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Optimal Control Strategy on Mathematical Model for the Dynamics of Mastitis

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Abstract: In this study, a nonlinear mathematical model for the transmission dynamics of mastitis diseases is formulated and analyzed. The local and global stability analysis of mastitis-free equilibrium and endemic equilibrium is obtained using the stability theory of differential equation. It was established that the mastitis-free equilibrium is locally stable if the basic reproduction number is less than unity. The endemic equilibrium, which exists only when the basic reproduction number is greater than unity, is globally asymptotically stable. Sensitivity analysis of the reproduction number suggested that the concentration of bacteria in the environment has a high impact on the dynamics of mastitis. Furthermore, an optimal control problem is formulated by applying Pontryagin's minimum principle with three control strategies, namely, prevention strategy, screening strategy, and treatment strategy. Therefore, based on optimal control problem simulation results and analysis of cost-effectiveness prevention strategy is the most effective and least costly to eradicate the transmission of mastitis from the cattle.

Keywords: Mastitis; Stability; Model; Optimal control; Simulation.

1 Introduction

Infectious diseases caused by bacteria, viruses and parasites easily affect humans and animals. Mastitis is a disease caused by bacteria staphylococcus and streptococcus that affects mammal glands of the animal [1]. The mastitis arises from poor environmental sanitation and the location of the cow is the main facilitator of herd infection [2]. In addition, it is often transmitted through environments contaminated with staphylococcus and streptococcus bacteria from infected cattle. Mastitis symptoms may be clinical or subclinical. Clinical mastitis is characterized by visible symptoms such as rupture or leakage in the milk, swelling and gut discoloration of the breast, as well as abnormal discharge. Also Mastitis with no obvious symptoms and known to cause breast cancer is called subclinical Mastitis [3]. The standard method of detecting SCM is to measure the Somatic Cell Count (SCC). Currently, the SCC threshold of 100,000 cells/ml in first-quarter milk is accepted internationally, but an SCC greater than 50,000 cells/ml in composite milk is considered to indicate SCM [4]. Ethiopia has an estimated 57.83 million cattle. This makes it the most cattle-rich country in Africa. Mastitis accounts for 78% of total milk production losses in Ethiopia. In addition to reproductive diseases, approximately USD/cow/ approximately 140 to 200 USD per year is the main reason for the economic decline in Ethiopia. Mastitis causes an economic loss of 58 and 78.65 USD per cow and 78.65 USD per calf respectively in the urban and suburban areas of Addis Ababa [5].
Mathematical modeling plays an important role in analyzing the understanding and control of infectious diseases. It also helps us to predict inexpensive ways to control disease. Understanding this, many researchers have conducted various studies at different times. Among them [[6], [7],[8],[9],[10],[11],] are researchers who have tried to develop mathematical modeling of mastitis using

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by different aspects.
All of the above studies consider the context of different countries and reveal the dynamics of mastitis with important consequences. But no mathematical model has been developed on Mastitis investigate using optimal control strategies. In our study, we developed a deterministic mathematical model of mastitis with optimal control strategies and also the cost-effectiveness of the implemented control strategies was investigated.

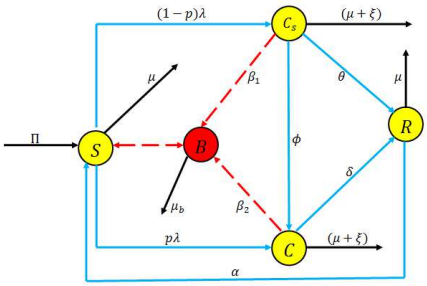


Fig. 1: Schematic Diagram of Mastitis Model

2 Model Assumption and Formulation

The model assumes cattle populations as well as bacteria population (B). The cattle populations divided into four classes with respect to their mastitis status. The notations and description of this classes are as follows; Susceptible class (S); this class contains those cattles who are at a risk of infected by mastitis disease. Subclinical class (C_s); are infectious cattles that is active but does not produce noticeable symptoms of mastitis. Clinical class (C); this class contains all cattles who are showing the symptom of the mastitis. Recovered class (R); this class contains all cattles that have recovered from the mastitis and got temporary immunity.
Susceptible cattle increased by recruited rate Π and also from recovered cattles by losing temporary immunity with α rate. Susceptible cattles acquired mastitis through contaminated environment by staphylococcus and streptococcus bacteria. The force of infection of the model is $\lambda = \frac{B\gamma}{K+B}$, where γ is ingestion rate, K is the concentration of staphylococcus and streptococcus bacteria in environment and $\frac{B\gamma}{K+B}$ is the probability of cattles contaminated with mastitis. Susceptible cattles progress to the clinical infectious class with probability p and to the subclinical infectious class with probability $(1-p)$. The subclinical cattles can develop mastitis symptom and join the clinical class with a rate ϕ and others join the recovered class at rate θ. Cattles in clinical class can get treatment and join the recovered class with rate δ. In all infectious cattles ξ is the disease induced mortality rate and μ is the natural death rate of individuals. The model assumed that the bacteria population in contaminated environment, where subclinical and clinical can contribute to increasing the number of bacteria population in environment without proper sanitation with a discharge rate of β_1 and β_2 respectively. We also considered μ_b to be the death rate of bacterial and all parameters in the model are positive. This assumption can be described below in Figure 1.

Based on the model assumptions and the schematic diagram, the mastitis model equations are formulated as follows;

$$\begin{aligned}
\frac{dS}{dt} &= \Pi + \alpha R - (\lambda+\mu)S,\\
\frac{dC_s}{dt} &= (1-p)\lambda S - (\theta+\phi+\beta_1+\mu+\xi)C_s,\\
\frac{dC}{dt} &= p\lambda S + \phi C_s - (\delta+\beta_2+\mu+\xi)C,\\
\frac{dR}{dt} &= \theta C_s + \delta C - (\alpha+\mu)R,\\
\frac{dB}{dt} &= \beta_1 C_s + \beta_2 C - \mu_b B,
\end{aligned} \tag{1}$$

where $\lambda = \frac{B\gamma}{K+B}$ with initial condition $S(0) = S_0, C_{s0} = C_{s0}, C(0) = C_0, R(0) = R_0$ and $B(0) = B_0$.

3 Analysis of Mastitis Model

3.1 Invariant Region

We obtained a region in which the solutions of model equation (1) is bounded. To obtain this, first we consider the total cattle population N, where $N = S + C_s + C + R$. Then, differentiating N both sides with respect to t, we get,

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dC_s}{dt} + \frac{dC}{dt} + \frac{dR}{dt}. \tag{2}$$

By combining equation (1) and (2), we get;

$$\frac{dN}{dt} = \Pi - \mu N - \xi(C_s + C). \tag{3}$$

In the absence of death due to mastitis disease $(\xi = 0)$, equation (3) becomes;

$$\frac{dN}{dt} \leq \Pi - \mu N. \tag{4}$$

After solving equation (4) and equating it as time tends to infinity, we get $0 \leq N(t) \leq \frac{\Pi}{\mu}$. Hence, the feasible solution set of model equation (1) remains in the region;

$$\Omega = \{(S,C_s,C,R,B) \in \mathbb{R}^5_+ : N \leq \frac{\Pi}{\mu}\}.$$

Therefore, the model is well posed epidemiologically and mathematically. Hence, it is sufficient to study the dynamics of the model in Ω.

3.2 Positivity of the Solution

We assumed that the initial condition of the model is positive, and now we showed all the solution of the model equation (1) remain positive for future time.

Theorem 1: Let $\Omega = \{(S,C_s,C,R,B) \in \mathbb{R}^5_+ : S(t) > S_0, C_s(t) \geq C_{s0}, C(t) \geq C_0, R(t) \geq R_0, B(t) \geq B_0\}$ then the solution of $\{S,C_s,C,R,B\}$ are positive for all $t \geq 0$.

