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Mathematical Model for Curtailing Neurosyphilis Through Early Treatment

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Abstract: Syphilis, caused by Treponema pallidum, remains a major global health burden with millions of new cases annually and severe complications, including neurosyphilis, if left untreated. This study develops an eight-compartment deterministic ODE model to examine syphilis transmission dynamics and quantify the effect of early treatment in preventing progression to neurosyphilis. The model incorporates susceptible, primary, secondary, latent, treated (early), recovered, neurosyphilis, and treated-neurosyphilis compartments. The disease-free equilibrium (DFE) is shown to be locally asymptotically stable by Jacobian analysis and globally asymptotically stable via the Castillo-Chavez framework when $R_0 < 1$. Global stability of the endemic equilibrium when $R_0 > 1$ is established using a Lyapunov function. The basic reproduction number, computed via the next-generation matrix method, yields $R_0 = 0.09975$ under baseline parameters ($\mu = 0.0143/year$), confirming disease-free conditions under current treatment coverage. Sensitivity analysis identifies the primary treatment rate β_1 (index −0.5566) and primary infectivity η_1 (index +0.6984) as the most influential parameters. Numerical simulations confirm that scaling-up early treatment dramatically reduces neurosyphilis incidence. Model limitations and future extensions are discussed.

Keywords: syphilis, neurosyphilis, mathematical modeling, stability analysis, sensitivity analysis

1. Introduction

Syphilis is a sexually transmitted disease (STD) caused by the bacterium Treponema pallidum. According to the World Health Organization's estimate in 2020, there were approximately 7.1 million reported cases of active syphilis infections among individuals between the ages of 15 and 49. It remains a significant public health concern worldwide [1]. Syphilis was found in 176,713 people in the U.S. in 2021, according to the Centres for Disease Control and Prevention. These cases were broken down into 53,767 primary and secondary cases, which are the early stages of the disease. Syphilis incidence in the United States, like in many other countries, is closely monitored to track the spread of the disease [2]. These statistics underscore the ongoing challenge of addressing and monitoring syphilis on both a global and national scale.

Syphilis progresses through several stages if left untreated, each with distinct clinical manifestations and timeframes. Primary Syphilis typically occurs 10 to 90 days after initial infection. This stage is characterized by a single, painless sore or ulcer at the site of infection, known as a chancre. It is usually firm, round, and not accompanied by other symptoms. The chancre can heal on its own, even without treatment. Secondary Syphilis can occur 6 to 12 weeks after the appearance of the chancre. It causes skin rashes, mucous membrane lesions, sore throat, fever, enlarged lymph nodes, and malaise. Skin rashes may appear anywhere on the body and are often the most noticeable feature. Without therapy, secondary syphilis symptoms might go away, but the infectious agent remains inside the body. The duration of latent syphilis can vary from a few years to many decades. During this phase, there are no noticeable symptoms. The infection is present in the body, but individuals are often asymptomatic. Syphilis can remain in this stage for an extended period. In the absence of treatment, one-third of individuals who contract syphilis can progress to tertiary disease. Tertiary Syphilis can develop many years after the initial infection, often spanning decades. This advanced stage of the disease is characterized by severe and potentially life-threatening complications that can affect multiple organs, including the heart, brain, eyes, nerves, and blood vessels. Tertiary syphilis can manifest in various forms, such as neurosyphilis (6.5% incidence), cardiovascular syphilis (10% incidence), and gummatous syphilis (15% incidence). It is important to note that individuals with tertiary syphilis are generally considered non-contagious, with sexual transmission occurring predominantly during the primary and secondary stages of infection [3, 4].

To achieve this objective, an in-depth understanding of the disease's transmission routes is essential. This article focuses on the significance of treating the latent phase of syphilis, since failure to do so may result in the development of neurosyphilis in affected persons. After infection, it might manifest at any

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moment. Neurosyphilis in early syphilis may be asymptomatic or cause meningitis, stroke, and/or cranial neuropathies. Neurosyphilis in late syphilis generally manifests as dementia or sensory ataxia [5]. It is a serious condition that requires medical treatment to reduce neurological damage and infection. Neurosyphilis is treated with antibiotics in larger dosages and for longer periods than the preceding stages. The specific treatment regimen and duration depend on the stage and severity of the disease. Individuals with syphilis need to receive appropriate treatment to prevent the progression of neurosyphilis and the associated neurological complications [6]. The major purpose of this research is to evaluate whether early treatment is successful in reducing neurosyphilis in the community.

Syphilis remains a significant global public health concern despite the availability of effective diagnostic and therapeutic interventions. Its transmission is influenced by sexual behavior, inadequate screening, delayed treatment, and insufficient treatment coverage. Recent epidemiological studies have emphasized the continuing global burden and clinical complexity of syphilis, highlighting the need for improved prevention, diagnosis, and treatment strategies [7–9]. Public health guidelines further emphasize early diagnosis, systematic screening, and timely treatment as essential measures for reducing transmission and preventing disease-related complications.

Mathematical modeling has provided an important framework for understanding syphilis transmission dynamics and evaluating intervention strategies. Early stage-structured modeling demonstrated that treatment during the primary and secondary stages can substantially reduce progression to subsequent stages of infection [10]. Subsequent studies have extended syphilis models by incorporating different population structures, transmission pathways, behavioral factors, and intervention strategies. Momoh et al. [11] developed a sex-structured model with three infection stages and demonstrated the effectiveness of combined prevention and treatment strategies. de Albuquerque and Dias [12] incorporated vertical transmission, highlighting the importance of considering multiple transmission pathways. Jing et al. [13] examined the effects of public health awareness and behavioral changes on syphilis transmission using a multi-stage model, while Hui et al. [14] evaluated enhanced testing and test-and-treat strategies. Gabrick et al. [15] further applied fractal and fractional modeling approaches to syphilis data, demonstrating the usefulness of advanced mathematical frameworks for analyzing transmission dynamics. More recent research has emphasized the importance of integrating real-world data into modeling frameworks to design effective public health strategies [16, 17].

Syphilis progresses through primary, secondary, latent, and tertiary stages, with the latent stage being particularly important because individuals may remain asymptomatic for prolonged periods. Untreated or inadequately treated infection can result in serious systemic and neurological complications. Recent epidemiological studies have emphasized the continuing global burden and clinical complexity of syphilis [8, 18]. More recent mathematical models have incorporated co-infection and stage-specific treatment. Teklu & Terefe [19] investigated the co-dynamics of COVID-19 and syphilis, while Wang et al. [20] developed a model of syphilis and HIV co-infection. Olopade et al. [21] examined the effects of multi-stage treatment, and Luo et al. [22] investigated control measures in a sex-structured syphilis model. Similarly, Yao et al. [23] emphasized the role of the early latent stage in syphilis transmission. Collectively, these studies demonstrate the importance of representing disease stages and treatment processes when analyzing syphilis dynamics.

Neurosyphilis represents an important neurological manifestation of Treponema pallidum infection and may occur during different stages of syphilis. Its diverse clinical manifestations, diagnostic difficulties, and potential for long-term neurological consequences have attracted increasing research attention. Zhou et al. [24] reviewed recent advances in neurosyphilis, including its pathogenesis, diagnosis, treatment, and prevention. Further clinical reviews by Wu et al. [25] and Hamill et al. [26] provided comprehensive insights into its clinical characteristics and management, while Wei & Wei [27] demonstrated the increasing research interest in neurosyphilis through a bibliometric analysis. More recent clinical studies have further examined its complexity. Sethi & Marks [28] and Minter & Chow [29] discussed contemporary diagnostic and therapeutic challenges, while Marra [30] provided an updated clinical overview. Orlova et al. [31] investigated clinical and laboratory characteristics and associated risk factors. In addition, Daza-Ovalle et al. [32] examined stroke associated with neurosyphilis, and Aznar et al. [33] analyzed its clinical presentation, diagnosis, treatment, and outcomes.

