# Combating tuberculosis: using time-dependent sensitivity analysis to develop strategies for treatment and prevention

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## Background

- Tuberculosis (TB) is a potentially fatal, airborne infection caused by the bacillus, *Mycobacterium tuberculosis,* that typically affects the respiratory system.
  - Some individuals become infectious immediately after encountering the bacterium (fast-track TB), while others enter an exposed, or latent, state (slow-track TB).
- Although many organizations throughout the world have worked tirelessly to control TB epidemics, no country has yet been able to eradicate the disease completely.
- TB has made a recent resurgence in the developing world, specifically in the regions of Sub-Saharan Africa, Eastern Europe, and Asia.
- TB incidence rate has doubled overall in the past fifteen years.
- In regions severely affected by both TB and HIV, the rate has quadrupled.
- In the early twentieth century, William Kermack and Anderson McKendrick introduced a simplistic compartmental model used for disease modeling, called the Susceptible - Infectious - Recovered (SIR) model.
  - Basic SIR models account for two types of transitions: the transition from susceptible (S) to infectious (I) and from infectious (I) to recovered (R).
- For the purpose of our research, we use a modified version: the Susceptible - Exposed - Infectious - Recovered (SEIR) model.
  - The addition of the exposed (E) state takes into account those with slow-track TB, who enter a latent stage after coming into contact with the bacteria.

## Goals

- Construct two compartmental models representing the spread of a TB epidemic in a population: a general model and one accounting for HIV/TB co-infection
- Determine the parameters with the most impact upon the exposed and infectious populations using active subspaces to conduct time-dependent sensitivity analysis
- Expand upon previous research, introducing a new use for time-dependent sensitivity analysis: to pinpoint the exact times during an epidemic in which treatment strategies are most effective

## Ordinary Differential Equations (General TB Model)

$$\frac{dS}{dt} = \beta - \lambda SI - \delta S - \nu S$$

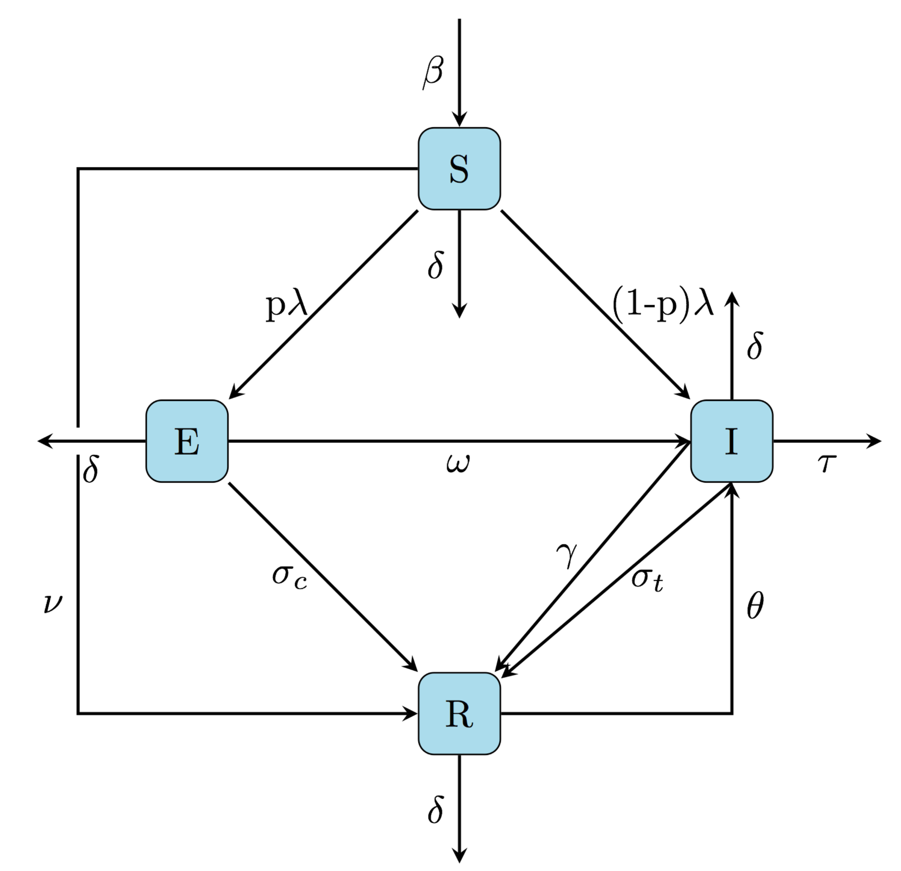
$$\frac{dE}{dt} = p\lambda SI - (\omega + \sigma_c + \delta)E$$

$$\frac{dI}{dt} = (1-p)\lambda SI + \omega E - (\delta + \tau + \gamma + \sigma_t)I + \theta R$$