Proof: Consider $\frac{dS}{dt}$ in model equation (1);

$\frac{dS}{dt} = \Pi + \alpha R - (\lambda + \mu)S$, eliminating the positive terms $\Pi + \alpha R$ we obtain

$\frac{dS}{dt} \geq -(\lambda + \mu)S$, using variables separable method we get,

$\frac{dS}{S} \geq -(\lambda + \mu)dt$ integrating both side we can get,

$\int \frac{dS}{S} \geq -\int(\lambda + \mu)dt$ we obtain,

$\ln(S) \geq -(\lambda + \mu)t + \ln(A)$ where $ln(A)$ is any arbitrary constant,

Then after solving for S we obtain:

$S(t) \geq S_0 e^{-(\lambda+\mu)t}$.

Recall that an exponential function is always non-negative irrespective of the sign of the exponent, i.e., the exponential function $e^{-(\lambda+\mu)t}$ is a non-negative quantity. Hence,it can be concluded that $S(t) > Ce^{-(\lambda+\mu)t} \geq 0$. Therefore $S(t) > 0$ for all $t \geq 0$. Similarly using the other equations of system (1), positivity of solutions can be established. Hence, all the solutions of the model equation (1) are positive for all $t \geq 0$.

3.3 Mastitis Free Equilibrium

Mastitis free equilibrium points are steady state solutions where there is no mastitis in the cattles. Absence of mastitis implies that $C_s(t) = C(t) = 0$ and the equilibrium points require that the right hand sides of the model equations set equal to zero. Therefore, the mastitis free equilibrium $E_0 = (\frac{\Pi}{\mu}, 0, 0, 0, 0)$.

3.4 Basic Reproduction Number

The basic reproduction number is the number of people getting secondary infection among the whole susceptible cattle. It is determined using the next generation matrix method so that it is the largest eigenvalue of the next generation matrix [12]. Using the notation as in [12] for the model equation (1) the associated matrices f and v for the newly infectious terms and the remaining transition terms are respectively given as;

$$f_i = \begin{bmatrix} \frac{(1-p)(B\gamma)S}{K+B} \\ \frac{(B\gamma)S}{K+B} \\ 0 \end{bmatrix}, v_i = \begin{bmatrix} (\theta+\phi+\beta_1+\mu+\xi)C_s \\ -\phi C_s + (\delta+\beta_2+\mu+\xi)C \\ -\beta_1 C_s - \beta_2 C + \mu_b B \end{bmatrix}. \tag{5}$$

The Jacobian matrices of f and v evaluated at mastitis free equilibrium are given by F and V respectively, such that;

$$F(E_0) = \begin{bmatrix} 0 & 0 & \frac{(1-p)\Pi\gamma}{\mu K} \\ 0 & 0 & \frac{\Pi\gamma}{\mu K} \\ 0 & 0 & 0 \end{bmatrix} \text{ and}$$

$$V(E_0) = \begin{bmatrix} (\theta+\phi+\beta_1+\mu+\xi) & 0 & 0 \\ -\phi & (\delta+\beta_1+\mu+\xi) & 0 \\ -\beta_1 & -\beta_2 & \mu_b \end{bmatrix}.$$

It can be verified that that the matrix $V(E_0)$ is non-singular as its determinant $\det(V(E_0)) = (\theta+\phi+\beta_1+\mu+\xi)(\delta+\beta_1+\mu+\xi)\mu_b \neq 0$ is non-zero. That is $V(E_0) \neq 0$ then it is invertible and the inverse is given by;

$$[V(E_0)]^{-1} = \begin{bmatrix} \frac{1}{r_1} & 0 & 0 \\ \frac{\phi}{r_1 r_2} & \frac{1}{r_1} & 0 \\ \frac{r_1\beta_1+\phi\beta_2}{r_1 r_2 \mu_b} & \frac{\beta_2}{r_2\mu_b} & \frac{1}{\mu_b} \end{bmatrix}$$

where $r_1 = (\theta+\phi+\beta_1+\mu+\xi)$ and $r_2 = (\delta+\beta_1+\mu+\xi)$. Then

$$F[V(E_0)]^{-1} = \begin{bmatrix} \frac{(1-p)\Pi\gamma(r_2\beta_1+\phi\beta_2)}{\mu K r_1 r_2 \mu_b} & \frac{(1-p)\Pi\gamma\beta_2}{\mu K r_2 \mu_b} & \frac{(1-p)\Pi\gamma}{\mu K \mu_b} \\ \frac{p\Pi\gamma(r_2\beta_1+\phi\beta_2)}{\mu K r_1 r_2 \mu_b} & \frac{p\Pi\gamma\beta_2}{\mu K r_2 \mu_b} & \frac{p\Pi\gamma}{\mu K \mu_b} \\ 0 & 0 & 0 \end{bmatrix}$$

Thus, the eigenvalues are computed by evaluating $det(FV^{-1} - \lambda I) = 0$. Then we obtained the characteristic equation;

$$\lambda^2(\lambda - (\frac{(1-p)\Pi\gamma(r_2\beta_1+\phi\beta_2)}{\mu K r_1 r_2 \mu_b} + \frac{p\Pi\gamma\beta_2}{\mu K r_2 \mu_b})) = 0.$$

The eigenvalues are $\lambda_1 = \lambda_2 = 0$ and $\lambda_3 = \frac{(1-p)\Pi\gamma(r_2\beta_1+\phi\beta_2)}{\mu K r_1 r_2 \mu_b} + \frac{p\Pi\gamma\beta_2}{\mu K r_2 \mu_b}$. However, the largest eigenvalue here is λ_3. Thus, it can be concluded that the basic reproduction number $\Re_0$ of the model after substituting r_1 and r_2 is;

$$\Re_0 = \frac{(1-p)\Pi\gamma((\delta+\beta_1+\mu+\xi)\beta_1+\phi\beta_2)}{\mu K(\theta+\phi+\beta_1+\mu+\xi)(\delta+\beta_1+\mu+\xi)\mu_b} + \frac{p\Pi\gamma\beta_2}{\mu K(\delta+\beta_1+\mu+\xi)\mu_b}.$$

3.5 Local Stability of Mastitis Free Equilibrium

Theorem 2: The mastitis free equilibrium point of model equation (1) is locally asymptotically stable if $\Re_0 < 1$ and unstable if $\Re_0 > 1$.

Proof: To proof this theorem first we obtain the Jacobian

matrix of model equation (1) at mastitis free equilibrium E_0 as follows;

$$J(E_0)=\begin{bmatrix} -\mu & 0 & 0 & \alpha & \frac{\gamma\Pi}{K\mu} \\ 0 & -r_1 & 0 & 0 & \frac{(1-p)\gamma\Pi}{K\mu} \\ 0 & \phi & -r_2 & 0 & \frac{p\gamma\Pi}{K\mu} \\ 0 & \theta & \delta & -(\alpha+\mu) & 0 \\ 0 & \beta_1 & \beta_2 & 0 & -\mu_b \end{bmatrix}. \quad (6)$$

From the Jacobian matrix of (6), we obtained a characteristic equations;

$$(-\lambda-\mu)(-\lambda-(\alpha+\mu))[[\lambda^3+\lambda^2(r_1+r_2+\mu_b)+ \lambda[r_1r_2+\mu_b(r_1+r_2)-((1-p)\beta_1+p\beta_2)\tfrac{\Pi\gamma}{K\mu}]]+ r_1r_2\mu_b(1-\Re_0)]=0.$$

