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

**Aaron Andersona,\*, Johann Kotzéb, Brody Hatcha, Chris Slootmakera, Stephanie A. Shwiffa, Anne Conanc, Darryn Knobelc, Louis H. Neld,e**

a USDA National Wildlife Research Center, Fort Collins, CO, USA

b MSD Animal Health Malelane Research Unit, South Africa

c Ross University School of Veterinary Medicine, Basseterre, St Kitts and Nevis

d Department of Microbiology and Plant Pathology, University of Pretoria, Pretoria, South Africa

e Global Alliance for Rabies Control SA NPC, Pretoria, South Africa

\* Tel: + 1-970-266-6264 Fax: +1-970-266-6157 Email: Aaron.M.Anderson@aphis.usda.gov

**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. Furthermore, 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, Vigilato et al. 2013).

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 results 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 canine rabies management funding and planning is often 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 (https://bioecon.shinyapps.io/CanineRabiesWebApp) as well as a complementary command-line interface. The model 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 (https://github.com/anderaa/BioEcon\_CanineRabies) 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 only requires 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.

To illustrate application of the model, we investigate several aspects of rabies management in free-ranging dog populations in South Africa. Specifically, we investigate the optimality of puppy vaccination and of combining sterilization and vaccination to minimize the impacts of the disease. The manuscript proceeds with a description of the model and the details of its various mechanisms. This is followed by the presentation of the case study. We provide details of the process of parameterizing the model for a region in South Africa and of examining alternative management strategies within this region. After presenting and analyzing the results of our application, 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. Notably, the user can 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.

|  |  |  |
| --- | --- | --- |
| **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 mitigate this concern here. Our model is written in the R language (R Core Team 2014) using the Shiny framework for the web application. 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 for the web app model 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.

**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 given 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***

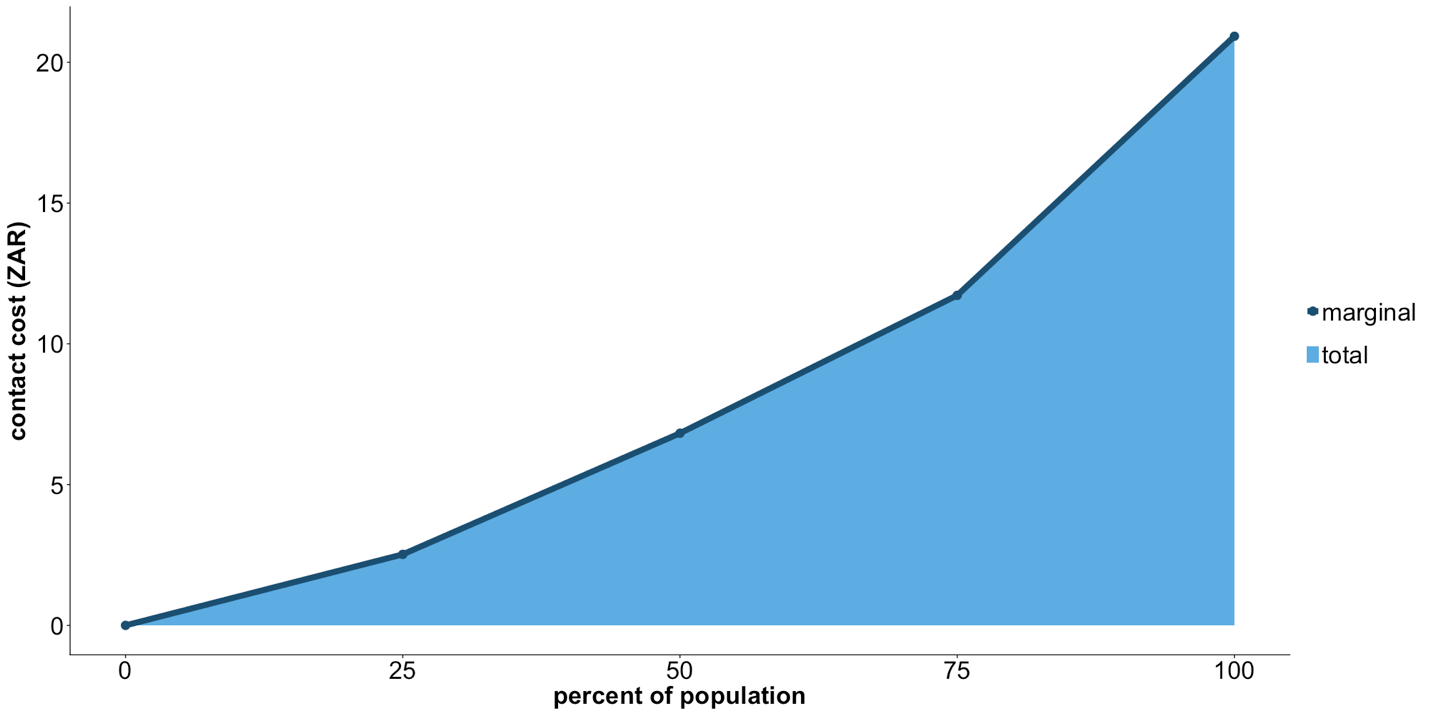
The user can specify two impacts to humans: PEP applications and mortality. To enable estimation of these impacts, the user first specifies the number of bites per day by rabid and non-rabid dogs. Then the probability of PEP applications for each bite type, as well as the cost of each PEP application, 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***

