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A model for leptospire dynamics and control in the Norway rat (*Rattus norvegicus*) the reservoir host in urban slum environments

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Highlights

- R_0 for *Leptospira* infection in rodents is a non-linear function of multiple transmission routes
- Environmental transmission plays an important role in the maintenance of infection
- Infection in the host population can be reduced using rodent or environmental controls

Abstract

Leptospirosis is a zoonosis that humans can contract via contact with animal reservoirs directly or with water contaminated with their urine. The primary reservoir of pathogenic leptospires within urban slum environments is the Norway rat (*Rattus norvegicus*). Motivated by the annual outbreaks of human leptospirosis in slum urban settings, the within population infection dynamics of the Norway rat were investigated in Pau da Lima, an community in Salvador, Brazil. A mechanistic model of the dynamics of leptospire infection was informed by extensive field and laboratory data was developed and explored analytically. To identify the intraspecific transmission route of most importance, a global sensitivity analysis of the basic reproduction number to its components was performed. In addition, different methods of rodent control were investigated by calculating target reproduction numbers. Our results suggest environmental transmission plays an important role in the maintenance of infection in the rodent population. To control numbers of wild Norway rats, combinations of controls are recommended but environmental control should also be investigated to reduce prevalence of infection in rats.

Keywords: Leptospirosis, Norway rats, target reproduction number

Abbreviations: NGM, next generation matrix; LH, Latin hypercube.

1. Introduction

Leptospirosis is a widespread zoonotic disease (Pappas *et al.*, 2008), in part because a high diversity of domestic and wild animals act as reservoirs (Ellis, 2015). Humans become infected with pathogenic leptospires (of the genus *Leptospira*) either by direct contact with an animal reservoir or contact with environment (water or soil) that has been contaminated with leptospira shed in animal urine (Haake and Levett, 2015). More than one million cases and 58,000 deaths are reported annually worldwide (Costa, Hagan, *et al.*, 2015). However, in developing tropical countries this is certainly an underestimate as studies of acute febrile illnesses without any identifiable etiologic agent have implicated leptospirosis as the cause, based on detailed followup laboratory confirmation, in as many as 40% of cases. Leptospirosis burden affects both rural and urban poor communities of tropical climates (Costa, Hagan, *et al.*, 2015; Torgerson *et al.*, 2015).

Outbreaks of leptospirosis have been increasingly reported in slum urban communities of tropical developing nations (Ko *et al.*, 1999; Sarkar *et al.*, 2002; Reis *et al.*, 2008; Costa, Hagan, *et al.*, 2015). This increase has been related to urban expansion, where one billion of the world's population (or one in three urban dwellers) now live in slums (UN-Habitat, 2007). In those settings *Leptospira* transmission is associated with poverty, inadequate sanitation and transmission occurring in peridomestic environment (Sclar, Garau and Carolini, 2005; Reis *et al.*, 2008; Hagan *et al.*, 2016). Those characteristics provide optimal habitats for Norway rats (*Rattus norvegicus*) (Santos *et al.*, 2017) the major reservoir host for leptospires of the *icterohaemorrhagiae* serovar and environmental conditions suitable for transmission to humans (eg peridomestic rat infestations and seasonal flooding). A Norway rat population of 82 animals studied in Salvador, Brazil, shed close to a

trillion (9.1×10^{10}) infectious leptospires in their urine each day (Costa, Wunder, *et al.*, 2015). Although the survivorship rate of leptospires in soil is being investigated (Casanovas-Massana, unpublished results) the infectious burden will be high with this level of urinary excretion .

Without effective human vaccination (Ko, Goarant and Picardeau, 2009), prevention of infection is key to reducing the burden of disease. In order to prevent outbreaks of human leptospirosis, the cycle of transmission must be broken. For leptospirosis, this means reducing contact with contaminated environment and reducing Norway rat populations. Despite being one of the most frequent strategies to prevent human transmission, rodent control has not been proven to be effective. Populations tend to rebound rapidly when control efforts reduce only a fraction of the population (Glass *et al.*, 2009). Rodent control strategies for leptospirosis are hampered by our insufficient knowledge of population ecology of rodent populations and defining effective 'eradication units', although detailed genetic studies of rat populations at varying distance from core sampling points are helping to assess the issue of defining eradication units within Salvador (Kajdacsi *et al.*, 2013; Richardson *et al.*, 2016). Pau da Lima, an urban slum community Salvador city, Brazil, divided into a number of valleys, has been used as a model to study the epidemiology of leptospirosis in urban slums (Reis *et al.*, 2008). This community registers high annual incidence of leptospirosis (Felzemburgh *et al.*, 2014) where flooding events wash contaminated soil and water into areas of potential human use. Previous studies have identified that risk of leptospire infection in humans is associated with the presence of rats, almost all of which are Norway rats (Costa, Ribeiro, *et al.*, 2014), and residence in areas prone to flooding (Reis *et al.*, 2008; Felzemburgh *et al.*, 2014). Prevalence of leptospire infection in the rodent population in Salvador is between 60-80% (Costa,

Porter, *et al.*, 2014) and currently there is no evidence of seasonality in prevalence (Minter *et al.*, 2017) .

The Pau da Lima neighbourhood in Salvador, Brazil is comprised of multiple valleys separated by roads which rodents are unlikely to cross (Feng and Himsworth, 2014). Within a valley, environmental factors of urban slums mean that rodents have access to food and water, leading to high levels of rat infestation (Santos *et al.*, 2017). Recent estimates show that on occasion, rat population sizes within the trapping areas of the valleys surpass 100 (Pedra et al, unpublished results) though the population size of the entire valley will be much larger than this value.

