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2. Modelling the impact of a live vaccine for Tularemia

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Abstract. Tularemia is an infectious disease caused by the bacteria *Francisella tularensis*. The disease is naturally occurring the the wild and primarily carried by animals and arthropods, but can also infect humans. Vectors include ticks, deer flies, horse flies and mosquitoes. A live attentuated vaccine has been available for decades, but has only received limited distribution to high-risk individuals. We develop a mathematical model for tularemia in order to examine the effects of pulse vaccination using impulsive differential equations. We develop thresholds for the frequency of vaccination and proportion of vaccinated individuals that will reduce human infection below a desired level. We also illustrate our results with numerical simulations and show that a 15% reduction in infectibility is achievable with modest (60%) coverage if vaccinations occurs three times a year. However, annual vaccination, even if coverage was high, is unlikely to have much impact on the disease.

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1. Introduction

Tularemia is an infectious disease caused by the bacteria *Francisella tularensis*. Typically found in North America, Europe and Asia, the spread and incidence of the disease has been steadily decreasing in recent years [12]. Tularemia occurs primarily in the Northern Hemisphere, with regular incidence of disease in the Czech Republic, Finland, Japan, Kazakhstan, Slovakia, Sweden, Russia, the US and Uzbekistan [2]. In particular, tularemia cases in the US are mainly concentrated in Arkansas, Missouri and Oklahoma, which accounted for 42.45% of all cases from 2000-2008 [16]. Nowadays, the prevalence and incidence of tularemia is fairly low, though it is endemic in certain rural regions and numerous small outbreaks have been reported in recent decades.

Several animals and arthropods can carry the disease, and the disease itself naturally occurs in the wild. In particular, ticks, deer flies, horse flies and mosquitoes are known to contribute significantly to the transmission of the disease [15]. The animal population can contract the disease due to interaction with infected arthropods or with the contaminated environment. As environmental factors and arthropods are wide ranging, the disease has been noted in domestic animals, wild small mammals and fish [3]. While human-to-human transmission has not yet been reported, humans can contract tularemia through a number of different methods, including [12]:

- Fly and tick bites spreading the disease from animals to humans
- Contact with infected animals, including consumption of infected meat
- Drinking contaminated water or inhaling infected particles.

Tularemia in humans can manifest in several different forms: ulceroglandular, oculoglandular, pneumonic, oropharyngeal, gastrointestinal and typhoidal [3]. The most common form is ulceroglandular, which accounts for 80% of cases and has a fatality rate of 5% in untreated cases [3]. If tularemia has been ingested through contaminated meat or infected water, then it will likely display itself as either oropharyngeal or gastrointestinal tularemia [3]. Cases of oropharyngeal and gastrointestinal tularemia have the highest untreated fatality rate of 60%. Contact with airborne tularemia in the eyes may lead to oculoglandular or pneumonic tularemia, the latter of which has an untreated fatality rate of 40% [3].

Current methods of prevention for the general public are limited to techniques that reduce their exposure to infected animals and ticks [12]. Once infected, there is an effective antibiotic regimen that limits the mortality rate to below 2% [12]. Recovery for most individuals results in long-lasting immunity to the disease [12]. As the bacteria are highly infective and easy to aerosolise, the disease has been recognised as a potential bioterrorism weapon.

This has led to increased interest in the development and production of vaccines [5]. Current vaccines include an attenuated form of the *Francisella tularensis* Live Vaccine Strain (LVS), which has been available for several decades. This vaccine, while efficacious against non-aerosol forms of transmission, offers less protection against aerosol transmission. Furthermore, as the basis for the immune response and rate of reversion are unknown, it has not been deemed safe enough to distribute to the general public and has only been distributed to individuals of high risk who are in constant contact with the disease [2,5].

Most studies of tularemia to date have been clinical in nature. Past studies have addressed the disease, vaccine and drug options [2, 3, 12], as well as transmission and infection sources during an outbreak [6]. Studies have also focused on the clinical diagnosis of tularemia [7], and verifying the efficacy of the live vaccine [4]. Mathematical modelling of this disease has received relatively little attention.

This chapter will attempt to model tularemia within a small group of organisms. We will first consider the model without vaccination to examine various dynamics of the system before extending the model to include impulsive vaccinations occuring at regular intervals. Numerical simulations of the system will then illustrate the effect of the vaccine.

2. The system without vaccination

For the basic model of tularemia, we consider eight populations, listed in Table 1. Contamination of the environment, in the form of infected airborne particles or contaminated water, will be treated as a population in order to consider its effects on the dynamics of the other three populations.

By using a system of ordinary differential equations (ODEs) to characterize the system, we assume that the populations mix homogeneously. This is valid for the population of animals, insects and the environment, as they are in constant contact with each other. This may also hold for the human population when considering an isolated rural village.

For this model, we assume that there are constant birth rates within the insect, animal and human populations (π_I, π_A, π_H), and that all offspring are born susceptible to the disease. There is also constant background or decay rates within the insect, animal, human and environment populations $(\mu_I, \mu_A, \mu_H, \mu_E)$.

Susceptible individuals become infected through mass-action transmission after interaction with infected organisms in the other populations(α_i, for i = 1 to 7) and subsequently move into their respective infected populations.

Table 1. State variables.

Populations	
S_I	Susceptible insect population
I_I	Infectious insect population
S_A	Susceptible animal population
I_A	Infectious animal population
S_H	Susceptible human population
I_H	Infectious human population
R_H	Recovered human population
E	Contaminated environment

Susceptible animals can become infected through exposure to the contaminated environment (ρ_1), and susceptible humans can become infected through exposure to contaminated water (ρ_2) and air (ρ_3). Infected animals and humans can recover from the disease (β_A, β_H), though only humans recover with lifelong immunity. Finally, infected animals and humans can die at a disease-specific death rate that is higher than the background death rate (γ_A, γ_H).

These interactions produce the following model:

$$\begin{aligned}
S_I' &= \pi_I - \alpha_2 I_A S_I - \alpha_6 I_H S_I - \mu_I S_I \\
I_I' &= \alpha_2 I_A S_I + \alpha_6 I_H S_I - \mu_I I_I \\
S_A' &= \pi_A - \alpha_1 I_I S_A - \alpha_3 I_A S_A - \rho_1 E S_A + \beta_A I_A - \mu_A S_A \\
I_A' &= \alpha_1 I_I S_A + \alpha_3 I_A S_A + \rho_1 E S_A - \beta_A I_A - \gamma_A I_A - \mu_A I_A \\
S_H' &= \pi_H - \alpha_4 I_A S_H - \alpha_5 I_I S_H - (\rho_2 + \rho_3) E S_H - \mu_H S_H \\
I_H' &= \alpha_4 I_A S_H + \alpha_5 I_I S_H + (\rho_2 + \rho_3) E S_H - \beta_H I_H - \gamma_H I_H - \mu_H I_H \\
R_H' &= \beta_H I_H - \mu_H R_H \\
E' &= \alpha_7 I_A - \mu_E E
\end{aligned} \tag{1}$$

where the all of the parameters are nonnegative. The interactions between the different populations are illustrated in Figure 1.

Using Model (1), the disease-free equilibrium population values are:

$$\{S_I^*, I_I^*, S_A^*, I_A^*, S_H^*, I_H^*, R_H^*, E^*\} = \{\frac{\pi_I}{\mu_I}, 0, \frac{\pi_A}{\mu_A}, 0, \frac{\pi_H}{\mu_H}, 0, 0, 0\}.$$

The endemic equilibrium values are:

$$S_I^* = \frac{\mu_I I_I^*}{\alpha_2 I_A^* + \alpha_6 I_H^*}$$

$$S_A^* = \frac{(\beta_A + \gamma_A + \mu_A) I_A^*}{\alpha_1 I_I^* + \alpha_3 I_A^* + \rho_1 \dfrac{\alpha_7 I_A^*}{\mu_E}}$$

$$S_H^* = \frac{\pi_H}{\alpha_4 I_A^* + \alpha_5 I_I^* + (\rho_2 + \rho_3)\dfrac{\alpha_7 I_A^*}{\mu_E} + \mu_H}$$

$$R_H^* = \frac{\beta_H I_H^*}{\mu_H}$$

$$E^* = \frac{\alpha_7 I_A^*}{\mu_E}$$

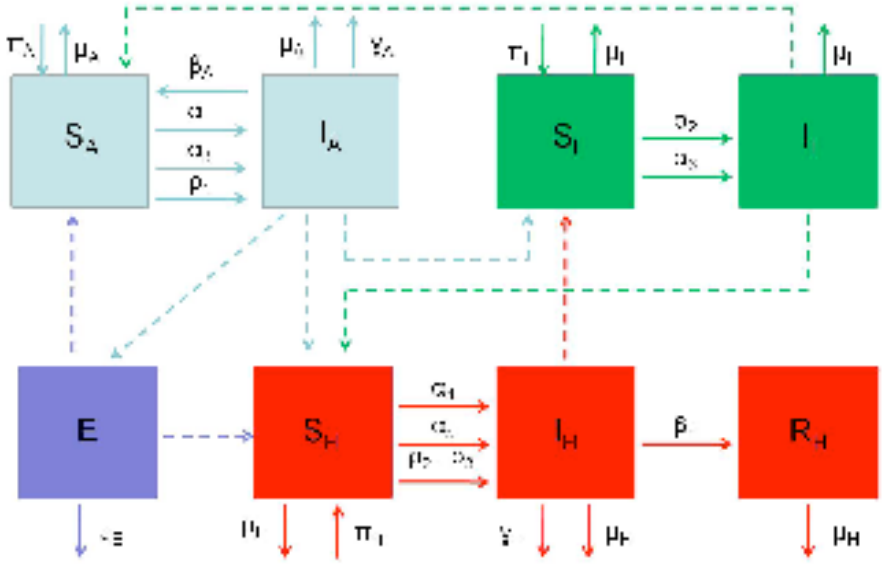

Figure 1. Flowchart of the model without vaccination. The dashed lines represent routes of transmission, while the solid lines represent transfer of individuals from one compartment to another.

