

A mathematical epidemiological model of gram-negative *Bartonella* bacteria: does differential ectoparasite load fully explain the differences in infection prevalence of *Rattus rattus* and *Rattus norvegicus*?

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We postulate that the large difference in infection prevalence, 24% versus 5%, in *R. norvegicus* and *R. rattus*, respectively, between these two co-occurring host species may be due to differences in ectoparasite and potential vector infestation rates. A compartmental model, representative of an infectious system containing these two *Rattus* species and two ectoparasite vectors, was constructed and the coefficients of the forces of infection determined mathematically. The maximum difference obtained by the model in the prevalence of *Bartonella* in the two *Rattus* species amounts to 4.6%, compared to the observed mean difference of 19%. Results suggest the observed higher *Bartonella* infection prevalence in *Rattus norvegicus* compared to *Rattus rattus*, cannot be explained solely by higher ectoparasite load. The model also highlights the need for more detailed biological research on *Bartonella* infections in *Rattus* and the importance of the flea vector in the spread of this disease.

Keywords: *Bartonella*; *Rattus*; mathematical epidemiological model; ectoparasites; infection prevalence; South Africa

1. Introduction

More than 20 diseases caused by bacterial, viral and protozoal infections are spread to humans by rodents, either directly or indirectly [21]. Due to their frequent association with human settlements, and status as natural reservoir of infections, they are often implicated in outbreaks of bacterial diseases, including plague (caused by *Yersinia pestis*), Lyme disease (*Borrelia burgdorferi*), Typhus (*Rickettsia typhi*) and the spotted fevers (*Rickettsia* spp.) [16,51]. The gram-negative bacterium,

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Bartonella, is no exception and rodents have been found to host several species, including *Bartonella elizabethae*, *Bartonella grahamii*, *Bartonella tribocorum*, *Bartonella rattimassiliensis*, *Bartonella rattiaustraliani*, *Bartonella taylorii*, *Bartonella doshiae*, *Bartonella cooperplainensis*, *Bartonella queenslandensis* and *Bartonella phoceensis* [2,22,32,33]. Although not all of these *Bartonella* species are associated with human illnesses, it has been suggested that most *Bartonella* species are capable of infecting humans and that lack of exposure to current reservoirs is the only obstacle preventing this [11]. This is highlighted by the observation that some *Bartonella* infections in humans only came to light after their initial detection in rodents (e.g. *B. grahamii*, *B. elizabethae* and *B. vinsonii arupensis*) [27].

Invasive members of the *Rattus* genus, viz. *Rattus rattus* and *Rattus norvegicus*, are known to harbour *Bartonella* species with documented zoonotic potential [32]. These two *Rattus* species, which, essentially have a worldwide distribution due to increased trade and favourable living conditions created by human presence, occur in South Africa [9]. Hsieh *et al.* [26] report a 43% higher *Bartonella* prevalence in *R. norvegicus* than in *R. rattus*, while Ellis *et al.* [19] similarly show a 7.4% higher prevalence in the former species. Data on *Bartonella* in *Rattus* from South Africa concur with that of Northern hemisphere data, indicating that bacterial prevalence differs markedly in the two species [13,42].

These differences in infection rates between *R. norvegicus* and *R. rattus* suggest a constantly higher infection prevalence in the former species despite the co-occurrence of both species in the countries under study. This is of interest as one would anticipate that related species with similar biologies that occur in the same area, would have comparable susceptibility to infection. This suggests some extrinsic factor is likely to be responsible for the observed differences in *Bartonella* prevalence in these two species. Therefore, an investigation into the dynamics of *Bartonella* infections in these rodents, linked to a mathematical epidemiological model for *Bartonella* infections in *R. rattus* and *R. norvegicus* was initiated.

More detailed investigation of the factors mediating *Bartonella* infections, revealed a lack of biological information on this infectious system. The available peer-reviewed studies on rodent hosts did, however, confirm the following: (1) *Bartonella* is a vector-borne bacterial infection transmitted by haematophagous arthropod vectors such as fleas and ticks [25,35,41,45], (2) natural *Bartonella* infections seem to have little effect on the mortality of rodents ([19], (3) vertical transmission of *Bartonella* occurs in some rodent species [11,19,28], (4) individual rodents can display super-infection with different *Bartonella* species [53], (5) rodent hosts acquire immunity following exposure to a *Bartonella* species, but are not protected from subsequent infection by a different species [11] and (6) *Bartonella* can exhibit host-specificity although this has not been shown for *Rattus* specifically [1,8,25,46].

Seasonal variation in *Bartonella* infections which could possibly be attributed to seasonal fluctuation of rodent and ectoparasite population numbers has been demonstrated for the Tunisian fat sand rat (*Psammomys obesus*, [20]). Studies investigating the known and possible vectors of *Bartonella* (mostly ticks and fleas) show large variation in *Bartonella* infection rates [25,35,41,45]. These typically range from 5% to 40% in ticks (mainly Ixodidae) and between 13% and 60% for fleas (mainly *Xenopsylla*) [5,12,15,23,29,41,43,45]. Studies also suggest an age, sex and seasonal bias in the *Bartonella* infection rates of these blood-sucking arthropods [23,25]. Additionally, co-infection of different *Bartonella* species at a rate of 30% in ticks and a sex-biased co-infection rate in adult ticks of 44% in females compared to 11% in males has also been reported [23,25].

To this end, the aim of this work is firstly, to study mathematically the relationships between the contributing factors of *Bartonella* infections in a commensal rat population in South Africa, in an effort to explain the differences in infections rates between two different species of *Rattus* with respect to their ectoparasite infestation levels. Secondly, this work aims to assess the most crucial factors and biological parameters for which information is presently lacking, that may prove vital in the understanding of *Bartonella* infections in carrier rodents and their consequent zoonotic

threat to humans. To this end, this work will lay the foundation for directing future biological and epidemiological research.

2. The *Bartonella* model

Mathematical modelling has become a major tool for studying the evolution of infectious diseases in general [4,17], and vector-borne diseases in particular [14,18,36,37]. The mathematical model developed for this study is in the form of a system of ordinary differential equations involving two hosts (*R. rattus* and *R. norvegicus*) and two vectors (Ixodid ticks (potential vector) and *Xenopsyllid* fleas (known vector)). Although ticks have not been proven vectors of *Bartonella*, their ability to pick up the bacterium from the host has been confirmed [13] and this, along with available biological data (as opposed to other known vectors) justified the inclusion of this ectoparasite in the model. Considering this, both ectoparasites will be considered as vectors of the disease for the remainder of this paper. In constructing the model, we use the well-known SEI compartmental approach with three compartments for each population, namely susceptible (S), exposed (E) and infective (I); 12 compartments in total. The mathematical model, therefore, comprises 12 ordinary differential equations defining a dynamical system. The parameters of the model are related to the transfer rates to and from compartments as determined by the vital dynamics (birth and deaths) of the populations as well as the course of the infection. Numerical simulations confirmed the stability of final states of the model in the case of stable population sizes for both hosts and vectors and also in the case of periodic changes in the populations of the ectoparasite vectors. Furthermore, we computed sensitivity indices of the prevalence rates with respect to all parameters of the model which will aid in directing future research. Extended mathematical details for modelling of host and vector populations are detailed in [6].

