

# Summary of BTB-brucellosis coinfection model and assumptions

23-April-2016

## Overview

Bovine tuberculosis (bTB) and brucellosis are positively associated at the population level. Age prevalence curves show a shift in the peak age of brucellosis infection in co-infected animals (Figure 1). We want to know why, so we investigate the costs of co-infection on three parameters relevant for disease dynamics.

1. *Host mortality rates*: bTB was associated with a 2.81 (95%CI 1.47 – 6.82) fold increase in mortality hazard and infection with brucellosis was associated with an 3.00 (95%CI 1.50 – 6.01) fold increase in mortality hazard compared to uninfected buffalo. We did not find support for an interaction between bTB and brucellosis on mortality, indicating that the mortality effects of both infections are additive in co-infected buffalo.

2. *Incidence rates*: bTB was associated with a 1.37 fold increase in the rate at which animals acquire brucellosis. This pattern occurred in one site but not the second. I think this is because the higher baseline mortality in the second site means we do not catch and diagnose infected individuals before they die and hope to test this with the model.

3. *Pregnancy rates*: These analyses are still in prep- in general we see declines with infection. The model then asks, (1) are changes in these rates sufficient to generate the age prevalence patterns observed and (2) what is the consequence of co-infection for disease invasion?

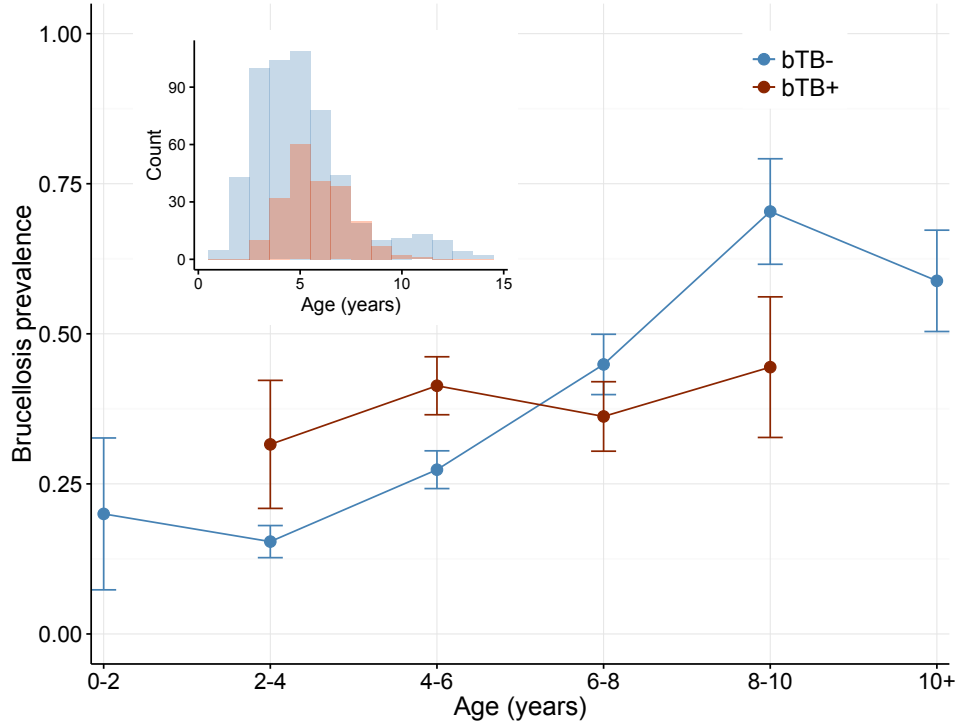


Figure 1: Age, brucellosis-prevalence curves in buffalo simultaneously uninfected (blue) or infected (red) with bTB. The inset figure shows the distribution of ages in our sample, which best cover buffalo between two and eight years old and include 796 samples from 151 repeatedly captured individuals. 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.

## 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 brucellosis ( $C_B$ ), infected with bTB ( $I_T$ ), co-infected with both pathogens ( $I_C$ ), or in the chronic stages of brucellosis and infected with bTB ( $C_C$ ).

Our model is not spatially explicit. Buffalo herds within the regions studied have fission-fusion behavior, where herds come together and fragment over time (Cross et al. 2005). Dispersal between regions also occurs (Spaan, Masters thesis). If data become available to parameterize aggregation patterns and movement rates between herds during birthing periods, it is possible to extend this framework in a spatially explicit context. We represent regional differences in the underlying survival and fecundity rates observed in our statistical analyses by considering parameters for both the Lower Sabie and Crocodile Bridge region.

