1.7 and 3.3 per 100,000 population, under continuous and 10-year vaccination, respectively.

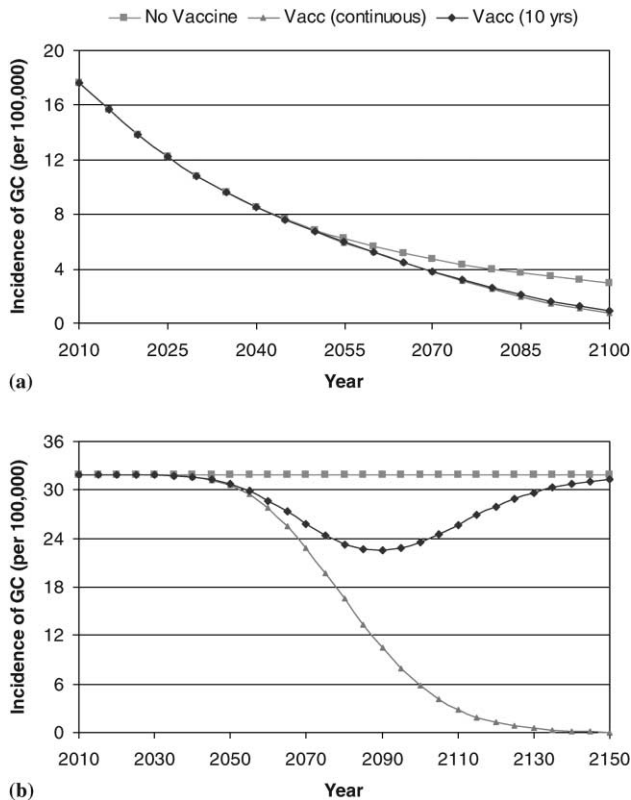


Fig. 3. Effect of a prophylactic *H. pylori* vaccine for infants in other countries. (a) Incidence of *H. pylori*-associated GC in Japan; (b) incidence of *H. pylori*-associated GC in a prototypical developing country. Legend applies to both graphs and are similar to Fig. 2. In a Japan-like country, *H. pylori*-associated GC is still high because the age-cohort phenomenon started several decades later than the US; prophylactic vaccine would accelerate the disappearance of *H. pylori* and, similar to the US, a 10-year vaccination program would achieve almost the same benefits as a vaccination effort that extends beyond 10 years. In a typical developing country, *H. pylori* is still endemic; because transmissibility is still high, a continuous vaccination effort that extends beyond 10 years would be necessary in order to eradicate *H. pylori*.

Next, we tested the sensitivity to the maximum coverage of vaccine. If the coverage were 50%, prevalence of *H. pylori* would decrease to 0.4% under continuous vaccination and 1.3% under a 10-year vaccination, by the end of the 21st century. In the same time period, incidence of *H. pylori*-attributable GC would drop to 0.4 and 0.6 per 100,000, and incidence of DU would decrease to 1.7 and 4.2 per 100,000 under continuous and 10 years of vaccination, respectively.

Finally, we tested how duration of the vaccination program would change the outcome. The prevalence of *H. pylori* would decrease to 2.2% by year 2100 if vaccination were in effect for only 5 years, 0.7% if vaccination extended for 10 years, and 0.4% if it extended for 15 years. The incidence of *H. pylori*-attributable GC would drop to 0.8, 0.4 and 0.3 per 100,000 population by century-end, under 5-, 10-, and 15-year vaccination program. The model was insensitive to all other variables.

3.4. Sensitivity analyses — other countries

In Japan, if efficacy were lowered to 50%, prevalence of *H. pylori* would decrease, by the end of the 21st century, to 0.9% under continuous vaccination and 3.0% under 10 years of vaccination. Similarly, the incidence of *H. pylori*-attributable GC would decrease to 0.9 and 1.3 per 100,000 population. If maximum coverage of vaccine were 50%, we obtained similar results as the 50% efficacy scenario.

