Modeling Co-infection of Bovine Brucellosis and Tuberculosis

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Authors’ contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Abstract

Bovine tuberculosis and bovine brucellosis continue to cause serious economic and public health burden in low-income countries, especially in many regions of sub-Saharan Africa where the diseases are co-endemic. The economic burden of the two infections in low-income countries trigger important questions about the optimal intervention strategies in co-endemic regions. Hence, the need for comprehensive modelling studies to address such questions is therefore essential, yet only a limited of such studies exist to date despite the power of models to predict the future and, most importantly, to quantify the uncertainty in these predictions. Here, we develop a brucellosis-tuberculosis co-infection modelling framework that incorporates all relevant biological factors and culling of infectious animals as the sole intervention strategy. We performed an optimal control study to assess the impact of culling infectious animals on controlling the prevalence of the two infections. Two objective functions have been considered, a linear and a quadratic.

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Existence and the characterization of the optimal control has been determined. Numerical results are carried out to illustrate the main findings. Our findings highlight the importance of optimal culling on controlling the spread of two infections.

Keywords: Brucellosis; tuberculosis; co-infection; mathematical model; optimal control strategies.

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1 Introduction

Bovine tuberculosis (BTB) and brucellosis remain important zoonotic bacterial infections in developing countries especially in Sub-Saharan nations [1]. BTB is caused by *Mycobacterium bovis* whereas brucellosis is caused by various species of the bacteria known as *Brucella*. Both diseases affect domesticated animals, wildlife and humans [1]. In animals BTB transmission predominantly occurs through aerosols [2, 3]. In humans, contaminated dairy products are regarded as the main source of BTB infection [3]. In animals, brucellosis is transmitted by direct contact transmission through the brucella carriers or indirect contact transmission when animal ingest contaminated forages or the excrement containing large quantities of bacteria, generally discharged by infected animals [4]. Humans acquire brucellosis infection through close contact with infected animals or animal tissue such as placental membranes [1]. Unlike BTB, human-to-human transmission of brucellosis is considered negligible [4].

In areas where both BTB and brucellosis are endemic, cases of simultaneous colonization of the single host (also know as co-infection) with both infections has been reported [5, 6, 7]. In order to explore on whether co-infection BTB and brucellosis has adverse effects to the host, Gorisch and co-workers [5] monitored 126 buffalo for both tuberculosis and brucellosis infection and they observed that animals co-infected with both infections had the highest mortality rate.

Apart from being public health hazards, both diseases can have enormous economic effects to the farmer, regional and national economies through: (i) decreased animal productivity and market/trade impairments, and, (ii) resources allocation aimed at effective disease control or eradication [1]. For instance, it is estimated that approximately US$ 200 million was spent on BTB eradication program in Michigan state between 1994 and 2010 [2]. In addition, in most developing nations where these two diseases are endemic there is inadequate veterinary services [3].

The immeasurable contribution of mathematical models on providing insights to epidemiologists and policy makers on how to prevent and control epidemics is well documented [8]. Although, there are plenty of mathematical models for brucellosis infection only [4, 9, 10, 11, 12, 13, 14, 15], and tuberculosis infection only [3, 16, 17, 18] not much has been done on modelling tuberculosis and brucellosis co-infection. The purpose of the present paper is to assess the impact of optimal culling on co-dynamics of tuberculosis and brucellosis among animals in a periodic environment. Like many other infectious diseases, tuberculosis and brucellosis are significantly influenced by seasonality [12, 13, 19, 20]. Factors such as the seasonal availability of forage which in turn lead to nomadic animal farming may be attributed to seasonal-induced prevalence of animal infections. Thus, we developed a dynamic co-infection model for tuberculosis and brucellosis with a goal to assess the effectiveness of culling strategy. Two objective functions have been considered, a linear and a quadratic. Existence and the characterization of the optimal control has been determined.

