

**Statistical and mathematical modeling to evaluate the
cost-effectiveness of *Helicobacter pylori* screening and treating
strategies in Mexico in the setting of antibiotic resistance**

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Dedication

To my grandmother, Irene Mandujano Tovar.

Abstract

Helicobacter pylori (*H. pylori*), a bacterium that is present in the stomach of half of the world's population with disproportionate burden in developing countries, is the strongest known biological risk factor for gastric cancer. Gastric cancer is the fourth most common type of cancer and the second cause of cancer death in the world. In particular, in Mexico gastric cancer is the third highest cause of cancer death in adults, with some regions having cancer mortality rates that are twice the national average (8.0 vs. 3.9 per 100,000, respectively). *H. pylori* can be treated with antibiotics, but widespread treatment may lead to significant levels of antibiotic resistance (ABR). ABR is one of the main causes of *H. pylori* treatment failure and represents one of the greatest emerging global health threats.

In this thesis, we use statistical and mathematical modeling to investigate the health benefits, harms, costs and cost-effectiveness of screen-and-treat strategies for identifying and treating persons with *H. pylori* to inform public health practice in three steps. First, we estimated the age-specific force of infection of *H. pylori*—defined as the instantaneous per capita rate at which susceptibles acquire infection—using a novel hierarchical nonlinear Bayesian catalytic epidemic model with data from a national *H. pylori* seroepidemiology survey in Mexico.

Second, we developed an age-structured, susceptible-infected-susceptible (SIS) transmission model of *H. pylori* infection in Mexico that included both treatment-sensitive and treatment-resistant strains. Model parameters were derived from the published literature and estimated from primary data. Using the model, we projected *H. pylori* infection and resistance levels over 20 years without treatment and for three hypothetical population-wide treatment policies assumed to be implemented in 2018. In sensitivity analyses, we considered different mixing patterns and trends of background antibiotic use. We validated the model against historical values of prevalence of infection and ABR of *H. pylori*.

Third, we expanded the SIS model to incorporate the natural history of gastric carcinogenesis including gastritis, intestinal metaplasia, dysplasia and ultimately non-cardia gastric cancer. We then estimated the cost-effectiveness of various screen-and-treat strategies for *H. pylori* infection and ABR in the Mexican population from the health sector perspective.

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Chapter 1

Introduction

Helicobacter pylori (*H. pylori*), a gram-negative microaerophilic bacterium that is present in the stomach of half of the world's population with disproportionate burden in developing countries, is the strongest known biological risk factor for gastric cancer.[1, 2] Gastric cancer is the fourth most common type of cancer and the second leading cause of cancer death in the world, with almost 70% of cases occurring in developing countries. Gastric cancer is associated with poor survival and reduced quality of life, as a high percentage of gastric cancer cases are detected at a late stage. Latin America has the second highest rate of gastric cancer mortality in the world. In particular, in Mexico gastric cancer is the third highest cause of cancer death in adults, with some regions having cancer mortality rates that are twice the national average (8.0 vs. 3.9 per 100,000, respectively).[3] Therefore, gastric cancer represents a major public health problem in regions with high prevalence of *H. pylori*

The mode of transmission of *H. pylori* remains unclear. Transmission is believed to occur through close personal contact, such as oral-oral or fecal-oral, particularly within the family and typically in early childhood.[1, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16] Once infected with *H. pylori*, individuals will experience life-long infection in the absence of antibiotic treatment.[17, 18]

The force of infection is the instantaneous rate at which susceptible individuals acquire infection. It is an important epidemiological quantity and a key parameter for mathematical models of disease transmission, which are used to estimate disease burden and the effectiveness and cost-effectiveness of infectious disease treatment and prevention.[19, 20, 21] Like many infectious diseases, it is infeasible to directly measure the force of infection of *H. pylori*. [22,

23, 24]

H. pylori infection can be cleared with antibiotics, which in theory can reduce the risk of gastric cancer, duodenal and gastric ulcers, but previously infected individuals are at risk of reinfection.[25, 26] In addition, antibiotic treatment can result in antibiotic resistance (ABR), which is the natural response of bacteria to resist the threats designed to eliminate them. Non-adherence and ABR are the main causes of *H. pylori* treatment failure.[26, 27, 28, 29, 30, 31] ABR reduces the effectiveness of treatment and represents one of the greatest emerging global health threats.[32, 33, 34] Resistant strains of *H. pylori* have been identified in Latin American to most antibiotics typically used to treat it.[35]

Given the high burden of *H. pylori* infection in the population, the idea of antibiotic-based mass eradication in developing regions has been suggested, and even implemented in targeted high-risk populations.[36] However, the modest benefits of *H. pylori* mass eradication programs may be outweighed by the development of treatment-induced ABR. Therefore, it is important to only treat appropriate cases with selected regimens based on the observed patterns of ABR in the target population. Under a "screen-and-treat" approach asymptomatic individuals (i.e., individuals without symptoms of having the disease of interest) are subjected to a screening test and treatment decisions are based on the test result, which should be provided soon or, ideally, immediately after a positive screening test.[37]

In this thesis, we address these issues across three different chapters.

In Chapter 2, we showed that under certain assumptions the age-specific force of infection of *H. pylori* can be estimated from national seroprevalence data. Specifically, we estimated the age-specific force of *H. pylori* infection in Mexico (a middle-income country with a high prevalence of infection). We used data from a nationally representative seroepidemiology survey conducted in Mexico prior to widespread antibiotic treatment of *H. pylori* with rich geographical variation. Given the large heterogeneity in the number of samples obtained in each state, we used a nonlinear Bayesian hierarchical catalytic model that allows us to estimate the force of infection in each state in Mexico while simultaneously estimating the national average force of infection. We demonstrate that this method dramatically stabilizes estimation by shrinking the state-specific force of infection toward the national estimate, particularly on states with low data.

We modeled the number of individuals with *H. pylori* at a given age in each state as a binomial random variable. We assumed that the cumulative risk of infection by a given age

follows a modified exponential distribution, allowing some fraction of the population to remain uninfected. The cumulative risk of infection was modeled for each state in Mexico and these state-specific cumulative risk curves were shrunk toward the overall national cumulative risk curve using Bayesian hierarchical models. These parameters were used to estimate the force of infection by age in each Mexican state. Models were estimated using Markov chain Monte Carlo (MCMC) methods.

We found that national *H. pylori* prevalence estimates plateau at 86.1% [95% credible interval (CR): 84.2%-88.2%]. The rate of increase of prevalence per year of age is 0.093 [95%CR: 0.084-0.103]. We estimated an average age at infection of the population eventually infected of 12.5 [95%CR: 11.3-13.8] and the age-specific force of infection was highest at birth 0.080 [95%CR: 0.089-0.071] and decreased to zero with increasing age.

This chapter presents the first estimation of the force of infection of *H. pylori* using seroepidemiologic data.

In Chapter 3, we developed an age-structured, susceptible-infected-susceptible (SIS) transmission model of *H. pylori* infection in Mexico that included both treatment-sensitive and treatment-resistant strains. Antibiotic treatment was assumed to either clear sensitive strains or induce acquired resistance (and had no effect on resistant strains). In addition, the model included the effects of both background antibiotic use and antibiotic treatment specifically intended to treat *H. pylori* infection. Model parameters were derived from the published literature and estimated from primary data. Using the model, we projected *H. pylori* infection and resistance levels over 20 years without treatment and for three hypothetical population-wide treatment policies assumed to be implemented in 2018: (1) treat children only (2-6 year-olds); (2) treat older adults only (>40 years old); (3) treat everyone regardless of age. Clarithromycin—introduced in Mexico in 1991—was the antibiotic considered for the treatment policies. In sensitivity analyses, we considered different mixing patterns and trends of background antibiotic use. We validated the model against historical values of prevalence of infection and ABR of *H. pylori*.

We found that in the absence of a mass-treatment policy, our model predicts infection begins to rise in 2022, mostly caused by treatment-induced resistant strains as a product of background use of antibiotics. The impact of the policies is immediate on decreasing infection but also increasing ABR. For example, policy 3 decreases infection by 21% but increases ABR by 57% after the first year of implementation. The relative size of the decrease in infection vs. the

increase in ABR for policy 3 is 37%. These results were robust across all scenarios considered in sensitivity analyses.

In summary, mass-treatment policies have a greater effect on increasing ABR, allowing resistant strains take over infection. Given the high proportion of ABR at the time of the policy implementation, mass treatment strategies are not recommended for Mexico.

In Chapter 4, we conducted a cost-effectiveness analysis (CEA) to compare the costs, life years and quality-adjusted life years (QALYs) of different screen-and-treat strategies for *H. pylori* infection and ABR in the Mexican population from the health sector perspective. We considered different testing strategies including those used to identify ABR strains.

We expanded the SIS model from Chapter 3 to incorporate the natural history of gastric carcinogenesis including gastritis, intestinal metaplasia, dysplasia and ultimately non-cardia gastric cancer. We calibrated the parameters describing gastric disease dynamics using a Bayesian approach. We then implemented alternative screen-and-treat strategies with two different testing algorithms: (1) test only for *H. pylori* infection and treat if positive, and (2) test for *H. pylori* infection and if positive, test for susceptibility to clarithromycin.

All screening policies produced higher effectiveness compared to a no-screen-and-no-treat policy. However, all policies were costlier compared to a do-nothing strategy. Using a cost-effectiveness threshold of the GDP per capita (MXN\$132,000 in Mexico), we found screening and treating for *H. pylori* all the population would be considered cost-effective.

Chapter 2

Force of infection of *Helicobacter pylori* in Mexico: Evidence from a national survey using a hierarchical Bayesian model

2.1 Introduction

H. pylori is one of the most prevalent global pathogens, the strongest known biological risk factor for gastric cancer (about a six-fold increase of risk) and is responsible for approximately 80% of gastric ulcers.[1, 2, 38, 39] Gastric cancer is the fourth most common type of cancer and the second cause of cancer death globally.[40] *H. pylori* is a gram-negative, microaerophilic bacterium commonly found in the epithelial lining of the human stomach.[41]

The mode of transmission of *H. pylori* remains unclear. Transmission appears to occur through close personal contact, such as oral-oral or fecal-oral, particularly within the family and typically in early childhood.[1, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16] Once infected with *H. pylori*, individuals will experience life-long infection in the absence of antibiotic treatment.[17, 18] The global burden of disease is substantial, with *H. pylori* present in the stomach of half of the world's population; however, *H. pylori* most heavily burdens low- and middle-income countries (LMICs) where the proportion of people infected is approximately 70%.[42, 43, 44]

For example, a prevalence study in Mexico showed that 66% of the Mexican population was infected with *H. pylori* and that this prevalence increases with age, reaching up to 80% in adults 25 years old and older.[45] However, this study also found significant variation in prevalence by age, socioeconomic status and geography (e.g., state-level prevalence ranged from 48% to 85%).

The force of infection is the instantaneous rate at which susceptible individuals acquire infection. It is an important epidemiological quantity and a key parameter for mathematical models of disease transmission, which are used to estimate disease burden and the effectiveness and cost-effectiveness of infectious disease treatment and prevention.[19, 20, 21] Like many infectious diseases, it is infeasible to directly measure the force of infection of *H. pylori*. [22, 23, 24] However, under certain assumptions, it can be estimated using population-level seroprevalence data.[19, 46, 47, 48] Despite the existence of seroprevalence data of *H. pylori* its force of infection has not been previously estimated.

In this paper, we show how the age-specific force of infection of *H. pylori* can be estimated from national seroprevalence data. The purpose of this paper is to estimate the age-specific force of *H. pylori* infection in Mexico (a middle-income country with a high prevalence of infection). We used data from a nationally representative seroepidemiology survey conducted in Mexico prior to widespread antibiotic treatment of *H. pylori* with rich geographical variation. Given the large heterogeneity in the number of samples obtained in each state, we used a nonlinear Bayesian hierarchical catalytic model that allows us to estimate the force of infection in each state in Mexico while simultaneously estimating the national average force of infection. We demonstrate that this method dramatically stabilizes estimation by shrinking the state-specific force of infection toward the national estimate, particularly on states with low data.

2.2 Methods

2.2.1 Force of infection as a catalytic model

The force of infection is the key quantity governing disease transmission within a given population and is defined as the instantaneous per capita rate at which susceptible individuals acquire infection (i.e., the hazard of infection). It reflects both the degree of contact between susceptible and infected individuals and the transmissibility of the pathogen per contact. In cases where contact is age dependent, the force of infection is itself a function of age analogous to the hazard

rate being a function of time in a survival model.[46]

Formally, let $P(a)$ denote the probability that an individual susceptible at birth is still susceptible at age a ; this is identical to the cumulative survival function in a survival analysis. Let $\lambda(a)$ denote the force of infection at age a , which represents the rate of infection of the susceptible population $P(a)$. In terms of a survival model, the force of infection $\lambda(a)$ represents the instantaneous infection hazard rate. Therefore, for lifelong infections (or infections conferring lifelong immunity) that do not significantly affect mortality, $\lambda(a)$ can be defined as

$$\lambda(a) = -\frac{1}{P(a)} \frac{dP(a)}{da}, \quad (2.1)$$

under the assumption that the population is in dynamic equilibrium (meaning that $P(a)$ is constant over time and not changing generation to generation).

Equation (2.1) specifies a so-called *catalytic epidemic model*, first defined by Muench.[48] The term *catalytic model* derives from its origins in chemistry, where these models were used to study chemical reaction kinetics. Catalytic epidemic models have been widely used to estimate the force of infection of different infectious disease such as measles, rubella, mumps, hepatitis A and yellow fever using seroprevalence epidemiological data from settings where these diseases do not significantly affect mortality.[19]

Catalytic models can easily be written in terms of the cumulative probability of infection by age a , $F(a) = 1 - P(a)$, which more directly corresponds to how seroprevalence data is collected.[46, 48] In terms of $F(a)$, the force of infection, $\lambda(a)$, becomes:

$$\lambda(a) = \frac{1}{1 - F(a)} \frac{dF(a)}{da}. \quad (2.2)$$

Note that rearranging Equation (2.2) we can solve for $F(a)$ as a function of $\lambda(a)$, which is equivalent to a survival model where the probability of infection by age a is the cumulative distribution function of the time to infection:

$$F(a) = 1 - \exp \left[- \int_0^a \lambda(s) ds \right]. \quad (2.3)$$

Further, it is possible to estimate the average age of infection, A , which is equivalent to the average time spent in the susceptible group before becoming infected:

$$A = \int_0^L (1 - F(a)) da, \quad (2.4)$$

where L is the life expectancy of the population of interest. The average age, A at infection is a parameter of considerable epidemiological significance for *H. pylori* since low values of A are associated with high infectivity during childhood.[49] A could be a useful summary measure of the FOI to easily compare across settings (e.g., across states and countries). And also, could have policy implications like deciding optimal age of screening or treatment.

It is possible that some individuals never end up infected over their lifetimes. If this is the case, A is a combination of the average age at infection of individuals who eventually become infected, A_e , and life expectancy, L , for those who are never infected. A_e can be calculated as[46]

$$A_e = \frac{A - L(1 - \alpha)}{\alpha}, \quad (2.5)$$

where α is the proportion of the population who ultimately becomes infected. The difference between A and A_e decreases as the proportion of the population eventually infected α increases.

2.2.2 Seroprevalence of *H. pylori* in Mexico

In 1987-1988, the National Seroepidemiological Survey (NSS) was conducted in Mexico as a nationally representative survey of *H. pylori* infection.[45, 50] The survey was designed to represent the country by including all 32 states of Mexico, all ages, all socioeconomic levels and both sexes.[50] In total, 32,200 households were surveyed and more than 70,000 serum samples were collected. Of these samples, 11,605 individuals were used for *H. pylori* testing and out of these, 7,720 (66%) were seropositive for *H. pylori*. *H. pylori* infection was determined by ELISA detection of IgG antibodies to specific *H. pylori* antigens. *H. pylori* prevalence in Mexico varies by state and can be as low as 48% in the state of Chihuahua and as high as 83% in the state of Baja California Sur, Figure 2.1.

2.2.3 Functional form of catalytic model of *H. pylori* infection in Mexico

The NSS data were collected prior to widespread antibiotic treatment of *H. pylori* so we can assume that the prevalence of infection as a function of age is cumulative and that the population is in steady state. The age-specific prevalence measured nationally and in three states is shown in Figure 2.2 and it is clear that the trend is monotonically non-decreasing. Based on the shape of these data, we assume that the state-specific cumulative probability of *H. pylori* infection,

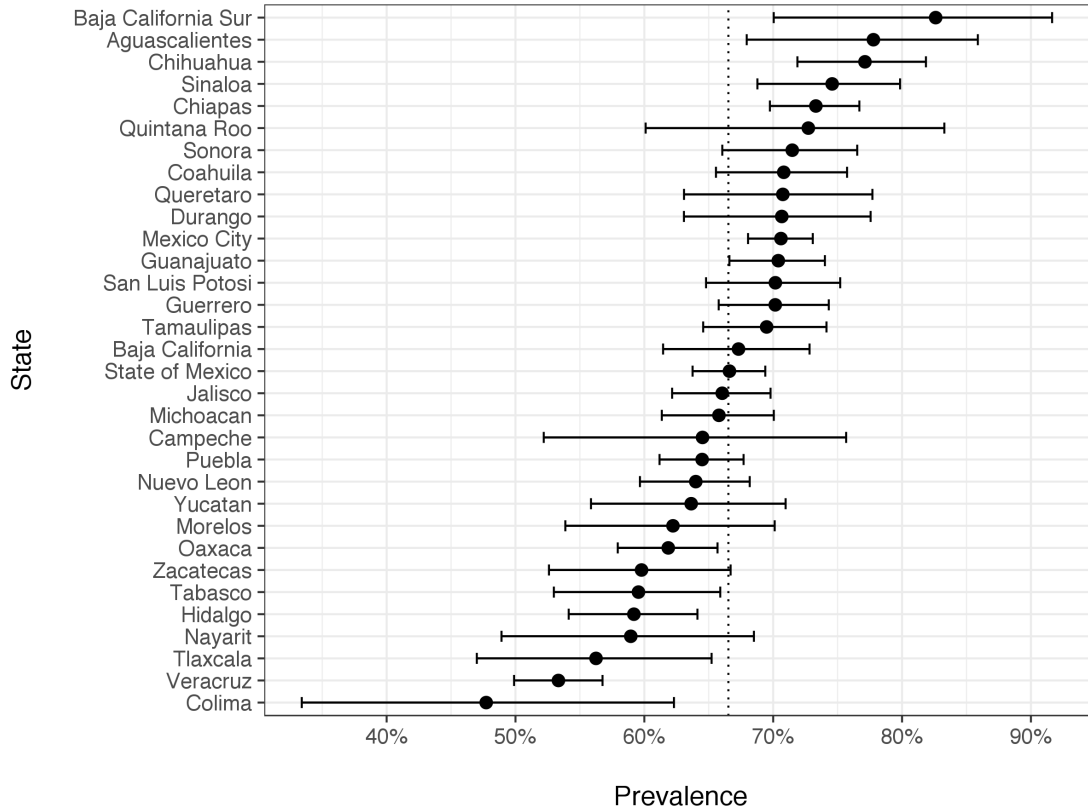


Figure 2.1: Observed prevalence of *H. pylori* in Mexico by state in 1987-88 with 95% CI

$F_i(a)$, for each state i follow a constrained exponential functional form:

$$F_i(a) = \alpha_i(1 - e^{-\gamma_i a}), \quad (2.6)$$

where $\alpha_i \leq 1$ is the state-specific proportion of the population who eventually becomes infected and γ_i is the state-specific rate of infection among those who eventually become infected. We allow α and γ to vary by state to reflect the heterogeneity in *H. pylori* prevalence trends resulting from differences in socioeconomic and environmental factors. Note that for all states, we assume that no children are infected at birth ($F_i(0) = 0$) since there is no biological evidence for vertical transmission of *H. pylori* from mother to child during pregnancy, labor, or delivery.[51]

Based on this functional form for the cumulative probability of infection, we use equation

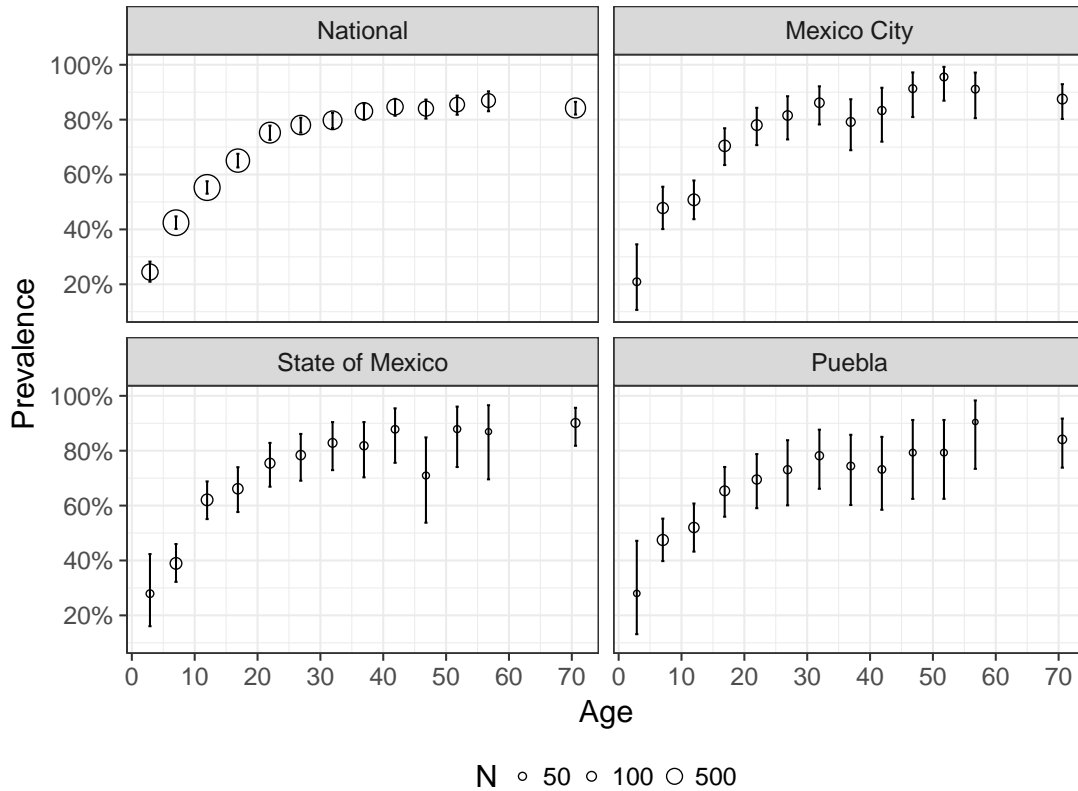


Figure 2.2: Empirical prevalence of *H. pylori* in Mexico by age nationally and in three different states.

(2.2) to solve for the state-specific force of infection, $\lambda_i(a)$, in terms of α_i and γ_i :

$$\lambda_i(a) = \frac{\alpha_i \gamma_i e^{-\gamma_i a}}{1 - \alpha_i (1 - e^{-\gamma_i a})}. \quad (2.7)$$

Note that if the entire population is eventually infected in a given state (i.e., $\alpha_i = 1$), $\lambda_i(a) = \gamma_i$ and Equation (2.6) reduces to a traditional exponential model in survival analysis. The average age at infection can be calculated from Equations (2.4) and (2.6) for each state i :

$$A_i = \frac{L(1 - \alpha_i) \gamma_i - e^{-\gamma_i L} + 1}{\gamma_i}, \quad (2.8)$$

where life expectancy, L , is 70 years for Mexico in 1987-88 and assumed to be the same for all states.[52]

2.2.4 Statistical estimation of the force of infection of *H. pylori* infection

We used statistical methods to estimate the parameters α and γ that best fit the cumulative probability of infection in each state and then calculated the corresponding force of infection. Due to the high degree of variation in sample composition for each state in the NSS, traditional nonlinear least-squares (NLS) estimation yielded imprecise, unstable, or unrealistic estimates of the α and γ . This could translate into estimates of force of infection that are implausibly high or low with wide confidence intervals when only a small number of people are sampled (and, for instance, none are infected). For example, some states had individuals sampled at all ages and while others had limited data for certain ages. In Figure 2.2 we show the empirical prevalence in four different states with varying amounts of data and the predicted prevalence for these states using NLS. Nuevo Leon and Mexico City have more data and more variability in terms of disease status compared to the states of Baja California Sur and Morelos. The state of Baja California Sur is a state where all adults sampled older than twenty years old ($n=24$) are positive for *H. pylori*. The resulting parameter estimates are implausibly high based on our current knowledge of *H. pylori*.

In order to solve these issues, we instead implemented a hierarchical Bayesian nonlinear model that "borrows" information from all states when estimating state-specific effects. Such models have been described in detail elsewhere [53] and are known to reduce mean squared error of model estimates in some settings. We are unaware of these models having been applied to catalytic models to estimate force of infection. We first use hierarchical Bayesian nonlinear models to estimate the posterior distribution of the α and γ parameters of model (2.6) for each of the 32 states. We then estimate the aggregated and state-specific force of infection of *H. pylori* in Mexico.

2.2.5 Hierarchical nonlinear Bayesian model

We assume that for each state $i = 1, \dots, 32$ the number of infected individuals $y_i(a)$ at age a follows a binomial distribution where $n_i(a)$ is the sample size and $p_i(a)$ is the cumulative

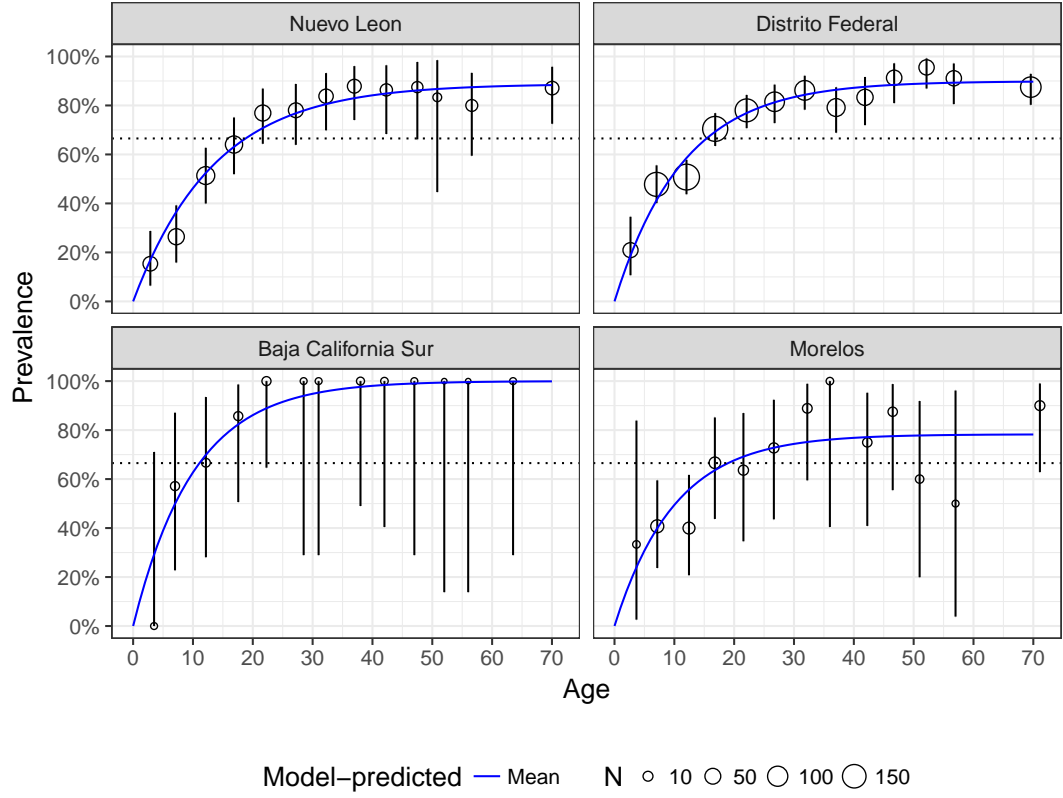


Figure 2.3: Empirical prevalence of *H. pylori* in Mexico by age in four different states with different amount of data, together with model-predicted prevalence using NLS. The upper two reflect states with data for all ages and the lower two reflect states with limited amount of data for some ages.

probability of infection (i.e., $F_i(a)$) in state i :

$$\begin{aligned}
 y_i(a) &\sim \text{Binomial}(n_i(a), p_i(a)), \\
 p_i(a) &= F_i(a) = \alpha_i (1 - e^{-\gamma_i a}), \\
 \begin{bmatrix} \alpha_i \\ \gamma_i \end{bmatrix} &\sim \text{MVN} \left(\begin{bmatrix} \alpha^0 \\ \gamma^0 \end{bmatrix}, \Sigma \right), \\
 \Sigma &\sim \text{IW} \left(\begin{bmatrix} 10^3 & 0 \\ 0 & 10^3 \end{bmatrix}, 2 \right),
 \end{aligned} \tag{2.9}$$

Note that each of the 32 states has its own set of parameters α_i and γ_i , but these state-specific parameters "borrow" information from each other by assuming that they collectively follow a multivariate Normal (*MVN*) distribution centered at α^0 and γ^0 , which can be interpreted as the average total infection probability and infection rate for all of Mexico.

