An intrinsic analysis of human brucellosis dynamics in Africa

Abstract
Brucellosis is one of the most common zoonotic infections globally. It a_ects humans, domestic animals and wildlife. In this paper, we conduct an intrinsic analysis of human brucellosis dynamics in non-periodic and periodic environments. As such we propose and study two mathematical models for human brucellosis transmission and control, in which humans acquire infection from cattle and wildlife. The _rst model is an autonomous dynamical system and the second is a non-autonomous dynamical system in which the seasonal transmission of brucellosis is incorporated. Disease intervention strategies incorporated in this study are cattle vaccination, culling of infectious cattle and human treatment. For both models we conduct both epidemic and endemic analysis, with a focus on the threshold dynamics characterized by the basic reproduction numbers. Using sensitivity analysis we established that R_0 is most sensitive to the rate of brucellosis transmission from bu_alos to cattle, the result suggest that in order to control humant brucellosis there is a need to control cattle infection. Based on our models, we also formulate an optimal control problem with cattle vaccination and culling of infectious cattle as control functions. Using reasonable parameter values, numerical simulations of the optimal control demonstrate the possibility of reducing brucellosis incidence in humans, wildlife and cattle, within a _nite time horizon, for both periodic and non-periodic environments.

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1 Introduction

Globally, human brucellosis remains an important and widespread infection [1]. The infection is more common in Mediterranean areas, the south and the center of America, Africa, Asia, Arab peninsula, Indian subcontinent and the Middle East [2]. In 2012, reported brucellosis incidence in some endemic regions were as follows: Saudi Arabia (214.4), Iran (238.6), Turkey (262.2), Iraq (278.4), and Syria (1603.4) [3]. However, the World Health Organization (WHO) believes that the real incidence is 10{25 times more than what have been reported [2]. Although, human brucellosis in rampant in many developing nations it is also a severe public health problem in China where 160 214 brucellosis cases were observed in the period 2005{2010
[4].

In animals, brucellosis is transmitted by direct contact transmission through the brucella carriers or indirect contact transmission when animals ingest contaminated forages or the excrement containing large quantities of bacteria, generally discharged by infected animals [5]. Domesticated
species such as cattle, sheep, horse and goats are regarded as the main source of human brucellosis [2], in which transmission may occur directly or through the consumption of unpasteurised
dairy products [5]. The cross-transmission of brucellosis between domesticated animals and wildlife is well documented [6, 7]. However, the debate on whether wildlife is the reservoir of infection for domestic animals or vice versa continues [6]. One wild animal that is a villain for inter-species spread of many infectious disease such as brucellosis, foot-and-mouth disease-virus (FMDV) in many Africa nations is the African bu_alo [6]. African bu_aloes have several intrinsic behavioural characteristics which are key to inter-species spread of infectious diseases. They are highly mobile and sociable species and they often move in large herds of 1000 or more [8].

Recently, a number of veterinary scientists have suggested that bu_alo, a preferred source of bush meat could be another source of human brucellosis in many developing nations [6].

Bu_alo meat is highly preferred bush meat in many African countries [9]. Since bush meat is consumed and handled (legally and illegally) in many developing nations its contribution to human brucellosis cannot be ignored.
Several mathematical models have been proposed to study the dynamics of brucellosis outbreaks
[5, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27]. Undeniably, these studies have produced many useful results and improved the existing knowledge on brucellosis dynamics. One of the limitations of these models, however, is that none of them incorporated the aspect of bush meat on modeling the transmission dynamics of human brucellosis. In this paper we develop a novel mathematical model that evaluates the impact of bush meat on human
brucellosis dynamics. Our model will incorporate human population, cattle and wildlife (African bu_alo). In addition, we will explore optimal disease control measures based on cattle vaccination, culling of infectious cattle and treatment of infected humans.
The remainder of this paper is organized as follows. In section 2 we formulate and comprehensively
analyze the transmission dynamics of brucellosis in non-periodic environments. We provide sensitivity analysis of the basic reproductive number on various model parameters in non-periodic environments, identifying the parameters to which reproductive number is most sensitive, we use this information to suggest strategies for controlling brucellosis using techniques
from optimal control theory. In section 3, we extend the autonomous brucellosis models formulated in section 2, to incorporate seasonal variations on disease transmission. We then conduct mathematical analyses, including the computation of the basic reproductive number, and the stability analysis of equilibria. In Section 4, we formulate an optimal control problem with cattle vaccination and culling of infectious cattle as control functions. Finally, a brief discussion in Section 5 rounds up the paper.

2 An autonomous brucellosis model

We propose an autonomous dynamical system that comprise of cattle population, human population and African bu_alo population. The African bu_alo population constitute three compartments: susceptible $S_b(t)$, symptomatic infectious $I_b(t)$ and carrier state - asymptomatic persistent infection $A(t)$. Thus the total population of bu_aloes at time t is $N_b(t) = S_b(t) +$

$I_b(t) + A(t)$: The cattle population is subdivided into classes of: susceptible $S_c(t)$, infectious $I_c(t)$, and the total cattle population at time t is $N_c(t) = S_c(t) + I_c(t)$: Further, the human population constitute: susceptible $S_h(t)$ and infectious $I_h(t)$. The total human population at time t is $N_h(t) = S_h(t) + I_h(t)$: There are some assumptions for our model:
(1) Brucellosis in the exposure period is hardly detected, and animals in this period can also infect susceptible animal and humans. Hence, we ignored the exposed/latent period in both human and animal population (see for example [20, 21, 22, 24]);
(2) Prior studies suggest that African bu_aloes have more chances of becoming chronic carriers of the disease [6, 28]. As such we omitted the carrier compartment on describing brucellosis transmission dynamics in cattle and humans;
(3) Here, brucellosis transmission rate is being modeled by the mass action incidence since it is appropriate when N(t) is not too large [29]. We assume that the transmission rate is dependent on the size of the population which implies that the contact rate is an increasing function of the population. The mass action incidence is density- dependent since contact rate per infective is proportional to the density of the infectious host
. In all the discussions to follow we will denote the African bu_alo, cattle and human by

subscripts b, c and h, respectively. A ow diagram describing the model is given in Figure 1 and the model equations are:

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$\frac{dS_b}{dt} = \__b \square [\__{bb}(I_b + \_A) + \__{cb}I_c]S_b \square \__bS_b;$

$\frac{dI_b}{dt} = [\__{bb}(I_b + \_A) + \__{cb}I_c]S_b \square [\__b +]I_b;$

$\frac{dA}{dt} = fI_b \square [\__b + d_b]A;$

$\frac{dS_c}{dt} = \__c \square [\__{bc}(I_b + \_A) + \__{cc}I_c]S_c \square [\_ + \__c]S_c;$

$\frac{dI_c}{dt} = [\__{bc}(I_b + \_A) + \__{cc}I_c]S_c \square [\__c + d_c]I_c;$

$\frac{dS_h}{dt} = \__h \square \__{bh}(I_b + \_A)S_h \square \__{ch}I_cS_h \square \__hS_h + \_I_h;$

$\frac{dI_h}{dt} = \__{bh}(I_b + \_A)S_h + \__{ch}I_cS_h \square (\_ + \__h)I_h;$

(1)

