Modeling the Dynamics of Canine Rabies and Policy Analysis under Uncertainty

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Abstract: *Rabies is a viral fatal disease transmitted to humans mainly from dogs. Human deaths due to rabies have been increasing in recent years, especially in Africa and Asia where socioeconomic factors play an important role in the revival of the epidemic. In the current situation, it is unknown how the epidemic will evolve and which policies can prevent undesired futures. Therefore, the dynamics of rabies are investigated with a system dynamics model and several policy options are tested in this study. An exploratory approach is adopted to deal with uncertainties associated with model formulation, lack of data and the epidemic characteristics. The results showed a wide variety of future dynamics for possible human deaths, and following dog culling, human vaccination resulted to be the best policy to decrease the maximum possible number of casualties. However, when the cost effectiveness is taken into account, high rates of dog vaccination and high levels of human hospitalization upon exposure to a dog were found as the policy that maximizes the number of future favorable cases in terms of human casualties and costs. Future research can include extending the model with underlying socioeconomic factors and multiple species.*

Keywords: *Rabies, epidemics, system dynamics, exploratory modeling and analysis, uncertainty, model structure uncertainty*

1. Introduction

Rabies is a viral zoonotic disease that has threatened human health throughout history. It is transmitted to humans from warm-blooded animals, mainly from dogs due to their intense interaction with humans. The rabies virus is almost entirely fatal once it enters the body, unless a Post-exposure Prophylaxis (PEP) treatment is applied to prevent the virus from reaching the brain.

Despite the eradication of the virus in North America and Europe, the World Health Organization reported 61000 human deaths due to rabies in 2010, of which 95% was in Africa and Asia (WHO, 2013). Increasing numbers of canine-related human rabies cases especially in India and China in recent years have drawn worldwide attention and revealed the complexity of the problem. On the one hand, the epidemic is attributed to several socioeconomic and cultural factors. In China, pet ownership attempts of the growing middle class which result in more stray dogs when the attempts fail is mentioned as an important factor (McKenna, 2013), whereas poor waste management systems which attract dogs to garbage mounds and facilitate dog-human interaction in

India are acknowledged as the problem underlying the rabies epidemic (Harris, 2012). On the other hand, policy makers face several problems in decision making, such as cultural and religious factors that oppose culling of dogs, and the dilemma of vaccinating dogs or humans, before or after exposure to a rabid animal. Yet, the major problem of policy making is the lack of data which stems either from unreported cases due to people's religious beliefs or ignorance, or from the absence of expensive surveillance activities (Knobel *et al.,* 2005; Beyer *et al.*, 2011; Lembo *et al.,* 2010).

Quantitative modeling has long been used to investigate the dynamics of rabies and to compare the well-known policy options such as culling and vaccination. Early models were based on ordinary differential equations (ODE's) and the well-known *Susceptible-Infected-Recovered (SIR)* framework for epidemic models. Anderson *et al.* (1981) presented a simple but useful model based on this framework of density-dependent transmission for fox rabies in Europe. This approach has been adopted by several recent studies, especially for canine rabies (Zhang *et al.*, 2011; Zhang *et al.*, 2012; Hou *et al.*, 2012; Zinsstag *et al.*, 2009; Deal *et al.,* 2000). Among these, only Deal et al. (2000) and Zinsstag et al. (2009) used system dynamics tools (software) although the models were not built with a system dynamics perspective. Stochastic inference and simulation models based on state-space distribution or Bayesian networks, have constituted the second major branch of rabies models, and are used mainly to deal with the absence of reported data (Hampson *et al.,* 2009; Beyer et al., 2011). For a more detailed review of mathematical models built for rabies, the reader is referred to Sterner and Smith (2006) and Panjeti and Real (2011). These studies indicate a wide variety of modeling methodologies that can be used and a high complication level that can be represented thanks to the advancements in computation technology. However, as Panjeti and Real (2011) argue, the availability of data lags behind the advancement in modeling techniques, and this impedes providing improvement over the early simple ODE models.

System dynamics has been successfully implemented to several epidemic diseases such as dengue (Ritchie-Dunham and Mendez Galvan, 1999), AIDS (Roberts and Dangerfield, 1990; Lounsbury and Levine, 2002) and flu pandemics (Eskici and Turkgulu, 2007; Pruyt and Hamarat, 2010; Duggan, 2012). These studies generated useful insights for understanding the transmission dynamics and comparing policy options. Following this, it is believed that system dynamics can also assist decision making to deal with rabies, and a twofold purpose for this paper is set: Firstly, this study aims at capturing additional nonlinearities present in the rabies transmission mechanism which are not included in the early ODE models found in the literature. The second purpose of this study is to use this model to explore future dynamics and relative performance of policy options in these futures, in order to deal with the uncertainties caused especially by the lack of data.

With these purposes, first, the system dynamics model developed for rabies will be described in the next section. The base run behavior of this model will be discussed in Section 3, with a comparison to the behavior of existing rabies models based on ODE. In Section 4, an uncertainty analysis for the exploration of future dynamics and comparison of several policy options will be presented. The paper will end with discussions and conclusions in Section 5.

2. Model Description

Since this paper is focused only on the canine rabies and its effects on human population, other species that can infect humans or dogs with rabies virus are excluded from the model scope. Therefore, only human and dog species are included in this study and the model is divided into two main parts, namely the 'dog' and 'human' sub-models:

- In the 'dog' sub-model, transmission within the dog population is modeled as a *Susceptible-Exposed-Infected-Vaccinated* (SEIV) model, which is a modified version of SIR model but assumes a 100% mortality rate of infected dogs, hence no recovered population.
- In the 'human' sub-model, the rabies epidemic in the human population is also modeled as a SEIV model, but another stock variable is added to represent the *Hospitalized* population group.

The link between the two sub-models is certainly the transmission of the virus from dogs to humans through biting.

Dog sub-model

The stock-flow diagram of this sub-model that shows the susceptible, exposed, infected and vaccinated (immune) population groups and movements between these can be seen in Figure 1. Rabid animals exhibit three different behaviors during the disease (Hemachudha *et al.*, 2002). Upon infection, they enter the prodromal phase associated with shyness and isolation. After that, they become furious and exhibit high aggressiveness. Lastly, they enter the paralytic stage and die. Since their contact behavior is very different, the infected population is divided into two groups for prodromal and furious dogs. The paralytic stage is excluded since dogs are assumed not to bite any human or dog under paralysis.

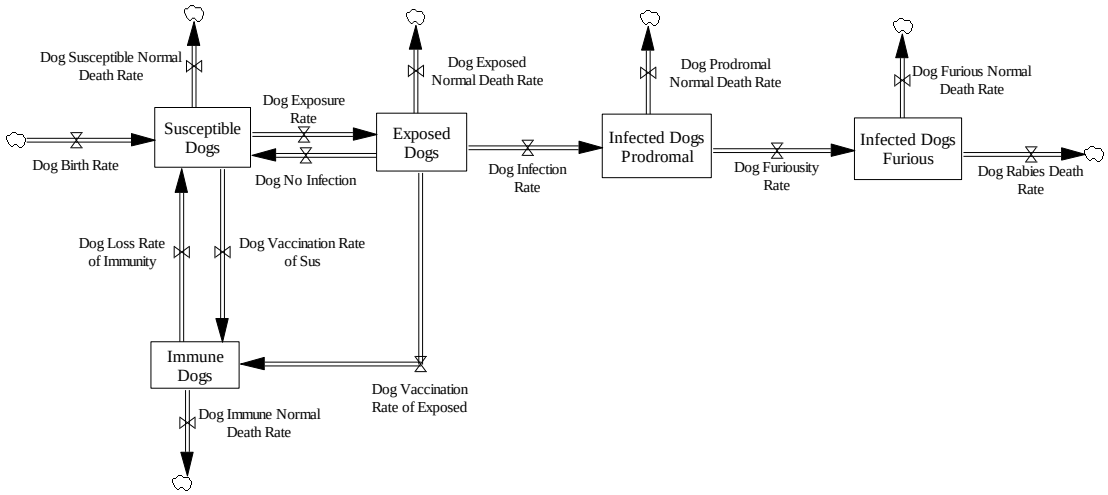

Figure 1: Stock-flow Diagram of the Dog Sub-model

All normal death, vaccination, immunity loss, furiousity and rabies-related death rates are formulated fractionally or as a first order material delay. Infection rate is formulated

as a fraction of exposed population, where this fraction is the infectivity, and divided by the average duration of incubation, as Equation 1 shows.