2.1. Host

The host animal is specified to be a commensal population of co-occurring *R. rattus* and *R. norvegicus* in South Africa. Both species are invasive rodents in South Africa. *R. norvegicus* is typically larger, heavier and more aggressive than *R. rattus* [21,49]. They are found in out-buildings, stores and houses, occasionally nesting in well-covered natural habitats [7]. They are nocturnal omnivorous pests that can live for up to two years. They show year-round reproductive ability in human populated areas, and are capable of producing litters of 5–10 pups every two months [7], corresponding to between 30 and 60 pups per female per year, under natural conditions. Differences between the two species mainly relate to their body size, their general behaviour and ectoparasite load. *R. norvegicus* spends most of its time on the ground, foraging and also nesting in self-constructed burrows in the soil [21,49,52]. Possibly due to this ground-dwelling behaviour and their larger size, they are infected with up to 1.4 times more ectoparasites than *R. rattus* [21,40,49]. *R. rattus* on the other hand, spends most of its time in trees and raised surfaces, especially in the presence of *R. norvegicus*, due to the aggressive nature of the latter larger rat. It is presumed this evasive behaviour limits the exposure to ectoparasites (especially ticks) which often search for their host on the ground where they hatch from eggs and molt [21].

If the numbers of the rodents are not controlled via natural predators or pest control measures, the rat population will be expected to increase exponentially. As this is generally not the case, we assume that the populations of the two species are in equilibrium. This means that the death rate and the birth rate, μ , are equal. We calculate μ by using the well-known Partial Differential Equation (PDE) population model [24]:

$$\frac{\partial p}{\partial t} + \frac{\partial p}{\partial x} = -\mu p,$$

where $p(t, x)$ is the population density at time t with respect to age x . In terms of the population density, the number of rats at time t between the ages \underline{a} and \bar{a} is given by $\int_{\underline{a}}^{\bar{a}} p(t, x) dx$. The differential equation is coupled with the boundary condition

$$p(t, 0) = \frac{1}{2}b \int_a^A p(t, x) dx,$$

which represents the fact that those of age zero are the newly born to all females at reproductive age which is between a and A . Here b is the fertility rate and it is assumed that females constitute approximately half of the population. Since the equilibrium population density $p(x) = p(t, x)$ satisfies the time-independent equation $\partial p / \partial x = -\mu p$, we have $p(x) = p(0) e^{-\mu x}$. Substituting in the boundary condition, we obtain

$$\phi(\mu) := \frac{1}{\mu} (e^{-\mu a} - e^{-\mu A}) = \frac{2}{b}.$$

For the considered *Rattus* species, we have $a = 61$, $A = 730$, $b \in [b_1, b_2] = [\frac{30}{365}, \frac{60}{365}]$. The left-hand side and the lower and upper bounds for the right-hand side are plotted in Figure 1. Where the value of μ is between 0.01072 and 0.01575, we take the average, $\mu = 0.01324$. Taking into account that the population does not have individuals older than 730 days, the recruitment/death rate needs to be modified to

$$\frac{p(0)}{\int_0^{730} p(x) dx} = \frac{\mu}{1 - e^{-730\mu}} = 0.01324084. \quad (1)$$

However, the change is small and within the round-off error to four significant figures. Therefore, we assume that the recruitment/death rate for each of the *Rattus* species is $\mu_R = 0.01324$. Additionally, the assumption was made that rats can transmit *Bartonella* to their unborn offspring through vertical transmission [30]. Experimental infection of rodents with low and high concentrations of *Bartonella* [31] showed rodents to recover from *Bartonella* after about 6–9 weeks. This study also shows that the rodents become immune to challenge with the same species of *Bartonella* after recovery, but that they are susceptible to alternate *Bartonella* species, suggesting

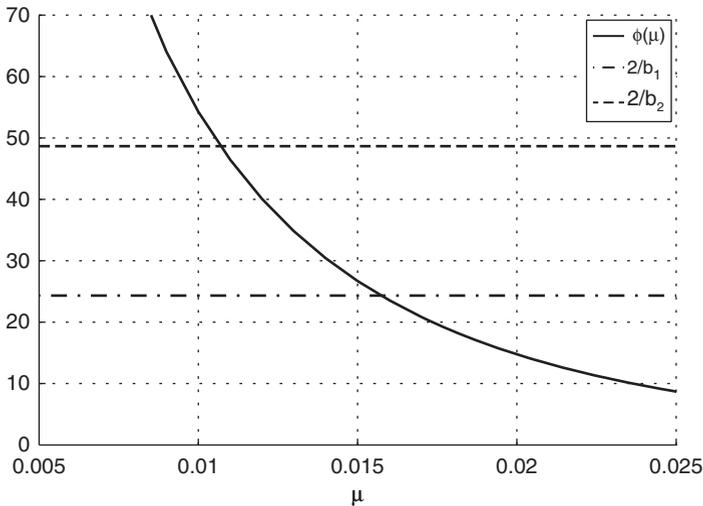


Figure 1. Determining values, μ , for the birth and death rates of invasive *Rattus* from South Africa.

full recovery and potential re-infection. Added to this is evidence from the literature [1,25,46] of co-infections with different species of *Bartonella* in individual rodents – suggesting that a full recovery is not needed for super-infection by another *Bartonella* species. Given the above background, we considered the available data from South Africa on *Bartonella* diversity in *Rattus* [13,42], which suggests that the diversity of bacterial strains to which rats are potentially exposed is probably quite limited, with only three species of *Bartonella* documented in rats thus far [13,42] and one of the three pre-dominating with a prevalence of 85% of infected rats. Therefore, we propose that if a rat in South Africa recovers from a *Bartonella* infection, although it is likely to be exposed to *Bartonella* again, it is very unlikely that it would be exposed to a different species which it would be susceptible to. We, therefore, modelled the reduced probability of being re-infected as shown in Section 2.4.

2.2. Flea vector

Rodent fleas mostly belong to the genus *Xenopsylla* that will hatch from eggs within 2–12 days and undergo three moults before pupating into adults [44]. The larvae of fleas are rarely parasitic and feed on organic debris in the burrow/nest of the host [34], and are therefore, not considered vectors of *Bartonella*. After taking a blood meal, females can lay up to 50 eggs per day [44,48]. On average, these fleas will live up to one year, which may or may not include an extended pupal phase, depending on environmental factors [48]. Due to temperature and humidity constraints on development, adult fleas exhibit a defined periodic abundance, which falls within the spring and summer months that run from September to February in South Africa [44,48]. As adult females produce an enormous number of eggs, it can safely be assumed that the amount of new recruits in the epidemiologically relevant population does not depend on its current population size, but only on the prevailing environmental conditions at the given time which we model through the carrying capacity of the environment. The epidemiologically relevant population consists of all adult fleas that feed on the population of rats that we consider. From this, we can make the inevitable assumption that this population is to a large extent separated from the rest of the fleas in the world. Therefore, the maximum carrying capacity is determined by the maximum (on time) average (over the modelled rat population) number of fleas and/or ticks per rat. Here, we assume that about 10% of adult fleas can be between hosts at any time. The transition between maximum abundance during spring and summer and low abundance in autumn and winter (set at about 20%) is modelled by using a periodic environmental carrying capacity of the form

$$C_F(t) = (N_r \xi_{Fr} + N_n \xi_{Fn}) \min \left\{ 1.1, \max \left\{ 0.65 + \cos \frac{2\pi t}{365}, 0.2 \right\} \right\}, \quad (2)$$

where N_r is the size of the population of *R. rattus*, N_n is the size of the population of *R. norvegicus*, ξ_{Fr} and ξ_{Fn} are the maximum (on time) average (on the modelled rat population) numbers of fleas per rodent for each one of the *Rattus* populations, respectively. Based on previous studies, we use the following values of the flea parasite load as $\xi_{Fr} = 8.8$, $\xi_{Fn} = 12.37$ [21,49], assuming that fleas readily switch hosts. The graph of C_F with $N_r = N_n = 1000$ is given in Figure 2.

