

Monte Carlo simulation of Rabies dynamics: effects of constant rate of vaccination and single vaccination campaign

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Running head: Effect of vaccination in Rabies dynamics

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Summary

Rabies is an important zoonosis and a major public health concern. Latin American countries have adopted rabies control strategies but these are often only partially successful and are rarely sustained over time. Human, canine and bovine cases of rabies are still reported. This paper aims to apply mathematical modeling to the transmission of rabies in canines and simulate the behavior of the disease under various scenarios to find the best control strategy. Monte Carlo simulations enable us to represent well an epidemic outbreak of rabies. We modeled an epidemic that started quickly in a susceptible unvaccinated population and reached a high level of prevalence. The canine population declined drastically but the original population level was later recovered. We incorporated different rates of vaccination (sustained campaign) into the model. The epidemic magnitude was lower at higher vaccination rates. When a single large-scale vaccination campaign (once-off) was introduced, the magnitude of the epidemic was reduced in proportion to the number of susceptible individuals that were vaccinated. A higher level of security for eradication of rabies epidemics is achieved considering the 95th percentile for eradication: 42% of coverage was obtained for a realistic value $R_0 = 1.58$. Our results suggest i) that both strategies may be equally efficient to eradicate rabies epidemics, being constant rates of vaccination more applicable for dog population in cities and massive campaigns for wild reservoir; ii) that the 70% coverage proposed by WHO is considerably greater than the coverage necessary to interrupt the transmission chain for the R_0 level reported today and iii) that birth rate (a), transmission coefficient (β) and reservoir immunity coverage (ϕ or P) are the key factors for rabies control. Key words: Chagas disease, *Trypanosoma cruzi* strains, histopathological study, inflammatory infiltrate.

Key words: Monte Carlo method – Rabies - Vaccination

Introduction

Rabies continues to be a zoonosis of major public health importance, with a worldwide distribution and an increasing wild reservoir (Favi & Durán 1991, Plotkin 2000). Its impact can be distressing: there were 217 human deaths in America in 1993 in, 45% of whom were of children less than one year of age (Knobel et al. 2005). Since 2010, 111 cases of human Rabies transmitted by dogs or bats have been reported in Latin America and Caribbean (Vigilato et al. 2013). Human infection that is often lethal can result by accidental dispersion from animal reservoirs (Smith & Seidel 1993, Favi et al. 2011, Favi & Durán 1991, Ribas et al. 2013) and there are 55000 human deaths/year in the world (Knobel et al. 2005). All mammals are potential hosts of the disease (Acha & Szyfres 2003), although few species are able to maintain endemic cycles independently (Clark 1988). In Brazil, 28 cases of human rabies were reported between 1981 and 1998. Transmission by simians, raccoons, and foxes accounted for 2.5% of all reported human cases during this period, with even more suspected unreported cases caused by these wild animals (Batista-Morais et al. 2000). An

epidemic which started in the red fox (*Vulpes vulpes*) in Poland (1940) spread across much of the European continent and is still active today. Rabies remains associated with the gray fox *Pseudalopex griseus* in South America. In southern Chile, 58 foxes were captured and their brains were studied with direct immunofluorescence and mouse inoculation; 8.6% were found to be positive for Rabies (Durán & Favi 1989). Hematophagous and non-hematophagous bats of South America provide another example of Rabies circulation in wild populations (Acha & Szyfres 2003, Soares et al. 2002) and, in Chile, the prevalence in non-hematophagous bats has increased (Favi et al. 2011, Aguilar-Setien et al. 2002).

