

A STRUCTURED MODELING APPROACH OF PEPTIC ULCERS AND H. PYLORI INFECTION

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ABSTRACT. Current therapies against ulcers caused by *H. pylori* infection consist of antibiotics, an acid reducer, and some clinical trials underway to develop a *H. pylori* vaccine. We develop a structured model with age-dependent mortality of peptic ulcers and *H. pylori* infection. Our main goal is to analyze our structured model mathematically and to compare it to our previously unstructured model to examine the disease transmission dynamics in terms of annual prevalence and annual incidence of the disease.

1. INTRODUCTION

A peptic ulcer is a sore on the lining of the stomach or duodenum, which is the beginning of the small intestine. *Helicobacter pylori* (*H. pylori*) is an emerging, spiral-shaped pathogen. The connection between peptic ulcers and *H. pylori* bacterium was discovered in 1983. It is now believed that most ulcers are caused by *H. pylori* infection or the use of common nonsteroidal anti-inflammatory drugs instead of stress, acid, and spicy foods.

Approximately two-thirds of the world's population is infected with *H. pylori* [1]. In the United States, 20% of people under 40 years old and 60% of people over 60 years old are infected [2]. United States military personnel on foreign deployments have been found to have an increased risk of acquiring *H. pylori* infection, with an annual infection rate of between 1.9% and 7.3% [3] since it is widespread in the developing countries as high as 80% to 90% [4]. About 10% of Americans suffer from peptic ulcers during their lifetime.

It is not known why *H. pylori* does not cause ulcers in every infected person. Most likely, infection depends on characteristics of the infected person, the type of *H. pylori*, and other factors yet to be discovered. About 15%-20% of subjects with *H. pylori* colonization will

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develop ulcers in their lifetimes [5][6]. In the United States, there are 500,000 to 850,000 new cases of peptic ulcer disease each year [1]. The infection is found in 90% to 95% of patients with duodenal ulcers and 75% to 80% of patients with stomach ulcers [5][6]. Current therapies against ulcers caused by *H. pylori* infection consists of antibiotics and an acid reducer. A test for *H. pylori* infection and two or three weeks of medication cure 90% of the disease and the recurrence of ulcer after successful eradication of *H. pylori* is rare, compared with up to 80% when the infection persists [7]. The efficacy at the level of general practitioners is lower due to poor compliance and increasing antibiotics resistance [8][9]. Also, many doctors are still treating ulcers without antibiotics. The fact that the prevalence of peptic ulcers in the United States is 4.5 millions with less than 850,000 new cases annually shows that changing medical belief and practice takes time.

We assume that 10% of the population is not susceptible to *H. pylori* based on [6]. Although *H. pylori* can be transmitted from person to person by a fecal-oral or oral-oral route and the infection is decreasing due to sanitary awareness, prevention is difficult. In some endemic developing countries, reinfection after eradication is serious. Recent studies have shown promise with attenuated live vaccines used in combination with *H. pylori* antigens [10][11] and recently it is shown that Mongolian gerbil can be successfully vaccinated against the infection [12]. Clinical trials are underway with the goal of producing an inexpensive, safe, and effective vaccine in the near future.

Our previous work [13] developed an unstructured model of peptic ulcers and *H. pylori* with vaccination to discuss the disease transmission dynamics through stability and sensitivity analysis. Rupnow et al [15][16] had quantified the population dynamics by modeling three different age groups using partial differential equations. These and the cohort theory on peptic ulcers developed by [14] motivated us to develop a structured model with age-dependent mortality. Our main goal is to analyze our structured model mathematically and then compare it to our previously unstructured model.

We organize our paper as follows: Section 2 introduces two models, one new structured and one previously unstructured, and reduces the structured model to an integral equation, Section 3 contains our mathematical analysis of the structured model, Section 4 estimates our parameters for numerical analysis, and the last section concludes with the comparison of the two models.