Early diagnosis and timely treatment are essential for reducing syphilis transmission and preventing disease progression. Mathematical modeling studies have demonstrated that enhanced testing and increased treatment coverage can substantially influence transmission dynamics [14]. Olopade et al. [19] further highlighted the importance of treatment across different stages of syphilis, while García-Luna & Maldonado [34] demonstrated mathematically that reducing treatment delay can decrease predicted syphilis prevalence. These findings provide quantitative support for investigating early treatment as an important intervention for limiting transmission and reducing the likelihood of advanced disease. Thus, treatment should not only be considered as a mechanism for reducing infectiousness but also as an important factor influencing disease progression.

Despite advances in treatment, the diagnosis of neurosyphilis remains challenging because of its heterogeneous clinical presentation and limitations of conventional diagnostic approaches. Cerebrospinal fluid investigations, including CSF-VDRL, are commonly used, but their diagnostic performance may be limited. Consequently, recent studies have investigated non-invasive and predictive approaches for improving early identification. Yan et al. [35] identified clinical and laboratory predictors associated with neurosyphilis, while Yang et al. [36] developed a prediction model based on demographic and clinical parameters for neurosyphilis risk stratification. Zhang et al. [37] further evaluated a novel diagnostic criterion and reported improved diagnostic performance. These studies demonstrate the growing importance of quantitative and predictive approaches in supporting early diagnosis and clinical decision-making.

Recent developments in epidemiological modeling have also incorporated spatial heterogeneity, nonlinear transmission, and data-driven approaches. Reaction–diffusion and spatial epidemic models have demonstrated that population heterogeneity and spatial variability can influence disease persistence and stability [38–41]. Such approaches provide useful methodological foundations for representing more complex epidemic systems. In parallel, artificial intelligence and machine-learning techniques have expanded the predictive capability of infectious-disease models. Guedri et al. [42] developed an artificial neural-network approach to analyze syphilis progression and disability risk, demonstrating the potential of AI-based methods for disease prediction. Although these approaches provide valuable predictive information, mechanistic compartmental models remain

particularly useful for explicitly representing transmission, disease progression, treatment, and recovery processes.

Overall, the existing literature demonstrates substantial progress in mathematical modeling of syphilis transmission, particularly through the incorporation of multiple disease stages, behavioral factors, co-infections, testing, treatment, and control interventions. At the same time, clinical research has substantially improved the understanding of neurosyphilis, including its pathogenesis, diagnosis, treatment, and neurological complications. However, comparatively limited mathematical work has explicitly incorporated neurosyphilis as a distinct advanced compartment within a stage-structured syphilis transmission model while simultaneously considering treatment and disease progression. In particular, the quantitative effect of early treatment on the progression of syphilis to neurosyphilis remains insufficiently investigated within an integrated transmission framework.

Therefore, the present study develops a nonlinear compartmental model incorporating the major stages of syphilis together with neurosyphilis as an advanced disease compartment. The model is used to derive the basic reproduction number using the next-generation matrix approach, analyze the stability properties of the equilibria, identify influential epidemiological parameters through sensitivity analysis, and investigate the effect of early treatment on syphilis transmission and progression to neurosyphilis. By integrating transmission dynamics, disease progression, treatment, and neurosyphilis within a unified mathematical framework, this study provides quantitative insight into the importance of timely treatment and offers a basis for developing effective strategies for syphilis control and prevention.

The paper is structured as follows. Section 2 presents the model formulation, compartment definitions, assumptions, parameter values, equilibrium analysis, and derivation. Section 3 provides local and global stability analysis. Section 4 presents numerical simulations. Section 5 reports sensitivity analysis. Section 6 discusses limitations and future directions. Section 7 concludes the work.

2. Model Formulation

The proposed model employs compartments of deterministic ordinary differential equations to categorize the population into eight distinct subgroups at a given time. These subgroups together constitute the total population, denoted as $N(t)$. Among these divisions, we have susceptible individuals $S(t)$ who have not yet been infected but are at risk of contracting the acquiring syphilis. Infected individuals in the primary $I_P(t)$, secondary $I_S(t)$, and latent $L(t)$ stages of syphilis have the ability to transmit the disease to those who are susceptible. Treated individuals $T_1(t)$, who have received early treatment at various stages, especially in the latent stage. Recovered individuals $R(t)$ who have contracted the infection and have successfully recovered from the disease are immune to reinfection. Individuals who remained untreated and, over time, progressed to neurosyphilis $I_{NS}(t)$, a more severe form of the disease, before seeking treatment $T_2(t)$. This model helps us better understand the dynamics of disease transmission within a mixed population by tracking these distinct subgroups and their interactions over time. The model uses a system of ordinary differential equations to describe the transitions between these compartments, incorporating recruitment rate B, natural death rate μ, progression rates$(\alpha_1, \alpha_2, \alpha_3)$, treatment rates$(\beta_1, \beta_2, \beta_3, \beta_4)$, recovery rate from early treatment γ_1, and γ_2 the rate at which recovered individuals revert to the susceptible class, reflecting possible waning immunity or other factors that might lead to loss of immunity. The model helps understand the dynamics of syphilis transmission and the impact of early treatment interventions on reducing the incidence of neurosyphilis.

2.1. Assumptions

1) The population is assumed to be well-mixed, so individuals have an equal probability of contacting any other individual. Disease transmission occurs through direct contact.
2) The model typically does not consider demographic factors such as age, gender, or socio-economic status. Instead, it treats individuals as a homogeneous group with uniform susceptibility to infection and response to treatment.
3) The disease's transmission rate is assumed to be constant across the population. In reality, transmission rates may vary with factors such as behavior, location, and access to healthcare.
4) Syphilis is transmitted only horizontally (i.e., through sexual contact) and not vertically (from mother to child during childbirth).
5) Treatment reduces infectiousness and advances individuals towards recovery.
6) Uniform natural mortality: A constant natural death rate $\mu = 0.0143$/year applies to all compartments, corresponding to a mean lifespan of approximately 70 years.

2.2. Model equations

The force of infection $\psi = \frac{\phi}{N}(\eta_1 I_P + \eta_2 I_S + \eta_3 L)$ represents the rate at which susceptible individuals become infected, depending on the number of infectious individuals in various stages (I_P, I_S, L) and their respective transmission coefficients η_i. The parameter ϕ is the effective contact rate for transmission of syphilis, while the parameter (η_1, η_2, η_3) reflects how contagious people with other phases of the disease are compared to people who are already sick with that phase.

The compartmental flow diagram illustrating all transitions between the eight subgroups is shown in Figure 1. A uniform natural mortality rate μ applies to all compartments.

The system of ordinary differential equations governing the dynamics, with all parameters in per-year units, is:

$$\begin{aligned}
\frac{dS}{dt} &= B + \gamma_2 R - (\psi + \mu) S;\\
\frac{dI_P}{dt} &= \psi S - (\alpha_1 + \beta_1 + \mu) I_P;\\
\frac{dI_S}{dt} &= \alpha_1 I_P - (\alpha_2 + \beta_2 + \mu) I_S;\\
\frac{dT_1}{dt} &= \beta_1 I_P + \beta_2 I_S + \beta_3 L - (\gamma_1 + \mu) T_1;\\
\frac{dR}{dt} &= \gamma_1 T_1 - (\gamma_2 + \mu) R;\\
\frac{dL}{dt} &= \alpha_2 I_S - (\alpha_3 + \beta_3 + \mu) L;\\
\frac{dI_{NS}}{dt} &= \alpha_3 L - (\beta_4 + \mu) I_{NS};\\
\frac{dT_2}{dt} &= \beta_4 I_{NS} - \mu T_2.
\end{aligned} \tag{1}$$

Initial conditions (all nonnegative):

$$S(0) \geq 0,\ I_P(0) \geq 0,\ I_S(0) \geq 0,\ L(0) \geq 0,\ T_1(0) \geq 0,$$
$$R(0) \geq 0,\ I_{NS}(0) \geq 0,\ T_2(0) \geq 0.$$