We organize the remainder of this paper as follows. In Section 2, we present the main result of this study. More specifically, we introduce the brucellosis-tuberculosis model and then formulate
the optimal control problems. Further, we present results for the existence and the characterization of the optimal controls. Numerical results are carried out to illustrate the main findings. Finally, Section 3, contains discussion and conclusions.

2 Materials and Methods

2.1 Model framework

The purpose of this section is to formulate a mathematical model for bovine tuberculosis and brucellosis co-infection in a periodic environment, with a goal to investigate the strength of culling infectious animals as a control measure. Although, there are several modes of transmission for the aforementioned diseases we will consider direct transmission only. Let $S(t)$, $I_{11}(t)$, $I_{22}(t)$ and $I_{12}(t)$ denote proportions of the susceptible, animals singly infected with brucellosis, animals singly infected with tuberculosis and dually infected animals, respectively. As in [21], we assume that contact between susceptible and co-infected animals can result on either single or dual infection. The influence of seasonal variations on the dynamics of the two diseases is captured by periodic functions $\beta_{ii}(t)$ $(i = 1, 2,)$ and $\beta_{0i}(t)$ $(i = 1, 2)$. Thus, we assume that $\beta_{ii}(t)$ $(i = 1, 2)$ and $\beta_{0i}(t)$ $(i = 1, 2,)$ are periodic continuous functions in $t$ with a period, $\omega > 0$ (specifically, $\omega = 12$ months). Consequently, animals singly infected with brucellosis are assumed to transmit the infection at rate $\beta_{11}(t)$, while those singly infected with tuberculosis transmit the disease at rate $\beta_{22}(t)$, thus,

$$\beta_{ii}(t) = \bar{\beta}_{ii} \left[ 1 + a_{ii} \sin \left( \frac{2\pi t}{12} \right) \right], \quad i = 1, 2, \quad (2.1)$$

where $\bar{\beta}_{ii}$ denotes the basic contact rate without seasonal forcing and $0 \leq a_{ii} \leq 1$ denotes the magnitude of seasonal fluctuations. Further, co-infected animals are assumed to transmit both infections at rate $\beta_{12}(t)$, given by

$$\beta_{12}(t) = \bar{\beta}_{12} \left[ 1 + a_{12} \sin \left( \frac{2\pi t}{12} \right) \right], \quad (2.2)$$

where $\bar{\beta}_{12}$ denotes the basic contact rate without seasonal forcing and $0 \leq a_{12} \leq 1$ denotes the magnitude of seasonal fluctuations. In addition, co-infected animals can transmit either brucellosis or tuberculosis at rates $\beta_{01}(t)$ and $\beta_{02}(t)$, respectively. Thus,

$$\beta_{0i}(t) = \bar{\beta}_{0i} \left[ 1 + b_{0i} \sin \left( \frac{2\pi t}{12} \right) \right], \quad i = 1, 2, \quad (2.3)$$

where $\bar{\beta}_{0i}$ denotes the basic contact rate without seasonal forcing and $0 \leq b_{0i} \leq 1$ denotes the magnitude of seasonal fluctuations.

Our model is governed by the following system of equations:

$$
\begin{align*}
S'(t) &= \mu - [\beta_{11}(t)I_{11} + \beta_{22}(t)I_{22} + \beta_{01}(t)I_{12} + \beta_{02}(t)I_{12} - \mu]S - \mu S, \\
I'_{11}(t) &= [\beta_{11}(t)I_{11} + \beta_{22}(t)I_{22} + \beta_{01}(t)I_{12} - \mu]S - \mu \mu S, \\
I'_{22}(t) &= [\beta_{12}(t)I_{12} + \beta_{02}(t)I_{12}]S - [\beta_{11}(t)I_{12} + \beta_{01}(t)I_{12}]I_{11} - \mu c(u(t) + d_{12})I_{11}, \\
I'_{12}(t) &= [\beta_{12}(t)I_{12} + \beta_{02}(t)I_{12}]S - [\beta_{11}(t)I_{12} + \beta_{01}(t)I_{12}]I_{11} - \mu c(u(t) + d_{12})I_{11}.
\end{align*}
$$

