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A model of Leptospirosis infection in an African rodent to determine risk to humans: Seasonal fluctuations and the impact of rodent control

J. Holt [a,*], S. Davis [b], H. Leirs [b,c]

[a] *Natural Resources Institute, University of Greenwich, Central Avenue, Chatham Maritime, Chatham, Kent ME4 4TB, UK*
[b] *Evolutionary Biology Group, Department of Biology, University of Antwerp, Groenenborgerlaan 171, B-2020 Antwerp, Belgium*
[c] *Danish Institute for Agricultural Sciences, Department of Integrated Pest Management, Danish Pest Infestation Laboratory, Skovbrynet 14, DK-2800 Kongens Lyngby, Denmark*

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Abstract

Human leptospirosis (*Leptospira* spp. infection) is a worldwide public health problem that is of greatest concern for humid tropical and subtropical regions. The magnitude of the problem in these areas is larger because of the climatic and environmental conditions the bacterium face outside their hosts but also because of the frequency of contacts between people and sources of infection. Rodents are thought to play the most important role in the transmission of human leptospirosis. We here model the dynamics of infection in an African rodent (*Mastomys natalensis*) that is thought to be the principal source of infection in parts of Tanzania. Our model, representing the climatic conditions in central Tanzania, suggests a strong seasonality in the force of infection on humans with a peak in the abundance of infectious mice between January and April in agricultural environments. In urban areas the dynamics are predicted to be more stable and the period of high numbers of infectious animals runs from February to July. Our results indicate that removal of animals by trapping rather than reducing the suitability of the environment for rodents will have the greater impact on reducing human cases of leptospirosis.

Keywords: Zoonosis; *Mastomys natalensis*; Epidemiology; Population dynamics; Mathematical model; Tanzania

1. Introduction

Leptospirosis affects all mammals and can spread between domestic pets, livestock, wild animals and humans. In Africa, it is thought that commensal rodents are the most important source of transmission to humans (WHO Leptospirosis Manual, 2003; Dalu and Feresu, 1997; Machangu et al., 1997). Leptospirosis infection in humans presents with symptoms that are similar to that of other better known parasitic, viral and bacterial infections such as malaria, Rift valley fever and brucellosis. Hence it is frequently misdiagnosed and its impact on African communities is largely undocumented.

Perhaps with the exception of Caley and Ramsey (2001), who modelled transmission of letpospirosis in brushtail possums (*Trichosurus vulpecula*), there are no published mathematical models for the spread and maintenance of leptospirosis infection in wildlife. This is not too surprising since so little is understood about

* Corresponding author. Tel.: +44 1634 883225; fax: +44 1634 883379.
E-mail address: j.holt@gre.ac.uk (J. Holt).

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how it maintains itself in natural populations; whether there is competition between serovars, whether infection or immunity is passed from mother to offspring, what determines survival of leptospires in the environment, and whether animals recover and become immune.

Mathematical models of the type used here (a deterministic model consisting of a set of differential equations) have a long tradition in the study of wildlife diseases (for reviews see Heesterbeek and Roberts, 1995; Barlow, 1995; Swinton et al., 2002). For the majority of models the primary motivation is to predict the impact of intervention by either culling or vaccination (e.g. Roberts and Aubert, 1995) and a universal motivation is a better understanding of the dynamics of infection (e.g. Sauvage et al., 2003).

Here we present a basic model for the dynamics of leptospirosis infection in a common African rodent, the multimammate mouse (*Mastomys natalensis*). Though similar to other models in the literature, the epidemiological characteristics of leptospirosis and the life history of *M. natalensis* have resulted in a model of unique form. The multimammate mouse has long been recognised as a serious agricultural pest (Fiedler, 1988; Leirs et al., 1996) and is hence well studied (Leirs et al., 1990, 1993). The basis for our model is a population dynamics model developed by Leirs et al. (1997) for *Mastomys* populations in maize fields in Tanzania. In crop habitat *M. natalensis* populations undergo predictable seasonal fluctuations but they may also respond to high rainfall and can irrupt to very high densities. Commensal rodent populations are likely to be more stable and we also explore model results when the infection circulates in a population of relatively constant abundance. Seasonality in leptospirosis risk and the potential effects of management interventions were investigated in model simulations.