In system (1), $\__i$ denote the constant recruitment rate into the population through birth, $\__i$ is the natural-related death rate (i = b; c; h), d_b is the disease-related mortality rate for bu_alo population, $d_c = \_ + \_$, where _ is the culling rate and _ is the disease-related mortality rate, _ is the vaccination rate, _ accounts for the unequal chances of disease transmission between symptomatic and asymptomatic bu_aloes, $\__{ij}$ (i; j = b; c) denotes disease transmission rate,

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with i = j implying bu_alo{to{bu_alo or cattle{to{cattle transmission and i 6= j signify cross-transmission, respectively, $\__{bh}$ and $\__{ch}$ denotes transmission rate from bu_alo and cattle, respectively, to humans. Further, infected African bu_aloes display clinical signs of the disease for $\square_1$ days after which a fraction f become chronic carriers and the complementary (1 □ f) succumb to disease-related death. Infected human displaying clinical signs of the disease are treated at rate _. Prior studies suggests that the optimal treatment of uncomplicated brucellosis should be based on a six-week regimen of doxycycline combined either with streptomycin for 2{3 weeks, or rifampicin for six weeks [30].

Although, species can be infected by the brucella through indirect transmission (environmental transmission), prior studies suggests that this form of infection plays a relatively small role on the spread of brucellosis [11, 14]. In addition, prior studies also suggests that humans rarely transmit the disease [11, 14].

Figure 1: Flow diagram representing the transmission routes and other processes model by system (1).

Since the last two equations are independent of the _rst _ve equations of model (1), without

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loss of generality, in our mathematical analysis we will consider only the _rst _ve equations :

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>>>>>>>>>>>:

$\frac{dS_b}{dt} = \__b \square [\__{bb}(I_b + \_A) + \__{cb}I_c]S_b \square \__bS_b;$

$\frac{dI_b}{dt} = [\__{bb}(I_b + \_A) + \__{cb}I_c]S_b \square [\__b +]I_b;$

$\frac{dA}{dt} = fI_b \square [\__b + d_b]A;$

$\frac{dS_c}{dt} = \__c \square [\__{bc}(I_b + \_A) + \__{cc}I_c]S_c \square [\_ + \__c]S_c;$

$\frac{dI_c}{dt} = [\__{bc}(I_b + \_A) + \__{cc}I_c]S_c \square [\__c + d_c]I_c:$

(2)
It can easily be veri_ed that model (2) has a unique and bounded solutions with initial value in R_5
$_+$: Further, the compact set
□ =
_
(S_b; I_b; A; S_c; I_c) 2 R_5
$_+$: N_b _
_b
_b
; N_c _
_c
_c
:
_
; (3)
is positively invariant and attracting with respect to model (2).

2.1 The reproductive number

It is evident that (2) always has a disease-free equilibrium (DFE) given by
E_0 :
_
S_0
b ; I_0
b ;A_0; S_0
c ; I_0
c
_
=
_
_b
_b
; 0; 0;
_c
(_ + _c)
; 0
_
:
One measure of the severity of a disease is the basic reproductive number, R_0, which is de_ned as the average number of secondary infections caused by a single infected animal in a completely
susceptible population. Using the second generation matrix approach [31], the non-negative matrix F that denotes the generation of new infection terms and the non-singular matrix V that denotes the remaining transfer terms are respectively, given (at the disease-free equilibrium) by
F =
2
66664
_bb_b
_b
__bb_b
_b
_cb_b
_b

0 0 0
_bc_c
(_+_c)
__bc_c
(_+_c)
_cc_c
(_+_c)
3
77775
; and V =
2
66664
(_b +) 0 0
□f (_b + db) 0
0 0 (_c + dc)
3
77775
: (4)
Thus, the next generation matrix of system (2) is
6
FV □1 =
2
66664
M11 M12 M13
M21 M22 M23
0 0 0
3
77775
;
where 8>>>>>>>>>>>>>>>>>>>>><
>>>>>>>>>>>>>>>>>>>>>:
M11 =
_b_bb
(_b +)_b
+
f_b__bb
(_b +)(_b + db)_b
;
M21 =
_c_bc
(_b +)(_ + _c)
+
f_c__bc
(_b +)(_b + db)(_ + _c)
;
M12 =
_b__bb
_b(_b + db)
; M22 =
_c__bc
(_ + _c)(_b + db)
;

$M_{13} =$
$\__b\__{cb}$
$\__b(\__c + d_c)$
; $M_{23} =$
$\__c\__{cc}$
$(\_ + \__c)(\__c + d_c)$
:
It follows that the basic reproductive number is
$R_0 = \_(FV \square_1) =$
$M_{11} + M_{22} +$
p
$(M_{11} \square M_{22})^2 + 4M_{12}M_{21}$
2
;
De_ning the appropriate value of R_0 for a disease characterized by hidden infections is challenging
but essential in developing control measures. The reproductive number is the key threshold parameter whose values determine the global dynamics of system (2). A disease is considered to be endemic if $R_0 > 1$. However, if $R_0 \_ 1$ it implies that the disease dies out.

2.2 Equilibrium analysis

Theorem 2.1. If $R_0 \_ 1$, the system (2) has a unique DFE that is globally asymptotically stable in the region $\square$.
Proof. Let $Y(t) = [I_b(t); A(t); I_c(t)]$: Since
8>>>><
>>>>:
$I\__b \_ [\__{bb}(I_b + \_A) + \__{cb}I_c]S_0$
$_b \square [\__b +]I_b$;
$\_A$
$\_ fI_b \square [\__b + d_b]A$;
$I\__c \_ [\__{bc}(I_b + \_A) + \__{cc}I_c]S_0$
$_c \square [\__c + d_c]I_c$;
(5)
it follows that
$\_Y$
$\_ (F \square V)Y$;
7
where F and V are de_ned in Eq. (4). One can easily deduce that, both F and $V \square_1$ are nonnegative.
By the Perron-Frobenius Theorem, the non-negative matrix $V \square_1 F$ has a non-negative left eigenvector $w \_ 0$ with respect to $\_(V \square_1 F) = \_(FV \square_1) = R_0$; that is $w^T V \square_1 F = R_0 w^T$:
Motivated by [32], we de_ne a Lyapunov function as follows:
$L = w^T V \square_1 Y$:
Di_erentiating L along solutions of (2), we have
$\_L$
$= w^T V \square_1 \_Y \_ w^T V \square_1(F \square V)Y = (R_0 \square 1)w^T Y$:
If $R_0 < 1$, $\_L = 0$ implies that $w^T Y = 0$ and hence $I_b = A = I_c = 0$: It follows from the _rst and fourth equations of (2) that $S_b = S_0$
$_b$ and $S_c = S_0$
$_c$: Hence, the only invariant set where $\_L = 0$
is the singleton fS_0
$_b$; 0; 0; S_0

