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OPTIMAL CONTROL STRATEGY FOR A DISCRETE TIME EPIDEMIC MODELS OF MYCOBACTERIUM TUBERCULOSIS INFECTIONS

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Abstract. In this paper, our aim is to study the optimal control strategy of a mathematical model of the tuberculosis transmission in the discrete case, and to investigate, in discrete time, optimal control strategy in which the controls are: vaccination and treatment and sensibilisation. The studied population is divided into five compartments SL_1IL_2R. Our objective is to find the best strategy to reduce the number of S, L_1, I and L_2. So, the Pontryagin's maximum principle, in discrete time, is used to characterize the optimal control. The numerical simulation is carried out using MATLAB. The obtained results confirm the performance of the optimization strategy.

Keywords: optimal control; discrete epidemic model; vaccination; treatment; Pontryagin's maximum principal.

2010 AMS Subject Classification: 92B05, 92D30, 93C55.

1. INTRODUCTION

"Just sleep and eat nutritious foods" was the advice given to patients in the 1800s infected with tuberculosis, or formerly known for a long time as consumption [12]. Tuberculosis (TB) has never stopped making victims through the times and in all known human civilizations. Even today it is considered as the most infectious disease that has led to the most deaths in the history of humanity. TB remains one of the leading causes of illness and death in the world, estimated

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one third of the world's population is infected with TB. Such a human reservoir triggers about 8 million new TB cases and 2 million deaths each year according to WHO [26]. The identification of Mycobacterium tuberculosis "MTB" (or Bacillus of Koch "BK") on March 24, 1882, by biologist Robert Koch, followed by the invention of The BCG vaccine starts with Albert Calmette and Camille Guerin, thy were two French scientists who from 1905 had been working on developing a vaccine against TB. BCG is abbreviation of Bacillus Calmette-Guerin, meaning the bacilli of Calmette and Guerin, then the discovery of streptomycin in 1943 by Selman Waksman, have eventually allowed to revolutionize the vital and functional prognosis of patients with TB [12]. Tuberculosis is a contagious disease, secondary to infection with "bacillus of Koch" (Mycobacterium tuberculosis). This bacterial agent is transmitted by air via the droplets contaminated by the bacterium, which are suspended in the exhaled air by patients, especially during coughing. Inhaling a small number of contaminated droplets is enough to infect an individual. The displacement of populations (travelers, refugees) has largely contributed recently in the spread of the disease in the world, People who are more likely to acquire TB infection are the following:

(1) People recently exposed to someone who has symptomatic TB disease;

(2) People who live in congregate settings with high risk persons;

(3) People who live or have lived in countries where TB is common;

(4) People who are health care workers who are in contact with TB patients when proper infection control procedures are not followed.

Many people who acquire TB infection do not have symptoms and may never develop TB disease. These people have latent TB infections (LTBI) [24]. After exposure to the bacillus of tuberculosis, some people develop a primary infection, the "primary infection", which is controlled by the immune system in 90% of cases: tuberculosis is labeled "latent". The bacillus remains in the body, but the immune system prevents its multiplication.

In 10% of infected people, the bacillus is not sufficiently controlled by the immune system and these people develop a form of so-called "active" tuberculosis, which will cause illness and complications. The organs most often affected by tuberculosis infection are the lungs (more than two-thirds of cases): it is "pulmonary tuberculosis", which is also the contagious form

of the disease, Tuberculosis can also infect lymph nodes (”lymphadenopathy”), skin, kidneys, brain (”meningitis”), bones, intestines: it is ”extra-pulmonary tuberculosis”, which is the non-contagious form . After contact with the bacillus of Koch occurs an incubation phase where the bacteria fight against the immune defenses of the infected person in order to develop. It lasts from one to three months and usually goes unnoticed, but Koch's bacillus, which can remain dormant in the body for years, can also wake up to develop the infection because of the secondary weakening of the immune system of the person affected (HIV, chemotherapy, immunosuppressive treatments) [3]. With early antibiotic treatment and well followed, ”tuberculosis disease” usually heals without leaving sequelae (treatment combining 4 antibiotics = quadrotherapy). On the other hand, if the treatment is not treated correctly, the cure will not be obtained and the bacillus will become resistant to the usual antibiotics obliging to resort to heavier and more complicated treatments [8].

In Morocco, tuberculosis remains a major public health problem,. The last World Health Organization WHO estimates reported 36.000 incident TB cases for the year 2016 (vs.37.000 for the year 2015), with a per capita rate of 103 per 100.000 population (vs.107 for the year 2015). The TB death toll for the same year is estimated at 3300 deaths (vs. 3200 for the year 2015) with a mortality rate of 9.3 per 100.000 population (vs. 9.4 for the year 2015) [27].

However, in Morocco, families cannot declare a birth at the civil registry (30 days delay) if they do not provide a BCG vaccination certificate. This makes this immunization mandatory for the first month .

TB control is organized in the framework of the National TB Program (NTP). The efforts undertaken through the NTP activities resulted in increasing TB case detection by 1.5% per year since 2009. In 2016, the number of patients with a new TB episode who were notified reached 31.542 (vs. 30.636 for the year 2015). It is estimated that more than 87% of incident TB cases are detected and treated. Furthermore, the treatment success rate is more than 88% among TB patients who are put on treatment. These high rates in detection and treatment success are likely to contribute to significantly decreasing TB-related deaths. The analysis of the data generated by the NTP information system suggests that the transmission of TB is likely declining in general population. Even though there is a steady annual decrease in TB incidence, this decrease is

low in general population. At this decrease pace, the decline in TB burden is likely to remain significant for many of the coming years.

The goal of this national strategic plan (NSP), which covers the timeframe from 2018 to 2021, is to fit within the sustainable development goals and to reduce the number of TB deaths by 40% in 2021 compared to 2015. Indeed, this NSP aims at increasing more TB case detection and treatment success rate, especially in highly urbanized regions, through the improvement and strengthening of the existing NTP services, the involvement of all care providers and the reinforcement of TB services for high-risk groups and vulnerable populations.

Moreover, in order to reduce the number of TB deaths, this NSP also aims at improving and strengthening TB/HIV joint activities and the programmatic management of drug-resistant TB. To develop and implement these interventions, highlighted above, it is clear that the managerial capacities of the NTP need to be improved and reinforced at all levels [27] and [16].[2].

Mathematical modeling of tuberculosis has been studied by many researchers [[1] - [3], [7]- [10], [12], [19]- [25], [28]]. We observe that most of those researchers focused on the continuous-time models described by the differential equations. It is noted that, in recent years, more and more attention has been given to discrete time models (see [[11], [18] and the references cited therein).

The reasons for adopting discrete modeling are as follows: Firstly, the statistical data are collected at discrete moments (day, week, month, or year). So, it is more direct and more accurate and timely to describe the disease using discrete time models than continuous time models. Secondly, the use of discrete time models can avoid some mathematical complexities such as choosing a function space and regularity of the solution. Thirdly, the numerical simulations of continuous time models are obtained by the way of discretization.

