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OPTIMAL CONTROL PROBLEM OF A TUBERCULOSIS MODEL WITH SPATIAL DYNAMICS

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Abstract. Tuberculosis is an ancient contagious disease, and it causes more deaths worldwide than any other infectious diseases. Based on the fact that it is spread from person to person through the air, the tuberculosis can emerge in one region and spread to its neighbors in unprecedented durations. we propose here a Susceptible-Exposed-Infected-Recovered (SEIR) spatiotemporal model that characterizes the dynamics of tuberculosis disease by taking into consideration the spatial heterogeneity; in order to provide a realistic description of this disease. Then, controls on treatment, chemoprophylaxis are incorporated to reduce the latently infected (exposed) and actively infected individual populations to fight against the spread of the disease. Theoretically, we have proved the existence of optimal controls, and we have given a characterization of controls in terms of states and adjoint functions based on a discrete version of Pontryagin's maximum principle. To illustrate the effectiveness of our theoretical results, we give numerical simulations for several scenarios. Our results indicate that the control effect is effective if controls on treatment and chemoprophylaxis strategies are used simultaneously.

Keywords: spatiotemporal SEIR model; tuberculosis; chemoprophylaxis; treatment; optimal control.

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1. INTRODUCTION

Tuberculosis probably accompanies us from the beginning of humanity, it is considered to be responsible for one of the deadliest infectious disease epidemics. Currently, there are more than 10.4 millions new tuberculosis cases and about 1.7 million tuberculosis patients die every year [1]. The microbe *Mycobacterium tuberculosis* (mtp) is the main agent of tuberculosis human (abbreviated TB), which mainly attacks the lungs (for pulmonary tuberculosis). In addition, tuberculosis could affect the central nervous system, the circulatory system, the genitourinary, bones, joints and even the skin. It is transmitted during the expectoration of droplets of bronchial secretions from people with TB disease and can also be spread by coughing, sneezing, kissing, spitting of people with pulmonary tuberculosis, as well as by using unsterilized utensils (plates, glasses of water) from an infected person. In rare case, a pregnant woman with active tuberculosis can infect the fetus [2]. On the one hand, Tuberculosis can develop quickly after first contact with the microbe; Symptoms of active tuberculosis depend on the part of the body infected. When tuberculosis lodges in the lungs (pulmonary tuberculosis), the main symptoms often observed by a cough, sometimes productive or bloody chest pain, fatigue, weight loss and night sweats. On the other hand, it can also appear several years later and it has no symptoms.

As a matter of fact, mathematical models especially compartmental models, have played an essential role in fighting against infectious diseases since their birth by Kermack 1927. Several infectious diseases have been modeled using compartmental mathematical models, particularly tuberculosis [3, 4, 5, 6, 7, 8], then it is no longer necessary to justify the importance of mathematical models in the investing and controlling the spread of human infectious diseases, enabling governments and public health officials to predict the impact of specific vaccination and treatment programs or to develop more effective strategies based on different mathematical methods [9, 10]. Relatively little of this mathematical models focus on the fact that the population is extremely mobile, and this mobility increases the complexity of the transmission dynamics of infectious diseases. It exists in the history of epidemics several cases of infection spatially spread. For instance, the case of SARS epidemic of spring 2003 clearly showed that human diseases spread in space, over large areas and often jumping continents [11]. These cases also includes the influenza pandemic (H1N1) 2009 [12], first appeared in Mexico and

then spread rapidly throughout the world, the Black Death that appeared in the 1300s in Europe [13], followed by Measles and smallpox in the New World between the 1500s and 1600s [14, 15] and most recent one Ebola which appeared in the Democratic Republic of the Congo in 1977, in Sudan in 1979 as well as in North America in the late 1990s [16, 17] and HIV / AIDS appeared in 1981 [18]. In most mathematical models, the existence of a spatial component has a remarkable probability due to the mobility of thousands of people moving from one region to another. In this case, an epidemic can spread rapidly around a vast area given regardless of the border. The geographic scale is therefore at the heart of a multitude of studies of diseases that are becoming spatially mobile to different regions because of the population's movement from one region to another. We believe that there is a need to develop a new generation of models that include spatial spread of an infectious disease; current tuberculosis models are based on models developed by Blower and colleagues almost 25 years ago [19, 5]. We predict that modeling spatial spread of the disease will lead to the design of more effective tuberculosis control strategies. In fact, several types of interventions exist, including short-term treatment strategy under direct surveillance, that have so far failed in the fight against tuberculosis in areas with a high prevalence of HIV / AIDS (De Cock and Chaisson, 1999) [20]. The question is whether the fight against tuberculosis should remain a biomedical strategy only, focusing on the trait effortless treatment to understand and meet the needs of patients (social and economic needs).

After studying several papers taking into account the spatial aspect of the spread of an epidemic [21, 22, 23, 17, 26]. New models should include the movement of people from one region to another. A multiregional discrete-time SEIR model is designed here for the tuberculosis epidemic in which a control variable is introduced represents the effort on chemoprophylaxis. the second control is used to show the effect of treatment after infection, knowing that the treatment of tuberculosis has saved 53 million lives between 2000 and 2018 [1].

The rest of the manuscript is organized as follows: Section 2 is devoted to the basic mathematical model . In Section 3, we announce a theorem of necessary conditions and characterization of the sought optimal controls functions related to the chemoprophylaxis and treatment strategies, with the introduction of numerical simulations. Finally, we conclude our work in Section 4.

2. MATHEMATICAL MODEL SEIR

In this section, Based on the (TB) model formulated by C.P. Bhunu and al.[10] and as mentioned above in the introduction, statistics showed that in several regions in the world, the spatial factor plays a major role in the transmission and the propagation of the disease. We consider a discrete-time tuberculosis model, which describes the spatial-temporal and regional spread of an epidemic based on *SEIR* interactions within a global domain of interest Ω , divided to M^2 regions that are uniform in size. This domain can be represented by the union $\Omega = \bigcup_{j=1}^M \Omega_j$, and let $N_i^{\Omega_j}$ be the population of Ω_j at time i , i.e., the number of individuals in Ω_j , with $(\Omega_j)_{j=1, \dots, M}$ a spatial location or region. We note that $(\Omega_j)_{j=1, \dots, M}$ could represent a country, a city, a town, or a small domain such as neighborhoods, that belong respectively to the global domain of interest which could in turn represent a part of continent or even a whole continent a part of country or a whole country.

The $S - E - I - R$ dynamics associated to a region Ω_j are noted by the states $S^{\Omega_j}, E^{\Omega_j}, I^{\Omega_j}$ and R^{Ω_j} . We noted susceptible individuals by S^{Ω_j} , and exposed to (TB) are E^{Ω_j} (latently infected), The infected individuals with Mtb presenting symptoms of (TB) are I^{Ω_j} , and those who have recovered from sickness are R^{Ω_j} . We note that the transition between them, is probabilistic, with probabilities being determined by the observed characteristics of specific diseases. In addition to the death, there are population movements among those four epidemiological compartments, from time unit i to time $i + 1$. The unit of time i can correspond to days, months or years, it depends on the frequency of data collection and statistics.

