Qualitative analysis of a stochastic SEITR epidemic model with multiple stages of infection and treatment

Olusegun Michael Otunuga a, *, Mobolaji O. Ogunsolu b

a Department of Mathematics, Marshall University, One John Marshall Drive, Huntington, WV, USA
b Department of Mathematics and Statistics, University of South Florida, 4202, E Fowler Ave, Tampa, FL, USA

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Abstract

We present a mathematical analysis of the transmission of certain diseases using a stochastic susceptible-exposed-infectious-treated-recovered (SEITR) model with multiple stages of infection and treatment and explore the effects of treatments and external fluctuations in the transmission, treatment and recovery rates. We assume external fluctuations are caused by variability in the number of contacts between infected and susceptible individuals. It is shown that the expected number of secondary infections produced (in the absence of noise) reduces as treatment is introduced into the population. By defining $R_{T,n}$ and $\mathcal{R}_T,n$ as the basic deterministic and stochastic reproduction numbers, respectively, in stage $n$ of infection and treatment, we show mathematically that as the intensity of the noise in the transmission, treatment and recovery rates increases, the number of secondary cases of infection increases. The global stability of the disease-free and endemic equilibrium for the deterministic and stochastic SEITR models is also presented. The work presented is demonstrated using parameter values relevant to the transmission dynamics of Influenza in the United States from October 1, 2018 through May 4, 2019 influenza seasons.

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1. Introduction

Numerous mathematical models have been developed to study the transmission dynamics of emerging and re-emerging diseases (Diekmann, Heesterbeek, & Metz, 1990; Driessche & Watmough, 2002; Etbaigha, Willms, & Poljak, 2018; Feng, Towers, & Yang, 2011; Hollingsworth, Anderson, & Fraser, 2008; Huo, Chen, & Wang, 2016; Korobeinikov, 2009; LaSalle, 1976; Li, Xiao, Zhang, & Yang, 2012; Melesse & Gumel, 2010; Mendez, Campos, & Horsthemke, 2012; Tornatore, Buccellato, & Vetro, 2005; Otunuga, 2017; Otunuga, 2018; West, Bulsara, Lindenberg, Seshadri, & Shuler, 1979; Yang & Mao, 2013, Mummert & Otunuga, 2019). Without treatment of such diseases, infection advances in stages and infected individuals typically die within certain years. Several authors (Birrell, Presanis, & De Angelis, 2012; Hollingsworth et al., 2008; Korobeinikov, 2009; Melesse & Gumel, 2010; Otunuga, 2018) have studied extensively epidemic models with various stages of infection. Influenza has various stages of infection ranging from the contagious stage before any symptoms appear (period
when the flu virus is entering and multiplying in only a few cells in the respiratory tract) to the stage when the flu virus has proliferated enough for the immune system to notice. The general incubation period for Influenza (typically known as the flu) varies for different individuals, usually between one to four days with average incubation period of about two days. This suggests that it is important to study the different stages of flu infection while studying transmission of infectious diseases. Although it might be impossible to avoid certain infectious diseases, there are different strategies available that protect individuals from infection and treat disease once it has developed. It is of high importance to study how such disease reacts to treatments, and the analysis of treatment stages and treatment effects on infected individuals should be included in models describing the transmission dynamics of treatable diseases. Several programs such as the Biomedical Advanced Research and Development Authority have been developed by the U.S. Department of Health and Human Services to provide an integrated, systematic approach to the development and purchase of vaccines, drugs, therapies, and diagnostic tools necessary for public health medical emergencies.

According to the work of Hu et al. (Hu, Nigmatulina, & Eckhoff, 2013), contact rates and patterns among individuals in a geographic area drive transmission of directly-transmitted pathogens, making it essential to understand and estimate contacts for simulation of disease dynamics. In their work, Grassly et al. (Grassly & Fraser, 2006) explains different causes of seasonality in infectious diseases of humans. They give different representations of the transmission rate based on the causes of seasonality in the infectious diseases. In this work, we study the global dynamics of a deterministic and stochastic SEITR epidemic model with multiple stages of infection and treatments. We assume the population is completely susceptible at the beginning of the epidemics and derive the measure of the power of an infectious disease to attack a completely susceptible population using the deterministic model. In the absence of noise, we compare mathematically the expected number of secondary cases of infection in the presence and absence of treatments and show that the number decreases as the treatment rate increases. We study the case where the transmission, treatments and recovery rates are assumed to be influenced by external fluctuations caused by variability in the number of contacts between infected and susceptible individuals due to weather patterns, school terms, etc. We assume fluctuations in the treatment rates may be caused by limited availability of drugs or effect of seasonality and this may result in fluctuations in the recovery rates. Such random variations can be modeled by a Gaussian white noise process causing the rate to fluctuate around a mean value. The external noise is able to modify the dynamical behavior of the model by transforming the deterministic SEITR epidemic model to a stochastic epidemic model. We derive the basic reproduction number in the presence of noise and analyze how the presence of noise in the transmission, treatments and recovery rates affects the number of infections produced by an infected individual. The paper is organized as follows. In Section 2, we formulate the deterministic model describing the transmission and spread of certain diseases, as well as its treatments and recovery. In Section 3, the existence of equilibrium points, and derivation of reproduction number using next generation method in the presence and absence of treatments are analyzed. Analysis of the effect of treatments and effect of dropping out of treatment on the number of infection produced by an infected individual are investigated analytically and numerically in Section 4. The local and global stability of the disease-free and endemic equilibriums are discussed in Section 5. By introducing noise in the transmission, treatment and recovery rates, we formulate and derive a stochastic model analogous to the deterministic model in Section 6. The effects of noise on the transmission, treatment and recovery rates, together with the existence and stability of the disease-free equilibrium point in the presence of noise are investigated analytically and numerically.

2. Deterministic model formulation

By assuming the human population is completely susceptible at the beginning of an epidemics and sub-dividing the total population, $N(t)$, into susceptible humans $S(t)$, exposed humans $E(t)$, infected untreated $I_j(t)$ humans in stage $j$ of infection, infected humans under treatment and in stage $j$ of infection $T_j(t)$, and the recovered population $R(t)$, at time $t$, we investigate the transmission and treatment of certain infectious diseases. We assume the total human population $N(t)$ satisfies $N(t) = S(t) + E(t) + \sum_{j=1}^{n} (I_j(t) + T_j(t)) + R(t)$ and humans are recruited into the susceptible population at a rate $\Lambda$. The general population is reduced by natural death at a rate $\mu$. The population of susceptible humans is reduced by infection due to contact with infectious (untreated or treated) individual at a full rate $\beta \sum_{j=1}^{n} h_j I_j$. It is well known (Godoy et al., 2018) that influenza vaccination may not prevent infection but reduces the severity of the disease. The Center for Disease and Control \(^2\) claimed that in randomized clinical trials, there was evidence that some influenza viruses developed resistance or reduced susceptibility to one or more influenza antiviral CDC recommended FDA-approved drugs like oseltamivir (Tamiflu), zanamivir (Relenza), peramivir (Rapivab), and baloxavir (Xofluza) drugs\(^2\). Several authors (Feng et al., 2011; Gani et al., 2005; Kretzschmar, Schim van der Loeff, Birrell, Angelis, & Coutinho, 2013; Liu and Zhang, 2011; Otunuga, 2018; Qiu & Feng, 2010) have considered introducing parameter that accounts for the reduction in infectiousness due to treatments among individuals in their model. In our model, we let $e_j$ be the reduced infectiousness due to treatment in stage $j$ of infection and include the reduced rate $\beta \sum_{j=1}^{n} h_j l_j$.

\(^1\) Prevention and treatment, https://www.ncbi.nlm.nih.gov/books/NBK209704/, accessed 5.12.2019.

\(^2\) https://www.cdc.gov/flu/treatment/baloxavir-marboxil.htm. Page last reviewed: November 18, 2019.
$\varepsilon_j T_j$ due to treatment. Infected (but not yet infectious) individuals become untreated infectious individuals in stage 1 of infection at a rate $\pi$. Untreated infected individuals in stage $k$ of infection migrate into stage $k+1$ of untreated infection at a rate $\rho_k$ and die of infection at a rate $\delta_k$. These individuals receive treatment (and migrate to stage $k$ of treated infected compartment) at a rate $\tau_k$. Treated infected individuals in stage $k$ of infection migrate to stage $k+1$ of treated infection at a rate $\gamma_k$ and die of infection at a rate $\delta_k$. Individuals that stop receiving treatment migrate to stage $k$ of untreated infected compartment at a rate $\phi_k$. Untreated and treated infected individuals in stage $k$ of infection recover and migrate to the recovered compartment at a rate of $\psi_k$ and $\eta_k$, respectively. The schematics describing the transmission described above is given in Fig. 1.

The deterministic model governing $S$, $E$, $I_k$, $T_k$, $R$ for $k = 1, 2, \ldots, n$, is described as follows:

\begin{align}
    dS &= \left( \Lambda - \beta S \sum_{j=1}^{n} (h_j I_j + \varepsilon_j T_j) - \mu S \right) dt, \quad S(t_0) = S_0, \\
    dE &= \left( \beta S \sum_{j=1}^{n} (h_j I_j + \varepsilon_j T_j) - (\mu + \pi) E \right) dt, \quad E(t_0) = E_0, \\
    dI_1 &= \left( \pi E - (\mu + \delta_1 + \rho_1 + \tau_1 + \psi_1) I_1 + \varphi_1 T_1 \right) dt, \quad I_1(t_0) = I_{01}, \\
    dI_k &= \left( \rho_{k-1} I_{k-1} - (\mu + \delta_k + \rho_k + \tau_k + \psi_k) I_k + \varphi_k T_k \right) dt, \quad I_k(t_0) = I_{0k}, \quad k = 2, 3, \ldots, n, \\
    dT_1 &= \left( \tau_1 I_1 - (\mu + \delta_1 + \gamma_1 + \varphi_1 + \eta_1) T_1 \right) dt, \quad T_1(t_0) = T_{01}, \\
    dT_k &= \left( \tau_k I_k + \gamma_{k-1} T_{k-1} - (\mu + \delta_k + \gamma_k + \varphi_k + \eta_k) T_k \right) dt, \quad T_k(t_0) = T_{0k}, \quad k = 2, 3, \ldots, n, \\
    dR &= \left( \sum_{j=1}^{n} (\psi_j I_j + \eta_j T_j) - \mu R \right) dt, \quad R(t_0) = R_0.
\end{align}

Fig. 1. Schematic diagram for the SEITR model. The circle compartments represent group of individuals.
where the parameters in the model are described in Table 2, with \( \gamma_n = \rho_n = 0 \). Since the limit \( \lim_{t \to \infty} \sup N(t) \leq \Lambda/\mu \), we consider the solution of the model (2.1) in the feasible region

\[
\mathcal{F} = \{ (S, E, I_1, \ldots, I_n, T_1, \ldots, T_n, R) \in \mathbb{R}_{+}^{2n+3} : 0 \leq S + E + \sum_{j=1}^{n} (I_j + T_j) + R = N \leq \frac{\Lambda}{\mu} \},
\]

where \( \mathbb{R}_+ \) denotes set of nonnegative real numbers. For the rest of this work, we define \( \pi = \Lambda/\mu \). It can be shown that \( \mathcal{F} \) is positively invariant with respect to (2.1). We set the sizes of \( S, E, I_k, T_k, R, \) for \( k = 1, 2, \ldots, n \) as percentages by setting \( L = m \).

3. Existence of equilibrium points in the presence and absence of treatments

We discuss the existence and stability of the equilibrium points of (2.1) in the presence and absence of treatment. Under certain conditions (which are discussed in (3.14) and Section 5), system (2.1) has two unique equilibrium points namely, the disease-free (denoted \( P_0 \)) and endemic (denoted \( P_1 \)) equilibrium points described as

\[
P_0 = \left( \begin{array}{cccccc}
S^0 & E^0 & I_1^0 & \cdots & I_n^0 & T_1^0 & \cdots & T_n^0 & R^0
\end{array} \right)^{\top},
\]

\[
P_1 = \left( \begin{array}{cccccc}
S^* & E^* & I_1^* & \cdots & I_n^* & T_1^* & \cdots & T_n^* & R^*
\end{array} \right)^{\top}.
\]

The equilibrium points \( P_0 \) and \( P_1 \) are derived in Subsections 3.1 and 3.2, respectively.

3.1. Disease-free equilibrium \( P_0 \)

The disease-free equilibrium \( P_0 \) of (2.1) has entries

\[
S^0 = \pi, \quad E^0 = 0, \quad I_j^0 = 0, \quad T_j^0 = 0, \quad R^0 = 0, \quad j = 1, 2, \ldots, n.
\]

In the following, we derive the measure of the power of an infectious disease to attack a completely susceptible population. It is the expected number of secondary cases produced, in a completely susceptible population, by a typical infective individual. This number, called the basic reproduction number and denoted by \( R_{T,n} \), is calculated explicitly considering \( n \) stages of infection and treatment. The endemic equilibrium, \( P_1 \), is expressed in terms of \( R_{T,n} \). We also discuss a case where no treatment is received in the population and denote the corresponding reproduction number by \( R_0 \). We show that in order for the number of infection to diminish to zero on the long run, appropriate parameters in the model must be controlled so that the number \( R_{T,n} \) is at most one. That is, as long as the number of secondary infection produced by an infected individual is not more than one, the number of infections diminish to zero on the long run. Above the number \( R_{T,n} = 1 \), disease endemic persist.