$_c$; 0g. By LaSalle's invariance principle [33], the DFE is globally
asymptotic all stable in □ if $R_0 < 1$:
If $R_0 = 1$, _L = 0 implies that $S_b = S_0$
$_b$ and $S_c = S_0$
$_c$, by the _rst and third equations of
(5) and the fact that $w_T Y > 0$: Then, from the _rst and fourth equations of (2) we have,
[$_{bb}(I_b$ + _A) + $_{cb}I_c]S_b = 0$ and [$_{bc}(I_b$ + _A) + $_{cc}I_c]S_c = 0$, respectively. This can only
happen if $I_b = A = I_c = 0$: Therefore, the largest invariant set where _L = 0 is the singleton
fS_0
$_b$; 0; 0; S_0
$_c$; 0g, and by LaSalle's invariance principle, the DFE is globally asymptotic all stable
in □ if $R_0 = 1$:
Theorem 2.2. If $R_0 > 1$, there exists a unique endemic equilibrium of the system (2) which
is globally asymptotically stable in the region □:
Proof. In order to analyze the global asymptotic stability of the endemic equilibrium of system
(2) we set:
x =
S_b
S_
$_b$
; y =
I_b
I_
$_b$
; z =
A
A_ ; u =
S_c
S_
$_c$
and v =
I_c
I_
$_c$
:
8
Thus, system (2) is transformed into the following form:
dx
dt
= x
_
_$_b$
S_
$_b$
_
1
x
□ 1
_
□ $_{bb}$I_
$_b$ (y □ 1) □ $_{bb}$_A_(z □ 1) □ $_{cb}$I_
$_c$ (v □ 1)

_
;
dy
dt
= y

_
bbS
b (x □ 1) +
_bb_A_S_
b
I_
b

_
zx
y
□ 1

_
+
cbI
c S_
b
I_
b

_
vx
y
□ 1

__
;
du
dt
= u

_
_c
S_
c

_
1
u
□ 1

_
□ _bcI_
b (y □ 1) □ _bc_A_(z □ 1) □ _ccI_
c (v □ 1)

_
;
dv
dt
= v

_
ccS
c (u □ 1) +

_bc_A_S_
c
I_
c
_zu
v
□ 1
_
+
bcI
b S_
c
I_
c
_yu
v
□ 1
__
;
dz
dt
= z
_
fI_
b
A_
_y
z
□ 1
__
:
(6)
It can easily be veri_ed that model (6) has a unique endemic equilibrium E_(1; 1; 1; 1; 1), and that the global stability of E_ is the same as that of system (2). Consider the Lyapunov function
U = S_
b [x □ 1 □ ln x] + I_
b [y □ 1 □ ln y]
+
[_bb_A_S_
b + _bc_A_S_
c]A_
fI_
b
[z □ 1 □ ln z]
+S_
c [u □ 1 □ ln u] + I_
c [v □ 1 □ ln v]:
Di_erentiating U with respect to t along solutions of (6) gives:
9
dU
dt

= +(x □ 1)

_
_b

_
1
x
□ 1

_
□ _bbl_
b S_
b (y □ 1) □ _bb_A_S_
b (z □ 1) □ _cbl_
c S_
b (v □ 1)

_
+(y □ 1)

_
bbl
b S_
b (x □ 1) + _bb_A_S_
b

_
zx
y
□ 1

_
+ _cbl_
c S_
b

_
vx
y
□ 1

___
+(u □ 1)

_
_c

_
1
u
□ 1

_
□ _bcl_
b S_
c (y □ 1) □ _bc_A_S_
c (z □ 1) □ _ccl_
c S_
c (v □ 1)

_
+(v □ 1)
h

ccI
c S_
c (u □ 1) + _bc_A_S_
c
_zu
v
□ 1
_
+ _bcI_
b S_
c
_yu
v
□ 1
_i
+
[_bb_A_S_
b + _bc_A_S_
c]
fI_
b
(z □ 1)
h
fI_
b
_y
z
□ 1
_i
= F(x; y; z; u; v):
(7)
At endemic point we have the following identities:
_b =
_b
S_
b
□ [_bbI_
b + _bb_A_ + _cbI_
c];
(_b +) = _bbS_
b +
_bb_A_S_
b
I_
b
+
cbI
c S_
b
I_
b
;
(_ + _c) =

_c
S_
c
 [_bcI_
b + _bc_A_ + _ccI_
c];
(_c + dc) = _ccS_
c +
_bc_A_S_
c
I_
c
+
bcI
b S_
c
I_
c
;
(_b + db) =
fI_
b
A_ :
(8)
To assure that F(x; y; z; u; v) _ 0 for x > 0; y > 0; z > 0; u > 0; v > 0, the following condition must be satis_ed _cbI_
c S_
b = _bc(I_
b + _A_)S_
c (see [35]). After some algebraic manipulations,
we have
dU
dt
= (_bS_
b + _bbI_
b S_
b)
_
2 x
1
x
_
+
_
(_ + _c)S_
c + _ccI_
c S_
c
__
2 u
1
u
_

+_bb_A_S_
b
_
3 □
1
x
□
y
z
□
zx
y
_
+ _bcl_
b S_
c
_
4 □
1
x
□
1
u
□
vx
y
□
yu
v
_
+_bc_A_S_
c
_
5 □
1
x
□
1
u
□
vx
y
□
zu
v
□
y
z
_
:
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Since the arithmetic mean is greater or equal to the geometric mean, it can easily be veri_ed

that _U _ 0 provided that S_
$_b$, I_
$_b$,A_, S_
$_c$, I_
$_c$ are positive, where the equality _U = 0 holds only
for x = y = z = u = v = 1. Therefore _U _ 0 holds. Then the endemic equilibrium point _ is globally asymptotically stable if R_0 > 1 by LaSalle's invariance principle [33].

2.3 Sensitivity analysis of the reproduction number

In this section we perform the sensitivity analysis of the model system (1). The threshold quantity R_0 known as basic reproduction number is an important parameter to determine the persistence and extinction of brucellosis disease transmission in the population. To be able to suggest the most e_cient way of controlling the disease we need to determine the parameters we can control and to which R_0 is more sensitive. Therefore we perform the sensitivity analysis of the model system (1) using partial rank correlated coe_cient (PRCC) developed in [34] and the values of the parameters used in the model simulations are in Table (2) to demonstrate the inuence of each parameter in the size of threshold quantity R_0: PRCC is an e_cient sensitivity analysis method based on sampling. PRCC assigns a value between □1 to +1 for each parameter. Positive PRCC value indicates a positive correlation of the parameter with the disease maintenance, whereas a negative value indicates a negative correlation with the infectiousness of the diseases. The Parameters studied are: $_b$, $_c$, $_h$, $_b$, $_c$, $_h$, d_b, $_{bc}$, $_{bb}$, $_{cc}$, $_{bh}$, $_{ch}$, f, _, , _, $_{bc}$, d_c, _.

De_nition 1. (See, [34]) The normalized sensitivity index of R_0 which depends on di_erentiability of parameter, ! is de_ned as follows:

R_0

! =

@R_0

@!

_

!