2. TWO EPIDEMIOLOGICAL MODELS OF *H. PYLORI*

We consider two different models, one unstructured and one structured, for the dynamics of *H. pylori* infection and related peptic disease. Both models include four classes: susceptible (S), infective and asymptomatic (H), infective and symptomatic (U), and removed (R). The unstructured model allows for investigation of dynamics that can occur if a vaccine is developed for *H. pylori*; hence, it has an additional class (V) which we omit from the structured population model. It will also be frequently useful to consider a combined infective class $I = H + U$ and the total population N .

Individuals move among the classes by a number of different processes. A natural death process removes individuals from all classes at a rate μ per capita. It is widely held that 10% to

20% of people are naturally resistant to *H. pylori* infection; hence, the birth process adds people into the removed class, as well as the susceptible and vaccinated classes, at rates $(1 - n)bN$, $n(1 - p)bN$, and $npbN$ respectively. Both models have a transmission process by which susceptibles become asymptomatic infectives at rate $\beta' SI$ and a progression process by which asymptomatics become symptomatic at rate αH . In the otherwise more complicated structured model, we assume a curative process by which symptomatics become removed at rate ρU . In the unstructured model, we assume that symptomatics move into the vaccinated class when cured; we also include a loss of immunity process by which vaccinated individuals move into the susceptible class at rate $\gamma' V$. See the schematic diagrams of Figures 1 and 2.

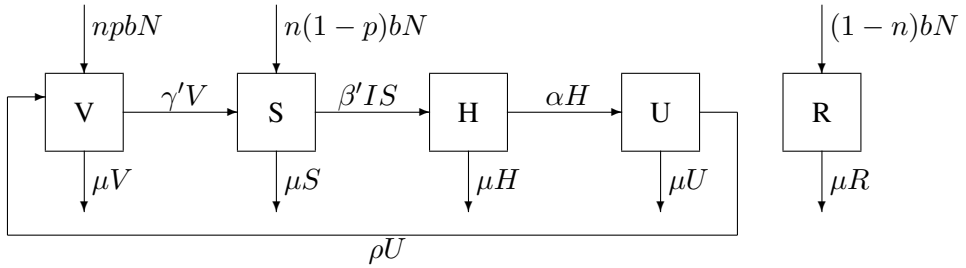


FIGURE 1. A schematic diagram of the unstructured model

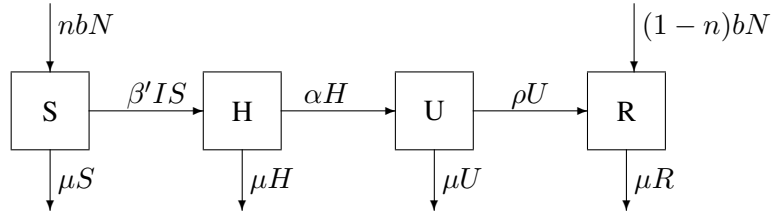


FIGURE 2. A schematic diagram of the structured model

2.1. The Unstructured Model. Letting $r = b - \mu$, the unstructured model consists of the equations

$$\frac{dN}{dt} = rN, \quad (1)$$

$$\frac{dS}{dt} = n(1 - p)(r + \mu)N + \gamma'V - \beta'S \frac{I}{N} - \mu S, \quad (2)$$

$$\frac{dI}{dt} = \beta'S \frac{I}{N} - \rho U - \mu I, \quad (3)$$

$$\frac{dU}{dt} = \alpha H - \rho U - \mu U, \quad (4)$$

$$\frac{dR}{dt} = (1 - n)(r + \mu)N - \mu R, \quad (5)$$

$$H = I - U, \quad V = N - S - I - R. \quad (6)$$

2.2. The Structured Model. As an alternative *H. pylori* model, we consider a structured model that accounts for age-dependent mortality. For simplicity, we assume that the parameters α , β , and ρ are age-independent, that immunity is permanent ($\gamma = 0$), and that there is no vaccination ($p = 0$). Thus, the patients cured of ulcers move into the removed class (see the schematic in Figure 2). Let S_a , H_a , U_a , R_a , and N_a be the age-density functions for the susceptible, asymptomatic, symptomatic, removed, and total populations, where a measures the age from birth, not the age from entry into a particular class. Thus, the total population of all ages and the total infective population of all ages are

