Analysis of a SEIT compartmental model of transmission of Tuberculosis with treatment

III International conference

« Mathematical Physics, Dynamical systems, Infinite-Dimensional Analysis »

Dedicated to the 100th anniversary of V.S. Vladimorov, the 100th anniversary L.D. Kudryavstev, and the 85th anniversary of O.G. Smolyanov

July 5-13, Dolgoprudny

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III Международная конференция

«Математическая физика, динамические системы, бесконечномерный анализ»,

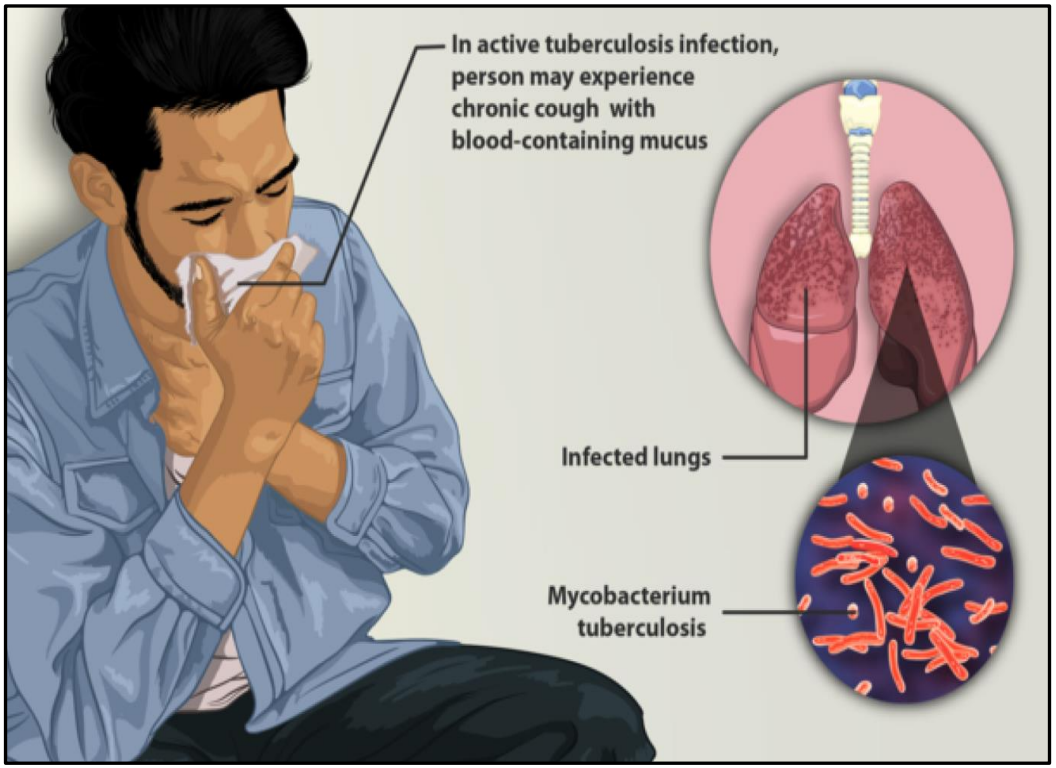
посвященная 100-летию В.С. Владимирова, 100-летию Л.Д. Кудрявцева и 85-летию О.Г. Смолянова

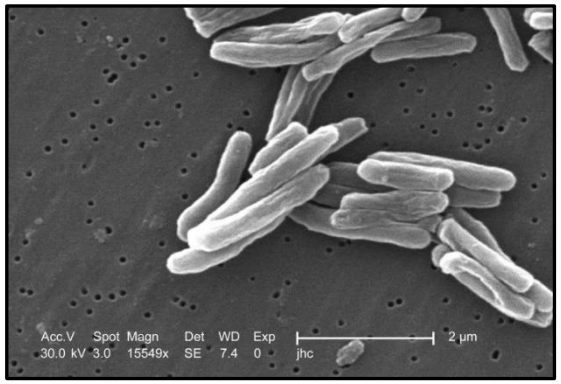
Уважаемые коллеги, Уважаемые организаторы, сегодня для меня, большая честь и большое счастье, что меня пригласили выступить с этой презентацией.

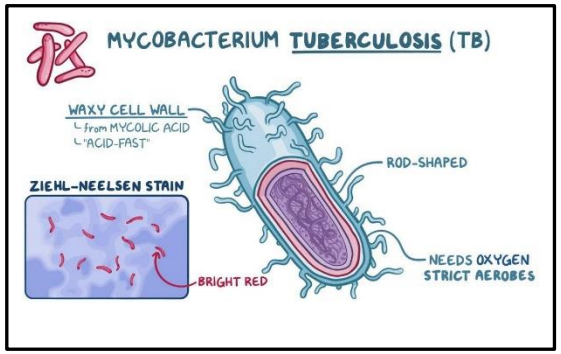
Dear colleagues, Dear organizers, today it is a great honor and great happiness for me that I was invited to make this presentation.

What is exactly Tuberculosis?

Tuberculosis (TB) is an airborne infectious disease that is transmitted between individuals via droplets with TB bacilli, that is, Mycobacterium tuberculosis. The disease is characterized by the presence of this bacteria, which Dr. Robert Koch discovered in 1882.



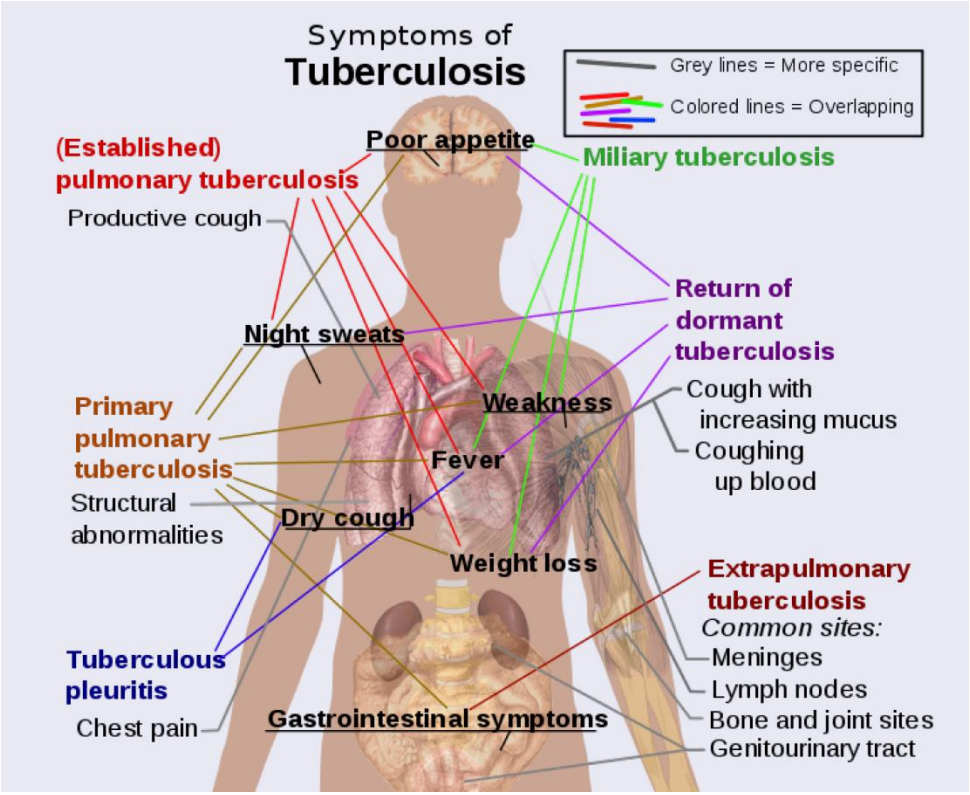




Туберкулез (ТБ) – это воздушно-капельное инфекционное заболевание, которое передается между людьми воздушно-капельным путем с бациллами туберкулеза, то есть микобактериями туберкулеза. Болезнь характеризуется наличием этой бактерии, которую доктор Роберт Кох открыл в 1882 году.