(2.4)

The constant parameter $\mu$ denotes the constant rate of entry for new animals into the susceptible class. We assume that it also equals the non-disease related death rate and is assumed to be the same for all classes; $c$ is the culling rate; $d_{11}$ denotes brucellosis related mortality rate; $d_{22}$ denotes tuberculosis related mortality rate; $d_{12}$ is the disease related mortality rate for dual infected animals. The effects of the optimal strategy are captured by the control function $u(t)$ which will be assigned reasonable upper and lower bounds.
As highlighted earlier, our goal is to determine a control strategy (culling effort) that minimizes the proportions of all infected animals over a finite time interval $[0, T]$ at minimal costs. In what follows we introduce two possible objective functions $J_1$ and $J_2$ formulated to achieve the desired goal. In the objective functional $J_1$ the control effort is assumed to be linear while in $J_2$ the control effort is a combination of linear and quadratic functions.

### 2.2 Linear dependence on the control

In this section, we develop an optimal control problem, to investigate the effects of optimal culling on controlling the spread of the two aforementioned diseases. We assumed a linear dependence on the control, thus we have ruled out the potential of non-linearities in the costs. A successful control strategy is one that reduces the population of infectious animals and maximize the susceptible population while minimizing the cost of control. Our objective functional is therefore formulated as follows:

$$J_1(u(t)) = \int_0^T \left[ C_1 I_{11}(t) + C_2 I_{22}(t) + C_3 I_{12} - C_4 S(t) + C_5 u(t) \right] dt,$$

subject to the constraints of the Ordinary differential equations (ODEs) in system (2.4) and where $C_j$, $j = 1, 2, 3, 4, 5$, are balancing coefficients (positive) transforming the integral into monetary quantity over a finite period of $T$ days. The control set is given by

$$\Gamma = \left\{ u(t) \mid u(t) \text{ is Lebesgue measurable on } [0, T], \ 0 \leq U_1 \leq u(t) \leq U_2 \leq 1 \right\}.$$

where $U_1$ and $U_2$ denote the lower and upper bounds of the control. In what follows, we derive the necessary conditions for our optimal control and corresponding states by using Pontryagin’s Principle in [22, 23, 24]. We consider the following Hamiltonian $H_L$:

$$H_L = C_1 I_{11}(t) + C_2 I_{22}(t) + C_3 I_{12} - C_4 S(t) + C_5 u(t) + \lambda_1(t) \left( \mu - \beta_{11} I_{11} + \beta_{01} I_{12} + \beta_{202} I_{22} + \beta_{02} I_{12} + \beta_{12} I_{12} S - \mu S \right), + \lambda_2(t) \left( \beta_{11} I_{11} + \beta_{01} I_{12} S - \beta_{202} I_{22} + \beta_{02} I_{12} I_{11} - \mu + cu(t) + d_{11} I_{11} \right), + \lambda_3(t) \left( \beta_{22} I_{22} + \beta_{02} I_{12} S - \beta_{11} I_{11} + \beta_{01} I_{12} I_{22} - \mu + cu(t) + d_{22} I_{22} \right), + \lambda_4(t) \left( \beta_{12} I_{11} S + \beta_{22} I_{22} + \beta_{02} I_{12} I_{11} + \beta_{11} I_{11} + \beta_{01} I_{12} I_{22} - \mu + cu(t) + d_{12} I_{12} \right).$$