$$N(t) = \int_0^\infty N_a(a, t) da, \quad I(t) = \int_0^\infty [H_a(a, t) + U_a(a, t)] da, \quad (7)$$

and the totals for the other groups are computed similarly. Because the infection process is age-independent, the rate at which susceptibles of age a are infected is proportional to the total fraction of infectives. Thus, we have the equations

$$\frac{\partial N_a}{\partial t} + \frac{\partial N_a}{\partial a} = -\mu(a)N_a, \quad N_a(0, t) = bN(t), \quad (8)$$

$$\frac{\partial S_a}{\partial t} + \frac{\partial S_a}{\partial a} = -\beta' S_a \frac{I}{N} - \mu(a)S_a, \quad S_a(0, t) = nbN(t), \quad (9)$$

$$\frac{\partial H_a}{\partial t} + \frac{\partial H_a}{\partial a} = \beta' S_a \frac{I}{N} - \alpha H_a - \mu(a)H_a, \quad H_a(0, t) = 0, \quad (10)$$

$$\frac{\partial U_a}{\partial t} + \frac{\partial U_a}{\partial a} = \alpha H_a - \rho U_a - \mu(a)U_a, \quad U_a(0, t) = 0, \quad (11)$$

$$R_a = N_a - S_a - H_a - U_a. \quad (12)$$

Suppose now that the population is constant. Equation 8 then becomes

$$\frac{dN_a}{da} + \mu(a)N_a = 0, \quad N_a(0) = bN,$$

with solution

$$N_a = bN e^{-\int_0^a \mu(\bar{a}) d\bar{a}}.$$

Given that the total population is N , we obtain

$$\frac{1}{b} = \int_0^\infty e^{-M(a)} da, \quad M(a) = \int_0^a \mu(\bar{a}) d\bar{a}. \quad (13)$$

The survival probability to age a is

$$\frac{N_a(a)}{N_a(0)} = e^{-M(a)}.$$

Thus, equation (13) expresses the life expectancy $1/b$ in terms of survival probability.

We complete the steady-state model by normalizing all of the populations, as with the structured model. With $\beta = n\beta'$, $S_a = nNs_a$, $I = nNi$, and so on, we obtain the model

$$\frac{ds_a}{da} + [\beta i + \mu(a)] s_a = 0, \quad s_a(0) = b, \quad (14)$$

$$\frac{dh_a}{da} + [\alpha + \mu(a)] h_a = \beta i s_a, \quad h_a(0) = 0, \quad (15)$$

$$\frac{du_a}{da} + [\rho + \mu(a)] u_a = \alpha h_a, \quad u_a(0) = 0, \quad (16)$$

$$h = \int_0^\infty h_a(a) da, \quad u = \int_0^\infty u_a(a) da, \quad i = h + u. \quad (17)$$

2.3. Reduction of the structured model to an integral equation. The solution of Equation (14) is

$$s_a = be^{-M(a)} e^{-xa}, \quad x = \beta i.$$

We can now solve Equations (15)–(16) with the following computational lemma.

Lemma 2.1. *If $\frac{dz_a}{da} + [c + \mu(a)] z_a = Ae^{-M(a)} e^{-ka}$ and $z_a(0) = 0$, then*

$$z_a = \frac{A}{k-c} e^{-M(a)} (e^{-ca} - e^{-ka}), \quad \int_0^\infty z_a(a) da = A \frac{L(c) - L(k)}{k-c},$$

where

$$L(y) = \int_0^\infty e^{-M(a)} e^{-ya} da. \quad (18)$$

From Lemma 2.1, we obtain the desired solutions for h and u as

$$h_a = \frac{b\beta i}{x-\alpha} e^{-M(a)} (e^{-\alpha a} - e^{-xa}), \quad h = \frac{b\beta i}{x-\alpha} [L(\alpha) - L(x)],$$

$$u = \frac{\alpha b\beta i}{x-\alpha} \left(\frac{L(\rho) - L(\alpha)}{\alpha - \rho} - \frac{L(\rho) - L(x)}{x - \rho} \right).$$