Understanding the within-population dynamics of leptospire infection for Norway rats is critical for improving leptospirosis control strategies. Norway rats are able to shed leptospires throughout their life without showing any symptoms of the disease (Bharti *et al.*, 2003; Ellis, 2015). The presence of leptospires in the mammary glands and semen of rats provides biological evidence that perinatal, vertical and sexual transmission may occur (De Oliveira *et al.*, 2016). Outside the burrow, rats may become infected via contact with contaminated environment and through direct transmission through wounds inflicted by other rats (Costa, Wunder, *et al.*, 2015). Inside the burrow, rats have frequent contact with each other through adult grooming, orogenital grooming of pups by the dam (Bolles, 1960) and with shed urine (Grant, 1963). Functionally, this can be represented as direct transmission: infection risk increasing with the frequency of infected rats as opposed to the number of free living leptospires in the environment. Recent analyses of the age-prevalence profiles of rodents trapped in Salvador suggest these multiple routes of transmission do occur in wild rodent populations (Minter *et al.*, 2017). However, the relative

importance of these multiple transmission routes in the maintenance of endemic infection in the rodent population is unknown.

Previous modelling studies for leptospire infection in reservoir host include one for African multimammate mice (Holt, Davis and Leirs, 2006), rat to human infection models in Thailand (Triampo *et al.*, 2007; Pongsumpun, Manmai and Kongnuy, 2008; Kongnuy and Naowanich, 2012; Pongsumpun, 2012, 2014; Zaman, Khan and Islam, 2012; Pimpunchat, Wake and Modchang, 2013; Khan, Islam and Khan, 2014) and a multiple reservoir to human model (Baca-Carrasco, Olmos and Barradas, 2015). However, none look in detail at infection dynamics within Norway rat populations and all lack empirical information to inform model parameters.

Herein, a model is presented to describe the dynamics of leptospire infections in Norway rats in the urban slum environment of Salvador, Brazil. The model incorporates empirical data on rat population demography and characteristics of leptospiral acquisition and maintenance collected through several field and laboratory studies conducted in the Pau da Lima slum area of Salvador (Costa, Porter, *et al.*, 2014; Costa, Wunder, *et al.*, 2015; De Oliveira *et al.*, 2016; Jesús A. Panti-May *et al.*, 2016). We characterise the basic reproduction number, R_0, and investigate the contribution of the multiple transmission routes in the occurrence of endemic infection. We then go on to utilise recent developments of the concept of targeted control efforts aimed at sub-populations of the host (Shuai, Heesterbeek and van den Driessche, 2013) and quantify percentage reductions needed to control leptospirosis based on target reproduction numbers representing different rodent management programs tailored to urban Norway rats. We include the important elements needed to describe the dynamics of infection but in a model simple enough

to maintain analytical tractability, aiding its application to other water-borne or environmentally transmitted pathogens.

2. Methods and Analytical results

2.1.Model formulation

Figure 1 is a schematic representation of *Leptospira* infection in rats. There is no evidence of seasonal patterns in Norway rat reproductive parameters in Salvador (J.A. Panti-May *et al.*, 2016) and so we assume rats are born at a constant rate b. A proportion of the infected rats, υ_1 give rise to infected offspring by vertical or perinatal (pseudo-vertical) transmission. There is assumed to be no time delay between acquiring infection and becoming infected, and once infected, rats are infected for their entire lifetime. Susceptible rats can become infected via direct transmission υ_2 (representing a combination of sexual contact and direct contact in a shared nest), or environmental transmission υ_3. Direct transmission is assumed to be frequency dependent as it is largely a result of sexual and social contact (Begon *et al.*, 2002); environmental transmission is assumed to be density dependent, increasing with the numbers of susceptibles and free-living leptospires. Once infected, rats shed leptospires at a rate λ. In the environment, leptospires die at a rate μ. In the absence of evidence of disease, susceptible and infected rats suffer mortality at the same rate m (Ellis, 2015).

Given rodents are unlikely to cross the roads that separate the valleys (Feng and Himsworth, 2014) we assume there is no migration between valleys. Our model represents a closed population of rodents within one valley of Pau da Lima where the number of animals is at a self-regulated carrying capacity (rate of birth is equal to the mortality rate) (Davis, 1953).

Given the high prevalence of infection and the large rates at which rats shed leptospires, υ_3 will be low in absolute value. However, dealing with parameter values so low in numerical analysis, such as parameter estimation, can be problematic. Therefore, we re-scale the free number of living leptospires, otherwise L, to $L' = L/\lambda$, and the environmental transmission rate to $\upsilon_3' = \upsilon_3\lambda$, where □ is the shedding rate of leptospires. We can then describe these processes using a system of ordinary differential equations, where Y denotes the number of infected animals, H the total population size and L' is the number of free living leptospires expressed in shedding units.

$$\frac{dY}{dt} = b\upsilon_1 Y + \upsilon_2 \frac{(H-Y)Y}{H} + \upsilon_3'(H-Y)L' - mY \quad (1)$$

$$\frac{dL'}{dt} = Y - \mu L' \quad (2)$$

The model has two equilibrium states: infection free and endemic infection. See Supplementary materials S1 for details of the equilibrium states and analysis of their stability.

2.2.Importance of transmission routes

In determining the drivers of endemic infection, it is of interest to understand the relative importance of the different transmission routes. The basic reproduction number R_0 gives 'the average number of secondary cases arising from an average primary case in an entirely susceptible population', and so the infection can invade and then spread for as long as the reproduction number remains greater than one (Keeling and Rohani, 2008). We can investigate the importance of different transmission routes by studying the contributions of the different components of the basic reproduction number.