3.1.1. Elimination threshold quantity, \( R_{T,n} \), in the presence of treatments

Define

\[
\begin{align*}
a_k &= \mu + \delta_k + \rho_k + \tau_k + \psi_k, \\
b_k &= \mu + \delta_k + \gamma_k + \phi_k + \eta_k, \\
c &= \mu + \pi, \\
\pi &= \Lambda/\mu.
\end{align*}
\]

In the presence of treatments, we write (2.1) in the form

\[
dx = (\mathcal{F}(x) - \mathcal{V}(x)) \, dt,
\]

using the next-generation matrix (Driessche & Watmough, 2002), where.
The derivatives $D \mathcal{F}(P_0) = \frac{\partial \mathcal{F}}{\partial x}$ and $D \mathcal{F}(P_0) = \frac{\partial \mathcal{F}}{\partial x}$ respectively, are evaluated at $P_0$ and partitioned so that $F_n = \beta \pi$, and

$$V_n = \begin{pmatrix} c & 0_{1 \times n} & 0_{1 \times n} \\ \sigma & M_j & -\mathcal{J}_{\varphi} \\ 0_{n \times 1} & -\mathcal{J}_{\tau} & M_T \end{pmatrix}, \quad \sigma = (-\pi \ 0 \ 0)^T n \times 1, \quad J_3 = \begin{pmatrix} 0 & -\psi_1 & -\psi_2 & \ldots & -\psi_n & -\eta_1 & -\eta_2 & \ldots & -\eta_n \\ 0 & \beta \pi h_1 & \beta \pi h_2 & \ldots & \beta \pi h_n & \beta \pi \epsilon_1 & \beta \pi \epsilon_2 & \ldots & \beta \pi \epsilon_n \end{pmatrix},$$

$$J_4 = \begin{pmatrix} \mu & 0 & 0 \end{pmatrix},$$

and

$$M_l = \begin{pmatrix} a_1 & 0 & 0 & 0 & 0 & \cdots & 0 \\ -\rho_1 & a_2 & 0 & 0 & 0 & \cdots & 0 \\ 0 & -\rho_2 & a_3 & 0 & 0 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & -\rho_{n-1} & a_n \end{pmatrix}, \quad M_T = \begin{pmatrix} b_1 & 0 & 0 & 0 & 0 & \cdots & 0 \\ -\gamma_1 & b_2 & 0 & 0 & 0 & \cdots & 0 \\ 0 & -\gamma_2 & b_3 & 0 & 0 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & -\gamma_{n-1} & b_n \end{pmatrix}.$$ (3.5)

The spectral radius of the matrix $F_nV_n^{-1}$ is given by

$$R_{T,n} = \frac{\pi}{C} \sum_{k=1}^{n} \frac{u_k \beta k + v_k \gamma k}{\prod_{j=1}^{n} \left[ a_j b_j - \tau_j \varphi_j \right]}.$$ (3.6)

where $u_k$ and $v_k$ satisfy

$$\begin{cases} u_k = b_k \rho_{k-1} u_{k-1} + \phi_k \gamma_{k-1} v_{k-1}, \\ v_k = \gamma_k \rho_{k-1} u_{k-1} + \phi_k \gamma_{k-1} v_{k-1} \end{cases} \text{ for } k = 1, 2, \ldots, n,$$ (3.7)

and $\rho_0 = \gamma_0 = 1; \ u_0 = 1; \ v_0 = 0$. We note here that $a_j b_j - \tau_j \varphi_j = \sigma_j b_j + \tau_j \beta_j > 0$ for $j = 1, 2, \ldots, n$.

**Remark 3.1.1.** The reproduction number (3.6) can be re-written in matrix form as

$$R_{T,n} = \frac{\pi}{C} \sum_{k=1}^{n} \left( \frac{h_k e_k}{\tau_k} \begin{pmatrix} b_k & \phi_k \gamma_{k-1} \\ \tau_k & a_k \end{pmatrix} \begin{pmatrix} \rho_{k-1} & 0 \\ 0 & \gamma_{k-1} \end{pmatrix} \begin{pmatrix} u_k \gamma_{k-1} \end{pmatrix} \right),$$ (3.8)

where $u_{k-1}$ and $v_{k-1}$ are defined in (3.7) and the matrices $\begin{pmatrix} b_k & \phi_k \gamma_{k-1} \\ \tau_k & a_k \end{pmatrix}$ and $\begin{pmatrix} \rho_{k-1} & 0 \\ 0 & \gamma_{k-1} \end{pmatrix}$ are coefficient matrices of the differential equation.
Remark 3.1.2. Description of the derivation of $R_{T,n}$

For a model with one stage of infection, if $i,j=1,2,3$ represent compartments $E$, $I_1$ and $T_1$, respectively, then the $(i,j)$ entry of the inverse $V_1^{-1}$ of the matrix $V_1$ defined in (3.5), and obtained as

$$V_1^{-1} = \begin{pmatrix}
\frac{1}{c} & 0 & 0 \\
\frac{\tau}{a_1b_1 - \tau_1\varphi_1} & \frac{1}{a_1b_1 - \tau_1\varphi_1} & \frac{1}{a_1b_1 - \tau_1\varphi_1} \\
\frac{\tau}{a_1b_1 - \tau_1\varphi_1} & \frac{1}{a_1b_1 - \tau_1\varphi_1} & \frac{1}{a_1b_1 - \tau_1\varphi_1}
\end{pmatrix},$$

is the average time an individual introduced into compartment $j$ spent in compartment $i$. It follows directly from (3.9) that the average time an individual introduced into the exposed compartment spent in the untreated infected compartment $I_1$ is

$$\frac{1}{\tau_1} = \frac{1}{\tau_1} \sum_{j=0}^{\infty} \left( \frac{\tau_1}{\tau} \right)^j = \frac{1}{\tau_1} \frac{1}{1 - \left( \frac{\tau}{\tau_1} \right)},$$

while the average time an individual introduced into the exposed compartment spent in the treated infected compartment $T_1$ is

$$\frac{1}{\tau_1 - \tau_j\varphi_j} = \frac{1}{\tau_1 - \tau_j\varphi_j} \sum_{j=0}^{\infty} \left( \frac{\tau_j\varphi_j}{\tau_1} \right)^j = \frac{1}{\tau_1 - \tau_j\varphi_j} \frac{1}{1 - \left( \frac{\tau_j\varphi_j}{\tau_1} \right)}.$$

An infected individual in the untreated and treated compartments $I_1$ and $T_1$ produces new infection in the exposed compartment $E$ at a rate $\beta_h$ and $\beta_e$, respectively. Thus, the number $R_{T,n} = \beta_t\varphi_1 \sum_{j=0}^{\infty} \left( \frac{\tau_j}{\tau_1} \right)^j$ is the expected number of secondary cases produced, in a completely susceptible population, by a typical infective individual in compartment $1$. In general, the average time an individual introduced into the exposed compartment spent in the untreated infected compartment $I_k$ is

$$\frac{1}{\tau_k} \frac{u_k}{\prod_{j=1}^{k} (a_j b_j - \tau_j \varphi_j)},$$

while the average time an individual introduced into the exposed compartment spent in the treated infected compartment $T_k$ is

$$\frac{1}{\tau_k} \frac{u_k}{\prod_{j=1}^{k} (a_j b_j - \tau_j \varphi_j)}.$$

Remark 3.1.3. Reproduction number $R_{0,n}$ in the absence of treatment

Define

$$\begin{cases}
\bar{\tau}_k = \mu + \delta_k + \rho_k + \psi_k, \\
\bar{\beta}_k = \mu + \psi_k + \gamma_k + \eta_k.
\end{cases}$$

(3.10)

In the absence of treatment (that is, $\tau_k = 0$ for $k=1,2,\ldots,n$) we have $u_k = \prod_{j=1}^{k} (\beta_j b_j - 1)$, $v_k = 0$ for $k=1,2,\ldots,n$, and the reproduction number $R_{T,n}$ simplifies to the treatment free reproduction number $R_{0,n}$ given by

$$R_{0,n} = \frac{\bar{\beta} \bar{\tau}}{\bar{\beta}} \sum_{k=1}^{n} \left[ h_k \prod_{j=1}^{k} \left( \frac{\beta_j b_j - 1}{\bar{\beta}_j} \right) \right].$$

(3.11)

This is the reproduction number associated with the model without treatment.
\[dS = \left( \Lambda - \beta S \sum_{j=1}^{n} (h_j I_j) - \mu S \right) dt,\]
\[dE = \left( \beta S \sum_{j=1}^{n} (h_j I_j) - (\pi + \mu) E \right) dt,\]
\[dI_1 = \left( \pi E - (\mu + \delta_1 + \rho_1 + \psi_1) I_1 \right) dt,\]
\[dI_k = \left( \rho_{k-1} I_{k-1} - (\mu + \delta_k + \rho_k + \psi_k) I_k \right) dt, \quad k = 2, \ldots, n\]
\[dR = \left( \sum_{j=1}^{n} (\psi_j I_j - \mu R) \right) dt.\]  

(3.12)

In a completely susceptible population receiving no treatment, we describe the quantity \( R_{0,n} \) as the expected number of secondary infection produced by a typical untreated infected individual in a completely susceptible population.

The disease-free equilibrium point of (3.12) reduces to

\[\hat{P}_0 = \left( \begin{array}{cccc} S_0^0 & E_0^0 & I_1^0 & \cdots & I_n^0 & R_0^0 \end{array} \right)^T.\]  

(3.13)

3.2. Endemic equilibrium point, \( P_1 \), in the presence of treatment

The endemic equilibrium \( P_1 = (S^* \ E^* \ I_1^* \ \cdots \ I_n^* \ \cdots \ T_n^* \ R^*)^T \) of system (2.1) described in (3.1) is obtained as

\[
\begin{align*}
S^* &= \frac{\Lambda}{R_{T,n}}, \\
E^* &= \frac{\Lambda}{c} \left( 1 - \frac{1}{R_{T,n}} \right), \\
I_1^* &= \frac{\pi}{c} \frac{\Lambda u_k}{\prod_{j=1}^{k} (a_j b_j - \tau \phi_j)} \left( 1 - \frac{1}{R_{T,n}} \right), \\
T_k^* &= \frac{\pi}{c} \frac{\Lambda v_k}{\prod_{j=1}^{k} (a_j b_j - \tau \phi_j)} \left( 1 - \frac{1}{R_{T,n}} \right), \quad k = 1, 2, \ldots, n, \\
R^* &= \frac{\Lambda}{\mu} \frac{\pi}{c} \sum_{k=1}^{n} \left( \frac{u_k \psi_k + v_k \eta_k}{\prod_{j=1}^{k} (a_j b_j - \tau \phi)} \right) \left( 1 - \frac{1}{R_{T,n}} \right),
\end{align*}
\]  

(3.14)

provided \( R_{T,n} > 1 \), where \( u_k \) and \( v_k \) are defined in (3.7).

Remark 3.2.1. Endemic equilibrium in the absence of treatment.

In the absence of treatment, the endemic equilibrium \( P_1 \) reduces to

\[\hat{P}_1 = \left( \begin{array}{cccc} S^* & E^* & I_1^* & \cdots & I_n^* & R^* \end{array} \right)^T,\]  

(3.15)

where \( \hat{P}_1 \) is derived from (3.14) by setting \( \tau_k = 0 \) and obtained as
\[
\begin{align*}
S^* &= \frac{\pi}{R_{0,n}}, \\
E^* &= \frac{\Lambda}{c} \left( 1 - \frac{1}{R_{0,n}} \right), \\
I_k^* &= \frac{\pi}{c} \Lambda \left[ \prod_{j=1}^{k} \left( \frac{\rho_{j-1}}{\alpha_j} \right) \right] \left( 1 - \frac{1}{R_{0,n}} \right), \\
R^* &= \frac{\Lambda}{\mu} \frac{\pi}{c} \sum_{k=1}^{n} \left( \psi_k \prod_{j=1}^{k} \left( \frac{\rho_{j-1}}{\alpha_j} \right) \right) \left( 1 - \frac{1}{R_{0,n}} \right),
\end{align*}
\]

(3.16)

provided \(R_{0,n} > 1\).

4. Effect of treatment and dropping out treatment in the system

In this section, we study how receiving treatment and dropping out of treatment affect the system.

4.1. Effect of treatment of infection in the system

Consider the reproduction number \(R_{T,j}\) corresponding to model (2.1) with \(j\) stage(s) of infection (derived by setting \(n = j\) in (3.6)). Write \(R_{T,j}(\tau_i)\equiv R_{T,j}\) as a function of \(\tau_i\) for \(1 \leq i \leq n\). We define the quantities \(R_{T,j}(\tau_i \to \infty) \equiv \lim_{\tau_i \to \infty} R_{T,j}(\tau_i)\) and \(R_{T,j}(r_i = 0) \equiv R_{T,j}(\tau_i) |_{\tau_i = 0}\) as the expected number of secondary infection produced by a typical infected individual (in a completely susceptible population with \(j \leq n\) stages of infection) as treatment capacity \(r_i\) goes to infinity and as no treatment is administered in stage \(i\) of infection, respectively.

We can show, after rigorous calculations, that

\[
\begin{align*}
R_{T,j}(\tau_i \to \infty) &= \tilde{\tau} \tilde{\beta} \frac{\pi}{cb_i} \sum_{k=1}^{j} \frac{\tilde{u}_k h_k + \tilde{v}_k e_k}{\prod_{r=1}^{k} (\tilde{a}_r b_r + \tilde{b}_r \tau_r)} , \\
\tilde{u}_1 &= 0, \quad \tilde{v}_1 = 1, \quad \text{and} \quad \tilde{u}_k, \tilde{v}_k, k \neq 1 \text{ are defined in (4.3)}
\end{align*}
\]

(4.1)

\[
\begin{align*}
R_{T,j}(\tau_i \to \infty) &= R_{T,j-1} + \tilde{\tau} \tilde{\beta} \frac{\pi}{cb_i} (u_{i-1} p_{i-1} + v_{i-1} q_{i-1}) \sum_{k=1}^{j} \frac{\tilde{u}_k h_k + \tilde{v}_k e_k}{\prod_{r=1}^{k} (\tilde{a}_r b_r + \tilde{b}_r \tau_r)} , \\
\tilde{u}_i &= 0, \quad \tilde{v}_i = 1, \quad \text{and} \quad \tilde{u}_k, \tilde{v}_k, k \neq i \text{ are defined in (4.3)}
\end{align*}
\]
where \( u_i, v_i \) are defined in (3.7) for \( i = 1, 2, \ldots, n \), \( u_0 = 1 \), \( v_0 = 0 \), and

\[
\begin{align*}
\hat{u}_k &= b_i \rho_{i-1} \hat{u}_{i-1} + \varphi_i \gamma_{i-1} \hat{v}_{i-1}, \\
\hat{v}_k &= \tau_k \rho_{i-1} \hat{u}_{i-1} + d_k \gamma_{i-1} \hat{v}_{i-1}, \quad \text{for } k = i+1, \ldots, n, \quad 1 \leq i \leq n \\
\hat{u}_k &= b_i \rho_{i-1} \hat{u}_{i-1} + \varphi_i \gamma_{i-1} \hat{v}_{i-1}, \\
\hat{v}_k &= \tau_k \rho_{i-1} \hat{u}_{i-1} + d_k \gamma_{i-1} \hat{v}_{i-1}, \quad \text{for } k \neq i.
\end{align*}
\]

Furthermore,

\[
\begin{align*}
\frac{dR_{T_j}}{dt} &= \frac{\bar{a}_i \bar{b}_i b_i}{(\bar{a}_i b_i + \bar{b}_i \tau_i)^2} (R_{T_j}(\tau_i \rightarrow \infty) - R_{T_j}(\tau_i = 0)), \\
\frac{d^2R_{T_j}}{dt^2} &= -\frac{2\bar{a}_i \bar{b}_i b_i}{(\bar{a}_i b_i + \bar{b}_i \tau_i)^3} (R_{T_j}(\tau_i \rightarrow \infty) - R_{T_j}(\tau_i = 0)), \quad \text{for } 1 \leq i, j \leq n.
\end{align*}
\]

It follows from (4.4) that the derivative \( \frac{dR_{T_j}}{dt} < 0 \) and the graph of \( R_{T_j}(\tau_i) \) concaves up for all \( \tau_i \geq 0 \) if and only if \( R_{T_j}(\tau_i \rightarrow \infty) < R_{T_j}(\tau_i = 0) \), for \( 1 \leq i \leq j \leq n \). Likewise, \( \frac{d^2R_{T_j}}{dt^2} > 0 \) and the graph of \( R_{T_j}(\tau_i) \) concaves down for all \( \tau_i \geq 0 \) if and only if \( R_{T_j}(\tau_i \rightarrow \infty) > R_{T_j}(\tau_i = 0) \), for \( 1 \leq i \leq j \leq n \). By definition, we expect \( R_{T_j}(\tau_i \rightarrow \infty) < R_{T_j}(\tau_i = 0) \), for \( 1 \leq i, j \leq n \). This shows that in a population with \( j \) stages of infection, the number of secondary infection, \( R_{T_j} \), produced by an infected individual in a completely susceptible population decreases as the treatment rate \( \tau_i \) increases.