$$Dog\ Infection\ Rate(t) = \frac{Exposed\ Dogs\ (t) * Infectivity}{Average\ Incubation\ Period} \quad \text{[Dogs/year]} \quad (1)$$

"Dog No Infection" shows the rate of dogs that are not actually infected after being exposed and join the susceptible group again. It is formulated as:

$$Dog\ Infection\ Rate(t) = \frac{Exposed\ Dogs(t) * (1 - Infectivity)}{Average\ Incubation\ Period} \quad \text{[Dogs/year]} \quad (2)$$

In several ODE models found in the literature (Zhang et al., 2011; Zhang et al., 2012; Hou et al., 2012; Zinsstag et al., 2009; Deal et al., 2000), the birth rate is assumed to be a constant rather than a fraction. Although this formulation is expected to yield unrealistic results when the dog population decreases and cannot reproduce to the extent assumed by the constant value, the ability of these authors to use their modes successfully is interpreted as an uncertainty in the model formulation. Therefore, two alternative formulations of birth rate are assumed as follows:

$$Dog\ Birth\ Rate(t) = Dog\ Birth\ Rate\ Constant \quad \text{[Dogs/year]} \quad (3)$$

$$Dog\ Birth\ Rate(t) = b_{dog} * \left(S_{dog}(t) + V_{dog}(t)\right) \quad \text{[Dogs/year]} \quad (4)$$

In Equation 4, b_{dog} is the birth rate constant and only susceptible (S_{dog}) and immune (V_{dog}) dogs are assumed to be included in the reproductive population.

"Dog Exposure Rate" is one of the most important formulations since it directly determines how the virus is transmitted among dogs. In the existing ODE models (Zhang et al., 2011; Zhang et al., 2012; Hou et al., 2012; Zinsstag et al., 2009; Deal et al., 2000), this rate is formulated as a fraction of all possible contact between susceptible and infected populations. In other words, the exposure rate is assumed to be equal to the multiplication of susceptible and infected population variables by a constant determined by statistical approximation. However, in the system dynamics studies on epidemics, the transmission or infection rate is formulated in a density dependent manner, with the most well-known form being

$$IR(t) = S(t) * contact\ rate * \frac{I(t)}{T} * infectivity \quad \text{[Dogs/year]} \quad (5)$$

in the simple SIR model (Sterman, 2000, pp. 303). In this formulation, IR stands for the infection rate, S for the susceptible population, I for the infected and T for the total. This duality in the existing transmission formulations indicates another model structure uncertainty, and the following two formulations are assumed to be the two alternatives of the Dog Exposure Rate.

$$Dog\ Exposure\ Rate(t) = S_{dog}(t) * I_{dog}(t) * \beta_{1,dog} \quad \text{[Dogs/year]} \quad (6)$$

$$Dog\ Exposure\ Rate(t) = S_{dog}(t) * \beta_{2,dog} * \frac{I_{dog}(t)}{T_{dog}(t)} \quad \text{[Dogs/year]} \quad (7)$$

In Equation 6, $\beta_{1,dog}$ stands for the transmission fraction, so does $\beta_{2,dog}$ in Equation 7 for the contact rate. In Figure 2, the addition of a positive feedback loop by the density-dependent formulation besides a positive loop via susceptible population and a negative one via infected population can be seen. The interaction of these three loops is expected to create the dynamics of the exposure rate.

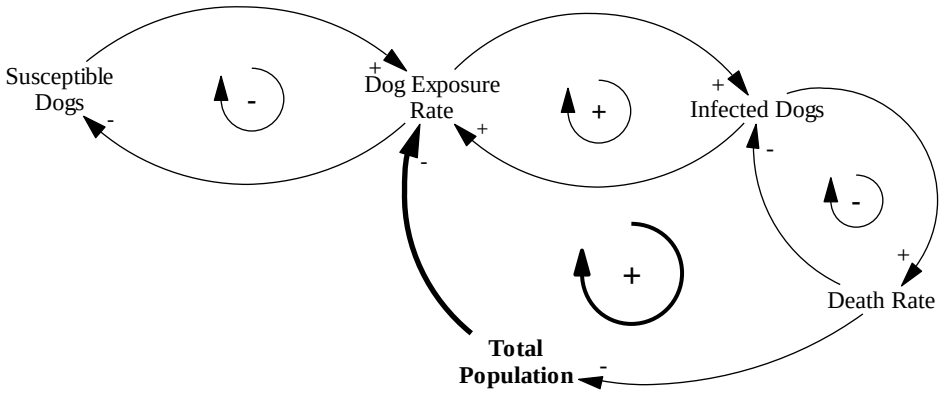

Figure 2: Causal loop diagram for the exposure rate with two alternative formulations

In addition to these two alternatives for the dog exposure rate, we propose a third one, which takes the differences in the behavior of dogs in the prodromal and furious stages of rabies into account. (Note that in the previous formulations I_{dog} refers to the sum of prodromal and furious dogs.) Due to the timid behavior of dogs in the prodromal stage and the aggressive behavior of the ones in the furious stage, the contact rate used in the density-dependent transmission formulation (Equation 7) is assumed to be a variable which depends on the fraction of prodromal or furious dogs in the total population. In the formulation of this contact rate variable, the normal contact rate is multiplied by the effects of prodrome and furiousity, which are formulated as lookup functions of which inputs are the fractions of these dog groups in the total dog population. Following this, the third alternative of dog exposure rate can be denoted as:

$$Dog\ Exposure\ Rate(t) = S_{dog}(t) * \left(\beta_{p,dog}(t) * \frac{I_p(t)}{T_{dog}(t)} + \beta_{f,dog}(t) * \frac{I_f(t)}{T_{dog}(t)}\right) \quad \text{[Dogs/year]} \quad (8)$$

$$\beta_{p,dog}(t) = \beta^*_{p,dog} * f_p\left(\frac{I_p(t)}{T_{dog}(t)}\right) \quad \text{[1/year]} \quad (8)$$

$$\beta_{f,dog}(t) = \beta^*_{f,dog} * f_f\left(\frac{I_f(t)}{T_{dog}(t)}\right) \quad \text{[1/year]} \quad (8)$$

f_p and f_f are the lookup functions used to represent the effect of prodrome and furiousity on the contact rate, respectively, and they can be seen in Appendix I.