Based on the aforementioned reasons, we will develop in this paper a discrete time model studying the dynamics of Koch bacillus spread and introduce a mortality rate due to active MTB infection. In addition, in order to find the best strategy to reduce the number of susceptible, infected who have active MTB or recently and persistent infected latent, we will use four control strategies, namely vaccination and treatment programs, tests to detect the disease and take the TB drugs regularly and to complete them. In this paper, we construct a discrete SL_1IL_2R

Mathematical TB Model. In Section 2, the mathematical model is proposed. In Section 3, we investigate the optimal control problem for the proposed discrete mathematical model. Section 4 consists of numerical simulation through MATLAB.The conclusion is given in Section 5.

2. FORMULATION OF THE MATHEMATICAL MODEL

In the present paper, following, we consider a TB mathematical model taken from [7],where reinfection and post-exposure interventions, consisting of a system of non-linear ordinary differential equations representing population dynamics. in The model without controls, the population total is divided into five categories:

(S) : susceptible, who have never encountered the Mycobacterium;

(L_1): early latent, that is, individuals recently infected (less than two years) but not infectious;

(I): infected, that is, individuals who have active tuberculosis and are infectious;

(L_2): persistent latent, that is, individuals who were infected and remain latent;

(R): recovered, that is, individuals who were previously infected and treated.

Individuals in the early latent compartment L_1 can progress either to active disease (I) with rate $\phi\delta$ or to a persistent latent infection (L_2) with rate $(1-\phi)\delta$, following the approach in [28]. Parameter ϕ reflects that only 5% of infected individuals will ever develop active TB [21] , [20]. We choose δ such that the progression rate from early infections to active disease is $\phi\delta = 0.6yr^{-1}$, which roughly approximates the data by [22] , describing the proportions of disease development after conversion. For the rates of reactivation we adopt $\omega = 0.0002yr^{-1}$ for untreated latent infections [23] , [25] and $\omega_R = 0.00002yr^{-1}$. for those who have undergone a therapeutic intervention. As in Gomes et al. (2004a) [9], the partial susceptibility factor affecting the rate of exogenous reinfection of untreated individuals, σ, is fixed at 0.25, in accordance to the highest estimates of protection conferred by BCG vaccination see [1] .In treated patients this factor becomes σ_R, for which several exploratory values are adopted. Treatment of different infection stages is implemented at specific rates: τ_0 applies to active TB and represents the rate of recovery (typically as a result of treatment, though here it also accounts for the infrequent natural recovery); τ_1 and τ_2 apply, respectively, to the latent classes L_1 and L_2 as the rates at which chemotherapy or a post-exposure vaccine is applied. The rate τ_0 is fixed at $2yr^{-1}$, corresponding to an average duration of infectiousness of 6 months, while τ_1 and τ_2 are considered

at different exploratory values. see [10].

The total population, N, is assumed to be constant, so, $N = S(t) + L_1(t) + I(t) + L_2(t) + R(t)$. The proportions of the population in each category change, as represented by the diagram in Fig. 1; According to Silva and Torres [See [19]] , the Tuberculosis modelled is described by the nonlinear time-varying state equations:

$$
(1) \quad \begin{cases} S(t+1) &= S(t) + \Lambda - \frac{\beta}{N} I(t) S(t) - \mu S(t), \\ L_1(t+1) &= L_1(t) + \frac{\beta}{N} I(t) \left(S(t) + \sigma L_2(t) + \sigma_R R(t)\right) - (\delta + \tau_1 + \mu) L_1(t)), \\ I(t+1) &= I(t) + \phi \delta L_1(t) + \omega L_2(t) + \omega_R R(t) - \tau_0 I(t) - (\mu + d) I(t), \\ L_2(t+1) &= L_2(t) + (1-\phi)\delta L_1(t) - \sigma \frac{\beta}{N} I(t) L_2(t) - (\omega + \tau_2 + \mu) L_2(t), \\ R(t+1) &= R(t) + \tau_0 I(t) + \tau_1 L_1(t) + \tau_2 L_2(t) - \left(\sigma_R \frac{\beta}{N} I(t) + \omega_R + \mu\right) R(t). \end{cases}
$$

where Λ is the recruitment rate, μ is the natural per-capita mortality rate, d is the per-capita TB induced mortality rate, β is the transmission rate, with The initial conditions for system (1) are: $S(0) = (\frac{76}{120})N$, $L_1(0) = (\frac{36}{120})N$, $L_2(0) = (\frac{2}{120})N$, $R(0) = (\frac{1}{120})N$, and $I(0) = (\frac{5}{120})N$.

The values of the model parameters presented in the control system (1) are given in Table 1. The values of the rates $\beta, \delta, \mu, \sigma, \sigma_R, \omega, \omega_R, \phi, \tau_0, \tau_1$, and τ_2 are taken from [10] and the references cited therein.

