A model for Tuberculosis epidemics endemicity and control strategies

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Some references:

▶ **B. Ainseba, Z. Feng, M. Iannelli and F. A. Milner**,  

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▶ **Z. Feng, M. Iannelli and F. A. Milner**,  

▶ **V. Barbu, M. Iannelli**,  

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Key facts on tuberculosis
(WHO fact sheet, January 2018)

- Tuberculosis (TB) is one of the top 10 causes of death worldwide.
- In 2016, 10.4 million people fell ill with TB, and 1.7 million died from the disease.
- In 2016, an estimated 1 million children became ill with TB and 250,000 children died of TB.
- TB is a leading killer of HIV-positive people: in 2016, 40% of HIV deaths were due to TB.
- Multidrug-resistant TB (MDR-TB) remains a public health crisis and a health security threat. WHO estimates that there were 600,000 new cases with resistance to rifampicin.
- Globally, TB incidence is falling at about 2% per year. This needs to accelerate to a 4-5% annual decline to reach the 2020 milestones of the End TB Strategy.
- An estimated 53 million lives were saved through TB diagnosis and treatment between 2000 and 2016.
- Ending the TB epidemic by 2030 is among the health targets of the Sustainable Development Goals.
About Tuberculosis

Disease details

- Tuberculosis (TB) is caused by bacteria (Mycobacterium tuberculosis) that most often affect the lungs. Tuberculosis is curable and preventable.

- TB is spread from person to person through the air. When people with lung TB cough, sneeze or spit, they propel the TB germs into the air. A person needs to inhale only a few of these germs to become infected.

- About one-quarter of the world's population has latent TB, which means people have been infected by TB bacteria but are not (yet) ill with the disease and cannot transmit the disease.

- People infected with TB bacteria have a 5-15% lifetime risk of falling ill with TB. However, persons with compromised immune systems, such as people living with HIV, malnutrition or diabetes, or people who use tobacco, have a much higher risk of falling ill.

- When a person develops active TB disease, the symptoms (such as cough, fever, night sweats, or weight loss) may be mild for many months. This can lead to delays in seeking care, and results in transmission of the bacteria to others. People with active TB can infect 10-15 other people through close contact over the course of a year. Without proper treatment, 45% of HIV-negative people with TB on average and nearly all HIV-positive people with TB will die.
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▶ TB is spread from person to person through the air. When people with lung TB cough, sneeze or spit, they propel the TB germs into the air. A person needs to inhale only a few of these germs to become infected.

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▶ When a person develops active TB disease, the symptoms (such as cough, fever, night sweats, or weight loss) may be mild for many months. This can lead to delays in seeking care, and results in transmission of the bacteria to others. People with active TB can infect 10-15 other people through close contact over the course of a year. Without proper treatment, 45% of HIV-negative people with TB on average and nearly all HIV-positive people with TB will die.
From observation data we have the fraction of infected individuals of age-of-infection $\theta$ showing symptoms of the disease

$$p(\theta) = \begin{cases} 
0.06 & \theta \in [0,1), \\
0.084 & \theta \in [1,2), \\
0.093 & \theta \in [2,3), \\
0.097 & \theta \in [3,4), \\
0.098 & \theta \in [4,5), \\
0.099 & \theta \in [5,6), \\
0.1 & \theta \in [6,\infty),
\end{cases}$$

Thus, if $i(\theta, t)$ is the density of infected individuals with age of infection $\theta$ at time $t$, then

$$p(\theta)i(\theta, t)$$

is the density of infectious individuals with age of infection $\theta$ at time $t$. 
The model

We shall consider a population of otherwise healthy individuals, of size $N(t)$ at time $t \geq 0$, some of whom are infected by a single drug-sensitive strain of *Mycobacterium tuberculosis*.