Given an optimal control $u^*(t)$, there exists adjoint functions, $\lambda_i(t)$, for $i = 1, 2, 3, 4$, corresponding to the states $S$, $I_{11}$, $I_{22}$, and $I_{12}$ respectively satisfying

$$\frac{d\lambda_1}{dt} = C_4 + \mu \lambda_1 + \left( \beta_{11} I_{11} + \beta_{01} I_{12} \right) \left( \lambda_1 - \lambda_2 \right) + \left( \beta_{22} I_{22} + \beta_{02} I_{12} \right) \left( \lambda_1 - \lambda_3 \right) + \beta_{12} I_{12} \left( \lambda_1 - \lambda_4 \right),$$

$$\frac{d\lambda_2}{dt} = -C_2 + \beta_{11} S \left( \lambda_1 - \lambda_2 \right) + \left( \beta_{22} I_{22} + \beta_{02} I_{12} \right) \left( \lambda_2 - \lambda_4 \right) + \left( \mu + cu(t) + d_{11} \right) \lambda_2 + \beta_{11} I_{22} \left( \lambda_3 - \lambda_4 \right),$$

$$\frac{d\lambda_3}{dt} = -C_2 + \beta_{22} S \left( \lambda_1 - \lambda_3 \right) + \left( \beta_{11} I_{11} + \beta_{01} I_{12} \right) \left( \lambda_3 - \lambda_4 \right) + \left( \mu + cu(t) + d_{22} \right) \lambda_3 + \beta_{22} I_{11} \left( \lambda_2 - \lambda_4 \right),$$

$$\frac{d\lambda_4}{dt} = -C_3 + \beta_{01} S \left( \lambda_1 - \lambda_2 \right) + \beta_{02} S \left( \lambda_1 - \lambda_3 \right) + \beta_{12} S \left( \lambda_1 - \lambda_4 \right) + \beta_{02} I_{11} \left( \lambda_2 - \lambda_4 \right) + \left( \mu + cu(t) + d_{12} \right) \lambda_4 + \beta_{01} I_{22} \left( \lambda_3 - \lambda_4 \right).$$

where $\lambda_i(T) = 0$ for $i = 1, 2, 3, 4$, are transversality conditions. Furthermore, the optimal controls are characterized by the optimality conditions:
The singular case could occur if the slope or the switching function
\[
\frac{\partial H_L}{\partial u} = C_5 - c[\lambda_2(t)I_{11}(t) + \lambda_3(t)I_{22}(t) + \lambda_4(t)I_{12}(t)],
\]
(2.9)
is zero on non-trivial interval of time, and the optimal would be at its upper bound or its lower bound according to:
\[
\frac{\partial H_L}{\partial u} < \text{ or } > 0
\]
To investigate the singular case, let us claim \(\frac{\partial H_L}{\partial u} = 0\) on some non-trivial interval. In this case we calculate
\[
0 = \frac{d}{dt}\left(\frac{\partial H_L}{\partial u}\right) = \Phi_1(t)u(t) + \Phi_2(t)
\]
(2.11)
with
\[
\Phi_1(t) = -c\left[C_1I_{11} + C_2I_{22} + C_3I_{12}\right] + c^2\left[\beta_{11}\lambda_1\right]S_{11} + c^2\left[\beta_{22}\lambda_1\right]S_{22}
\]
\[
+ c^2\left[\beta_{11}\lambda_1\right]SI_{12} + c^2\left[\beta_{11}(\lambda_3 - \lambda_4)\right]I_{11}I_{22} + c^2\left[\beta_{22}(\lambda_2 - \lambda_4)\right]I_{22}I_{12},
\]
and,
\[
\Phi_2(t) = -c\left[C_1(\mu + d_{11})I_{11} + C_2(\mu + d_{22})I_{22} + C_3(\mu + d_{12})I_{12}\right] - c\mu\lambda_1\left[\beta_{11}I_{11} + \beta_{22}I_{22} + (\beta_{11} + \beta_{22} + \beta_{12})I_{12}\right] + c\left[\beta_{11}(C_1 - C_4)\right]S_{11}
\]
\[
+ c\left[\beta_{11}\lambda_1\right]SI_{11} + c\beta_{11}\lambda_2\left[\beta_{11}I_{11} + \beta_{22}I_{22}\right]SI_{11}
\]
\[
+ c\beta_{11}\lambda_1\left[\beta_{22}I_{22} + \beta_{12}I_{12}\right]SI_{11} + c\beta_{22}\lambda_1\left[\beta_{22}I_{22} + \beta_{12}I_{12}\right]SI_{11}
\]
\[
+ c\beta_{11}\lambda_1\left[\beta_{22}I_{22} + \beta_{12}I_{12}\right]SI_{11} + c\beta_{11}\lambda_1\left[\beta_{22}I_{22} + \beta_{12}I_{12}\right]SI_{11}
\]
\[
+ c\beta_{11}\lambda_4\lambda_3\beta_{11}I_{11} + c\left[\beta_{22}(C_2 - C_4)\right]SI_{22} + c\left[\beta_{22}\lambda_1(\mu + d_{22})\right]SI_{22}
\]
\[
+ c\beta_{11}\lambda_3\lambda_4\beta_{11}I_{11} + c\left[\beta_{22}(C_2 - C_4)\right]SI_{22} + c\left[\beta_{22}\lambda_1(\mu + d_{22})\right]SI_{22}
\]
\[
+ c\beta_{11}\lambda_4\left[\beta_{22}I_{22} + \beta_{12}I_{12}\right]SI_{22} + c\beta_{22}\lambda_1\left[\beta_{22}I_{22} + \beta_{12}I_{12}\right]SI_{22}
\]
\[
+ c\beta_{11}\lambda_4\left[\beta_{22}I_{22} + \beta_{12}I_{12}\right]SI_{22} + c\left[\beta_{22}(C_2 - C_4)\right]SI_{22} + c\left[\beta_{22}\lambda_1(\mu + d_{22})\right]SI_{22}
\]
\[
- c\beta_{11}\lambda_3\left[\beta_{11}I_{11} + \beta_{22}I_{22}\right]SI_{22} + c\beta_{11}\lambda_3\left[\beta_{22}I_{22} + \beta_{12}I_{12}\right]SI_{22} + c\left[\beta_{11}(C_1 - C_4)\right]SI_{12}
\]
Then we can solve for the singular control as