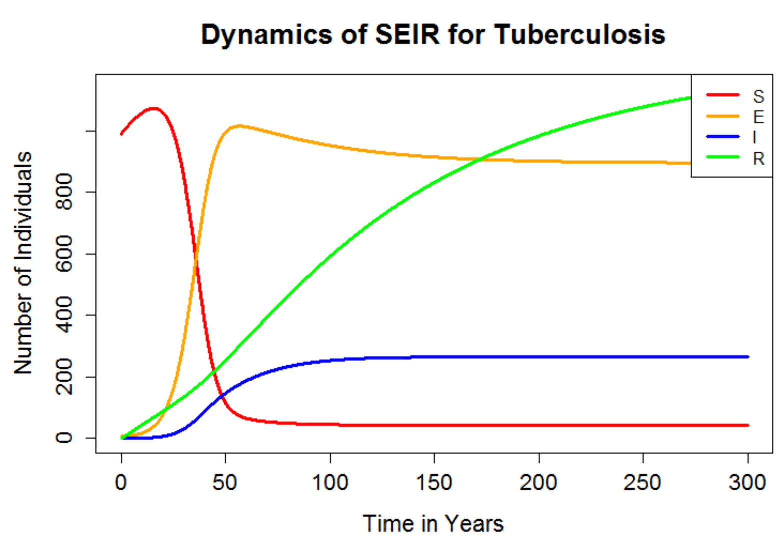
$$\frac{dR}{dt} = \nu S + \sigma_c E + (\sigma_t + \gamma)I - (\delta + \theta)R$$

Assumptions:
1) Everyone is born susceptible to TB
2) Relapse from the recovered state means re-contracting active TB
3) Drug treatment for both latent and active TB is available but not administered to the entire E and I populations
4) There are no drug-resistant TB strains present

## General TB Model




## Population Dynamics




- SEIR dynamics of a population at pre-determined parameter values
- Initial population of 1000 people: 990 susceptible and 10 exposed
- Susceptible population begins very high and over time decreases
- Exposed, infectious and recovered populations increase over time