Human sub-model

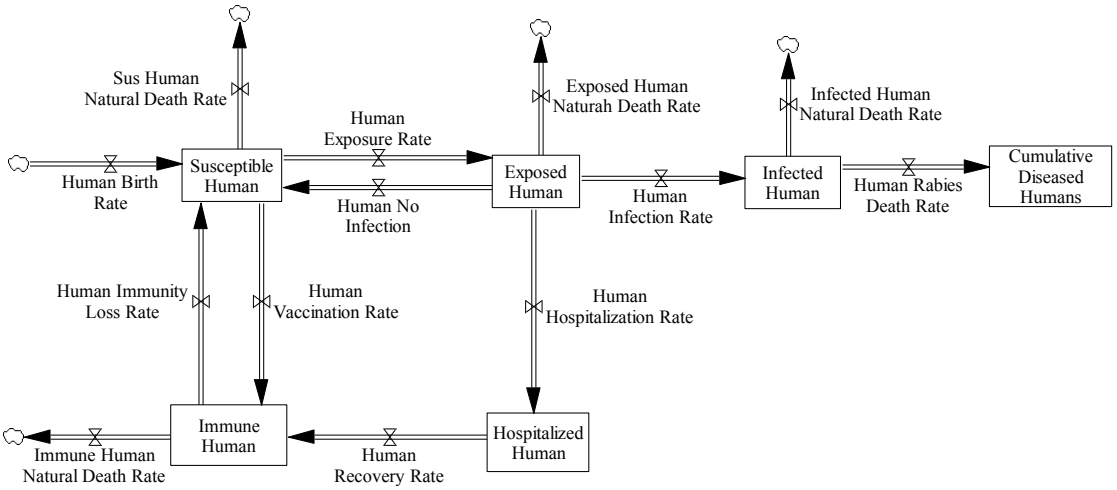

Figure 3: Stock-flow diagram of the human sub-model

The structure of the human sub-model is different from the dog sub-model in terms of having an additional stock variable for the hospitalized population, and a single stock variable for the infected population since interspecies transmission does not exist for humans. Infected people are assumed not to be hospitalized, because once the virus reaches the brain and people are counted as infected, hospitalization cannot provide recovery. All the rate variables in this sub-model are formulated similar to those of dogs, with fractional or durational parameters which can be seen in Appendix I.

As for the dog birth rate, human birth rate has two alternatives: A constant birth rate as used in some rabies models in the literature, and a fractional birth rate as used in the system dynamics literature.

The three alternative formulations for the dog-to-dog exposure rate listed above hold for the dog-to-human exposure rate, too. Whether it is not density-dependent, density-dependent or stage-dependent, the exposure occurs due to the infected dogs biting susceptible humans. The formulations for these three alternatives can be seen in the equations below.

$$Human\ Exposure\ Rate(t) = S_{hum}(t) * I_{dog}(t) * \beta_{1,hum} \quad \text{[Humans/year]} \quad (9)$$

$$Human\ Exposure\ Rate(t) = S_{hum}(t) * \beta_{2,hum} * \frac{I_{dog}(t)}{T_{dog}(t)} \quad \text{[Humans/year]} \quad (10)$$

$$Human\ Exposure\ Rate(t) = S_{hum}(t) * \left(\beta_{p,hum}(t) * \frac{I_p(t)}{T_{dog}(t)} + \beta_{f,hum}(t) * \frac{I_f(t)}{T_{dog}(t)}\right) \quad \text{[Humans/year]} \quad (11)$$

$$\beta_{p,hum}(t) = \beta^*_{p,hum} * f_p\left(\frac{I_p(t)}{T_{dog}(t)}\right) \quad \text{[1/year]} \quad (11)$$

$$\beta_{f,hum}(t) = \beta^*_{f,hum} * f_f\left(\frac{I_f(t)}{T_{dog}(t)}\right) \quad \text{[1/year]} \quad (11)$$

3. Comparison of the Base Run Behavior of Alternative Model Formulations

As mentioned before, there are several ODE models that have been built to study the transmission dynamics of rabies, and we proposed three alternative formulations to these models: First, density dependency of the transmission rate, second, fractional dog and human death rates instead of constant ones, and third, different contact behavior of dogs in different stages of the disease. To demonstrate the effects of these alternative formulations on the behavior, we use the data set of Zhang et al. (2011) and compare our model results to theirs. We calibrated our contact rate parameters and graphical function ($\beta_{2,dog}$, $\beta^*_{p,dog}$, $\beta^*_{f,dog}$, f_p, f_f, $\beta_{2,hum}$, $\beta^*_{p,hum}$, $\beta^*_{f,hum}$) by using the optimization tool of Vensim DSS with respect to the historical data of 14 years Zhang et al. (2011) used. This data for the Infected Humans in China from 1996 to 2010 can be seen in Figure 4.

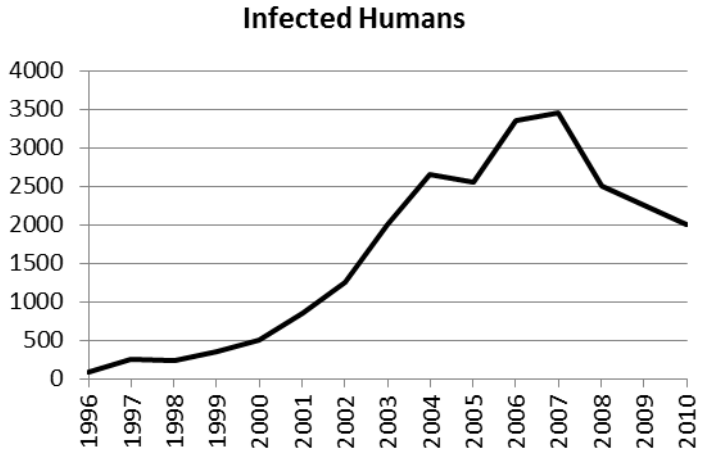

Figure 4: Data values for the Infected Human for 14 years (Zhang et al., 2011)

In Figure 5, Line 3 belongs the dynamics of the model of Zhang et al. (2011), which shows fading oscillations following an overshoot-and-decline. A density-dependent formulation for the transmission rate soothes these oscillations as Line 2 shows, since the fraction of infected dogs in the total population remains stable as they die and the transmission rate is stabilized. As for the fractional formulation of birth rates, as Line 1 shows, the number of infected humans eventually reaches zero, since infected dogs demonstrate the same behavior and susceptible dogs reach zero as well due to low birth rates. In Figure 6, the behavior of the model when these two modifications are simultaneously applied can be seen. In this case, the peak is delayed, the time span in which infected people exist is prolonged, but still the number of infected people reaches zero eventually.

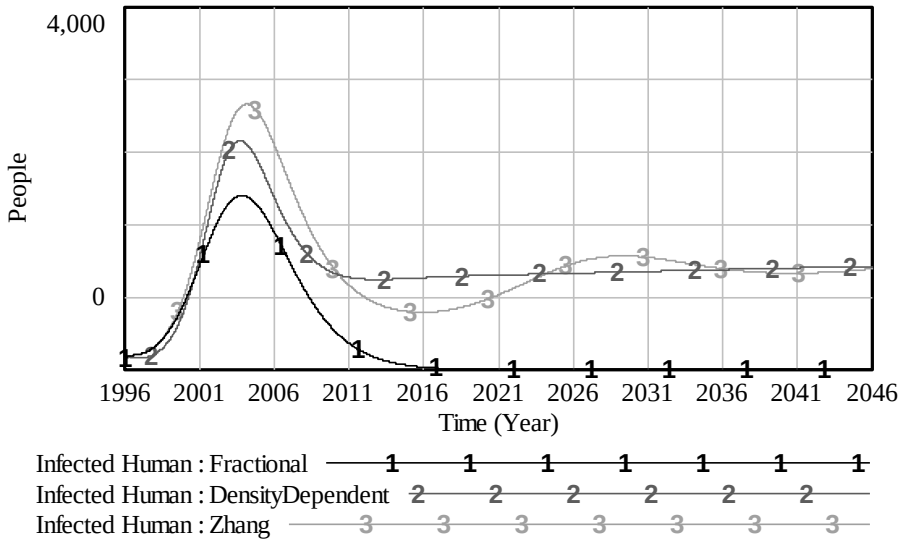

Figure 5: Dynamics of the Infected Humans resulting from the original model (3), density dependent transmissions (2) and fractional birth rates (1)