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 cost 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.

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.

**Figure 2 – The stepwise-linear function for capture or contact costs used in our application**



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***

Rabies remains endemic in South Africa, and is relatively common in KwaZulu-Natal, Eastern Cape, Mpumalanga, Free State and Limpopo Provinces (NHLS 2016). From 2012 to 2015, 30 human cases were reported, although this likely represents an underestimate of the true number (Kotze 2017, NHLS 2016). Historically, the dogs have been responsible for the vast majority of human cases in South Africa, and most victims have been children under 10 years of age (Bishop et a. 2010).

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

The economic burden of PEP is substantial, amounting to R70 million per year, much of which falls on an already-stressed public healthcare system (Kotze 2017). In addition to the burden of PEP, several government entities contribute significant resources to control efforts. Roughly XXXX is spent each year by the South African government on vaccination campaigns and public education. Much of the effort devoted to vaccination is coordinated by a network of state veterinarians employed by the South African Department of Agriculture.

***Objectives***

Managers tasked with minimizing canine rabies prevalence in South Africa (and elsewhere) face a variety of strategic choices. These choices include the type and timing of vaccination campaigns. Central-point vaccination campaigns can be advantageous because they rely on owners to bring dogs for vaccination. As a result, contact costs are relatively low. In some areas, dogs will often be brought by children, so operating these campaigns when school is not in session will further increase coverage. However, in areas with a high abundance of free-ranging or semi-owned dogs, this type of campaign may be less useful and more active contact and capture efforts may be required.

In addition to the type and timing of campaigns, managers must also decide the amount of resources to allocate to a specific area and how often to repeat campaigns. It is typically recommended that managers attempt to achieve 70% vaccination coverage, but it is often unclear what sort of funding will be required to reach this objective. Furthermore, there is high-turnover in dog populations in southern Africa, and vaccination coverage declines rapidly. Quantifying this rate of decline would assist managers in planning future vaccination plans.

Besides these broader questions related to resources requirements and vaccination campaigns, there are a variety of more specific choices related to what to do with dogs that are captured or contacted. These questions include which demographic groups to vaccinate, whether to give booster vaccinations to previously vaccinated dogs, and whether there is a role for population and fertility control. Although our objective was to design a tool that would help managers answer any of these questions, we limited the application that we present here two important questions.

The first question that we addressed is whether it is beneficial to vaccinate puppies (<90 days old). Historically, puppies have been excluded from mass vaccination campaigns on the grounds that their immature immune systems may not reliably respond to the vaccine. However, recent evidence (e.g. Morters et al. 2015) suggests that puppies do reliably respond to vaccination and current guidelines recommend vaccination at 4-6 weeks (MSD Animal Health).

Barring differences in vaccine response, 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 would desirable. If excess vaccination resources are available after all juvenile and 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 desirable. 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. There is substantial debate about the role of sterilization and other population management strategies within dog vaccination programs (Taylor et al. 2017). The OIE recommends dog population control as an integral part of vaccination programs (OIE), but Cleaveland et al. 2014 offers an opposing view based on the fact that there is no evidence that rabies transmission depends on dog density. Our interest in examining female sterilization is based on evidence that suggests female sterilization is much more effective than male sterilization at reducing abundance (Barlow et al. 1997, Fitzpatrick et al. 2016)

The answer to the question of whether and to what extent female sterilization should be integrated into vacation campaigns involves tradeoffs similar to those of the puppy vaccination question. Of course, if sufficient resources are available to vaccinate all dogs in the population, then any additional resources devoted to sterilization will reduce the need to vaccinate in the future because population turnover and growth will slow. In absence of sufficient resources to vaccinate all dogs, a manager will face a choice between vaccinating relatively more dogs or vaccinating fewer dogs but also sterilizing the females that are contacted. Although vaccination of single dog will reduce rabies prevalence and sterilization will not, sterilization might still be preferred if the effect on population growth makes the population substantially less susceptible to disease or if it makes high levels of vaccination much less costly in the future. Furthermore, if marginal contact costs increase as more dogs are captured, it may have been possible for the manager to sterilize many dogs rather than vaccinate only a few additional dogs.