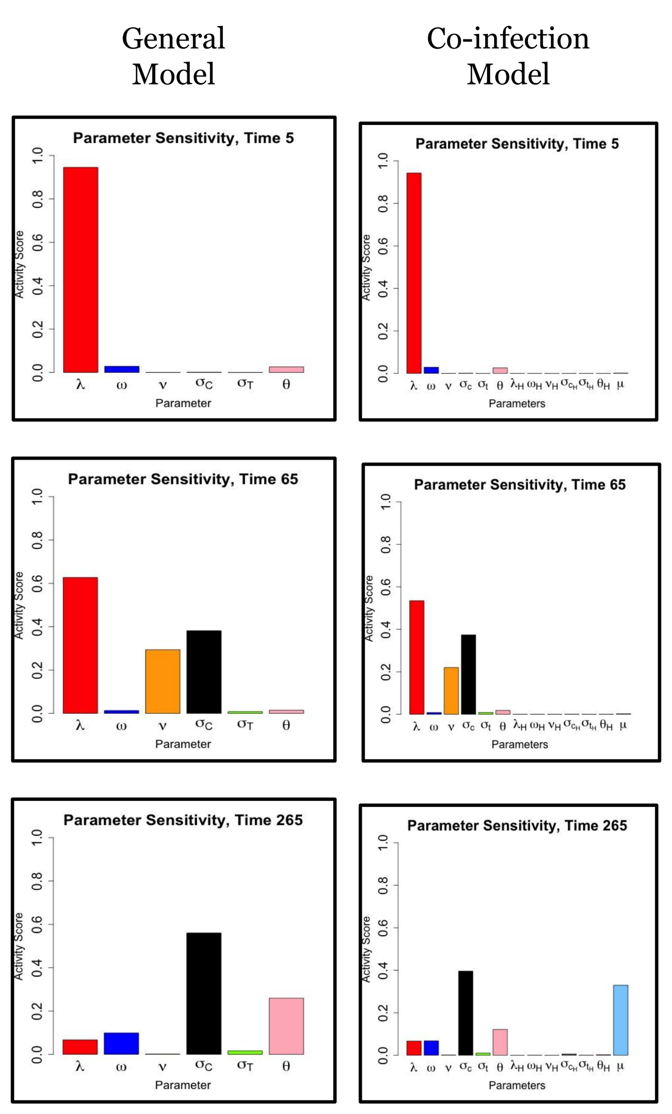
## Results

In the beginning of the epidemic
- The rate of infection ($\boldsymbol{\lambda}$) is the most significant parameter.
- Focus resources on: quarantine and vaccinations

Around year 50
- The significance of the rates of latent treatment ($\boldsymbol{\sigma_c}$) and vaccination ($\boldsymbol{\nu}$) increase dramatically.
- Focus resources on: increasing access to latent treatment and vaccinations, while improving both latent treatments and vaccines

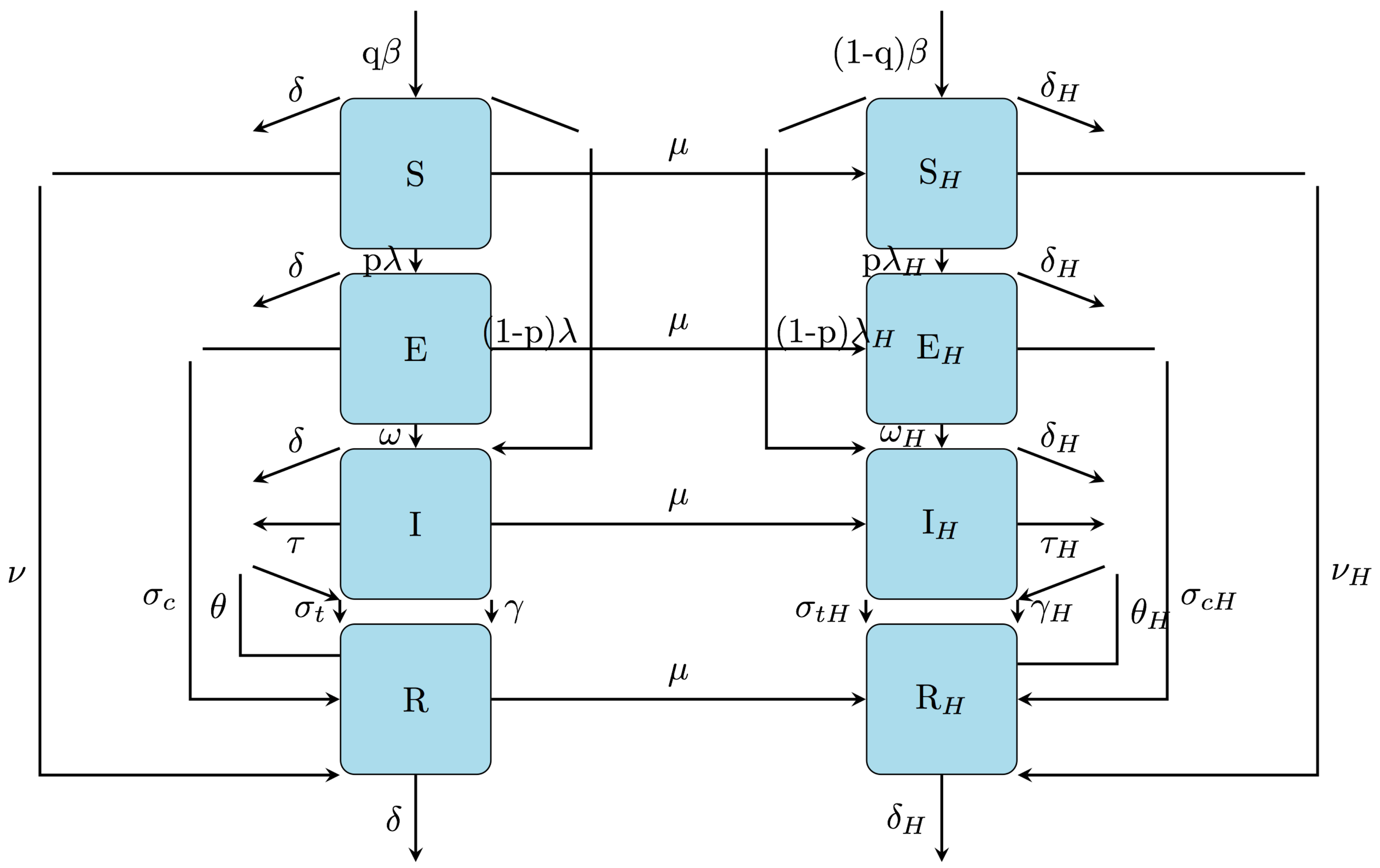
Towards the end of the epidemic
- The significance of $\boldsymbol{\sigma_c}$ remains high, however the relapse rate ($\boldsymbol{\theta}$) and rate of deterioration ($\boldsymbol{\omega}$), i.e. the rate of exposed individuals becoming infectious, also become important.
- Focus resources on: keeping recovered individuals from relapsing, reducing the number of latent people becoming infectious and researching for a long-lasting cure or better treatment