For the covariance matrix, we use an inverse Wishart (*IW*) distribution of two degrees of freedom. The *IW* is a widely-used prior distribution for covariance matrices; the large diagonal entries and the zero off-diagonal entries in the matrix represent an uninformative prior on the variances and no prior correlation between α and γ parameters.[54] Uniform prior distributions (0-1) were specified for α and γ parameters.

Parameters of model (2.9) were estimated through Gibbs sampling, using Just Another Gibbs Sampler (JAGS).[55] We ran two Markov Chain Monte Carlo (MCMC) chains. For each chain 50,000 iterations were used to generate a posterior distribution after a 10,000 iterations burn-in period. The mean estimates and 95% credible intervals (CR) were derived from posterior distributions. For each chain, we used starting values computed from the solution of model (2.6) using NLS. To confirm whether the model provides a reasonable fit of the data, we plotted the observed prevalence by age with 95% confidence intervals, together with the model-predicted prevalence.

The force of *H. pylori* infection, $\lambda(a)$ and the average age of infection overall, A , and among those eventually becoming infected, A_e , were estimated within the MCMC model by evaluating Equations (2.7), (2.8) and (2.5) at each parameter set draw from the posterior distribution, respectively. We then calculated their posterior predicted mean and 95% credible interval. All statistical modeling was conducted in JAGS [55] and R version 3.2.4 (<http://www.r-project.org>).[56]

2.2.6 Model validation

To confirm the model provides a reasonable estimate of the force of infection, we compare the model-predicted $\lambda(a)$ to previous estimates of *H. pylori* infection incidence in 0-2 year-olds and in 5-13 year-olds in the states of Chihuahua and Mexico City, respectively.

2.3 Results

Table 2.1 presents the posterior summaries of the national-level α^0 and γ^0 parameters of the hierarchical nonlinear Bayesian model, and the average age of infection overall, A , and for those eventually infected, A_e . The posterior mean of the overall proportion of the population eventually infected (α^0) is 0.861 [95%CR:0.841-0.882]. The posterior mean of the overall constant infection rate (γ^0) is 0.093 [95%CR: 0.083-0.103]. We estimated an average age at infection overall, A , of 20.5 years [95%CR: 19.0-22.0] and for those eventually infected, A_e , of 12.5 years [95%CR: 11.3-13.8].

Table 2.1: Posterior mean estimates, SD, and lower and upper bounds of the 95% credible interval of the national-level asymptote and rate parameters of the catalytic epidemic model, average age at infection and average age at infection of those eventually infected

Parameter	Estimate	SD	LB	UB
α^0	0.861	0.010	0.841	0.882
γ^0	0.093	0.005	0.083	0.103
A	20.488	0.759	19.026	22.014
A_e	12.513	0.621	11.344	13.791

Figure 2.4 shows the α and γ parameter estimates by state. Parameter estimates exhibit substantial heterogeneity between states. More than a third of the states have posterior means of the proportion of population eventually infected outside the 95% credible interval of the national average [95%CR: 0.841-0.881]. Six states (Baja California Sur, Coahuila, Sinaloa, San Luis Potosi, Sonora and Mexico City) have posterior means above the upper bound of the national average while seven other states (Nayarit, Hidalgo, Tlaxcala, Tabasco, Oaxaca, Puebla and Veracruz) have estimates below the lower bound of the national average. Half of the states have posterior means of the infection rate parameter outside the 95% credible interval of the estimated national average [95%CR: 0.084-0.103]. Eight states (Chiapas, Chihuahua, Guanajuato, Guerrero, Baja California Sur, Tamaulipas, Queretaro and Aguascalientes) have posterior means above the upper bound of the national average and eight other states (Michoacan, Nayarit, Zacatecas, Yucatan, Nuevo Leon, Hidalgo, Veracruz and Colima) have lower estimates than the lower bound of the national average.

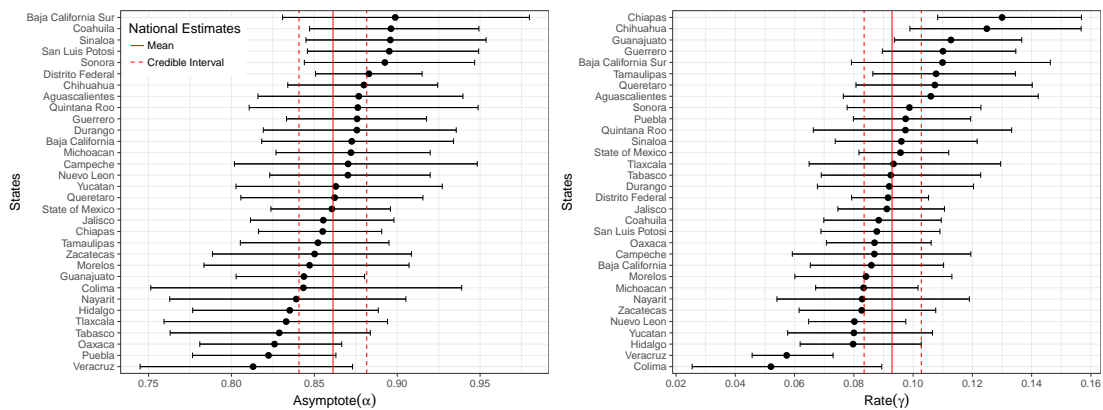


Figure 2.4: State-specific posterior mean and 95% credible interval for the asymptote and rate parameters. Solid and dashed vertical lines represent the national-level posterior mean and 95% credible interval, respectively.

Figure 2.5 shows the observed national prevalence of *H. pylori* by age in Mexico, together with the model-predicted prevalence. All but three model-predicted prevalence lie between the 95% confidence bounds of the empirical data. For one- and two-year olds the model-predicted prevalence lies below the bounds, favoring lower prevalence than those observed for these ages. Figure 2.6 shows the observed and model-predicted state-specific prevalence of *H. pylori* by age using both the hierarchical Bayesian and the NLS models. The width of the model-predicted credible bounds is a function of the amount of data used to estimate the state-specific prevalence. States for which more data is available have tighter credible bounds than states with limited data. The predicted prevalence from the NLS model are sensitive to small sample sizes overestimating the prevalence on ages for which data are skewed towards infection. The hierarchical Bayesian model shrinks the estimated prevalence for states with limited data towards the overall mean.

2.3.1 Force of infection

Figure 2.7 shows the model-predicted national force of infection of *H. pylori* by age in Mexico. The force of infection starts at 0.08 right after birth and decreases to zero as age increases. Like α_i and γ_i , the state-specific force of infection varies considerably across states (Figure 2.8). At birth, estimates of the force of infection were as high as 0.10 (Chiapas and Chihuahua) and as low as 0.04 (Colima and Veracruz).

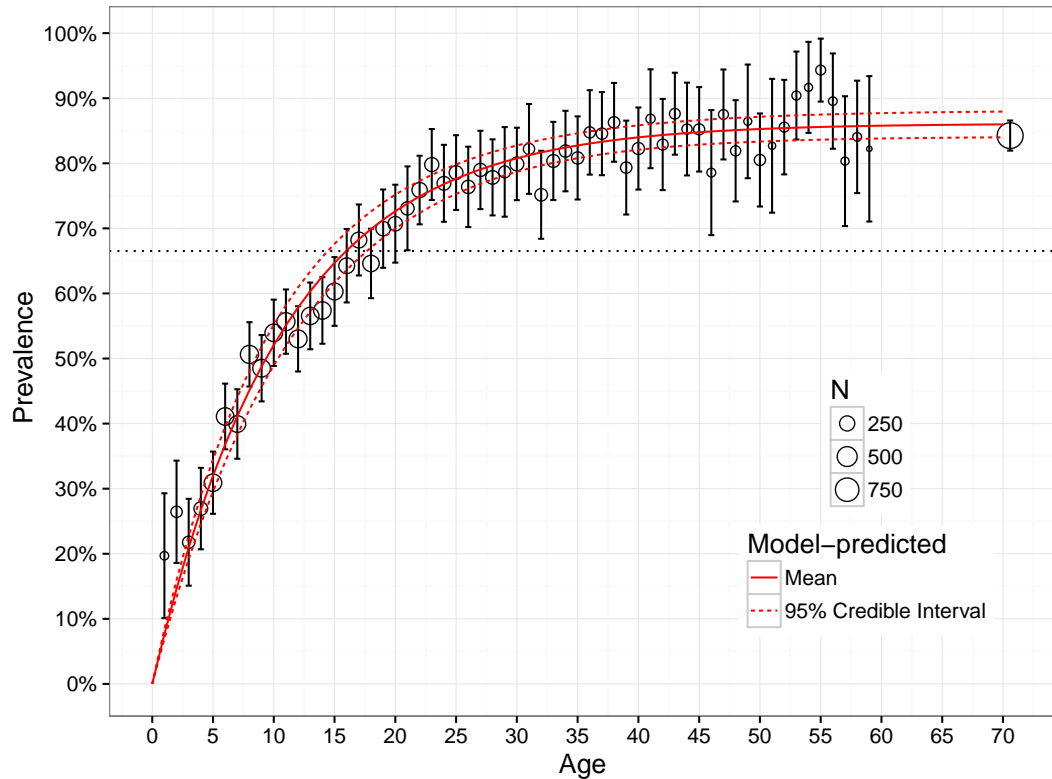


Figure 2.5: Model fit to the national prevalence of *H. pylori* by age in Mexico in 1987-88. Gray circles denote empirical prevalence with size proportional to sample size, and 95% confidence interval per 1-year age group. The red solid line denotes the model-predicted posterior mean and the red dashed lines denote the 95% credible bounds.

2.3.2 Model validation

The model-predicted force of infection is comparable with annual incidence rates of 6.56% [95%CI: 4.6%-8.53%] in 5-8 years old and 6.01% [95% CI: 3.52% - 8.5%] in 9-13 years old obtained by observing *H. pylori* incidence over time in Mexican school children who initially tested negative for the infection.[57] Another study estimated the infection rate to be 19.84% [95%CI: 16.43%-23.25%] from birth to two years old in a cohort of children in El Paso, Texas, and Ciudad Juárez (Chihuahua), which is consistent with our assumption that the force of infection is highest at birth and decreases with age.[58]

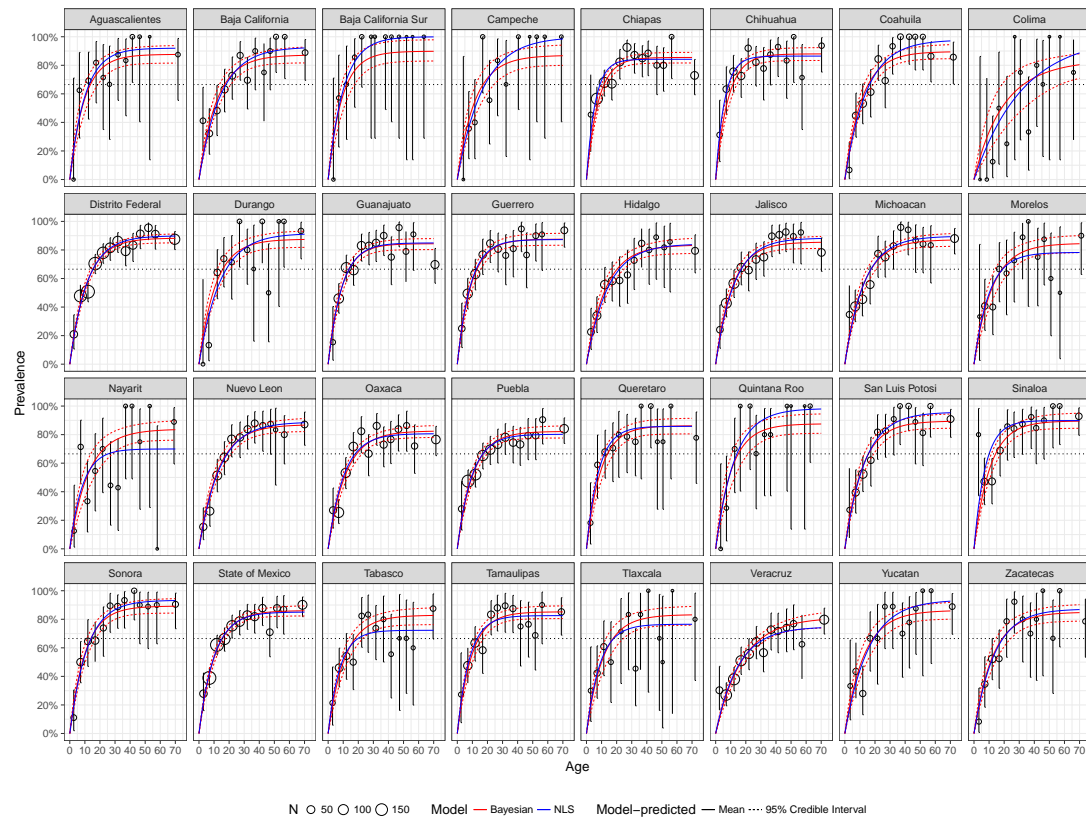


Figure 2.6: Model fit to the state-specific prevalence of *H. pylori* by age in Mexico in 1987-88. Gray circles denote empirical prevalence with size proportional to sample size, and 95% confidence interval. The red solid line denotes the model-predicted posterior mean and the red dashed lines denote the 95% credible bounds.

2.4 Discussion

In this study, we used catalytic models to estimate the force of infection of *H. pylori* in Mexico at the national level, but also at the state level, accounting for state-level heterogeneity. By estimating state-specific parameters simultaneously using a hierarchical nonlinear Bayesian model, we obtained reasonable parameter estimates even for states that were sparsely sampled in a national seroprevalence survey. Sero-epidemiologic studies offer a rich source for understanding infection dynamics, and under certain assumptions these can be used to estimate the force of infection. Catalytic models have been previously used to estimate the force of infection of other

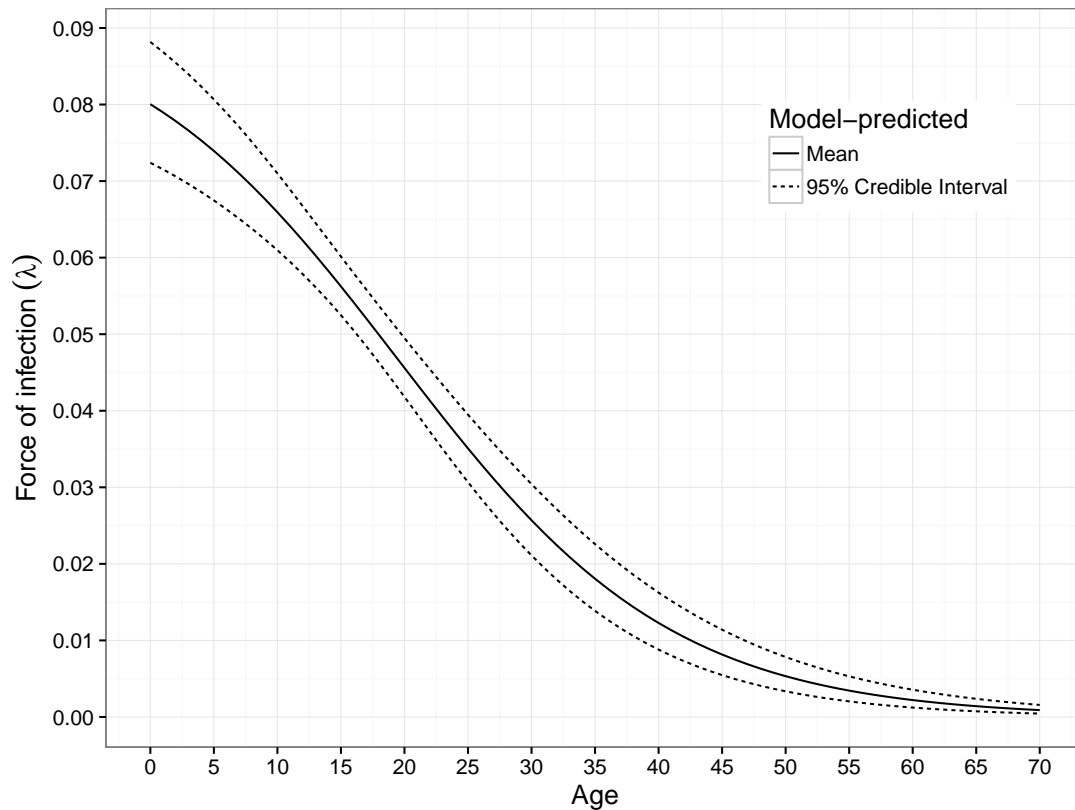


Figure 2.7: Model-predicted national force of infection of *H. pylori* by age in Mexico in 1987-88. The solid line denotes the model-predicted posterior mean and the dashed lines denote the 95% credible bounds.

diseases but have not previously been applied of *H. pylori*.

The hierarchical Bayesian approach used to estimate the catalytic model of *H. pylori* allowed us to account for state-specific heterogeneity in the force of infection. Specifically, we obtained better inference for under sampled states and quantified the variation across states.

We found that age-specific prevalence of *H. pylori* varies greatly by state. In addition, we found great variation in the proportion of the population who eventually becomes infected (α) and the rate of infection among those who eventually become infected (γ) across states. These contrasting differences translate into high variation in the force of infection, which can have implications in prevention and treatment strategies and highlights the need of state-specific interventions.

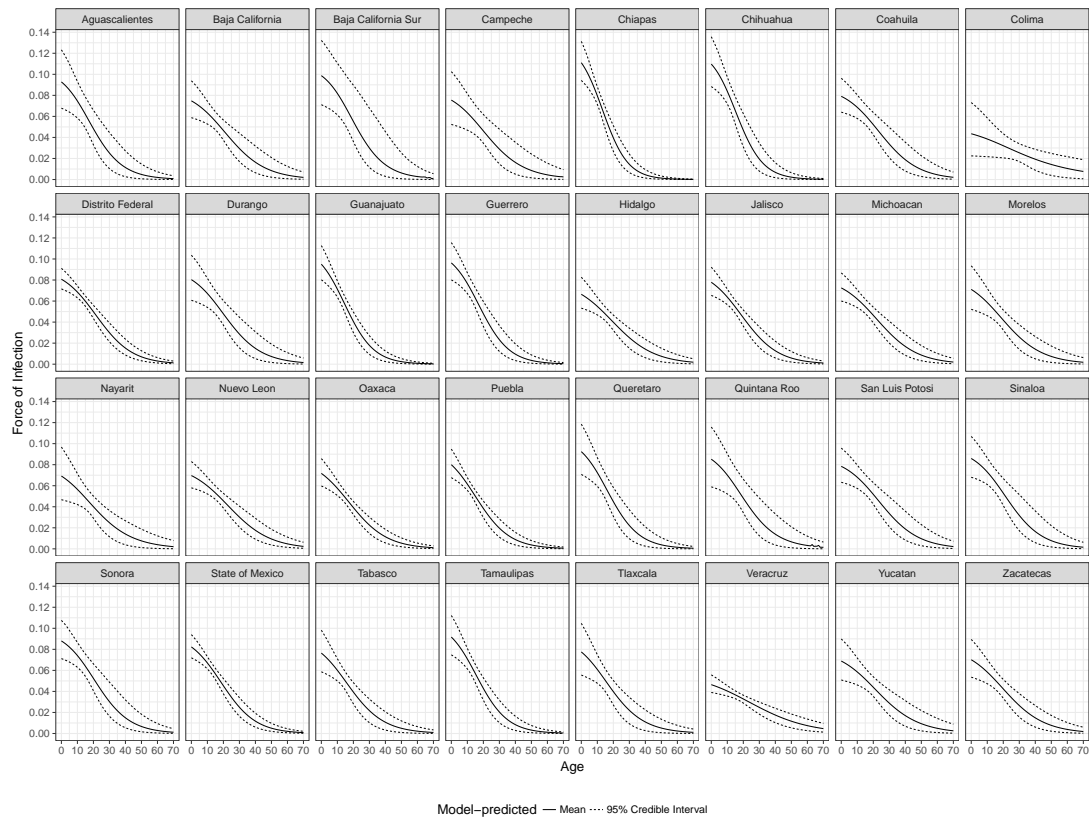


Figure 2.8: Model-predicted state-specific force of infection of *H. pylori* by age in Mexico in 1987-88. The solid line denotes the model-predicted posterior mean and the dashed lines denote the 95% credible bounds.

Our study does have several limitations. We imposed a constrained exponential functional form on the cumulative probability of infection, which may have overly restricted our parameter estimates and the predicted force of infection. For example, the model-predicted *H. pylori* prevalence consistently falls below observed prevalence for children under 2 years old, nationally and for many states, which may indicate that the force of infection at these ages is being underestimated. A more flexible catalytic model, such as a piecewise or a spline model, could have provided a better fit to the data.[59, 60] However, by using these more flexible models we lose the ability to link the model parameters directly to the disease process. We also assumed that the Mexican population is in endemic equilibrium with respect to *H. pylori* infection, which means that there the force of infection does not change over time. While antibiotic treatment

for *H. pylori* was not widespread prior to 1991,[61, 62] this assumption could still be violated if other factors related to *H. pylori* transmission, such as improved sanitation, have changed prior to 1987 (the year when NSS started collection). In addition, we assumed that disease-related mortality is negligible compared to all-cause mortality. This would seem reasonable in the case of *H. pylori*, but because it is a carcinogenic agent, there is a small fraction of the infected population who will develop gastric cancer and face an elevated mortality risk.

Despite these limitations, we believe this work represents a proof of principle for the use of catalytic epidemic models to estimate the force of infection of *H. pylori* using national seroepidemiologic data.

Although we found and quantified the high variation across states, we did not explain potential sources for this variation. Some of these state-level explanatory variables might include level of socioeconomic development, sanitation, education and percentage of population living in rural areas. These factors could be used to model both the proportion of the population who eventually becomes infected (α) and the rate of infection among those who eventually become infected (γ). Mexico has a high sociodemographic variation in its states, so the estimated influence of state-level characteristics on the force of infection might be relevant to other Latin American countries. This, however, is a topic of further research.

While our analysis relied on data specifically from Mexico, there are many other low-to-middle income countries that face a similar burden of gastric cancer, where *H. pylori* is thought to be the dominant cause.[63, 64, 65] Many of these countries are in Latin America and likely have similar transmission dynamics.[1]

Application of our model to more recent sero-epidemiologic data in Mexico could help assess if the force of infection of *H. pylori* has changed in time because of antibiotic treatment, cohort effects or changes in other sociodemographic variables. In addition, serological data have been employed to estimate the parameters of dynamic transmission models[66, 67] that are then used to estimate the effectiveness and cost-effectiveness of different treatment or vaccination strategies.[21, 68, 69] The methodology and results of this study could be used to estimate the transmission parameters for dynamic transmission models of *H. pylori* to evaluate different screen-and-treat strategies or estimate the benefits of a potential vaccine, which are currently under development.[70, 71, 72, 73] Identifying populations at greatest risk of *H. pylori* infection will further the development of appropriately targeted prevention, screening, and treatment strategies.

Chapter 3

Modeling the impact of antibiotic consumption on the epidemiology of *Helicobacter pylori* in the presence of antibiotic resistance

3.1 Introduction

3.1.1 *H. pylori*

Helicobacter pylori (*H. pylori*) is one of the most prevalent chronic bacterial infections in the world and poses a significant public health threat. The gram-negative, microaerophilic bacterium is commonly found in the epithelial lining of the human stomach.[41] *H. pylori* is a risk factor for gastric cancer and gastric ulcers.[1, 2, 38, 39]

Once infected, the human immune response to *H. pylori* is often not sufficient to clear the infection and individuals who do not receive antibiotic treatment may experience life-long infections,[18] because spontaneous clearance is rare.[17] The global burden of disease is substantial, with *H. pylori* present in the stomach of half of the world's population; however, infection is much more common in developing than in developed countries. [12, 74, 75, 76] *H. pylori* most heavily burdens low- and middle-income countries (LMICs) where the proportion of people infected is approximately 70%.[42, 43]

The mode of transmission of *H. pylori* remains unclear, though it appears to occur through close personal contact, such as oral-oral or fecal-oral, particularly within the family and typically in early childhood.[1, 4, 5, 7, 8, 9, 10, 11, 13] Infection risk peaks in early childhood and risk seems to decrease with age.[12, 16]

3.1.2 Antibiotic treatment and resistance

H. pylori infection can be cleared with antibiotics, which in theory can reduce the risk of gastric cancer, duodenal and gastric ulcers, but previously infected individuals are at risk of reinfection.[25, 26] Several population-wide mass treatment programs have been implemented or proposed to eradicate *H. pylori* infection with the goal of reducing gastric cancer burden.[1, 36, 44, 77, 78, 79] However, no study has shown definitive evidence on reducing incidence of gastric cancer.[80] For example, a population-based mass eradication of *H. pylori* infection was undertaken in Taiwan from 2004 to 2008.[81] This program showed reductions in the incidence of *H. pylori* infection, gastric atrophy and peptic ulcer disease, but the incidence and severity of premalignant lesions such as intestinal metaplasia remained unchanged.[36] Model-based cost-effectiveness analyses have shown that *H. pylori* eradication programs would be cost-effective if they prevented at least 10% of gastric-cancer deaths and peptic ulcer disease.[82, 83, 84, 85, 86, 87]

However, the modest benefits of *H. pylori* mass eradication programs may be outweighed by the development of treatment-induced antibiotic resistance (ABR), which was not accounted for in these prior studies. Antibiotic treatment induces ABR by imposing a selective pressure for bacteria to mutate and develop resistance while eliminating susceptible strains. An indiscriminate use of antibiotics may lead to widespread ABR. Non-adherence and ABR are the main causes of *H. pylori* treatment failure.[26, 27, 28, 29, 30, 31] ABR reduces the effectiveness of treatment and represents one of the greatest emerging global health threats.[32, 33, 34] Resistant strains of *H. pylori* have been identified to most antibiotics typically used to treat it, particularly in Latin America.[35] Compared to other antibiotics, the prevalence of clarithromycin-resistant *H. pylori* has been one of the most rapidly increasing in many countries over the past decade.[88] Furthermore, the World Health Organization (WHO) recently published a priority pathogens list that includes clarithromycin-resistant *H. pylori*. [89] Policies aimed at population-wide *H. pylori* eradication could have serious repercussions.[90] The impact of the increased antibiotic consumption resulting from the mass treatment of *H. pylori* on *H. pylori* resistance is unknown

and difficult to assess using standard study designs.

The purpose of this chapter is twofold: 1) to develop a dynamic mathematical model of the infection and resistance of *H. pylori* that represents the Mexican population, and 2) to apply the model to evaluate the impact of different antibiotic usage strategies on the prevalence of *H. pylori* infection and resistance. The mathematical model is comprised of three main components to simulate the Mexican population over time. The first component describes the epidemiologic model specifying how *H. pylori* is transmitted from person to person as a function of age. The second component describes the background use of antibiotics in the population over time and the mechanism by which ABR of *H. pylori* arises. And finally, the third component evaluates different policies of targeted antibiotic use for *H. pylori*. This will be the first model to comprehensively combine these components in one model.

3.2 Methods

Our transmission dynamic model has demographic, epidemiologic and resistance components. The demographic model defines the demographic characteristics of the population being simulated and describes how persons enter, age, and exit various categories. The epidemiologic and resistant model simulates *H. pylori* infection in the Mexican population over time. We divided the population into distinct epidemiologic categories, according to the person's status with respect to infection, type of infection strain (i.e., sensitive or resistant) and treatment.

3.2.1 The epidemiologic model

The epidemiologic model of *H. pylori* in the absence of treatment can be described as a susceptible -infected (SI) model.[24, 91] In a simple SI model the population is divided into two compartments: susceptibles (S) and infected (I).[92, 93, 94, 95] Each of these compartments represent an epidemiologic variable as a function of time. The transmission dynamics in a simple SI model can be described by the following system of ordinary differential equations (ODEs)

$$\begin{aligned}\frac{dS}{dt} &= b - (\beta I + \mu)S, \\ \frac{dI}{dt} &= \beta IS - \mu I,\end{aligned}\tag{3.1}$$

where susceptibles become infected at a rate βI through contact with infected individuals, new individuals enter the population into the susceptible compartment at a rate b , and all individuals face a mortality rate of μ . Figure 3.1 illustrates the transmission dynamics of a simple ODE SI model.

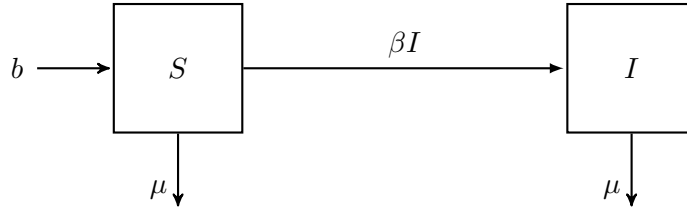


Figure 3.1: Simplified diagram of a SI model describing the transmission dynamics of *H. pylori*.