4.1.1. Case where \( \tau_i = \tau \) for all \( i = 1, 2, \ldots, n \)

Define

\[
R_{\infty,n} = \frac{\beta^2 \gamma}{C} \sum_{k=1}^{n} \prod_{j=1}^{k} \left( \frac{\gamma_j}{b_j} \right).
\]

where \( b_j \) is defined in (3.10). For fixed \( \tau = \tau \), \( j = 1, 2, \ldots, n \), we write \( R_{T,n} = R_{\infty,n} (\tau) \) (defined in (3.6)) as a function of \( \tau \). The number of secondary infection, \( R_{T,n}(\tau) \), has the property:

\[
R_{T,n} \rightarrow R_{\infty,n} \text{ as } \tau \rightarrow \infty.
\]

The function

\[
f(\tau) = \frac{R_{T,n}(\tau)}{R_{\infty,n}},
\]

is a rational function of \( \tau \) referred to as the relative elimination threshold. The graph of the function has \( y \)-intercept \( f(0) = 1 \) (following directly from Remark 3.1.1) and negative zeros. The vertical asymptotes are the negative vertical lines \( \tau = -\frac{b_j}{b_i} \), for \( j = 1, 2, \ldots, n \). Define

\[
\hat{u}_1 = 1, \quad \hat{v}_1 = 0, \quad \text{and} \quad \hat{u}_k, \hat{v}_k, k \neq 1 \text{ are defined in (4.3)}.
\]

\[
\begin{align*}
\hat{u}_i &= b_i \rho_{i-1} \hat{u}_{i-1} + \varphi_i \gamma_{i-1} \hat{v}_{i-1}, \\
\hat{v}_i &= \tau_i \rho_{i-1} \hat{u}_{i-1} + d_i \gamma_{i-1} \hat{v}_{i-1}, \quad \text{for } 1 \leq i \leq n
\end{align*}
\]
The function $f(\tau) \rightarrow \bar{f}$ as $\tau \rightarrow \infty$. The value $\bar{f}$ is the horizontal asymptote of $f(\tau)$. It measures the infection transmission potential when treatment capacity goes to infinity relative to the transmission potential when no treatment is administered. It follows from property of rational functions that $\bar{f} R_0, n < R_T, n(\tau) \leq R_0, n$ (that is, $R_{\infty, n} < R_T, n \leq R_0, n$) if $\bar{f} < 1$ and $R_0, n \leq R_T, n(\tau) < \bar{f} R_0, n$ if $\bar{f} > 1$. This is represented in Fig. 2 below.

Fig. 2 (a) and (b) show the trajectory of $f(\tau)$ for the cases where $\bar{f} < 1$ and $\bar{f} > 1$, respectively.

**Remark 4.1.1.** The quantity $R_{\infty, n}$ can be described as the expected number of secondary infection produced by a typical infected individual as the treatment capacity goes to infinity. From the description of $R_{0, n}$ in Remark 3.1.1, we expect $R_{\infty, n} = \bar{f} R_0, n$ that is, we expect the expected number of secondary infection produced when the treatment capacity goes to infinity to be smaller than the expected number of secondary infection produced when no treatment is administered. This implies $\bar{f} < 1$, so that $R_T, n < R_0, n$. This shows that as the treatment rate increases, the expected number of infection decreases. The highest expected number of infection produced by an infected individual in a completely susceptible population is $R_0, n$ (which is attained when $\tau = 0$) while the lowest expected number of infection is $R_{\infty, n}$ (attained as $\tau \rightarrow \infty$).

### 4.2. Effect of dropping out of treatment

Write $R_{T, j}(\varphi_1) \equiv R_{T, j}$ as a function of $\varphi_1$ for $1 \leq i, j \leq n$. Using similar definition in Subsection 4.1, we define the quantities $R_{T, j}(\varphi_1 \rightarrow \infty)$ and $R_{T, j}(\varphi_1 = 0)$ as the expected number of secondary infection produced by a typical infected individual (in a completely susceptible population with $j \leq n$ stages of infection) as drop out treatment rate $\varphi_1$ goes to infinity and as no one drops out of treatment in stage $i$ of infection, respectively.

We obtain, after rigorous calculations

$$R_{T, j}(\varphi_1 \rightarrow \infty) = \bar{f} R_0, n \prod_{k=1}^{j} \frac{\hat{u}_k h_k + \hat{v}_k e_k}{\prod_{r=1}^{k} (a_r \bar{b}_r + \bar{a}_r \varphi_r)}$$

for $1 \leq i \leq j$, and $\hat{u}_k, \hat{v}_k, k \neq 1$ are defined in (4.10),

$$R_{T, j}(\varphi_1 = 0) = R_{T, j-1} + \bar{f} R_0, n \prod_{k=1}^{j} \frac{\hat{u}_k h_k + \hat{v}_k e_k}{\prod_{r=1}^{k} (a_r \bar{b}_r + \bar{a}_r \varphi_r)}$$

for $2 \leq i \leq j \leq n$,

$$R_{T, j}(\varphi_1 \rightarrow \infty) = R_{T, i-1} + \bar{f} R_0, n \prod_{k=1}^{j} \frac{\hat{u}_k h_k + \hat{v}_k e_k}{\prod_{r=1}^{k} (a_r \bar{b}_r + \bar{a}_r \varphi_r)}$$

for $2 \leq i \leq j \leq n$,

$\hat{u}_i = 1, \hat{v}_i = 0$, and $\hat{u}_k, \hat{v}_k, k \neq i$ are defined in (4.10),

$$f(\tau) \rightarrow \bar{f} \text{ as } \tau \rightarrow \infty.$$  

![Fig. 2. Graphs of $f(\tau)$ against $\tau$ for the cases where $\bar{f} < 1$ and $\bar{f} > 1$.](image-url)
expected number of secondary infection produced by an infected individual increases to

\[ \beta_2 \frac{\pi}{C} \sum_{k=1}^{j} \frac{\bar{u}_k h_k + \bar{v}_k e_k}{(\beta_i \bar{B}_i + \bar{a}_i \phi_i)} \]

\[ \tau = 1 \]

\[ \bar{u}_1 = \bar{B}_i, \quad \bar{v}_1 = \tau_1, \quad \text{and} \quad \bar{u}_k, \bar{v}_k, k \neq 1 \text{ are defined in (4.10).} \]

\[ R_{T,j}(\phi_1 = 0) = R_{T,j-1} + \beta_2 \frac{\pi}{C} \sum_{k=1}^{j} \frac{\bar{u}_k h_k + \bar{v}_k e_k}{(\beta_i \bar{B}_i + \bar{a}_i \phi_i)} \quad \text{for} \quad 2 \leq i \leq j \leq n, \]

\[ \tau \neq 1 \]

\[ \bar{u}_i = \bar{B}_i \bar{u}_{i-1}, \quad \bar{v}_i = \tau_i \bar{u}_{i-1} + a_i \gamma_{i-1} \bar{v}_{i-1}, \quad \text{and} \quad \bar{u}_k, \bar{v}_k, k \neq i \text{ are defined in (4.10),} \]

where \( u_i, v_i \) are defined in (3.7) for \( i = 1, 2, \cdots, n \), \( u_0 = 1, v_0 = 0 \), and

\[ \begin{cases} 
\bar{u}_k = b_k \bar{u}_{k-1} + \phi_k \gamma_{k-1} \bar{v}_{k-1}, \\
\bar{v}_k = \tau_k \bar{u}_{k-1} + a_k \gamma_{k-1} \bar{v}_{k-1}, \\
\bar{u}_k = b_k \bar{u}_{k-1} + \phi_k \gamma_{k-1} \bar{v}_{k-1}, \\
\bar{v}_k = \tau_k \bar{u}_{k-1} + a_k \gamma_{k-1} \bar{v}_{k-1}, \\
\end{cases} \quad \text{for} \quad k = i + 1, \cdots, n, \quad 1 \leq i \leq n \]

Furthermore,

\[ \frac{dR_{T,j}}{d\phi_i} = \frac{a_i \bar{a}_i \bar{B}_i}{(a_i \bar{B}_i + \bar{a}_i \phi_i)^2} (R_{T,j}(\phi_i \rightarrow \infty) - R_{T,j}(\phi_i = 0)), \]

\[ \frac{d^2R_{T,j}}{d\phi_i^2} = -\frac{2a_i \bar{a}_i \bar{B}_i}{(a_i \bar{B}_i + \bar{a}_i \phi_i)^3} (R_{T,j}(\phi_i \rightarrow \infty) - R_{T,j}(\phi_i = 0)), \quad \text{for} \quad 1 \leq i, j \leq n. \]

It follows from (4.11) that the derivative \( \frac{dR_{T,j}(\phi_i)}{d\phi_i} > 0 \) and the graph of \( R_{T,j}(\phi_i) \) concaves down for all \( \phi_i \geq 0 \) if and only if \( R_{T,j}(\phi_i \rightarrow \infty) > R_{T,j}(\phi_i = 0) \), for \( 1 \leq i \leq j \leq n \). Likewise, \( \frac{d^2R_{T,j}}{d\phi_i^2} < 0 \) and the graph of \( R_{T,j}(\phi_i) \) concaves up for all \( \phi_i \geq 0 \) if and only if \( R_{T,j}(\phi_i \rightarrow \infty) < R_{T,j}(\phi_i = 0) \), for \( 1 \leq i \leq j \leq n \). By definition, we expect \( R_{T,j}(\phi_i \rightarrow \infty) > R_{T,j}(\phi_i = 0) \), for \( 1 \leq i \leq j \leq n \). This shows that in a population with \( j \) stages of infection, the number of secondary infection, \( R_{T,j} \), produced by an infected individual in a completely susceptible population increases as the treatment dropout rate \( \phi_i \) increases.

### 4.2.1. Case where \( \phi_i \equiv \phi \) for all \( i = 1, 2, \cdots, n \)

Assume \( \phi_i \equiv \phi \) for \( j = 1, 2, \cdots, n \), and write \( R_{T,n}(\phi) \). We see that

\[ R_{T,n}(\phi) \rightarrow R_{0,n}, \quad \text{as} \quad \phi \rightarrow \infty, \]

and

\[ R_{T,n}(\phi = 0) = \beta_2 \frac{\pi}{C} \sum_{k=1}^{n} \left[ \frac{\phi_{j-1}}{a_j} \right] h_k + \frac{v_k}{\prod_{j=1}^{k} (a_j \bar{B}_j) \right] \]

where \( v_k \) is defined in (3.7) for \( k = 1, 2, \cdots, n \). The vertical asymptotes of the rational function \( R_{T,n}(\phi) \) are the negative vertical lines \( \phi = -a_j \bar{B}_j / \gamma_j \), for \( j = 1, 2, \cdots, n \). Since \( R_{T,n}(\phi) \) is a rational function of \( \phi \) whose numerator and denominator have the same degree, it follows that \( R_{T,n}(\phi) \) is an increasing function of \( \phi \) if and only if \( R_{T,n}(\phi = 0) \leq R_{T,n}(\phi \rightarrow \infty) = R_{0,n} \), for \( \phi \geq 0 \). By definition, we expect \( R_{T,n}(\phi = 0) \leq R_{T,n}(\phi \rightarrow \infty) \). This shows that as the rate of dropping out of treatment increases, the expected number of secondary infection produced by an infected individual increases to \( R_{0,n} \).
4.2.2. Numerical results verifying the effects of treatment and dropping out of treatment on the number of infections

Here, we use relevant parameters to the transmission dynamics of influenza disease in the United States for the numerical simulations of the reproduction number as a function of the treatment and dropout rates. We set the life expectancy of the United States population to 80 years\(^3\) and the total population to be 329, 256, 465 as of July 2018.\(^4\) Using the parameters collected from the Center for Disease Control and Prevention (CDC), the time from when a person is exposed and infected with flu to when symptoms begin is about 2 days, but can range from about 1 to 4 days\(^5\) and uncomplicated influenza signs and symptoms typically resolve after 3–7 days for the majority of people.\(^6\) Antiviral drugs, when used for treatment, can reduce symptoms and shorten sick time by 1 or 2 days\(^6\).