where $I_H^* = \left(\dfrac{\alpha_4 I_A^* + \alpha_5 I_I^* + (\rho_2 + \rho_3)\dfrac{\alpha_7 I_A^*}{\mu_E}}{\alpha_4 I_A^* + \alpha_5 I_I^* + (\rho_2 + \rho_3)\dfrac{\alpha_7 I_A^*}{\mu_E} + \mu_H} \right) \left(\dfrac{\pi_H}{\beta_H + \gamma_H + \mu_H} \right)$, and I_A^* and I_I^* are obtained by solving

$$I_I^* = \frac{\pi_I(\alpha_2 I_A^* + \alpha_6 I_H^*)}{\mu_I(\alpha_2 I_A^* + \alpha_6 I_H^* + \mu_I)}$$

and $$\frac{\pi_A + \beta_A I_I^*}{\alpha_1 I_I^* + \alpha_3 I_A^* + \rho_1 \dfrac{\alpha_7 I_A^*}{\mu_E} + \mu_A} = \frac{\pi_A - I_A^*(\gamma_A + \mu_A)}{\mu_A}$$

for given parameters.

Theorem 2.1. *Define*

$$
\begin{aligned}
A &= \mu_I - \alpha_3\frac{\pi_A}{\mu_A} + \beta_A + \gamma_A + \mu_A + \mu_E + \beta_H + \gamma_H + \mu_H \\
B &= -\alpha_6\alpha_5\frac{\pi_I}{\mu_I}\frac{\pi_H}{\mu_H} + (\mu_E + \beta_H + \gamma_H + \mu_H)\left(\mu_I - \alpha_3\frac{\pi_A}{\mu_A} + \beta_A + \gamma_A + \mu_A\right) \\
&\quad + \mu_I\left(\beta_A + \gamma_A + \mu_A - \alpha_3\frac{\pi_A}{\mu_A}\right) + \mu_E(\beta_H + \gamma_H + \mu_H) + \alpha_1\alpha_2\frac{\pi_A}{\mu_A}\frac{\pi_I}{\mu_I} \\
C &= \alpha_6\frac{\pi_I}{\mu_I}\frac{\pi_H}{\mu_H}\left(\alpha_5(\alpha_3\frac{\pi_A}{\mu_A} - \mu_E - \beta_A - \gamma_A - \mu_A) - \alpha_1\alpha_4\frac{\pi_A}{\mu_A}\right) \\
&\quad + \mu_E(\beta_H + \gamma_H + \mu_H)\left(\mu_I - \alpha_3\frac{\pi_A}{\mu_A} + \beta_A + \gamma_A + \mu_A\right) \\
&\quad + \mu_I\left(\beta_A + \gamma_A + \mu_A - \alpha_3\frac{\pi_A}{\mu_A}\right)(\beta_H + \gamma_H + \mu_H + \mu_E) \\
&\quad - \rho_1\alpha_7\frac{\pi_A}{\mu_A}(\mu_I + \beta_H + \gamma_H + \mu_H) \\
D &= \alpha_6\frac{\pi_I}{\mu_I}\frac{\pi_H}{\mu_H}\left(\alpha_5\mu_E\left(\alpha_3\frac{\pi_A}{\mu_A} - \beta_A - \gamma_A - \mu_A\right) + \rho_1\alpha_5\alpha_7\frac{\pi_A}{\mu_A}\right. \\
&\quad \left.-\alpha_1\frac{\pi_A}{\mu_A}(\alpha_4\mu_E + \alpha_7(\rho_2 + \rho_3))\right) \\
&\quad + \mu_E(\beta_H + \gamma_H + \mu_H)\left(\mu_I\left(\beta_A + \gamma_A + \mu_A - \alpha_3\frac{\pi_A}{\mu_A}\right) - \alpha_1\alpha_2\frac{\pi_A}{\mu_A}\frac{\pi_I}{\mu_I}\right) \\
&\quad - \rho_1\alpha_7\mu_I\frac{\pi_A}{\mu_A}(\beta_H + \mu_H + \gamma_H).
\end{aligned}
$$

If $h_0 = min\{A,D,AB - C,C(AB - C) - A^2D\} > 0$, *the disease-free equilibrium is stable. Otherwise, the disease-free equilibrium is unstable*.

Proof. It suffices to provide the conditions in which all of the eigenvalues of the Jacobian matrix of Model (1) when evaluated at the disease-free equilibrium have a negative real part. The Jacobian matrix for Model (1) is $J = [J_1|J_2]$ where J_1 and J_2 are as follows:

$$
J_1 = \begin{bmatrix}
-\alpha_2 I_A - \alpha_6 I_H - \mu_I & 0 & 0 & -\alpha_2 S_I \\
\alpha_2 I_A + \alpha_6 I_H & -\mu_I & 0 & \alpha_2 S_I \\
0 & -\alpha_1 S_A & -\alpha_1 I_I - \alpha_3 I_A - \rho_1 E - \mu_A & -\alpha_3 S_A + \beta_A \\
0 & \alpha_1 S_A & \alpha_1 I_I + \alpha_3 I_A + \rho_1 E & \alpha_3 S_A - \beta_A - \gamma_A - \mu_A \\
0 & -\alpha_5 S_H & 0 & -\alpha_4 S_H \\
0 & \alpha_5 S_H & 0 & \alpha_4 S_H \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & \alpha_7
\end{bmatrix}
$$

$$J_2 = \begin{bmatrix} 0 & -\alpha_6 S_I & 0 & 0 \\ 0 & \alpha_6 S_I & 0 & 0 \\ 0 & 0 & 0 & -\rho_1 S_A \\ 0 & 0 & 0 & \rho_1 S_A \\ -\alpha_4 I_A - \alpha_5 I_I - \rho_2 E - \rho_3 E - \mu_H & 0 & 0 & -\rho_2 S_H - \rho_3 S_H \\ \alpha_4 I_A + \alpha_5 I_I + \rho_2 E + \rho_3 E & -\beta_H - \gamma_H - \mu_H & 0 & \rho_2 S_H + \rho_3 S_H \\ 0 & \beta_H & -\mu_H & 0 \\ 0 & 0 & 0 & -\mu_E S \end{bmatrix}.$$

When evaluated at the disease-free equilibrium, the eigenvalues satisfy roots of the characteristic equation

$$0 = (-\mu_H - \lambda)^2(-\mu_A - \lambda)(-\mu_I - \lambda)M$$

where

$$M = \begin{vmatrix} -\mu_I - \lambda & \alpha_2 \frac{\pi_I}{\mu_I} & \alpha_6 \frac{\pi_I}{\mu_I} & 0 \\ \alpha_1 \frac{\pi_A}{\mu_A} & \alpha_3 \frac{\pi_A}{\mu_A} - \beta_A - \gamma_A - \mu_A - \lambda & 0 & \rho_1 \frac{\pi_A}{\mu_A} \\ \alpha_5 \frac{\pi_H}{\mu_H} & \alpha_4 \frac{\pi_H}{\mu_H} & -\beta_H - \gamma_H - \mu_H - \lambda & \rho_2 \frac{\pi_H}{\mu_H} + \rho_3 \frac{\pi_H}{\mu_H} \\ 0 & \alpha_7 & 0 & -\mu_E - \lambda \end{vmatrix}.$$

By assumption, μ_I , μ_A and μ_H are all strictly positive, so it suffices to examine the determinant of the matrix. This is a quartic of the form $\lambda^4 + A\lambda^3 + \mathrm{B}\lambda^2 + C\lambda + D$, where A, B, C and D are equal to the following:

