New Trends in Mathematical Sciences
http://dx.doi.org/10.20852/ntmsci.2019.380

Mathematical model for the infectiology of brucellosis with some control strategies

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Received: 21 June 2019, Accepted: 8 October 2019
Published online: 25 December 2019.

Abstract: Brucellosis is a neglected zoonotic infection caused by gram-negative bacteria of genus brucella. In this paper, a deterministic mathematical model for the infectiology of brucellosis with vaccination of ruminants, culling of seropositive animals through slaughter, and proper environmental hygiene and sanitation is formulated and analyzed. A positive invariant region of the formulated model is established using the Box Invariance method, the effective reproduction number, R_e of the model is computed using the standard next generation approach. We prove that the brucellosis free equilibrium exists, locally and globally asymptotically stable if $R_e < 1$ while the endemic equilibrium point exists, locally and globally asymptotically stable if $R_e > 1$. Sensitivity analysis of the effective reproductive number shows that, natural mortality rate of ruminants, recruitment rate, ruminant to ruminant transmission rate, vaccination rate, and disease induced culling rate are the most sensitive parameters and should be targeted in designing of the control strategies for the disease. Numerical simulation is done to show the variations of each subpopulation with respect to the control parameters.

Keywords: Brucellosis, mathematical model, infectiology, environmental hygiene.

1 Introduction

Brucellosis is a zoonotic infection caused by gram-negative bacteria of genus brucella (*B. abortus* primarily from cattle, *B. melitensis* from small ruminants, *B. suis* from swine, and *B. canis* from dogs) [14,34,52,57]. It is considered by the Food and Agriculture Organisation (FAO), the World Health Organisation (WHO) and World Organization for Animal Health (Office International des Epizooties (OIE)) as one of the most widespread zoonoses in the world alongside bovine tuberculosis and rabies [45]. The disease is an ancient one that was described more than 2000 years ago by the Romans [24] and has been known by various names, including Mediterranean fever, Malta fever, gastric remittent fever, bang's disease, crimean fever, gibraltar fever, rock fever, lazybones disease and undulant fever [55]. A British military medical officer David Bruce isolated brucella bacteria from an infected individual's blood for the first time in 1887 and hence the disease was named brucellosis to honor his contribution [54]. Furthermore, in 1905 Zamitt carried out an experiment on goats to investigate the origin of human brucellosis, and found that, human brucellosis originates from goats [2]. To date, eight species have been identified and named primarily for the source animal or features of infection. Of these, the following four have moderate-to-significant human pathogenicity: *Brucella melitensis* (highest pathogenicity), *Brucella suis* (high pathogenicity) named after the source animal (swine), *Brucella abortus* (moderate pathogenicity) named after the feature of infection, *Brucella canis* named after the source animal (moderate pathogenicity) [37,38,56].

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In animals, brucellosis is transmitted when susceptible animals ingest contaminated materials like tissues or discharges from infected animals while in humans the bacteria is transmitted by ingestion of contaminated unpasteurized milk or other dairy products. Furthermore, direct contact with aborted fetuses, discharges and occupational accidents through needle injection during mass vaccination and during laboratory manipulation is another route of brucellosis transmission in the human population. In this view, farmers, laboratory personnels, abattoir workers and veterinarians are more susceptible to the disease. Infected animals exhibit clinical signs that are of economic significance to stakeholders and include reduced fertility, abortion, poor weight gain, lost draught power, and a substantial decline in milk production [21, 53]. Symptoms in humans include: continuous or intermittent fever, headache, weakness, profuse sweats, chills, joint pains, aches, weight loss as well as devastating complications in pregnant women. Neurological complications, endocarditis and testicular or bone abscess formation can also occur [13, 16]. The infection can also affect the liver and spleen, it may last for days or months, and sometimes for a year or more if not treated. The clinical signs in human present diagnostic difficulties because the disease can be confused with typhoid fever, malaria, rheumatic fever, joint diseases and relapsing fever. Human brucellosis is debilitating and requires prolonged treatment with combination of antibiotics [27].

The global burden of human brucellosis remains enormous: The infection causes more than 500,000 cases per year worldwide. The annual number of reported cases in United States (now about 100) has dropped significantly because of aggressive animal vaccination programs and milk pasteurization. Most US cases are now due to the consumption of illegally imported unpasteurized dairy products from Mexico. Approximately 60% of human brucellosis cases in the United States now occur in California and Texas [43].

In Africa Brucellosis exists throughout sub-Saharan Africa, but the prevalence is unclear and poorly understood with varying reports from country to country, geographical regions as well as animal factors [50]. Most African countries are of poor socioeconomic status, with people living with and by their livestock, while health networks, surveillance and vaccination programs are virtually non-existent. In Tanzania, the first outbreak of brucellosis was reported in Arusha in 1927 [48]. Previous surveys in Tanzania have demonstrated the occurrence of the disease in cattle in various production systems, regions and zones with individual animal level seroprevalence varying from 1 to 30%. There has been isolation of *Brucella* for more than 50 years ago and at that time *B. abortus* and *B. melitensis* were isolated from cattle and small ruminants respectively. In humans, the average prevalence varies from 1 to 5% [49], a recent study by [8]shows that brucellosis incidence is moderate in northern Tanzania and suggests that the disease is endemic and an important human health problem in this area. Moreover, special cases had been reported in areas of northern, eastern, lake and western zones with seroprevalence varying from 0.7 to 20.5%. [46].

Despite the WHO, FAO, OIE efforts and interventions are available, brucellosis continues to pose great economic threat by affecting livelihood and food security in both developed and developing countries; it is endemic in most of the developing world and causes devastating losses to the livestock industry especially small-scale livestock holders, thereby limiting economic growth and hindering access to international markets [21] from generation to generation. Thus, there is a need to assess the current control strategies and their cost-effectiveness if we are to control or eradicate the disease. So far few studies [3, 25, 33, 39, 40, 44, 56], have been developed to analyze dynamics of and spread of brucellosis in a homogeneous/heterogeneous populations. However, none of these studies have considered the mathematical approach for the impact of vaccination of ruminants, culling of seropositive animals through slaughter, and proper environmental hygiene and sanitation in reducing or eradicating the disease in cattle, small ruminants and human populations using mathematical models. This paper is at hand to fill the gap.

2 Model formulation

2.1 Dynamics of brucellosis

In this section, we formulate a deterministic mathematical model for the transmission dynamics of Brucellosis in domestic small ruminants, cattle and human populations. The model includes: direct transmission of brucellosis within the cattle population, within small ruminants (sheep and goats) and from both species to human and indirect transmission from the environment to livestock and humans. Cattle and small ruminants newborns are either vaccinated or remain susceptible. Based on the epidemiological status, the cattle population at any time t is divided into vaccinated $V_c(t)$, susceptible $S_c(t)$, and infective $I_c(t)$ classes. Similarly, the small ruminant population at any time t is divided into vaccinated $V_s(t)$, susceptible $S_s(t)$, and infectious $I_s(t)$ subpopulations while the total human population, $N_h(t)$ at any time t is divided into susceptible, $S_h(t)$, infected, $I_h(t)$ and recovered, $R_h(t)$ individuals. Susceptible cattle become infected when they are in contact with infected cattle (direct transmission) at the rate of β_c or through contact with infected raw blood, meat, placentas, aborted fetus, unpasteurized milk or other dairy products (indirect transmission) at the rate α_c, and susceptible small ruminants become infected when they are in contact with infectious small ruminants at the rate of β_s or through contact with their products at the rate α_s while the transmission to humans is expressed as additive contributions of transmission from infective cattle, small ruminants and their products. Appertaining to the fact that it is very difficult to determine the quantity of brucella in environment, we define the average number of brucella that is enough for a host to be infected with brucellosis as an infectious unit and let $B(t)$ to be the number of infectious units in the environment. During the incubation period, Brucellosis is hardly detected, but individuals at this period can infect the susceptible individuals at the same transmission rate as the infectious individual and discharge the same quantity of brucella into the environment per unit time. It is against this background, we assume that individuals in the incubation period and post incubation period are hosted in the same population compartment called infectious. The interaction within and between the four populations shows that, veterinary surgeons, laboratory assistants, and farmers are predominantly exposed to the pathogen (See Figure 1).

