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Modeling and analysis of the transmission dynamics of tuberculosis without and with seasonality

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Abstract A deterministic model of tuberculosis without and with seasonality is designed and analyzed into its transmission dynamics. We first present and analyze a tuberculosis model without seasonality, which incorporates the essential biological and epidemiological features of the disease. The model is shown to exhibit the phenomenon of backward bifurcation, where a stable disease-free equilibrium coexists with one or more stable endemic equilibria when the associated basic reproduction number is less than unity. The statistical data of tuberculosis (TB) cases show seasonal fluctuations in many countries. Then, the extension of our TB model by incorporating seasonality is developed and the basic reproduction ratio is defined. Parameter values of the model are estimated according to demographic and epidemiological data in Cameroon. The simulation results are in good accordance with the seasonal variation of the reported cases of active TB in Cameroon.

Keywords Tuberculosis · Mathematical models · Backward bifurcation · Stability · Seasonal pattern

1 Introduction

The global burden of tuberculosis (TB) has increased over the past two decades, despite widespread implementation of control measures including BCG vaccination and the World Health Organization's DOTS strategy which focuses on case finding and short-course chemotherapy [1]. This rise has been attributed to the spread of HIV, the collapse of public health programs and the emergence of drug-resistant strains of *Mycobacterium tuberculosis*. At present, about 95% of the estimated 8 million new cases of tuberculosis (TB) occurring each year are in developing countries, where 80% occur among people between the ages of 15–59 years [2]. In Sub-Saharan Africa, TB is the leading cause of mortality, and in developing countries it accounts for an estimated 2 million deaths which accounts for a quarter of avoidable adult deaths [3]. TB was assumed to be on its way out in developed countries until the number of TB cases began to increase in the 1980s. With this return, we face the paradox of well-known bacteria, fully treatable with efficient and

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affordable drugs according to internationally recommended guidelines, which yet cause increasing human suffering and death. As the world is experiencing the devastating effects of HIV/AIDS epidemic, it is now necessary to ask why we have so far failed to control TB and define the limits of the global TB control programs [4]. Currently, half of the people living with HIV are TB co-infected and three quarters of all dually infected people live in Sub-Saharan Africa [5]. Another issue that is essential to the epidemiology of TB is the exogenous reinfection, where a latently infected individual acquires a new infection from another infectious (see [6, 7] and references therein).

Although TB is not widely recognized as having seasonal trends like measles, diphtheria, chickenpox, cholera, rotavirus, malaria, and even sexually transmitted gonorrhea [8, 9], some studies have shown variable periods of peak seasonality in TB incidence rates in late winter to early spring in South Africa [10], during summer in UK [11] and Hong Kong [12], during summer and autumn in Spain [13], and during spring and summer in Japan [14]. In northern India, it was indicated that TB diagnosis peaked between April and June, and reached a nadir between October and December, and magnitude of seasonal variation had important positive correlation with rates of new smear-positive TB cases [15]. Quite recently, it was demonstrated that there was a spring peak (late April) in TB cases detected among migrant workers entering Kuwait from high TB burden countries [16]. Liu et al. [17] have developed a TB model that incorporates seasonality and found that there is a seasonal pattern of new TB cases, and the number of new TB cases peak in late spring to early summer, and reach a nadir in late winter and early spring in the mainland of China.

The real causes of seasonal patterns of TB remain unknown, but the seasonal trend, with higher incidence rate in winter, may be relevant to the increased periods spent in overcrowded, poorly ventilated housing conditions, these phenomena much more easily seen than in warm seasons [10, 13], and/or vitamin D deficiency leading to reactivation of latent/exposed infection, which may have been the basic causes for observed TB seasonality [15, 18]. Furthermore, in winter and spring, the viral infections like flu are more frequent and cause immunological deficiency leading to reactivation of the *M. Tuberculosis* [13]. There is a growing awareness that seasonality can cause population fluctuations ranging from annual cycles to multi-year oscillations, and even chaotic dynamics [19, 20]. From an applied perspective, clarifying the mechanisms that link seasonal environmental changes to diseases dynamics may aid in forecasting the long-term health risks, in developing an effective public health program, and in setting objectives and utilizing limited resources more effectively [13, 21]. For these reasons, we need to identify possible seasonal patterns in the incidence rate for pulmonary tuberculosis.

It is worth emphasizing that mathematical analysis of biomedical and disease transmission models can contribute to the understanding of the mechanisms of those processes and to design potential therapies (see [22–26] and references therein). A number of theoretical studies have been carried out on the mathematical modeling of TB transmission dynamics [27–38].

The purpose of the current study is to complement and extend the aforementioned studies, by designing and qualitatively analyzing a new and more comprehensive deterministic model for gaining insights into the transmission dynamics and control of TB in a population. However, to our knowledge, no studies so for have described TB seasonality in Cameroon. But from the quarterly reported data (2003–2007) of the National Committee to Fight against Tuberculosis [39] there is also a seasonal pattern in new TB cases.

The rest of the paper is organized as follows. In Sect. 2, a model without seasonality for the dynamics of TB is formulated and rigorously analyzed. Section 3 extends the model formulated in Sect. 2 to describe seasonal incidence rate by incorporating periodic coefficients. Numerical results are presented to illustrate analytical results. Finally, Sect. 4 contains discussions and conclusion.

2 The model

2.1 Model construction

In this section, we process to the construction of a mathematical model for the spread of tuberculosis that incorporates constant recruitment, slow or fast progression, effective chemoprophylaxis, diagnostic and treatment of infectious and exogenous reinfections. Based on epidemiological status, the simplest models include classes of susceptible, infected and infective individuals, and hence are known as SEI (Susceptible-Exposed-Infective) models [27–38].

We consider a finite population of N people. The infective class is divided into two subclasses with different properties: diagnosed and undiagnosed infectious. At any given time, an individual is therefore in one of the following states: susceptible, latently infected (exposed to TB but not infectious), diagnosed infectious (has active TB confirmed after a sputum examination in the hospital) and undiagnosed infectious (i.e., have active TB not confirmed by a sputum examination in hospital), and we will denote these states by S, E, I and J, respectively.

All recruitment is into the susceptible class and occurs at a constant rate Λ. The rate constant for non-disease related death is μ; thus, $1/\mu$ is the average lifetime. Diagnosed and undiagnosed infectious have addition death rates due to the disease with constant rates d_1 and d_2, respectively. Transmission of *M. Tuberculosis* occurs due to adequate contacts between susceptible, diagnosed or undiagnosed infectious. Then, susceptible individuals acquire TB infection from individuals with active TB at a rate λ, given by

$$\lambda = \frac{\beta(I + \varepsilon J)}{N}, \tag{1}$$

where β is the effective contact rate of diagnosed or undiagnosed infectious that is sufficient to transmit infection to susceptible, and the parameter $\varepsilon > 1$ accounts for the high infectiousness of undiagnosed infectious with respect to diagnosed infectious. On adequate contacts with active TB, a susceptible individual becomes infected but not yet infectious. Proportion p of newly infected individuals is assumed to undergo a fast progression directly to the diagnosed and undiagnosed infectious classes I and J, respectively, while the remainder is latently infected and enters the latent class E. Among the newly infected individuals that undergo a fast progression to TB, a proportion f of them are detected and will enter the diagnosed infectious class I and the remaining proportion $1 - f$ is undetected and will be transferred in the undiagnosed infectious class J. Once latently infected with *M. Tuberculosis*, an individual will remain so for life unless reactivation occurs. Latently infected individuals are assumed to acquire some immunity as a result of infection, which reduces the risk of subsequent infection but does not fully prevent it. To account for treatment, we define by $r_1 E$, latently infected individuals receiving effective chemoprophylaxis, and r_2 as the rate of effective per capita therapy of diagnosed infectious. We assume that chemoprophylaxis of latently infected individuals reduces their reactivation and that the initiation of therapeutics of diagnosed infectious immediately removes individuals from active status I and places them into a latent state E. We also assume that undiagnosed infectious can naturally recover and will be transferred into the latent class E at a constant rate r_3. Due to endogenous reactivation, latently infected individuals who did not receive effective chemoprophylaxis become infectious with a constant rate $k(1 - r_1)$, and reinfected (exogenously) after effective contact with individuals in the active TB classes at a rate $\sigma(1 - r_1)\lambda$, where σ is the factor reducing the risk of infection as a result of acquiring immunity for latently infected individuals. Among latently infected individuals who become infectious, the proportion h of them are diagnosed and treated, while the complementary part $1 - h$ are not diagnosed and enter the class of undiagnosed infectious J.

The model flow diagram is shown in Fig. 1.

This yields the following differential equations:

$$\begin{cases} \dot{S} = \Lambda - \lambda S - \mu S, \\ \dot{E} = (1-p)\lambda S + r_2 I + r_3 J \\ \qquad - \sigma(1 - r_1)\lambda E - A_1 E, \\ \dot{I} = pf\lambda S + h(1 - r_1)(k + \sigma\lambda)E - A_2 I, \\ \dot{J} = p(1-f)\lambda S + (1-h)(1 - r_1)(k + \sigma\lambda)E \\ \qquad - A_3 J, \end{cases} \tag{2}$$

where

$$A_1 = \mu + k(1 - r_1), \qquad A_2 = \mu + d_1 + r_2 \quad \text{and}$$
$$A_3 = \mu + d_2 + r_3.$$

System (2) can be written in the following compact form:

$$\begin{cases} \dot{x} = \varphi(x) - \lambda x, \\ \dot{y} = \lambda\big[B_1 x + B_2\langle e_2 \mid y\rangle\big] + Ay, \end{cases} \tag{3}$$

where $x = S \in \mathbb{R}_+$ is a state representing the compartment of non-transmitting individuals (susceptible), $y = (y_1, y_2, y_3) = (E, I, J)^T \in \mathbb{R}^3_+$ is the vector representing the state compartment of different infected individuals (latently infected, diagnosed and undiagnosed infectious), $\varphi(x) = \Lambda - \mu x$ is a function that depends on x, $\lambda = \langle e_1 \mid y\rangle / N$ is the force of infection, $N = x + y_1 + y_2 + y_3$ is the size of the total popu-

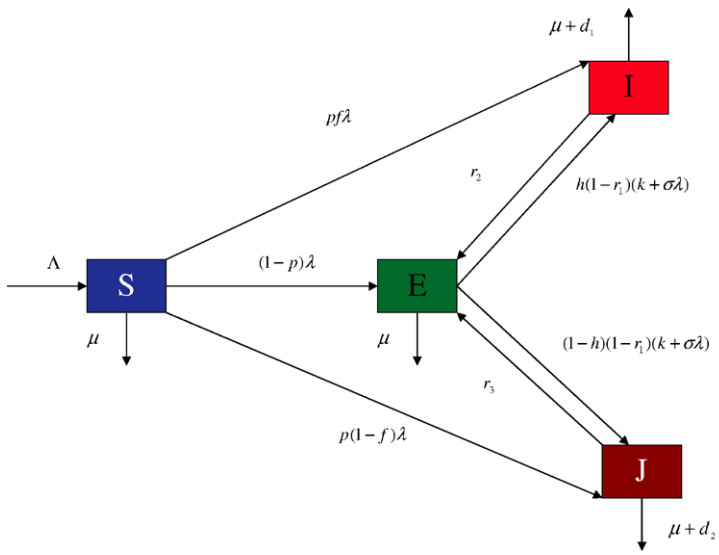

Fig. 1 Transfer diagram for a dynamics transmission of tuberculosis where $\lambda = \beta(I + \varepsilon J)/N$

lation, $e_1 = (0, \beta, \beta\varepsilon)$, $e_2 = (1, 0, 0)$, $B_1 = (1 - p, pf, p(1 - f))^T$, $B_2 = (-\sigma(1 - r_1), \sigma h(1 - r_1), \sigma(1 - h)(1 - r_1))^T$, $\langle \cdot \mid \cdot \rangle$ is the usual scalar product and A is the constant matrix

$$A = \begin{bmatrix} -A_1 & r_2 & r_3 \\ kh(1-r_1) & -A_2 & 0 \\ k(1-h)(1-r_1) & 0 & -A_3 \end{bmatrix}$$

with A_1, A_2 and A_3 defined as in (2).

It should be pointed out that A is a Metzler matrix, i.e., a matrix with all its off-diagonal entries non-negative [40, 41]. Using the fact that A is a non-singular Metzler matrix, $-A^{-1}$ is non-negative [42, 43]. We will need this property later.

We give the explicit expression of $-A^{-1}$ since we will need it later.

$$-A^{-1} = \frac{1}{\tau} \begin{bmatrix} A_2A_3 & r_2A_3 & r_3A_2 \\ hk(1-r_1)A_3 & A_1A_3 - kr_3(1-h)(1-r_1) & -hkr_3(1-r_1) \\ kA_2(1-h)(1-r_1) & kr_2(1-h)(1-r_1) & A_1A_2 - hkr_2(1-r_1) \end{bmatrix},$$

where

$$\tau = A_1A_2A_3 - k(1-r_1)\big[hr_2A_3 + A_2r_3(1-h)\big].$$

The TB model (2) was simulated with the parameters given in Table 1.

Due to lack of data, the parameters that are not estimated are assumed within realistic ranges (for the purpose of illustration) based on current understanding of the qualitative and the essential biological and epidemiological features of TB.

2.2 Properties of the model

2.2.1 *Positivity and boundedness of solutions*

For model system (2) to be epidemiologically meaningful, it is important to prove that all its state variables are non-negative for all time. In other words, solutions of model system (2) with positive initial data remain positive for all time $t > 0$.