Substituting these results into $i = h + u$, we obtain an integral equation for x :

$$(\rho + \alpha - x)L(x) - \frac{x^2}{b\beta} + \left[\frac{\rho + \alpha}{b\beta} + \frac{\rho L(\alpha) - \alpha L(\rho)}{\rho - \alpha} \right] x = \frac{\rho^2 L(\alpha) - \alpha^2 L(\rho)}{\rho - \alpha} + \frac{\alpha\rho}{b\beta}. \quad (19)$$

If there is an endemic equilibrium, it can be found by solving Equation (19), after which we have

$$i = \frac{x}{\beta}, \quad h = bx \frac{L(\alpha) - L(x)}{x - \alpha}, \quad u = i - h. \quad (20)$$

The number of new ulcer cases per year and the total prevalence of ulcers, both relative to the total population, are

$$C = \frac{\alpha H}{N} = \alpha nh, \quad P = \frac{U}{N} = nu. \quad (21)$$

3. ANALYSIS OF THE STRUCTURED MODEL

We now examine the qualitative behavior of the model of Equations (18)–(20) by focusing on the issue of existence of the endemic disease equilibrium (EDE), which is determined from Equation (19). Consider first the limiting case $\beta' \rightarrow \infty$, which corresponds to $\beta \rightarrow \infty$ while keeping x/β constant. In this limit, Equation (19) reduces to

$$-\frac{x^2}{b\beta} + \frac{\rho L(\alpha) - \alpha L(\rho)}{\rho - \alpha} x = 0,$$

from which we obtain a solution for x and the corresponding equilibrium result

$$i^* \sim b \frac{\rho L(\alpha) - \alpha L(\rho)}{\rho - \alpha}, \quad \beta' \rightarrow \infty.$$

In this special case, we have $i^* \rightarrow 1$ as $\rho \rightarrow 0$ and $i^* \rightarrow bL(\alpha) < 1$ as $\rho \rightarrow \infty$. Thus, the combination of infinite transmission coefficient and no treatment leads to infection of the entire population, while the size of the infective class is positive but bounded as treatment becomes standard and instantaneous. These results are consistent with the model assumptions and the results of the unstructured model; the combination of infinite transmission coefficient and treatment speed leads to an EDE with $0 < i^* < 1$ owing to the lag between infection and development of symptoms.

It also follows immediately from (19) that there is no EDE in the limit $\beta' \rightarrow 0$. As we lower β' from a value sufficient for EDE, we gradually reduce i^* to 0, at which point the EDE disappears. Thus, the critical case is when $x = 0$ in Equation (19). The criterion for elimination of the EDE is therefore

$$\frac{1}{bn\beta'} > \frac{\rho^2[L(0) - L(\alpha)] - \alpha^2[L(0) - L(\rho)]}{\alpha\rho(\rho - \alpha)} \equiv F(\rho; \alpha), \quad (22)$$

where the notation for F indicates that we are thinking of the treatment rate ρ as variable while the ulcer-development rate α is fixed. The remainder of the analysis of the structured model will consist in determining the properties of the function F to see if the EDE elimination criterion (22) indicates properties similar to the corresponding criterion $n\beta' < b\phi$ of the unstructured model. To that end, we begin by computing $F(\rho)$ for the case $\mu(a) = b$, which makes the structured model equivalent to the unstructured model. Indeed, with $\mu = b$, we have $L(y) = (b + y)^{-1}$, and F reduces to

$$F(\rho) = \frac{\rho + \alpha + b}{b(\alpha + b)(\rho + b)} = \frac{1}{b^2\phi},$$

making the criteria for the two models identical.

Additional properties of F are summarized in Theorem 1.

Theorem 3.1. *F is positive, continuous, and decreasing for $\rho \geq 0$, with $F(0)$ the average age of the population and $F(\infty) = \alpha^{-1}[L(0) - L(\alpha)]$. The range of F decreases as $\alpha \rightarrow 0$, with $\lim_{\alpha \rightarrow 0}[F(0) - F(\infty)] = 0$.*

Two important corollaries follow immediately from Theorem 1:

- (1) Existence of the EDE is possible only if $n\beta'$ is greater than the ratio of life expectancy $1/b$ to the average age $\int_0^\infty ae^{-M(a)} da$.
- (2) $bn\beta' > \alpha/[L(0) - L(\alpha)]$ is sufficient to guarantee existence of the EDE, regardless of ρ .