***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 2). 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 estimates. However, parameters and settings that define disease introductions are based on specific assumptions we make for our application. Because we wanted to investigate both pre-emptive and reactive management strategies, we assumed 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***

We set the cost of dog treatment (vaccination, sterilization, contraception, and euthanasia) and the cost of human PEP based on communication with experts in South Africa. The cost of contacting dogs was estimated based on data we collected during mass vaccination campaigns in 37 different villages in the Bushbuckridge and Mbombela municipalities during 2015. Specifically, we recorded labor hours, wages, and kilometers driven from efforts that included both central-point and door-to-door campaigns. Typical of vaccination efforts in the region, central-point campaigns were used to contact approximately the first 25% of dogs, with door-to-door campaigns accounting for the remainder. Vaccination campaigns in this area were concentrated in the months of April, June, and September, and these are the months in which we assume management will occur in our application.

***Human impacts***

The number of human bites was based on estimate of approximately 423 bites per 100k human population (Hampson et al. 2015). From this we calculated 213,583 total bites based on a human population of just over 50 million. Hampson et al. (2015) also provides an estimate of the probability that a bite is from a rabid dog of 0.111. We leverage this to split total bites into rabid and non-rabid. Following Hampson et al. 2015, we then calculate the number of rabid dogs per year as

where 0.63 is the average vaccination coverage in South Africa. Finally, given a total dog population of 8,897,064 (South African Companion Animal Council (SACAC, 2011) and our total number of bites, we estimated the number of human bites per rabid dog per day to be 0.02252 and the number of human non-rabid bites per dog per day to be 0.00006. Unfortunately, we lack data to relate the probability of receiving PEP to the rabies status of the dog. As a result, we assume a probability of 0.991 of receiving PEP as a result of a dog bite (Hampson et al. 2015). To the extent that this is inaccurate, the model will underestimate the number of PEP applications given non-zero disease prevalence. However, all other results of the modeling exercises are unaffected. Finally, based on communication with the National Institute for Communicable Disease, we assumed per-person PEP costs to be R754.92 based on the current retail price of the vaccine in South Africa (4 x R188.73).