2.2.1. Basic reproduction number

Due to the multiple routes of transmission, the expression for the reproduction number was found using the next generation matrix (NGM) method (Diekmann, Heesterbeek and Metz, 1990). First, the terms responsible for new infections need to be distinguished from all other terms in the system. The matrix F comprises these 'new infection terms' while the matrix V comprises all other additions and removals from the number of infected and free living leptospires. Taking the partial derivatives of the components of F and V with respect to Y and L' gives matrices F and V, respectively. The next generation matrix is defined as $F.V^{-1}$. The choice of F and V, with particular reference to treatment of the state variable for the free-living pathogens, will lead to different expressions for R_0 (Bani-Yaghoub *et al.*, 2012). In the present case the free-living leptospires act as an environmental reservoir, and so secondary free-living leptospires should be added to the leptospire state via shedding, and shedding placed in the F matrix. The basic reproduction number is then:

$$R_0 = \frac{1}{2}\left(R_{\upsilon_1} + R_{\upsilon_2} + \sqrt{4R_{\upsilon_3'} + (R_{\upsilon_1} + R_{\upsilon_2})^2}\right). \quad (3)$$

Where $R_{\upsilon_1} = \upsilon_1, R_{\upsilon_2} = \upsilon_2/m$ and $R_{\upsilon_3'} = (1/m).(H\upsilon_3'/\mu)$ are the individual reproduction numbers for the three different transmission routes (for full derivation see Supplementary materials S2). The first infections in a susceptible population occur via vertical or sexual transmission, shedding from these first infections leads to additional risk from environmental transmission, hence the non-linear expression of the basic reproduction number.

An infected animal will give birth to infected animals at a rate of bv_1 over its lifetime $1/m$. Hence the basic reproduction number for vertical and pseudo-vertical transmission is $\frac{bv_1}{m}$, but given that the system is at its carrying capacity, $b = m$, and so $\frac{bv_1}{m}$ becomes v_1. Given that v_1. is a proportion, the basic reproduction number for the route of vertical transmission can never be more than one. For direct transmission, the basic reproduction number is the rate at which direct transmission occurs over the lifespan of an infected rat $(1/m)$. The basic reproduction number for environmental transmission can be interpreted as the rate at which leptospires are shed λ (after re-scaling this as a rate of 1 per rat in L' units), over the lifespan of an infected rat $(1/m)$, which will either infect new hosts (Hv_3') or die at rate μ.

2.2.2. Global sensitivity analysis of R_0

To investigate the global sensitivity of R_0, we used the Sobol (2001) method, which calculates sensitivity 'indices' by dividing up the variance of the output of a function into fractions, to be attributed to the inputs. The first order indices (main effects) are the effects of the various parameters of a function (here, R_0). The total indices (total effects) measure the overall effect of a parameter, including all the variance caused by its interactions with other parameters. When the output is binary (here, whether $R_0 > 1$) the total effect is of most interest: is there a component which contributes most to the occurrence of endemic infection? The method requires, as inputs, parameter ranges on which to perform the sensitivity analysis. The parameter ranges specified in Table 1 were used in a Latin hypercube (LH) design (Latinhyper, R package FME) to ensure that the entire parameter space was sampled (McKay, Beckman and Conover, 1979).

The rate of infection from the environment, υ_3', is not easily measured, so it is necessary to estimate a value for it in order to achieve a realistic output. In the absence of longitudinal data on infection dynamics in rats, and with no evidence that prevalence is seasonal, prevalence data from the field is considered a stable value. Given the midpoint of the ranges for the birth/mortality rate (b/m) and mortality rate of leptospires (μ), and transmission parameters set to zero (Table 1), values of υ_3' were found such that the model could achieve realistic prevalence. Specifically, the endemic equilibrium was calculated for given values of the environmental transmission rate υ_3, and the values were 'accepted' if the resulting prevalence of infection was projected to be in the range 60-80% (as found by (Costa, Porter, *et al.*, 2014)). The highest value accepted was $2.12\text{x}10^{-5}$, which was used as the upper limit of the range for environmental transmission rate υ_3'. The lower limit was zero.

Using the ranges as shown in Table 1, global sensitivity analysis of R_0 to its different components was performed using $2\text{x}10^5$ LH samples based on previously proposed formulas (Jansen, 1999; Saltelli *et al.*, 2010) (soboljansen, R package sensitivity). Regardless of the formulation of R_0 using the NGM method, the two formulations of the basic reproduction number agree at the threshold $R_0 = 1$, so it was only necessary to perform the sensitivity analysis on one formulation (see Supplementary material S3).

2.2.3. Target reproduction numbers

In the control of any infectious disease, there may be multiple control strategies available, which, for example, instead of targeting both the host and the environment, may target just one of these, or even target one sub-population of either. The type

reproduction number (Roberts and Heesterbeek, 2003) is an expression that provides a threshold for the occurrence of infection in the host population for different population types, e.g. the host population or the environment. If control measures for the environment are cheaper or easier to implement, a type reproduction number for the environment might be of more use than the basic reproduction number. The target reproduction number (Shuai et al., 2013) extends this approach. Target reproduction numbers provide a threshold value similar to the basic and type reproduction numbers, but here a sub-population within a population type is targeted in order to eradicate infection in the host population.

The elements of the NGM describe the secondary infections of different population types in the present case, as follows.

$$\text{NGM}=\begin{bmatrix} \upsilon_1 + \frac{\upsilon_2}{m} & \frac{H\upsilon_3'}{\mu m} \\ \frac{1}{m} & 0 \end{bmatrix}.$$

The columns refer to the host and to the environment, respectively. The first row of the NGM thus describes the secondary infections, either by vertical and direct transmission ($\upsilon_1 + \upsilon_2/m$) or environmental transmission ($H\upsilon_3'/\mu$). Secondary free-living leptospires are only generated by shedding (we do not include any kind of bacterial growth within the environment), and so the only entry in the second row is the average lifetime of an infected rat ($1/m$).