To appropriately model the age-dependent dynamics of *H. pylori* infection, we expanded the simple SI model to include a realistic age structure (RAS) and heterogeneous age-structured mixing. We divided the population into n age groups and each age group, i , has its own set of susceptible and infected compartments, S_i and I_i , respectively, for $i = 1 \dots, n$. The RAS SI model for *H. pylori* is described by the following system of $2n$ ODEs:

$$\begin{aligned} \frac{dS_i}{dt} &= b_i + d_{i-1}S_{i-1} - \lambda_i S_i - (d_i + \mu_i)S_i, \\ \frac{dI_i}{dt} &= d_{i-1}I_{i-1} + \lambda_i S_i - (d_i + \mu_i)I_i, \end{aligned} \quad (3.2)$$

which are parameterized by the age-specific force of infection (λ_i), aging rate (d_i), mortality rate (μ_i), and birth rate (b_i). New individuals are assumed to enter the model only through birth into the youngest age group, so b_i is defined as

$$b_i = \begin{cases} b & \text{if } i = 1 \\ 0 & \text{otherwise} \end{cases} \quad (3.3)$$

The demographic parameters d_i , μ_i and b are calculated using the methods described in section 3.2.3.

Force of infection

The force of infection (FOI), λ , is the key quantity governing the transmission of infection within a given population, defined as the instantaneous per capita rate at which susceptibles

acquire infection. FOI reflects both the degree of contact between susceptibles and infected and the transmissibility of the pathogen per contact. Since contact is age dependent, typically higher in children than in infants or adults, the force of infection of *H. pylori* is itself a function of age [46]. In Chapter 2, we estimated the age-specific FOI of *H. pylori* in Mexico using a catalytic epidemic modeling approach on a nationally representative seroepidemiology survey conducted prior to widespread antibiotic treatment.

The age and time dependent force of *H. pylori* infection is defined as

$$\lambda(a, t) = \sum_{a'=1}^N \beta(a, a') I(a', t), \quad a = 1, \dots, N, \quad (3.4)$$

where the transmission rate, $\beta(a, a')$, describes the probability that an infected individual of age a' will infect a susceptible of age a per unit of time.

The elements $\beta(a, a')$ will be estimated from the pre-antibiotic treatment force of infection using Equation (3.4) assuming steady state, which means that FOI varies by age but does not change over time (i.e., calendar year). That is,

$$\lambda(a, t) = \lambda(a) = \sum_{a'=1}^N \beta(a, a') I(a'), \quad a = 1, \dots, N \quad (3.5)$$

To simplify notation and manipulation, we express the FOI in the following matrix notation

$$\lambda = \beta I$$

$$\begin{bmatrix} \lambda(1) \\ \lambda(2) \\ \vdots \\ \lambda(N) \end{bmatrix} = \begin{bmatrix} \beta_{1,1} & \beta_{1,2} & \cdots & \beta_{1,N} \\ \beta_{2,1} & \beta_{2,2} & \cdots & \beta_{2,N} \\ \vdots & \vdots & \ddots & \vdots \\ \beta_{N,1} & \beta_{N,2} & \cdots & \beta_{N,N} \end{bmatrix} \begin{bmatrix} I(1) \\ I(2) \\ \vdots \\ I(N) \end{bmatrix}, \quad (3.6)$$

where $\beta_{a,a'} = \beta(a, a')$. The FOI $\lambda(a)$ represents the rate of disease transmission from infected people in all age groups to susceptibles in age group a . [96]

The standard technique to take account of mixing patterns between members of a population based on different characteristics, such as age, is to use a Who-Acquired-Infection-From-Whom (WAIFW) matrix. The WAIFW matrix has N^2 elements, representing mixing between each pair of age groups in the model. The FOI in Equation (3.6) is therefore a system of N equations. Fixing λ to the FOI estimated in Chapter 2 and I to *H. pylori* prevalence data, equation (3.6)

can be solved to uniquely estimate WAIFW matrix values as long as the WAIFW structure can be specified in terms of up to N parameters. We consider four types of mixing structures that meet this criterion.

Who-acquires-infection-from-whom (WAIFW) matrix

The WAIFW matrix represents the effective contact rate between age groups a and a' , and the probability of infection of an individual in age group a given a contact with an infected of age a' . That is, each element of the WAIFW matrix is the rate at which an infected individual of age a' will infect a susceptible of age a per unit time. The elements of the WAIFW matrix cannot be observed directly so they must be estimated, ideally from the FOI in the absence of antibiotic treatment.

Data on how the population in Mexico mixes across ages are limited, therefore it is necessary to assess how different mixing structures influence results. As a structural sensitivity analysis, we proposed four different WAIFW matrices with six different transmission parameters each shown in Table 3.1. We divided the population into $N = 6$ discrete age classes guided by the age groupings of the educational system in Mexico: $[0, 2)$, $[2, 6)$, $[6, 12)$, $[12, 19)$, $[19, 45)$, $[45, 70)$. Notice that these age groups are coarser than are modeled in the demographic model. The 6×6 WAIFW matrix represents mixing across age groups. To simplify the number of different elements in the WAIFW matrices, we assume that interactions between age groups are symmetric such that $\beta_{a,a'} = \beta_{a',a}$.

The first two WAIFW matrices, W_1 and W_2 , represent different social mixing behaviors that differ between age groups. The third WAIFW matrix, W_3 , represents similar behavior across all age groups of infected individuals for each age group of susceptibles. The WAIFW matrix with zeros in the off-diagonals represents a fully assortative matrix where individuals interact with other individuals only within the same age group.

Table 3.1: Four different WAIFW matrix structures

$$\begin{aligned}
W_1 &= \begin{pmatrix} \beta_1 & \beta_1 & \beta_3 & \beta_4 & \beta_5 & \beta_6 \\ \beta_1 & \beta_2 & \beta_3 & \beta_4 & \beta_5 & \beta_6 \\ \beta_3 & \beta_3 & \beta_3 & \beta_4 & \beta_5 & \beta_6 \\ \beta_4 & \beta_4 & \beta_4 & \beta_4 & \beta_5 & \beta_6 \\ \beta_5 & \beta_5 & \beta_5 & \beta_5 & \beta_5 & \beta_6 \\ \beta_6 & \beta_6 & \beta_6 & \beta_6 & \beta_6 & \beta_6 \end{pmatrix}, & W_2 &= \begin{pmatrix} \beta_1 & \beta_1 & \beta_1 & \beta_4 & \beta_5 & \beta_6 \\ \beta_1 & \beta_2 & \beta_3 & \beta_4 & \beta_5 & \beta_6 \\ \beta_1 & \beta_3 & \beta_3 & \beta_4 & \beta_5 & \beta_6 \\ \beta_4 & \beta_4 & \beta_4 & \beta_4 & \beta_5 & \beta_6 \\ \beta_5 & \beta_5 & \beta_5 & \beta_5 & \beta_5 & \beta_6 \\ \beta_6 & \beta_6 & \beta_6 & \beta_6 & \beta_6 & \beta_6 \end{pmatrix}, \\
W_3 &= \begin{pmatrix} \beta_1 & \beta_1 & \beta_1 & \beta_1 & \beta_1 & \beta_1 \\ \beta_2 & \beta_2 & \beta_2 & \beta_2 & \beta_2 & \beta_2 \\ \beta_3 & \beta_3 & \beta_3 & \beta_3 & \beta_3 & \beta_3 \\ \beta_4 & \beta_4 & \beta_4 & \beta_4 & \beta_4 & \beta_4 \\ \beta_5 & \beta_5 & \beta_5 & \beta_5 & \beta_5 & \beta_5 \\ \beta_6 & \beta_6 & \beta_6 & \beta_6 & \beta_6 & \beta_6 \end{pmatrix}, & W_4 &= \begin{pmatrix} \beta_1 & 0 & 0 & 0 & 0 & 0 \\ 0 & \beta_2 & 0 & 0 & 0 & 0 \\ 0 & 0 & \beta_3 & 0 & 0 & 0 \\ 0 & 0 & 0 & \beta_4 & 0 & 0 \\ 0 & 0 & 0 & 0 & \beta_5 & 0 \\ 0 & 0 & 0 & 0 & 0 & \beta_6 \end{pmatrix}.
\end{aligned}$$

3.2.2 Resistance model

Resistance develops from an evolutionary perspective as a consequence of the mutation of the bacteria in response to antibiotic therapy and of the selection pressure that provides a competitive advantage for mutations that result in resistance.[97] Based on molecular studies, drug resistance in *H. pylori* is predominantly due to mutations rather than the transfer of genetic material from a resistant strain to a sensitive strain.[98, pg. 216], [99, pg. 304],[100], [101, pg. 703] and [102, pg. 1278]. This means that resistance in *H. pylori* is mainly caused when sensitive strains are exposed to antibiotics as opposed to sensitive strains picking up resistance genes when infecting individuals harboring other resistant bacteria (due to recent past antibiotic use, for example). If a small proportion of susceptible *H. pylori* bacteria develop a resistant mutation, it will survive a course of treatment and then repopulate the stomach.[27] Therefore, treating again with the same antibiotic will have a significant reduction in effectiveness and *H. pylori* infection will persist with the possibility of spreading the resistant bacteria to other individuals.

Studies looking at the dynamics of antibiotic resistance in *H. pylori* are scarce and have been conducted mostly in non-human settings. One study estimated that mutation frequencies

to the development of clarithromycin resistance in mice initially infected with clarithromycin-sensitive *H. pylori* range from 1×10^{-7} to 5×10^{-9} per hour.[103] In humans, some insight can be gained from a study that estimated a probability of 0.375 of sensitive strains becoming resistant after an initial course of treatment.[104]

To represent the dynamics of ABR in *H. pylori* we expanded the SI model described in section 3.2.1 into a susceptible-infected-susceptible (SIS) model[92, 94, 95, 105, 106] with additional compartments to represent sensitive and resistant infections, and states for active treatment.[107, 108, 109, 110] In the SIS model, individuals are born into an antibiotic-free susceptible class (S^0). When individuals become infected, they may be colonized by either sensitive (I_w) or resistant strains (I_r). Infected states are further divided into untreated (I_r^0 or I_w^0) and treated (S^0 or I_r^1) states, where $I_r = I_r^0 + I_r^1$. Susceptible individuals in the absence of treatment may be infected by either sensitive I_w^0 or resistant I_r bacteria.

Antibiotic treatment is applied at a rate ψ_p (which depends on the treatment policy) and is assumed to clear sensitive strains with probability $(1 - \sigma)$ or induce acquired resistance with probability σ . In addition, the model allows for background use of antibiotics; which may or may not be related to *H. pylori* infection but that can induce resistance,[111] at a rate α . Thus, individuals are prescribed antibiotics at a rate $\alpha + \psi_p$ and enter either a treated susceptible compartment S^1 (from both S^0 and I_w^0) or a treated resistant compartment I_r^1 (only from I_w^0 if resistance is developed).

Generally, there are two mechanisms by which resistance can be conferred: (i) selection of resistant mutants during treatment ($I_w^0 \rightarrow I_r^1$), which follows the model above; and (ii) plasmid transfer from hosts colonized with resistant strains ($I_w^0 \rightarrow I_r^0$). Given the lack of information for plasmid transfer in the case of *H. pylori* we will only consider treatment-induced resistance.

Following the introduction of antibiotic treatment for either other infections not related to *H. pylori* or targeted specifically for *H. pylori* infection, a proportion $p_a = S^1 + I_r^1$ are being treated with antibiotics at all times. This model structure for representing antibiotic resistant infections was originally proposed by Austin et al. (1997) [107] and further described in a subsequent article.[109] The dynamics of these compartments are described by the following

ODEs:

$$\begin{aligned}
\frac{dS^0}{dt} &= b - [\beta I_w^0 + \beta' I_r + \alpha + \psi_p + \mu] S^0 + f I_w^0 + \gamma S^1 + f' I_r^0, \\
\frac{dI_w^0}{dt} &= -[\xi I_r + \alpha + \psi_p + f + \mu] I_w^0 + \beta I_w^0 S^0, \\
\frac{dI_r^0}{dt} &= -[\alpha + \psi_p + f' + \mu] I_r^0 + \beta' I_r S^0 + \xi I_r I_w^0 + \gamma I_r^1, \\
\frac{dS^1}{dt} &= -[\beta' I_r + \gamma + \mu] S^1 + f' I_r^1 + (\alpha + \psi_p) S^0 + (\alpha + \psi_p)(1 - \sigma) I_w^0, \\
\frac{dI_r^1}{dt} &= -[\gamma + f' + \mu] I_r^1 + (\alpha + \psi_p) I_r^0 + (\alpha + \psi_p) \sigma I_w^0 + \beta' I_r S^1,
\end{aligned} \tag{3.7}$$

where $I_r = I_r^0 + I_r^1$ and primes denote parameters for resistant strains, α is the prescribing rate (per unit time), $1/\gamma$ the average length of treatment (typically days) and $1/f$ the average duration of infection (typically months or years). In the case of *H. pylori* we assume that individuals remain infected in the absence of treatment (i.e., $f = 0$). Resistance is assumed to be associated with some fitness cost, which could be in the form of either reduced transmissibility via $\beta' \leq \beta$ (where $\beta' = \phi\beta$ and $\phi \in [0, 1]$) or decreased duration of infection via $f' \geq f$, or both. The parameter ϕ represents the protection provided by treatment as reduced infectivity. Plasmid transfer is measured by the transmission parameter, ξ which is analogous to β' , equal to the contact rate between infected multiplied by the probability that the plasmid is transferred between infected. Typically, $\xi \leq \beta'$. Demographics are described in more detail in section 3.2.3. Figure 3.2 describes the transmission dynamics of the SIS ODE model of ABR in *H. pylori* defined in Equation (3.7).

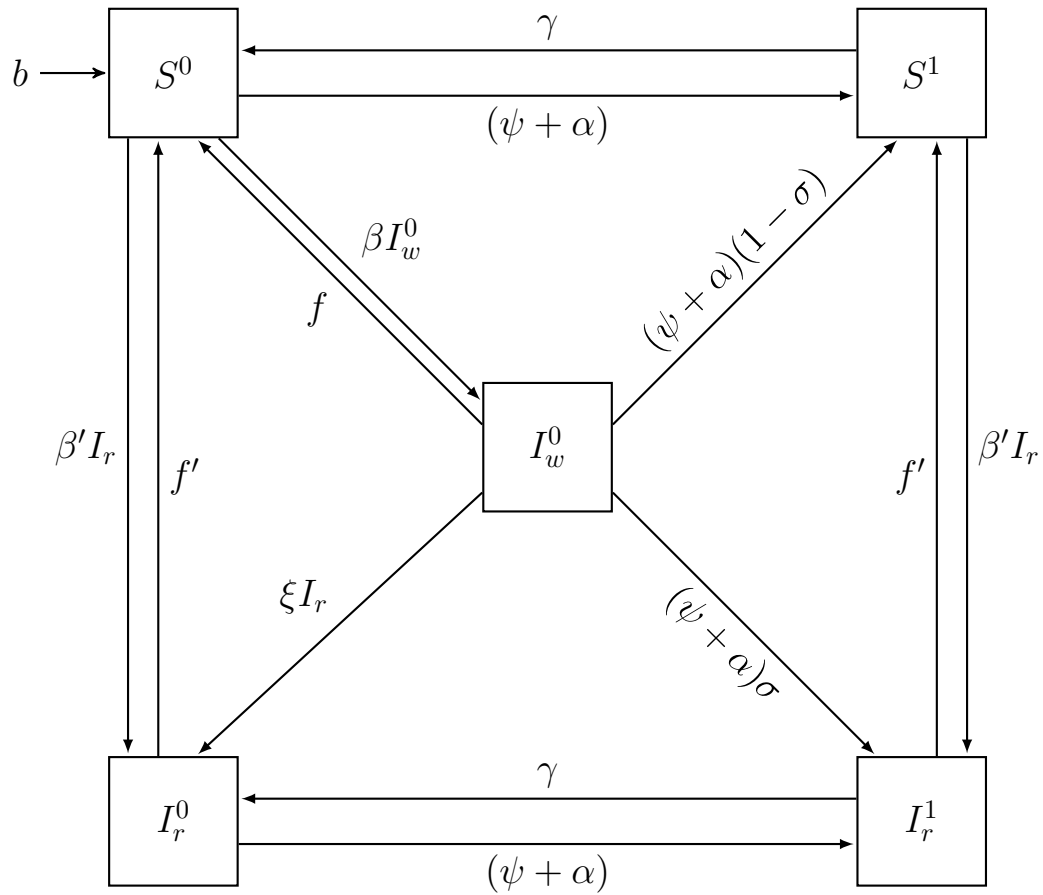


Figure 3.2: SIS model of antibiotic therapy and infection incorporating drug-sensitive and resistant strains. $I_r = I_r^0 + I_r^1$ and primes denote parameters for resistant strains, α is the prescribing rate (per unit time), $1/\gamma$ the average length of treatment (typically days) and $1/f$ the average duration of infection (typically months or years). Antibiotic treatment is assumed to either clear sensitive strains or induce acquired resistance with probability σ .

A **key assumption** of model (3.7) is that treatment is completely ineffective at clearing resistant *H. pylori* strains.

In the case of *H. pylori* we assume that there is no fitness cost to resistance (i.e., $\phi = 1$) and that resistance does not occur through plasmid transfer (i.e., $\xi = 0$). The probability at which infected individuals with *H. pylori* become resistant after an initial course of treatment, σ , equals 0.375 (95%CI: [0.04, 0.71]). This value was obtained from a study where three individuals out

of eight total infected with *H. pylori* sensitive strains prior to treatment developed resistance after treatment.[104]

The description of the variables, subscripts and superscripts of the SIS model in the presence of ABR are shown in Table 3.2

Table 3.2: Description of variables, subscripts and superscripts

Symbol	Description
Subscripts	
i, j	Age groups
k	Treatment status (no treatment=0, treatment=1)
m	Type of strain (sensitive = w , resistant = r)
p	Antibiotic treatment policy
Variables	
λ_i	Force of infection at age i
S_i^k	Susceptible with treatment status k in age group i
I_{mi}^k	Infected with type of strain m and treatment status k in age group i
A_i	Antibiotic consumption

3.2.3 Parameters

The SIS model has two sets of parameters that require estimation. The first set consists of parameters reflecting the demographic dynamics of the Mexican population (birth, death and aging). The second set consist of the transmission parameters of the WAIFW matrices.

Demographic parameters

The demographic dynamics can be thought as independent from the infection dynamics. As such, these can be represented through the demographic model described in Appendix A.

We estimated the demographic parameters that describe the proportion of the population in each age group, their corresponding aging and death rates, and the rate at which new individuals enter the youngest age group (i.e., the birth rate) using the equations shown in Appendix A.

We divided the population into yearly age groups from ages 0 to 69 and a single age group for those aged 70 years or older. This yielded a total of 71 age groups. The death rates were

obtained from vital statistics from Mexico's 2012 life tables.[112] The annual growth rate q of this demographic model was set to zero and b was derived so that the population would be stable in the absence of deaths from gastric cancer (Equation (A.5)). This will ensure that variation in the results across strategies is mainly due to epidemiologic and program features rather than peculiar characteristics of the demographic model.[113]

WAIFW matrix parameters

To estimate the six transmission parameters $[\beta_1, \beta_2, \beta_3, \beta_4, \beta_5, \beta_6]$ of the WAIFW matrices, we used a maximum likelihood estimation (MLE) approach where we assumed the FOI estimated with the catalytic model comes from a normal distribution with mean defined by the multiplication of the WAIFW matrix β and the proportion of individuals infected at each age $I(a)$, that is

$$\begin{aligned} \lambda^{CM}(a) &\sim \text{Normal}(\hat{\lambda}(a), \sigma_a^{CM}), \\ \hat{\lambda}(a) &= \beta I(a), \end{aligned} \tag{3.8}$$

where $\lambda^{CM}(a)$ is the mean and σ_a^{CM} is the standard deviation of the estimated FOI from the catalytic model described in section 2.3.1 with data from a nationally representative survey of *H. pylori* infection in Mexico.[45, 50]

All the parameters of the SIS model are described in Table 3.3.

Table 3.3: Description of parameters

Symbol	Description	Value	Source	Range
Demographic parameters				
b	Birth rate; entry rate into youngest age group (i.e., newborns)	0.014	Section 3.2.3	-
μ_i	Background mortality for age group i	age-specific	[112]	-
d_i	Aging rate of age group i (i.e., transfer rate between age groups)	age-specific	Section 3.2.3	-
l_i	Number of years within age group i	[1, 30]	Section 3.2.3	-
q	Annual rate of population growth	0	Assumed	-
Behavioral parameters				
β	Vector of transmission parameters of WAIFW matrix	Table 3.4	Section 3.2.3	95% CI
Biological parameters				
ϕ	Protection provided by treatment as reduced infectivity	1	Assumed	-
β'	Vector of transmission parameters of WAIFW matrix on treated individuals equal to $\phi\beta$	β	Section 3.2.3	-
ϕ_ξ	Reduction of infectivity due to plasmid transfer	0	Assumed	-
ξ	Plasmid transfer rate, equal to the contact rate multiplied by the probability that the plasmid is transferred between hosts (typically, $\xi = \phi_\xi\beta' \leq \beta'$)	0	Assumed	-
Treatment parameters				
α	Prescribing rate (per unit time)	0.3*	[114]	$[0, \infty)$

Description of parameters (continued)

Symbol	Description	Value	Source	Range
α_i	Prescribing rate (per unit time) for age group i	-	-	$[0, \infty)$
ψ_{pi}	Antibiotic treatment policy p for age group i	-	Section 3.2.4	$[0, \infty)$
$1/\gamma$	Average length of treatment (days)	14	[115]	-
σ	Probability that treatment induces mutation on sensitive strains and therefore does not clear colonization	0.375 [†]	[104]	[0.04, 0.71]

* DDDs/1000 per day

[†] From a study where three individuals out of eight total infected with *H. pylori* sensitive strains prior to treatment developed resistance after treatment.

3.2.4 Antibiotic treatment policies

We compared three different population-wide *H. pylori* treatment policies: a mass treatment strategy (AB all), where everyone in the population is treated with clarithromycin, and age-targeted treatment strategies focusing on 2 to 6 year-old children (AB 2-6 yo) or adults aged 40 years and older (AB 40+). We also simulated a no-treatment strategy as the base case. We assume that these mass-treatment programs are a one-time occurrence, are carried out over a single year and only apply to persons not already on antibiotics during the year. Following the one year intervention period, we then simulate the population (without further treatment) for X years (analytic horizon) to estimate the impact of different one-time mass-*H. pylori* treatment initiatives.[116]

3.2.5 Epidemiologic outcomes

Different antibiotic treatment policies could impact both prevalence of the disease and the prevalence of resistance. We assessed the epidemiologic impact of different patterns of antibiotic usage on the total antibiotic consumption and two epidemiological outcomes by age groups and on all the population over time: (1) prevalence of infection, and (2) prevalence of resistant

infection.

Antibiotic consumption

We calculated the volume of antibiotics consumed under each treatment strategy in terms of defined daily doses per 1000 adults (DDDs/1000) and is equivalent to the proportion of the population receiving treatment at any time. The age-specific antibiotic consumption, A_i , is given by

$$A_i = S_i^1 + I_{ri}^1, \quad (3.9)$$

and overall total consumption, A , is calculated as

$$A = \sum_{i=1}^n [S_i^1 + I_{ri}^1]. \quad (3.10)$$

Prevalence of infection

The age-specific prevalence of infection, PI_i , is given by

$$PI_i = \frac{\sum_{k=0}^1 \sum_{m \in \{w,r\}} I_{mi}^k}{\sum_{k=0}^1 (S_i^k + \sum_{m \in \{w,r\}} I_{mi}^k)}, \quad (3.11)$$

where I_{mi}^k is the proportion of the population infected with strain m , in a treatment status k and in age group i , and S_i^k is the proportion of the population susceptible in a treatment status k and in age group i .

The prevalence of infection on all the population PI is calculated as

$$PI = \frac{\sum_{i=1}^n \sum_{k=0}^1 \sum_{m \in \{w,r\}} I_{mi}^k}{\sum_{i=1}^n \sum_{k=0}^1 (S_i^k + \sum_{m \in \{w,r\}} I_{mi}^k)}. \quad (3.12)$$

Prevalence of resistant infection

The prevalence of resistant infection is defined as the proportion of infected individuals with a resistant strain of all the infected population. The age-specific prevalence of resistant infection, PIR_i , is given by

$$PIR_i = \frac{\sum_{k=0}^1 I_{ri}^k}{\sum_{k=0}^1 \sum_{m \in \{w,r\}} I_{mi}^k}, \quad (3.13)$$

where I_{ri}^k is the proportion of the population infected with a resistant strain, in a treatment status k and in age group i .

The prevalence of resistant infection on all the population, PIR , is given by

$$PIR = \frac{\sum_{i=1}^n \sum_{k=0}^1 I_{ri}^k}{\sum_{i=1}^n \sum_{k=0}^1 \sum_{m \in \{w,r\}} I_{mi}^k}. \quad (3.14)$$

3.2.6 Model validation

To validate the epidemiologic SI model of *H. pylori* infection, we compared the age-specific observed prevalence in Mexico 1988-89 that was used to estimate the force of infection with the model-predicted prevalence in the absence of treatment using Equation (3.11).

To validate the SIS model of antibiotic resistance for *H. pylori* in Mexico, we implemented an antibiotic consumption pattern observed in the country between 1991 and 2017 and compared the model results to two different observed epidemiologic outcomes in the presence of treatment: (1) age-specific prevalence of infection, and (2) prevalence of resistant infection, described in sections 3.2.5 and 3.2.5, respectively. For both outcomes, we simulated a population that reflected the demographic and epidemiologic profile at 1988.

Background consumption of antibiotic

To model the background consumption of antibiotic, we considered the consumption of clarithromycin. Consumption of macrolide antibiotics between 1997 and 2007 remained constant at approximately 1 defined daily doses (DDD) per 1,000 inhabitants per day.[114, 117, 118] Clarithromycin is a special type of macrolide antibiotic and its consumption in Mexico in 2007 was approximately 0.2 DDDs/1000 per day, which represents 20% of all macrolides. [114]. The estimated annual rate of clarithromycin consumption of 0.073/year was obtained by multiplying 0.2 DDDs/1000 per day times 365 divided by 1,000. Clarithromycin was introduced in Mexico in 1991.[61, 62] To validate, the model we assumed that consumption of clarithromycin also remained constant between 1997 and 2010. Mexico implemented a policy to enforce prohibition of over the counter antibiotic sales, reduced consumption of macrolides by 5%.[118] Accordingly, we ran the model for three years without antibiotic consumption and on 1991 we impose an increase until 1997 and fix it at a constant level until 2010, where it is decreased by a factor of 0.95% (i.e., the impact of over-the-counter restrictions on antibiotic consumption in Mexico). To account for different patterns in the uptake of clarithromycin since its introduction

in Mexico in 1991, we assumed two different increasing patterns between 1991 and 1997: (1) linear and (2) quadratic. Figure 3.3 shows the assumed patterns of antibiotic consumption of clarithromycin from 1997 to 2017.

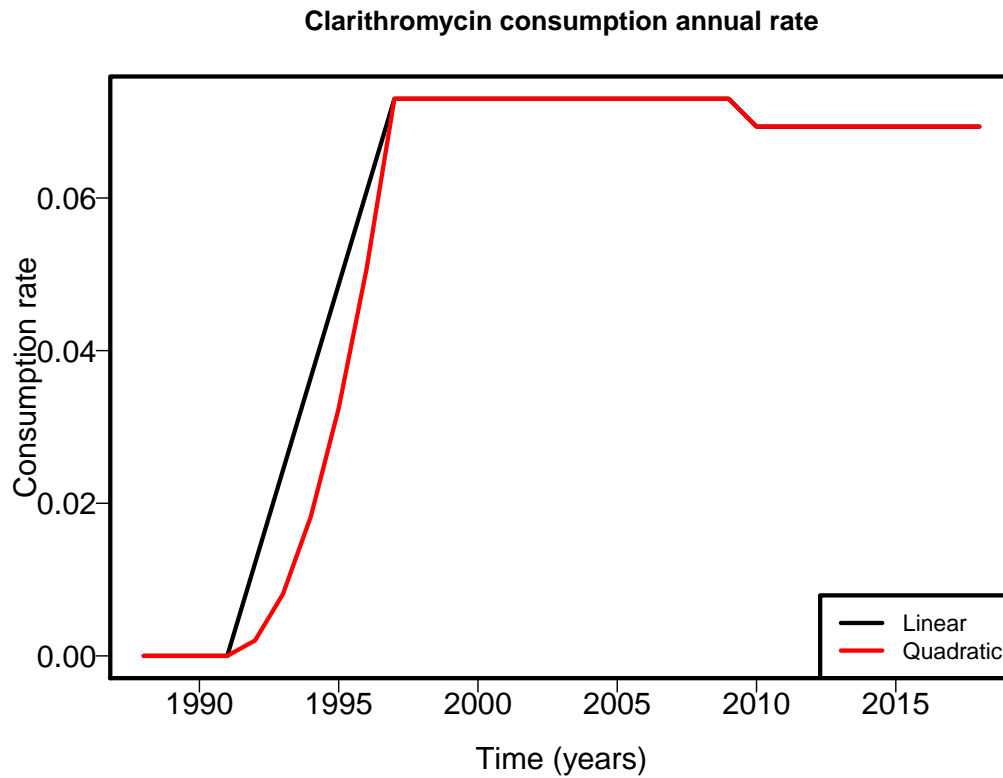


Figure 3.3: Average consumption rate of clarithromycin over time in Mexico

To account for differences in antibiotic consumption rates by age, we used a relative rate (RR) of consumption of macrolides in the US by age groups calculated from a sample of oral antibiotic prescriptions dispensed in the US during 2011 (see Figure 3.4).[119] To apply these RR, we impose two assumptions: (1) the RR of consumption of macrolides is the same as that for clarithromycin and (2) the RR in the US is a proxy of the RR in Mexico.