### *Brucellosis*

We model the transmission of brucellosis by assuming the time course of infection in African buffalo is comparable with infection in cattle and bison (*Bison bison*) and by following model structures developed in those systems (Treanor et al. 2010, Vaccine, Ebinger et al. 2011, Hobbs et al. 2015). Clinical signs of brucellosis infection in cattle and bison include abortions and decreased milk production (Olsen and Tatum, 2010; Samartino and Enright 1993; Rhyan et al. 1994). In natural populations of African buffalo, infection is also associated with declines in condition in the dry season and mortality independent of host condition (Gorsich et al. 2015). (Note this is similar to Moose! Forbes et al. 1996, Experimental studies on *Brucella abortus* in moose, JWD).

In bison, brucellosis is associated with lower calving rates following sero-conversion. Calving rates were also overall lower in some age classes with brucellosis, although the effect was

non-significant (age < 4, uninfected 0.64 (95% CI: 0.52?0.76); test positive: 0.81 (95% CI: 0.73?0.89); after sero-conversion 0.22 (95% CI: 0.00?0.46) )

The survival and reproductive costs of infection in bison (Fuller et al.2007)

”However, some animals may completely clear the bacterium and recover (John and Samuel 2000, Ficht 2003), while other animals appear have a natural resistance to the disease (Templeton et al. 1988, Derr et al. 2002).”

Transmission of brucellosis to susceptible bison or cattle occurs primarily through ingestion of the bacteria shed in association with an aborted fetus, reproductive tissues or discharges during birthing (Samartino and Enright 1993). The bacteria has been isolated from placental samples after brucella-induced abortions and milk (Alexander et al. 1981; Capparelli et al. 2009). Thus, although males acquire infection, pregnant females are assumed to transmit the infection (seaman source). In bison, risk of shedding the bacteria is highest 2 years after infection After 2 years, xxxx abortions??? .

The incubation period ranges with age, sex, stage of gestation, and susceptibility (Nicoletti).

Based on the ranging behavior and size of buffalo herds (Ryan et al. 2007), we assume contact patterns are constant across a range of host densities and model transmission as frequency dependent. Animals remain infected and infectious with brucellosis for two years following seroconversion (Rhyan et al. 2009). During this time, they suffer decreased birth and survival rates. Recovered animals are associated with similar pregnancy rates as uninfected buffalo and do not contribute to transmission. A small percentage of recovered buffalo,  $\eta$ , can recrudescence and actively transmit the infection. (Note: this assumptions about time course of infection are why I am redoing my pregnancy analyses so is subject to change) More on latency from Ray et al., 1988; Dolan et al. 1980. We also represent the possibility of vertical transmission of brucellosis because bacteria have been detected in the placenta, fetal fluid, and colostrum of infected cattle and bison (cattle: Alexander et al. 1981; Emminger and Schalm 1943, bison: Davis et al. 1990, Xavier et al. 2009). Experimental evidence from

Figure 2: Schematic representation of model structure

cattle suggests vertical transmission is infrequent (Fensterbank 1978; Plommet et al. 1973). Similarly, maternal immunity in bison calves wanes after 5-6 months and is no difference in the rate that calves borne to seronegative and seropositive mothers become infected (Fuller et al. 2007, Ryan et al. 2009). Serological evidence suggests that vertical transmission is also rare in African buffalo (Gorsich et al. 2015). Thus, we allow a small proportion of African buffalo calves,  $\rho$ , to acquire the infection.

bTB infection in African buffalo is a lifelong infection (Bengis 1999) so we do not include a recovered class or clearance of the infection for bTB. Our assumptions about how bTB infection and co-infection with brucellosis effect survival, fecundity and transmission rates are detailed in the analyses section. Together, the statistical results identified in this paper and these assumptions generate the following model:

$$\begin{aligned}
 N &= \sum_{i=1}^4 S_i + I_{T_i} + I_{B_i} + I_{C_i} + C_{B_i} + C_{C_i} \\
 N_b &= \sum_{i=1}^4 S_i + b_{1_i} I_{T_i} + b_{2_i} I_{B_i} + b_{3_i} I_{C_i} + C_{B_i} + b_{1_i} C_{C_i} \\
 \lambda_T &= \frac{\beta_T \sum_{i=1}^4 (I_{T_i} + I_{C_i} + C_{C_i})}{N} \\
 \lambda'_T &= \frac{\beta'_T \sum_{i=1}^4 4(I_{T_i} + I_{C_i} + C_{C_i})}{N} \\
 \lambda_B &= \frac{\beta_B \sum_{i=1}^4 (I_{B_i} + I_{C_i})}{N} \\
 \lambda'_B &= \frac{\beta'_B \sum_{i=1}^4 4(I_{B_i} + I_{C_i})}{N}
 \end{aligned}$$