$$\begin{aligned} A &= \mu_I - \alpha_3 \frac{\pi_A}{\mu_A} + \beta_A + \gamma_A + \mu_A + \mu_E + \beta_H + \gamma_H + \mu_H \\ B &= -\alpha_6 \alpha_5 \frac{\pi_I}{\mu_I} \frac{\pi_H}{\mu_H} + (\mu_E + \beta_H + \gamma_H + \mu_H) \left(\mu_I - \alpha_3 \frac{\pi_A}{\mu_A} + \beta_A + \gamma_A + \mu_A \right) \\ &\quad + \mu_I \left(\beta_A + \gamma_A + \mu_A - \alpha_3 \frac{\pi_A}{\mu_A} \right) + \mu_E (\beta_H + \gamma_H + \mu_H) + \alpha_1 \alpha_2 \frac{\pi_A}{\mu_A} \frac{\pi_I}{\mu_I} \\ C &= \alpha_6 \frac{\pi_I}{\mu_I} \frac{\pi_H}{\mu_H} \left(\alpha_5 (\alpha_3 \frac{\pi_A}{\mu_A} - \mu_E - \beta_A - \gamma_A - \mu_A) - \alpha_1 \alpha_4 \frac{\pi_A}{\mu_A} \right) \\ &\quad + \mu_E (\beta_H + \gamma_H + \mu_H) \left(\mu_I - \alpha_3 \frac{\pi_A}{\mu_A} + \beta_A + \gamma_A + \mu_A \right) \\ &\quad + \mu_I \left(\beta_A + \gamma_A + \mu_A - \alpha_3 \frac{\pi_A}{\mu_A} \right) (\beta_H + \gamma_H + \mu_H + \mu_E) \\ &\quad - \rho_1 \alpha_7 \frac{\pi_A}{\mu_A} (\mu_I + \beta_H + \gamma_H + \mu_H) \\ D &= \alpha_6 \frac{\pi_I}{\mu_I} \frac{\pi_H}{\mu_H} \left(\alpha_5 \mu_E \left(\alpha_3 \frac{\pi_A}{\mu_A} - \beta_A - \gamma_A - \mu_A \right) + \rho_1 \alpha_5 \alpha_7 \frac{\pi_A}{\mu_A} \right. \\ &\quad \left. - \alpha_1 \frac{\pi_A}{\mu_A} (\alpha_4 \mu_E + \alpha_7 (\rho_2 + \rho_3)) \right) \\ &\quad + \mu_E (\beta_H + \gamma_H + \mu_H) \left(\mu_I \left(\beta_A + \gamma_A + \mu_A - \alpha_3 \frac{\pi_A}{\mu_A} \right) - \alpha_1 \alpha_2 \frac{\pi_A}{\mu_A} \frac{\pi_I}{\mu_I} \right) \\ &\quad - \rho_1 \alpha_7 \mu_I \frac{\pi_A}{\mu_A} (\beta_H + \mu_H + \gamma_H). \end{aligned}$$

According to the Routh-Hurwitz stability criterion, all of the roots will have negative real part if $A > 0$, $D > 0$, $AB - C > 0$, and $C(AB - C) > A^2D$, which provides us with the conditions outlined in the theorem.

Note that the criterion $A > 0$ is unlikely to hold if $\alpha_3 > 0$, as $\alpha_3 \frac{\pi_A}{\mu_A}$ is likely much larger than $\mu_I + \beta_A + \gamma_A + \mu_A + \mu_E + \beta_H + \gamma_H + \mu_H$ in which case $A = \mu_I - \alpha_3 \frac{\pi_A}{\mu_A} + \beta_A + \gamma_A + \mu_A + \mu_E + \beta_H + \gamma_H + \mu_H < 0$.

3. The system with vaccination

We will now turn our attention to the system with pulse vaccinations given at regular time intervals (τ) to a proportion of the susceptible human population (p). This vaccine has different efficacies for aerosol transmission (θ_2) and for the other methods of transmission (θ_1), and also reverts to the original viral strain at a given rate (ϕ). This system, in ODE form, is illustrated below.

For $t \neq t_k$:

$$\begin{aligned}
S_I' &= \pi_I - \alpha_2 I_A S_I - \alpha_6 I_H S_I - \mu_I S_I \\
I_I' &= \alpha_2 I_A S_I + \alpha_6 I_H S_I - \mu_I I_I \\
S_A' &= \pi_A - \alpha_1 I_I S_A - \alpha_3 I_A S_A - \rho_1 E S_A + \beta_A I_A - \mu_A S_A \\
I_A' &= \alpha_1 I_I S_A + \alpha_3 I_A S_A + \rho_1 E S_A - \beta_A I_A - \gamma_A I_A - \mu_A I_A \\
S_H' &= \pi_H - \alpha_4 I_A S_H - \alpha_5 I_I S_H - (\rho_2 + \rho_3) E S_H - \mu_H S_H \\
I_H' &= \alpha_4 I_A S_H + \alpha_5 I_I S_H + \rho_2 E S_H + \rho_3 E S_H - \beta_H I_H - \gamma_H I_H - \mu_H I_H \\
&\quad + (1-\theta_1)(\alpha_4 I_A V_H + \alpha_5 I_I V_H + \rho_2 E V_H) + (1-\theta_2)\rho_3 E V_H + \phi V_H \\
R_H' &= \beta_H I_H - \mu_H R_H \\
E' &= \alpha_7 I_A - \mu_E E \\
V_H' &= -(1-\theta_1)(\alpha_4 I_A V_H + \alpha_5 I_I V_H + \rho_2 E V_H) \\
&\quad - (1-\theta_2)\rho_3 E V_H - \phi V_H - \mu_H V_H.
\end{aligned} \tag{2}$$

The impulsive conditions are given by

$$\begin{aligned}
\Delta S_H &= -p S_H^- \\
\Delta V_H &= p S_H^-
\end{aligned} \tag{3}$$

for $t = t_k$.

The inherent assumption in adding an impulsive component to the model is that the changes happen instantaneously, which is a relatively safe assumption if enough clinics are set up so that all of the vaccinations can occur simultaneously. Due to the impulsive effects, the populations do not reach an equilibrium. However, we may attempt to find impulsive orbits for these populations and arrive at a bound for the infected human population as $t \to \infty$.

For notational purposes, define $c_1 \equiv \alpha_4 I_A^* + \alpha_5 I_I^* + \rho_2 E^* + \rho_3 E^* + \mu_H$ and $c_2 \equiv (1-\theta_1)(\alpha_4 I_A^* + \alpha_5 I_I^* + \rho_2 E^*) + (1-\theta_2)\rho_3 E^* + \phi + \mu_H$, where I_A^*, where I_A^*, I_I^*, E^* are the equilibrium values of the populations in the model without vaccination.

Theorem 3.1. *Let $X(t_k^-)$ denote the k[th] endpoint immediately before the impulse. Then*

$$S_H^*(t_k^-) = \frac{\pi_H}{c_1}\left(1 - \frac{pe^{-c_1\tau}}{1-(1-p)e^{-c_1\tau}}\right)$$

and

$$V_H^*(t_k^-) = \frac{pe^{-c_2\tau}}{1-e^{-c_2\tau}} S_H^*(t_k^-)$$

are globally asymptotically stable fixed points for the endpoint before the impulse for S_H and V_H.

Proof. First, consider the susceptible human population. Let $f_1(t) \equiv \alpha_4 I_A(t) + \alpha_5 I_I(t) + \rho_2 E(t) + \rho_3 E(t) + \mu_H$. Then, from Model (2):

$$S' = \pi_H - \alpha_4 I_A S_H - \alpha_5 I_I S_H - \rho_2 E S_H - \rho_3 E S_H - \mu_H S_H = \pi_H - f_1(t) S_H(t),$$

which implies that

$$\frac{d}{dt}\left(S_H e^{\int f_1(s)\,ds}\right) = \pi_H e^{\int f_1(s)\,ds}.$$

Then it follows that, for $t_k < t \leq t_{k+1}$:

$$S_H(t) = \frac{1}{e^{\int f_1(s)\,ds}\Big|_{s=t}} \left[S_H(t_k^+) e^{\int f_1(s)\,ds}\Big|_{s=t_k} + \int_{t_k}^{t} \pi_H e^{\int f_1(s)\,ds} ds \right]$$

and, after factoring in the impulsive effect and setting $t = t_k+1$,

$$S_H(t_{k+1}^-) = \frac{1}{e^{\int f_1(s)\,ds}\Big|_{s=t_{k+1}}} \left[(1-p) S_H(t_k^-) e^{\int f_1(s)\,ds}\Big|_{s=t_k} + \int_{t_k}^{t_{k+1}} \pi_H e^{\int f_1(s)\,ds} ds \right].$$

Let $S_H(t_0) = \frac{1}{1-p} S_H(0)$, where S_H (0) is the initial population of S_H.

Then

$$S_H(t_1^-) = \frac{1}{e^{\int f_1(s)\,ds}\Big|_{s=t_1}} \left[(1-p) S_H(t_0) e^{\int f_1(s)\,ds}\Big|_{s=t_0} + \int_{t_0}^{t_1} \pi_H e^{\int f_1(s)\,ds} ds \right]$$

$$S_H(t_2^-) = \frac{1}{e^{\int f_1(s)\,ds}\Big|_{s=t_2}} \left[(1-p) \left[(1-p) S_H(t_0) e^{\int f_1(s)\,ds}\Big|_{s=t_0} + \int_{t_0}^{t_1} \pi_H e^{\int f_1(s)\,ds} ds \right] + \int_{t_1}^{t_2} \pi_H e^{\int f_1(s)\,ds} ds \right]$$

$$\vdots$$

$$S_H(t_k^-) = \frac{1}{e^{\int f_1(s)\,ds}\Big|_{s=t_k}} \left[(1-p)^k S_H(t_0) e^{\int f_1(s)\,ds}\Big|_{s=t_0} + \sum_{j=0}^{k-1} (1-p)^j \int_{t_{k-j-1}}^{t_{k-j}} \pi_H e^{\int f_1(s)\,ds} ds \right].$$