Latin American countries have adopted various strategies to control rabies for decades. These have focused primarily on urban Rabies (associated with dogs) and while some have achieved partial successes, this is rarely sustained over time. The cyclical behavior of Rabies has been described in countries such as Argentina and Paraguay (Ernst & Fabrega 1989), probably associated to interactions between host and viral population and the renovation of the canine population (Piza et al. 2002, Rosatte et al. 2001, Anderson et al. 1981,

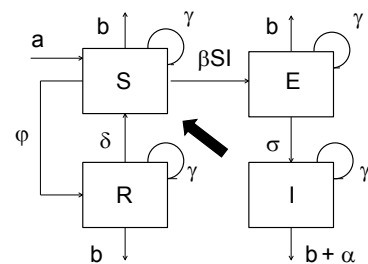
Scortti et al. 1997). The first successful control programme in South America was carried out in Uruguay during the 1950s using avianized vaccines and culling. In the third Special Session on Rabies in Chile (1972), the health ministries of the Americas set out a plan which included recommendations to control and eradicate rabies within ten years (Baez 1984). Coordinated actions for regional elimination of human Rabies transmitted by dogs began in 1983 in Latin America and Caribbean. This effort has led to an 90% reduction of human and canine Rabies (Vigilato et al. 2013). However, this could only be partially fulfilled in some countries: there were still 67 cases of human Rabies (the largest numbers of cases in Brazil and Colombia), 1590 cases of canine Rabies and despite cattle vaccination programmes 3136 of bovine Rabies reported in Latin America in 2000 (Acha & Szyfres 2003, Piza et al. 2002). In Chile, urban Rabies was endemic between 1950 and 1960 with large numbers of cases recorded in both humans and animals (Favi et al. 2008, Laval & Lepe 2008). Mass immunisation and increased diagnostic coverage by active surveillance was introduced as part of a control programme in 1960 which aimed to reduce the prevalence of rabies in the dog population. This led to a large decline in cases of human Rabies without human cases from 1972 and only low number of cases reported in animals (low endemic condition). However, in August of 2013 a case of human rabies surprisingly caused by dog bite was confirmed (MINSAL 2013). The currently increasing canine and feline population (Acosta-Jamett et al. 2010, Urcelay & Di Silvestri 1990) could make it more difficult to control the disease. It is therefore necessary to review and optimise mass immunisation campaigns that can be carried out on animals, using tools such as mathematical modeling (Fitzpatrick et al. 2012, Morters et al. 2013, Townsend et al. 2013, Zhang et al. 2011).

The mathematical modeling of infectious diseases is well developed and models can incorporate complexities in biological organizations and environmental stochasticity and heterogeneity. Such models can be powerful and provide good predictive capabilities, for example in the dynamics of rabies (Anderson et al. 1981, Fitzpatrick et al. 2012, Morters et al. 2013, Townsend et al. 2013, Zhang et al. 2011, Panjeti & Real 2011), and other diseases (Canals et al. 2012). New tools, for an optimal control, may be used by public health agencies to direct

the management and strategic planning of disease control. This paper applies mathematical models to the transmission of rabies in canines and simulates its behavior under various scenarios to identify the best control strategies.

Material and methods

We used the Anderson et al. (Anderson et al. 1981) model for Rabies as the base model in this study. It considers susceptible (S), non-infectious infected or latent (E) and infective (I) groups in the population ($N = S + E + I$). By introducing a vaccination programme in this system a recovered sub-population was created (R) (Fig. 1).



Individuals gain immunity with a vaccination rate ϕ and lose immunity at a rate of δ . In this modified model the dynamics of Rabies is expressed by the following differential equations:

$$\frac{dS}{dt} = a(S + R) - (b + \gamma N)S - \beta SI - \phi S + \delta R$$

$$\frac{dE}{dt} = \beta SI - (\sigma + b + \gamma N)E$$

$$\frac{dI}{dt} = \sigma E - (\alpha + b + \gamma N)I$$

$$\frac{dR}{dt} = \phi S - (\delta + b + \gamma N)R$$

where a is the birth rate and b is the mortality rate of the population, γ is the density-dependent effect, β is the transmissibility, σ is the transfer rate from latent to infectious and α is the specific death rate from Rabies. Using the next generation matrix method we compute the reproductive number R_0 . The next generation operator is fully described in Diekmann & Heesterbeek (2000). The formation of the operator involves determining two compartments, infected and non-infected, from the model. Let us assume that there are n compartments of which m are infected. We define the vector $X = x_i$, $i = 1, 2, \dots, n$, where x_i denotes the number or proportion of individuals in the i th compartment. Let $F_i(X)$ be the rate of appearance of new infections in compartment i and let $V_i(X)$

=Vi(-)-Vi(+) where Vi(+) is the rate of transfer of individuals into compartment i by all other means and Vi(-) is the rate of transfer of individuals out of the ith compartment. The difference Fi(X)-Vi(X) gives the rate of change of xi. Assuming that Fi and Vi meet the conditions outlined by Diekmann et al. (1990) and van den Driessche & Watmough (2002), we can form the next generation matrix (operator) FV-1 from matrices of partial derivatives of Fi and Vi and R0 is given by the spectral radius (dominant eigenvalue) of the matrix FV-1(34).