Note that $\Omega_j = \Omega_{(p,q)}$ and $\Omega_k = \Omega_{(r,s)}$, we define the Vicinity set of Ω_j ; $V(\Omega_j) = \{\Omega_k \in \Omega, r = p + l', s = q + l', (l, l') \in \{-1, 0, 1\}\}$. We assume that the susceptible individuals are those who are not yet infected with the Tuberculosis, but can be infected only through contacts with I^{Ω_k} , coming from $V(\Omega_j)$ (Vicinity set or Neighborhood of a region Ω_j). Thus the transmission of infection is assumed to occur between individuals that are present in a given region Ω_j , and it is given by $\sum_{\Omega_k \in V(\Omega_j)} \frac{\beta_{jk} c_{jk} S_i^{\Omega_j} I_i^{\Omega_k}}{N_i^{\Omega_j}}$ where the disease transmission coefficient $\beta_{jk} > 0$, is the proportion of contacts in the region Ω_j between a susceptible from Ω_j and

an infective from its neighbor $\Omega_k \in V(\Omega_j)$, and c_{jk} is the per capita contact rate between a susceptible from a region Ω_j and an infective from its neighbor $\Omega_k \in V(\Omega_j)$.

The latently infected progress to active through contacts with I^{Ω_k} coming from $V(\Omega_j)$ (Vicinity set or Neighborhood of a region Ω_j). Thus the transmission of infection is assumed to occur between individuals that are present in a given region Ω_j , and it is given by

$\sum_{\Omega_k \in V(\Omega_j)} \delta_1 \frac{\beta_{jk} c_{jk} E_i^{\Omega_j} I_i^{\Omega_k}}{N_i^{\Omega_j}}$ where the disease transmission coefficient $\beta_{jk} > 0$, is the proportion of contacts between a latently infected from a region Ω_j and an infected from its neighbor

$\Omega_k \in V(\Omega_j)$, c_{jk} is the per capita contact rate between an exposed from a region Ω_j and an infected from its neighbor $\Omega_k \in V(\Omega_j)$ and δ_1 for exogenous re-infection. And we assume the susceptible individuals can be infected only through contacts with individuals in recovered R^{Ω_k} (though they may contain some live bacilli) coming from $V(\Omega_j)$ are not totally immune to Mtb

infection, and its given by $\sum_{\Omega_k \in V(\Omega_j)} \gamma_{jk} \frac{\beta_{jk} S_i^{\Omega_j} R_i^{\Omega_k}}{N_i^{\Omega_j}}$ where the disease transmission coefficient $\beta_{jk} > 0$, here is the proportion of contacts in the region Ω_j between a susceptible from Ω_j and a recovered from its neighbor $\Omega_k \in V(\Omega_j)$, and c_{jk} is the per capita contact rate between an susceptible from a region Ω_j and a recovered from its neighbor $\Omega_k \in V(\Omega_j)$. The following system describes the discrete tuberculosis model corresponding to region Ω_j , for $j = 1, \dots, M$, given by

$$\begin{aligned}
(1) \quad S_{i+1}^{\Omega_j} &= S_i^{\Omega_j} + \Lambda^{\Omega_j} - \sum_{\Omega_k \in V(\Omega_j)} \frac{\beta_{jk} c_{jk} S_i^{\Omega_j} I_i^{\Omega_k}}{N_i^{\Omega_j}} - \mu^j S_i^{\Omega_j} \\
(2) \quad E_{i+1}^{\Omega_j} &= \sum_{\Omega_k \in V(\Omega_j)} \theta \frac{\beta_{jk} c_{jk} S_i^{\Omega_j} I_i^{\Omega_k}}{N_i^{\Omega_j}} - \sum_{\Omega_k \in V(\Omega_j)} \delta_1 \frac{\beta_{jk} c_{jk} E_i^{\Omega_j} I_i^{\Omega_k}}{N_i^{\Omega_j}} - (k^j + r_1^j + \mu^j) E_i^{\Omega_j} \\
&\quad + \sum_{\Omega_k \in V(\Omega_j)} \gamma_{jk} \frac{\beta_{jk} c_{jk} S_i^{\Omega_j} R_i^{\Omega_k}}{N_i^{\Omega_j}} \\
(3) \quad I_{i+1}^{\Omega_j} &= \sum_{\Omega_k \in V(\Omega_j)} (1 - \theta) \frac{\beta_{jk} c_{jk} S_i^{\Omega_j} I_i^{\Omega_k}}{N_i^{\Omega_j}} + \sum_{\Omega_k \in V(\Omega_j)} \delta_1 \frac{\beta_{jk} c_{jk} E_i^{\Omega_j} I_i^{\Omega_k}}{N_i^{\Omega_j}} + k^j E_i^{\Omega_j} \\
&\quad - (p^j + r_2^j + \mu^j + d^j) I_i^{\Omega_j} + q^j R_i^{\Omega_j} \\
(4) \quad R_{i+1}^{\Omega_j} &= r_1^j E_i^{\Omega_j} + (p^j + r_2^j) I_i^{\Omega_j} - (q^j + \mu^j) R_i^{\Omega_j} - \sum_{\Omega_k \in V(\Omega_j)} \gamma_{jk} \frac{\beta_{jk} c_{jk} S_i^{\Omega_j} R_i^{\Omega_k}}{N_i^{\Omega_j}}
\end{aligned}$$

where $S_0^{\Omega_j}, E_0^{\Omega_j}, I_0^{\Omega_j}$ and $R_0^{\Omega_j}$ are the given initial states in the region Ω_j .

where θ is the probability that the infected enters the latent stage. The latently infected progress to active (TB) at rates k^j for endogenous reactivation. Susceptible individuals infected with Mtb are moved into the infective class at a rate $(1 - \theta)$ and these form the primary active TB cases. Once in active stage of the disease, an individual may recover naturally at rate p^j and move into the recovered class R^{Ω_j} (though they may contain some live bacilli). Individuals in R^{Ω_j} are not totally immune to Mtb infection and are infected at rate γ_{kj} and move into E^{Ω_j} , since primary infection confers some immunity. Some individuals in R^{Ω_j} relapse back into the infective state at rate q^j . The natural death rate in each class is assumed to be $\mu^j > 0$ and infectives have an additional TB induced death rate, $d^j > 0$. The treatment rates for the latently infected and the infectives are assumed to be r_1^j and r_2^j , respectively.

$N_i^{\Omega_j}$ is the population size corresponding to region Ω_j at time i . It is clear that the population size remains constant if $\mu_j = \frac{\Lambda^{\Omega_j}}{N_i^{\Omega_j}}$, in fact

$$\begin{aligned} N_{i+1}^{\Omega_j} &= S_{i+1}^{\Omega_j} + E_{i+1}^{\Omega_j} + I_{i+1}^{\Omega_j} + R_{i+1}^{\Omega_j} \\ &= S_i^{\Omega_j} + E_i^{\Omega_j} + I_i^{\Omega_j} + R_i^{\Omega_j} + \Lambda_j - \mu_j \left(S_i^{\Omega_j} + E_i^{\Omega_j} + I_i^{\Omega_j} + R_i^{\Omega_j} \right) \\ &= N_i^{\Omega_j} + \Lambda^{\Omega_j} - \mu^j N_i^{\Omega_j} = N_i^{\Omega_j}. \end{aligned}$$

In order to show the effect of the spatial factor, and the contribution of the mobility in the transmission of the tuberculosis, we give a simulation of our model along a period of 5 years, for more details about parameters values and numerical method in section 3 entitled (Numerical results). Figure 1 is a graphical representation showing the trend of all the classes where Fig.1(a), Fig.1(b), Fig.1(c), Fig.1(d) describe the dynamics of susceptible, exposed, infected, and recovered people in the case where no control strategy is yet suggested (see the differential system (1) - (4)), and we note that in all these figures represent simulations that give us an idea of the propagation of the disease in the case where the infection begins in the corner.