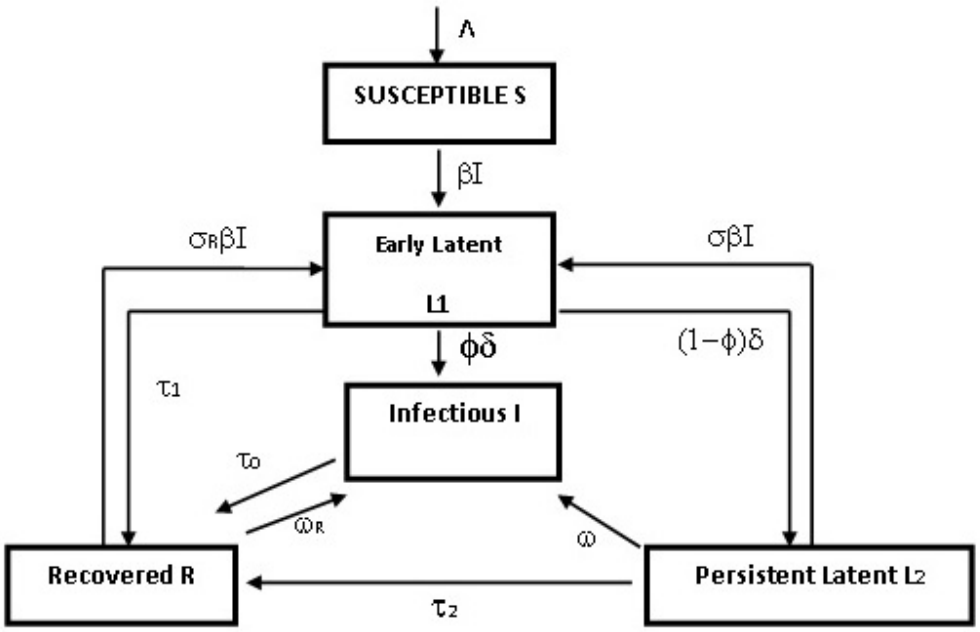

FIGURE 1. Diagram

Symbol	Description	Value
β	transmission coefficient	0.01
Λ	Recruitment rate	1203.75
μ	Naturral death rate	0.04
d	Death rate due to infection	0.005
δ	rate at which individuals leave L_1	$12yr^{-1}$
ϕ	proportion of individuals going to compartment I	0.05
ω	rate of endogenous reactivation for persistent latent infections	$0.0002yr^{-1}$
ω_R	rate of endogenous reactivation for treated individuals	$0.00002yr^{-1}$
σ	factor reducing the risk of infection an a result of acquired immunity to a previous infection for persistent latent individuals	0.25
σ_R	factor reducing the risk of infection an a result of acquired immunity to a previous infection for treated individuals	0.25
τ_0	rate of recovery under treatment of active TB	$2yr^{-1}$
τ_1	rate of recovery of early latent individuals under post-exposure interventions	$2yr^{-1}$
τ_2	rate of recovery of persistent latent individuals under post-exposure interventions	$1yr^{-1}$
N	total population	30000
T	total simulation duration	$20yr$

Table - Parameter Values

3. THE OPTIMAL CONTROL OF A TUBERCULOSIS MODEL

The model includes control variables representing vaccination or prevention and treatment measures, which are continuously implemented during a considered period of disease treatment: We now consider the TB model (1) and introduce four control functions $u_1(.), u_2(.), u_3(.)$ and $u_4(.)$, and four real positive model constants $\varepsilon_1, \varepsilon_2, \varepsilon_3$ and ε_4,

The resulting model is given by the following system of non-linear differential equations:

$$
(2) \quad \begin{cases}
S(t+1) &= S(t) + \Lambda - \frac{\beta}{N} I(t) S(t) - (\mu + \varepsilon_1 u_1(t)) S(t), \\
L_1(t+1) &= L_1(t) + \frac{\beta}{N} I(t)(S(t) + \sigma L_2(t) + \sigma_R R(t)) - (\delta + \tau_1 + \varepsilon_2 u_2(t) + \mu) L_1(t)), \\
I(t+1) &= I(t) + \phi \delta L_1(t) + \omega L_2(t) + \omega_R R(t) - (\tau_0 + \varepsilon_3 u_3(t) + \mu + d) I(t), \\
L_2(t+1) &= L_2(t) + (1-\phi)\delta L_1(t) - \sigma \frac{\beta}{N} I(t) L_2(t) - (\omega + \tau_2 + \varepsilon_4 u_4(t) + \mu) L_2(t), \\
R(t+1) &= R(t) + \varepsilon_1 u_1(t) S(t) + (\tau_0 + \varepsilon_3 u_3(t)) I(t) + (\tau_1 + \varepsilon_2 u_2(t)) L_1(t) \\
&+ (\tau_2 + \varepsilon_4 u_4(t)) L_2(t) - \sigma_R \frac{\beta}{N} I(t) R(t) - (\omega_R + \mu) R(t).
\end{cases}
$$

where

$$
\varepsilon_i = \begin{cases} 1 \\ 0 \end{cases} \quad \text{for i } \in \{1,2,3,4\}
$$

there are four controls $u_i = (u_{i,0}, u_{i,1}, ..., u_{i,T-1})$ with $i = 1,2,3,4$.

u_1(t) : represents the BCG vaccination for new-borne.

u_2(t) : represents the effort on early detection and treatment of recently infected individuals L_1,

u_3(t) : represents the effort that prevents the failure of treatment in active TB infectious individuals I, e.g. supervising the patients, helping them to take the TB drugs regularly and to complete the TB treatment;

u_4(t) : represents the fraction of persistent latent individuals L_2, that is identified and put under treatment.

So the first control, we note that $u_{1,i}S_i$ individuals move from the susceptible class to the removed class at time step i. The second control we note that $u_{2,i}L_{1,i}$ individuals move from the early latent class to the removed class at time step i. The third control we note that $u_{3,i}I_i$ individuals move from the infected class to the removed class at time step i. The fourth control we note that $u_{4,i}L_{2,i}$ individuals move from the persistent latent class to the removed class at time step i .

Indeed, the system above (2) presents five different models as the table 2 explains.

ε_1	ε_2	ε_3	ε_4	interpretations
0	0	0	0	Discrete TB model without control
1	1	0	0	Discrete TB model with BCG vaccination and the effort on early detection and treatment of recently infected
1	0	1	0	Discrete TB model with BCG vaccination and treatment in active TB infectious individuals
1	0	0	1	Discrete TB model with BCG vaccination and the effort for identified the persistent latent and put under treatment
1	1	1	1	Discrete TB model with four controls

Table - Interpretations according to the values of epsilons

3.1. The Optimal Control Problem: Our goal is reducing the number of S, L_1, I and L_2 during the times steps $t = 0$ to T and also minimizing the cost of treatment and the cost of vaccination. To simplify, we assume that the costs of administering the controls are quadratic. Then, the objective functional is presented as follows:

$$\begin{aligned} J(u_1,u_2,u_3,u_4) &= A_{1,T}S_T + A_{2,T}L_{1,T} + A_{3,T}I_T + A_{4,T}L_{2,T} \\ &+ \sum_{t=0}^{T-1}(A_{1,t}S_t + A_{2,t}L_{1,t} + A_{3,t}I_t + A_{4,t}L_{2,t} + \frac{1}{2}B_t u_{1,t}^2 + \frac{1}{2}C_t u_{2,t}^2 + \frac{1}{2}D_t u_{3,t}^2 + \frac{1}{2}E_t u_{4,t}^2) \end{aligned} \tag{3}$$

where the parametrs $B_t > 0, C_t > 0, D_t > 0, E_t > 0$ and $A_{i,t} > 0$, for $i = 1,2,3,4$ are the cost coefficients. They are selected to weigh the relative importance of $S_t, L_{1,t}, I_t, L_{2,t}$ and $u_{1,t}, u_{2,t}, u_{3,t}, u_{4,t}$ at time t.

T is the final time. We are minimizing the number of susceptible individuals, early latent individuals, infected individuals and persistent latent individuals during the time steps $t = 0$ to $T-1$, and at the final time and also minimizing the cost of administering the control.

In other words, we seek the optimal control $u^* = (u_1^*, u_2^*, u_3^*, u_4^*)$ such that :

$$J(u^*) = \min_{u \in U_{ad}} J(u) \tag{4}$$

Where U_{ad} is the set of admissible controls defined by:

$$U_{ad} = \{u_{i,t} : 0 \leq U_{min} \leq u_{i,t} \leq U_{max} \leq 1, i = 1,2,...,4, t = 0,1,...,T-1\} \tag{5}$$

The sufficient condition for the existence of optimal controls (u_1, u_2, u_3, u_4) for problem (2) and (3) comes from the following theorem:

Theorem 1. *There exists an optimal control* $(u_1^*, u_2^*, u_3^*, u_4^*)$ *such that:*

$$J(u_1^*, u_2^*, u_3^*, u_4^*) = \min_{(u_1,u_2,u_3,u_4) \in U_{ad}} J(u_1, u_2, u_3, u_4) \tag{6}$$

subject to the control system (2) with initial conditions.