Sub-populations, or target sets, denoted S, correspond to entries of the NGM which are being targeted. For example, when the target set, $S = \{(1,1)\}$, the target population is the entry in the first row and first column of the NGM, the vertical and direct transmission routes. The target reproduction number T_S for target set S can be used to calculate the percentage of target set S entries that need to be removed in

order to eradicate infection in the host population. The proportion is given by $p_s = 1 - 1/T_s$ (Shuai, Heesterbeek and van den Driessche, 2013). Different control methods can be used to reduce different target populations. In the case $S = \{(1,1)\}$, the control method would be to destroy burrows (reducing vertical transmission) and pre-emptive removal of susceptible rats (reducing direct transmission). Table 2 shows these target populations, the control methods, target sets S, and target reproduction numbers T_s, along with the proportion p_s and corresponding conditionalities. For example, the target reproduction number in the present case requires that $R_{v_3'} < 1$. Infection could be eradicated by controlling direct and vertical transmission only if environmental transmission would not otherwise sustain infection.

Results

2.3.Quantifying R_0

The range of the basic reproduction number for vertical transmission [illegible]ted by the parameter values in Table 2 does not include one (Table 3, Figure 2), so vertical transmission alone cannot be responsible for the occurrence of endemic infection. The range for direct transmission does include one, but the mean is 0.36 (Table 3, Figure 2), so for most of the parameter values, direct transmission will not be solely responsible for endemic infection. For environmental transmission, the highest basic reproduction number observed was 6.54, but the mean was much lower (0.62, Table 3, Figure 2). Environmental transmission does have the potential to be solely responsible for endemic infection. The mean value for $R_0$was greater than one, which held for 46% of the calculated basic reproduction numbers of the $2x10^5$ LH samples.

2.4.Global sensitivity analysis of R_0

The main effect for R_{υ_1} was very low, indicating that varying this component alone had little effect on going over the threshold $R_0 > 1$ (Figure 3). The component R_{υ_2} had a higher main effect, and $R_{\upsilon_3'}$ the highest. The same pattern holds for the total effect, but with R_{υ_1}having a relatively higher value than its main effect when its role is considered in combination with the other transmission routes.

Given the simplicity of the formulations of $R_{\upsilon_1}$and R_{υ_2} , we chose to only explore the relationship beween paramaters enerteing R_{υ_3} (Figure 4). The changes in the magnitude of the overall basic reproduction number and the basic reproduction number for environmental transmission were investigated in respect to changes in parameters which contribute to $R_{\upsilon_3'}$ (Figure 4). When changes in a parameter value result in a non-linear decrease in $R_{\upsilon_3'}$, the

same relationship is observed between changes in that parameter value and R_0 (Figure 4). This is true for mortality rate of rats m, and mortality rate of leptospires μ. For changes in the value of environmental transmission rate v_3', there is a non-linear increase in R_0 and a linear increase in $R_{v_3'}$, whereas for changes in population size, H, there is a linear increase in $R_0$and $R_{v_3'}$.

3.3 Quantifying control efforts

The percentage of entries that need to be reduced is on average lower when all transmission routes exist, and the additive reproduction number is more than one (Figure 5a), whereas when only environmental transmission exists, a higher percentage of entries must be reduced. The LH samples generated $R_{v_1} + R_{v_2} < 1$ in approximately 95% of the parameter sets. Therefore, the most likely scenarios are that all transmission routes can exist (a) and only environmental transmission exists (c). Given our uncertainty in the model parameters, it is likely that a control applied to the environment would reduce infection successfully. However, it should be acknowledged that there are occasions where it could not.

For environmental controls, the percentage of entries that need to be removed has a heavily skewed distribution (Figure 5d). When both rats and the environment are targeted (Figure 5e) the corresponding target reproduction number does not have the constraint that only environmental transmission exists. Hence the conditions for this scenario are met more often. In addition, targeting rats and leptospires simultaneously had, on average, the lowest percentage requiring removal.

4. Discussion

In both temperate and tropical regions, the Norway rat is a significant reservoir for human and animal leptospirosis (Bharti et al., 2003, Costa et al. 2014a). In many of these settings, controlling the reservoir host in order to reduce levels of human infection is the most viable option (Costa *et al.*, 2017). The model framework presented here has been developed specifically to describe leptospire dynamics in *Rattus norvegicus*. The basic reproduction number was characterised for our study system, urban slums in Salvador, Brazil. Our results suggest that environmental transmission contributes most to the occurrence of endemic infection in the rodent population, and that controls related to the environment, such as improving drainage, would be most effective in reducing infection in the rodent population.

Global sensitivity analysis was performed on the basic reproduction number as a binary value (Davis, Aksoy and Galvani, 2010). This suggested that all transmission routes have the potential to play a role in the occurrence of endemic infection. Importantly, vertical transmission cannot be solely responsible for the occurrence of endemic infection (Table 3, Figure 3), but may contribute when accompanied by other transmission routes. Changes in the rate of direct transmission will have a greater effect on the occurrence of endemic infection than vertical transmission, but changes in the rate of environmental transmission will have an even greater effect. Similar results were found by (Xiao *et al.*, 2007) who investigated the contribution of different transmission routes on the dynamics of *Salmonella* infection in an unmanaged animal population. They concluded that vertical transmission had little effect on the model dynamics, whereas changes in direct and indirect transmission led to changes in the behaviour of the model at equilibrium. Additionally, in the Holt et al. (2006) framework for leptospire infection in the African multimammate mouse, their analysis revealed that most important transmission route for affecting the prevalence of leptospirosis in rats was indirect (via the environment).

Disease control can only be considered for implementation when the required effort is judged to be realistic or feasible in the given setting. However, as illustrated by this analysis, it is necessary to take into consideration how often the conditions are met on the target reproduction number and the corresponding level of reduction required to eradicate infection. Controlling leptospirosis by targeting vertical, pseudo-vertical and direct transmission is not a viable option in the slums. Even when the condition for the environmental transmission is met, which is unlikely to occur (Costa *et al.*, 2017), there is no guarantee that percentage reduction will be low. Often the conditions for vertical and direct transmission are met, but then the percentage reductions needed to implement control via environmental transmission only are too high to be considered feasible.

