**A bioeconomic model for the optimization of local and regional canine rabies control**

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**Abstract**

**Introduction**

The World Health Organization estimates that about 55,000 people die from rabies each year. Although the mortality risk from rabies infection is relatively small compared to some other diseases, rabies is distinctive because infection in humans is both easily prevented with vaccination and easily treated after exposure. Additionally, a low-cost, effective vaccine is available for managing and eliminating the disease in dogs, which are the primary source of human exposure in much of the developing world. Successful management of the disease has been demonstrated in many developed countries, where post-exposure prophylaxis (PEP) is readily available and vaccination of dogs is common practice. In the United States, canine rabies was eliminated in the 1970s after extensive public education and mass vaccination of dogs (Blanton et al. 2010). Much of Western and Central Europe is also free from the disease, and many countries in Latin America have made substantial progress in recent years (Bourhy et al. 2005, Schneider et al. 2007, Global Alliance for Rabies Control 2012).

Nearly all human deaths from canine rabies occur in Africa and parts of Asia, where several obstacles to successful management persist. These obstacles include the prevalence of inaccessible dogs, the inability or unwillingness of owners to bring dogs in for vaccination, lack of information about rabies, lack of surveillance and diagnostic capabilities, and insufficient resources for veterinary services. In many regions, a lack of education about the need for PEP and an inability to access PEP are also sources of human mortality. Regardless of the particular impediments to successful management, the fundamental problem is insufficient resources. Public health issues are pervasive in much of the developing world, and rabies management is simply not a priority. Furthermore, many regions lack the basic infrastructure and institutions necessary for effective management. Successful dog vaccination campaigns require functioning transportation and communications infrastructure, and widespread PEP availability requires the existence of clinics or hospitals that are accessible by much of the population.

Our focus in this paper is based on two observations. First, the elimination of human exposure in the developing world comes from the elimination of the disease in dogs. Eliminating the disease in dogs provides ongoing benefits by avoiding the relatively high and unending costs of human treatment. Furthermore, in any population, there will always be people who are unwilling or unable to obtain PEP in response to a potential exposure. Thus, elimination of the disease in dogs will reduce human mortality even if access to PEP is widespread. Our second observation is that funding for canine rabies management is typically haphazard. Coordinated international efforts are rare, and even efforts within a single country may not be well-coordinated. With these observations in mind, and given the near universal lack of sufficient management resources, our goal was to develop a tool that can be used to maximize the impact of whatever canine rabies management resources are available at the local and regional levels.

The tool we have developed is a bioeconomic model that can be accessed through a web-based graphical user interface. The model itself is an individual-based, stochastic simulation model that explicitly accounts for the links between management effort, management cost, and biological outcomes. Additionally, our objective was to construct a model that (1) accounts for population and disease dynamics, (2) allows vaccination, permanent sterilization, temporary contraception, and removal, (3) allows strategies to vary temporally and demographically, (4) allows combination strategies, and (5) is flexible enough to allow parameterization for many different canine rabies management scenarios. Although all our code is freely available and can be modified by a user if desired, our model can be used in applied settings by users without computer programming experience. The web-based framework was chosen over an installable desktop application because it requires nothing more than an internet connection and a web browser. The performance of the model is not affected by the speed of the internet connection or the hardware of the user’s computer because all computations are performed remotely. Additionally, the model will run on any operating system, even those that are substantially outdated.

The manuscript proceeds with a description of the model and the details of its various mechanisms. This is followed by a case study in which we use the model to examine alternative strategies for managing rabies in a free-ranging dog population in South Africa. Specifically, we investigate the optimality of combining sterilization and vaccination to minimize the impacts of the disease in the village of Hluvukani, Mpumalanga Province. We close with a discussion of the various ways the model can be used and the shortcomings that users should be aware of.

**Methods**

*Model Overview*

There are several key characteristics of the model. First, the model tracks individual dogs and their traits through time. This is performed via a matrix that contains a row for each living individual and a column for each trait associated with individuals (Table 1). Second, the model operates on a daily time step. This minimizes bias that results from discrete time steps, and allows the model to more precisely consider management efforts that vary temporally. Third, nearly all of the processes that occur in the model are stochastic. A stochastic model provides important benefits because it allows a user to examine the tradeoffs between management costs and the certainty with which a management goal is successfully achieved. Fourth, the model allows nearly any combination of vaccination, fertility control, and removal, and these treatments can be demographic-specific. Finally, the model separates the cost of capturing or contacting dogs and the cost of applying the treatment. Furthermore, the model allows the user to easily specify a non-linear relationship between the cost of capturing dogs and the number of dogs captured. The separation of costs and ability to specify non-linear capture costs are critical to a proper understanding of the economics of management, and we are unaware of the existence of any other model of rabies management that does this.

