Parameter estimation and optimal control of the dynamics of transmission of tuberculosis with application to Cameroon

Samuel Bowong and Jean Jules Tewa

UMI 209 IRD/UPMC UMMISCO, Bondy, Projet MASAIE INRIA Grand Est, France and Projet Grimcape, LIRIMA, Cameroun

COMMISCO 2010, 11-13 Octobre, Bondy, France

Outline

Outline

- Introduction

Outline

- Introduction
- Epidemiology of Tuberculosis

Outline

- Introduction
- Epidemiology of Tuberculosis
- Model formulation and analysis of the model

Outline

- Introduction
- Epidemiology of Tuberculosis
- Model formulation and analysis of the model
- Estimation of unknown parameters

Outline

- Introduction
- Epidemiology of Tuberculosis
- Model formulation and analysis of the model
- Estimation of unknown parameters
- Optimal intervention strategies

Outline

- Introduction
- Epidemiology of Tuberculosis
- Model formulation and analysis of the model
- Estimation of unknown parameters
- Optimal intervention strategies
- Summary

Introduction

Introduction

- Tuberculosis (TB) is one of the most wide spread infectious diseases, and the leading cause of death due to a single infectious agent among adults in the world.

Introduction

- Tuberculosis (TB) is one of the most wide spread infectious diseases, and the leading cause of death due to a single infectious agent among adults in the world.
- It is estimated that a third of the world population is infected with Mycobacterium tuberculosis and 1.3 billion live in developing countries.

Introduction

- Tuberculosis (TB) is one of the most wide spread infectious diseases, and the leading cause of death due to a single infectious agent among adults in the world.
- It is estimated that a third of the world population is infected with Mycobacterium tuberculosis and 1.3 billion live in developing countries.
- It is responsible for approximately three million deaths each year.

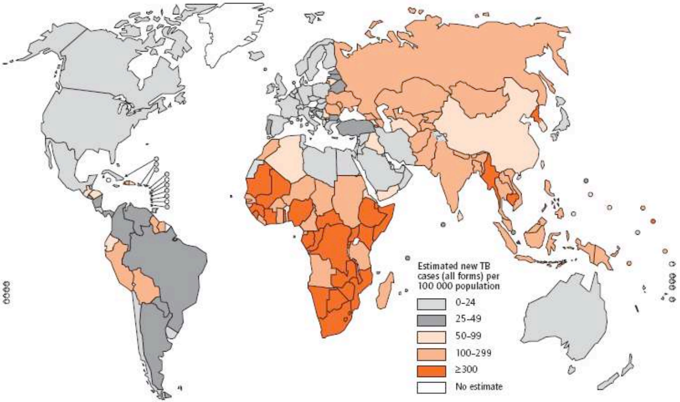
Introduction

- Tuberculosis (TB) is one of the most wide spread infectious diseases, and the leading cause of death due to a single infectious agent among adults in the world.
- It is estimated that a third of the world population is infected with Mycobacterium tuberculosis and 1.3 billion live in developing countries.
- It is responsible for approximately three million deaths each year.
- In 1993, the World Health Organization (WHO) declared TB as a global emergency because of the rising deaths and infection rates.

Worldwide TB (WHO)

Worldwide TB (WHO)

- Estimated TB incidence rates, 2008



Introduction

Factors that have called for improved control strategies for TB are

Introduction

Factors that have called for improved control strategies for TB are

- Endogenous reactivation

Introduction

Factors that have called for improved control strategies for TB are

- Endogenous reactivation
- Emergence of multi-drug resistant

Introduction

Factors that have called for improved control strategies for TB are

- Endogenous reactivation
- Emergence of multi-drug resistant
- Exogenous re-infection, where a latently-infected individual acquires a new infection from another infectious