2. Materials and methods

Our model is a system of differential equations (Appendix A) representing both the changes in total numbers of rodents and in the numbers of rodents carrying leptospirosis. The rodent population is divided into three age classes (juveniles, sub-adults and adults), each of which is further divided into two disease classes (susceptible and infectious). It is assumed in the model that once infected, individuals are chronically infected for their lifetime, and that there is no delay between becoming infected and being infectious. In the absence of evidence to the contrary, we have chosen to ignore the possible occurrence of recovery.

The model includes three potential routes of transmission for leptospirosis; from mother to offspring, direct (sexual) contact, and via the external environment (WHO Leptospirosis Manual, 2003). The relative importance of these routes is unknown and this uncertainty is represented in the model by including parameters that allow their importance to be varied. Direct transmission via sexual contact is modelled as frequency-dependent (Begon et al., 2002) as it is thought that for multimammate mice the frequency of sexual contact is unaffected by population abundance.

There are several differences between the three rodent age classes. Only the adult age-class is able to reproduce and hence transmission via sexual contact only applies to this age-class. Juveniles are generally confined to the nest so infectious juveniles are assumed not to shed leptospires into the environment and susceptible juveniles not to be exposed to free-living leptospires. Juveniles become sub-adults after 3–4 weeks but maturation rate of sub-adults has been found to be sensitive to the amount of rainfall in the previous month as well as the abundance of adults (Leirs et al., 1997). In the model, adult abundance provides a source of density-dependence which essentially determines a carrying capacity and prevents the population from reaching unreasonably high numbers.

A seventh differential equation represents the abundance of leptospires in the external environment. Free-living leptospires are shed in the urine of infectious animals and though the period they survive depends very much on whether they are shed into water or on dry ground, a mean survival time is assumed in the model. The rate at which susceptible sub-adults and adults become infected via free-living leptospires is expected to increase with the abundance of leptospires in the external environment, described by a simple non-linear term so that eventually additional free-living leptospires have a negligible effect on the rate of transmission.

The parameter values associated with *Mastomys* population dynamics can be estimated accurately and seasonal variation in these parameters is also well understood (Leirs et al., 1997). In contrast, there is little information about the leptospire parameters, especially the infection rates, ν_i, and mortality of free-living leptospires, μ. In the absence of directly relevant data, order of magnitude estimates were chosen for the epidemiological parameters (Table 1). It appears that Leptospirosis fails to persist in rodent populations in the absence of an environmental infection source (R. Hartskeerl, personal communication) and indirect transmission, i.e. via free-living leptospires shed by infectious hosts into surface water, has usually been assumed to be the most important transmission route (Ward, 2002; Meites et al., 2004).

Table 1
Parameter values used in the simulations

Parameter	Symbol	Value	Units	Source
Per capita birth rate	β	0.28 or 0 variable; 0.12 constant	day^{-1}	Leirs et al. (1997)
Number of leptospires at which transmission rate from the environment is $0.5\nu_3$	h	10^6	ha^{-1}	Estimated[a]
Shape-parameter for density-dependence in maturation of sub-adults	c	0.04	Dimensionless	Estimated from Leirs et al. (1997)
Leptospires shed per day per infected individual	k	10^3	day^{-1}	Estimated[a]
Mortality rate of leptospires in the environment	μ	0.2 or 0.05 variable; 0.1 constant	day^{-1}	Estimated[a]
Maturation rate of juveniles	Ψ_0	0.04	day^{-1}	Leirs et al. (1997)
Maturation rate of sub-adults	Ψ_1	0.01	day^{-1}	Leirs et al. (1997)
Mortality of juveniles	s_0	0.01	day^{-1}	Leirs et al. (1997)
Mortality of sub-adults and adults	s_1	0.013	day^{-1}	Leirs et al. (1997)
Proportion of pups infected from suckling	ν_1	0.01	day^{-1}	R. Hartskeerl (personal communication)
Transmission co-efficient for sexual transmission	ν_2	0.01	day^{-1}	R. Hartskeerl (personal communication)
Transmission via the environment	ν_3	0.005	day^{-1}	R. Hartskeerl (personal communication)

[a] Estimation of epidemiological parameters was informed by R. Hartskeerl (personal communication), but no basis existed for an accurate quantification.

