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THE DYNAMICS OF PEPTIC ULCERS AND H. PYLORI WITH VACCINATION

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Abstract: The majority of peptic ulcers are caused by H. pylori infection. Since clinical trials are underway to develop a H. pylori vaccine, we have developed a VSHUR model. The model examines the disease transmission dynamics with treatment and vaccination through analytical stability analysis and numerical simulation of a system of ordinary differential equations.

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Key Words: treatment, vaccination

1. Introduction

One out of ten Americans suffers from peptic ulcer diseases during their lifetime. People of any age can get an ulcer. 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. Until

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1983, before the discovery of the connection between peptic ulcers and H. pylori bacterium, stress, acid, and spicy foods were considered the major causes of peptic ulcers. Now it is believed that most ulcers are caused by H. pylori infection or the use of common nonsteroidal anti-inflammatory drugs.

Approximately two-thirds of the world's population is infected with H. pylori. About 15%-20% of subjects with H. pylori colonization will develop ulcers in their lifetimes [8, 4]. The infection is found in 90% to 95% of patients with duodenal ulcers and 75% to 80% of patients with stomach ulcers [8, 4]. We assume that 10% of the population is not susceptible to H. pylori based on [4]. Since recent studies have shown promise with attenuated live vaccines used in combination with H. pylori agents [1, 2], we consider vaccination in our discussion.

We create a simple model of peptic ulcers caused by H. pylori. Our deterministic model is heterogeneous mixing and consists of ordinary differential equations. Through the mathematical stability analysis and numerical simulation of the model, we investigate the ulcer prevalence and the sensitivity of the basic reproductive number with respect to the rates of treatment and vaccination. Previous works of Rupnow et al [5, 6] had quantified the population dynamics by modeling three different age groups using partial differential equations.

2. Model

The model we consider for the dynamics of H. pylori infection and related peptic disease include five classes: vaccinated (V), susceptible (S), infective and asymptomatic (H), infective and symptomatic (U), and removed (R). 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. 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 $\gamma' V$.

Letting $r = b - \mu$, the model consists of the equations

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

$$\frac{dI}{dt} = \beta' S\frac{I}{N} - \rho U - \mu I, \tag{2}$$

$$\frac{dU}{dt} = \alpha H - \rho U - \mu U, \tag{3}$$

$$\frac{dR}{dt} = (1-n)(r+\mu)N - \mu R, \tag{4}$$

$$H = I - U, \qquad V = N - S - I - R. \tag{5}$$

The box diagram in Figure 1 illustrates the flow of individuals as an epidemic progresses.

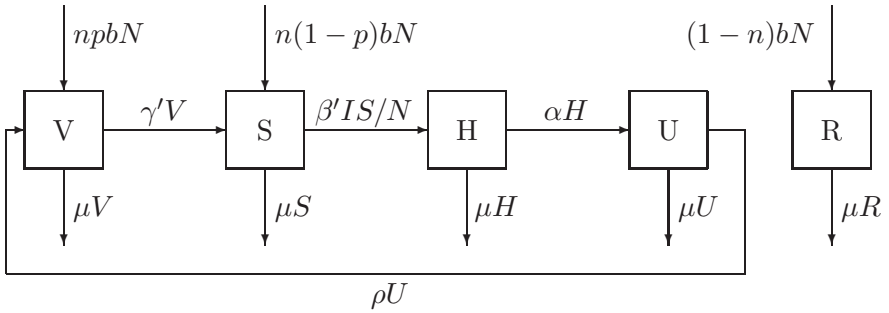

Figure 1: A schematic diagram of the model

3. Analysis of the Model

For the subsequent analysis, we assume $r = 0$, whence N is constant. Assuming that the initial fraction of removed individuals is $1 - n$, then $R = (1-n)N$ is also constant. These assumptions lead to a system of differential equations for S, I, and U, which we nondimensionalize using the substitutions

$$S = nNs,\ I = nNi,\ q = \frac{\alpha}{\rho + \mu + \alpha},\ U = qnNu,\ \tau = \mu t. \tag{6}$$

Note that q is the endemic equilibrium ratio of symptomatics to asymptomatics. The substitutions yield the dimensionless model

$$\frac{ds}{d\tau} = (1+\gamma)(\sigma - s) - \gamma i - \beta s i, \tag{7}$$

$$\frac{di}{d\tau} = \beta s i - i - \nu u, \tag{8}$$

$$\frac{du}{d\tau} = \eta(i-u), \tag{9}$$

where

$$\gamma = \frac{\gamma'}{\mu},\ \beta = \frac{n\beta'}{\mu},\ \nu = \frac{\rho q}{\mu},\ \eta = \frac{\alpha}{q\mu} > 1,\ \sigma = 1 - \frac{p}{1+\gamma}. \tag{10}$$

We now examine the qualitative behavior of the model of equations (7)-(9).