**Results**

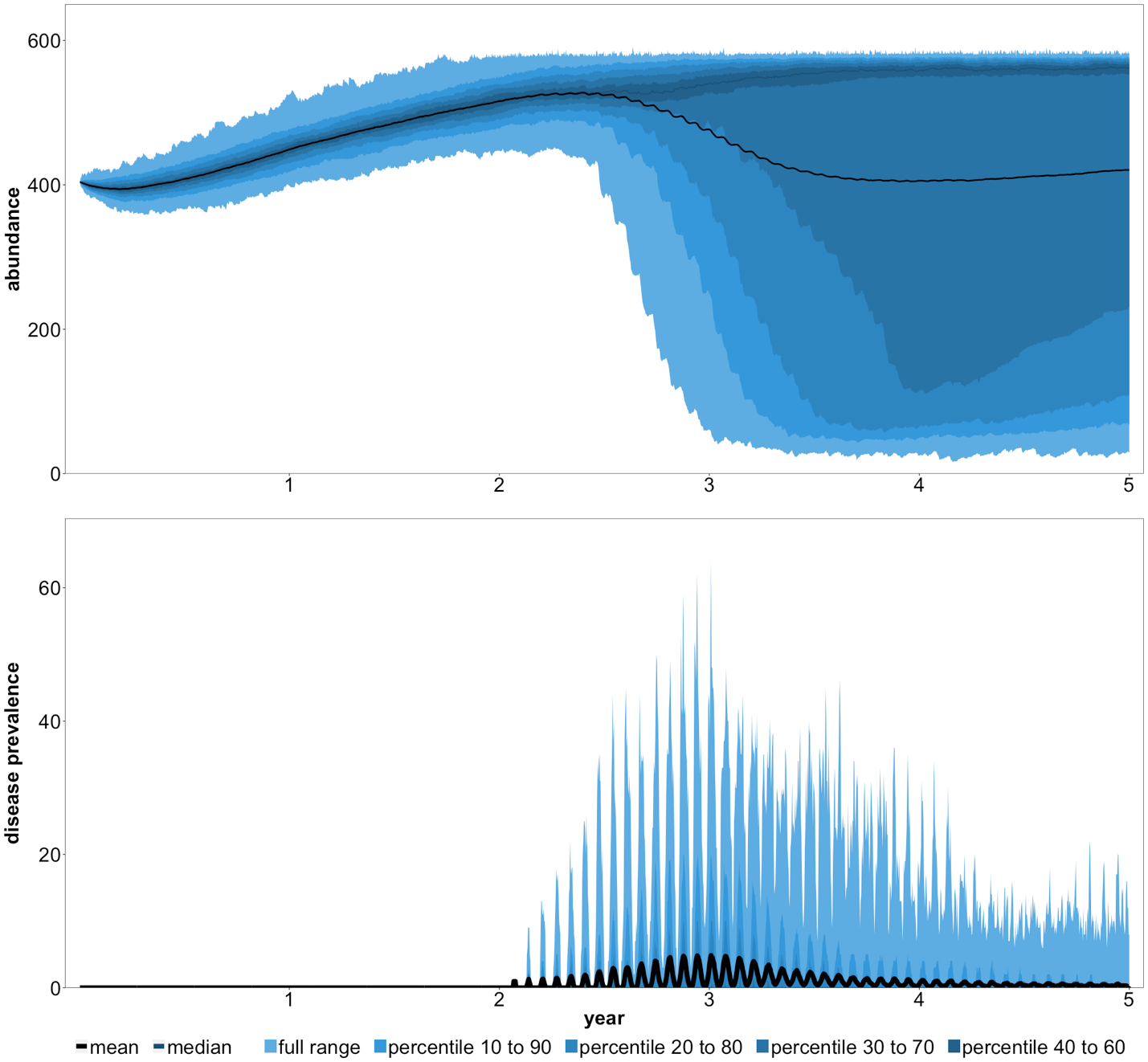
*Baseline*

Before addressing the questions of puppy vaccination and female sterilization, we investigated a number of baseline scenarios. In these scenarios, and in all others we present, we relied on the command-line version of the model.[[1]](#footnote-1) First, we examined population and disease dynamics in the absence of any management (Figure 3). Rabies was introduced by a single infectious dog at the beginning of year three. To gain a clear understanding of the benefits of vaccination, we assumed no existing vaccination coverage. Thus, disease prevalence should be higher than is currently observed in many areas of South Africa. Furthermore, note that disease prevalence should be higher than indicated by Equation 1 with vaccination coverage set to zero. If Equation 1 is reasonable for all of South Africa over a period of months or years, we would expect maximum (or even average) disease prevalence during an outbreak in a smaller area to be substantially higher.

The key result from the no management scenario was 1,062 dog-days of infection[[2]](#footnote-2). Across 250 iterations of the simulation, the average maximum daily rabies prevalence was 13 dogs. However, not all rabies introductions resulted in an outbreak; maximum prevalence never exceeded a single dog in 51% of the iterations. In the iterations that we observed disease transmission to multiple dogs, the average maximum prevalence was 25 dogs. The total cost of rabies in this scenario was R51,877 which was made up entirely of PEP costs. Finally, we observed no human deaths in any of the observed scenarios.

Next, we investigated a suite of baseline management scenarios in which we applied vaccination to juvenile and adult dogs (Table 3). Specifically, we defined three different total budgets for the five-year simulation period: R5,000, R15,000, and R30,000. At each total budget, we additionally examined annual, biennial, and reactive management. In the annual management scenarios, the budget is spread evenly over the entire five-year period; in the biennial scenarios, the budget is spread over years one, three, and five. The reactive scenarios assume that management only occurs once the disease is detected and continues to occur thereafter. Thus, in the reactive scenarios, the management budget is spread evenly over years three, four, and five.

The metric by which we judge the relative merits of the baseline strategies is dog-days of infection. This is equivalent to assuming the sole objective of management is to minimize disease prevalence. We focus on dog-days of infection because PEP costs and human mortality risk are highly related to it. Baseline results indicate that even very low levels of vaccination will substantially reduce rabies prevalence and burden. Even the worst performing of the baseline scenarios (reactive management with a budget of R5,000) provided a 74% decline in dog-days of infection and reduced the combined cost of PEP and management.