The model was used to simulate the dynamics of canine rabies using the Monte Carlo method (35). Elementary transformations T(i) were disaggregated and the resulting probability for each transformation, was estimated as $p_i = T(i)/T$, where $T = \sum_i T(i)$. The transformation T(j) was executed when $\sum_{p_i \leq RN} \sum_{p_i}$ where RN are randomly generated numbers between 0 and 1 (Table 1). Time was measured in days.

Table 1.- Elementary transformations to generate probability distributions in Monte Carlo simulations. Here $T = \sum_i T(i)$ and $p_i = T(i)/T$

Event loading	Elementary transformation	Event (i)
$T(1) = a * (S(i) + R(i))$	$S(i+1) = S(i) + 1$	Susceptible born
$T(2) = (b + \gamma * N(i)) * S(i)$	$S(i+1) = S(i) - 1$	Susceptible dies
$T(3) = (b + \gamma * N(i)) * E(i)$	$E(i+1) = E(i) - 1$	Latent dies
$T(4) = (a + b + \gamma * N(i)) * I(i)$	$I(i+1) = I(i) - 1$	Infected dies
$T(5) = (b + \gamma * N(i)) * R(i)$	$R(i+1) = R(i) - 1$	Recovered dies
$T(6) = \beta * S(i) * I(i)$	$S(i+1) = S(i) - 1, E(i+1) = E(i) + 1$	Susceptible infected (bite)
$T(7) = \phi * S(i)$	$S(i+1) = S(i) - 1, R(i+1) = R(i) + 1$	Susceptible immunised (vaccine)
$T(8) = \delta * R(i)$	$S(i+1) = S(i) + 1, R(i+1) = R(i) - 1$	Recovered lose immunity
$T(9) = \sigma * E(i)$	$E(i+1) = E(i) - 1, I(i+1) = I(i) + 1$	Latent ill

We simulated the introduction of 10 infected animals in two situations, considering a total population of i) 3000 and ii) 5000 susceptible animals. The population was considered to be growing with rates $a = 0.000468$ and $b = 0.000356$ individuals / population day, based on data from domestic dogs (Morales & Ibarra 1979) in Santiago of Chile, a realistic value that agrees with recently estimations (see Favi & Durán 1991). We assumed a specific mortality rate of $\alpha = 100b$ and no effect of density dependence ($\gamma = 0$). We defined $\sigma = 0.0333$ day⁻¹ since the latency period of rabies is about 30 days (Acha & Szyfres 2003). The transmission coefficient was estimated from the relationship $R_0 = \frac{\sigma \beta K}{(\sigma + a)(\alpha + a)}$, where R0 is the reproductive number (number of secondary cases from an index case) for the dynamics of rabies in natural conditions (without vaccination) and K is a population threshold size needed to cause an epidemic. We arbitrarily chose K = 3000, thus, $\beta = 0.00001452$ individuals/(infected)

(susceptible)day. The rate of loss of immunity used was $\delta = 0.000877$ day⁻¹ (immunity of 3.12 years post vaccine))(Chomel et al. 1988) (Table 2).

Table 2.- Values of the parameters used in the numerical simulations.