The percentage entries that need to be reduced to eradicate infection was on average lowest when both rats (reduction by removing rats) and leptospires shedding (reduction by improving drainage) were targeted at the same time. The target reproduction number for control via shedding was the same expression as for control by environmental transmission. That is, a measure to reduce leptospires in the environment would require the same level of reduction as a control measure to reduce contact between rats and leptospires. But in reality, applying environmental controls would be most difficult in terms of allocation of resources and organisation. Removal of rats via trapping or rodenticide is a control measure that has already been applied by the city Government at the Pau da Lima site with limited results. Holt et al. (2006) recommended removing multimammate mice, as opposed to habitat management, as the more effective control strategy, but they did not investigate any environmental control.

In our study, the removal of rats when the reproduction number is more than one would require on average a lower level of reduction than targeting solely the environment. Though controlling via environmental transmission and the reservoir would on average require a

smaller reduction than solely removing rats, removing rats is easier to implement. However, the effect of removing rodents is temporary control as rodents recover quickly from population decrease (Shilova & Tchabovsky, 2009). Due to its ease of application, we recommend removal of rodents as a control measure but only as a first line strategy. Environmental control, though more difficult to achieve in practice, would result in a permanent reduction in risk. In addition, given that both rodents and humans acquire infection via the environmental reservoir, targeting the environmental would reduce risk for both populations. Application of rodent removal alongside an environmental control would have the dual effect of reducing environmental transmission risk in rodents, reducing the rodent population and at the same time reducing human risk from infection.

Our identification of the importance of environmental transmission is supported by other modelling studies with multiple transmission routes, but we note, nonetheless, that its rate was the only parameter that had to be estimated. We treated all other parameters as fixed and known and estimated the environmental transmission rate according to whether model predictions of prevalence were within the range found in animals trapped in the field and tested for infection. This analysis of the transmission routes was based on parameter ranges passed to R_0, and not a fixed value of the environmental transmission rate. Model validation is an important step in the development of a mathematical framework (Restif *et al.*, 2012). The global sensitivity analysis was used for finding which transmission route was most important in the occurrence of endemic infection, but it also directs us to which parameters we should have most certainty in, which in this case are those parameters related to environmental transmission.

The sensitivity results were based on parameter ranges that were deemed realistic for leptospire infection in rats in the slums based on our current knowledge of the system but not equally likely to occur. In some cases, the biology behind the parameter value is well understood, whereas in others, the range was assigned based on studies on other reservoirs or given a wide range to accommodate all possible scenarios. Whereas the sensitivity results do suggest that the environmental transmission route is most important for a wide range of scenarios, if some parameters had a better biological basis and so a narrower parameter range, then the conclusions related to direct transmission could change. For example, direct transmission was assumed to occur through direct contact with other rodents. It may not be sexual, but via biting or other close contact; wounding has been a consistent factor associated with leptospiral prevalence among Norway rats in Salvador (Costa, Porter, *et al.*, 2014; Minter *et al.*, 2017). The value of the direct transmission basic reproduction number can be affected both by the rate of direct transmission and the average lifespan of a rat. Small variations in mortality rate by system are expected, but in general the mortality rate of rats in wild systems is high (Feng & Himsworth, 2014) and thought not to differ much across different settings (Glass *et al.*, 1989). The rate of direct transmission here was adopted from Holt et al. (2006), as there are no existing quantitative studies on sexually transmitted leptospire infection in rats. We expect the contact rate of adult rats to remain constant, but the probability of successful infection and hence the sensitivity analysis results could change if we could confirm whether infection was sexual, biting, grooming, urine marking or a combination of these.

Rodent control strategies often fail to eradicate the population as rodents have shown resistance to rodenticide (Shilova and Tchabovsky, 2009)and can recover from severe population decreases (Hein and Jacob, 2015). Environmental control will reduce infection in the rat population and also reduce human risk of leptospire infection. Our modelling approach

has allowed us to characterize analytical expressions for the target reproduction numbers. The conditions of target reproduction numbers provide information as to when a control measure can be effective. For example, environmental control will only be effective when infection would otherwise not persist in the rodent population. Given these conditions, we were able to quantify the amount of reduction needed in the host population or environmental reservoir. However, ultimately, these numbers should be interpreted alongside both the cost and the feasibility of the different controls. For example, removal of rats may be easier to implement than the removal of leptospires in an urban slum setting. In addition, exploration of the time dependent effects of these controls should be explored in a more complex mathematical model framework. Future studies should incorporate the present work into these broader settings.

Urbanisation together with climate change is expected to increase the global incidence of leptospirosis (Lau *et al.*, 2010). Incidence of rat-borne zoonoses has increased with changes in climate and urbanisation (Himsworth *et al.*, 2013). To understand the infection dynamics within the Norway rat population a theoretical approach was taken. For controlling leptospire infection in the slums, removal of rats is easy to implement but does not have long lasting effects. Improved methods such as reducing the carrying capacity of the rodent population or combinations of rodent and environmental control must be considered. The target reproduction number provides a useful threshold of whether infection can be eradicated by applying different types of control. However, this approach does not take into account the success of such control measures, the effect of removing both susceptible and infected rats, or consider a non-constant application of control. A priority for future work is to explore the effects of controls applied at different timescales whilst accounting for cost and the effect on human risk of infection. Decisions regarding the best measures to control infection need to be based on numerical results, availability resources and ease of implementation. Approaches

that utilise mathematical models of infection while accommodating for the difference in costs of multiple controls could be used to inform zoonotic control strategies.