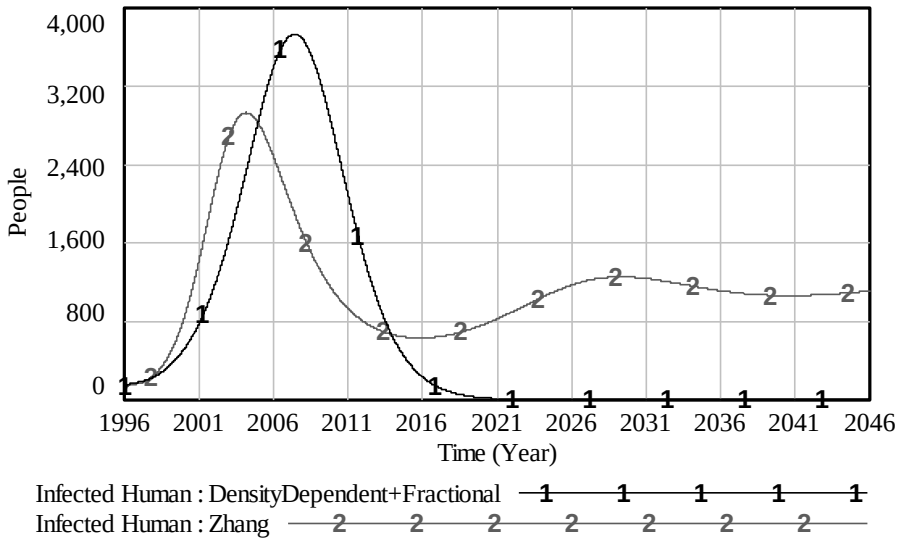

Figure 6: Dynamics of the Infected Humans when density-dependency and fractional births are implemented together (1) compared to the original model (2)

The third alternative formulation we proposed is the distinction between the stages of rabies in dogs since their contact behavior is different in each stage. Line 1 in Figure 7 shows the outcome of this formulation in addition to the density-dependency and fractional birth rates. This formulation yields a more rapid increase in Infected Humans although the rabies epidemic lasts shorter compared to previous versions of the model.

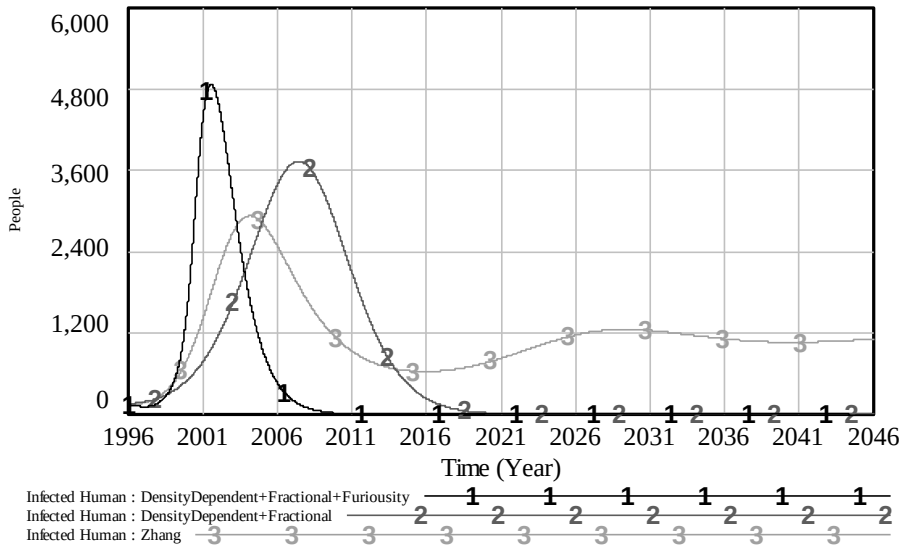

Figure 7: Dynamics of the Infected Humans in the case of staged infected population (1) compared to the original model (3) and the model with density-dependency and fractional births (2)

As seen in the figures above, these alternative formulations generate considerably different dynamics on one hand, especially in terms of the eradication of the virus or the continuation of the epidemic in a stable manner. On the other hand, they are all able generate outcomes sufficiently resembling the available data. Since the data is available for a rather short period and does not provide any information about long-term dynamics, and the proposed alternative formulations are successfully used in previous system dynamics studies, there is no indication of which model structure better represents the rabies epidemic. This uncertainty in the model structure, together with other uncertainties related to the characteristics of rabies and to the initial conditions which are not fully known due to lack of reporting, makes it possible to observe various dynamics and prevents reaching a 'best-estimate' future with a simulation model. Due to these uncertainties, the model-based comparison of policies based on a single future is not expected to yield reliable insights. Therefore, we adopt an exploratory approach in order to generate several possible and plausible dynamics of the rabies transmission and to compare policies based on their ability to deal with uncertainty, which will be delineated in the following section.

4. Uncertainty Analysis

In this section, to deal with uncertainties associated with the characteristics of rabies and data problems, we follow an Exploratory Modeling and Analysis (Bankes, 1993; Bankes *et al.*, 2013; Agusdinata, 2008) approach. This approach is based on Bankes (1993) who state that a 'best estimate' future can be reached neither with an extensive modeling study nor with stochastic methods under deep uncertainty. Therefore, the future should be explored rather than estimated by comprehensively taking uncertainties into account. In the system dynamics field, Exploratory Modeling and Analysis (EMA) has raised interest in recent years. Being based on causal relations, system dynamics

models enable exploring the future by generating plausible future dynamics, therefore they can be reliably used for exploration purposes. In addition to Kwakkel and Pruyt (2013a, 2013b) who discussed the benefits of this approach and presented several cases to demonstrate these benefits, more studies in which EMA is used can be found in the system dynamics literature of the past few years (Auping *et al.*, 2012; Eker and Daalen, 2013; Pruyt and Hamarat, 2010).

In order to explore possible future dynamics created by alternative models with possible values of uncertain parameters, we run 10000 simulations each with a different combination of the possible input values selected from their uncertainty ranges with Latin Hypercube Sampling. Each combination of the uncertain inputs, parameter or model structure, can be considered as a scenario as well. An interface written in the Python programming language is used to control Vensim DSS and run and analyze these simulations automatically. In addition to the uncertainty ranges assigned to the parameters which can be seen in Appendix I, we take four alternative model formulations into account based on the discussion in the previous section. These are:

(1) Original model of Zhang et al. (2011).
(2) Density-dependent transmission formulation
(3) Density-dependent transmission and fractional birth rates of humans and dogs
(4) Density-dependent transmission, fractional birth rates and different contact behavior of dogs in different stages of the disease

Exploration

In Figure 8, the dynamics of *Infected Human* generated by each model formulation can be seen. Due to visualization limits, only 250 simulations are shown in these figures. According to these results, each model repeats the base run behavior with numeric differences most of the time. For instance in Model 3, the number of infected humans becomes zero sooner or later. However, oscillatory behavior is not observed in some simulations of Model 1, or the decline phase is not observed in some runs of Model 2. Briefly, these results show that a variety of possible outcomes, not only numerically but also behaviorally different, is possible due to the uncertainties in the parameter values and model structures. In Figure 9, the grey shaded area shows the envelope that encompasses these 4 sets of simulations. In particular, this envelope depicts the range between minimum and maximum values that *Infected Humans* takes over 50 years in these 10000 experiments. Within this shaded area, 10 simulations randomly selected from this ensemble are shown, and at the right hand side a density graph of the end states of these 10000 simulations is depicted. These results indicate that there is a wide variety in the peak time and magnitude of the epidemic. Also, as the density graph shows, in the majority of the scenarios the final number of infected people is close to zero, which points out the eradication of rabies. However, there are still many possible undesirable cases in which a significant amount people are infected by the rabies virus.