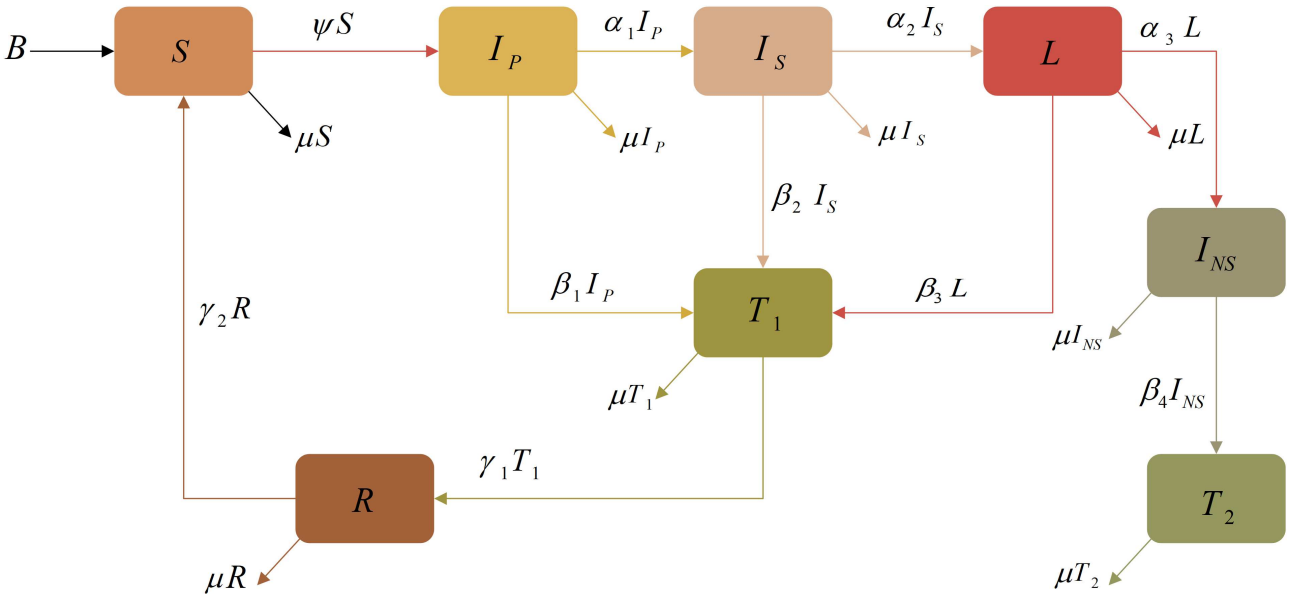

Figure 1. The flow chart for syphilis transmission

2.3. Data and fixed-parameter values

The treatment rates $\beta_1 = 0.896$, $\beta_2 = 0.807$, and $\beta_3 = 0.759/year$ are sourced from Garnett et al. (1997) and CDC surveillance data and reflect treatment coverage under actively managed public health programs. These near-optimal values yield $R_0 = 0.09975 < 1$. In resource-limited settings where coverage drops to $\beta_1 \approx 0.30$, R_0 rises to approximately 0.12; at $\beta_1 \approx 0.05$, R_0 exceeds 1, leading to endemic disease. This analysis reinforces the critical importance of maintaining high treatment coverage and provides quantitative targets for program managers.

2.4. Analysis of the model (Well-Posedness: Positive Invariant Region)

Theorem 1 (Positive Invariance): About the model (1), the closed set $\Lambda = \left\{(S, I_P, I_S, T_1, R, L, I_{NS}, T_2) \in R_+^8 : N \le \frac{B}{\mu}\right\}$ is positively invariant.

Proof: The summation of each equation in the model (1) yields:

It should be noted that $N(t)$. This represents the entire population.

$$\begin{aligned} N(t) &= S(t) + I_P(t) + I_S(t) + T_1(t) + R(t) \\ &\quad + L(t) + I_{NS}(t) + T_2(t) \\ N'(t) &= S'(t) + I_P'(t) + I_S'(t) + T_1'(t) + R'(t) \\ &\quad + L'(t) + I_{NS}'(t) + T_2'(t) \\ N'(t) &= B - \mu(S + I_P + I_S + T_1 + R + L + I_{NS} + T_2) \\ N'(t) &= B - \mu N(t) \end{aligned} \tag{2}$$

Since $N'(t) = B - \mu N(t)$, it follows that $N'(t) < 0$ whenever $N(t) > \frac{B}{\mu}$. Thus,

$$\begin{aligned} N(t) &\le N(0)e^{-\mu t} + \frac{B}{\mu}(1 - e^{-\mu t}). \text{ In particular } N(t) \\ &\le \frac{B}{\mu} \text{ if } N(0) \le \frac{B}{\mu} \end{aligned}$$

Therefore, Λ is positively invariant.

Hence, the mathematical model may be considered well-posed and epidemiologically reasonable since all variables preserve nonnegative values over the whole period $t \ge 0$. Model (1) with initial value

$$S(0) \ge 0,\ I_p(0) \ge 0,\ I_S(0) \ge 0,\ T_1(0) \ge 0,\ R(0) \ge 0,$$
$$L(0) \ge 0,\ I_{NS}(0) \ge 0,\ T_2(0) \ge 0.$$

Therefore, it is enough to examine the dynamics of the model (1) inside the domain Λ.

2.5. Equilibrium analysis

The following sections determine the syphilis-free equilibrium phase, the syphilis-present equilibrium phase, the basic reproduction number, and the stability analysis.

By setting it to zero, the equilibrium points of system (1) are established:

1) System (1) reaches a stable condition when there is no syphilis infection, known as the syphilis-free equilibrium. i.e., $I_P = I_S = T_1 = R = L = I_{NS} = T = 0$.

$$E_0 = (S, I_P, I_S, T_1, R, L, I_{NS}, T_2) = \left(\frac{B}{\mu}, 0, 0, 0, 0, 0, 0, 0\right)$$

When syphilis is absent, the proportion of susceptible individuals varies in direct proportion to the ratio of their recruitment to mortality rates.

2) To determine the endemic equilibrium where the disease persists for the given system of differential equations, we need to set the derivatives to zero and solve for the non-zero steady-state values of the compartments. i.e., finding the value $S, I_P, I_S, T_1, R, L, I_{NS}, and\ T_2$ that satisfied the system (1).

Let E_{end}^* it be syphilis-present equilibrium $E_{end}^* = (S^*, I_P^*, I_S^*, T_1^*, R^*, L^*, I_{NS}^*, T_2^*)$

$S^* = \frac{N(\alpha_1+\beta_1+\mu)}{\phi k}$, where $k = \eta_1 + \frac{\eta_2\alpha_1}{(\alpha_2+\beta_2+\mu)} + \frac{\eta_3\alpha_1\alpha_2}{(\alpha_2+\beta_2+\mu)^2}$

$I_P^* = \frac{\psi S^*}{(\alpha_2+\beta_2+\mu)}$, $I_S^* = \frac{\alpha_1 I_P^*}{(\alpha_2+\beta_2+\mu)}$, $L^* = \frac{\alpha_3 I_S^*}{(\alpha_3+\beta_3+\mu)}$, $I_{NS}^* = \frac{\alpha_3 L^*}{\beta_4+\mu}$, $T_1^* = \frac{\beta_1 I_P^* + \left(\beta_2 + \frac{\beta_3}{\alpha_3+\beta_3+\mu}\right) I_S^*}{(\gamma_1+\mu)}$, $R^* = -\frac{\gamma_1 T_1^*}{(\gamma_2+\mu)}$, $T_2{}^* = \frac{\beta_4 I_{NS}{}^*}{\mu}$.