CDC\(^7\) estimates that, from October 1, 2018, through May 4, 2019, there have been 37.4 – 42.9 million flu illness, 17.3 – 20.1 million flu medical visits, 531 – 647 thousand flu hospitalizations and 36.4 – 61.2 thousand flu death. We define \(e_j\) as a reduction factor in infectiousness (in stage \(j\) of infection) due to flu treatment and it reduces the infectious period to \(\frac{1}{\eta_j} < \frac{1}{\eta}\). For more information about the parameter \(e_j\), we refer readers to the work of Lipsitch et al. (Liu and Zhang, 2011), Feng et al. (Feng et al., 2011), Kretzschmar et al. (Kretzschmar et al., 2013) and CDC\(^2\). In their work, Lipsitch (Liu and Zhang, 2011) introduced a parameter which is the reduction in hazard of infection for an individual on prophylaxis. They claimed with probability \(e_p\), transmission is blocked and of those blocked infections, a proportion \(a_p\) are only partially blocked. Using two infectious stages, we set \(\frac{1}{\eta_1} = 4, \frac{1}{\eta_2} = 3, \frac{1}{\eta_3} = 4, \frac{1}{\eta_4} = 2, \beta = 0.8, h_1 = 0.5, h_2 = 0.106, e_1 = 0.2, e_2 = 0.05, \tau_1 = 0.08, \tau_2 = 0.12, \varphi_1 = 1/3, \varphi_2 = 1/4, \psi_1 = 1/5, \psi_2 = 1/10, \eta_1 = 1/4, \eta_2 = 1/8, \delta_1 = 1.43 \times 10^{-4}, \delta_2 = 1.1 \times 10^{-4}, \delta_3 = 0.925 \times 10^{-4}, \delta_4 = 0.8 \times 10^{-4}.\)

The value \(\sum_{j=1}^{n} T_j(0)\) of individuals under treatment is close to the number reported by Biggerstaff et al. (Biggerstaff, Jhung, Kamimoto, Balluz, & Finelli, 2012). According to the paper published by Tokars at al. (Tokars, Olsen, & Reed, 2018), between 3% and 11.3% of the U.S. population gets infected and develops flu symptoms each year. The value \(\sum_{j=1}^{n} T_j(0)\) is approximately in this reported range. See Tables 1, 2 and 3 for parameter values and descriptions.

Fig. 3 (a) shows the graph of \(R_T,1 = RT,1(\tau)\) against \(\tau = \tau_1\), Fig. 3 (b) shows the graph of \(R_T,2 = RT,2(\tau)\) against \(\tau = \tau_1 = \tau_2\). The graphs show that with no treatment, the reproduction number is \(R_0,n\), and as more treatment is introduced into the population the number of secondary infection \(R_T,n\) reduces until it approaches \(R_\infty,n\), which is the least number of secondary infection that can be produced by an infected individuals when introduced into susceptible population. This is explained in Subsection 4.1.

Fig. 4 (a) shows the graph of \(R_T,1 = RT,1(\varphi)\) against \(\varphi = \varphi_1\), Fig. 4 (b) shows the graph of \(R_T,2 = RT,2(\varphi)\) against \(\varphi = \varphi_1 = \varphi_2\). The graphs show that the number of secondary infection \(R_T,n\) increases to \(R_0,n\) as individuals drop out of treatment. This is explained in Subsection 4.2.

Fig. 5 (a) shows the graph of \(R_T,1 = RT,1(\varphi, \tau)\) against \(\tau = \tau_1 \) and \(\varphi = \varphi_1\), Fig. 5 (b) shows the graph of \(R_T,2 = RT,2(\tau, \varphi)\) against \(\tau = \tau_1 = \tau_2\) and \(\varphi = \varphi_1 = \varphi_2\).

5. Existence and stability of equilibrium points

In this section, we discuss the endpoint behavior of the solution of (2.1). We give conditions under which the solution converges on the long run to the disease-free or endemic equilibrium.

5.1. Existence and stability of disease-free equilibrium \(P_0\) in the presence of treatment

The following theorems show the condition for the local and global stability of the disease-free equilibrium, \(P_0\). We study condition(s) under which disease elimination exists on the long run. The idea presented here is similar to the work in Otunuga (Otunuga, 2018). To analyze the local asymptotic stability of \(P_0\), we linearize (2.1) about \(P_0\) and show that the real part of all eigenvalues of the coefficient matrix of the linear associated system is negative.

Define \(\Psi = (S - \pi E I_1 \ldots I_n T_1 \ldots T_n R)^T\). The linearization of (2.1) along the disease-free equilibrium \(P_0\) is obtained as

\[
\frac{d \Psi}{dt} = A \Psi, \quad \Psi(t_0) = \Psi_0.
\]

\(^3\) https://www.cia.gov/library/publications/the-world-factbook/rankorder/2102rank.html.

\(^4\) https://www.cia.gov/library/publications/the-world-factbook/geos/us.html.

\(^5\) https://www.cdc.gov/flu/about/keyfacts.htm. Page last reviewed: August 27, 2018.

\(^6\) https://www.cdc.gov/flu/professionals/acip/clinical.htm. Page last reviewed: March 8, 2019

\(^7\) https://www.cdc.gov/flu/about/burden/preliminary-in-season-estimates.htm. Page last reviewed: May 9, 2019
where \[ A = \begin{pmatrix} A_{11} & A_{12} & A_{13} & A_{14} \\ A_{21} & A_{22} & A_{23} & A_{24} \\ A_{31} & A_{32} & A_{33} & A_{34} \\ A_{41} & A_{42} & A_{43} & A_{44} \end{pmatrix} \]

with \[ A_{1,1} = \begin{pmatrix} -\mu & 0 & 0 \\ 0 & 0 & -c \end{pmatrix}, \quad A_{1,2} = \beta\pi \begin{pmatrix} -h_1 & -h_2 & \ldots & -h_n \end{pmatrix}, \]

\[ A_{1,3} = \beta\pi \begin{pmatrix} -e_1 & -e_2 & \ldots & -e_n \end{pmatrix}, \quad A_{1,4} = \begin{pmatrix} 0 \\ 0 \end{pmatrix}, \quad A_{2,1} = \begin{pmatrix} 0 & \pi & 0 \end{pmatrix}, \quad A_{2,2} = -M_1, \quad A_{2,3} = \psi_1, \quad A_{2,4} = A_{3,4} = \begin{pmatrix} 0 & \pi & 0 \end{pmatrix}, \quad A_{3,1} = (0_n \times 1), \quad A_{3,2} = \beta\pi, \quad A_{3,3} = -M_T, \quad A_{4,1} = (0_1 \times 2), \quad A_{4,2} = (\psi_1 \psi_2 \psi_3), \quad A_{4,3} = (\eta_1 \eta_2 \eta_n), \quad A_{4,4} = -d, \quad \text{and} \quad M_1, M_T, \psi_1, \psi_2, \psi_3, \eta_1, \eta_2, \eta_n \text{ are defined in (3.5).} \]

We can express the characteristic polynomial of \( A \) in the form

\[ \det(\mathbf{A} - r \mathbf{I}) = \det(\mathbf{A} - r \mathbf{I}) = (r + \mu) \det(\mathbf{A} - r \mathbf{I}) \]

where \( \mathbf{A} \) is the square matrix formed by deleting the first row and column of \( \mathbf{A} \) in (5.1) and \( r \) is the eigenvalue of \( \mathbf{A} \).
Theorem 5.1. The real part of all eigenvalues of $A$ is negative if $R_{T,n} < 1$. One of the eigenvalues of $A$ is zero if $R_{T,n} = 1$ and at least one of the eigenvalues is positive real if $R_{T,n} > 1$.

Proof. It suffices to show that the maximum real part of all eigenvalues of $A$, denoted, $\sigma(A)$, is less than zero if $R_{T,n} < 1$. To do this, we use relations $D_{12}$ and $J_{20}$ in (Plemmons, 1977) to show that the real part of each eigenvalues of the matrix $B = -A$ is positive. The matrix can be written in the form

$$B = \mathcal{L} \mathcal{U},$$

(5.3)

where $\mathcal{L}$ and $\mathcal{U}$ are lower and upper diagonal matrices, respectively, with positive diagonals. The matrices $\mathcal{L} = (\mathcal{L}_{ij})$ and $\mathcal{U} = (\mathcal{U}_{ij})$ are computed rigorously as follows:

$$\mathcal{L}_{ij} = \frac{1}{\mathcal{F}_j} \begin{bmatrix} R_{1,1} & R_{1,2} & \ldots & R_{1,j} \\ R_{2,1} & R_{2,2} & \ldots & R_{2,j} \\ \vdots & \vdots & \ddots & \vdots \\ R_{j-1,1} & R_{j-1,2} & \ldots & R_{j-1,j} \\ R_{j,1} & R_{j,2} & \ldots & R_{j,j} \end{bmatrix},$$

for $i \geq j \neq 1$, $\mathcal{L}_{i,1} = \frac{1}{\mathcal{F}_1} R_{i,1}$ for $i = 1, 2, \ldots, 2n + 2$, and 0 elsewhere.
conditions in diagonal entries $U_j$, for $j = 1, 2, \ldots, 2n + 2$, and 0 elsewhere.

Proof. The proof follows from (5.2) and Theorem 5.1.

Proof. The disease-free equilibrium $P_0$ of (2.1) is globally stable in the feasible region $\mathcal{T}$ if $R_{t,n} \leq 1$.

Proof. Define the Lyapunov function $L : \mathbb{R}_{2n+2} \to \mathbb{R}^+$ by
where $\mathbb{R}^+$ is the set of positive real numbers, $\sigma$, $\hat{\phi}_k$ and $\hat{\theta}_k$ satisfy

$$\sigma = 1,$$

$$\begin{pmatrix} \hat{\phi}_n \\ \hat{\theta}_n \end{pmatrix} = \frac{\tilde{\beta} n b_n + \tau_n e_n}{h_n b_n - \tau_n \phi_n} \begin{pmatrix} h_n \phi_n + \alpha n e_n \\ \hat{\phi}_n - \hat{\theta}_n \end{pmatrix},$$

$$\begin{pmatrix} \hat{\phi}_{n-k} \\ \hat{\theta}_{n-k} \end{pmatrix} = \frac{1}{\alpha n - b_n - \tau_n \phi_{n-k}} \left[ \begin{pmatrix} b_n \phi_{n-k} - \gamma_{n-k} \tau_{n-k} \\ \phi_{n-k} - \gamma_{n-k} \alpha_n \end{pmatrix} \begin{pmatrix} \hat{\phi}_{n-k+1} \\ \hat{\theta}_{n-k+1} \end{pmatrix} + \tilde{\beta} n h_{n-k} b_{n-k} + \tau_{n-k} e_{n-k} \right],$$

for $k \in \{1, 2, 3, \ldots, n-1\}$, and $(\hat{\phi}_1 \hat{\theta}_1)^T$ reduces to

$$\begin{pmatrix} \hat{\phi}_1 \\ \hat{\theta}_1 \end{pmatrix} = \frac{c}{\pi} \begin{pmatrix} R_{\tau n} \\ R_{\tau n} \end{pmatrix},$$

where

$$R_{\tau n} = \pi \tilde{\beta} \sum_{k=1}^{n} \left[ \frac{h_k \bar{a}_k + \epsilon_k \bar{b}_k}{\prod_{j=1}^{k} (a_j b_j - \gamma_j e_j)} \right],$$

and $\bar{a}_k$ and $\bar{b}_k$ are recursive sequences defined by

$$\begin{align*}
\bar{a}_1 &= \phi_1; \\
\bar{a}_k &= b_k \phi_{k-1} \bar{a}_{k-1} + \gamma_k \bar{b}_{k-1}; \\
\bar{b}_1 &= \tau_1 \phi_{k-1} \bar{a}_{k-1} + \gamma_k \bar{b}_{k-1},
\end{align*}$$

for $k \in \{2, 3, \ldots, n\}$.

The coefficients $\sigma$, $\hat{\phi}_k$ and $\hat{\theta}_k$ satisfy $\hat{\phi}_k a_k - \hat{\theta}_k b_k - \beta n \hat{\phi}_k - \gamma_k \tau_k \hat{\theta}_k = 0$, $\hat{\theta}_k b_k - \hat{\phi}_k - \beta n \hat{\phi}_k - \gamma_k \tau_k \hat{\theta}_k = 0$ for $k \in \{1, 2, \ldots, n-1\}$, and $\hat{\phi}_n a_n - \tau_n \hat{\theta}_n - \beta \hat{\phi}_n - \gamma_n \tau_n \hat{\theta}_n = 0$ and $\hat{\theta}_n b_n - \tau_n \hat{\theta}_n - \beta \hat{\phi}_n = 0$. It follows from (5.5) and (5.6) that the derivative of $L$ computed along solution of (2.1) is

$$\frac{dl}{dt} = \Lambda + \mu S^0 - \mu S^0 \left[ S - \mu S - (1 - \mu) \beta n \sum_{k=1}^{n} (h_k I_k + \epsilon_k T_k) - (\sigma C - \hat{\phi}_1 \pi) E - \sum_{k=1}^{n-1} (\hat{\phi}_k a_k - \hat{\phi}_{k+1} \mu b_k - \beta n \hat{\phi}_k - \gamma_k \tau_k \hat{\theta}_k) I_k \right]$$

$$- \sum_{k=1}^{n-1} (\hat{\phi}_k b_k - \hat{\phi}_{k+1} \gamma_k \tau_k \hat{\theta}_k - \beta n \hat{\phi}_k - \gamma_k \tau_k \hat{\theta}_k) I_k - \hat{\phi}_n b_n - \beta \hat{\phi}_n \epsilon_n.$$

If $R_{\tau n} \leq 1$, then $(\sigma C - \hat{\phi}_1 \pi) \geq 0$. Thus, it follows from (5.6) and (5.7) that $\hat{\phi}_k$ and $\hat{\theta}_k$ are positive for $k \in \{1, 2, \ldots, n\}$ and

$$\frac{dl}{dt} \leq - \Lambda \left( \frac{S^0 \mu}{\sigma} + \frac{S^0}{\sigma^2} - 2 \right) \leq 0$$

using the fact that $S^0 = \pi / (\mu \pi) = 1$.

The above theorem shows that disease can be eliminated on the long run from the population if parameters are controlled so that the elimination threshold $R_{\tau n}$ is at most 1. This elimination is independent of the initial number of infection. The global stability of the disease-free equilibrium $P_0$ of system (3.12) without treatment follows immediately from Theorem 5.4 by setting $\tau_k = 0$ for all $k \in \{1, 2, \ldots, n\}$. We state the theorem below without proof.