After some simplification we obtain;

$$(-\lambda-\mu)(-\lambda-(\alpha+\mu))[\lambda^3+L_1\lambda^2+L_2\lambda+L_3]=0 \quad (7)$$

where, $r_1=(\theta+\phi+\beta_1+\mu+\xi)$ and $r_2=(\delta+\beta_1+\mu+\xi)$,
$L_1=r_1+r_2+\mu_b$,
$L_2=r_1r_2+\mu_b(r_1+r_2)-[(1-p)\beta_1+p\beta_2]\frac{\Pi\gamma}{K\mu}$,
$L_3=r_1r_2\mu_b(1-\Re_0)$.
From equation (7) we obtained;

$$-\lambda-\mu=0,$$
$$\text{or } -\lambda-(\alpha+\mu)=0,$$
$$\text{or } \lambda^3+L_1\lambda^2+L_2\lambda+L_3=0.$$

This implies,$\lambda_1=-\mu,\lambda_2=-(\alpha+\mu)$ and for the last expression $\lambda^3+L_1\lambda^2+L_2\lambda+L_3=0$, we applied Routh Hurwitz criteria. By the principle of Routh Hurwitz criteria $\lambda^3+L_1\lambda^2+L_2\lambda+L_3=0$ has strictly negative real root if and only if $L_1>0,L_3>0$, and $L_1L_2>L_3$. Clearly we see that L_1 is positive because it is a sum of positive variables, but L_3 to be positive $(1-\Re_0)$ must be positive, which leads to $\Re_0<1$. Therefore, mastitis free equilibrium will be locally asymptotically stable if and only if $\Re_0<1$.

3.6 Global Stability of Mastitis Free Equilibrium

The global stability of disease free equilibrium was implemented by Castillo-Chavez and Song technique [13]. The model equation (1) can be re-written as

$$dX/dt=F(X,Z),$$

$$dZ/dt=G(X,Z),G(X,0)=0.$$

Where, X stands for the uninfected population, that is $X=(S,\ R)$ and Z also stands for the infected population, that is $Z=(C_s,C,B)$. The disease free equilibrium point of the model is denoted by $U=(X^*,\ 0)$. The point $U=(X^*,\ 0)$ to be globally asymptotically stable equilibrium for the model provided that $\Re_0<1$ and the following conditions must be met:
(H_1). For $dX/dt=F(X,0)$, X^* is globally asymptotically stable.
(H_2). $G(X,Z)=AZ-\tilde{G}(X,Z),\quad \tilde{G}(X,Z)=0$ for $(X,Z)\subset\Omega$.
where $A=D_ZG(U,0)$ a Metzler matrix is i.e. the off diagonal elements of A are non-negative and G is the region where the model makes biologically sense. If the model (1) met the above two criteria then the following theorem holds.
Theorem 3: The point $U=(X^*,\ 0)$ is globally asymptotically stable equilibrium provided that $\Re_0<1$ and the condition (H_1) and $(H_2)$are satisfied.
Proof: From system (1) we can get $F(X,Z)$ and $G(X,Z)$;

$$F(X,Z)=\begin{bmatrix}\Pi+\alpha R-(\lambda+\mu)S \\ \theta C_s+\delta C-(\alpha+\mu)R\end{bmatrix}$$

and $G(X,Z)=\begin{bmatrix}(1-p)\lambda S-(\theta+\phi+\beta_1+\mu+\xi)C_s \\ p\lambda S+\phi C_s-(\delta+\beta_2+\mu+\xi)C \\ \beta_1C_s+\beta_2C-\mu_bB\end{bmatrix}$

Consider the reduced system

$$\frac{dX}{dt}_{|Z=0}=\begin{bmatrix}\Pi-\mu S \\ 0\end{bmatrix} \quad (8)$$

From equation (8) above it is obvious that $X^*=\left\{\frac{\Pi}{\mu},0\right\}$ is the global asymptotic point. This can be verified from the solution, namely, $S=\frac{\Pi}{\mu}+\left[S(0)-\frac{\Pi}{\mu}\right]e^{-\mu t}$. As $t\longrightarrow\infty$ the solution $S\longrightarrow\frac{\Pi}{\mu}$ implying that the global convergence of (8) in Ω. From the equation for infected compartments in the model we have:

$$A=\begin{bmatrix}-(\theta+\phi+\beta_1+\mu+\xi) & 0 & \frac{(1-p)\Pi\gamma}{K\mu} \\ \phi & -(\delta+\beta_2+\mu+\xi) & \frac{p\Pi\gamma}{K\mu} \\ \beta_1 & \beta_2 & -\mu_b\end{bmatrix}$$

Since A is Metzler matrix, i.e. all off diagonal elements are nonnegative. Then, $G(X,Z)$ can be written as,$G(X,Z)=AZ-\tilde{G}(X,Z)$, where

$$\tilde{G}(X,Z)=\begin{bmatrix}(1-p)\gamma B(\frac{\Pi}{K\mu}-\frac{S}{K+B}) \\ p\gamma B(\frac{\Pi}{K\mu}-\frac{S}{K+B}) \\ 0\end{bmatrix}=\begin{bmatrix}\tilde{G}_1(X,Z) \\ \tilde{G}_2(X,Z) \\ \tilde{G}_3(X,Z)\end{bmatrix} \quad (9)$$

It follows that, in equation (9) $\tilde{G}_1(X,Y)\geq 0,\tilde{G}_2(X,Y)\geq 0$ and $\tilde{G}_3(X,Y)=0$ and. Hence, $\tilde{G}(X,Y)\geq 0$. Therefore, condition (H_1) and (H_2) are satisfied and we conclude that U is globally asymptotically stable for $\Re_0<1$.

3.7 Endemic Equilibrium Point

Endemic equilibrium point E_1 is a steady state solution where the mastitis persists in the cattle. Then it is obtained

by setting left hand sides of equations of the system (1) equal to zero. Thus, solving for state variables we obtained the following;

$$S^* = \frac{\lambda^*+\mu}{\Pi+\alpha R^*},$$
$$C_s^* = \frac{(1-p)\lambda^*}{(\theta+\phi+\beta_1+\mu+\xi)}(\frac{\lambda^*+\mu}{\Pi+\alpha R^*}),$$
$$C^* = (\frac{\lambda^*+\mu}{\Pi+\alpha R^*})(\frac{p\lambda^*(\theta+\phi+\beta_1+\mu+\xi)+\phi(1-p)\lambda^*}{(\theta+\phi+\beta_1+\mu+\xi)(\delta+\beta_2+\mu+\xi)}),$$
$$R^* = \frac{\theta C_s^*+\delta C^*}{(\alpha+\mu)},$$
$$B = \frac{\beta_1}{\mu_b}(\frac{(1-p)\lambda S^*}{(\theta+\phi+\beta_1+\mu+\xi)}) +$$
$$\frac{\beta_2}{\mu_b}((\frac{\lambda^*+\mu}{\Pi+\alpha R^*})(\frac{p\lambda^*(\theta+\phi+\beta_1+\mu+\xi)+\phi(1-p)\lambda^*}{(\theta+\phi+\beta_1+\mu+\xi)(\delta+\beta_2+\mu+\xi)})).$$

On substituting the expression for B into the force of infection, that is, $\lambda^* = [B\gamma]/K + B$, characteristic polynomial of force of infection is obtained as

$$p(\lambda^*) = D_1\lambda^{*2} + D_2\lambda^*,$$

Here $D_1 = (\delta\alpha((p\beta_1+\mu+\phi)+(1-p)\phi)+\alpha\theta p(\beta_2+\mu+\delta+\xi))+\Re(\beta_2+\delta+\mu+\xi)(\beta_1+\phi+\mu)\mu\mu_b K+1$ and $D_2 = \mu(\alpha+\mu)(1-\Re_0)$.
Clearly, $D_1 > 0$ and $D_2 \geq 0$, when $\Re_0 < 1, \lambda^* = -D_2/D_1 = 0$. From this, we see that, for, there is no endemic equilibrium for this model. Therefore, this condition shows that it is not possible for backward bifurcation in the model if $\Re_0 < 1$.
Lemma 1: A unique endemic equilibrium point E_1 exists and is positive if $\Re_0 > 1$.