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| **Table 1 – Columns of the population matrix** | | |
|  | **trait** | **notes** |
|  | age | integer – days |
|  | puppy | bool – yes/no |
|  | adult | bool – yes/no |
|  | female | bool – yes/no |
|  | sterilized | bool – yes/no |
|  | contracepted | bool – yes/no |
|  | time contracepted | integer – days |
|  | booster vaccine received | bool – yes/no |
|  | exposed | bool – yes/no |
|  | infective | bool – yes/no |
|  | time infective | integer – days |
|  | immune | bool – yes/no |
|  | month | integer – month number |

We are acutely aware of the perception that many individual-based models are not amenable to fast and thorough investigation and thus considered black boxes. We have taken a number of steps to address this concern here. Our model is written in the R language (R Core Team 2014). R was chosen over other languages because its use by researchers is common and growing, it is free and open-access, and the code is relatively easy to read. Additionally, we have also structured the code in a way that facilitates easy understanding. The code consists of two scripts, one that creates the user interface and one that defines the model. The script that defines the model consists of four main sections (Figure 1). All code has been carefully annotated to ease understanding. Additionally, major mechanisms within the model are contained in their own functions. While this structure eases understanding, it also makes the code modular and easy to modify. If a user want to change a mechanism, a single function can be changed without the risk of interfering with other mechanisms. Finally, there were a number of situations where we faced a choice of employing code that was faster or employing code that was easier to understand. In most cases, we chose the latter. In the following sections, we provide brief descriptions of the major mechanisms of the model.

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| **Figure 1 – Outline of code in the model script** |
| 1. **Inputs**   *When the model is run, inputs are passed from the user interface to the model.**Some inputs are hidden from the user but can be adjusted within the code.*   1. **Mechanism functions**    1. **Initial population function**   *Called at the start of each iteration, builds the initial population.*   * 1. **Annual strategy function**   *Called at the start of each year, determines the number of dogs that can be treated give the annual budget.*   * 1. **Strategy schedule function**   *Takes the number of dogs that can be treated and determines when that treatment will occur during the year.*   * 1. **Census function**   *Counts and retains results.*   * 1. **Mortality function**   *Calculates mortality and out-migration probabilities, applies them to the current population, and removes individuals that do not survive or that leave the population.*   * 1. **Reproduction function**   *Calculates reproduction probabilities for fertile, adult females, applies them to the current population, and produces new litters if necessary.*   * 1. **Immigration function**   *Adds new dogs to the population based on the probability of in-migration.*   * 1. **Disease progression function**   *Transitions individuals from exposed and infective disease states.*   * 1. **Disease spread function**   *Calculates probabilities of exposure, and moves individuals from the susceptible to exposed states based on these probabilities.*   * 1. **Management function**   *Carries out the appropriate treatment based on the schedule provided by the strategy schedule function.*   * 1. **Time function**   *Updates time-related traits in the population matrix.*   1. **Iteration and time loops**   *Each iteration is performed sequentially. Within each iteration, a loop runs through each day of the 5-year time period.*   1. **Results organization**   *Calculates results that depend on disease prevalence (e.g. PEP applications), calculates averages across the iterations, produces plots.* |

*Mortality and Reproduction Processes*

Non-rabies mortality is caused by two mechanisms. First, a user-specified, annual mortality rate is converted to a daily mortality probability for puppies, juveniles, and adults. Individuals in the population face this probability on each day, and random draws determine their fates. Additionally, if the abundance exceeds the user-specified carrying capacity after probabilistic mortality has occurred, individuals are randomly removed from the population until carrying capacity is reached.

Reproduction is governed by a user-specified probability that a fertile adult female has a litter in a year, as well as average litter size. Additionally, the user can specify certain months in which litters are more likely. This is performed with month check boxes and a parameter that specifies the fraction of all litters during a year that occur in the selected months. The model takes the selected months and fraction of litters born during those months and calculates, for each fertile adult female, the probability of producing a litter during each month of the year. Finally, random draws determine the number of litters produced each month, and new puppies are added to the population.

*Disease Introduction*

In some cases, canine rabies management may only occur in response to a known outbreak. In other cases, management may be an ongoing attempt to minimize the threat posed by a potential introduction. Our model can be used to investigate either type of management. Rabies can be introduced at any time during the five-year simulation period. Additionally, the user can specify the number of dogs that are exposed during the introduction event, as well as the number of sequential months that introductions occur. This arrangement allows the user to investigate management that is implemented before or after an introduction occurs.