Proof. Note first that L is decreasing, with

$$L'(y) = - \int_0^\infty ae^{-M(a)-ya} da,$$

and $L(\infty) = 0$. From the definition of F and the properties of L , we then have

$$\begin{aligned} \lim_{\rho \rightarrow \infty} F(\rho) &= \frac{L(0) - L(\alpha)}{\alpha} > 0, \\ \lim_{\rho \rightarrow 0} F(\rho) &= \lim_{\rho \rightarrow 0} \frac{L(0) - L(\rho)}{\rho} = -L'(0) = \int_0^\infty ae^{-M(a)} da, \\ \lim_{\alpha \rightarrow 0} [F(0) - F(\infty)] &= \lim_{\rho \rightarrow 0} \frac{L(0) - L(\rho)}{\rho} - \lim_{\alpha \rightarrow 0} \frac{L(0) - L(\alpha)}{\alpha} = 0, \\ \lim_{\rho \rightarrow \alpha} F(\rho) &= \lim_{\epsilon \rightarrow 0} \frac{(\alpha + \epsilon)^2[L(0) - L(\alpha)] - \alpha^2[L(0) - L(\alpha + \epsilon)]}{\epsilon\alpha^2} = \frac{2}{\alpha}[L(0) - L(\alpha)] + L'(\alpha). \end{aligned}$$

□

It remains to show that $F' < 0$. We begin with two computational lemmas.

Lemma 3.2. $xye^{-x} + e^{-yx} \geq (1+x)e^{-x} \forall x, y \geq 0$.

Proof. The statement is immediately true for $x = 0$. Let $x > 0$ be given and define $f(y) = xye^{-x} + e^{-yx}$. Then $f'(y) = x(e^{-x} - e^{-yx})$, so $f' < 0$ for $y < 1$ and $f' > 0$ for $y > 1$. Hence, $f(y) \geq f(1) = (1+x)e^{-x}$. □

Lemma 3.3. $y[(y-1)x + y - 2]e^{-x} + e^{-yx} \leq (y-1)^2 \forall x, y \geq 0$.

Proof. The statement is immediately true for $y = 0$. Let $y > 0$ be given and define $f(x) = y[(y-1)x + y - 2]e^{-x} + e^{-yx}$. Then $f(0) = (y-1)^2$ and $f'(x) = y[(1+x)e^{-x} - xye^{-x} - e^{-yx}]$; by Lemma 3.2, $f' \leq 0$. Hence, $f(x) \leq f(0) = (y-1)^2$. □

Now let ρ and α be chosen such that $F' > 0$. Then

$$(\rho^2 - \alpha\rho)[2\rho L(0) + \alpha^2 L'(\rho) - 2\rho L(\alpha)] > (2\rho - \alpha)[(\rho^2 - \alpha^2)L(0) + \alpha^2 L(\rho) - \rho^2 L(\alpha)].$$

After some algebraic simplification, this inequality reduces to

$$(\alpha\rho - \alpha^2)\rho L'(\rho) + (\alpha^2 - 2\alpha\rho)L(\rho) + \rho^2 L(\alpha) > (\alpha - \rho)^2 L(0).$$

From the definition of L , we have

$$\int_0^\infty [(\alpha^2 - \alpha\rho)\rho ae^{-\rho a} + (\alpha^2 - 2\alpha\rho)e^{-\rho a} + \rho^2 e^{-\alpha a}]e^{-M(a)} da > \int_0^\infty (\alpha - \rho)^2 e^{-M(a)} da.$$

Now let $x = \rho a$ and $y = \alpha/\rho$. With these substitutions, we have the inequality

$$\int_0^\infty (y[(y-1)x + y - 2]e^{-x} + e^{-yx}) e^{-M(a)} da > \int_0^\infty (y-1)^2 e^{-M(a)} da.$$

However, this inequality contradicts the result of Lemma 3.3; hence, there are no values of ρ and α for which $F' > 0$.

