2. Modelling the impact of a live vaccine for Tularemia

Kar-Fai Gee¹, Kristen Addison¹ and Robert Smith²

¹Department of Mathematics The University of Ottawa 585 King Edward Ave Ottawa ON K1N 6N5 Canada ²Department of Mathematics and Faculty of Medicine The University Ottawa 585 King Edward Ave Ottawa ON K1N 6N5, Canada

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 attenuated 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.

Correspondence/Reprint request: Dr. Robert Smith?, Department of Mathematics and Faculty of Medicine The University Ottawa 585 King Edward Ave Ottawa ON K1N 6N5, Canada. E-mail: rsmith43@uottawa.ca
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 occurring 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 \((\pi_I, \pi_A, \pi_H)\), 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 \((\alpha_i, \text{for } i = 1 \text{ to } 7)\) and subsequently move into their respective infected populations.
Susceptible animals can become infected through exposure to the contaminated environment ($\rho_1$), and susceptible humans can become infected through exposure to contaminated water ($\rho_2$) and air ($\rho_3$). Infected animals and humans can recover from the disease ($\beta_A$, $\beta_H$), 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 ($\gamma_A$, $\gamma_H$).

These interactions produce the following model:

\begin{align*}
S'_I &= \pi_I - \alpha_2 I_A S_I - \alpha_6 I_H S_I - \mu I_I \\
I'_I &= \alpha_2 I_A S_I + \alpha_6 I_H S_I - \mu I_I \\
S'_A &= \pi_A - \alpha_1 I_I S_A - \alpha_3 I_A S_A - \rho_1 ES_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 ES_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) ES_H - \mu H S_H \\
I'_H &= \alpha_4 I_A S_H + \alpha_5 I_I S_H + (\rho_2 + \rho_3) ES_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{align*}

where 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:

$$\{S^*_I, I^*_I, S^*_A, I^*_A, S^*_H, I^*_H, R^*_H, E^*\} = \{\frac{\pi_I}{\mu_I}, 0, \frac{\pi_A}{\mu_A}, 0, \frac{\pi_H}{\mu_H}, 0, 0, 0\}.$$
Modelling Tularemia vaccination

\[ S_I^* = \frac{\mu_I I_I^*}{\alpha_2 I_A^* + \alpha_6 I_H^*} \]
\[ S_A^* = \frac{(\beta_A + \gamma_A + \mu_A) I_A^*}{\alpha_1 I_I^* + \alpha_3 I_A^* + \rho_1 \alpha_7 I_A^*} \]
\[ S_H^* = \frac{\pi_H}{\alpha_4 I_A^* + \alpha_6 I_I^* + (\rho_2 + \rho_3) \frac{\alpha_7 I_A^*}{\mu_E} + \mu_H} \]
\[ R_H^* = \frac{\beta_H I_H^*}{\mu_H} \]
\[ E^* = \frac{\alpha_7 I_A^*}{\mu_E} \]

**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.

\[
I_H^* = \left( \frac{\alpha_4 I_A^* + \alpha_6 I_I^* + (\rho_2 + \rho_3) \frac{\alpha_7 I_A^*}{\mu_E}}{\alpha_4 I_A^* + \alpha_6 I_I^* + (\rho_2 + \rho_3) \frac{\alpha_7 I_A^*}{\mu_E} + \mu_H} \right) \left( \frac{\pi_H}{\beta_H + \gamma_H + \mu_H} \right), \text{ and}
\]

$I_A^*$ 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

\[
I_A^* = \frac{\pi_A + \beta_A I_I^*}{\mu_A (\alpha_2 I_A^* + \alpha_6 I_H^* + \mu_A)} = \frac{\pi_A - I_A^*(\gamma_A + \mu_A)}{\mu_A}
\]
for given parameters.