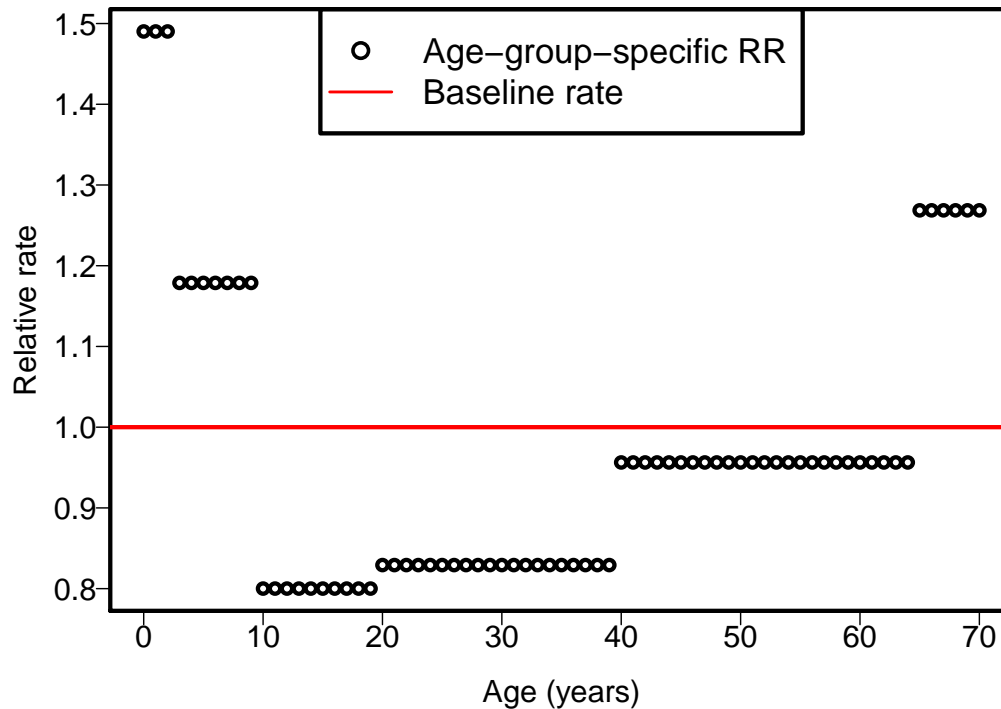


Figure 3.4: Relative rate of antibiotic consumption of clarithromycin by age group

Age-specific prevalence of *H. pylori* infection in the presence of treatment

We compared the model-predicted age-specific prevalence of infection to the observed seroprevalence of the state of Morelos, Mexico in 1999 in the presence of background use of antibiotic for any reason. We constructed a state-specific SIS model for the state of Morelos by estimating four different WAIFW matrices (with the same structure of the national-level SIS model described in section 3.2.1) using the state-specific prevalence and FOI estimated in chapter 2. The observed seroprevalence was obtained from a study conducted in the state of Morelos in 1999 in 5,299 adolescents 11-24 years old where the overall prevalence was 47.6% (95%CI: [46.9%, 48.2%]).[120] We imposed the rate of background use of antibiotic for any reason described in section 3.2.6 in the state of Morelos-specific SIS model. Figure 3.5 shows the comparison of the observed seroprevalence of *H. pylori* infection by age among adolescents in

the state of Morelos, Mexico in 1987–88 and 1999 with the prevalence predicted for the state of Morelos with the catalytic model of Chapter 2.

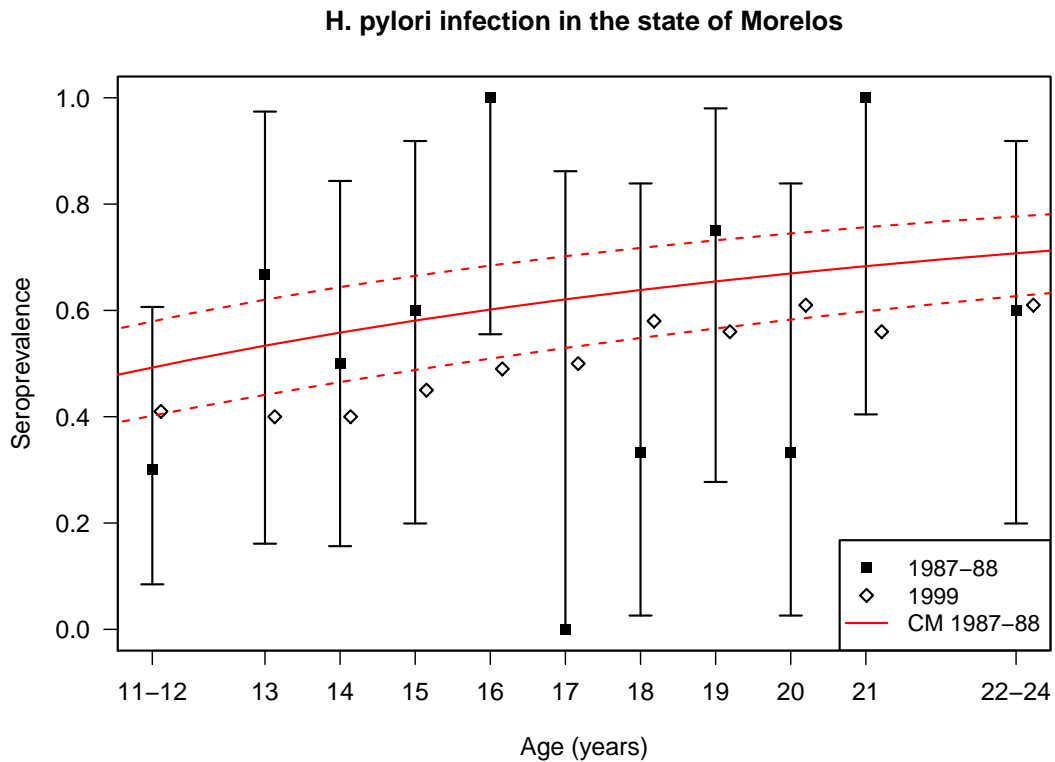


Figure 3.5: Comparison of observed seroprevalence of *H. pylori* infection by age among adolescents in the state of Morelos, Mexico in 1987–88 and 1999 with the prevalence predicted for the state of Morelos with the catalytic model of Chapter 2. Dotted lines represent the 95%CR of the prevalence predicted by the catalytic model.

Prevalence of resistance

We compared the model-predicted prevalence of resistant infection to that observed in different epidemiologic studies in Mexico. The prevalence of clarithromycin-resistant *H. pylori* in Mexico in 1995, 1996 and 1997 was 10%, 21% and 26%, respectively, obtained from epidemiologic studies in Mexico city.[35, 121]

To account for the uncertainty of the transmission parameters, β , and the probability of treatment-induced resistance, σ , on all validation results, we ran the model 1,000 times for different combinations of these parameters. Different parameter combinations were drawn from probabilistic distributions that reflect the nature of the parameters. For example, the transmission parameters β were obtained from a multivariate Normal distribution with mean and covariance matrix given by the mean estimates, standard errors and correlations shown in Table 3.4 and Figure 3.7 for the national estimates, respectively, and Table 3.5 for the Morelos-specific estimates, all obtained from the MLE approach described in section 3.2.3. The samples for parameter σ were obtained from a Beta distribution with parameter $\alpha_1 = 3$ and $\alpha_2 = 5$ (reflecting the 8-person sample size of the study from which σ was estimated). We then calculated the mean and the 95% model-predicted CI of the prevalence of *H. pylori* infection in adolescents by running the SIS model at each of the 1,000 parameter sets.

The ODE model was constructed in the R program version 3.2.4[56] and solved using the function `lsoda` from the package `deSolve`. [122] The function `lsoda` solves ODEs by switching automatically between stiff and non-stiff methods. [123, 124]

3.2.7 Cohort effects

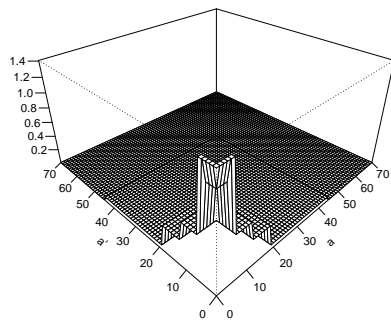
Different mixing structures through WAIFW matrices might yield different direct and indirect effects. To do so, we compared the effects of the proposed antibiotic mass-treatment policies on the cohort of newborns and 40 year olds at the time of the policy implementation under different WAIFW matrices. We evaluated the effects of the policies on these two cohorts by following them until age 70 and computing the cumulative prevalence of *H. pylori* infection and resistance over this period. We then compared these two outcomes for all the policies to the no-treatment scenario.

3.3 Results

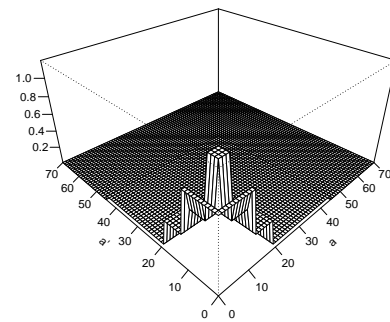
3.3.1 Estimates of WAIFW matrices and transmission parameters

We estimated the β parameters of the four different WAIFW matrices using a maximum likelihood estimation (MLE) approach described in section 3.2.3. Table 3.4 shows the point estimates and standard errors of the β parameters, and the negative log-likelihood value of each WAIFW

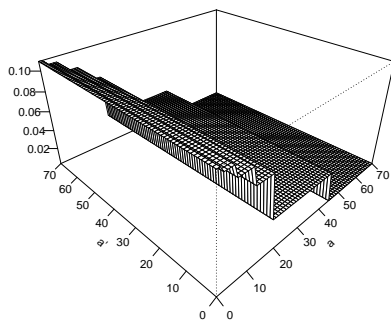
matrix. The perspective plots of the four different WAIFW matrices on the point estimates from Table 3.4 are shown in Figure 3.6. Three different WAIFW matrices, W_1 , W_2 and W_3 , have the best fit with equal negative log-likelihood values of 173.8 and thus provide no basis to guide the choice of mixing pattern. WAIFW matrix W_4 has a higher negative log-likelihood value of 321.1.



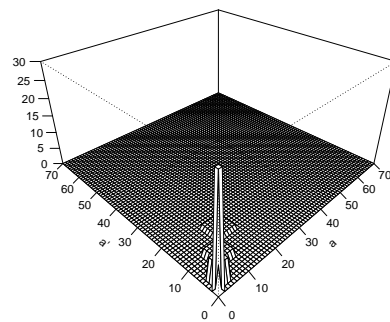
(a) WAIFW = 1



(b) WAIFW = 2



(c) WAIFW = 3



(d) WAIFW = 4

Figure 3.6: Perspective plots of the WAIFW matrices for *H. pylori* infection in Mexico.

Table 3.4: Point estimates and standard errors in parentheses of the β transmission parameters for different WAIFW matrices for *H. pylori* in Mexico.

Parameter	WAIFW structure			
	W_1	W_2	W_3	W_4
β_1	1.408 (0.209)	0.800 (0.054)	0.109 (0.004)	30.000 (2.651)
β_2	1.122 (0.150)	1.185 (0.152)	0.104 (0.002)	5.872 (0.137)
β_3	0.576 (0.023)	0.572 (0.024)	0.093 (0.002)	1.786 (0.029)
β_4	0.342 (0.007)	0.342 (0.007)	0.076 (0.001)	0.917 (0.012)
β_5	0.063 (0.001)	0.063 (0.001)	0.033 (0.001)	0.093 (0.002)
β_6	0.003 (0.000)	0.003 (0.000)	0.003 (0.000)	0.005 (0.000)
Neg-Llk	173.821	173.821	173.821	321.097

Neg-llk: Negative log-likelihood. The lower the value the better fit.

Different WAIFW matrices can yield different correlation among their parameters. The correlations between the β parameters of the four WAIFW matrices considered are shown in Figure 3.7. WAIFW matrices W_1 and W_2 represent different social mixing behaviors that differ between age groups of both infected and susceptible individuals, which allows correlations different than zero for some combinations of their β parameters. The correlation between the β parameters for these two matrices is negative. WAIFW matrices W_3 and W_4 do not allow different mixing across age groups and therefore they don't have correlation among their β parameters.

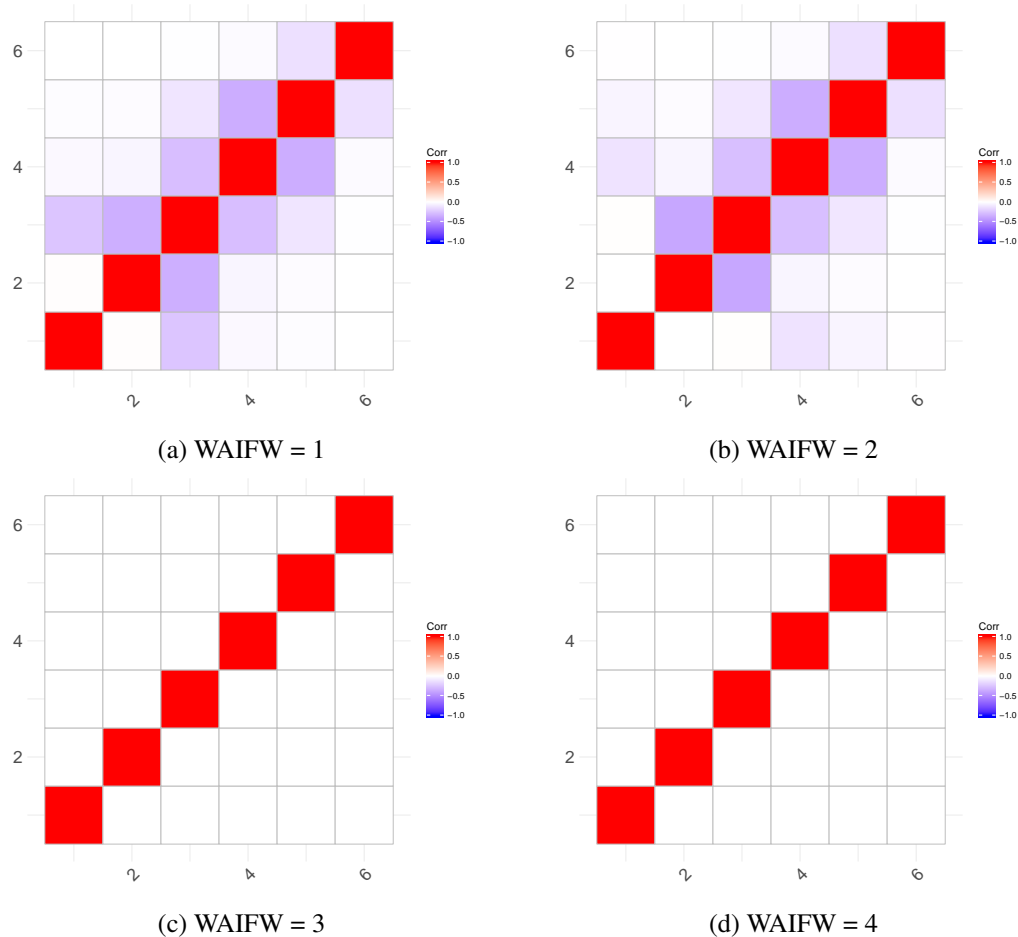


Figure 3.7: Correlations between the β parameters of different WAIFW matrices.

Transmission parameters for the state of Morelos, Mexico

To validate the transmission model over time on the prevalence of *H. pylori* infection, we compared the prevalence predicted by the state-specific transmission model of Morelos to data of prevalence of *H. pylori* infection in Morelos in the late 1990's. We constructed a state-specific model for the state of Morelos by estimating different state-specific WAIFW matrices using the MLE approach described in Section 3.2.3 using the state-specific FOI of Morelos estimated in Chapter 2. The point estimates and standard errors of the β parameters, and the negative log-likelihood value of each WAIFW matrix of the state of Morelos, Mexico are shown in Table

3.5. Two different WAIFW matrices, W_2 and W_3 , have the best fit with equal negative log-likelihood values of -258.3 and thus provide no basis to guide the choice of mixing pattern. WAIFW matrix W_1 had a slightly higher negative log-likelihood. WAIFW matrix, W_4 , had the highest value of -242.1 providing evidence that this mixing structure is the least likely given the data.

Table 3.5: Point estimates and standard errors in parentheses of the β transmission parameters for different WAIFW matrices for the state of Morelos, Mexico.

Parameter	WAIFW structure			
	W_1	W_2	W_3	W_4
β_1	1.673 (0.618)	0.737 (0.159)	0.101 (0.011)	30.000 (7.945)
β_2	0.402 (0.441)	1.114 (0.445)	0.096 (0.007)	5.785 (0.403)
β_3	0.538 (0.066)	0.516 (0.067)	0.086 (0.004)	1.735 (0.084)
β_4	0.302 (0.020)	0.302 (0.020)	0.071 (0.003)	0.885 (0.034)
β_5	0.068 (0.003)	0.068 (0.003)	0.037 (0.002)	0.104 (0.004)
β_6	0.005 (0.001)	0.005 (0.001)	0.005 (0.001)	0.011 (0.002)
Neg-LLk	-257.034	-258.270	-258.271	-242.074

Neg-llk: Negative log-likelihood. The lower the value the better fit.

3.3.2 FOI with estimated WAIFW matrices

The estimation of the WAIFW matrices impose a piecewise age-structure on transmission dynamics, which translates into a piecewise FOI. Therefore, we compared the piecewise FOI of *H. pylori* predicted with each of the WAIFW matrices using Equation (2.1) to the continuous FOI estimated in Mexico in 1987-88 at a national level and for the state of Morelos with the

catalytic model in Chapter 2. The comparison between the predicted piecewise FOI from the national WAIFW matrices to the estimated FOI is shown in Figure 3.8.

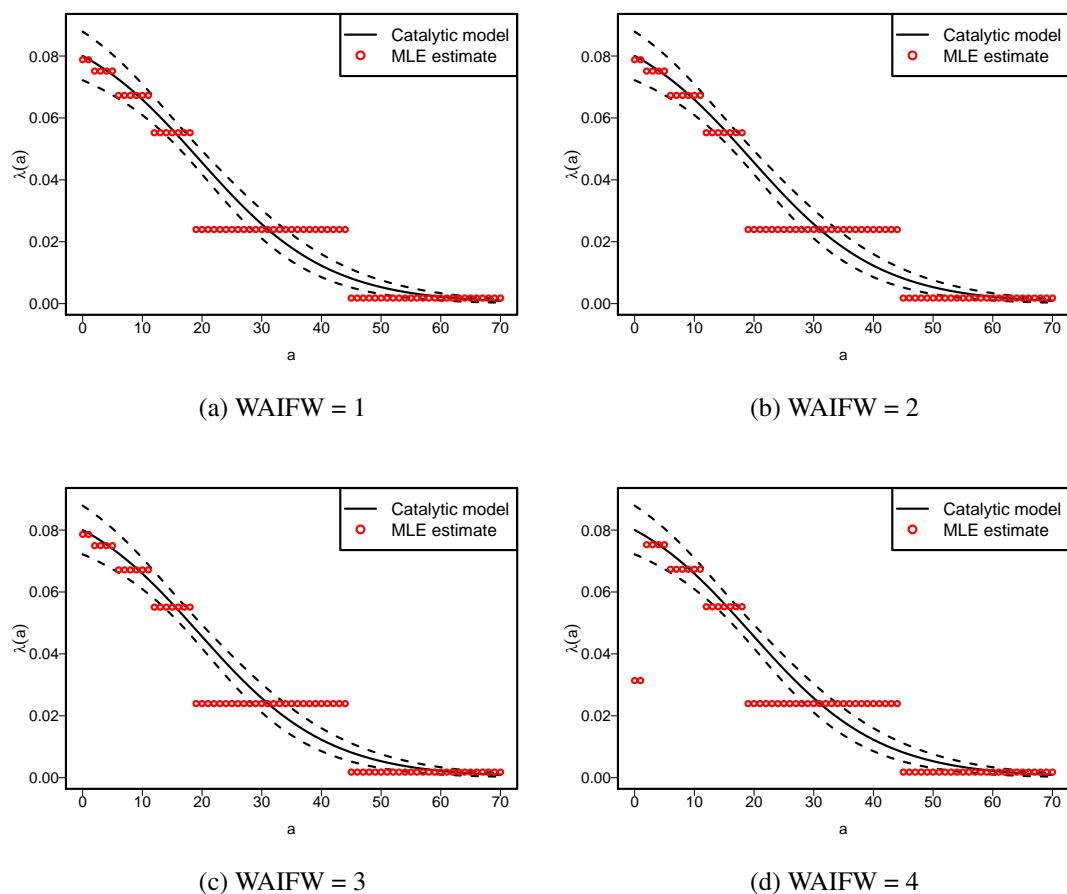


Figure 3.8: Comparison of the piecewise FOI of *H. pylori* predicted with each of the national-level WAIFW matrices using Equation (2.1) to the continuous FOI estimated in Mexico in 1987-88 with the catalytic model in Chapter 2.

The FOI predicted with the national-level WAIFW matrices W_1 , W_2 and W_3 had similar fit to the continuous FOI estimated with the catalytic model. They all predict a decreasing pattern on the FOI by age. The fully assortative WAIFW matrix, W_4 , predicts a notably lower FOI on the youngest age group, 0-2 year-old, compared to the continuous FOI.

The comparison between the predicted piecewise FOI from the Morelos-specific WAIFW

matrices to the estimated FOI is shown in Figure 3.9.

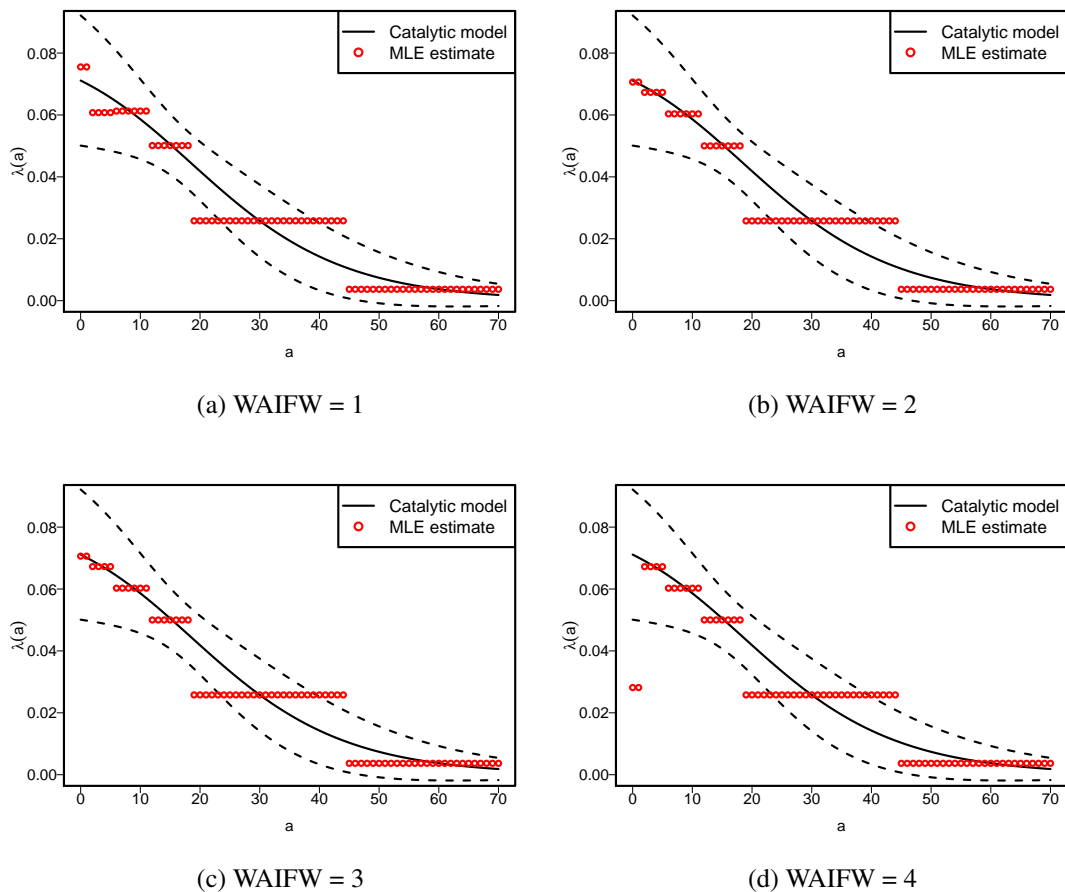


Figure 3.9: Comparison of the piecewise FOI of *H. pylori* predicted with each of the Morelos-specific WAIFW matrices using Equation (2.1) to the continuous FOI estimated in the state of Morelos, Mexico in 1987-88 with the catalytic model in Chapter 2.

Similar to the national-level predicted piecewise FOI, the FOI predicted with the Morelos-specific WAIFW matrices W_1 , W_2 and W_3 had the best fit with the equivalent age-decreasing pattern. The fully assortative WAIFW matrix, W_4 , also predicts a lower FOI on the 0-2-year-old age group compared with the estimated continuous FOI. Notice that the confidence intervals of the continuous FOI of the state of Morelos estimated with the catalytic model are wider compared to the national-level because the state-specific FOI are estimated with fewer data

than the national-level FOI.

3.3.3 Validation

We ran the SI model of *H. pylori* infection using the WAIFW matrix W_2 described in section 3.2.1. The mean and covariance of the multivariate normal distribution are given by the point estimates and standard errors in Table 3.4 and correlation matrix of Figure 3.7, all obtained from the MLE approach described in section 3.2.3. The age-specific prevalence of *H. pylori* predicted by the SI model with their corresponding 95% predicted CI compared to the age-specific observed prevalence of *H. pylori* in Mexico in 1987-88 is shown in Figure 3.10.

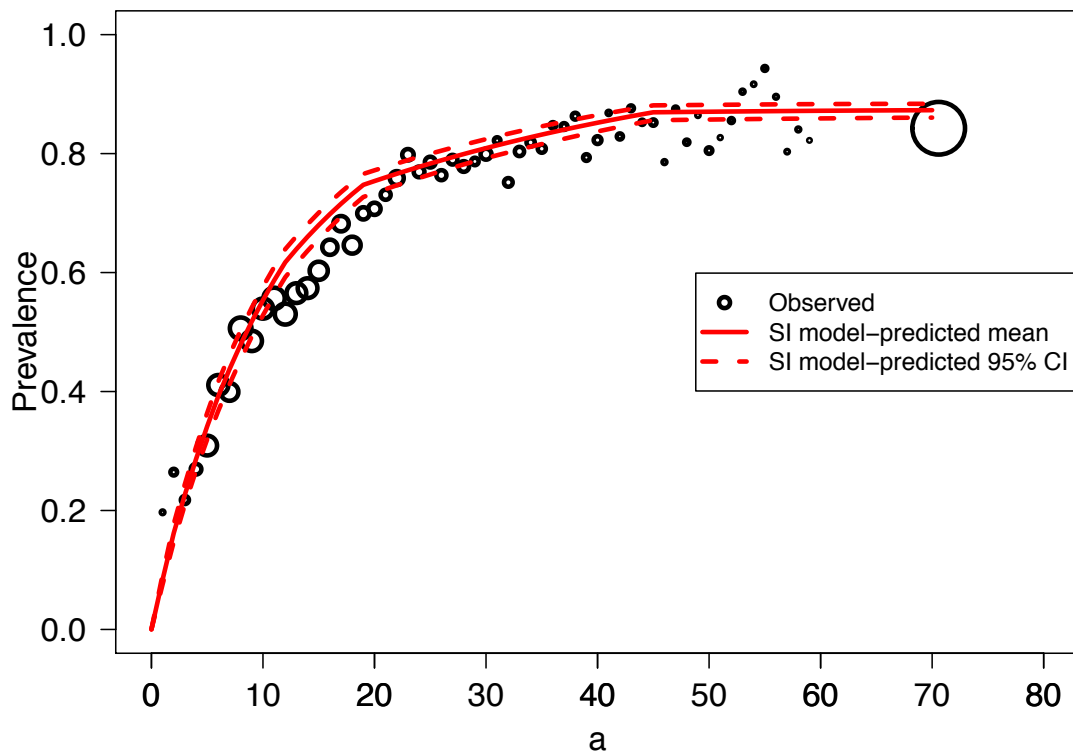


Figure 3.10: Comparison of observed age-specific prevalence of *H. pylori* in Mexico in 1987-88 with the age-specific prevalence predicted with the SI model.