\[ u_{\text{singular}}(t) = -\frac{\Phi(t)}{\Phi'(t)}, \quad \text{if } \Phi_1(t) \neq 0 \text{ and } U_1 \leq \Phi_1(t) \leq U_2. \]

By Legendre-Clebsch condition in [25], for singular control to be optimal, we require

\[ \frac{d}{dt} \left( \frac{\partial H}{\partial u} \right) = \Phi_1(t) \]

to be negative. We can summarize, our control characterization is: On a nontrivial interval,

\[ \frac{\partial H}{\partial u} < 0 \quad \text{at } t \quad \text{then } u^*(t) = U_2 \]
if \( \frac{\partial H_L}{\partial u} > 0 \) at \( t \) then \( u^*(t) = U_1 \)

if \( \frac{\partial H_L}{\partial u} < 0 \) at \( t \) then \( u_{\text{singular}}(t) = -\frac{\Phi_2}{\Phi_1} \)

Thus, our control is optimal at \( t \) provided \( \Phi_1(t) < 0 \) and \( U_1 \le -\frac{\Phi_2(t)}{\Phi_1(t)} \le U_2 \).

### 2.3 Quadratic and linear dependence on the control

In this section, we propose a new objective functional that has a quadratic dependence on the control. The quadratic functions account for the potential non-linearities in the costs. Our objective functional is:

\[
J_2(u(t)) = \int_0^T \left[ I_{11}(t) + I_{22}(t) + I_{12}(t) + Au(t)\{I_{11}(t) + I_{22}(t) + I_{12}(t)\} + Bu^2(t) \right] dt \quad (2.12)
\]

subject to the constraints of the ordinary differential equations in system (2.4) and where \( A \) and \( B \) are balancing coefficients (positive) transferring the integrals into monetary quantity over a finite period of \( T \) days. The terms with coefficient \( A \) represent the cost associated with culling of infectious animals. Our objective functional (2.12) also include a quadratic term with coefficient \( B \) to indicate potential non-linearities in the costs. The weights, constant over the prescribed time frame, are a measure of the relative costs of the interventions over a finite time horizon. The optimal control problem hence becomes that we seek optimal function, \((u^*(t))\), such that

\[
J_2(u^*(t)) = \min_{u} J_2(u(t)) \quad (2.13)
\]

subject to the state equations in system (2.4) with initial conditions, with the control set 2.6.