How seasonality in rainfall and other climatic variables affects free-living leptospires may be complex. In the wet season, leptospire survival was expected to be better, as moisture and humidity are greater and water bodies would usually be fresher and cleaner. In the dry season, initial leptospire survival is likely to be poor as most rodent urine would be shed on dry ground. Water quality would also be expected to be poorer with an additional negative influence on leptospire survival (R. Hartskeerl, personal communication). We have ignored the potential for seasonal effects on leptospire survival and the associated infection rate to be more complex, e.g. shedding of leptospires in the dry-season into water bodies may be high because animals will visit and contaminate those few remaining.

As well as analysis with constant parameter values (see Table 1), simulations were carried out in which seasonal cycles were incorporated into the *Mastomys*/leptospirosis model. These were introduced with a switch in both rodent reproduction and leptospire survival. All other parameters remained constant. The reproduction period (based on field data) begins in mid June and continues until mid October and corresponds to the period when the amount of food available for rodents is high. The survival of leptospires in the environment was assumed to depend on the period of the rainy season, mortality being lower in wet conditions and higher in dry conditions. The wet season was assumed to last from the beginning of October–May. A time lag was assumed such that mean leptospire survival was assumed to be higher (20 days = 1/0.05) between mid November and early July and lower (5 days = 1/0.2) at other times (Table 1). Although it is possible for leptospires to survive in the environment for several months (R. Hartskeerl, personal communication) it is likely that on average leptospires survive for a much shorter time.

Sensitivity analysis was carried out by examining the proportional change in model variables which resulted from a given proportional change in a parameter value. This is termed elasticity (De Kroon et al., 1986), defined by $e_a = (a/\lambda)(d\lambda/da)$ where a is the parameter and λ is the variable of interest. Following the example of Sauvage et al., 2003, a $\pm$ 10% change in the parameter value was used. Model variables were abundance of leptospires in the environment, abundance of rodents and leptospirosis prevalence in rodents. Elasticity analysis was carried out on both the constant and seasonal versions of the model, in the latter cases recording the maximum value of the variable over the seasonal cycle.

3. Results

Commensal rodent populations may be relatively stable, but this is not so for rodents in agricultural environments. Indeed not only the rodent populations but the abundance of leptospires in the environment may exhibit

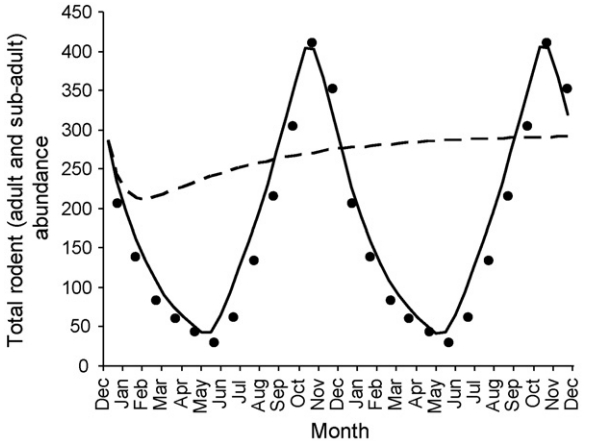

Fig. 1. Annual cycle of *Mastomys* number ha^{-1} based on a 10-year mean calculated from data published in Leirs et al., 1997 ●. Model results where rodent reproduction is seasonal (rural situation) — and continuous - - - - - (possible urban situation).

a seasonal cycle. A good fit of the model to the seasonal cycle of *M. natalensis* abundance was obtained when the reproductive rate was 0.28 per day between mid June and mid October and 0 otherwise (Fig. 1).

