Summary of BTB-brucellosis co-infection model and assumptions

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We observed a positive association between BTB and brucellosis in our field data. Longitudinal observation showed that this pattern was age-specific, with the positive association occurring only in younger buffalo. We developed a model for BTB-brucellosis co-infection to understand the mechanisms and consequences of co-infection. Parameter values representing the consequences of co-infeciton in this model are estimated from field data. We and use the model to ask, (1) are the observed changes in transmission and mortality rates sufficient to generate the positive co-infection patterns observed; (2) what is the consequence of brucellosis infection for the invasion of bTB; and (3) what is the consequence of bTB invasion for the dynamics of brucellosis (endemic equilibrium values)?

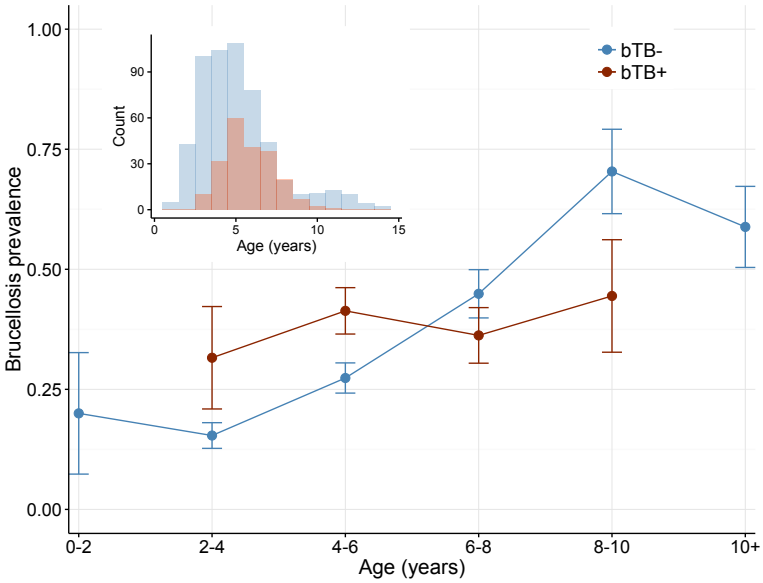

Figure 1: Age, brucellosis-prevalence curves in buffalo simultaneously uninfected (blue) or infected (red) with bTB. The inset figure shows the distribution of ages in our sample, which best cover buffalo between two and eight years old and include 796 samples from 151 repeatedly captured individuals. Ages are binned for visualization and animals that test positive are assumed to remain positive for the duration of the study. Sample sizes for TB- are: 10, 182, 209, 103, 27, 35 buffalo. Sample sizes for TB+ animals are: 0, 21, 108, 75, 21, 1 for ages 0-2, 2-4, 4-6, 6-8, 8-10, and 10+ respectively.

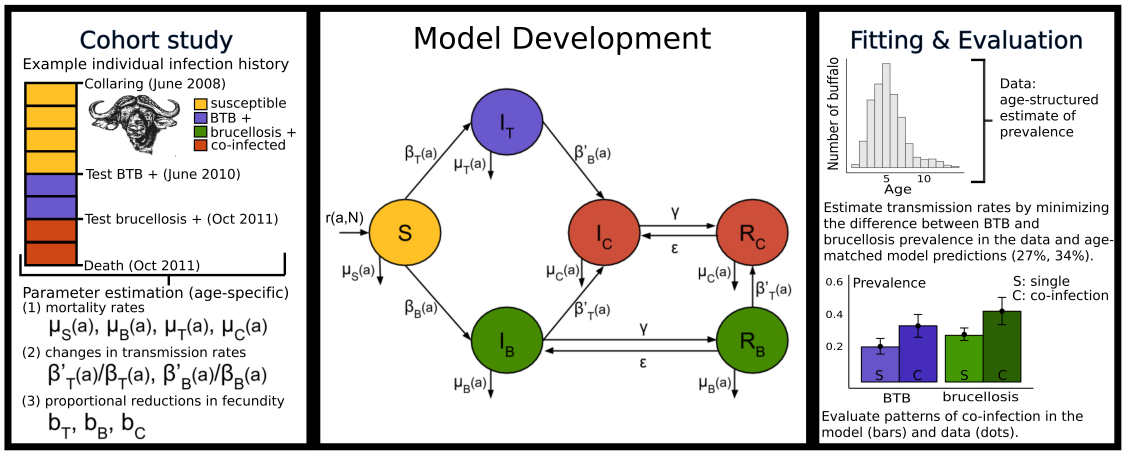

Figure 2: (center) Schematic representation of the disease model defined in SI Appendix 3. Hosts are represented as Susceptible (S), infected with TB only (IT), infected with brucellosis only (IB), co-infected with both infections (IC), persistently infected with brucellosis only but no longer infectious (RB), and persistently infected with brucellosis and co-infected with BTB (RC). (left) A detailed cohort study informs model parameterization, including the mortality, transmission, and fecundity consequences of co-infection as well as the (right) transmission parameters for both infections. The prevalence plot illustrates that the model accurately reproduces the observed co-infection patterns in the data. Bars represent model results and dots represent the data.