As we can see susceptible individuals become exposed and after an incubation period become infected, thus the disease spreads rapidly to reach the entire population, which indicates the danger of the disease. This shows the importance of the spatial approach that has been applied. Concerning the recovered class, there is a few recovered people (about 5 individuals). The

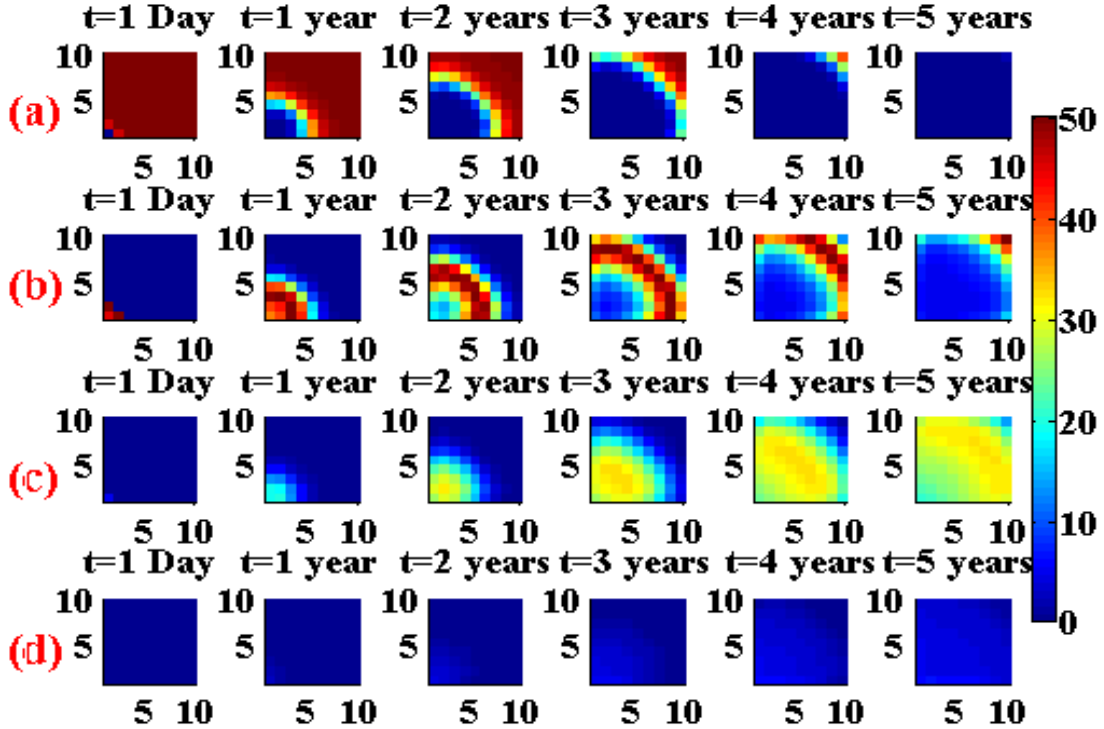


FIGURE 1. States of system (1)–(4) without controls. (a) Susceptibles behavior in the absence of control. (b) Exposed behavior in the absence of control. (c) Infectives behavior in the absence of control. (d) Removed behavior in the absence of control.

remarks observed in these simulations motivate us to think of defining a suitable control strategy taking these remarks into consideration. The strategy chosen here is the introduction of two controls, the first one is chemoprophylaxis to reduce the exposed (latently infected) individual and the second one is treatment incorporated to reduce the actively infected individual.

3. AN OPTIMAL CONTROL PROBLEM

In this section, we introduce a control strategy which consists in involving two kinds of treatments. The first one u^{Ω_j} , represents the effort on chemoprophylaxis r_1 , of latently infected individuals to reduce the number of individuals that may be infectious. While the control v^{Ω_j} is the effort on treatment r_2 , of actively infected individuals to increase the number of recovered individuals. These new assumptions, we will get $r_1 u^{\Omega_j}$ individuals who will leave the class $E_i^{\Omega_j}$

(latently infected) to the class of recovered $R_i^{\Omega_j}$, and $r_2 v_i^{\Omega_j}$ will enter to the class $R_i^{\Omega_j}$ from the class of infected $I_i^{\Omega_j}$. With the new changes, our controlled system becomes as follows :

$$\begin{aligned}
(5) \quad S_{i+1}^{\Omega_j} &= S_i^{\Omega_j} + \Lambda^{\Omega_j} - \sum_{\Omega_k \in V(\Omega_j)} \frac{\beta_{jk} c_{jk} S_i^{\Omega_j} I_i^{\Omega_k}}{N_i^{\Omega_j}} - \mu^j S_i^{\Omega_j} \\
(6) \quad E_{i+1}^{\Omega_j} &= \sum_{\Omega_k \in V(\Omega_j)} \theta \frac{\beta_{jk} c_{jk} S_i^{\Omega_j} I_i^{\Omega_k}}{N_i^{\Omega_j}} - \sum_{\Omega_k \in V(\Omega_j)} \delta_1 \frac{\beta_{jk} c_{jk} E_i^{\Omega_j} I_i^{\Omega_k}}{N_i^{\Omega_j}} - \left(k^j + r_1^j u_i^{\Omega_j} + \mu^j \right) E_i^{\Omega_j} \\
&\quad + \sum_{\Omega_k \in V_{\Omega_j}} \gamma_{jk} \frac{\beta_{jk} c_{jk} S_i^{\Omega_j} R_i^{\Omega_k}}{N_i^{\Omega_j}} \\
(7) \quad I_{i+1}^{\Omega_j} &= \sum_{\Omega_k \in V(\Omega_j)} (1 - \theta) \frac{\beta_{jk} c_{jk} S_i^{\Omega_j} I_i^{\Omega_k}}{N_i^{\Omega_j}} + \sum_{\Omega_k \in V(\Omega_j)} \delta_1 \frac{\beta_{jk} c_{jk} E_i^{\Omega_j} I_i^{\Omega_k}}{N_i^{\Omega_j}} + k^j E_i^{\Omega_j} \\
&\quad - \left(p^j + r_2^j v_i^{\Omega_j} + \mu^j + d^j \right) I_i^{\Omega_j} + q^j R_i^{\Omega_j} \\
(8) \quad R_{i+1}^{\Omega_j} &= r_1^j E_i^{\Omega_j} + \left(p^j + r_2^j \right) I_i^{\Omega_j} - \left(q^j + \mu^j \right) R_i^{\Omega_j} - \sum_{\Omega_k \in V(\Omega_j)} \gamma_{jk} \frac{\beta_{jk} c_{jk} S_i^{\Omega_j} R_i^{\Omega_k}}{N_i^{\Omega_j}}
\end{aligned}$$

We are interested in controlling the population of regions Ω_j . Then, the problem is to minimize the objective function given by

$$(9) \quad J(u^{\Omega_j}, v^{\Omega_j}) = \Psi_1 E_N^{\Omega_j} + \Psi_2 I_N^{\Omega_j} + \sum_{i=1}^{N-1} \left(\Psi_1 E_i^{\Omega_j} + \Psi_2 I_i^{\Omega_j} + \frac{A_1}{2} (u_i^{\Omega_j})^2 + \frac{A_2}{2} (v_i^{\Omega_j})^2 \right)$$

subject to system (5)-(8). Ψ_1 and Ψ_2 are positive constants to keep a balance in the size of $E_i^{\Omega_j}$ and $I_i^{\Omega_j}$ respectively. In the objective function, A_1 and A_2 are positive weight parameters which are associated with the controls $u_i^{\Omega_j}$ and $v_i^{\Omega_j}$.

