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A mathematical model of syphilis transmission in an MSM population

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ABSTRACT

Syphilis is caused by the bacterium *Treponema pallidum* subspecies *pallidum*, and is a sexually transmitted disease with multiple stages. A model of transmission of syphilis in an MSM population (there has recently been a resurgence of syphilis in such populations) that includes infection stages and treatment is formulated as a system of ordinary differential equations. The control reproduction number is calculated, and it is proved that if this threshold parameter is below one, syphilis dies out; otherwise, if it is greater than one, it is shown that there exists a unique endemic equilibrium and that for certain special cases, this equilibrium is globally asymptotically stable. Using data from the literature on MSM populations, numerical methods are used to determine the variation and robustness of the control reproduction number with respect to the model parameters, and to determine adequate treatment rates for syphilis eradication. By assuming a closed population and no return to susceptibility, an epidemic model is obtained. Final outbreak sizes are numerically determined for various parameter values, and its variation and robustness to parameter value changes is also investigated. Results quantify the importance of early treatment for syphilis control.

1. Introduction

Various sexually transmitted diseases are caused by bacteria; for example, *Neisseria gonorrhoeae* causes gonorrhea [27], and *Treponema pallidum* subspecies *pallidum* causes syphilis [21]. *T. pallidum* is classified as a spirochetes (family *Spirochaetaceae*), and measures 6–20 μm in length and 0.18 μm in diameter [26]. It cannot be successfully continually cultured *in vitro* outside of the mammalian host; thus for experimental purposes, *T. pallidum* is usually first obtained from inoculated rabbits. This slows the research process and has been suggested as the greatest setback in terms of syphilis research [21].

In humans, an untreated syphilis infection progresses through multiple stages. After infection, the exposed (infected but not yet infectious) stage lasts an average 28 days [13]. The primary stage is characterized by a single chancre at the source of inoculation (*i.e.*, where *T. pallidum* penetrated dermal microabraisons or mucous membranes) appearing after the exposed period. This painless chancre eventually heals, and the individual progresses to the secondary stage [21,35] after an average of 46 days [13]. The secondary stage is characterized by multiple symptoms, most of which are nonspecific (*i.e.*, sore throat, muscle aches, etc.). Most secondary infections of syphilis also result in copper colored skin lesions that tend to be universally distributed. This rash heals after a few weeks, and the individual progresses to latency [21,35] after an average of about 15 weeks [13]. The latency period of syphilis is divided into two stages: the early latent stage, and the late latent stage. Early latency represents the first year of latency; late latency represents the remainder, until progression to the tertiary stage in 1–46 years [21,35]. The tertiary stage can have multiple presentations, ranging from cardiovascular syphilis to neurosyphilis. Progression to the tertiary stage is poorly understood; only about 30% of untreated cases progress from latency to the tertiary stage [21]. Disease caused mortality also occurs at this stage [35].

Fortunately, treatment for syphilis does exist. For treatment success, usually in the primary, secondary, and early latent stage, a single dose of Benzanthine penicillin G, 2.4 mU is administered; whereas for patients in the late latent stage, treatment is more strenuous, namely three doses of 2.4 mU at 1 week intervals of Benzanthine penicillin G are administered [35,44]. While treatment in the tertiary stage is available, not only is it much more intensive than in previous stages, it often is not as successful [35]. Moreover, the damage (*i.e.*, neurological for neurosyphilis) caused by tertiary syphilis cannot be undone. For appropriate treatment, accurate diagnosis of syphilis and the presenting stage is needed; Smith et al. [37] identified appropriate proteins as diagnostic candidates. It is also important to mention that a human vaccine for syphilis

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does not currently exist on the market, but Cameron and Lukehart [5] outline the needs and potential prospects for a vaccine.

Throughout the 1990s, there had been a decrease in overall cases of syphilis worldwide [15]. In the early 2000s, the homosexual male population (hereafter referred to as the MSM population) has seen resurgence of syphilis; see, for *e.g.*, Heffelfinger et al. [15], Read et al. [31], Simms et al. [34] and Stolte et al. [38]. Moreover, specific outbreaks in MSM communities have been identified and quantified; see, for *e.g.*, Hopkins et al. [16] for study on an outbreak in Ireland; Hourihan et al. [17] for one in East London and Weerakoon et al. [43] for details of syphilis cases in Melbourne. While syphilis itself can be a debilitating disease if not treated early (*i.e.*, allowed to progress to its later stages), it has also been linked to more susceptibility for infection by other serious sexually transmitted diseases such as the Human Immunodeficiency Virus (HIV); see Karp et al. [19], Lynn and Lightman [23] and Tuite et al. [39]. Clearly, control of syphilis is of importance.

Some deterministic mathematical models of syphilis have been formulated and analyzed. Garnett et al. [13] introduced a model that includes the stages of syphilis but does not differentiate between early and late latency. They also include treatment, but treated individuals in the primary and secondary stages do not go into a treated class but return directly to susceptibility; treated individuals in latency and in the tertiary stage flow into the same 'immune' class, from which individuals then return to susceptibility. Pourbohloul et al. [30] formulated an ordinary differential equations (ODE) model with 210 differential equations to model heterosexual syphilis transmission in East Vancouver where they combine the later stages of syphilis but partition the population into multiple groups based on sex, sexual activity and age. The results of published mathematical models of syphilis up to 2008 are reviewed in Fenton et al. [12]. More recently, Milner and Zhao [25] presented an ODE model based on partial immunity and vaccination (assuming a successful vaccine is developed), and showed that there exists backward bifurcation for some parameter values. Their model includes removed classes that contain individuals that have recovered from infection, those that removed themselves from susceptibility, and those that were vaccinated. Recently, Tuite et al. [40] considered an agent based model for the MSM population in Toronto, and concluded that more frequent screening of high-risk males is more effective in reducing syphilis than screening a larger population.