The size N_F of the flea population is obtained from the differential equation

$$\frac{dN_F(t)}{dt} = \alpha_F(t) - \mu_F(t)N_F(t), \quad (3)$$

where $\alpha_F(t) = \bar{\mu}_F C_F(t) + a_F \max\{C_F(t) - N_F(t), 0\}$ represents recruitment to adults in the population while $\mu_F(t) = \bar{\mu}_F + a_F \max\{1 - C_F(t)/N_F(t), 0\}$ represents the removal rate (deaths) from

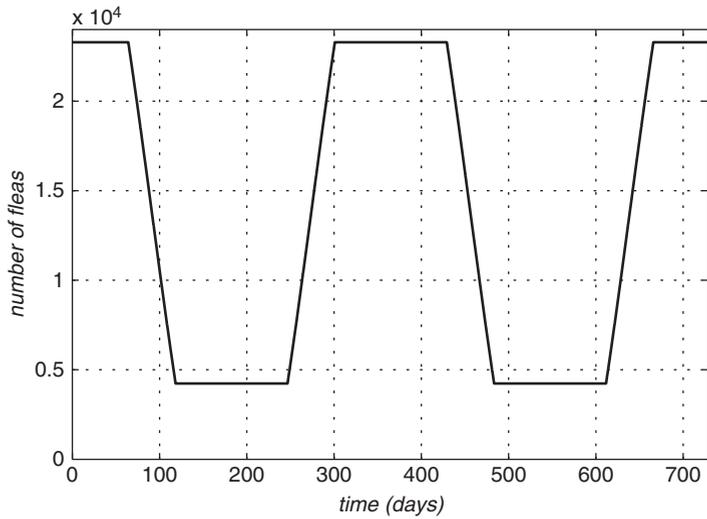


Figure 2. Changes in flea carrying capacity over time.

the population. If we combine the two terms, the equation simplifies to a linear differential equation

$$\frac{dN_F(t)}{dt} = (\bar{\mu}_F + a_F)(C_F(t) - N_F(t))$$

with a stable equilibrium C_F whenever $C_F = C_F(t)$ is a constant. However, it is important that these two terms are kept separate since later on we split the population into compartments. The new recruits all go to the susceptible class while the deaths are deducted proportionately from all compartments. Here, $\bar{\mu}_F = \frac{1}{365} = 0.00273$ is the death rate when the carrying capacity is reached and relates to an expected lifespan of one year. If the population is not at carrying capacity, the death rate $\mu_F(t)$ is higher than $\bar{\mu}_F$ in the case of over-capacity and lower than $\bar{\mu}_F$ in the case of under-capacity. The coefficient a_F relates to the response of the population to the changing environment (carrying capacity).

We should remark that with seasonal change of the environment, the average lifespan is much shorter than one year since the death rate can be significantly higher than $\bar{\mu}_F$ in adverse conditions (over-capacity). Irrespective of its initial size, the population of fleas reaches a stable periodical cycle within a year, as shown in Figure 3, where the seasonal amount of fleas on a 1000-strong population of each of the *Rattus* species is plotted. Here and in the sequel, we use $a_F = 0.04 - \bar{\mu}_F$.

2.3. Tick vector

Ticks of the family Ixodidae are known carriers of *Bartonella* and considered potential vectors in most areas [10,15,23,29,41,45,50]. The Ixodid tick population exhibits a three-host life cycle in which the immatures only feed on murid rodents mainly during the dry or winter months [38,55]. The adults of these ticks parasitize larger hosts such as cattle, ungulates, goats and domestic cats and dogs [38,55]. In South Africa, these fall within the genera *Rhipicephalus*, *Haemaphysalis*, *Hyalomma* and *Ixodes* of the family Ixodidae (hard ticks) [38,55]. They commonly display adult activity in the spring and summer months of the year, while larvae and nymphs are active during the autumn and winter months [38,55]. In this three-host life cycle, six-legged larvae will hatch on the ground from eggs, find a suitable host (typically a rodent) and attach for about a week. Once engorged, the larvae will drop from the host, moult on the ground and after a few days,

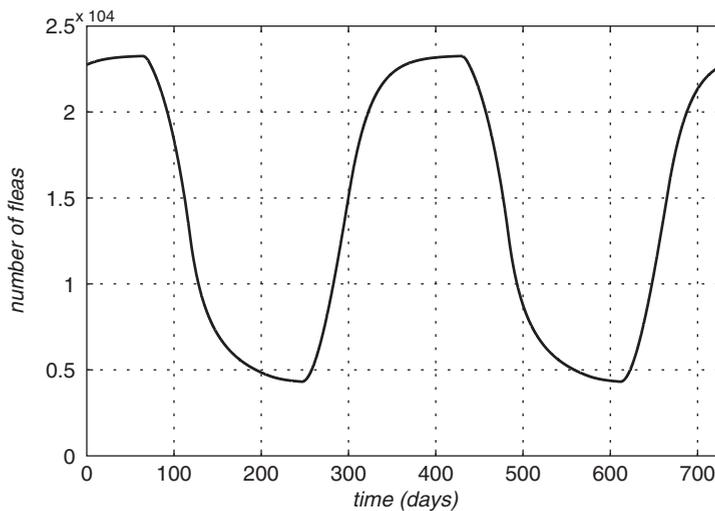


Figure 3. Flea population size variation on a 1000-strong population of each of three *Rattus* species is plotted over time.

will find a second host to attach to [38,55]. They will remain on this host for about a week, and once engorged, drop to the ground to moult to adults [38,55]. These adults will locate a larger, non-rodent host after a couple of days, attach, mate and once the female is engorged, it will drop to the ground to lay a single batch of about 2000–5000 eggs [38,55]. The female will die after oviposition, while males can remain on the host for several months, sometimes switching between individuals of the same host species [38,55].