The mean prevalence of *H. pylori* infection and the 95% predicted CI in adolescents age 11-24 years old with the state-specific SIS model for the state of Morelos between 1988 and 1999 compared with the observed prevalence in 1998 and 1999 of the state of Morelos, Mexico,[120]

is shown in Figure 3.11. The model predicted prevalence in adolescents 11-24 years old for the state of Morelos seem to mimic the observed prevalence over time. The wide confidence intervals of the observed prevalence in Morelos in 1988 relative to 1999 is attributed to the difference in sample sizes of that state between both years. The data collected in Morelos in 1988 was part of a national representative sample while in 1999 the data was collected specifically for that state.

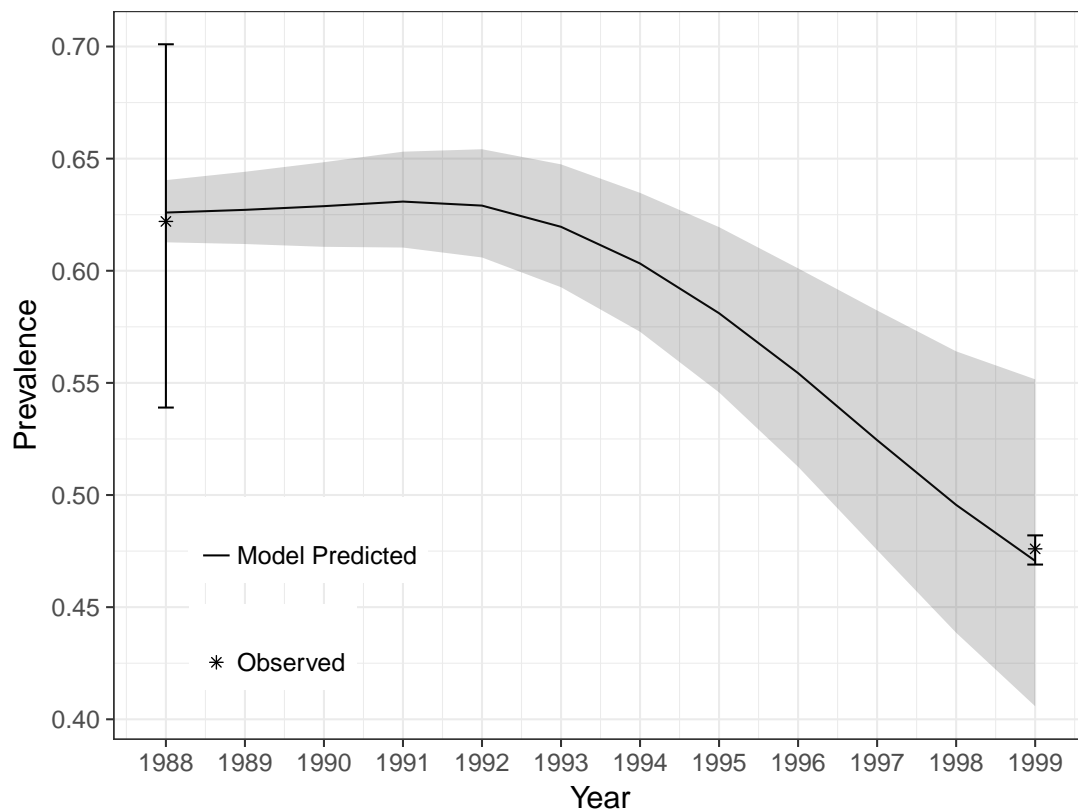


Figure 3.11: Comparison of model-predicted prevalence of *H. pylori* between 1988 and 1999, and observed prevalence with 95% CI in 1988 and 1999 in the state of Morelos, Mexico in adolescents age 11-24 years old.

The predicted prevalence of clarithromycin-resistant *H. pylori* in Mexico between 1988 and 1999 and the observed resistance prevalence in Mexico city between 1995-97 [121] are shown in Figure 3.12.

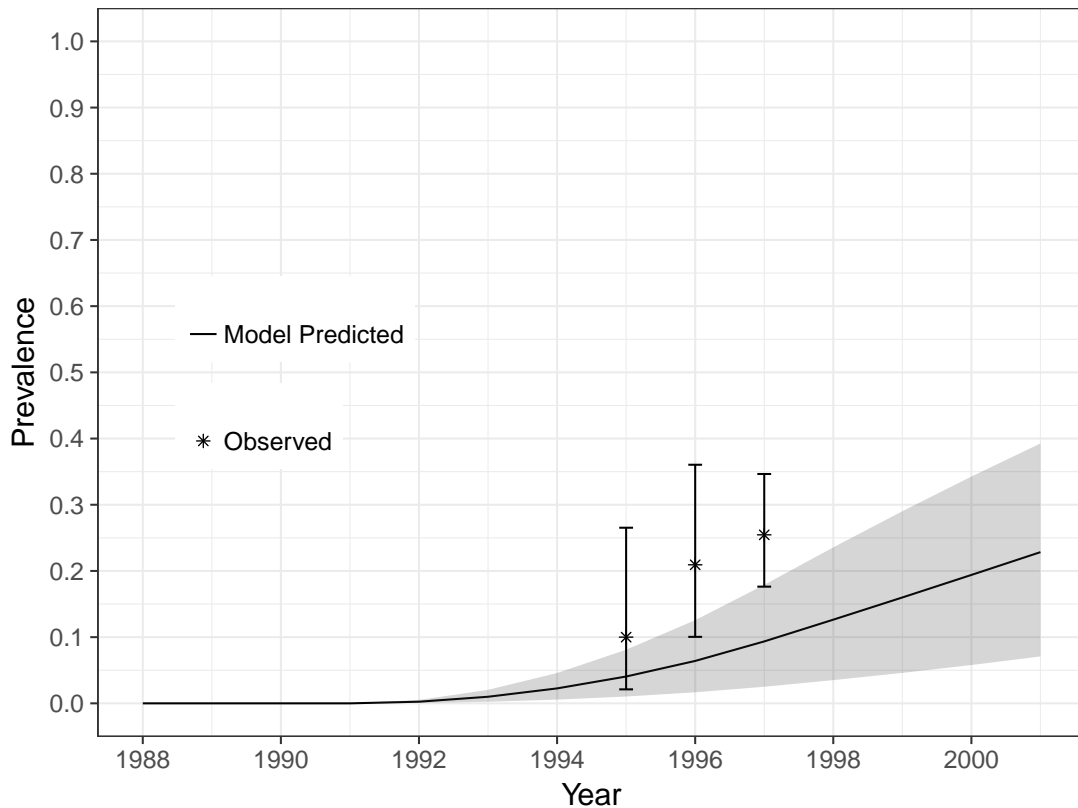


Figure 3.12: Mean and 95% model-predicted CI of prevalence of clarithromycin-resistant *H. pylori* in Mexico between 1988 and 1999, and observed prevalence resistance in Mexico City. Confidence intervals of observed resistance were computed using the Binomial exact method.

The model-predicted prevalence of resistance is lower than the observed prevalence. The main differences occur on the years 1996 and 1997.

3.3.4 Impact of different antibiotic mass-treatment policies on epidemiologic outcomes

In this section, we present the simulation results for the antibiotic treatment policies described in section 3.2.4 for our base-case analysis (i.e., WAIFW matrix W_2 and a quadratic uptake in background use of antibiotic). We first simulated the population using the SIS model described in section 3.2.2 from 1988 to 2018 considering the background use of antibiotic described in section 3.2.6. We then implemented the one-year long antibiotic treatment policies in 2018.

Following the one-year intervention period, we then simulated the population (without further treatment) for 22 years to estimate the impact of one-time population-wide treatment initiatives on different epidemiologic outcomes.

In the absence of a mass-treatment policy, our model predicts infection begins to rise in 2022, mostly caused by treatment-induced resistant strains as a product of background use of antibiotics. The impact of the policies is immediate on decreasing infection but also increasing ABR (see Figure 3.13). After the first year of implementation, policy 3 (AB all) decreases infection by 21% but increases ABR by 57%. The relative size of the decrease in infection vs. the increase in ABR is highest for policy 2 (AB 40+ year-olds), 39%, and lowest for policy 1 (AB 2-6 year-olds), 23%. The relative size of the decrease in infection vs. the increase in ABR for policy 3 (AB all) is 37%. These results agree across all scenarios considered in sensitivity analysis for different WAIFW matrices and antibiotic treatment background uptake shown in Appendix B.

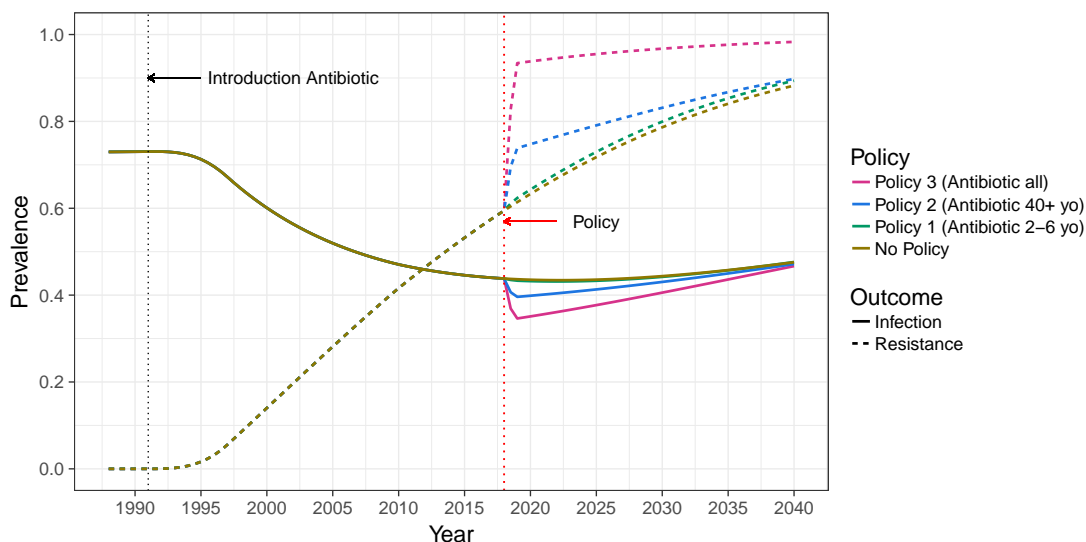


Figure 3.13: Impact of different antibiotic treatment policies on prevalence of *H. pylori* infection and resistance for different antibiotic mass-treatment policies.

3.3.5 Cohort effects of different antibiotic mass-treatment policies

In this section, we compare the cohort effects of different antibiotic mass-treatment policies for all the WAIFW matrices described in section 3.2.1. We computed the cumulative prevalence of

H. pylori infection and resistance for a cohort born in 2018 (i.e., the year when the policies are implemented) over 70 years. For all the policies, WAIFW matrices W_1 and W_2 have similar effects. WAIFW matrix W_3 consistently estimates the lowest prevalence of *H. pylori* infection and resistance while W_4 estimates the highest values for both epidemiologic outcomes (see Figures 3.14 and 3.15).

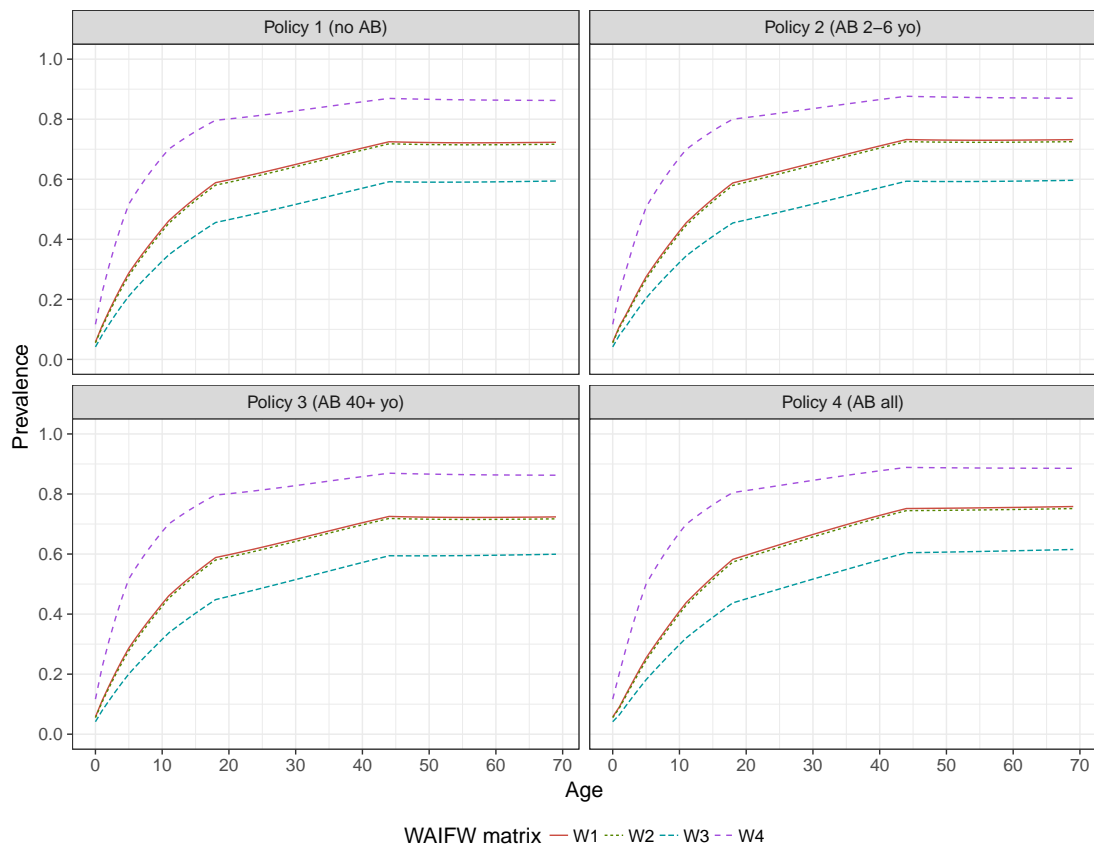


Figure 3.14: Cohort effects of different antibiotic mass-treatment policies on prevalence of *H. pylori* infection.

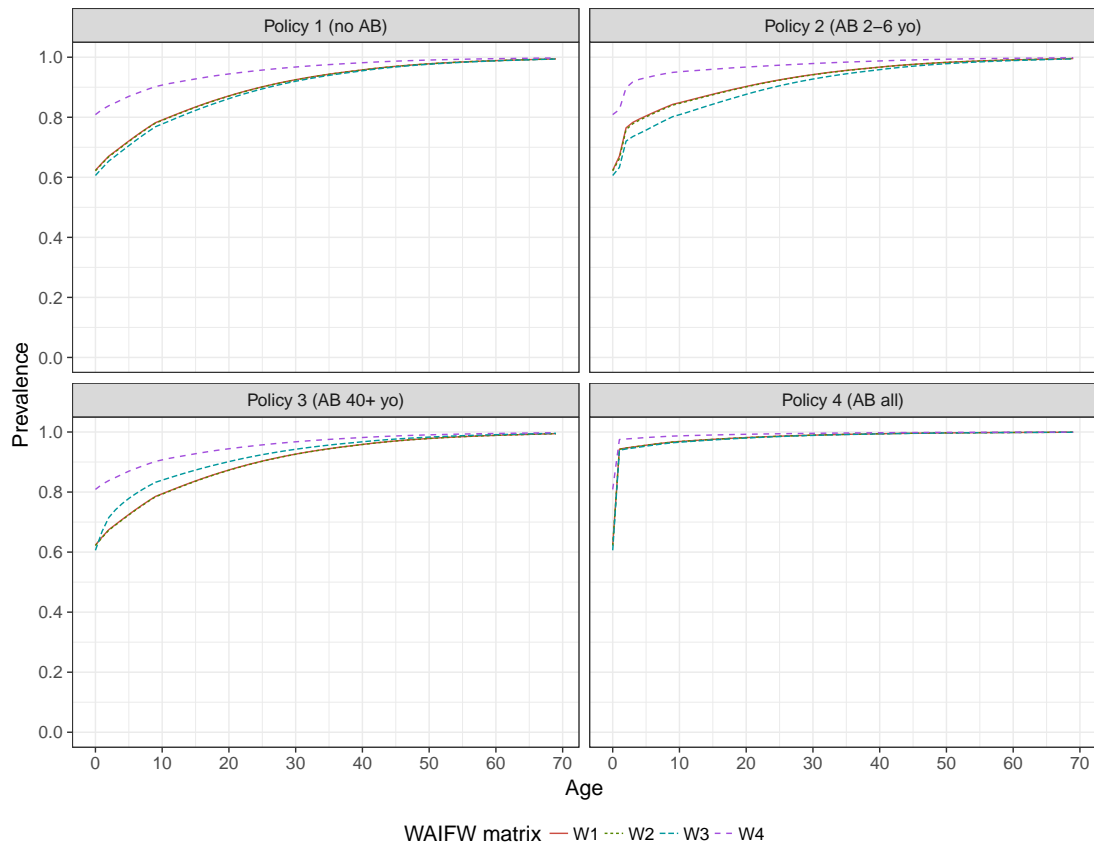


Figure 3.15: Cohort effects of different antibiotic mass-treatment policies on prevalence of resistance.

3.4 Discussion

In this chapter, we developed an integrated transmission dynamic model of *H. pylori* infection and resistance to represent the Mexican population. We estimated the transmission parameters of different mixing matrices based on different structures of how the population mixes across age. We validated the model by comparing model-predicted age-specific and aggregated prevalence of *H. pylori* infection in steady state and over time, respectively, to observed prevalence from different studies. In addition, we also compared the model-predicted prevalence of resistant infection to that observed in Mexico City in the mid 1990's. We then used this model to evaluate different antibiotic mass-treatment policies on several epidemiologic outcomes such as

prevalence of infection and resistance.

We gained valuable insights by comparing various antibiotic mass-treatment strategies. In general, the results suggest that any mass-treatment policy will have a higher effect on increasing resistance than on reducing infection. In fact, as the proportion of *H. pylori* resistant strains increases and becomes more prevalent than sensitive strains, *H. pylori* infection starts rising again.

Most validation results from this model were qualitatively similar to the observed epidemiologic outcomes on the age-specific and aggregated prevalence of *H. pylori* infection and prevalence or resistance. However, we were not able to validate the model-predicted prevalence of resistance to data in more recent years due to the lack of recent studies that report prevalence of resistance to clarithromycin in Mexico. Thus, we had to predict current levels of resistance in Mexico (60%) before simulating the antibiotic mass-treatment policies in 2018. Model-predicted levels of resistance seem higher compared to published estimates for Mexico,[35] although most of these studies were conducted more than a decade ago. However, our predicted prevalence of resistance for more recent years is not far off from other studies reporting high levels of resistance in similar years.[125] For example, in Iran, a study reported a resistance to clarithromycin of 45.2% [95%CI: 38.3%-52.2%] on 197 individuals in 2009.[126] A larger study in Southeast China from 2010 to 2012 found that *H. pylori* resistance to clarithromycin was 21.5% [95%CI: 20.9%-22.1%].[127] Another study conducted in 71 children in Beijing, China, from 2009 to 2010 found a much higher clarithromycin resistance of 84.9% [95%CI: 76.7%-93.3%].[128] In addition, our model-predicted prevalence of resistance over time in more recent years is in line with resistance in other countries, such as in South Korea where resistance increased from 22.9% [95%CI: 13.1%-32.9%] in 2003 to 37.0% [95%CI: 29.6%-44.4%] in 2012 [129], and in Japan where *H. pylori* resistance went from 1.8% [95%CI: 0.0%-3.8%] in 1996 to 27.1% [95%CI: 21.2%-33.0%] in 2008.[130] These studies provide evidence on the quick rise of clarithromycin resistance in the last few years.

Our current analysis has several limitations. First, there is limited data on the background use of clarithromycin in Mexico over time. Therefore, we had to make assumptions on the uptake of clarithromycin since its introduction to the Mexican health care sector in 1991; although different assumptions on the antibiotic uptake did not change the results. Second, data on treatment-induced resistance for *H. pylori* infection are also limited, with only one study

reporting the probability of clarithromycin-induced resistance. Uncertainty around this parameter has a big effect on the predicted prevalence of resistance over time, as shown in Figure 3.12. Thus, more studies are needed to more accurately estimate antibiotic-treatment-induced mutation rate. Third, the assumption of mixing of the population has differential cohort effects. Different WAIFW matrices predict different levels of infection and resistance across a lifetime for different mass-treatment policies. Therefore, care should be taken when choosing the mixing structure across age of the population of interest. More accurate data on how the Mexican population mixes across age would help refining our current results.

Mass-treatment policies have a higher effect on increasing ABR letting resistant strains take over infection. Given the high predicted prevalence of ABR at the time of the policy implementation, mass treatment strategies are unlikely to be optimal in Mexico.

Chapter 4

Cost-effectiveness analysis of population screening and treatment of *Helicobacter pylori* in the setting of antibiotic resistance

4.1 Introduction

Gastric cancer is the fourth most common type of cancer and the second cause of cancer death globally. Latin America has the second highest rate of gastric cancer mortality in the world. In particular, in Mexico gastric cancer is the third highest cause of cancer death in adults, with some regions having cancer mortality rates that are twice the national average (8.0 vs. 3.9 per 100,000, respectively).[3]

Helicobacter pylori (*H. pylori*) is the strongest known biological risk factor for gastric cancer (about a six-fold increase of risk compared to *H. pylori* negative individuals) and causes the majority of peptic ulcers.[2, 1] In 2008, more than 79% of the 989,000 gastric cancer cases and most ulcer cases in the world could be attributed to chronic infection with *H. pylori*. [2] *H. pylori* is one of the most prevalent chronic bacterial infections in the world and most heavily burdens low- and middle-income countries (LMICs) where the proportion of people infected is approximately 70%. The current understanding is that *H. pylori* causes gastritis and chronic

inflammation, which significantly increases the risk of developing an ulcer, followed by atrophy of the gastric glands leading to precancerous lesions, and ultimately resulting in gastric cancer.[131]

H. pylori infection can be cleared with antibiotics, and in theory reduce the risk of gastric cancer and peptic ulcers.[25, 26] However, antibiotic treatment can result in antibiotic resistance (ABR), which is the natural response of bacteria to resist the threats designed to eliminate them. ABR is one of the main causes of *H. pylori* treatment failure [27] and represents one of the greatest emerging global health threats.[32, 33] *H. pylori* has developed resistance to most antibiotics typically used to treat it,[132] including in the Latin American region.[35]

Given the high burden of *H. pylori* infection in the population, a policy of antibiotic-based mass eradication in developing regions has been proposed, and even implemented in targeted high-risk populations.[36] However, the adverse consequences of mass use of antibiotics, such as ABR, might outweigh the benefits. It is crucial to investigate this issue further in order to choose the best policy to treat *H. pylori* infection.[1] Therefore, it is important to only treat appropriate cases with selected regimens based on the observed patterns of ABR in the target population.[1] Failing to do so may lead to overtreatment and increase of ABR, especially in developing countries where prevalence of *H. pylori* infection is high. Current guidelines for North America and other western countries, do not suggest universal treatment for *H. pylori* but rather to those who may benefit from treatment; the key task is to determine who these individuals are, which is an important contribution of this research.[26, 133] However, there are recommendations to intervene to prevent gastric cancer in subpopulations with high background rates of *H. pylori* in western countries.[134, 135]

Under a “screen-and-treat” approach, asymptomatic individuals (i.e., individuals with out symptoms of having the disease of interest) are subjected to a screening test and treatment decision is based on the test result, which should be provided soon or, ideally, immediately after a positive screening test.[37] The goal of a screen-and-treat approach for *H. pylori* infection is to reduce gastric malignancies and cancer, and related mortality with relatively few adverse effects, such as ABR. The screen-and-treat approach for *H. pylori* infection must include a screening test or strategy (sequence of tests) and be linked to appropriate treatments for *H. pylori* infection.[136] There are several test for *H. pylori* infection that could be either invasive or noninvasive. Invasive tests are done via endoscopy and include culture, histology, rapid urease testing (RUT) and polymerase chain reaction (PCR).[137] For screening, noninvasive

tests are preferred, such as urea breath test (UBT), stool antigen and serology.[137, 138, 139, 140, 141, 142]

Efforts to combat resistance in the treatment of *H. pylori* focus on the development of new combinations of drugs, but few focus on optimizing use of existing antibiotics.[27] Screening policies of early detection of *H. pylori* have proven cost-effective, but most have failed to consider both the broader benefits in terms of reduction of the infection in the population, as well as the adverse effects of widespread use of antibiotics, such as resistance.[82] Therefore, the design of *H. pylori* screen-and-treat strategies must fit the narrow criteria to be an acceptable compromise between cancer prevention aims [143] and infection prevention, with the containment of ABR.[1, 144] Therefore, the design of *H. pylori* screen-and-treat strategies must, fit the narrow criteria to be an acceptable compromise between cancer prevention aims (cost-effectiveness)[143] and infection prevention (mass eradication reduces sources of infection), with the containment of ABR. [1, 144]

Susceptibility to different antibiotics can be assessed using a susceptibility test, which improves prediction on antibiotic treatment outcomes and guide clinicians in their choice of therapy.[145] In the case for *H. pylori* infection, there are basically two different susceptibility testing methods: (1) phenotypic methods and (2) genotypic methods.[99] Phenotypic methods include agar dilution method (usually considered the gold-standard to compare other techniques) and Etest.[137] Genotypic detection of resistance includes the real-time PCR method. [146]

Recent recommendations from the Maastricht IV Consensus Report on diagnosing *H. pylori* infection, suggest that culture and antibiotic susceptibility testing should be performed if primary resistance to clarithromycin is higher than 20% in a given geographical area or after failure of second-line treatment.[26] Although this recommendation explicitly mentions a threshold of resistance to recommend susceptibility testing, there is no evidence on whether the 20% threshold is appropriate. Other recommendations mention that treatment with clarithromycin is restricted to geographical areas with low prevalence of resistance without mention of any specific threshold.[147] Susceptibility testing could be considered as part of a screening strategy, but there is lack of evidence on its effectiveness and cost-effectiveness.

Epidemiological models of infectious diseases are mathematical representations of the dynamics and subsequent disease progression. These models are widely used for many conditions including human immunodeficiency virus (HIV),[148] human papillomavirus (HPV)

[149, 150, 151, 152] and hepatitis C [153, 154, 155], and provide information about the underlying mechanisms that influence the spread of disease and may suggest control strategies.[156]

Current models of *H. pylori* do not incorporate transmission dynamics, effects of antibiotic treatment and ABR in one single model.[91, 24] Previous analyses that have evaluated benefits of treatment have used either decision trees [157, 158] or Markov models that simulate fixed cohorts without accounting for transmission between the population, background use of antibiotic and ABR.[83, 159, 86] Previous transmission models of *H. pylori* have evaluated the benefits and cost-effectiveness of potential vaccines but have not evaluated mass antibiotic treatment or screen-and-treat strategies.[160, 161]

The purpose of this paper is to directly inform the design and implementation of public health interventions and clinical practice to prevent gastric cancer in a population with a high prevalence of *H. pylori* infection where ABR is present. In addition, we explore the potential benefits in different settings such as prevalence of infection, mutation rates and background use of antibiotics. We estimated the cost-effectiveness of various screen-and-treat strategies for *H. pylori* infection and ABR in the Mexican population from the health sector perspective.[85, 87] We considered different testing strategies including those used to identify ABR strains.[162, 163]

4.2 Methods

4.2.1 Mathematical model

We developed a mathematical model to simulate the Mexican population over time to replicate outcomes in Mexico. The mathematical model consists of several components, such as *H. pylori* infection, ABR, and gastric disease dynamics. The first and second components described in Chapter 3 model the transmission dynamics of *H. pylori* infection and ABR at a population level using an epidemiologic model of *H. pylori*. The third component described in section 4.2.1 below, describes the progression of underlying gastric disease following Correa's natural history model of gastric carcinogenesis including gastritis, intestinal metaplasia, dysplasia and ultimately cardia gastric cancer (NCGC).[131, 164, 165, 166, 167, 168]

Susceptible-infected-susceptible model with antibiotic resistance

We expanded the system of ordinary differential equations (ODEs) of the susceptible-infected-susceptible (SIS) model described in Chapter 3 to account for each gastric disease state g described in Section 4.1 above and different screen-and-treat strategies. The transmission dynamics of *H. pylori* infection have been described in more detail in Chapter 3. Briefly, individuals are born into an antibiotic-free susceptible class with normal mucosa (S_N^0) and infected individuals may be colonized by either sensitive (I_{wg}^0) or resistant strains (I_{rg}). Furthermore, (I_{rg}) is divided into untreated-resistant (I_{rg}^0) and treated-resistant (I_{rg}^1), where $I_{rg} = I_{rg}^0 + I_{rg}^1$. Susceptible individuals in the absence of treatment, S_g^0 , may be infected by either sensitive I_{wg}^0 or resistant bacteria I_{rg} . Antibiotic treatment is assumed to either clear sensitive strains with probability $(1 - \sigma)$ or induce acquired resistance with probability σ . Once accounting for all age groups, infected and gastric disease states, the system of ODEs had 2,130 equations.