R_0

(9)

From (9), the value of normalized sensitivity index for each parameter used in the model (1) is summarized in Table (1):

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Table 1: Sensitivity analysis of parameters for the model system (1)

Parameter $_b$ $_c$ $_h$ $_b$ $_c$ $_h$ d_b

Index +0.7399 +0.2601 0 -1.0476 -0.1141 0 □0:4615

Parameter $_{bc}$ $_{bb}$ $_{cc}$ $_{bh}$ $_{ch}$ f _

Index +0.1937 +0.7399 0 0 0 +0.64 0

Parameter _ $_{bc}$ d_c _

Index -0.2308 -0.1460 +0.2601 0 +0.7691

Figure 2: Sensitivity analysis of the model system (1)

In Fig. 2, we observed that model parameters such as $_b$, $_c$, $_{bc}$, $_{bb}$, _, and f, have a positive inuence on the R_0, that is, whenever they are increased, the size of R_0 increases. For example, an increase in recruitment rate of Bu_alo $_b$ by 73.99% will lead to an increase in the size of R_0 by 73:99%: In the other-hand, model parameters with negative index values have a negative inuence on R_0, for example, an increase in mortality rate of Bu_alo d_b by 46:15% will lead to a decrease on the magnitude of R_0 by 46:15%.

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(a)

(b)

Figure 3: E_ects of varying (a) progression rate of infected cattle to chronic stage modeled by parameter on R_0 (b) vaccinate rate of susceptible cattle modeled by parameter _ on R_0

Numerical results in Fig. 3 (a) shows the progression rate of cattle from susceptible to chronic stage modeled by parameter on R_0. Overall, we noted that increase on progression rate of infected cattle to chronic stage reduce the size of R_0. In particular, one can note that whenever the progression rate is greater than 0:5 the disease dies in the community. Figure 3 (b) demonstrates
the e_ect of vaccination rate of susceptible cattle on the spread of brucellosis disease in the population. Overall, we observed that whenever the vaccination rate of susceptible cattle is less than 0:5 the disease persists in the community.

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Figure 4: E_ects of varying rate modifying factor for disease transmission modeled by parameter
_ on R_0

Figure 4 demonstrates the e_ects of modifying factor in the dynamics of brucellosis disease transmission. Overall, one can note that whenever the modifying factor for disease transmission is less then 0:5 the magnitude of R_0 is less than unit and thus, the disease dies in the population.

Figure 5: Contour plot of the basic reproduction number R_0 as the function of treatment rate of infected cattle (modeled by parameter _) and vaccination rate of susceptible cattle (modeled by parameter _)

Figure (5) shows the contour plot of basic reproduction number R_0 as the function of treatment rate of infected cattle (modeled by parameter _) and vaccination rate of susceptible cattle

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(modeled by parameter _). Overall, we noted that, increase on vaccination rate of susceptible and treatment of infected cattle reduce the size of R_0. In particular one can note that whenever _ is greater than 0:5 the disease dies in the population.

3 A periodic brucellosis model

Infectious disease dynamics are often strongly inuenced by seasonal patterns, irrespective pathogen transmission mode [7, 36]. The breadth and consistency of these patterns suggest that seasonal inuence on host and pathogen biology can have signi_cant e_ects on patterns of pathogen invasion and transmission [37]. The relationship between host abundance and pathogen transmission, inuenced strongly by seasons in some environments such as the semi-arid, is central to understanding infectious disease ecology and patterns and processes of pathogen invasion [7].

In fact, like many other infectious diseases, brucellosis is signi_cantly inuence by seasonal variations, and prior studies have demonstrated a strong connection between brucellosis infection
and seasonal variations [7, 38, 39]. Factors such as the seasonal availability of forage which in turn lead to nomadic animal farming may be attributed to seasonality of brucellosis dynamics. Botswana provides an important example of this potential inuence with extreme seasonal climatic variation, which occurs within and between years. In Botswana water availability
is highly variable in time and space in relation to rainfall patterns and this can strongly inuence density and spatial distribution of domestic animals and wildlife including bu_alo over the whole year including bu_alo calving periods [6].

Against this background, in this section, we extend model (2) to incorporate seasonality. Thus

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we introduce seasonal-induced transmission rate. Our new model takes the form:

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>>>>>>>>>>>>>>>>>>:

$\frac{dS_b}{dt} = \__b \square [\__{bb}(t)(I_b + \_A) + \__{cb}(t)I_c]S_b(t) \square \__b S_b(t);$

$\frac{dI_b}{dt} = [\__{bb}(t)(I_b + \_A) + \__{cb}(t)I_c]S_b(t) \square [\__b +]I_b;$

$\frac{dA}{dt} = fI_b \square [\__b + d_b]A(t);$

$\frac{dS_c}{dt} = \__c \square [\__{bc}(t)(I_b + \_A) + \__{cc}(t)I_c]S_c(t) \square [\_ + \__c]S_c(t);$

$\frac{dI_c}{dt} = [\__{bc}(t)(I_b + \_A) + \__{cc}(t)I_c]S_c(t) \square [\__c + d_c]I_c(t);$

$\frac{dS_h}{dt} = \__h \square \__{bh}(t)(I_b + \_A)S_h \square \__{ch}(t)I_cS_h \square \__hS_h + \_I_h;$

$\frac{dI_h}{dt} = \__{bh}(t)(I_b + \_A)S_h + \__{ch}(t)I_cS_h \square (\_ + \__h)I_h:$

(10)

All the variables and model parameters are assumed to be positive and they retain the same de_nitions as in model (2). Further, we assume that $\__{ij}(t)$, (i; j = b; c; h) are periodic continuous functions in t with a period ! > 0 (speci_cally, ! = 12 months). Thus,

$\__{ij}(t) = \__{ij}$

$\frac{\_}{1} + a_k \sin$

$\frac{\_}{2}\_t$

$\frac{12}{\_\_}$

; k = 1; 2; 3; 4; 5; 6 (11)

where $\__{ij}$ denotes the basic contact rate without seasonal forcing and $0 < a_k < 1$ denotes the magnitude of seasonal uctuations.

3.1 The reproductive number

To introduce the basic reproduction number in the uctuating environment Wang and Zhao [40], extended the general procedure presented by Driessche andWatmough [31] by introducing the next infection operator

$(L\_)(t) =$

$\int_0^1$

$Y(t; t \square s)F(t \square s)\_(t \square s)ds$ (12)

Assume that Y (t; s); t _ s, is the evolution operator of the linear ! -periodic system $\frac{dy}{dt} = V(t)y$

and _(t), the initial distribution of infectious animals, is ! -periodic and always positive. Then e_ective reproductive number of the system (10) is then established by calculating the spectral radius of the next infection operator,

$R_s = \_(L):$

16

Thus, the evolution operator Y (t; s), for the system (10) is

Y (t; s) =

2

66664

$e^{\square(\__b+)(t\square s)}$ 0 0

$f^{(\square d_b)}[e^{\square(\__b+d_b)(t\square s)} \square e^{\square(\__b+)(t\square s)}]$ $e^{\square(\__b+d_b)(t\square s)}$ 0

0 0 $e^{\square(\__c+d_c)(t\square s)}$

3

77775
: (13)
The next infection operator can be numerically evaluated by
(L_(t) =
Z 1
0
Y (t; t □ s)F(t □ s)_(t □ s)ds =
Z T
0
G(t; s)_(t □ s)ds;
where
G(t; s) _
MX
k=0
Y (t; t □ s □ k!)F(t □ s)
_
MX
k=0
2
66664
l_{11} l_{12} l_{13}
l_{21} l_{22} l_{23}
l_{31} l_{32} l_{33}
3
77775
;
for some positive integer M large enough, and
8>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>><
>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>:
_l_{11} = l_{12} = _ _bb(t□s)_b
_b
e□(_b+)(s+k!);
l_{13} = _cb(t□s)_b
_b
e□(_b+)(s+k!);
_l_{21} = l_{22} = _ f
(□db)
h
_bb(t□s)_b
_b
e□(_b+db)(s+k!) □ l_{11}
i
;
l_{23} =
h
_cb(t□s)_b
_b
e□(_b+db)(s+k!) □ l_{13}
i
;
_l_{31} = l_{32} = _ _bc(t□s)_c
(_+_c) e□(_c+dc)(s+k!);
l_{33} = _cc(t□s)_c
(_+_c) e□(_c+dc)(s+k!):