**Corollary 5.5.** The disease-free equilibrium $P_0$ of (3.12) is globally asymptotically stable in the feasible region $\mathcal{F}$ if $R_{\tau n} \leq 1.$
### Table 3
Parameter values for the epidemic model: Case study Influenza.

| Parameter Description                                      | Default Value | References               |
|------------------------------------------------------------|---------------|--------------------------|
| \( \Lambda \) Recruitment rate into the population            | \( \frac{1}{80 \times 365} \) day\(^{-1} \) | CIA\(^3\)                |
| \( \beta \) Transmission rate of infection                  | \( \sum_{j=1}^{n} \beta h_j = 0.5 \) | Feng et al. (2011)        |
| \( h_k \) Infectivity of untreated individuals in stage \( k \) of infection | 0.5           | (Feng et al., 2011; Roosa & Chowell, 2019) |
| \( r_k \) Reduced infectiousness due to treatment in stage \( k \) of infection | 0.2           | Feng et al. (2011)        |
| \( \pi \) Infectious rate for exposed individuals            | \( \frac{1}{\pi} = 2 \) (days) | CDC\(^5\)                |
| \( \mu \) Natural death rate                                | \( \Lambda \) | CIA\(^3\)                |
| \( \delta_k \) Death rate associated with untreated infection | \( 1.43 \times 10^{-4} \) | Assumed                  |
| \( \tau_k \) Death rate associated with treated infection   | \( \sum_{j=1}^{n} \tau_j = [0.05, 0.2] \) (day\(^{-1} \)) | CDC\(^5\)                |
| \( \psi_k \) Rate of dropping out of treatment in stage \( k \) | \( \sum_{j=1}^{n} \frac{1}{\psi_j} = 7 \) (days) | Assumed                  |
| \( \rho_k \) Average duration of untreated infection         | \( \sum_{j=1}^{n} \frac{1}{\rho_j} \equiv [3, 7] \) (days) | CDC\(^6\)                |
| \( \gamma_k \) Average duration of treated infection        | \( \sum_{j=1}^{n} \frac{1}{\gamma_j} \equiv [1, 6] \) (days) | CDC\(^6\)                |
| \( \psi_k \) Recovery rate for untreated individuals in stage \( k \) of infection | \( \sum_{j=1}^{n} \frac{1}{\psi_j} \equiv [3, 1.5] \) (days) | Assumed                  |
| \( \eta_k \) Recovery rate for treated individuals in stage \( k \) of infection | \( \sum_{j=1}^{n} \frac{1}{\eta_j} \equiv [2, 1.4] \) (days) | Assumed                  |
| \( S(0) \) Initial susceptible Population                   | Assumed       |                          |
| \( E(0) \) Initial Exposed Population                        | Assumed       |                          |
| \( \sum_{j=1}^{n} I_j(0) \) Initial Untreated Infected Population | 37.4          | CIA\(^3\), CDC\(^2\) |
| \( R(0) \) Initial Recovered Population                      | Assumed       |                          |

#### 5.1.1. Numerical results verifying global stability of disease-free equilibrium \( P_0 \)

Here, we use relevant parameters (given in Table 3) to the transmission dynamics of influenza disease in the United States for the numerical simulations of the number of susceptible, untreated infected, treated infected and recovered individuals satisfying the SEITR models (2.1) and (3.12).

Fig. 6 (a) shows the comparison of the trajectories of the number (in percentages) of exposed (\( E_n \)), untreated infected (\( I_{1n} \)) population in stage 1 of infection for model (3.12) (no treatment) with the trajectories of the number of exposed (\( E \)), untreated infected (\( I_1 \)) and treated infected (\( T_1 \)) population in stage 1 of infection for model (2.1) (with treatment) for the case where \( n = 1 \). Fig. 6 (b) shows the comparison of the trajectories of the number of exposed (\( E_n \)), untreated infected (\( I_{1n} \)) and treated infected (\( I_2n \)) population in stages 1 and 2 of infection, respectively, for model (3.12) with the trajectories of the number of exposed (\( E \)), untreated infected (\( I_1 \)), (\( I_2 \)) and treated infected (\( T_1 \)), (\( T_2 \)) populations in stages 1 and 2 of infection, respectively, for model (2.1) with the case \( n = 2 \). It is clear from the graph that the introduction of treatment in the system reduces the number of exposed and infected individuals (that is, \( E < E_n, I_1 < I_{1n} \) and \( I_2 < I_{2n} \)) after some days. The number of exposed and infected individuals tends to zero on the long run and the number of susceptible individuals tends to 1. In this case, \( R_{01} = 0.8885, R_{02} = 0.9971, R_{71} = 0.8337, \) and \( R_{72} = 0.9255 \). The graph of the solution \((S(t), E(t), I_1(t), I_2(t), T_1(t), T_2(t), R(t))\) of system (3.12) converges to \( P_0 \) as \( t \to \infty \). This confirms Corollary 5.5. Likewise, the graph of the solution \((S(t), E(t), I_1(t), \ldots, I_n(t), T_1(t), \ldots, T_n(t), R(t))\) of system (2.1) converges to \( P_0 \) as \( t \to \infty \). This confirms Theorem 5.4.

#### 5.2. Existence and stability of endemic equilibrium \( P_1 \) in the presence of treatment

**Theorem 5.6.** The endemic equilibrium \( P_1 \) (given in (3.14)) of (2.1) exists if and only if \( R_{T,n} > 1 \) and does not exist if \( R_{T,n} < 1 \). It becomes disease-free (that is, \( P_1 = P_0 \)) if \( R_{T,n} = 1 \).

Proof. It follows directly from (3.14) that \( S > 0, E^* > 0, T_k^* > 0, \tilde{T}_k > 0 \) and \( \tilde{R}^* > 0 \) for \( k = 1, 2, \ldots, n \) if \( R_{T,n} > 1 \). The result for the case where \( R_{T,n} \leq 1 \) follows from (3.14). \( \blacksquare \)
The following theorem gives the threshold for persistence of endemic (considered independent of the initial number of infection).

**Theorem 5.7.** The endemic equilibrium $P_1$ of the system (2.1) is globally stable in the feasible region $\mathcal{F}$ if $R_{T,n} > 1$ and $f_k > 0$, $m_k > 0$, where $f_k$ and $m_k$ are given in (5.11).

Proof. The existence of the endemic equilibrium $P_1$ follows from Theorem 5.6 if $R_{T,n} > 1$. Assume $R_{T,n} > 1$. Define the Lyapunov function $L : \mathbb{R}^{n+2} \rightarrow \mathbb{R}^+$ by

$$L(S, I_1, ..., I_n, T_1, ..., T_n) = \left( S - \bar{S} \right)^{a} \ln \frac{S}{\bar{S}} + \bar{\sigma}^{*} \left( E - \bar{E} \right)^{a} \ln \frac{E}{\bar{E}} + \sum_{k=1}^{n} p_{k} \left( I_{k} - \bar{T}_{k} \right)^{a} \ln \frac{I_{k}}{\bar{T}_{k}},$$

where $\bar{\sigma}^{*}$, $p_{k}$, $k = 1, 2, ..., n$, are positive constants defined by

$$\bar{\sigma}^{*} = 1,$$

$$\binom{p_{n}}{p_{n}} = \frac{\beta S^{a}}{a_{n}b_{n} - \tau_{n}a_{n}} \left( h_{n}b_{n} + \tau_{n}a_{n} \right),$$

$$\binom{\bar{p}_{n-k}}{\bar{p}_{n-k}} = \frac{1}{a_{n-k}b_{n-k} - \tau_{n-k}a_{n-k}} \left( \begin{array}{cc} h_{n-k}b_{n-k} & \gamma_{n-k}\tau_{n-k} \\ \gamma_{n-k}b_{n-k} & \gamma_{n-k}a_{n-k} \end{array} \right) \binom{\bar{p}_{n-k+1}}{\bar{p}_{n-k+1}} + \beta S^{a} \left( \begin{array}{cc} h_{n-k}b_{n-k} + \tau_{n-k}a_{n-k} \\ \gamma_{n-k}b_{n-k} + \gamma_{n-k}a_{n-k} \end{array} \right),$$

for $k = 1, 2, 3, ..., n - 1,$

and $(\bar{\varphi}_{1} \bar{\varphi}_{1})^{T}$ reduces to

$$\binom{\bar{\varphi}_{1} \bar{\varphi}_{1}}{\bar{\varphi}_{1}} = S^{a} \frac{c}{\pi \pi} \left( R_{T,n} \right),$$

where $R_{T,n}$ is given in (5.7). It follows from (5.9) and (3.14) that $\bar{\sigma}^{*}c - \bar{\varphi}_{1}^{T} \pi = 0$, $\bar{\varphi}_{k}a_{k} - \bar{\varphi}_{k+1}b_{k} - \beta S^{a} h_{k} - \tau_{k} \bar{\varphi}_{k} = 0$, $\bar{\varphi}_{k}b_{k} - \bar{\varphi}_{k+1}b_{k} \gamma_{k} - \beta S^{a} \gamma_{k} \bar{\varphi}_{k} = 0$ for $k = 1, 2, ..., n - 1$, $\bar{\varphi}_{n}a_{n} - \beta S^{a} h_{n} - \tau_{n} \bar{\varphi}_{n} = 0$, and $\bar{\varphi}_{n}b_{n} - \beta S^{a} \gamma_{n} \bar{\varphi}_{n} = 0$.

The derivative of $L$ computed along solution of (2.1) is
\[
\frac{dE}{dt} = \Lambda - \Lambda \frac{S}{S^*} - \mu S + \mu S^* - (1 - \bar{\rho}^*) \beta S \sum_{k=1}^{n} (h_k I_k + e_k T_k) - (\bar{\sigma}^* c - \bar{\sigma}^* \pi) E - \sum_{k=1}^{n-1} (\bar{\phi}^*_k a_k - \bar{\phi}^*_k \rho_k - \beta S^* h_k - \tau_k T_k)
\]

\[
- \sum_{k=1}^{n} (\bar{\phi}^*_k b_k - \bar{\phi}^*_k \gamma_k) T_k - (\bar{\phi}^*_n a_n - \beta S^* h_n - \tau_n T_n) I_n - (\bar{\phi}^*_n b_n - \beta S^* e_n - \phi_n \bar{\mu}_n) T_n - \bar{\sigma}^* \pi \frac{T_k}{t_k}
\]

\[
- \sum_{k=1}^{n} \left( \bar{\phi}^*_k \rho_k T_k + \bar{\phi}^*_k \gamma_k T_k \right) - \sum_{k=2}^{n} \left( \bar{\phi}^*_k \rho_k T_k + \bar{\phi}^*_k \gamma_k T_k \right) - \bar{\sigma}^* E \sum_{k=1}^{n} \left( h_k \frac{S_k}{E} + e_k \frac{T_k}{E} \right),
\]

\[
+ \sum_{k=1}^{n} (\bar{\phi}^*_k a_k + \bar{\phi}^*_k b_k T_k) + \bar{\sigma}^* c E^*.
\]

Define

\[
s = \frac{S}{S^*}, \quad e = \frac{E}{E^*}, \quad i_k = \frac{i_k}{T_k} \quad \text{and} \quad t_k = \frac{T_k}{T_k} \quad \text{for} \quad k = 1, 2, \ldots, n,
\]

\[
T = \Lambda + \mu S^* + \sum_{k=1}^{n} (\bar{\phi}^*_k a_k + \bar{\phi}^*_k b_k T_k) + \bar{\sigma}^* c E^*.
\]

We have

\[
\frac{dE}{dt} = \frac{T}{s} - \frac{A}{s} - \mu S^* s - (1 - \bar{\rho}^*) \beta S^* \sum_{k=1}^{n} (h_k I_k + e_k T_k) - (\bar{\sigma}^* c - \bar{\sigma}^* \pi) E^* e
\]

\[
- \sum_{k=1}^{n} (\bar{\phi}^*_k a_k - \bar{\phi}^*_k \rho_k - \beta S^* h_k - \tau_k T_k) I_k - \sum_{k=1}^{n-1} (\bar{\phi}^*_k b_k - \bar{\phi}^*_k \gamma_k) T_k - (\bar{\phi}^*_n a_n - \beta S^* h_n - \tau_n T_n) I_n
\]

\[
- (\bar{\phi}^*_n b_n - \beta S^* e_n - \phi_n \bar{\mu}_n) T_n - \bar{\phi}^* T_n + \bar{\sigma}^* c E^* t_k - \sum_{k=2}^{n} \left( \bar{\phi}^*_k \rho_k T_k + \bar{\phi}^*_k \gamma_k T_k \right) - \sum_{k=2}^{n} \left( \bar{\phi}^*_k \rho_k T_k + \bar{\phi}^*_k \gamma_k T_k \right) - \bar{\sigma}^* E \sum_{k=1}^{n} \left( h_k \frac{S_k}{E} + e_k \frac{T_k}{E} \right),
\]

\[
= -z \left( s + \frac{1}{s} - 2 \right) - \sum_{k=2}^{n} g_k \left( \frac{1}{s} + \frac{s}{s} + \frac{e}{t_k} + \frac{k}{j} - (k + 2) \right) - g_k \left( \frac{1}{s} + \frac{s}{s} + \frac{e}{t_k} + \frac{k}{j} - (k + 1) - 3 \right)
\]

\[
- \sum_{k=2}^{n} f_k \left( \frac{1}{s} + \frac{s}{s} + \frac{e}{t_k} + \frac{k}{j} - \frac{2}{l} + \frac{2}{l} - (k + 1) \right) - f_k \left( \frac{1}{s} + \frac{s}{s} + \frac{e}{t_k} + \frac{k}{j} - \frac{2}{l} - 4 \right) - \sum_{k=2}^{n} d_k \left( \frac{i_k}{l} + \frac{i_k}{l} - 2 \right)
\]

\[
- \sum_{k=2}^{n} m_k \left( \frac{1}{s} + \frac{s}{s} + \frac{e}{t_k} + \frac{k}{j} - \frac{2}{l} + \frac{2}{l} - (k + 3) \right).
\]