We implemented screen-and-treat strategies on the SIS model by adding a screening rate η that gets applied to individuals in all gastric disease states g that are currently not being treated for *H. pylori* S_g^0 , I_{wg}^0 and I_{rg}^0 . We assumed that screening is performed using an imperfect test with sensitivity ρ and specificity θ . In addition, we also incorporated a susceptibility test with sensitivity ρ^s and specificity θ^s . In section 4.2.3 we describe in more detail the screen-and-treat strategies. Figure 4.1 shows the diagram of the SIS model accounting for ABR and screen-and-treat strategies for each gastric disease state g .

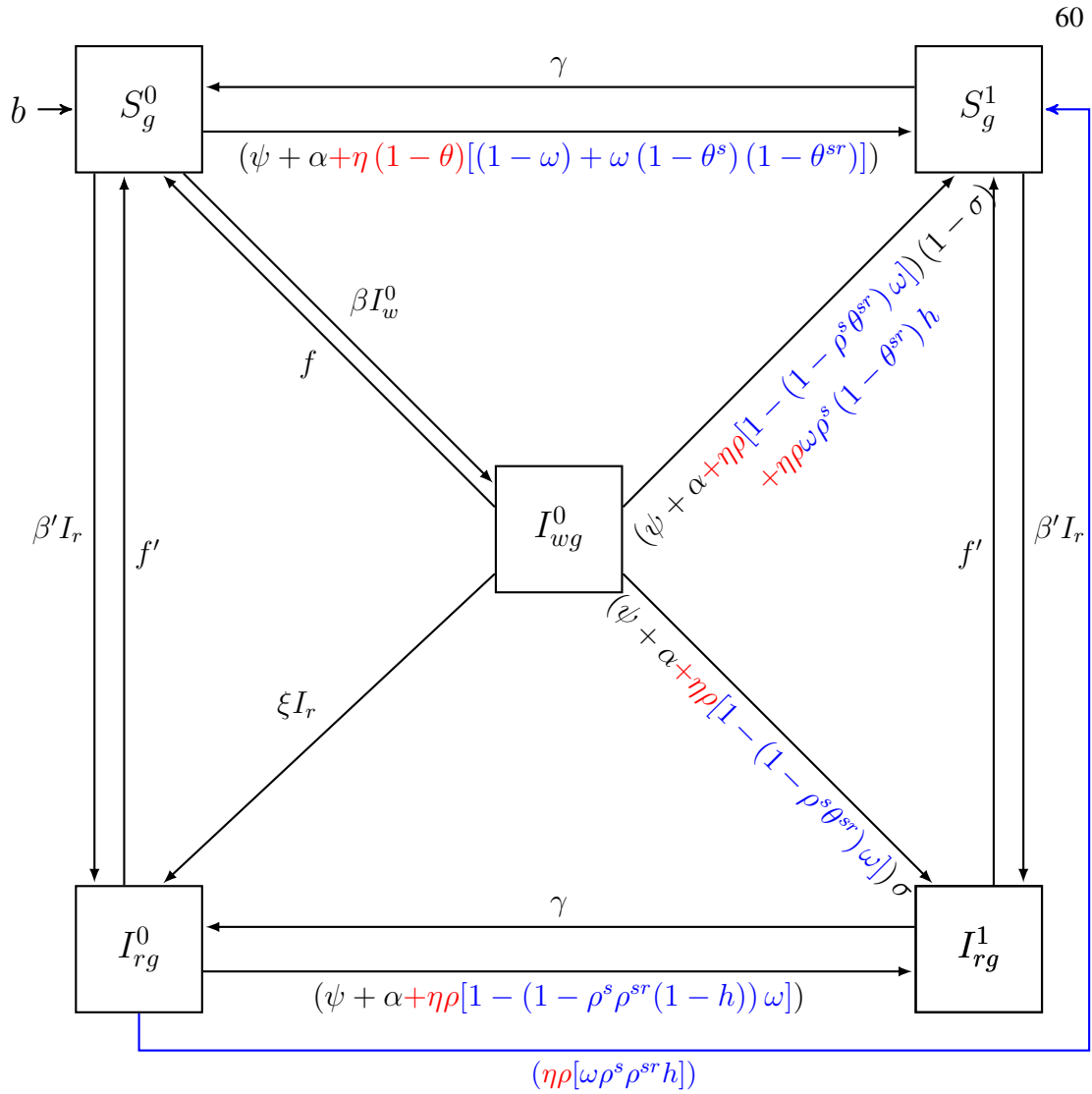


Figure 4.1: SIS model of screen-and-treat with antibiotic therapy incorporating drug-sensitive and resistant strains for each gastric disease state $g \in \{N, G, A, M, D, NCGC\}$. Primes denote parameters for resistant strains. Parameters in red refer to screening parameters and those in blue refer to susceptibility test.

Gastric disease dynamics

To accurately quantify the effects of screen-and-treat strategies for *H. pylori* infection it is important to model the effect of *H. pylori* infection on the natural history of gastric cancer. *H. pylori* causes gastritis and chronic inflammation, followed by atrophy of the gastric glands leading to precancerous lesions such as intestinal metaplasia and dysplasia, ultimately leading to gastric cancer.[18, 164, 165, 169, 170] Gastritis is an inflammation of the gastric mucosa without causing serious complications.[131, 171] Chronic atrophic gastritis is characterized by the ‘loss of appropriate glands’, mostly of parietal and principal cells that drive a reduction in the secretion of peptic acid and increases the risk of developing gastric cancer.[167, 172]. Intestinal metaplasia is considered a pre-cancerous lesion, which is usually caused by chronic *H. pylori* infection and is considered as a condition that predisposes to malignancy.[172, 173] Gastric dysplasia is defined as intraepithelial or intraglandular neoplasia and is considered as the immediate precursor to gastric cancer.[167]

The population in steady state is distributed across six different health states that include a normal gastric mucosa (N) state and five gastric precancerous states, which include, non-atrophic gastritis (G), atrophic gastritis (A), intestinal metaplasia (M), and intestinal dysplasia (D). New individuals are born into a normal gastric mucosa (N) state at an annual rate b (same rate calculated in Chapter 3). Furthermore, individuals residing in one state face a transition rate to either progress or regress to a consecutive state. For example, individuals with atrophic gastritis can either regress to non-atrophic gastritis at a rate λ_{AG} , progress to intestinal metaplasia at a rate λ_{AM} or remain with atrophic gastritis. Individuals who develop dysplasia face a rate λ_{NCGC} of developing non-cardia gastric cancer. The dynamics of precancerous gastric disease are shown in Figure 4.2.

Progression transition rates λ_{NG} and λ_{GA} (depicted with dashed lines) are higher for *H. pylori* infected individuals (i.e., hazard ratio (HR) greater than 1). Treatment for *H. pylori* influences these transitions but not those in solid lines.[174] That is, once individuals develop intestinal metaplasia, it is considered a point of no return.[173, 175]

The simulated population face an age-specific mortality from other causes according to country-specific life tables. We assumed that neither *H. pylori* infection nor any precancerous condition increases a person’s age-specific mortality.

There are limited individual level data to estimate the progression and regression rates of the

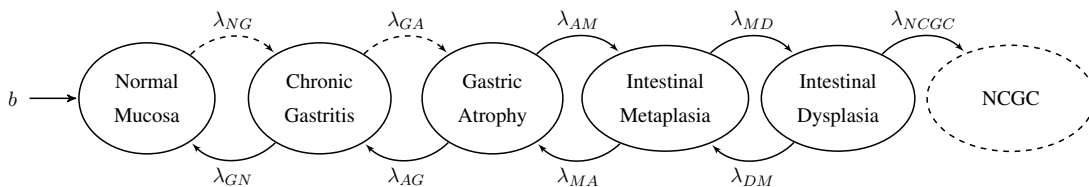


Figure 4.2: Diagram of gastric disease dynamics

natural history model of gastric cancer in Mexico. Therefore, we used a model calibration approach to estimate the parameters of the natural history model of gastric cancer using available epidemiologic data. In section 4.2.2 below, we describe in more detail the calibration approach we used to estimate these parameters.

4.2.2 Calibration of gastric disease dynamics

Parameters of mathematical models could be either unobserved or unobservable due to different reasons (e.g., financial, practical or ethical). Model calibration is the process of estimating values for unknown or uncertain parameters of a mathematical model by matching model outputs to observed clinical or epidemiological data (known as calibration targets). The goal is to identify parameter values that maximize the fit between model outputs and the calibration targets.[176, 177, 178]

Current guidelines suggest that model calibration should be performed where there are existing data on outputs.[179] And more importantly, uncertainty around calibrated parameters should be reported and reflected in both deterministic and probabilistic sensitivity analysis.[180]

There are several calibration techniques but not all of them are able to fully reveal both the uncertainty and correlation among the input parameters. Bayesian methods are naturally suited for calibration because they reveal the posterior joint and marginal distributions of the input parameters.[54, 181] A posterior distribution from a Bayesian analysis is synonymous with the distribution of the calibrated parameters.[182, 183]

In its simplest form, Bayes' theorem is defined as

$$p(\theta|y) = \frac{l(y|\theta)p(\theta)}{p(y)}, \quad (4.1)$$

where θ is a set of unknown parameters of the mathematical and y is the observed target data. The posterior distribution $p(\theta|y)$ is the conditional probability of the parameters after observing

y . The prior distribution $p(\theta)$ represents the uncertainty of θ before observing any target data. $p(\theta)$ could be a vague distribution represented by a uniform distribution where all the values are equally likely within a pre-specified range. Alternatively, $p(\theta)$ can have certain values more likely than others that could be represented by a normal distribution, for example. The likelihood function $l(y|\theta)$ represents the data generation mechanism of the targets y and is usually represented by either a probability density function (pdf) if y are continuous or a probability mass function (pmf) if y are discrete.

Because the denominator is not a function of θ , we can rewrite Equation (4.1) as

$$p(\theta|y) \propto l(y|\theta)p(\theta), \quad (4.2)$$

which means that the posterior distribution is equal up to a proportional constant to the prior times the likelihood.

In the context of model calibration, $Y \sim f(y; \phi)$, where f denotes a either a probability density function (pdf) if y are continuous or a probability mass function (pmf) if y are discrete, ϕ are the model outputs, which in turn depend on θ . Given that y is observed, the likelihood function can be defined as $l(y|\theta) = f(y; \phi)$. The posterior distribution $p(\theta|y)$, represents the updated distribution of θ after the model fits the target data y . Notice that this is equivalent to the definition of a calibrated parameter because it represents the updated distribution of that parameter after we incorporate the observed data. Thus, Bayes' formula can be viewed as defining a calibrated parameter as a function of the prior parameter distributions and the simulation model.

Each term in Equation (4.2) could be translated to a component in a calibration framework. Table 4.1 relates each term in Bayes' theorem with its counterpart in a calibration process. That is, Bayes theorem is naturally suited for calibration as it produces the distribution of the parameters accounting for previous knowledge about them and the targets of interest.

Table 4.1: Contrasting Bayes theorem with a calibration process.

Term	Bayesian Context	Calibration Context
$p(\theta)$	Prior distribution of θ	Pre-calibrated parameters
$l(y \theta)$	Likelihood of the data given θ	Goodness-of-fit for a parameter set
$p(\theta y)$	Posterior distribution of θ given targets y	Calibrated model parameters

There are multiple methods to obtain the posterior distribution. Some of them could be computationally expensive such as a Markov chain Monte Carlo (MCMC) method that simulates the posterior distribution by jumping (i.e., sampling) the parameter space in a stochastic fashion. MCMC techniques require a high number of model runs in order for the algorithm to converge.[183] Other approaches use importance sampling, such as the sampling-importance-resampling (SIR) algorithm [184] or an improved version that combines sequential importance sampling with optimization methods called incremental-mixture importance sampling (IMIS), developed specifically for mechanistic models.[185]

To calibrate the progression and regression rates of the gastric disease natural history model described in section 4.2.1, we used a different calibration Bayesian approach that aims to identify the parameter set that maximizes the posterior parameter distribution. Specifically, we adopted a Laplace approximation where we computed the posterior mode often called the maximum a posteriori (MAP) point, by maximizing the logarithm of the posterior, and use the MAP point (instead of the mean) as an approximation of the parameter set θ . The inverse of the negative Hessian of the logarithm of the posterior can be used to measure the uncertainty of this approximation.[186, 187, 188, 189, 190]

Because the population model has a constant inflow of individuals --at a birth rate b -- that then age, we initialize the model at a defined distribution of the population across all age groups, infection and treatment status, and gastric disease rates. We then identify the parameters that maintain this distribution in steady state. To solve for the steady state of the gastric disease natural history model, we used the function `runsteady` from R package `rootSolve`. The function `runsteady` solves the steady-state condition of ODEs by dynamically running till the summed absolute values of the derivatives become smaller than some predefined tolerance.[191, 192]

Calibration targets

We used data from different epidemiologic and population studies as calibration targets, such as the prevalence of total gastritis (i.e., a combination of both chronic non-atrophic and atrophic gastritis), the proportions of gastric lesions by age and *H. pylori* infection status, and the age-specific gastric cancer incidence. At the time of this study, we could not find studies that report the prevalence of gastritis by age for the Mexican population. Therefore, we had to use data

from a different country. Specifically, we used data from a Finnish study that reported prevalence of total gastritis by age groups.[193] We used data for Mexico on the proportion of gastric lesions and gastric cancer incidence.

Prevalence of gastritis The prevalence of total gastritis (i.e., a combination of both chronic non-atrophic and atrophic gastritis) by age groups was obtained from biopsy samples from ~500 consecutive endoscopy Finnish outpatients in the late 80s (Jorvi hospital, Espoo, Finland).[193] These data might be an underrepresentation of the prevalence of total gastritis in Mexico because the prevalence of *H. pylori* in Finland has been consistently lower compared to Mexico, particularly in the lower age groups.[194, 195] Figure 4.3 shows the prevalence increases with age.

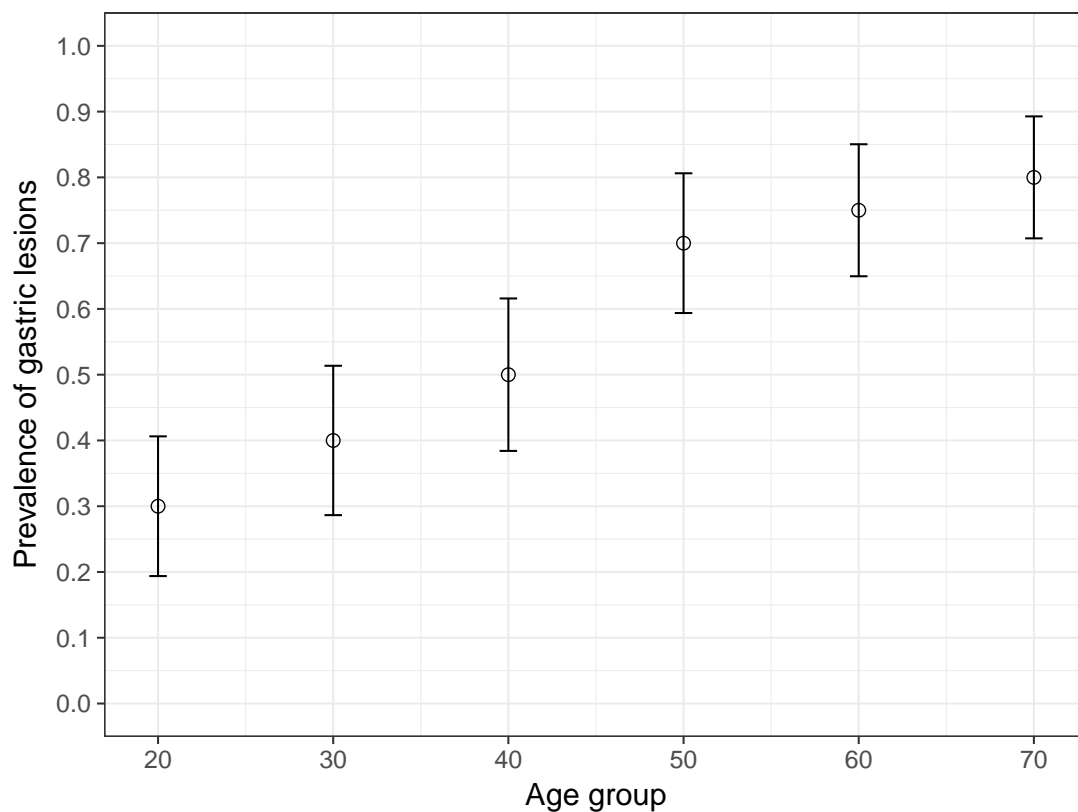


Figure 4.3: Prevalence of gastric lesions by age

Proportion of gastric lesions The proportion of the population with each of the gastric lesions by age group came from study conducted in patients who consulted because of gastroduodenal symptoms or because of a probable gastric cancer, programmed for endoscopy and biopsy for diagnostic purposes in two oncology hospitals in Mexico City from 1999 to 2002.[196] Table 4.2 shows the number of patients with different gastric lesions by age group and *H. pylori* status.

Table 4.2: Gastric lesions by age and *H. pylori* status for a sample of patients in Mexico in 1999-2002.

<i>H. pylori</i> status	Age(y)	Lesion			
		Non-atrophic gastritis	Atrophic gastritis	Intestinal metaplasia	Dysplasia
Negative	30-44	40	0	5	0
	45-54	27	2	2	0
	55-64	17	0	5	0
	65+	14	0	7	1
Positive	30-44	131	1	14	0
	45-54	71	6	21	0
	55-64	39	2	25	0
	65+	29	3	31	1

The proportion of the population with each gastric lesion by age group and *H. pylori* status with their corresponding 95% CI is shown in Figure 4.4. We estimated the 95%CI using the Sison-Graz method assuming proportions of gastric lesions within each age group and *H. pylori* status follow a multinomial distribution.[197, 198] We used the R package `MultinomialCI` to compute these 95% CI.[199]

gastric cancer incidence Age-specific gastric cancer incidence estimates for Mexico came from GLOBOCAN 2012.[200, 201, 202] The rate, cases, standard errors and 95% CI are shown in Table 4.3. We estimated the 95% CI using an exact method assuming cancer cases within each age group follow a Poisson distribution. We used the R package `epitools` to compute these 95% CI.[203]

Figure 4.5 shows cancer incidence by age group with their corresponding 95% CI.

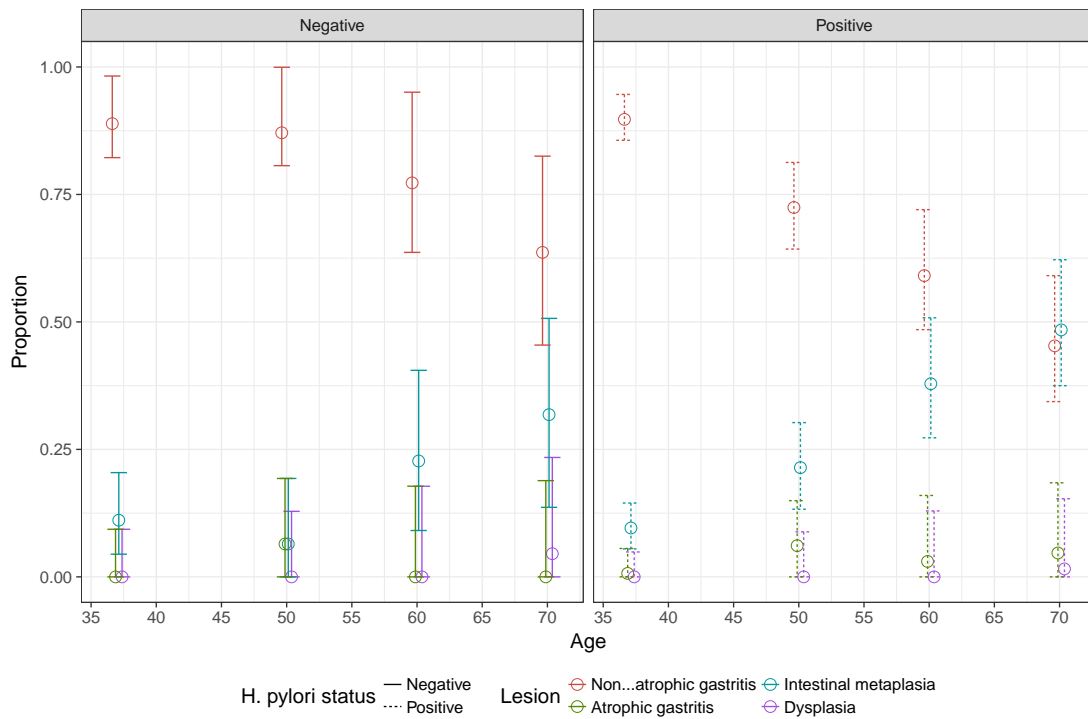


Figure 4.4: Proportion of gastric lesions by age and *H. pylori* status for a sample in Mexico in 1999-2002 with multinomial confidence intervals.

Likelihood functions

We assigned a likelihood function to each type of target. To compute an aggregated likelihood measure across all targets, we added the log-likelihoods of each target. For the proportion of gastric lesions by age, we assumed that the number of individuals with a gastric lesion g for age group i , N_{gi} with $g \in \{G, A, M, D\}$ follow a multinomial distribution

$$[N_{Gi}, N_{Ai}, N_{Mi}, N_{Di}] \sim \text{Multinomial}(N_i; [p_{Gi}, p_{Ai}, p_{Mi}, p_{Di}]), \quad (4.3)$$

where N_i is the total number of individuals in age group i and p_{gi} is the model predicted-proportion of individuals with gastric lesion g for age group i .

To compute the likelihood for cancer incidence and prevalence of gastritis for age group i , we assumed that they follow a normal distribution. For example, let gastric cancer incidence

Table 4.3: Gastric cancer incidence in Mexico in 2012 by age group with corresponding standard errors (SE), and 95% CI lower bounds (LB) and upper bounds (UB). Rates per 100,000

Age group	Rate	Cases	SE	LB	UB
15-39	1.10	509	0.05	1.01	1.20
40-44	5.00	394	0.25	4.52	5.52
45-49	8.20	537	0.35	7.52	8.92
50-54	12.30	688	0.47	11.40	13.25
55-59	17.60	815	0.62	16.41	18.85
60-64	25.10	856	0.86	23.45	26.84
65-69	35.80	914	1.18	33.52	38.20
70+	58.31	2964	1.07	56.23	60.44

and prevalence of total gastritis for age group i be denoted by y_i :

$$y_i \sim \text{Normal}(\phi_i, \sigma_i), \quad (4.4)$$

where ϕ_i is the model predicted-incidence and σ_i is the standard error of the target for age group i .

Prior distributions

All the parameters that need to be calibrated are defined over positive numbers. Thus, we assumed that their prior distributions follow a log-normal distribution. The ranges given in Table 4.6 are assumed to represent the 95% equal-tailed interval for a log-normal distribution.

Steady state distribution of the population

The demographic and infection steady state distributions are detailed in Chapter 3. For the distribution of the population in each gastric disease state, we estimated the proportion of the population with each gastric lesion for ages 0-70 by fitting a multinomial logistic regression [204] on an expanded dataset based on the aggregated data for the proportion of gastric lesions in Mexico shown in Table 4.2 and Figure 4.4. Briefly, we expanded the aggregated data by generating repeated observations by the number of individuals with each gastric lesion $k =$

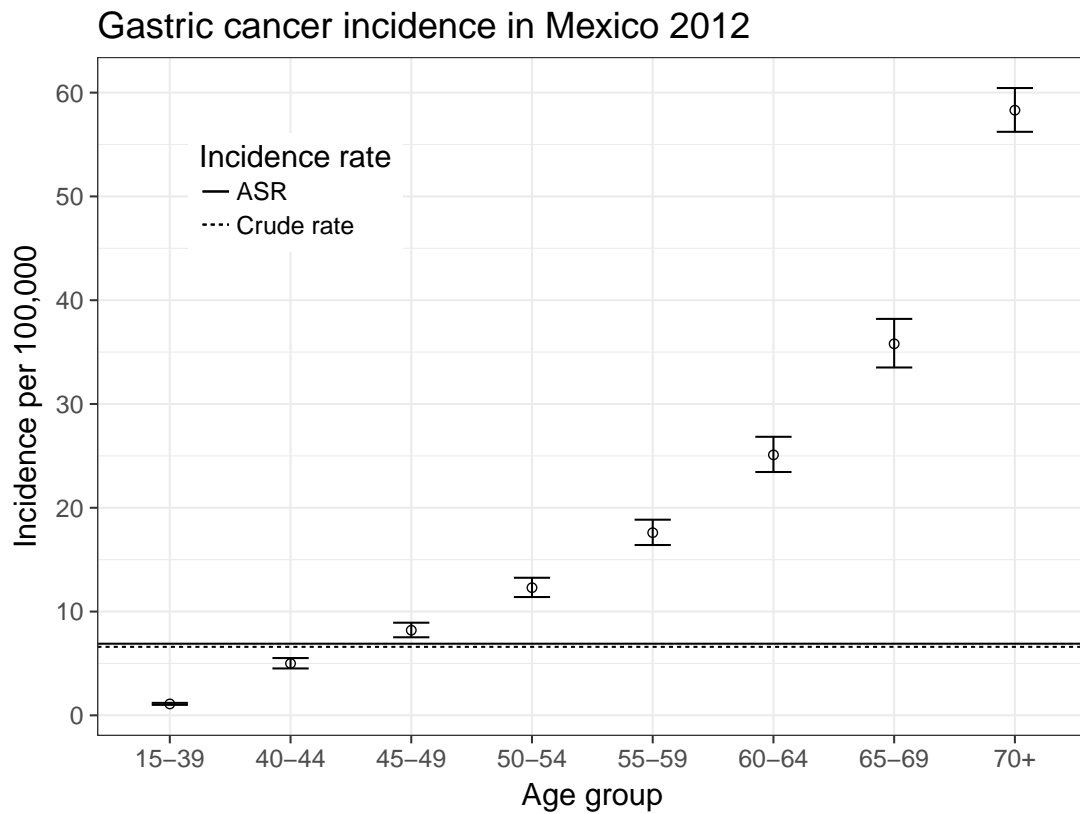


Figure 4.5: Gastric cancer incidence in Mexico in 2012 by age group with confidence intervals, and crude and age-standardized rates (ASR).

0, . . . , 3, *H. pylori* infection status and age group, and assigned them the median age for each age group. For example, for the 131 individuals in Table 2 in the category with non-atrophic gastritis, positive *H. pylori* infection in age group 30-44, we created 131 identical observations with non-atrophic gastritis, positive *H. pylori* infection and age 37. We then modeled each gastric lesion k with independent binary logistic regression models as a function of age and *H. pylori* status, in which non-atrophic gastritis, $k = 0$, is chosen as the reference category. The

other three categories are separately regressed against the reference category. That is,

$$\begin{aligned}\ln \frac{Pr(Y_i = 1)}{Pr(Y_i = 0)} &= \beta_1 X_i, \\ \ln \frac{Pr(Y_i = 2)}{Pr(Y_i = 0)} &= \beta_2 X_i, \\ \ln \frac{Pr(Y_i = 3)}{Pr(Y_i = 0)} &= \beta_3 X_i,\end{aligned}\tag{4.5}$$

where $Y_i = k$ represents individual i has gastric lesion k , β_k is a vector of coefficients including the intercept and X_i is a vector of covariates for individual i , such as age and *H. pylori* infection status.