*Disease Transmission*

We assume that the number of bites per rabid dog per day follows a negative binomial distribution. Thus, on each day that at least one rabid dog exists, random draws determine the total number of bites that rabid dogs inflict on other dogs. These bites are allocated across the population randomly. Susceptible dogs that receive a bite face a user-specified probability of infection. If a random draw implies infection, the dog is moved from the susceptible state to the exposed state. Dogs remain in the exposed state for a specified period before moving to the infectious state. Although these values are not adjustable in the user interface, they are clearly marked and easily adjusted within the code. There are also several additional transmission-related inputs that are adjustable within the code. By default, the probability of survival is zero, by this can adjusted so that some small percentage of dogs recover with immunity. Additionally, the number of dogs immune (either from recovery or vaccination) in the initial population can be specified.

*Disease Impacts*

The user can specify two impacts to humans: PEP applications and mortality. To enable estimation of these impacts, the user first specifies the number of bites per day by rabid and non-rabid dogs. Then the number of PEP applications for each bite type, as well as the cost of each PEP application, is specified. Finally, the probability of human death, given a bite from a rabid dog, is specified. Given these inputs and the number of rabid and non-rabid dogs on each day of the simulation period, the model calculates the number of PEP applications and human deaths on each day.

*Management Costs*

To facilitate understanding, we define marginal strategy cost as the cost of applying a chosen strategy to an additional dog. Furthermore, the marginal strategy cost is the sum of the marginal treatment cost and the marginal contact (i.e. capture) cost. The separation of treatment costs and contact costs and the ease with which a user can specify a non-linear marginal contact function are important characteristics of the model. The model assumes marginal treatment (i.e. vaccination, sterilization, contraception, removal) costs are constant as the number of dogs treated varies. These are specified on a per-dog basis and sterilization and contraception costs are sex-specific. Marginal contact costs are derived by estimating the cost of contacting or capturing 25%, 50%, 75%, and 100% of the population (Figure 2). Because the resulting function may be non-linear (technically piecewise-linear), the marginal cost of the chosen strategy may be both an increasing and non-linear function of the number of dogs treated. This contrasts with most existing models of rabies control, which only incorporate constant costs of treatment.

Figure 2 – An example of a stepwise-linear function for capture or contact costs

It is intuitive that marginal strategy costs are not typically constant. Some dogs are quite easy to capture or contact, while other dogs are very difficult or time-consuming. This can have important implications for optimizing management strategies. For example, a manager choosing a mix of vaccination and fertility control may choose to devote all resources to vaccination if contact costs are ignored. Alternatively, if contact costs are considered, and if those costs sharply increase beyond a certain point, it may be beneficial to capture fewer dogs and instead apply vaccination *and* fertility control to the dogs that do get captured. In other words, it may be preferable to apply fertility control to many dogs rather than vaccination to only a few additional dogs. A variety of similar tradeoffs exist. As a result, when there is a choice between concentrating resources on a specific treatment, demographic group, or time period or, instead, spreading resources more broadly, it is imperative that the increasing, non-linear nature of contact and strategy costs is accounted for.

Although we believe the ability to account for non-linear strategy costs is an important part of the model, we also recognize that sufficient data must be available to properly estimate such a relationship. As a result, the model can also accommodate constant capture and strategy costs. This can be done by setting all of the points that produce Figure 2 to zero, and including capture costs in the specified treatment costs. For example, a user may only have an estimate of the average cost of capturing a dog. In this case, the average cost can be added to the cost of whatever treatment options are being employed.

*Management Budget*

The user specifies a management budget is for each year of the 5-year simulation period. At the beginning of each year, the model estimates the number of dogs that can be contacted and treated by considering the budget, specified strategy, and current demographics. The estimation occurs by an iterative process that splits the available budget between contact and treatment. In the first iteration, all of the budget is allocated to contact effort, and the contacted dogs receive treatment. The total cost of this is calculated based on the allocation to contact and the treatment costs. If the total cost exceeds the annual budget, the allocation to contact effort is slightly reduced. This process continues until the total cost does not exceed the available budget. Once the allocation to contact effort and the number of dogs treated has been estimated, the treatment events are spread randomly across the days of the months that the user specified and the dogs that exist on those days.

**Application**

*Status of rabies and its management in South Africa*

* To what extent is the disease still a problem?

Rabies remains endemic in South Africa, and is relatively common in eastern Cape Province, eastern Mpumalanga Province, northern Limpopo Province, the Rustenburg area of North West Province , and rural KwaZulu-Natal Province (NHLS). From 2012 to 2015, 30 human cases were reported, although this likely represents an underestimate of the true number (Kotze 2017, NHLS). Generally, about half of all human cases are children. Historically, dogs have accounted for 37% of all animal cases in South Africa, but they account for 95% of human cases. It is thus imperative to reduce rabies prevalence in dogs to reduce the risk of human mortality.

Although the number of reported human cases each year is relatively small, many people receive PEP…

* How are people affected (deaths, PEPs)?
* How much is spent on PEP and who pays for it?
* How much money is being spent on management?
* How is management coordinated nationally and regionally?