****

**Figure 3 – Abundance and disease prevalence with no vaccination coverage and no management**

At all budget levels, the annual management strategies were superior to their biennial and reactive budget-equivalents. There are several reasons for this. First, when resources are more concentrated in certain years (as in biennial and reactive), it pushes contact costs onto the steeper portion of the marginal cost curve. This means that it becomes costlier to find an additional dog to vaccinate. Second, annual management makes it more likely to re-contact dogs and apply a booster vaccine, which we assume provides an additional three years of protection. The preceding comparison notwithstanding, our objective here is not to provide guidance on management timing across years. These decisions often depend on factors besides cost effectiveness. For example, annual vaccination in a local area may not be feasible given the resources available and the total size of the area under management. Or reactive management may be required when a dog tests positive in an area that had been rabies-free for some time.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Table 3 – Baseline scenario results** | | | | | |
|  | **dog-days**  **of infection** | **probability**  **of outbreak** | **max prev.**  **of outbreak** | **max vacc.**  **coverage** | **total**  **cost** |
| **no management** | 1,018 | 49% | 25 | - | R51,877 |
| **annual** |  |  |  |  |  |
| **budget = R5,000** | 154 | 31% | 9 | 21% | R46,564 |
| **budget = R15,000** | 20 | 23% | 4 | 45% | R54,895 |
| **budget = R30,000** | 6 | 13% | 3 | 69% | R69,634 |
| **biennial** |  |  |  |  |  |
| **budget = R5,000** | 240 | 38% | 10 | 22% | R47,537 |
| **budget = R15,000** | 46 | 40% | 5 | 45% | R55,143 |
| **budget = R30,000** | 22 | 30% | 5 | 64% | R69,815 |
| **reactive** |  |  |  |  |  |
| **budget = R5,000** | 268 | 48% | 11 | 32% | R47,778 |
| **budget = R15,000** | 62 | 42% | 6 | 60% | R55,480 |
| **budget = R30,000** | 47 | 46% | 6 | 82% | R70,271 |

*Puppy Vaccination*

The observation that puppies respond well to rabies vaccination is not sufficient evidence to justify puppy vaccination during mass vaccination campaigns. There are two additional factors that must be considered. First, if the slope of the marginal contact cost curve is positive, it becomes costlier to contact additional dogs as a campaign continues. If these costs are sufficiently large, the suggestion is that puppies that happen to be contacted should be vaccinated because it will become increasingly costly to contact additional juveniles and adults. However, this must be weighed against fact that the mortality rate of puppies is often much higher. In our target population, puppy mortality is nearly three times higher than adult mortality. Thus, even if a manager can forego a relatively small number of adult vaccinations and gain a relatively larger number of puppy vaccinations, mortality differences will cause the vaccinated puppies to exit the population earlier and potentially negate any advantage.

To investigate the optimality of puppy vaccination, we modified our baseline scenarios by vaccinating all puppies that are contacted (Table 4). The results provide evidence of the tradeoff we discuss above. Puppy vaccination reduces dog-days of infection in every scenario except annual vaccination with a budget or R5,000. Although we also investigate biennial and reactive scenarios with total budgets of R5,000, the annual scenario is the only scenario that spreads this budget over all five years of the timeframe. Thus, the annual budget is lower in the annual/R5,000 scenario that in any other. The observation that this is the only scenario in which it is not beneficial to vaccinate puppies suggests that this only scenario in which the contact costs are sufficiently low….

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Table 4 – Puppy vaccination results** | | | | | |
|  | **dog-days**  **of infection** | **probability**  **of outbreak** | **max prev.**  **of outbreak** | **max vacc.**  **coverage** | **total**  **cost** |
| **annual** |  |  |  |  |  |
| **budget = R5,000** | 174 | 34% | 10 | 22% | R46,829 |
| **budget = R15,000** | 16 | 20% | 4 | 48% | R54,945 |
| **budget = R30,000** | 7 | 13% | 3 | 73% | R69,750 |
| **biennial** |  |  |  |  |  |
| **budget = R5,000** | 181 | 40% | 7 | 25% | R46,939 |
| **budget = R15,000** | 39 | 36% | 5 | 49% | R55,210 |
| **budget = R30,000** | 20 | 25% | 5 | 69% | R69,846 |
| **reactive** |  |  |  |  |  |
| **budget = R5,000** | 247 | 49% | 10 | 33% | R47,611 |
| **budget = R15,000** | 73 | 54% | 6 | 63% | R55,548 |
| **budget = R30,000** | 34 | 46% | 5 | 87% | R70,043 |