\[
N(t) = S(t) + \int_0^\infty i(\theta, t) d\theta
\]

\[
S'(t) = M_S + \beta N(t) - [\mu + \lambda(t)] S(t) + \int_0^\infty \kappa(\theta) i(\theta, t) d\theta
\]

\[
\frac{\partial}{\partial t} i(\theta, t) + \frac{\partial}{\partial \theta} i(\theta, t) + \mu i(\theta, t) + \gamma(\theta) i(\theta, t) = m_i(\theta),
\]

\[
i(0, t) = \lambda(t) S(t),
\]

\[
S(0) = S_0 > 0, \quad i(\theta, 0) = i_0(\theta) \geq 0.
\]
The model

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\frac{\partial}{\partial t} i(\theta, t) + \frac{\partial}{\partial \theta} i(\theta, t) + \mu i(\theta, t) + \gamma(\theta) i(\theta, t) &= m_i(\theta), \\
i(0, t) &= \lambda(t) S(t), \\
S(0) &= S_0 > 0, \quad i(\theta, 0) = i_0(\theta) \geq 0.
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S(0) &= S_0 > 0, \quad i(\theta, 0) = i_0(\theta) \geq 0.
\end{aligned}
\]
The model

\[ S(t) - i(\theta, t) \]

\[ \lambda(t) \]

\[ \mu, \beta, M_S \]

\[ \int_0^{\theta^\dagger} \chi p(\theta) i(\theta, t) d\theta \]

\[ \int_0^{\theta^\dagger} \nu p(\theta) i(\theta, t) d\theta \]
The model

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\begin{cases}
S'(t) = M_S + \beta N(t) - [\mu + \lambda(t)] S(t) + \int_{0}^{\infty} \kappa(\theta) i(\theta, t) d\theta \\
\frac{\partial}{\partial t} i(\theta, t) + \frac{\partial}{\partial \theta} i(\theta, t) + \mu i(\theta, t) + \gamma(\theta) i(\theta, t) = m_I(\theta), \\
i(0, t) = \lambda(t) S(t), \\
S(0) = S_0 > 0, \quad i(\theta, 0) = i_0(\theta) \geq 0.
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S'(t) = M_S + \beta N(t) - [\mu + \lambda(t)] S(t) + \int_{0}^{\infty} \kappa(\theta) i(\theta, t) \, d\theta
\]

\[
\frac{\partial}{\partial t} i(\theta, t) + \frac{\partial}{\partial \theta} i(\theta, t) + \mu \, i(\theta, t) + \gamma(\theta) i(\theta, t) = m_1(\theta),
\]

\[
i(0, t) = \lambda(t) S(t), \quad m_1(\theta) = M \phi_1 q_1(\theta)
\]

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S(0) = S_0 > 0, \quad i(\theta, 0) = i_0(\theta) \geq 0.
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\frac{\partial}{\partial t} i(\theta, t) + \frac{\partial}{\partial \theta} i(\theta, t) + \mu i(\theta, t) + \gamma(\theta) i(\theta, t) = m_i(\theta),
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\frac{\partial}{\partial t} i(\theta, t) + \frac{\partial}{\partial \theta} i(\theta, t) + \mu i(\theta, t) + (\chi + \nu) p(\theta) i(\theta, t) = m_i(\theta), \\
i(0, t) = \lambda(t) S(t), \\
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$$N(t) = S(t) + \int_0^\infty i(\theta, t) d\theta$$

$$S'(t) = M_S + \beta N(t) - [\mu + \lambda(t)] S(t) + \int_0^\infty \chi p(\theta) i(\theta, t) d\theta$$

$$\frac{\partial}{\partial t} i(\theta, t) + \frac{\partial}{\partial \theta} i(\theta, t) + \mu i(\theta, t) + (\chi + \nu)p(\theta) i(\theta, t) = m_I(\theta),$$

$$i(0, t) = \lambda(t) S(t),$$

$$S(0) = S_0 > 0, \quad i(\theta, 0) = i_0(\theta) \geq 0.$$
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We shall consider a population of otherwise healthy individuals, of size \( N(t) \) at time \( t \geq 0 \), some of whom are infected by a single drug-sensitive strain of *Mycobacterium tuberculosis*.