2.2 Model assumptions

In formulation of the model, the following assumptions are taken into consideration:

(i) There is no direct transmission between cattle and small ruminants.
(ii) Infected animals shed the brucellosis pathogen in the environment.
(iii) Livestock seropositivity is a life-long lasting.
(iv) Immunized individuals cannot be infected unless their vaccine efficacy wanes.
(v) There is constant natural mortality rate in each of the species.
(vi) The mixing in each population is homogeneous.
(vii) The birth rate for each population is greater than natural mortality rate.

The variables and parameters used in this model are respectively summarized in Table 1 and Table 2.

2.3 Compartmental Flow Diagram for the Disease Dynamics

The interactions between the human, cattle, small ruminants populations and the brucella in the environment are illustrated in Figure 1.

Table 1: Model Variables

Variable	Description
$S_h(t)$	Number of susceptible humans at time t
$I_h(t)$	Number of infected human at time t
$R_h(t)$	Number of recovered humans at time t
$S_c(t)$	Number of susceptible cattle at time t
$I_c(t)$	Number of infected cattle at time t
$V_c(t)$	Number of vaccinated cattle at time t
$S_s(t)$	Number of susceptible small ruminants at time t
$I_s(t)$	Number of infected small ruminants at time t
$V_s(t)$	Number of vaccinated small ruminants at time t
$B(t)$	Number of brucella bacteria load per unit volume in the environment at time t

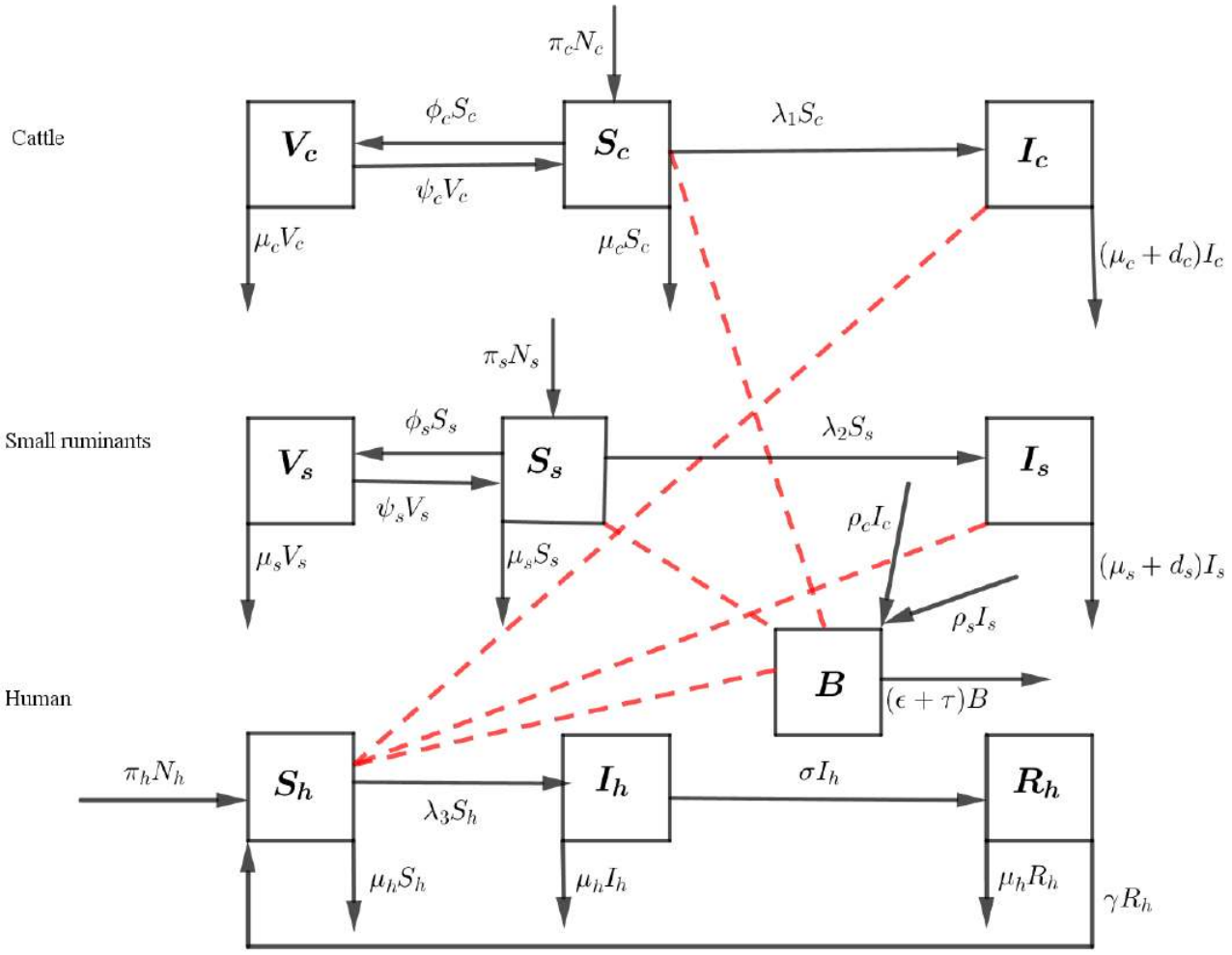


Fig. 1: A schematic diagram for direct and indirect transmission of brucellosis in cattle, small ruminants and human populations. Solid arrows represent transfer of individuals from one subpopulation to another while dotted lines represent interactions leading to infections.

Table 2: Model Parameters used in the model and their description

Parameter	Description
π_c	Per capita cattle birth rate
ϕ_c	Cattle vaccination rate
π_h	Per capita human birth rate
σ	Human recovery rate
μ_h	Per capita human natural death rate
ψ_c	Cattle vaccine efficacy waning rate
β_c	Within cattle transmission rate
d_c	Culling rate of seropositive cattle
μ_c	Per capita cattle natural death rate
α_c	Brucella from the environment to cattle transmission rate
α_s	Brucella from the environment to small ruminants transmission rate
α_h	Brucella from the environment to human transmission rate
ρ_c	Brucella shedding rate by infected cattle
ρ_s	Brucella shedding rate by infected small ruminants
β_{ch}	Cattle to human transmission rate
β_{sh}	Small ruminants to human transmission rate
γ	The rate at which recovered human become susceptible
ε	Decaying rate of brucella in the environment
τ	Environmental hygiene and sanitation rate
π_s	Small ruminants per capita birth rate
ϕ_s	Vaccination rate of small ruminants
ψ_s	Small ruminant vaccine efficacy
β_s	Within small ruminants transmission rate
d_s	Culling rate of seropositive small ruminants
μ_s	Per capita small ruminants natural mortality rate