4 Sensitivity Analysis of Model Parameters

We carried out a sensitivity analysis in order to determine the relative significance of model parameters on mastitis transmission. The analysis will enable us to find out parameters that have a high impact on the basic reproduction number and which should be targeted by intervention strategies. We perform sensitivity analysis by calculating the sensitivity indices of the basic reproduction number $\Re_0$ in order to determine whether mastitis can be spread in the cattles or not. These indices tell us how crucial each parameter is in the transmission of mastitis. To investigate which parameters in the model system (1) have high impact on the $\Re_0$, we apply the approach presented by [14].
The explicit expression of $\Re_0$ is given by$\Re_0 = \frac{(1-p)\Pi\gamma((\delta+\beta_1+\mu+\xi)\beta_1+\phi\beta_2)}{\mu K(\theta+\phi+\beta_1+\mu+\xi)(\delta+\beta_1+\mu+\xi)\mu_b} + \frac{p\Pi\gamma\beta_2}{\mu K(\delta+\beta_1+\mu+\xi)\mu_b}$. Since $\Re_0$ depends only on seven parameters; $p = 0.6, \Pi = 500, \gamma = 0.09, \delta = 0.998, \beta_1 = 0.009, \mu = 0.02, \xi = 0.9992, \phi = 0.999, \beta_2 = 0.008, K = 1000, \theta = 0.98, \mu_b = 0.01$ we derive an analytical expression for its sensitivity to each parameter using the normalized forward sensitivity index as by Chitnis [14] as follows:

The sensitivity indices of the reproductive number with respect to parameters are arranged orderly in Table 1 and as shown in Figure 2. Those parameters that have positive indices i.e. $\Pi, \gamma, \beta_1, \phi$, and β_2 show that they have a great impact on expanding the disease in the cattle if their values are increasing. The reason that the basic reproduction number increases as their values increase, means that the number of secondary cases of infection increases in the community. Furthermore, parameters in which their sensitivity indices are negative i.e. δ, θ, ξ, K and μ_b have an influence of minimizing the burden of the disease in the cattle as their values increase while the others are left constant. And also as their values increase, the basic reproduction number decreases, which leads to minimizing the endemicity of the disease in the cattle.

Table 1: Sensitivity indices Table.

Parameter Symbol	Sensitivity indices
Π	+1
γ	+1
β_1	0.4743
ϕ	0.191
β_2	0.00955
δ	-0.25758
θ	-0.32589
ξ	-0.56
μ	-1
K	-1
μ_b	-1

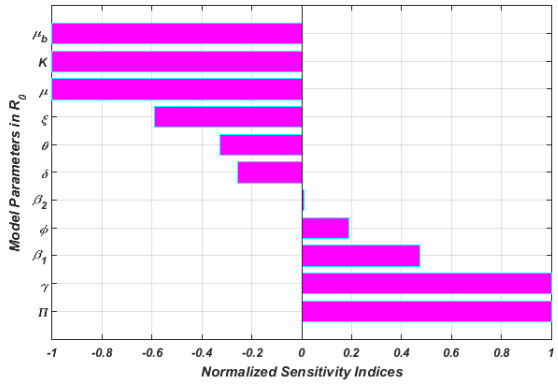


Fig. 2: Sensitivity indices of basic reproduction number $\Re_0$.

5 Optimal Control Problem Formulation

In this section, mathematical model of mastitis (1) is extended to optimal control model by including the following three controls;

1. u_1 is the prevention efforts that protect susceptible individuals from contracting the mastitis disease.
2. u_2 is the screening for subclinical individuals which helps them to get proper treatment if they are aware of their status.

3.u_3 is the treatment for clinical individuals who develop symptoms of mastitis disease.

After incorporating the controls into the model equations (1) we obtain the following equation;

$$\begin{aligned}
\frac{dS}{dt} &= \Pi + \alpha R - (1-u_1)\lambda S - \mu S,\\
\frac{dC_s}{dt} &= (1-u_1)(1-p)\lambda S - (u_2+\phi)C_s - (\theta+\beta_1+\mu+\xi)C_s,\\
\frac{dC}{dt} &= (1-u_1)p\lambda S + (1-u_2)\phi C_s - (u_3+\delta)C - (\beta_2+\mu+\xi)C,\\
\frac{dR}{dt} &= \theta C_s + (u_2+\delta)C - (\alpha+\mu)R,\\
\frac{dB}{dt} &= \beta_1 C_s + \beta_2 C - \mu_b B,
\end{aligned} \tag{10}$$

with a bounded Lebesgue measurable control set $U = \{(u_1,u_2,u_3) : 0 \le u_i \le u_{imax}, i = 1,2,3, 0 \le t \le T\}$. The main objective is to minimize the number of infected cattle while minimizing the rate of interventions u_1, u_2 and u_3 on a fixed time period T. Therefore, the optimal control problem for model equation (10) is to minimize the objective functional;

$$J(u_1,u_2,u_3) = min_{(u_1,u_2,u_3)} \int_0^T \left(M_1 C_s + M_2 C + \frac{1}{2}\sum_{i=1}^{3} w_i u_i^2(t) \right) dt. \tag{11}$$

The constants w_1, w_2 and w_3 measures the cost or effort required for the implementation of each of the three control measures adopted while M_1 and M_2 measures the relative importance of reducing subclinical and clinical classes on the spread of the mastitis disease. Thus, we need to find the optimal controls $u^* = (u_1^*, u_2^*, u_3^*)$ such that;

$$J(u^*) = min_U J(u_1,u_2,u_3).$$

5.1 Optimal Control Problem Analysis

5.1.1 Existence of an optimal Controls

The existence of the optimal control can be showed by using an approach of [15]. We have already justified the boundedness of the solution of the basic mastitis model. This results can be used to prove the existence of optimal control. For detailed proof, see [15][Theorem 4.1, p68-69].

5.1.2 The Hamiltonian and Optimality System

To obtain the Hamiltonian (H), we follow the approach of [16] such that;

$$H = \frac{dJ}{dt} + \lambda_1\frac{dS}{dt} + \lambda_2\frac{dC_s}{dt} + \lambda_3\frac{dC}{dt} + \lambda_4\frac{dR}{dt} + \lambda_5\frac{dB}{dt} \tag{12}$$

That is,

$$\begin{aligned}
H(S,C_s,C,R,B,t) = (M_1 C_s + M_2 C + \frac{w_1 u_1^2}{2} + \frac{w_2 u_2^2}{2} + \\
\frac{w_3 u_3^2}{2}) + \lambda_1[\Pi + \alpha R - (1-u_1)\lambda S - \mu S] + \lambda_2[(1-u_1)(1- \\
p)\lambda S - (u_2+\phi)C_s - (\theta+\beta_1+\mu+\xi)C_s] + \lambda_3[(1- \\
u_1)p\lambda S + (1-u_2)\phi C_s - (u_3+\delta)C - (\beta_2+\mu+\xi)C] + \\
\lambda_4[\theta C_s + (u_2+\delta)C - (\alpha+\mu)R] + \lambda_5[\beta_1 C_s + \beta_2 C - \mu_b B].
\end{aligned}$$