*Need for / value of a tool to optimize management*

* Background on how management is performed at the local-level?
  + What is a campaign and who runs it?
* Explain how local and regional managers could benefit from using BioEcon.
  + Generally, maximizing the benefits from management
  + Seasonal timing
  + Resources needed
  + Benefits of vaccinating puppies
  + Benefits of booster vaccine
  + Benefits of sterilization – we will answer this question in the application.

*Importance of the question (vaccination vs. vaccination and sterilization)*

* Given a fixed budget, is it beneficial to vaccinate puppies? Does this answer depend on the budget? Does it depend on whether management is pre-emptive or reactive?
* Given a fixed budget, is it beneficial to sterilize females that are being vaccinated? Does this answer depend on the budget? Does it depend on whether puppies are being vaccinated? Does it depend on whether management is pre-emptive or reactive?

There are two key questions we sought to answer in our application of the model. The first question was whether it is beneficial to vaccinate puppies (<90 days old)? Given a choice between vaccinating a puppy or an adult, the adult would be preferred due the lower mortality rate of adult dogs. A puppy is more likely to exit the population during a given time period, and any vaccination resources devoted to that dog would be wasted if the dog died or otherwise left the population. However, there are certain conditions under which vaccinating puppies may be desirable. If excess vaccination resources are available after all juvenile or adult dogs have been vaccinated and the goal is to minimize disease prevalence or human risk, then puppy vaccination is clearly desirable. Even if insufficient vaccination resources are available for juvenile and adult dogs, the nature of contact costs may make puppy vaccination cost-effective. This would occur if the marginal cost of contacting additional dogs increased sharply enough. In this situation, a manager would face a choice between vaccinating many puppies or only a few additional non-puppies. Thus, even if vaccinating a single puppy does not provide the same benefits as vaccinating a single adult, the fact that many more puppies can be vaccinated may lead to an optimal strategy that includes puppy vaccination. A final consideration would be how the population responds to a rabies outbreak. Adult vaccination ensures a relatively large population of fertile dogs, which could lead to longer-lasting outbreaks or a population that recovers faster and is therefore more susceptible to subsequent rabies introductions.

The second question we sought to answer is whether female dogs that are contacted during vaccination efforts should be sterilized at the same time.

*Study Area*

In 2011, we established a health and demographic surveillance system (HDSS-Dogs) in a population of owned, largely free-roaming dogs in a low-income community in the village of Hluvukani, Mpumalanga Province, South Africa. We defined a demographic surveillance area (DSA) using natural and artificial boundaries, and monitored all of the approximately 2,500 households in the DSA through regular visits, every five to six months. In each household, we collected data on entry and exit events of owned dogs (birth, death, in- and out-migration). Dogs that entered this population were uniquely and permanently identified by subcutaneous implantation of a radio frequency identification microchip, or through photo identification if they could not be handled. Dates of events were estimated by owners, with uncertainty reflected by a lower and upper estimate of the time since the event. We considered the midpoint between the estimates to be the estimated event date. At each visit, we recorded the rabies vaccination status of new dogs, and updated the vaccination history of dogs in the household since the previous visit. To date, the HDSS-Dogs has provided data on the lives of over 3,000 dogs in the DSA.

*Parameter Estimation*

The data collected from the study area provided the basis for many of the parameters used in the model (Table 1). Although data collection began in 2011, all parameter estimation was based on data collected from January 2012 to January 2017 to minimize any bias introduced by irregular reporting early in the study period. Daily mortality probabilities were estimated using binary-outcome probit models estimated via maximum likelihood. The daily predicted probabilities for each age class were then annualized for use in the model. There were many cases when a dog exited the population for unknown reasons. As result, we chose to include all exit events in the mortality analysis. Thus, we set out-migration to zero in our application of the model, and our mortality parameters reflect mortality as well as all other types of exit events.

Three reproduction parameters were estimated from the HDSS data: expected litters per female per year, mean litter size, and the fraction of puppies that are female. These were simple calculations from the data collected from January 2012 to January 2017. We also investigated the data for evidence of a seasonal variation in reproduction, but no strong evidence was found. As a result, we chose not to include any birth pulse in our application of the model. In addition to these reproduction parameters, we also calculated the average number of dogs moving into the population over the five-year observation period. We then annualized this result for use in the model.

The parameters that govern disease transmission and progression were based on previously-published studies. However, parameters and settings that define disease introductions are based on specific assumptions we make for our application. Because we wish to investigate both pre-emptive and reactive management strategies, we assume disease is introduced by a single rabid dog (perhaps from outside the area the occupied by the modeled population) at the beginning of the third year.

* Cost estimates
* Human impacts
  + Bites
  + PEPs

**Results**

**Discussion**

**References**