2.4 Model equations

Based on the assumptions and the inter-relations between the variables and the parameters as shown in Figure 1, the transmission dynamics of Brucellosis can be described by the following ordinary differential equations:

$$
\begin{aligned}
\frac{dV_c}{dt} &= \phi_c S_c - (\mu_c + \psi_c)V_c, \\
\frac{dS_c}{dt} &= \pi_c N_c + \psi_c V_c - (\lambda_1 + \phi_c + \mu_c)S_c, \\
\frac{dI_c}{dt} &= \lambda_1 S_c - (\mu_c + d_c)I_c, \\
\frac{dV_s}{dt} &= \phi_s S_s - (\mu_s + \psi_s)V_s, \\
\frac{dS_s}{dt} &= \pi_s N_s + \psi_s V_s - (\lambda_2 + \phi_s + \mu_s)S_s, \\
\frac{dI_s}{dt} &= \lambda_2 S_s - (\mu_s + d_s)I_s, \\
\frac{dB}{dt} &= \rho_c I_c + \rho_s I_s - (\varepsilon + \tau)B, \\
\frac{dS_h}{dt} &= \pi_h N_h + \gamma R_h - (\lambda_3 + \mu_h)S_h, \\
\frac{dI_h}{dt} &= \lambda_3 S_h - (\sigma + \mu_h)I_h, \\
\frac{dR_h}{dt} &= \sigma I_h - (\gamma + \mu_h)R_h,
\end{aligned}
\tag{1}
$$

where, $\lambda_1 = \beta_c I_c + \alpha_c B, \lambda_2 = \beta_s I_s + \alpha_s B$ and $\lambda_3 = \beta_{hc} I_c + \beta_{hs} I_s + \alpha_h B$.

3 Model properties

Basing on the fact that the first seven equations of system (1) are independent of the last three equations, let us first consider the following model for cattle and the ruminants:

$$\begin{aligned}
\frac{dV_c}{dt} &= \phi_c S_c - (\mu_c + \psi_c) V_c, \\
\frac{dS_c}{dt} &= \pi_c N_c + \psi_c V_c - (\lambda_1 + \phi_c + \mu_c) S_c, \\
\frac{dI_c}{dt} &= \lambda_1 S_c - (\mu_c + d_c) I_c, \\
\frac{dV_s}{dt} &= \phi_s S_s - (\mu_s + \psi_s) V_s, \\
\frac{dS_s}{dt} &= \pi_s N_s + \psi_s V_s - (\lambda_2 + \phi_s + \mu_s) S_s, \\
\frac{dI_s}{dt} &= \lambda_2 S_s - (\mu_s + d_s) I_s, \\
\frac{dB}{dt} &= \rho_c I_c + \rho_s I_s - (\varepsilon + \tau) B.
\end{aligned} \tag{2}$$

3.1 Invariant region

In this subsection we use Box Invariance method proposed by [1] to assess the well-posedness of the model by investigating the existence and feasibility of its solution. In other words, we investigate whether the solutions are epidemiologically (variables have biological interpretation) and mathematically well-posed (a unique bounded solution exists for all the time). That is solutions of model system (2) with nonnegative initial data remain nonnegative for all time $t \geq 0$. The model system (2) can be expressed in the compact form as:

$$\frac{dX}{dt} = A(X) + F.$$

where, $X = (V_c, S_c, I_c, V_s, S_s, I_s, B)$, F is a column vector given by $F = (0, \pi_c N_c, 0, 0, \pi_s N_s, 0, 0, 0)^T$ and

$$A = \begin{bmatrix}
-(\mu_c + \psi_c) & \phi_c & 0 & 0 & 0 & 0 & 0 \\
\psi_c & -(\lambda_1 + \phi_c + \mu_c) & 0 & 0 & 0 & 0 & 0 \\
0 & \lambda_1 & -(\mu_c + d_c) & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & -(\mu_s + \psi_s) & \phi_c & 0 & 0 \\
0 & 0 & 0 & \psi_s & -(\lambda_2 + \phi_s + \mu_s) & 0 & 0 \\
0 & 0 & 0 & 0 & \lambda_2 & -(\mu_s + d_s) & 0 \\
0 & 0 & \rho_c & 0 & 0 & \rho_s & -(\varepsilon + \tau)
\end{bmatrix}.$$

It can be noticed that $A(X)$ is Meltzer matrix since all of its off diagonal entries are non negative, for all $X \in \mathbb{R}^7_+$. Therefore, using the fact that $F \geq 0$, the model system (2) is positively invariant in $\mathbb{R}^7_+$ which means that an arbitrary trajectory of the system starting in $\mathbb{R}^7_+$ remains in $\mathbb{R}^7_+$ forever. In addition, the right hand F is Lipschitz continuous. Thus, a unique maximal solution exists and so

$$\Omega = \{(V_c, S_c, I_c, V_s, S_s, I_s, B) \geq 0\} \in \mathbb{R}^7_+,$$

is the feasible region for the model (2). Thus, the model (2) is epidemiologically and mathematically well-posed in the region Ω.

4 Model analysis

4.1 Disease free equilibrium

The Brucellosis free equilibrium point is obtained by setting the right hand side of equations in model system (2) to zero, that is:

$$\frac{dV_c}{dt} = \frac{dS_c}{dt} = \frac{dI_c}{dt} = \frac{dV_s}{dt} = \frac{dS_s}{dt} = \frac{dI_s}{dt} = \frac{dB}{dt} = 0.$$

Let the disease free equilibrium point of Brucellosis model be E^0. In case there is no disease $I_c = I_s = B = 0$ that is, the sum of susceptible and vaccinated populations is equal to total population. There exists a disease free equilibrium $E^0 = (V_c^0, S_c^0, 0, V_s^0, S_s^0, 0, 0)$ for model system (2) where:

$$S_c^0 = \frac{(\mu_c + \psi_c)\pi_c N_c^0}{\mu_c(\phi_c + \psi_c + \mu_c)}, \qquad S_s^0 = \frac{(\mu_s + \psi_s)\pi_s N_s^0}{\mu_s(\phi_s + \psi_s + \mu_s)}, \qquad V_c^0 = \frac{\phi_c \pi_c N_c^0}{\mu_c(\phi_c + \psi_c + \mu_c)},$$

$$V_s^0 = \frac{\phi_s \pi_s N_s^0}{\mu_s(\phi_s + \psi_s + \mu_s)}.$$

4.2 The effective reproduction number

In this subsection, we compute the effective reproduction number for model system (2) using the standard method of the next generation matrix developed in [17,18]. The effective reproduction number, R_e is defined as the measure of average number of infections caused by a single infectious individual introduced in a community in which intervention strategies are administered [41]. Its magnitude is a useful indicator of both the risk of an epidemic and the effort required to control an infection [58]. When there are no interventions or controls, the number of secondary infections caused by typical infected individual in a completely susceptible population during its entire period of infectiousness is called basic reproduction number, R_0. It is the threshold parameter to determine whether or not the disease can invade the susceptible population successfully. Due to the natural history of some infections, transmissibility is better quantified by the effective reproduction number rather than the basic reproduction number [15]. Considering the system for the infective variables:

$$\begin{aligned}
\frac{dI_c}{dt} &= (\beta_c I_c + \alpha_c B)S_c - (\mu_c + d_c)I_c, \\
\frac{dI_s}{dt} &= (\beta_s I_s + \alpha_s B)S_s - (\mu_s + d_s)I_s, \\
\frac{dB}{dt} &= \rho_c I_c + \rho_s I_s - (\varepsilon + \tau)B.
\end{aligned} \tag{3}$$