The results for the HIV/TB co-infection model are very similar. The difference is that towards the end of the co-infection epidemic, the HIV contraction rate ($\boldsymbol{\mu}$) becomes very significant.



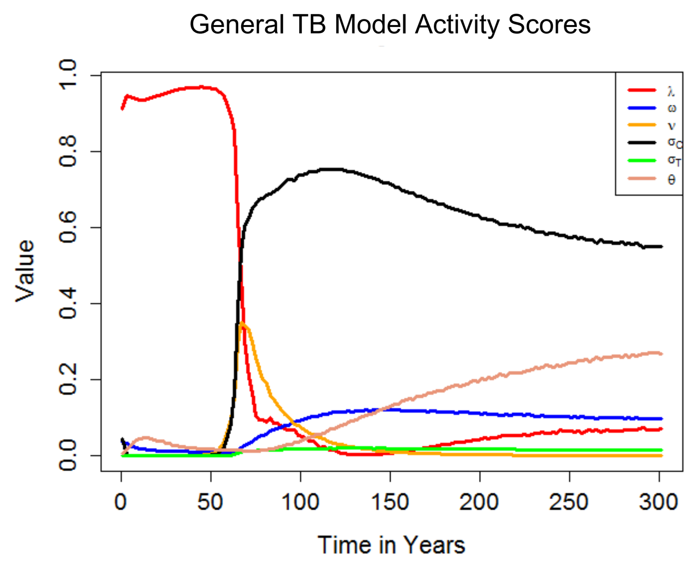

## HIV/TB Co-infection Model

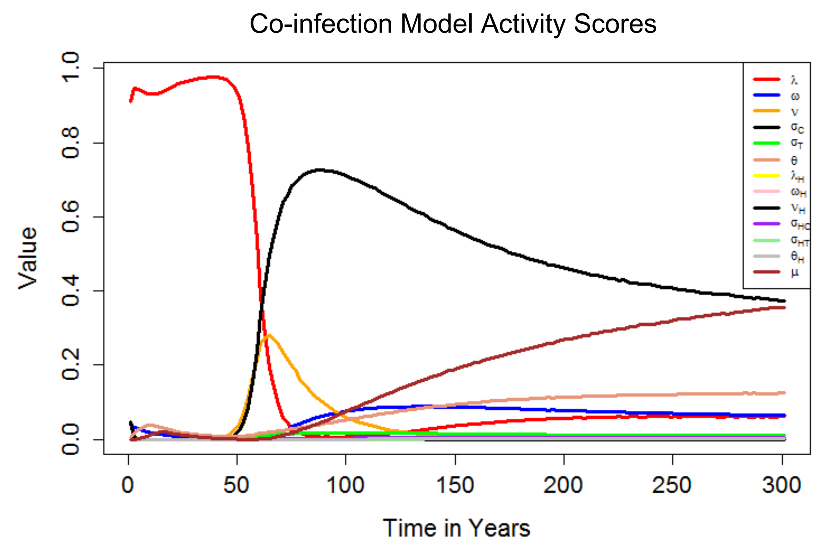
We kept the assumptions from the general TB model. One additional assumption was added: the HIV incidence rate remains the same for all four HIV- populations.




## Parameter Significance Over Time

Activity scores are a way for us to take into account multi-dimensional active subspaces. This ensures our sensitivity metrics are correctly weighted.

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