**Theorem 2.1.** Define

$$A = \mu_I - \alpha_3 \frac{\pi_A}{\mu_A} + \beta_A + \gamma_A + \mu_A + \mu_E + \beta_H + \gamma_H + \mu_H$$

$$B = -\alpha_6 \alpha_5 \frac{\pi_I}{\mu_H} + \left(\mu_E + \beta_H + \gamma_H + \mu_H\right) \left(\mu_I - \alpha_3 \frac{\pi_A}{\mu_A} + \beta_A + \gamma_A + \mu_A\right) + \mu_I \left(\beta_A + \gamma_A + \mu_A - \alpha_3 \frac{\pi_A}{\mu_A}\right) + \mu_E \left(\beta_H + \gamma_H + \mu_H\right) + \alpha_1 \alpha_2 \frac{\pi_A}{\mu_A} \frac{\pi_I}{\mu_I}$$

$$C = \alpha_6 \frac{\pi_I}{\mu_I} \frac{\pi_H}{\mu_H} \left(\alpha_5 \left(\alpha_3 \frac{\pi_A}{\mu_A} - \mu_E - \beta_A - \gamma_A - \mu_A\right) - \alpha_1 \alpha_4 \frac{\pi_A}{\mu_A}\right) + \mu_E \left(\beta_H + \gamma_H + \mu_H\right) \left(\mu_I - \alpha_3 \frac{\pi_A}{\mu_A} + \beta_A + \gamma_A + \mu_A\right) + \mu_I \left(\beta_A + \gamma_A + \mu_A - \alpha_3 \frac{\pi_A}{\mu_A}\right) \left(\beta_H + \gamma_H + \mu_H + \mu_E\right) - \rho_1 \alpha_7 \frac{\pi_A}{\mu_A} \left(\mu_I + \beta_H + \gamma_H + \mu_H\right)$$

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

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 $J = [J_1 \mid J_2]$ where $J_1$ and $J_2$ are as follows:

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

\[
M = \begin{bmatrix}
-\mu_I - \lambda & \alpha_2 \frac{\pi A}{\mu_A} & \alpha_3 \frac{\pi A}{\mu_A} & \alpha_4 \frac{\pi A}{\mu_A} & 0 \\
\alpha_1 \frac{\pi A}{\mu_B} & -\beta_A - \gamma_A - \mu_A - \lambda & \alpha_6 \frac{\pi A}{\mu_H} & 0 & 0 \\
\alpha_5 \frac{\pi A}{\mu_H} & 0 & -\beta_H - \gamma_H - \mu_H - \lambda & \rho_1 \frac{\pi A}{\mu_A} & 0 \\
0 & \alpha_7 & 0 & 0 & -\mu_E - \lambda
\end{bmatrix}
\]

By assumption, \( \mu_I, \mu_A \) and \( \mu_H \) are all strictly positive, so it suffices to examine the determinant of the matrix. This is a quartic of the form

\[ A\lambda^4 + B\lambda^3 + C\lambda^2 + D, \]

where \( A, B, C \) and \( D \) are equal to the following:

\[
A = \mu_I - \alpha_3 \frac{\pi A}{\mu_A} + \beta_A + \gamma_A + \mu_A + \mu_E + \beta_H + \gamma_H + \mu_H \\
B = -\alpha_2 \alpha_3 \frac{\pi A}{\mu_B} \mu_H + (\mu_E + \beta_H + \gamma_H + \mu_H) \left( \mu_I - \alpha_3 \frac{\pi A}{\mu_A} + \beta_A + \gamma_A + \mu_A \right) \\
\quad + \mu_H \left( \beta_A + \gamma_A + \mu_A - \alpha_2 \frac{\pi A}{\mu_A} \right) + \mu_E (\beta_H + \gamma_H + \mu_H) + \alpha_2 \alpha_3 \frac{\pi A}{\mu_A} \mu_H \\
C = \alpha_1 \alpha_4 \frac{\pi H}{\mu_B} \left( \alpha_5 \frac{\pi A}{\mu_A} - \beta_A - \gamma_A - \mu_A \right) - \alpha_1 \alpha_4 \frac{\pi A}{\mu_A} \\
\quad + \mu_E (\beta_H + \gamma_H + \mu_H) \left( \mu_I - \alpha_3 \frac{\pi A}{\mu_A} + \beta_A + \gamma_A + \mu_A \right) \\
\quad + \mu_H \left( \beta_A + \gamma_A + \mu_A - \alpha_2 \frac{\pi A}{\mu_A} \right) (\beta_H + \gamma_H + \mu_H + \mu_E) \\
\quad - \rho_2 \alpha_1 \alpha_3 \frac{\pi A}{\mu_H} (\beta_H + \gamma_H + \mu_H) + \mu_H (\beta_A + \gamma_A + \mu_A - \alpha_2 \frac{\pi A}{\mu_A}) - \rho_2 \alpha_3 \frac{\pi A}{\mu_H} (\beta_H + \gamma_H + \mu_H) \\
D = \alpha_6 \alpha_7 \frac{\pi A}{\mu_B} \mu_H \left( \alpha_5 \frac{\pi A}{\mu_A} - \beta_A - \gamma_A - \mu_A \right) + \rho_4 \alpha_5 \frac{\pi A}{\mu_A} \\
\quad - \alpha_4 \frac{\pi_A}{\mu_A} (\alpha_5 \mu_E + \alpha_7 (\rho_2 + \rho_3)) \\
\quad + \mu_E (\beta_H + \gamma_H + \mu_H) \left( \mu_I (\beta_A + \gamma_A + \mu_A - \alpha_3 \frac{\pi A}{\mu_A}) - \alpha_3 \alpha_5 \frac{\pi A}{\mu_A} \right) \\
\quad - \rho_2 \alpha_1 \frac{\pi A}{\mu_H} (\beta_H + \gamma_H + \mu_H),
\]
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 \( \frac{\pi A}{\mu A} \) is likely much larger than \( \mu I + \beta A + \gamma A + \mu A + \mu E + \beta H + \gamma H + \mu H \)
in which case \( A = \mu I - \alpha_3 \pi A + \beta A + \gamma A + \mu A + \mu E + \beta H + \gamma H + \mu H < 0. \)

3. The system with vaccination

We will now turn our attention to the system with pulse vaccinations given at regular time intervals (\( \tau \)) to a proportion of the susceptible human population (\( p \)). This vaccine has different efficacies for aerosol transmission (\( \theta_2 \)) and for the other methods of transmission (\( \theta_1 \)), and also reverts to the original viral strain at a given rate (\( \phi \)). This system, in ODE form, is illustrated below.

For \( t \neq t_k \):

\[
\begin{align*}
S'_I &= \pi I - \alpha_2 I_A S_I - \alpha_6 I_H S_I - \mu I S_I \\
I'_I &= \alpha_2 I_A S_I + \alpha_6 I_H S_I - \mu I I_I \\
S'_A &= \pi_A - \alpha_1 I_I S_A - \alpha_3 I_A S_A - \rho_1 ES_A + \beta_A I_A - \mu_A S_A \\
I'_A &= \alpha_1 I_I S_A + \alpha_3 I_A S_A + \rho_1 ES_A - \beta_A I_A - \gamma A I_A - \mu A I_A \\
S'_H &= \pi_H - \alpha_4 I_A S_H - \alpha_6 I_I S_H - (\rho_2 + \rho_3) ES_H - \mu_H S_H \\
I'_H &= \alpha_4 I_A S_H + \alpha_6 I_I S_H + \rho_2 ES_H + \rho_3 ES_H - \beta_H I_H - \gamma H I_H - \mu_H I_H \\
&\quad + (1 - \theta_1)(\alpha_4 I_A V_H + \alpha_6 I_I V_H + \rho_2 EV_H) + (1 - \theta_2)\rho_3 EV_H + \phi V_H \\
R'_H &= \beta_H I_H - \mu_H R_H \\
E' &= \alpha_7 I_A - \mu E E \\
V'_H &= - (1 - \theta_1)(\alpha_4 I_A V_H + \alpha_6 I_I V_H + \rho_2 EV_H) \\
&\quad - (1 - \theta_2)\rho_3 EV_H - \phi V_H - \mu_H V_H.
\end{align*}
\]

The impulsive conditions are given by

\[
\begin{align*}
\Delta S_H &= -pS_H^- \\
\Delta V_H &= pS_H^-
\end{align*}
\]

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 $I_A^*, I_I^*, E^*$ 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