The numbers of leptospirosis-infected rodents and the abundance of leptospires in the environment are both potential indicators of risk of leptospirosis infection to humans. When neither rodent population processes nor leptospire epidemiology exhibited seasonal variation, then both disease prevalence in the rodent population and leptospire concentration in the environment reached constant values after a short time, the model being asymptotically stable with these parameter values. Non-juvenile rodent abundance stabilized at approximately 300 ha^{-1} (Fig. 1) and leptospirosis prevalence at 8.2%. Different patterns were found when either or both were seasonal. In the absence of any seasonal variation in leptospire survival in the environment, leptospire abundance simply tracked the seasonal cycle of the infected rodents (Fig. 2a) which itself followed the cycle of total rodent abundance with a lag of approximately two months (Fig. 1). In this situation therefore, the period of peak infection risk to humans occurred about two months after the seasonal peak in rodent abundance. Leptospirosis prevalence in the rodents varied between 2.5% and 19% over the course of the year.

Fig. 2b represents a more urban situation where rodent reproduction occurs continuously. In the absence of any seasonal variation in rodent reproduction, a constant (non-juvenile) rodent population of approximately 300 ha^{-1} was maintained (Fig. 1). Infected rodent numbers varied between approximately 30 and 50, prevalence therefore being 10–17%, and in this situation the cycle was driven by seasonal variation in leptospire survival. The cycle in the number of infected rodents followed that of leptospires in the environment. The constant rodent population allowed both a much higher abundance of infected rodents and environmental leptospires to persist throughout the year but with particular periods of high Leptospirosis risk between February and July, a rather different situation from that where rodent population dynamics are seasonal. In this urban situation, the degree to which infected rodent numbers fluctuated over the annual cycle was dependent on the infection relationship; if h was increased, fewer leptospires were required to achieve the same rate of infection and for sufficiently high values, $h > 10^5$ approximately, leptospires remain effectively in excess throughout the year so that the rate of infection was near-constant.

When both rodent reproduction and leptospire survival exhibited seasonal variation, the combined effect of the two cycles was to create a period of high leptospirosis risk to humans between January and April (Fig. 2c). Both infected rodent and environmental leptospire numbers increased sharply following the onset of the rainy season. The peak in infected rodents occurred in February. With higher survival throughout the wet season, leptospire abundance in the environment remained high for longer, extending the period of potential high risk to humans. Leptospirosis prevalence in the rodents varied between 2.5% and 25%.

The elasticity analysis provided an indication of the importance of the different parameters. Similar results were obtained for both the constant and seasonal versions of the model; a 10% increase and a 10% decrease in parameter values also gave similar results. Fig. 3 shows the impact of a 10% increase in parameter values on the version of the model incorporating seasonal variation in both rodent reproduction and leptospire survival. The most sensitive parameter was the mortality of adults and sub-adults s_1. This parameter had a large impact on the three key variables: leptospire abundance, rodent number and leptospire prevalence in the rodents. An increase in adult and sub-adult mortality is therefore expected to have an important effect in reducing all variables associated with high leptospirosis risk to humans. Trapping or baiting to kill rodents is therefore expected to offer a potentially highly effective way to reduce leptospirosis infection risk.

An alternative to rodent control is to reduce the suitability of the habitat to rodents by reducing their access to potential nesting sites and food supplies. The model parameter c controls the density dependent maturation of sub-adults thereby limiting rodent population size. Changes to the parameter c can be regarded as repre-