Our goal is to minimize the infected population and the cost of implementing the control. In other words, we are seeking optimal controls $(u_i^{\Omega_j*})$ and $(v_i^{\Omega_j*})$ such that

$$(10) \quad J(u^{\Omega_j*}, v^{\Omega_j*}) = \min \left\{ J_{pq}(u^{\Omega_j}, v^{\Omega_j}) \mid u^{\Omega_j*} \in U, v^{\Omega_j*} \in V \right\}$$

Where U and V are the sets of admissible controls defined by :

$$U = \{ (u) \mid u^{min} \leq u_i \leq u^{max}, i \in \{0, \dots, N-1\} \},$$

$$V = \{(v) \mid v^{min} \leq v_i \leq v^{max}, i \in \{0, \dots, N-1\}\},$$

where $(u^{min}, u^{max}) \in]0, 1[^2$ and $(v^{min}, v^{max}) \in]0, 1[^2$.

The sufficient condition for existence of an optimal control for the problem is a result of the following theorem.

Theorem 3.1. (*Sufficient conditions*)

For the optimal control problem given by (10) along with the state equations (5)-(8), there exists optimal controls $(u_i^{\Omega_j^*})$ and $(v_i^{\Omega_j^*})$ such that

$$J(u^{\Omega_j^*}, v^{\Omega_j^*}) = \min \left\{ J_{pq}(u^{\Omega_j}, v^{\Omega_j}) \mid u^{\Omega_j^*} \in \mathcal{U}, v^{\Omega_j^*} \in \mathcal{V} \right\}$$

Proof. See Dabbs, K [[24], Theorem 1]. □

At the same time by using Pontryagin's Maximum Principle[25] we derive necessary conditions for our optimal controls. For this purpose we define the Hamiltonian as:

$$\begin{aligned} \mathcal{H}(\Omega) &= \left(\Psi_1 E_i^{\Omega_j} + \Psi_2 I_i^{\Omega_j} + \frac{A_1}{2} (u_i^{\Omega_j})^2 + \frac{A_2}{2} (v_i^{\Omega_j})^2 \right) \\ &+ \zeta_{1,i+1} \left[S_i^{\Omega_j} + \Lambda^{\Omega_j} - \sum_{\Omega_k \in V(\Omega_j)} \frac{\beta_{jk} c_{jk} S_i^{\Omega_j} I_i^{\Omega_k}}{N_i^{\Omega_j}} - \mu^j S_i^{\Omega_j} \right] \\ &+ \zeta_{2,i+1} \left[\sum_{\Omega_k \in V(\Omega_j)} \theta \frac{\beta_{jk} c_{jk} S_i^{\Omega_j} I_i^{\Omega_k}}{N_i^{\Omega_j}} - \sum_{\Omega_k \in V(\Omega_j)} \alpha_{jk} \frac{\beta_{jk} c_{jk} E_i^{\Omega_j} I_i^{\Omega_k}}{N_i^{\Omega_j}} \right. \\ &\quad \left. - \left(k^j + r_1^j u_i^{\Omega_j} + \mu^j \right) E_i^{\Omega_j} + \sum_{\Omega_k \in V(\Omega_j)} \gamma_{jk} \frac{\beta_{jk} c_{jk} S_i^{\Omega_j} R_i^{\Omega_k}}{N_i^{\Omega_j}} \right] \\ &+ \zeta_{3,i+1} \left[\sum_{\Omega_k \in V(\Omega_j)} (1-\theta) \frac{\beta_{jk} c_{jk} S_i^{\Omega_j} I_i^{\Omega_k}}{N_i^{\Omega_j}} + \sum_{\Omega_k \in V(\Omega_j)} \alpha_{jk} \frac{\beta_{jk} c_{jk} E_i^{\Omega_j} I_i^{\Omega_k}}{N_i^{\Omega_j}} \right. \\ &\quad \left. + k E_i^{\Omega_j} - \left(p^j + r_2^j v_i^{\Omega_j} + \mu^j + d^j \right) I_i^{\Omega_j} + q R_i^{\Omega_j} \right] \\ &+ \xi_{4,i+1} \left[u_i^{\Omega_j} r_1^j E_i^{\Omega_j} + \left(p^j + v_i^{\Omega_j} r_2^j \right) I_i^{\Omega_j} - \left(q^j + \mu^j \right) R_i^{\Omega_j} - \sum_{\Omega_k \in V(\Omega_j)} \gamma_{jk} \frac{\beta_{jk} c_{jk} S_i^{\Omega_j} R_i^{\Omega_k}}{N_i^{\Omega_j}} \right] \end{aligned}$$

Theorem 3.2. (Necessary Conditions)

Given optimal controls $(u_i^{\Omega_j^*})$, $(v_i^{\Omega_j^*})$ and solutions $S_i^{\Omega_j^*}$, $E_i^{\Omega_j^*}$, $I_i^{\Omega_j^*}$ and $R_i^{\Omega_j^*}$, there exists $\xi_{k,i}$, $i = 1 \dots N$, $k = 1, 2, 3, 4$, the adjoint variables satisfying the following equations:

$$\left\{ \begin{array}{l} \Delta \xi_{1,i}^{\Omega_j} = (1 - \mu^j) \xi_{1,i+1}^{\Omega_j} + \left(\theta \xi_{2,i+1}^{\Omega_j} + (1 - \theta) \xi_{3,i+1}^{\Omega_j} - \xi_{1,i+1}^{\Omega_j} \right) \left(\beta_j I_i^{\Omega_j} + \sum_{\Omega_k \in V(\Omega_j)} \beta_{jk} I_i^{\Omega_k} \right), \\ \Delta \xi_{2,i}^{\Omega_j} = (1 - \mu^j) \xi_{2,i+1}^{\Omega_j} + \left(\xi_{3,i+1}^{\Omega_j} - \xi_{2,i+1}^{\Omega_j} \right) \left(\sum_{\Omega_k \in V(\Omega_j)} \alpha_{jk} I_i^{\Omega_k} + k^{\Omega_j} \right) \\ \quad + \left(\xi_{4,i+1}^{\Omega_j} - \xi_{2,i+1}^{\Omega_j} \right) \left(r_1^j u_i^{\Omega_j} \right) + \Psi_1 \\ \Delta \xi_{3,i}^{\Omega_j} = (1 - \mu^j - d^j) \xi_{3,i+1}^{\Omega_j} + \left(\theta \xi_{2,i+1}^{\Omega_j} + (1 - \theta) \xi_{3,i+1}^{\Omega_j} - \xi_{1,i+1}^{\Omega_j} \right) \beta_j S_i^{\Omega_j} \\ \quad + \left(\xi_{4,i+1}^{\Omega_j} - \xi_{3,i+1}^{\Omega_j} \right) \left(p + r_2 v_i^{\Omega_j} \right) + \Psi_2 \\ \Delta \xi_{4,i}^{\Omega_j} = \xi_{4,i+1}^{\Omega_j} (1 - \mu^j) + \left(\xi_{2,i+1}^{\Omega_j} - \xi_{4,i+1}^{\Omega_j} \right) \sum_{\Omega_k \in V(\Omega_j)} \gamma_{jk} I_i^{\Omega_k} + q^j \left(\xi_{3,i+1}^{\Omega_j} - \xi_{4,i+1}^{\Omega_j} \right), \end{array} \right.$$