The effective reproduction number is obtained by taking the spectral radius of the next generation matrix

$$FV^{-1} = \left[\frac{\partial \mathscr{F}_i(E^0)}{\partial t}\right]\left[\frac{\partial \mathscr{V}_i(E^0)}{\partial t}\right]^{-1},$$

where E^0 is the brucellosis-free equilibrium point while $\mathscr{F}_i$ and $\mathscr{V}_i$ are vectors representing respectively, the rate of appearance of new infection in compartment i and the transfer of infections from one compartment i to another, such that:

$$\mathscr{F}_i = \begin{bmatrix} (\beta_c I_c + \alpha_c B)S_c \\ (\beta_s I_s + \alpha_s B)S_s \\ 0 \end{bmatrix},$$

$$\mathscr{V}_i = \begin{bmatrix} (\mu_c + d_c)I_c \\ (\mu_s + d_s)I_s \\ -\rho_c I_c - \rho_s I_s + (\varepsilon + \tau)B \end{bmatrix}.$$

It is important to note that $\mathscr{V}_i$ is a resultant vector of the two vectors $\mathscr{V}_i^+$ defined as the rate of transfer of individuals into compartment i by all other means, and $\mathscr{V}_i^-$ which is the rate of transfer of individuals out of compartment i. That is:

$$\mathscr{V}_i = \mathscr{V}_i^- - \mathscr{V}_i^+, i = \{1,2,3\}.$$

The Jacobian matrices F of $\mathscr{F}_i$ and V of $\mathscr{V}_i$ evaluated at E^0 are respectively:

$$F = \begin{bmatrix} \beta_c S_c^0 & 0 & \alpha_c S_c^0 \\ 0 & \beta_s S_s^0 & \alpha_s S_s^0 \\ 0 & 0 & 0 \end{bmatrix},$$

and

$$V = \begin{bmatrix} \mu_c + d_c & 0 & 0 \\ 0 & \mu_s + d_s & 0 \\ -\rho_c & -\rho_s & (\varepsilon + \tau) \end{bmatrix}.$$

Referring to the infected states with indices i and j, for $i, j \in [1,2,3]$, the entry F_{ij} is the rate at which individuals in infected state j give rise or produce new infections to individuals in infected state i, in the linearized system. Thus, when there is no new cases produced in infected state i by an individual in infected state j immediately after infection, we have $F_{ij} = 0$. The inverse of V is found to be

$$V^{-1} = \begin{bmatrix} \frac{1}{\mu_c + d_c} & 0 & 0 \\ 0 & \frac{1}{\mu_s + d_s} & 0 \\ \frac{\rho_c}{(\mu_c + d_c)(\varepsilon + \tau)} & \frac{\rho_s}{(\mu_s + d_s)(\varepsilon + \tau)} & \frac{1}{\varepsilon + \tau} \end{bmatrix}.$$

The entry $\left(V^{-1}\right)_{ij}$ is the average length of time an infected individual spends in compartment j during its lifetime when introduced into the compartment i of disease free equilibrium, assuming that the population remains near the disease free equilibrium and barring reinfection. In particular, $\frac{1}{\mu_c + d_c}$ is an average time an infectious cattle spends in the state of being infective, $\frac{1}{\mu_s + d_s}$ is the average time spent by an infective small ruminant in the infectious state and $\frac{1}{\varepsilon + \tau}$ is the average time *brucella* spend in the environment. Furthermore, $\frac{\rho_c}{(\mu_c + d_c)}$ is the probability that an infective cattle will shed *brucella* into the environment while $\frac{\rho_s}{(\mu_s + d_s)}$ is the probability that an infected small ruminant will shed *brucella* into the environment. Moreover, the Next Generation Matrix is calculated to be:

$$FV^{-1} = \begin{bmatrix} \frac{\beta_c S_c^0}{\mu_c + d_c} + \frac{\alpha_c \rho_c S_c^0}{(\mu_c + d_c)(\varepsilon + \tau)} & \frac{\alpha_c \rho_s S_c^0}{(\mu_s + d_s)(\varepsilon + \tau)} & \frac{\alpha_c S_c^0}{\varepsilon + \tau} \\ \frac{\alpha_s \rho_c S_s^0}{(\mu_c + d_c)(\varepsilon + \tau)} & \frac{\beta_s S_s^0}{\mu_s + d_s} + \frac{\alpha_s \rho_s S_s^0}{(\mu_s + d_s)(\varepsilon + \tau)} & \frac{\alpha_s S_s^0}{\varepsilon + \tau} \\ 0 & 0 & 0 \end{bmatrix}.$$

The matrix FV^{-1} can be written as:

$$FV^{-1} = \begin{bmatrix} R_{11} & R_{12} & R_{13} \\ R_{21} & R_{22} & R_{23} \\ 0 & 0 & 0 \end{bmatrix}.$$

The (i,k) entry of the Next Generation Matrix FV^{-1} is the expected number of secondary infections in compartment i produced by individuals initially in compartment k assuming that the environment seen by the individual remains homogeneous for the duration of its infection [51]. In particular; R_{11} is the expected number of infected cattle produced by one infectious cattle, R_{12} is the expected number of infected cattle produced by one infectious small ruminant via consumption of brucella from the environment, R_{21} is the expected number of infected small ruminant as a result of one infected cattle, and R_{22} is the expected number of infected small ruminant as a result of one infected small ruminant. It can further be noticed that, matrix FV^{-1} is non-negative and therefore, has a nonnegative eigenvalue. The non-negative eigenvalue is associated with a non-negative eigenvector which represents the distribution of infected individuals that produces the greatest number R_e of secondary infections per generation [42]. Thus, the spectral radius for our Next Generation Matrix is

$$\rho(FV^{-1}) = R_e = \frac{R_{11}+R_{22}+\sqrt{(R_{22}-R_{11})^2+4R_{12}R_{21}}}{2} \tag{4}$$

where,

$$R_{11} = \frac{(\beta_c(\varepsilon+\tau)+\alpha_c\rho_c)(\psi_c+\mu_c)\pi_c N_c^0}{\mu_c(\mu_c+d_c)(\varepsilon+\tau)(\phi_c+\psi_c+\mu_c)}, \quad R_{22} = \frac{(\beta_s(\varepsilon+\tau)+\alpha_s\rho_s)(\psi_s+\mu_s)\pi_s N_s^0}{\mu_s(\mu_s+d_s)(\varepsilon+\tau)(\phi_s+\psi_s+\mu_s)},$$

$$R_{12} = \frac{(\psi_c+\mu_c)\alpha_c\rho_s\pi_c N_c^0}{\mu_c(\mu_s+d_s)(\varepsilon+\tau)(\phi_c+\psi_c+\mu_c)}, \quad R_{21} = \frac{(\psi_s+\mu_s)\alpha_s\rho_c\pi_s N_s^0}{\mu_s(\mu_c+d_c)(\varepsilon+\tau)(\phi_s+\psi_s+\mu_s)},$$

When there is no livestock vaccination: $\psi_c = \psi_s = \phi_c = \phi_s = 0$ and

$$R_{11} = \frac{(\beta_c(\varepsilon+\tau)+\alpha_c\rho_c)\pi_c N_c^0}{\mu_c(\mu_c+d_c)(\varepsilon+\tau)}, \quad R_{22} = \frac{(\beta_s(\varepsilon+\tau)+\alpha_s\rho_s)\pi_s N_s^0}{\mu_s(\mu_s+d_s)(\varepsilon+\tau)},$$