(5.10)

where
\[ z = \mu S^*, \]
\[ d_k = \tilde{\sigma}_k \phi_k T^*_k, \quad \text{for} \quad k = 1, 2, \ldots, n, \]
\[ g_k = \tilde{\sigma}^* \tilde{\epsilon}_k T^*_k, \quad \text{for} \quad k = 1, 2, \ldots, n, \]
\[ m_k = \tilde{\sigma}_k \gamma_{k-1} T^*_{k-1} - \tilde{\sigma}_k \gamma_k T^*_k, \quad \text{for} \quad k = 2, 3, \ldots, n - 1, \]
\[ m_n = \tilde{\sigma}_n \gamma_{n-1} T^*_{n-1}, \]
\[ f_1 = \tilde{\sigma}^* \tilde{\epsilon}_1 T^*_1, \]
\[ f_k = \tilde{\sigma}_k \tau_k T^*_k - d_k > 0, \quad \text{for} \quad k = 2, 3, \ldots, n. \]
\[ \mathcal{C} = 2z + \sum_{k=1}^{n} (2+k)g_k + (3+k)f_k + 2d_k + \sum_{k=2}^{n} (3+k)m_k. \]

hence, from (5.10)–(5.11) and the fact that the arithmetic mean of a list of non-negative real numbers is greater than or equal to the geometric mean of the same list (Steele, 2004), it follows that

\[ 1 = \left( \frac{\frac{1}{3} + \frac{\mu_1 \phi_1}{S^*} + \frac{\mu_2 \phi_2}{S^*}}{3} \right)^\frac{1}{3} \leq \frac{1}{3} \left( \frac{1}{3} + \frac{\mu_1 \phi_1}{S^*} + \frac{\mu_2 \phi_2}{S^*} \right); \]
\[ 1 = \left( \frac{\frac{1}{3} + \frac{\mu_1 \phi_1}{S^*} + \frac{\mu_2 \phi_2}{S^*} + \frac{\mu_3 \phi_3}{S^*}}{3} \right)^\frac{1}{3} \leq \frac{1}{3} \left( \frac{1}{3} + \frac{\mu_1 \phi_1}{S^*} + \frac{\mu_2 \phi_2}{S^*} + \frac{\mu_3 \phi_3}{S^*} \right); \]
\[ 1 = \left( \frac{\frac{1}{3} + \frac{\mu_1 \phi_1}{S^*} + \frac{\mu_2 \phi_2}{S^*} + \sum_{j=2}^{n} \frac{\mu_j \phi_j}{S^*}}{3} \right)^\frac{1}{3} \leq \frac{1}{3} \left( \frac{1}{3} + \frac{\mu_1 \phi_1}{S^*} + \frac{\mu_2 \phi_2}{S^*} + \sum_{j=2}^{n} \frac{\mu_j \phi_j}{S^*} \right); \]

for \( k = 2, \ldots, n \), and \( 1 = \left( \frac{\mu_1 \phi_1}{S^*} \right)^\frac{1}{3} \leq \frac{1}{3} \left( \frac{\mu_1 \phi_1}{S^*} \right), \) for \( k = 1, 2, \ldots, n \), and

\[ \frac{d\mathcal{L}}{dt} \leq 0. \]

Equality holds if and only if \( S = S^* \), \( E/E^* = I_{j-1}/T_{j-1} = I_j/T_j = T_{j-1}/T_j = T_j/T_j' = 1 \) for \( j = 2, 3, \ldots, n \). Using (3.14) and the fact that \( R(t) \) satisfies (2.1), it follows that \( R(t) \to R^* \) as \( t \to \infty \). The largest invariant set of (2.1) contained in \( \{ (S, E, I_1, \ldots, I_n, T_1, \ldots, T_n, R) \in \mathcal{S} : d\mathcal{L}/dt = 0 \} \) is the singleton \( \{ P_1 \} \). By the LaSalle’s Invariance Principle (LaSalle, 1976), it follows that \( P_1 \) is globally stable in the feasible region if \( R_{T,n} > 1 \).

---

**Fig. 7.** Graphs of comparison of deterministic trajectories of solution of system (2.1) and (3.12) for the cases where \( n = 1 \) and \( n = 2 \), with \( R_{T,n} > 1 \).
The global stability of the endemic equilibrium \( \hat{P}_1 \) of system (3.12) without treatment follows immediately from Theorem 5.7 by setting \( \tau_k = 0 \) for all \( k = 1, 2, \ldots, n \). We state the theorem below without proof.

**Corollary 5.8.** The endemic equilibrium \( \hat{P}_1 \) (given in (3.16)) of (3.12) is globally asymptotically stable if \( R_{0,n} > 1 \).

5.2.1. Numerical results verifying the global stability of \( P_1 \) and effect of treatment

Using two infectious stages, we use the same values of parameters given in Table 3 except that we set \( \beta = 0.5 \), \( h = 1.5 \), \( h_2 = 0.5 \), \( \varepsilon_1 = 0.5 \), \( \varepsilon_2 = 0.01 \), \( \mu = 0.0125 \).

Fig. 7(a) shows the comparison of the trajectories of the number of exposed \( (E_n) \), untreated infected \( (I_1n) \) individuals for model (3.12) with trajectories of the number of exposed \( (E) \), untreated infected \( (I_1) \) and treated infected \( (T_1) \) individuals for model (2.1) for the case where \( n = 1 \) and \( R_{T,1} > 1 \). Fig. 7(b) shows the comparison of the trajectories of the number of exposed \( (E_n) \), untreated infected \( (I_1n), (I_2n) \) individuals for model (3.12) with trajectories of the number of exposed \( (E) \), untreated infected \( (I_1), (I_2) \), and treated infected \( (T_1), (T_2) \) individuals for model (2.1) for the case where \( n = 2 \) and \( R_{T,2} > 1 \). It is clear from the graph that the introduction of treatment in the system reduces the number of exposed and infected individuals (that is, \( E < E_n, I_1 < I_1n \) and \( I_2 < I_2n \)) after some days. In this case, \( R_{01} = 1.7397, R_{02} = 1.9549, R_{T1} = 1.5934 \), and \( R_{T2} = 1.7665 \). The endemic equilibrium point for system (3.12) is \( (S^* = 0.5748, E^* = 0.0104, I_1^* = 0.0112, T_1^* = 0.1475) \) for the case \( n = 1 \) and \( (S^* = 0.5115, E^* = 0.0119, I_1^* = 0.0129, T_1^* = 0.0053, \hat{R}^* = 0.1983) \) for the case \( n = 2 \). Likewise, the endemic equilibrium points for system (2.1) for cases \( n = 1 \) and \( n = 2 \) are \( (S^* = 0.6276, E^* = 0.0091, I_1^* = 0.0087, T_1^* = 0.0010, \hat{R}^* = 0.1594) \) and \( (S^* = 0.5661, E^* = 0.0106, I_1^* = 0.0101, T_1^* = 0.0037, \hat{T}_1^* = 0.0012, \hat{T}_2^* = 0.000842, \hat{R}^* = 0.2240) \), respectively. The graph of the solution \( (S(t), E(t), I_1(t), \ldots, I_n(t), T(t)) \) of system (3.12) converges to \( \hat{P}_1 \) as \( t \to \infty \). This confirms Corollary 5.8. Likewise, the graph of the solution \( (S(t), E(t), I_1(t), \ldots, I_n(t), T_1(t), \ldots, T_n(t), R(t)) \) of system (2.1) converges to \( P_1 \) as \( t \to \infty \). This confirms Theorem 5.7.

Fig. 8(a) shows the graph of \( R_{T,1}(\tau, \varphi) \) against \( \tau = \tau_1 \) and \( \varphi = \varphi_1 \). Fig. 8(b) shows the graph of \( R_{T,2}(\tau, \varphi) \) against \( \tau = \tau_1 = \tau_2 \) and \( \varphi = \varphi_1 = \varphi_2 \). The graphs show that for fixed \( \varphi \), as more (less) treatment is introduced into the population, the number of secondary infection \( R_{T,n} \) reduces (increases) until it approaches \( R_{T,n}(R_{0,n}) \), which is the least (highest) number of secondary infection that can be produced by an infected individuals when introduced into susceptible population. This is explained in Subsection 4.1. Also, the number of secondary infection \( R_{T,n} \) increases to \( R_{0,n} \) as individuals drop out of treatment. This is explained in Subsections 4.1 and 4.2.

6. Derivation of stochastic model: effect of fluctuations and stability of disease-free equilibrium

In this section, we study the effect of noise on the transmission rates and infectivities, \( \{\beta h_k, \beta e_k\} \); the treatment rates \( \{\tau_k\} \); the recovery rates \( \{\psi_k\} \) and \( \{\eta_k\} \) in stage \( k \) of untreated and treated individuals, respectively, for \( k = 1, 2, \ldots, n \). We assume the noise/external fluctuations in the system is caused by variability in the number of contacts between infected and susceptible individuals and such random variations can be modeled by a Gaussian white noise (Mendez et al., 2012). We also assume that fluctuations in the treatment rates may be caused by limited availability of drugs or effect of seasonality. This, in turn, causes...
fluctuations in the recovery rates. By allowing these rates to fluctuate about a mean value, we introduce external fluctuations in the model as follows:

\[
\begin{align*}
\begin{cases}
\beta & = \beta + \tilde{\beta}(t), \\
\tau_k & = \tau_k + \tilde{\tau}_k(t), \\
\psi_k & = \psi_k + \tilde{\psi}_k(t), \\
\eta_k & = \eta_k + \tilde{\eta}_k(t), \quad \text{for } k = 1, 2, \ldots, n.
\end{cases}
\end{align*}
\]

(6.1)

where $\tilde{\beta}, \tilde{\tau}_k, \tilde{\psi}_k, \tilde{\eta}_k$ are independent Gaussian noise terms with zero mean, and $\tilde{\beta}, \tilde{\tau}_k, \tilde{\psi}_k, \tilde{\eta}_k$ are the noise intensities, a measure of the amplitude of fluctuations, for $k = 1, 2, \ldots, n$. By substituting (6.1) into (2.1), we get a Langevin equation. The resulting equation is a stochastic differential equation. It is important to be able to interpret and evaluate the noise structure of this equation. The Ito approach on stochastic differential equation depends on Markovian and Martingale properties. These properties do not obey the traditional chain rule. Whereas, the Stratonovich approach obeys the traditional chain rule and allows white noise to be treated as a regular derivative of a Brownian or Wiener process. It has been suggested by several authors like West et al., Wong et al. (West et al., 1979; Wong & Zakai, 1965) that Stratonovich calculus is appropriate for Langevin equations with both internal and external noise. For this reason, by substituting (6.1) into (2.1), we extend the result to the equation on a stochastic model of the form

\[
dS = \left( A - \beta S \sum_{j=1}^{n} (h_jI_j + \varepsilon_jT_j) - \mu S \right) dt - S \sum_{j=1}^{n} (r_jI_j + \bar{r}_jT_j) \ast dC_j(t),
\]

\[
dE = \left( \beta S \sum_{j=1}^{n} (h_jI_j + \varepsilon_jT_j) - (\pi + \mu) E \right) dt + S \sum_{j=1}^{n} (r_jI_j + \bar{r}_jT_j) \ast dC_j(t),
\]

\[
dl_k = (\rho_{k-1}I_{k-1} - (\mu + \tilde{\delta}_k + \rho_k + \tilde{\tau}_k + \tilde{\psi}_kI_k + \tilde{\varphi}_kT_k) - \tilde{\tau}_kI_k) \ast dW_k(t) - \tilde{\varphi}_kI_k \ast dZ_k(t), \quad k = 2, 3, \ldots, n,
\]

\[
dT_k = (\tau_1I_1 - (\mu + \tilde{\beta}_1 + \tau_1 + \tilde{\psi}_1I_1 + \tilde{\varphi}_1T_1)) dt + \tau_1I_1 \ast dW_1(t) - \tilde{\varphi}_1I_1 \ast dZ_1(t),
\]

\[
dR = \left( \sum_{j=1}^{n} (\tilde{\psi}_jI_j + \tilde{\eta}_jT_j) - \mu R \right) dt + \sum_{j=1}^{n} \tilde{\varphi}_jI_j \ast dZ_j(t) + \sum_{j=1}^{n} \tilde{\eta}_jT_j \ast dZ_j(t),
\]

where $\ast$ denotes the Stratonovich integral (Arnold, 1974); $C(t), W_i(t), Z_i(t), Z_i(t)$, $i = 1, 2, \ldots, n$ are standard Wiener process on a filtered probability space $(\Omega, (\mathcal{F}_t)_{t \geq 0}, \mathbb{P})$; the initial process $x(t_0) = (S(t_0), E(t_0), I_1(t_0), \ldots, I_n(t_0), T_1(t_0), \ldots, T_n(t_0), R(t_0))$ is $\mathcal{F}_{t_0}$ measurable and independent of $C(t) - C(t_0), W_i(t) - W_i(t_0), Z_i(t) - Z_i(t_0)$ and $Z_i(t) - Z_i(t_0)$, $i = 1, 2, \ldots, n$.

The Stratonovich dynamic model (6.2) is converted to its Ito’s equivalent (stated below) using the Stratonovich-Itô conversion theorem given in Bernardi et al. (Bernardi, Madday, Blowey, Coleman, & Craig, 2001) and Kloeden et al. (Kloeden & Platen, 1995).

**Theorem 6.1.** The Ito stochastic differential equation having the same solution as the $2n + 3$-dimensional Stratonovich stochastic differential equation (6.2) is given by
\[
\begin{align*}
    dS &= \left( A - \beta S \sum_{j=1}^{n} (h_j I_j + e T_j) - \mu S + \frac{1}{2} S \sum_{j=1}^{n} (\sigma_{ij} + \bar{\sigma}_{ij})^2 \right) dt - S \sum_{j=1}^{n} (\sigma_{ij} + \bar{\sigma}_{ij}) dC_j(t), \\
    dE &= \left( \beta S \sum_{j=1}^{n} (h_j I_j + e T_j) - (\pi + \mu) E - \frac{1}{2} S \sum_{j=1}^{n} (\sigma_{ij} + \bar{\sigma}_{ij})^2 \right) + S \sum_{j=1}^{n} (\sigma_{ij} + \bar{\sigma}_{ij}) dC_j(t), \\
    dl_1 &= \left( \pi E - a_1 l_1 + \varphi_1 T_1 + \frac{1}{2} \left( \tau_1^2 + \bar{\tau}_1^2 \right) I_1 \right) dt - \tau_1 l_1 dW_1(t) - \chi_l l_1 dZ_1(t), \\
    dl_k &= \left( \rho_{k-1} l_{k-1} - a_k l_k + \varphi_k T_k + \frac{1}{2} \left( \tau_k^2 + \bar{\tau}_k^2 \right) k \right) dt - \tau_k l_k dW_k(t) - \chi_k l_k dZ_k(t), \\
    dT_1 &= \left( \tau_1 l_1 - b_1 T_1 + \frac{1}{2} \left( - \tau_1^2 l_1 + \bar{\tau}_1^2 T_1 \right) \right) dt + \tau_1 l_1 dW_1(t) - \eta_1 T_1 dZ_1(t), \\
    dT_k &= \left( \tau_k l_k + \gamma_{k-1} l_{k-1} - b_k T_k + \frac{1}{2} \left( - \tau_k^2 l_k + \bar{\tau}_k^2 T_k \right) \right) dt + \tau_k l_k dW_k(t) - \eta_k T_k dZ_k(t), \quad k = 2, 3, \ldots, n, \\
    dR &= \left( \sum_{j=1}^{n} (\psi_{ij} I_j + \eta_j T_j) - \mu R - \frac{1}{2} \sum_{j=1}^{n} (\psi_{ij}^2 I_j + \bar{\psi}_{ij}^2 T_j) \right) dt + \sum_{j=1}^{n} (\psi_{ij} I_j dZ_j(t) + \bar{\psi}_{ij} T_j dZ_j(t)).
\end{align*}
\]

\[ (6.3) \]

Proof. The proof follows using the Stratonovich-Itô conversion theorem given in Bernardi et al. (Bernardi et al., 2001) and Kloeden et al. (Kloeden & Platen, 1995).