Let w be the smallest integer such that, for $t \geq t_w$, I_I, I_A and E all approximately at their equilibrium values. We will now make the assumption that the equilibrium values for these populations are the same as in the model without vaccination and, moreover, are constant. This assumption was because the infected populations are dependent upon multiple populations, of which only a couple are directly affected by

the impulses.Then, for $t \geq t_w$, $f_1(t) \approx \alpha_4 I_A^* + \alpha_5 I_I^* + \rho_2 E^* + \rho_3 E^* + \mu_H = c_1$ and so, for $k \geq w$:

$$
\begin{aligned}
S_H(t_k^-) &\approx \frac{(1-p)^k S_H(t_0) e^{\int f_1(s)\,ds}\Big|_{s=t_0}}{e^{c_1 t_k}} + \sum_{j=0}^{w-1} \frac{\pi_H (1-p)^{k-w+j} \int_{t_{w-j-1}}^{t_{w-j}} e^{\int f_1(s)\,ds} ds}{e^{c_1 t_k}} \\
&\quad + \sum_{j=0}^{k-w-1} \frac{\pi_H (1-p)^j}{c_1} \left(\frac{e^{c_1 t_{k-j}} - e^{c_1 t_{k-j-1}}}{e^{c_1 t_k}} \right) \\
&= \frac{(1-p)^k S_H(t_0) e^{\int f_1(s)\,ds}\Big|_{s=t_0}}{e^{c_1 t_k}} + \pi_H (1-p)^{k-w} \sum_{j=0}^{w-1} \frac{(1-p)^j \int_{t_{w-j-1}}^{t_{w-j}} e^{\int f_1(s)\,ds} ds}{e^{c_1 t_k}} \\
&\quad + \sum_{j=0}^{k-w-1} \frac{\pi_H (1-p)^j}{c_1} \left(e^{-c_1 (t_k - t_{k-j})} - e^{-c_1 (t_k - t_{k-j-1})} \right) \\
&= \frac{(1-p)^k S_H(t_0) e^{\int f_1(s)\,ds}\Big|_{s=t_0}}{e^{c_1 t_k}} + \pi_H (1-p)^{k-w} \sum_{j=0}^{w-1} \frac{(1-p)^j \int_{t_{w-j-1}}^{t_{w-j}} e^{\int f_1(s)\,ds} ds}{e^{c_1 t_k}} \\
&\quad + \sum_{j=0}^{k-w-1} \frac{\pi_H (1-p)^j}{c_1} \left(e^{-c_1 (t_k - t_{k-j})} - e^{-c_1 (t_k - t_{k-j-1})} \right) \\
&= \frac{(1-p)^k S_H(t_0) e^{\int f_1(s)\,ds}\Big|_{s=t_0}}{e^{c_1 t_k}} + \pi_H (1-p)^{k-w} \sum_{j=0}^{w-1} \frac{(1-p)^j \int_{t_{w-j-1}}^{t_{w-j}} e^{\int f_1(s)\,ds} ds}{e^{c_1 t_k}} \\
&\quad + \sum_{j=0}^{k-w-1} \frac{\pi_H (1-p)^j e^{-c_1 j \tau}}{c_1} \left(1 - e^{-c_1 \tau} \right) \\
&= \frac{(1-p)^k S_H(t_0) e^{\int f_1(s)\,ds}\Big|_{s=t_0}}{e^{c_1 t_k}} + \pi_H (1-p)^{k-w} \sum_{j=0}^{w-1} \frac{(1-p)^j \int_{t_{w-j-1}}^{t_{w-j}} e^{\int f_1(s)\,ds} ds}{e^{c_1 t_k}} \\
&\quad + \frac{\pi_H (1 - e^{-c_1 \tau})}{c_1} \left(\frac{1 - (1-p)^{k-w} e^{-c_1 \tau (k-w)}}{1 - (1-p) e^{-c_1 \tau}} \right)
\end{aligned}
$$

As $k \to \infty$, $(1-p)^k \to 0$, $(1-p)^{k-w} \to 0$ and $e^{-c_1 \tau (k-w)} \to 0$, so:

$$
\begin{aligned}
S_H^*(t_k^-) &\to \frac{\pi_H (1 - e^{-c_1 \tau})}{c_1} \left(\frac{1}{1 - (1-p) e^{-c_1 \tau}} \right) \\
&= \frac{\pi_H}{c_1} \left(1 - \frac{p e^{-c_1 \tau}}{1 - (1-p) e^{-c_1 \tau}} \right).
\end{aligned}
$$

We apply a similar treatment to the vaccinated human population: Let $f_2(t) \equiv (1-\theta_1)(\alpha_4 I_A + \alpha_5 I_I V_H + \rho_2 E V_H) + (1-\theta_2)\rho_3 E V_H + \phi V_H + \mu_H V_H$. From

Model (2), $V' = -(1-\theta_1)(\alpha_4 I_A V_H + \alpha_5 I_I V_H + \rho_2 E V_H) - (1-\theta_2)\rho_3 E V_H - \phi V_H - \mu_H V_H = -f_2 V_H$ and so $\frac{dV_H}{dt}\frac{1}{V_H} = -f_2(t)$; or, for $t_k < t \leq t_{k+1}$, $V_H(t) = V_H(t_k^+)e^{-\int_{t_k}^{t} f_2(s)ds}$. After accounting for the impulsive effects and setting $t = t_{k+1}$:

$$V_H(t_{k+1}^-) = \left(V_H(t_k^-) + pS_H(t_k^-)\right) e^{-\int_{t_k}^{t_{k+1}} f_2(s)ds}.$$

Then, if $V_H(t_0) = V_H(0) - pS_H(t_0)$, we have

$$V_H(t_1^-) = \left(V_H(t_0) + pS_H(t_0)\right) e^{-\int_{t_0}^{t_1} f_2(s)ds}$$

$$V_H(t_2^-) = \left[\left(V_H(t_0) + pS_H(t_0)\right) e^{-\int_{t_0}^{t_1} f_2(s)ds} + pS_H(t_1^-)\right] e^{-\int_{t_1}^{t_2} f_2(s)ds}$$

$$\vdots$$

$$V_H(t_k^-) = V_H(t_0)\prod_{l=1}^{k} e^{-\int_{t_{k-l}}^{t_{k-l+1}} f_2(s)ds} + \sum_{j=0}^{k-1} pS_H(t_j^-)\prod_{l=1}^{k-j} e^{-\int_{t_{k-l}}^{t_{k-l+1}} f_2(s)ds}.$$

For $t \geq t_w$, $f_2(t) \approx (1-\theta_1)(\alpha_4 I_A^* + \alpha_5 I_I^* + \rho_2 E^*) + (1-\theta_2)\rho_3 E^* + \phi + \mu_H = c_2$

and so, as $k \to \infty$, $V_H(t_0)\prod_{l=1}^{k} e^{-\int_{t_{k-l}}^{t_{k-l+1}} f_2(s)ds} \to 0$. Furthermore, as seen above, for given values of I_A^*, I_I^*, E^*, $S_H(t_k^-)$ converges to a single fixed point and so $V_H(t_k^-)$ will also converge to a single fixed point. It remains to find this fixed point, which will occur where

$$\begin{aligned} V_H(t_k^-) &= V_H(t_{k+1}^-) \\ &= \left(V_H(t_k^-) + pS_H^*(t_k^-)\right) e^{-c_2\tau} \end{aligned}$$

which implies that $V_H^*(t_k^-) = \dfrac{pe^{-c_2\tau}}{1-e^{-c_2\tau}} S_H^*(t_k^-)$.

Using these endpoints, we can make inferences about the infected human population, which is our population of interest. This analysis will use the following lemma.

Lemma 3.1. *If $X' \leq k - lX(t)$ for constants $k > 0$ and $l > 0$, then X(t) will converge to a value that is less than or equal to $\frac{k}{l}$. Furthermore, if*

$X' \geq k - lX(t)$, *then X(t) will converge to a value that is larger than or equal to* $\frac{k}{l}$.

Proof. Given that $\frac{dX(t)}{dt} \leq k - lX(t)$, this implies that $\frac{dX(t)}{dt} + lX(t) \leq k$ or $\frac{d}{dt}X(t)e^{lt} \leq ke^{lt}$. Therefore, $X(t) \leq X(0)e^{-lt} + \frac{k}{l}(1 - e^{-lt})$. As t $\to \infty$, $e^{-lt} \longrightarrow 0$ and so *X*(*t*) will converge to a value that is less than $\frac{k}{l}$. The second part of the theorem follows by reversing the inequalities above.

This will be used to help prove that, with appropriate vaccination parameters, we can reduce the infected human population below any given threshold as $t \longrightarrow \infty$.

Theorem 3.2. *Let* I_A^*, I_I^*, E^* *be the equilibrium values of* I_A, I_I *and E, respectively, in the model without vaccination. Then* $I_H(t)$ *can be reduced below any threshold as* $t \longrightarrow \infty$ *with appropriate* p, τ, θ_1, θ_2, *and* ϕ.

Proof. Let $\epsilon > 0$ denote the desired threshold of infected humans, and I_A^*, I_I^* and E^* be the equilibrium values of I_A, I_I and E respectively in model without vaccination. Furthermore, note that, by Model (2),

$$\begin{aligned} I_H' = {} & S_H(f_1 - \mu_H) + (1 - \theta_1)(\alpha_4 I_A V_H + \alpha_5 I_I V_H + \rho_2 E V_H) \\ & + (1 - \theta_2)\rho_3 E V_H + \phi V_H - \beta_H I_H - \gamma_H I_H - \mu_H I_H \end{aligned}$$

where $f_3(t) = \alpha_4 I_A(t) + \alpha_5 I_I(t) + \rho_2 E(t) + \rho_3 E(t) - \mu_H$.

Then let *w* be the smallest integer such that for $t \geq t_w$, I_I, I_A and *E* all attain their equilibrium values and $S_H(t_w^-)$ and $V_H(t_w^-)$ are both at their impulsive orbits. Similar to our previous analysis, we will assume that the population equilibrium values are approximately the same as in the model without vaccination so that we can treat it as a constant and $f_1 \approx c_1$. Therefore, consider $t \geq t_w$.