2.6. Basic reproduction number (R_0)

To determine the threshold value for the transmission of syphilis, researchers employ a basic reproduction number R_0 calculated through the next-generation matrix (NGM) algorithm [43–45]. This number represents the expected number of secondary infections generated by a single infectious individual in a susceptible population. Obtaining the basic reproduction number involves computing the spectral radius of the matrix describing disease transmission dynamics centered around the disease-free equilibrium point. Let the infectious compartment $X = (I_P, I_S, L)$ be rewritten as $X' = F(X) - V(X)$ in the model, where $F(X)$ represents the rate of new infections appearing in the compartment and $V(X)$ represents the rate of transfer of individuals. The epidemiological threshold for syphilis is represented by the equation $R_0 = \rho\left(fv^{-1}\right)$,which ρ represents the dominant eigenvalue.

$$F(X) = \begin{bmatrix} \frac{(\eta_1 I_P + \eta_2 I_S + \eta_3 L)\phi S}{N} \\ 0 \\ 0 \end{bmatrix}, \text{ and}$$

$$V(X) = \begin{bmatrix} (\alpha_1+\beta_1+\mu) I_P \\ -\alpha_1 I_P + (\alpha_2+\beta_2+\mu) I_S \\ -\alpha_2 I_S - (\alpha_3+\beta_3+\mu) L \end{bmatrix}$$

By calculating the Jacobian matrices at E_0, we find that $D(F(E_0)) = \begin{bmatrix} f & 0 \\ 0 & 0 \end{bmatrix}$ and $D(V(E_0)) = \begin{bmatrix} v & 0 \\ J_1 & J_2 \end{bmatrix}$, where, f and v are 3×3 matrices defined as $f = \left(\frac{\partial F_i}{\partial X_j}\right)\Big|_{E_0}$ and $v = \left(\frac{\partial V_i}{\partial X_j}\right)\Big|_{E_0}$. Finding f and v we get,

$$f = \begin{bmatrix} \frac{\phi\eta_1 S}{N} & \frac{\phi\eta_2 S}{N} & \frac{\phi\eta_3 S}{N} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \text{ and}$$

$$v = \begin{bmatrix} \alpha_1+\beta_1+\mu & 0 & 0 \\ -\alpha_1 & \alpha_2+\beta_2+\mu & 0 \\ 0 & -\alpha_2 & \alpha_3+\beta_3+\mu \end{bmatrix}$$

$$fv^{-1} = \begin{bmatrix} \frac{\phi\eta_1 S}{N(\alpha_1+\beta_1+\mu)} + \frac{\phi\eta_2 S\alpha_1}{N(\alpha_2+\beta_2+\mu)(\alpha_1+\beta_1+\mu)} + \frac{\phi\eta_3 S\alpha_1\alpha_2}{N(\alpha_1+\beta_1+\mu)(\alpha_2+\beta_2+\mu)^2} & 0 & 0 \\ \frac{\phi\eta_2 S}{N(\alpha_2+\beta_2+\mu)} + \frac{\phi\eta_3 S\alpha_2}{N(\alpha_2+\beta_2+\mu)^2} & 0 & 0 \\ \frac{\phi\eta_3 S}{N(\alpha_2+\beta_2+\mu)} & 0 & 0 \end{bmatrix}$$

The basic reproduction number R_0 is defined as the spectral radius (fv^{-1}) or the maximal eigenvalue of the next-generation matrix (NGM). i.e., $R_0 = \rho\left(fv^{-1}\right)$. where B is the population recruitment rate (new individuals entering per year), $N = B/\mu$ is the total population at the disease-free equilibrium, and μ is the natural mortality rate.

$$R_0 = \frac{\phi B}{N\mu(\alpha_1+\beta_1+\mu)}\left(\eta_1 + \frac{\eta_2\alpha_1}{(\alpha_2+\beta_2+\mu)} + \frac{\eta_3\alpha_1\alpha_2}{(\alpha_2+\beta_2+\mu)^2}\right) = 0.09975 \tag{3}$$

This R_0 gives the expected number of secondary cases produced by a single infection in a fully susceptible population.

3. Stability Analysis

3.1. Local asymptotic stability

Theorem 2: The syphilis-free equilibrium point E_0 of the model (1) is locally asymptotically stable Λ if and only if $R_0 < 1$, and unstable if $R_0 > 1$.

Proof: To analyze the local stability at the syphilis-free equilibrium point. This involves evaluating the Jacobian matrix at the equilibrium point and analyzing its eigenvalues. The Jacobian matrix J of system (1) evaluated at $E_0 = (B/\mu, 0, 0, 0, 0, 0, 0, 0)$ is the 8×8 block-structured matrix below. Ordering state variables as $(S, I_P, I_S, T_1, R, L, I_{NS}, T_2)$: The Jacobian Matrix at the syphilis-free equilibrium point is given by,

$$J = \begin{pmatrix} -\mu & 0 & 0 & 0 \\ 0 & -\alpha_1-\beta_1-\mu & 0 & 0 \\ 0 & \alpha_1 & -\alpha_2-\beta_2-\mu & 0 \\ 0 & \beta_1 & \beta_2 & -\gamma_1-\mu \\ 0 & 0 & 0 & \gamma_1 \\ 0 & 0 & \alpha_2 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \begin{pmatrix} \gamma_2 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & \beta_3 & 0 & 0 \\ -\gamma_2-\mu & 0 & 0 & 0 \\ 0 & -\alpha_3-\beta_3-\mu & 0 & 0 \\ 0 & \alpha_3 & -\beta_4-\mu & 0 \\ 0 & 0 & \beta_4 & -\mu \end{pmatrix}$$

The eigenvalue of the Jacobian matrix is $\lambda_{1,2} = -\mu, \lambda_3 = -\gamma_1-\mu, \lambda_4 = -\gamma_2-\mu, \lambda_5 = -\beta_4-\mu, \lambda_6 = -\alpha_1-\beta_1-\mu, \lambda_7 = -\alpha_2-\beta_2-\mu, \lambda_8 = -\alpha_3-\beta_3-\mu$. They are all negative. If the eigenvalues of the Jacobian matrix are entirely negative, then the equilibrium point of the system is considered stable. Hence, the syphilis-free equilibrium point is locally asymptotically stable [46].

3.2. Global asymptotic stability of the DFE

Theorem 3: The syphilis-free equilibrium points E_0 of the syphilis model (1) are globally asymptotically stable Λ if $R_0 < 1$.

Proof: To achieve the global stability of the syphilis-free equilibrium point, model (1) applied the two conditions for global stability [43, 44]. The global asymptotic stability of the disease-free equilibrium was proved using the Castillo–Chavez approach

that was widely used in recent compartmental epidemic models [47, 48]. The model (1) may be rewritten in the following manner.

$$\frac{dX_0}{dt} = F(X_0, I_0) \tag{A1}$$

$$\frac{dI_0}{dt} = G(X_0, I_0)\ ,\quad G(X_0, 0) = 0 \tag{A2}$$

Given the nonnegative initial conditions $X(0) = X_0 \in R^m$ and $I(0) = I_0 \in R^n$, where the elements of the vector X represent the number of uninfected individuals (e.g., susceptible, treated, recovered, etc.), and the elements of I represent the count of infected and infectious individuals (i.e., those capable of transmitting the disease, such as asymptomatic but infectious individuals and actively infected individuals). Furthermore, it is assumed that the function F is continuous, the function G belongs to the class C_1, and the fractional differential system (1) with the initial conditions $X(0) = X_0\ I(0) = I_0$ has a unique solution.

where $X = (S, T_1, R, T_2)$ represents non-infectious compartments and $I = (I_P, I_S, L, I_{NS})$ represents infectious compartments.

In this study, we represent the syphilis-free equilibrium point of the system (1) $E_0 = (X^*, 0) \in R^{m+n}$.

i.e., $F(X^*, 0) = G(X^*, 0) = 0$

The following two conditions ensure the global stability of the given equilibrium point,

I) $\frac{dX}{dt} = F(X, 0)$, E_0 is the global asymptotically stable
II) $G(X, I) = AI - \hat{G}(X, I)$, *where* $\hat{G}(X, I) \geq 0$ *for all* $(X, I) \in \Lambda$.