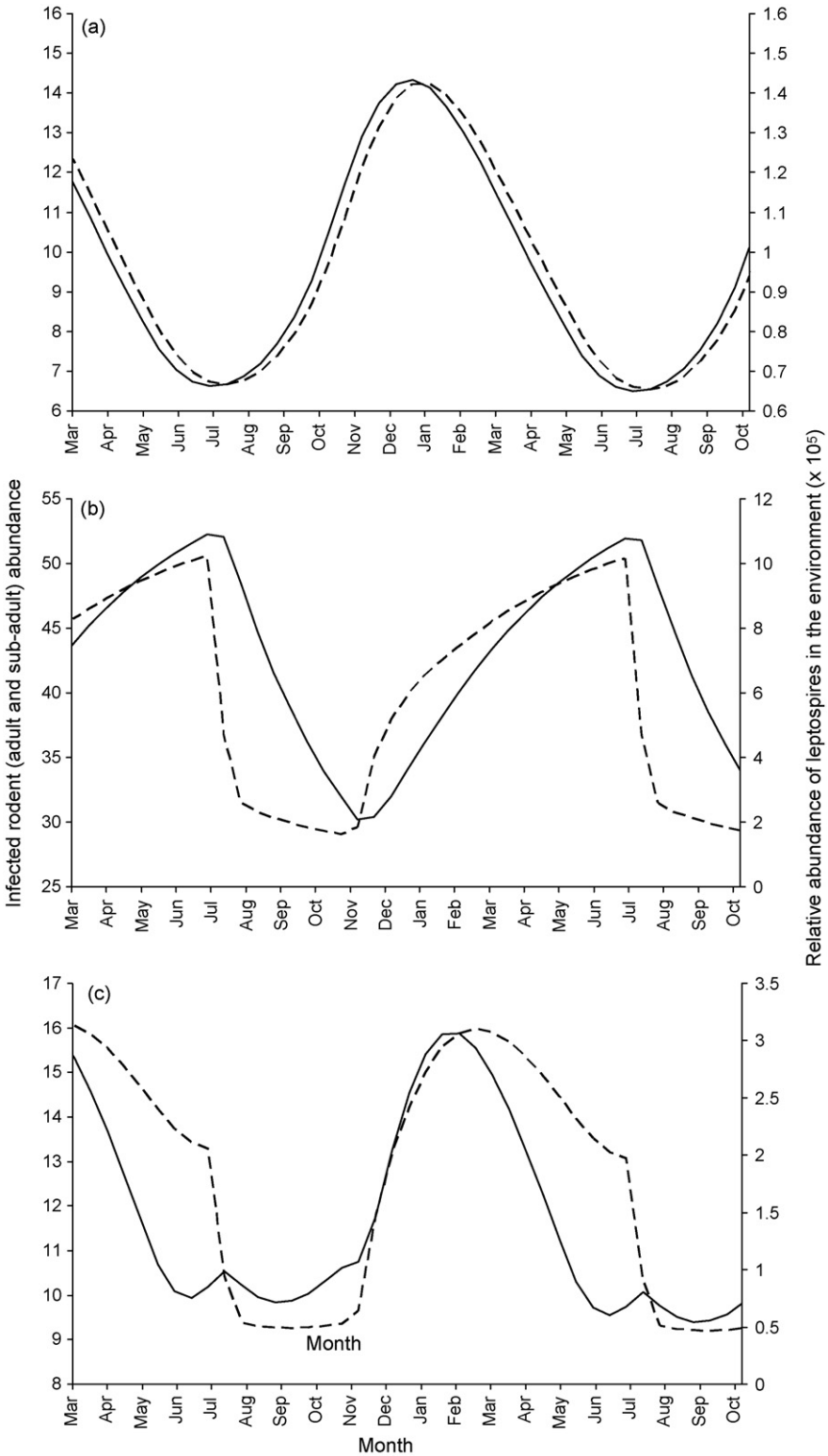

Fig. 2. Simulated seasonal cycle of leptospire-infected rodents (—) and leptospire abundance in the environment (- - - - -): (a) when rodent reproduction is seasonal, (b) leptospire survival in the environment is seasonal and (c) both are seasonal (see text for details).