What are its symptoms?

Tuberculosis can affect almost any part of the human body. However, in this presentation, we will only consider pulmonary tuberculosis



In the 19th century, it was not possible to cure such a disease, rich people were looking for a place with mild winters, like the French Riviera. Nicholas Alexandrovich, Tsesarevich of Russia died on 24 April 1865 in Nice (France).

A chapel named in his honor was built near the Russian Saint Nicholas Cathedral.

Туберкулез может поразить практически любую часть человеческого тела. Однако в данной презентации мы будем рассматривать только туберкулез легких.

В 19 веке вылечить такое заболевание было невозможно, богатые люди искали место с мягкими зимами, вроде Французской Ривьеры. Николай Александрович, цесаревич России, умер 24 апреля 1865 года в Ницце (Франция). Рядом с Никольским собором в России построена часовня, названная в его честь.

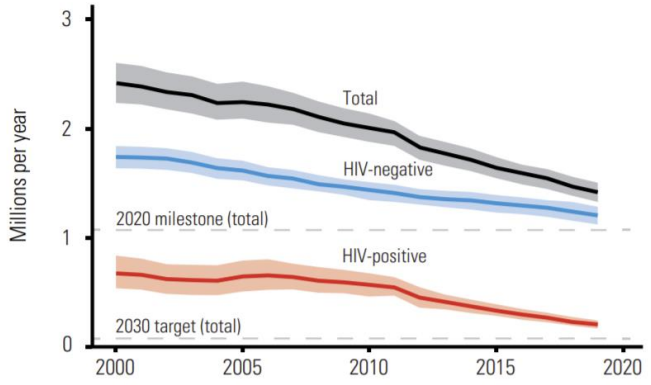
Global Tuberculosis Report 2020 of World Health Organization (WHO)

Tuberculosis is a still deadly active general pandemy

Each year, the WHO commemorates the World Tuberculosis (TB) Day on March 24

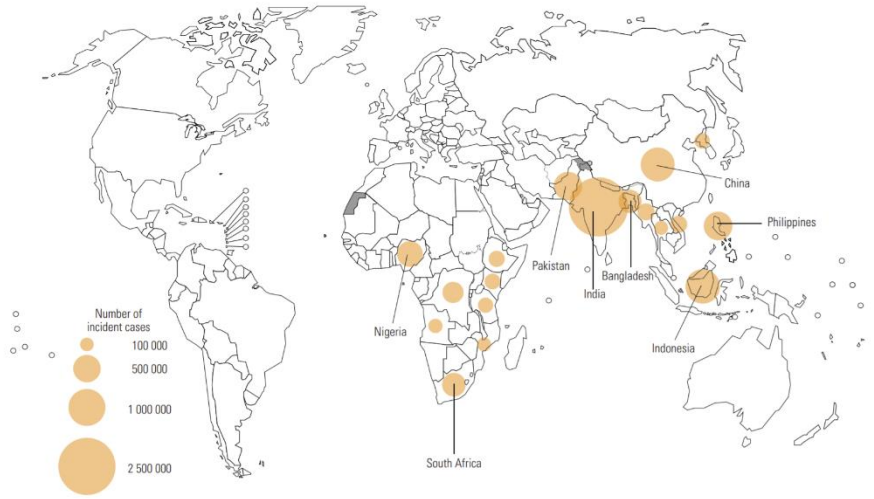
Global trend in the estimated number of TB deaths, 2000–2019

The shaded areas are uncertainty intervals. Horizontal dashed lines mark the 2020 milestone and 2030 target of the End TB Strategy.



Countries that had at least 100 000 incident cases of TB in 2019

The eight countries that rank first to eighth in terms of numbers of cases, and that accounted for two thirds of global cases in 2019, are labelled.



Tuberculosis symptoms: infected versus infectious

Symptoms: Although a person's body can harbor Mycobacterium tuberculosis, their immune system can usually prevent that person from getting sick. This is why doctors make a distinction between:

Latent TB (or inactive TB, or TB infection): a person has a TB infection, but the bacteria are inactive and cause no symptoms,

Active TB (or TB disease): this condition makes the person sick and can spread to others through droplets. It can occur weeks or years after infection

We define a compartmental SEI model with three compartments:

S stands for Susceptible people

E for Exposed (infected but not yet infectious: latent TB)

I for Infectious (active TB)

Three versions of this model are considered:

1/ the endogenous model for which it is assumed that postprimary tuberculosis is usually caused by reactivation of endogenous infection rather than by a new, exogenous infection.

2/ the exogenous model for which it is assumed that postprimary tuberculosis is also caused by new, exogenous infection due to a new contact with infectious

3/ the model with treatment in which a fourth compartment **T for Treated** is added

The endogenous model

Let Λ be the recruitment rate of the population, d be the natural death rate, γ be the death rate caused by the disease, and the mean exposed period is $1/\alpha$, where $\alpha > 0$ is the rate of loss of latency. In nearly 5-10 % of susceptible people, latent TB may be activated due to immune evasion by Mtb (Mycobacterium tuberculosis) from intracellular phagosome within macrophage, perpetrating TB.

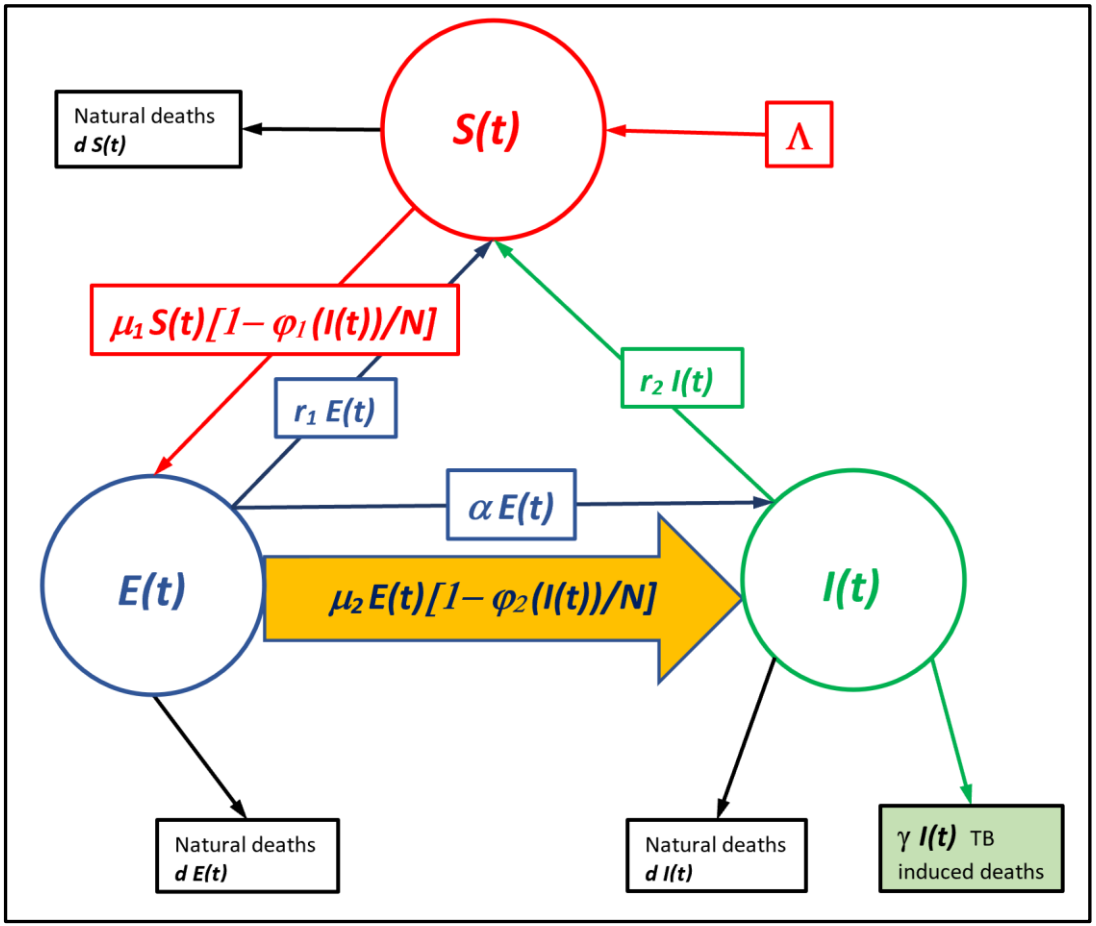
$$
\begin{aligned}
S(t+1) &= \Lambda + (1-\mu_1 - d)S(t) + \mu_1\varphi_1(I(t)/N(t))S(t) + r_1E(t) + r_2I(t) \\
E(t+1) &= \mu_1(1-\varphi_1(I(t)/N(t)))S(t) + (1-d-\alpha-r_1)E(t) \\
I(t+1) &= \alpha E(t) + (1-d-\gamma-r_2)I(t)
\end{aligned}
$$