<insert analysis of budget threshold for puppy vaccination>

*Female Sterilization*

In these scenarios, we assume any non-sterilized juvenile or adult female dog that is contacted during a vaccination campaign is surgically sterilized. Sterilization could be beneficial if reduction in population growth and turnover reduce future vaccination costs enough to justify forego vaccinating some dogs in earlier periods. Based on the time period we examine, it is intuitive that sterilization will not be effective at reducing the burden or total cost in the reactive scenario. In the reactive scenarios, management only occurs in response to an outbreak, before sterilization could slow growth and turnover. However, we choose to present the results here because they illustrate how sterilization can affect expected abundance and vaccine coverages in latter half of the timeframe.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Table 5 – Female sterilization results** | | | | | |
|  | **dog-days**  **of infection** | **probability**  **of outbreak** | **max prev.**  **of outbreak** | **max vacc.**  **coverage** | **total**  **cost** |
| **annual** |  |  |  |  |  |
| **budget = R5,000** | 771 | 44% | 21 | 5% | R53,750 |
| **budget = R15,000** | 669 | 46% | 18 | 11% | R62,398 |
| **budget = R30,000** | 300 | 40% | 11 | 16% | R72,288 |
| **biennial** |  |  |  |  |  |
| **budget = R5,000** | 899 | 21% | 51 | 6% | R55,087 |
| **budget = R15,000** |  | % |  | % | R |
| **budget = R30,000** |  | % |  | % | R |
| **reactive** |  |  |  |  |  |
| **budget = R5,000** |  | % |  | % | R |
| **budget = R15,000** |  | % |  | % | R |
| **budget = R30,000** |  | % |  | % | R |

**<insert analysis of budget threshold for female sterilization>**

To maximize the chances of female sterilization providing a net benefit, we examine a set of additional scenarios in which budget are larger and rabies is introduced at the beginning of year 5. Larger budgets will potentially push contact costs onto the steepest portion of the marginal cost curve, which increases the cost of vaccinating an additional dog relative to sterilizing females that are contacted earlier in vaccination campaigns. Furthermore, pushing the time of introduction back two years allows more time for the benefits of sterilization to be realized. After four potential years of sterilization, abundance should be substantially lower.

**Discussion**

Besides answering several important strategic questions related to rabies management in South Africa, our over-arching objective was to build a tool that can be used in applied settings to answer practical questions about how to best manage canine rabies in South Africa and elsewhere. The tool we provide is more accessible and more flexible than any other modeling tool for canine rabies management that we are aware of. Users can access the model easily and the interface allows many parameters to be tuned for the specific application. Furthermore, a huge variety of strategic options can be investigated. Any combination of vaccination, sterilization, contraception, and euthanasia can be specified, and these can be set specifically for each of six different demographic groups.

The other substantial advantage of our model is the sophistication and realism of the economic and cost components of the model. Accounting for increasing marginal costs of contact or capture is of central importance when a manager is considering diverting resources to options such as fertility control, booster vaccination, or vaccination of puppies. Additionally, the ability to specify sex-specific fertility control costs and adjust these costs is important. Male and female sterilization are not equally costly, and chemo-sterilization is an evolving technology with sex-specific costs that are likely to change substantially as the technology is refined and becomes more widely available.

There are several shortcomings of the model that users should be aware of. Although we have carefully parameterized the model based on previously-published information and data we have collected, the suitability of these parameters for modeling populations that differ substantially from the population we modeled in our application is an unanswered question. There two additional concerns related to modeling large populations. First, the model we have built has no spatial detail other than a concept of dogs entering and exiting the population. In large populations with substantial spatial heterogeneity, the suitability of our model should be carefully considered. Second, because our model is a stochastic simulation model, it is quite slow and computation time will increase approximately linearly with both the size of the population and the number of iterations specified.

**References**

Cleaveland, S., Lankester, F., Townsend, S., Lembo, T., Hampson, K. (2014) Rabies control and elimination: a test case for One Health Veterinary Record 175, 188-193.

NHLS (National Health Laboratory Service). 2016. Rabies Frequently Asked Questions. http://www.nicd.ac.za/assets/files/RabiesFAQ\_20160609\_final.pdf. Accessed January 2018.

Morters, M. K., McNabb, S., Horton, D. L., Fooks, A. R., Schoeman, J. P., Whay, H. R., … Cleaveland, S. (2015). Effective vaccination against rabies in puppies in rabies endemic regions. The Veterinary Record, 177(6), 150. http://doi.org/10.1136/vr.102975

MSD ANIMAL HEALTH Nobivac Puppy DP data sheet. http://www.msd-animal-health.co.in/Products/Nobivac\_Puppy\_DP/020\_Product\_Details.aspx. Accessed January 12, 2018.

OIE. Infection with rabies virus. Terrestrial Animal Health Code. (Chap. 8.13), OIE; (2015). Available from: http://www.oie.int/index.php?id=169&L=0&htmfile=chapitre\_rabies.htm

Taylor, L. H., Wallace, R. M., Balaram, D., Lindenmayer, J. M., Eckery, D. C., Mutonono-Watkiss, B., … Nel, L. H. (2017). The Role of Dog Population Management in Rabies Elimination—A Review of Current Approaches and Future Opportunities. Frontiers in Veterinary Science, 4, 109. http://doi.org/10.3389/fvets.2017.00109

Barlow ND, Kean JM, Briggs CJ. Modelling the relative efficacy of culling and sterilisation for controlling populations. Wildlife Res (1997) 24:129–41.10.1071/WR95027

Bourhy, H., Dacheux, L., Strady, C. & Mailles, A. ( 2005 ). Rabies in Europe in 2005. Euro Surveillence 10(11), 213–216.