Let the initial data be $S(0) > 0$, $E(0) > 0$, $I(0) > 0$ and $J(0) > 0$. Then, one can easily prove that the solutions (S, E, I, J) of model system (2) are positive for all $t > 0$. Assume that $\bar{t} = \sup\{t > 0 : S > 0, E > 0, I > 0, J > 0\} \in [0, t]$. Thus, $\bar{t} > 0$ and it fol-

Table 1 Numerical values for the parameters of model

Parameters	Symbol	Estimate	Source
Recruitment rate of susceptible	Λ	397800/yr	[44]
Transmission rate	β	Variable	Assumed
Fast route to active TB	p	0.015	Assumed
Fast route to diagnosed infectious class	f	0.7	Assumed
Infectivity of undiagnosed infectious	ε	1.5	Assumed
Reinfection parameter of latently infected individuals	σ	2	Assumed
Slow route to active TB class	k	0.05/yr	Assumed
Natural mortality	μ	0.019896/yr	[44]
TB mortality of diagnosed infectious	d_1	0.0575/yr	[39]
TB mortality of undiagnosed infectious	d_2	0.24/yr	Assumed
Chemoprophylaxis of latently infected individuals	r_1	0/yr	[39]
Detection rate of active TB	h	0.69/yr	[39]
Treatment rate of diagnosed infectious	r_2	0.8625/yr	[39]
Recovery rate of undiagnosed infectious	r_3	0.49/yr	Assumed

lows from the first equation of model system (2) that

$$\frac{dS}{dt} = \Lambda - (\mu + \lambda)S,$$

which can be rewritten as

$$\frac{d}{dt}\left[S(t)\exp\left\{\mu t + \int_0^t \lambda(s)\,ds\right\}\right] = \Lambda \exp\left\{\mu t + \int_0^t \lambda(s)\,ds\right\}.$$

Hence,

$$S(\bar{t})\exp\left\{\mu\bar{t} + \int_0^{\bar{t}} \lambda(s)\,ds\right\} - S(0) \geq \int_0^{\bar{t}} \Lambda \exp\left\{\mu u + \int_0^u \lambda(w)\,dw\right\} du,$$

so that

$$S(\bar{t}) \geq S(0)\exp\left\{-\left(\mu\bar{t} + \int_0^{\bar{t}} \lambda(s)\,ds\right)\right\} + \exp\left\{-\left(\mu\bar{t} + \int_0^{\bar{t}} \lambda(s)\,ds\right)\right\} \times \int_0^{\bar{t}} \Lambda \exp\left\{\mu u + \int_0^u \lambda(w)\,dw\right\} du > 0.$$

Similarly, it can be shown that $E(t) > 0$, $I(t) > 0$ and $J(t) > 0$ for all $t > 0$.

Now, adding the four equations in the differential system (2), one gets

$$\dot{N} = \Lambda - \mu(S + E + I + J)(t) - d_1 I(t) - d_2 J(t).$$

Thus, we can deduce that $\dot{N}(t) \leq \Lambda - \mu N(t)$. It then follows that $\lim_{t\to+\infty} N(t) \leq \frac{\Lambda}{\mu}$ which implies that the trajectories of model system (2) are bounded. On the other hand, one has $N(t) \leq N(0)e^{-\mu t} + \frac{\Lambda}{\mu}(1 - e^{-\mu t})$. In particular, $N(t) \leq \frac{\Lambda}{\mu}$ if $N(0) \leq \frac{\Lambda}{\mu}$. Then, the simplex

$$\Omega = \left\{(S, E, I, J) \in \mathbb{R}^4_+,\ N(t) \leq \frac{\Lambda}{\mu}\right\} \tag{4}$$

is a compact forward invariant set for the system (2). So, we limit our study to this simplex.

2.2.2 *Local stability of the disease-free equilibrium (DFE)*

Model system (2) has a DFE given by $Q_0 = (\frac{\Lambda}{\mu}, 0, 0, 0)$. The stability of this equilibrium will be investigated using the next generation operator [45]. Using the notations in [45] on model system (2), the matrices F and V for the new infection terms and the remaining transfer terms are, respectively, given by

$$F = B_1 e_1 \quad \text{and} \quad V = -A.$$

Then, the basic reproduction ratio is defined, following [45], as the spectral radius of the next generation

matrix, FV^{-1}:

$$\mathcal{R}_0 = \rho\big(FV^{-1}\big) = \big\langle e_1 | \big(-A^{-1}\big)B_1 \big\rangle, \tag{5}$$

where ρ represents the spectral radius (the dominant eigenvalue in magnitude) of FV^{-1}. We use the expression $(-A^{-1})$ to emphasize that $(-A^{-1}) \geq 0$ because the matrix A is Metzler stable.

Using the expression of $(-A^{-1})$, the explicit expression of the basic reproduction ratio is

$$\mathcal{R}_0 = \frac{\beta[(1-p)\mathcal{R}_{01} + pf\mathcal{R}_{02} + p(1-f)\mathcal{R}_{03}]}{A_1A_2A_3 - k(1-r_1)[hr_2A_3 + A_2r_3(1-h)]}, \tag{6}$$

where

$$\begin{aligned}
\mathcal{R}_{01} &= hk(1-r_1)A_3 + \varepsilon A_2(1-h)(1-r_1),\\
\mathcal{R}_{02} &= A_1A_3 - kr_3(1-h)(1-r_1)\\
&\quad + \varepsilon kr_2(1-h)(1-r_1),\\
\mathcal{R}_{03} &= -hkr_3(1-r_1) + \varepsilon\big[A_1A_2 - hkr_2(1-r_1)\big].
\end{aligned}$$

The following result is established (from Theorem 2 of [45]):

Lemma 1 *The disease-free equilibrium Q_0 of model system (2) is locally asymptotically stable whenever $\mathcal{R}_0 < 1$, and instable if $\mathcal{R}_0 > 1$.*

The threshold quantity $\mathcal{R}_0$ is the reproduction number for TB. Biologically speaking, Lemma 1 implies that TB can be eliminated from the community (when $\mathcal{R}_0 < 1$) if the initial size of the population of the model is in the basin of attraction of Q_0. Since TB models may undergo the phenomenon of backward bifurcation (see [46]), it is instructive to determine whether the present model exhibits this phenomenon.

2.3 Equilibria and bifurcation

Model system (2) has one disease-free equilibrium, $Q_0 = (S_0, 0, 0, 0)$ with $S_0 = \Lambda/\mu$, and one or two endemic equilibria of the form $Q^* = (S^*, E^*, I^*, J^*)$. On the other hand, from Lemma 1, the DFE of model system (2) is locally asymptotically stable (LAS) if $\mathcal{R}_0 < 1$. However, this equilibrium may not be globally asymptotically stable (GAS) in Ω for $\mathcal{R}_0 < 1$, owing to the possibility of the backward bifurcation phenomenon, where the stable DFE coexists with a stable endemic equilibrium when $\mathcal{R}_0 < 1$ (see for instance [47–51] and the references therein). The public health implication of the backward bifurcation phenomenon is that the classical requirement of having the basic reproductive number less than unity, although necessary, is no longer sufficient for curtailing the outbreak of the disease [51]. The possibility of this phenomenon in model system (2) is investigated below.

Let $Q^* = (x^*, y^*)$ be any arbitrary equilibrium point of model system (3). To find conditions for the existence of an equilibrium for which tuberculosis is endemic in the population (steady state with y^* nonzero), the equations in model system (3) are set at zero, i.e.,

$$\begin{cases}
\varphi(x^*) - \lambda^* x^* = 0,\\
\lambda^*\big[B_1x^* + B_2\langle e_2 \mid y^*\rangle\big] + Ay^* = 0,
\end{cases} \tag{7}$$

where

$$\lambda^* = \frac{\langle e_1 \mid y^*\rangle}{N^*} \tag{8}$$

is the force of infection at the steady state. Multiplying the second equation of (7) by $-A^{-1}$, one obtains

$$y^* = \lambda^*\big[x^*\big(-A^{-1}\big)B_1 + \big(-A^{-1}\big)B_2\langle e_2 \mid y^*\rangle\big]. \tag{9}$$

Then, one can deduce that

$$\begin{aligned}
&\langle e_1 \mid y^*\rangle = \lambda^*\big[x^*\langle e_1 \mid \big(-A^{-1}\big)B_1\rangle + a_1\langle e_2 \mid y^*\rangle\big] \quad \text{and}\\
&\langle e_2 \mid y^*\rangle = \lambda^*\big[a_3x^* + a_4\langle e_2 \mid y^*\rangle\big],
\end{aligned} \tag{10}$$

where

$$\begin{aligned}
a_1 &= \langle e_1 \mid \big(-A^{-1}\big)B_2\rangle,\\
a_3 &= \langle e_2 \mid \big(-A^{-1}\big)B_1\rangle \quad \text{and}\\
a_4 &= \langle e_2 \mid \big(-A^{-1}\big)B_2\rangle.
\end{aligned}$$

Now, using the second and third equations of (10), one can prove that

$$\langle e_2 \mid y^*\rangle = \frac{a_3\lambda^*x^*}{1 - a_4\lambda^*}. \tag{11}$$

Combining the first equation of (10) and the force of infection at the steady state (8) yields

$$N^* = x^*\mathcal{R}_0 + a_1\langle e_2 \mid y^*\rangle. \tag{12}$$

Table 2 Number of possible real roots of $f(\lambda^*)$ for $\mathcal{R}_0 < 1$ and $\mathcal{R}_0 > 1$

Cases	c_2	c_1	c_0	$\mathcal{R}_0$	Number of sign changes	Number of possible positive real roots
1	−	−	−	$\mathcal{R}_0 > 1$	0	0
	−	−	+	$\mathcal{R}_0 < 1$	1	1
2	+	−	−	$\mathcal{R}_0 > 1$	1	1
	+	−	+	$\mathcal{R}_0 < 1$	2	0.2
3	−	+	−	$\mathcal{R}_0 > 1$	2	0.2
	−	+	+	$\mathcal{R}_0 < 1$	1	1
4	+	+	−	$\mathcal{R}_0 > 1$	1	1
	+	+	+	$\mathcal{R}_0 < 1$	0	0

Now, let $e_2 = (1,0,0)$, $e_3 = (0,1,0)$ and $e_4 = (0,0,1)$. Using (9), one can deduce that

$$\begin{aligned}
E^* &= \langle e_2 \mid y^* \rangle \\
&= \lambda^* \big[x^* \langle e_2 \mid \left(-A^{-1}\right) B_1 \rangle \\
&\quad + \langle e_2 \mid \left(-A^{-1}\right) B_2 \rangle \langle e_2 \mid y^* \rangle \big], \\
I^* &= \langle e_3 \mid y^* \rangle \\
&= \lambda^* \big[x^* \langle e_3 \mid \left(-A^{-1}\right) B_1 \rangle \\
&\quad + \langle e_3 \mid \left(-A^{-1}\right) B_2 \rangle \langle e_2 \mid y^* \rangle \big], \\
J^* &= \langle e_4 \mid y^* \rangle \\
&= \lambda^* \big[x^* \langle e_4 \mid \left(-A^{-1}\right) B_1 \rangle \\
&\quad + \langle e_4 \mid \left(-A^{-1}\right) B_2 \rangle \langle e_2 \mid y^* \rangle \big].
\end{aligned}$$

Then, the size of the total population can be written as follows:

$$\begin{aligned}
N^* &= x^* + \sum_{k=2}^{4} \langle e_k \mid y^* \rangle \\
&= x^* + \lambda^* \big[x^* g_0 + g_1 \langle e_2 \mid y^* \rangle \big], \qquad (13)
\end{aligned}$$

where

$$g_0 = \sum_{k=2}^{4} \langle e_k \mid \left(-A^{-1}\right) B_1 \rangle \quad \text{and}$$

$$g_1 = \sum_{k=2}^{4} \langle e_k \mid \left(-A^{-1}\right) B_2 \rangle.$$

Equalizing (12) and (13), and using (11), it can be shown that the non-zero equilibria of the model satisfy the following quadratic equation in term of λ^*:

$$c_2 \left(\lambda^*\right)^2 + c_1 \left(\lambda^*\right) + c_0 = 0, \qquad (14)$$

where

$$c_2 = g_1 a_3 - a_4,$$

$$c_1 = g_0 - a_1 a_3 - a_4 (1 - \mathcal{R}_0) \quad \text{and} \quad c_0 = 1 - \mathcal{R}_0.$$

Thus, positive endemic equilibria Q^* are obtained by solving for λ^* from the quadratic equation (14) and substituting the result (positive values of λ^*) into the expression in (8). Clearly, c_0 is positive or negative if $\mathcal{R}_0$ is respectively less than or greater than unity. Thus, the number of possible real roots of the polynomial (14) can depend on the signs of c_2, c_1 and c_0. This can be analyzed using the Descartes Rule of Signs on the cubic polynomial $f(\lambda^*) = c_2(\lambda^*)^2 + c_1(\lambda^*) + c_0$ given in (14). The various possibilities for the roots of $f(\lambda^*)$ are tabulated in Table 2.

The following result follows from various possibilities enumerated in Table 2.

Lemma 2 *The TB model* (2)

(i) *could have a unique endemic equilibrium if* $\mathcal{R}_0 > 1$ *and whenever Cases* 2 *and* 4 *are satisfied*;
(ii) *could have more than one endemic equilibrium if* $\mathcal{R}_0 > 1$ *and Case* 3 *is satisfied*;
(iii) *could have a unique endemic equilibrium if* $\mathcal{R}_0 < 1$ *and whenever Cases* 1 *and* 2 *are satisfied*;
(iv) *no endemic equilibria in the other cases*.