As S_H has attained its impulsive periodic orbit, it follows that, as $S_H' > 0$ for $t_k < t \leq t_{k+1}$ then, for all $t \geq t_w$, $S_H(t) \leq S_H^*(t_k^-) = \frac{\pi_H}{c_1}\left(1 - \frac{pe^{-c_1\tau}}{1 - (1-p)e^{-c_1\tau}}\right)$.

This can be made arbitrarily small for *p* close to 1 and τ close to 0. Therefore, choose an appropriate *p* and τ such that $S_H^*(t_k^-) \leq \frac{\epsilon(\beta_H + \mu_H + \gamma_H)}{4(c_1 - \mu_H)}$.

Furthermore, as V_H is also at its impulsive orbit, note that $V_H' < 0$ for

$$t_k < t \leq t_{k+1} \text{ or that, for all } t \geq t_w,$$

$$\begin{aligned} V_H(t) &\leq V_H^*(t_k^+) \\ &= V_H^*(t_k^-) + pS_H^*(t_k^-) \\ &= \frac{pe^{-c_2\tau}}{1-e^{-c_2\tau}} S_H^*(t_k^-) + pS_H^*(t_k^-) \\ &= S_H^*(t_k^-)\frac{p}{1-e^{-c_2\tau}}. \end{aligned}$$

This is well-defined for the values of p and τ chosen above. Therefore, we can choose θ_1 such that

$$(1-\theta_1) \leq \frac{\epsilon(\beta_H + \mu_H + \gamma_H)}{4V_H^*(t_k^+)(\alpha_4 I_A^* + \alpha_5 I_I^* + \rho_2 E^*)}.$$

Similarly, choose θ_2 such that $(1-\theta_2) \leq \frac{\epsilon(\beta_H + \mu_H + \gamma_H)}{4V_H^*(t_k^+)\rho_3 E^*}$. Finally, choose ϕ such that $\phi \leq \frac{\epsilon(\beta_H + \mu_H + \gamma_H)}{4V_H^*(t_k^+)}$.

Therefore, for $t \geq t_w$, using the values of p, τ, θ_1, θ_2 and ϕ above:

$$\begin{aligned} I_H'(t) &\approx S_H(t)(c_1 - \mu_H) + (1-\theta_1)V_H(t)(\alpha_4 I_A^* + \alpha_5 I_I^* + \rho_2 E^*) \\ &\quad + (1-\theta_2)V_H(t)\rho_3 E^* + \phi V_H(t) - (\beta_H + \gamma_H + \mu_H)I_H(t) \\ &\leq S_H^*(t_k^-)(c_1 - \mu_H) + (1-\theta_1)V_H^*(t_k^+)(\alpha_4 I_A^* + \alpha_5 I_I^* + \rho_2 E^*) \\ &\quad + (1-\theta_2)V_H^*(t_k^+)\rho_3 E^* + \phi V_H^*(t_k^+) - (\beta_H + \gamma_H + \mu_H)I_H(t) \\ &\leq \epsilon(\beta_H + \mu_H + \gamma_H) - I_H(\beta_H + \mu_H + \gamma_H). \end{aligned}$$

From Lemma 3.1, it follows that I_H will converge to a value less than ϵ.

Therefore, provided that we can control τ, p, θ_1, θ_2 and ϕ, the infected human population can be reduced below a given threshold as $t \to \infty$. The following theorem will provide other bounds for p, τ and the infected human population under certain conditions as $t \to \infty$.

Theorem 3.3. *a*) Let θ_1, θ_2 and ϕ be given. Then, as $p \to 1$ and $\tau \to 0$, I_H will converge to $\dfrac{\pi_H}{\beta_H + \gamma_H + \mu_H}\left(\dfrac{c_2 - \mu_H}{c_2}\right)$.

b) If $\theta_1 = \theta_2 = 1$ *and* $\phi = 0$ *then, for a given threshold* ϵ *for* I_H*, the minimum threshold for p is:*

$$p = 1 - \left[1 - \frac{\pi_H}{\epsilon(\beta_H + \gamma_H + \mu_H)}\left(\frac{c_1 - \mu_H}{c_1}\right)\left(1 - e^{-c_1\tau}\right)\right] e^{c_1\tau}.$$

c) Similarly, the minimum threshold for τ *is:*

$$\tau = \frac{1}{c_1} \ln\left[\frac{\epsilon c_1(\beta_H + \gamma_H + \mu_H)(1-p) - \pi_H(c_1 - \mu_H)}{\epsilon c_1(\beta_H + \gamma_H + \mu_H) - \pi_H(c_1 - \mu_H)}\right].$$

Proof. a) Note that, at their impulsive orbits, S_H is bounded below by $S_H^*(t_k^+)$ and V_H is bounded below by $V_H^*(t_k^-)$. Therefore, for large enough t such that I_A, I_I and E are all at their equilibrium values, and S_H and V_H are at their impulsive orbits:

$$\begin{aligned}
I_H'(t) &\approx S_H(t)(c_1 - \mu_H) + (1-\theta_1)V_H(t)(\alpha_4 I_A^* + \alpha_5 I_I^* + \rho_2 E^*) \\
&\quad + (1-\theta_2)V_H(t)\rho_3 E^* + \phi V_H(t) - (\beta_H + \gamma_H + \mu_H)I_H(t) \\
&\geq S_H^*(t_k^+)(c_1 - \mu_H) + V_H^*(t_k^-)\big[(1-\theta_1)(\alpha_4 I_A^* + \alpha_5 I_I^* + \rho_2 E^*) \\
&\quad + (1-\theta_2)\rho_3 E^* + \phi\big] - (\beta_H + \gamma_H + \mu_H)I_H(t) \\
&= (1-p)\, S_H^*(t_k^-)(c_1 - \mu_H) + V_H^*(t_k^-)\,(c_2 - \mu_H) - (\beta_H + \gamma_H + \mu_H)I_H(t) \\
&= (1-p)\,\frac{\pi_H}{c_1}\left(\frac{1 - e^{-c_1\tau}}{1 - (1-p)e^{-c_1\tau}}\right)(c_1 - \mu_H) + S_H^*(t_k^-)\left(\frac{pe^{-c_2\tau}}{1 - e^{-c_2\tau}}\right)(c_2 - \mu_H) \\
&\quad - (\beta_H + \gamma_H + \mu_H)I_H(t) \\
&= (1-p)\,\frac{\pi_H(c_1 - \mu_H)}{c_1}\left(\frac{1 - e^{-c_1\tau}}{1 - (1-p)e^{-c_1\tau}}\right) \\
&\quad + \frac{\pi_H}{c_1}\left(\frac{pe^{-c_2\tau}}{1 - (1-p)e^{-c_1\tau}}\right)\left(\frac{1 - e^{-c_1\tau}}{1 - e^{-c_2\tau}}\right)(c_2 - \mu_H) - (\beta_H + \gamma_H + \mu_H)I_H(t).
\end{aligned}$$

Similarly, at their impulsive orbits, S_H is bounded above by $S_H^*(t_k^+)$ and V_H is bounded above by $V_H^*(t_k^+)$. Therefore:

$$
\begin{aligned}
I'_H(t) &\leq S^*_H(t_k^-)(c_1-\mu_H) + V^*_H(t_k^+)\,(c_2-\mu_H) - (\beta_H+\gamma_H+\mu_H)I_H(t) \\
&= \frac{\pi_H(c_1-\mu_H)}{c_1}\left(\frac{1-e^{-c_1\tau}}{1-(1-p)e^{-c_1\tau}}\right)c_1 + S^*_H(t_k^-)\left(\frac{p}{1-e^{-c_2\tau}}\right)(c_2-\mu_H) \\
&\quad -(\beta_H+\gamma_H+\mu_H)I_H(t) \\
&= \frac{\pi_H(c_1-\mu_H)}{c_1}\left(\frac{1-e^{-c_1\tau}}{1-(1-p)e^{-c_1\tau}}\right) \\
&\quad + \frac{\pi_H}{c_1}\left(\frac{p}{1-(1-p)e^{-c_1\tau}}\right)\left(\frac{1-e^{-c_1\tau}}{1-e^{-c_2\tau}}\right)(c_2-\mu_H) \\
&\quad -(\beta_H+\gamma_H+\mu_H)I_H(t).
\end{aligned}
$$

Note that, as $p \to 1$ and $\tau \to 0$, then $\left(\frac{1-e^{-c_1\tau}}{1-(1-p)e^{-c_1\tau}}\right) \to 0$, $\left(\frac{pe^{-c_2\tau}}{1-(1-p)e^{-c_1\tau}}\right) \to 1$ and, by L'Hopital's rule, $\left(\frac{1-e^{-c_1\tau}}{1-e^{-c_2\tau}}\right) \to \frac{c_1}{c_2}$.

Therefore, as $p \to 1$ and $\tau \to 0$, the upper and lower bounds of I'_H will converge to $\frac{\pi_H}{c_2}(c_2-\mu_H) - (\beta_H+\gamma_H+\mu_H)I_H(t)$. Therefore, I_H will converge to $\frac{\pi_H}{\beta_H+\gamma_H+\mu_H}\left(\frac{c_2-\mu_H}{c_2}\right)$.

Parts b) and c) of the theorem follow by noting that if $\theta_1 = \theta_2 = 1$ and $\phi = 0$ then, for large t, as $I'_H(t) \approx S_H(t)(c_1-\mu_H) - (\beta_H+\gamma_H+\mu_H)I_H(t)$ and S_H is bounded above by $S^*_H(t_k^-)$, it suffices to lower $S^*_H(t_k^-)$ below the threshold of $\frac{\epsilon(\beta_H+\gamma_H+\mu_H)}{c_1-\mu_H}$.