Proof. Since the coefficients of the state equations are bounded and there are finite number of time steps, $S = (S_0, S_1, ..., S_T)$, $L_1 = (L_{1,0}, L_{1,1}, ..., L_{1,T})$, $I = (I_0, I_1, ..., I_T)$, $L_2 =$

$(L_{2,0}, L_{2,1}, ..., L_{2,T})$ and $R = (R_0, R_1, ..., R_T)$ are uniformly bounded for all $(u_1, u_2, u_3, u_4) \in U_{ad}$; thus $J(u_1, u_2, u_3, u_4)$ is bounded, $\inf_{(u_1,u_2,u_3,u_4)\in U_{ad}} J(u_1, u_2, u_3, u_4)$ is finite, and there exists a sequence $(u_1^j, u_2^j, u_3^j, u_4^j) \in U_{ad}$ such that $\lim_{j\to+\infty} J(u_1^j, u_2^j, u_3^j, u_4^j) = \inf_{(u_1,u_2,u_3,u_4)\in U_{ad}} J(u_1, u_2, u_3, u_4)$ and corresponding sequences of states S^j, L_1^j, I^j, L_2^j, and R^j . Since there is a finite number of uniformly bounded sequences, there exist $(u_1^*, u_2^*, u_3^*, u_4^*) \in U_{ad}$ and S^*, L_1^*, I^*, L_2^*, and $R^* \in \mathbb{R}^{T+1}$ such that, on a subsequence, $(u_1^j, u_2^j, u_3^j, u_4^j) \longrightarrow (u_1^*, u_2^*, u_3^*, u_4^*)$,
$S^j \longrightarrow S^*$, $L_1^j \longrightarrow L_1^*$, $I^j \longrightarrow I^*$, $L_2^j \longrightarrow L_2^*$, and $R^j \longrightarrow R^*$. Finally, due to the finite dimensional structure of system (2) and the objective function $J(u_1, u_2, u_3, u_4)$, $(u_1^*, u_2^*, u_3^*, u_4^*)$ is an optimal control with corresponding states S^*, L_1^*, I^*, L_2^*, and R^*. Therefore $\inf_{(u_1,u_2,u_3,u_4)\in U_{ad}} J(u_1, u_2, u_3, u_4)$ is achieved. see [14] □

In order to derive the necessary conditions for optimal control, the Pontryagin's maximum principle, in discrete time, given in [17] was used. This principle converts into a problem of minimizing a Hamiltonian, H_t at time step t defined by:

$$H_t = A_{1,t}S_t + A_{2,t}L_{1,t} + A_{3,t}I_t + A_{4,t}L_{2,t} + \frac{1}{2}B_t u_{1,t}^2 + \frac{1}{2}C_t u_{2,t}^2 + \frac{1}{2}D_t u_{3,t}^2 + \frac{1}{2}E_t u_{4,t}^2 + \sum_{j=1}^{5} \lambda_{j,t+1} f_{j,t+1} \tag{7}$$

where $f_{j,t+1}$ is the right side of the system of difference equations (2) of the j^{th} state variable at time step t+1 .

Theorem 2. *Given an optimal control $(u_1^*, u_2^*, u_3^*, u_4^*) \in U_{ad}$ and the solutions $S_t^*, L_{1,t}^*, I_t^*, L_{2,t}^*$ and R_t^* of the corresponding state system (2), there exists adjoint functions $\lambda_{1,t}$, $\lambda_{2,t}$, $\lambda_{3,t}$, $\lambda_{4,t}$ and $\lambda_{5,t}$ satisfying:*

$$\lambda_{1,t} = A_{1,t} + (1-\mu)\lambda_{1,t+1} + \frac{\beta}{N} I_t(\lambda_{2,t+1} - \lambda_{1,t+1}) + \varepsilon_1 u_{1,t}(\lambda_{5,t+1} - \lambda_{1,t+1})$$

$$\lambda_{2,t} = A_{2,t} + (1-\mu)\lambda_{2,t+1} + (\tau_1 + \varepsilon_2 u_{2,t})(\lambda_{5,t+1} - \lambda_{2,t+1}) + \phi\delta(\lambda_{3,t+1} - \lambda_{4,t+1}) + \delta(\lambda_{4,t+1} - \lambda_{2,t+1})$$

$$\lambda_{3,t} = A_{3,t} + (1-\mu-d)\lambda_{3,t+1} + \frac{\beta}{N} S_t(\lambda_{2,t+1} - \lambda_{1,t+1}) + \sigma\frac{\beta}{N} L_{2,t}(\lambda_{2,t+1} - \lambda_{4,t+1}) + (\tau_0 + \varepsilon_3 u_{3,t})(\lambda_{5,t+1} - \lambda_{3,t+1}) + \sigma_R \frac{\beta}{N} R_t(\lambda_{2,t+1} - \lambda_{5,t+1})$$

$$\lambda_{4,t} = A_{4,t} + (1-\mu)\lambda_{4,t+1} + \sigma\frac{\beta}{N} I_t(\lambda_{2,t+1} - \lambda_{4,t+1}) + \omega(\lambda_{3,t+1} - \lambda_{4,t+1}) + (\tau_2 + \varepsilon_4 u_{4,t})(\lambda_{5,t+1} - \lambda_{4,t+1})$$

$$\lambda_{5,t} = (1-\mu)\lambda_{5,t+1} + \sigma_R \frac{\beta}{N} I_t(\lambda_{2,t+1} - \lambda_{5,t+1}) + \omega_R(\lambda_{3,t+1} - \lambda_{5,t+1})$$

with the following transversality conditions at time T,

$$\lambda_{1,T} = A_{1,T},\ \lambda_{2,T} = A_{2,T},\ \lambda_{3,T} = A_{3,T},\ \lambda_{4,T} = A_{4,T} \text{ and } \lambda_{5,T} = 0 \tag{8}$$