We estimated the coefficients of the multinomial model in Equation (4.5) using the function `vglm` of the package `VGAM` via maximum likelihood (ML).[205] We then predicted the proportion of each gastric lesion by *H. pylori* status and for ages 0 to 70 years, $\hat{Pr}(Y_{age, Hp} = k)$, using the following expression

$$\begin{aligned}\hat{Pr}(Y_{age, Hp} = 0) &= \frac{1}{1 + \sum_{k=0}^3 e^{\hat{\beta}_k X}}, \\ \hat{Pr}(Y_{age, Hp} = 1) &= \frac{e^{\hat{\beta}_1 X}}{1 + \sum_{k=0}^3 e^{\hat{\beta}_k X}}, \\ \hat{Pr}(Y_{age, Hp} = 2) &= \frac{e^{\hat{\beta}_2 X}}{1 + \sum_{k=0}^3 e^{\hat{\beta}_k X}}, \\ \hat{Pr}(Y_{age, Hp} = 3) &= \frac{e^{\hat{\beta}_3 X}}{1 + \sum_{k=0}^3 e^{\hat{\beta}_k X}},\end{aligned}\tag{4.6}$$

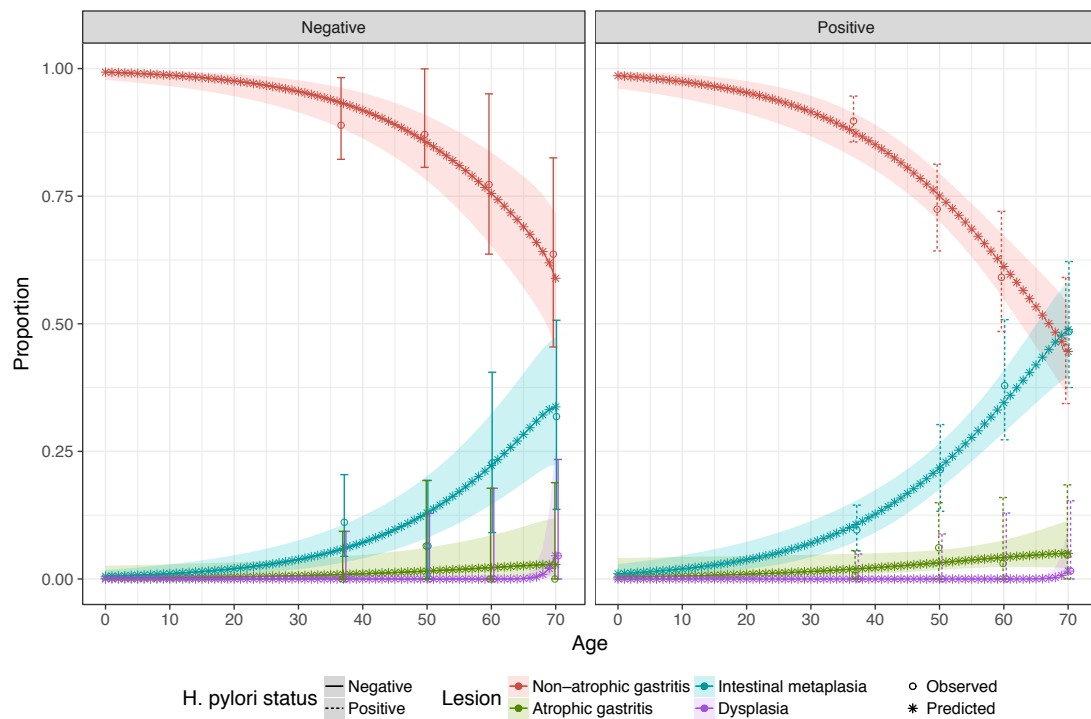
where $\hat{\beta}_k$ is the estimated vector of coefficients for gastric lesion k and X is the design matrix with the values of interest of age and *H. pylori* infection status.

The estimated parameters of the multinomial model described in Equation (4.5) are shown in Table 4.4.

The trend in growth of the predicted proportions of gastric lesions by age does not vary by *H. pylori* infection status. Non-atrophic gastritis declines with age and the rest of gastric lesions increase with age. Intestinal metaplasia has the highest increase and dysplasia has the lowest increase. The predicted and observed proportions of all gastric lesions by age and *H. pylori* status are shown in Figure 4.6.

Table 4.4: Estimated coefficients of the multinomial model.

Coefficient	Estimate	Std. Error	z value	Pr(> z)
β_1^0	-6.448	1.444	-4.464	0.000
β_2^0	-5.210	0.610	-8.542	0.000
β_3^0	-108.735	5080.855	-0.021	0.983
β_1^{Age}	0.049	0.022	2.174	0.030
β_2^{Age}	0.066	0.010	6.861	0.000
β_3^{Age}	1.517	72.584	0.021	0.983
β_1^{Hp}	0.850	0.777	1.094	0.274
β_2^{Hp}	0.650	0.293	2.216	0.027
β_3^{Hp}	-0.789	1.442	-0.547	0.584

Figure 4.6: Predicted proportion of gastric lesions by age and *H. pylori* status with 95% CI error bands from a sample of patients in Mexico in 1999-2002.

The rate of growth of gastric lesions by age varies by *H. pylori* infection status. The decrease in non-atrophic gastritis is more pronounced in patients *H. pylori*-positive patients compared to *H. pylori*-negative patients. In both atrophic gastritis and intestinal metaplasia, the increase is higher in *H. pylori*-positive patients compared to *H. pylori*-negative patients. The increase in dysplasia by age is higher in *H. pylori*-negative patients compared to *H. pylori*-positive patients. The difference in predicted gastric lesions by *H. pylori* infection status is shown in Figure 4.7.

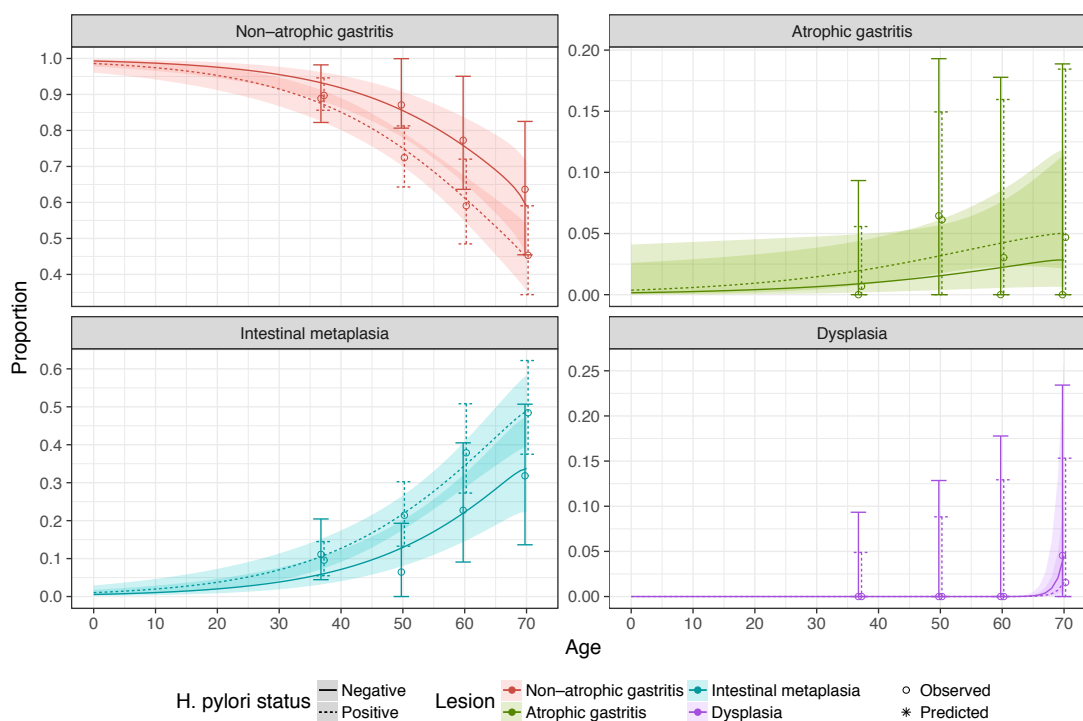


Figure 4.7: Difference in predicted proportion of gastric lesions by age and *H. pylori* status with 95% CI error bands from a sample of patients in Mexico in 1999-2002.

For the distribution of the population in at least one gastric lesion state, we estimated the prevalence of the population with total gastritis for ages 0-70 by fitting a linear regression on the aggregated data shown in Figure 4.3. That is, we modeled the prevalence of total gastritis for age group i denoted by y_i with a linear regression model as a function of age:

$$y_i = b_0 + b_1 x_i + \epsilon_i, \quad (4.7)$$

where b_0 is the intercept, b_1 is the coefficient representing the effect of age on the prevalence

of total gastritis, x_i is the median age in age group i , and ϵ_i is the error term. We estimated the coefficients of the linear model in Equation 4.7 using ordinary least squares (OLS). We then predicted the prevalence of total gastritis for ages 0 to 70 years using the following expression

$$\hat{y} = \hat{b}_0 + \hat{b}_1 x, \quad (4.8)$$

where $x = 0, \dots, 70$.

4.2.3 Screen-and-treat algorithms

We implemented different screen-and-treat strategies with two different testing algorithms: (1) test only for *H. pylori* infection and treat if positive (SnT), and (2) test for *H. pylori* infection and if positive, test for susceptibility and if test indicates susceptibility to clarithromycin, treat with clarithromycin; otherwise, treat with second line treatment (SnT-ST). We assume that screening will only be implemented in the population currently not getting any antibiotics (i.e., S_g^0 , I_{wg}^0 and I_{rg}^0).

For the screening test, we considered the urea breath test (UBT). UBT is a popular and accurate noninvasive test for diagnosis of *H. pylori* infection and can be safely used in children and women of childbearing age.[137] We used the test characteristics of UBT from a recent meta-analysis with a pooled sensitivity of 96% (95%CI: 0.95-0.97) and a pooled specificity of 93% (95%CI: 0.91-0.94).[140]

The susceptibility test actually tests for both susceptibility and *H. pylori* infection status, but it requires a biopsy, which is why we do not consider using it as a single test. To detect for susceptibility to clarithromycin, we used the GenoType HelicoDR assay, which is a molecular test that combines polymerase chain reaction (PCR) and hybridization, allowing the molecular identification of *H. pylori* as well as clarithromycin resistance within 6 hours. In previous studies, the GenoType HelicoDR assay using bacterial strains or gastric biopsy specimens was highly accurate for clarithromycin resistance with 94%-100% sensitivity and 86%-99% specificity respectively.[137, 206, 207, 208] We assumed that testing for infection using a susceptibility test has a sensitivity of 100% and specificity of 90%, based on the test characteristics of culture.[209]

For the second line treatment, we assume an effectiveness of 0.80 based on recent reports of effectiveness of Bismuth-containing quadruple therapy (PPI, bismuth, tetracycline, metronidazole) after failure of clarithromycin-based therapy.[210] These screening algorithms will be

applied to the simulated population at a rate η .

4.2.4 Screen-and-treat policies

We implemented six different population-wide *H. pylori* screen-and-treat policies, three for each of the two testing algorithms described in section 4.2.1. We also simulated a do-nothing strategy (i.e., non *H. pylori* screening or treatment) to have a common comparator in the absence of any policy. The different screen-and-treat policies evaluated are:

- Policy 1: No screen-and-treat (No SnT)
- Policy 2: Screen-and-treat 2-6 year olds (SnT 2-6 yo)
- Policy 3: Screen-and-treat 40+ year olds (SnT 40+)
- Policy 4: Screen-and-treat all the population (SnT all)
- Policy 5: Screen-and-treat with susceptibility test 2-6 year olds (SnT-ST 2-6 yo)
- Policy 6: Screen-and-treat with susceptibility test 40+ year olds (SnT-ST 40+)
- Policy 7: Screen-and-treat with susceptibility test all the population (SnT-ST all)

We assume these policies are implemented in 2018 and are carried out over 13 years (i.e., implementation period). Individuals who are not receiving antibiotics during the year are assumed to be screened each year. Following the introduction of the screen-and-treat policies, we then simulate the population for 70 years (i.e., analytic horizon, T) to capture the long-term impact of these policies.[116] Note that for 57 years (i.e., 70-13) the impact of the policies will be quantified following the implementation period.

4.2.5 Variables and Parameters

The variables, subscripts and superscripts of the mathematical model are described in Table 4.5.

Table 4.5: Description of variables, subscripts and superscripts

Symbol	Description
Subscripts	
i, j	Age groups
g	Gastric disease state ($N, G, A, M, D, NCGC$)
k	Treatment status (no treatment=0, treatment=1)
m	Type of strain (sensitive = w , resistant = r)
p	Antibiotic treatment policy
Variables	
λ_i	Force of infection at age i
S_{gi}^k	Susceptible with gastric lesion g and treatment status k in age group i
I_{mgi}^k	Infected with type of strain m , gastric lesion g and treatment status k in age group i
A_i	Antibiotic consumption

The parameters of the different components of the mathematical model, such as the gastric disease dynamics, screening and treatment, and the cost-effectiveness analysis are shown in Table 4.6.

Table 4.6: Description of parameters

Symbol	Description	Value	Source	Range
Gastric Disease Dynamics				
Transition rates (annual)				
λ_{NG}	Normal Mucosa to non-atrophic gastritis	0.0052	Calibrated Section 4.2.2	[0.001, 0.01]
λ_{GA}	Non-atrophic gastritis to atrophic gastritis	0.0043	Calibrated Section 4.2.2	[0.001, 0.01]
λ_{AM}	Atrophic gastritis to intestinal metaplasia	0.0300	Calibrated Section 4.2.2	[0.001, 0.05]
λ_{MD}	Intestinal metaplasia to dysplasia	0.0002	Calibrated Section 4.2.2	[0.001, 0.01]
λ_{NCGC}	Dysplasia to gastric cancer	0.0054	Calibrated Section 4.2.2	[0.001, 0.01]
λ_{GN}	Non-atrophic gastritis to normal mucosa	0.0032	Calibrated Section 4.2.2	[0.001, 0.01]
λ_{AG}	Atrophic gastritis to non-atrophic gastritis	0.0018	Calibrated Section 4.2.2	[0.001, 0.01]
λ_{MA}	Intestinal metaplasia to atrophic gastritis	0.0018	Calibrated Section 4.2.2	[0.001, 0.01]
λ_{DM}	Dysplasia to intestinal metaplasia	0.0021	Calibrated Section 4.2.2	[0.001, 0.01]
μ_{NCGC}	Gastric cancer mortality rate	0.3238	[211]	[0.023, 0.033]
Hazard ratios				
HR_{NG}	Normal mucosa to non-atrophic gastritis	5.2	Calibrated Section 4.2.2	[1, 5]
HR_{GA}	Non-atrophic gastritis to atrophic gastritis	1.9	Calibrated Section 4.2.2	[1, 15]
HR_{AM}	Atrophic gastritis to intestinal metaplasia	1.0	Assumed Section 4.2.2	[1, 5]

Description of parameters (continued)

Symbol	Description	Value	Source	Range
Screening parameters				
η	Screening rate (per unit time)	1	Assumed	–
η_i	Screening rate (per unit time) for age group i	1	Assumed	–
ρ	Sensitivity of screening UBT	0.96	[140]	[0.95, 0.97]
θ	Specificity of screening UBT	0.93	[140]	[0.91, 0.94]
ω	Susceptibility test	0–1	Assumed	–
ρ^s	Sensitivity of susceptibility test to identify infection	1.00	[209]	–
θ^s	Specificity of susceptibility test to identify infection	0.90	[209]	–
ρ^{sr}	Sensitivity of susceptibility test to identify resistance	0.97	[137, 206, 207]	[0.94, 1.00]
θ^{sr}	Specificity of susceptibility test to identify resistance	0.93	[137, 206, 207]	[0.86, 0.99]
Treatment parameters				
α	Prescribing rate (per unit time)	0.3*	[114]	–
α_i	Prescribing rate (per unit time) for age group i	–	–	–
ψ_{pi}	Antibiotic treatment policy p for age group i	–	Section 3.2.4	–
$1/\gamma$	Average length of treatment (days)	14	[115]	–
σ	Probability that treatment induces mutation on sensitive strains and therefore does not clear colonization	0.375 [†]	[104]	[0.04, 0.71]
h	Effectiveness of 2nd line treatment	0.80	[210]	[0.70, 0.92]
Cost-effectiveness parameters				
Costs (MXN\$) [‡]				

Description of parameters (continued)

Symbol	Description	Value	Source	Range
c_{HpRx}	Cost of <i>H. pylori</i> treatment	\$780	[212]	–
c_{Dx}	Cost of screening test of <i>H. pylori</i>	\$165	[213]	–
c_{Dx}^s	Cost of susceptibility test	\$252	[213]	–
c_{GC}	Cost of gastric cancer treatment	\$66,303	[212]	–
Health utilities				
u_N	Utility for normal	0.95	[214]	[0.94, 0.96]
u_G	Utility for non-atrophic gastritis	0.79	[215]	[0.77, 0.81]
u_A	Utility for atrophic gastritis	0.79	[215]	[0.77, 0.81]
u_M	Utility for intestinal metaplasia	0.79	[215]	[0.77, 0.81]
u_D	Utility for dysplasia	0.79	[215]	[0.77, 0.81]
u_{NCGC}	Utility for NCGC	0.68	[215]	[0.55, 0.81]
Discount factors (annual)				
δ_c	Discount factor for costs	3%	[216]	[3%, 7%]
δ_e	Discount factor for effectiveness	3%	[216]	[3%, 7%]

* DDDs/1000 per day

† From a study where three individuals out of eight total infected with *H. pylori* sensitive strains prior to treatment developed resistance after treatment.

‡ In 2015 Mexican pesos (MXN\$).

4.2.6 Epidemiologic impact of screen-and-treat strategies

To assess the epidemiologic impact of each screen-and-treat strategy we use two main outcome measures of effectiveness: life years (LY) and quality-adjusted life years (QALYs).

Years of life

The total number of undiscounted and discounted years spent alive by the active population, LY and LY^d , respectively, under strategy x given by

$$LY_x = \int_0^T \left(\sum_{i=1}^{71} N_i \right) dt, \quad (4.9)$$

$$LY_x^d = \int_0^T e^{-\delta_e t} \left(\sum_{i=1}^{71} N_i \right) dt, \quad (4.10)$$

where N_i is the size of the population in age group i , δ_e is the discount rate for effectiveness and T is the analytic horizon. All the parameters and state variables are described in more detail in Table 4.6

Quality-adjusted life years

The second outcome considers the quality of life weight associated to different health states into a QALY. Let u_g be the utility assigned to spend one year in a gastric disease state g , where $g \in \{N, G, A, M, D, NCGC\}$. The undiscounted and discounted QALYs under strategy x over the analytic horizon, T , are given by

$$QALY_x = \int_0^T \left(\sum_{g=1}^6 \sum_{i=1}^{71} u_g N_{gi} \right) dt, \quad (4.11)$$

$$QALY_x^d = \int_0^T e^{-\delta_e t} \left(\sum_{g=1}^6 \sum_{i=1}^{71} u_g N_{gi} \right) dt, \quad (4.12)$$

where N_{gi} is the size of the population in gastric disease state g and age group i calculated as

$$N_{gi} = S_{gi}^0 + S_{gi}^1 + I_{wgi}^0 + I_{rgi}^0 + I_{rgi}^1. \quad (4.13)$$

All the parameters and state variables are described in more detail in Table 4.6

Estimates of health utilities

There are no health utility estimates for the Mexican population for either the general population or any of the gastric disease states. Therefore, we used health utility estimates for these

health states from other populations. For the normal gastric mucosa states, we used a health utility u_N of 0.95 from the general population obtained from recently published article that estimated health utilities for the Uruguayan population.[214] We used the same health utility for all asymptomatic precancerous gastric lesions of 0.79 (i.e., $u_G = u_A = u_M = u_D = 0.79$), obtained from a multicenter study of gastric premalignant conditions and malignant lesions in Portugal.[215] This study used the EQ-5D-5L questionnaire developed by the EuroQol Group, which is a standardized measure to provide utilities for clinical and economic appraisal.[217] The health utilities were estimated by converting the responses to the EQ-5D-5L questionnaire by setting preferences for the general population using the time trade-off technique. The estimate of the health utility associated to gastric cancer u_{NCGC} of 0.68 was also obtained from this study.[215]

4.2.7 Costs of screen-and-treat strategies

Screening costs

The cost of screening per unit time is the product of the cost per screening test c_{Dx} , the screening rate η_i per unit time (e.g., every year), and the size of the population eligible for screening $\sum_{i=1}^{71} \{S_i^0 + I_{wi}^0 + I_{ri}^0\}$. For simplicity, we assumed that the population under treatment will not be eligible for screening. Thus, the total screening costs associated with strategy x at time t are

$$Screen_x(t) = c_{Dx} \left(\sum_{g=1}^6 \sum_{i=1}^{71} \eta_i \{S_{gi}^0 + I_{gwi}^0 + I_{gri}^0\} \right). \quad (4.14)$$

Susceptibility test costs

The cost of susceptibility testing per unit time is the product of the cost per susceptibility test c_{Dx}^s , the screening rate η_i per unit time (e.g., every year), and the size of the population assigned to receive the susceptibility test, which are those with a positive screening test result $\sum_{i=1}^{71} \{(1 - \theta)\omega S_{gi}^0 + \rho\omega [I_{gwi}^0 + I_{gri}^0]\}$. Thus, the total susceptibility test costs associated with strategy x at time t are

$$SusTest_x(t) = c_{Dx}^s \left(\sum_{g=1}^6 \sum_{i=1}^{71} \eta_i \{(1 - \theta)\omega S_{gi}^0 + \rho\omega [I_{gwi}^0 + I_{gri}^0]\} \right). \quad (4.15)$$

Costs of *H. pylori* antibiotic treatment

Treatment costs of *H. pylori* are the product of the population on the treated states and the cost of treatment c_{HpRx} . Thus, the total treatment costs of strategy x at time t are

$$Treat_x(t) = c_{HpRx} \left(\sum_{g=1}^6 \sum_{i=1}^{71} \{S_{gi}^1 + I_{gri}^1\} \right). \quad (4.16)$$

Costs of gastric cancer treatment

Treatment costs of gastric cancer are the product of the population in the gastric cancer disease state (i.e., $g = 6$) across all infection status and the cost of gastric cancer treatment c_{GC} . Thus, the total treatment costs of gastric cancer of strategy x at time t are

$$CancerTreat_x(t) = c_{GC} \left(\sum_{i=1}^{71} \{S_{6i}^0 + S_{6i}^1 + I_{6wi}^0 + I_{6ri}^0 + I_{6ri}^1\} \right). \quad (4.17)$$

Note that people with precancerous lesions are assumed to remain asymptomatic; therefore, they are never identified nor treated.

Total costs

The discounted total cost of strategy x over the planning horizon, T , is

$$Cost_x = \int_0^T e^{-\delta_c t} (Screen_x(t) + SusTest_x(t) + Treat_x(t) + CancerTreat_x(t)) dt, \quad (4.18)$$

where δ_c is the discount rate for costs.

Incremental cost-effectiveness ratio

To compare mutually exclusive non-dominated screen-and-treat strategies we first calculated the incremental cost-effectiveness ratio (ICER) by taking the difference in discounted total costs and divide it by the difference in discounted total QALYs of strategy x and its next best strategy x' ,

$$ICER_{x,x'} = \frac{Cost_x - Cost_{x'}}{QALY_x^d - QALY_{x'}^d}. \quad (4.19)$$

Second, we identified the strategies on the cost-effectiveness frontier using an efficient non-iterative algorithm [218] and finally, selected the optimal strategy with the highest ICER that falls at or below the threshold willingness to pay (WTP) for additional QALY.[216]

4.2.8 Methodological assumptions

We adopted a health care sector perspective. Other methodological assumptions used in the cost-effectiveness analysis followed the updated recommendations by the Second Panel on Cost-Effectiveness in Health and Medicine.[216] In particular, we adopted a discount rate of 3% for both costs and health effects on a lifetime time horizon. Costs are expressed in 2015 Mexican pesos (MXN\$). In Mexico, an intervention is considered to be cost-effective if the ICER is less than or equal to 1-times GDP per capita.[219, 220] Mexico's GDP per capita for 2013 was MXN\$132,000.[221]

4.3 Results

4.3.1 Model fit

The calibrated parameters are shown in Table 4.6. Figures 4.8, 4.9 and 4.10 depict the model output for the prevalence of total gastritis, proportions of gastric lesions and cancer incidence using the MAP estimate in comparison to the observed target data. The majority of model-predicted outputs from the MAP estimate fell within the 95% confidence intervals of the target data.

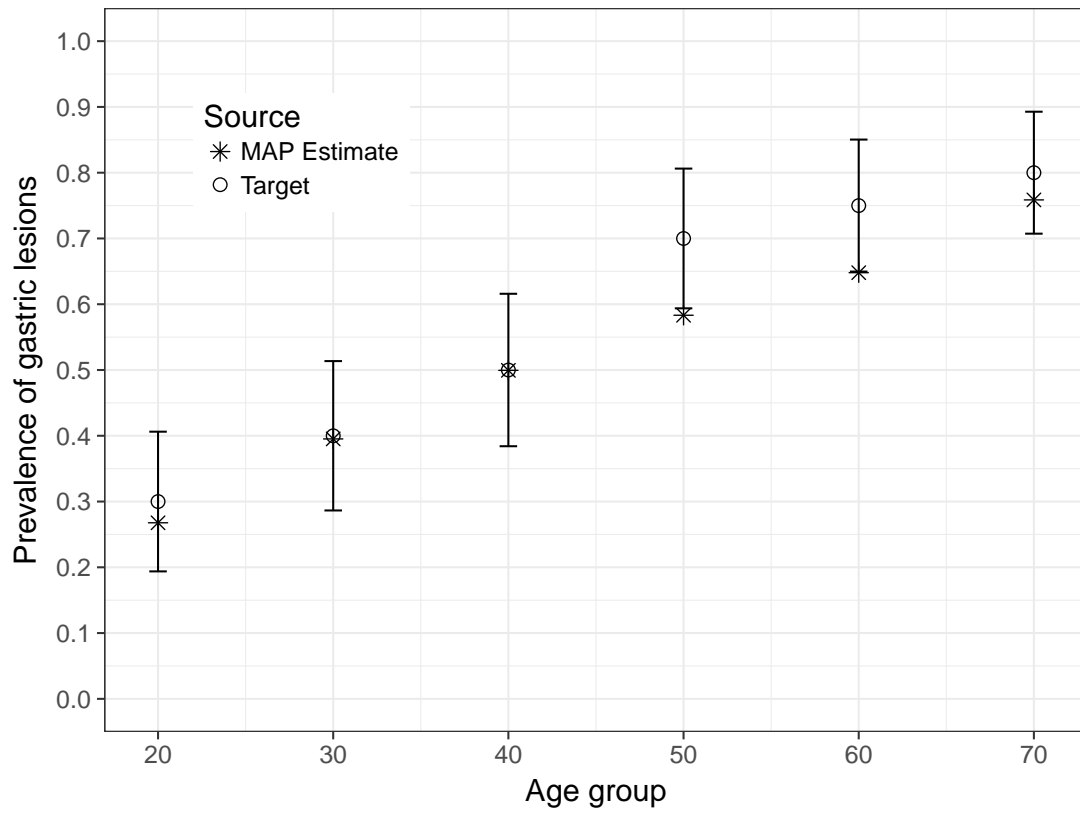


Figure 4.8: Observed and model-predicted prevalence of gastritis using MAP estimate.

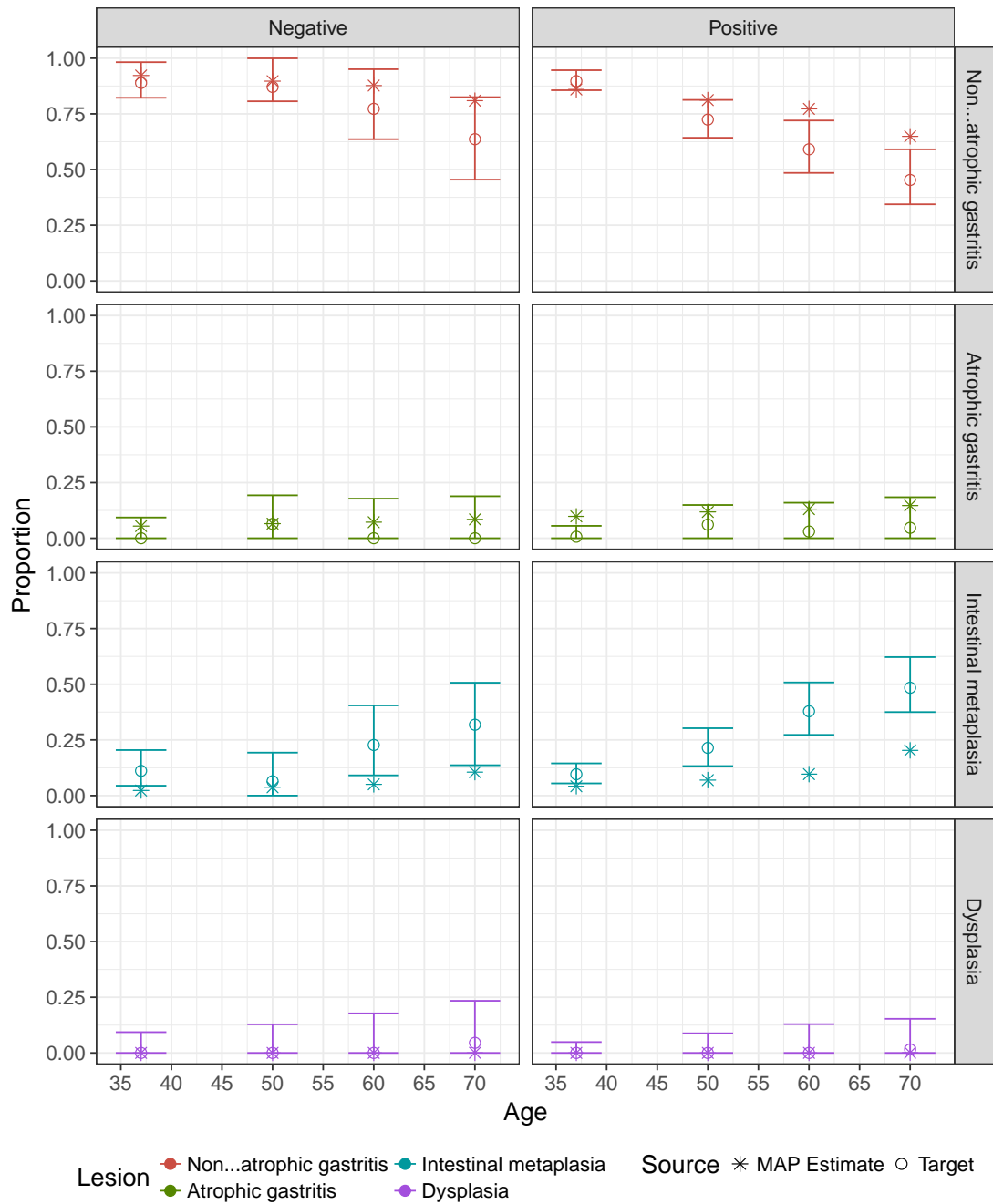


Figure 4.9: Observed and model-predicted proportions of gastric lesions by age and *H. pylori* infection status using MAP estimate for the population in Mexico

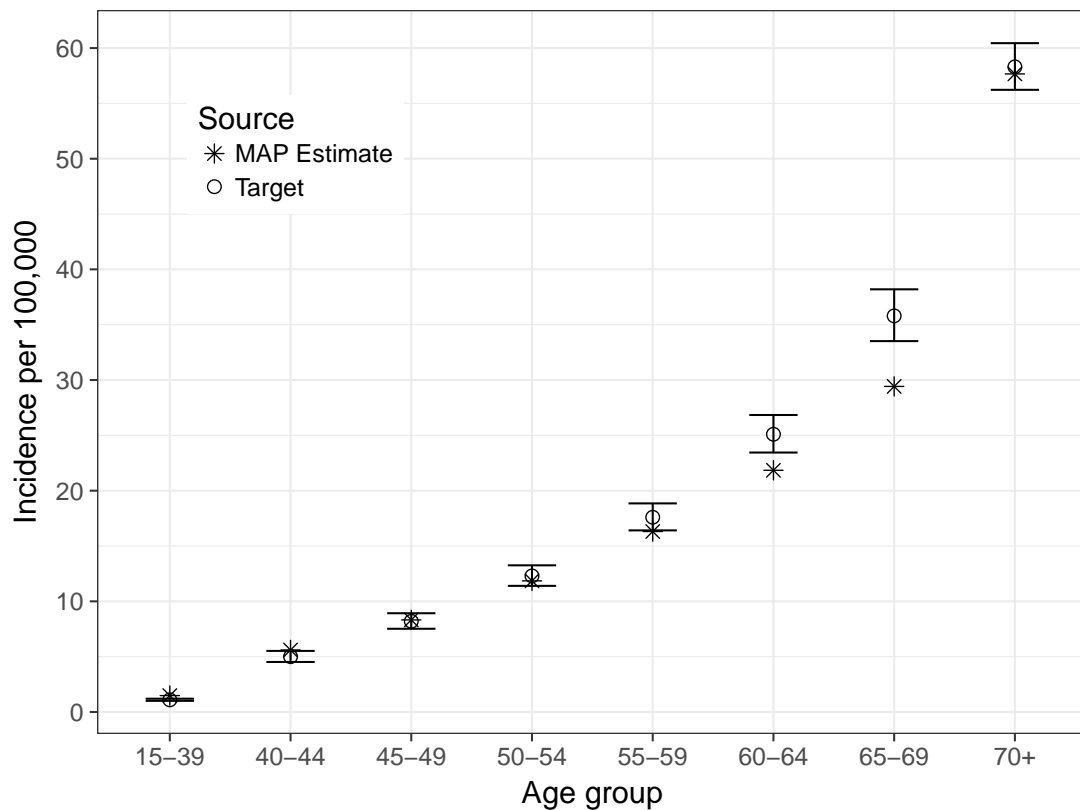


Figure 4.10: Observed and model-predicted gastric cancer incidence using MAP estimate for the population in Mexico.