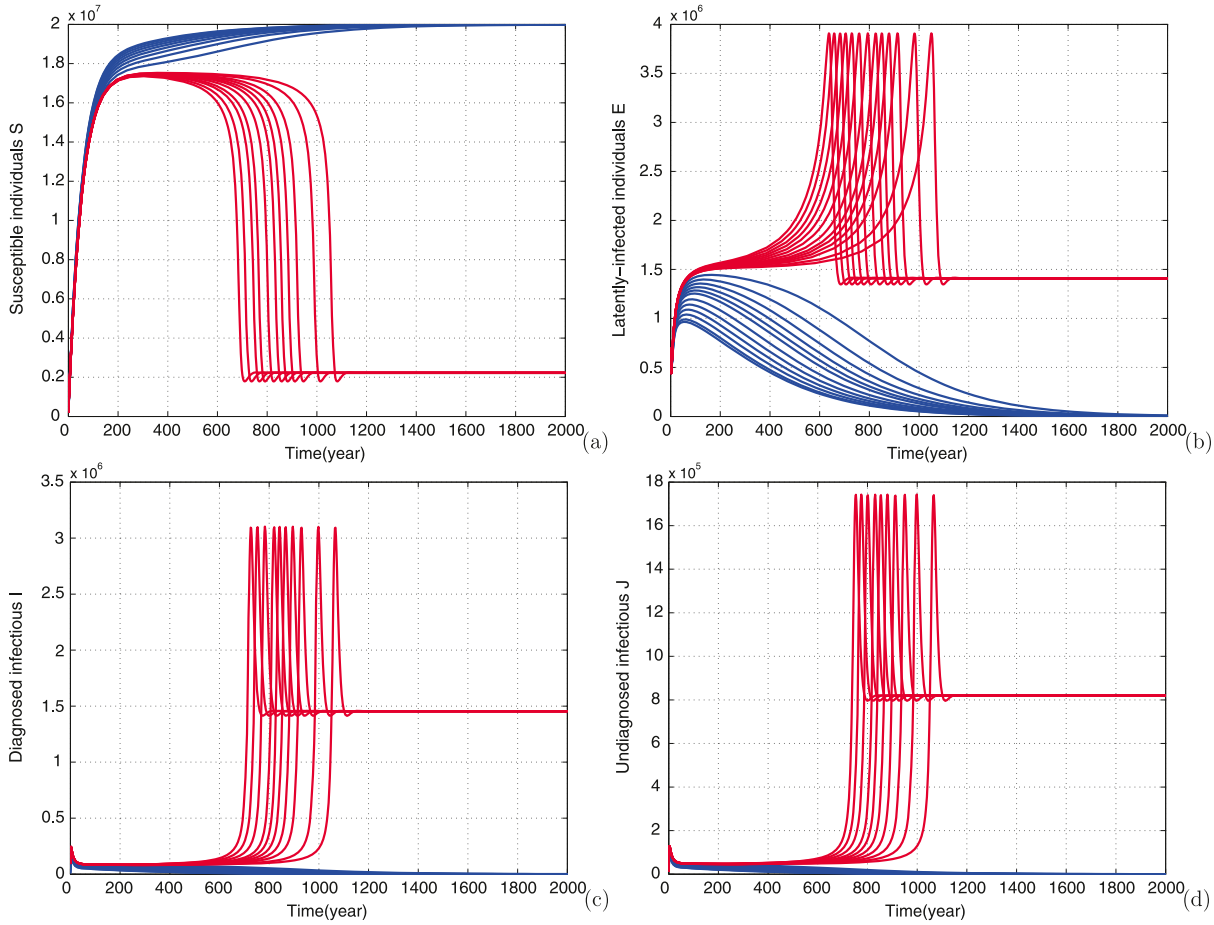

Fig. 2 Simulation of model system (2). Time series of (**a**) susceptible individuals, (**b**) latently infected individuals, (**c**) diagnosed infectious and (**d**) undiagnosed infectious when $\beta = 0.35$ (so that $\mathcal{R}_0 = 0.8733$). All other parameters are as in Table 1

It should be pointed out that the case (iii) indicates the possibility of the backward bifurcation phenomenon (where locally asymptotically stable DFE coexists with a locally asymptotically stable endemic equilibrium when $\mathcal{R}_0 < 1$, see for instance, [47–51]) in the TB model (2) when $\mathcal{R}_0 < 1$.

The backward bifurcation phenomenon is illustrated by simulating system (2) with the parameters of Table 1 and $\beta = 0.35$ (so that $\mathcal{R}_0 = 0.8481$).

Figure 2 shows the convergence to both the disease-free equilibrium and the endemic equilibrium for model system (2) when $\mathcal{R}_0 < 1$. In other words, the profiles can converge to either the disease-free equilibrium or an endemic equilibrium point for the trajectories of model system (2), depending on the initial sizes of the population of the model (owing to the phenomenon of backward bifurcation).

The epidemiological significance of the phenomenon of backward bifurcation is that the classical requirement of $\mathcal{R}_0 < 1$ is, although necessary, no longer sufficient for disease eradication. In such a scenario, disease elimination would depend on the initial sizes of the population (state variables) of the model. That is, the presence of backward bifurcation in the TB transmission model (2) suggests that the feasibility of controlling TB when $\mathcal{R}_0 < 1$ could be dependent on the initial sizes of the population. Further, as a consequence, it is instructive to try to determine the "cause" of the backward bifurcation phenomenon in model system (2). This is explored below.

2.4 Role of exogenous reinfections

Herein, the role of exogenous reinfections on backward bifurcation will be investigated. We consider the

case where there are not exogenous reinfections in the population. In this case, $\sigma = 0$ (so that $B_2 = 0$) and model system (3) becomes

$$\begin{cases} \dot{x} = \varphi(x) - \lambda x, \\ \dot{y} = \lambda B_1 x + Ay, \end{cases} \tag{15}$$

where $\varphi(x)$, B_1, λ and A are defined as in (3).

The above model has the same disease-free equilibrium Q_0 than model system (3). Apart from this equilibrium state, the model can also have an unique positive endemic equilibrium state. In the absence of exogenous reinfections $\sigma = 0$ (so that $B_2 = 0$), the coefficients c_0, c_1 and c_2 in (14) reduce to

$$c_2 = 0, \qquad c_1 = g_0 \quad \text{and} \quad c_0 = 1 - \mathcal{R}_0.$$

In this case, the force of infection at the steady state is

$$\lambda^* = \frac{\mathcal{R}_0 - 1}{g_0},$$

which is positive when $\mathcal{R}_0 > 1$. Then, one can tediously prove that an endemic equilibrium $Q^* = (x^*, y^*)$ exists and is unique, and, x^* and y^* are given by

$$\begin{aligned} x^* &= \frac{g_0 \Lambda}{\mu g_0 + \mathcal{R}_0 - 1} \quad \text{and} \\ y^* &= \frac{\Lambda(\mathcal{R}_0 - 1)(-A^{-1})B_1}{\mu g_0 + \mathcal{R}_0 - 1}. \end{aligned} \tag{16}$$

Hence, in this case (with $\sigma = 0$), no endemic equilibrium exists whenever $\mathcal{R}_0 \leq 1$. It follows then that, owing to the absence of multiple endemic equilibria for model system (2) with $\sigma = 0$ and $\mathcal{R}_0 \leq 1$, a backward bifurcation is unlikely for model system (2) with $\sigma = 0$ and $\mathcal{R}_0 \leq 1$.

The absence of multiple endemic equilibria suggests that the disease-free equilibrium of model system (15) is globally asymptotically stable when $\mathcal{R}_0 < 1$. Then, we claim the following:

Theorem 1 *Consider model system* (2) *with* $\sigma = 0$. *The disease-free equilibrium is globally asymptotically stable in* Ω *whenever* $\mathcal{R}_0 \leq 1$.

Proof All solutions starting in Ω remain in Ω, and all other solutions approach Ω. Thus, it may be assumed that $S/N \leq 1$, for all $t \geq 0$. Consequently, the last three equations of model system (2) in the absence of exogenous reinfections can be expressed in the following differential inequality:

$$\begin{pmatrix} \dot{E} \\ \dot{I} \\ \dot{J} \end{pmatrix} \leq (F - V) \begin{pmatrix} E(t) \\ I(t) \\ J(t) \end{pmatrix}. \tag{17}$$

Consider the linear ODE system given by inequality in (17). If $\mathcal{R}_0 < 1$, $F - V$ has all its eigenvalues in the left-half plane [45]. It follows that the linear system given by the inequality (17) is stable whenever $\mathcal{R}_0 < 1$, thus $(E(t), I(t), J(t)) \to (0, 0, 0)$ as $t \to \infty$ for this linear ODE system. Consequently, after using a standard comparison theorem [42, 52], the variables $(E(t), I(t), J(t)) \to (0, 0, 0)$ as well for the nonlinear system given by the last three equations of model system (2). Returning now to the first equation of model system (2) and substituting $E = I = J = 0$ in this equation gives a linear system with $S \to S_0$ as $t \to \infty$. Thus, $(S(t), E(t), I(t), J(t)) \to (S_0, 0, 0, 0)$ as $t \to \infty$ for $\mathcal{R}_0 < 1$, so that Q_0 is globally asymptotically stable if $\mathcal{R}_0 < 1$. This achieves the proof. □

Numerical results for model system (2) without exogenous reinfections are depicted in Fig. 3. Figure 3(a) shows simulation results converging to the disease-free equilibrium of the total cases of infection using various initial conditions when $\beta = 0.2$ (so that $\mathcal{R}_0 = 0.4846$). This means that the disease disappears in the population. Figure 3(b) shows the convergence to the endemic equilibrium of the total cases of infection using various initial conditions for $\beta = 0.6$ (so that $\mathcal{R}_0 = 1.4539$). This implies that the disease persists in the population. Although the stability analysis of the endemic equilibrium of model system (2) without exogenous reinfections has not been carried out in this study, this result is certainly expected (since the DFE is unstable in this case, and, typically, the disease persists when the reproduction threshold ($\mathcal{R}_0$) exceeds unity; as is the case in this particular simulation).

The above results show that, for the model without exogenous reinfections, TB can be eliminated from the community if the associated threshold quantity, $\mathcal{R}_0$, can be brought to a value less than unity (that is, unlike in the model (2), where exogenous reinfections are used, the classical epidemiological requirement of $\mathcal{R}_0 < 1$ is both necessary and sufficient for TB elimination from the community if there is no exogenous reinfections in the model formulation).

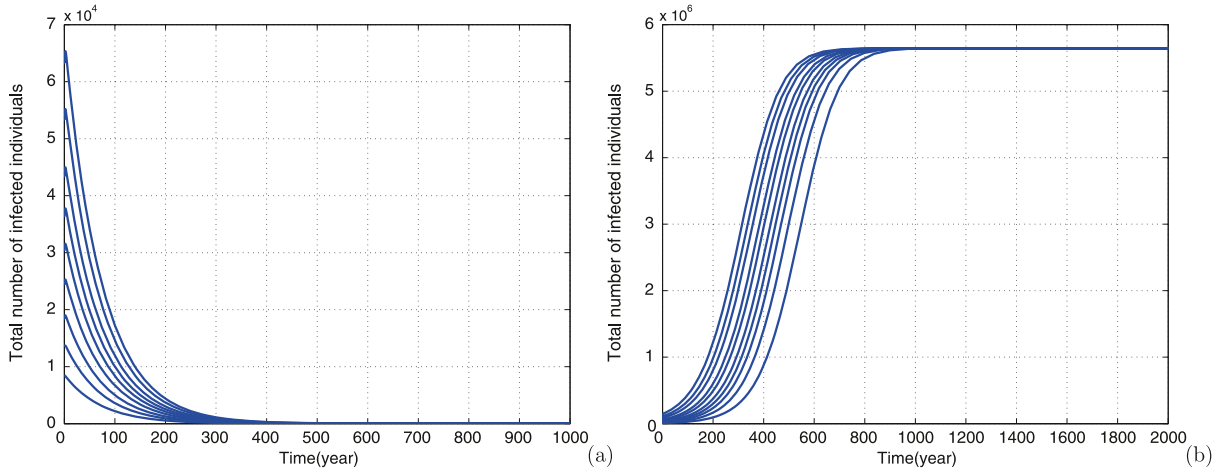

Fig. 3 Time series of model system (2) with $\sigma = 0$ showing the total number of infected individuals as a function of time, using various initial conditions. (**a**) When $\beta = 0.2$ (so that $\mathcal{R}_0 = 0.4846$) and (**b**) when $\beta = 0.6$ (so that $\mathcal{R}_0 = 1.4539$). All other parameters are as in Table 1

Figure 4 shows the impact of varying the detection parameter h in the model (2) with $\sigma = 0$. The model was simulated with the following initial conditions: $S(0) = 200000$, $E(0) = 700000$, $I(0) = 90000$ and $J(0) = 10000$.

From this figure, one can see that as the value of h increases, the population of diagnosed infectious increases (Fig. 4(b)), while the populations of undiagnosed and latently infected decrease (Figs. 4(a) and (c)). This demonstrates the importance of diagnosis. This is due to the fact that diagnosis leads to the treatment of patients, resulting in less latently infected individuals, that do not lead to an epidemic. Care then should be taken to prevent a failure of treatment and a relapse of the disease after treatment.

2.5 Analysis of the mass action model

Consider model system (2) in the absence of exogenous reinfections. Thus, the force of infection λ reduces to $\lambda = \beta(I + \varepsilon J)$. Then, model system (2) becomes

$$\begin{cases} \dot{S} = \Lambda - \beta(I + \varepsilon J)S - \mu S, \\ \dot{E} = \beta(1-p)(I + \varepsilon J)S + r_2 I + r_3 J - A_1 E, \\ \dot{I} = \beta p f (I + \varepsilon J)S + kh(1-r_1)E - A_2 I, \\ \dot{J} = \beta p(1-f)(I + \varepsilon J)S \\ \qquad + k(1-h)(1-r_1)E - A_3 J, \end{cases} \tag{18}$$

where A_1, A_2 and A_3 are defined as in (2) or in compact form

$$\begin{cases} \dot{x} = \varphi(x) - x\langle e_1 \mid y\rangle, \\ \dot{y} = x\langle e_1 \mid y\rangle B_1 + Ay, \end{cases} \tag{19}$$

where $\varphi(x)$, e_1, B_1 and A are defined as in (3).