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\end{aligned}
\]

\[
i(0, t) = \lambda(t)S(t),
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S(0) = S_0 > 0, \quad i(\theta, 0) = i_0(\theta) \geq 0.
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$$\frac{\partial}{\partial t} i(\theta, t) + \frac{\partial}{\partial \theta} i(\theta, t) + \mu i(\theta, t) + \gamma(\theta) i(\theta, t) = m_I(\theta),$$

$$i(0, t) = \lambda(t) S(t), \quad \lambda(t) = \frac{1}{N(t)} \int_0^\infty \rho(\theta) p(\theta) i(\theta, t) d\theta,$$

$$S(0) = S_0 > 0, \quad i(\theta, 0) = i_0(\theta) \geq 0.$$
The model

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i(0, t) = \lambda(t) S(t), \quad \lambda(t) = \frac{1}{N(t)} \int_{0}^{\infty} \rho(\theta) p(\theta) i(\theta, t) d\theta,
\]

\[
S(0) = S_0 > 0, \quad i(\theta, 0) = i_0(\theta) \geq 0.
\]

\[
c(\theta) \delta(\theta) \frac{p(\theta) i(\theta, t) d\theta}{N(t)}
\]
The model

the transformed and scaled model

\[
\begin{aligned}
n'(t) &= 1 + (R_d - 1)n(t) - \nu \int_0^\infty p(\theta)u(\theta, t)d\theta, \\
\frac{\partial}{\partial t}u(\theta, t) + \frac{\partial}{\partial \theta}u(\theta, t) + u(\theta, t) + \gamma(\theta)u(\theta, t) &= \phi_I q_I(\theta), \\
u(0, t) &= \left(1 - \frac{U(t)}{n(t)}\right) \int_0^{\infty} \rho(\theta)\rho(\theta)u(\theta, t)d\theta, \\
u(\theta, 0) &= u_0(\theta) \geq 0, \quad n(0) = n_0 > 0
\end{aligned}
\]

- demographic reproduction number $R_d = \frac{\beta}{\mu}$
- scaled total population $n(t)$
- scaled infected $u(\theta, t)$
- scaled total infected $U(t) = \int_0^{\theta_1} u(\theta, t)d\theta$
The model

The transformed and scaled model

\[
\begin{align*}
n'(t) &= 1 + (R_d - 1)n(t) - \nu \int_0^\infty p(\theta)u(\theta, t)d\theta, \\
\frac{\partial}{\partial t} u(\theta, t) + \frac{\partial}{\partial \theta} u(\theta, t) + u(\theta, t) + \gamma(\theta)u(\theta, t) &= \phi_1 q_1(\theta), \\
u(0, t) &= \left(1 - \frac{U(t)}{n(t)}\right) \int_0^\infty \rho(\theta)p(\theta)u(\theta, t)d\theta, \\
\frac{\partial}{\partial \theta} u(\theta, t) + \gamma(\theta)u(\theta, t) &= \phi_1 q_1(\theta), \\
\end{align*}
\]

\[
\begin{align*}
\quad u(\theta, 0) &= u_0(\theta) \geq 0, \quad n(0) = n_0 > 0
\end{align*}
\]

- demographic reproduction number \( R_d = \frac{\beta}{\mu} \)
- scaled total population \( n(t) \)
- scaled infected \( u(\theta, t) \)
- scaled total infected \( U(t) = \int_0^{\theta_+} u(\theta, t)d\theta \)
The endemic state

\[
\begin{aligned}
1 + (R_d - 1)n^* - \nu \int_0^\infty p(\theta)u^*(\theta)d\theta &= 0 \\
\frac{d}{d\theta}u^*(\theta) &= -(1 + \gamma(\theta)u^*(\theta) + \phi_I q_I(\theta), \\
u^*(0) &= \left(1 - \frac{U^*}{n^*}\right) \int_0^\infty \rho(\theta)p(\theta)u^*(\theta)d\theta, \\
U^* &= \int_0^\infty u^*(\theta)d\theta.
\end{aligned}
\]
For any set of parameters, with $\phi_I > 0$, there exists a unique steady state:

$$ u^*(\theta) = v^* K_0(\theta) + \phi_I \int_0^\theta \frac{K_0(\theta)}{K_0(s)} q_I(s) ds, $$

where

$$ K_0(\theta) = e^{-\theta} e^{-\int_0^\theta \gamma(\sigma) d\sigma}, $$

is the probability of remaining infected at age $\theta$, and $v^*$ is the (unique) solution of

$$ b(\Pi_0 v + \Pi_I \phi_I)(R_0 v + R_I \phi_I) = (Q - \nu J_0 v)((R_0 - 1)v + R_I \phi_I) $$
The endemic state