Under natural conditions, ticks show a very pronounced periodic cycle of abundance due to their alternate adult host preference. In this case, where the nymphs specifically are being modelled, there is a marked increase of larvae and nymphs in the dry cold months in South Africa [38,55]. These stages decrease dramatically during the wet warm months of the year, which represents the dominant time for adult ticks [38,55]. Thus, we should observe a high abundance of larvae and nymphs on rodents during winter, and a low abundance in summer when adult ticks can be found in high numbers on larger mammals [38,55]. The epidemiologically relevant part of the population, namely the immature nymphs, is modelled in the same way as the fleas, but the cycle is shifted six months due to their high abundance in the dry cold months in South Africa [38,55] rather than in the summer months as for fleas. Furthermore, individuals are transferred out of the population not only due to death but also due to maturation. Hence, the rate of removal from the population is the sum of the death rate μ_T and maturation rate $\alpha_T = 0.024$, the latter reflecting a duration of the larval stage of the tick of about 42 days [38,55]. In the absence of any precise data, we take rather arbitrarily $\mu_T = 0.002$. However, due to its relatively smaller contribution to the removal rate, it is expected that the possible error in the value of μ_T does not have a significant impact.

2.4. The model

We assumed no significant difference between the level of ectoparasite infection on male and female rats [39]. Although there is evidence of increased ectoparasite infection on juvenile rats, this was assumed to be constant for the sake of simplicity [39]. Although it has been suggested that there is an age, sex and seasonal bias in the infection rates of blood-sucking arthropods with *Bartonella* [23,25], we also assumed no such bias, again, for the sake of simplicity. The

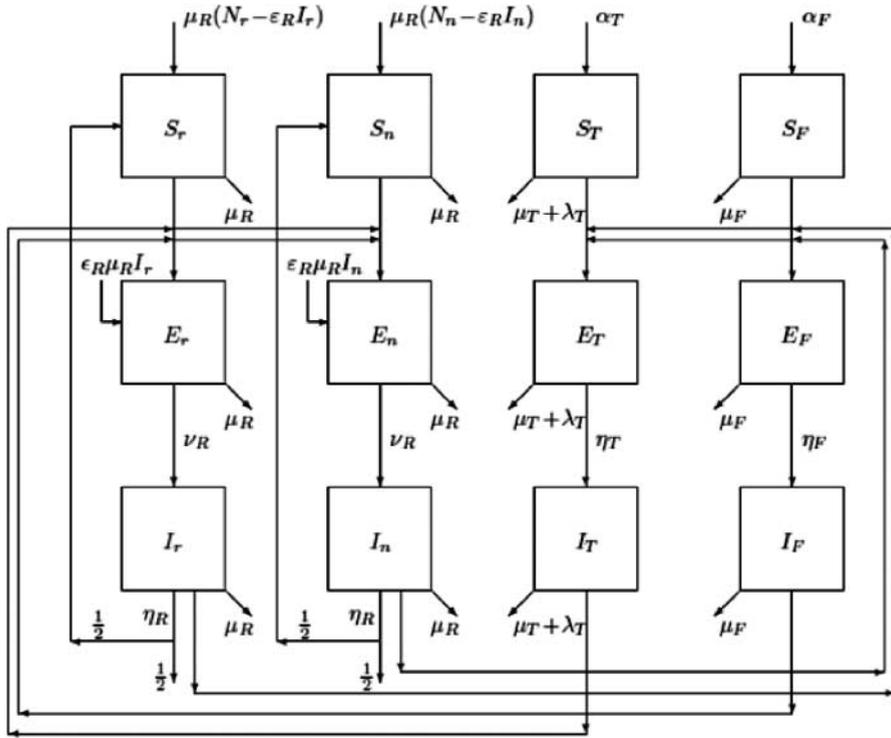


Figure 4. Compartmental structure and epidemiological flow between the compartments of *Bartonella* infections in *Rattus*.

assumption was made that vertical transmission of *Bartonella* occurs in rats, but not in the tick or flea vector [30] and that *Bartonella* does not significantly alter the death rate of either the rats or their ectoparasites [11,19,28]. The four populations are compartmentalized using the usual SEI approach with S , E and I denoting the number of susceptible, exposed (carriers not yet infective) and infective individuals, respectively. The indices denote the species (r for *R. rattus*, n for *R. norvegicus*, T for ticks and F for fleas). The compartmental structure with the epidemiological flow between the compartments is presented in Figure 4. A key issue in the modelling of diseases are the transfer rates from susceptible compartments to exposed compartments, also known as the forces of infection. In order to model these transfer rates, we apply the method of standard incidence [24]. Suppose, for simplicity that there is one host, for example, *R. rattus* and one vector, for example, flea, then the force of infection acting on the host population should be proportional to the number of fleas per rat and the prevalence of the infection among the fleas resulting in a transfer from S_r to E_r of the form

$$\sigma_F \frac{N_F}{N_r} \frac{I_F}{N_F} S_r = \sigma_F \frac{I_F}{N_r} S_r, \quad (4)$$

where the coefficient σ_F takes into account other factors, for example, the probability of infection in a single bite. We may note that this type of force of infection appears often in the modelling of mosquito-borne human diseases [18]. Alternately, the force of infection acting on the flea population is modelled differently since the carrying capacity for this population is based on the number of rat hosts available. Therefore, the number of interactions with the rat population is fixed depending on the physiological needs of the flea. Then, the force of infection is proportional only to the prevalence of the infection in the host population, that is, the transfer from S_F to E_F is

of the form

$$\theta_F \frac{I_r}{N_r} S_F. \quad (5)$$

In the more complicated situation of two host species, we apply the same approach as in Equations (4) and (5), but taking into account that the flea population is split between the two hosts in the ratio $(\xi_{Fr}N_r) : (\xi_{Fn}N_n)$. We have

$$S_r \longrightarrow E_r : \sigma_F \frac{\xi_{Fr}I_F}{\xi_{Fr}N_r + \xi_{Fn}N_n} S_r, \quad (6)$$

$$S_n \longrightarrow E_n : \sigma_F \frac{\xi_{Fn}I_F}{\xi_{Fr}N_r + \xi_{Fn}N_n} S_n, \quad (7)$$

$$S_F \longrightarrow E_F : \theta_F \frac{\xi_{Fr}I_r + \xi_{Fn}I_n}{\xi_{Fr}N_r + \xi_{Fn}N_n} S_F. \quad (8)$$

The forces of infection related to the tick population are modelled in the same way using constants σ_T and θ_T . The transfer rates from exposed to infective reflects the latent period of the infection for the respective species. The removal from each population is proportionally applied to all compartments. The recruitment in a population is placed in the respective susceptible compartment except for the host species where, due to vertical transmission, a certain proportion (ε_R) is placed in the exposed compartment. Once infective, the fleas and ticks remain so for the rest of their lives.

The rats, however, recover in 42 days and are no longer infective [30]. Rodents also acquire life-long immunity against the particular strain of *Bartonella* they have been infected with. Since there are two dominant types of *Bartonella* in South African *Rattus* (a third type has only a marginal distribution) [13,42], a rat which is recovered from one infection can be infected again with the other *Bartonella* species. Instead of complicating the model, we assume that on the recovered, there is a force of infection which is 1/2 of the original one or alternatively that 1/2 of the recovered return to the susceptible population. A compartment for the recovered is not explicitly included since it does not interact with any other compartment. However, the number of recovered can always be obtained as $N_r - S_r - E_r - I_r$ or $N_n - S_n - E_n - I_n$ for each one of the host species. A complete list of the parameters, short description and values are given in Table 1.