With r_1 and r_2 the rate of recovering. The fractions of susceptible that escapes the infection at time t is given by $\varphi_1(I(t)/N(t)) = e^{-\beta_1 I(t)/N(t)}$ with μ_1 the level of infection $0 \leq \mu_1 \leq 1$ and β_1 with $0 \leq \beta_1 \leq 1$ is called the transmission coefficient

$$
\begin{aligned}
S(t+1) &= \Lambda + (1-\mu_1 - d)S(t) + \mu_1 e^{-\beta_1 I(t)/N(t)}S(t) + r_1E(t) + r_2I(t) \\
E(t+1) &= \mu_1(1-e^{-\beta_1 I(t)/N(t)})S(t) + (1-d-\alpha-r_1)E(t) \\
I(t+1) &= \alpha E(t) + (1-d-\gamma-r_2)I(t)
\end{aligned}
\qquad (1)
$$

Diagram of tuberculosis transmission

Both endogenous and exogenous model (with no treatment) are represented in this chart flow. The chartflow of the non-exogenous model is obtained by deleting the arrow whose interior is colored in orange.



We assume that the contact between susceptible and infected individuals is assumed to be a Poisson process given by

$$\varphi_i(I(t)/N(t)) = e^{-\beta_i I(t)/N(t)}$$

where β_i $i = 1, 2$ is called the transmission coefficient which will be used here.

The exogenous model

For decades it has been assumed that postprimary tuberculosis is usually caused by reactivation of endogenous infection rather than by a new, exogenous infection. However, exogenous reinfection appears to be a major cause of postprimary tuberculosis after a previous cure in an area with a high incidence of this disease. This finding emphasizes the importance of achieving cures and of preventing anyone, with infectious tuberculosis from exposing others to the disease.

$$
\begin{aligned}
S(t+1) &= \Lambda + (1-\mu_1 - d)S(t) + \mu_1\varphi_1(I(t)/N(t))S(t) + r_1E(t) + r_2I(t) \\
E(t+1) &= \mu_1(1-\varphi_1(I(t)/N(t)))S(t) + \mu_2\varphi_2(I(t)/N(t))E(t) + (1-\mu_2 - d - \alpha - r_1)E(t) \\
I(t+1) &= \alpha E(t) + \mu_2(1-\varphi_2(I(t)/N(t)))E(t) + (1-d-\gamma-r_2)I(t)
\end{aligned}
$$

with $\varphi_2(I(t)/N(t)) = e^{-\beta_2 I(t)/N(t)}$ and μ_2 the level of reinfection $0 \leq \mu_2 \leq 1$

$$
\begin{aligned}
S(t+1) &= \Lambda + (1-\mu_1 - d)S(t) + e^{-\beta_1 I(t)/N(t)}S(t) + r_1E(t) + r_2I(t) \\
E(t+1) &= \mu_1(1-e^{-\beta_1 I(t)/N(t)})S(t) + \mu_2 e^{-\beta_2 I(t)/N}E(t) + (1-\mu_2 - d - \alpha - r_1)E(t) \\
I(t+1) &= \alpha E(t) + \mu_2(1-e^{-\beta_2 I(t)/N(t)})E(t) + (1-d-\gamma-r_2)I(t)
\end{aligned}
\qquad (2)
$$

Mathematical results

A/ Endogenous SEI model : Study of existence and stability of the Disease Free Equilibrium ($\mathcal{E}_0$) and the Endemic Equilibrium ($\mathcal{E}^*$) and the reproduction number R_0

A.1/ - Computation of R_0,

A.2a/ - Local stability of ($\mathcal{E}_0$) **A.2b/** - Global stability of ($\mathcal{E}_0$)

A.3a/ - Existence of ($\mathcal{E}^*$) **A.3b/** - Unicity of ($\mathcal{E}^*$)

A.4a/ - Local stability of ($\mathcal{E}^*$) (Global stability of ($\mathcal{E}^*$) is not yet proved)

B/ Exogenous SEI model:

B.1/ - Computation of R_0 and comparison with the **exogenous model**

B.2a/ - Local stability of ($\mathcal{E}_0$)

C/ SEIT Model with treatment:

C.1/ - Computation of R_0,

C.2a/ - Local stability of ($\mathcal{E}_0$) **A.2b/** - Global stability of ($\mathcal{E}_0$)

C.3a/ - Existence of ($\mathcal{E}^*$) **C.3b/** - Unicity of ($\mathcal{E}^*$)

C.4a/ - Local stability of ($\mathcal{E}^*$) (Global stability of ($\mathcal{E}^*$) is not yet proved)

A/ Properties of the endogenous model
Basic reproduction number and equilibrium points

We consider now that $N(t+1) = \Lambda + (1-d)\,N(t) - \gamma\, I$. Then $0 < N(t) \leq \Lambda/d$ and if we assume that $\gamma = 0$, then $N(t) \to \Lambda/d$ as $t \to \infty$. Henceforth, we assume that N is fixed and equal to $N^* = \Lambda/d$.

Let us recall that the threshold parameter R_0 is called the net reproduction number (or basic reproduction number or ratio) and is defined as the expected number of infections produced by a single infectious individual introduced into a totally susceptible population.

Consequently, when $R_0 < 1$, it is expected to imply that the number of infections will decrease over time and the disease will eventually die out. However, when $R_0 > 1$, a disease outbreak will occur.

Equilibrium points

Now, we consider the properties of the two equilibria: the Disease Free Equilibrium ($\mathcal{E}_0$) for which there is no Infected (E = 0) or Infectious (I = 0):

$$(\mathcal{E}_0) = (0, 0, N^*)$$

and the Endemic Equilibrium ($\mathcal{E}^*$)

$$(\mathcal{E}^*) = (E^*, I^*, S^*)$$

A.1/ The basic reproduction number
Computation of R_0 using the next generation matrix

Let $X_0 = (E, I)^T$, $X_1 = S^T$, $X = (X_0, X_1) \in R^3_+$. Hence system (1) may be written as

$$X_0(t+1) = G_0(X(t))$$
$$X_1(t+1) = G_1(X(t))$$

where $G_0(X(t)) = \begin{pmatrix} E(t+1) \\ I(t+1) \end{pmatrix} = \mathcal{F}(t) + \mathcal{T}(t)$, and $G_1(X(t)) = S(t+1)$, where

$$\mathcal{F}(t) = \begin{pmatrix} \mu_1(1 - \varphi_1(I(t)/N)S(t) \\ 0 \end{pmatrix} = \begin{pmatrix} \mathcal{F}_1(t) \\ \mathcal{F}_2(t) \end{pmatrix}$$

is the vector of new infections that survive in the time interval $[0, t]$, and

$$\mathcal{T}(t) = \begin{pmatrix} (1 - d - \alpha - r_1)E(t) \\ \alpha E(t) + (1 - d - \gamma - r_2)I(t) \end{pmatrix} = \begin{pmatrix} \mathcal{T}_1(t) \\ \mathcal{T}_2(t) \end{pmatrix}$$

is the vector of all other transitions.