Significant parameters:

- **epidemiological reproduction numbers:**
  
  \[ R_0 = \int_0^\infty \rho(\theta)p(\theta)K_0(\theta)d\theta \]
  
  \[ R_I = \int_0^\infty \rho(\theta)p(\theta) \int_0^\theta \frac{K_0(\theta)}{K_0(s)} q_I(s)dsd\theta. \]

- **expected duration of latency:**
  
  \[ \Pi_0 = \int_0^\infty K_0(\theta)d\theta \]
  
  \[ \Pi_I = \int_0^\infty \int_0^\theta \frac{K_0(\theta)}{K_0(s)} q_I(s)dsd\theta. \]

- **expected duration of infectivity:**
  
  \[ \mathcal{I}_0 = \int_0^\infty p(\theta)K_0(\theta)d\theta \]
  
  \[ \mathcal{I}_I = \int_0^\infty p(\theta) \int_0^\theta \frac{K_0(\theta)}{K_0(s)} q_I(s)dsd\theta. \]
The endemic state

If $\phi_I = 0$ then

$$u^*(\theta) = v^*(R_0)K_0(\theta)$$
The endemic state

If $\phi_I = 0$ then

$$u^*(\theta) = v^*(R_0)K_0(\theta)$$

If $\phi_I > 0$ then

$$u^*(\theta) = v^*(R_0)K_0(\theta) + \phi_I \int_0^\theta \frac{K_0(\theta)}{K_0(s)}q_1(s)ds$$
The endemic state

stability of the endemic state by the characteristic equation

\[ \rho \hat{K}_1(\lambda) = \frac{\lambda + 1 + \rho K^*}{(\lambda + 1) \left(1 - h^* - \frac{\nu K^* h^*}{\lambda + b}\right) + (\chi + \nu) K^*} \]

proving (for small \( \nu \)) that all roots have \( \Re \lambda < 0 \)
Screening strategies

We consider two possible interventions

- screening of the resident population
- screening of the immigrant group

\[
n'(t) = 1 + (R_d - 1)n(t) - \nu \int_0^\infty p(\theta)u(\theta, t)d\theta,
\]

\[
\frac{\partial}{\partial t}u(\theta, t) + \frac{\partial}{\partial \theta}u(\theta, t) + u(\theta, t) + \gamma(\theta)u(\theta, t) = \phi I q_I(\theta),
\]

\[
u(0, t) = \left(1 - \frac{U(t)}{n(t)}\right) \int_0^\infty \rho(\theta)p(\theta)u(\theta, t)d\theta,
\]

\[
u(\theta, 0) = u_0(\theta) \geq 0, \quad n(0) = n_0 > 0
\]

\(\sigma(t)\): the fraction of individuals screened per unit time

\[\sigma \in \mathcal{U} = \{f \in L^\infty(0, T); 0 \leq f(t) \leq \sigma_{\text{max}}\}\]
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\frac{\partial}{\partial t} u(\theta, t) + \frac{\partial}{\partial \theta} u(\theta, t) + \left[1 + \gamma(\theta) + \sigma(t)(1 - p(\theta))\right] u(\theta, t) = \phi_I q_I(\theta), \\
u(0, t) &= \left(1 - \frac{U(t)}{n(t)}\right) \int_0^\infty \rho(\theta)p(\theta)u(\theta, t)d\theta, \\
u(\theta, 0) &= u_0(\theta) \geq 0, \quad n(0) = n_0 > 0
\end{align*}
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\begin{align*}
n'(t) & = 1 + (R_d - 1) n(t) - \nu \int_0^\infty p(\theta) u(\theta, t) d\theta, \\
\frac{\partial}{\partial t} u(\theta, t) + \frac{\partial}{\partial \theta} u(\theta, t) + [1 + \gamma(\theta)] u(\theta, t) & = (1 - \sigma(\theta)) \phi_1 q_1(\theta), \\
\rho(\theta) p(\theta) u(\theta, t) d\theta, \\
\end{align*}
\]

\[
\begin{align*}
\rho(\theta) p(\theta) u(\theta, t) d\theta, \\
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\[
\begin{align*}
u(\theta, 0) & = u_0(\theta) \geq 0, \quad n(0) = n_0 > 0
\end{align*}
\]
Screening strategies

