Optimal control and cost-effectiveness analysis for a tuberculosis model

P. Rodrigues, C. J. Silva and D. F. M. Torres

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Motivation: some Tuberculosis (TB) numbers

In 2013:

- 9 million people fell ill with TB
- 1.5 million people died from TB
- over 95% of TB deaths occur in low- and middle-income countries, and it is among the top 5 causes of death for women aged 15 to 44
- an estimated 550 000 children became ill with TB
- 80 000 HIV-negative children died of TB
- an estimated 480 000 people developed multidrug resistant TB
Motivation
TB model
OC problem
Numerical results
Conclusion

Tuberculosis: causes and transmission

Mycobacterium tuberculosis
(Image from Wikipedia)

TB transmission
Acquired via airborne infection from someone who has active TB
(Image from http://linssky.com)
• Mycobacterium tuberculosis is the **second cause of death worldwide** from a single infectious agent, after Human immunodeficiency virus (HIV);
Some more Tuberculosis numbers

✓ The TB death rate dropped 45% between 1990 and 2013.
✓ An estimated 37 million lives were saved through TB diagnosis and treatment between 2000 and 2013.
✓ The estimated number of people falling ill with TB each year is declining.

The world is on track to achieve the Millennium Development Goal: reverse the spread of TB by 2015!

The Global Plan to Stop TB 2006–2015

The Global Plan to Stop TB launched worldwide

The Global Plan to Stop TB 2006-2015 Actions for Life, was launched at the World Economic Forum in Davos, Switzerland, in January 2006, following 18 months of consultation and research. WHO Stop TB staff were heavily involved in the Global Plan’s development, and took part in a series of high profile launches.

Following WHO: “2015 is seen as a critical year for action to adapt and roll out the strategy in diverse country settings.”


(Image from http://www.who.int/tb/en/)
OC and cost-effectiveness analysis for a TB model

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This model considers:

- treatment of active infectious individuals;
- post-exposure interventions to prevent endogenous reactivation (treatment of latent infectious with anti-TB drugs or apply prophylactic vaccine).
Divide the total population $N$ in:

$\uparrow S$: susceptible;

$\uparrow L_1$: early latent, i.e., individuals recently infected (less than 2 years) but not infectious;

$\rightarrow I_T$: infected, i.e., individuals who have active TB and are infectious;

$\downarrow L_2$: persistent latent, i.e., individuals who were infected and remain latent;

$\downarrow R$: recovered, i.e., individuals who were previously infected and treated.
Assumptions:

- At birth, all individuals are equally susceptible and differentiate as they experience infection and respective therapy.
- The rates of birth and death, $\mu$, are equal, and no disease-related deaths are considered.

Total population, $N$, is constant

$$N = S(t) + L_1(t) + I(t) + L_2(t) + R(t)$$
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P. Rodrigues, C. J. Silva and D. F. M. Torres

Motivation
TB model
OC problem
Numerical results
Conclusion

Mathematical model for TB

\[
\begin{align*}
\dot{S}(t) &= \mu N - \frac{\beta}{N} I(t)S(t) - \mu S(t) \\
\dot{L}_1(t) &= \frac{\beta}{N} I(t) (S(t) + \sigma L_2(t) + \sigma R R(t)) - (\delta + \tau_1 + \mu)L_1(t) \\
\dot{I}(t) &= \phi \delta L_1(t) + \omega L_2(t) + \omega R R(t) - (\tau_0 + \mu)I(t) \\
\dot{L}_2(t) &= (1 - \phi) \delta L_1(t) - \sigma \frac{\beta}{N} I(t)L_2(t) - (\omega + \tau_2 + \mu)L_2(t) \\
\dot{R}(t) &= \tau_0 I(t) + \tau_1 L_1(t) + \tau_2 L_2(t) - \sigma R \frac{\beta}{N} I(t)R(t) - (\omega_R + \mu)R(t).
\end{align*}
\]
TB mathematical model with controls

P. Rodrigues, C. J. Silva and D. F. M. Torres

Motivation
TB model
OC problem
Numerical results
Conclusion

- $u_1$: intensity of the post-exposure interventions (chemotherapy with anti-TB drugs) to early latent individuals $L_1$
- $u_2$: intensity of the post-exposure interventions (post-exposure vaccine) to persistent latent individuals $L_2$

Why treat latent individuals?