Model Structure and Assumptions

We developed a continuous time differential equation model to evaluate the disease dynamic consequence of bTB invasion on brucellosis dynamics and vice versa. Our model structure reflects the costs of co-infection identified for each parameter: host mortality rate, host birth rate, and disease transmission rates (Figure 2). Animals are represented with six groups: susceptible to both infections(S), acutely infected with brucellosis (I_B), chronically infected with or recovered from acute brucellosis (R_B), infected with bTB (I_T), co-infected with both pathogens (I_C), or in the chronic stages of brucellosis and infected with bTB (R_C).

$$
\begin{aligned}
\frac{dS(a)}{dt} &= r(a,N) - \beta_T T S(a) - \frac{\beta_B(a)B}{N} S(a) - \mu_S(a)S(a) \\
\frac{dI_T(a)}{dt} &= \beta_T T S(a) - \frac{\beta'_B(a)B}{N} I_T(a) - \mu_T(a) I_T(a) \\
\frac{dI_B(a)}{dt} &= \frac{\beta_B(a)B}{N} S(a) - \beta'_T T I_B(a) + \epsilon R_B(a) - (\gamma + \mu_B(a)) I_B(a) \\
\frac{dI_C(a)}{dt} &= \beta'_T T I_B(a) + \frac{\beta'_B(a)B}{N} I_T(a) + \epsilon R_C(a) - (\gamma + \mu_C(a)) I_C(a) \\
\frac{dR_B(a)}{dt} &= \gamma I_B(a) - (\epsilon + \mu_B(a)) R_B(a) \\
\frac{dR_C(a)}{dt} &= \beta'_T T R_B(a) + \gamma I_C(a) - (\epsilon + \mu_C(a)) R_C(a)
\end{aligned}
$$

Parameter table - not yet updated Parameter table- not yet updated

	Value	Meaning
b	0.54	maximum natural birth rate for uninfected adults
b1	1	proportional reduction in births for adults with bTB
b2	1	proportional reduction in births for adults with brucellosis.
b3	1	proportional reduction in births with chronic brucellosis.
b4	1	proportional reduction in births for co-infected adults.
b5	assume= b4	proportional reduction in births for co-infecteds with chronic brucellosis.
μ_{S_i}	$0.12, 0.04$	annual mortality rate for uninfected juveniles and adults
μ_{T_i}	$2.82\mu_{S_i}$	annual mortality rate for animals with bTB
μ_{B_i}	$3.02\mu_{S_i}$	annual mortality rate for animals with brucellosis
$\mu_{R_{B_i}}$	μ_{B_i}	annual mortality rate for animals with chronic brucellosis
μ_{C_i}	$5.84\mu_{S_i}$	annual mortality rate for animals with bTB-brucellosis co-infection
$\mu_{R_{C_i}}$	μ_{C_i}	annual mortality rate for co-infecteds with chronic brucellosis
β_T	fit to data	transmission rate for bTB in susceptible animals
β_B	fit to data	transmission rate for brucellosis in susceptible animals
$\beta_T^{'}$	β_T	transmission rate for the bTB in animals infected with brucellosis
$\beta_B^{'}$	$2.1\beta_B$	transmission rate for brucellosis in animals infected with bTB
γ	1/2	1/duration of infectious period for brucellosis
ϵ	0.01	recrudescence rate
ρ	0.05	proportion of births from animals with brucellosis that result in infection