By Theorem 3.1, we note that $S^*_H(t_k^-) = \frac{\pi_H}{c_1}\left(\frac{1-e^{-c_1\tau}}{1-(1-p)e^{-c_1\tau}}\right)$. Therefore, setting $S^*_H(t_k^-) = \frac{\epsilon(\beta_H+\gamma_H+\mu_H)}{c_1-\mu_H}$:

$$
\begin{aligned}
\frac{\epsilon(\beta_H+\gamma_H+\mu_H)}{c_1-\mu_H} &= \frac{\pi_H}{c_1}\left(\frac{1-e^{-c_1\tau}}{1-(1-p)e^{-c_1\tau}}\right) \\
1-(1-p)e^{-c_1\tau} &= \frac{\pi_H}{\epsilon(\beta_H+\gamma_H+\mu_H)}\left(\frac{c_1-\mu_H}{c_1}\right)\left(1-e^{-c_1\tau}\right).
\end{aligned}
$$

Thus

$$
1-\frac{\pi_H}{\epsilon(\beta_H+\gamma_H+\mu_H)}\left(\frac{c_1-\mu_H}{c_1}\right)\left(1-e^{-c_1\tau}\right) = (1-p)e^{-c_1\tau}.
$$

It follows that

$$p = 1 - \left[1 - \frac{\pi_H}{\epsilon(\beta_H + \gamma_H + \mu_H)}\left(\frac{c_1 - \mu_H}{c_1}\right)\left(1 - e^{-c_1\tau}\right)\right] e^{c_1\tau}$$

Similarly, we isolate τ to obtain the other identity:

$$1 - \frac{\pi_H}{\epsilon(\beta_H + \gamma_H + \mu_H)}\left(\frac{c_1 - \mu_H}{c_1}\right) = \left[1 - p - \frac{\pi_H}{\epsilon(\beta_H + \gamma_H + \mu_H)}\left(\frac{c_1 - \mu_H}{c_1}\right)\right] e^{-c_1\tau}$$

$$\epsilon c_1(\beta_H + \gamma_H + \mu_H) - \pi_H(c_1 - \mu_H) = [\epsilon c_1(\beta_H + \gamma_H + \mu_H)(1 - p) - \pi_H(c_1 - \mu_H)]\, e^{-c_1\tau}$$

and hence

$$\tau = \frac{1}{c_1} \ln\left[\frac{\epsilon c_1(\beta_H + \gamma_H + \mu_H)(1 - p) - \pi_H(c_1 - \mu_H)}{\epsilon c_1(\beta_H + \gamma_H + \mu_H) - \pi_H(c_1 - \mu_H)}\right]$$

Note that, if $\theta_1 = \theta_2 = 1$ and $\phi = 0$, then $c_2 = \mu_H$. Therefore, Theorem 3.3a indicates that, as $p \to 1$ and $\tau \to 0$, I_H converges to 0. Otherwise, given vaccine parameters θ_1, θ_2 and ϕ, Theorem 3.3a provides a lower bound for the infected human population using pulse vaccinations.

4. Numerical simulations

As known carriers of the disease, tick and rabbit populations were chosen to illustrate the model. However, the lack of reliable records for this disease and the number of different transmission routes make it difficult to accurately estimate the transmission parameters of the ODE model. Nonetheless, using the parameter values outlined in Table 3 (in the appendix), we will illustrate the effects of a live vaccine on the populations of interest. These results are specific to the parameters chosen and are meant to only be illustrative; the exact scale of the effects may drastically change with different parameters.

For the purposes of numerical simulations, we assume that the populations are at the endemic equilibrium, that no other populations can be affected by the disease and the human population is a rural community that has approximately 1120 individuals. The vaccine is 97% effective against nonaerosol transmission, so θ_1 =0.97 [1]. Tests indicate that, when challenged, 75% of unvaccinated individuals contracted aerosol tularemia compared to 17%

of individuals vaccinated with the live vaccine strain (LVS) [14]. Therefore, θ_2 was estimated to be (1 - 17/75) = 0.773. The capacity for reversion is unknown so, although biologically unlikely, ϕ was taken to be 0 [14].

We performed a sensitivity analysis on the value of h_0 defined in Theorem 2.1 using Latin Hypercube Sampling for the range of values outlined in Table 2. The results are given in Figure 2, which shows that the parameters that would have the largest effects on the system are α_1, α_2, μ_A and μ_I . Therefore, the transmission parameters – the variables that we have difficulty estimating – and the relative sizes of the human, animal and insect populations are the most crucial to the behaviour of the system. It follows that we are unlikely to control the disease in the absence of a vaccine.

To examine the effects of vaccination, we varied the vaccination period and the proportion of individuals vaccinated for likely values. Our outcome was the relative infectability of infected vaccinated individuals compared to infected unvaccinated individuals. All simulations began at the endemic equilibrium without vaccination.

Table 2. Parameter ranges.

Variable	Definition	Lower	Upper
π_I	Insect birth rate	11.568	19.28
π_A	Animal birth rate	0.57534	0.9589
π_H	Human birth rate	0.02740	0.04658
α_1	Insect to animal transmissibility	0.00001	0.001
α_2	Animal to insect transmissibility	0.00001	0.001
α_3	Animal to animal transmissibility	0	0
α_4	Animal to human transmissiblity	0.0000001	0.00001
α_5	Insect to human transmissibility	0.0000001	0.00001
α_6	Human to insect transmissibility	0.0000001	0.00001
α_7	Animal to environment transmissibility	0.00001	0.001
ρ_1	Environment to animal transmissibility	0.00001	0.001
ρ_2	Waterborne environment to human transmissibility	0.00001	0.001
ρ_3	Airborne environment to human transmissibility	0.00001	0.001
β_A	Recovery rate of animals	0	0.005
β_H	Recovery rate of humans	0.01282	0.02381
γ_A	Disease death rate of animals	0.05	0.15
γ_H	Disease death rate of humans	0.0001667	0.000666
μ_I	Background insect death rate	0.00068493	0.002740
μ_A	Background animal death rate	0.00054794	0.001370
μ_H	Background human death rate	0.0000332232	0.0000391389
μ_E	Environment decay rate	0.0055556	0.0102

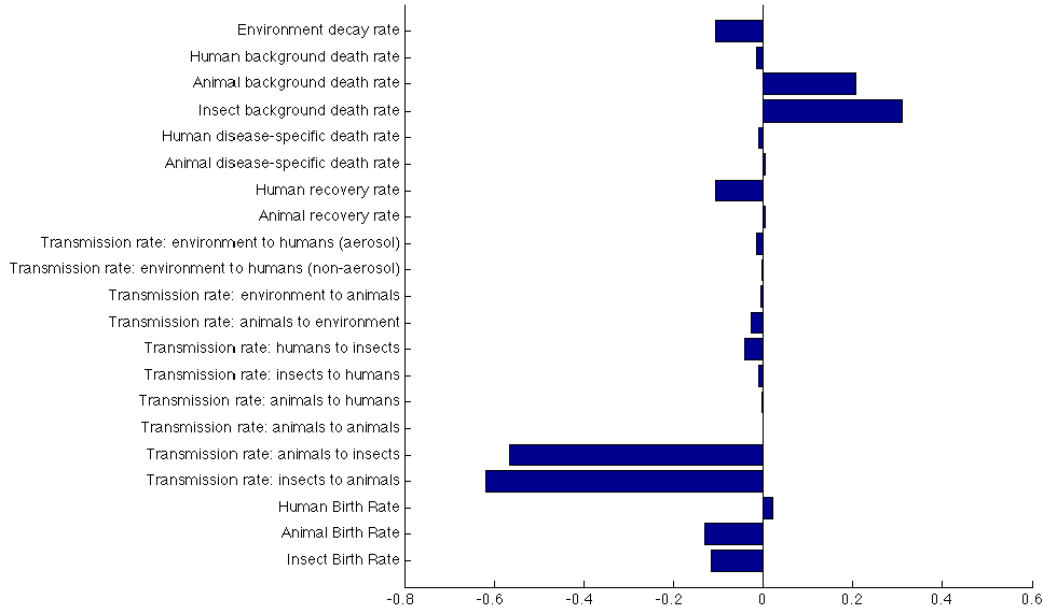

Figure 2. Results of parameter sensitivity analysis using Latin Hypercube Sampling.

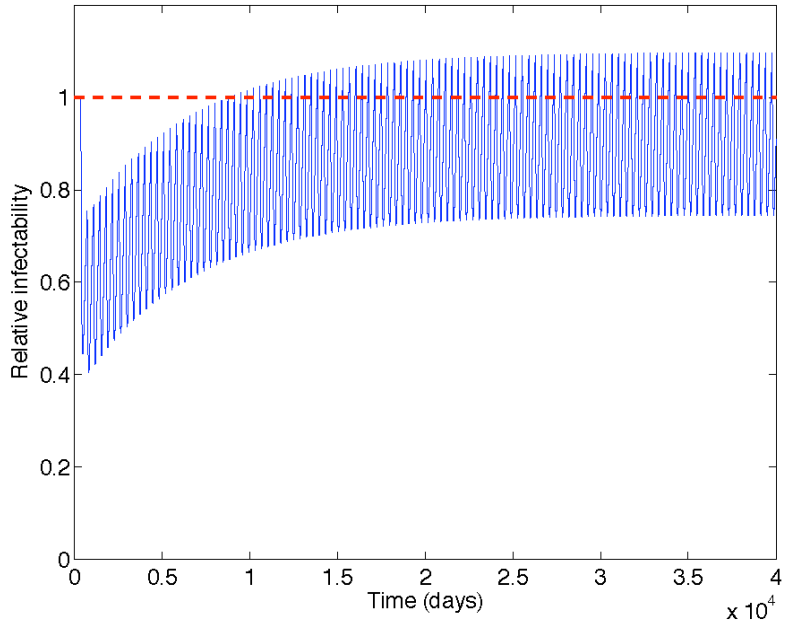

Figure 3. Relative infectability of infected vaccinated individuals compared to infected unvaccinated individuals. The vaccine was given to 90% of the population, every 365 days.