Parameter	Value
Birth rate (a)	0.000468 day ⁻¹
Mortality rate (b)	0.000356 day ⁻¹
Specific mortality rate (α)	0.0356 day ⁻¹
Density parameter (γ)	0
Transfer rate (E-I) (σ)	0.000333 day ⁻¹
Transmissibility (β)	0.00001452 infected ⁻¹ day ⁻¹
Rate of loss of immunity (δ)	0.000877 day ⁻¹

We simulated: A) sustained campaign: a completely susceptible population with vaccination rates varying from $\phi = 0$ to $\phi > (a + \delta)(R_0 - 1)$ animals/day (Vigilato et al. 2013) and B) Once-off: a completely susceptible population with mass vaccination at $t = 120$ days, varying the proportion of susceptible vaccinated from 0 to $P > 1 - 1/R_0$ (Anderson et al. 1981).

A sensitivity analysis of R_0 as function of the parameters of the model was performed considering the standardized sensitivity (or elasticity): $\gamma_{\theta}^{R_0} = \frac{\partial R_0}{\partial \theta} \frac{\theta}{R_0}$, where θ is the studied parameter, and then evaluated for the particular values of the parameters (following Shah & Gupta 2013). We also performed a sensitivity analysis of the presence of rabies epidemics to the values of ϕ and P estimating the critical values (ϕ^* and P^*) (20) by means of the probit model (Canals & Solís 2014). We performed simulations for different values of P and ϕ to detect the presence of rabies epidemics (30 simulations for each value), determining the probability of rabies epidemics (PE) for a particular value of the parameter θ (P or ϕ). We consider the relationship $\text{Probit}(pa) = \beta_0 + \beta_1 \theta$, with $\text{Probit}(pa) = z + 5$, where pa is the probability for abort a Rabies epidemics ($= 1 - PE$) and z is the value for pa in the cumulative standardized Gauss distribution density. With this analysis we determine the critical value θ^* as the value for which $\text{Probit}(pa) = 5$, and the 95th percentile to eradicate the epidemics θ^*_{95} as the values for which $\text{Probit}(pa) = 6.64$ ($= 1.64 + 5$).

Results

For our model we obtain $F = \begin{bmatrix} 0 & \frac{\beta \lambda}{(b + \phi)} \\ 0 & 0 \end{bmatrix}$ and $V = \begin{bmatrix} \sigma + b & 0 \\ -\sigma & \alpha + b \end{bmatrix}$, and the first eigenvalue of FV^{-1} was $R_0 = \frac{\beta \lambda \sigma}{(\phi + b)(\sigma + b)(\alpha + b)}$, where $\lambda = a(S+R)$. The sensitivity indices of R_0 ($\gamma_{\theta}^{R_0}$) to the parameters are show in Table 3.

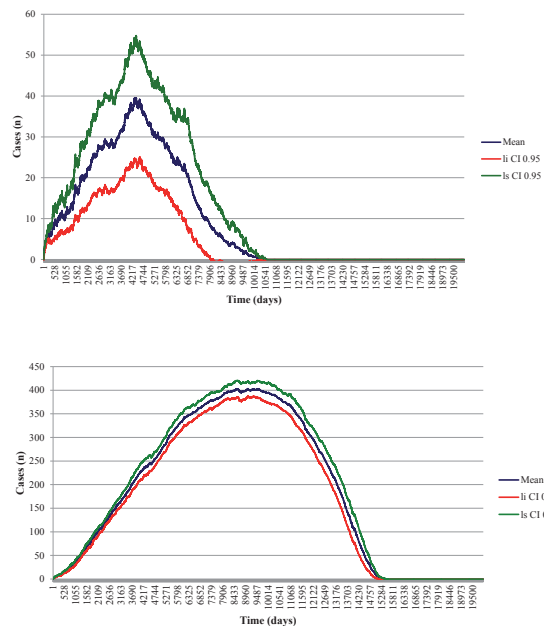
The highest sensitivity values of R_0 were related to the parameters β , a , and α .