In the special case of _ij(t) _ _ij ; 8t _ 0, we obtain F(t) _ F; and V (t) _ V , 8t _ 0; then
Rs = R0:
17
3.2 Brucellosis extinction and persistence
In this section, we present that if Rs < 1, then DFE is globally stable and the disease dies out. Then, if Rs > 1 the disease persist.
In the special case of _ij(t) _ _ij ; 8t _ 0, we obtain F(t) _ F; and V (t) _ V , 8t _ 0; then
Rs = R0:
It can easily be veri_ed that system (10) satis_es assumptions (A1)-(A7) in Wang and Zhao (2008) [40]. Thus, we have the following results , which are crucial for our simulations and the main analytical results in this section.
Lemma 1. (Wang and Zhao Theorem 2.2 in [40]). The following statements are valid:
(i) R0 = 1 if and only if _(_(F□V)(!)) = 1:
(ii) R0 > 1 if and only if _(_(F□V)(!)) > 1:
(ii) R0 < 1 if and only if _(_(F□V)(!)) < 1:
We now proceed to prove Theorem 3.1.
Proof. In the case where Rs < 1, Lemma 1 implies that E0 is locally asymptotically stable. It su_ces to prove that E0 is globally attractive in □:
Assume that Rs < 1; By Lemma 1, it follows that for any ' > 0, there exists large t0 > 0 such that Sb(t) < S0
b + ' and Sc < S0
c + ', when t > t0: Then for system (10), we have, when
t > t0; that
8>>>><
>>>>:
I_b(t) _ [_bb(t)(Ib + _A) + _cb(t)Ic][S0
b (t) + '] □ [_b +]Ib;
_A
(t) = fIb □ [_b + db]A(t);
I_c(t) _ [_bc(t)(Ib + _A) + _cc(t)Ic][S0
c (t) + '] □ [_c + dc]Ic(t):
(14)
Considering the comparison system,
dh
dt
= (F(t) □ V (t) +M')h(t); h(t) = (Ib(t); Ic(t);A(t)): (15)
By Lemma 2.1 in [41], it follows that there exists a positive !-periodic function _h
(t) such that
h(t) = e t_ h(t) is a solution of the system (15) where = 1
! ln _(_(F□V +M')(_)(!)). Further,
18
we know that Rs < 1, if and only if _(_(F□V +M')(_)(!)) < 1. Since _(_(F□V +M')(_)(!)) < 1,
it follows that, is a negative constant. Therefore, we have h(t) □! 0 as t □! +1. This implies that the zero solution o f system (15) is globally asymptotically stable. For any nonnegative
initial value (Ib(0);A(0); Ic(0))T for system (14), there a su_cient large M_ > 0 such that (Ib(0);A(0); Ic(0))T _ M_h
(0) holds. Following the comparison principle [42], we have
(Ib(t);A(t); Ic(t))T _ M_h(t) for all t > 0 where M_h(t) is also a solution of system (15).
Therefore, we get Ib(t) □! _____0, A(t) □! 0 and Ic(t) □! 0 , as t □! +1. By the theory of asymptotic autonomous systems [49], it then follows that Sb(t) □! S0

$_b$ and $S_c(t)$ □! S_0
$_c$. So
E_0 is globally attractive when $R_s < 1$: It follows that E_0 is globally asymptotically stable when $R_s < 1$:
De_ne:
$X_0 = f(S_b; S_c; A; I_b; I_c)$ 2 R_5
$_+$: $A > 0$; $I_b > 0$; $I_c > 0g$: @$X_0 = R_5$
$_+$nX_0:
Let P : R_5
$_+$ □! R_5
$_+$ be the Poincar_e map associated with system (10) such that
$P(x_0) = u(!; x_0)$; $8x_0$ 2 R_5
$_+$;
where $u(t; x_0)$ denotes the unique solution of the system (10) with $u(0; x_0) = x_0$. It is easy to verify that
$P_m(x_0) = u(m!; x_0)$; $8m > 0$;
Lemma 2. When $R_s > 1$, then there exists a _ > 0 such that when
k(S_0
$_b$; I_0
$_b$;A_0; S_0
$_c$; I_0
$_c$) □ P_0k _ _
for any (S_0
$_b$; I_0
$_b$;A_0; S_0
$_c$; I_0
$_c$) 2 X_0, we have
lim sup
$_{m!1}$
d[P_m(S_0
$_b$; I_0
$_b$;A_0; S_0
$_c$; I_0
$_c$); P_0] _ _ (16)
where P_0 = (S_0
$_b$; 0; 0; S_0
$_c$; 0):
19
Proof. If $R_0 > 1$; we obtain _(_(F□V (!)) > 1 by Lemma 1. Choose ~_ small enough such that _(_(F□V □M~_(!)) > 1, where
M~_ =
2
66664
~_ ~_ ~_
~_ ~_ ~_
0 0 0
3
77775
:
Now we proceed by contradiction to prove that
lim sup

$m!1$
$d[P_m(S_b^0; I_b^0; A_c^0; S_c^0; I_c^0); P_0] \_ \_:$
If not, then
lim sup
$m!1$
$d[P_m(S_b^0; I_b^0; A_c^0; S_c^0; I_c^0); P_0] < \_;$
for some $(S_b^0; I_b^0; A_c^0; S_c^0; I_c^0) \in X_0$: Without loss of generality, we assume that $d[P_m(S_b^0; I_b^0; A_c^0; S_c^0; I_c^0); P_0] <$
$\_$ for all $m \_ 0$: By the continuity of the solution with respect to the initial values, we obtain
$ku(t; P_m(S_b^0; I_b^0; A_c^0; S_c^0; I_c^0)) \leq u(t_1; P_0)k \_ \sim\_; \forall m \_ 0; \forall t_1 \in [0; !]:$
For any $t \_ 0$, let $t = m! + t_1$, where $t_1 \in [0; !]$ and $m = [\frac{t}{!}]$, which the greatest integer less
than or equal to $\frac{t}{!}$: Then we have
$ku(t; (S_b^0; I_b^0; A_c^0; S_c^0; I_c^0)) \leq u(t; P_0)k = ku(t_1; P_m(S_b^0; I_b^0; A_c^0; S_c^0; I_c^0)) \leq u(t_1; P_0)k \_ \sim\_$
for any $t \_ 0$, which implies that $S_b^0 \sim\_ < S_b(t) < S_b^0 + \sim\_$, $S_c^0 \sim\_ < S_c(t) < S_c^0 + \sim\_$, $t \_ 0$: Then
for $k(S_b^0; I_b^0; A_c^0; S_c^0; I_c^0)$