,

$$R_{12} = \frac{\alpha_c\rho_s\pi_c N_c^0}{\mu_c(\mu_s+d_s)(\varepsilon+\tau)}, \quad R_{21} = \frac{\alpha_s\rho_c\pi_s N_s^0}{\mu_s(\mu_c+d_c)(\varepsilon+\tau)},$$

When there is no intervention: $\psi_c = \psi_s = \phi_c = \phi_s = \tau = 0$, the effective reproduction number becomes the basic reproduction number:

$$R_0 = \frac{R_{11}^0+R_{22}^0+\sqrt{(R_{22}^0-R_{11}^0)^2+4R_{12}^0R_{21}^0}}{2}, \tag{5}$$

where,

$$R_{11}^0 = \frac{(\beta_c\varepsilon+\alpha_c\rho_c)\pi_c N_c^0}{\mu_c(\mu_c+d_c)\varepsilon}, R_{22}^0 = \frac{(\beta_s\varepsilon+\alpha_s\rho_s)\pi_s N_s^0}{\mu_s(\mu_s+d_s)\varepsilon}, R_{12}^0 = \frac{\alpha_c\rho_s\pi_c N_c^0}{\mu_c(\mu_s+d_s)\varepsilon},$$

and

$$R_{21}^0 = \frac{\alpha_s\rho_c\pi_s N_s^0}{\mu_s(\mu_c+d_c)\varepsilon}.$$

In view of the fact that, the first seven equations of model system (1) are independent of the last three equations, system (1) and system (2) have the same effective reproduction and the same basic reproduction number. Thus, the effective reproduction and basic reproduction number for system (1) are R_e and R_0, respectively.

4.3 Local stability of the disease free equilibrium

In this subsection we use the trace-determinant method to investigate the local stability of the brucellosis free equilibrium point.

Theorem 1. *The disease free equilibrium for the brucellosis model system(2) is locally asymptotically stable if* $R_0 < 1$ *and unstable if* $R_0 > 1$.

Proof. We show that, variational matrix $J(E_0)$ of the brucellosis model at DFE has a negative trace and positive determinant.
The Jacobian matrix for system 3.2 is given by:

$$J(E_0) = \begin{bmatrix} -(\mu_c+\psi_c) & \phi_c & 0 & 0 & 0 & 0 & 0 \\ \psi_c & -(\phi_c+\mu_c) & -\beta_c S_c^0 & 0 & 0 & 0 & -\alpha_c S_c^0 \\ 0 & 0 & a_0 & 0 & 0 & 0 & \alpha_c S_c^0 \\ 0 & 0 & 0 & -(\mu_s+\psi_s) & \phi_s & 0 & 0 \\ 0 & 0 & 0 & \psi_s & -(\phi_s+\mu_s) & -\beta_s S_s^0 & -\alpha_s S_s^0 \\ 0 & 0 & 0 & 0 & 0 & a_1 & \alpha_s S_s^0 \\ 0 & 0 & \rho_c & 0 & 0 & \rho_s & -(\varepsilon+\tau) \end{bmatrix}$$

where,

$$a_0 = \beta_c S_c^0 - (\mu_c + d_c),$$

$$a_1 = \beta_s S_s^0 - (\mu_s + d_s).$$

The trace of the Jacobian matrix $J(E_0)$ is given by:

$$\begin{aligned} Tr(J(E_0)) =& -(\phi_c+\psi_c+2\mu_c+\varepsilon+\tau+\phi_s+\psi_s+2\mu_s)+\beta_c S_c^0-(\mu_c+d_c)+\beta_s S_s^0-(\mu_s+d_s), \\ =& -(\phi_c+\psi_c+2\mu_c+\varepsilon+\tau+\phi_s+\psi_s+2\mu_s), \\ & -(\mu_c+d_s)\left(1-\frac{\beta_c S_c^0}{\mu_c+d_c}\right)-(\mu_s+d_s)\left(1-\frac{\beta_s S_s^0}{\mu_s+d_s}\right). \end{aligned}$$

Thus, the trace of the Jocobian matrix is the less than zero, that is $Tr(J(E_0)) < 0$, if:

$$\frac{\beta_c S_c^0}{\mu_c+d_c} < 1 \text{ and } \frac{\beta_s S_s^0}{\mu_c+d_s} < 1.$$

On the hand, the determinant of matrix $J(E_0)$ is:

$$\begin{aligned} Det(J(E_0)) =& \mu_c\mu_s(\phi_c+\psi_c+\mu_c)(\phi_s+\psi_s+\mu_s)[(\mu_s+d_s)(\varepsilon+\tau)\beta_c S_c^0\left(1-\frac{\beta_s S_s^0}{\mu_s+d_s}\right) \\ & +(\mu_c+d_c)\rho_s\alpha_s S_s^0\left(1-\frac{\beta_c S_c^0}{\mu_c+d_c}\right)+(\mu_s+d_s)\rho_c\alpha_c S_c^0\left(1-\frac{\beta_s S_s^0}{\mu_s+d_s}\right) \\ & -(\mu_c+d_c)(\mu_s+d_s)(\varepsilon+\tau)\left(1-\frac{\beta_s S_s^0}{\mu_s+d_s}\right)], \\ =& \mu_c\mu_s(\phi_c+\psi_c+\mu_c)(\phi_s+\psi_s+\mu_s)(\mu_c+d_c)(\mu_s+d_s)(\varepsilon+\tau) \\ & \left(\frac{\alpha_c\rho_c S_c^0\left(1-\frac{\beta_s S_s^0}{\mu_s+d_s}\right)}{(\varepsilon+\tau)(\mu_s+d_s)}-\left(1-\frac{\beta_c S_c^0}{\mu_c+d_c}\right)\left(1-\frac{(\beta_s(\varepsilon+\tau)+\alpha_s\rho_s)S_s^0}{(\varepsilon+\tau)(\mu_s+d_s)}\right)\right). \end{aligned}$$

The determinant of the Jacobian matrix is positive (i.e. $J(E_0) > 0$) iff:

$$\left(\frac{\alpha_c \rho_c S_c^0 \left(1 - \frac{\beta_s S_s^0}{\mu_s + d_s}\right)}{(\varepsilon + \tau)(\mu_s + d_s)} > \left(1 - \frac{\beta_c S_c^0}{\mu_c + d_c}\right)\left(1 - \frac{(\beta_s(\varepsilon + \tau) + \alpha_s \rho_s) S_s^0}{(\varepsilon + \tau)(\mu_s + d_s)}\right) \right),$$

$$\frac{\beta_c S_c^0}{\mu_c + d_c} < 1, \qquad \frac{\beta_s S_s^0}{\mu_c + d_s} < 1,$$

and

$$\frac{((\varepsilon + \tau)\beta_c + \rho_c \alpha_c) S_c^0}{(\varepsilon + \tau)(\mu_c + d_c)} < 1.$$

Furthermore, $\frac{\beta_c S_c^0}{\mu_c + d_c}$ and $\frac{\beta_s S_s^0}{\mu_c + d_s}$ are respectively the average number of cattle infections as a result of direct contact between susceptible and infected cattle and the average number of small ruminant infections as a result of direct contact between susceptible and infected small ruminant, and $\frac{((\varepsilon + \tau)\beta_c + \rho_c \alpha_c) S_c^0}{(\varepsilon + \tau)(\mu_c + d_c)}$ is the expected number of infected cattle caused directly or indirectly by one infectious cattle. Thus, the brucellosis free equilibrium for each population is locally asymptotically stable if and only if the number of secondary infections, (R_e) is less than unit, that is $R_0 < 1$. This completes the proof.