Table 3.- Sensitivity indices of R_0 to the parameters (θ) for the Rabies model

θ	Sign	Value
B	+	1
A	+	1
Σ	+	0.011
Φ	-	0.360
Λ	-	0.990
B	-	0.661

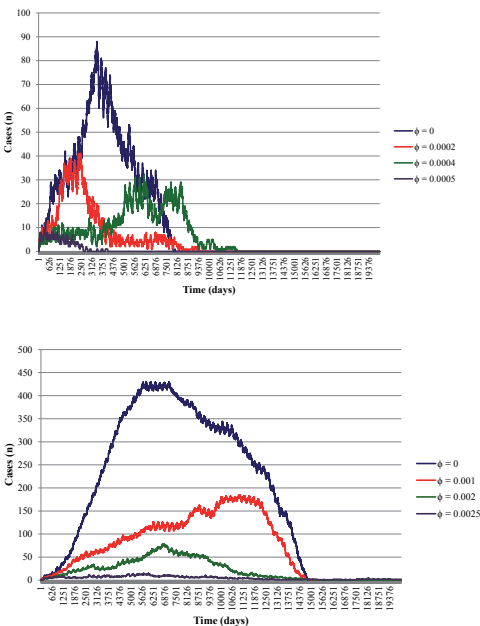
In the simulations, when the initial number of susceptible $S = 3000$, we obtained $R_0 = 1.576$, and for $S = 5000$ we obtain $R_0 = 2.626$.

Monte Carlo simulations enabled us to represent an epidemic phenomenon well. With the first initial condition $R_0 = 1.576$ an epidemic (with values above the 10 initial latent individuals) started in the susceptible population without vaccination at around 500 days, reaching 40 ± 15 cases/day 12.3 years after $t = 0$ and lasting 28.21 years (10297 days). With the second initial condition, $R_0 = 2.626$, the epidemic started in the susceptible population without vaccination quickly, reaching 400 ± 20 cases/day 27.4 years after the beginning of the epidemics and lasting at 42.65 years (15569 days) (Fig. 2).

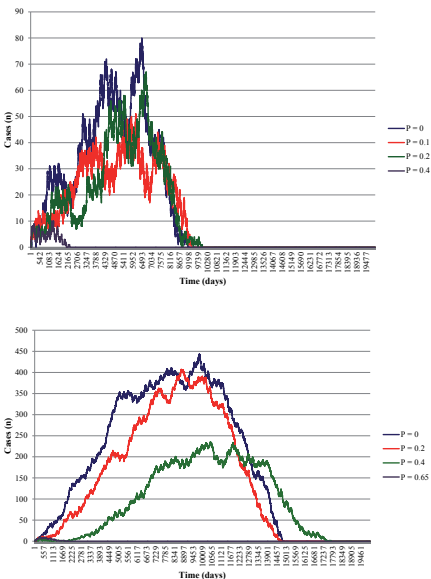


During an epidemic the canid population declined drastically, making population recovery longer to achieve. The epidemics decreased in magnitude when constant rates of vaccination were introduced, and disappeared with a high vaccination rate. The time at which the epidemic started was

similar in all cases, but more vaccination led to a reduced epidemic (Fig. 3).

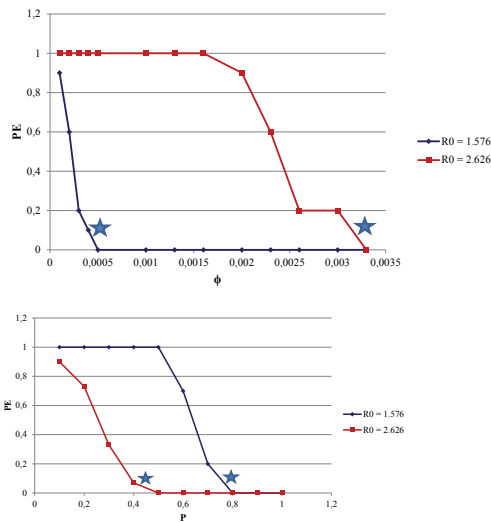


When we modeled a once-off campaign at 120 days from the beginning of the epidemic there was a reduction in epidemic magnitude due to the proportion of susceptible individuals being vaccinated (Fig. 4).