Next, we compute the Jacobian matrix of $\mathcal{T}(t)$ and $\mathcal{F}(t)$ at the disease-free equilibrium (DFE) $\mathcal{E}_0 = (0, 0, S^*) = (0, 0, N)$

$$F(t)|_{(0,0,S^*)} = \begin{pmatrix} \frac{\partial \mathcal{F}_1(t)}{\partial E} & \frac{\partial \mathcal{F}_1(t)}{\partial I} \\ \frac{\partial \mathcal{F}_2(t)}{\partial E} & \frac{\partial \mathcal{F}_2(t)}{\partial I} \end{pmatrix} = \begin{pmatrix} 0 & \mu_1\beta_1\frac{S^*}{N^*} \\ 0 & 0 \end{pmatrix} = \begin{pmatrix} 0 & \mu_1\beta_1 \\ 0 & 0 \end{pmatrix}$$

$$T(t)|_{(0,0,S^*)} = \begin{pmatrix} \frac{\partial \mathcal{T}_1(t)}{\partial E} & \frac{\partial \mathcal{T}_1(t)}{\partial I} \\ \frac{\partial \mathcal{T}_2(t)}{\partial E} & \frac{\partial \mathcal{T}_2(t)}{\delta I} \end{pmatrix} = \begin{pmatrix} 1 - d - \alpha - r_1 & 0 \\ \alpha & 1 - d - \gamma - r_2 \end{pmatrix}.$$

A.1/ The basic reproduction number

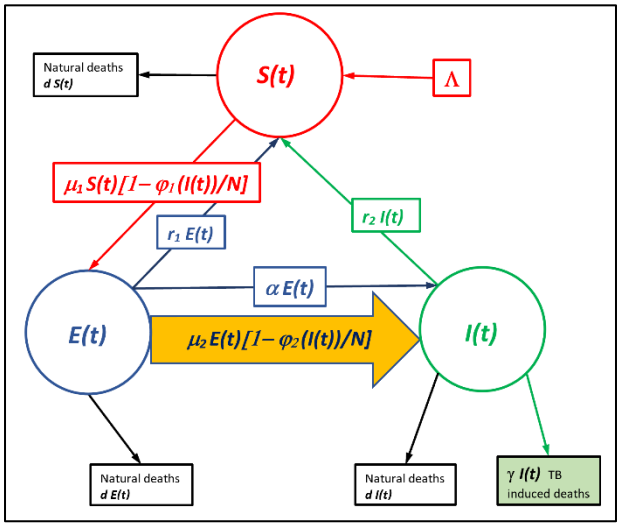
Now the basic reproduction number is given by $\mathcal{R}_0(\mathcal{E}_0) = \rho(F(I-T))^{-1})$, where ρ denotes the spectral radius of a matrix

$$F(I-T)^{-1} = \begin{pmatrix} 0 & \mu_1\beta_1 \\ 0 & 0 \end{pmatrix} \begin{pmatrix} \frac{1}{d+\alpha+r_1} & 0 \\ \frac{\alpha}{(d+\alpha+r_1)(d+\gamma+r_2)} & \frac{1}{d+\gamma+r_2} \end{pmatrix}$$

$$= \begin{pmatrix} \frac{\mu_1\alpha\beta_1}{(d+\alpha+r_1)(d+\gamma+r_2)} & \frac{\beta_1}{(d+\gamma+r_2)} \\ 0 & 0 \end{pmatrix}.$$

Hence

$$\mathcal{R}_0(\mathcal{E}_0) = \frac{\mu_1\alpha\beta_1}{(d+\alpha+r_1)(d+\gamma+r_2)}.$$



Remark: R_0 is generally computed using the DFE and considered fro the whole space of solutions of system (1). It is why we denote it $R_0(\mathcal{E}_0)$.

We introduce a new concept: the basic reproduction number at the endemic equilibrium $R_0(\mathcal{E}^*)$: using the same method it is possible to proof that:

$$\mathcal{R}_0(\mathcal{E}^*) = \frac{\alpha\beta_1\left[(\mu_1+d+r_1)\mathcal{S}^* - \Lambda\right]}{N^*(d+\alpha+r_1)(d+\gamma+r_2)}$$

or

$$\mathcal{R}_0(\mathcal{E}^*) = \mathcal{R}_0(\mathcal{E}_0)\frac{\left[(\mu_1+d+r_1)\mathcal{S}^* - \Lambda\right]}{N^*\mu_1}$$

A/ Properties of the endogenous model

A.2a/ Local Stability of the Disease Free Equilibrium (DFE) ($\mathcal{E}_0$)

Local Stability:

Theorem 1 *The DFE* $(\mathcal{E}_0)$ *of system* (1) *is locally asymptotically stable if* $\mathcal{R}_0(\mathcal{E}_0) \leq 1$ *and a saddle if* $\mathcal{R}_0(\mathcal{E}_0) > 1$.

Proof. Jacobian matrix of system (1) at $\mathcal{E}_0$ represented by $J(\mathcal{E}_0)$ is given by

$$J(\mathcal{E}_0) = \begin{pmatrix} 1-d & r_1 & r_2 - \mu_1\beta_1 \\ 0 & 1-(d+\alpha+r_1) & \mu_1\beta_1 \\ 0 & \alpha & 1-(d+\gamma+r_2) \end{pmatrix}$$

The first eigenvalue of the Jacobian matrix is $\lambda_1 = 1 - d < 1$.

The remaining two eigenvalues are the eigenvalues of the matrix

$$A = \begin{pmatrix} 1-(d+\alpha+r_1) & \mu_1\beta_1 \\ \alpha & 1-(d+\gamma+r_2) \end{pmatrix},$$

We now use the determinant-trace criteria to show that the two eigenvalues of this matrix lie inside the unit disk and thus the DFE is locally asymptotically stable.

A/ Properties of the endogenous model

A.2b/ Global Stability of the Disease Free Equilibrium (DFE) ($\mathcal{E}_0$)

Global Stability: It is possible to proof the global stability of the DFE if $R_0(\mathcal{E}_0) < 1$ using the Lasalle Invariant principle

Theorem 2 (LaSalle Invariance Principle) *Consider the difference equation*

$$\mathbf{x}(t+1) = F(\mathbf{x}(t))$$

where $F : \mathbb{R}^n_+ \to \mathbb{R}^n_+$ *is continuous on a subset* G *of* $\mathbb{R}^n_+$. *Suppose there is a Liapunov function* $V : G \to \mathbb{R}$ *such that* V *is continuous on the closure* $\overline{G}$ *of* G. *Let* $E = \{\mathbf{x} : \Delta V(\mathbf{x}(t)) = 0\}$ *and* M *be the largest positively invariant subset of* E. *Assume that for every point* $\mathbf{x} \in G$, *its orbit* $O(\mathbf{x})$ *is bounded and is a subset of* G. *Then there exists* $c \in R$ *such that for every* $x \in G$, $\omega(x) \subset M \cap V^{-1}(c)$.

and Lyapunov function

$$V(X_0, X_1) = \left(\frac{1}{d+\alpha+r_1} + \frac{\alpha^2}{(d+\gamma+r_2)(d+\alpha+r_1)}, \frac{\alpha}{d+\gamma+r_2} \right) X_0$$

with $X_0 \in \mathbf{R}^2_+ | \{0\}$.