4. PARAMETER ESTIMATION

We can estimate the values of the parameters from the following data:

life expectancy	μ^{-1}	77 yr
U.S. population	N	300M
H. pylori prevalence	I	90M
ulcer prevalence	U	15M
new cases per year	αH	0.6M
susceptibility	n	0.9

TABLE 1. Primary data for H pylori

Assuming the data for I , U , and αH represent equilibrium values, we have

$$\mu \approx 0.013, \quad i^* = \frac{I^*}{nN} \approx \frac{1}{3}, \quad q = \frac{U^*}{I^*} \approx \frac{1}{6}, \quad \alpha = \frac{\alpha H^*}{I^* - U^*} \approx 0.008, \quad (23)$$

$$\rho = \frac{\alpha}{q} - \alpha - \mu \approx 0.027, \quad \nu = \frac{\rho q}{\mu} \approx 0.346, \quad \beta = \frac{1}{(1 + \nu)^{-1} - i^*} \approx 2.44. \quad (24)$$

The estimate for α is consistent with that of Rupnow et al.

5. COMPARISON OF THE TWO MODELS

Figure 3 shows a comparison of the structured and unstructured models. In each case, we let β_0 be the value estimated from the data. Figures 3a and 3b show the effect of changes in treatment rate on ulcer prevalence and incidence rate. In both cases, the upper curves, which were calculated with $\beta = \beta_0$, are comparable, indicating that the effect of ρ is the same for both models. Specifically, increasing the treatment rate up to about 0.2 has a significant impact on peptic disease, but further increases in treatment rate make little difference. This is easily explained by the unstructured model, where the parameter q , representing the fraction of infectives who are symptomatic, is easily calculated. Treatment of ulcer sufferers with antibiotics decreases the number of symptomatics, but cannot decrease the number of asymptomatics. The effect on the infection rate is noticeable only until q is very small. With $\rho = 0.2$, only 3% of infectives are symptomatic. Even the rather low value of ρ estimated from the current data is large enough for treatment to have already had most of its demographic impact.

The lower curves in Figures 3a and 3b show that the effect of changes in β are qualitatively similar, but quantitatively different, for the two models. A 20% decrease in transmission makes