Based on [17], if the control u^* and the corresponding state ϕ^* are an optimal couple, necessarily there exists a non trivial adjoint vector $\lambda = (\lambda_1,\lambda_2,\lambda_3,\lambda_4,\lambda_5)$ satisfying the following equality;

$$\begin{aligned}
\frac{d\Phi}{dt} &= \frac{\partial H(\Phi,u,\lambda)}{\partial \lambda},\\
\frac{d\lambda}{dt} &= -\frac{\partial H(\Phi,u,\lambda)}{\partial \Phi},\\
\frac{\partial H(\Phi,u,\lambda)}{\partial u} &= 0,
\end{aligned} \tag{13}$$

which gives after derivatives;

$$\begin{aligned}
u_i^* &= 0, \text{ if } \tfrac{\partial H}{\partial u_i} < 0,\\
0 \le u_i^* &\le u_{imax}, \text{ if } \tfrac{\partial H}{\partial u_i} = 0,\\
u_i^* &= u_{imax}, \text{ if } \tfrac{\partial H}{\partial u_i} > 0.
\end{aligned}$$

Theorem 5: There exist an optimal control set of u_1, u_2 and u_3 and corresponding solutions,S, C_s, C, R and B, that minimize $J(u_1,u_2,u_3)$ over U. Furthermore, there exist adjoint functions $\lambda_1,\lambda_2,\lambda_3,\lambda_4$ and λ_5 such that;

$$\begin{aligned}
\frac{d\lambda_1}{dt} &= \lambda_1[\frac{(1-u_1)B\gamma}{K+B} + \mu] - \lambda_2[\frac{(1-u_1)(1-p)B\gamma}{K+B}] - \lambda_3[\frac{(1-u_1)B\gamma}{K+B}],\\
\frac{d\lambda_2}{dt} &= -M_1 + \lambda_2(u_2+\phi+\theta+\beta_1+\mu+\xi) - \lambda_3(1-u_2)\phi - \lambda_4\theta - \lambda_5\beta_1,\\
\frac{d\lambda_3}{dt} &= -M_2 + \lambda_3(u_3+\delta+\beta_2+\mu+\xi) - \lambda_4(u_3+\delta) - \lambda_5\beta_2,\\
\frac{d\lambda_4}{dt} &= -\lambda_1\alpha + \lambda_4(\alpha+\mu),\\
\frac{d\lambda_5}{dt} &= \lambda_1[\frac{(1-u_1)\gamma KS}{(K+B)^2}] - \lambda_2[\frac{(1-p)(1-u_1)\gamma KS}{(K+B)^2}] - \lambda_3[\frac{(1-u_1)p\gamma KS}{(K+B)^2}]\\
&+\lambda_5\mu_b,
\end{aligned} \tag{14}$$

with transversality conditions;

$$\lambda_i(T) = 0, i = 1,2,3,4,5. \tag{15}$$

And the characterized control set of (u_1^*, u_2^*, u_3^*) is;

$$\begin{aligned}
u_1^*(t) &= max\{0, min(1, \tfrac{S(\lambda_3 pB\gamma - \lambda_2 B\gamma + \lambda_2 pB\gamma) - \lambda_1 B\gamma}{(K+B)w_1})\}\\
u_2^*(t) &= max\{0, min(1, \tfrac{C_s(\lambda_2+\phi\lambda_3)}{w_2})\}\\
u_3^*(t) &= max\{0, min(1, \tfrac{C(\lambda_3-\lambda_4)}{w_3})\}.
\end{aligned}$$

Proof: To prove this theorem, we used the classical result of [16]. Accordingly, to get the system of adjoint variables,

we differentiate the Hamiltonian (12) with respect to each state as follows;

$$\begin{aligned}
\frac{d\lambda_1}{dt} &= \lambda_1[\frac{(1-u_1)B\gamma}{K+B}+\mu]-\lambda_2[\frac{(1-u_1)(1-p)B\gamma}{K+B}]-\lambda_3[\frac{(1-u_1)B\gamma}{K+B}],\\
\frac{d\lambda_2}{dt} &= -M_1+\lambda_2(u_2+\phi+\theta+\beta_1+\mu+\xi)-\lambda_3(1-u_2)\phi-\lambda_4\theta-\lambda_5\beta_1,\\
\frac{d\lambda_3}{dt} &= -M_2+\lambda_3(u_3+\delta+\beta_2+\mu+\xi)-\lambda_4(u_3+\delta)-\lambda_5\beta_2,\\
\frac{d\lambda_4}{dt} &= -\lambda_1\alpha+\lambda_4(\alpha+\mu),\\
\frac{d\lambda_5}{dt} &= \lambda_1[\frac{(1-u_1)\gamma KS}{(K+B)^2}]-\lambda_2[\frac{(1-p)(1-u_1)\gamma KS}{(K+B)^2}]-\lambda_3[\frac{(1-u_1)p\gamma KS}{(K+B)^2}]+\lambda_5\mu_b.
\end{aligned} \tag{16}$$

And the optimal controls u_i^* are obtained from the optimality conditions and using the property of the control space U. The optimality condition of the Hamiltonian gives $\frac{\partial H}{\partial u_i}=0$. That is;

$$\frac{\partial H}{\partial u_i}=0, \text{ at } u_i=u_i^*, \text{ where } i=1,2,3.$$

For

$$\begin{aligned}
i=1, \frac{\partial H}{\partial u_1}=0, \text{ at } u_1^*, u_1^* &= \frac{S(\lambda_3 pB\gamma-\lambda_2 B\gamma+\lambda_2 pB\gamma)-\lambda_1 B\gamma}{(K+B)w_1},\\
i=2, \frac{\partial H}{\partial u_2}=0, \text{ at } u_2^*, u_2^* &= \frac{C_s(\lambda_2+\phi\lambda_3)}{w_2},\\
i=3, \frac{\partial H}{\partial u_3}=0, \text{ at } u_3^*, u_3^* &= \frac{C(\lambda_3-\lambda_4)}{w_3}.
\end{aligned}$$

Since, $0\le u_i^*\le u_{imax}$, we can write in a compact notation;

$$\begin{aligned}
u_1^*(t) &= max\{0, min(1, \frac{S(\lambda_3 pB\gamma-\lambda_2 B\gamma+\lambda_2 pB\gamma)-\lambda_1 B\gamma}{(K+B)w_1})\},\\
u_2^*(t) &= max\{0, min(1, \frac{C_s(\lambda_2+\phi\lambda_3)}{w_2})\},\\
u_3^*(t) &= max\{0, min(1, \frac{C(\lambda_3-\lambda_4)}{w_3})\}.
\end{aligned} \tag{17}$$

5.2 The Optimality System

The optimality system consists of the state system (10) with its initial conditions coupled with the adjoint system (14) with its transversality conditions together with the characterization of the optimal controls. It is written as follows:

$$\begin{aligned}
\frac{dS}{dt} &= \Pi+\alpha R-(1-u_1)\lambda S-\mu S,\\
\frac{dC_s}{dt} &= (1-u_1)(1-p)\lambda S-(u_2+\phi)C_s-(\theta+\beta_1+\mu+\xi)C_s,\\
\frac{dC}{dt} &= (1-u_1)p\lambda S+(1-u_2)\phi C_s-(u_3+\delta)C-(\beta_2+\mu+\xi)C,\\
\frac{dR}{dt} &= \theta C_s+(u_3+\delta)C-(\alpha+\mu)R,\\
\frac{dB}{dt} &= \beta_1 C_s+\beta_2 C-\mu_b B\\
\frac{d\lambda_1}{dt} &= \lambda_1[\frac{(1-u_1)B\gamma}{K+B}+\mu]-\lambda_2[\frac{(1-u_1)(1-p)B\gamma}{K+B}]-\lambda_3[\frac{(1-u_1)B\gamma}{K+B}],\\
\frac{d\lambda_2}{dt} &= -M_1+\lambda_2(u_2+\phi+\theta+\beta_1+\mu+\xi)-\lambda_3(1-u_2)\phi-\lambda_4\theta-\lambda_5\beta_1,\\
\frac{d\lambda_3}{dt} &= -M_2+\lambda_3(u_3+\delta+\beta_2+\mu+\xi)-\lambda_4(u_3+\delta)-\lambda_5\beta_2,\\
\frac{d\lambda_4}{dt} &= -\lambda_1\alpha+\lambda_4(\alpha+\mu),\\
\frac{d\lambda_5}{dt} &= \lambda_1[\frac{(1-u_1)\gamma KS}{(K+B)^2}]-\lambda_2[\frac{(1-p)(1-u_1)\gamma KS}{(K+B)^2}]-\lambda_3[\frac{(1-u_1)p\gamma KS}{(K+B)^2}]+\lambda_5\mu_b,
\end{aligned} \tag{18}$$

with transversality conditions;

$$\begin{aligned}
\lambda_i(T)=0, i=1,2,3,4,5,\\
S(0)=S_0, C_{s0}=C_{s0}, C(0)=C_0, R(0)=R_0, B(0)=B_0.
\end{aligned}$$