Table 1. Model parameters and baseline values for *Bartonella* in *Rattus*.

	Description	Value	Reference
<i>R. rattus</i> (5%), <i>R. norvegicus</i> (24%)			
μ_R	Birth/death rate	0.01324	
ν_R	Transfer rate to infective	0.143	
ε_R	Rate of vertical transmission	0.48	[31]
η_R	Recovery rate	0.0238	[31]
<i>Ticks</i> (4.4%)			
$\bar{\mu}_T$	Birth/death rate at carrying capacity	0.002	
ν_T	Transfer rate to infective	0.0714	
λ_T	Transfer rate to adult	0.024	
ξ_{Tr}	Average load on <i>R. rattus</i>	0.2	[29]
ξ_{Tn}	Average load on <i>R. norvegicus</i>	0.28	$\xi_{Tr} \times 1.4$ (see above)
<i>Fleas</i> (61%)			
$\bar{\mu}_F$	Birth/death rate at carrying capacity	0.00273	
ν_F	Transfer rate to infective	0.2	
ξ_{Fr}	Average load on <i>R. rattus</i>	8.8	[21,49]
ξ_{Fn}	Average load on <i>R. norvegicus</i>	12.37	[21,49]

In our search for biological data, we aimed for values obtained from peer-reviewed studies where there was evidence of co-habitation of *R. rattus* and *R. norvegicus*. Flea infestation data were obtained from [21,49] where *R. rattus* and *R. norvegicus* co-occur. Values in these studies ranged from *R. norvegicus* = 12.14–12.6 and *R.rattus* = 7.18–10.42 fleas per rat. The average values were used to determine the difference in infestation rates between the two *Rattus* species, which amounted to a factor of 1.4. The average number of ticks found on *R. rattus*, was obtained from [3,29,54] and corresponds to 0.2 ticks for every rat collected. As no biological data are available for tick infestation rates in *R. norvegicus*, we therefore extrapolated the number of ticks per *R. norvegicus* based on the factor of difference between flea infestation numbers in *R. rattus* and *R. norvegicus*. On this basis, the calculated tick infestation data for *R. norvegicus* was calculated to be 0.28 (1.4×0.2).

Preliminary prevalence estimates of *Rattus*–*Bartonella* infections in South Africa concur with prevalence estimates for these two species found in the literature, when one considers those studies that investigated both species using the same methodology and for which 10 or more animals were screened, viz. [13,19,26,42]. Together, the preliminary South African studies yield prevalence estimates of 24% for *R. norvegicus* and 5% for *R. rattus* (i.e. nearly a five-fold difference in prevalence between the two host species). These values were used in this model and were obtained for co-occurring species in South Africa [13,42]. Infection rates of ticks and fleas were obtained as far possible from studies that removed these ectoparasites from rats, and where possible, were limited to studies where the two *Rattus* species co-occur. This produces an infection estimate of 4.4% [29] and 61% for Xenopsylid fleas [10].

Bartonella seems to have little effect on the mortality rates of rodents and several authors have suggested infections may be maintained in the population by vertical transmission from mother to offspring in the womb [11,19,28]. Vertical transmission was, therefore, included in our model, and the parameter value based on the study by Kosoy *et al.* [31], where 48% of rodent neonates were shown to be infected with *Bartonella* through their mother before birth. We assume that at birth, the infection is at the start of its progression. Hence, the affected neonates are place in the exposed compartment of infected but not yet infective individuals. Experimental infection done by Kosoy *et al.* [31] shows that *bartonellae* can be detected from the blood of rodents after seven days of incubation. Using this value, we obtain a probability of $\nu_R = 1/7 = 0.143$ for a rat becoming infective. The probability of an exposed tick becoming infective is calculated based on the same principle as the corresponding parameter for rats. The incubation period of the bacteria in ticks, unfortunately, has no experimental substantiation.

For the purpose of this model however, we have considered the life cycle of these ticks. These ticks feed on a single host for a week at a time, and only after molting will attach to a new host and have the ability to spread the disease [38,55]. Although the incubation period is likely to be much shorter than that in rats (due to lack of immune response), the tick can only transmit the pathogen after about two weeks due to its method of feeding. From this, the actual incubation time in the ticks is not important for our model, and we can assume an ‘incubation period’ of 14 days before a tick becomes ‘infective’. This results in a probability of $\nu_T = 1/14 = 0.0714$. There is also no scientific data available for the time, it takes for *Bartonella* to incubate in a flea, that is, the time it takes for an exposed flea to become infective. This parameter was, therefore, estimated and tested with a sensitivity analysis.

The mathematical model describing the flow in the diagram on Figure 4 is the following system of 12 differential equations defining a dynamical system on the non-negative cone of \mathbb{R}^{12} :

$$\frac{dS_r}{dt} = \mu_R(N_r - S_r - \varepsilon_R I_r) + \frac{1}{2} \eta_R I_r - \left(\frac{\sigma_T \xi_{Tr} I_T}{\xi_{Tr} N_r + \xi_{Tn} N_n} + \frac{\sigma_F \xi_{Fr} I_F}{\xi_{Fr} N_r + \xi_{Fn} N_n} \right) S_r, \quad (9)$$

$$\frac{dE_r}{dt} = \left(\frac{\sigma_T \xi_{Tr} I_T}{\xi_{Tr} N_r + \xi_{Tn} N_n} + \frac{\sigma_F \xi_{Fr} I_F}{\xi_{Fr} N_r + \xi_{Fn} N_n} \right) S_r - (\nu_R + \mu_R) E_r + \varepsilon_R \mu_R I_r, \quad (10)$$

$$\frac{dI_r}{dt} = \nu_R E_r - (\eta_R + \mu_R) I_r, \quad (11)$$

$$\frac{dS_n}{dt} = \mu_R (N_n - S_n - \varepsilon_R I_n) + \frac{1}{2} \eta_R I_n - \left(\frac{\sigma_T \xi_{Tn} I_T}{\xi_{Tr} N_r + \xi_{Tn} N_n} + \frac{\sigma_F \xi_{Fn} I_F}{\xi_{Fr} N_r + \xi_{Fn} N_n} \right) S_n, \quad (12)$$

$$\frac{dE_n}{dt} = \left(\frac{\sigma_T \xi_{Tr} I_T}{\xi_{Tr} N_r + \xi_{Tn} N_n} + \frac{\sigma_F \xi_{Fn} I_F}{\xi_{Fr} N_r + \xi_{Fn} N_n} \right) S_n - (\nu_R + \mu_R) E_n + \varepsilon_R \mu_R I_n, \quad (13)$$

$$\frac{dI_n}{dt} = \nu_R E_n - (\eta_R + \mu_R) I_n, \quad (14)$$

$$\frac{dS_T}{dt} = \alpha_T(t) - \theta_T \frac{\xi_{Tr} I_r + \xi_{Tn} I_n}{\xi_{Tr} N_r + \xi_{Tn} N_n} S_T - (\lambda_T + \mu_T(t)) S_T, \quad (15)$$