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

and

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

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

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

Then it follows that, for $t_k < t \leq t_{k+1}$:
\[ S_H(t) = \frac{1}{e^{\int f_1(s)\,ds}} \left[ S_H(t_k^+) e^{\int f_1(s)\,ds} \bigg|_{s=t_k} + \int_{t_k}^{t} \pi_H e^{\int f_1(s)\,ds} \, ds \right] \]

and, after factoring in the impulsive effect and setting \( t = t_k + 1 \),

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

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

Then

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

\[ S_H(t_2^-) = \frac{1}{e^{\int f_1(s)\,ds}} \left[ (1 - p) \left( (1 - p) S_H(t_0) e^{\int f_1(s)\,ds} \bigg|_{s=t_0} \right. \right. \]

\[ + \int_{t_0}^{t_1} \pi_H e^{\int f_1(s)\,ds} \, ds + \int_{t_1}^{t_2} \pi_H e^{\int f_1(s)\,ds} \, ds \bigg] \]

\[ \vdots \]

\[ S_H(t_k^-) = \frac{1}{e^{\int f_1(s)\,ds}} \left[ (1 - p)^k S_H(t_0) e^{\int f_1(s)\,ds} \bigg|_{s=t_0} \right. \]

\[ + \sum_{j=0}^{k-1} (1 - p)^j \int_{t_{k-j-1}}^{t_{k-j}} \pi_H e^{\int f_1(s)\,ds} \, ds \bigg] . \]

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 $k \geq w$:

$$
S_H(t_k) \approx \frac{(1 - p)^k S_H(t_0) e^{f t_0} f_1(s) ds}{e^{ct_k}} \bigg|_{t_0}^{t_k} + \sum_{j=0}^{w-1} \frac{\pi_H(1 - p)^{k-w+j} \int_{t_{w-j-1}}^{t_{w-j}} e^{f t} f_1(s) ds ds}{e^{ct_k}} \\
+ \sum_{j=0}^{k-w-1} \frac{\pi_H(1 - p)^j}{c_1} \left( e^{ct_{k-j}} - e^{ct_{k-j-1}} \right) \\
= \frac{(1 - p)^k S_H(t_0) e^{f t_0} f_1(s) ds}{e^{ct_k}} \bigg|_{t_0}^{t_k} + \pi_H(1 - p)^k \sum_{j=0}^{w-1} \frac{(1 - p)^j \int_{t_{w-j-1}}^{t_{w-j}} e^{f t} f_1(s) ds ds}{e^{ct_k}} \\
+ \sum_{j=0}^{k-w-1} \frac{\pi_H(1 - p)^j}{c_1} \left( e^{-\alpha_1 t_{k-j}} - e^{-\alpha_1 t_{k-j-1}} \right) \\
= \frac{(1 - p)^k S_H(t_0) e^{f t_0} f_1(s) ds}{e^{ct_k}} \bigg|_{t_0}^{t_k} + \pi_H(1 - p)^k \sum_{j=0}^{w-1} \frac{(1 - p)^j \int_{t_{w-j-1}}^{t_{w-j}} e^{f t} f_1(s) ds ds}{e^{ct_k}} \\
+ \sum_{j=0}^{k-w-1} \frac{\pi_H(1 - p)^j e^{-\alpha_1 \tau}}{c_1} (1 - e^{-\alpha_1 \tau}) \\
= \frac{(1 - p)^k S_H(t_0) e^{f t_0} f_1(s) ds}{e^{ct_k}} \bigg|_{t_0}^{t_k} + \pi_H(1 - p)^k \sum_{j=0}^{w-1} \frac{(1 - p)^j \int_{t_{w-j-1}}^{t_{w-j}} e^{f t} f_1(s) ds ds}{e^{ct_k}} \\
+ \pi_H \frac{1 - e^{-\alpha_1 \tau}}{c_1} \frac{1 - (1 - p)^{k-w} e^{-\alpha_1 (k-w)}}{1 - (1 - p)e^{-\alpha_1 \tau}} \\
As k \to \infty, (1 - p)^k \to 0, (1 - p)^{k-w} \to 0 and e^{-\alpha_1 (k-w)} \to 0, so:

$$
S_H^* (t_k) \to \frac{\pi_H(1 - e^{-\alpha_1 \tau})}{c_1} \left( \frac{1}{1 - (1 - p)e^{-\alpha_1 \tau}} \right) \\
= \frac{\pi_H}{c_1} \left( 1 - \frac{pe^{-\alpha_1 \tau}}{1 - (1 - p)e^{-\alpha_1 \tau}} \right).
$$