As pointed out by a reviewer, a very recent multistage model for syphilis is formulated and analyzed by Iboi and Okuonghae [18]. Their model includes early and late latent stages as well as individuals who acquire transitory (natural) immunity following successful treatment in an infectious or latent stage. Loss of transitory immunity is shown to allow the possibility of backward bifurcation. If this loss is ignored and individuals in the early latent stage do not revert to the infectious stages, then Iboi and Okuonghae provide a complete global analysis, calculating a basic reproduction number threshold that determines whether syphilis dies out or becomes endemic in the population.

We focus our modeling on an MSM population because of the resurgence of syphilis in such groups. In Section 2, we formulate an ODE model for an MSM population that includes all the stages of syphilis (including exposed, early and late latency), as well as treatment in the latent and infectious stages. Due to different numbers of contact, we assume that the infectivity rates in the primary and secondary infectious stages may be different. Then in Section 3 we calculate the control reproduction number $\mathcal{R}_c$ for our model, which is shown to be a threshold parameter. In Section 4, we address the stability of the disease-free equilibrium, and in Section 5, we show that, for certain parameter values, there exists an endemic equilibrium. We also discuss stability of this equilibrium for various epidemiologically meaningful cases. In Section 6, we give baseline parameter values and perform numerics for our model, including sensitivity analysis by Latin Hypercube Sampling. Final size calculations (assuming constant population) are presented in Section 7. Finally, in Section 8, we draw our conclusions.

2. Formulation of a syphilis model

We first split an MSM population into eleven classes with the numbers in each class given as follows: S denotes susceptible males, E denotes exposed males, I_1 denotes infectious males who are in the primary stage of syphilis, I_2 denotes infectious males who are in the secondary stage of the infection, L_1 denotes males who are in the early latent stage, L_2 denotes males who are in the late latent stage, and X denotes males who are in the tertiary (and final) stage of syphilis. The classes T_1, T_2, T_3 and T_4 denote effectively treated males from the primary, secondary, early latency, and late latency stages of infection, respectively. We assume a constant recruitment Λ into the susceptible class, and m denotes the human natural death rate. We assume that only individuals in the primary and secondary stage of the infection are infectious, and the infectivity rates are denoted β_1, β_2, for the primary and secondary stage, respectively. Note here that β_i, $i = 1, 2$, is equal to the probability of transmission from one contact between an individual in S and in I_i, times the number of contacts per day per individual. Bilinear incidence is assumed, that is, an average male in I_i makes $\beta_i N$ contacts with other males in the population per unit time, and the probability that such a contact is with a susceptible male is $\frac{S}{N}$. We also assume that treatment only occurs for individuals in I_1, I_2, L_1, L_2, at rates τ_1, τ_2, τ_3, τ_4, respectively and these effectively treated individuals return to susceptibility at rates δ_1, δ_2, δ_3, δ_4, respectively. Since our model is for an MSM population, this return could be due to risky behavior or to loss of immunity. The average incubation time before developing the disease is denoted by $\frac{1}{\eta}$. We assume that the disease progresses from the primary stage to the secondary stage at rate γ_1, from the secondary stage to the early latent stage at rate γ_2, from the early latent stage to late latent stage at rate γ_3, and from the late latent stage to the tertiary stage at rate γ_4. We also consider death due to disease only in the final (tertiary) stage of the infection, where α denotes the death rate due to syphilis of individuals in X. A summary of the parameters used is presented in Table 1.

We formulate the dynamics of the model changing with time as a system of ordinary differential equations, as seen in (1).

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - mS - (\beta_1 I_1 + \beta_2 I_2)S + \delta_1 T_1 + \delta_2 T_2 + \delta_3 T_3 + \delta_4 T_4 \\
\frac{dE}{dt} &= (\beta_1 I_1 + \beta_2 I_2)S - (\eta + m)E \\
\frac{dI_1}{dt} &= \eta E - (\gamma_1 + \tau_1 + m)I_1 \\
\frac{dI_2}{dt} &= \gamma_1 I_1 - (\gamma_2 + \tau_2 + m)I_2 \\
\frac{dL_1}{dt} &= \gamma_2 I_2 - (\gamma_3 + \tau_3 + m)L_1 \\
\frac{dL_2}{dt} &= \gamma_3 L_1 - (\gamma_4 + \tau_4 + m)L_2 \\
\frac{dT_1}{dt} &= \tau_1 I_1 - (\delta_1 + m)T_1 \\
\frac{dT_2}{dt} &= \tau_2 I_2 - (\delta_2 + m)T_2 \\
\frac{dT_3}{dt} &= \tau_3 L_1 - (\delta_3 + m)T_3 \\
\frac{dT_4}{dt} &= \tau_4 L_2 - (\delta_4 + m)T_4 \qquad (1)
\end{aligned}$$

and

$$\frac{dX}{dt} = \gamma_4 L_2 - (\alpha + m)X \qquad (2)$$

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