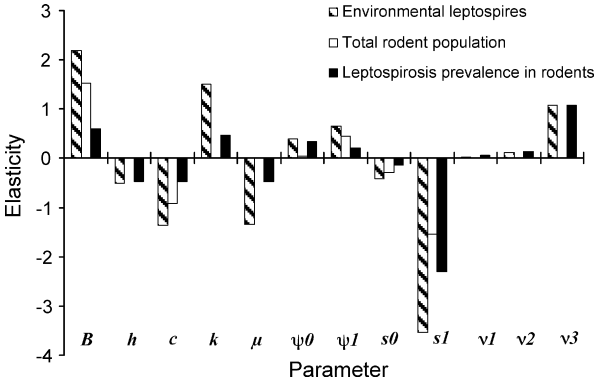

Fig. 3. Elasticity values for parameters for the version of the model in which both rodent reproduction and leptospire survival exhibit yearly cycles, using a variation of +10% according to the elasticity analysis (see text). The impacts on maximum abundance of leptospires in the environment, rodents and leptospirosis prevalence in rodents reached during the yearly cycle are presented. The higher the absolute elasticity, the more sensitive the model to the corresponding parameter.

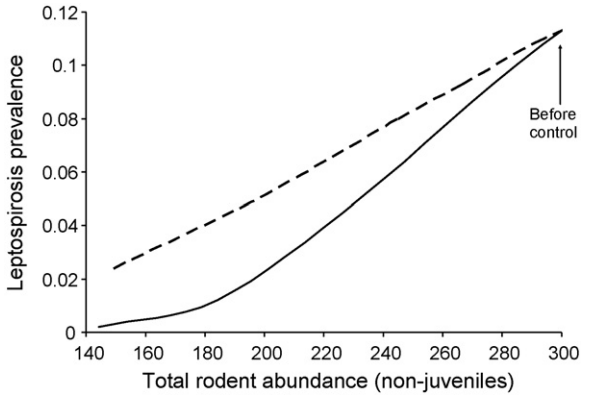

Fig. 4. Response of leptospirosis disease prevalence in rodents to a reduction in their abundance achieved by either trapping or baiting to increase mortality (—) or by managing the environment to reduce its suitability for rodents (- - - - -); the former has a larger impact on leptospirosis prevalence in rodents and therefore potential infection risk to humans.

senting a change in rodent habitat suitability such that the same area can support fewer rodents. In the elasticity analysis, an increase in c did reduce variables associated with leptospirosis risk but the sensitivity was somewhat less than that for s_1; in particular the effect on prevalence was much less than that of s_1.

The epidemiological parameters, h, k, μ, ν_1, ν_2 and ν_3 had varying effects on leptospire abundance and prevalence but as expected, no effect on rodent abundance. The elasticity analysis reflected our assumption that indirect transmission from the environment ν_3 was more important than the two direct routes of transmission, 'maternal' and sexual. With these parameter values, only when the infection rate from environmental sources was reduced substantially ($\nu_3 < 0.001$ day^{-1}), did prevalence start to become more sensitive to the other transmission routes. If indirect transmission is indeed overwhelmingly important, management interventions which target this transmission route, e.g. by removal of sources of standing water which are likely to harbor leptospires, are likely to be effective.

Considering further the two potential approaches to rodent control: killing and reducing habitat suitability, Fig. 4 compares the impact on prevalence when rodent numbers are reduced by each of these means. Using trapping or baiting to reduce numbers has the added advantage that leptospirosis prevalence in the remaining rodent population is reduced to a greater degree. Of course, the two approaches to rodent control are not mutually exclusive and actions to reduce habitat suitability to rodents may also impact on other important parameters, for example leptospire survival in the environment may be reduced when the habitat for rodents is reduced.

The impact of control interventions also depended on other parameters, in particular the ease with which rodents acquire infection from environmental sources. If the infection rate due to environmental leptospires was very high with consequent high prevalence (60–90%) then increased rodent mortality had comparatively little impact on prevalence. This is likely to be an unrealistic situation because though the number of studies is few, leptospirosis prevalence in African rodent populations is in the range 5–15% (Dalu and Feresu, 1997; unpublished data). Under such circumstances, a doubling of mortality would be very effective in reducing disease prevalence in the population.