Introduction

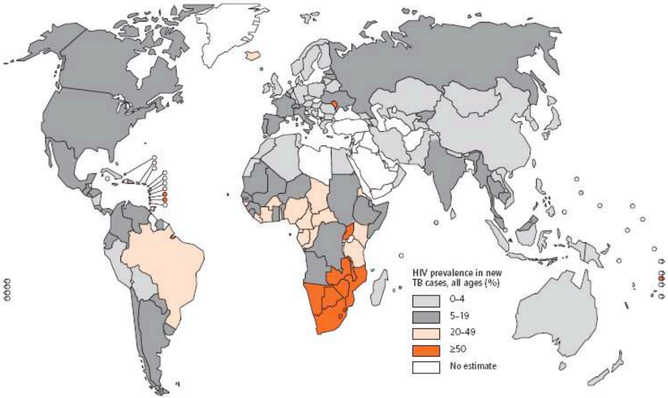
Factors that have called for improved control strategies for TB are

- Endogenous reactivation
- Emergence of multi-drug resistant
- Exogenous re-infection, where a latently-infected individual acquires a new infection from another infectious
- Increase in HIV incidence

Worldwide TB (WHO)

Worldwide TB (WHO)

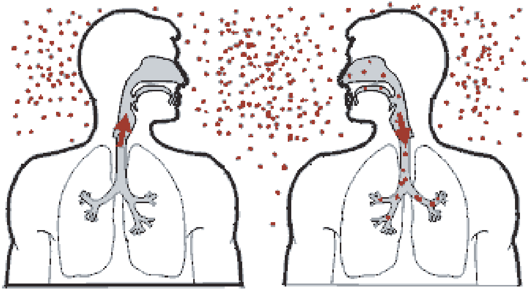
- Estimated HIV prevalence in new TB cases, 2008



A short biological background

A short biological background

- Tuberculosis (TB) is a contagious bacteria disease caused by inhaling the tubercle bacillus in the droplet nucleus form.



A short biological background

A short biological background

- When infectious people cough, sneeze, talk or spit, they propel TB germs, known as bacilli, into the air. A person needs only to inhale a small number of these to be infected.

A short biological background

A short biological background

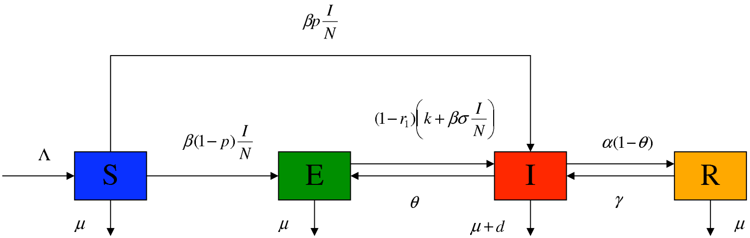
- An infected person may have latent TB infection or active TB infection.

A short biological background

- An infected person may have latent TB infection or active TB infection.
- A latent TB infected person does not show any symptoms of the disease and cannot infect others, though may live as long as possible without it degenerating into active TB

Transfert diagram

The transfer diagram is as follows



The equations

The corresponding equations are

$$\begin{cases} \dot{S} &= \Lambda - \lambda S - \mu S, \\ \dot{E} &= (1-p)\lambda S + \theta I - \sigma(1-r_1)\lambda E - [\mu + k(1-r_1)]E, \\ \dot{I} &= p\lambda S + \gamma R + (1-r_1)(k+\sigma\lambda)E - [\mu + d + \theta + \alpha(1-\theta)]I, \\ \dot{R} &= \alpha(1-\theta)I - [\mu+\gamma]R. \end{cases}$$

where

$$\lambda = \beta \frac{SI}{N},$$

is the force of infection.

Positive invariance of the nonnegative orthant and Boundedness of the trajectories

For the model to be epidemiologically meaningful, it is important to prove that all its state are non-negative for all time.
We have the following result :

Proposition

The nonnegative orthant $\mathbb{R}^4_+$ is positively invariant for the model.

The closed set

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

is a compact forward invariant set for the system and for $\varepsilon > 0$, this set is absorbing.