WORK STOPS HERE

$$
\begin{aligned}
N &= S + I_T + I_B + R_B + I_C + R_C \\
T &= I_T + I_C + R_C \\
B &= I_B + I_C \\
N_b &= S + b_1 I_T + b_2 I_B + b_3 R_B + b_4 I_C + b_5 R_C \\
\frac{dS}{dt} &= bN_b\big(1 - \frac{r}{b}\frac{N}{K}\big) - \beta_T TS - \beta_B BS - \mu_S S \\
\frac{dI_T}{dt} &= \beta_T TS - \beta'_B BI_T - \mu_T I_T \\
\frac{dI_B}{dt} &= \beta_B BS - \beta'_T TI_B - \gamma I_B + \epsilon R_B - \mu_B I_B \\
\frac{dI_C}{dt} &= \beta'_T TI_B + \beta'_B BI_T - \gamma I_C + \epsilon R_C - \mu_C I_C \\
\frac{dR_B}{dt} &= \gamma I_B - \epsilon R_B - \mu_{RB} R_B \\
\frac{dR_C}{dt} &= \beta'_T TR_B + \gamma I_C - \epsilon R_C - \mu_{R_C} R_C
\end{aligned}
$$

where N is the total host population and T, B, and N_b are the numbers of buffalo contributing to tuberculosis transmission, brucellosis transmission, and births respectively.

To evaluate the consequences of co-infection for disease invasion, we evaluate how co-infection alters the basic reproduction number (R_o^T) of bTB.

Lets first consider the bTB only model:

$$
\begin{aligned}
\frac{dS}{dt} &= b(S + b_1 I_T)\left(1 - \frac{r}{b}\frac{S + I_T}{K}\right) - \beta_T SI_T - \mu S \\
\frac{dI_T}{dt} &= \beta_T SI_T - \mu_T I_T
\end{aligned}
$$

R_o^T for bTB in the case when brucellosis is absent is, $R_o^T = \frac{\beta_T K}{\mu_T}$. The disease free equilibrium is $E_o = (K, 0)$, where the variables are denoted $x_o = (S, I_T)$. The endemic

equilibrium for bTB when brucellosis is absent is, $E^* = (S_T^*, I_T^*)$, where $S_T^* = K\frac{1}{R_o^T}$ and

$$I_T^* = \frac{K}{2}\frac{1}{b_1}\left[\left(\frac{bb_1 - \mu - \alpha_T}{r} - \frac{1+b_1}{\mathcal{R}_0^T}\right) + \sqrt{\left(\frac{bb_1 - \mu - \alpha_T}{r} - \frac{1+b_1}{\mathcal{R}_0^T}\right)^2 + 4\frac{b_1}{\mathcal{R}_0^T}\left(1 - \frac{1}{\mathcal{R}_0^T}\right)}\right].$$

Now consider the brucellosis only model:

$$\begin{aligned}
\frac{dS}{dt} &= b(S + b_2 I_B + b_3 R_B)\big(1 - \frac{r}{b}\frac{(S + I_B + R_B)}{K}\big) - \beta_B I_B S - \mu_S S \\
\frac{dI_B}{dt} &= \beta_B I_B S - \gamma I_B + \epsilon R_B - \mu_B I_B \\
\frac{dR_B}{dt} &= \gamma I_B - \epsilon R_B - \mu_{RB} R_B
\end{aligned}$$

R_o^B for brucellosis in the case that bTB is absent is, $R_o^B = \frac{\beta_B K(\epsilon+\mu_R)}{(\gamma+\mu_B)(\epsilon+\mu_{RB})+\epsilon\gamma}$

The endemic equilibrium for brucellosis when bTB is absent is $E* = (S_t^*, I_{Bt}^*, R_{Bt}^*)$, where

$S_t^* = \frac{K}{R_o^B}$,

$I_{Bt}^* = \frac{K}{2}\frac{1}{b_2(1+\delta)+b_3(\delta+\delta^2)} + \left[bb_2 + bb_3\delta - \frac{\beta_B K}{R_o} - \frac{r+r\delta+b_2+b_3\delta}{R_o}\right] +$

$\sqrt{4 + \frac{K}{b_2(1-\delta)+b_3(\delta+\delta^2)}\left[bb_2 + bb_3\delta - \frac{\beta_B K}{R_o} - \frac{r+r\delta+b_2+b_3\delta}{R_o}\right]^2}$,

$R_{Bt}^* = \frac{\gamma I_{Bt}^*}{\epsilon-\mu_R}$.

R_o for bTB when brucellosis is present is evaluated at these conditions, where $\delta = \frac{\gamma}{\epsilon-\mu_R}$.

$R_o^T = 2$.

CHECK THIS WITH NUMERICAL INTEGRATION!!

Notes on deriving R_o^T:

1. Note there are $n = 6$ components of this model, $m = 3$ of which are infected with bTB. Define the vector, $x_o = [I_T, I_C, R_C, S, I_B, R_B]^T$, such that x_i contains the huber of individuals in each component.