In a prototypical developing country, if the efficacy of vaccine were 50%, prevalence of *H. pylori* would decrease continuously to 8.6% by year 2100 under a continuous vaccination; under a 10-year vaccination, however, prevalence would reach a minimum of 66.7% around 2030, rapidly increasing to over 70% by year 2100. The incidence of *H. pylori*-attributable GC would decrease to 8.3 per 100,000 in 2100, to 0.3 per 100,000 in 2150, under continuing vaccination program; a 10-year vaccination would make the GC incidence drop to 26.4 per 100,000 population, but the incidence would increase again to the original level by 2150. If the coverage of vaccine were limited to 50%, the effect on *H. pylori* prevalence and associated GC would also be comparable to the 50% efficacy scenario.

4. Discussion

In this work, we quantified the potential health impact of a prophylactic *H. pylori* vaccine, by estimating how the incidence of *H. pylori*-attributable diseases would change if infants received vaccine, compared to the baseline curves of intrinsic dynamics. Because *H. pylori* appears to be disappearing without targeted intervention, we used this methodological approach in an attempt to provide realistic projections of vaccine benefits.

In the US, although vaccination would have an early impact on the overall *H. pylori* prevalence statistics, differences in incidence of disease would not be significant until at least five decades later for GC, and three decades for DU. Interestingly, a vaccination of limited time span (10 years) resulted in curves of *H. pylori* prevalence and incidence of *H. pylori*-attributable GC and DU similar to a vaccination of unlimited time span. There appears to be a maximum reduction from the baseline curve that a prophylactic vaccine can achieve, and the maximum reduction can be accomplished with a vaccination program that extends only for a short time. An explanation for this finding is that *H. pylori* is disappearing without mass intervention, which indicates that the transmissibility of the pathogen is already low enough to set a decreasing trend. If most children — among whom risk for new infection remains the highest — get vaccine and become immune to *H. pylori*, we accelerate the disappearance of *H. pylori* from the population. After 10 years, when vaccination is phased out, newborns would

not get the infection because *H. pylori* transmissibility would already be very low, most children would be vaccinated (i.e. there would be few susceptibles), and the overall prevalence would be very low (i.e. there would be few transmitters).

In developed countries with high GC rate, conclusions similar to the US apply. In a typical developing country, however, a temporary vaccination program would not eradicate the organism from the population. Because transmissibility is still high in such a country, once the vaccination were interrupted, new susceptible individuals (newborns) would quickly acquire *H. pylori*, and the number of transmitters (*H. pylori* prevalence) would remain high enough to perpetuate transmission return to the original level. In developing countries, a continuing vaccination effort would be required, unless those countries undergo rapid socio-economic development, which is believed to be responsible for the natural decrease in the incidence of *H. pylori* that occurred in industrialized countries in the 20th century.

Sensitivity analyses showed that in the US and Japan, the model is minimally sensitive to the vaccine efficacy and coverage. This indicates that in countries where the intrinsic transmissibility of the pathogen is already low (i.e. the pathogen is disappearing on its own without intervention), the vaccine does not have to be very efficacious, or the vaccination coverage in the population does not have to be very comprehensive. In a prototypical developing country, however, the outcomes are sensitive to these variables, and it is important that the vaccine be very effective and have a broad population coverage. The difficulty to obtain effective protection in infants and young children, and the need for large amounts of resources to achieve good coverage pose enormous challenge to the implementation of a successful vaccination program in developing countries.

In the present study, we evaluated the impact of a prophylactic *H. pylori* vaccine for infants, not older groups such as adolescents. A large proportion of infections occurs earlier in life, and if vaccine were administered to adolescents, a proportion of children would still acquire *H. pylori*. In this situation, the *H. pylori* vaccine would have much less impact on the overall disease prevention.

Animal models have also shown the possibility of curing — rather than preventing — *H. pylori* infection with a vaccine [12–14]. Such therapeutic vaccine would have several advantages: (1) the time lag between administration of vaccine and realization of health benefits would be much shorter; and (2) clinical trials would be easier to design, because the vaccine could target infected adults (instead of infants) and the follow-up time could be much shorter than that required for a prophylactic vaccine. Although benefits of a therapeutic vaccine for DU patients may be assessed with available data, benefits for patients with other clinical conditions cannot be estimated with current state of knowledge. Moreover, therapeutic vaccines developed to date

decrease colonization of human stomach but do not cure infection [15]. Better understanding is required on the benefit of *H. pylori* eradication in dyspepsia patients and individuals with pre-cancerous conditions.