$$\frac{dS_i}{dt} = b_i(1 - \rho)N_b \left(1 - \frac{r}{b} \frac{N}{K}\right) - \lambda_T S_i - \lambda_B S_i - \mu_{S_i} S_i - \nu_i S_i \quad (1)$$

$$\frac{dI_{T_i}}{dt} = \lambda_T S_i - \lambda'_B I_{T_i} - \mu_{T_i} I_{T_i} - \nu_i I_{T_i} \quad (2)$$

$$\frac{dI_{B_i}}{dt} = b_i \rho N_b \left(1 - \frac{r}{b} \frac{N}{K}\right) + \lambda_B S_i + \epsilon C_{B_i} - \gamma I_{B_i} - \lambda'_T I_{B_i} - \mu_{I_{B_i}} I_{B_i} - \nu_i I_{B_i} \quad (3)$$

$$\frac{dI_{C_i}}{dt} = \lambda'_T I_{B_i} + \lambda'_B I_{T_i} + \epsilon C_{C_i} - \gamma I_{C_i} - \mu_{I_{C_i}} I_{C_i} - \nu_i I_{C_i} \quad (4)$$

$$\frac{dC_{B_i}}{dt} = \gamma I_{B_i} - \epsilon C_{B_i} - \mu_{C_{B_i}} C_{B_i} - \nu_i C_{B_i} \quad (5)$$

$$\frac{dC_{C_i}}{dt} = \lambda'_T C_{B_i} + \gamma I_{C_i} - \epsilon C_{C_i} - \mu_{C_{C_i}} C_{C_i} - \nu_i C_{C_i} \quad (6)$$

$$(7)$$

where  $N$  is the total host population and  $r = b - \mu$  is the natural growth rate without density dependence.

## 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)?

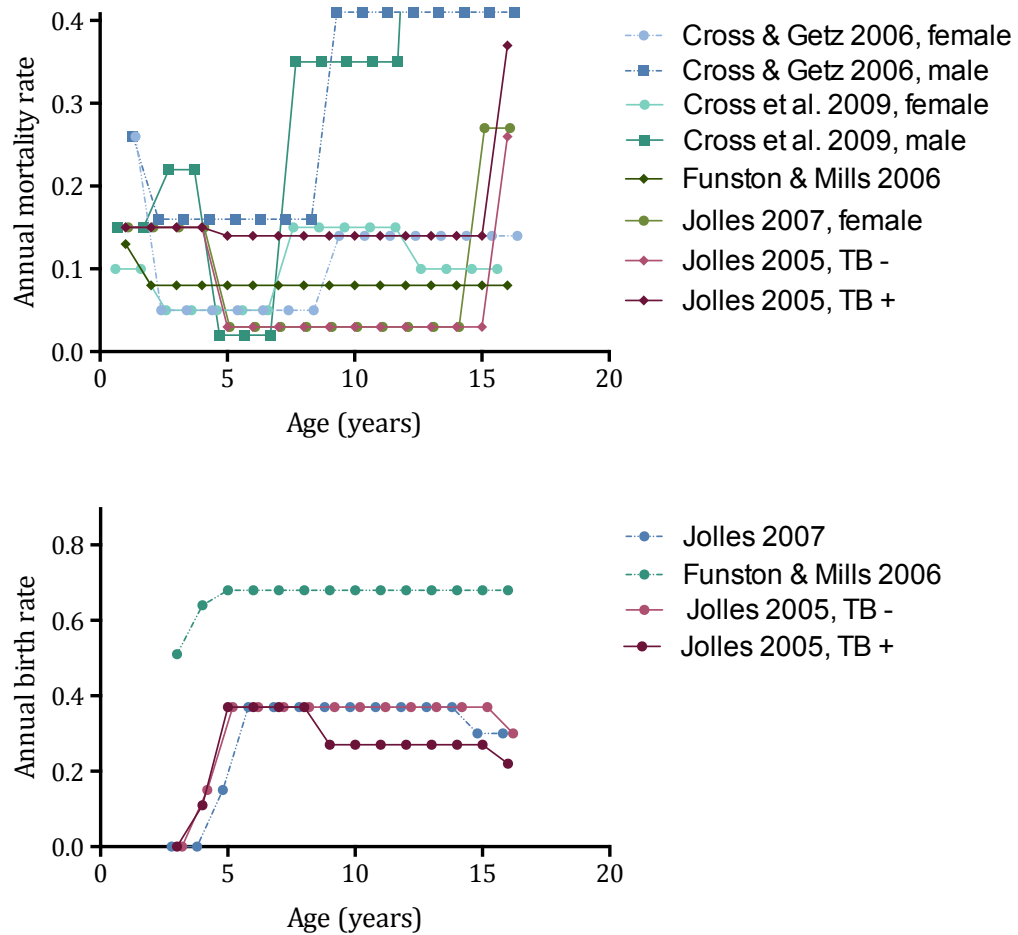
Parameters relevant to the time course of brucellosis are limited to cattle and U.S. bison:

- Pull  $\gamma$  and  $\epsilon$  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  $\beta_B$  and  $\beta_T$  from the time sequence data.



Note: In our study, 31% of buffalo captured right before the birthing season were pregnant.

Figure 3: Survival and fecundity parameters estimated on buffalo in South Africa

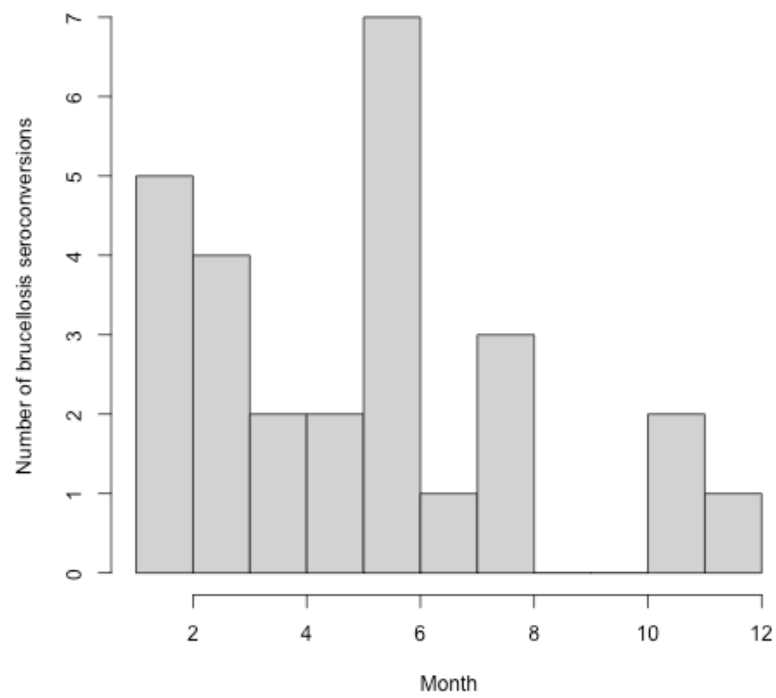


Figure 4: Month when incidences occurred



Parameter table

	Value	Unit	Meaning
b	<i>figure</i>	1/d	natural birth rate for uninfected animals
b <sub>1</sub>	?	1/d	proportional reduction in birth rate for animals with bTB
b <sub>4</sub>	?	1/d	proportional reduction in birth rate for animals with brucellosis.
b <sub>5</sub>	?	1/d	proportional reduction in birth rate for co-infected animals.
$\mu$	0.067/365.25	1/d	natural death rate for uninfected animals.
K	1000	indiv	carrying capacity
$\beta_T$	0.0001/365.25	1/d	transmission rate for bTB
$\beta_A$	0.01/365.25	1/d	transmission rate for the acute infection
$\beta_{T_A}$	0.02/365.25	1/d	transmission rate for the acute infection for animals with bTB
$\gamma_A$	1/3	1/d	1/duration of infection for acute pathogens
$\gamma_{T_A}$	1/3	1/d	1/duration of infection for acute pathogens for individuals with bTB
$\alpha_T$	0.001/365.25	1/d	increase in the mortality rate due to bTB infection
$\alpha_T$	0.001/365.25	1/d	increase in the mortality rate due to bTB infection
$\alpha_T$	0.001/365.25	1/d	increase in the mortality rate due to bTB infection
r	b− $\mu$	1/d	population growth rate at small population sizes

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Let's consider first the TB-only model:

$$\frac{dS}{dt} = bN_b \left( 1 - \frac{r}{b} \frac{N}{K} \right) - \beta_T S I_T - \mu S \quad (8)$$

$$\frac{dI_T}{dt} = \beta_T S I_T - \alpha_T I_T - \mu I_T \quad (9)$$

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

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

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

## Citations

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