By applying the Pontryagin’s Maximum Principle [22], system (2.4) is converted into an equivalent problem, namely the problem of minimizing the Hamiltonian \( H_Q \) given by:

\[
H_Q = I_{11}(t) + I_{22}(t) + I_{12}(t) + Au(t)\{I_{11}(t) + I_{22}(t) + I_{12}(t)\} + Bu^2(t) \\
\hat{\lambda}_1(t)\left\{ \mu - [\beta_{11}(t)I_{11} + \beta_{01}(t)I_{12} + \beta_{22}(t)I_{22} + \beta_{02}(t)I_{22}]I_{12} - \beta_{12}(t)I_{12}S - \mu S \right\}, \\
\hat{\lambda}_2(t)\left\{ [\beta_{22}(t)I_{22} + \beta_{02}(t)I_{22}]S - [\beta_{22}(t)I_{22} + \beta_{02}(t)I_{12}]I_{11} - [\mu + cu(t)] + d_{11}I_{11} \right\}, \\
\hat{\lambda}_3(t)\left\{ [\beta_{22}(t)I_{22} + \beta_{02}(t)I_{12}]I_{11} + [\beta_{22}(t)I_{22} + \beta_{02}(t)I_{22}]I_{12} - [\mu + cu(t)] + d_{22}I_{22} \right\}, \\
\hat{\lambda}_4(t)\left\{ \beta_1(t)I_{11}S + [\beta_{22}(t)I_{22} + \beta_{02}(t)I_{12}]I_{11} + [\beta_{22}(t)I_{22} + \beta_{02}(t)I_{22}]I_{12} - [\mu + cu(t)] + d_{22}I_{22} \right\},
\]

where \( \hat{\lambda}_i(t) \), \( (i = 1, 2, 3, 4) \) denote the adjoint functions associated with the states \( S, I_{11}, I_{22}, \) and \( I_{12}, \) respectively. Note that, in \( H_Q(t) \), each adjoint function multiplies the right-hand side of the differential equation of its corresponding state function. The first term in \( H_Q(t) \) comes from the integrand of the objective functional.

Given an optimal control solution \((u^*)\) and corresponding states \((S, I_{11}, I_{22}, I_{12})\), there exist adjoint functions [24] satisfying

\[
\frac{d\hat{\lambda}_1(t)}{dt} = -\frac{\partial H_Q}{\partial S}, \quad \frac{d\hat{\lambda}_2(t)}{dt} = -\frac{\partial H_Q}{\partial I_{11}}, \quad \frac{d\hat{\lambda}_3(t)}{dt} = -\frac{\partial H_Q}{\partial I_{22}}, \quad \frac{d\hat{\lambda}_4(t)}{dt} = -\frac{\partial H_Q}{\partial I_{12}}. \quad (2.15)
\]

These yield

\[
\frac{d\hat{\lambda}_1}{dt} = \mu \hat{\lambda}_1 + \left( \beta_{11}I_{11} + \beta_{01}I_{12} \right) \left( \hat{\lambda}_1 - \hat{\lambda}_2 \right) + \left( \beta_{22}I_{22} + \beta_{02}I_{22} \right) \left( \hat{\lambda}_1 - \hat{\lambda}_3 \right) + \beta_{12}I_{12} \left( \hat{\lambda}_1 - \hat{\lambda}_4 \right).
\]
Baseline values for model parameters are in Table 1. For results in Figs. 1-3, we set the amplitude of oscillations decreases with time. The amplitude of the oscillation remains almost constant while in the presence of optimal control the infectious population oscillates for the entire time horizon. However, without optimal control to a level close to 0 when $t > t_0$ is evident that the optimal control strategy can significantly reduce the infectious animal population.