Beneficial and perverse effects of isoniazid preventive therapy for latent tuberculosis infection in HIV–tuberculosis coinfected populations

Ted Cohen,*†, Marc Lipsitch†, Rochelle P. Walensky*, and Megan Murray*‡

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Edited by John J. Mekalanos, Harvard Medical School, Boston, MA, and approved March 8, 2006 (received for review January 13, 2006)
TB mathematical model with controls

\[
\begin{align*}
\dot{S}(t) &= \mu N - \frac{\beta}{N} I(t) S(t) - \mu S(t) \\
\dot{L}_1(t) &= \frac{\beta}{N} I(t) (S(t) + \sigma L_2(t) + \sigma_R R(t)) - (\delta + \tau_1 u_1(t) + \mu) L_1(t) \\
\dot{I}(t) &= \phi \delta L_1(t) + \omega L_2(t) + \omega_R R(t) - (\tau_0 + \mu) I(t) \\
\dot{L}_2(t) &= (1 - \phi) \delta L_1(t) - \sigma \frac{\beta}{N} I(t) L_2(t) - (\omega + \tau_2 u_2(t) + \mu) L_2(t) \\
\dot{R}(t) &= \tau_0 I(t) + \tau_1 u_1(t) L_1(t) + \tau_2 u_2(t) L_2(t) - \sigma_R \frac{\beta}{N} I(t) R(t) \\
&\quad - (\omega_R + \mu) R(t).
\end{align*}
\]
Optimal control problem

Set of admissible controls functions

\[ \Omega = \left\{ (u_1(\cdot), u_2(\cdot)) \in (L^\infty(0, t_f))^2 \mid 0 \leq u_1(t), u_2(t) \leq 1, \forall t \in [0, t_f] \right\} \]

Control system (CS)

\[
\begin{align*}
\dot{S}(t) &= \mu N - \frac{\beta}{N} l(t) S(t) - \mu S(t) \\
\dot{L}_1(t) &= \frac{\beta}{N} l(t) (S(t) + \sigma L_2(t) + \sigma_R R(t)) - (\delta + \tau_1 u_1(t) + \mu)L_1(t) \\
\dot{I}(t) &= \phi \delta L_1(t) + \omega L_2(t) + \omega_R R(t) - (\tau_0 + \mu)I(t) \\
\dot{L}_2(t) &= (1 - \phi) \delta L_1(t) - \sigma \frac{\beta}{N} l(t)L_2(t) - (\omega + \tau_2 u_2(t) + \mu)L_2(t) \\
\dot{R}(t) &= \tau_0 I(t) + \tau_1 u_1(t)L_1(t) + \tau_2 u_2(t)L_2(t) - \sigma_R \frac{\beta}{N} l(t)R(t) - (\omega_R + \mu)R(t)
\end{align*}
\]

Cost function: minimize

\[
\mathcal{J}(u_1(\cdot), u_2(\cdot)) = \int_0^{t_f} \left[ W_0 I(t) + \frac{W_1}{2} u_1^2(t) + \frac{W_2}{2} u_2^2(t) \right] dt
\]

\(W_0\): weight constant on active infectious individuals \(I\).
\(W_1, W_2\): relative cost of the interventions associated to control \(u_1, u_2\), respectively.
Optimal control problem

Optimal control problem (OCP)

Determine \((S^*(\cdot), L_1^*(\cdot), I^*(\cdot), L_2^*(\cdot), R^*(\cdot))\), associated to an admissible control pair \((u_1^*(\cdot), u_2^*(\cdot)) \in \Omega\) on the time interval \([0, t_f]\), satisfying \((CS)\), given initial conditions \(S(0), L_1(0), I(0), L_2(0)\) and \(R(0)\) and minimizing the cost function \(\mathcal{J}\), i.e.,

\[
\mathcal{J}(u_1^*(\cdot), u_2^*(\cdot)) = \min_{\Omega} \mathcal{J}(u_1(\cdot), u_2(\cdot)).
\]  