To find the basic reproduction number, we use the next generation matrix method [7]. Define a vector $X = (i,u)^T$ and separate the new infections from the rest. Let f and w denote the new infection vector and the vector of the negative of the remaining terms, respectively. Now let $F = \frac{\partial f}{\partial X}$ and $W = \frac{\partial w}{\partial X}$ and evaluate the matrices with $s = \sigma$ since the infection free equilibrium (IFE) is $(\sigma, 0, 0)$. Finally, compute FW^{-1}. Since the spectral radius of the FW^{-1} is the basic reproductive number R_0, $R_0 = \frac{\beta\sigma}{1+\nu}$, which is the number of new infections produced by a typical infective individual.

For the equilibria of the model and stability we note first that

$$\eta - \nu = \eta\left[\frac{(\rho+\mu+\alpha)^2 - \alpha\rho}{(\rho+\mu+\alpha)^2}\right] > \frac{\eta\alpha\rho}{(\rho+\mu+\alpha)^2} = \nu. \tag{11}$$

The model has two equilibria: an infection-free equilibrium (IFE) and an endemic disease equilibrium (EDE). The IFE $(\sigma, 0, 0)$ exists for all sets of parameter values. The associated characteristic equation is

$$\lambda^3 + c_2\lambda^2 + c_1\lambda + c_0 = 0,$$

where $c_2 = 1 + \gamma + (\eta + 1 - \beta\sigma)$, $c_1 = (1+\gamma)(\eta + 1 - \beta\sigma) + \eta(\phi - \beta\sigma)$, and $c_0 = \eta(1+\gamma)(\phi - \beta\sigma)$. By the Routh-Hurwitz criteria, the IFE is asymptotically stable if and only if $c_2 > 0$, $c_1c_2 > c_0 > 0$. The last condition means that $\beta\sigma < \phi$ is necessary for stability. It is also seen to be sufficient, as then $\eta + 1 - \beta\sigma > \eta + 1 - \phi = \eta - \nu > \nu$ and $c_1c_2 > [\eta(\phi - \beta\sigma)](1+\gamma) > c_0$.

The EDE

$$\left(\frac{\phi}{\beta}, i^\star, i^\star\right), \qquad i^\star = \frac{(1+\gamma)(\beta\sigma - \phi)}{\beta(\phi+\gamma)}, \qquad \beta\sigma > \phi \tag{12}$$

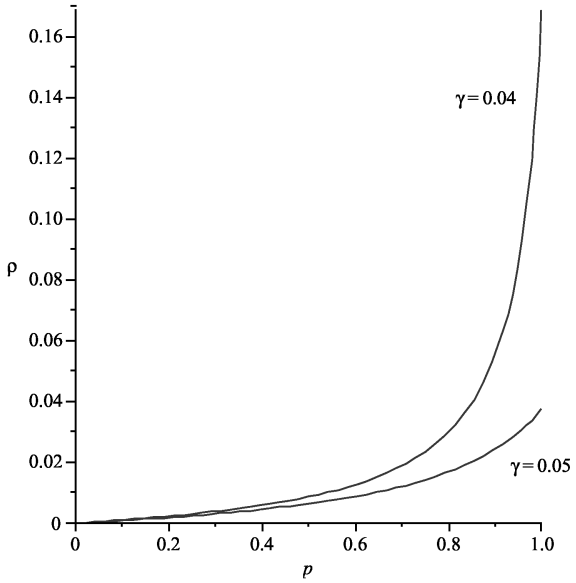

Figure 2: Sensitivity of $R_0(p,\rho)$: $|S_\rho| = |S_p|$ with $n = 0.9$, $\mu = b = 0.013$, $\alpha = 0.007$

has the cubic characteristic equation with

$$c_2 = \eta - \nu + 1 + \gamma + \beta i^\star > \phi + \gamma, \qquad c_0 = \eta(\phi+\gamma)\beta i^\star,$$
$$c_1 + (\eta - \nu)(1 + \gamma + \beta i^\star) + (\phi + \gamma)\beta i^\star > (\eta + 1 + \gamma)\beta i^\star,$$

which satisfies the Routh-Hurwitz conditions. Thus, the IFE is asymptotically stable when the basic reproductive number is less than 1 and the EDE is asymptotically stable when it is more than 1.

For the sensitivity analysis we focus on the transmission rate ρ and the vaccination rate p since they are the only parameters that can be influenced by exterior forces such as vaccination and treatment policies.

Figure 2 plots the points at which the sensitivity of the basic reproductive number with respect to the treatment rate is equal to the one with respect to the the vaccination rate. The parameter values used in the figure are estimated based on the data from Centers for Disease Control and Prevention, National Digestive Disease Information Clearinghouse, and [3]. It clearly shows that an increase in the value of ρ has a greater impact in decreasing $R(\rho, p)$. In our subsequent paper we discuss the effect of changes in ρ on ulcer prevalence and

annual incidence in depth.

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