2. The rate of change of x_i (e.g. the differential equations) can be represented as, $\mathcal{F}_i(x) - \mathcal{V}_i(x)$. Here $\mathcal{F}_i(x)$ is the rate of appearance of new infections in compartment i and $\mathcal{V}_i(x)$ is the rate of transfer by all other means. Noting the negative sign with $\mathcal{V}_i(x)$ and that $\mathcal{F}_i(x)$ only includes infections that are newly arising and does not include terms which describe the transfer of infectious individuals from one infected compartment to another.
Here, $\mathcal{F}_i(x) = \left[\frac{\beta_T S(I_t+I_C+R_C)}{S+I_T+I_B+I_C+R_B+R_C}, \frac{\beta_T I_B(I_t+I_C+R_C)}{S+I_T+I_B+I_C+R_B+R_C}, \frac{\beta_T R_B(I_t+I_C+R_C)}{S+I_T+I_B+I_C+R_B+R_C}, 0, 0, 0\right]^T$.
$\mathcal{V}_i(x) = \left[2\right]^T$

3. Check $\mathcal{F}_i$ and $\mathcal{V}_i$ meet the conditions outlined by van den Driessche and Watmough (2002) so you can use the next generation matrix, FV^{-1}, from m by m matrices of partial derivatives of F_i and V_i. (CHECK ME) $F_i = \left[\frac{\partial \mathcal{F}_i(x_o)}{\partial x_i}\right]$. $V_i = \left[\frac{\partial \mathcal{V}_i(x_o)}{\partial x_i}\right]$. x_o are the disease free equilibrium values of x.

4. Define bTB free equilibrium values $x_o = [I_T = 0, I_C = 0, R_C = 0, S = S*, I_B = I_B*, R_B = R_B*]^T$. Where $S*$, I_B*, and R_B* are the equilibrium values of brucellosis in the absence of bTB.

5. Evaluate the F and V matrices at x_o.
Here, $F_i = \begin{bmatrix} \frac{\beta_T S*}{(S*+I_B*+R_B*)} & \frac{\beta_T S*}{(S*+I_B*+R_B*)} & \frac{\beta_T S*}{(S*+I_B*+R_B*)} \\ \frac{\beta'_T I_B*}{(S*+I_B*+R_B*)} & \frac{\beta'_T I_B*}{(S*+I_B*+R_B*)} & \frac{\beta'_T I_B*}{(S*+I_B*+R_B*)} \\ \frac{\beta'_T R_B*}{(S*+I_B*+R_B*)} & \frac{\beta'_T R_B*}{(S*+I_B*+R_B*)} & \frac{\beta'_T R_B*}{(S*+I_B*+R_B*)} \end{bmatrix}$
Here, $V_i = \begin{bmatrix} a & b & c \\ d & e & f \\ g & h & i \end{bmatrix}$

6. Calculate FV^{-1}

7. The dominant eigenvalue of FV^{-1} is xxx.

Approach

Mortality and Fecundity parameters:

- Data analyses informs mortality rates for each disease category in *young females aged 2-8)*.

- Data analysis informs fecundity rates for each disease category in *young females aged 2-8)*.

- How to extrapolate to males and other age groups (Figure 3)?

Parameters relevant to the time course of brucellosis are limited to cattle and U.S. bison:

- Pull γ and ϵ from the literature.

- Few animals were followed less than 2 years so assume our estimates are relevant for I_B.

Still thinking about this.

Transmission:

- Data analyses inform the proportional increase in transmission with co-infection (e.g. that $\beta'_B = 2.8 * \beta_B$). I hope to estimate β_B and β_T from the time sequence data.

Let's consider first the TB-only model:

$$\frac{dS}{dt} = bN_b\left(1 - \frac{r}{b}\frac{N}{K}\right) - \beta_T S I_T - \mu S \tag{1}$$

$$\frac{dI_T}{dt} = \beta_T S I_T - \alpha_T I_T - \mu I_T \tag{2}$$

Then the disease free equilibrium is $E^0 = (K, 0)$ where the population is $x = (S, I_T)$. The basic reproduction number is $\mathcal{R}_0 = \frac{\beta_T K}{\alpha_T + \mu}$. The endemic equilibrium is $E^* = (S^*, I_T^*)$ where $S^* = K\frac{1}{\mathcal{R}_0}$ and

$$I^* = K\left(\frac{r - \alpha_T}{2r} - \frac{1}{\mathcal{R}_0} + \frac{1}{2r}\sqrt{(r - \alpha_T)^2 + \frac{4r\alpha_T}{\mathcal{R}_0}}\right).$$

When $\alpha_T = 0$, then $I^* = K(1 - 1/\mathcal{R}_0)$. We fix other parameters and vary β_T to get endemic levels such that $I^*/N = 10\%$, etc.

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