Furthermore, the optimal controls $(u_i^{\Omega_j^*})$ and $(v_i^{\Omega_j^*})$ are given by

$$u_i^{\Omega_j^*} = \min \left\{ \max \left\{ u^{\min}, \frac{\left(\xi_{2,i+1}^{\Omega_j} - \xi_{1,i+1}^{\Omega_j} \right)}{A_1} r_1 E_i^{\Omega_j} \right\}, u^{\max} \right\}, \quad i = 1, \dots, n.$$

$$v_i^{\Omega_j^*} = \min \left\{ \max \left\{ v^{\min}, \frac{\left(\xi_{3,i+1}^{\Omega_j} - \xi_{4,i+1}^{\Omega_j} \right)}{A_2} r_2 I_i^{\Omega_j} \right\}, v^{\max} \right\}, \quad i = 1, \dots, n.$$

Proof. Using Pontryagin's Maximum Principle [25], and setting $S_i^{\Omega_j} = S_i^{\Omega_j^*}$, $E_i^{\Omega_j} = E_i^{\Omega_j^*}$, $I_i^{\Omega_j} = I_i^{\Omega_j^*}$, $R_i^{\Omega_j} = R_i^{\Omega_j^*}$, $u_i^{\Omega_j} = u_i^{\Omega_j^*}$ and $v_i^{\Omega_j} = v_i^{\Omega_j^*}$. we obtain the following adjoint equations:

$$\left\{ \begin{array}{l} \Delta \xi_{1,i}^{\Omega_j} = \frac{-\partial H}{\partial S^{\Omega_j}} = (1 - \mu^j) \xi_{1,i+1}^{\Omega_j} + \left(\theta \xi_{2,i+1}^{\Omega_j} + (1 - \theta) \xi_{3,i+1}^{\Omega_j} - \xi_{1,i+1}^{\Omega_j} \right) \left(\beta_j I_i^{\Omega_j} + \sum_{\Omega_k \in V(\Omega_j)} \beta_{jk} I_i^{\Omega_k} \right), \\ \Delta \xi_{2,i}^{\Omega_j} = \frac{-\partial H}{\partial E^{\Omega_j}} = (1 - \mu^j) \xi_{2,i+1}^{\Omega_j} + \left(\xi_{3,i+1}^{\Omega_j} - \xi_{2,i+1}^{\Omega_j} \right) \left(\sum_{\Omega_k \in V(\Omega_j)} \alpha_{jk} I_i^{\Omega_k} + k^{\Omega_j} \right) \\ \quad + \left(\xi_{4,i+1}^{\Omega_j} - \xi_{2,i+1}^{\Omega_j} \right) \left(r_1^j u_i^{\Omega_j} \right) + \Psi_1, \\ \Delta \xi_{3,i}^{\Omega_j} = \frac{-\partial H}{\partial I^{\Omega_j}} = (1 - \mu^j - d^j) \xi_{3,i+1}^{\Omega_j} + \left(\theta \xi_{2,i+1}^{\Omega_j} + (1 - \theta) \xi_{3,i+1}^{\Omega_j} - \xi_{1,i+1}^{\Omega_j} \right) \beta_j S_i^{\Omega_j}, \\ \quad + \left(\xi_{4,i+1}^{\Omega_j} - \xi_{3,i+1}^{\Omega_j} \right) \left(p + r_2 v_i^{\Omega_j} \right) + \Psi_2 \\ \Delta \xi_{4,i}^{\Omega_j} = \frac{-\partial H}{\partial R^{\Omega_j}} = \xi_{4,i+1}^{\Omega_j} (1 - \mu^j) + \left(\xi_{2,i+1}^{\Omega_j} - \xi_{4,i+1}^{\Omega_j} \right) \sum_{\Omega_k \in V(\Omega_j)} \gamma_{jk} I_i^{\Omega_k} + q \left(\xi_{3,i+1}^{\Omega_j} - \xi_{4,i+1}^{\Omega_j} \right), \end{array} \right.$$

then

$$\left\{ \begin{array}{l} \xi_{1,i}^{\Omega_j} = (2 - \mu^j) \xi_{1,i+1}^{\Omega_j} + \left(\theta \xi_{2,i+1}^{\Omega_j} + (1 - \theta) \xi_{3,i+1}^{\Omega_j} - \xi_{1,i+1}^{\Omega_j} \right) \left(\beta_j I_i^{\Omega_j} + \sum_{\Omega_k \in V(\Omega_j)} \beta_{jk} I_i^{\Omega_k} \right), \\ \xi_{2,i}^{\Omega_j} = (2 - \mu^j) \xi_{2,i+1}^{\Omega_j} + \left(\xi_{3,i+1}^{\Omega_j} - \xi_{2,i+1}^{\Omega_j} \right) \left(\sum_{\Omega_k \in V(\Omega_j)} \alpha_{jk} I_i^{\Omega_k} + k^{\Omega_j} \right) \\ + \left(\xi_{4,i+1}^{\Omega_j} - \xi_{2,i+1}^{\Omega_j} \right) \left(r_1 u_i^{\Omega_j} \right) + \Psi_1, \\ \xi_{3,i}^{\Omega_j} = (2 - \mu^j - d^j) \xi_{3,i+1}^{\Omega_j} + \left(\theta \xi_{2,i+1}^{\Omega_j} + (1 - \theta) \xi_{3,i+1}^{\Omega_j} - \xi_{1,i+1}^{\Omega_j} \right) \beta_j S_i^{\Omega_j} \\ + \left(\xi_{4,i+1}^{\Omega_j} - \xi_{3,i+1}^{\Omega_j} \right) \left(p^j + r_2^j v_i^{\Omega_j} \right) + \Psi_2, \\ \xi_{4,i}^{\Omega_j} = \xi_{4,i+1}^{\Omega_j} (2 - \mu^j) + \left(\xi_{2,i+1}^{\Omega_j} - \xi_{4,i+1}^{\Omega_j} \right) \sum_{\Omega_k \in V(\Omega_j)} \gamma_{jk} I_i^{\Omega_k} + q^j \left(\xi_{3,i+1}^{\Omega_j} - \xi_{4,i+1}^{\Omega_j} \right), \end{array} \right.$$