Following similar approach presented in Otunuga (Otunuga, 2018), we can show, using the function \( V(t, x) = \ln(S + E + \sum_{j=1}^{n} (I_j + T_j) + R + e^x), \) that \( \mathbb{I}V < V \) and \( \inf_{|x| > M} V(t, x) \to \infty, \) as \( M \to \infty, \) where \( \mathbb{I} \) is a differential operator called the \( \mathbb{I}- \) operator defined by

\[
\mathbb{I}V(t, u) = \frac{\partial V(t, u)}{\partial t} + \frac{\partial V(t, u)}{\partial u} A + \frac{1}{2} \text{trace} \left[ B + \frac{\partial^2 V(t, u)}{\partial u^2} B \right],
\]

where \( \frac{\partial V(t, u)}{\partial u} = \left( \frac{\partial V(t, u)}{\partial u_1}, \ldots, \frac{\partial V(t, u)}{\partial u_n} \right) \) and \( \frac{\partial^2 V(t, u)}{\partial u^2} = \left( \frac{\partial^2 V(t, u)}{\partial u_i \partial u_j} \right)_{2n \times 2n}. \) It follows from Theorem 3.5 of Khasminskii (Rafail, 2012) that there exists a solution \( x(t) = (S(t), E(t), I_1(t), \ldots, I_n(t), T_1(t), \ldots, T_n(t), R(t)) \) of (6.3) which is almost surely continuous stochastic process and is unique up to equivalence if \( x(t_0) \in \mathcal{F} \) is independent of the processes \( C_j(t) - C_j(t_0), W_i(t) - W_i(t_0), Z_i(t) - Z_i(t_0), \) \( i = 1, 2, \ldots, n. \) The solution described above can be shown to be nonnegative and in the feasible region \( \mathcal{F} \) using a similar idea presented in (Yang & Mao, 2013).

6.1. Equilibrium points and basic reproduction number in the presence of noise

The point \( P_0 \) defined in (3.1)–(3.2) is also the disease-free equilibrium of system (6.3). We calculate an equivalent of \( R_{\mathcal{T}, n} \) in (3.6), denoted by \( R_{\mathcal{T}, n} \) and derive threshold under which system (6.3) becomes disease-free on the long run. We first linearize the non-linear stochastic system about the disease-free system and study the solution of the linear system.

Define \( \Psi = (S - R \ E \ I_1 \ldots I_n \ T_1 \ldots T_n \ R)^T. \) The linearization of (6.3) about the disease-free equilibrium \( P_0 \) results in

\[
    d \Psi = \mathcal{A} \Psi dt + \sum_{i=1}^{n} \left( C_i dC_i(t) + \overline{C}_i dW_i(t) + H_i dZ_i(t) + \overline{H}_i dZ_i(t) \right) \Psi,
\]

where \( \mathcal{A} = \begin{pmatrix} \mathcal{A}_{11} & \mathcal{A}_{12} & \mathcal{A}_{13} & \mathcal{A}_{14} \\ \mathcal{A}_{21} & \mathcal{A}_{22} & \mathcal{A}_{23} & \mathcal{A}_{24} \\ \mathcal{A}_{31} & \mathcal{A}_{32} & \mathcal{A}_{33} & \mathcal{A}_{34} \\ \mathcal{A}_{41} & \mathcal{A}_{42} & \mathcal{A}_{43} & \mathcal{A}_{44} \end{pmatrix} \) with \( \mathcal{A}_{11} = A_{11}, \mathcal{A}_{12} = A_{12}, \mathcal{A}_{13} = A_{13}, \mathcal{A}_{14} = A_{14}, \mathcal{A}_{21} = A_{21}, \mathcal{A}_{23} = A_{23}, \mathcal{A}_{24} = A_{24}, \mathcal{A}_{31} = A_{31}, \mathcal{A}_{34} = A_{34}, \mathcal{A}_{41} = A_{41} \) and \( \mathcal{A}_{44} = A_{44} \) defined in (5.1).
\[
\mathcal{A}_2 = -\begin{pmatrix}
\alpha_1 - \frac{\tau_1^2 + \psi_1^2}{2} & 0 & 0 & 0 & \cdots & 0 & 0 \\
-\rho_1 & \alpha_2 - \frac{\tau_2^2 + \psi_2^2}{2} & 0 & 0 & \cdots & 0 & 0 \\
0 & -\rho_2 & \alpha_3 - \frac{\tau_3^2 + \psi_3^2}{2} & 0 & \cdots & 0 & 0 \\
\vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\
0 & 0 & \cdots & \cdots & \cdots & 0 & -\rho_{n-1} \\
0 & 0 & \cdots & \cdots & \cdots & 0 & \alpha_n - \frac{\tau_n^2 + \psi_n^2}{2}
\end{pmatrix}
\]

\[
\mathcal{A}_3 = -\begin{pmatrix}
\beta_1 - \frac{\eta_1^2}{2} & 0 & 0 & 0 & \cdots & 0 & 0 \\
-\gamma_1 & \beta_2 - \frac{\eta_2^2}{2} & 0 & 0 & \cdots & 0 & 0 \\
0 & -\gamma_2 & \beta_3 - \frac{\eta_3^2}{2} & 0 & \cdots & 0 & 0 \\
\vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\
0 & 0 & \cdots & \cdots & \cdots & 0 & -\gamma_{n-1} \\
0 & 0 & \cdots & \cdots & \cdots & 0 & \beta_n - \frac{\eta_n^2}{2}
\end{pmatrix}
\]

\[
\mathcal{A}_3 = \mathcal{A} - \mathbf{1} \mathbf{1}^T, \quad \mathcal{A}_2 = \mathcal{A} - \mathbf{2} \mathbf{2}^T, \quad \mathcal{A}_3 = \mathcal{A} - \mathbf{3} \mathbf{3}^T
\]

where

\[
\mathcal{A} = \max(\mathcal{A}), \quad \mathbf{1} = \begin{pmatrix} 1 & 1 & \cdots & 1 \end{pmatrix}, \quad \mathbf{2} = \begin{pmatrix} 2 & 2 & \cdots & 2 \end{pmatrix}, \quad \mathbf{3} = \begin{pmatrix} 3 & 3 & \cdots & 3 \end{pmatrix}
\]

The characteristic polynomial of \( \mathcal{A} \) can be expressed as

\[
\det(\mathcal{A} - \lambda I) = - (\tau + \mu) \det(\mathcal{A} - \lambda I_{2n-2}).
\]

where \( \tau \) is the matrix obtained by deleting the first row and column of \( \mathcal{A} \) in (6.5), and \( \tau \) is the eigenvalue.

Using the idea presented in Mendez et al. (Mendez et al., 2012) and in Section 3.1.1, we calculate the reproduction number \( R_{2n,n} \) with respect to the deterministic model (6.6) in the presence of treatment as

\[
R_{2n,n} = \frac{\pi \beta \pi}{c} \sum_{k=1}^{n} \frac{\delta_k h_k + \epsilon_k \psi_k}{\prod_{j=1}^{k} (\hat{\delta}_j - \hat{\gamma}_j \hat{\gamma}_j)}
\]

where
\[ \tilde{\alpha}_j = a_j - \frac{\tau_j^2}{2} \]
\[ \tilde{\beta}_j = b_j - \frac{\eta_j^2}{2} \]
\[ \tilde{\tau}_j = \tau_j - \frac{\eta_j^2}{2} \]

\[ \tilde{u}_k = \tilde{\beta}_k p_{k-1} \tilde{u}_{k-1} + \varphi_k \gamma_{k-1} \tilde{v}_{k-1}, \]
\[ \tilde{v}_k = \tilde{\tau}_k p_{k-1} \tilde{u}_{k-1} + \tilde{\alpha}_k \gamma_{k-1} \tilde{v}_{k-1}, \quad \text{for } k = 1, \ldots, n. \]

with \( \tilde{u}_0 = 1, \tilde{v}_0 = 0 \). We note here that the threshold \( \mathcal{R}_{T,n} \) is nonnegative provided

\[ \tilde{\tau}_j \geq 0, \quad \tilde{\eta}_j = \eta_j - \frac{\eta_j^2}{2} \geq 0, \quad \tilde{\psi}_j = \psi_j - \frac{\psi_j^2}{2} / 2 \geq 0. \] (6.9)

For the rest of this work, we assume condition (6.9) is satisfied.

**Remark 6.1.1.** We note here that the number \( \mathcal{R}_{T,n} \) reduces to \( R_{T,n} \) if \( \eta_j = \tilde{\eta}_j = \tilde{\psi}_j = 0 \) for all \( j = 1, 2, \ldots, n \).

**Remark 6.1.2.** Condition (6.9) indicates that the noise intensities \( \tau_j, \tilde{\eta}_j \) and \( \tilde{\psi}_j \) must not exceed the rates \( \sqrt{2\tau_j}, \sqrt{2\tilde{\eta}_j} \) and \( \sqrt{2\tilde{\psi}_j} \), respectively, for the model to be well defined.

6.2. Effect of noise in the treatment, and recovery rates

In this section, we study the effect of fluctuations in the treatment and recovery rates.

6.2.1. Effect of noise in the treatment rates

Assuming condition (6.9) is satisfied, and \( \tilde{\eta}_j = \tilde{\psi}_j = 0 \) for \( j = 1, 2, \ldots, n \), we wish to study how the number of infection changes due to changes in the treatment intensity rates \( \{\tilde{\tau}_j\} \). Define \( R_{T,n} = R_{T,n}(\tau_i) \) (given in (3.6)) and \( \mathcal{R}_{T,n} = \mathcal{R}_{T,n}(\tau_i) \). It is easy to show that \( R_{T,j}(\tau_i - \tau_j^2 / 2) = \mathcal{R}_{T,j}(\tau_i) \). As discussed in Subsection 4.1, the derivative \( \frac{\partial R_{T,j}}{\partial \eta_i} < 0 \) if and only if \( R_{T,j}(\tau_i \rightarrow \infty) \leq R_{T,j}(\tau_i = 0) \) for \( 1 \leq i \leq j \leq n \), that is, \( R_{T,j}(\tau_i) \) is a decreasing function of \( \tau_i \) if and only if \( R_{T,j}(\tau_i \rightarrow \infty) \leq R_{T,j}(\tau_i = 0) \), for \( 1 \leq i \leq j \leq n \).

It follows that \( R_{T,j}(\tau_i) \leq \mathcal{R}_{T,j}(\tau_i) \) provided \( R_{T,j}(\tau_i \rightarrow \infty) \leq R_{T,j}(\tau_i = 0) \), for \( 1 \leq i \leq j \leq n \). The same result follows for the case where \( \tau_i \equiv \tau \) for all \( i = 1, 2, \ldots, n \), that is, \( R_{T,n}(\tau) \leq \mathcal{R}_{T,n}(\tau) \equiv \mathcal{R}_{T,n}(\tau) \equiv R_{T,n} \). An increase in the noise intensity in the treatment rate increases the number of secondary infection cases produced by a typical infective individual.

6.2.2. Effect of noise in the recovery rates of untreated infected individual

Assuming condition (6.9) is satisfied, and \( \tilde{\eta}_j = \tilde{\psi}_j = 0 \) for \( j = 1, 2, \ldots, n \). We wish to study how the number of infection changes due to changes in the untreated recovery intensity rates \( \{\tilde{\psi}_j\} \) of infected individual. Write \( \mathcal{R}_{T,n} = \mathcal{R}_{T,n}(\tilde{\psi}_j) \) as a function of \( \tilde{\psi}_j \). Since the functions \( g_j(t) = \tilde{\psi}_j t - \frac{\tilde{\psi}_j^2}{2} - \tilde{\psi}_j \) and \( g_j(t) = \tilde{\psi}_j t^2 - \frac{\tilde{\psi}_j^2}{2} - \tilde{\psi}_j \) are increasing functions of \( t \) for \( j = 1, 2, \ldots, n \), and \( \mathcal{R}_{T,n}(\tilde{\psi}_j, \ldots, \tilde{\psi}_n) \) can be expressed in terms of \( g_j(\tilde{\psi}_j) \) and \( g_j(\tilde{\psi}_j) \), it follows from the increasing property of \( g_j(\tilde{\psi}_j) \) that \( \mathcal{R}_{T,n}(\tilde{\psi}_j, \ldots, \tilde{\psi}_n) \geq \mathcal{R}_{T,n}(0, 0, \ldots, 0) = R_{T,n} \). The higher the noise intensity in the untreated infected recovery rates, the higher the number of secondary infection cases produced by a typical infective individual.