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 \( \frac{dV_H}{dt} = -f_2(t) \); 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 \( t = t_{k+1} \):
\[ V_H(t_{k+1}^-) = (V_H(t_k^-) + pS_H(t_k^-)) e^{- \int_{t_k}^{t_{k+1}} f_2(s) \, ds}. \]

Then, if \( V_H(t_0) = V_H(0) - pS_H(t_0) \), we have
\[ V_H(t_1^-) = (V_H(t_0) + pS_H(t_0)) e^{- \int_{t_0}^{t_1} f_2(s) \, ds} \]
\[ V_H(t_2^-) = \left[ (V_H(t_0) + pS_H(t_0)) e^{- \int_{t_0}^{t_1} f_2(s) \, ds} + pS_H(t_1^-) \right] e^{- \int_{t_1}^{t_2} f_2(s) \, ds} \]
\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
\[ V_H(t_{k^-}) = V_H(t_{k+1}^-) = (V_H(t_k^-) + pS_H(t_k^-)) e^{-c_2 \tau} \]
which implies that \( V_H(t_{k^-}) = \frac{pe^{-c_2 \tau}}{1 - e^{-c_2 \tau}} S_H(t_{k^-}) \).

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 \( X' \leq k - l X(t) \) 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
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 $t \to \infty$, $e^{-lt} \to 0$ 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 $t \to \infty$.

**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 $t \to \infty$ with appropriate $p$, $\tau$, $\theta_1$, $\theta_2$, and $\phi$.

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),

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

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 $\tau$ close to 0. Therefore, choose an appropriate $p$ and $\tau$ such that $S_H^*(t_k^-) \leq \frac{e(\beta_H + \mu_H + \gamma_H)}{4(c_1 - \mu_H)}$. 

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

$$t_k < t \leq t_{k+1}$$

or that, for all $t \geq t_w$,

$$V_H(t) \leq V_H^*(t_k^+)$$

$$= V_H^*(t_k^-) + pS_H^*(t_k^-)$$

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

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

This is well-defined for the values of $p$ and $\tau$ chosen above. Therefore, we can choose $\theta_1$ such that

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

Similarly, choose $\theta_2$ such that $(1 - \theta_2) \leq \frac{\varepsilon(\beta_H + \mu_H + \gamma_H)}{4V_H^*(t_k^+)(\alpha_4 I_A^* + \rho_3 E^*)}$. Finally, choose $\phi$ such that

$$\phi \leq \frac{\varepsilon(\beta_H + \mu_H + \gamma_H)}{4V_H^*(t_k^+)}.$$

Therefore, for $t \geq t_w$, using the values of $p$, $\tau$, $\theta_1$, $\theta_2$ and $\phi$ above:

$$I_H'(t) \approx S_H(t)(c_1 - \mu_H) + (1 - \theta_1)V_H(t)(\alpha_4 I_A^* + \alpha_5 I^*_I + \rho_2 E^*)$$

$$+ (1 - \theta_2)V_H(t)p_3 E^* + \phi V_H(t) - (\beta_H + \gamma_H + \mu_H) I_H(t)$$

$$\leq S_H^*(t_k^-)(c_1 - \mu_H) + (1 - \theta_1)V_H^*(t_k^+)(\alpha_4 I_A^* + \alpha_5 I^*_I + \rho_2 E^*)$$

$$+ (1 - \theta_2)V_H^*(t_k^+)(\rho_3 E^* + \phi V_H^*(t_k^+) - (\beta_H + \gamma_H + \mu_H) I_H(t)$$

$$\leq \varepsilon(\beta_H + \mu_H + \gamma_H) - I_H(\beta_H + \mu_H + \gamma_H).$$

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

Therefore, provided that we can control $\tau$, $p$, $\theta_1$, $\theta_2$, and $\phi$, the infected human population can be reduced below a given threshold as $t \to \infty$. The following theorem will provide other bounds for $p$, $\tau$ and the infected human population under certain conditions as $t \to \infty$. 
Theorem 3.3. a) Let $\theta_1, \theta_2$ and $\phi$ be given. Then, as $p \to 1$ and $\tau \to 0$, $I_H$ will converge to \[ \frac{\pi_H}{\beta_H + \gamma_H + \mu_H} \left( \frac{c_2 - \mu_H}{c_2} \right). \]

