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Mathematical model and intervention strategies for mitigating tuberculosis in the Philippines

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ABSTRACT

Tuberculosis (TB) is the sixth leading cause of morbidity and mortality in the Philippines. Although significant progress has been made in the detection and cure of TB under the Directly Observed Treatment Short Course, battling against the disease is still a burdensome task. It demands a concerted effort for specific and effective interventions. In this work, a mathematical TB model fitted to the Philippine data is developed to understand its transmission dynamics. Different control strategies such as distancing, latent case finding, case holding, active case finding controls, and combinations thereof are investigated within the framework of optimal control theory. This study proposes optimal control strategies for reducing the number of high-risk latent and infectious TB patients with minimum intervention implementation costs. Results suggest that distancing control is the most efficient control strategy when a single intervention is utilized. However, full scale employment of the distancing control measure is a daunting task. This burden can be circumvented by the combination of other control interventions. Our noble finding in this study is that enhancing active case finding control instead of case holding control together with distancing and latent case finding control is shown to have significant potential for curtailing the spread of TB in the Philippines.

1. Introduction

Tuberculosis (TB) is an infectious disease caused by the bacillus *Mycobacterium tuberculosis* (MTB), which typically attacks the lungs (pulmonary TB) but can also affect other sites (extrapulmonary TB) including the central nervous system, lymphatic system, brain, spine, or kidneys. The bacterial disease is acquired through airborne infection. That is, people with lung TB can propel MTB into the air and spread the disease through coughing, sneezing, spitting, or speaking. Approximately one-third of the world's population has been infected by MTB but are not (yet) ill and cannot transmit the disease (*latent TB*). Those who are infected have a 10% lifetime risk of falling ill (*active TB*). TB causes ill-health in millions of people each year and, in 2015, was considered one of the top 10 causes of death worldwide, ranking above HIV/AIDS as one of the leading causes of death from an infectious disease (World Health Organization, 2016a). This is despite the fact that, with a timely diagnosis and correct treatment, most people who develop active TB can be cured.

In the Philippines, TB is a major public health problem and one of the leading causes of morbidity and mortality among Filipinos. Despite the intensive effort of the National Tuberculosis Program and various non-governmental organizations to eradicate TB, it ranks sixth among the World Health Organization (WHO) leading causes of death in the country. The Philippines is the ninth out of the 22 highest TB-burden countries and eighth among the 27 high priority countries for multi-drug resistant (MDR) TB (Department of Health, Philippines, 2013). Since the adoption of Directly Observed Treatment Short Course (DOTS) strategy in 1996, significant progress has been achieved. Nationwide coverage was reached in 2002, and subsequently, targets for cure and case detection rates have been attained. However, with the advent of MDR TB, the country will need the concerted effort of all government and non-government stakeholders both in the public and private sectors to meet its target of reducing incidence and TB-associated mortality.

Tuberculosis is a disease with intrinsic dynamics. On average, the incubation period, latent period, and infectious period span years. The progression of TB leads to long-term outcomes of tuberculosis at the population level. Hence, mathematical models are utilized to estimate prolonged results and future trends of the

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disease (Aparicio et al., 2002; Aparicio and Castillo-Chavez, 2009; Brauer, 2009; Ozcaglar et al., 2012). The first mathematical model for TB dynamics was introduced by Waaler et al. (1962). They divided the population into three classes and constructed the model according to the epidemiological characteristics of TB transmission. Revelle et al. (1967) developed a model using a nonlinear system of ordinary differential equations. This model first introduced that TB transmission is dependent on the proportion of its prevalence (Revelle et al., 1967). Castillo et al. presented several mathematical models for TB: a two-strain TB model, a distributed delay TB model, an exogenous reinfection TB model, and an age-structured TB model (Castillo-Chavez and Feng, 1997; Castillo-Chávez et al., 1998). They analyzed each model with the basic reproductive number and the stability of model system. Castillo and Song also collected various dynamical models of TB transmission and developed a theoretical framework (Castillo-Chavez and Song, 2004).

Optimal control framework has also been used to propose control measures for mitigating TB disease. Jung et al. suggested optimal control strategies in a two-strain TB model (Jung et al., 2002). It was the first study that applied optimal control theory to a TB transmission model. Whang et al. developed a mathematical TB model for the Republic of Korea and suggested optimal TB intervention strategies (Whang et al., 2011). Choi and Jung also proposed a practical intervention policy through a comparison of the government TB budget with the optimal control results (Choi et al., 2015). Villasin et al. (2017) developed a mathematical model for TB dynamics in the Philippines, considering BCG vaccination and estimating parameters from available data. Intervention strategies were investigated by varying various parameters. The study concludes that increasing partial immunity and decreasing the treatment success rate, treatment duration, and case detection rate are effective to reduce TB incidence and prevalence rather than increasing vaccine coverage.