$_c$) □ P_0k _ _, we have
8>>>><
>>>>:
I_b(t) _ [$_{bb}$(t)(I_b + _A) + $_{cb}$(t)I_c][S_0
$_b$ (t) □ ~_] □ [$_b$ +]I_b;
_A
(t) = fI_b □ [$_b$ + d_b]A(t);
I_c(t) _ [$_{bc}$(t)(I_b + _A) + $_{cc}$(t)I_c][S_0
$_c$ (t) □ ~_] □ [$_c$ + d_c]I_c(t):
(17)
Next we consider the linear system
8>>>><
>>>>:
I_b(t) = [$_{bb}$(t)(I_b + _A) + $_{cb}$(t)I_c][S_0
$_b$ (t) □ ~_] □ [$_b$ +]I_b;
_A
(t) = fI_b □ [$_b$ + d_b]A(t);
I_c(t) = [$_{bc}$(t)(I_b + _A) + $_{cc}$(t)I_c][S_0
$_c$ (t) □ ~_] □ [$_c$ + d_c]I_c:
(18)
20
Once again by Lemma 1, it follows that there exists a positive !□ periodic function ~g(t) such that g(t) = e^{pt}~g(t) is a solution of system (18), where p = $_1$
! ln _(_F□V □M~_(!)): Because
_(_F□V □M~_(!)) > 1, when g(0) > 0, g(t) ! 1 as t ! : Applying the comparison principle [42], we know that when I_b(0) > 0, A(0) > 0 and I_c(0) > 0, I_b(t) ! 1, A(t) ! 1 and I_c(t) ! 1 as t ! 1. This is a contradiction. This completes the proof.
Theorem 3.1. If the basic reproduction number R_s < 1, then the unique DFE is globally asymptotically stable in □. Further, if R_s > 1 the disease persists.

4 Optimal control

In this section, we turn to an optimal control study of our brucellosis models, with an aim of exploring e_ective prevention and intervention strategies that could best balance the outcomes and costs of the control. To that end, we will perform the optimal control study both the autonomous model (1) and non-autonomous model (10). We introduce two time-dependent control strategies, u_1(t) and u_2(t) which are represented as functions of time and assigned reasonable upper and lower bounds. The control function u_1(t) measures the rate at which susceptible cattle are vaccinated during each time period, while control function u_2(t) accounts for the impact of detection and culling of infectious cattle. Since humans do not transmit the disease we did not consider time dependent intervention strategy. Retaining the same variable and parameter names as in (1), the system of di_erential equations describing our model with controls is: 8>>>>>>>>>>>>>>>>>>< >>>>>>>>>>>>>>>>>>>:
dS_b
dt = $_b$ □ [$_{bb}$(I_b + _A) + $_{cb}I_c$]S_b □ $_bS_b$;
dI_b
dt = [$_{bb}$(I_b + _A) + $_{cb}I_c$]S_b □ [$_b$ +]I_b;
dA
dt = fI_b □ [$_b$ + d_b]A;
dS_c
dt = $_c$ □ [$_{bc}$(I_b + _A) + $_{cc}I_c$]S_c □ [$_u$1(t) + $_c$]S_c;
dI_c
dt = [$_{bc}$(t)(I_b + _A) + $_{cc}I_c$]S_c □ [$_c$ + $_u$2(t) + _]I_c;
dS_h

dt = _h □ _bh(Ib + _A)Sh □ _chIcSh □ _hSh + _Ih;
dIh
dt = _bh(Ib + _A)Sh + _chIcSh □ (_ + _h)Ih:
(19)
According to the extended model above, an optimal control problem with the objective function
21
is formulated by
Minimize J
_
u1(t); u2(t)
_
=
Z T
0
h
BIc(t) +
W1
2
u21
(t) +
W2
2
u22
(t)
i
dt : (20)
The objective is to minimize infected cattle population over a _nite time interval [0; T] at minimal costs. In equation (20), B1 represent weight constant of the infected cattle. In addition, W1 and W2 are weight for cattle vaccination and cattle culling. The control e_orts in equation (20) are assumed to be nonlinear-quadratic, since a quadratic structure in the control has mathematical advantages, such as: if the control set is compact and convex it follows that the Hamiltonian attains its minimum over the control set at a unique point [43, 44, 45, 46, 47, 48]. Further, W1u21
(t), and W2u22
(t) describe the costs associated with vaccination and culling,
respectively. We assumed that the costs are proportional to the square of the corresponding control function.
The control set is de_ned as
=
n
(u1(t); u2(t))
__
1 _ u1(t) _ U1; 1 _ u2(t) _ U2g; (21)
where U1, and U2 denote the upper bounds for the e_orts of vaccination, culling and human treatment, respectively. The bounds reect practical limitation on the maximum rate of control that can be implemented in a given time period. If, however, u1(t) = u2(t) = 1 for all t, then the model (19) is reduced to the original model (1) or (10), with regular (i.e., minimum) controls.
The optimal control problem hence becomes that we seek optimal functions, (u_1 (t); u_2 (t)), such
that

J

_

u_

1 (t); u_

2(t)

_

= min

J

_

u1(t); u2(t)

_

(22)

subject to the state equations in system (19) with initial conditions. The existence of optimal control follows from standard results in optimal control theory [50, 51]. The necessary conditions that optimal controls must satisfy are derived using Pontryagin's Maximum Principle [52]. Thus, system (2) is converted into an equivalent problem, namely the problem of

22

minimizing the Hamiltonian H given by:

H(t) = BIc(t) +

W1

2

u21

(t) +

W2

2

u22

(t)

+_Sb(t)

h

_b □ (_bb(Ib + _A) + _cbIc)Sb □ _bSb

i

+_Ib(t)

h

(_bb(Ib + _A) + _cbIc)Sb □ (_b +)Ib

i

+_A(t)

h

fIb □ (_b + db)A

i

+_Sc(t)

h

_c □ (_bc(Ib + _A) + _ccIc)Sc □ (_u1(t) + _c)Sc

i

+_Ic(t)

h

(_bcu2(t)(Ib + _A) + _ccIc)Sc □ (_c + _u2(t) + _)Ic

i

+_Sh(t)

h

_h □ _bh(Ib + _A)Sh □ _chIcSh □ _hSh + _Ih

i
+ _I_h(t)
h
_$_{bh}$(I_b + _A)S_h + _$_{ch}$$I_c$$S_h$ □ (_ + _$_h$)I_h
i
;
where _S_b(t), _I_b(t), _A(t), _S_c(t), _I_c(t), _S_h(t) and _I_h(t) denote the adjoint functions associated with the states S_b, I_b, A, S_c and I_c, respectively. Note that, in H(t), each adjoint function multiplies the right-hand side of the di_erential equation of its corresponding state function. The _rst term in H(t) comes from the integrand of the objective functional.
Given an optimal control treble ($u_{\_1}$; $u_{\_2}$; $u_{\_3}$) and corresponding states (S_b; I_b; A; Sc; I_c), there exist adjoint functions [50] satisfying
d_S_b(t)
dt
= □
@H
@S_b
;
d_I_b(t)
dt
= □
@H
@I_b
;
d_A(t)
dt
= □
@H
@A
;
d_S_c(t)
dt
= □
@H
@S_c
;
d_I_c(t)
dt
= □
@H
@I_c
;
d_S_h(t)
dt
= □
@H
@S_h
;
d_I_h(t)
dt
= □