Theorem (existence and uniqueness)

\((OCP)\) admits an unique optimal solution.
Pontryagin maximum principle: 1st order necessary optimality condition

For (OCP) there exists adjoint functions $\lambda_i^*(\cdot)$, $i = 1, \ldots, 5$ such that

\[
\begin{aligned}
\dot{\lambda}_1^*(t) &= \lambda_1^*(t) \left( \frac{\beta}{N} I^*(t) + \mu \right) - \lambda_2^*(t) \frac{\beta}{N} I^*(t) \\
\dot{\lambda}_2^*(t) &= \lambda_2^*(t) (\delta + \tau_1 + \mu) - \lambda_3^*(t) \phi \delta - \lambda_4^*(t) (1 - \phi) \delta - \lambda_5^*(t) \tau_1 u_1^*(t) \\
\dot{\lambda}_3^*(t) &= -W_0 + \lambda_1^*(t) \frac{\beta}{N} S^*(t) - \lambda_2^*(t) \frac{\beta}{N} (S^*(t) + \sigma L_2^*(t) + \sigma_R R^*(t)) \\
&\quad + \lambda_3^*(t) (\tau_0 + \mu) + \lambda_4^*(t) \sigma \frac{\beta}{N} L_2^*(t) - \lambda_5^*(t) \left( \tau_0 - \sigma_R \frac{\beta}{N} R^*(t) \right) \\
\dot{\lambda}_4^*(t) &= -\lambda_2^*(t) \frac{\beta}{N} I^*(t) \sigma - \lambda_3^*(t) \omega + \lambda_4^*(t) \left( \sigma \frac{\beta}{N} I^*(t) + \omega + \tau_2 u_2^*(t) + \mu \right) \\
&\quad - \lambda_5^*(t) (\tau_2 u_2^*(t)) \\
\dot{\lambda}_5^*(t) &= -\lambda_2^*(t) \sigma_R \frac{\beta}{N} I^*(t) - \lambda_3^*(t) \omega_R + \lambda_5^*(t) \left( \sigma_R \frac{\beta}{N} I^*(t) + \omega_R + \mu \right),
\end{aligned}
\]
Optimal control problem

Pontryagin maximum principle: 1\textsuperscript{st} order necessary optimality condition

with transversality conditions

\[
\lambda_i^*(t_f) = 0, \quad i = 1, \ldots, 5.
\]

Furthermore,

\[
\begin{align*}
    u_1^*(t) &= \min \left\{ \max \left\{ 0, \frac{\tau_1 L_1^* (\lambda_2^* - \lambda_5^*)}{W_1} \right\}, 1 \right\}, \\
    u_2^*(t) &= \min \left\{ \max \left\{ 0, \frac{\tau_2 L_2^* (\lambda_4^* - \lambda_5^*)}{W_2} \right\}, 1 \right\}.
\end{align*}
\]
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Motivation