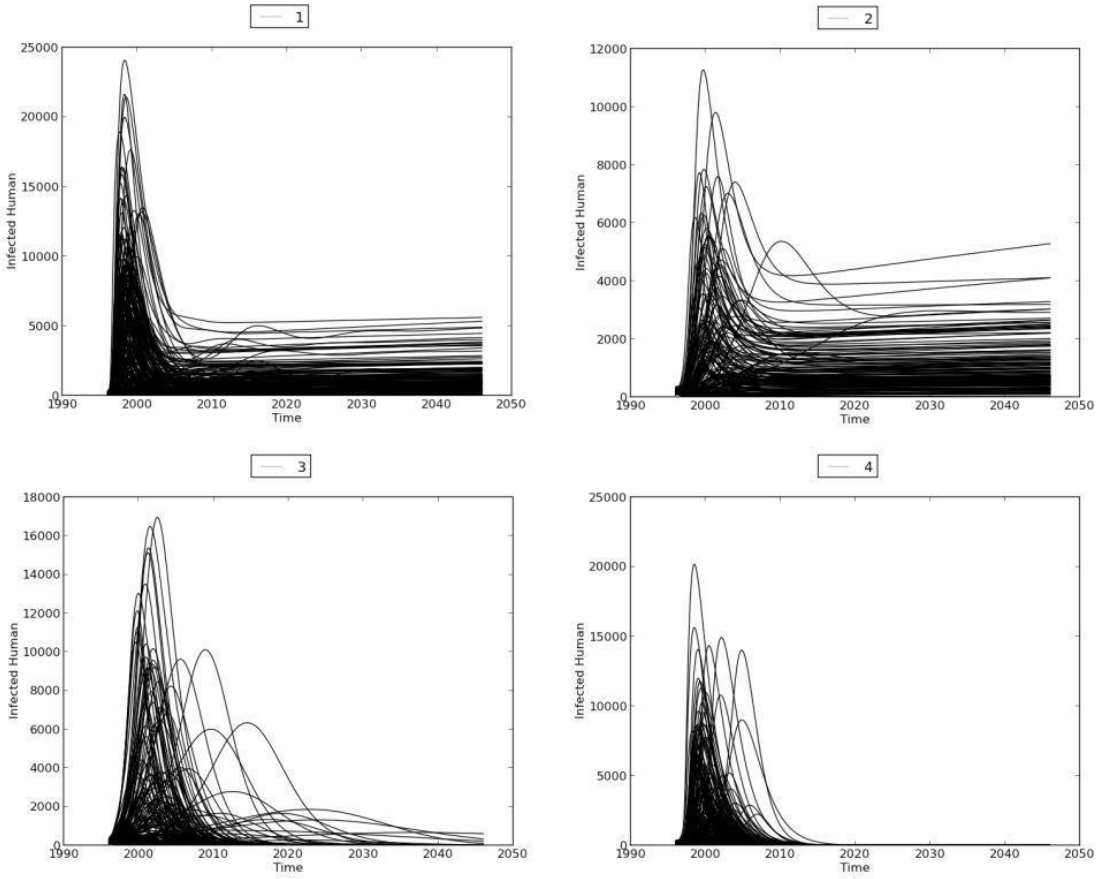

Figure 8: Dynamics of *Infected Human* in 250 simulations for each alternative model formulation

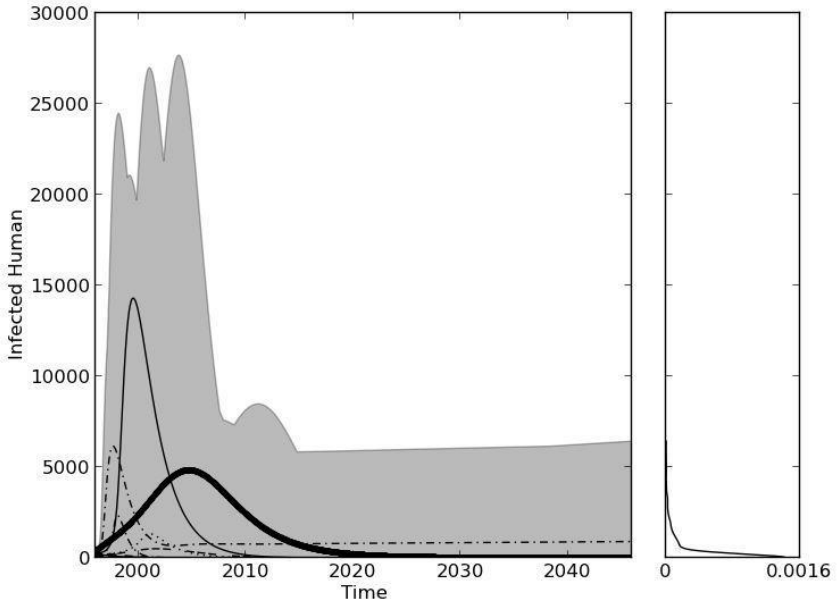

Figure 9: Envelope of 10000 runs and 10 exemplar behaviors of Infected Humans

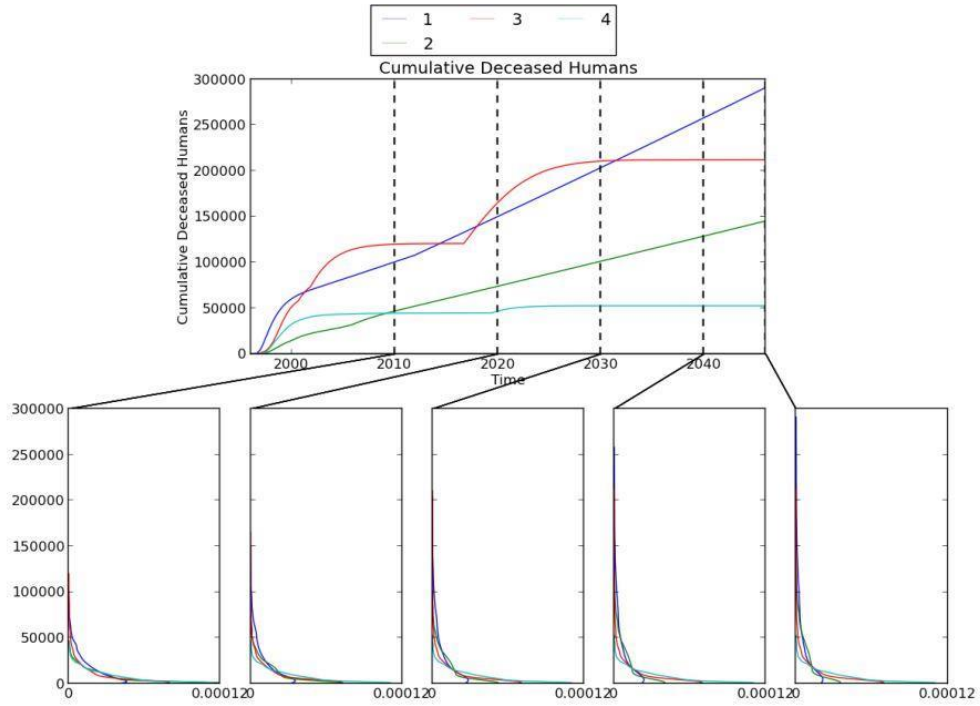

Figure 10: Envelopes of Total Deceased Human for each model structure and the density graphs over time

In Figure 10, the envelopes belonging to the cumulative number of people deceased due to rabies for each model structure can be seen. The curve generated by the maximum possible values over time is plotted with the color corresponding to each model structure. In particular, the dark blue is for the base model of Zhang, the green for the second alternative with density dependency, the red one for the combination of density dependency and fractional births, and the fourth for the addition of different contact behavior to these. Since the curves generated by the minimum possible values are all at the zero line, they are not seen on this plot. With the third and fourth model, the maximum number of total deaths stabilizes since the fractional formulation generates the eradication behavior, whereas it keeps growing with the first and second model. Besides, as the density graphs show, the cases in which the first and second models generate low numbers of deaths at any time point shown are less than the other two models.

Policy Comparison

Vaccination policies are the most common interventions to deal with an epidemic. In the case of rabies, it is possible to vaccinate both dogs and humans before the infection. Public campaigns to enhance the awareness of people to go to a hospital after exposure and receive a Post-Exposure Treatment are mentioned as well, as a promising policy option (Hou et al., 2012). Besides, culling of infected dogs is another common mean used by authorities or citizens to deal with rabies, although it is controversial in terms of animal rights. These interventions were included in the base model to some extent as a fraction of the corresponding stock variables, but as a policy option, we propose

different values to these fractions. Table 2 below summarizes the base run and policy values of these parameters.