$$\frac{dE_T}{dt} = \theta_T \frac{\xi_{Tr} I_r + \xi_{Tn} I_n}{\xi_{Tr} N_r + \xi_{Tn} N_n} S_T - (\lambda_T + \nu_T + \mu_T(t)) E_T, \quad (16)$$

$$\frac{dI_T}{dt} = \nu_T E_T - (\lambda_T + \mu_T(t)) I_T, \quad (17)$$

$$\frac{dS_F}{dt} = \alpha_F(t) - \theta_F \frac{\xi_{Fr} I_r + \xi_{Fn} I_n}{\xi_{Fr} N_r + \xi_{Fn} N_n} S_F - \mu_F(t) S_F, \quad (18)$$

$$\frac{dE_F}{dt} = \theta_F \frac{\xi_{Fr} I_r + \xi_{Fn} I_n}{\xi_{Fr} N_r + \xi_{Fn} N_n} S_F - (\nu_F + \mu_F(t)) E_F, \quad (19)$$

$$\frac{dI_F}{dt} = \nu_F E_F - \mu_F(t) I_F. \quad (20)$$

3. Numerical simulations

A numerical solution of the system (9)–(20) can be obtained with any prescribed accuracy through a large variety of methods. We use the Matlab procedure `ode45` which implements a fourth-order

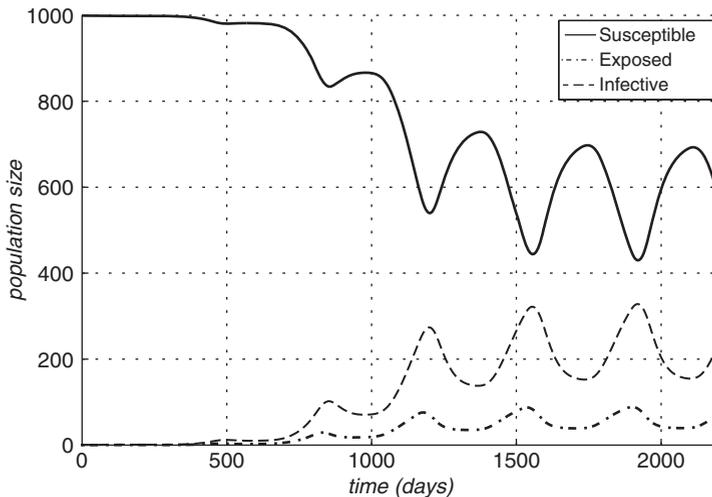


Figure 5. Changes in compartment sizes over time for *Rattus rattus*: (a) Case A: in an infection-free environment, the infection is introduced through a single infected individual and (b) Case B: both host and vector populations are initially completely infective.

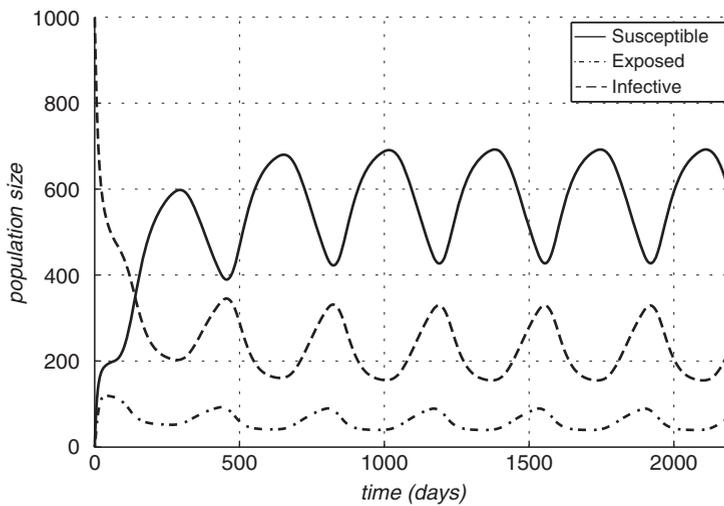


Figure 6. Changes in compartment sizes over time for *R. norvegicus*: (a) Case A: in an infection-free environment, the infection is introduced through a single infected individual and (b) Case B: both host and vector populations are initially completely infective.

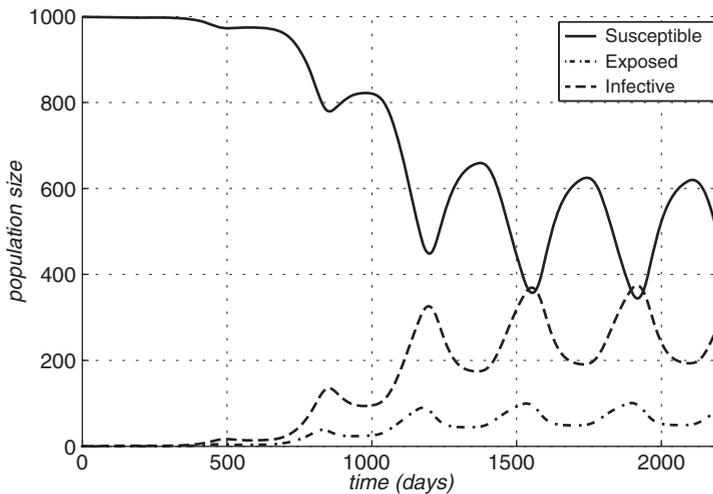


Figure 7. *Bartonella* infection prevalence rates over time for two host species, *R. rattus* and *R. norvegicus* and two vectors, Ixodid ticks and Xenopsylid fleas: (a) Case A: in an infection-free environment, the infection is introduced through a single infected individual and (b) Case B: both host and vector populations are initially completely infective.

Runge–Kutta method with automatic step-size adjustment. Note that at this stage, we do not know the coefficients σ_T , σ_F , θ_T and θ_F of the forces of infection. Nevertheless, numerical simulations indicate that for all values of these coefficient, in some realistic range, the solution of Equations (9)–(20) approaches a limit cycle (periodic solution) as time increases. Typical results are shown in Figures 5–7 which are plotted from the numerical solutions in two extreme cases:

- (A) In an infection-free environment, the infection is introduced through a single infected individual in each one of the *Rattus* populations.
- (B) Both host and vector populations are initially completely infective.

In both cases, we consider a 1000-strong population of each of the *Rattus* hosts and the values of the coefficients of the forces of infection are arbitrarily set to 0.01. We observe that in 3–4 years, the solution sets into a periodic pattern which is eventually the same in both cases.

Due to the arbitrary values of $\sigma_T, \sigma_F, \theta_T$ and θ_F in this simulation, one cannot claim any strong biological relevance of the concrete values of the solution. However, the important point here is their qualitative behaviour. The empirical evidence suggests that for any set of values of $\sigma_T, \sigma_F, \theta_T, \theta_F$ and initial population sizes, the model (9)–(20) admits a stable limit cycle so that for any non-zero initial infection prevalence, the respective solution of Equations (9)–(20) approaches this limit cycle.

4. Determining the unknown parameters

The parameters $\sigma_T, \sigma_F, \theta_T$ and θ_F reflect unknown characteristics of the infection transmission such as the probability of transmission to or from the host over a single blood meal. Since currently there are no data from which the values of these parameters can be calculated directly, we use other observable data, namely the average infection prevalence in the two host species, *R. rattus* and *R. norvegicus* and two vectors, Ixodid ticks and Xenopsylid fleas (see Table 2).