Fitzpatrick MC, Shah HA, Pandey A, Bilinski AM, Kakkar M, Clark AD, et al. One Health approach to cost-effective rabies control in India. Proc Natl Acad Sci USA (2016) 113(51):14574–81.10.1073/pnas.1604975113

Blanton JD1, Palmer D, Rupprecht CE. Rabies surveillance in the United States during 2009.

J Am Vet Med Assoc. 2010 Sep 15;237(6):646-57. doi: 10.2460/javma.237.6.646.

Schneider MC, Belotto A, Ade MP, Hendrickx S, Leanes LF, de Freitas Rodrigues MJ, et al. Current status of human rabies transmitted by dogs in Latin America. Cadernos De Saude Publica. 2007;23(9):2049–63. pmid:17700940

Vigilato, M. A. N., Clavijo, A., Knobl, T., Silva, H. M. T., Cosivi, O., Schneider, M. C., … Espinal, M. A. (2013). Progress towards eliminating canine rabies: policies and perspectives from Latin America and the Caribbean. Philosophical Transactions of the Royal Society B: Biological Sciences, 368(1623), 20120143. http://doi.org/10.1098/rstb.2012.0143

R Core Team. 2014. R: A language and environment for statistical computing. R Foundation for Statistical Computing. Vienna, Austria. http://www.R-project.org.

Kotze, J.L. 2017. Rabies in South Africa: Report from the RAG for 2015-2016. Department of Agriculture, Forestry, and Fisheries, Republic of South Africa.