The resulting (mass action) model has the same disease-free equilibrium given by Q_0. The associated next generation matrices, F and V, are, respectively, given by

$$F = x_0 B_1 e_1 \quad \text{and} \quad V = -A,$$

where $x_0 = \Lambda/\mu$. It follows that the associated basic reproduction ratio for the mass action model without exogenous reinfections, denoted by $\mathcal{R}_0 = \rho(FV^{-1})$, is given by

$$\mathcal{R}_0 = x_0\langle e_1 \mid (-A^{-1})B_1\rangle. \tag{20}$$

2.5.1 Non-existence of endemic equilibria for $\mathcal{R}_0 < 1$

In this section, the non-existence of endemic equilibria of model system when $\mathcal{R}_0 \leq 1$ will be explored. To this end, let $Q^* = (x^*, y^*)$ be the positive endemic equilibrium of model (19). Then, the positive endemic equilibrium (steady state with $y^* > 0$) can be obtained by setting the right-hand side of all equations in model

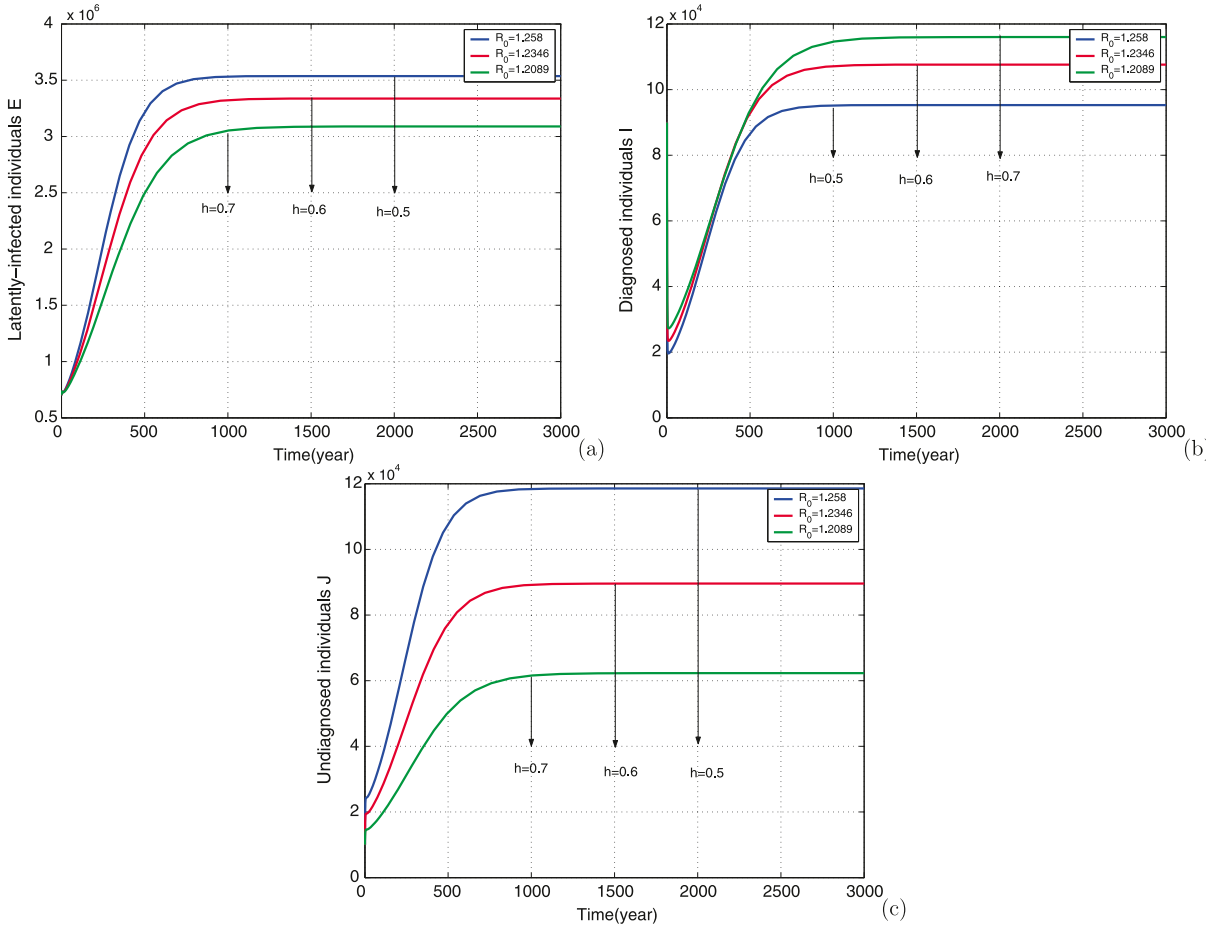

Fig. 4 Time series of (**a**) latently infected individuals, (**b**) diagnosed infectious and (**c**) undiagnosed infectious of model system (2) with $\sigma = 0$ showing the impact of varying h when $\beta = 0.5$. All other parameters are as in Table 1

system (19) equal to zero, i.e.,

$$\begin{cases} \varphi(x^*) - x^*\langle e_1 \mid y^*\rangle = 0, \\ x^*\langle e_1 \mid y^*\rangle B_1 + Ay^* = 0. \end{cases} \tag{21}$$

From the second equation of (21), one has $y^* = x^*(-A^{-1})B_1\langle e_1 \mid y^*\rangle$, and replacing in $\langle e_1 \mid y^*\rangle$ yields

$$\langle e_1 \mid y^*\rangle = x^*\langle e_1 \mid (-A^{-1})B_1\rangle\langle e_1 \mid y^*\rangle.$$

The case $\langle e_1 \mid y^*\rangle = 0$ implies that $\varphi(x^*) = 0$ and $-Ay^* = 0$. Since A is non-singular, this gives the disease-free equilibrium Q_0. For the other case, simplifying by $\langle e_1 \mid y^*\rangle$ gives

$$x^* = \frac{1}{\langle e_1 \mid (-A^{-1})B_1\rangle} = \frac{x_0}{\mathcal{R}_0} > 0.$$

With $\mathcal{R}_0 > 1$, one has $x^* < x_0$, $\varphi(x^*) > 0$ and

$$y^* = (-A^{-1})B_1\varphi(x^*).$$

Hence, model system (19) has a unique endemic equilibrium $Q^* = (x^*, y^*)$ where x^* and y^* are given by

$$x^* = \frac{1}{\langle e_1 \mid (-A^{-1})B_1\rangle} = \frac{x_0}{\mathcal{R}_0} \quad \text{and} \quad y^* = (-A^{-1})B_1\varphi(x^*). \tag{22}$$

The above result suggests the impossibility of a backward bifurcation in the mass balance action model, since no endemic equilibrium exists when $\mathcal{R}_0 \leq 1$ (and backward bifurcation requires the presence of at least two endemic equilibria when $\mathcal{R}_0 \leq 1$). A global stability result is established for the disease-

free equilibrium of the mass balance action model without exogenous reinfections below.

2.5.2 Global stability of the DFE

Consider model system (3) with mass balance incidence in the absence of the exogenous reinfections. We have the following result.

Theorem 2 *If $\mathcal{R}_0 \leq 1$, then model system (2) with mass balance incidence in the absence of exogenous reinfections has no positive equilibrium states and the disease-free equilibrium Q_0 is globally asymptotically stable on the non-negative orthant $\mathbb{R}^4_+$. This means that the disease naturally dies out.*

Proof Let us consider the following LaSalle–Lyapunov candidate function:

$$V(x,y) = \frac{1}{x_0}(x - x_0 \ln x) + e_1^T\left(-A^{-1}\right)y - \frac{1}{x_0}(x_0 - x_0 \ln x_0). \tag{23}$$

It is easy to see that at the disease-free equilibrium Q_0, the function $V(x,y)$ reaches its global minimum in $\mathbb{R}^4_{\geq 0}$, and hence $V(x,y)$ is a Lyapunov function, since we know that $e_1^T(-A^{-1}) > 0$. Its time derivative along the trajectories of model system (19) satisfies

$$\begin{aligned}
\dot{V}(x,y) &= \frac{1}{x_0}\left(1 - \frac{x_0}{x}\right)\dot{x} + e_1^T\left(-A^{-1}\right)\dot{y},\\
&= \frac{1}{x_0}\left(1 - \frac{x_0}{x}\right)\left[\varphi(x) - x\langle e_1 \mid y\rangle\right]\\
&\quad + e_1^T\left(-A^{-1}\right)\left[B_1\langle e_1 \mid y\rangle x + Ay\right],\\
&= \frac{1}{x_0}\left(1 - \frac{x_0}{x}\right)\varphi(x) - \frac{x}{x_0}e_1^T y + e_1^T y\\
&\quad + e_1^T\left(-A^{-1}\right)B_1\langle e_1 \mid y\rangle x - e_1^T y,\\
&= \frac{(x - x_0)}{x_0 x}\varphi(x) - \frac{x}{x_0}\langle e_1 \mid y\rangle + \frac{x}{x_0}\langle e_1 \mid y\rangle\mathcal{R}_0,\\
&= \frac{(x - x_0)}{x_0 x}\varphi(x) + \frac{x}{x_0}\langle e_1 \mid y\rangle(\mathcal{R}_0 - 1).
\end{aligned} \tag{24}$$

Recalling that at the disease-free equilibrium $\Lambda = \mu x_0$ so that $\varphi(x) = \mu(x_0 - x)$, one finally obtains

$$\dot{V}(x,y) = \frac{-\mu(x - x_0)^2}{x_0 x} + \frac{x}{x_0}\langle e_1 \mid y\rangle(\mathcal{R}_0 - 1). \tag{25}$$

Thus, $\mathcal{R}_0 \leq 1$ ensures that $\dot{V}(x,y) \leq 0$ for all $x, y \geq 0$, and that $\dot{V}(x,y) = 0$ holds when $\mathcal{R}_0 = 1$ for $x = x_0$. It is easy to verify that the disease-free equilibrium state Q_0 is the only fixed point of the system in the space $x = x_0$, and hence the system has no equilibria in Ω apart from Q_0. Then, by the Lyapunov–LaSalle's asymptotic stability theorem [53–55], the equilibrium state Q_0 is globally asymptotically stable in Ω. This proves the global asymptotic stability on Ω and then in the non-negative orthant $\mathbb{R}^4_+$ (see [55], Theorem 3.7.11, p. 346). This achieves the proof. □

2.5.3 Global stability of the unique endemic equilibrium

The global stability of the endemic equilibrium of model system (18) is given by Theorem 3, stated below and proved in Appendix.

Theorem 3 *If $\mathcal{R}_0 > 1$, then the positive endemic equilibrium state Q^* of model system (2) with mass balance incidence in the absence of exogenous reinfections is globally asymptotically stable on the set Ω whenever*

$$\frac{S^*}{S} \leq \frac{J^*}{J} \leq \frac{I^*}{I} \leq \frac{E^*}{E}. \tag{26}$$

Remark 1 It is possible for the inequality (26) to fail, in which case the global stability of Q^* has not been established. The local stability result and numerical simulations, however, seem to support the idea that Q^* is still globally asymptotically stable even in this case.

Numerical results for model system (2) without exogenous reinfections and mass balance incidence are depicted in Figs. 5 and 6.

Figure 5 presents the trajectories plot of the 2-D and 3-D planes of model system (2) with mass balance incidence in the absence of exogenous reinfections when $\mathcal{R}_0 \leq 1$ using various initial conditions. From Fig. 5(a), one can observe that the trajectories of the model in the plane (E, S) converge to a point in the S-axis which is the DFE, while from Fig. 5(b), the trajectories of the model converge to the origin. This illustrates that the trajectories of model system (2) with mass balance incidence in the absence of the exogenous reinfections converge to the disease-free equilibrium. This means that the disease disappears in

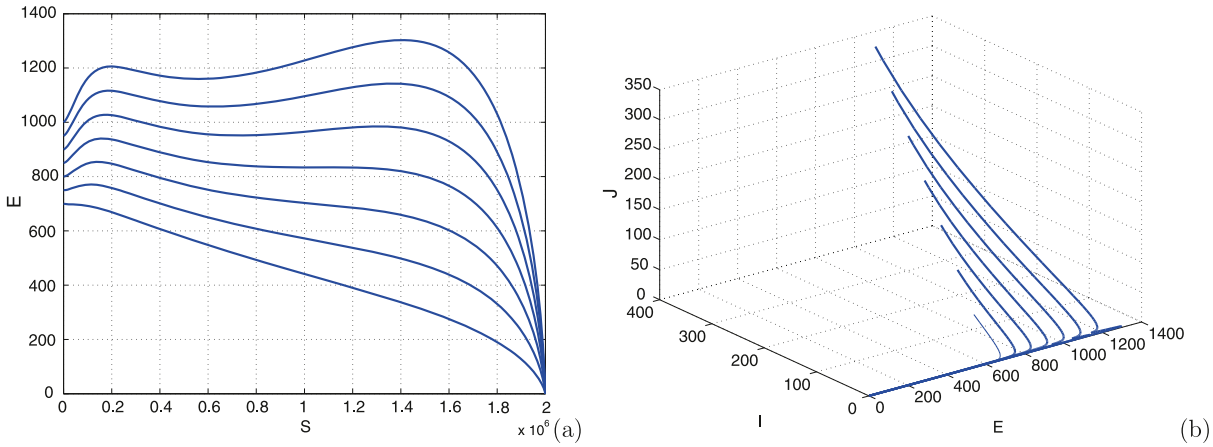

Fig. 5 Trajectories of model system (2) with mass balance incidence in the absence of exogenous reinfections for different initial conditions when $\beta = 0.01$ (so that $\mathcal{R}_0 \leq 1$). All other parameters are as in Table 1