**respective cost functions**

- screening of the resident population
  
  treatment of active-TB individuals
  \[
  \tau_{+} \frac{M}{\mu} \chi \int_{0}^{T} \int_{0}^{\infty} p(\theta) u^{\sigma}(\theta, t) d\theta dt,
  \]

- screening of the immigrant group
  
  treatment of non-infectious screened
  \[
  \tau_{-} \frac{M}{\mu} \int_{0}^{T} \sigma(t) \int_{0}^{\infty} (1 - p(\theta)) u^{\sigma}(\theta, t) d\theta dt.
  \]

  social cost of the disease
  \[
  \zeta \int_{0}^{T} \int_{0}^{\infty} u^{\sigma}(\theta, t) d\theta dt,
  \]

  fixed cost of the screening procedure
  \[
  \frac{\alpha}{2} \int_{0}^{T} \sigma^{2}(t) dt,
  \]

  cost of screening the population
  \[
  c \frac{M}{\mu} \int_{0}^{T} \sigma(t) n^{\sigma}(t) dt.
  \]
Screening strategies

- screening of the resident population
- screening of the immigrant group

\[
C_l(\sigma) = \int_0^T \int_0^\infty [A(\theta) + \sigma(t)B(\theta)] u^\sigma(\theta, t) d\theta dt
+ \int_0^T \left[ \frac{\alpha}{2} \sigma^2(t) + c \sigma(t)n^\sigma(t) \right] dt,
\]

where

\[
A(\theta) = \zeta + \tau_+ \chi p(\theta), \quad B(\theta) = \tau_-(1 - P(\theta))
\]
Screening strategies

respective cost functions

- screening of the resident population
- screening of the immigrant group

Treatment of active-TB individuals:
\[ \tau_+ \frac{M}{\mu} \chi \int_0^T \int_0^\infty p(\theta)u^\sigma(\theta, t)d\theta dt, \]

Treatment of non-infectious screened:
\[ \tau_- \frac{M}{\mu} \phi I \int_0^T \sigma(t) \int_0^\infty (1 - p(\theta))q_I(\theta)d\theta dt. \]

Social cost of the disease:
\[ \zeta \int_0^T \int_0^\infty u^\sigma(\theta, t)d\theta dt, \]

Fixed cost of the screening procedure:
\[ \frac{\alpha}{2} \int_0^T \sigma^2(t) dt, \]

Cost of screening the population:
\[ c \frac{M}{\mu} \phi I \int_0^T \int_0^\infty \sigma(t)q_I(\theta)d\theta dt. \]
Screening strategies

respective cost functions

- screening of the resident population
- screening of the immigrant group

\[ C_{II}(\sigma) = \int_0^T \int_0^\infty A(\theta) u^\sigma(\theta, t) d\theta dt \]

\[ + B \int_0^T \sigma(t) dt + \frac{\alpha}{2} \int_0^T \sigma^2(t) dt \]

where

\[ A(\theta) = \zeta + \tau_+ \chi p(\theta), \quad B = \phi I(\tau_+ - \tau_-) \int_0^\infty p(\theta) q I(\theta) d\theta + \phi I(\tau_- + c) \]
About existence and uniqueness of an optimal control

either (local existence and uniqueness)


or (existence)