Local stability of the disease-free equilibrium (DFE)

Local stability of the disease-free equilibrium (DFE)

- The model has an evident equilibrium called the disease-free equilibrium $Q^0 = \left(\frac{\Lambda}{\mu}, 0, 0, 0\right)$

Local stability of the disease-free equilibrium (DFE)

- The model has an evident equilibrium called the disease-free equilibrium $Q^0 = \left(\frac{\Lambda}{\mu}, 0, 0, 0\right)$
- Using the method of van den Driessche and Watmough, the basic reproduction ratio is defined as follows :

$$\mathcal{R}_0 = \frac{\beta(\mu+\gamma)[p\mu + k(1-r_1)]}{D},$$

where

$$D = (\mu+\gamma)[\mu(\mu+d+\theta) + k(1-r_1)(\mu+d)] + \mu\alpha(1-\theta)[\mu+k(1-r_1).$$

Local stability of the disease-free equilibrium (DFE)

- The model has an evident equilibrium called the disease-free equilibrium $Q^0 = \left(\frac{\Lambda}{\mu}, 0, 0, 0\right)$
- Using the method of van den Driessche and Watmough, the basic reproduction ratio is defined as follows :

$$\mathcal{R}_0 = \frac{\beta(\mu+\gamma)[p\mu + k(1-r_1)]}{D},$$

where

$$D = (\mu+\gamma)[\mu(\mu+d+\theta)+k(1-r_1)(\mu+d)]+\mu\alpha(1-\theta)[\mu+k(1-r_1).$$

- We can claim the following result about the local stability of the DFE

Lemma

: The disease-free equilibrium of the model is locally asymptotically stable whenever $\mathcal{R}_0 < 1$, and instable if $\mathcal{R}_0 > 1$.

Equilibria and bifurcation

Apart the disease-free equilibrium, the model also has a positive endemic equilibrium $Q^* = (S^*, E^*, I^*, R^*)$ where

$$S^* = \frac{\Lambda}{\mu + \lambda^*}, \quad E^* = \frac{\Lambda\lambda^*[(1-p)(\beta\mu + d\lambda^*) + \theta(\mu + \lambda^*)]}{(\mu + \lambda^*)(\beta\mu + d\lambda^*)[A_1 + \sigma(1 - r_1)\lambda^*]},$$

$$I^* = \frac{\Lambda\lambda^*}{\beta\mu + d\lambda^*} \text{ and } R^* = \frac{\alpha\Lambda(1-\theta)\lambda^*}{A_3(\beta\mu + d\lambda^*)}.$$

Endemic equilibria and bifurcation

λ^* is the force of infection at the steady state which satisfies the following quadratic equation :

$$a_2(\lambda^*)^2 + a_1(\lambda^*) + a_0 = 0,$$

where

$$\begin{aligned}
a_2 &= \sigma(1-r_1)[\mu+\gamma+\alpha(1-\theta)],\\
a_1 &= \sigma(1-r_1)[\mu[\mu+d+\alpha(1-\theta)+\gamma(\mu+d)-\beta(\mu+\gamma)]\\
&+ (\mu+\gamma)(\mu+d+\theta-pd)+\mu\alpha(1-\theta)\\
&+ k(1-r_1)[\mu+\gamma+\alpha(1-\theta)],\\
a_0 &= (\mu+\gamma)[\mu(\mu+d+\theta)+k(1-r_1)(\mu+d)]\\
&+ \mu\alpha(1-\theta)[\mu+k(1-r_1)](1-\mathcal{R}_0).
\end{aligned}$$

Endemic equilibria and bifurcation

The number of possible real roots of the polynomial $P(\lambda^*) = a_2(\lambda^*)^2 + a_1(\lambda^*) + a_0 = 0$ can have depends on the signs of a_2, a_1 and a_0.

Then, we claim the following result

Lemma

The TB model
(i) a unique endemic equilibrium when $a_0 < 0$*, i.e.,* $\mathcal{R}_0 > 1$ *;*
(ii) a unique endemic equilibrium when $a_1 < 0$*, and* $a_0 = 0$ *or* $a_1^2 - 4a_2a_0 = 0$*,*
(iii) two endemic equilibria when $a_0 > 0$*,* $a_1 < 0$ *and* $a_1^2 - 4a_2a_0 > 0$ *;*
(iv) no endemic equilibria in the other cases.

Numerical studies

The model is simulated with parameter values using real data of Cameroon and summarize in the following table.