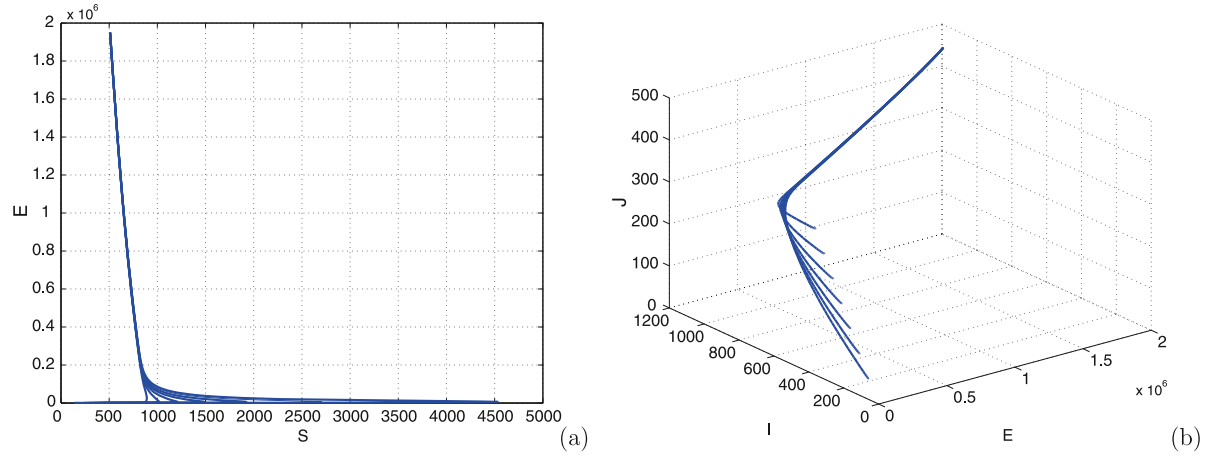

Fig. 6 Trajectories of model system (2) with mass balance incidence in the absence of exogenous reinfections for different initial conditions when $\beta = 1$ (so that $\mathcal{R}_0 > 1$). All other parameters are as in Table 1

the host population. Figure 6 gives the trajectories plot in the 2-D and 3-D planes of model system (2) with mass balance incidence in the absence of exogenous reinfections when $\mathcal{R}_0 > 1$ using various initial conditions. Figures 6(a) and (b), gives the trajectories of the model in the (E, S) and (E, I, J) planes, respectively. From the figure, it clearly appears that the trajectories of model system (2) with mass balance incidence in the absence of the exogenous reinfections converge to the unique endemic equilibrium point. Thus, when $\mathcal{R}_0 > 1$, the disease persists in the host population as shown in Theorem 3.

In model system (2), we have assumed that all parameters are positive and constants. Indeed, some of the parameters may vary. Then, we need to extend model system (2) to take into account the seasonality. This is the aim of the next section.

3 The seasonal TB model

In this section, we extend the model proposed in the previous section by incorporating periodic coefficients based on the possible fact that there is a seasonal trend in the new TB cases. In view of the periodic trend of quarterly new TB cases in Cameroon [39] and the possible causes of the seasonal pattern [17], a model with periodic infection rate $\beta(t)$ and reactivation rate

$k(t)$ may be a natural choice to describe the TB transmission. Thus, we assume that $k(t)$ and $\beta(t)$ are periodic positive continuous functions in t with period ω for some $\omega > 0$. Then, the compartmental model (2) is now described by the following system of non-autonomous differential equations:

$$\begin{cases} \dot{S} = \Lambda - \lambda(t)S - \mu S, \\ \dot{E} = (1-p)\lambda(t)S + r_2 I + r_3 J \\ \qquad - \sigma(1-r_1)\lambda(t)E - A_1(t)E, \\ \dot{I} = pf\lambda(t)S + h(1-r_1)\big(k(t)+\sigma\lambda(t)\big)E \\ \qquad - A_2 I, \\ \dot{J} = p(1-f)\lambda(t)S \\ \qquad + (1-h)(1-r_1)\big(k(t)+\sigma\lambda(t)\big)E - A_3 J, \end{cases} \tag{27}$$

where

$$\lambda(t) = \beta(t)(I + \varepsilon J)/N,$$
$$A_1(t) = \mu + k(t)(1-r_1),$$
$$A_2 = \mu + d_1 + r_2 \quad \text{and} \quad A_3 = \mu + d_2 + r_3.$$

From Smith [42], it follows that for any $(S_0, E_0, I_0, J_0) \in \mathbb{R}^4_+$, model system (27) has unique local non-negative solution $(S(t), E(t), I(t), J(t))$ through the initial value $(S(0), E(0), I(0), J(0)) = (S_0, E_0, I_0, J_0)$.

By adding all equations in model system (27), we have

$$\frac{dN}{dt} = \Lambda - \mu N - d_1 I - d_2 J \le \Lambda - \mu N.$$

It is easy to see that the linear differential equation $\frac{dN}{dt} = \Lambda - \mu N$ has a unique equilibrium $N_0 = \Lambda/\mu$, which is globally asymptotically stable. The comparison principle [42] implies that $N(t)$ is ultimately bounded, and hence, the solutions of model system (27) exist globally on the interval $[0, \infty)$. We summarize these discussions as follows.

Proposition 1 *Model system (27) has a unique and bounded solution with the initial value*

$$(S_0, E_0, I_0, J_0) \in \mathbb{R}^4_+ \in \big\{\big(S(t), E(t), I(t), J(t)\big) \in \mathbb{R}^4_{\ge 0}, \; S + E + I + J \le N\big\}.$$

Further, the compact set

$$\Gamma = \big\{(S, E, I, J) \in \mathbb{R}^4_+, \; N(t) \le \Lambda/\mu\big\} \tag{28}$$

is positively invariant and attracts all positive orbits of model system (27) in $\mathbb{R}^4_+$.

3.1 Local stability of the disease-free equilibrium

We introduce the basic reproduction ratio $\mathcal{R}_0$ for model system (27) according to the general procedure presented in [56]. It is easy to see that model system (27) has exactly one disease-free equilibrium $Q_0 = (\Lambda/\mu, 0, 0, 0)$ and the equations for latent and infectious compartments of the linearized system of model system (27) at Q_0 are

$$\begin{cases} \dot{E} = (1-p)\beta(t)(I + \varepsilon J) + r_2 I \\ \qquad + r_3 J - A_1(t)E, \\ \dot{I} = pf\beta(t)(I + \varepsilon J) + h(1-r_1)k(t)E \\ \qquad - A_2 I, \\ \dot{J} = p(1-f)\beta(t)(I + \varepsilon J) \\ \qquad + (1-h)(1-r_1)k(t)E - A_3 J, \end{cases} \tag{29}$$

where $A_1(t)$, A_2 and A_3 are defined as in (27). Now, we introduce

$$F(t) = \begin{pmatrix} 0 & \beta(t)(1-p) & \beta(t)\varepsilon(1-p) \\ 0 & \beta(t)pf & \beta(t)\varepsilon pf \\ 0 & \beta(t)p(1-f) & \beta(t)\varepsilon p(1-f) \end{pmatrix} \quad \text{and}$$

$$V(t) = \begin{pmatrix} -A_1(t) & r_2 & r_3 \\ k(t)h(1-r_1) & -A_2 & 0 \\ k(t)(1-h)(1-r_1) & 0 & -A_3 \end{pmatrix}.$$

Let $\Phi_V(t)$ and $\rho(\Phi_V(\omega))$ be the monodromy matrix of the linear ω-periodic system $\frac{dz}{dt} = V(t)z$ and the spectral radius of $\Phi_V(\omega)$, respectively. Assume that $Y(t, s)$, $t \ge s$, is the evolution operator of the linear ω-periodic system

$$\frac{dy}{dt} = -V(t)y. \tag{30}$$

That is, for each $s \in \mathbb{R}$, the 3×3 matrix $Y(t, s)$ satisfies

$$\frac{d}{dt}Y(t,s) = -V(t)Y(t,s), \quad \forall t \ge s, \qquad Y(s,s) = I_3, \tag{31}$$

where I_3 is the identity matrix of dimension 3. Thus, the monodromy matrix $\Phi_{-V}(t)$ of (30) is equal to $Y(t,0)$, $t \geq 0$.

In view of the periodic environment, we assume that $\phi(s)$, ω-periodic in s, is the initial distribution of infectious individuals. Then, $F(s)\phi(s)$ is the rate of new infections produced by the infected individuals who were introduced at time s. Given $t \geq s$, then $Y(t,s)F(s)\phi(s)$ gives the distribution of those infected individuals who were newly infected at time s and remain in the infected compartments at time t. It follows that

$$\begin{aligned}\psi(t) &= \int_{-\infty}^{t} Y(t,s)F(s)\phi(s)\,ds \\ &= \int_{0}^{\infty} Y(t,t-a)F(t-a)\phi(t-a)\,da\end{aligned}$$

is the distribution of accumulative new infections at time t produced by all those infected individuals $\phi(s)$ introduced at time previous to t.

Let C_ω be the ordered Banach space of all ω-periodic functions from $\mathbb{R}$ to $\mathbb{R}^3$, which is equipped with the maximum norm $\|\cdot\|$ and the positive cone $C_\omega^+ = \{\phi \in C_\omega,\ \phi(t) \geq 0,\ \forall t \in \mathbb{R}\}$. Then, we can define a linear operator $L : C_\omega \to C_\omega$ by

$$\begin{aligned}(L\phi)(t) &= \int_{0}^{\infty} Y(t,t-a)F(t-a)\phi(t-a)\,da, \\ &\forall t \in \mathbb{R},\ \phi \in C_\omega. \end{aligned} \tag{32}$$

Following Wang and Zhao [56], we call L the next infection operator, and define the basic reproduction ratio as

$$\mathcal{R}_0 = \rho(L),$$

the spectral radius of L.

It should be pointed out that in the special case of $\beta(t) \equiv \beta$, and $k(t) \equiv k$, $\forall t \geq 0$, we obtain $F(t) \equiv F$ and $V(t) \equiv V$, $\forall t \geq 0$. By van den Driessche and Watmough [45] (see also Wang and Zhao [56], Lemma 2.2(ii)), we further obtain the basic reproduction ration defined as in (5).

In the periodic case, we let $W(t,\zeta)$ be the monodromy matrix of the linear ω-periodic system:

$$\frac{du}{dt} = \left(-V(t) + \frac{1}{\zeta}F(t)\right)u, \quad t \in \mathbb{R},$$

with parameter $\zeta \in (0,\infty)$. Since $F(t)$ is non-negative and $-V(t)$ is cooperative, it follows that $\rho(W(\omega,\zeta))$ is continuous and non-increasing in $\zeta \in (0,\infty)$, and $\lim_{\zeta\to\infty}\rho(W(\omega,\zeta)) < 1$. It is easy to verify that model system (27) satisfies assumptions (A_1)–(A_7) of Theorem 2.1 in Wang and Zhao [56]. Thus, applying the results in [56] (Theorem 2.1), the following three statements are valid:

1. If $\rho(W(\omega,\zeta)) = 1$ has a positive solution ζ_0, then ζ_0 is an eigenvalue of the operator L, and hence $\mathcal{R}_0 > 1$.
2. If $\mathcal{R}_0 > 1$, then, $\zeta = \mathcal{R}_0$ is the unique solution of $\rho(W(\omega,\zeta)) = 1$.
3. $\mathcal{R}_0 = 0$ if and only if $\rho(W(\omega,\zeta)) < 1$ for all $\zeta > 0$.

Applying the results of Wang and Zhao [56] (Theorem 2.2), once again, we claim the following.

1. $\mathcal{R}_0 = 1$ if and only if $\rho(\Phi_{F-V}(\omega)) = 1$.
2. $\mathcal{R}_0 > 1$ if and only if $\rho(\Phi_{F-V}(\omega)) > 1$.
3. $\mathcal{R}_0 < 1$ if and only if $\rho(\Phi_{F-V}(\omega)) < 1$.

Thus, the disease-free equilibrium Q_0 of model system (27) is locally asymptotically stable if $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$.

3.2 A study case

From the National Committee for Fight against Tuberculosis in Cameroon [39], we have obtained the quarterly numbers of newly reported TB cases from January 2003 to December 2007. The quarterly reported TB cases in Cameroon from 2003 and 2007 show an obvious seasonal fluctuation, with the seasonality peak in the first quarterly. This seasonal trend may be mainly attributed to increase times spent in overcrowded, poorly ventilated housing conditions [10, 13, 21], and/or more frequent viral infections, with immunological deficiency leading to reactivation of the *M. Tuberculosis* [13]. The quarterly reported TB cases in Cameroon from 2003 to 2007 are given in Table 3.

Table 3 The numbers of quarterly reported new TB cases

Trimester	2003	2004	2005	2006	2007
First trimester	3032	2875	3334	3703	3491
Second trimester	2778	2854	3323	3626	3160
Third trimester	2475	2655	3187	3171	3157
Four trimester	2624	3122	3325	3315	3208

The quarterly numbers of new TB cases in Table 2 correspond to the term

$$g(t) = pf\lambda(t)S(t) + h(1-r_1)\big(k(t)+\sigma\lambda(t)\big)E(t) \tag{33}$$

in the third equation of model system (27). Since variables and parameters in model system (27) are continuous functions of t, we use trigonometric functions to fit $g(t)$ as a periodic function with period 5. Let

$$g(t) = c_0 + \sum_{m=1}^{7}(d_m \cos mLt + e_m \sin mLt), \tag{34}$$

in order to let the expression of $g(t)$ be simpler and exacter, where $L = \frac{2\pi}{5}$ is the fundamental frequency. We use the software Mathematica to determine those coefficients d_k and e_k, which yields the function $g(t)$ given as follows:

$$\begin{aligned} g(t) \approx\ & 3120.75 - 232.102\cos(2\pi t/5) \\ & + 44.9921\cos(4\pi t/5) + 37.0004\cos(6\pi t/5) \\ & - 32.8381\cos(8\pi t/5) + 179\cos(10\pi t/5) \\ & + 19.7421\cos(12\pi t/5) \\ & - 68.5405\cos(14\pi t/5) \\ & - 313.023\sin(2\pi t/5) - 63.8465\sin(4\pi t/5) \\ & - 54.4061\sin(6\pi t/5) - 47.7114\sin(8\pi t/5) \\ & + 14.7\sin(10\pi t/5) - 29.9372\sin(12\pi t/5) \\ & + 12.4314\sin(14\pi t/5). \end{aligned} \tag{35}$$

The comparison of the data with the curve is shown in Fig. 7. The data and the curve match quite well.

