Effect of population structure, parameter estimation of complex model, and LTBI on TB dynamics

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I. Extended Abstract

The intricate nature of Tuberculosis (TB) infection requires further research to better understand the relationship between the disease mechanisms and the population structure. The influence of the population structure and the role of the infected population on the TB incidence is still not clear. In this study, mathematical modelling techniques are used to elucidate those questions and contribute to understand TB complexity. The work examines the complexity of TB dynamics by using SEI models of different levels of complexity to study the effect of both structure of population and the role of the infected population in TB dynamics. It presents a step by step procedure of how to develop and estimate parameters of complex model for TB transmission. We performed different experiment on more than 20 different countries in order to elucidate if the increase in complexity of the models increases the model accuracy and provides more information about the disease. Our results indicate that parameter estimation could be made easy by the gradual development of simple models. In addition we showed the importance of more complex model over simple model and our result indicate that, unlike simple models, complex model could explain characteristic of the disease such as diagnosis delay time and reinfection. We illustrate how the model without population as a limiting factor dramatic change in behaviour when implemented in high burden incidence. We also demonstrate how the change in age of infection in the latent TB could dramatically alter the dynamics of the disease.

A. Introduction

Tuberculosis (TB) is still a major global health concern and one of the leading causes of death. As reported by WHO, there were an estimated 10.4 million new incident TB cases and 1.7 million deaths worldwide in 2015[1]. Even though most TB cases occur in resource-limited countries, it is still a threat to higher-resource countries. This is due to the nature of the disease's strong interaction with HIV dynamics and also the recently world-wide emergence of drug-resistant TB [2], [3].

The main manifestation and the only infectious form of TB is the pulmonary form, hence worthy of study. Pulmonary TB is an infectious disease caused by *Mycobacterium tuberculosis (Mtb)* and it is transmitted via air borne droplets of the saliva of the sick host. When a sick host sneezes, coughs or talks it can infect susceptible individuals sharing the same environment who inhale the saliva droplets containing the bacterium. The inhalation of the bacilli will usually lead to the initiation of an immune response that can have one of the 3 different clinical outcomes: (1) Complete clearance of the pathogen (2) Latent TB infection (LTBI) or (3) Progression to primary active disease [4], [5]. The objectives of this study are: (i) To understand how the structure of the population that can shape the dynamics of the disease.(i) To show the importance of both complex and simple models depending on each given situation, and to elucidate how parameter estimation can be easily achieved when developing gradually more complex models.(iii) To show the role and importance of the latent infected population and the age of infection in understanding the dynamics of TB. The epidemiological evolution of 20 different countries will be analyzed to exemplify the importance of each type of model to achieve the aims set above.

B. Methodology

TB dynamics presents several characteristics that greatly contribute to its complexity. Compartmental models facilitate obtaining a good understanding of these complexity. Fig. 1 proposed several compartmental models that were used to described the dynamics of TB with different complexity level. In each of the model, starting with the most simple form SEI, population were divided into different compartment, namely Susceptible S, latent infected (exposed) E, Sick (infectious) I, and Reinfection R. We formulated five different models (SEI, SEI2, SE8I, SE8I2, SE8IR), each model was formulated with two different force of infection $\Lambda = \frac{\alpha IS}{N}$ and $\Lambda^* = \alpha I$ to allow the evaluation of effect of population on the dynamics of the disease. Model equation for each model were formulated, and the spectral radius was analyzes.

C. Results

TB epidemiological data from countries all around the world was analyzed and 20 (10 LBC and 10 HBC) different countries were selected to test and validate the models.

Comparison of models performance between low and high incidence burden setting to illustrate the effect of population on Tb dynamics: To address the long over due question of how the population can affect the dynamics of TB, we adhere to our strategy by fitting both set of models with population as limiting factor and without to both LBC and HBC. Fig. 2 illustrate the difference between the two sets of models when implemented in low burden and high burden countries.