If the vaccination period was large (say, a year), then even a vaccine given to 90% of the population would produce results little better than not vaccinating at all and in some cases worse, due to forced oscillations in the system. See Figure 3.

Conversely, a vaccine with a short vaccination period (say, two months), but given to only 30% of the population would result in a significant improvement over a widespread but infrequent vaccine. See Figure 4.

Keeping the coverage at 30% but increasing the vaccination period to 120 days saw only a modest increase in the relative infectability. See Figure 5.

Keeping the vaccination period at 120 days but increasing the proportion of individuals vaccinated to 60% resulted in only a slight decrease in the relative infectability. See Figure 6.

Increasing the vaccination coverage to 90% resulted in only a small further decrease in the relative infectability. See Figure 7.

Finally, we investigated the effect of the efficacy against non-aerosol transmission, as simulations suggested this was a crucial parameter. If a vaccine were developed that could prevent 100% of non-aerosol infections, then it would have a significant impact on the relative infectability of tularemia. See Figure 8.

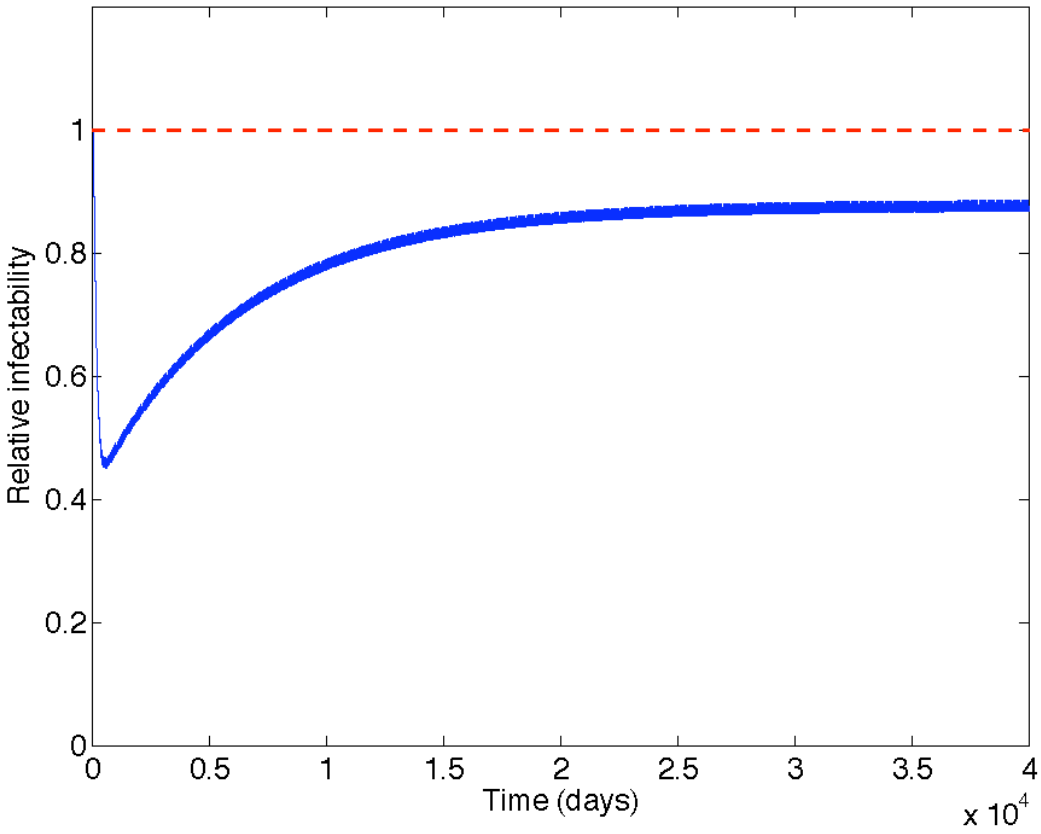

Figure 4. Relative infectability of infected vaccinated individuals compared to infected unvaccinated individuals. The vaccine was given to 30% of the population, every 60 days.

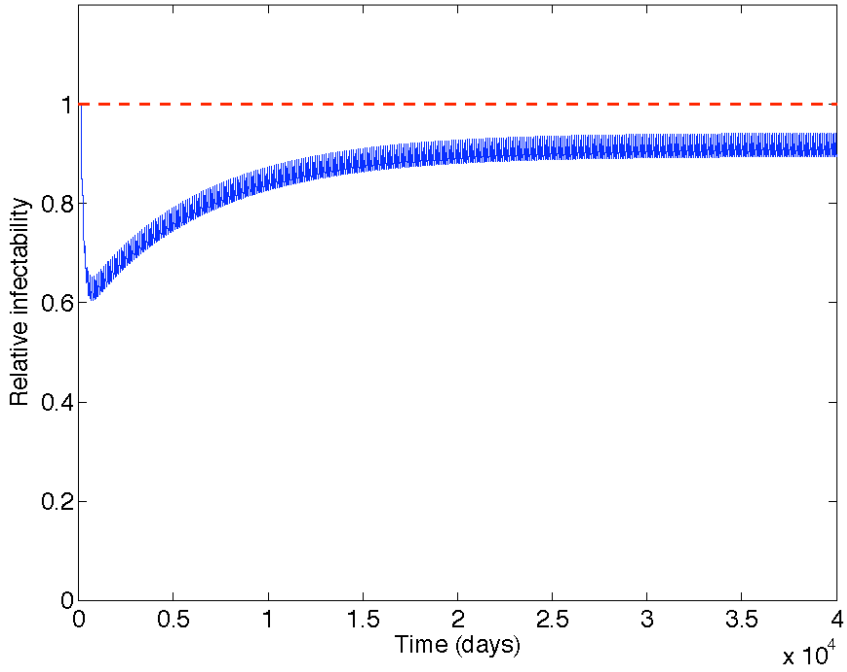

Figure 5. Relative infectability of infected vaccinated individuals compared to infected unvaccinated individuals. The vaccine was given to 30% of the population, every 120 days.

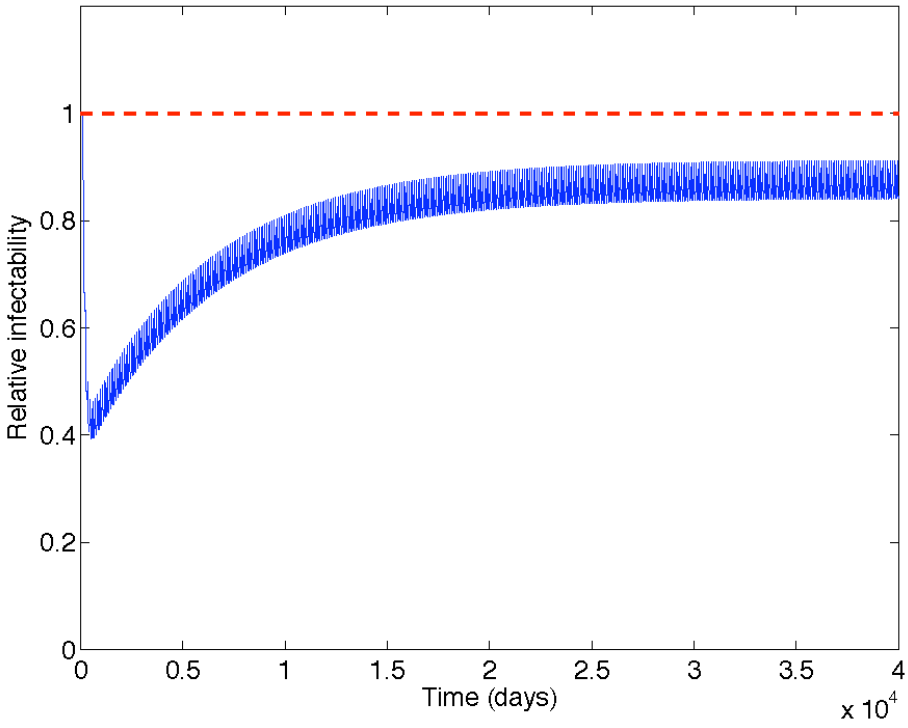

Figure 6. Relative infectability of infected vaccinated individuals compared to infected unvaccinated individuals. The vaccine was given to 60% of the population, every 120 days.