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

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

c) Similarly, the minimum threshold for $\tau$ is:

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

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:

\[
I'_H(t) \approx S_H(t)(c_1 - \mu_H) + (1 - \theta_1)V_H(t)(\alpha_4 I_A^* + \alpha_5 I_I^* + \rho_2 E^*)
+ (1 - \theta_2)V_H(t)\rho_3 E^* + \phi V_H(t) - (\beta_H + \gamma_H + \mu_H)I_H(t)
\geq S^*_H(t_k^-)(c_1 - \mu_H) + V^*_H(t_k^-)(c_2 - \mu_H) - (\beta_H + \gamma_H + \mu_H)I_H(t)
= (1 - p) S^*_H(t_k^-)(c_1 - \mu_H) + V^*_H(t_k^-)(c_2 - \mu_H) - (\beta_H + \gamma_H + \mu_H)I_H(t)
= (1 - p) \frac{\pi_H}{c_1} \left( \frac{1 - e^{-\varepsilon \tau}}{1 - (1 - p)e^{-\varepsilon \tau}} \right) (c_1 - \mu_H) + S^*_H(t_k^-) \left( \frac{p e^{-\varepsilon \tau}}{1 - e^{-\varepsilon \tau}} \right) (c_2 - \mu_H)
- (\beta_H + \gamma_H + \mu_H)I_H(t)
= (1 - p) \frac{\pi_H}{c_1} \left( \frac{1 - e^{-\varepsilon \tau}}{1 - (1 - p)e^{-\varepsilon \tau}} \right) (c_1 - \mu_H)
+ \pi_H \left( \frac{p e^{-\varepsilon \tau}}{1 - (1 - p)e^{-\varepsilon \tau}} \right) \left( \frac{1 - e^{-\varepsilon \tau}}{1 - e^{-\varepsilon \tau}} \right) (c_2 - \mu_H) - (\beta_H + \gamma_H + \mu_H)I_H(t).
\]

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:
\[ I'_H(t) \leq S^*_H(t_k^-)(c_1 - \mu_H) + V^*_H(t_k^+)(c_2 - \mu_H) - (\beta_H + \gamma_H + \mu_H)I_H(t) \]
\[ = \frac{\pi_H(c_1 - \mu_H)}{c_1} \left( \frac{1 - e^{-c_1 \tau}}{1 - (1-p)e^{-c_1 \tau}} \right) c_1 + S^*_H(t_k^-) \left( \frac{p}{1 - e^{-c_2 \tau}} \right)(c_2 - \mu_H) \]
\[ - (\beta_H + \gamma_H + \mu_H)I_H(t) \]
\[ = \frac{\pi_H(c_1 - \mu_H)}{c_1} \left( \frac{1 - e^{-c_1 \tau}}{1 - (1-p)e^{-c_1 \tau}} \right) + \frac{\pi_H}{c_1} \left( \frac{p}{1 - (1-p)e^{-c_1 \tau}} \right) \left( \frac{1 - e^{-c_1 \tau}}{1 - e^{-c_2 \tau}} \right)(c_2 - \mu_H) \]
\[ - (\beta_H + \gamma_H + \mu_H)I_H(t). \]

Note that, as \( p \to 1 \) and \( \tau \to 0 \), then 
\[ \left( \frac{1 - e^{-c_1 \tau}}{1 - (1-p)e^{-c_1 \tau}} \right) \to 0, \quad \left( \frac{p e^{-c_1 \tau}}{1 - (1-p)e^{-c_1 \tau}} \right) \to 1 \]
and, by L’Hôpital’s rule, 
\[ \left( \frac{1 - e^{-c_1 \tau}}{1 - e^{-c_2 \tau}} \right) \to \frac{c_1}{c_2}. \]

Therefore, as \( \bar{p} \to 1 \) 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 
\[ \frac{c_1 - \mu_H}{c_1} \]

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 
\[ S^*_H(t_k^-) = \frac{\epsilon(\beta_H + \gamma_H + \mu_H)}{c_1 - \mu_H}; \]

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

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

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

Similarly, we isolate \( \tau \) to obtain the other identity:

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

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

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 \( \theta_1 \), \( \theta_2 \) and \( \phi \), 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 non-aerosol transmission, so \( \theta_1 = 0.97 \) [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, \( \theta_2 \)
was estimated to be \((1 - 17/75) = 0.773\). The capacity for reversion is unknown so, although biologically unlikely, \( \phi \) was taken to be 0 [14].