@H
@Ih
: (23)
These yield
d_Sb(t)
dt
= _Sb(t)
_
_bb(Ib + _A) + _cbIc + _b
_
 _Ib(t)
_
_bb(Ib + _A) + _cbIc
_
;
d_Ib(t)
dt
= _Sb_bbSb + _Ib(t)
_
_b + _bbSb
_
 f_A(t) + _Sc(t)_bc(t)Sc _Ic(t)_bc(t)Sc
+_Sh(t)_bhSh _Ih(t)_bhSh;
d_A(t)
dt
= _Sb(t)_bb_Sb + _Sc(t)_bc_Sc _Ic(t)_bc_Sc _Ib(t)_bb_Sb + _A(_b + db);
+_Sh_bh_Sh _Ih_bh_Sh;
d_Sc(t)
dt
= _Sc(t)
_
_bc(Ib + _A) + _ccIc + _c + _u1(t)(t)
_
 _Ib(t)
_
_bc(Ib + _A) + _ccIc
_
;
d_Ic(t)
dt
= B + _Sb(t)_cbSb _Ib(t)_cbSb + _Sc(t)_ccSc + _Ic(t)
_
_c + _u2(t) + _ _ccSc
_
23
+_Sh_chSh _Ih_chSh;
d_Sh(t)
dt
= _Sh(_bh(Ib + _A) + _chIc + _h) _Ih(_bh(Ib + _A) + _chIc);
d_Ih(t)
dt

= $\_{I_h}(t)(\_ + \_h)$ □ $\_{S_h}(t)\_$;
with transversality conditions $\_i(T) = 0$, for i = $S_b(t)$; $I_b(t)$;A(t); $S_c(t)$; $I_c(t)$; $S_h(t)$; $I_h(t)$. Furthermore, the optimal controls are characterized by the optimality conditions:
$u\_{1}(t) = \max[1; \min(\_{u_1}(t);U_1)]$; $u\_{2}(t) = \max[1; \min(\_{u_2}(t);U_2)]$: (24)
where
$\_{u_1}(t) = \frac{\_{S_c}\_{S_c}}{2W_1}$; $\_{u_2}(t) = \frac{\_{I_c}\_{I_c}}{2W_2}$: (25)
While it is known that wildlife can be important in brucellosis transmission dynamics, lack of data present an enormous challenge to modellers on evaluating animal and public health control strategies. Wildlife present a complex component of transmission that can be di_cult to characterize and there is a need for surveillance data to be coupled with molecular, genetic, and dynamical modeling tools in order to begin to unravel this complexity [7]. Despite the unavailability of surveillance data we proceed to explore the numerical solutions to our autonomous
model. Parameter values and variables used in our simulations are listed in Table 2.
In the formulation above, the parameters $\_{ij}$, (i; j = b; c; h) can be either constants, for the autonomous model (1), or periodic functions in the form of equation (11), for the periodic model (10). For each case, the state equations, adjoint equations and optimality conditions constitute an optimal control problem, which is then solved numerically.
We adopted the following initial population levels from [13], $S_c(0) = 1:33 \_ 10^6$, $I_c(0) = 3:3 \_ 10^5$, $S_h(0) = 1:618 \_ 10^6$, $I_h = 0$ and estimate the African bu_alo population levels as follows $S_b(0) = 4:341\_10^7$, $I_b(0) = 1:33\_10^6$ and A(0) = 0: For simplicity we set B = 1. We further assume that vaccination incurs higher costs than those for culling so that $W_1 > W_2$. More speci_cally we set $W_1 = 10^6$ and $W_2 = 10^3$: In addition, we set the control bound of $u_1(t)$ and $u_2(t)$ as follows $U_1 = 20$ and $U_2 = 3$, respectively.
Baseline values for our model parameter have been adopted from various source abound in literature as indicated in Table 2. Since prior studies suggests that the optimal treatment of uncomplicated brucellosis should be based on a six-week regimen of doxycycline combined
24
either with streptomycin for 2{3 weeks, or rifampicin for six weeks [30], we assume that the average treatment duration is 4 weeks and then $\_ = \frac{52}{4} = 13$:
Table 2: Parameters and values

Symbol	De_nition	Value	Units	Source
($\_b$;$\_c$;$\_h$)	Recruitment rate	(1680000,1976000,9150)	year□1	[13]
($\_b$; $\_c$; $\_h$)	Natural elimination rate	(0.04,0.22,0.02)	year□1	[12, 53]
(d_b; d_c)	Disease-related death rate	(0.35, 0.2)	year□1	[12]
a_k(k = 1; 2; 3; 4)	Amplitude of oscillation	0:8		
($\_{bc}$; $\_{cb}$)	Averaged direct transmission rate	0:135 _ 10□6	animal□1year□1	[13]
$\_{bb}$	Averaged direct transmission rate	0:21 _ 10□6	animal□1year□1	[13]
$\_{cc}$	Averaged direct transmission rate	0:18 _ 10□6	animal□1year□1	[13]
$\_{bh}$	Averaged direct transmission rate	1:3458 _ 10□9	animal□1year□1	[13]
$\_{ch}$	Averaged direct transmission rate	0:5896 _ 10□9	animal□1year□1	[13]
f	Proportion of new infections that			

develop into chronic 0.8 [11]
Rate of progression to chronic
carrier state African bu_aloes 0.67 year□1 [54]
_ Human treatment rate 13 year□1 [30]
_ Modi_cation factor 0.5
_ Vaccination rate 0.316 year□1 [11]

Figure 6 depict the numbers of infected wildlife, cattle and human over _nite time interval in the presence and absence of optimal control. The results demonstrate that optimal control strategy a signi_cant e_ect on the numbers of infected wildlife, cattle and humans, though, these control strategies are targeting cattle population only. Similar behavior is also present on the results for the periodic model (see Figure 7), but with oscillatory patterns indicate the inuence of seasonality on brucellosis dynamics. Results in both Figure 6 and Figure 7 shows that the implementation of time dependent intervention strategies aimed targeting domesticated

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livestock may not be su_cient to control the spread of human brucellosis in communities where cattle, wildlife and human interact. However, when there is extremely minimum interaction between wildlife and both cattle and humans (we set $\_{cb} = \_{bc} = 0{:}21\_10\square_{10}$) we observe that optimal vaccination and culling of cattle will lead to brucellosis elimination (see Figure 8).

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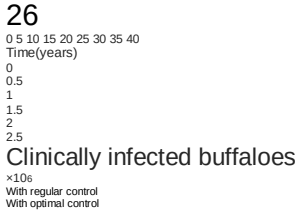
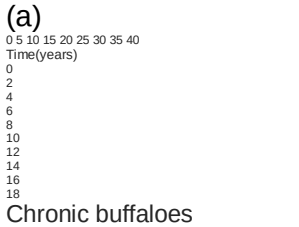
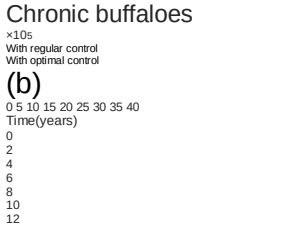


(a)



(b)



(c)

(d)

Figure 6: The numbers of infected wildlife, cattle and human for the autonomous model (1): (a) clinically infected bu_aloes (b) chronically infected bu_aloes; (c) infected cattle; (d) infected humans.