5.3 Uniqueness of the optimality system

In order to successively discuss uniqueness of the optimality system we notice that the adjoint system is also linear in λ_i for $i=1,2,3,4,5$ with bounded coefficients. Thus, there exists a $M>0$ such that $|\lambda_i(t)|<M$ for $i=1,2,3,4,5$ on $[0,T]$.

Theorem 6: For T sufficiently small the solution to the optimality system is unique [17].

6 Numerical Results and Discussion

In this section, the result obtained by numerically solving the optimality system was presented. In an optimal control problem, we have initial conditions for the state variables and terminal conditions for the adjoints. That is, the optimality system is a two-point boundary value problem with separated boundary conditions at times step $i=0$ and $i=T$. The numerical simulation was carried out using the software MATLAB 2015b. To conduct the study, a set of meaningful values are assigned to the model parameters. These values are either taken from literature or estimated or assumed. Using the parameter values given in Table 2 and the initial

Table 2: Parameter values used in Numerical Simulations

Para meter	Description	Value	Reference
Π	Recruited rate	500	Assumed
μ	Natural death rate	0.02	[8]
α	Recovered rate	0.99	Estimated
γ	Ingestion rate	0.09	Estimated
p	Probability of susceptible joining clinical individuals	0.6	Assumed
K	Concentration of bacteria in environment	1000	Assumed
ξ	Induced mortality rate	0.9992	Estimated
δ	Treatment rate of clinical individuals	0.998	Estimated
ϕ	Screening rate	0.999	Assumed
θ	Recovered rate of subclinical individuals	0.98	Estimated
β_1	Discharge rate of bacteria from subclinical individuals	0.009	Estimated
β_2	Discharge rate of bacteria from clinical individuals	0.008	Estimated
μ_b	Natural death rate of bacteria	0.01	Assumed

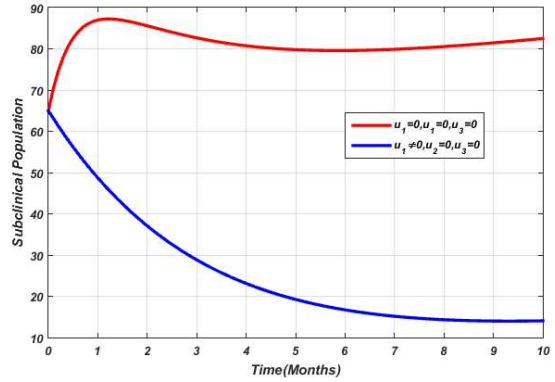
conditions
$S(0) = 1000,\ C_s(0) = 65,\ C(0) = 70, R(0) = 30$ and $B_c(0) = 20$ and also coefficients of the state and controls that we used are $M_1 = 25,\ M_2 = 25,\ W_1 = 10, W_2 = 10, W_3 = 10$ the simulation study is conducted and the results are given below in Figures.

A. Control strategy with prevention

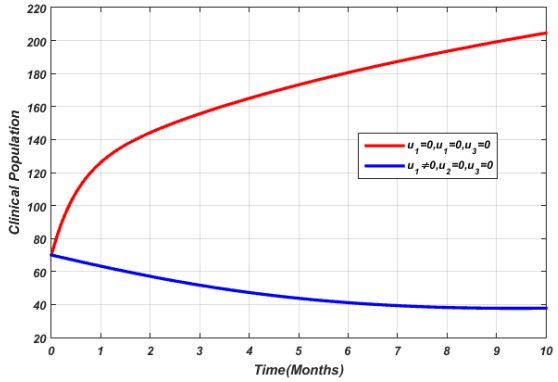
We simulated the optimality system by incorporating a prevention strategy only. Figures 3(a) and 3(b) show the decrease in subclinical and clinical individuals in the specified time. We conclude that prevention that includes sanitation and other techniques is a vital method to reduce Mastitis infection. The number of individuals who have been with Mastitis disease before the implementation of prevention control has gone down due to disease-induced and natural deaths. Therefore, applying optimized prevention control can eradicate Mastitis disease.

B. Control strategy with screening

As we know screening helps subclinical to identify their status as they are leaving with the bacteria or not. Therefore, Figures 4(a) and 4(b) show that the subclinical and clinical individuals go down by screening strategy but their number cannot be zero. New infection always appears in cattle because the diseases are not avoided and those who broaden the symptom of mastitis are not getting treatment. Therefore, control with screening only eradicates the burden to some extent but it is not helpful to eradicate mastitis disease totally from the cattle.



(3a)



(3b)

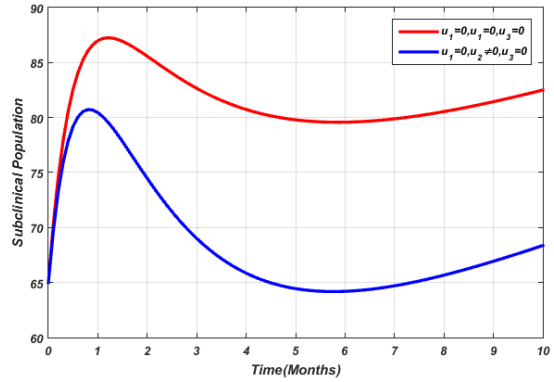
Fig. 3: Simulation of Mastitis model with prevention

C. Control strategy with prevention and screening

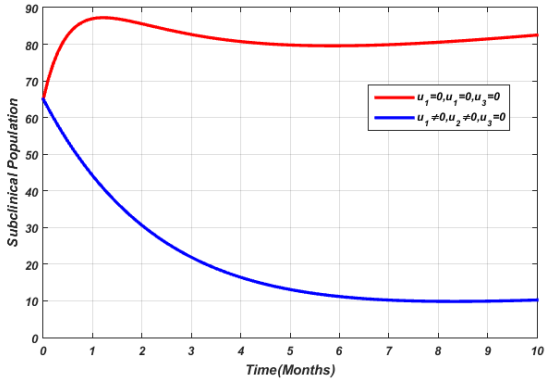
We simulated the model by incorporating prevention and screening efforts as a mastitis control strategy. Figures (5a) and (5b) show that the subclinical and clinical individuals go to zero at the end of the implementation of intervention time. From this, we can conclude that applying prevention and screening can reduce the disease even if without treating individuals that have mastitis symptoms. Therefore, applying prevention and screening efforts as strategies will reduce mastitis disease in cattle.