Table 1: Policy Variables and Their Values

Policy	***Corresponding Parameter***	***Target Population Groups***	***Base Value (No policy)***	***Policy Value***
Dog Vaccination	Vaccination Fraction of Dogs	Susceptible and Exposed Dogs	0.09	0.5
Human Vaccination	Vaccination Fraction of Humans	Susceptible Humans	0.54	0.8
Human Awareness	Hospitalization Fraction of Humans	Exposed Humans	0.5	0.9
Dog Culling	Culling Rate of Furious Dogs and Prodromal Dogs	Infected Prodromal and Furious Dogs	0	0.6 and 0.5

In Figure 11, the influence of these policies on the uncertainty range of *Cumulative Deceased Humans* can be seen, when the four models are used as alternatives together with all other uncertain parameters to create this range. Each color corresponds to a policy and each line shows the upper border of the envelope encompassing 2500 simulations. *Dog Culling* (dark blue line) results to be the most effective policy to reduce the uncertainty range as its envelope shows, and to increase the number of simulations resulting in lower deaths as the density graphs indicate. *Human Vaccination* (light blue line) is the second most effective policy, followed by *Dog Vaccination* (green line) and *Human Awareness* (red line), while the last two do not considerable differ from the *No Policy* (pink) case.

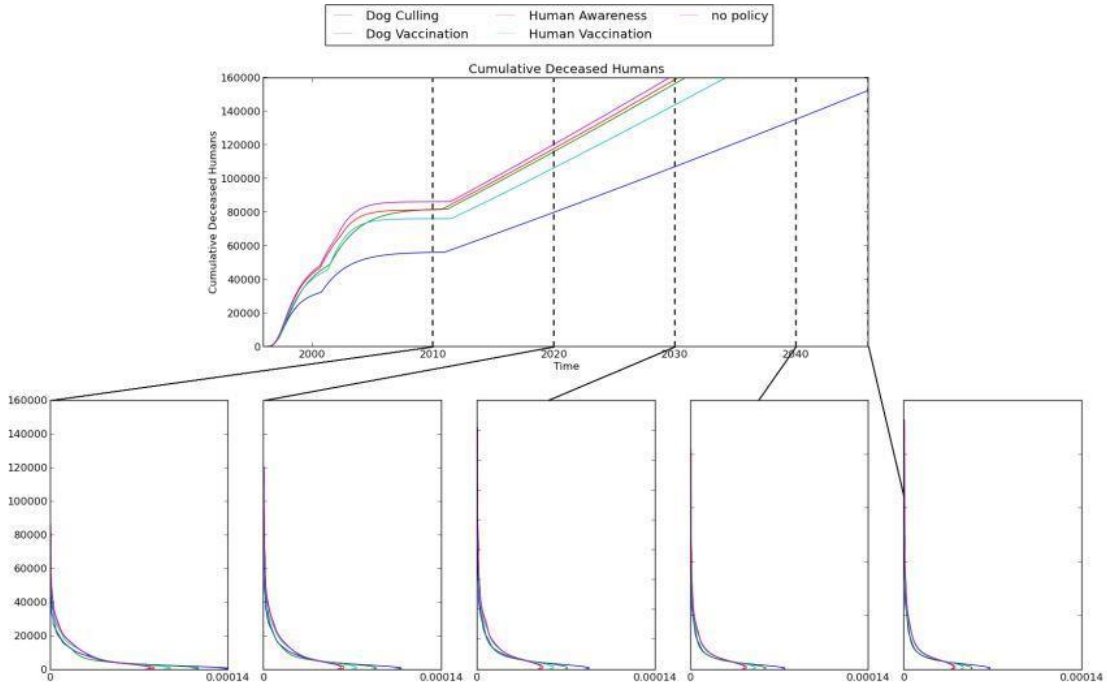

Figure 11: Effects of Policies on the Uncertainty Range of *Cumulative Deceased Humans*

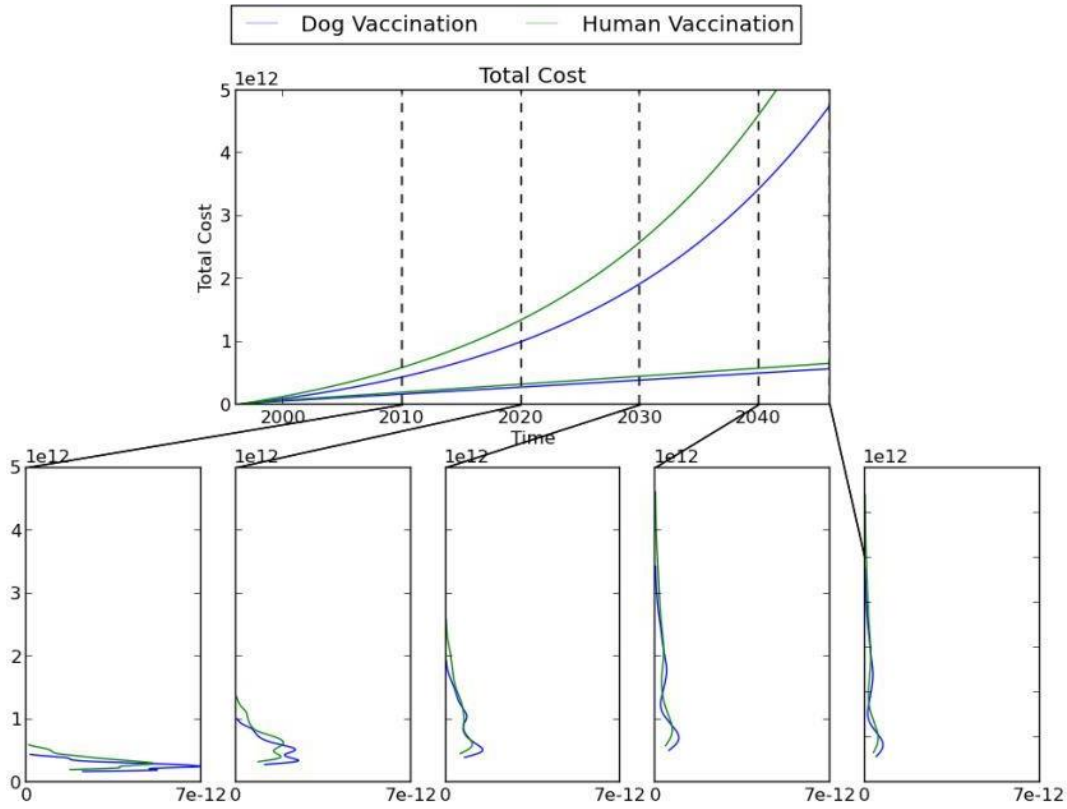

Figure 12: Effects of Policies on the Uncertainty Range of *Total Costs*

Besides the effect of them on the mean outcome of interest, which is the total number of human deaths, the costs of these policies are also an important measure policy makers

take into account to compare them. We assume the (cumulative) *Total Cost* of policies to be the sum of dog vaccination costs, human vaccination costs and human PEP Treatment costs, excluding the relatively low costs of dog culling and public campaigns. Having the cost of vaccinating a dog 2 USD (Kayali *et al.*, 2006), that of a human 40 USD and the cost of PEP Treatment 49 USD (Zinsstag et al., 2009), dog vaccination, culling and human awareness policies yield the same cost values as the 'no policy' option, as can be seen in Figure 12 where they overlap on the lower (pink) line. This finding is interesting for the *Dog Vaccination* policy, because it implies that the expenses of dog vaccination covers the costs of human PEP treatment in the case of no dog vaccination, which means that human deaths are reduced, although the money spent is not more than the amount spent in the case of no policy. Despite its higher effectiveness in terms of reducing human deaths, the uncertainty range of the costs of the *Human Vaccination* policy (upper, light blue line) is wider than the other four options, and as the density graphs show, the simulations tend to accumulate around higher values.