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Figures captions

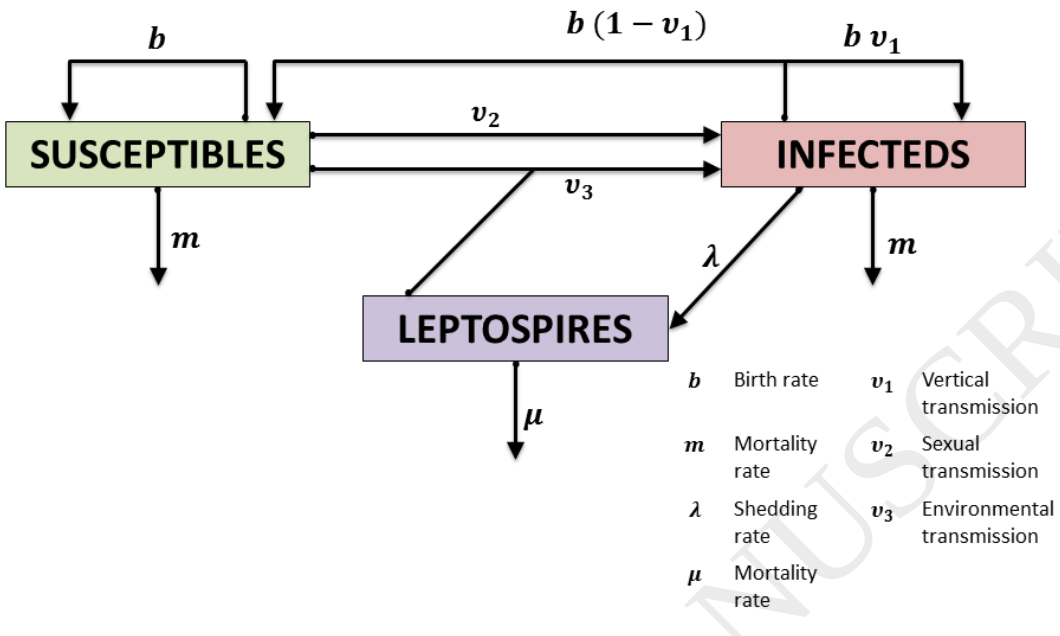

Figure 1: Flow diagram of leptospire dynamics in rats.

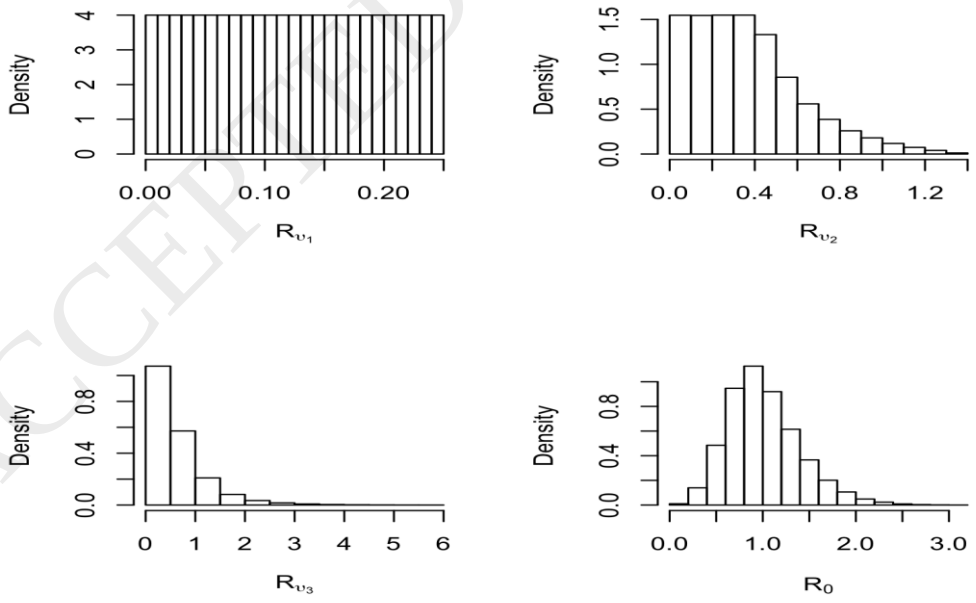

Figure 2: Histograms of the distributions of basic reproduction numbers for each transmission route based on LH samples used in sensitivity analysis.

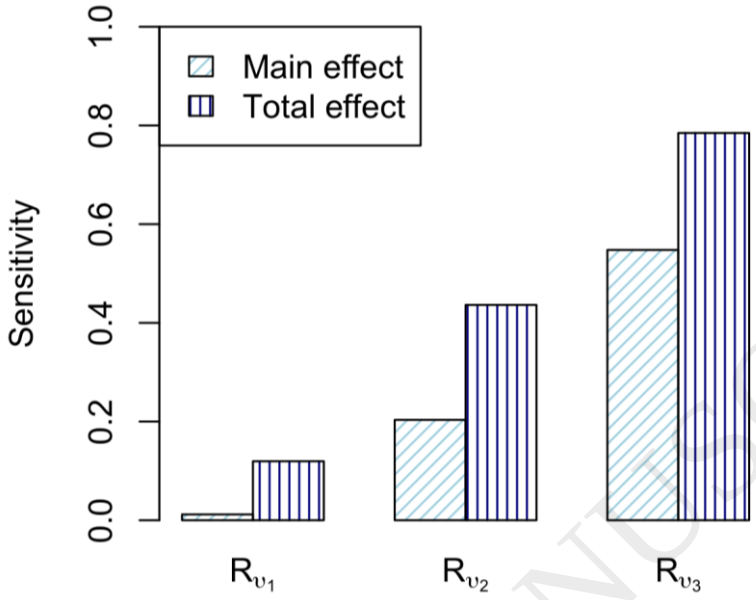

Figure 3: Main and total effect for the different components of $\boldsymbol{R_0 > 1}$.