Furthermore, for $t = 0,1,2...,T-1$, the optimal control $u^*_{1,t}, u^*_{2,t}, u^*_{3,t}, u^*_{4,t}$ are given by:

$$\begin{aligned}
u^*_{1,t} &= min\left[U_{max}, max\left(U_{min}, \frac{\varepsilon_1 S_t(\lambda_{1,t+1} - \lambda_{5,t+1})}{B_t}\right)\right],\\
u^*_{2,t} &= min\left[U_{max}, max\left(U_{min}, \frac{\varepsilon_2 L_{1,t}(\lambda_{2,t+1} - \lambda_{5,t+1})}{C_t}\right)\right],\\
u^*_{3,t} &= min\left[U_{max}, max\left(U_{min}, \frac{\varepsilon_3 I_t(\lambda_{3,t+1} - \lambda_{5,t+1})}{D_t}\right)\right],\\
u^*_{4,t} &= min\left[U_{max}, max\left(U_{min}, \frac{\varepsilon_4 L_{2,t}(\lambda_{4,t+1} - \lambda_{5,t+1})}{E_t}\right)\right].
\end{aligned} \tag{9}$$

Proof. The Hamiltonian at time t is given by:

$$\begin{aligned}
H_t &= A_{1,t}S_t + A_{2,t}L_{1,t} + A_{3,t}I_t + A_{4,t}L_{2,t} + \tfrac{1}{2}B_t u^2_{1,t} + \tfrac{1}{2}C_t u^2_{2,t} + \tfrac{1}{2}D_t u^2_{3,t} + \tfrac{1}{2}E_t u^2_{4,t}\\
&+ \lambda_{1,t+1}[S_t + \Lambda - \tfrac{\beta}{N}I_t S_t - \mu S_t - \varepsilon_1 u_{1,t} S_t]\\
&+ \lambda_{2,t+1}[L_{1,t} + \frac{\beta}{N}I_t(S_t + \sigma L_{2,t} + \sigma_R R_t) - (\delta + \tau_1 + \varepsilon_2 u_{2,t} + \mu)L_{1,t}]\\
&+ \lambda_{3,t+1}[I_t + \phi\delta L_{1,t} + \omega L_{2,t} + \omega_R R_t - (\tau_0 + \varepsilon_3 u_{3,t} + \mu + d)I_t]\\
&+ \lambda_{4,t+1}[L_{2,t} + (1-\phi)\delta L_{1,t} - \sigma\frac{\beta}{N}I_t L_{2,t} - (\omega + \tau_2 + \varepsilon_4 u_{4,t} + \mu)L_{2,t}]\\
&+ \lambda_{5,t+1}[R_t + \varepsilon_1 u_{1,t} S_t + (\tau_1 + \varepsilon_2 u_{2,t})L_{1,t} + (\tau_0 + \varepsilon_3 u_{3,t})I_t + (\tau_2 + \varepsilon_4 u_{4,t})L_{2,t}\\
&- (\omega_R + \sigma_R\frac{\beta}{N}I_t + \mu)R_t]
\end{aligned} \tag{10}$$

By the bias of Pontryagin's Maximum Principle, in discrete time, the adjoint equations and corresponding final time conditions (transversality conditions) are given:

$$\begin{cases}
\lambda_{1,t} = \dfrac{\partial H_t}{\partial S_t},\ \lambda_{1,T} = A_{1,T}\\
\lambda_{2,t} = \dfrac{\partial H_t}{\partial L_{1,t}},\ \lambda_{2,T} = A_{2,T}\\
\lambda_{3,t} = \dfrac{\partial H_t}{\partial I_t},\ \lambda_{3,T} = A_{3,T}\\
\lambda_{4,t} = \dfrac{\partial H_t}{\partial L_{2,t}},\ \lambda_{4,T} = A_{4,T}\\
\lambda_{5,t} = \dfrac{\partial H_t}{\partial R_t},\ \lambda_{5,T} = 0
\end{cases}$$

for $t = 0, 1.....,T-1$; the optimal control $u^* = (u^*_{1,t}, u^*_{2,t}, u^*_{3,t}, u^*_{4,t})$ is obtained as well $\frac{\partial H_t}{\partial u_{i,t}} = 0$ *for* $t = 0, 1, ..., T-1$ *and* $i = 1, 2, 3, 4$.

$$
(11) \qquad \begin{cases} \dfrac{\partial H_t}{\partial u_{1,t}} = B_t u_{1,t} - \varepsilon_1 S_t \lambda_{1,t+1} + \varepsilon_1 S_t \lambda_{5,t+1} = 0 \\ \dfrac{\partial H_t}{\partial u_{2,t}} = C_t u_{2,t} - \varepsilon_2 L_{1,t} \lambda_{2,t+1} + \varepsilon_2 L_{1,t} \lambda_{5,t+1} = 0 \\ \dfrac{\partial H_t}{\partial u_{3,t}} = D_t u_{3,t} - \varepsilon_3 I_t \lambda_{3,t+1} + \varepsilon_3 I_t \lambda_{5,t+1} = 0 \\ \dfrac{\partial H_t}{\partial u_{4,t}} = E_t u_{4,t} - \varepsilon_4 L_{2,t} \lambda_{4,t+1} + \varepsilon_4 L_{2,t} \lambda_{5,t+1} = 0 \end{cases}
$$

So, for $\varepsilon_1 = \varepsilon_2 = \varepsilon_3 = \varepsilon_4 = 1$,we have:

$$
(12) \qquad \begin{cases} u_{1,t} &= \dfrac{1}{B_t}(\lambda_{1,t+1} - \lambda_{5,t+1}) S_t \\ u_{2,t} &= \dfrac{1}{C_t}(\lambda_{2,t+1} - \lambda_{5,t+1}) L_{1,t} \\ u_{3,t} &= \dfrac{1}{D_t}(\lambda_{3,t+1} - \lambda_{5,t+1}) I_t \\ u_{4,t} &= \dfrac{1}{E_t}(\lambda_{4,t+1} - \lambda_{5,t+1}) L_{2,t} \end{cases}
$$

□

However, if $\varepsilon_i = 0$ for i=1,2,3,4 the control attached to this case will be eliminated and removed.

By the bounds in U_{ad} of the controls, it is easy to obtain $u^*_{1,t}, u^*_{2,t}, u^*_{3,t}$, and $u^*_{4,t}$ in the forme of (9).□

4. NUMERICAL SIMULATIONS

4.1. Algorithm: In this section, we present the result obtained by solving numerically the optimality system.

This system consists of the state system, adjoint system, initial and final time conditions, and the controls characterization. So, the optimality system is given by the following:

Step 1:

$S(0)=S_0, \quad L_1(0)=L_{1,0}, \quad I(0)=I_0, \quad L_2(0)=L_{2,0}, \quad R(0)=R_0, \quad \lambda_{1,T}=A_{1,T},\ \lambda_{2,T}=A_{2,T},\ \lambda_{3,T}=A_{3,T},\ \lambda_{4,T}=A_{4,T}$ *and* $\lambda_{5,T}=0$, and given $\quad u^*_{1,0}, \quad , u^*_{2,0}, \quad , u^*_{3,0}, \quad$ *and* $\quad u^*_{4,0}$.