27

0 5 10 15 20 25 30 35 40
Time(years)
0
0.5
1
1.5
2
2.5
Clinically infected buffaloes
×10^6
With regular control
With optimal control
(a)
0 5 10 15 20 25 30 35 40
Time(years)
0
2
4
6
8
10
12
14
16
18
Chronic buffaloes
×10^5
With regular control
With optimal control
(b)
0 5 10 15 20 25 30 35 40
Time(years)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
Infected cattle
×10^6
With regular control
With optimal control
(c)
0 5 10 15 20 25 30 35 40
Time(years)
0
2000
4000
6000
8000
10000
12000
Infected human population
With regular control
With optimal control
(d)

Figure 7: The numbers of infected wildlife, cattle and human for the periodic model (10): (a) clinically infected bu_aloes (b) chronically infected bu_aloes; (c) infected cattle; (d) infected humans.

28

0 5 10 15 20 25 30 35 40
Time(years)
0
1000
2000
3000
4000
5000
6000
Infected cattle
With regular control
With optimal control

Figure 8: The numbers of infected cattle for the autonomous model (1) with extremely minimal interaction between wildlife and both cattle and humans.

0 5 10 15 20 25 30 35 40
Time(years)
0
5
10
15
20
25
Optimal control rates
$u_1(t)$
$u_2(t)$

Figure 9: Control pro_les for the periodic model (10)

Figure 9 depicts the optimal control pro_les for $u_1(t)$ and $u_2(t)$ for the periodic model (10). As we can observe, both u_1 and u_2 starts at the maximum and remain there for a period of 18 years. There after both controls (u_1 and u_2) begin to oscillate with time for all the remaining period. These results suggest a maximum e_ort for vaccination and culling for the entire horizon. A similar remark can be drawn for an autonomous model (1) since both controls u_1 and u_2 start at the maximum and remain there for the entire time horizon (see Figure 10).

0 5 10 15 20 25 30 35 40
0
5
10
15
20
25
Optimal control rates
Time(years)
$u_1(t)$
$u_2(t)$

Figure 10: Control pro_les for the periodic model (1)

To explore the e_ects of costs on the implementation of control strategies, we varied W_1 and W_2. Suppose $W_1 = 10_{10}$ and $W_2 = 10_5$. Then as illustrated in Figure 11 control u_1 and u_2 will not stay at the maximum for the entire time horizon as we have observed earlier. More speci_cally, u_1 will stay at the maximum for a period of 2 years while u_2 will stay at the maximum for about 7 years and this is due to the relatively lower value of W_2:

0 2 4 6 8 10 12 14 16 18 20
Time(years)
0
5
10
15
20
25
Optimal control rates
u
1
(t)
u
2
(t)

Figure 11: Control pro_les for the periodic model (10) with high costs.

5 Concluding remarks

In this paper, we constructed a theoretical framework to investigate the transmission dynamics of human brucellosis in periodic and non-periodic environments. We also investigated the

implications of intervention strategies on controlling the spread of brucellosis. To explore brucellosis dynamics in non-periodic environments we developed an autonomous dynamical system with constant parameters that account for all the essential biological dynamics of brucellosis.

Our model incorporated human population, cattle population and wildlife population (African bu_aloes). We conducted thorough analysis of the model, including computation of the basic reproduction number and stability analysis of the model steady states. Particularly, we demonstrated that when the basic reproduction number is less than unity then our autonomous

model has globally stable disease free equilibrium. This implies that the disease dies out in the community. However, if the basic reproduction number is greater than unity then there exists a unique endemic equilibrium that is globally asymptotically stable.

Extensive investigation of the relationship between reproduction number R_0 and model parameters, we observed that model parameters such as $\__b$, $\__c$, $\__{bc}$, $\__{bb}$, _, and f, have a positive inuence on the R_0, that is, whenever they are increased, the size of R_0 increases. For example, an increase in recruitment rate of Bu_alo $\__b$ by 73.99% will lead to an increase in the size of R_0 by 73:99%: In the other-hand, model parameters with negative index values have a negative inuence on R_0, for example, an increase in mortality rate of Bu_alo d_b by 46:15% will lead to a decrease on the magnitude of R_0 by 46:15%. Overall, we noted that increase on

progression rate of infected cattle to chronic stage reduce the size of R_0. In particular, one can note that whenever the progression rate is greater than 0:5 the disease dies in the community. Furthermore, we observed that whenever the vaccination rate of susceptible cattle is less than 0:5 the disease persists in the community.

The model allowed us to demonstrate the implications of time dependent controls. Specifically we have shown that time dependent intervention strategies for cattle population could minimized brucellosis incidence in both humans and wildlife. In addition, our optimal control simulations demonstrate that if humans and cattle have extremely minimal interaction then brucellosis can be e_ectively controlled in both humans and cattle and it may require a period of 5 years to successful contain the disease. However, if the intervention strategies are regular the disease may not be successful contained even if the strategies are implemented for a time period of 40 years.

In the second model, we extended the autonomous system to a periodic environment to analyze

the impacts of seasonal variation that may a_ect the movements of animals and, consequently, brucellosis transmission. We derived an expression for the seasonal-induced basic reproductive number and showed that the basic reproductive number remains a sharp threshold for brucellosis dynamics even in a periodic environment. Thus, if the basic reproduction number is less than unity brucellosis will be eradicated. We also proved uniform persistence of the disease as well as the existence of a nontrivial periodic solution when the basic reproduction number is greater than unity. In a similar manner, to our autonomous model, we explored the implication of time dependent cattle vaccination and culling of infected cattle. Our optimal control simulations in this case concurred with our earlier _ndings on the autonomous model, that optimal control can greatly reduce brucellosis incidence among human, wildlife and cattle. However, our optimal control simulations of the periodic model also exhibited annual oscillations which reect the e_ect of seasonality on brucellosis dynamics in periodic environments.

In conclusion, our study demonstrate that, in all scenarios, the optimal control can greatly reduce the burden of brucellosis in the community and most importantly if wildlife and cattle and humans and cattle have extremely minimal contacts then the disease can be e_ectively controlled in a shorter period of time.

A potential limitation of the present paper is that we have employed the mass action incidence for the direct transmission route for both the autonomous and time-periodic model. Such mass action forms, with the advantage of making model calculations more tractable, have been extensively used in previously published brucellosis modeling work (see, e.g., [12, 11, 16, 18]). On the other hand our model did not include indirect transmission, for realistic applications, the indirect (i.e., environment-to host) transmission it would have been better if it is included in our model and represented by saturated type functional responses, and such type of incidence forms have been used in modeling some other environmentally transmitted diseases (such as cholera [55, 56]). It would be interesting to employ saturated type incidence in our future work on brucellosis modeling, for both the autonomous and time-periodic cases. Our study can be extended by assessing the impact of intervention strategies that minimize cattle and wildlife interactions such as maintenance of game fencing. Also the study can be strengthened by incorporating heterogeneous interaction between cattle, wildlife and humans. It is also undeniable that _tting those key model parameters with realistic seasonal data will

improve our model and its applicability.

Availability of Data

All data have been included in the manuscript.

Competing Interest

The authors declare that they have no conicts of interest.

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