We performed a sensitivity analysis on the value of \( \hat{h}_0 \) 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 \( \alpha_1, \alpha_2, \mu_A \) and \( \mu_f \). 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.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Definition</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \pi_I )</td>
<td>Insect birth rate</td>
<td>11.568</td>
<td>19.28</td>
</tr>
<tr>
<td>( \pi_A )</td>
<td>Animal birth rate</td>
<td>0.57534</td>
<td>0.9589</td>
</tr>
<tr>
<td>( \pi_H )</td>
<td>Human birth rate</td>
<td>0.02740</td>
<td>0.04658</td>
</tr>
<tr>
<td>( \alpha_1 )</td>
<td>Insect to animal transmissibility</td>
<td>0.000001</td>
<td>0.001</td>
</tr>
<tr>
<td>( \alpha_2 )</td>
<td>Animal to insect transmissibility</td>
<td>0.000001</td>
<td>0.001</td>
</tr>
<tr>
<td>( \alpha_3 )</td>
<td>Animal to animal transmissibility</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>( \alpha_4 )</td>
<td>Animal to human transmissibility</td>
<td>0.00000001</td>
<td>0.00001</td>
</tr>
<tr>
<td>( \alpha_5 )</td>
<td>Insect to human transmissibility</td>
<td>0.0000001</td>
<td>0.00001</td>
</tr>
<tr>
<td>( \alpha_6 )</td>
<td>Human to insect transmissibility</td>
<td>0.0000001</td>
<td>0.00001</td>
</tr>
<tr>
<td>( \alpha_7 )</td>
<td>Animal to environment transmissibility</td>
<td>0.00001</td>
<td>0.001</td>
</tr>
<tr>
<td>( \rho_1 )</td>
<td>Environment to animal transmissibility</td>
<td>0.00001</td>
<td>0.001</td>
</tr>
<tr>
<td>( \rho_2 )</td>
<td>Waterborne environment to human transmissibility</td>
<td>0.00001</td>
<td>0.001</td>
</tr>
<tr>
<td>( \rho_3 )</td>
<td>Airborne environment to human transmissibility</td>
<td>0.00001</td>
<td>0.001</td>
</tr>
<tr>
<td>( \beta_A )</td>
<td>Recovery rate of animals</td>
<td>0</td>
<td>0.005</td>
</tr>
<tr>
<td>( \beta_H )</td>
<td>Recovery rate of humans</td>
<td>0.01282</td>
<td>0.02381</td>
</tr>
<tr>
<td>( \gamma_A )</td>
<td>Disease death rate of animals</td>
<td>0.05</td>
<td>0.15</td>
</tr>
<tr>
<td>( \gamma_H )</td>
<td>Disease death rate of humans</td>
<td>0.0001667</td>
<td>0.0006666</td>
</tr>
<tr>
<td>( \mu_I )</td>
<td>Background insect death rate</td>
<td>0.00068493</td>
<td>0.002740</td>
</tr>
<tr>
<td>( \mu_A )</td>
<td>Background animal death rate</td>
<td>0.00054794</td>
<td>0.001370</td>
</tr>
<tr>
<td>( \mu_H )</td>
<td>Background human death rate</td>
<td>0.0000332232</td>
<td>0.0000391389</td>
</tr>
<tr>
<td>( \mu_E )</td>
<td>Environment decay rate</td>
<td>0.0055585</td>
<td>0.0102</td>
</tr>
</tbody>
</table>
Modelling Tularemia vaccination

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 number 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 $\theta_1$ 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

RJS? is supported by an NSERC Discovery Grant, an Early Researcher Award and funding from MITACS.