Condition (I): The sub-system $dX/dt = F(X, 0)$ governs uninfected individuals when $I = 0$. Setting I = 0 in the S equation gives dS/dt $= B + \gamma\_2\, R - \mu\, S$ and the T_1 and R equations decouple. It is straightforward to show that this linear sub-system has a unique globally asymptotically stable equilibrium at $X^* = (B/\mu, 0, 0, 0)^T$, since all eigenvalues of the sub-system Jacobian are $-\mu$, $-(\gamma_1 + \mu)$, $-(\gamma_2 + \mu)$, and $-\mu$, all strictly negative. Hence, condition (I) is satisfied.

Condition (II): We must show $G(X, I) = AI - \hat{G}(X, I)$, *where* $\hat{G}(X, I) \geq 0$ *for* $(X, I) \in \Lambda$

Let A be defined as the partial derivative of G with respect to I $(A = \partial G/\partial I)$, evaluated at $(X^*, 0)\left(i.e,\ A = \frac{\partial G}{\partial I}(X^*, 0)\right)$.

$$A = \begin{bmatrix} -(\alpha_1 + \beta_1 + \mu) & \phi\eta_2 & \phi\eta_3 & 0 \\ \alpha_1 & -(\alpha_2 + \beta_2 + \mu) & 0 & 0 \\ 0 & \alpha_2 & -(\alpha_3 + \beta_3 + \mu) & 0 \\ 0 & 0 & \alpha_3 & -(\beta_4 + \mu) \end{bmatrix}$$

The off-diagonal entries of − A are non-positive, the diagonal entries are positive, and A is diagonally dominant (since $R_0 < 1$), confirming −A is an M-matrix (i.e., A is Metzler stable).

The residual term is $\hat{G}(X, I) = AI - G(X, I)$, *Computing explicity:*

$$\hat{G}_1 = \varphi\eta_1 (1 - S/N) I_P + \varphi\eta_2 (1 - S/N) I_S + \varphi\eta_3 (1 - S/N) L \geq 0,$$

$$\hat{G}_2 = \hat{G}_3 = \hat{G}_4 = 0.$$

Since $S \leq N$in Λ, we have $\hat{G}(X, I) \geq 0$ *for all* $(X, I) \in \Lambda$. Also, $G(X, 0) = 0$ is verified directly from (A2). Both conditions of Castillo-Chavez et al. [44](2002) are satisfied, so E_0 is globally asymptotically stable when $R_0 < 1$.

3.3. Global stability of the endemic equilibrium

Theorem 4: The global stability of the endemic equilibrium point E^*_{end} of the syphilis model is examined when $R_0 > 1$.

Proof: A Lyapunov function L_y is a scalar function that helps to analyze the stability of an equilibrium point. The function should be positive definite, and its time derivative along the trajectories of the system should be negative definite [49, 50].

Let us assume the Lyapunov function L_y(Quadratic (sum of squared deviations)) at the syphilis-present equilibrium point E^*_{end} as,

$$L_y = \frac{1}{2}\left[((S - S^*)) + \left(I_P - I_P^*\right) + \left(I_S - I_S^*\right) + (L - L^*) + \left(T_1 - T_1^*\right) + (R - R^*) + \left(I_{NS} - I_{NS}^*\right) + \left(T_2 - T_2^*\right)\right]^2$$

$$\frac{dL_y}{dt} = \left[((S - S^*)) + \left(I_P - I_P^*\right) + \left(I_S - I_S^*\right) + (L - L^*) + \left(T_1 - T_1^*\right) + (R - R^*) + \left(I_{NS} - I_{NS}^*\right) + \left(T_2 - T_2^*\right)\right] \times \left(S' + I_P' + I_S' + T_1' + R' + L' + I_{NS}' + T_2'\right)$$

$$\frac{dL_y}{dt} = \left[((S - S^*)) + \left(I_P - I_P^*\right) + \left(I_S - I_S^*\right) + (L - L^*) + \left(T_1 - T_1^*\right) + (R - R^*) + \left(I_{NS} - I_{NS}^*\right) + \left(T_2 - T_2^*\right)\right] \times [B - \mu(S + I_P + I_S + T_1 + R + L + I_{NS} + T_2)]$$

If, take $B = \mu\left(S^* + I_P^* + I_S^* + T_1^* + R^* + L^* + I_{NS}^* + T_2^*\right)$ then,

$$\frac{dL_y}{dt} = -\mu\left[((S - S^*)) + \left(I_P - I_P^*\right) + \left(I_S - I_S^*\right) + (L - L^*) + \left(T_1 - T_1^*\right) + (R - R^*) + \left(I_{NS} - I_{NS}^*\right) + \left(T_2 - T_2^*\right)\right]^2$$

Here, $\frac{dL_y}{dt} < 0$. Therefore, according to LaSalle's Invariance principle [51], the current equilibrium point of syphilis is globally asymptotically stable.

4. Numerical Simulation

This section presents an analysis of numerical simulation results that illustrate the diverse outcomes of the model for individual observations. Model (1) is now being simulated using the parameter estimations provided in Table 1.

We validated the deterministic ODE approximation by implementing a Gillespie-type continuous-time Markov chain (CTMC) model with the same 8-compartment structure and baseline parameter values (Table 2), scaled to a population of individuals. The Gillespie direct approach was used to simulate 200 independent CTMC trajectories over 20 years. For each compartment, the median trajectory and the 2.5th and 97.5th percentiles were calculated to obtain the 95% simulation range. Stochastic compartmental modeling provides a complementary framework for assessing uncertainty and validating deterministic epidemic dynamics [52–54].

Figure 2 Deterministic ODE solution (red line) overlaid on the 95% stochastic band (shaded area) for (a) primary syphilis $I_P(t)$ and (b) latent syphilis $L(t)$. The deterministic trajectory is inside the 95% CTMC simulation band across the simulation time. This shows the validity of the mean-field ODE approximation for the population scale investigated. The finding offers a solid validation for the use of the deterministic framework as the main analytical tool in this study.

Table 1. Model variables and their full epidemiological definition with stratification criteria

Symbol	Compartment Name	Epidemiological Definition	Clinical Basis	Inclusion Criteria
$S(t)$	Susceptible	Sexually active individuals with no current syphilis infection who are at risk of acquiring the disease through sexual contact	No prior syphilis infection or fully waned immunity	Sexually active adults aged 15–64 years; no active syphilis; includes MSM and heterosexual populations
$I_P(t)$	Primary Syphilis	Individuals with confirmed or probable primary syphilis, characterized by the presence of a chancre at the infection site	CDC primary syphilis case definition; VDRL/RPR reactive or clinical chancre	Onset 10–90 days post-infection; highest infectivity; includes all transmission risk groups
$I_S(t)$	Secondary Syphilis	Individuals with confirmed secondary syphilis, characterized by disseminated rash, mucous membrane lesions, or systemic symptoms	CDC secondary syphilis case definition; serological titer rise	Onset 6–12 weeks after primary; systemic dissemination; high sexual infectivity
$L(t)$	Latent Syphilis	Serologically reactive individuals with no clinical symptoms of active syphilis; includes early latent (< 1 year) and late latent (≥ 1 year) phases	Positive treponemal and non-treponemal serology without active signs	Early latent: residual sexual infectivity retained; late latent: non-infectious sexually; stratified here as combined latent pool
$T_1(t)$	Early-Treated	Individuals who have received and are receiving antibiotic treatment for primary, secondary, or latent syphilis before progression to neurosyphilis	WHO/CDC treatment guidelines: benzathine penicillin G or equivalent	Treatment initiated at any pre-neurosyphilis stage; reduces infectivity to zero during treatment
$R(t)$	Recovered	Individuals who have successfully completed treatment and are temporarily immune to reinfection	Post-treatment serological decline; temporary immunity documented in literature (Garnett et al., 1997)	Immunity wanes at rate $\gamma_2 = 0.75$/yr (~16 months); individuals re-enter S(t) after immunity loss
$I_{NS}(t)$	Neurosyphilis	Individuals who progressed to neurosyphilis due to untreated or inadequately treated latent infection	CDC/WHO neurosyphilis case definition: positive CSF-VDRL or clinical neurological involvement with reactive serology	Progression from untreated L(t) at rate $\alpha_3 = 0.10$/yr; non-sexually infectious; requires IV treatment
$T_2(t)$	Treated Neurosyphilis	Individuals receiving high-dose IV antibiotic therapy for neurosyphilis	Aqueous crystalline penicillin G IV per CDC neurosyphilis treatment guidelines (Jay, 2006)	Treatment at rate $\beta_4 = 0.70$/yr; long-duration therapy; outcome modeled as removal from I_NS