We did not model immigration in the present study due mainly to lack of data and understanding on how it affects the disease dynamics. If a US born infant moves to a developing country and adopts the local hygiene practices as well as contact with other local children, it is likely that this infant will acquire *H. pylori*. On the other hand, if an infant born in a developing country moves to the US and enjoys the improved hygiene and infrastructure, would the child acquire *H. pylori*? If already infected, would the child transmit infection to other children? How important is the socio-economic class of the immigrant family to the likelihood of acquiring *H. pylori* and developing the associated diseases? These are questions that need to be investigated through epidemiological research, before we embark in a more complex modeling exercise to examine how immigration would affect the outcome of a vaccination program.

Finally, we should point out the recently raised concern that *H. pylori* eradication may lead to an increase in the incidence of gastroesophageal diseases. Many studies are limited to the short-term impact of *H. pylori* eradication (as opposed to protective immunization) on the incidence of gastroesophageal reflux disease (GERD). It is still controversial whether avoidance of initial *H. pylori* infection would lead to GERD, and possibly distal esophageal adenocarcinomas. Given that *H. pylori* infection has been decreasing in the US since beginning of the century while the rise in gastroesophageal problems started occurring after 1970s, we speculate that a prophylactic vaccine will have little impact on the incidence of these clinical conditions. If we wish to analyze the benefits of a therapeutic vaccine, however, the corresponding model should probably incorporate the risk of developing gastroesophageal problems in a subset of patients who receive the vaccine.

Acknowledgements

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Appendix A

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

$$\frac{\partial I}{\partial t} + \frac{\partial I}{\partial a} = -\mu(a)I(a, t)$$

$$\frac{\partial S}{\partial t} + \frac{\partial S}{\partial a} = -[\lambda_1(a, t) + \lambda_2(a, t) + \mu(a)]S(a, t)$$

$$\frac{\partial AG}{\partial t} + \frac{\partial AG}{\partial a} = \lambda_1(a, t)S(a, t) - [\delta_1(a) + \delta_2(a) + \mu(a)]AG(a, t)$$

$$\frac{\partial CG}{\partial t} + \frac{\partial CG}{\partial a} = \lambda_2(a, t)S(a, t) + \delta_1(a)AG(a, t) - [\delta_4(a) + \mu(a)]CG(a, t)$$

$$\frac{\partial DU}{\partial t} + \frac{\partial DU}{\partial a} = \delta_2(a)AG(a, t) - [\delta_3(a) + \mu_{DU} + \mu(a)]DU(a, t)$$

$$\frac{\partial CAG}{\partial t} + \frac{\partial CAG}{\partial a} = \delta_3(a)DU(a, t) + \delta_4(a)CG(a, t) - [\delta_5(a) + \mu_{GU} + \mu(a)]CAG(a, t)$$

$$\frac{\partial GC}{\partial t} + \frac{\partial GC}{\partial a} = \delta_5(a)CAG(a, t) - [\mu_{GC} + \mu(a)]GC(a, t)$$

where

$$\lambda_1(a, t) = p(a) \int_0^{\infty} \beta(a, a') [AG(a', t) + CG(a', t) + DU(a', t) + \alpha CAG(a', t) + GC(a', t)] da'$$

$$\lambda_2(a, t) = (1 - p(a)) \int_0^{\infty} \beta(a, a') [AG(a', t) + CG(a', t) + DU(a', t) + \alpha CAG(a', t) + GC(a', t)] da'$$

The boundary conditions without vaccine are as follows:

$$I(0, t) = p_I \Pi$$

$$S(0, t) = (1 - p_I) \Pi$$

$$AG(0, t) = CG(0, t) = DU(0, t) \\ = CAG(0, t) = GC(0, t) = 0$$

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

$$I(0, t) = p_I \Pi + (1 - p_I) \Pi \phi \chi(t)$$

$$S(0, t) = (1 - p_I) \Pi - (1 - p_I) \Pi \phi \chi(t)$$

where $\chi(t)$ corresponds to the Gompertz function that govern the increase in vaccine coverage upon introduction

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

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

$$Z(t) = \Pi \chi(t)$$

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