To obtain the optimality conditions we take the variation with respect to controls $u_i^{\Omega_j}$ and $v_i^{\Omega_j}$ and set it equal to zero

$$\frac{\partial H}{\partial u_i^{\Omega_j}} = A_1 u_i^{\Omega_j} - \xi_{2,i+1} \left(r_1^j E_i^{\Omega_j} \right) + \xi_{4,i+1} \left(r_1^j E_i^{\Omega_j} \right) = 0$$

$$\frac{\partial H}{\partial v_i^{\Omega_j}} = A_2 v_i^{\Omega_j} - \xi_{3,i+1} \left(r_2^j I_i^{\Omega_j} \right) + \xi_{4,i+1} \left(r_2^j I_i^{\Omega_j} \right) = 0$$

Then we obtain the optimal controls

$$\begin{aligned} u_i^{\Omega_j} &= \frac{\left(\xi_{2,i+1}^{\Omega_j} - \xi_{1,i+1}^{\Omega_j} \right)}{A_1} r_1^j E_i^{\Omega_j} \\ v_i^{\Omega_j} &= \frac{\left(\xi_{3,i+1}^{\Omega_j} - \xi_{4,i+1}^{\Omega_j} \right)}{A_2} r_2^j I_i^{\Omega_j} \end{aligned}$$

By the bounds in U and V of the controls, it is easy to obtain $u_i^{\Omega_j^*}$ and $v_i^{\Omega_j^*}$ in the following form

$$u_i^{\Omega_j^*} = \min \left\{ \max \left\{ u^{min}, \frac{\left(\xi_{2,i+1}^{\Omega_j} - \xi_{1,i+1}^{\Omega_j} \right)}{A_1} r_1^j E_i^{\Omega_j} \right\}, u^{max} \right\}, \quad i = 1, \dots, n \quad / \quad \Omega_j \in \Omega$$

$$v_i^{\Omega_j^*} = \min \left\{ \max \left\{ v^{min}, \frac{\left(\xi_{3,i+1}^{\Omega_j} - \xi_{4,i+1}^{\Omega_j} \right)}{A_2} r_2^j I_i^{\Omega_j} \right\}, v^{max} \right\}, \quad i = 1, \dots, n \quad / \quad \Omega_j \in \Omega$$

□

3.1. Numerical simulation. In this section, we present the numerical results that illustrate and reinforce the effect of our control strategy. This strategy consists in applying two kinds of treatment respectively to the exposed individuals and to the infected ones in order to fight against the spread of the tuberculosis disease. We have developed a code in MATLABTM and we have simulated our results using different data. We solve the optimality system using an iterative method. Where the state system with an initial guess is solved forward in time and then the adjoint system is solved backward in time because of the transversality conditions. Afterwards, we updated the optimal controls values using the values of state and costate variables obtained in the previous steps. Finally, we execute the previous step still a tolerance criterion is reached.

In order to show the importance of our work, and without lose of generality, we consider here that a 10×10 grid denoted Ω which $\Omega = \bigcup_{j=1}^{10} \Omega_j$. All simulations are performed using the parameter values in Table (1) taken from [10]. At day $t = 1$ we assume that the susceptible people are homogeneously distributed with 45 in each cell except at the lower right corner cell Ω_1 where we introduce 5 infectives, and keep 40 susceptible there. In all of the figures below, the redder part of the color bars contains larger numbers of individuals while the bluer part contains the smaller numbers. To illustrate and show the effect of each control and its influence on the spread of the disease, we choose to adopt three scenarios. In the first scenario, we optimized simultaneously the controls on chemoprophylaxis (u) and treatment (v). However, in the 2nd case, the control (v) on treatment is not optimized but held constant while the control on chemoprophylaxis (u) is optimized, and finally in the 3rd case, we use constant chemoprophylaxis and optimal treatment given to the infected people.

- Case 1: Applying two controls : chemoprophylaxis and treatment.
- Case 2: Constant treatment.

3.1.1. Case 1 : Applying two controls : chemoprophylaxis and treatment. In figures 2, 3, 4 and 5 when we use our spatiotemporal control strategy based on two treatments. We admit that optimal treatments begin on day $t = 1$ which is the same day that infection is detected in Ω . The impact of spatiotemporal treatment controls is very remarkable in slowing the spread of infection.

TABLE 1. Initial conditions and parameters values

Parameter	Value	Description
$S_0^{\Omega_j}$	50 for Ω_j 45 for Ω_1	Initial susceptible population
$E_0^{\Omega_j}$	0	Initial exposed population
$I_0^{\Omega_j}$	0 for Ω_j 5 for Ω_1	Initial infected population
$R_0^{\Omega_j}$	0	Initial immune population
Λ	3000	Birth rate
μ	0.01	Natural mortality rate
c	21	Contact rate
d	0.3	TB induced death rate
β	0.35	Probability of being infected
k	0.00013	Natural rate of progression to active TB
p	0.2	Natural recovery rate
q	0.005	Relapsing rate
r_1	0.7	Treatment rate for the latently infected
r_2	0.55	Treatment rate for the infectives
δ_1	0.7	Modification parameter
δ_2	0.9	Modification parameter
f	0.99	Probability that the infected will enter the latent stage of the disease

In Fig.1 (b), We can observe that the latently infected population, in the absence of chemoprophylaxis and treatment of infective, increases as susceptible are infected, and reaches its maximum, then gradually falls and then reaches a stable state where it remains constant. Upon the implementation of chemoprophylaxis and treatment as shown in Fig.3, the latent infected population has decreased to low levels as the infectious are treated, which leads to decrease in contagiousness.

In figure 4, after 4 years, the density of the infected population falls from 35 infected in absence of treatment and chemoprophylaxis, to 2 infected in the presence of optimal controls as shown in Fig.1(c). In fact, in the absence of treatment and chemoprophylaxis, the infective population increases from the onset due to some of the latently infected becoming infectious, and reaches its peak and then falls and reaches a state where it remains constant as shown in Fig.1(c). In Fig.4, in the presence of chemoprophylaxis and treatment of the infectives, the population falls off and are reduced to low levels as chemoprophylaxis will reduce the number of individuals progressing to active (TB). The treatment is also impeding those that develop active (TB) to infect others.

In figure 5, the maximum number of people eliminated reaches approximately 43 individuals compared to less than 4 in the absence of controls, which is very beneficial and reflects the importance of our control strategy. We can observe in figures 1 and 5 the disappearance of the recovered population in the two cases either in absence or in the presence of the control. In the first case, recovered individuals are transferred to the infected class (see figures 2 and 3), but in the second case recovered individuals are transferred to the recovered class (see figure.5) through the mechanisms of treatments adopted in this case. This implies that the holistic approach of the intervention strategies is the most effective way in combating the (TB) epidemic.

3.1.2. Case 2 : Constant treatment. In figures 2-9, we investigate numerical results with only one chemoprophylaxis of exposed population and a constant treatment for the infected population. We observe that in this case, the number of exposed decreases but in a way less than the first scenario, however the number of infected remains high and the number of removed increases relatively without reaching the same number as in the use of both treatments.