TB model

OC problem

Numerical results

Conclusion

### Numerical Results and Cost-Effectiveness Analysis

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \beta )</td>
<td>Transmission coefficient</td>
<td>Variable</td>
</tr>
<tr>
<td>( \mu )</td>
<td>Death and birth rate</td>
<td>1/70 year(^{-1} )</td>
</tr>
<tr>
<td>( \delta )</td>
<td>Rate at which individuals leave ( L_1 )</td>
<td>12 year(^{-1} )</td>
</tr>
<tr>
<td>( \phi )</td>
<td>Proportion of individuals going to ( I )</td>
<td>0.05</td>
</tr>
<tr>
<td>( \omega )</td>
<td>Rate of endogenous reactivation for persistent latent infections</td>
<td>0.0002 year(^{-1} )</td>
</tr>
<tr>
<td>( \omega_R )</td>
<td>Rate of endogenous reactivation for treated individuals</td>
<td>0.00002 year(^{-1} )</td>
</tr>
<tr>
<td>( \sigma )</td>
<td>Factor reducing the risk of infection as a result of acquired immunity to a previous infection for ( L_2 )</td>
<td>0.25</td>
</tr>
<tr>
<td>( \sigma_R )</td>
<td>Rate of exogenous reinfection of treated patients</td>
<td>( \alpha; 2\alpha; \alpha/2 )</td>
</tr>
<tr>
<td>( \tau_0 )</td>
<td>Rate of recovery under treatment of active TB</td>
<td>2 year(^{-1} )</td>
</tr>
<tr>
<td>( \tau_1 )</td>
<td>Rate of recovery under treatment of latent individuals ( L_1 )</td>
<td>2 year(^{-1} )</td>
</tr>
<tr>
<td>( \tau_2 )</td>
<td>Rate of recovery under treatment of latent individuals ( L_2 )</td>
<td>1 year(^{-1} )</td>
</tr>
<tr>
<td>( N )</td>
<td>Total population</td>
<td>30,000</td>
</tr>
<tr>
<td>( t_f )</td>
<td>Total simulation duration</td>
<td>5 years</td>
</tr>
<tr>
<td>( W_0 )</td>
<td>Weight constant on active infectious individuals ( I(t) )</td>
<td>50</td>
</tr>
<tr>
<td>( W_1 )</td>
<td>Weight constant on control ( u_1(t) )</td>
<td>50</td>
</tr>
<tr>
<td>( W_2 )</td>
<td>Weight constant on control ( u_2(t) )</td>
<td>50</td>
</tr>
</tbody>
</table>
Numerical Results and Cost-Effectiveness Analysis

(OCP): example for a period of 5 years

Particular epidemiological scenario:

- $\beta = 100$
- $\sigma_R = \sigma$

Initial conditions (the values are obtained as the endemic equilibria values for (CS) before the introduction of post-exposure interventions (i.e., $u_1 = 0 = u_2$)):

<table>
<thead>
<tr>
<th></th>
<th>$S(0)$</th>
<th>$L_1(0)$</th>
<th>$I(0)$</th>
<th>$L_2(0)$</th>
<th>$R(0)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>4 554</td>
<td>72</td>
<td>24</td>
<td>23 950</td>
<td>1 400</td>
</tr>
</tbody>
</table>

**Numerical Results and Cost-Effectiveness Analysis**

*(OCP): example for a period of 5 years*

Control $u_1$ (continuous line); control $u_2$ (dashed line).

Active infected individuals $I$. 

Motivation

TB model

OC problem

Numerical results

Conclusion
Numerical Results and Cost-Effectiveness Analysis

(OCP): example for a period of 5 years

Control $u_1$ (continuous line); control $u_2$ (dashed line).

Efficacy function:

$$E(t) = \frac{l(0) - l^*(t)}{l(0)} = 1 - \frac{l^*(t)}{l(0)}$$
Sensitivity Analysis to the Duration of Intervention $t_f$

Particular epidemiological scenario:
- $\beta = 100$
- $\sigma_R = \sigma$
- $t_f \in \{5, 7, 10, 12, 15, 17, 20, 22, 25\}$

Proportion of infectious individuals for the optimal solution $I(t)$. 
Numerical Results and Cost-Effectiveness Analysis

Sensitivity Analysis to the Weight Constants on the Objective Functional $\mathcal{J}$ (vary $W_0$, $W_1$ and $W_2$)

Particular epidemiological scenario:

- $\beta = 100$
- $\sigma_R = \sigma$
- $t_f = 5$

$W_0 = 50$ and $W_1 = W_2 = 5, 25, 50, 100, 200, 500$.  

$W_0 = W_2 = 50$ and varying $W_1$.  

![Graph 1](image1.png)  

![Graph 2](image2.png)
Numerical Results and Cost-Effectiveness Analysis

Sensitivity Analysis to the Weight Constants on the Objective Functional $\mathcal{J}$ (vary $W_0$, $W_1$ and $W_2$)

Particular epidemiological scenario:

- $\beta = 100$
- $\sigma_R = \sigma$
- $t_f = 5$

$W_0 = W_2 = 50$ and $W_1 = 5, 25, 50, 100, 200, 500$. $W_0 = W_1 = 50$ and $W_2 = 5, 25, 50, 100, 200, 500$. 