Step 2:

for i=0;1;....;T-1,**do**:

(13)

$$
\begin{aligned}
S_{i+1} &= S_i+\Lambda-\tfrac{\beta}{N}I_iS_i-(\mu+\varepsilon_1u_{1,i})S_i,\\
L_{1,i+1} &= L_{1,i}+\tfrac{\beta}{N}I_i(S_i+\sigma L_{2,i}+\sigma_RR_i)-(\delta+\tau_1+\varepsilon_2u_{2,i}+\mu)L_{1,i},\\
I_{i+1} &= I_i+\phi\delta L_{1,i}+\omega L_{2,i}+\omega_RR_i-(\tau_0+\varepsilon_3u_{3,i}+\mu+d)I_i,\\
L_{2,i+1} &= L_{2,i}+(1-\phi)\delta L_{1,i}-\sigma\tfrac{\beta}{N}I_iL_{2,i}-(\omega+\tau_2+\varepsilon_4u_{4,i}+\mu)L_{2,i},\\
R_{i+1} &= R_i+\varepsilon_1u_{1,i}S_i+(\tau_0+\varepsilon_3u_{3,i})I_i+(\tau_1+\varepsilon_2u_{2,i})L_{1,i}+(\tau_2+\varepsilon_4u_{4,i})L_{2,i}\\
&- \left(\sigma_R\tfrac{\beta}{N}I_i+\omega_R+\mu\right)R_i,\\
\lambda_{1,T-i} &= A_{1,i}+(1-\mu)\lambda_{1,T-i+1}+\frac{\beta}{N}I_i(\lambda_{2,T-i+1}-\lambda_{1,T-i+1})\\
&+ \varepsilon_1u_{1,i}(\lambda_{5,T-i+1}-\lambda_{1,T-i+1}),\\
\lambda_{2,T-i} &= A_{2,i}+(1-\mu)\lambda_{2,T-i+1}+(\tau_1+\varepsilon_2u_{2,i})(\lambda_{5,T-i+1}-\lambda_{2,T-i+1})\\
&+ \phi\delta(\lambda_{3,T-i+1}-\lambda_{4,T-i+1})+\delta(\lambda_{4,T-i+1}-\lambda_{2,T-i+1}),\\
\lambda_{3,T-i} &= A_{3,i}+(1-\mu-d)\lambda_{3,T-i+1}+\frac{\beta}{N}S_i(\lambda_{2,T-i+1}-\lambda_{1,T-i+1})\\
&+ (\sigma\frac{\beta}{N}L_{2,i})(\lambda_{2,T-i+1}-\lambda_{4,T-i+1})+(\tau_0+\varepsilon_3u_{3,i})(\lambda_{5,T-i+1}-\lambda_{3,T-i+1})\\
&+ \sigma_R\frac{\beta}{N}R_i\left(\lambda_{2,T-i+1}-\lambda_{5,T-i+1}\right),\\
\lambda_{4,T-i} &= A_{4,i}+(1-\mu)\lambda_{4,T-i+1}+\sigma\frac{\beta}{N}I_i(\lambda_{2,T-i+1}-\lambda_{4,T-i+1})+\omega(\lambda_{3,T-i+1}-\lambda_{4,T-i+1})\\
&+ (\tau_2+\varepsilon_4u_{4,i})(\lambda_{5,T-i+1}-\lambda_{4,T-i+1}),\\
\lambda_{5,T-i} &= (1-\mu)\lambda_{5,T-i+1}+\sigma_R\frac{\beta}{N}I_i(\lambda_{2,T-i+1}-\lambda_{5,T-i+1})+\omega_R(\lambda_{3,T-i+1}-\lambda_{5,T-i+1}),\\
u_{1,i+1} &= min\left[U_{max},max\left(U_{min},\frac{S_i(\lambda_{1,T-i+1}-\lambda_{5,T-i+1})}{B_i}\right)\right],\\
u_{2,i+1} &= min\left[U_{max},max\left(U_{min},\frac{L_{1,i}(\lambda_{2,T-i+1}-\lambda_{5,T-i+1})}{C_i}\right)\right],\\
u_{3,i+1} &= min\left[U_{max},max\left(U_{min},\frac{I_i(\lambda_{3,T-i+1}-\lambda_{5,T-i+1})}{D_i}\right)\right],\\
u_{4,i+1} &= min\left[U_{max},max\left(U_{min},\frac{L_{2,i}(\lambda_{4,T-i+1}-\lambda_{5,T-i+1})}{E_i}\right)\right],
\end{aligned}
$$

end **for**

Step 3:

for i=0;1;....;T **write**:

$$S_i^* = S_i, \quad L_{1,i}^* = L_{1,i}, \quad I_i^* = I_i, \quad L_{2,i}^* = L_{2,i}, \quad R_i^* = R_i, \quad u_{1,i}^* = u_{1,i}, \quad u_{2,i}^* = u_{2,i}, \quad u_{3,i}^* = u_{3,i},$$

$\mathrm{u}_{4,i}^* = u_{4,i}(14)$

end **for**.

4.2. The different control strategies: In the following, four different control strategies are investigated and compared. This approach can be used to test various control options. Here, we only look at how the state variables change under the different strategies.

4.2.1. *The first strategy:* In this strategy, we use only two controls: the BCG vaccination u_1 and the effort on early detection and treatment of recently infected u_2 to optimize the objective function $J(u)$ while the controls u_3 and u_4 are set to zero. In Fig.2, we observe that there is a significant decrease in the number of susceptible individuals vaccinated compared with those not vaccinated, with a slight decrease in the number of early latent individuals and an increase the number of recovered individuals.

4.2.2. *The second strategy:* In this strategy, we use only two controls: the BCG vaccination u_1 and the effort that prevents the failure of treatment in active TB infectious individuals u_3 to optimize the objective function $J(u)$ while the controls u_2 and u_4 are set to zero. In Fig.3, we observe that there is a significant decrease in the number of susceptible individuals vaccinated compared with those not vaccinated, with a slight decrease in the number of infected individuals and an increase the number of recovered individuals.