For simplicity in the notation, let q be a vector of the unknown parameters and let y be the vector of the state variables, that is $q = (\sigma_T, \sigma_F, \theta_T, \theta_F)'$ and $y = (S_r, E_r, I_r, S_n, E_n, I_n, S_T, E_T, I_T, S_F, E_F, I_F)'$. Then the system (9)–(20) can be written in the form

$$\frac{dy}{dt} = g(t, q, y), \tag{21}$$

where function g is defined through the right-hand side of Equations (9)–(20). As it was demonstrated, for every value of q after some time period, which we denote here by T , the solution $y = y(q, t)$ of Equations (21) settles at a periodic pattern. Since there is little seasonal data for infection prevalence, we calculate the average infection prevalence over one year:

$$\begin{aligned} \tilde{p}_r(q) &= \frac{1}{365} \int_T^{T+365} \frac{y_3(q, t)}{N_r} dt, \\ \tilde{p}_n(q) &= \frac{1}{365} \int_T^{T+365} \frac{y_6(q, t)}{N_n} dt, \\ \tilde{p}_T(q) &= \frac{1}{365} \int_T^{T+365} \frac{y_9(q, t)}{y_7(q, t) + y_8(q, t) + y_9(q, t)} dt, \\ \tilde{p}_F(q) &= \frac{1}{365} \int_T^{T+365} \frac{y_{12}(q, t)}{y_{10}(q, t) + y_{11}(q, t) + y_{12}(q, t)} dt. \end{aligned}$$

Then, the most suitable values of the unknown parameters are determined via an optimization problem: find a value of q which minimizes the function

$$h(q) = (\tilde{p}_r(q) - p_r)^2 + (\tilde{p}_n(q) - p_n)^2 + (\tilde{p}_F(q) - p_F)^2 + (\tilde{p}_T(q) - p_T)^2.$$

Table 2. Observed average infection prevalence for two *Rattus* host species and two ectoparasite vectors.

	<i>R. rattus</i>	<i>R. norvegicus</i>	Ticks	Fleas
Notation	p_r	p_n	p_T	p_F
Mean prevalence	5%	24%	4.4%	61%

Table 3. Optimal coefficients and model prevalence rates.

<i>Coefficients</i>	
σ_T	0.00375579689
σ_F	0.00219432281
θ_T	0.01225593860
θ_F	0.06451837275
<i>Infection prevalence</i>	
\tilde{p}_R	13.4%
\tilde{p}_N	16.7%
\tilde{p}_T	4.5%
\tilde{p}_F	61.0%

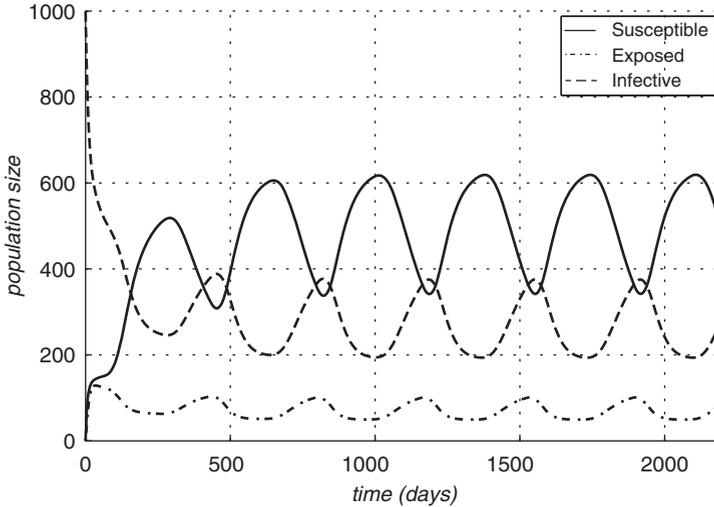


Figure 8. Prevalence rates over time for optimal value of parameters estimated for *Bartonella* infections in *Rattus* and two vectors (Ixodid ticks and Xenopsylid fleas).

Applying a Monte Carlo approach, we obtain the optimal values for the coefficients given in Table 3. The infection prevalence rates for the two host (*R. rattus* and *R. norvegicus*) species and two vectors (Ixodid ticks and Xenopsylid fleas) are plotted against time in Figure 8.

One can observe the high oscillations in the infection prevalence in the flea population, oscillations of lesser amplitude in the infection prevalence of the rodent populations and almost no oscillation in the infection prevalence of the ticks (see Figure 8). This leads to the conclusion that the fleas are the primary vector in the sylvatic cycle of *Bartonella*. Similar conclusions can also be obtained by calculating the forces of infection for the obtained values of the parameters. However, it should be noted that this model does not explain the large difference in the observed infection prevalence between *R. rattus* and *R. norvegicus*. While the average infection prevalence of the two host species combined is captured in the model (14.5% average in data versus 15% average for model), the difference in the infection prevalence between the two host species captured by the models is only 3.3% compared to the observed difference between the two of nearly 19%. Some of the difference can be explained when we assume that the populations of the ectoparasites living on the two host species are to some extent separated. When modelled so, this leads to higher prevalence rates of the ectoparasite in *R. norvegicus* than the corresponding rates of those on *R. rattus*. The exact values of prevalence rates for the same values of the parameters are given in

Table 4. Prevalence rates in the model of two *Rattus* hosts with disjunct vector populations.

Infection prevalence	
\tilde{p}_R	12.6%
\tilde{p}_N	17.2%
\tilde{p}_T	4.5%
\tilde{p}_F	60.5%

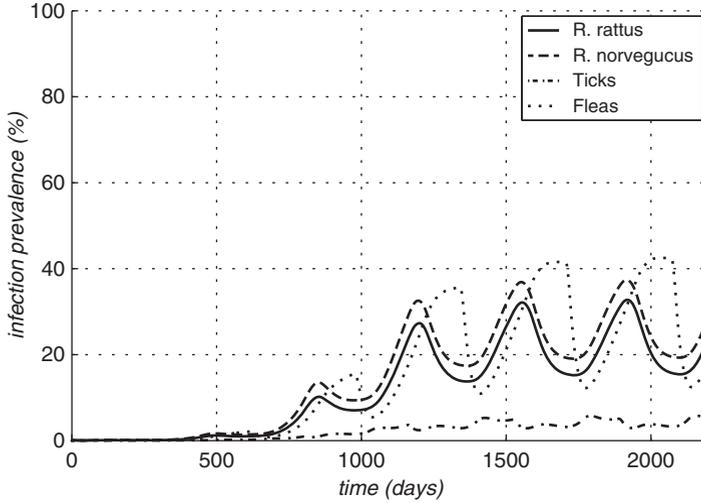


Figure 9. *Bartonella* infection prevalence rates for (a) *R. rattus* and (b) *R. norvegicus* and their respective ectoparasite populations as simulated by the mathematical epidemiological model.

Table 4 with the respective plots against time presented in Figure 9. The difference of 4.6% shown by this version of the model is still much smaller than the observed difference in infection rates.