Numerics

Numerical scheme for the state equation (strategy I)

\[
\begin{align*}
    u_j^0 &= u_0(jh), \\
    U^i &= h \sum_{j=1}^{N_a} u_j^i, \\
    V^i &= h \sum_{j=1}^{N_a} \rho_j p_j u_j^i, \\
    u_0^i &= \left(1 - \frac{U^i}{N^i}\right) V^i, \\
    u_{j+1}^i - u_j^i &= \frac{h}{1} + u_{j+1}^{i+1} + \sigma^{i+1}(1 - p_{j+1}) u_{j+1}^{i+1} \\
    &\quad + (\chi + \nu) p_{j+1} u_{j+1}^{i+1} = \phi_I \ q_{j+1}, \\
    W^{i+1} &= h \sum_{j=1}^{N_a} p_j u_{j+1}^{i+1}, \\
    N^{i+1} - N^i &= \frac{h}{1} = 1 - bN^{i+1} - \nu W^{i+1}.
\end{align*}
\]
Numerics

discrete cost function (strategy I)

\[ C_{lh} = h^2 \sum_{i=0}^{N_t-1} \sum_{j=0}^{N_a-1} \left[ (\zeta + \tau + \chi p_j) + \tau_-(1 - p_j)\sigma_i \right] u_j^i + h \sum_{i=0}^{N_t-1} \left[ \frac{\alpha}{2} \sigma_i^2 + c\sigma_i N^i \right] \]

discrete adjoint equation (strategy I)

\[
\begin{align*}
\sum_{j=0}^{N_a-1} & \frac{z_j^{Nt+1}}{h} + z_j^i + \sigma^i (1 - p_j) z_j^i + (\chi + \nu) p_j z_j^i + \nu h p_j w^i \\
& = \left( -\frac{V^i}{n^i} + (1 - \frac{U^i}{n^i}) p_j p_j \right) z_1^{i+1} - (A_j + B_j \sigma^i) \\
\sum_{j=0}^{N_a-1} & \frac{w_j^{i+1} - w_j^i}{h} + bw^i = \frac{U^i V^i}{2(n^i)^2} z_1^{i+1} - h c \sigma^i
\end{align*}
\]

discrete gradient (strategy I)

\[
\frac{\partial C_{lh}}{\partial \sigma_i}(\sigma) = \sum_{j=0}^{N_a-1} (1 - p_{j+1}) u_{j+1}^i z_{j+1}^i + \alpha \sigma^i + c w^i
\]
The algorithm (strategy I)

- **Step 1** Choose an initial screening effort $\sigma_0$ and a tolerance $\varepsilon > 0$;
- **Step 2** solve the discrete state system with $\sigma_0$;
- **Step 3** solve the discrete adjoint system with $\sigma_0$;
- **Step 4** compute the cost $C_{lh}(\sigma_0)$ and the gradient $\frac{\partial C_{lh}}{\partial \sigma}(\sigma_0)$;
- **Step 5** compute the next iteration screening effort using a gradient descent method $\sigma_{n+1} = \sigma_n - \rho \frac{\partial C_{lh}}{\partial \sigma}(\sigma_n)$. Here $\rho$ represents the path of descent, which is internally chosen by the routine ”Uming” of the International Mathematics and Statistics Library (IMSL);
- **Step 5** if $\|\sigma_{n+1} - \sigma_n\| < \varepsilon$ then stop; else go to Step 1.
Data from Italy 2012

resident population

\[ N = 59.54 \times 10^6, \quad \beta = 0.009, \quad \mu = 0.01 \quad (R_d = 0.9 < 1) \]
\[ \nu = 0.065, \quad \chi = 1.34, \quad \rho = 0.81, \quad \ell_0 = 4.9 \times 10^4 \]
\[ R_0 = 0.54 < 1 \]

immigrant population

\[ M = 0.37 \times 10^6, \quad M_I = 2.4 \times 10^3, \]
strategy I: fixed screening rate

\[ \sigma = 0/\text{year} \]

\[ \sigma = 0.25/\text{year} \]

\[ \sigma = 1/\text{year} \]
Simulations

in decreasing order: same social cost and, increasing fixed cost of screening + increasing single cost
Simulations

the respective infected fractions
strategy II: fixed screening rate

\[ \sigma = 0 \]
\[ \sigma = 0.5 \]
\[ \sigma = 1 \]
in decreasing order: same social cost and, increasing fixed cost of screening + increasing single cost
Simulations

the respective infected fractions
Simulations

Summary with respective efficacy (difference between the cost when no control is performed and the cost of the particular strategy, normalized by the cost without control)

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THANK YOU FOR YOUR ATTENTION