A/ Properties of the endogenous model

A.2b/ Global Stability of the Disease Free Equilibrium (DFE) ($\mathcal{E}_0$)

Now let $\mathbf{f}(X_0, X_1) = (F+T)X_0 - G_0(X_0, X_1)$. Then $X_0(t+1) = (F+T)X_0(t) - \mathbf{f}(X_0(t), X_1(t))$ since $G_0(0, X_1^*) = 0$, $\mathbf{f}(0, X_1^*) = \mathbf{0}$.

Theorem 3 *Assume that $\mathcal{R}_0 \leq 1$. Then $X^* = (0, X_1^*)$ is globally asymptotically stable.*

Proof. Now

$$\begin{aligned}
\Delta V(X_0, X_1) &= V(G_0(X_0, X_1), G_1(X_0, X_1)) - V(X_0, X_1) \\
&= W^T(I-T)^{-1}X_0(t+1) - W^T(I-T)^{-1}X_0(t) \\
&= W^T(I-T)^{-1}(F+t)X_0(t) - W^T(I-T)^{-1}\mathbf{f}(X_0(t), X_1(t)) - W^T(I-T)^{-1}X_0(t) \\
&= W^T(I-T)^{-1}(T-I+F+I)X_0(t) - W^T(I-T)^{-1}\mathbf{f}(X_0(t), X_1(t)) - W^T(I-T)^{-1}X_0(t) \\
&= W^T(-1+\mathcal{R}_0)X_0(t) - W^T(I-T)^{-1}\mathbf{f}(X_0(t), X_1(t))
\end{aligned}$$

since $\mathcal{R}_0 \leq 1$ and $W^T(I-T)^{-1}f(X_0(t), X_1(t)) \geq 0$. It follows that $\Delta V(X_0, X_1) \leq 0$.

By the LaSalle Invariance Principle, $X(t) = \begin{pmatrix} X_0(t) \\ X_1(t) \end{pmatrix}$ approaches the largest positively invariant subset M of the set $E = \{X \in \mathbb{R}_+^3 | \Delta V(X) = 0\}$, where $M = \{(0, X_1) | X_1 \in \mathbb{R}_+^2\}$. Hence the only invariant set M is the disease-free equilibrium $(0, X_1^*)^T$. Therefore the disease-free equilibrium is globally asymptotically stable. Hence the only invariant set in M is the disease-free equilibrium $(0, X_1^*)^T$. Therefore the disease-free equilibrium is globally asymptotically stable. ■

A/ Properties of the endogenous model

A.3a/ Existence of the endemic equilibrium ($\mathcal{E}^*$)

There is no closed formula giving ($\mathcal{E}^*$) which is solution of the equation:

case $\gamma = 0,\ r_1 = r_2 = 0$ The proof is combinatoric, however tedious

Proposition 6 *Assume that* $r_1 = r_2 = 0$, *and* $\gamma = 0$. *Then every equilibrium point* $\mathcal{E}^* = (\mathcal{S}^* > 0\ ,\ E^* \geq 0,\ \mathcal{I}^* \geq 0)$ *of model* (1) *is of the form* $\mathcal{E}^* = (\mathcal{S}^*, \frac{\Lambda - d\mathcal{S}^*}{(d+\alpha)}, \frac{\alpha(\Lambda - d\mathcal{S}^*)}{d(d+\alpha)})$ *with* $\mathcal{S}^*$ *solution of*

$$d(d+\alpha)N^* \ln\left[\frac{\mu_1 \mathcal{S}^*}{(\mu_1 + d)\mathcal{S}^* - \Lambda}\right] + \alpha\beta_1 d\mathcal{S}^* = \alpha\beta_1\Lambda, \tag{20}$$

case $\gamma \neq 0,\ r_1 \neq 0\ ,\ r_2 \neq 0$

Proposition 9 *Assume that* $r_1 = 0$, $r_2 \neq 0$, *and* $\gamma \neq 0$. *Then every equilibrium point* $\mathcal{E}^* = (S^* > 0\ ,\ E^* \geq 0,\ I^* \geq 0)$ *of model* (1) *is of the form*

$$\mathcal{E}^* = (S^*, \tfrac{(d+\gamma+r_2)(\Lambda - d\mathcal{S}^*)}{K_1}, \tfrac{\alpha(\Lambda - d\mathcal{S}^*)}{K_1})$$

with $\mathcal{S}^*$ *solution of*

$$K_1' N^* \ln\left[\frac{\mu_1 K_1 \mathcal{S}^*}{K_1'\left((\mu_1 + d)\mathcal{S}^* - \Lambda\right) - \alpha r_2(\Lambda - d\mathcal{S}^*)}\right] + \alpha\beta_1 d\mathcal{S}^* = \beta_1\alpha\Lambda$$

with $K_1' = (r_1 - (d + \alpha + r_1))\,(d + \gamma + r_2) - r_2\alpha$

A/ Properties of the endogenous model
A.3b/ Unicity of the endemic equilibrium ($\mathcal{E}^*$)

To proof the unicity of ($\mathcal{E}^*$) we use the properties of a convex function:

case $\gamma = 0,\ r_1 = r_2 = 0$

Theorem 10 *Assume that* $r_1 = r_2 = 0$, $\gamma = 0$ *and* $\mathcal{R}_0 > 1$. *Then there exists a unique endemic equilibrium point* $\mathcal{E}^* = (S^*, E^*, I^*)$ *of System* (1)

Proof. *Consider the function*

$$f(x) = d(d+\alpha)N^* \ln\left[\frac{\mu_1 x}{(\mu_1+d)x - \Lambda}\right] + \alpha\beta_1 dx, \tag{49}$$

which is only defined for $x > \frac{\Lambda}{\mu_1+d}$.
Its derivative is:

$$f'(x) = -\frac{(d+\gamma)(d+\alpha)N\Lambda}{x\left[(\mu_1+d)x - \Lambda\right]} + \alpha\beta_1 d, \tag{50}$$

and its second derivative is:

$$f''(x) = \frac{(d+\gamma)(d+\alpha)N\Lambda\left[2(\mu_1+d)x - \Lambda\right]}{x^2\left[(\mu_1+d)x - \Lambda\right]^2}, \tag{51}$$

which is always positive because $(\mu_1+d)x - \Lambda > 0$
hence $\Lambda < (\mu_1+d)x < 2(\mu_1+d)x$
Therefore $f(x)$ *is convex and* $f'(x)$ *is always increasing.*

A/ Properties of the endogenous model

A.3b/ Unicity of the endemic equilibrium ($\mathcal{E}^*$)

Finally

The equation

$$f(x) = \alpha\beta_1\Lambda, \tag{52}$$

which represents the intersection of a convex curve with and horizontal straight line, and can have either zero, one, or two solutions. Clearly, $x = N^*$ satisfies equation (52), which gives us the disease equilibrium point $(S^*, 0, 0)$. Therefore this equation can have only one or two solutions. Moreover, if $\mathcal{R}_0 = 1$, and since $N^* = \Lambda/d$, it follows that

$$f'(N^*) = -\frac{(d+\gamma)(d+\alpha)d\Lambda}{\mu_1\Lambda} + d\frac{(d+\gamma)(d+\alpha)}{\mu_1} = 0, \tag{53}$$

Therefore the tangent to the convex curve is horizontal, and, consequently, there is only one point of intersection between the horizontal line and the curve which is the DFE.