Now, we need to estimate unknown parameters $\beta(t)$ and $k(t)$. This will be done via numerical simulations. We assume that the transmission rate $\beta(t)$ and the reactivation rate $k(t)$ are defined as

$$\beta(t) = \beta_0\beta_1(t) \quad \text{and} \quad k(t) = k_0k_1(t), \tag{36}$$

where β_0 and k_0 are related to the magnitudes of the seasonal fluctuation and $\beta_1(t)$ and $k_1(t)$ are periodic function to be determined. In the sensitivity analysis, those two parameters are varied to see the influences of the transmission rate and the reactivation rate on the new TB case numbers. For simulations, we take the first quarterly of 2003 as the start time of simulation.

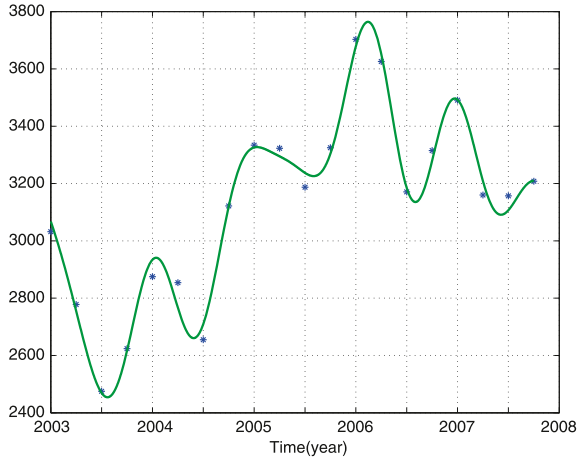

Fig. 7 The quarterly numbers of new TB cases and its fitted curve

The statistics of the National Institute of Statistics [44] show that the total population of the whole Cameroonian in 2003 is $N(0) = 15685000$. According to the National Committee of Fight against Tuberculosis in Cameroon, the number of new and relapse cases of TB was 3650, then we take $I(0) = 3650$. We assume that 70% of the Cameroonian population is infected with *M. Tuberculosis*, that is, $S(0) = 4705500$. We also assume that tenth of the new and relapse cases of TB are not diagnosed in the hospital so that $J(0) = 365$. Then, we can find that $E(0) = 10975485$. All other parameter values in the simulations are as in Table 1.

Without loss of generality, we assume that $\beta_1(t) = \theta g(t)$ where θ is a positive constant to be specified by the designer. Then, from (33) one can deduce that $k_1(t) = (g(t)/(h(1-r_1)\bar{E}))(1-\theta(\bar{I}+\varepsilon\bar{J})(pf\bar{S} + \sigma h(1-r_1)\bar{E})/\bar{N})$ where $\bar{S}$, $\bar{E}$, $\bar{I}$, $\bar{J}$ and $\bar{N}$ are the average number of susceptible, latently infected, diagnosed and undiagnosed infectious individuals and total population in the Cameroonian population between 2003 and 2009. After simulations and comparisons, $\theta = 0.0040879$, $\beta_0 = 0.0001$ and $k_0 = 0.71$ have been chosen, and $\beta_1(t)$ and $k_1(t)$ are the following two periodic functions:

$$\begin{aligned} \beta_1(t) = \big(& 12.7573 - 0.9488\cos(2\pi t/5) \\ & + 0.1839\cos(4\pi t/5) + 0.1513\cos(6\pi t/5) \\ & - 0.1342\cos(8\pi t/5) + 0.7317\cos(10\pi t/5) \\ & + 0.0807\cos(12\pi t/5) - 0.2802\cos(14\pi t/5) \\ & - 1.2796\sin(2\pi t/5) - 0.2610\sin(4\pi t/5) \end{aligned}$$

$$
\begin{aligned}
&- 0.2224\sin(6\pi t/5) - 0.1950\sin(8\pi t/5)\\
&+ 0.0601\sin(10\pi t/5) - 0.1224\sin(12\pi t/5)\\
&+ 0.0508\sin(14\pi t/5)\big) \qquad (37)
\end{aligned}
$$

and

$$
\begin{aligned}
k_1(t) = \big(10^{-5}\big)\big[&637.9488 - 47.4467\cos(2\pi t/5)\\
&+ 9.1974\cos(4\pi t/5) + 7.5637\cos(6\pi t/5)\\
&- 6.7128\cos(8\pi t/5) + 36.5915\cos(10\pi t/5)\\
&+ 4.0357\cos(12\pi t/5)\\
&- 14.0112\cos(14\pi t/5)\\
&- 63.9887\sin(2\pi t/5) - 13.0516\sin(4\pi t/5)\\
&- 11.1218\sin(6\pi t/5) - 9.7532\sin(8\pi t/5)\\
&+ 3.005\sin(10\pi t/5) - 6.1198\sin(12\pi t/5)\\
&+ 2.5412\sin(14\pi t/5)\big]. \qquad (38)
\end{aligned}
$$

Substituting these values of parameters and functions into model system (27), we obtain the following TB transmission model to simulation TB infection in Cameroon:

$$
\begin{cases}
\dot{S} = 397800 - \beta_0\beta_1(t)\dfrac{(I+1.5J)S}{N} - 0.01986S,\\
\dot{E} = 0.9850\beta_0\beta_1(t)\dfrac{(I+1.5J)S}{N} + r_2 I\\
\qquad + r_3 J - 2\beta_0\beta(t)\dfrac{(I+1.5J)E}{N}\\
\qquad - \big(0.01986 + k_0k_1(t)\big)E,\\
\dot{I} = 0.0105\beta_0\beta_1(t)\dfrac{(I+1.5J)S}{N}\\
\qquad + 0.69\left(k_0k_1(t) + 2\beta_0\beta(t)\dfrac{(I+1.5J)}{N}\right)E\\
\qquad - (0.01986 + 0.0575 + 0.8625)I,\\
\dot{J} = 0.0045\beta_0\beta_1(t)\dfrac{(I+1.5J)S}{N}\\
\qquad + 0.31\left(k_0k_1(t) + 2\beta_0\beta(t)\dfrac{(I+1.5J)}{N}\right)E\\
\qquad - (0.01986 + 0.24 + 0.49)J.
\end{cases} \qquad (39)
$$

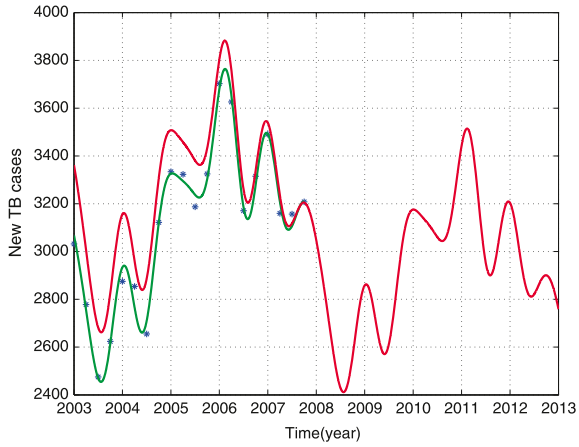

Fig. 8 New TB cases: reported number and simulation curve

Simulation results are reported in Figs. 8 and 9. Figure 8 illustrates the comparison of the quarterly reported data and the simulation curve of new TB cases in Cameroon. The stars in the curve stand for the reported new TB cases, from January 2003 to December 2006. The simulation result based on our model exhibits the seasonal fluctuation and matches the data with some small error between 2003 and 2007 but after the model matches the data well. This implies that the model is in transient period between 2003 and 2006. This can be due to the choice of the initial conditions which may not be the exact initial conditions corresponding to the first quarterly of 2003. To resolve this problem, we need more data. Figure 9 gives the trends of susceptible, latently infected, diagnosed and undiagnosed individuals in the future several years, respectively.

Sensitivity analysis of parameters is not only critical to model verification and validation in the process of model development and refinement, but also provides insight into the robustness of the model results when making decisions [57]. Figure 10 illustrates the impact of β_0 and k_0 on the quarterly new TB cases. From this figure, one can see that β_0 and k_0 have an evident impacts on the numbers of new TB cases. The number of new TB cases increases substantially with a rise in β_0 and k_0, and falls with a decrease in β_0 and k_0.

4 Discussions and conclusion

This paper presents a comprehensive, continuous and more realistic deterministic model for the transmission

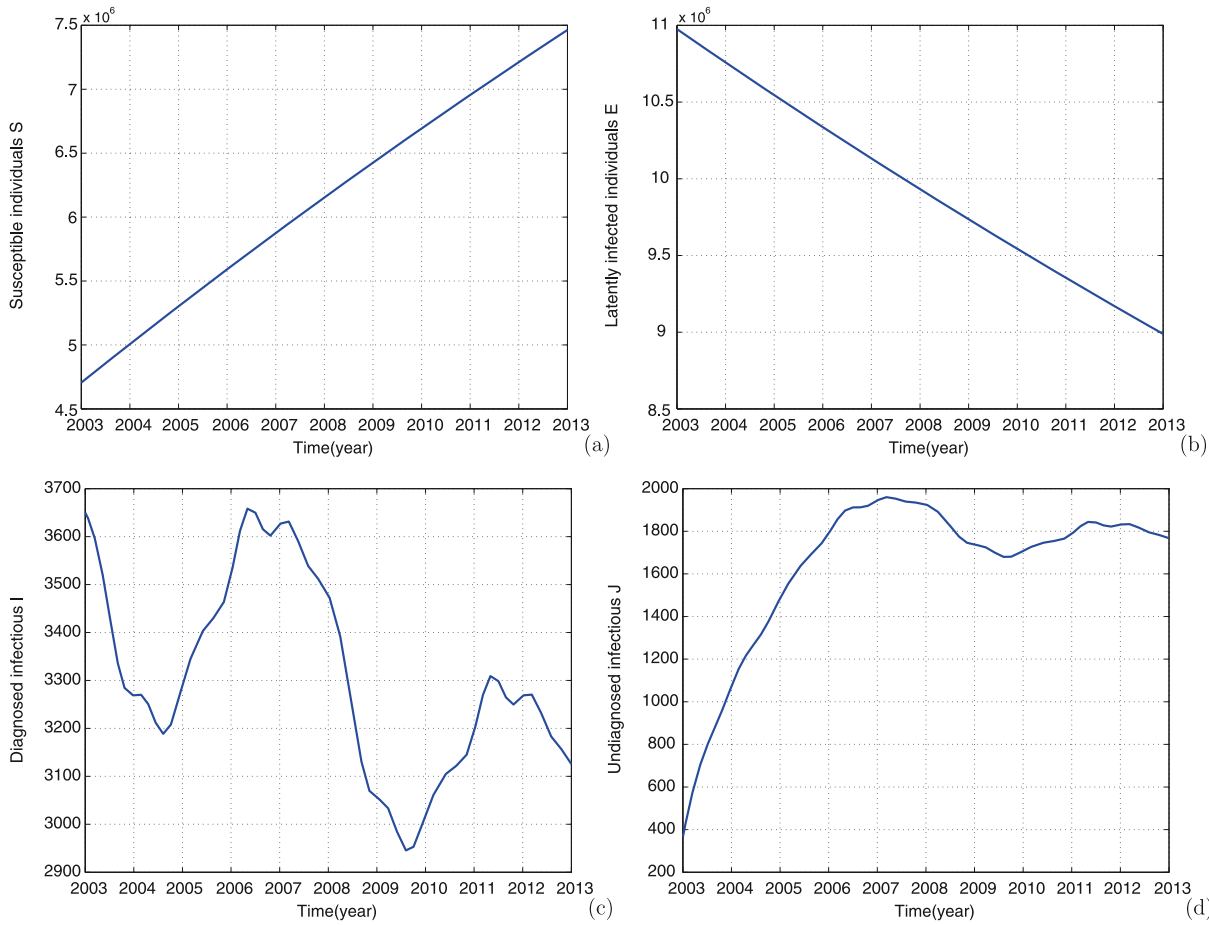

Fig. 9 Simulation of model system (27) performed with $\beta_0 = 0.0001$ and $k_0 = 0.71$. Time series of (**a**) susceptible individuals, (**b**) latently infected individuals, (**c**) diagnosed infectious and (**d**) undiagnosed infectious

dynamics of tuberculosis without and with seasonality. In contrast to many TB models in the literature, we have included two infective classes emanating from diagnosed and undiagnosed infectious. The undiagnosed subclass is of particular importance in modeling TB in developing countries like Sub-Saharan Africa where public health is under developed. In particular the proportion of individuals that present themselves to medical facilities, h, is worth noting. This parameter can be used to measure successes of educational campaigns that encourage individuals to go for TB screening. It can also be a measure of the level of awareness of the implications of not having TB diagnosis.

The model has been rigourously analyzed to gain insight into its qualitative dynamics. We have mainly found that the model exhibits the phenomenon of backward bifurcation, where the stable disease-free equilibrium coexists with a stable endemic equilibrium, when the basic reproduction ratio is less than unity. It is shown that this (backward bifurcation) dynamics feature is caused by the reinfection of latently infected individuals. By analyzing this model without exogenous reinfections and mass balance incidence, we have found that it is globally asymptotically stable and possesses only the globally stable equilibrium state. Depending on the basic reproduction ratio, this steady state is either the endemic or the disease-free one. The global stability of the infection-free equilibrium state implies that for any initial level of infection the disease will eventually fade out from the population when the condition for this stability, namely $\mathcal{R}_0 \leq 1$, holds. The condition $\mathcal{R}_0 > 1$ implies that the disease will persist in a population.