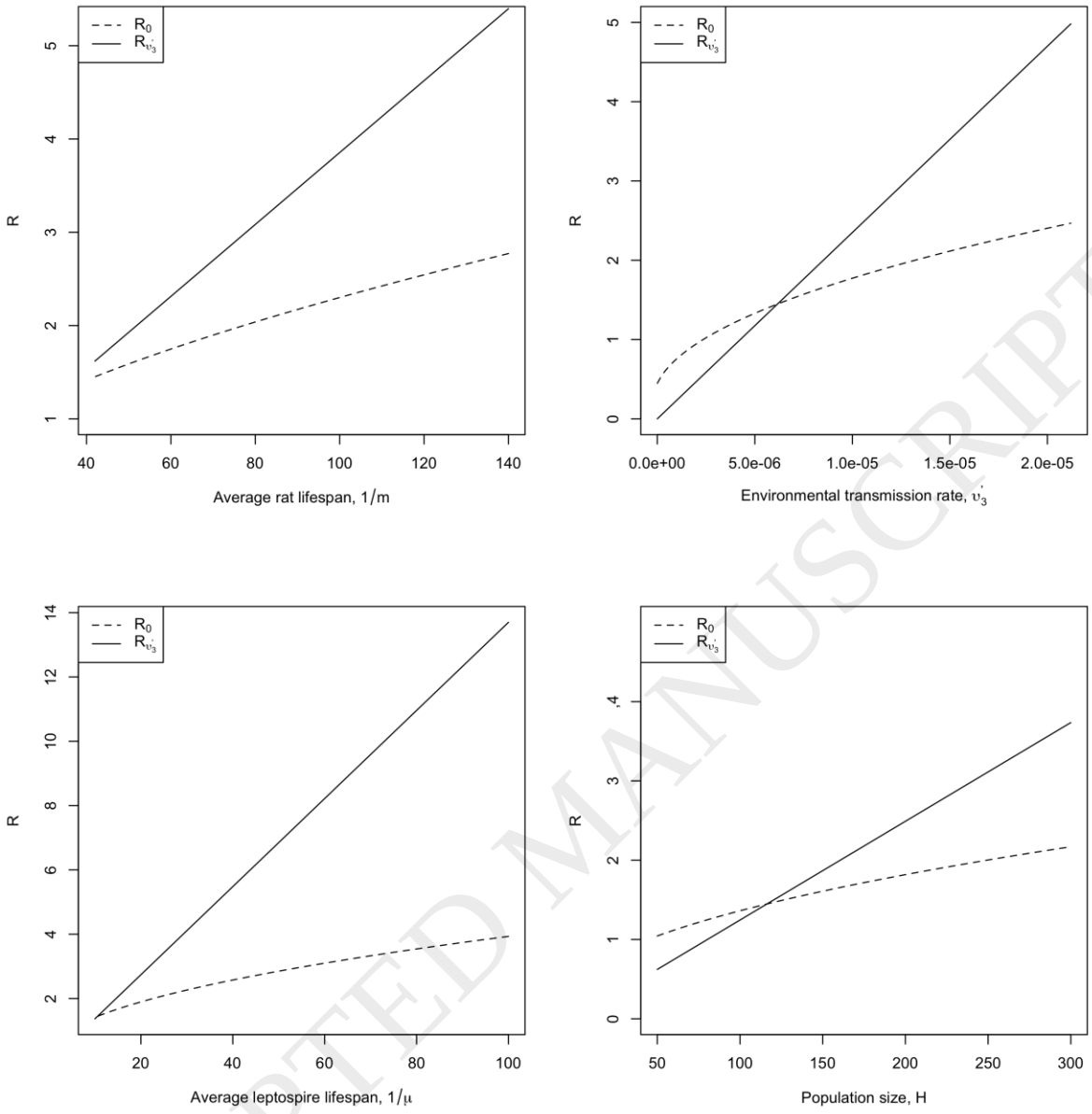

Figure 4: Changes in the basic reproduction number $\boldsymbol{R_0}$ (dashed line) and the basic reproduction number for environmental transmission only $\boldsymbol{R_{v_3'}}$ (solid line) and with respect to changes in mortality rate $\boldsymbol{m}$, environmental transmission rate $\boldsymbol{v_3'}$, leptospire mortality rate $\boldsymbol{\mu}$ and population size $\boldsymbol{H}$.