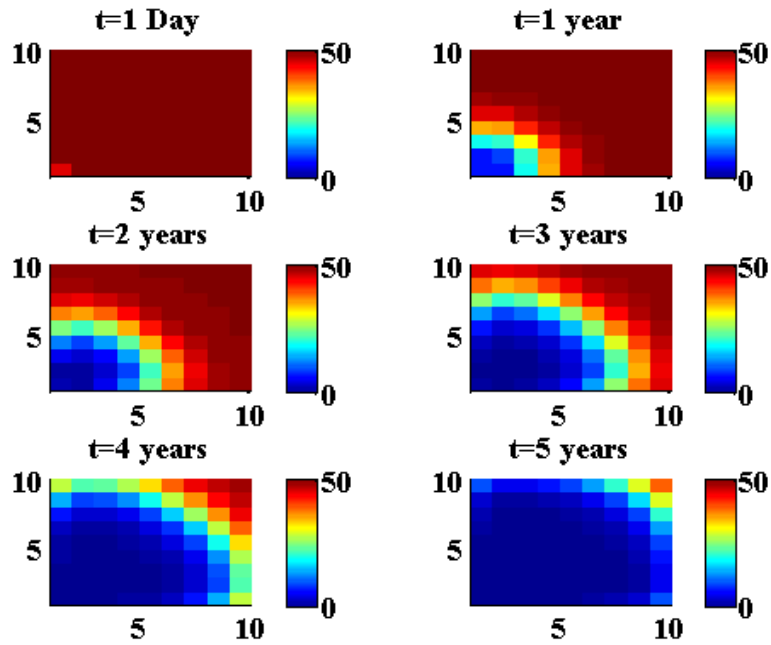


FIGURE 2. Susceptible behavior within Ω with control (Optimal chemoprophylaxis and treatment).

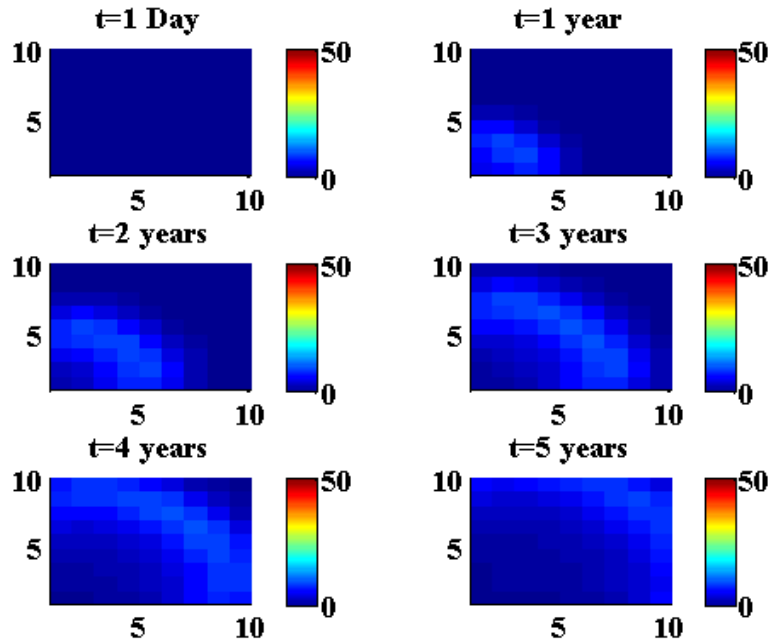


FIGURE 3. Exposed behavior within Ω with control (Optimal chemoprophylaxis and treatment).

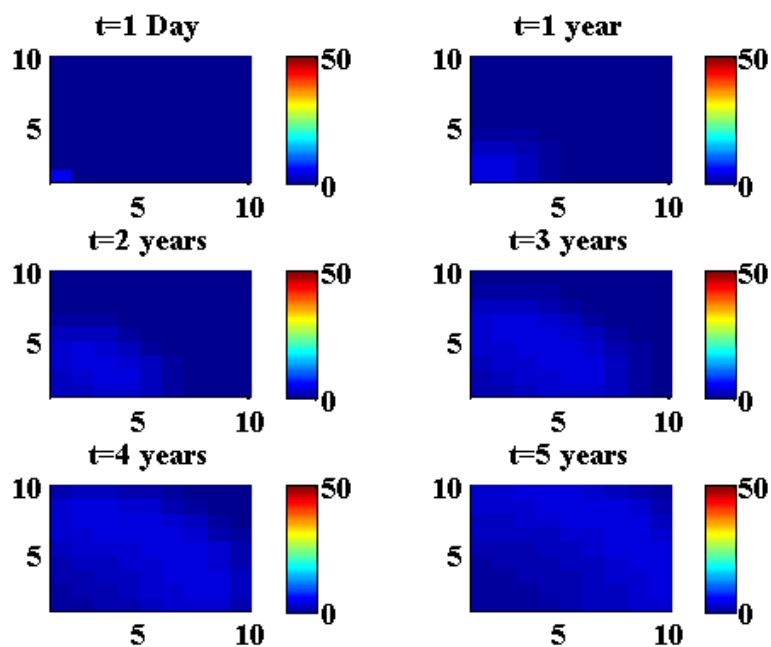


FIGURE 4. Infected behavior within Ω with control (Optimal chemoprophylaxis and treatment).

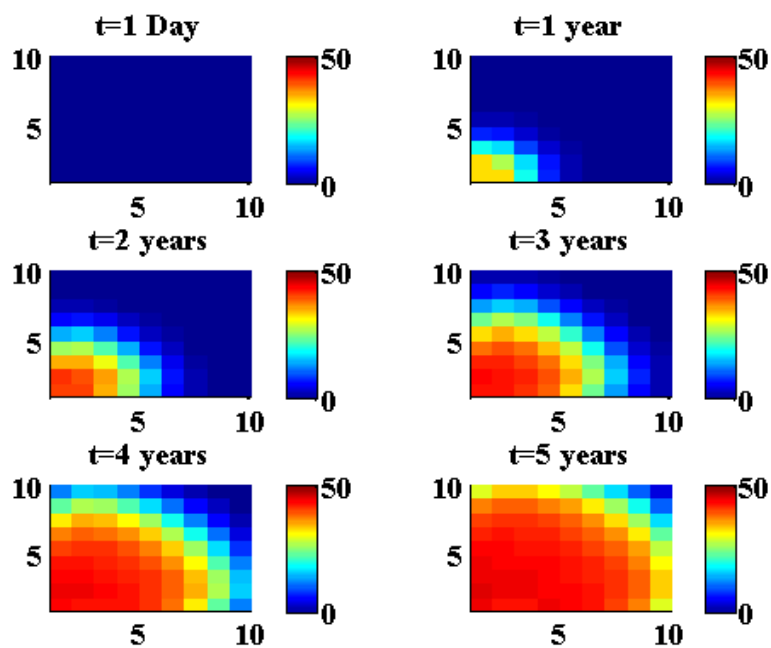


FIGURE 5. Recovered behavior within Ω with control (Optimal chemoprophylaxis and treatment).