It is easy to verify that if $\mathcal{R}_0 > 1$ or $\alpha\beta > \frac{d(d+\alpha)}{\mu}$, then $f'(N^*) > 0$ and, consequently, there is an equilibrium point on the left-hand side intersection between the convex curve and the horizontal straight line, with $\mathcal{S}^* < N^*$. This proves the existence and uniqueness of the endemic equilibrium point if $\mathcal{R}_0 > 1$. ■

The same kind of proof is done in the **case** $\gamma \neq 0$, $r_1 \neq 0$, $r_2 \neq 0$

A/ Properties of the endogenous model

A.4a/ Local stability of the endemic equilibrium ($\mathcal{E}^*$)

To proof the local stability of ($\mathcal{E}^*$) is done in two steps:

Step 1: $\gamma = 0$

Theorem 13 *Assume that $\gamma = 0$ and $\mathcal{R}_0(\mathcal{E}^*) < 1 < \mathcal{R}_0(\mathcal{E}_0)$. Then for sufficiently small r_1 and r_2 the endemic equilibrium of the endogenous system (1) is locally asymptotically stable.*

Proof. The Jacobian matrix of system (1) at $\mathcal{E}^*$ is given by

$$B = JF(\mathcal{E}^*) = \begin{pmatrix} 1-(\mu_1+d)+\mu_1 e^{-\beta_1 \frac{\mathcal{I}^*}{N^*}} & r_1 & r_2 - \frac{\mu_1\beta_1\mathcal{S}^*}{N^*}e^{-\beta_1\frac{\mathcal{I}^*}{N^*}} \\ \mu_1(1-e^{-\beta_1\frac{\mathcal{I}^*}{N^*}}) & 1-d-\alpha-r_1 & \frac{\mu_1\beta_1\mathcal{S}^*}{N}e^{-\beta_1\frac{\mathcal{I}^*}{N^*}} \\ 0 & \alpha & 1-d-r_2 \end{pmatrix}.$$

To find the eigenvalues of $B = JF(\mathcal{E}^*)$, we solve the characteristic equation $det(B-\lambda I) = 0$

$$\begin{vmatrix} 1-(\mu_1+d)+\mu_1 e^{-\beta_1 \frac{\mathcal{I}^*}{N^*}} - \lambda & r_1 & r_2 - \frac{\mu_1\beta_1\mathcal{S}^*}{N^*}e^{-\beta_1\frac{\mathcal{I}^*}{N^*}} \\ \mu_1(1-e^{-\beta_1\frac{\mathcal{I}^*}{N^*}}) & 1-d-\alpha-r_1-\lambda & \frac{\mu_1\beta_1\mathcal{S}^*}{N^*}e^{-\beta_1\frac{\mathcal{I}^*}{N^*}} \\ 0 & \alpha & 1-d-r_2-\lambda \end{vmatrix} = 0$$

A/ Properties of the endogenous model

A.4a/ Local stability of the endemic equilibrium ($\mathcal{E}^*$)

Step 1: $\gamma = 0$

The characteristic equation is given by

$$p(\lambda) = \lambda^2 - (2 - 2d - r_1 - \mu_1 - \alpha)\lambda + (1 - d - \alpha - r_2)(1 - \mu_1 - d + \mu_1\varphi_1) - \alpha\mu_1\beta_1\frac{S*}{N*}\varphi_1$$

which may be written as

$$p(\lambda) = \lambda^2 + a_1\lambda + a_0$$

We now apply the Jury test to show that the remaining two eigenvalues are inside the unit disk.

$p(1) = 1 - (2 - 2d - \mu_1 - \alpha - r_2 - r_1 - \alpha + \mu_1\varphi_1) + (1 - d - \alpha - r_2)((1 - \mu_1 - d - \mu_1\varphi_1) - r_1(1 - d - r_2) + \alpha r_2 - \mu_1\alpha\beta\frac{S*}{N*}\varphi_1$.

Thus

$p(1) > \mu_1(d+\alpha+r_2)(1-\varphi_1)+(d+r_2)(d+\alpha+r_1)-\alpha\mu_1\beta_1\frac{S*}{N*}\varphi_1 > (d+r_2)(d+\alpha+r_1)-\alpha\mu_1\beta_1\frac{S*}{N*}\varphi_1$.

Since $\mathcal{R}_0(\mathcal{E}^*) < 1$, it follows from formula (17) that $(d + r_2)(d + \alpha + r_1) > \alpha\mu_1\beta_1\frac{S*}{N*}\varphi_1$. Hence $p(1) > 0$. Clearly $p(-1) > 0$.

One may show that the constant term $a_0 < 1$. Therefore, the endemic equilibrium is locally asymptotically stable. ■

A/ Properties of the endogenous model

A.4a/ Local stability of the endemic equilibrium ($\mathcal{E}^*$)

Step 2: $\gamma \neq 0$

In the case $\gamma \neq 0$, we need the following perturbation theorem [8]

Theorem 14 *Consider the system $\mathbf{x}(t+1) = F(\mathbf{x}(t), \eta) = F_\eta$, where $\eta = (\eta_1, \eta_2, , \eta_m$, where $F : U \times G \to U$ is continuous, $U \subset \mathbb{R}^n$, $G \subset \mathbb{R}^{>}$. Let $\mathbf{x_0}^*$ be the interior equilibrium point of $F_{\mathbf{0}}(\mathbf{x})$. Assume that the spectral radius $\rho(JF(\mathbf{x}_0^*)) < 1$. Then there exists $\delta > 0$ and a unique $\mathbf{x}^*(\eta) \in U$ for $\eta \in \mathbf{B}(\eta_0, \delta)$ such that $F(\mathbf{x}^*, \eta)) = \mathbf{x}^*$ and $F^t(\mathbf{z}) \to \mathbf{x}^*(\eta))$ as $t \to \infty$ for all $\mathbf{z} \in U$.*

[8] S. Elaydi, Y. Kang, R. Luis, Global Asymptotic Stability of the Evolutionary Periodic Ricker Competition Model J. Difference Eq. Appl., submitted, 903-915.

And after a long reasoning we proof:

Theorem 15 *[19] Assume A_1 and A_2 and the limiting equation has an equilibrium point $\mathbf{x}^* \in \mathbb{R}^n_+$. Then*
(i) if $\mathbf{x}^* \in int(\mathbb{R}^n_+)$, and if it is locally asymptotically stable as an equilibrium point of the limiting equation, then $\mathbf{x}^*$ is locally asymptotically fixed point of the nonautonomous equation (56).

Based on this asymptotic theory we have the following final result on the local asymptotic stability of the system (3)

Theorem 16 *Assume that $\mathcal{R}_0(\mathcal{E}^*) < 1 < \mathcal{R}_0(\mathcal{E}_0)$. Then for sufficiently small r_1, r_2, and γ, the endemic equilibrium of the system (3) is locally asymptotically stable.*

B/ Properties of the exogenous model
B.1/ Basic reproduction number and equilibrium points

Using again the next generation matrix approach it is possible to proof that:

$$\mathcal{R}_0(\mathcal{E}_0) = \frac{\mu_2}{\mu_2 + d + \alpha + r_1} + \frac{\mu_1 \alpha \beta_1}{(\mu_2 + d + \alpha + r_1)(d + \gamma + r_2)}$$

Moreover, we can establish a relationship between endogenous and exogenous models

Theorem 4 *The basic reproduction number of the endogenous model is less (greater) than 1 if and only if the basic reproduction number of the exogenous model is less (greater) than 1. Moreover, they are equal if one of them is equal to 1.*

Proof. The proof is straightforward and will be omitted.

B/ Properties of the exogenous model

B.2a/ Local Stability of the Disease Free Equilibrium (DFE) ($\mathcal{E}_0$)

The proof of the following theorem,

Theorem 5 *The DFE* $(\mathcal{E}_0)$ *of System* (2) *is locally asymptotically stable if* $\mathcal{R}_0(\mathcal{E}_0) \leq 1$ *and a saddle if* $\mathcal{R}_0(\mathcal{E}_0) > 1$

is similar to the proof for the endogenous model, based on the computation of the eigenvalues of the same jacobian

The Jacobian matrix of system (2) at $\mathcal{E}_0$ represented by $J(\mathcal{E}_0)$ is given by

$$J(\mathcal{E}_0) = \begin{pmatrix} 1-d & r_1 & r_2 - \mu_1\beta_1 \\ 0 & 1-(d+\alpha+r_1) & \mu_1\beta_1 \\ 0 & \alpha & 1-(d+\gamma+r_2) \end{pmatrix}$$

Work in progress: Like for the endogenous case the global stability of the DFE, the existence and unicity of the endemic equilibrium and its local stability will be proved.