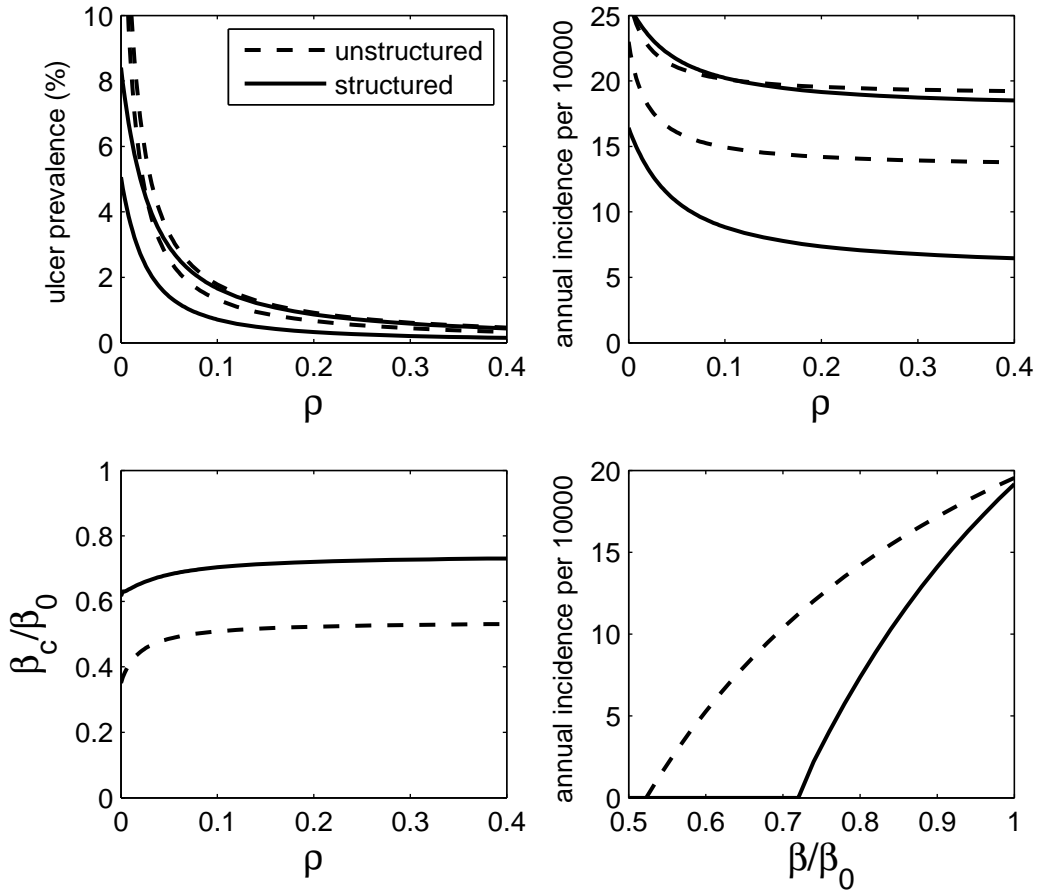


FIGURE 3. Comparison of the two models: a) ulcer prevalence with β_0 and $.8\beta_0$, with $\beta_0 = 1.5$ for the unstructured model and $\beta_0 = 2.52$ for the structured model, b) annual incidence with β_0 and $.8\beta_0$, c) critical β values for elimination of the endemic equilibrium, d) annual incidence with $\rho = 0.2$

a much larger difference when the age structure of the population is accounted for in the model. This effect is peculiar to diseases such as ulcers, in which all of the rates in the model are comparable in magnitude to the mortality rate. When the course of the disease is rapid compared to non-disease-related mortality, the effect of neglecting age structure is unimportant. The standard assumption of age-independent mortality yields a very unrealistic age structure. A simple calculation shows that if $\mu = 0.013$ is used in the structured model, the average of the population is identical to the expected lifespan. The population has a mean age of 77 years because

the age distribution includes a noticeable number of individuals who are more than 120 years old. This unrealistic structure only matters if the disease process is comparably slow, as in the case of peptic disease.

Figure 3c indicates the effect of changes in treatment on the critical degree of infectivity necessary to eliminate the endemic equilibrium. Once again, treatment makes little difference beyond about $\rho = 0.2$. The unstructured model presents an inaccurately bleak picture of the possibility of eliminating the endemic state through further reduction in the transmission rate. Based on the structured model, decreasing β by just over 25% would be sufficient to eliminate endemic peptic disease in the United States. Of course this is assuming no further increase in lifespan, which would allow infectives more time to transmit the infection. Figure 3d elaborates on the same theme by indicating the effect of β on the endemic ulcer incidence rate, given $\rho = 0.2$. The models agree at $\beta = \beta_c$ because the transmission coefficients were chosen to achieve the current incidence rate. Decreases in β reduce ulcer incidence markedly in the model that accounts for age structure, and much less so in the model that does not.

One could make a more sophisticated structured model by making parameters other than μ age-dependent. However, there are two reasons why it is probably not advantageous to do so. First, the other parameters are unlikely to be as strongly age-dependent as is the mortality rate. Second, the age-dependence of these parameters is not well known, while the age-dependence of mortality has the Makeham-Gompertz theoretical model with parameters that are relatively well-known, as compared with the crude estimate that 90 million U.S. residents are infected with *H. pylori*, for example. A further complication is that parameters having to do with infectivity and development of symptoms may depend as much on the amount of time since becoming infected as on the age of the patient. Even the relatively crude unstructured model used here displays the right qualitative behavior, so it is arguable that one could make better quantitative predictions than our structured model by using a model that is more precise but relies on extremely crude estimates of parameters. Our unstructured model is adequate for studies for which parameter values likely to be sensitive to population age structure are not changed much from current estimates. For studies that do make significant changes to such parameter values, our structured model gives sufficiently different results to warrant its use in spite of the mathematical complications.

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