We solved the optimality system numerically using the forward-backward sweep method. The optimality system is the state and adjoint systems coupled with the optimal control characterized by the optimality conditions:

$$
\frac{d\lambda_2}{dt} = -1 - A_u(t) + \beta_{11}S(\lambda_1 - \lambda_2) + (\beta_{22}I_{22} + \beta_{32}I_{12})(\lambda_2 - \lambda_4) + (\mu + cu(t) + d_{11})\lambda_2 + \beta_{11}I_{22}(\lambda_3 - \lambda_4),
$$

$$
\frac{d\lambda_3}{dt} = -1 - A_u(t) + \beta_{22}S(\lambda_1 - \lambda_3) + (\beta_{11}I_{11} + \beta_{30}I_{12})(\lambda_3 - \lambda_4) + (\mu + cu(t) + d_{22})\lambda_3 + \beta_{22}I_{11}(\lambda_2 - \lambda_4),
$$

$$
\frac{d\lambda_4}{dt} = -1 - A_u(t) + \beta_{30}S(\lambda_1 - \lambda_3) + \beta_{32}S(\lambda_3 - \lambda_4) + \beta_{32}I_{11}(\lambda_2 - \lambda_4) + (\mu + cu(t) + d_{12})\lambda_4 + \beta_{30}I_{22}(\lambda_3 - \lambda_4),
$$

with transversality conditions $\lambda_j(T) = 0$ for $j = 1, 2, 3, 4$. Furthermore, the optimal controls are characterized by the optimality conditions:

$$
u^* = \min\{U_2, \max\left(U_1, \frac{c(\lambda_2I_{11} + \lambda_4I_{22} + \lambda_4I_{12}) - A(I_{11} + I_{22} + I_{12})}{2B}\right)\}. \quad (2.17)
$$

### 2.4 Numerical illustrations

The optimality system is the state and adjoint systems coupled with the optimal control characterization. We solved the optimality system numerically using the forward-backward sweep method [24]. Baseline values for model parameters are in Table 1. For results in Figs. 1-3, we set $A = B = C_j = 1$, for $j = 1, 2, 3, 4$, and $C_5 = 10^3$. In addition, we assumed the following initial conditions $S = 0.96$, $I_{11} = I_{22} = 0.02$ and $I_{12} = 0$.

#### Table 1. Model parameters and their baseline values

| Symbol       | Description                                           | Value | Units | Source |
|--------------|-------------------------------------------------------|-------|-------|--------|
| $a_{11}, a_{02}$ | Amplitude of oscillation in transmission rates        | 0.8   | -     | [13]   |
| $a_{11}, a_{12}, a_{22}$ | Amplitude of oscillation in transmission rates        | 0.8   | -     | [13]   |
| $d_{11}$     | Elimination rate caused by brucellosis                 | 0.15  | year$^{-1}$ | [9]     |
| $d_{22}$     | Elimination rate caused by tuberculosis                | 0.2   | year$^{-1}$ | [17]   |
| $d_{12}$     | Elimination rate caused by dual infection              | 0.35  | year$^{-1}$ | [5]     |
| $\beta_{11}, \beta_{01}$ | Averaged brucellosis transmission rate            | 0.29  | animal$^{-1}$year$^{-1}$ | [14]   |
| $\beta_{22}, \beta_{02}$ | Averaged tuberculosis transmission rate            | 0.45  | animal$^{-1}$year$^{-1}$ | [17]   |
| $\beta_{12}$ | Averaged dual transmission rate                        | 0.65  | animal$^{-1}$year$^{-1}$ | Assumed |
| $c$          | The slaughter rate of infected animals                 | 0.0983 | year$^{-1}$ | [15]   |
| $\mu$        | Natural elimination rate                               | 0.22  | year$^{-1}$ | [9]     |