D. Control strategy with prevention and treatment

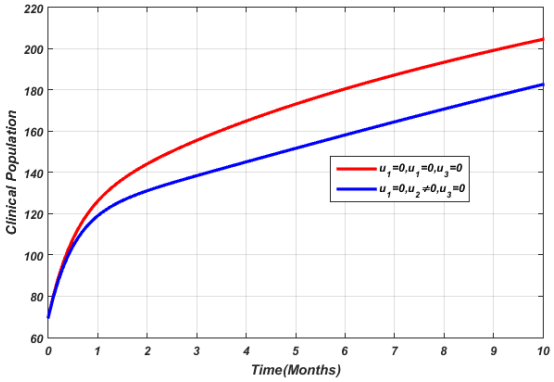
We simulate the model using prevention and treatment efforts as strategies for the control of mastitis disease in cattle. Figures (6a) and (6b) clearly show that the subclinical and clinical individuals have gone to zero at



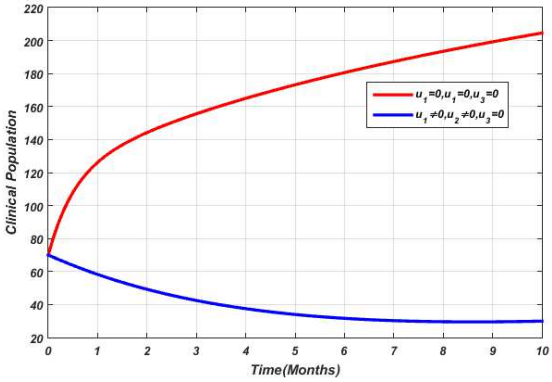
(4a)



(5a)



(4b)



(5b)

Fig. 4: Simulation of Mastitis model with screening

Fig. 5: Simulation of Mastitis model with prevention and screening

the end of the implementation period. Therefore, we conclude that this strategy is effective in reducing mastitis in cattle in a specified period of time.

E. Control strategy with screening and treatment

In this strategy, we used the combination of screening and treatment efforts as an intervention to control mastitis disease. Figures (7a) and (7b) show that optimized intervention by treating clinical individuals and screening of subclinical reduces the number of subclinical and clinical individuals but did not go to zero. Therefore, this strategy is not 100% effective in reducing mastitis in the specified period of time.

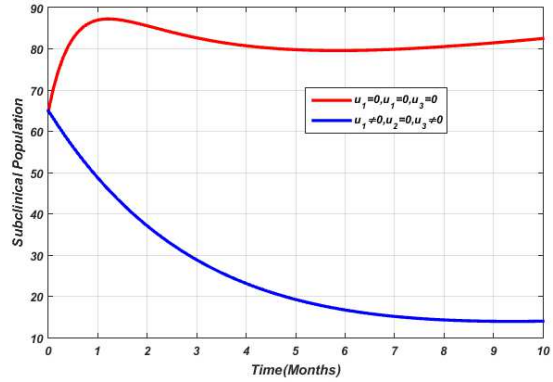
F. Control strategy with prevention, screening and treatment

In this strategy, we implemented all three controls prevention, treatment, and screening as interventions to reduce Mastitis from the cattle. Figures (8a) and (8b) show that the number of subclinical individuals and clinical goes to zero at the end of the implementation period.

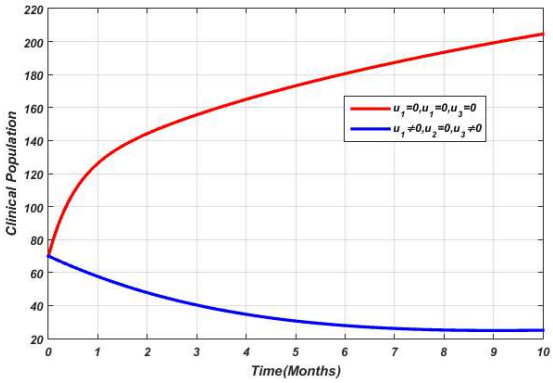
7 Cost-Effectiveness Analysis

We use cost-effectiveness analysis to determine the minimum cost-effective strategy to use to control the disease. To do this, we need to compare the differences between the costs and health outcomes of these interventions. This is done by calculating the incremental cost-effectiveness ratio (ICER) which is usually described as the additional cost of an additional health outcome. When two or more competing intervention strategies are progressively compared, an intervention must be compared with the next-less-effective alternative [18]. It is calculated using the following formula;

$$ICER = \frac{\text{Difference in costs between strategies}}{\text{Difference in health effects between strategies}}.$$

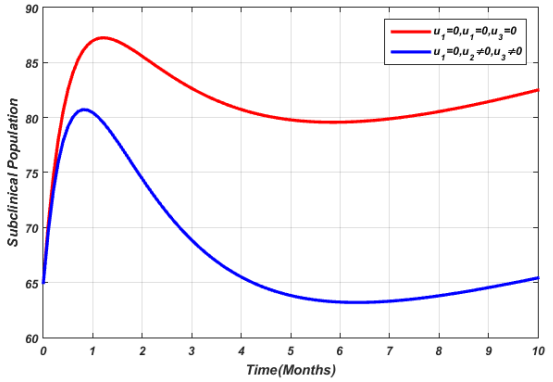


(6a)

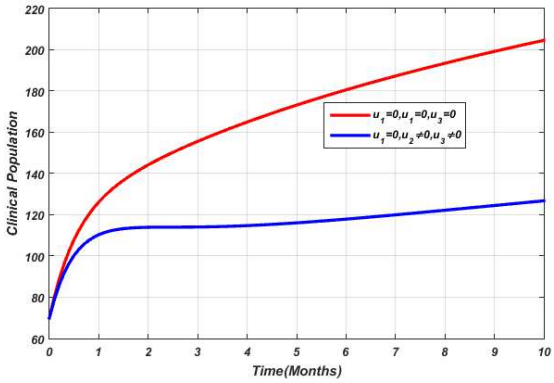


(6b)

Fig. 6: Simulation of Mastitis model with prevention and treatment



(7a)



(7b)

Fig. 7: Simulation of Mastitis model with screening and treatment

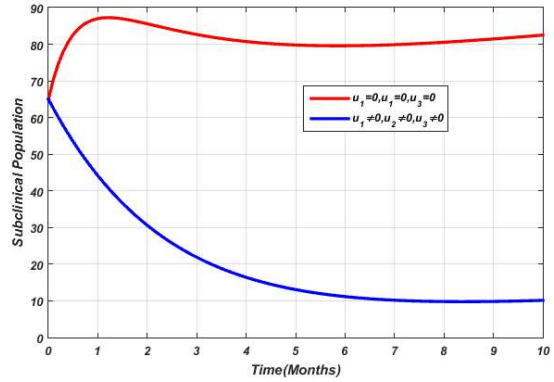
The infection averted is obtained by calculating the difference between the total number of individuals of species without control and the total number of individuals of species with control. The total control costs $w_1u_1^2, w_2u_2^2$ and $w_3u_3^2$ (where w_i for i = 1, 2, 3 are relative cost weight for each individual control measure, while u_1, u_2, u_3 are the prevention ($), Screening ($) and treatment ($) respectively) are calculated and estimated in ($) USD over the period of one year respectively. The control strategies are ranked in order of increasing infection averted as presented in Table and as shown in Figures 9,10 and 11.

Table 3: Total number of infections averted and total cost with their ICER

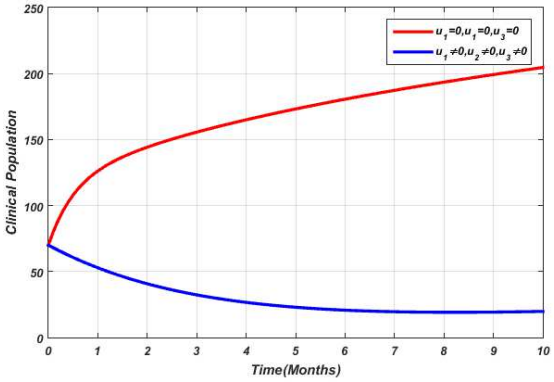
Strategies	**Total infectious averted**	**Total cost ($)**	**ICER**
Strategy B	6179.065	49.4943	0.008
Strategy E	6225.565	98.9841	1.064
Strategy A	6775.486	49.49	-0.8999
Strategy D	6808.605	98.99	1.4944
Strategy C	6833.069	98.99	0
Strategy F	6865.195	148.485	1.54

The comparison between ICER(B) and ICER(E) shows a cost saving of $0.008 for strategy B over strategy E. There is an additional $1.064 per infection averted as we move from strategy B to E. The small value ICER for strategy B indicates that strategy E is "strongly dominated". That is, strategy E is more costly and less effective than strategy B. Therefore, strategy E, the strongly dominated is excluded. Exclude strategy E, we now compare strategy B with A, D, C, and F. From the numerical results we have

The comparison between ICER(B) and ICER(A) shows a cost saving of $0.0000011736 for strategy A over strategy B. There is an additional $0.008 per infection averted as we move from strategy B to A. That is, strategy B is more costly and less effective than strategy A.