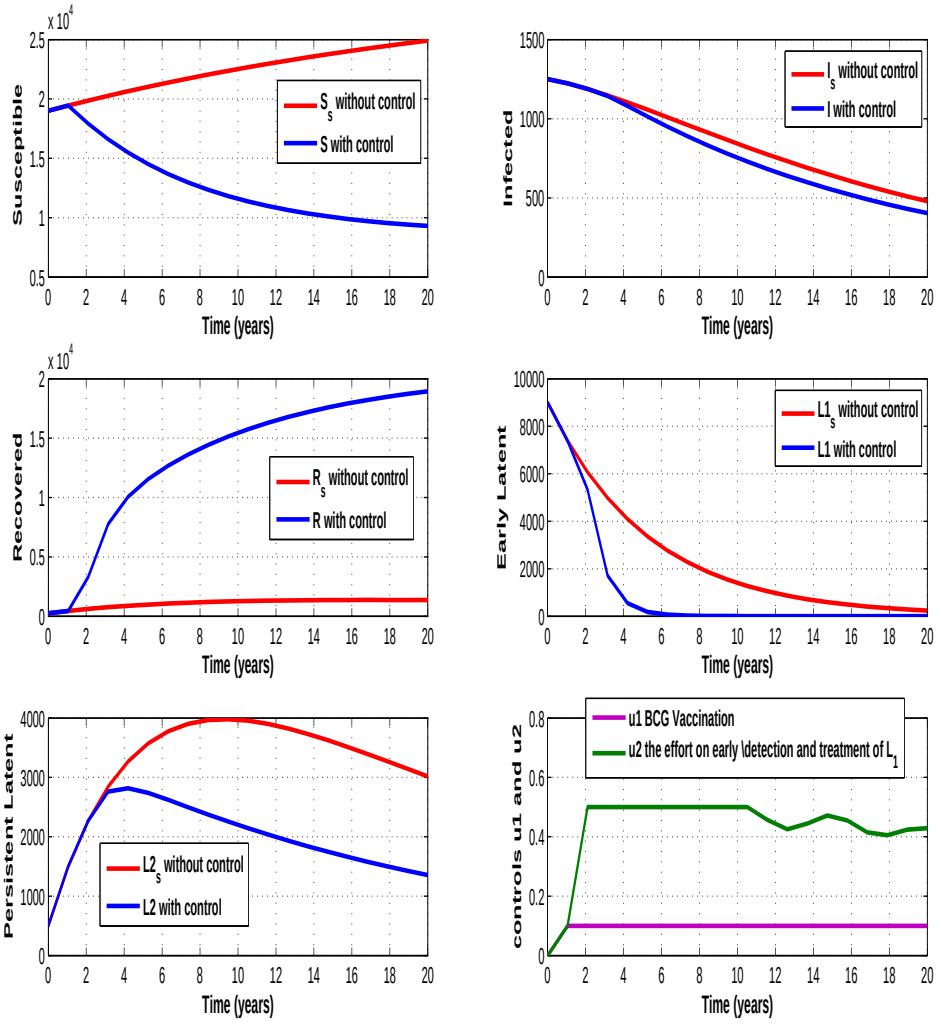

FIGURE 2. Curves without and with controls u_1 *and* u_2

4.2.3. *The third strategy:* In this strategy, another time we use only two controls: the BCG vaccination u_1 and the effort to identifying the persistent latent individuals and put them under treatment u_4 to optimize the objective function $J(u)$ while the controls u_2 and u_4 are set to zero. In Fig. 4, we observe that there is a significant decrease in the number of susceptible individuals vaccinated compared with those not vaccinated, with a slight decrease in the number of persistent latent individuals and an increase the number of recovered individuals.

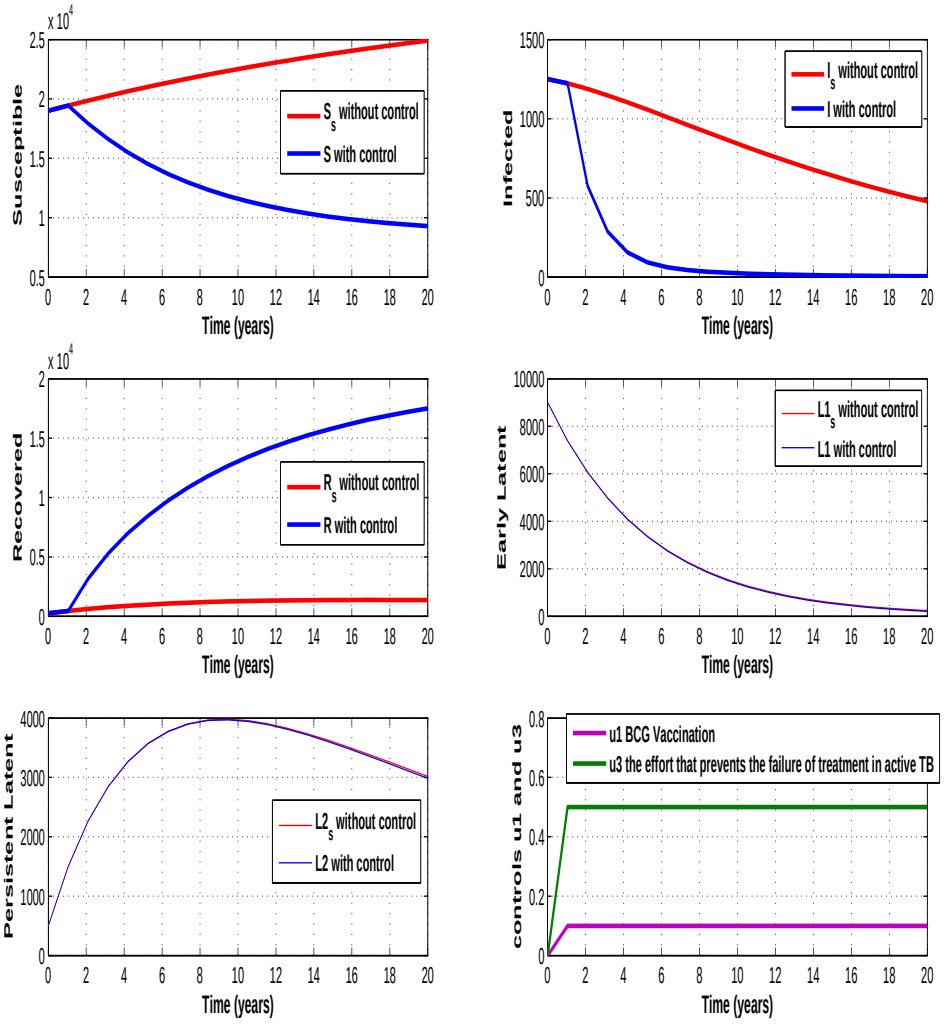

FIGURE 3. curves without and with controls u_1 and u_3

4.2.4. *The fourth strategy:* In this strategy,we will use four controls: the BCG vaccination u_1, the effort on early detection and treatment of recently infected u_2, the effort that prevents the failure of treatment in active TB infectious individuals u_3 and the effort to identified the persistent latent individuals and put them under treatments u_4 to optimize the objective function $J(u)$. In Fig. 5, we observe that there is a significant decrease in the number of susceptible individuals, early latent individuals, infected, and persistent latent individuals, controled compared with those not controled, and an increase the number of recovered individuals.