4.4 Global stability of the disease-free equilibrium

In this section, we analyze the global stability of the disease-free equilibrium point by applying the [11] approach. We write model system (2) in the form:

$$\begin{cases} \frac{dX_s}{dt} = A(X_s - X_{DFE,S}) + A_1 X_i, \\ \frac{dX_i}{dt} = A_2 X_i, \end{cases} \tag{6}$$

where X_s is the vector representing the non-transmitting compartments and X_i is the vector representing the transmitting components. The DFE is globally asymptotically stable if A has real negative eigenvalues and A_2 is a Metzler matrix (i.e. the off-diagonal elements of A_2 are non-negative). From model system (2) we have:

$$X_i = (I_c, I_s, B)^T, X_s = (V_c, S_c, V_s, S_s)^T, X_s - X_{DFE,s} = \begin{bmatrix} V_c - \frac{\phi_c \pi_c N_c^0}{\mu_c(\phi_c + \mu_c + \psi_c) + \psi_c} \\ S_c - \frac{(\phi_c + \mu_c)\pi_c N_c^0}{\mu_c(\phi_c + \mu_c + \psi_c) + \psi_c} \\ V_s - \frac{\phi_s \pi_s N_s^0}{\mu_s(\phi_s + \mu_s + \psi_s) + \psi_s} \\ S_s - \frac{(\phi_s + \mu_s)\pi_s N_s^0}{\mu_s(\phi_s + \mu_s + \psi_s) + \psi_s} \end{bmatrix},$$

and

$$A_1 = \begin{bmatrix} 0 & 0 & 0 \\ -\beta_c S_c & 0 & -\alpha_c \\ 0 & 0 & 0 \\ 0 & -\beta_s S_s & -\alpha_s \end{bmatrix}.$$

We need to check whether a matrix A for the non-transmitting compartments has real negative eigenvalues and that A_2 is a Metzler matrix. From the equation for non-transmitting compartments in (2) we have:

$$A = \begin{bmatrix} -(\psi_c+\mu_c) & \phi_c & 0 & 0 \\ \psi_c & -(\phi_c+\mu_c) & 0 & 0 \\ 0 & 0 & -(\psi_s+\mu_s) & \phi_s \\ 0 & 0 & \psi_s & -(\phi_s+\mu_s) \end{bmatrix},$$

with eigenvalues $\lambda_1 = -\mu_s, \lambda_2 = -(\psi_s+\phi_s+\mu_s), \lambda_3 = -\mu_c, \lambda_4 = -(\psi_c+\phi_c+\mu_c)$ and

$$A_2 = \begin{bmatrix} \beta_c S_c^0 - (\mu_c+d_c) & 0 & \alpha_c S_c^0 \\ 0 & \beta_s S_s^0 - (\mu_s+d_s) & \alpha_s S_s^0 \\ \rho_c & \rho_s & -(\varepsilon+\tau) \end{bmatrix}.$$

It can be seen that, A_2 which is a Metzler matrix, and A, have real negative eigenvalues. This implies that the disease free equilibrium for the model system (2) is globally asymptotically stable.

4.5 Global stability of endemic equilibrium

The local stability of the disease free equilibrium suggests local stability of the endemic equilibrium for the reverse condition [9,10,51]. In this subsection we study the global behaviour of the endemic equilibrium, E^* for the model system (2).

Theorem 2. *The endemic equilibrium point for the brucellosis model system (2) is globally asymptotically stable on Ω if $R_0 > 1$.*

Proof. We construction an explicit Lyapunov function for model system (2) using [7,30,31,32,36] approach as it is useful to most of the sophisticated compartmental epidemiological models. In this approach, we construct Lyapunov function of the form:

$$V = \sum a_i (x_i - x_i^* \ln x),$$

where a_i is a properly selected positive constant, x_i is the population of the i^{th} compartment and x_i^* is the equilibrium level. We define the Lyapunov function candidate V for model system (2) as:

$$\begin{aligned} L =& (S_c - S_c^* \ln S_c) + A_1 (V_c - V_c^* \ln V_c) + A_2 (I_c - I_c^* \ln I_c) + (S_s - S_s^* \ln S_s) \\ &+ A_3 (V_s - V_s^* \ln V_s) + A_4 (I_s - I_s^* \ln I_s) + A_5 (B - B^* \ln B), \end{aligned} \tag{7}$$

where A_1, A_2, A_3, A_4 and A_5 are positive constants. The time derivative of the Lyapunov function L is given by:

$$\begin{aligned} \frac{dL}{dt} =& \left(1 - \frac{S_c^*}{S_c}\right)\frac{dS_c}{dt} + A_1\left(1 - \frac{V_c^*}{V_c}\right)\frac{dV_c}{dt} + A_2\left(1 - \frac{I_c^*}{I_c}\right)\frac{dI_c}{dt} + \left(1 - \frac{S_s^*}{S_s}\right)\frac{dS_s}{dt} \\ &+ A_3\left(1 - \frac{V_s^*}{V_s}\right)\frac{dV_s}{dt} + A_4\left(1 - \frac{I_s^*}{I_s}\right)\frac{dI_s}{dt} + A_5\left(1 - \frac{B^*}{B}\right)\frac{dB}{dt}. \end{aligned} \tag{8}$$

Considering (2) at E^* we have:

$$\phi = \frac{(\psi_c + \mu_c)V_c^*}{S_c^*},$$

$$\pi_c N_c^* = (\beta_c I_c^* + \alpha_c B^* + \phi_c + \mu_c)S^* - \psi_c V_c^*,$$

$$\mu_c + d_c = \frac{(\beta_c I_c^* + \alpha_c B^*)S^*}{I_c^*},$$

$$(\varepsilon + \tau) = \frac{\rho_c I_c^* + \rho_s I_s^*}{I_c^*}.$$

Then, equation (8) may be re-written as:

$$\begin{aligned}
\frac{dL}{dt} =& -(\phi_c + \mu_c)S_c\left(1 - \frac{S_c^*}{S_c}\right)^2 - (\phi_s + \mu_s)S_s\left(1 - \frac{S_s^*}{S_s}\right)^2 \\
&- \left(1 - \frac{S_c^*}{S_c}\right)\left(\beta_c I_c S_c\left(1 - \frac{I_c^* S_c^*}{I_c S_c}\right) + \alpha_c B S_c\left(1 - \frac{B^* S_c^*}{B S_c}\right) + \psi_c V_c\left(\frac{V_c^*}{V_c} - 1\right)\right) \\
&- \left(1 - \frac{S_s^*}{S_s}\right)\left(\beta_s I_s S_s\left(1 - \frac{I_s^* S_s^*}{I_s S_s}\right) + \alpha_s B S_s\left(1 - \frac{B^* S_s^*}{B S_s}\right) + \psi_s V_s\left(\frac{V_s^*}{V_s} - 1\right)\right) \\
&- (\psi_c + \mu_c)BV_c A_1\left(1 - \frac{V_c^*}{V_c}\right)\left(1 - \frac{V_c^*}{V_c S_c^*}\right) - (\psi_s + \mu_s)BV_s A_3\left(1 - \frac{V_s^*}{V_s}\right)\left(1 - \frac{V_s^*}{V_s S_s^*}\right) \\
&+ A_2\left(1 - \frac{I_c^*}{I_c}\right)\left(\beta_c I_c S_c\left(1 - \frac{S_c^*}{S_c}\right) + \alpha_c B S_c\left(1 - \frac{B^* S_c^* I_c}{B S_c I_c^*}\right)\right) \\
&+ A_4\left(1 - \frac{I_s^*}{I_s}\right)\left(\beta_s I_s S_s\left(1 - \frac{S_s^*}{S_s}\right) + \alpha_s B S_s\left(1 - \frac{B^* S_s^* I_s}{B S_s I_s^*}\right)\right) \\
&+ A_5\left(1 - \frac{B^*}{B}\right)\left(\rho_c I_c\left(1 - \frac{B I_c^*}{B^* I_c}\right) + \rho_s I_s\left(1 - \frac{B I_s^*}{B^* I_s}\right)\right).
\end{aligned} \tag{9}$$