The SEIT model with treatment

Active TB infection can be treated by prolonged use of antibiotics. In 1943, Selman Waksman, Elizabeth Bugie, and Albert Schatz developed streptomycin, the first antibiotic, whereas rest and sunlight were prescribed in sanatoriums to alleviate TB. It was later abandoned because inducing permanent hearing loss, tinnitus, dizziness, and vertigo.

Now, four drugs are used in therapy: isoniazid (1951), pyrazinamide (1952), ethambutol (1961), and rifampin (1966). They remain the most common treatment for TB.

With that said, another difficulty is that many strains of TB are drug resistant. We conclude the SEIT model is sufficient to describe the transmission pattern of tuberculosis.
However, the reality is that while models assume we have access to complete data on TB cases, every active infection is not reported. Moreover, since latent TB carriers exhibit no symptoms, their exact number is far more difficult to estimate, and treatment often goes half-done because of its length or duration.

Above all, tuberculosis is a disease of poverty, which is not difficult to predict given that nations with higher living standards report fewer cases of TB.

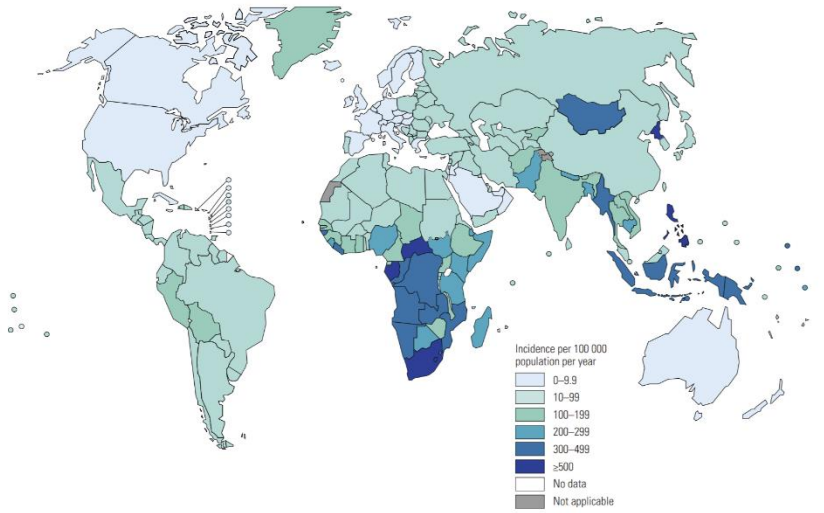
The SEIT model:

$$
\begin{aligned}
S(t+1) &= \Lambda + (1-\mu_1 - d)S(t) + \mu_1\varphi_1(I(t)/N^*)S(t) \\
E(t+1) &= \mu_1(1-\varphi_1(I(t)/N^*)S(t) + \mu_2\varphi_2(I(t)/N^*)E(t) + \mu_3(1-\varphi_3(I(t)/N^*)T(t) \\
&\quad + (1-d-\alpha-r_1-\mu_2)E(t) + pr_2I(t) \\
I(t+1) &= \alpha E(t) + \mu_2(1-\varphi_2(I(t)/N^*)E(t) + (1-d-r_2-\gamma)I(t) \\
T(t+1) &= r_1E(t) + qr_2I(t) + \mu_3\varphi_3(I(t)/N^*)T(t) + (1-\mu_3-d)T(t)
\end{aligned}
\tag{3}
$$