7. Appendix: Parameter estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimated Value</th>
<th>Derivation</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_1$</td>
<td>$10^{-4} \ast (\text{tick} \ast \text{day})^{-1}$</td>
<td>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.</td>
</tr>
<tr>
<td>$\alpha_2$</td>
<td>$10^{-4} \ast (\text{rabbit} \ast \text{day})^{-1}$</td>
<td>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.</td>
</tr>
<tr>
<td>$\alpha_3$</td>
<td>$0 \ast (\text{rabbit} \ast \text{day})^{-1}$</td>
<td>Rabbits do not exhibit carnivorous activity towards other rabbits.</td>
</tr>
<tr>
<td>$\alpha_4$</td>
<td>$10^{-6} \ast (\text{rabbit} \ast \text{day})^{-1}$</td>
<td>It was estimated that this rate would be approximately the same as the rate of transmission from ticks.</td>
</tr>
<tr>
<td>$\alpha_5$</td>
<td>$10^{-6} \ast (\text{tick} \ast \text{day})^{-1}$</td>
<td>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.</td>
</tr>
<tr>
<td>$\alpha_6$</td>
<td>$10^{-6} \ast (\text{person} \ast \text{day})^{-1}$</td>
<td>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.</td>
</tr>
<tr>
<td>$\alpha_7$</td>
<td>$10^{-4} \ast (\text{environment} \ast \text{rabbit} \ast \text{day})^{-1}$</td>
<td>Estimated variable. This was estimated to be the same rate as $\alpha_1$.</td>
</tr>
<tr>
<td>$\rho_1$</td>
<td>$10^{-4} \ast (\text{environment} \ast \text{day})^{-1}$</td>
<td>Estimated variable. This was estimated to be the same rate as $\alpha_1$.</td>
</tr>
<tr>
<td>$\rho_2$</td>
<td>$10^{-4} \ast (\text{environment} \ast \text{day})^{-1}$</td>
<td>Estimated variable. This was estimated to be the same rate as $\alpha_1$.</td>
</tr>
<tr>
<td>$\rho_3$</td>
<td>$10^{-4} \ast (\text{environment} \ast \text{day})^{-1}$</td>
<td>Estimated variable. This was estimated to be the same rate as $\alpha_1$.</td>
</tr>
<tr>
<td>$\beta_A$</td>
<td>$0 \ast \text{day}^{-1}$</td>
<td>We estimate that due to the susceptibility of rabbits to tularemia, they do not recover from the disease.</td>
</tr>
<tr>
<td>$\beta_B$</td>
<td>$1.6667 \ast 10^{-2} \ast \text{day}^{-1}$</td>
<td>The illness may continue for several weeks [13]. The variable was estimated at 1/60.</td>
</tr>
</tbody>
</table>
### Table 3. Continued

| \( \gamma_A \) | \( 10^{-1} \times day^{-1} \) | 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. |
| \( \gamma_H \) | \( 3.33 \times 10^{-4} \times day^{-1} \) | 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. |
| \( \pi_I \) | \( 1.5224 \times 10^3 \times ticks \times day^{-1} \) | We estimate that the tick birth rate is approximately 20 times that of the rabbit population. |
| \( \pi_A \) | \( 7.6712 \times 10^{-1} \times rabbits \times day^{-1} \) | We estimate that the rabbit birth rate within the area of consideration is approximately 20 times that of the human population. |
| \( \pi_H \) | \( 3.8356 \times 10^{-2} \times people \times day^{-1} \) | We estimate that the average crude birth rate is 14 per 1000 people per year. Therefore, the variable was estimated at 14/365. |
| \( \mu_I \) | \( 1.37 \times 10^{-3} \times day^{-1} \) | The average life cycle of a tick is approximately 2 years [11], so the variable was estimated at \( 1 \div (2 \times 365) \). |
| \( \mu_A \) | \( 1.191 \times 10^{-3} \times day^{-1} \) | The average lifespan of a rabbit is 2.3 years [10], so the variable was estimated at \( 1 \div (2.3 \times 365) \). |
| \( \mu_H \) | \( 3.4245 \times 10^{-5} \times day^{-1} \) | We estimate that the average lifespan is 80 years, so the variable was estimated at \( 1 \div (80 \times 365) \). |
| \( \mu_E \) | \( 7.52 \times 10^{-3} \times day^{-1} \) | 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. |

### References