Table 1 : Numerical values for the parameters of the model

Symbol	Estimate	Source
Λ	397800/yr	Estimated
β	Variable	Assumed
p	0.015/yr	Estimated
σ	0.7/yr	Assumed
k	0.00013/yr	Assumed
μ	0.019896/yr	Estimated
d	0.0575/yr	Estimated
r_1	0.001/yr	Estimated
α	0.7311/yr	Estimated
θ	0.1828/yr	Assumed
γ	0.0986/yr	Estimated

Bifurcation diagram

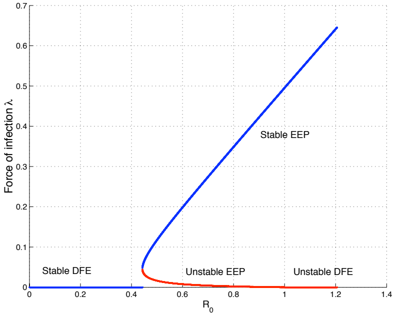


FIGURE: Bifurcation diagram for the model. The notation EEP stands for endemic equilibrium point. All other parameters are as in Table 1.

Trajectories of the model when $\mathcal{R}_0 \leq 0$

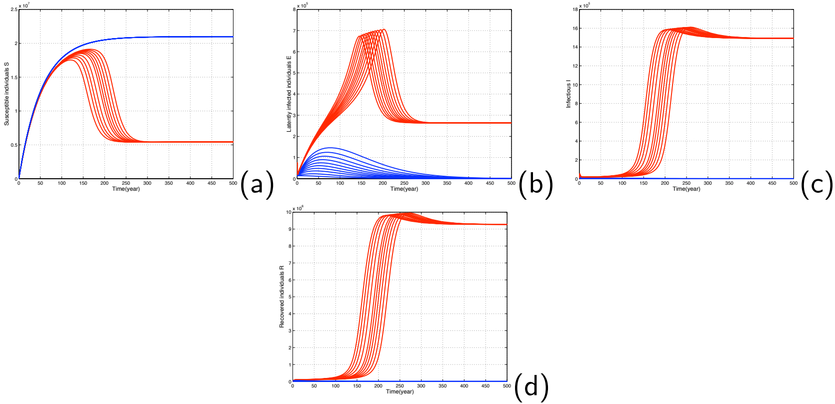


FIGURE: Simulation of system. Time series of (a) susceptible individuals, (b) latently infected individuals, (c) infectious and (d) recovered individual when $\beta = 0.6$ (so that $\mathcal{R}_0 = 0.1363$). All other parameters are as in Table 1.

Estimation of unknown parameters

In view of the periodic trend of quarterly new TB cases in Cameroon and the possible causes of the seasonal pattern, 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 is now described by the following system of non autonomous differential equations :

$$\begin{cases} \dot{S} &= \Lambda - \lambda(t)S - \mu S, \\ \dot{E} &= (1-p)\lambda(t)S + \theta I - \sigma(1-r_1)\lambda(t)E - [\mu + k(t)(1-r_1)]E, \\ \dot{I} &= p\lambda(t)S + \gamma R + (1-r_1)(k + \sigma\lambda(t))E - [\mu + d + \theta + \alpha(1-\theta)]I, \\ \dot{R} &= \alpha(1-\theta)I - [\mu + \gamma]R. \end{cases}$$

where

$$\lambda(t) = \beta(t)\frac{SI}{N},$$

Estimation of unknown parameters

The quarterly reported new TB cases in Cameroon from 2003 to 2007 are given in Table 2.

Table 2 : 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 :

$$f(t) = \lambda(t)pS(t) + (1 - r_1)[k(t) + \sigma\lambda(t)]E(t),$$

in the third equation of the model.

Estimation of unknown parameters

Since variables and parameters in the model are continuous functions of t, we use trigonometric functions to fit $f(t)$ as a periodic function with 5 years of observations. Let

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

in order to let the expression of $f(t)$ be simpler and exacter, where $L = \frac{2\pi}{5}$ is the fundamental frequency.

Estimation of unknown parameters

We use the software Mathematica to determine those coefficients d_m and e_m, which yields the function $f(t)$ given as follows :

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

UMMISCO
Unité Mixte Internationale

Estimation of unknown parameters

The comparison of the data with the curve is shown in the following figure.

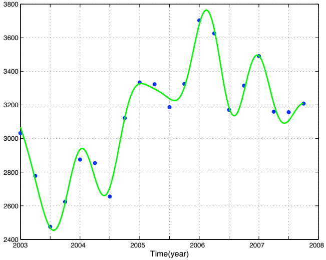


FIGURE: The quarterly numbers of new TB cases and its fitted curve.