Equation (9) can be written as:

$$\frac{dL}{dt} = -\left((\phi_c + \mu_c)S_c\left(1 - \frac{S_c^*}{S_c}\right)^2 + (\phi_s + \mu_s)S_s\left(1 - \frac{S_s^*}{S_s}\right)^2\right) + F(S_c, V_c, I_c, S_s, V_s, I_s, B),$$

where F is the balance of the right hand terms of equation (9). Following the approach of [7,30,31,32,33,36], F is a non-positive function for $S_c, V_c, I_c, S_s, V_s, I_s, B > 0$. Thus, $\frac{dL}{dt} < 0$ for $S_c, V_c, I_c, S_s, V_s, I_s, B > 0$ and is zero if $S_c = S_c^*, V_c = V_c^*, I_c = I_c^*, S_s = S_s^*, V_s = V_s^*, I_s = I_s^*$, and $B = B^*$. Therefore, if $R_e > 1$, model system (2) has a an endemic equilibrium point E^* which is locally and globally asymptotically stable.

5 Sensitivity analysis

In this section, we investigate the relative importance of the parameters featuring in the effective reproduction number. Brucellosis incidences and prevalences can best be reduced or eradicated if the parameters with significant impact in the transmission dynamics of the disease are taken into consideration when planning for and implementing intervention strategies. Sensitivity analysis is commonly used to determine the robustness of model predictions to parameter values, since there are usually errors in data collection and presumed parameter values [12]. Sensitivity indices provide information on how vital each parameter is to disease transmission and prevalence, and permits measurement of relative changes in a state variable when a parameter changes. Thus, we use sensitivity analysis to discover parameters that have

high impact on the reproduction number, R_e and that should be targeted by intervention strategies. We know that initial disease transmission is directly related to R_e, therefore we compute the sensitivity indices of R_e for the parameters in model 2. The explicit expression of R_e is given by equation 4. Since R_e depends only on twenty parameters, we derive an analytical expression for its sensitivity to each parameter using the normalized forward sensitivity index [35] as follows:

$$\Upsilon_{\mu_c}^{R_e} = \frac{\partial R_e}{\partial \mu_c} \times \frac{\mu_c}{R_e} = -0.84,$$

$$\Upsilon_{\pi_c}^{R_e} = \frac{\partial R_e}{\partial \pi_c} \times \frac{\pi_c}{R_e} = +0.69.$$

In a similar fashion, we compute the sensitivity indices for all parameters used in equation 4 and present the results in Table 3. Table 3 shows that the most sensitive parameters of the effective reproductive number in each population are natural

Table 3: Sensitivity indices for R_e parameters

Parameter	Value	Unit	Sensitivity Index
π_c	0.3	$year^{-1}$	0.69
β_c	0.0011	$year^{-1}$	0.54
ϕ_c	0.7	$year^{-1}$	-0.36
ψ_c	0.4	$year^{-1}$	0.22
μ_c	0.25	$year^{-1}$	-0.84
d_c	0.35	$year^{-1}$	-0.40
α_c	0.00035	$year^{-1}$	0.15
ρ_c	10	$year^{-1}$	0.15
ε	8	$year^{-1}$	-0.10
τ	12	$year^{-1}$	-0.16
π_s	0.4	$year^{-1}$	0.31
β_s	0.001	$year^{-1}$	0.20
ϕ_s	0.8	$year^{-1}$	-0.15
ψ_s	0.5	$year^{-1}$	0.09
μ_s	0.35	$year^{-1}$	-0.39
d_s	0.4	$year^{-1}$	-0.16
α_s	0.00032	$year^{-1}$	0.11
ρ_s	15	$year^{-1}$	0.11

death rate, birth rate, transmission rate, gradual culling rate of sero-positive ruminants through slaughter and vaccination rate. The positive sign in the sensitivity index means that an increase in that parameter leads to an increase in R_e and vise-versa. For instance, an increase or decrease of cattle birth rate by 10% leads to an increase or decrease of R_e by 6.9%. On the other hand, the negative sign in the sensitivity index of a parameter indicates that an increase or decrease in a parameter value leads to a decrease or increase in R_e respectively. For instance, a 10% increase in cattle natural mortality rate leads to a 8.4% decrease in the effective reproductive number. This implies that culling in large livestock flocks is inevitable if we want to control brucellosis transmissions.

6 Numerical Simulations

This section presents numerical simulations for model system 1 for the purpose of verifying some of the analytical results. The parameter values used in our computations are mainly from [34], a literature similar to this work. The parameter values are in Table 3. Figure 2 illustrates the variations in livestock and brucella subpopulations as time increases. Figure 2 shows that susceptible ruminants decrease rapidly due to brucellosis epidemic and vaccination of susceptible ruminants, while the infective subpopulations initially increase with time. However, after a two-year period these subpopulations start decreasing. The increase in the infective classes is due to high brucellosis transmission rate

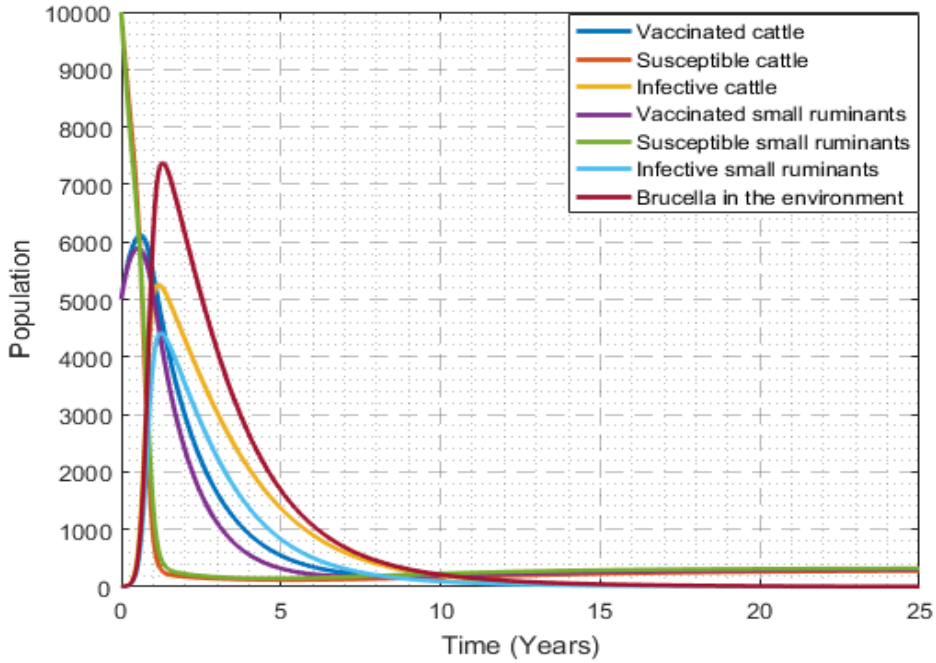


Fig. 2: Ruminants subpopulations variation

and the decrease is due to different interventions like gradual culling of infective ruminants, environmental hygiene and sanitation, and immunization of susceptible ruminants. The graph for vaccinated classes initially increase because large number of susceptible livestock are vaccinated at the beginning of any vaccination program and decrease due to reduction in the number of susceptible livestock. Furthermore, the number of all infective classes goes to zero after 10 years. From Figure 3 we see that the combination of timely environmental hygiene and sanitation and ruminants vaccination significantly controls the indirect transmission of brucella from cattle to small ruminants and vice versa. In addition, the disease can be eliminated from the population if gradual culling of seropositive ruminants through slaughter eliminates at least 35% and 40% of the infective cattle and small ruminants respectively.