![Graph](image1.png)  

![Graph](image2.png)
Summary measures

Total cases averted by the intervention

For each $\beta$ and $\sigma_R$ fixed, the total cases averted by the intervention during the time period $t_f$ is given by

$$A(\beta, \sigma_R) = t_f I(0; \beta, \sigma_R) - \int_0^{t_f} I^*(t; \beta, \sigma_R) dt,$$

where

- $I^*(t; \beta, \sigma_R) = I^*(t)$ is the optimal solution associated to the optimal controls $(u_1^*, u_2^*)$;
- $I(0; \beta, \sigma_R) = I(0)$ is the corresponding initial condition.
Summary measures

Effectiveness

We define effectiveness as the proportion of cases averted on the total cases possible under no intervention:

\[
\bar{E}(\beta, \sigma_R) = \frac{A(\beta, \sigma_R)}{t_f I(0; \beta, \sigma_R)} = 1 - \frac{\int_0^{t_f} l^*(t; \beta, \sigma_R) dt}{t_f I(0; \beta, \sigma_R)}.
\]
Numerical Results and Cost-Effectiveness Analysis

**Summary measures**

**Total cost**

The total cost associated to the intervention is

$$TC(\beta, \sigma_R) = \int_0^{t_f} C_1 u_1^*(t)L_1^*(t) + C_2 u_2^*(t)L_2^*(t)dt,$$

where $C_i$ correspond to the per person unit cost of the two possible interventions:

- detection and treatment of early latent individuals ($C_1$);
- chemotherapy/vaccination of persistent latent individuals ($C_2$).
Numerical Results and Cost-Effectiveness Analysis

Summary measures

Average cost-effectiveness ratio (Okosun et al., 2013)

Define the average cost-effectiveness ratio by

\[
ACER = \frac{TC}{A}.
\]

\(TC\): Total cost associated to the intervention.
\(A\): Total cases averted by the intervention.
Numerical Results and Cost-Effectiveness Analysis

**Relaxation-times**

The time at which the intensity of each intervention is relaxed:

\[ tr_i = tr_i(\beta, \sigma_R) = \max\{ t \in [0, t_f] : u_i(t; \beta, \sigma_R) = 1 \}, \quad i = 1, 2. \]
Numerical Results and Cost-Effectiveness Analysis

**(OCP): example for a period of 5 years**

Particular epidemiological scenario:

- $\beta = 100$
- $\sigma_R = \sigma$

**Summary of cost-effectiveness measures**

<table>
<thead>
<tr>
<th>$\beta$</th>
<th>$A$</th>
<th>$TC$</th>
<th>$ACER$</th>
<th>$\bar{E}$</th>
<th>$t_{r_1}$</th>
<th>$t_{r_2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>56</td>
<td>23 374</td>
<td>417</td>
<td>0.4691</td>
<td>4.1765</td>
<td>2.0</td>
</tr>
</tbody>
</table>

$A$: Total cases averted by the intervention.

$TC$: Total cost associated to the intervention.

$ACER$: Average cost-effectiveness ratio.

$\bar{E}$: Effectiveness.
Impact of transmission intensity on optimal control interventions

Consider:

- different epidemiological scenarios in terms of transmission intensity, by varying parameter $\beta$.

Assume:

- protection conferred by natural infection or by treatment is the same ($\sigma_R = \sigma$).
Numerical Results and Cost-Effectiveness Analysis

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Motivation
TB model
OC problem
Numerical results
Conclusion

Impact of transmission intensity on optimal control interventions

Effectiveness $\overline{E}$

Relaxation-times $t_i$, $i = 1, 2$ ($t_{r_1}$: full line; $t_{r_2}$: dashed line)

Dotted vertical line: reinfection threshold $RT$.