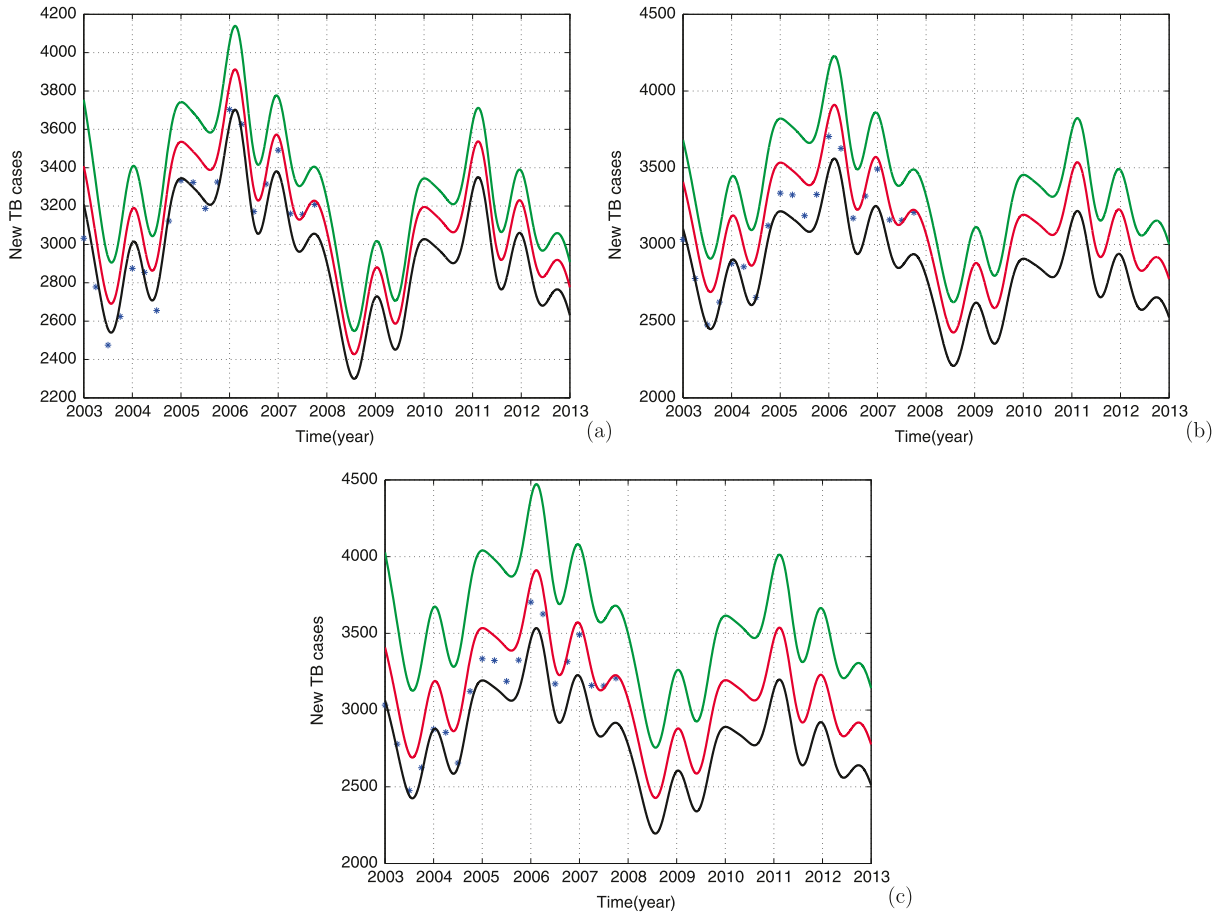

Fig. 10 (Color online) The relationship between new TB cases for different values of β_0 and k_0. (**a**) In the *green-line curve*, $\beta_0 = 0.001$ and in *black-line curve*, $\beta_0 = 0.00001$ when $k_0 = 0.71$; (**b**) in *green-line curve* $k_0 = 0.768$ and in *black-line curve* $k_0 = 0.645$ when $\beta_0 = 0.001$; and (**c**) in the *green-line curve* $\beta_0 = 0.001$ and $k_0 = 0.768$ and in *black-line curve* $\beta_0 = 0.00001$ and $k_0 = 0.645$. Other parameter values are given in Table 2. Here, the stars correspond to the real data from Cameroon and the red-line curve stands for $\beta_0 = 0.0001$ and $k_0 = 0.71$

This model has been extended to describe TB seasonal incidence rate by incorporating periodic coefficients. It has been found that there is a seasonal pattern of new TB cases in the mainland of Cameroon. Throughout numerical simulations, we found that the number of new TB cases is an increasing function of β_0 or k_0 and is more sensitive to k_0 than β_0.

From the practical viewpoint, the model formulated in this paper can be used to understand the transmission behaviors of the disease and to forecast the disease trends, which can help health program planners to implement more preventive interventions in TB control during the period of higher risk of infection.

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Appendix: Global stability of the endemic equilibrium of model (2) with mass balance incidence in the absence of the exogenous reinfections

In this appendix, we prove the global stability of the endemic equilibrium of model (2) with mass balance incidence in the absence of the exogenous reinfections. To this end, we use the same Lyapunov func-

tions as those used in [55, 58–62] to demonstrate the global stability of the endemic equilibrium of SEIR, SEIS, and SIR models.

Consider the following Lyapunov function candidate:

$$\begin{aligned} U(S,E,I,J) &= S - S^* \ln S + b_1\big(E - E^* \ln E\big) \\ &\quad + b_2\big(I - I^* \ln I\big) \\ &\quad + b_3\big(J - J^* \ln J\big), \end{aligned} \tag{40}$$

where

$$\begin{aligned} b_1 &= \frac{kh(1-r_1)A_3 + \beta\varepsilon S^* pk(1-r_1)(f-h)}{pf[(\mu+d_2)[\mu+k(1-r_1)] + r_3[\mu+kh(1-r_1)[1+p(1-f)]]]}, \\ b_2 &= \frac{1}{pfA_3}\big[A_3 - \beta\varepsilon S^* p(1-f) - b_1\big[A_3(1-p) + r_3 p(1-f)\big]\big], \\ b_3 &= \frac{\beta\varepsilon S^* + b_1 r_3}{A_3}. \end{aligned} \tag{41}$$

It is easy to show that the point Q^* is the only stationary point of this function and its global minimum, and the function $U(S,E,I,J)$ is a Lyapunov function. Indeed, the time derivative of this function satisfies

$$\begin{aligned} \dot{U} &= \left(1 - \frac{S^*}{S}\right)\dot{S} + b_1\left(1 - \frac{E^*}{E}\right)\dot{E} \\ &\quad + b_2\left(1 - \frac{I^*}{I}\right)\dot{I} + b_3\left(1 - \frac{J^*}{J}\right)\dot{J} \\ &= \left(1 - \frac{S^*}{S}\right)\big[\Lambda - \beta(I+\varepsilon J)S - \mu S\big] \\ &\quad + b_1\left(1 - \frac{E^*}{E}\right)\big[\beta(1-p)(I+\varepsilon J)S \\ &\quad + r_2 I + r_3 J - A_1 E\big] \\ &\quad + b_2\left(1 - \frac{I^*}{I}\right)\big[\beta pf(I+\varepsilon J)S \\ &\quad + kh(1-r_1)E - A_2 I\big] \\ &\quad + b_3\left(1 - \frac{J^*}{J}\right)\big[\beta p(1-f)(I+\varepsilon J)S \\ &\quad + k(1-h)(1-r_1)E - A_3 J\big], \end{aligned} \tag{42}$$

which may be rewritten as follows:

$$\begin{aligned} \dot{U} &= \left(1 - \frac{S^*}{S}\right)\big[\Lambda - \beta(I+\varepsilon J)S - \mu S\big] \\ &\quad + b_1\beta(1-p)(I+\varepsilon J)S + b_1 r_2 I + b_1 r_3)J \\ &\quad - b_1 A_1 E - b_1\beta(1-p)(I+\varepsilon J)S\frac{E^*}{E} \\ &\quad - b_1 r_2 I\frac{E^*}{E} - b_1 r_3 J\frac{E^*}{E} + b_1 A_1 E^* \\ &\quad + b_2\beta pf(I+\varepsilon J)S + b_2 kh(1-r_1)E \\ &\quad - b_2 A_2 I - b_2\beta pf(I+\varepsilon J)S\frac{I^*}{I} \\ &\quad - b_2 kh(1-r_1)E\frac{I^*}{I} + b_2 A_2 I^* \\ &\quad + b_3\beta p(1-f)(I+\varepsilon J)S \\ &\quad + b_3 k(1-h)(1-r_1)E - b_3 A_3 J \\ &\quad - b_3\beta p(1-f)(I+\varepsilon J)S\frac{J^*}{J} \\ &\quad - b_3 k(1-h)(1-r_1)E\frac{J^*}{J} + b_3 A_3 J^*, \end{aligned} \tag{43}$$

recalling that at the endemic equilibrium, one has

$$\begin{cases} \Lambda = \beta\big(I^* + \varepsilon J^*\big)S^* + \mu S^*, \\ A_1 E^* = \beta(1-p)\big(I^* + \varepsilon J^*\big)S^* \\ \qquad\quad + r_3 J^* + r_2 I^*, \\ A_2 I^* = \beta pf\big(I^* + \varepsilon J^*\big)S^* + kh(1-r_1)E^*, \\ A_3 J^* = \beta p(1-f)\big(I^* + \varepsilon J^*\big)S^* \\ \qquad\quad + k(1-h)(1-r_1)E^*. \end{cases} \tag{44}$$

With this in mind, (43) becomes

$$\begin{aligned}\dot{U} = {} & \left(1-\frac{S^*}{S}\right)\left[\beta\left(I^*+\varepsilon J^*\right)S^* \right.\\ & \left. +\mu S^* - \beta(I+\varepsilon J)S - \mu S\right]\\ & + b_1\beta(1-p)(I+\varepsilon J)S + b_1 r_2 I + b_1 r_3 J\\ & - b_1 A_1 E - b_1\beta(1-p)(I+\varepsilon J)S\frac{E^*}{E}\\ & - b_1 r_2 I\frac{E^*}{E} - b_1 r_3 J\frac{E^*}{E}\\ & + b_1\beta(1-p)\left(I^*+\varepsilon J^*\right)S^* + b_1 r_2 I^* + b_1 r_3 J^*\\ & + b_2\beta pf(I+\varepsilon J)S + b_2 kh(1-r_1)E - b_2 A_2 I\\ & - b_2\beta pf(I+\varepsilon J)S\frac{I^*}{I} - b_2 kh(1-r_1)E\frac{I^*}{I}\\ & + b_2\beta pf\left(I^*+\varepsilon J^*\right)S^* + b_2 kh(1-r_1)E^*\\ & + b_3\beta p(1-f)(I+\varepsilon J)S\\ & + b_3 k(1-h)(1-r_1)E - b_3 A_3 J\\ & - b_3\beta p(1-f)(I+\varepsilon J)S\frac{J^*}{J}\\ & - b_3 k(1-h)(1-r_1)E\frac{J^*}{J}\\ & + b_3\beta p(1-f)\left(I^*+\varepsilon J^*\right)S^*\\ & + b_3 k(1-h)(1-r_1)E^*. \end{aligned} \tag{45}$$

Rearranging, (45) gives

$$\begin{aligned}\dot{U} = {} & -\mu\frac{(S-S^*)^2}{S} + \left(1-\frac{S^*}{S}\right)\beta\left(I^*+\varepsilon J^*\right)S^*\\ & + \left[-1+b_1(1-p)+b_2 pf\right.\\ & \left. + b_3 p(1-f)\right]\beta(I+\varepsilon J)S\\ & + \left[b_1(1-p)+b_2 pf\right.\\ & \left. + b_3 p(1-f)\right]\beta\left(I^*+\varepsilon J^*\right)S^*\\ & + \left[-b_1 A_1 + b_2 kh(1-r_1)\right.\\ & \left. + b_3 k(1-h)(1-r_1)\right]E\\ & + \left[\beta S^* + b_1 r_2 - b_2 A_2\right]I\\ & + \left[\beta\varepsilon S^* + b_1 r_3 - b_3 A_3\right]J\\ & - b_1\beta(1-p)S^*I^*\frac{SI}{S^*I^*}\frac{E^*}{E}\\ & - b_1\beta\varepsilon(1-p)S^*J^*\frac{SJ}{S^*J^*}\frac{E^*}{E}\\ & - b_2\beta pf S^*I^*\frac{S}{S^*} - b_2\beta pf\varepsilon S^*J^*\frac{SJ}{S^*J^*}\frac{I^*}{I}\\ & - b_3\beta p(1-f)S^*I^*\frac{SI}{S^*I^*}\frac{J^*}{J}\\ & - b_3\beta p(1-f)\varepsilon S^*J^*\frac{S}{S^*}\\ & + b_1 r_2 I^*\left(1-\frac{I}{I^*}\frac{E^*}{E}\right) + b_1 r_3 J^*\left(1-\frac{J}{J^*}\frac{E^*}{E}\right)\\ & + b_2 kh(1-r_1)E^*\left(1-\frac{E}{E^*}\frac{I^*}{I}\right)\\ & + b_3 k(1-h)(1-r_1)E^*\left(1-\frac{E}{E^*}\frac{J^*}{J}\right). \end{aligned} \tag{46}$$

Now, the constants b_1, b_2 and b_3 can be chosen such that the coefficients of $\beta(I+\varepsilon J)S$, E, I and J are equal to zero, that is,

$$\begin{cases} b_1(1-p)+b_2 pf+b_3 p(1-f)=1,\\ -b_1 A_1 + b_2 kh(1-r_1)\\ \quad + b_3 k(1-h)(1-r_1)=0,\\ \beta S^* + b_1 r_2 - b_2 A_2 = 0,\\ \beta\varepsilon S^* + b_1 r_3 - b_3 A_3 = 0. \end{cases} \tag{47}$$