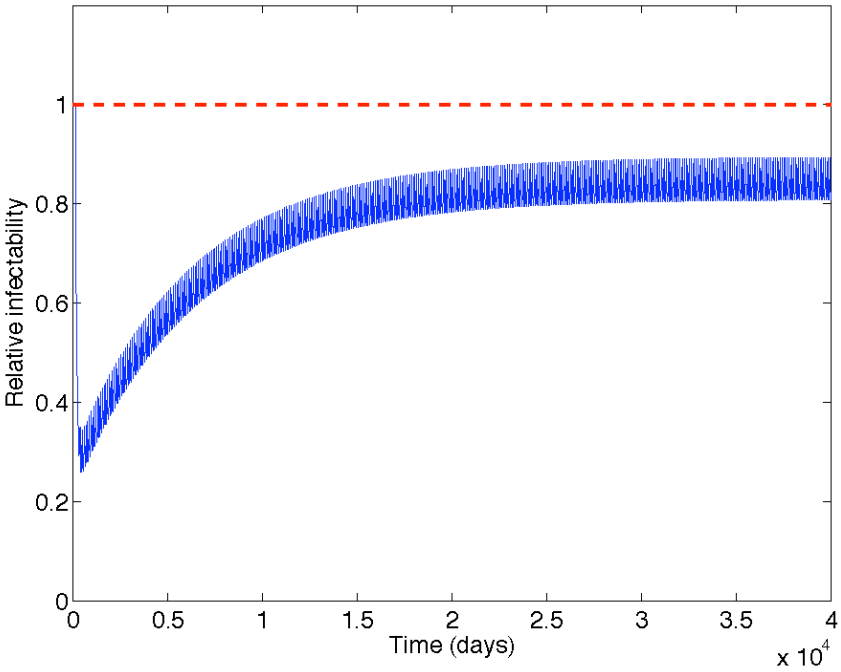

Figure 7. Relative infectability of infected vaccinated individuals compared to infected unvaccinated individuals. The vaccine was given to 90% of the population, every 120 days.

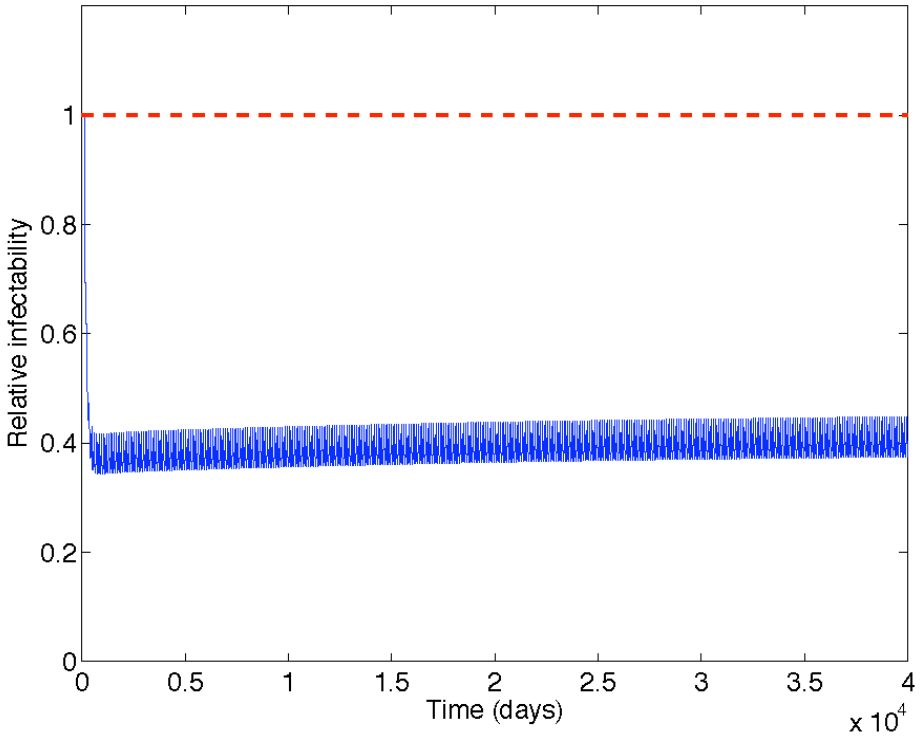

Figure 8. Relative infectability of infected vaccinated individuals compared to infected unvaccinated individuals. The vaccine was given to 60% of the population, every 120 days, but prevented 100% of non-aerosol infections.

5. Discussion

Numerical simulations illustrate that imperfect vaccines, even in the presence of an animal reservoir, can affect the outcome of an outbreak. The result is an initial drop in the number of infected vaccinated individuals, which gradually equilibrates at a reduced number of infections.

Variations in the coverage levels produced only modest changes in the relative infectability. A vaccine administered every four months would result in about a 15% reduction in the number of infected individuals. This outcome could be achieved with only 60% coverage. However, variations in the vaccination period had a significant effect on the outcome. A vaccine given to only 30% of the population could produce a 15% reduction in the nuber of infected individuals if given every two months. Conversely, a vaccine with 90% coverage could, at times, actually be worse than not vaccinating at all, if only given annually. This suggests that the vaccination period is critical and that the disease can be reduced if a core group of individuals is targeted, so long as efforts are made to follow up.

As predicted by theory, a live vaccine has the ability to decrease the infected human population below any given threshold. However, this requires control over the vaccination parameters, which is not always possible. For example, the current LVS vaccine is imperfect and it may not be possible to force the required proportion of the susceptible population to receive the vaccine. We also investigated the efficacy of the vaccine against non-aerosol infection. These suggested that θ_1 is a critical parameter; if it were lowered then vaccination efforts could be significantly compromised. Conversely, a vaccine which had 100% prevention of non-aerosol infection would be highly effective, as Figure 8 demonstrates.

Our model has a number of limitations, which should be noted. In the northern hemisphere, arthropods have seasonal patterns that can be accounted for and, depending on the length of the outbreak, may affect the outcome of the disease. There are also several species of animals and insects that can carry the disease, all of whom interact with each other, the disease and the environment in different ways. We assumed mass action transmission, which is appropriate for a small community, but which may break down for an outbreak in a larger urban centre. We also assumed vaccination occurred instantaneously, which is obviously not the case; however, impulsive differential equations have been shown to be quite robust to variations in the vaccination time [17].

In summary, vaccination against tularemia can reduce the infectability of the disease, but is unlikely to eradicate it. The vaccination period is critical,

suggesting that efforts should be put into vaccinating core groups with careful followup. However, an improved vaccine that prevented nonaerosol transmission would have a significant effect on controlling this disease.

6. Acknowledgements

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7. Appendix: Parameter estimates

Table 3. Parameter estimates.

Parameter	Estimated Value	Derivation
α_1	$10^{-4} * (tick * day)^{-1}$	Estimated variable. The order of magnitude was estimated from [8], after transforming it into a daily rate and accounting for the smaller size of the rabbits.
α_2	$10^{-4} * (rabbit * day)^{-1}$	Estimated variable. The order of magnitude was estimated from [8], after transforming it into a daily rate and accounting for the smaller size of the rabbits.
α_3	$0 * (rabbit * day)^{-1}$	Rabbits do not exhibit carnivorous activity towards other rabbits.
α_4	$10^{-6} * (rabbit * day)^{-1}$	It was estimated that this rate would be approximately the same as the rate of transmission from ticks.
α_5	$10^{-6} * (tick * day)^{-1}$	It was estimated that humans would have 100 times fewer tick bites than rabbits due to lower outdoor activity, clothing and diligent removal of ticks.
α_6	$10^{-6} * (person * day)^{-1}$	It was estimated that humans would have 100 times fewer tick bites than rabbits due to lower outdoor activity, clothing and diligent removal of ticks.
α_7	$10^{-4} * environment * (rabbit * day)^{-1}$	Estimated variable. This was estimated to be the same rate as α_1.
ρ_1	$10^{-4} * (environment * day)^{-1}$	Estimated variable. This was estimated to be the same rate as α_1.
ρ_2	$10^{-4} * (environment * day)^{-1}$	Estimated variable. This was estimated to be the same rate as α_1.
ρ_3	$10^{-4} * (environment * day)^{-1}$	Estimated variable. This was estimated to be the same rate as α_1.
β_A	$0 * day^{-1}$	We estimate that due to the susceptibility of rabbits to tularemia, they do not recover from the disease.
β_H	$1.6667 * 10^{-2} * day^{-1}$	The illness may continue for several weeks [13]. The variable was estimated at 1/60.

Table 3. Continued

γ_A	$10^{-1} * day^{-1}$	Rabbits with tularemia are typically found dead. Therefore, given the susceptibility of rabbits to the disease, we estimate that the average period before death is 10 days, or the variable is approximately 1/10.
γ_H	$3.33 * 10^{-4} * day^{-1}$	The fatality rate of tularemia has been reduced to less than 2% in the United States through the use of modern antibiotics [12]. Therefore, the variable was approximated as 2% of the rate at which people are cured of the disease
π_I	$1.5224 * 10 * ticks * day^{-1}$	We estimate that the tick birth rate is approximately 20 times that of the rabbit population.
π_A	$7.6712 * 10^{-1} * rabbits * day^{-1}$	We estimate that the rabbit birth rate within the area of consideration is approximately 20 times that of the human population.
π_H	$3.8356 * 10^{-2} * people * day^{-1}$	We estimate that the average crude birth rate is 14 per 1000 people per year. Therefore, the variable was estimated at 14/365.
μ_I	$1.37 * 10^{-3} * day^{-1}$	The average life cycle of a tick is approximately 2 years [11], so the variable was estimated at 1 / (2 * 365).
μ_A	$1.191 * 10^{-3} * day^{-1}$	The average lifespan of a rabbit is 2.3 years [10], so the variable was estimated at 1/ (2.3 * 365).
μ_H	$3.4245 * 10^{-5} * day^{-1}$	We estimate that the average lifespan is 80 years, so the variable was estimated at 1 / (80* 365).
μ_E	$7.52 * 10^{-3} * day^{-1}$	The organism can persist in water and mud for as long as 14 weeks, in straw for 6 months and in oats for 4 months [9]. An average of 133 days was chosen, so the variable was estimated at 1/133.

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