Furthermore, Figure 4a shows that an increase in cattle vaccination rate leads to a decrease in the effective reproduction number. For instance, the cattle population attains its disease free equilibrium at 10% vaccination rate provided that other controls are kept constant. This implies that cattle vaccination at some points plays a significant contribution in reducing the transmission dynamics of brucellosis. A similar trend is observed from Figure 4b that vaccination of small ruminants significantly reduces their secondary brucellosis infections and the small ruminants brucellosis free state is achieved at 9% vaccination rate. Moreover, if other control parameters are kept constant and disease-induced rate is varied, we obtain the brucellosis free equilibrium ($R_e < 1$) at 12.5% and 10% diseased induced elimination rates for cattle and small ruminants respectively (see Figure 5a and Figure 5b).

Generally, the combination of ruminants vaccination, test-and-slaughter and disinfection of the environment minimizes or eliminates the disease from the populations. In line with this [47] pointed out that, gradual culling of seropositive animals through slaughter, isolation and confinement of pregnant cows close to calving; proper disposal of placentas and aborted foetuses, the use of the S19 vaccine, and restricted introduction of new animals leads to brucellosis elimination in animal herds.

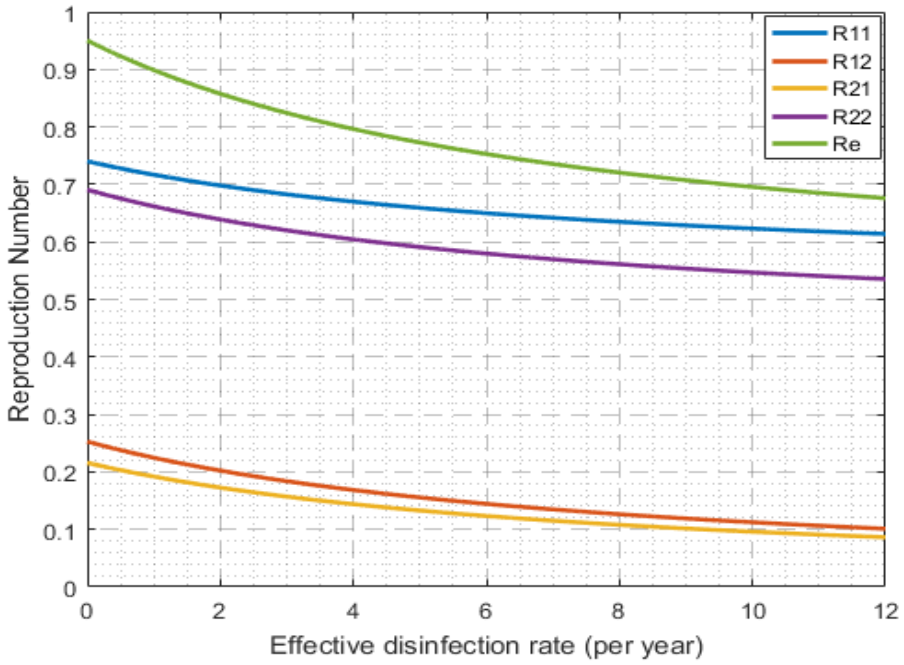
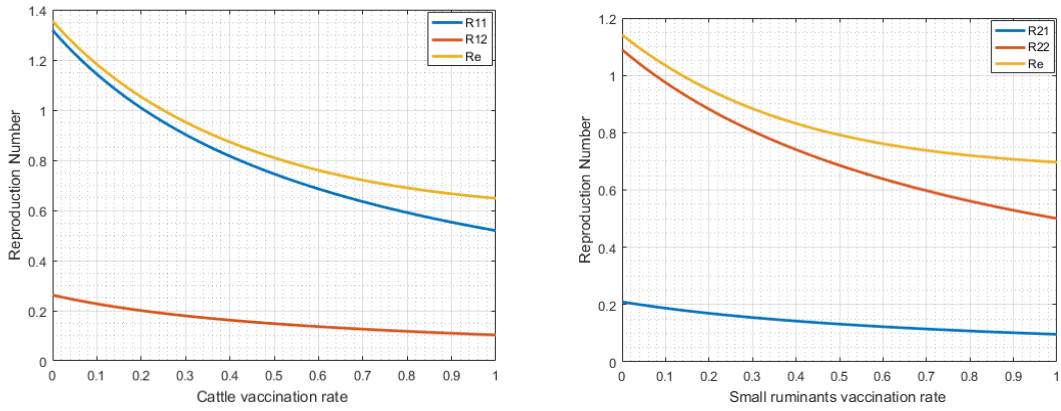


Fig. 3: The impact of environmental hygiene and sanitation on brucelosis transmission



(a) **(b)**

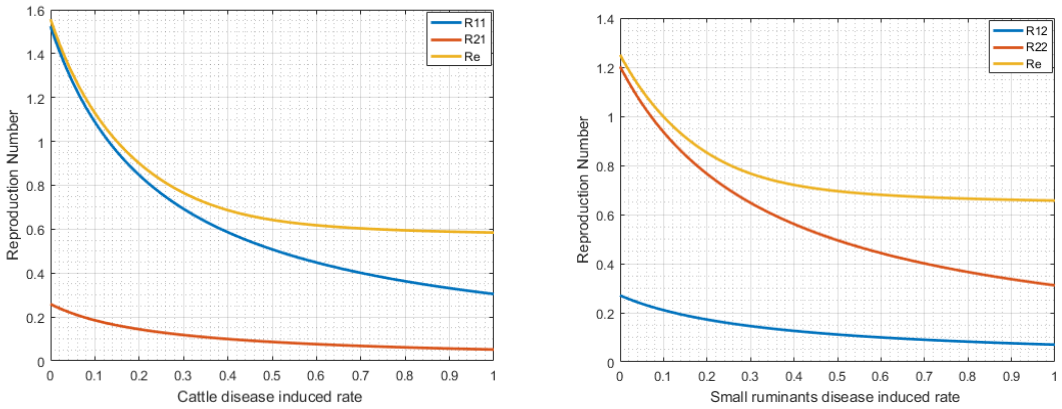
Fig. 4: The impact of ruminants vaccination on brucelosis transmission.

Conflict of Interest

The authors declares no conflict of interest regarding the publication of this manuscript.

Authors' contributions

All authors have contributed to all parts of the article. All authors read and approved the final manuscript.



(a) **(b)**

Fig. 5: The impact of seropositive ruminants culling on the transmission of brucellosis.

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