At this point, it is important to mention that when the third equation of (47) is satisfied, then all other equations of (47) are also satisfied. Indeed, multiplying the third equation of (47) by I^* and using the expression of $A_2 I^*$ defined as in (44), one obtains

$$\begin{aligned}&\beta S^*I^* + b_1 r_2 I^* - b_2 A_2 I^*\\ &\quad = \beta S^*I^* + b_1 r_2 I^* - b_2\beta pf\left(I^*+\varepsilon J^*\right)S^*\\ &\qquad - b_2 kh(1-r_1)E^*. \end{aligned} \tag{48}$$

On the other hand, from (44), one has

$$\begin{aligned}&b_1 A_1 E^* - b_1\beta(1-p)\left(I^*+\varepsilon J^*\right)S^*\\ &\quad - b_1 r_3 J^* - b_1 r_2 I^* + b_3 A_3 J^*\\ &\quad - b_3\beta p(1-f)\left(I^*+\varepsilon J^*\right)S^*\\ &\quad - b_3 k(1-h)(1-r_1)E^* = 0. \end{aligned} \tag{49}$$

Adding (49) in the right-hand side of (48) yields

$$\begin{aligned}&\left[1-b_1(1-p)-b_2 pf-b_3 p(1-f)\right]\beta\left(I^*+\varepsilon J^*\right)S^*\\ &\quad + \left[b_1 A_1 - b_2 kh(1-r_1) - b_3 k(1-h)(1-r_1)\right]E^*\\ &\quad + \left[-\beta\varepsilon S^* - b_1 r_3 + b_3 A_3\right]J^* = 0, \end{aligned} \tag{50}$$

which implies that when the third equation of (47) is satisfied, then all other equations of (47) are also satisfied. This is why we only consider the following system of equations:

$$\begin{cases} b_1(1-p)+b_2pf+b_3p(1-f)=1, \\ -b_1A_1+b_2kh(1-r_1) \\ \quad +b_3k(1-h)(1-r_1)=0, \\ \beta\varepsilon S^*+b_1r_3-b_3A_3=0. \end{cases} \tag{51}$$

Resolving the above system of equations gives the expressions of b_1, b_2 and b_3 defined as in (41). Plugging the expressions of b_1, b_2 and b_3 defined as in (41) into (46) gives

$$\begin{aligned} \dot{U} = & -\mu\frac{(S-S^*)^2}{S}+\left(2-\frac{S^*}{S}\right)\beta\left(I^*+\varepsilon J^*\right)S^* \\ & -b_1\beta(1-p)S^*I^*\frac{SI}{S^*I^*}\frac{E^*}{E} \\ & -b_1\beta\varepsilon(1-p)S^*J^*\frac{SJ}{S^*J^*}\frac{E^*}{E}-b_2\beta pfS^*I^*\frac{S}{S^*} \\ & -b_2\beta pf\varepsilon S^*J^*\frac{SJ}{S^*J^*}\frac{I^*}{I} \\ & -b_3\beta p(1-f)S^*I^*\frac{SI}{S^*I^*}\frac{J^*}{J} \\ & -b_3\beta p(1-f)\varepsilon S^*J^*\frac{S}{S^*}+b_1r_2I^*\left(1-\frac{I}{I^*}\frac{E^*}{E}\right) \\ & +b_1r_3J^*\left(1-\frac{J}{J^*}\frac{E^*}{E}\right) \\ & +b_2kh(1-r_1)E^*\left(1-\frac{E}{E^*}\frac{I^*}{I}\right) \\ & +b_3k(1-h)(1-r_1)E^*\left(1-\frac{E}{E^*}\frac{J^*}{J}\right). \end{aligned} \tag{52}$$

Now, let $(x_1,x_2,x_3,x_4)=(\frac{S^*}{S},\frac{E^*}{E},\frac{I^*}{I},\frac{J^*}{J})$. Then, (52) becomes

$$\begin{aligned} \dot{U} = & -\mu\frac{(S-S^*)^2}{S}+\beta\left[b_2pfI^*\right. \\ & \left.+b_3p(1-f)\varepsilon J^*\right]S^*\left(2-x_1-\frac{1}{x_1}\right) \\ & +b_1\beta(1-p)S^*I^*\left(2-x_1-\frac{x_2}{x_1x_3}\right) \\ & +b_1\beta\varepsilon(1-p)S^*J^*\left(2-x_1-\frac{x_2}{x_1x_4}\right) \\ & +b_2\beta pf\varepsilon S^*J^*\left(2-x_1-\frac{x_3}{x_1x_4}\right) \\ & +b_3\beta p(1-f)S^*I^*\left(2-x_1-\frac{x_4}{x_1x_3}\right) \\ & +b_3\beta p(1-f)\varepsilon S^*J^*\left(2-x_1-\frac{x_4}{x_1x_5}\right) \\ & +b_1r_2I^*\left(1-\frac{x_2}{x_3}\right)+b_1r_3J^*\left(1-\frac{x_2}{x_4}\right) \\ & +b_2kh(1-r_1)E^*\left(1-\frac{x_3}{x_2}\right) \\ & +b_3k(1-h)(1-r_1)E^*\left(1-\frac{x_4}{x_2}\right). \end{aligned} \tag{53}$$

Multiplying the second and third equations in (51) by E^* and J^*, respectively, yields

$$\begin{cases} -b_1A_1E^*+b_2kh(1-r_1)E^* \\ \quad +b_3k(1-h)(1-r_1)E^*+b_5r_1E^*=0, \\ \beta\varepsilon S^*J^*+b_1r_3J^*-b_3A_3J^*=0. \end{cases} \tag{54}$$

Then, using the expressions of A_1E^* and A_3J^* defined as in (44), (54) becomes

$$\begin{cases} -b_1\beta(1-p)\left(I^*+\varepsilon J^*\right)S^*-b_1r_3J^* \\ \quad -b_1r_2I^*+b_2kh(1-r_1)E^* \\ \quad +b_3k(1-h)(1-r_1)E^*=0, \\ \beta\varepsilon S^*J^*+b_1r_3J^*-b_3\beta p(1-f)\left(I^*+\varepsilon J^*\right)S^* \\ \quad -b_3k(1-h)(1-r_1)E^*=0. \end{cases} \tag{55}$$

Let $F_1(u)$ and $F_2(u)$ with $u=(x_1,x_2,x_3,x_4)^T$ be two functions to be determined later. Multiplying the first and second equations in (55) by $F_1(u)$ and $F_2(u)$, respectively, gives

$$\begin{cases} -b_1\beta(1-p)\left(I^*+\varepsilon J^*\right)S^*F_1-b_1r_3J^*F_1 \\ \quad -b_1r_2I^*F_1+b_2kh(1-r_1)E^*F_1 \\ \quad +b_3k(1-h)(1-r_1)E^*F_1+b_5r_1E^*F_1=0, \\ \beta\varepsilon S^*J^*F_2+b_1r_3J^*F_2 \\ \quad -b_3\beta p(1-f)\left(I^*+\varepsilon J^*\right)S^*F_2 \\ \quad -b_3k(1-h)(1-r_1)E^*F_2=0. \end{cases} \tag{56}$$

Adding (56) to the right-hand side of (57) yields

$$\begin{aligned}\dot{U} = &-\mu\frac{(S-S^*)^2}{S}\\ &+\beta\big(b_2pfI^*+b_3p(1-f)\varepsilon J^*\big)\\ &\times S^*\left(2-x_1-\frac{1}{x_1}\right)\\ &+b_1\beta(1-p)S^*I^*\left(2-x_1-\frac{x_2}{x_1x_3}-F_1\right)\\ &+b_1\beta\varepsilon(1-p)\\ &\times S^*J^*\left(2-x_1-\frac{x_2}{x_1x_4}-F_1+F_2\right)\\ &+b_2\beta pf\varepsilon S^*J^*\left(2-x_1-\frac{x_3}{x_1x_4}+F_2\right)\\ &+b_3\beta p(1-f)S^*I^*\left(2-x_1-\frac{x_4}{x_1x_3}-F_2\right)\\ &+b_1r_2I^*\left(1-\frac{x_2}{x_3}-F_1\right)\\ &+b_1r_3J^*\left(1-\frac{x_2}{x_4}-F_1+F_2\right)\\ &+b_2kh(1-r_1)E^*\left(1-\frac{x_3}{x_2}+F_1\right)\\ &+b_3k(1-h)(1-r_1)E^*\left(1-\frac{x_4}{x_2}+F_1-F_2\right).\end{aligned}\tag{57}$$

Now, we shall choose the functions $F_1(u)$ and $F_2(u)$, which make $\dot{U}$ non-positive. To this end, the function $F_1(u)$ is chosen such that the coefficient of $b_2kh(1-r_1)E^*$ is equal to zero and the function $F_2(u)$ is chosen such that the coefficient of $b_2\beta pf\varepsilon S^*J^*$ is non-positive, that is:

$$F_1=-1+\frac{x_3}{x_2}\quad\text{and}\quad F_2=1-\frac{x_4}{x_3}.\tag{58}$$

Substituting the above expressions of $F_1(u)$ and $F_2(u)$ into (57), one finally obtains

$$\begin{aligned}\dot{U} = &-\mu\frac{(S-S^*)^2}{S}+\beta\big(b_2pfI^*\\ &+b_3p(1-f)\varepsilon J^*\big)S^*\left(2-x_1-\frac{1}{x_1}\right)\\ &+b_1\beta(1-p)S^*I^*\left(3-x_1-\frac{x_2}{x_1x_3}-\frac{x_3}{x_2}\right)\\ &+b_1\beta\varepsilon(1-p)\\ &\times S^*J^*\left(4-x_1-\frac{x_2}{x_1x_4}-\frac{x_3}{x_2}-\frac{x_4}{x_3}\right)\\ &+b_2\beta pf\varepsilon S^*J^*\left(3-x_1-\frac{x_3}{x_1x_4}-\frac{x_4}{x_3}\right)\\ &+b_3\beta p(1-f)S^*I^*\left(1+\frac{x_4}{x_3}-x_1-\frac{x_4}{x_1x_3}\right)\\ &+b_1r_2I^*\left(2-\frac{x_2}{x_3}-\frac{x_3}{x_2}\right)\\ &+b_1r_3J^*\left(3-\frac{x_2}{x_4}-\frac{x_3}{x_2}-\frac{x_4}{x_3}\right)\\ &+b_3k(1-h)(1-r_1)\\ &\times E^*\left(-1-\frac{x_4}{x_2}+\frac{x_3}{x_2}+\frac{x_4}{x_3}\right).\end{aligned}\tag{59}$$

Since the arithmetic mean exceeds the geometrical mean, the following inequalities hold:

$$\begin{aligned}&3-x_1-\frac{x_2}{x_1x_3}-\frac{x_3}{x_2}\le 0,\\ &4-x_1-\frac{x_2}{x_1x_4}-\frac{x_3}{x_2}-\frac{x_4}{x_3}\le 0,\\ &3-x_1-\frac{x_3}{x_1x_4}-\frac{x_4}{x_3}\le 0,\\ &2-\frac{x_2}{x_3}-\frac{x_3}{x_2}\le 0,\qquad 3-\frac{x_2}{x_4}-\frac{x_3}{x_2}-\frac{x_4}{x_3}\le 0.\end{aligned}$$

Now let

$$\begin{aligned}f_1(u)&=1+\frac{x_4}{x_3}-x_1-\frac{x_4}{x_1x_3}\quad\text{and}\\ f_2(u)&=1-\frac{x_4}{x_2}+\left(\frac{x_3}{x_2}+\frac{x_4}{x_3}-2\right).\end{aligned}\tag{60}$$

The next step is to show that the functions $f_1(u)$ and $f_2(u)$ are non-positive for all $x_1,x_2,x_3,x_4\in\mathbb{R}_{\ge 0}$. Assume that $x_1\le x_4\le x_3\le 1$, then one has

$$\begin{aligned}f_1(u)&=1+\frac{x_4}{x_3}-x_1-\frac{x_4}{x_1x_3},\\ &\le 1+\frac{x_4}{x_3}-\left(\frac{x_1}{x_3}+\frac{x_4}{x_1}\right),\\ &\le \frac{x_4-x_3}{x_3}-\left(\frac{x_1-x_3}{x_3}+\frac{x_4-x_1}{x_1}\right),\\ &\le \frac{x_4-x_3}{x_3}-\left(\frac{x_1-x_3}{x_3}+\frac{x_4-x_1}{x_3}\right)=0.\end{aligned}$$

Also, if $x_4 \leq x_3 \leq x_2$, one has

$$\begin{aligned}\frac{x_3}{x_2}+\frac{x_4}{x_3}-2 &= \left(\frac{x_4}{x_3}-1\right)+\left(\frac{x_3}{x_2}-1\right),\\ &= \frac{x_4-x_3}{x_3}+\frac{x_3-x_2}{x_2},\\ &\leq \frac{x_4-x_3}{x_2}+\frac{x_3-x_2}{x_2}=\frac{x_4}{x_2}-1.\end{aligned}$$

It then follows that

$$f_2(u) \leq 1-\frac{x_4}{x_2}+\frac{x_4}{x_2}-1=0.$$

Therefore, when the condition (26) is satisfied, then $\dot{U} \leq 0$ for all $x_1, x_2, x_3, x_4 \geq 0$, provided that S^*, E^*, I^*, J^* are positive, where the equality $\dot{U}=0$ holds only on the straight line $S=S^*$, $E^*/E = I^*/I = J^*/J$. On the other hand, it is easy to see that for the system (2) with mass balance incidence in the absence of exogenous reinfections, Q^* is the only equilibrium state on this line. Thus, by Lyapunov–LaSalle asymptotic stability theorem [24–36], the positive equilibrium state Q^* is globally asymptotically stable in the positive region $\Omega \subset \mathbb{R}^4_{\geq 0}$, except on the S-axis which is the stable manifold for the fixed point Q_0. This achieves the proof.

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