In this study, a TB dynamic model is adapted from the works of Whang et al. (2011) and Choi and Jung (2014) to describe the transmission of TB in the Philippines in which TB-induced mortality is taken into account. Model parameters are estimated and fitted based on the available data collected from the WHO report (World Health Organization, 2016a). Using optimal control theory, four different control strategies are considered, namely, distancing, latent case finding, case holding, and active case finding control. Various scenarios are investigated to explore the optimal control scheme for reducing the transmission of the disease. The objective of optimal control is to reduce the number of high-risk latent and infectious TB individuals, and, at the same time, to minimize the cost incurred in the implementation of control measures. To the authors' best knowledge, the present study is the first TB model fitted with the Philippine data where optimal control theory is applied. It proposes different control strategies to meet the target of TB elimination. This study presents Philippine-specific mitigation control strategies that could provide insights on budget allocation and focus on more effective control policies.

This paper is organized as follows. The *Materials and methods* section provides information on the epidemiological data presented in this work and the adapted TB model. The estimation of parameters based on the available data is also discussed. In addition, parameter bootstrapping is considered to determine the reliability of the parameter estimates. The sensitivities of the parameters are also discussed using the partial rank correlation coefficient (PRCC) method and elasticity index. The section on *Optimal control strategies* presents the different control interventions that can be implemented to reduce the number of high-risk TB individuals and infectious TB patients. The *Results and discussion* section examines and discusses the various control strategies through numerical simulations and probable interpretations. The findings of this work is summarized in the last section.

2. Materials and methods

2.1. Epidemiological data

In 2016, the WHO published a global TB report that is based on the data collected from different countries and territories. Data are gathered according to the following topics: TB case notifications and treatment outcomes, including breakdowns by TB case type, age, sex, HIV status, and drug resistance; laboratory diagnostic services; monitoring and evaluation, including surveillance and surveys specifically related to drug-resistant TB; TB preventive therapy; TB infection control; the engagement of all public and private care providers in TB control; community engagement; the budgets of national TB control programs (NTPs); utilization of general health services (hospitalization and outpatient visits) during treatment; and NTP expenditures (World Health Organization, 2016b). A dedicated website for TB data collection was opened for reporting in April 2016 (World Health Organization, 2016d). The TB-related data from 1990 – 2014 presented in this study was downloaded from the WHO TB burden estimates (World Health Organization, 2016a).

2.2. Mathematical model of tuberculosis

The proposed dynamic model of TB disease transmission in the Philippines is adapted from the works of Whang et al. (2011) and Choi and Jung (2014), assuming constant epidemic parameters and taking into account the TB-induced mortality rate. This model divides the human population into the following epidemiological classes: susceptible (S), high-risk latent (E), infectious (or active TB) (I), and low-risk latent (L). Individuals who do not progress to the infectious state are moved from class E to low-risk latent class L. Recovered individuals, either by natural causes or treatment, are also moved from class I to class L because treatment cannot remove *tubercle bacilli*, the TB-causing bacteria. Hence, recovered and low-risk latently infected individuals are classified into a single class of low-risk latent individuals.

The TB model is governed by the following set of ordinary differential equations;

$$\begin{aligned}\frac{dS}{dt} &= bN - \beta\frac{SI}{N} - \mu S,\\ \frac{dE}{dt} &= \beta\frac{SI}{N} - (\alpha+\kappa+\mu)E + prI,\\ \frac{dI}{dt} &= \kappa E - (\mu + r + d)I,\\ \frac{dL}{dt} &= (1-p)rI + \alpha E - \mu L, \qquad (1)\end{aligned}$$

where $N = S + E + I + L$ represents the total population size. The per capita rates of birth and natural death are denoted by b and μ, respectively. Parameter β refers to the number of new infections caused by an infectious individual per unit time. The per capita rate of progression from latent class E to infectious class I is represented by parameter κ. The high-risk latent individuals E who do not progress to infectious class I are moved to low-risk latent class L at per capita rate α. In addition, the per capita rate at which I proceeds to L due to treatment is given by r. Parameter d denotes the per capita TB-induced mortality rate. The treatment success rate for infectious individuals is given by $1-p$. Fig. 1 depicts the flow diagram of the TB transmission model.

2.3. Parameter estimation

Model parameters are estimated based on the available data (World Health Organization, 2016a). The natural death rate μ is computed as the inverse of life expectancy. Here, life expectancy