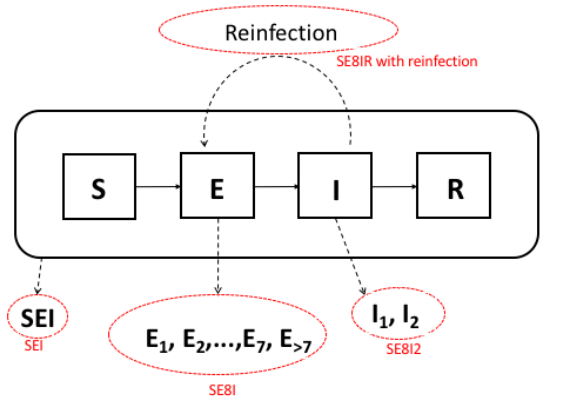

Fig. 1. **Overview of several proposed compartment models with different level of complexity.** SEI is the classical model of three compartments used to understand the epidemiological dynamics of TB in a given population. SEI2 applies to a general context of TB dynamics and has four compartments (Susceptible S; Exposed E; sick and infectious I_1; and sick but not infectious I_2). SE8I refers to a context where the time scale and age of infection in the latently infected population is considered due to its importance in understanding TB dynamics. In SE8I2 two main important features were also added, the diagnosis time delay and the probability of relapse. The sick population are dived into two sub-population, I_1 sick and infectious (thus, spreading the disease) and I_2 sick but under treatment. Finally, in contexts of high incidence, we introduce the concept of people reinfection so $E_i > 1 \rightarrow E_1$

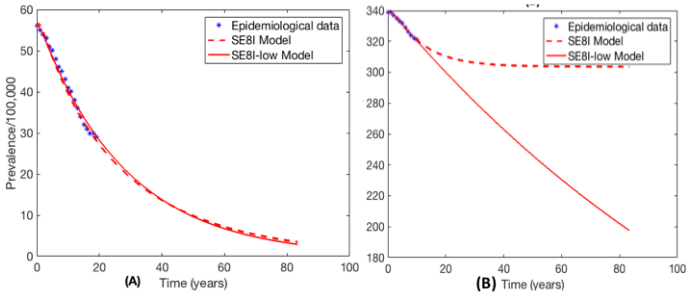

Fig. 2. **The effect of population structure on the dynamics of TB demonstrated in both low and high burden countries.** (A): The model simulation with population as a limiting factor (SE8I model) and model without population as a limiting factor (SE8I low model) in a low burden country. (B): The model with population as a limiting factor (SE8I model) and model without population as a limiting factor (SE8I low model) in a high burden country.

Model complexity and parameter derivation: Developing several models of increasing complexity in a gradual manner allowed the parameters to be derived from the simpler models. Fig 3 shows the simulation results for Argentina with different models of various complexity levels and contrast it with the epidemiological data during 20 years.

D. Conclusion

Our experiment provides a significant evidence that the structure of population plays a vital role in shaping the dynamics of the TB. Although simple models could describe the dynamics of the disease, we show that it is necessary to design more complex model in order to understand some of the more complex structure of the TB dynamics. We also showed that simple models can provide a significant aid in the estimation of

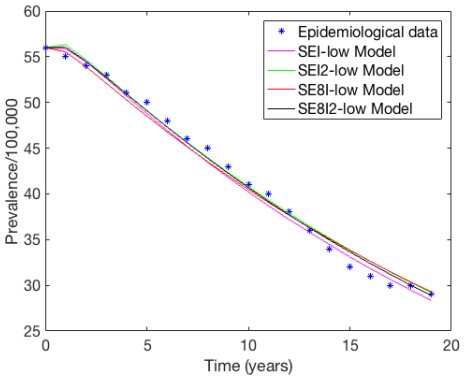

Fig. 3. **Comparison of low incidence models fittings for epidemiological data in Argentina.**

the parameter for more complex models. We finally conclude that the age of the infection and the structure of the latently infected population must to be taken into consideration while designing any TB intervention program

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