4.3.2 Cost-effectiveness analysis

Under base-case assumptions, the model predicts that from the health care payer's perspective, the screen-and-treat strategy with susceptibility test on children 2-6 year-olds (SnT-ST 2-6 yo) and the entire population (SnT-ST all) cost MXN\$2,277 and MXN\$7,796 per QALY gained, respectively (Table 4.7). Thus, taking MXN\$132,000 per QALY gained as upper limit for an intervention to be considered cost-effective, screening and treating the entire population with a susceptibility test would be worthwhile from the health care payer's perspective.

Table 4.7: Cost-effectiveness analysis of screen-and-treat strategies for *H. pylori* infection in the setting of antibiotic resistance. D: strongly dominated strategy; d: weakly dominated strategy.

Strategy	Costs (MXN\$)	Effectiveness (QALYs)	ΔC (MXN\$)	ΔEff (QALYs)	ICER (MXN\$/ QALYs)
Policy 1 (no screening)	126	14.4999	0	0	-
Policy 2 (screening 2-6 yo)	208	14.5000	82	0.0001	700,447
Policy 3 (screening 40+ yo)	699	14.5005	-	-	d
Policy 4 (screening all)	1,352	14.5014	1,144	0.0014	792,773

All screening policies produced higher effectiveness compared to a no-screen-and-no-treat policy. This means that regardless of the current predicted level of resistance, screening and treating for *H. pylori* infection will produce epidemiologic benefits at a population level. However, all policies were costlier than the do-nothing strategy. Policies including susceptibility test were more effective but also costed more than their counterparts without susceptibility test. In the case of policy 5 and policy 7, the additional benefits obtained with susceptibility test outweighed the additional costs. Figure 4.11 shows the cost-effectiveness plane with the cost-effectiveness efficiency frontier (represented by the solid line). Policies that lie on the frontier are considered the set of potentially cost-effective strategies. In our analysis, we found that when considered no SnT as the comparator, only two policies lie on the frontier: SnT-ST 2-6 yo and SnT-ST all.

4.4 Discussion

In this chapter, we expanded an integrated transmission dynamic model of *H. pylori* infection and resistance to simulate gastric disease dynamics of the Mexican population by incorporating multiple pre-cancerous gastric lesions and gastric cancer. We calibrated the parameters governing the natural history of gastric disease using a Bayesian approach that allowed us to weight the relevance of the targets based on their uncertainty using a likelihood function. In addition, we overlaid two different screening algorithms for *H. pylori* in which one accounts for susceptibility testing. Our model incorporates the known epidemiologic and economic consequences

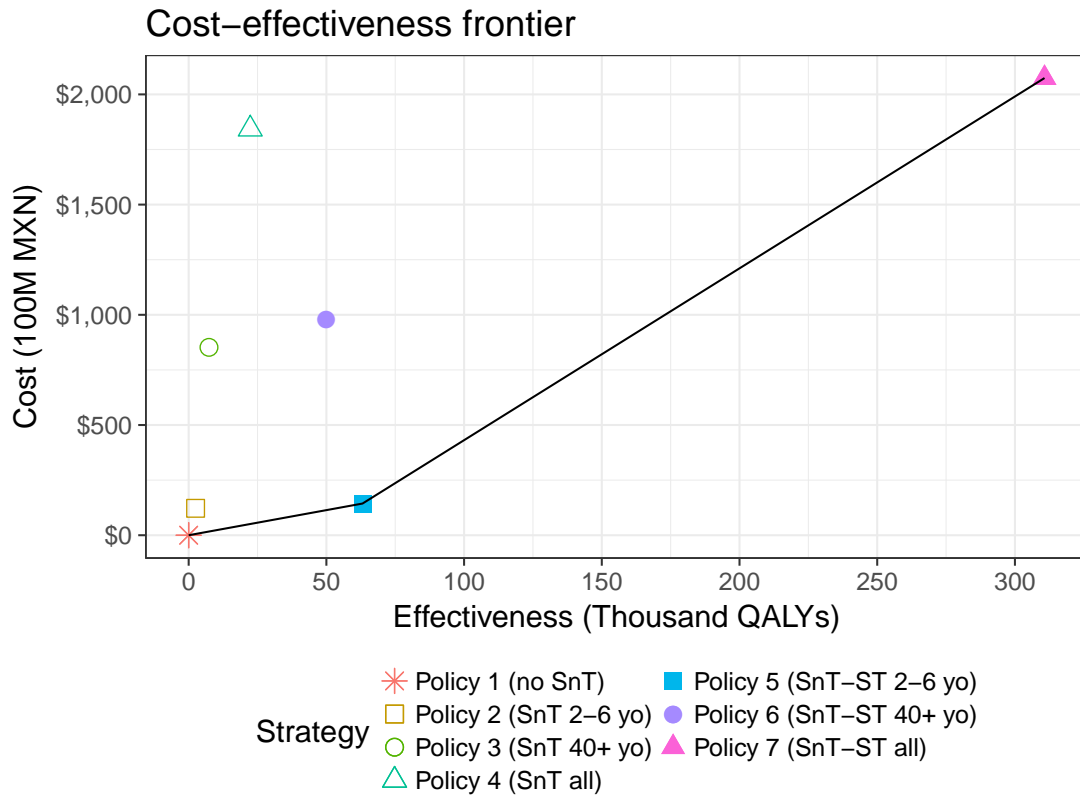


Figure 4.11: Cost-effectiveness frontier (represented by the solid line)

resulting from different screen-and-treat policies such as life years and QALYs, and costs of screening and treating for *H. pylori* and treating for gastric cancer. We used both costs and QALYs to compute the cost-effectiveness of such policies.

Currently, clinical guidelines do not recommend screening and treating for *H. pylori* in asymptomatic individuals.[26] Our results suggest that there appear to be *H. pylori* screening and treatment strategies that would be considered cost-effective in Mexico. Using a cost-effectiveness threshold of the GDP per capita (MXN\$132,000 in Mexico), we found screening and treating for *H. pylori* all the population would be considered cost-effective.

Our cost-effectiveness results are similar to other CEAs that found that screening and treating for *H. pylori* is cost-effective. However, given the high levels of resistance, screening for *H. pylori* has to be done with susceptibility tests. We acknowledge that conducting susceptibility tests could be costly and require medical equipment that is not readily available in most

of Mexico and that our results represent a scenario where technology to conduct biopsies and susceptibility tests does not require additional investment of infrastructure. Accounting for the need of investing in medical technology to conduct susceptibility testing will likely increase the ICER by making the policies costlier in terms of MEX\$/QALYs gained. However, the investment would only occur once while the returns would be carried over a long period. In addition, an investment in technology to test for clarithromycin resistance will have direct spillover effects such as being able to perform biopsies for reasons other than *H. pylori* infection and susceptibility testing, and will to test for resistance for other antibiotics with high resistance like metronidazole.

Our current analysis has several limitations. First, we do not account for non-adherence of treatment, which is also an important determinant of treatment failure.[26, 27, 28, 29, 30, 31] Therefore, our current analyses and results represent the maximum possible benefit. That is, by considering non-adherence the benefits of treatment could decrease. Second, we assumed the test characteristics of UBT and susceptibility testing does not vary across all ages. There is evidence that at least UBT can vary by age. Specifically, UBT test is less accurate in young children, but adjusting cutoff value, pretest meal, and urea dose, this accuracy can be improved.[222] Third, screening costs only include cost of screening and susceptibility tests but did not include any additional labor cost or cost of scaling up current infrastructure to meet demands of proposed policies. Fourth, we did not allow for the possibility of second line treatment to become resistant. Therefore, our results represent the maximum effectiveness of adding a second line treatment with less than perfect effectiveness. Fifth, we assumed that the prevalence of total gastritis using Finnish data was generalizable to Mexico. This is most likely not the case given that prevalence of *H. pylori* in Finland is notoriously lower than in Mexico; therefore, prevalence of total gastritis in Finland represents an under estimation or this prevalence in Mexico. Unfortunately, there are no available data either for the country or the region regarding these epidemiologic outcomes. Sixth, we assumed that the proportion of gastric lesions by age from the study conducted in Mexico City was generalizable to the whole Mexican population. Compared to another study conducted in Colombia in the 1980's,[223] our estimates of the proportion of atrophic gastritis in Mexico are significantly lower than those from Colombia and our estimates of intestinal metaplasia are significantly higher than the Colombian. This could have an effect on the calibrated parameters because the order between these two gastric lesions is reversed between countries. In addition, there is high variation of gastric cancer incidence

across Mexican states, which could also represent geographical variation in the proportion of gastric lesions. Therefore, a larger study to estimate the proportion of gastric lesions in Mexico could potentially benefit the calibration of the natural history model presented in this chapter. And lastly, we assumed that *H. pylori* infection increases the risk of non-atrophic and atrophic gastritis only. However, *H. pylori* may also promote progression to more advanced precancerous lesions. In such cases, our model-predicted benefits of antibiotic treatment for *H. pylori* infection represent a conservative estimate because we are not allowing for a reduction on the progression rates to more advanced gastric lesions from clearing *H. pylori* infection.

In summary, the results from this model suggest that in a setting of *H. pylori* screening, screening and treating with susceptibility test the entire population can substantially improve quality of life and be cost-effective. Model-based policy analyses using a decision-analytic framework allow for exploratory analyses of the potential health and economic outcomes of different screen-and-treat strategies of *H. pylori* infection for the prevention of gastric lesions and gastric cancer.

Chapter 5

Conclusion and discussion

This thesis investigates various aspects of the dynamics of *H. pylori* infection and ABR, and the impact of mass-treatment and screen-and-treat strategies on epidemiologic and economic outcomes in Mexico.

In Chapter 2, we used catalytic models to estimate the force of infection of *H. pylori* in Mexico at the national level, but also at the state level, accounting for state-level heterogeneity. By estimating state-specific parameters simultaneously using a hierarchical nonlinear Bayesian model, we obtained reasonable parameter estimates even for states that were sparsely sampled in a national seroprevalence survey. We found that age-specific prevalence of *H. pylori* varies greatly by state, which translates into high variation in the force of infection, which can have implications in prevention and treatment strategies and highlights the need of state-specific interventions. Seroepidemiologic studies offer a rich source for understanding infection dynamics, and under certain assumptions these can be used to estimate the force of infection. Catalytic models have been previously used to estimate the force of infection of other diseases but have not previously been applied to *H. pylori*. Our work represents a proof of principal for the use of catalytic epidemic models to estimate the force of infection of *H. pylori* using national seroepidemiologic data.

In Chapter 3, we developed an integrated transmission dynamic model of *H. pylori* infection and resistance to represent the Mexican population. We estimated the transmission parameters of different mixing matrices based on different structures of how the population mixes across age. We validated the model by comparing model-predicted age-specific and aggregated prevalence of *H. pylori* infection in steady state and over time, respectively, to observed prevalence

from different studies. We then used this model to evaluate different antibiotic mass-treatment policies on several epidemiologic outcomes such as prevalence of infection and resistance.

In general, the results suggest that any mass-treatment policy will have a higher effect on increasing resistance than on reducing infection. In fact, as the proportion of *H. pylori* resistant strains increases and becomes more prevalent than sensitive strains, *H. pylori* infection starts rising again. Given the high predicted prevalence of ABR at the time of the policy implementation, mass treatment strategies are unlikely to be optimal in Mexico.

In Chapter 4, we expanded an integrated transmission dynamic model of *H. pylori* infection and resistance to simulate gastric disease dynamics of the Mexican population by incorporating multiple pre-cancerous gastric lesions and gastric cancer. We calibrated the parameters governing the natural history of gastric disease using a Bayesian approach that allowed us to weight the relevance of the targets based on their uncertainty using a likelihood function. In addition, we overlaid two different screening algorithms for *H. pylori* in which one accounts for susceptibility testing. We then used this model to evaluate different screen-and-treat policies on several epidemiologic and economic outcomes such as life years and QALYs, and costs of screening and treating for *H. pylori* and treating for gastric cancer. We incorporated both costs and QALYs to compute the cost-effectiveness of such policies. Using a cost-effectiveness threshold of the GDP per capita (MXN\$132,000 in Mexico), we found screening and treating for *H. pylori* all the population would be considered cost-effective.

5.1 Implications

Introducing screen-and-treat strategies for *H. pylori* infection in Mexico may have important implications. A screening test will decrease the number of individuals exposed to *H. pylori* infection-targeted antibiotic, which will reduce the rate of treatment induced-resistance compared to treating the entire population. In addition, screening with an additional susceptibility test can optimize current lines of treatment by prescribing the right course of antibiotic treatment to infected individuals that who would truly benefit from it.

Because these strategies offer substantial public health impact, clinical studies to evaluate the long-term consequences of screening for *H. pylori* infection, treating infected individuals based on their susceptibility to the antibiotic and the impact of these treatments on overall resistance should be given the highest priority.

5.2 Future work

In this thesis, we simulated the whole Mexican population on the transmission model without accounting for any differences across states. Given the high variation of infection and gastric cancer mortality across geographical states in Mexico, state-specific transmission models could provide guidance on the optimal policy for each of state based on their state-specific infection dynamics. In Chapter 2, we estimated state-specific force of infection, which could be directly used to construct these state-specific transmission models, like the one we constructed for the state of Morelos on Chapter 3 for validation purposes.

In addition, some of the estimates are highly uncertain because they were either obtained from few studies with small sample sizes or obtained from different populations. This could have immediate consequences if different but equally good fitting parameters yield different recommendations. We plan to address this issue in future studies by conducting a value of information analysis (VOI) on key parameters with high uncertainty, such as the antibiotic treatment-induced mutation rate, assumptions on the different dynamics of resistance and natural history of gastric disease, and the background use on antibiotics. VOI is used to determine whether future research should be conducted based on the expected cost of uncertainty surrounding a decision with current information. VOI analysis is a quantification of the importance of reducing parameter uncertainty and avoiding the consequences of sub-optimal decisions.[224, 225]

5.3 Summary

In summary, using a simulation model-based policy analyses under a decision-analytic framework we found that given the high predicted prevalence of ABR at the time of the policy implementation, mass treatment strategies and screening without susceptibility test are unlikely to be optimal in Mexico. Screening and treating for *H. pylori* could be cost-effective. However, given the high levels of resistance, screening for *H. pylori* has to be done with susceptibility tests.

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Appendix A

Demographic model

A.1 Demographic model structure

The demographic model consists of a population that is divided into a finite number of n age groups defined by the age intervals $[a_{i-1}, a_i]$, where $0 = a_0 < a_1 < a_2 < \dots < a_{n-1} < a_n = \infty$, that moves across different age groups at aging rates d_i and face age-related causes of death rates d_i . All the symbols used to describe variables and parameters are defined in Tables 3.2 and 3.3.

Assuming that the population distribution has reached a steady state with exponential growth or decay of the form e^{qt} , Hethcote [95] provides a system of n ordinary differential equations (ODEs) for the sizes of the n age groups. In this formulation the maximum age is not explicitly defined because we assume that the last interval includes all the individuals over age a_{n-1} . [92, p. 267] and [95, p. 623]. Let $A(a)$ be the age-distribution function, and assume that it is piecewise constant, with a value in $[0, 1)$ for each year of age. Let P_i be the proportion of the population with ages in $[a_{i-1}, a_i]$. Then P_i is given by [95, p. 623]:

$$P_i = \int_{a_{i-1}}^{a_i} A(a) da \quad (\text{A.1})$$

In this case the age distribution is not explicitly calculated from data, but determined from the population's life tables. We assume that there is negligible population growth (population growth is denoted by q ; this assumption can be relaxed by allowing q to be nonzero) and that the population has reached an equilibrium age distribution. Using [95, Equation 4.11, p. 624],

the proportion in the youngest age group is

$$P_1 = \left(1 + \sum_{i=2}^n \frac{d_{i-1}}{(d_i + \mu_i)} \right)^{-1}, \quad (\text{A.2})$$

and the proportions in the following groups are

$$P_i = \frac{d_{i-1}P_{i-1}}{d_i + \mu_i}, \quad i = 2, \dots, n. \quad (\text{A.3})$$

For a multi-year age group, we take the mean of the rates. The aging rates are modified by the death rates, so that

$$d_i = \frac{\mu_i + q}{\exp[(\mu_i + q)l_i] - 1}, \quad (\text{A.4})$$

where l_i is the number of years in the i -th age group.

In this manuscript the birth rate b refers to the rate at which individuals enter the youngest age group (i.e. newborns) it is defined as

$$b = (d_1 + \mu_1 + q)P_1. \quad (\text{A.5})$$

Using Equations (A.2), (A.3), (A.4) and (A.5) the dynamics of the population can be described by the following system of n ordinary differential equations (ODE) [95, p. 623]:

$$\begin{aligned} \frac{dP_1}{dt} &= b - (d_1 + \mu_1)P_1, \\ &\vdots \\ \frac{dP_i}{dt} &= d_{i-1}P_{i-1} - (d_i + \mu_i)P_i, \\ &\vdots \\ \frac{dP_n}{dt} &= d_{n-1}P_{n-1} - (\mu_n + d_n)P_n, \end{aligned} \quad (\text{A.6})$$

where the population at each age group a_i either transfer to an older age group at age-specific rate d_i (equal to zero for the oldest age group) or die at rate μ_i .

Appendix B

Additional Figures

Care has been taken in this thesis to minimize the excess use of figures in the main text, but this cannot always be achieved. This appendix includes figures of additional analysis conducted in this thesis.

B.1 *H. pylori* SIS model in the setting of antibiotic resistance

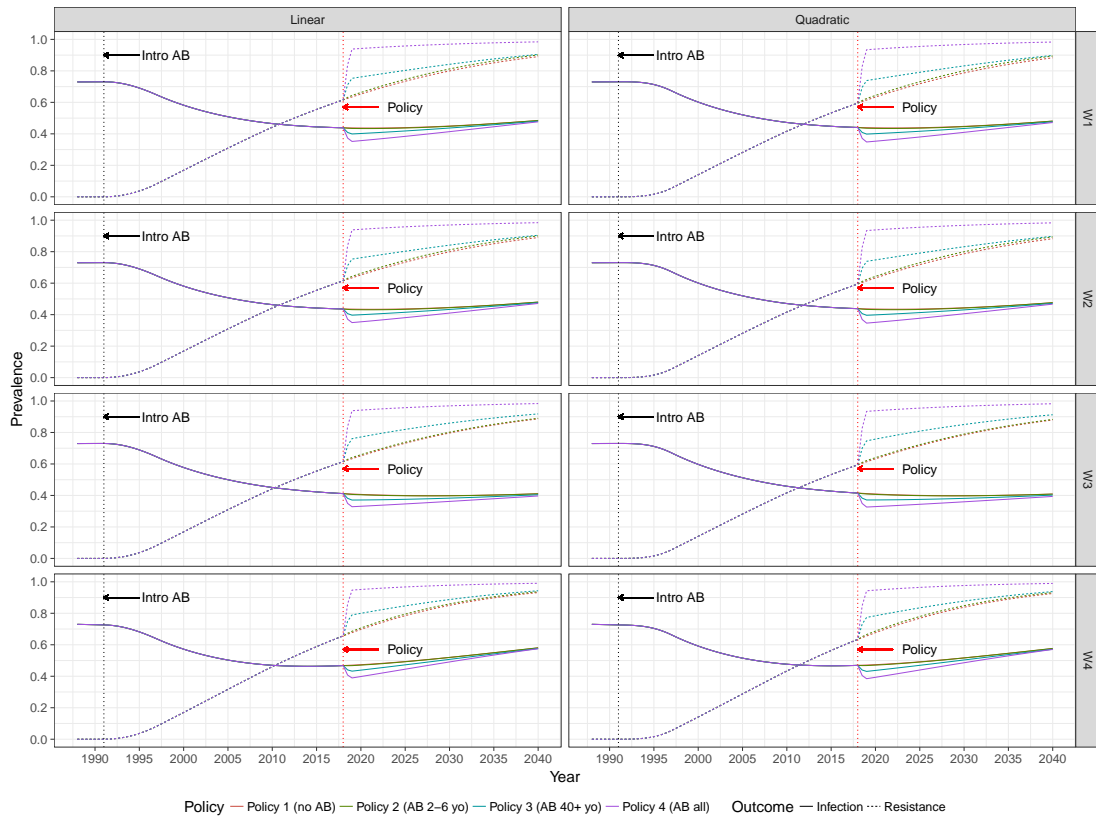


Figure B.1: Impact of different antibiotic treatment policies on prevalence of *H. pylori* infection and resistance for different antibiotic mass-treatment policies under different WAIFW matrices and background antibiotic uptakes.

Appendix C

Glossary and Acronyms

Care has been taken in this thesis to minimize the use of jargon and acronyms, but this cannot always be achieved. This appendix defines jargon terms in a glossary, and contains a table of acronyms and their meaning.

C.1 Glossary

- **Cost-effectiveness analysis (CEA)** is a form of economic evaluation that quantifies the health benefits and costs of interventions designed to improve the health of a population. [216]
- **Cost-effectiveness acceptability curves (CEAC)** is a graphical representation of the probability that interventions are cost-effective at different cost-effectiveness thresholds. [226, 227]
- **Cost-effectiveness acceptability frontier (CEAF)** indicates the probability of being cost-effective for the strategy with the highest expected net benefit.[228]
- **Confidence interval (CI)** is an interval in which a measurement or trial falls corresponding to a given probability.
- **Catalytic epidemic model (CM)** Catalytic epidemic models are concerned with the age by which individuals are or have been infected. For an age-dependent catalytic epidemic model it is assumed that the force of infection $\lambda(a)$ acts upon members of a susceptible

population of age a . Such would be the case if exposure to infection, the level of transmissibility remains constant in time and if infection were endemic in the population.[46, 48]

- **Credible interval (CR)** is an interval on the posterior probability distribution that includes a given probability.
- **Defined daily doses (DDD)** “Sales or prescription data presented in DDDs per 1000 inhabitants per day may provide a rough estimate of the proportion of the study population treated daily with a particular drug or group of drugs. As an example, the figure 10 DDDs per 1000 inhabitants per day indicates that 1% of the population on average might receive a certain drug or group of drugs daily. This estimate is most useful for chronically used drugs when there is good agreement between the average prescribed daily dose (see below) and the DDD. It may also be important to consider the size of the population used as the denominator. Usually the general utilization is calculated for the total population including all age groups, but some drug groups have very limited use among people below the age of 45 years. To correct for differences in utilization due to differing age structures between countries, simple age adjustments can be made by using the number of inhabitants in the relevant age group as the denominator.” [229] ATC/DDD Index 2017
- **Deterministic sensitivity analysis (DSA)** involves varying a parameter or set of parameters from their base-case values and reporting the implications for the results.[216]
- **Force of infection (FOI)** is the instantaneous rate at which susceptible individuals acquire infection.
- **Gastric cancer (GC)** is cancer developing from the lining of the stomach.[230]
- ***Helicobacter pylori* (*H. pylori*)** "is a spiral-shaped bacterium that grows in the mucus layer that coats the inside of the human stomach." [231]
- **Hazard ratio (HR)** is the ratio of the hazard rates.
- **Incremental cost-effectiveness ratio (ICER)** is calculated by taking the difference in discounted total costs and divide it by the difference in discounted total QALYs of strategy x and its next best strategy x' .[216]
- **Life years (LY)** represent the number of years that a population or an individual lives.

- **Minimal inhibitory concentration (MIC)** – Is the lowest concentration of antibiotic that inhibits the growth of a bacterium. Reports typically contain a quantitative result in $\mu\text{g/mL}$ and a qualitative interpretation. The interpretation usually categorizes each result as susceptible (S), intermediate (I), resistant (R), sensitive-dose dependent (SD), or no interpretation (NI)
- **Non-cardia gastric cancer (NCGC)** – Gastric cancer on the distal region.
- **Ordinary differential equation (ODE)** is a differential equation containing one or more functions of one independent variable and its derivatives.
- **Probabilistic sensitivity analysis (PSA)** is a method used to represent parameter uncertainty. In a PSA all parameters that are uncertain are varied simultaneously, with multiple sets of parameter values being sampled from priori-defined probability distributions. [180]
- **Quality-adjusted life years (QALY)** – A generic measure of disease burden, including both the quality and length of life.[216]
- **Relative rate (RR)** – A RR is a ratio of two different rates.
- **Susceptible-infected (SI) epidemiologic model** – A SI model represents the dynamics of interactions between susceptible and infected individuals to model the rate of emergence of new infectious individuals.[232]
- **Susceptible-infected-susceptible (SIS) epidemiologic model** – A model for a disease from which infected individuals recover with no immunity.[232]
- **Value of information (VOI)** – The value of acquiring more precise information about uncertain parameters of a decision model.[224]
- **Who-acquires-infection-from-whom (WAIFW) matrix** – Represents the effective contact rate between age groups (i.e. the rate at which an infective of age a' will infect a susceptible of age a). Contains the values of the transmission rates between groups: the element in the i -th row and j -th column denotes the probability that an infective in the j -th group will infect a susceptible in the i -th group per unit time.

- **The World Health Organization (WHO)**

– A specialized agency of the United Nations that is concerned with international public health.

C.2 Acronyms

Table C.1: Acronyms

Acronym	Meaning
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curves
CEAF	Cost-effectiveness acceptability frontier
CI	Confidence interval
CM	Catalytic epidemic model
CR	Credible interval
DDD	Defined daily doses
DSA	Deterministic sensitivity analysis
FOI	Force of infection
GC	Gastric cancer
<i>H. pylori</i>	<i>Helicobacter pylori</i>
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
LY	Life years
MIC	Minimal inhibitory concentration
NCGC	Non-cardia gastric cancer
ODE	Ordinary differential equation
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life years
RR	Relative Rate
SI	Susceptible-infected
SIS	Susceptible-infected-susceptible

Continued on next page

Table C.1 – continued from previous page

Acronym	Meaning
VOI	Value of information
WAIFW	Who-acquires-infection-from-whom matrix
WHO	The World Health Organization