To compare these four policy options, we chose to have a specific value of the policy leverages. However, different values, for example a higher dog vaccination or a lower human vaccination, could as well yield different results. In order to investigate the effects of different policy leverage levels, which are fractional parameters in this case, we ran the model(s) 5000 times, each with a different combination of the uncertain parameter values and a different value of the corresponding fractional policy parameter sampled for the range [0, 1]. The results are illustrated in Figures 13a-d as scatter plots of the total number of human deaths in 50 years and the corresponding fractional parameter of each policy. Looking at these figures, only human vaccination can be said to create more desirable results, namely lower deaths, as the vaccination percentage increases. Since there is no evident trend for the other policy variables, insights derived from these scatter plots are not adequate to determine vaccination fraction values which perform best under uncertainty. Therefore, to determine the values of policy parameters that perform well under uncertainty, we adopt a robust optimization approach (Rosenhead *et al.*, 1972; Lempert *et al.*, 2006). Specifically, we follow a cardinality-based robustness approach where the performance metric is the ratio of the number runs that meet certain thresholds to the total number of runs. These certain thresholds in our case are chosen as the final value of *Cumulative Deceased Human* being less than 1000 people, and the total costs of the policies being less than 1000 billion USD. These thresholds are chosen based on the uncertainty ranges of Figure 11 and 12. The decision variables are 'Dog Vaccination Fraction', 'Human Vaccination Fraction' and 'Human Hospitalization Fraction', excluding 'Dog Culling Fraction' due to its controversy. The list of equations in Figure 14 summarizes this optimization model.

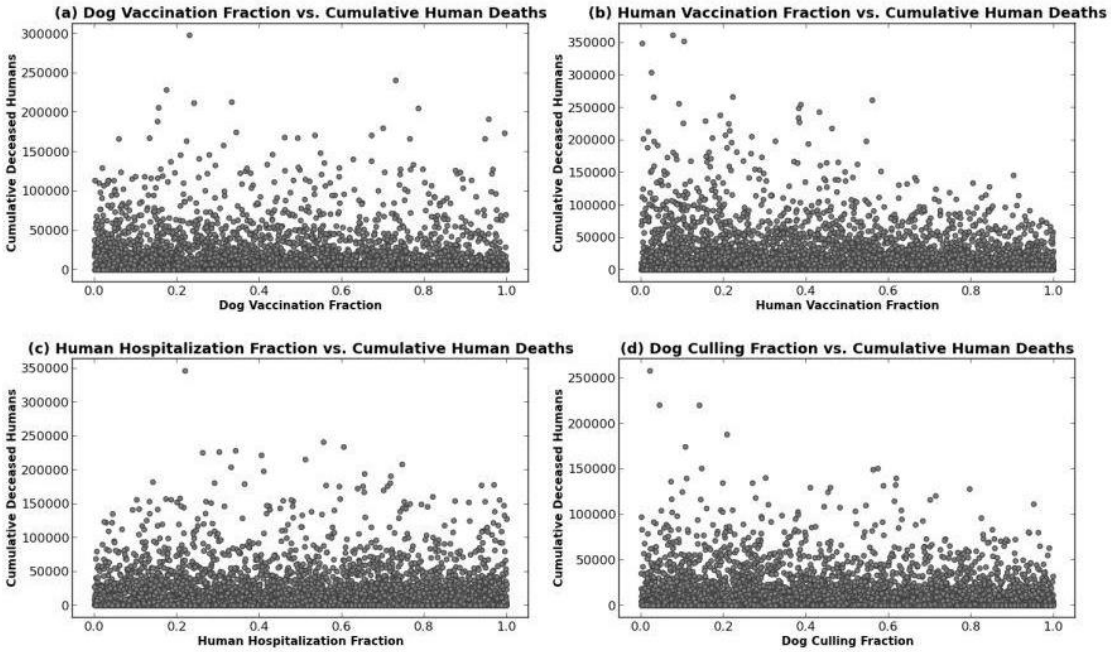

Figure 13: Scatter plots of policy parameters and Cumulative Deceased Humans

$$\text{maximize } \frac{N^*(x_1, x_2, x_3)}{N}$$

$$N^*(x_1, x_2, x_3) = \left|\left\{s_i(x_1, x_2, x_3):\ H_i(x_1, x_2, x_3) < 1000 \text{ and } C_i(x_1, x_2, x_3) < 10^{12},\ i = 1...N\right\}\right|$$

$$x_1, x_2, x_3 \in [0,1]$$

where

N : Number of simulations, constant for each combination of x_1, x_2 and x_3 values

$N^*(x_1, x_2, x_3)$: Number of simulations that meet the thresholds for (x_1, x_2, x_3)

$s_i(x_1, x_2, x_3)$: Simulation i with (x_1, x_2, x_3)

$H_i(x_1, x_2, x_3)$: Total number of human deaths in simulation i with (x_1, x_2, x_3)

$C_i(x_1, x_2, x_3)$: Total costs of policies in simulation i

Figure 14: Robust optimization problem

We solved this optimization problem by following the robust optimization procedure in (Hamarat *et al.*, 2013) which uses the Non-dominated Sorting Genetic Algorithm-II (Deb *et al.*, 2002) and generates a Pareto front that includes possible 60 (population size of the generic algorithm) Pareto solutions remained in the last generation of this algorithm. In this problem, all solutions resulted to be equal as seen in Figure 15, and the optimal values of *Dog Vaccination Fraction*, *Human Vaccination Fraction* and *Human Hospitalization Fraction* are found as 0.99, 0.06 and 0.93, respectively. This result can be interpreted as vaccinating almost all dogs, and increasing human awareness so that 93% of the people exposed to a dog bite would go the hospital creates favorable outcomes in terms of the human deaths and policy expenses without necessitating mass vaccination of humans before exposure, regardless of how future

will unfold. However, reaching almost 100% dog vaccination level is challenging in reality and this optimization procedure can be repeated by narrowing the range of *Dog Vaccination Fraction* in which the optimal value is to be searched.

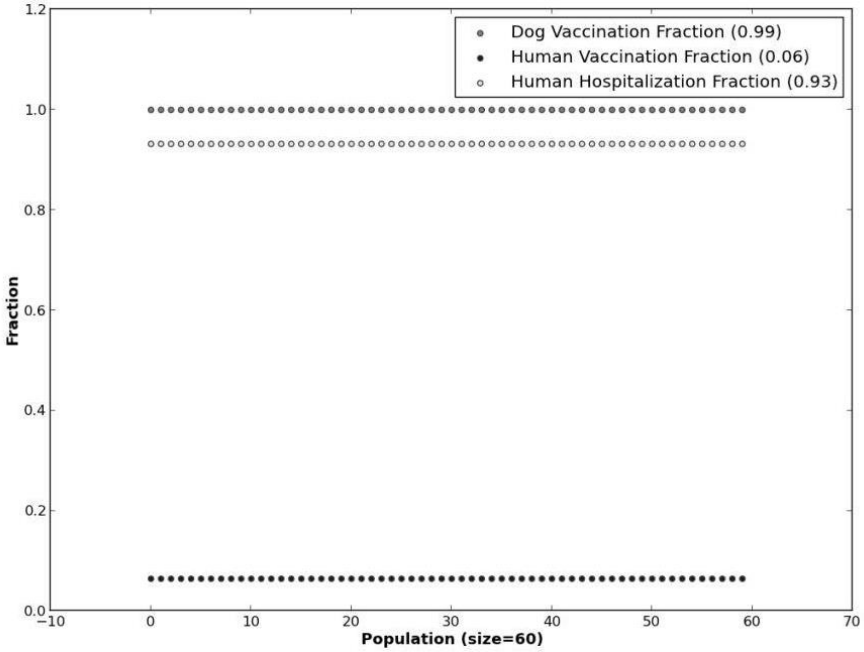

Figure 15: Robust Optimization results for the policy variables

5. Conclusion

In this paper, the dynamics of rabies are investigated with a system dynamics model based on the *Susceptible-Infected-Recovered* framework. Four alternative model formulations are included in the analysis of rabies dynamics and four policy options are tested based on these models. These models differ from each other in terms of the non-linearity incorporated in birth rate and transmission rate formulations. The four policy options considered were the dog vaccination, human vaccination, dog culling and increasing human hospitalization. Besides the uncertainties related to the characteristics of the disease, the lack of reporting causes severe data problems and uncertainties about the transmission dynamics, especially in Africa, India and China. To deal with these uncertainties, an exploratory approach is adopted in this study to examine the possible futures that may be created by these uncertainties and the policy options are compared based on their effectiveness in these multiple possible futures.