4. Discussion

To the authors' knowledge this work represents the first attempt to model the dynamics of leptospirosis infection in any wildlife host and is unusual in the wider context of wildlife disease modelling because the population dynamics of the host is based on a fully parameterised population model (Leirs et al., 1997). The model predicts seasonality in the force of infection on humans and a seasonal peak in numbers of human cases is often observed for rodent-borne zoonoses (Davis et al., 2005). This is certainly the case for plague in Africa where a distinct seasonality in human cases has been recorded in plague foci in Tanzania (unpublished data) and Madagascar (Chanteau et al., 2000). The seasonality in human leptospirosis predicted here arises partly from the sea-

sonality in rodent reproduction (a breeding season produces an annual pulse of young susceptible animals and this should affect a period of high transmission which in turn produces a seasonal peak in the abundance of infectious animals) but human behaviour, rodent movements and rodent behaviour can also be strongly seasonal and are often the explanation for seasonality in human cases of rodent-borne disease (Davis et al., 2005).

A number of simplifications have been made. We have modelled the dynamics of a single serovar in a single host while in reality there are over 200 pathogenic serovars (WHO Leptospirosis Manual, 2003) and there is a wide variety of domestic and wildlife animal hosts capable of harbouring and spreading the bacteria. We have no information on cross-species transmission and serovars have varying degrees of host specificity. In the locality in Morogoro, Tanzania on which the rodent model was based, *M. natalensis* was more abundant than all other rodent species added together. The seasonal fluctuations of the other species therefore contributed relatively little to overall rodent dynamics.

The model suggests that rodent removal methods, such as trapping, will be more effective in reducing leptospirosis risk. The biological reason for this result is that trapping reduces both survival and abundance while habitat reduction effectively reduces reproduction and after a short delay also reduces abundance. In the latter case the age structure shifts towards older individuals and prevalence remains relatively high. In the case of rodent removal, survival is reduced while recruitment continues such that the turnover in the population is high. For any infection a high population turnover represents difficult conditions in which to spread or persist because the mean period of infectiousness is short. Trapping hence lowers abundance but has an additional effect of lowering prevalence.

The model presented here offers testable predictions against which both human case data and the results of serological testing of rodent collections can be compared. In particular, expectations of seasonal patterns of leptospirosis prevalence in rodents and risk to humans have been shown to differ according to the situation considered. A framework is provided for the scientific evaluation of rodent control strategies as preventative measures against leptospirosis.

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Appendix A

The model is specified by the set of differential equations below. The numbers of animals in each age and disease class is represented by a J, U or A (denoting juvenile, sub-adult and adult states respectively) with a subsript of either an S or I to indicate susceptible or infectious disease classes, respectively. The abundance of free-living leptospires is represented by L. Parameter definitions and values are given in Table 1:

$$\frac{dJ_S}{dt} = B(A_S + (1-\nu_1)A_I) - \psi_0 J_S - s_0 J_S,$$

$$\frac{dJ_I}{dt} = B\nu_1 A_I - \psi_0 J_I - s_0 J_I,$$

$$\frac{dU_S}{dt} = \psi_0 J_S - \psi_1 \exp(-c(A_S + A_I))U_S - s_1 U_S - \frac{\nu_3 L}{L+h} U_S,$$

$$\frac{dU_I}{dt} = \psi_0 J_I + \frac{\nu_3 L}{L+h} U_S - \psi_1 \exp(-c(A_S + A_I))U_I - s_1 U_I,$$

$$\frac{dA_S}{dt} = \psi_1 \exp(-c(A_S + A_I))U_S - s_1 A_S - \frac{\nu_2 A_S A_I}{A_I + A_S} - \frac{\nu_3 L}{L+h} A_S,$$

$$\frac{dA_I}{dt} = \psi_1 \exp(-c(A_S + A_I))U_I + \frac{\nu_2 A_S A_I}{A_I + A_S} + \frac{\nu_3 L}{L+h} A_S - s_1 A_I,$$

$$\frac{dL}{dt} = k(U_I + A_I) - \mu L.$$

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