6.2.3. Effect of noise in the recovery rates of treated infected individual

Assuming condition (6.9) is satisfied and \( \tilde{\eta}_j = \tilde{\psi}_j = 0 \) for \( j = 1, 2, \ldots, n \). By writing \( \mathcal{R}_{T,n} = \mathcal{R}_{T,n}(\tilde{\eta}_j, \ldots, \tilde{\eta}_n) \) as a function of \( \tilde{\eta}_j \), we wish to show that \( \mathcal{R}_{T,n} \geq \mathcal{R}_{T,n}(0, \ldots, 0) = R_{T,n} \). Since the functions \( \frac{1}{a_j + b_j \tilde{\eta}_j + \tilde{\eta}_j^2} - \tilde{\tau}_j \) and \( \frac{1}{\tilde{\tau}_j + a_j \tilde{\eta}_j + \tilde{\eta}_j^2} - \tilde{\tau}_j \) are increasing function of \( \tilde{\eta}_j \) for \( j = 1, 2, \ldots, n \), it follows that \( \mathcal{R}_{T,n}(\tilde{\eta}_j, \ldots, \tilde{\eta}_n) \geq \mathcal{R}_{T,n}(0, 0, \ldots, 0) = R_{T,n} \), that is, as the noise intensity in the recovery rate \( \tilde{\eta}_j \) of treated infected individuals increases, the number of secondary infection cases produced by a typical infective individual increases.
6.2.4. Numerical analysis

We use the parameters presented in Table 3 to verify the results claimed in Subsubsections 6.2.1-6.2.3. Fig. 9 (a), (b) and (c) show the graphs of $R_{T,2} \equiv R_{T,2}(\bar{\tau})$, $R_{T,2} \equiv R_{T,2}(\bar{\psi})$ and $R_{T,2} \equiv R_{T,2}(\bar{\eta})$ against $\bar{\tau}$ (fixing $\bar{\psi} = \bar{\eta} = 0$), $\bar{\psi}$ (fixing $\bar{\tau} = \bar{\eta} = 0$) and $\bar{\eta}$ (fixing $\bar{\tau} = \bar{\psi} = 0$), respectively. Fig. 9 (d) shows the graph of $R_{T,2} \equiv R_{T,2}(\bar{\tau}, \bar{\psi})$ against $\bar{\tau}$ and $\bar{\psi}$. The trajectories of these graphs suggest that the higher the intensity of noise in the treatment rate, recovery rates of untreated and treated infected individuals, the higher the number of secondary infections produced by an infected individuals when introduced into a susceptible population.

Fig. 10 (a) and (b) show the graphs of $R_{T,2} \equiv R_{T,2}(\bar{\tau}, \bar{\eta})$ against $\bar{\tau}$ and $\bar{\eta}$ and $R_{T,2} \equiv R_{T,2}(\bar{\psi}, \bar{\eta})$ against $\bar{\psi}$ and $\bar{\eta}$. The trajectories of these graphs suggests that the higher the intensity of noise in the treatment rate, recovery rates of untreated and treated infected individuals, the higher the number of secondary infections produced by an infected individuals when introduced into a susceptible population.

6.3. Stability of infection-free equilibrium $P_0$ of (6.3)

In this section, we discuss conditions for stability of the infection-free equilibrium $P_0$ of (6.3) in the presence of noise. We study the conditions for stochastic stability of the disease-free equilibrium $P_0$ of the linear associated system (6.5) and later use Theorem A.2 in (Tornatore et al., 2005) to extend the result to that of the nonlinear system (6.3).

**Theorem 6.2.** Assume condition (6.9) is satisfied. The real part of all eigenvalues of $\mathcal{A}$ is negative if $R_{T,2} < 1$.

---

**Fig. 9.** Effect of noise on treatment rates and recovery rates of untreated and treated infected individuals for the case $n = 2$. 

---
Plot of reproduction number $R_{T2}(\tau, \eta)$ against $\tau$ and $\eta$

Plot of reproduction number $R_{T2}(\psi, \eta)$ against $\psi$ and $\eta$

Fig. 10. Effect of noise on treatment rates and recovery rates of untreated and treated infected individuals for the case $n = 2$.

Proof. The proof follows from (6.9) and Theorem 5.1 by setting $a_j \equiv a_j - \frac{\tau_j^2 + \psi_j^2}{2}$, $b_j \equiv b_j - \frac{\mu_j}{2}$, $\tau_j \equiv \tau_j - \frac{\tau_j^2}{2}$, $\psi_j \equiv \psi_j - \frac{\mu_j}{2}$, and $\eta_j \equiv \eta_j - \frac{\mu_j}{2}$ into matrix $A$ in (5.1).

Writing the system of non-linear stochastic differential equation (6.3) in terms of $\Psi$ reduces to

$$
\begin{align*}
\frac{d\Psi_1}{dt} &= \left( -\beta(\Psi_1 + \kappa) \sum_{j=1}^{n} (h_j \Psi_{j+2} + e_j \Psi_{n+j-2}) - \mu \Psi_1 + \frac{1}{2} (\Psi_1 + \kappa) \sum_{j=1}^{n} (\sigma_j \Psi_{j+2} + \sigma_j \Psi_{n+j-2})^2 \right) dt \\
&\quad - (\Psi_1 + \kappa) \sum_{j=1}^{n} (\sigma_j \Psi_{j+2} + \sigma_j \Psi_{n+j-2}) dC_j(t),
\end{align*}
$$

$$
\frac{d\Psi_2}{dt} = \left( \beta(\Psi_1 + \kappa) \sum_{j=1}^{n} (h_j \Psi_{j+2} + e_j \Psi_{n+j-2}) - c \Psi_2 - \frac{1}{2} (\Psi_1 + \kappa) \sum_{j=1}^{n} (\sigma_j \Psi_{j+2} + \sigma_j \Psi_{n+j-2})^2 \right) dt \\
&\quad + (\Psi_1 + \kappa) \sum_{j=1}^{n} (\sigma_j \Psi_{j+2} + \sigma_j \Psi_{n+j-2}) dC_j(t),
$$

$$
\begin{align*}
\frac{d\Psi_3}{dt} &= \left( \sigma_k \Psi_2 - a_1 \Psi_3 + \Psi_1 \Psi_{n+3} + \frac{1}{2} (\tau_1^2 + \psi_1^2) \right) dt - \tau_1 \Psi_3 dW_1(t) - \psi_1 \Psi_3 dZ_1(t),
\end{align*}
$$

$$
\begin{align*}
\frac{d\Psi_{k+2}}{dt} &= \left( \rho_{k-1} \Psi_{k+1} - a_k \Psi_{k+2} + \Psi_k \Psi_{n+k+2} + \frac{1}{2} (\tau_k^2 + \psi_k^2) \right) dt - \tau_k \Psi_{k+2} dW_k(t) - \psi_k \Psi_{k+2} dZ_k(t),
\end{align*}
$$

for $k = 2, \cdots, n$.

where $a_k$ and $b_k$ are defined in (3.3).
Let $F$ and $G$ be the drift and diffusion coefficients of the linear system (6.5), respectively, and $f$ and $g$ the drift and diffusion coefficients of the nonlinear system (6.10), respectively. We give a theorem concerning the global stability of the disease-free equilibrium point $P_0$ by showing that Theorems A.1 and A.2 of Tornatore et al., (2005) is satisfied with respect to systems (6.5) and (6.10).

**Theorem 6.3.** The disease-free equilibrium $P_0$ of the system (6.3) is globally asymptotically stable in the feasible region $\mathcal{F}$ if $\mathcal{R}_{T,n} < 1$.

To prove this, we first show that if $\mathcal{R}_{T,n} < 1$, the trivial solution $\Psi = 0$ of the linear stochastic differential equation (6.5) is asymptotically stable and later show that the drift and diffusion coefficients $f(t, \Psi)$ and $g(t, \Psi)$, respectively, of the nonlinear system (6.10) satisfy the inequality

$$
\|f(t, \Psi) - F(t, \Psi)\| + \|g(t, \Psi) - G(t, \Psi)\| < \xi \|\Psi\|
$$

(6.11) in a sufficiently small neighbourhood of $\Psi = 0$, with a sufficiently small constant $\xi$.

Proof. If $\mathcal{R}_{T,n} < 1$, it follows from Theorem 6.2 that the real part of all eigenvalues of $\mathcal{A}$ is negative. Hence, there exist a diagonal matrix $\Gamma$ (with positive diagonal entries, say, $r_1, r_2, \cdots, r_{2n+3}$) and a real number $\tilde{z} > 0$ such that $\mathcal{A} = (\Gamma \mathcal{A} + \Gamma^T \mathcal{A}) \mathcal{Y} \leq -\tilde{z} s^T s$ for every nonzero vector $s \in \mathbb{R}^{2n+3}$ (see relation $I_2$ of (Plemmons, 1977)). Let $\Psi = (\Psi_1, \Psi_2, \cdots, \Psi_{2n+3})^T$ be a vector satisfying the linear system (6.5) and define $V : [0, T] \times \mathbb{R}^{2n+3} \rightarrow \mathbb{R}^+$ by

$$
V(t, \Psi) = \Psi^T \Gamma \Psi.
$$

Let $\tilde{z} = \max_{1 \leq j \leq n} \{\sigma_j^2, \sigma_j^2, r_j, \sigma_j^2, \sigma_j^2\}$ such that $r_1 = r_2 = \frac{\tilde{z}}{10\kappa}, r_{2j+2} = r_{2j+3} = \frac{\tilde{z}}{10\kappa}$, for $j = 1, 2, \cdots, n$. Using (6.4), the $L$-operator defined in (6.4) satisfies

$$
\begin{align*}
\mathcal{L}V(t, \Psi) &= \Psi^T (\mathcal{Y} \mathcal{A} + \mathcal{A}^T \mathcal{Y}) \Psi + \Psi^T \sum_{i=1}^{n}\left(\mathcal{G}_i^T \mathcal{Y} \mathcal{G}_i + \mathcal{G}_i^T \mathcal{Y} \mathcal{G}_i + \mathcal{H}_i^T \mathcal{Y} \mathcal{H}_i + \mathcal{H}_i^T \mathcal{Y} \mathcal{H}_i\right) \Psi \\
&\leq -2\Psi^T \Psi + \Psi^T \sum_{i=1}^{n}\left(\mathcal{G}_i^T \mathcal{Y} \mathcal{G}_i + \mathcal{G}_i^T \mathcal{Y} \mathcal{G}_i + \mathcal{H}_i^T \mathcal{Y} \mathcal{H}_i + \mathcal{H}_i^T \mathcal{Y} \mathcal{H}_i\right) \Psi \\
&= -2\sum_{j=1}^{2n+3} \Psi_j^2 + \sum_{j=1}^{n} \left((r_1 + r_2)\kappa^2 \sigma_j^2 + (r_{2j+2} + r_{2j+3})\sigma_j^2 + r_{2j+3}\sigma_j^2\right) \Psi_{j+1}^2 \\
&+ \sum_{j=1}^{n} \left((r_1 + r_2)\kappa^2 \sigma_j^2 + r_{2j+2}\sigma_j^2 + (r_{2n+3} + r_{2n+3})\sigma_j^2\right) \Psi_{j+n+2}^2 \\
&\leq -2\sum_{j=1}^{2n+3} \Psi_j^2 + \frac{\tilde{z}}{2} \sum_{j=1}^{n} \Psi_j^2 + \frac{\tilde{z}}{2} \sum_{j=1}^{n} \Psi_{j+2}^2 + \frac{\tilde{z}}{2} \sum_{j=1}^{n} \Psi_{j+n+2}^2 < -2\Psi^T \Psi.
\end{align*}
$$

Let $r_1$ and $r_n$ be $\min\{r_1, \cdots, r_{2n+3}\}$ and $\max\{r_1, \cdots, r_{2n+3}\}$, respectively. Then $\eta_0 \|\Psi\|^2 \leq V(t, \Psi) \leq \eta_0 \|\Psi\|^2$. It follows from Theorem A.1 of Tornatore et al., (2005) that the trivial solution $\Psi = 0$ of (6.5) is asymptotically stable. We deduce from this result that if the initial condition (in $\mathcal{F}$) of system (6.5) is near 0, then the solution $(S(t), E(t), I_1(t), \cdots, I_n(t), T_1(t), \cdots, T_n(t), R(t))$ approaches $P_0$ on the long run if $\mathcal{R}_{T,n} < 1$. To prove the global stability of the solution $\Psi = 0$ of (6.10) (equivalent to the disease-free equilibrium $P_0$ of (6.3)), we choose $\tilde{z} > 0$ sufficiently small in a neighbourhood of $\Psi = 0$ so that $\|\Psi\| < \xi$ and $|f(t, \Psi) - F(t, \Psi)| + |g(t, \Psi) - G(t, \Psi)|$ reduces to

$$
\begin{align*}
&\sqrt{2\left(\beta \Psi_1 \sum_{j=1}^{n} \left(h_j \Psi_{j+2} + e_j \Psi_{n+j+2}\right) - \frac{1}{2} \left(\sigma_j \Psi_{j+2} + \sigma_j \Psi_{n+j+2}\right)\right)^2 + \sqrt{2\Psi_1^2 \left(\sum_{j=1}^{n} \left(\sigma_j \Psi_{j+2} + \sigma_j \Psi_{n+j+2}\right)\right)^2}} \\
&\leq \sqrt{2\left(\Psi_1^2 \left(\frac{1}{2} \sum_{j=1}^{n} \beta (h_j^2 + e_j^2) + (\sigma_j^2 + \sigma_j^2)\right) + \frac{1}{2} \left(\xi + \kappa\right) \sum_{j=1}^{n} \left(\sigma_j \Psi_{j+2}^2 + \sigma_j \Psi_{n+j+2}^2\right) + \frac{1}{2} \left(\beta + 1\right) \sum_{j=1}^{n} \left(\Psi_{j+2}^2 + \Psi_{n+j+2}^2\right)\right)}
\end{align*}
$$

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Plot of $E$, $I_1$, $T_1$: Case $R_{T1} < 1$

Plot of $E$, $I_2$, $T_1$, $T_2$: Case $R_{T2} < 1$

Fig. 11. Graphs of stochastic trajectories of solution of system (6.3) for the cases where $n = 1$ and $n = 2$, respectively, and $\mathcal{R}_T < 1$.

$$\frac{\bar{n}}{n} \leq \frac{\bar{E}}{E},$$

where $\bar{n} = \bar{\xi} \sqrt{2} \max\left\{ 1 \sum_{j=1}^{n} \beta \left( h_i^2 + \nu_i^2 \right) + \left( \sigma_j^2 + \tau_j^2 \right), \beta + 1, (\bar{\xi} + \bar{\tau}) \sigma_j, (\bar{\xi} + \bar{\tau}) \tau_j \right\}$ The global stability result follows from Theorem A.2 of (Tornatore et al., Vetro).

6.4. Numerical verification of global stability of infection-free equilibrium points for the stochastic model

Fig. 11 (a) shows the trajectories of $E$, $I_1$ and $T_1$ satisfying model (6.3) for the case where $n = 1$ and $\mathcal{R}_T < 1$. Fig. 11 (b) shows the trajectory of $E$, $I_2$, $T_1$, $T_2$ satisfying model (6.3) for the case where $n = 2$ and $\mathcal{R}_T < 1$. In this case, $\mathcal{R}_T = 0.8056$ and $\mathcal{R}_T = 0.8908$.

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