Estimation of unknown parameters

After simulations and comparisons, we choose

$$\beta(t) = \beta_0 \beta_1(t) \textit{ and } k(t) = k_0 k_1(t),$$

where β_0 and k_0 are related to the magnitudes of the seasonal fluctuation,

$$\begin{aligned}
\beta_1(t) &= 2.6006 - 0.1934\cos(2\pi t/5) + 0.0375\cos(4\pi t/5) \\
&+ 0.0308\cos(6\pi t/5) - 0.0274\cos(8\pi t/5) + 0.1492\cos(10\pi t/5) \\
&+ 0.0165\cos(12\pi t/5) - 0.0571\cos(14\pi t/5) - 0.2609\sin(2\pi t/5) \\
&- 0.0532\sin(4\pi t/5) - 0.0453\sin(6\pi t/5) - 0.0398\sin(8\pi t/5) \\
&+ 0.0122\sin(10\pi t/5) - 0.0249\sin(12\pi t/5) + 0.0104\sin(14\pi t/5),
\end{aligned}$$

and

Estimation of unknown parameters

$$
\begin{aligned}
k_1(t) &= (10^{-5})[9.3125 - 0.6926\cos(2\pi t/5) + 0.1343\cos(4\pi t/5)\\
&+ 0.1104\cos(6\pi t/5) - 0.098\cos(8\pi t/5) + 0.5343\cos(10\pi t/5)\\
&+ 0.0589\cos(12\pi t/5) - 0.2045\cos(14\pi t/5) - 0.9341\sin(2\pi t/5)\\
&- 0.1905\sin(4\pi t/5) - 0.1624\sin(6\pi t/5) - 0.1424\sin(8\pi t/5)\\
&+ 0.0439\sin(10\pi t/5) - 0.0893\sin(12\pi t/5) + 0.0371\sin(14\pi t/5)].
\end{aligned}
$$

Numerical Studies

After simulations and comparisons, we choose $\beta_0 = 0.01$ and $k_0 = 0.133$. We take the first quarterly of 2003 as the start time of simulation, i.e.,

$$N(0) = 15685000, \; I(0) = 3650, \; S(0) = 4705500,$$
$$R(0) = 2669 \; and \; E(0) = 10973681.$$

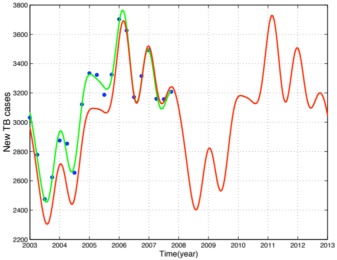


FIGURE: New TB cases : reported number and simulation curve.

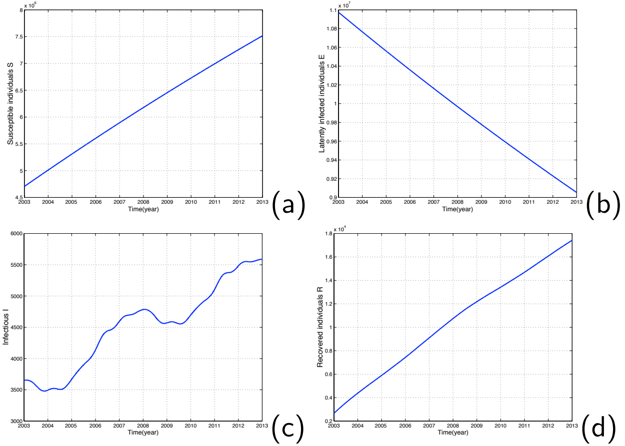


FIGURE: Simulation of the model performed with $\beta_0 = 0.01$ and $k_0 = 0.133$. Time series of (a) susceptible individuals, (b) latently infected individuals, (c) infectious and (d) recovered individuals.