Fig. 1 depicts the proportions of infectious animals over time, with and without optimal control. It is evident that the optimal control strategy can significantly reduce the infectious animal population to a level close to 0 when $t > 30$ years. Also, we can observe, with and without optimal control the infectious population oscillates for the entire time horizon. However, without optimal control the amplitude of the oscillation remains almost constant while in the presence of optimal control the amplitude of oscillations decreases with time.
Fig. 1. Disease dynamics among infected population with and without optimal control (a) animals singly infected with brucellosis $I_1(t)$, (b) animals singly infected with tuberculosis $I_2(t)$ and (c) dual infected animals $I_{12}(t)$

Fig. 2 shows the dynamics of the susceptible population over time with and without the optimal control. We observe that without the optimal control the susceptible population oscillates from the start with the amplitude decreasing with time for $0 \leq t \leq 10$, followed by a steady periodic oscillation with a maximum and minimum of close to 0.93 and 0.80, respectively. In contrast, with the optimal control implemented (both linear and quadratic), the susceptible population increases with a decreasing amplitude over time, eventually approaching a value close to 1.

Fig. 3 illustrates the optimal control profiles for system (2.4). As we can observe, the control profile associated with the linear objective functional starts from the maximum initially and stays there for about 32 years, followed by a decrease to the lower bound $u = 0$, where it stays till the final time horizon. In contrast, the control profile associated with the quadratic objective functional starts at its maximum and stays there for a slightly longer period (approximately 35 years) compared to the other control profile and there after it oscillates twice before settling at the lower bound $u = 0$. 
In Fig. 4 we explore the impact of costs on the controls, thus, we set $A = B = C_2 = 10^3$. Here we note that, the control profile associated with the linear objective functional stays at the maximum for a longer period compared to the other control profile. In addition, we note that the control profile for the linear objective functional switches between its maximum and minimum for $40 < t < 60$. This demonstrates that the optimal control strategy is dynamic and depends on cost parameters.

Fig. 2. Dynamics of the susceptible population with and without optimal control

Fig. 3. Control profiles
3 Discussion and Conclusions

We developed a mathematical model of brucellosis-tuberculosis infection, to investigate the impact of optimal intervention strategies on shaping the long-term dynamics of the two zoonotic diseases in the community. Although, these diseases affect humans our study focused on animal population only. Thus, we subdivided the animal population into categories of: susceptible, infectious animals singly infected with brucellosis, infectious animals singly infected with tuberculosis and dually infected animals. We performed an optimal control study to assess the impact of culling infectious animals on controlling the prevalence of two infections. Our control aims to minimize the proportions of infected animals as well as the cost associated to the implementation of the control strategy. We proposed two objective functions (i) control effort was assumed to be linear and (ii) control effort was assumed to be quadratic. We determined the existence and the characterization of the optimal control. Our results demonstrate that, in all the scenarios, the optimal control can significantly reduce the population of infected animals (both singly and dual), and keep them at low levels, a better outcome compared to the scenario when there is no optimal control. Further, we observed that the optimal control strategy is dynamic and it strongly depends on the cost parameters. With low costs, both control profiles for the two objective functions stay at the maximum for a longer period compared to the scenario when the costs are high. This demonstrates that with low costs the control strategy can be carried out at its maximum for a sufficiently long period of time despite on whether the implementation suits the linear or quadratic objective functional. In addition, we noted that for small cost parameters, the control profile associated with a linear objective function exhibits to a bang-bang solution, however, with high cost parameters the control does not exhibit this behavior.

Although, our study is not exhaustive, it has demonstrated the importance of optimal control theory as a tool to predict and to quantify the uncertainty in disease dynamics. The study can be extend to include aspects such as animal movement and the transmission of the two diseases to human.

Finally, we acknowledge that modeling the transmission and spread of infectious diseases, particularly bovine brucellosis and tuberculosis co-infection, would be of greater importance to public health and agriculture with the aid of realistic infection data. Unfortunately, the scarcity of seasonal brucellosis
and tuberculosis co-infection data at present limits our ability to calibrate some important seasonally varied parameters in our periodic model. We expect to improve this study in our future work with the availability of such data.

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**Competing Interests**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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