Table 2. Model parameters, descriptions, ranges, values and sources

Parameter	Description	Range	Value (/yr)	Source
B	Recruitment rate (new individuals entering population per year)	—	0.1	Assumed
ϕ	Effective contact rate for syphilis transmission	$(1.25–4.67) \times 10^{-1}$	0.5	Garnett et al. [55](1997)
η_1	Relative infectivity of primary syphilis contact	$(1.1–9.42) \times 10^{-1}$	0.08	Assumed
η_2	Relative infectivity of secondary syphilis contact	$(3.29–7.45) \times 10^{-1}$	0.05	Assumed
η_3	Relative infectivity of latent syphilis contact (residual; low)	$(5.35–9.75) \times 10^{-1}$	0.02	Assumed

(*Continued*)

Table 2. (*Continued*)

Parameter	Description	Range	Value (/yr)	Source
α_1	Progression rate: primary → secondary syphilis	$(2.19–9.52) \times 10^{-1}$	0.70	Garnett et al. [55]; Milner & Zhao [56]
α_2	Progression rate: secondary → latent syphilis	$(4.35–7.86) \times 10^{-1}$	0.30	Garnett et al. [55]; Milner & Zhao [56]
α_3	Progression rate: latent → neurosyphilis (approx. 10% over 10 years)	$(1.95–9.74) \times 10^{-1}$	0.10	Calculated; consistent with Clark & Danbolt [57]
β_1	Treatment rate at the primary stage	(0–1)	0.896	Garnett et al. [55]; CDC [2]
β_2	Treatment rate at the secondary stage	(0–1)	0.807	Garnett et al. [55]; CDC [2]
β_3	Treatment rate at the latent stage	(0–1)	0.759	Garnett et al. [55]; CDC [2]
β_4	Treatment rate for neurosyphilis	$(6.42–9.05) \times 10^{-1}$	0.70	Calculated
γ_1	Recovery rate from early treatment	(0–1)	0.70	Garnett et al. [55]; CDC [2]
γ_2	Rate of relapse from recovered to susceptible (waning immunity). Value $\gamma_2 = 0.75$/year implies a mean immunity duration of ~16 months, consistent with clinical reports of short-lived syphilis immunity (Garnett et al., 1997; Schaudinn & Hoffman, 1905).	(0–1)	0.75	Garnett et al. [55]; CDC [2]
μ	Natural mortality rate	—	0.0143	($\mu = 1/70 \approx 0.0143/year$; mean lifespan 70 years)

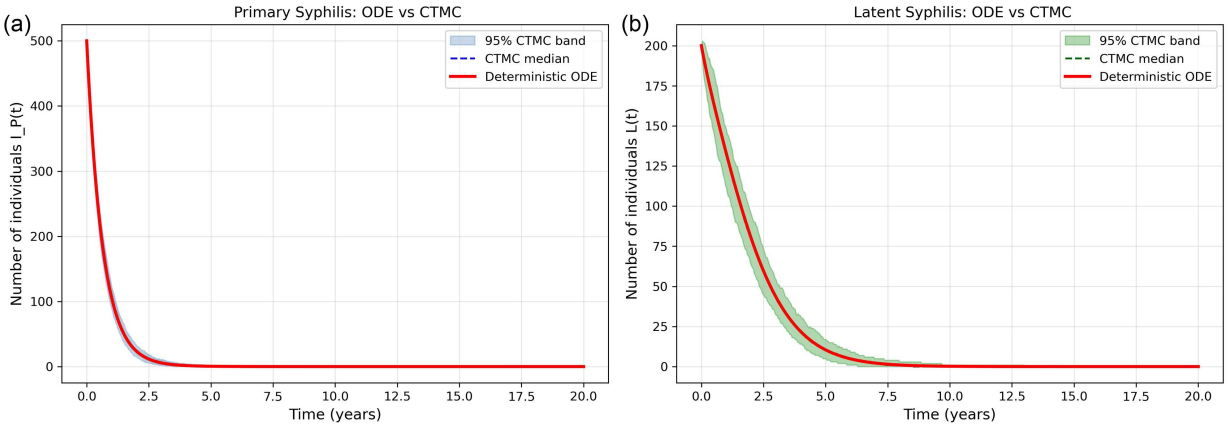

Figure 2. Stochastic robustness validation using Continuous-Time Markov Chain (CTMC) simulation

Figure 3 shows that a strong focus on treatment during the initial month is crucial in managing syphilis because this is the critical period when some susceptible individuals may progress from a latent or asymptomatic stage to primary syphilis. This early phase is a pivotal point in syphilis management, as untreated primary syphilis can potentially lead to the development of secondary syphilis over the next three to four months. Secondary syphilis is a more advanced stage of the disease characterized by a wide range of symptoms. The risk of complications and transmission to others is significantly higher during secondary syphilis. Therefore, early and effective treatment is required. As time progresses and treatment is initiated, recovery gradually occurs, and the treatment requirements tend to decrease. Regular medical monitoring is often required to ensure that the infection is fully eradicated and that the individual's health continues to improve.

Figure 4 indicates a higher prevalence of latent syphilis. It has been observed that individuals with untreated latent syphilis are at risk of developing neurosyphilis after a period of 8 to 10 years. As a result, a greater rate of therapy is required during the latent period. As a consequence, a higher treatment rate is necessary during the latent period.

Figure 5 illustrates the directional plot depicting the treatment trajectory of the primary I_P and secondary I_S syphilis. A higher treatment rate is necessary for those suffering from syphilis, particularly in cases of early stages of syphilis. It has been shown that the intensity of secondary syphilis has a greater rate of progression compared to primary syphilis.

As illustrated in Figure 6, individuals afflicted with latent syphilis actively pursue treatment. Syphilis treatment is crucial for curing the infection, preventing the disease's progression, and decreasing the likelihood of developing long-term complications. Individuals in the latent stage who do not receive treatment develop neurosyphilis after some time. Figure 6(B) demonstrates that effective syphilis therapy minimizes the probability of transmission to neurosyphilis. After receiving early treatment, an individual's contagiousness is eliminated, hence reducing the risk of neurosyphilis. The impact of early treatment on reducing the incidence of neurosyphilis in the population.