$RT$: critical transmissibility values above which there is a steep nonlinear increase in disease prevalence, corresponding to the increase contribute of reinfection cases to the disease load.
Impact of protection against reinfection of the treated individuals ($\sigma_R \neq \sigma$) on optimal control interventions

Explore two possibilities:

- treatment enhances protection against reinfection ($\sigma_R < \sigma$);
- protection is impaired by treatment ($\sigma_R > \sigma$).

Consider:

- $\sigma_R = \sigma / 2$;
- $\sigma_R = 2\sigma$. 
Impact of protection against reinfection of the treated individuals ($\sigma_R \neq \sigma$) on optimal control interventions.

Effectiveness $\bar{E}$ ($\sigma_R = \sigma/2$: full line; $\sigma_R = 2\sigma$: dashed line).
Impact of protection against reinfection of the treated individuals ($\sigma_R \neq \sigma$) on optimal control interventions

**Relaxation-time $t_{r_1}$**

($\sigma_R = \sigma/2$: full line; $\sigma_R = 2\sigma$: dashed line).

**Relaxation-time $t_{r_2}$**

($\sigma_R = \sigma/2$: full line; $\sigma_R = 2\sigma$: dashed line).
Numerical Results and Cost-Effectiveness Analysis

Optimal controls strategy and cost-effectiveness analysis

Control strategies:
- strategy **a**: implementing both controls $u_1$ and $u_2$;
- strategy **b**: implementing only control measure $u_1$;
- strategy **c**: only control measure $u_2$.

**Effectiveness $E$**
(Both controls $u_1$ and $u_2$: grey lines; only $u_1$: black full line; only $u_2$: black dashed line.)

**Relaxation-times, $t_{r1}$ or $t_{r2}$**
(Both controls $u_1$ and $u_2$: grey lines; only $u_1$: black full line; only $u_2$: black dashed line.)
Numerical Results and Cost-Effectiveness Analysis

Optimal controls strategy and cost-effectiveness analysis

Particular epidemiological scenario:

- $\beta = 100$
- $\sigma_R = \sigma$

Incremental cost effectiveness ratio (Okosun et al, 2013)

Incremental cost effectiveness ratio (ICER) :

$$ICER(b) = \frac{A(b) - A(a)}{TC(b) - TC(a)}.$$

A: Total cases averted by the intervention.
TC: Total cost associated to the intervention.
Numerical Results and Cost-Effectiveness Analysis

Optimal controls strategy and cost-effectiveness analysis

Particular epidemiological scenario:

- $\beta = 100$
- $\sigma_R = \sigma$
- $C_1 = C_2 = 1$

Incremental cost-effectiveness ratio for alternative strategies a, b and c.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>A</th>
<th>TC</th>
<th>ACER</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>c</td>
<td>24</td>
<td>35640</td>
<td>1485</td>
<td>1485</td>
</tr>
<tr>
<td>b</td>
<td>37</td>
<td>211</td>
<td>5.7</td>
<td>-1721</td>
</tr>
<tr>
<td>a</td>
<td>56</td>
<td>23374</td>
<td>417.4</td>
<td>1207</td>
</tr>
</tbody>
</table>

- Treatment of only early latent individuals is the more cost-effective strategy.
- Treatment of both early latent and persistent latent individuals has a higher effectiveness.
Some conclusions:

- Interventions impact can be sensitive to transmission intensity and reinfection.

- Effectiveness of optimal intervention decreases with transmission. In high transmission settings, the intensity of treatment of persistent latent individuals $u_2^*$ for the optimal solution is reduced. Since treatment of persistent latent individuals reduces the reactivation rate (from $\omega$ to $\omega_R$), when reinfection is very common and it overcomes reactivation impact, the advantage of treating this population group is less pronounced.

- Treatment of persistent latent individuals should be less intense or even absent for the case where treatment impairs protection.

- Reinfection has an important role in the determination of the optimal control strategy, by diminishing the intervention intensity on persistent latent individuals: first when transmission is very high corresponding to a very high reinfection rate and secondly when this population group has a lower susceptibility to reinfection ($\sigma < \sigma_R$).
Thank you!