Two intervention methods, called controls, are included in the model. The system of differential equations describing our model with controls is

$$\begin{cases} \dot{S} &=& \Lambda - \lambda(t)S - \mu S, \\ \dot{E} &=& \lambda(t)(1-p)S + \theta I - (1-ur_1)[k(t) + \sigma\lambda(t)]E - \mu E, \\ \dot{I} &=& \lambda(t)pS + \gamma R + (1-ur_1)[k(t) + \sigma\lambda(t)]E - v\alpha(1-\theta)I - (\mu + d) \\ \dot{R} &=& v\alpha(1-\theta)I - A_3 R, \end{cases}$$

where $u(t)$ represents the effort on the chemoprophylaxis parameter (r_1) of latently infected individuals to reduce the number of individuals that may be infectious and $v(t)$ is the effort on treatment (r_2) of infectious to increase the number of recovered individuals, i.e., to reduce the number of infectious.

Optimal intervention strategies

A control scheme is assumed to be optimal if it minimizes the objective functional :

$$J(u,v) = \int_0^T [B_1 I(t) + B_2 u^2(t) + B_3 v^2(t)]dt,$$

where B_1, B_2 and B_3 are balancing coefficients transforming the integral into Euros expended over a finite time period T years.

Optimal intervention strategies

We invoke Pontryagin's Maximum Principle to determine the precise formulation of our optimal controls $u^*(t)$ and $v^*(t)$. To do this, we note that our Hamiltonian is given by

$$
\begin{aligned}
H &= B_1 I(t) + B_2 u^2(t) + B_3 v^2(t) + w_S[\Lambda - \lambda(t)S(t) - \mu S(t)] \\
&+ w_E[\lambda(t)(1-p)S(t) + \theta I(t) - (1-u(t)r_1)[k(t)+\sigma\lambda(t)]E(t) - \mu E \\
&+ w_I[\lambda(t)pS(t) + \gamma R(t) + (1-u(t)r_1)[k(t)+\sigma\lambda(t)]E(t) \\
&- v(t)\alpha(1-\theta)I(t) - (\mu+d)I(t)] + w_R[v(t)\alpha(1-\theta)I(t) - A_3 R(t)],
\end{aligned}
$$

where w_S, w_E, w_I and w_R are the adjoint functions associated with their respective states to be determined later.

Characterization of optimal controls

Pontryagin's Maximum Principle states that the unconstrained optimal controls u^* and v^* satisfy

$$\frac{\partial H}{\partial u} = 0 \quad \text{and} \quad \frac{\partial H}{\partial v} = 0,$$

whenever $0 < u^*(t) < u_{\max}$ and $0 < v^*(t) < v_{\max}$, and taking the bounds into account. Thus, one obtains, in compact form :

$$u^*(t) = \min(u_{\max}, \max(\hat{u}(t), 0)) \text{ and } v^*(t) = \min(v_{\max}, \max(\hat{v}(t), 0)),$$

where

$$\hat{u} = \frac{r_1(w_I - w_E)[k(t) + \sigma\lambda(t)]E(t)}{2B_2} \text{ and } \hat{v} = \frac{\alpha(1-\theta)(w_I - w_R)I(t)}{2B_3}.$$

Characterization of optimal controls

The optimality system is defined as the state system together with the adjoint system and the optimal controls u^* and v^*. The adjoint system is given by

$$\frac{dw_S}{dt} = -\frac{\partial H}{\partial S}, \qquad \frac{dw_E}{dt} = -\frac{\partial H}{\partial E},$$

$$\frac{dw_I}{dt} = -\frac{\partial H}{\partial I} \qquad \text{and} \qquad \frac{dw_R}{dt} = -\frac{\partial H}{\partial R}.$$

Characterization of optimal controls

Then, given an optimal control double (u^*, v^*) and the corresponding states (S^*, E^*, I^*, R^*), there exists adjoint functions satisfying :