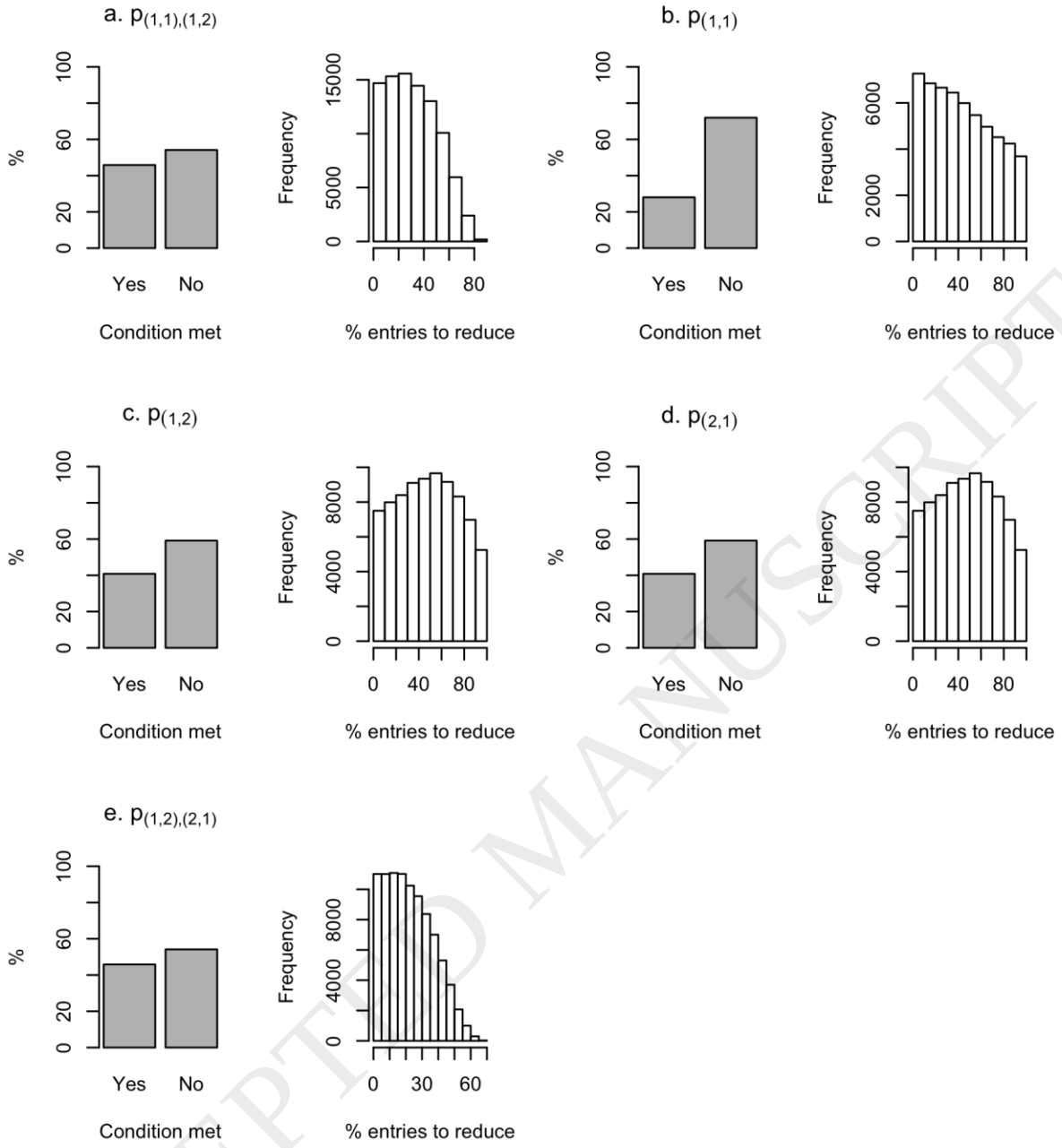

Figure 5: Percentage of the $2x10^5$ LH samples for which the conditions identified in Table 2 were met for the target reproduction number and corresponding percentage of *S* entries that need to be reduced to to eradicate infection via rodent control a) all transmission routes can exist, b) only vertical and direct transmission exist, and for environmental control c) only environmental transmission exists, d) environmental transmission exists, and e) no constraints on which infection routes exist.

Tables

Table 1: Ranges of parameter values used in the sensitivity analysis of $\boldsymbol{R_0}$.

Parameter	Definition	Units	Range	Source/Comments
b/m	Birth/Rat mortality rate	Day^{-1}	0.007-0.024	A mean'lifespan' of 20 to 6 weeks (Glass *et al.*, 1989) Note $b = m$.
υ_1	Proportion of pups infected from suckling and born infected	Day^{-1}	0-0.25	Around 20% pups are infected (Minter *et al.*, 2017).
υ_2	Transmission rate via direct transmission	Day^{-1}	0-0.01	Based on Holt et al. (2006).
υ_3'	Transmission rate via the environment	Day^{-1}	2.12x10^{-5}	Estimated in section 2.2.2.
μ	Mortality rate of leptospires in the environment	Day^{-1}	0.01-0.1	Long (approx. 100 days) or short lived (approx. 1 day).
H	Total population size	Number of rats	200*	The number of rats at carrying capacity in one valley.

* for this analysis, we investigate a population of rodents with a fixed size of 200.

Table 2: Target populations with corresponding control measure, target set and target reproduction number.

Target	**Control**	**Target set**	**Target reproduction number**	**Proportion p_S**	**Condition**
Host population	Remove rats	$S = \{(1,1),(1,2)\}$	$T_S = R_{v_1} + R_{v_2} + R_{v_3'}$	$p_S = \left(1 - \frac{1}{R_{v_1} + R_{v_2} + R_{v_3'}}\right).$	$R_{v_1} + R_{v_2} + R_{v_3'} > 1$
Control via direct and vertical transmission only	Remove rats	$S = \{(1,1)\}$	$T_S = \frac{\left(R_{v_1} + R_{v_2}\right)}{1 - R_{v_3'}}$	$p_S = \left(1 - \frac{1 - R_{v_3'}}{\left(R_{v_1} + R_{v_2}\right)}\right).$	$R_{v_3'} < 1$ and $R_{v_1} + R_{v_2} + R_{v_3'} > 1$
Control via environmental transmission	Remove rats or improve drainage	$S = \{(1,2)\}$ or $S = \{(2,1)\}$	$T_S = \frac{R_{v_3'}}{1 - \left(R_{v_1} + R_{v_2}\right)}$	$p_S = \left(1 - \frac{\left(R_{v_1} + R_{v_2}\right)}{R_{v_3'}}\right).$	$R_{v_1} + R_{v_2} < 1$ and $R_{v_1} + R_{v_2} + R_{v_3'} > 1$

only or control via shedding					
Control via environmental transmission and shedding	Remove rats and improve drainage	$S = \{(1,2),(2,1)\}$	$T_S = \frac{1}{2}\left(R_{v_1} + R_{v_2} + \sqrt{4R_{v_3'} + (R_{v_1} + R_{v_2})^2}\right)$	$p_S = 1 - \frac{1}{\frac{1}{2}\left(R_{v_1} + R_{v_2} + \sqrt{4R_{v_3'} + \left(R_{v_1} + R_{v_2}\right)^2}\right)}.$	$R_0 > 1$

Table 3: Ranges of the basic reproduction numbers for each transmission route based on LH samples used in sensitivity analysis.

Component	**Mean (Min, Max)**
Vertical transmission, R_{v_1}	0.13 (0,0.25)
Direct transmission, R_{v_2}	0.36 (0, 1.39)
Environmental transmission, $R_{v_3'}$	0.62 (0.02, 6.54)
R_0	1.01 (0.038, 3.11)