Bishop, G.C., D.N. Durrheim, P.E. Kloeck, J.D. Godlonton, J. Bingham, R. Speare. 2010. Guide for the Medical, Veterinary and allied Professions, Second Edition. Department of Agriculture, Forestry, and Fisheries, Republic of South Africa.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Table 2 – Model Parameters** | | | | | |
| **variable name** | **description** | **location** | **default value** | **source** | **notes** |
| ***simulation inputs*** | | | | | |
| simulationYears | number of years in the simulation | code | 5 | - | - |
| iterations | number of iterations | ui | 5 | - | - |
| ***initial population inputs*** | | | | | |
| initialPopSize | initial abundance | ui | 404 | HDSS data | mean abundance over observation period |
| initialFracAdult | fraction of initial population that are adult | ui | 0.49 | HDSS data | mean over observation period |
| initialFracPup | fraction of initial pop. of non-adults that are puppies | ui | 0.39 | HDSS data | mean over observation period |
| initialFracFemale | fraction of initial population that are female | code | 0.38 | HDSS data | mean over observation period |
| initialFracImmune | fraction of initial population that are immune | code | 0 | - | - |
| initialFracContra | fraction of initial pop. that have been contracepted | code | 0 | - | - |
| initialFracVacc | fraction of initial pop. that have been vaccinated | code | 0 | - | - |
| initialFracSter | fraction of initial population that have been sterilized | code | 0 | - | - |
| ***population model inputs*** | | | | | |
| maxJuvAge | day age at which juveniles transition to adult | code | 299 | expert opinion | approximate age of sexual maturity |
| maxPuppyAge | day age at which puppies transition to juveniles | code | 89 | expert opinion | approximate age of dispersal from litter |
| maxAge | maximum possible age of a dog in days | code | 4000 | expert opinion | - |
| carryingCap | carrying capacity | ui | 577 | HDSS data | maximum over observation period |
| pupAnnMortProb | annual mortality probability of a puppy | ui | 0.9 | HDSS data | estimated from data |
| juvAnnMortProb | annual mortality probability of a juvenile | ui | 0.63 | HDSS data | estimated from data |
| adultAnnMortProb | annual mortality probability of an adult | ui | 0.32 | HDSS data | estimated from data |
| emigrationProb | annual prob. of non-mortality exit from the pop. | ui | 0 | - | mortality probability incorporates non-mortality exit |
| immigrantDogs | number of dogs moving into the population annually | ui | 189 | HDSS data | annual average over observation period |
| expectedLittersPFY | expected litters per fertile female per year | ui | 0.31 | HDSS data | mean over observation period |
| meanLitterSize | mean litter size | code | 4.4 | HDSS data | mean over observation period |
| femalePupProb | fraction of puppies that are female | code | 0.38 | HDSS data | calculated from data |
| fractionBirthPulse | fraction of litters born during the birth pulse | ui | 0 | HDSS data | none observed in data |
| birthPulseVector | months that define the birth pulse | ui | [False, …, False] | HDSS data | none observed in data |
| ***disease model inputs*** | | | | | |
| monthsOfPressure | number of sequential months of introduction | ui | 0 | - | - |
| dogsPerMonthExposed | dogs per month exposed during introduction | ui | 0 | - | - |
| monthInitIntroduction | month of initial introduction | ui | 0 | - | - |
| timeLimitExposed | maximum days in exposed state | code | 22 | Hampson et al. 2009 | - |
| timeLimitInfective | maximum days in infective state | code | 3 | Hampson et al. 2009 | - |
| survivalProb | survival probability | code | 0 | asssumed | - |
| bitesPerRabidMean | bites per rabid mean | ui | 2.15 | Hampson et al. 2009 | - |
| bitesPerRabidShape | bites per rabid shape | code | 1.33 | Hampson et al. 2009 | - |
| probInfectionFromBite | probability of infection from bite | code | 0.49 | Hampson et al. 2009 | - |
| ***disease impact inputs*** | | | | | |
| bitesPerNonRabid | mean daily bites from a non-rabid dog | ui | 0.00005 | Hampson et al. 2015, SACAC 2011 | Calculated from Hamson et al. 2015 and est. dog pop. |
| bitesPerRabid | mean daily bites from a rabid dog | ui | 0.02252 | Hampson et al. 2015, SACAC 2011 | Calculated from Hamson et al. 2015 and est. dog pop. |
| PEPperNonRabidBite | PEP applications per bite from non-rabid dog | ui | 0.991 | Hampson et al. 2015, SACAC 2012 | Calculated from Hamson et al. 2015 and est. dog pop. |
| PEPperRabidBite | number of PEP applications per bite from rabid dog | ui | 0.991 | Hampson et al. 2015 | - |
| costPerPEP | cost per person treated with PEP | ui | R754.92 | expert opinion | - |
| lifeLossPerRabidBite | mean human deaths from a rabid dog bite | ui | 0.19 | Hampson et al. 2015 | - |
| ***management inputs*** | | | | | |
| vaccineCost | cost to vaccinate one dog, excluding contact cost | ui | R2.426 | expert opinion | - |
| contraceptionCostFemale | cost to contracept one female, excl. contact cost | ui | R150 | assumed | unused in current application |
| contraceptionCostMale | cost to contracept one male, excluding contact cost | ui | R150 | assumed | unused in current application |
| sterilizationCostFemale | cost to sterilize one female, excluding contact cost | ui | R300 | expert opinion | - |
| sterilizationCostMale | cost to sterilize one male, excluding contact cost | ui | R200 | expert opinion | - |
| euthanasiaCost | cost to euthanize one dog, excluding contact cost | ui | R30 | assumed | - unused in current application |
| timeVaccineEffective | years that the vaccine remains effective | ui | 2 | Hampson et al. 2007 | - |
| timeBoosterEffective | year that vaccine remains effective after booster | ui | 3 | expert opinion | - |
| timeContraEffectiveMales | years that male contraceptive remains effective | ui | 2 | assumed | unused in current application |
| timeContraEffectiveFemales | years that female contraceptive remains effective | ui | 2 | assumed | unused in current application |
| contactCost25 | cost of contacting 25% of the dogs in the population | ui | 1019.09 | MVC data | - |
| contactCost50 | cost of contacting 50% of the dogs in the population | ui | 2757.3 | MVC data | - |
| contactCost75 | cost of contacting 75% of the dogs in the population | ui | 4735.89 | MVC data | - |
| contactCost100 | cost of contacting all of the dogs in the population | ui | 8453.7 | MVC data | - |
| mgtMonthVector | vector of months that management will occur | ui | [0, …., 0] | - | - |
| annualBudget | vector with elements for each of 5 years | ui | [0, …., 0] | - | - |
| boosterGiven | booster given to already vaccinated dogs | ui | True | - | - |
| vacc<demographic><sex> | dogs in this group vaccinated if contacted | ui | False | - | - |
| ster<demographic><sex> | dogs in this group sterilized if contacted | ui | False | - | - |
| contra<demographic><sex> | dogs in this group contracepted if contacted | ui | False | - | - |
| euth<demographic><sex> | dogs in this group removed from pop. if contacted | ui | False | - | - |

1. Due to the stochastic nature of the models, results can be approximately but not exactly duplicated using the web-based model. [↑](#footnote-ref-1)
2. A single dog being infectious for one day results in one dog-day of infection. As an example, if an average of one dog of infectious on each day of a three-year period, the total dog-days of infection will be 1 x 3 x 365 = 1,095. [↑](#footnote-ref-2)