$$
\begin{aligned}
\frac{dw_S}{dt} &= \beta(t)\frac{I(N-S)}{N^2}[w_S-(1-p)w_E-pw_I] \\
&+ \beta(t)\sigma(1-ur_1)(w_I-w_E)\frac{EI}{N^2}+\mu w_S, \\
\frac{dw_E}{dt} &= \beta(t)\frac{SI}{N^2}[-w_S+(1-p)w_E+pw_I] \\
&+ \beta(t)\sigma(1-ur_1)(w_E-w_I)\frac{I(N-E)}{N^2}+k(t)(w_E-w_I)(1-ur_1)+\mu w_E, \\
\frac{dw_I}{dt} &= -B_1+\beta(t)\frac{S(N-I)}{N^2}[w_S-(1-p)w_E-pw_I] \\
&+ \beta(t)\sigma(1-ur_1)(w_E-w_I)\frac{E(N-I)}{N^2} \\
&- \theta w_E+\alpha(1-\theta)v(w_I-w_R)+(\mu+d)w_I, \\
\frac{dw_R}{dt} &= \beta(t)\frac{SI}{N^2}[-w_S+(1-p)w_E+pw_I] \\
&+ \beta(t)\sigma(1-ur_1)(w_E-w_I)\frac{EI}{N^2}-\gamma w_I+A_3 w_R.
\end{aligned}
$$

Optimal control numerical simulations

The initial conditions have been chosen to be

$$S(0) = 6600000,\ E(0) = 9600000,\ I(0) = 4600 \text{ and } R(0) = 13000,$$

which are the number of susceptible, latently-infected, infectious and recovered individuals in 2010 in the mainland of Cameroon.
We also choose

$$B_1 = 75,\ B_2 = 15,\ B_3 = 10,\ \ u_{\max} = v_{\max} = 1 \text{ and } T = 5\text{years}.$$

UMMISCO
Unite Mixte Internationale

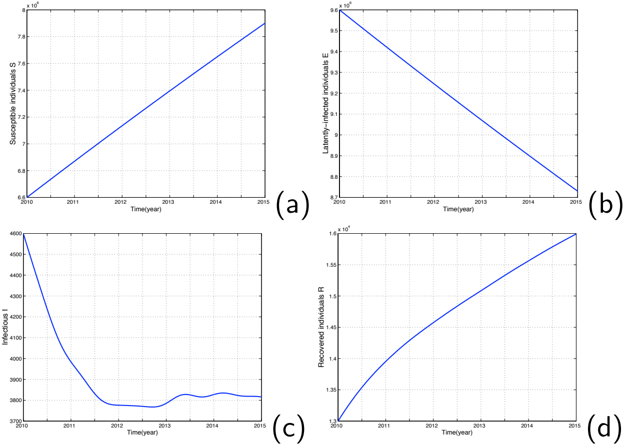


FIGURE: Dynamics of the model showing the effect of chemoprophylaxis and treatment rates on the host population. Time series of (a) susceptible individuals, (b) latently infected individuals, (c) infectious and (d) recovered individuals.

Summary

In summary

Summary

In summary

- We have presented an analysis of a simple model for the dynamics transmission of TB.

Summary

In summary

- We have presented an analysis of a simple model for the dynamics transmission of TB.
- We have mainly found that the model without seasonality exhibits the phenomenon of backward bifurcation, where the stable disease-free equilibrium co-exists with a stable endemic equilibrium, when the basic reproduction number is less than unity ;

Summary

In summary

- We have presented an analysis of a simple model for the dynamics transmission of TB.
- We have mainly found that the model without seasonality exhibits the phenomenon of backward bifurcation, where the stable disease-free equilibrium co-exists with a stable endemic equilibrium, when the basic reproduction number is less than unity ;
- This model has been extended to describe TB seasonal incidence rate by incorporating periodic coefficients. We have proposed a numerical study to estimate some parameters of the model from real data of the situation of TB in Cameroon. It has been found that there is a seasonal pattern of new TB cases in the mainland of Cameroon.

Summary

In summary

- We have presented an analysis of a simple model for the dynamics transmission of TB.
- We have mainly found that the model without seasonality exhibits the phenomenon of backward bifurcation, where the stable disease-free equilibrium co-exists with a stable endemic equilibrium, when the basic reproduction number is less than unity ;
- This model has been extended to describe TB seasonal incidence rate by incorporating periodic coefficients. We have proposed a numerical study to estimate some parameters of the model from real data of the situation of TB in Cameroon. It has been found that there is a seasonal pattern of new TB cases in the mainland of Cameroon.
- An optimal control strategy has been presented. An important result of this analysis is that a cost-effective balance of chemoprophylaxis and treatment methods can successfully control TB in Cameroon.

UMMISCO
Unité Mixte Internationale

Thanks for your attention !