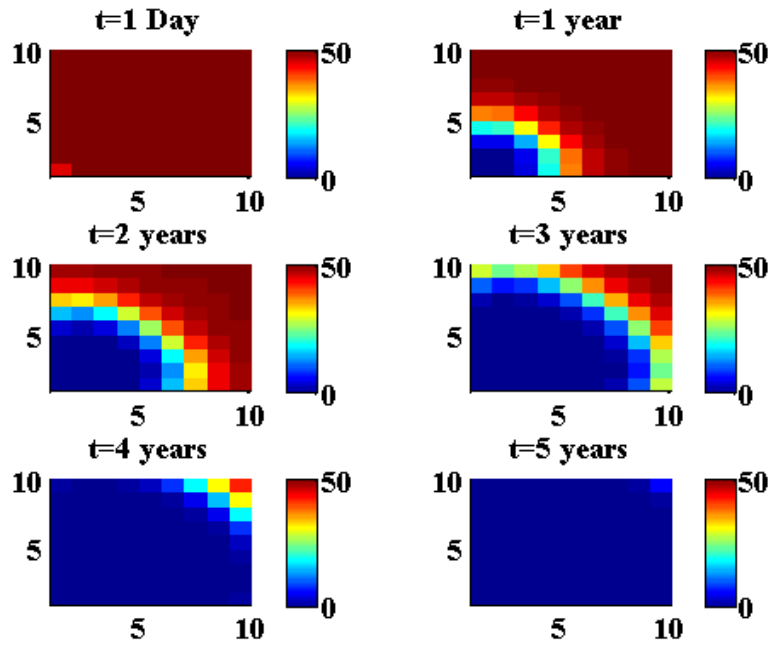


FIGURE 6. Susceptible behavior within Ω with control (Optimal chemoprophylaxis and treatment).

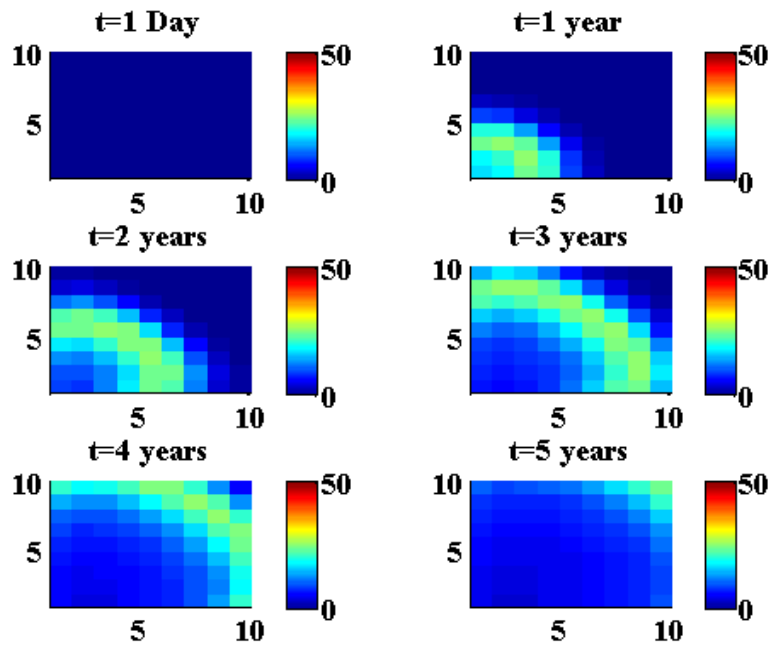


FIGURE 7. Exposed behavior within Ω with control (Optimal chemoprophylaxis and treatment).

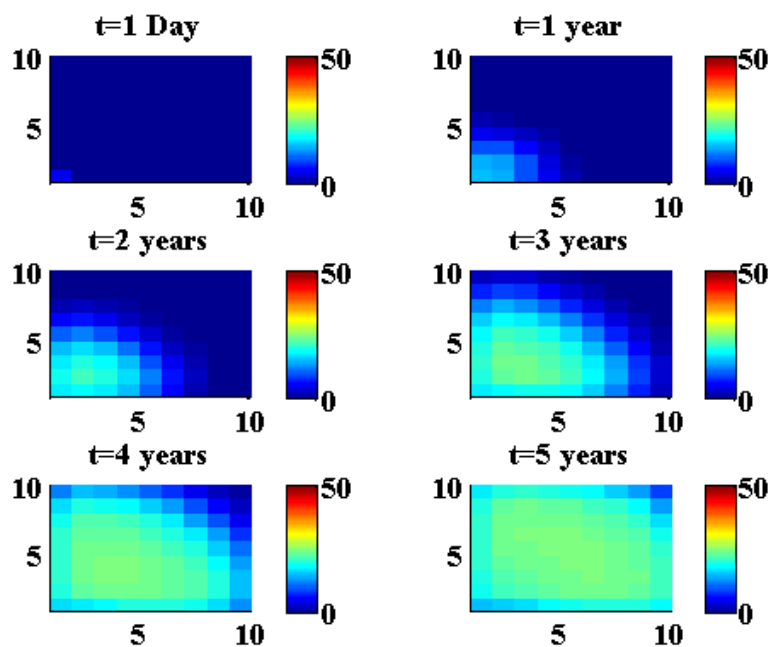


FIGURE 8. Infected behavior within Ω with control (Optimal chemoprophylaxis and treatment).

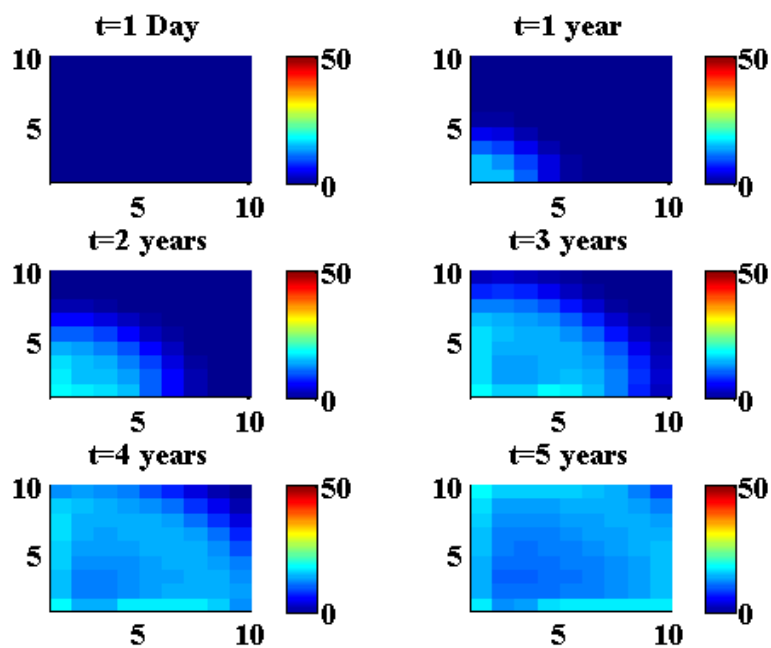


FIGURE 9. Recovered behavior within Ω with control (Optimal chemoprophylaxis and treatment).

4. CONCLUSION

The main idea of this article is to present an optimal strategy for controlling the spread of tuberculosis disease in a given region, based on a discrete time spatiotemporal model describing the evolution of the number of susceptible, exposed, infected and removed in different regions incorporating the movement of people from one region to another. The regions were assembled into a meshed cell surface where each cell represents a region, to show the impact of an infection that comes from a one cell to its vicinity. The optimal control approach is aiming at reducing the latently infected individuals (exposed) to avoid the transition, from tuberculosis infection to tuberculosis disease. This approach is suggested by looking at its effect when a treatment is supposed to be followed in the fight against the disease. According to the simulation results, it can be confirmed that the control effects will be effective by using controls on treatment and chemoprophylaxis simultaneously.

CONFLICT OF INTERESTS

The author(s) declare that there is no conflict of interests.

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