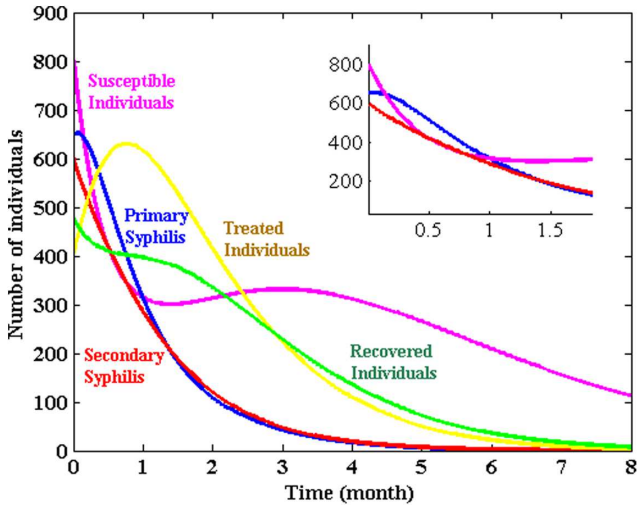

Figure 3. Transmission diagram of primary and secondary (P/S) syphilis

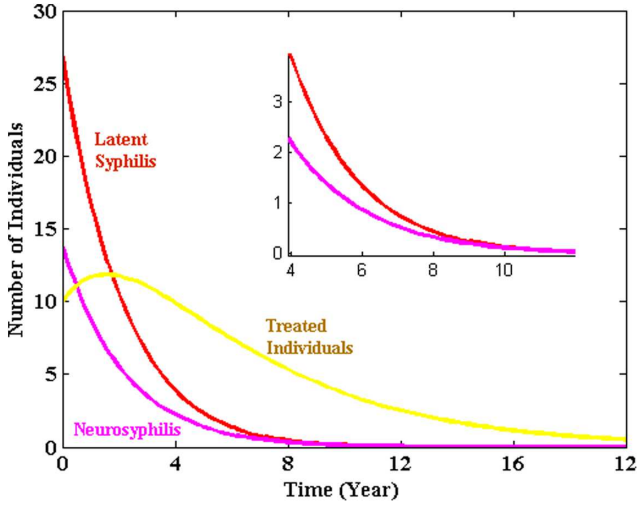

Figure 4. Transmission diagram of neurosyphilis

Figure 7(A) illustrates the distribution of individuals with primary, secondary, and latent syphilis, with percentages of 20%, 9%, and 2%, respectively. Among these individuals, 25% get early treatment, and within this subset, 15% successfully recovered. A higher treatment rate is necessary for those suffering from syphilis, particularly in cases of primary and secondary syphilis. Figure 7(B) illustrates the Percentage-wise distribution of other compartments. The treatment for neurosyphilis typically involves the use of antibiotics, usually in higher doses and for an extended duration compared to the treatment for other stages of syphilis.

5. Sensitivity Analysis

Sensitivity analysis helps us understand how variations in a specific parameter affect the model's output. Compartmental epidemic models depend on the reproduction number (threshold) to reflect transmission. Sensitivity analysis of R_0 involves studying how changes in model parameters affect R_0. This threshold value determines a parameter's importance and identifies the system's most sensitive parameter, enabling sensitivity analysis. Global sensitivity analysis using Latin Hypercube Sampling (LHS) and Partial Rank Correlation Coefficients (PRCC) has been widely applied in mathematical epidemic models to identify parameters that most strongly influence disease dynamics [58].

$\gamma_\alpha^{R_0} = \frac{\partial R_0}{\partial \alpha} . \frac{\alpha}{R_0}$, where α is the model parameter.

These parameters η_1,η_2,η_3 denote the efficacy of transmission given contact. The effective contact rate ϕ has the highest sensitivity index (+1.0000), as R₀ is directly proportional to ϕ. Positive values suggest that an increase in these parameters results in an increase in the transmission rate, with η_1 being the most significant (index = +0.6983), η_1 is the most sensitive parameter as compared to η_2 and η_3 having a positive impact on R_0, underscoring the importance of primary infections in spreading the disease. Treatment rate at the primary stage β_1 is the most impactful control parameter (index = −0.5566): a 10% increase in β_1 reduces R_0 by approximately 4.5%. Progression rates α_1 (−0.1329) and α_2 (−0.0593) have comparatively smaller effects. These results provide direct, quantitative targets for public health intervention: maximizing primary-stage treatment coverage and minimizing effective contact rates are the two highest-leverage strategies for keeping R_0 below unity.

6. Limitations and Future Directions

There are a number of key limitations to this study that should be noted:

(1) Vertical transmission excluded: The model considers only horizontal (sexual) transmission and excludes congenital/vertical (mother-to-child) syphilis transmission, which is a well-documented clinical entity [1]. This is a simplifying assumption; future models should incorporate vertical transmission pathways.

(2) Homogeneous mixing: The model assumes that all individuals mix uniformly, which is epidemiologically impractical for syphilis, a disease with substantial heterogeneity by sex, sexual network structure, and risk group. This assumption may overestimate or underestimate R_0 for heterogeneous populations or for core risk groups. This suggests that R_0 calculated here is an average quantity, and in practice, focused interventions in high-risk subgroups (e.g., men who have sex with men) may be more effective than population-average models predict.

(3) No sex or gender structure: Syphilis transmission varies greatly between males and females, and especially within high-risk groups. These dynamics would be better captured by a two-sex or multi-group model.

(4) No stochasticity: The deterministic framework does not consider stochastic fluctuations. In populations where one or more compartment(s) is small (e.g., a city-level high-risk group of a few thousand), stochastic extinction or outbreak effects may prevail. Future work includes a stochastic (e.g., continuous-time Markov chain)

(5) Assumed and unfitted parameters: Many parameters are taken from historical sources or assumed. The model has not been calibrated to today's incidence statistics. Future studies should calibrate the model to syphilis surveillance data at the national or municipal level, including explicit uncertainty quantification (e.g., Latin Hypercube Sampling or Bayesian inference).

(6) Backward bifurcation: The model has not been investigated for backward bifurcation, which will occur if a stable endemic equilibrium co-exists with the stable DFE for $R_0 < 1$. This may be attributable to a reduced immunity period (γ_2). In further investigation, a formal bifurcation analysis utilizing the

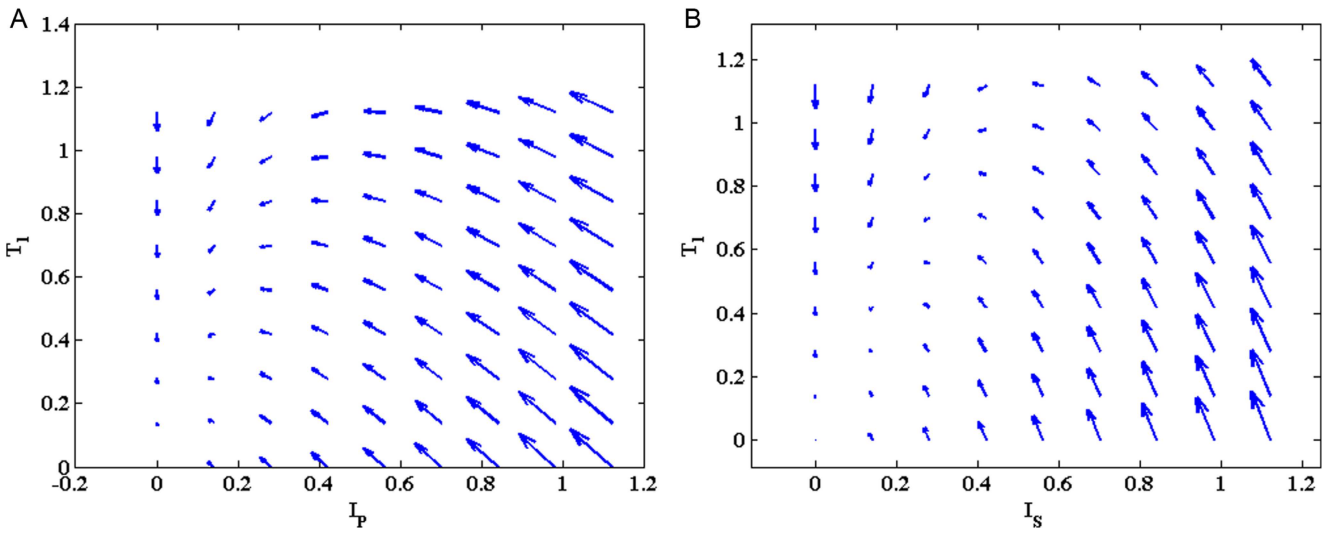

Figure 5. Phase-Plane Direction Fields of primary and secondary syphilis towards treatment T_1