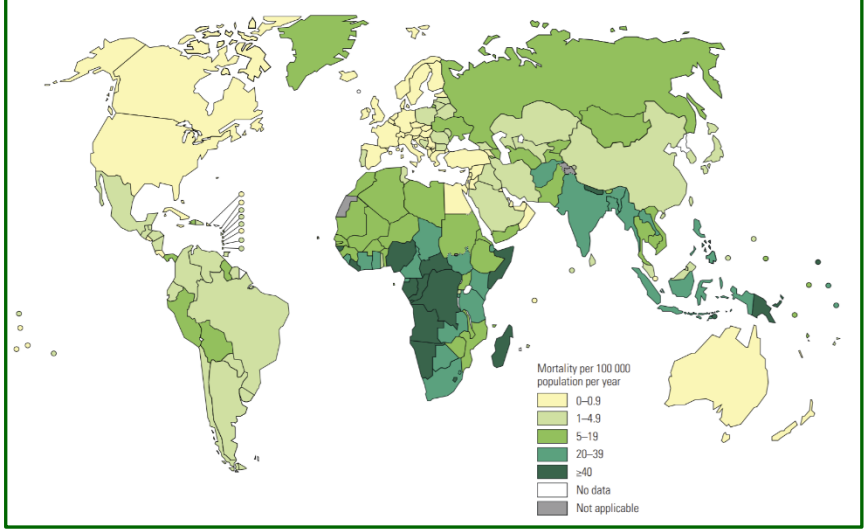
Tuberculosis a disease of poverty

Incidence and mortality rates

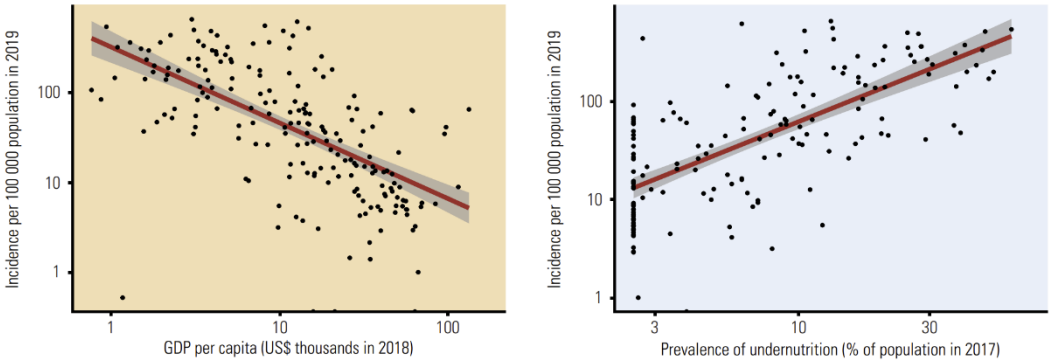
Estimated TB incidence rates, 2019



Estimated TB mortality rates in HIV-negative people, 2019

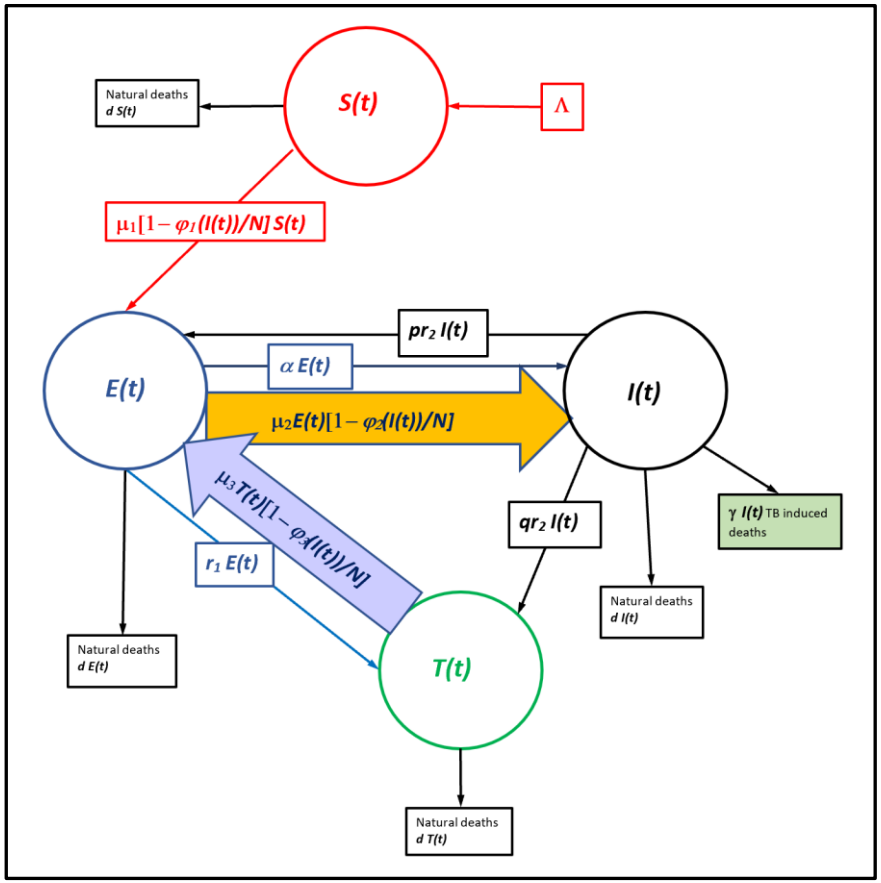


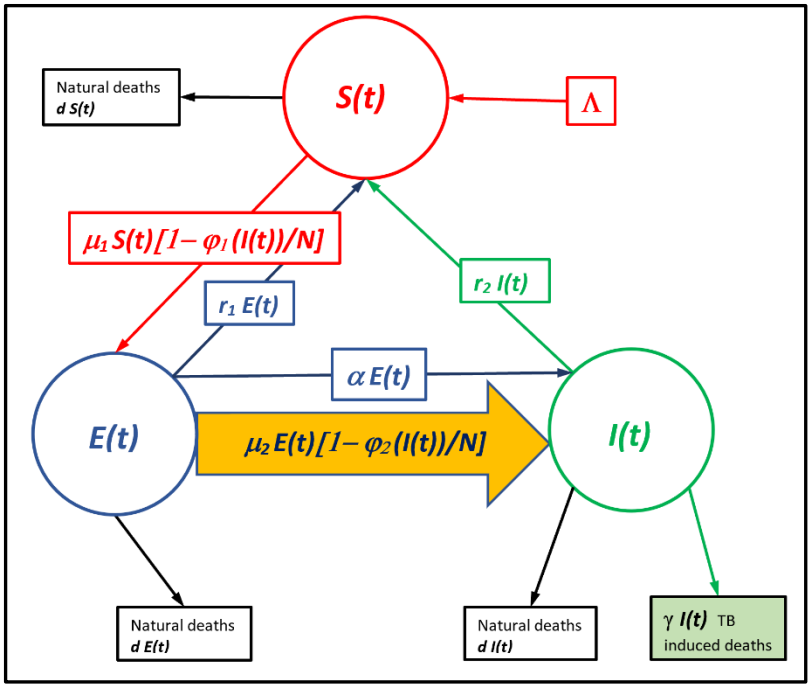
The relationship between GDP per capita and the prevalence of undernutrition, and TB incidence per 100 000 population



Chartflow of the SEIT model with treatment

Comparison between the SEI and the SEIT models:





The parameter p is the proportion of Infectious who does not complete treatment and relapse to the latent class, and $q = 1 - p$.

C.1/ The basic reproduction number

C.2a/ Local Stability of the Disease Free Equilibrium (DFE) ($\mathcal{E}_0$)

C.2b/ Global Stability of the Disease Free Equilibrium (DFE) ($\mathcal{E}_0$)

For the SEIT model we give only the results, the proofs being similar to the proofs of the SEI models.

Computation of R_0 using the next generation matrix:

$$\mathcal{R}_0 = \frac{\alpha(\mu_1\beta_1 + pr_2)}{(d+\alpha+r_1+\mu_2)(d+\gamma+r_2)}$$

Local Stability of ($\mathcal{E}_0$):

Theorem 17 *The DFE* $(\mathcal{E}_0)$ *of system* (3) *is locally asymptotically stable if* $\mathcal{R}_0(\mathcal{E}_0) \leq 1$ *and unstable if* $\mathcal{R}_0(\mathcal{E}_0) > 1$.

Global Stability of ($\mathcal{E}_0$):

Theorem 18 *Assume that* $\mathcal{R}_0 \leq 1$. *Then the DFE of* (3) *is globally asymptotically stable.*

C.3a/ Existence of the Endemic Equilibrium ($\mathcal{E}^*$)

C.3b/ Unicity of the Endemic Equilibrium ($\mathcal{E}^*$)

Existence of the Endemic Equilibrium ($\mathcal{E}^*$):

case $\gamma \neq 0$, $\mu_1 \neq 0$, $r_1 \neq 0$, $r_2 \neq 0$, $\mu_2 = 0$, $\mu_3 = 0$

Proposition 19 *Assume that* $\gamma \neq 0$, $\mu_1 \neq 0$, $r_1 \neq 0$, $r_2 \neq 0$, $\mu_2 = 0$ *and* $\mu_3 = 0$. *Then every equilibrium point* $\mathcal{E}^* = (\mathcal{S}^* > 0\ ,\ E^* \geq 0, \mathcal{I}^* \geq 0, \mathcal{T}^* \geq 0)$ *of model* (3) *is of the form*

$$\mathcal{E}^* = (S^*, \frac{(d + r_2 + \gamma))(\Lambda - d\mathcal{S}^*)}{L_1}, \frac{\alpha(\Lambda - d\mathcal{S}^*)}{L_1}, \frac{L_2(\Lambda - d\mathcal{S}^*)}{L_1}) \tag{62}$$

with $\mathcal{S}^*$ *solution of*

$$L_1 N^* \ln\left[\frac{\mu_1 \mathcal{S}^*}{(\mu_1 + d)\mathcal{S}^* - \Lambda}\right] + \alpha\beta_1 d\mathcal{S}^* = \alpha\beta_1\Lambda, \tag{63}$$

with $L_1 = ((d + \alpha + r_1)(d + r_2 + \gamma) - \alpha p r_2)\,,$

and $L_2 = (r_1(d + r_2 + \gamma) + q r_2 \alpha)\,.$

Unicity of the Endemic Equilibrium ($\mathcal{E}^*$):

Theorem 20 *Assume that* $\gamma \neq 0$, $\mu_1 \neq 0$, $r_1 \neq 0$, $r_2 \neq 0$, $\mu_2 = 0$, $\mu_3 = 0$ *and* $\mathcal{R}_0 > 1$. *Then there exists a unique endemic equilibrium point* $\mathcal{E}^* = (\mathcal{S}^* > 0\ ,\ E^* \geq 0, \mathcal{I}^* \geq 0, \mathcal{T}^* \geq 0)$ *of system* (3)

C.4a/ Local Stability of the Endemic Equilibrium ($\mathcal{E}^*$)

The proof is done in two steps:

Step 1:

Theorem 22 *Assume that* $\mu_2 = \mu_3 = r_1 = r_2 = 0$. *and* $\mathcal{R}_0(\mathcal{E}^*) < 1 < \mathcal{R}_0(\mathcal{E}_0)$. *Then for sufficiently small* r_1, r_2, *and* μ_2, *the endemic equilibrium of the system* (3) *is locally asymptotically stable.*

Step 2:

Theorem 23 *Assume that* $\mu_2 \neq 0$, $r_1 \neq 0$, $r_2 \neq 0$, *and* $\gamma \neq 0$, *and* $\mathcal{R}_0(\mathcal{E}^*) < 1 < \mathcal{R}_0(\mathcal{E}_0)$. *Then for sufficiently small* r_1, r_2, γ, *and* mu_2, *the endemic equilibrium of the system* (3) *is locally asymptotically stable.*

The global stability of ($\mathcal{E}^*$) is not yet proved,

Thank you for your attention

Спасибо за внимание