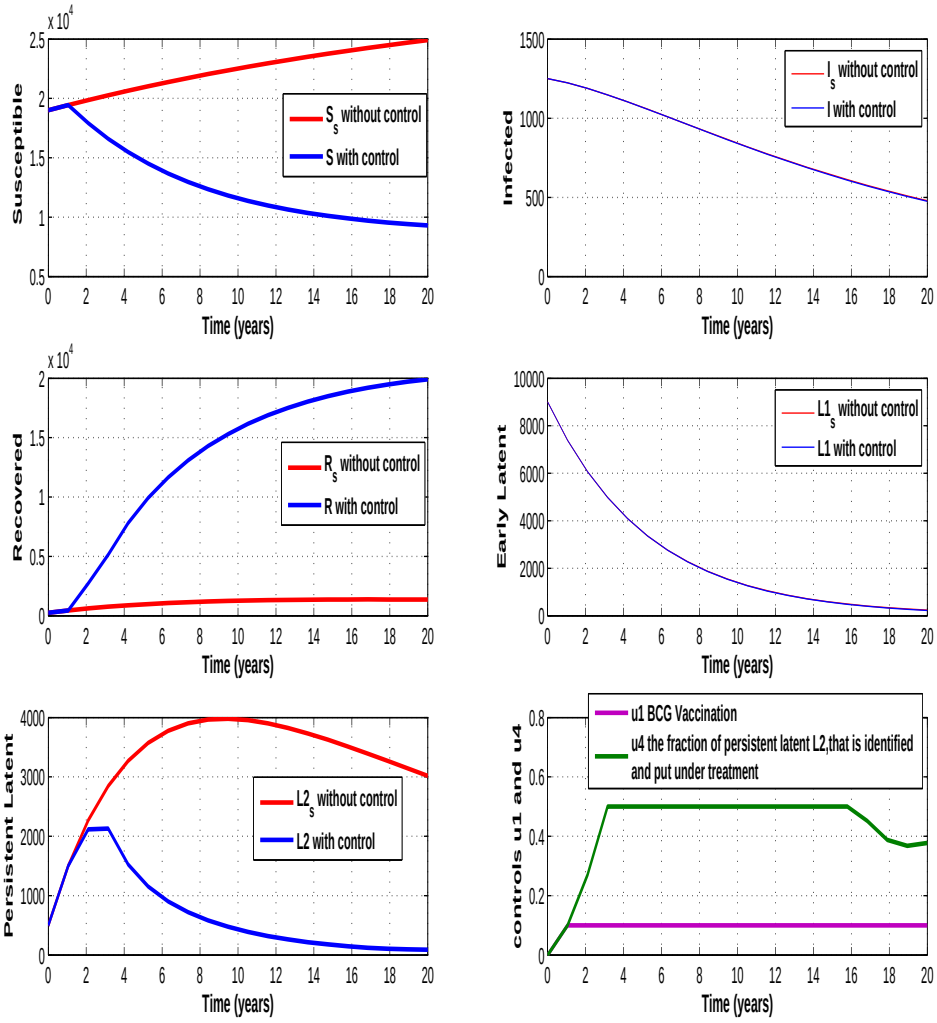

FIGURE 4. without or wih two controls u_1 and u_4

5. CONCLUSION

In this paper, we introduced a discrete modeling of TB tuberculosis in order to minimize the number of susceptible individuals, early latent individuals, infectious individuals, and persistent latent individuals, we also introduced four controls which, respectively, represent BCG vaccination, and the effort on early detection and treatment of recently infected, and the effort that prevents the failure of treatment in active TB infectious individuals, and the effort to identifie the persistent latent individuals and put them under treatment. We applied the results of the control theory and we managed to obtain the characterizations of the optimal controls. The

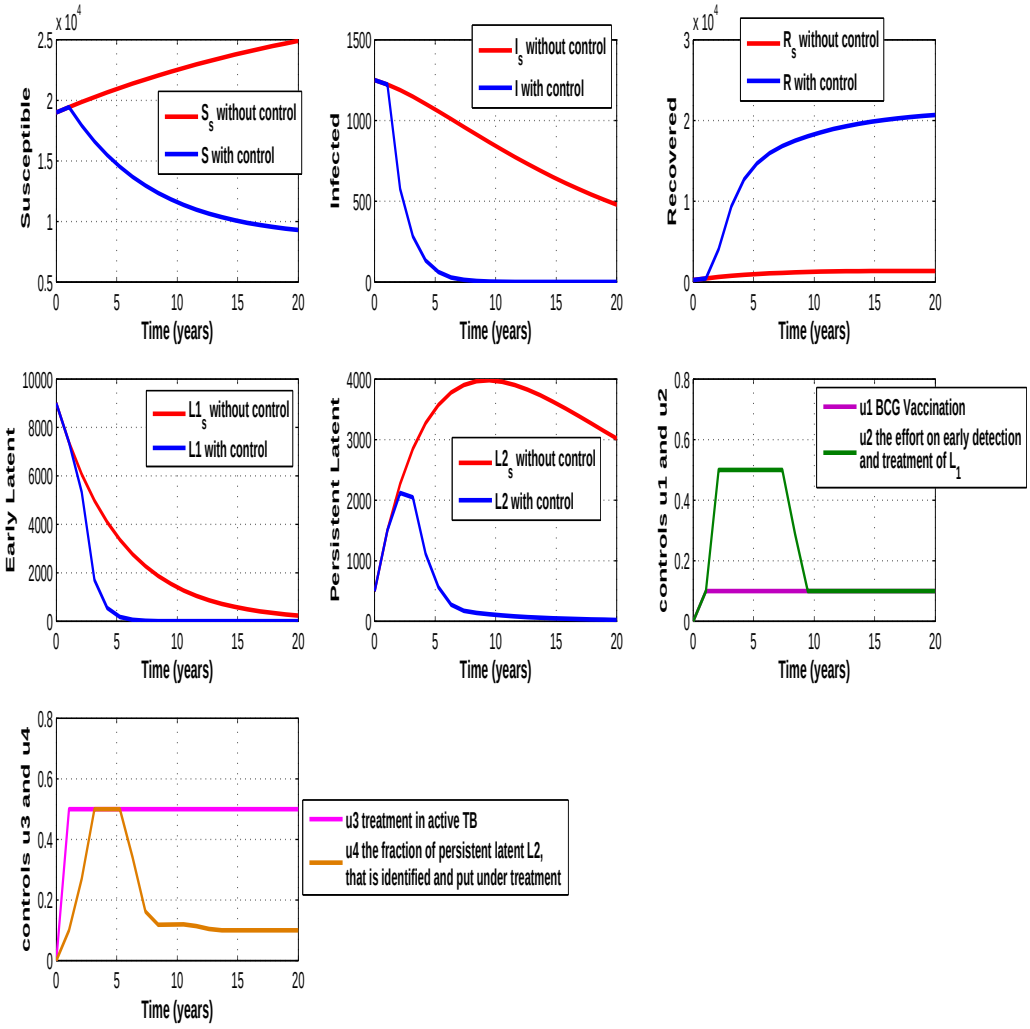

FIGURE 5. without or with four controls

numerical simulation of the obtained results showed the effectiveness of the proposed control strategies.

CONFLICT OF INTERESTS

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

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