Our results showed that the different behavior patterns generated by the four models are similar to the overshoot-and-decline behavior of the generic epidemics model, but they differ significantly in the long-term. The extent of possible deaths also exhibits a wide variety when all uncertainties are taken into account in addition to the model structure uncertainty. Our findings related to the effectiveness of policies favored the dog culling policy, but since it is controversial due to animal rights, we preferred to focus on the other three to obtain favorable results. Robust optimization of the variables of these three policies showed that almost full vaccination of dogs (99%), low vaccination of

humans (6%), and 93% hospitalization of humans upon exposure yield desirably low number of human casualties and low expenditure on policies in the maximal number of possible futures.

This study is not conducted for a particular city, region or country, although for the base run the data from China is used for the comparison of different model formulations. Yet, despite numerical differences, the structure of the models would be the same for any country since this framework represents the basic mechanism of the rabies epidemic. However, location specific models can include the socioeconomic factors behind the rabies epidemic, for instance the waste management system in India or pet abandoning in China. Therefore, studying the effects of such factors on rabies epidemics is a potential departure point for future research. Moreover, the rabies virus is spread by several other species including cats, foxes and bats. Extending the model to encompass more species and inter-species transmission among them could be a valuable future study to deal with rabies in a broader context.

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7. Appendix I: Data Set

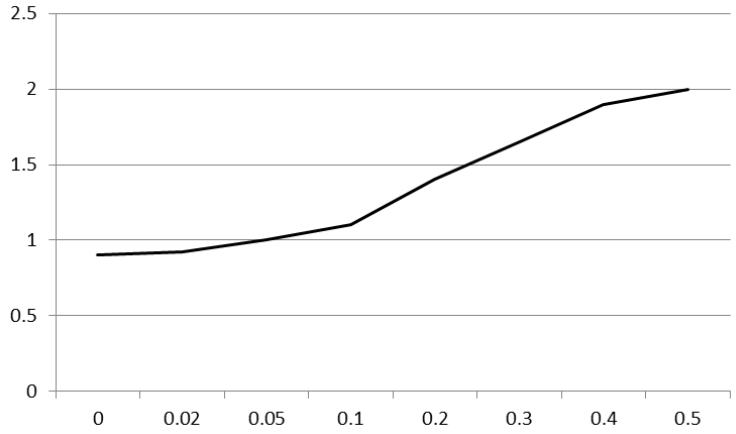
Below the values of the parameters and uncertainty ranges of them can be seen. Parameters related to the births and transmission are given for each alternative model formulation.

Parameter	*Unit*	*Base Value as in Zhang (2011)*	*Other Sources*	*Uncertainty Range Lower*	*Uncertainty Range Upper*
		DOGS			
Immunity Loss Fraction of Dogs	1/year	1	O.5 (Hou)	0.25	2
Infection Fraction of Exposed Domestic Dogs	Dmnl	0.4	0.37 (Hou), 0.49 (Hampson)	0.3	0.95
Incubation Period of Rabies in Dogs	Year	0.16	0.06 (Hampson)	0.05	0.3
Domestic Dog Natural Death Fraction	1/year	0.08	0.11, 0.24 (Hou), 0.45 (Hampson)	0.05	0.45
Vaccination Fraction of Domestic Dogs	1/year	0.09	0.133 (Hou)	This is a policy.	
Average Duration of Rabies in Dogs	Year	1	1 (Hou), 0.0085 (Hampson)	0.008	1
Initial Total Dog Population	Dogs	3.55E+07		3.00E+07	4.00E+07
Initial Exposed Dogs	Dogs	200000		0	400000
Initial Infected Dogs	Dogs	100000		50000	150000
Initial Immune Dogs	Dogs	200000		100000	300000
		HUMANS			
Average Immunity Duration in Humans	Year	1	1 (Hou)	0.5	3
Infection Fraction Humans	Dmnl	0.4	0.33 (Hou)	0.25	0.9
Average Incubation Period Humans	Year	0.16	0.083-0.166 (Hemachudha)	0.08	0.2
Human Natural Mortality Fraction	1/year	0.0066	0.0046 (Hou)	0.004	0.008
Human Vaccination Fraction	1/year	0.54	0.328 (Hou)	Policy	
Average Duration of Rabies in Humans	Year	1	1 (Hou), 1.75-2.6 (Hemachudha)	0.5	2.5
Initial Exposed Human	Humans	250		100	400

Initial Infected Human	Humans	89		No uncertainty here.	
Initial Hospitalized Human	Humans	0		0	100
Initial Immune Human	Humans	200000		100000	300000
Base Model of Zhang (2011)					
Dog Birth Rate	Dogs/year	3.00E+06		2.00E+06	4.00E+06
Dog Transmission Rate ($\beta_{1,dog}$)	1/(Dogs * year)	1.58E-07	3.2e-007, 8e-006 (Hou),	1.00E-07	1.00E-06
Human Birth Rate Constant	Humans /year	1.54E+07		1.00E+07	2.00E+07
Normal Dog to Human Transmission Fraction ($\beta_{1,hum}$)	1/(Dogs * year)	2.29E-12	4.8e-010, 3.6e-009 (Hou)	1.50E-12	3.00E-12
Density-Dependent Transmission Rate					
Dog Birth Rate	Dogs/year	3.00E+06		2.00E+06	4.00E+06
Dog Transmission Rate ($\beta_{2,dog}$)	1/ year	6		4	7
Human Birth Rate Constant	Humans /year	1.54E+07		1.00E+07	2.00E+07
Normal Dog to Human Transmission Fraction ($\beta_{2,hum}$)	1/ year	4.6E-05		3.50E-05	5.50E-05
Fractional					
Dog Birth Fraction (b_{dog})	1/year	5.00E-02		3.50E-02	6.50E-02
Dog Transmission Rate	1/(Dogs * year)	1.58E-07		1.00E-07	1.00E-06
Human Birth Fraction (b_{hum})	1 /year	4.7E-02		4.00E-02	5.5E-02
Normal Dog to Human Transmission Fraction	1/(Dogs * year)	6.00E-12		4.00E-12	8.00E-12
Density-Dependent and Fractional					
Dog Birth Fraction	1/year	5.00E-02		3.50E-02	6.50E-02
Dog Transmission Rate	1/ year	4.4		3.5	5.5
Human Birth Fraction	1 /year	4.7E-02		4.00E-02	5.5E-02
Normal Dog to Human Transmission Fraction	1/ year	1.05E-04		8.00E-05	2.00E-04
Density-Dependent, Fractional and with Furiousity Effect					
Dog Birth Fraction	1/year	5.00E-02		3.50E-02	6.50E-02

Dog Transmission Rate ($\beta^*_{p,dog} = \beta^*_{f,dog}$)	1/ year	7.5	5.0	10.0
Human Birth Fraction	1 /year	4.7E-02	4.00E-02	5.5E-02
Normal Dog to Human Transmission Fraction ($\beta^*_{p,hum} = \beta^*_{f,hum}$)	1/ year	3.44E-05	2.50E-05	4.50E-05

Effect of Furiousity: $f_f\left(\frac{I_f(t)}{T_{dog}(t)}\right)$



Effect of Prodrome: $f_p\left(\frac{I_p(t)}{T_{dog}(t)}\right)$