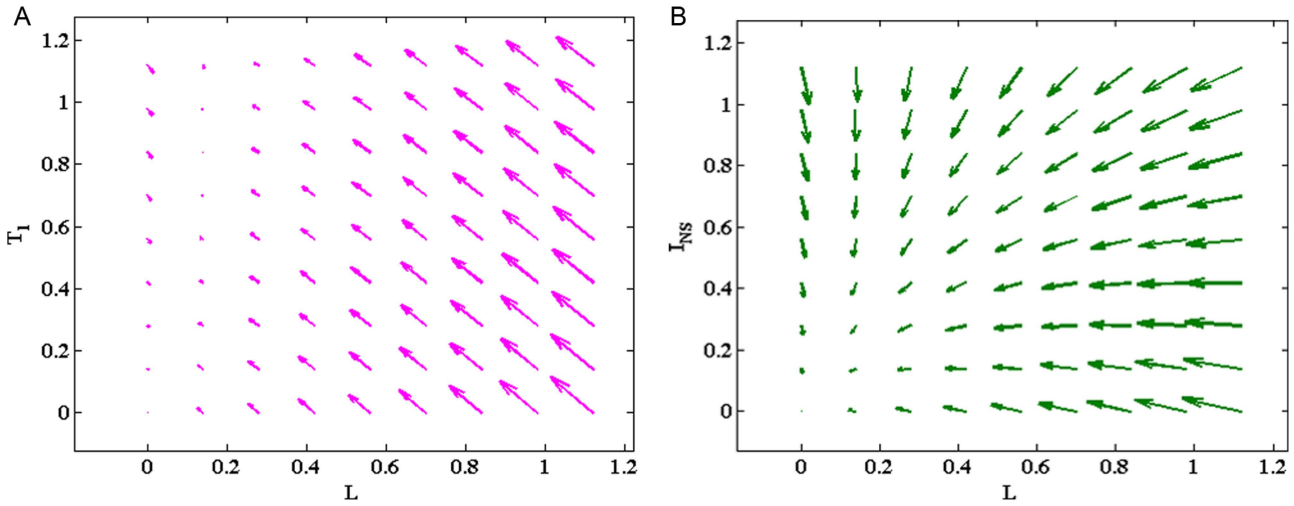

Figure 6. Phase-plane direction fields of latent syphilis towards treatment

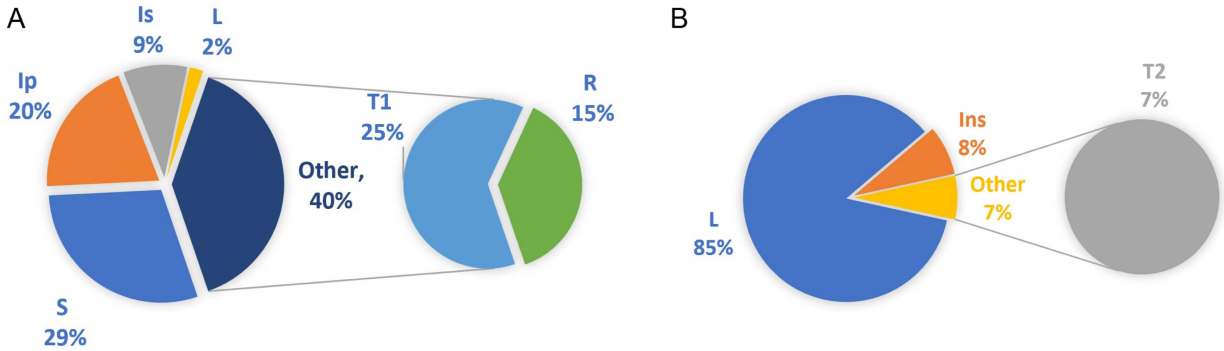

Figure 7. Distribution of syphilis in different stages

Table 3. Normalized forward sensitivity indices of R_0

Parameter	Description	Index	Direction
ϕ	Effective contact rate	+1	Positive
η_1	Primary syphilis infectivity	+0.698379	Positive
η_2	Secondary syphilis infectivity	+0.272464	Positive
η_3	Latent syphilis infectivity	+0.029156	Positive
α_1	Progression rate: primary → secondary	–0.13289	Negative
α_2	Progression rate: secondary → latent	–0.05933	Negative
β_1	Treatment rate at primary stage (MOST SENSITIVE negative)	–0.55661	Negative
β_2	Treatment rate at secondary stage	–0.23807	Negative

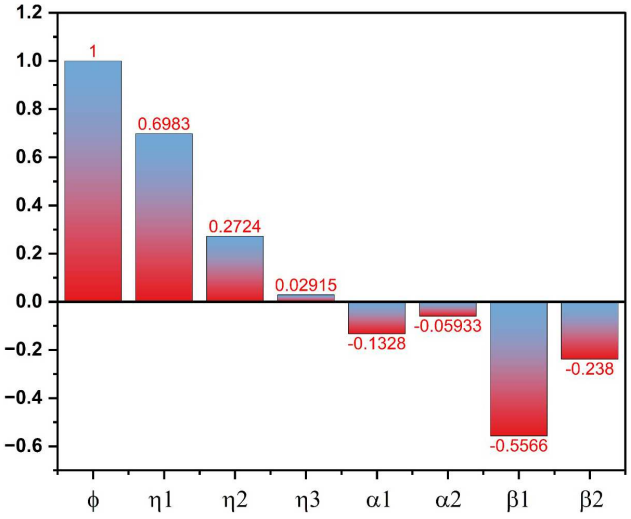

Figure 8. Normalized forward sensitivity indices of R_0 with respect to key model parameters

center manifold method should be carried out to evaluate whether $R_0 < 1$. [44]. It is adequate for disease elimination.

(7) Future directions: Extensions include a gender-stratified model, spatial heterogeneity via reaction-diffusion equations, optimal control analysis to minimize neurosyphilis incidence under budget constraints, integration with HIV co-infection dynamics, and AI/ML-based fitting to real-world surveillance data.

7. Discussion and Conclusion

In this paper, we created and analyzed an eight-compartment deterministic ODE model of syphilis transmission, explicitly representing neurosyphilis as a clinical consequence. The main mathematical contributions are:

If $R_0 < 1$, then the disease-free equilibrium E_0 is locally asymptotically stable and globally asymptotically stable. When $R_0 > 1$, the endemic equilibrium is globally asymptotically stable. Under baseline settings ($\mu = 0.0143/year$, all parameters per year), the basic reproduction number is $R_0 = 0.09975$, which means that the current treatment coverage is enough to keep the system below the epidemic threshold. The sensitivity analysis shows that the factors with the biggest impact on R_0 are the primary infectivity η_1 (index +0.69) and the primary treatment rate β_1 (index −0.55). A 10% increase in β_1 decreases R_0 by around 4.5%.

Numerical simulations indicate that treatment, particularly in the early primary and latent stages, markedly decreases the proportion of the population residing in the neurosyphilis compartment. It is important to distinguish between the model parameter $\alpha_3 = 0.10/year$(the annual per-individual rate of progression from untreated latent infection to neurosyphilis) and the simulation output in Figure 7(B), which reports compartment-level population distributions at steady state. Under untreated latent conditions, 85% of the relevant population is concentrated in $L(t)$, with 8% in $I_{NS}(t)$. Under active treatment, the latent fraction falls to 2%. These population fractions are fully consistent with $\alpha_3 = 0.10/year$ and do not imply that 85% of individuals progress to neurosyphilis. The results provide strong support for policy solutions based on prompt diagnosis, high treatment coverage, and ongoing screening programs.

The public health relevance is clear: the best intervention to limit the epidemic potential and avoid the terrible neurological sequelae associated with neurosyphilis is to increase therapy at the primary stage, where sensitivity is highest.

Ethical Statement

This study is a purely theoretical mathematical modeling investigation and did not involve human participants, animal subjects, or original data collection by the authors. All parameter values were sourced from previously published, ethically approved peer-reviewed studies and public surveillance datasets; no individual-level or identifiable data were accessed.

Conflicts of Interest

The authors declare that they have no conflicts of interest to this work.

Data Availability Statement

No new data were generated or analyzed in this study. All parameter values required to reproduce the results are provided within the manuscript (Table 2), sourced from publicly available peer-reviewed publications and surveillance reports cited in the reference list.

Author Contribution Statement

Nita H. Shah: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration. **Jalpa N. Vaghela:** Methodology, Software, Validation,

Formal analysis, Investigation, Resources, Writing – original draft, Writing – review & editing, Visualization. **Yash N. Shah:** Conceptualization, Investigation, Data curation, Writing – review & editing, Visualization.

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