(8a)



(8b)

Fig. 8: Simulation of Mastitis model with prevention, screening and treatment

Table 4: Total number of infections averted and total cost with their ICER

Strategies	**Total infectious averted**	**Total cost ($)**	**ICER**
Strategy B	6179.065	49.4943	0.008
Strategy A	6775.486	49.49	0.0000011736
Strategy D	6808.605	98.99	1.4944
Strategy C	6833.069	98.99	0
Strategy F	6865.195	148.485	1.54

Therefore, strategy B, the strongly dominated is excluded from the set of alternatives so it does not consume limited resources. We exclude strategy B and compare strategy A with D, C, and F. From the numerical results we have;

The comparison between ICER(A) and ICER(D) shows a cost saving of $0.0073 for strategy A over strategy D. There is an additional $1.4944 per infection averted as we move from strategy A to D. The small value ICER for strategy A indicates that strategy D is ”strongly dominated”. That is, strategy D is more costly and less effective than strategy A. Therefore, strategy D, the strongly dominated is excluded. Exclude strategy D, we now compare strategy A with C and F. From the numerical results we have;

Table 5: Total number of infections averted and total cost with their ICER

Strategies	**Total infectious averted**	**Total cost ($)**	**ICER**
Strategy A	6775.486	49.49	0.0073
Strategy D	6808.605	98.99	1.4944
Strategy C	6833.069	98.99	0
Strategy F	6865.195	148.485	1.54

Table 7: Total number of infections averted and total cost with their ICER

Strategies	**Total infectious averted**	**Total cost ($)**	**ICER**
Strategy A	6775.486	49.49	0.0073
Strategy F	6865.195	148.485	1.1034

Table 6: Total number of infections averted and total cost with their ICER

Strategies	**Total infectious averted**	**Total cost ($)**	**ICER**
Strategy A	6775.486	49.49	0.0073
Strategy C	6833.069	98.99	0.85954
Strategy F	6865.195	148.485	1.54

The comparison between ICER(A) and ICER(C) shows a cost saving of $0.0073 for strategy A over strategy C. There is an additional $0.85954 per infection averted as we move from strategy A to C. The small value ICER for strategy A indicates that strategy C is ”strongly dominated”. That is, strategy C is more costly and less effective than strategy A. Therefore, strategy C, the strongly dominated is excluded. Exclude strategy C, we now compare strategy A with F. From the numerical results we have; The comparison between ICER(A) and ICER(F) shows a cost saving of $0.0073 for strategy A over strategy F. There is an additional $1.1034 per infection averted as we move from strategy A to F. Similarly, the small value ICER for strategy A indicates the strategy F is ”strongly dominated”. That is, strategy F is more costly and less effective than strategy A. Therefore, strategy F, the strongly dominated is excluded. With this result, therefore, it is found that strategy A (prevention) is the best strategy to reduce mastitis disease

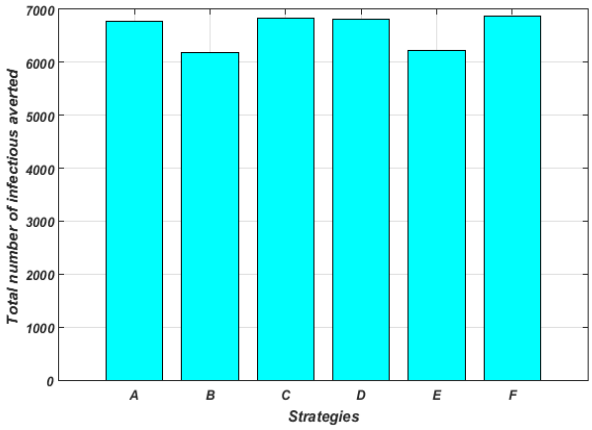


Fig. 9: Total infectious averted plots indicating the effect of control strategies A, B, C, D, E, and F.

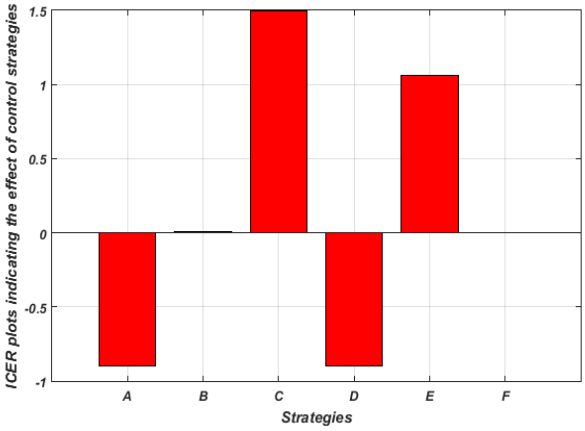


Fig. 11: Incremental cost-effective ration (ICER) plots indicating the effect of control strategies A, B, C, D, E, and F.

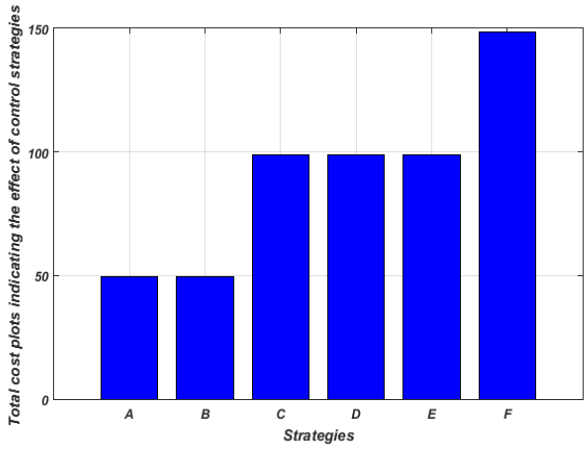


Fig. 10: The objective functional plots indicating the effect of control strategies A, B, C, D, E, and F.

in cattle. This result agrees with the results obtained in Figures 9, 10, and 11.

8 Conclusion

In this study, a mathematical model of mastitis with an optimal control strategy was formulated and analyzed using the stability theory of differential equations. First, we analyzed the invariant region and the positivity solution of the model.The primary reproduction range representing the epidemic indicator is obtained the use of the next-generation matrix. Both local and global stability of the disease-free equilibrium and endemic equilibrium point of the model equation was established. The results show that, if the basic reproduction number is less than one, then the solution converges to the disease-free steady-state, and the disease-free equilibrium is asymptotically stable. A sensitivity analysis of the model equation was performed on the key parameters in order to determine their impact on the disease transmission dynamics. Second, we apply optimal control theory to describe the model that incorporates three controls, namely using prevention of mastitis, screening of subclinical individuals, and treatment of clinical individuals. Pontryagin's maximum principle is introduced to obtain the necessary condition for the optimal control problem. Finally, the simulation result of the optimal control problem and analysis of cost-effectiveness show that using the prevention strategy is the most effective and least-cost strategy to prevent mastitis disease.

Data Availability

The data used in this paper is freely accessible for the user.

Conflicts of Interest

The authors state that there are no conflicts of interest concerning to the publication of this article.

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