This raises the question of the validity of the assumption in the model that the two rodent species are similar enough physiologically and behaviourally, that the probability of infection and the durations of exposure and recovery are the same. While indeed this is a fundamental assumption in the model, we need to note that its construction is based on little biological data. Verifying the optimal values of the coefficients obtained here would be a difficult task but the model gives predictions which may be easier to check experimentally. These include, for example, the periodicity of the infection prevalence in all host and vector species but more importantly in the fleas. If this periodicity is confirmed, then the relevant data will provide more complete information for refining the model and thus increasing the reliability of predictions.

Further research can also be guided by the sensitivity of the observable variables, namely the infection prevalences, on the parameters of the model. We characterize the sensitivity of the prevalence rates in terms of sensitivity indices. Let us recall that the sensitivity index of a variable u on a parameter q is defined as the relative change of u over the relative change of q , that is, $(\Delta u/u) \div (\Delta q/q) = q\Delta u/u\Delta q$. Naturally, the change of q is assumed to be small. If u is a differentiable function of q then letting $\Delta q \rightarrow 0$ the index is simply $(q/u)(du/dq) = \partial(\ln u)/\partial(\ln q)$. The sensitivity indices of the four infection prevalence rates with respect to the parameters of the model at their baseline values used thus far, are given in Table 5.

Values with the largest impact on the parameters of the model are highlighted as: (1) the recovery rate of the rats from *Bartonella* infection, (2) the flea infestation levels on each rat species and

Table 5. Sensitivity of the infection prevalence of *Bartonella* in *Rattus* on the model parameters at their baseline values.

Par	Value	\tilde{p}_r	\tilde{p}_n	\tilde{p}_T	\tilde{p}_F
μ_R	0.01324	-0.1715	-0.1146	-0.1315	-0.0486
ν_R	0.143	0.1563	0.1513	0.1337	0.0589
ε_R	0.48	0.1762	0.1564	0.1612	0.0561
η_R	0.0238	-0.9280	-0.8771	-0.8606	-0.3053
$\tilde{\mu}_T$	0.002	-0.0004	-0.0003	-0.0803	-0.0002
ν_T	0.0714	0.0007	0.0007	0.2729	-0.00001
λ_F	0.024	-0.0038	-0.0034	-0.9631	-0.0012
ξ_{Tr}	0.2	0.0029	0.0003	-0.0490	0.0005
ξ_{Tn}	0.28	0.0010	0.0033	0.0535	0.0008
$\tilde{\mu}_F$	0.00273	-0.1501	-0.1335	-0.1346	-0.2059
ν_F	0.2	0.0384	0.0336	0.0297	0.0411
ξ_{Fr}	8.8	0.7541	0.0705	0.2995	0.0972
ξ_{Fn}	12.37	0.1903	0.7645	0.5230	0.2258
σ_T	0.00375579689	0.0035	0.0032	0.0037	0.0012
σ_F	0.00219432281	0.9449	0.8352	0.8227	0.3231
θ_T	0.01225593860	0.0033	0.0031	0.9414	0.0011
θ_F	0.06451837275	0.3857	0.3367	0.3050	0.4761

(3) the force of infection from fleas to rats (Table 5). These should be investigated biologically to confirm their importance.

5. Discussion

Understanding the dynamics of zoonotic diseases provides the ability to put appropriate control measures in effect that will limit the potential for transmission at the rodent–human interface. Therefore, the large difference in *Bartonella* infection rates between two co-occurring commensal *Rattus* species in South Africa is an interesting phenomenon that is of veterinary and medical interest. Differences in the ectoparasite infestation rates (mainly fleas) between *R. rattus* and *R. norvegicus* has been proposed and observed for many years [21], and we would assume higher ectoparasite (vector) infestation rates would logically lead to higher *Bartonella* infection rates in *R. norvegicus*, as is observed biologically. Due to the ease of mathematical versus biological experimentation, this model was developed in order to assess if the proposed ectoparasite variation could fully explain the higher *Bartonella* infection prevalence in South African *R. norvegicus*. Construction of the model was based on two invasive *Rattus* species occurring in South Africa, and available and relevant peer-reviewed literature on the pathogen and vertebrate host.

The model revealed a striking need for more detailed biological research on *Bartonella* infections in *Rattus* and their role as carriers of this bacteria. Available data on the tick indices of rats, incubation periods of *Bartonella* in both vector and host as well as the forces of infection are for the most part not known. The likelihood of acquiring *Bartonella* per vector bite for the vector or the host has also not been investigated, as has the probability of recovering from *Bartonella* infection for the host. As mentioned before, data concerning the forces of infection (the likelihood of transmitting *Bartonella* per tick bite/feeding episode) is also needed. The model, however, allowed several interesting conclusions to be drawn regarding the epidemiological cycle of *Bartonella* in *Rattus*.

From the model, one can observe the importance of the flea vector of *Bartonella* due to the high oscillations in the infection prevalence in this ectoparasite population (see Figure 8) and from the results of the sensitivity analysis (Table 5). The sensitivity analysis indicates that the number of fleas per rat as well as the force of infection from these fleas are important in determining the

infection rates of the rats (Table 5). This leads to the conclusion that the fleas are the primary vector in the infectious cycle of *Bartonella* within the setting of this model, possibly due to their high mobility. The contribution of fleas to the infection of *Rattus* with *Bartonella* should, therefore, be investigated further, especially since fleas have been implicated in the zoonotic spread of other diseases such as plague. Furthermore, the sensitivity analysis also indicated the importance of the rate of recovery of the rats from *Bartonella* infection. Logically, the faster the recovery rate, the more resistant the population will be to high infection levels of *Bartonella*, since individuals recover relatively quickly. In our model, however, the rates of recovery were assumed to be constant for the two rat species due to their assumed similar biologies. Whether they in fact recover at different rates will have to be investigated and may provide a better understanding of the differences in infection prevalences between the two rat species. As expected, the model strongly depends on the coefficients of the forces of infection. However, our result is that by varying these coefficients alone, the model prevalence in the *Rattus* species does not approach the observed biological values. Table 5 also reveals strong dependence of the prevalence rates on the recovery rate of *Rattus*. This suggests further investigation into the infectiveness period for each species because any difference between the two species in this regard is likely to explain easily the difference in the prevalence rate. Differential susceptibility of rodent hosts to *Bartonella* infection can also not be overlooked.

Difference in ectoparasite infestation rates between the two *Rattus* species did not explain the observed difference in *Bartonella* infection prevalence between *R. rattus* and *R. norvegicus*. With the assumed shared ectoparasite population between the two rat populations, the maximal difference in infection prevalence that could be obtained with the model was about 3% compared to the observed 19%. When the ectoparasite populations are assumed to be disjunct, due to *R. rattus* avoiding *R. norvegicus*, the maximal difference in infection prevalence that could be obtained was almost 5%, which does explain all the variation we see in nature (see Table 4 and Figure 8).

There are thus additional factors involved in the infectious cycle of *Bartonella* in rodents that are not obvious. These may include a variety of factors such as the physiology and behaviour of the host and vector or presence of other competing bacteria [47]. Most importantly, this emphasizes the need for more detailed and extensive research on this, and other emerging zoonotic pathogens, and sets the foundation for directing future research.

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