When a constant rate of vaccination was used critical values to eliminate the rabies epidemics were

$\phi^* = 0.000233 \pm 0.00011$ and $\phi^{*95} = 0.000421 \pm 0.00011$ for $R_0 = 1.576$ and $\phi^* = 0.00246 \pm 0.0004$ and $\phi^{*95} = 0.00309 \pm 0.0004$ for $R_0 = 2.626$. When a massive vaccination at 120 days was used disease eradication was possible for critical values $P^* = 0.256 \pm 0.098$ and $P^{*95} = 0.418 \pm 0.098$ for $R_0 = 1.576$ and $P^* = 0.645 \pm 0.098$ and $P^{*95} = 0.752 \pm 0.098$ for $R_0 = 2.626$ (Fig.s 5).



Discussion

The model discussed in this paper simulates the spread of rabies in canine populations using demographic parameters for the dog populations of Chile. However the results can be extrapolated to the wild component of Rabies represented mainly by wild foxes in natural environments.

Vaccination is the most effective mean to control rabies in all species (Morters et al. 2013). Urban control and prevention of rabies through dog vaccination campaigns has been relatively efficient although a significant number of cases in humans and animals are still reported. Reported human cases in Latin America have fallen from an average of 270.4 per year between 1980 and 1989 to 67.0 per year in 2000. Annual cases of canine rabies in Latin America have fallen from an average of 9187 between 1990 and 1994 to 1590 in 2000. Excepting for a human case transmitted by a bat in 1996 (Favi 2000) and one recent case transmitted by a dog bite in 2013 (MINSAL 2013), no other human or canine cases have been reported in Chile since 1972 (Acha

& Szyfres 2003).

Our results suggest that constant vaccination of dog populations, at sufficiently high rates can maintain a disease-free population, requiring that urban dog population is sufficiently controlled by public health measures (such as Chile). However, other South American countries (such as Colombia, Ecuador, Peru, Venezuela, Paraguay, Guatemala, Mexico and the Caribbean) still reported tens of annual cases in 2000 and 111 human cases since 2010 (Vigilato et al. 2013).

Rabies in wild canines is much less controlled by public health systems and serves as a core reservoir for the maintenance of rabies, especially in places where there is contact between urban dog and wild fox populations (Acosta-Jamett et al. 2010). Disease control strategies initially looked to reduce or inhibit the reproduction of populations of wild canines, but now the use of vaccines is considered the most efficient mean of control (Fitzpatrick et al. 2012, Morters et al. 2013, Townsend et al. 2013, Zhang et al. 2011, Hanlon et al. 2002a,b). The first two methods affect the size of the rabies reservoir population but vaccination does not (Smith & Wilkinson 2003, Sterner & Smith 2006). Some European countries have implemented wild population vaccines. For example, the SAD-Bern vaccine was used to vaccinate foxes in Switzerland. SAD-B19 vaccine was distributed via 20 million baits in Germany, Belgium, France, Italy and Luxembourg, without causing the death of foxes or other animals in the area. France and Switzerland distributed 250,000 SAG-vaccine baits between 1989 and 1991 without causing secondary deaths (OPS/OMS 1994). The oral administration of SAG-2 was effective in skunks and raccoons in North America (Favi 2000) and another rabies vaccine was effective in bats (Aguilar-Setien et al. 2002). Canada and the United States have carried out major vaccination campaigns (Rosatte et al. 2001, Hanlon et al. 2002a, Sidwa et al. 2005, Slate et al. 2005). As a result of similar campaigns, a number of European countries remain free from rabies (Acha & Szyfres 2003, Freuling et al. 2013).

Our results show that both vaccination programmes, i) administered at constant rates (as used in urban populations) and ii) mass vaccination campaigns can be similarly useful to prevent rabies outbreaks. In wild populations, where transmission is mainly via foxes and rabies is either present in a wild reservoir, one-off large scale vaccination

campaigns could be particularly practical. However, mass vaccination campaigns should be repeated in several occasions to eliminate disease. For example, in Europe a median of 28 campaigns to achieve control and 17 for control of Rabies in foxes have been reported (Freuling et al. 2013).

The critical values found in our numerical simulations were lower than those proposed by the model of Anderson et al model: $P^* = 1 - 1/R_0$ and $\varphi^* = (a + \delta)(R_0 - 1)$ (Knobel et al. 2005) for $R_0 = 1.576$: the expected values were $P^* = 0.37$ and $\varphi^* = 0.00078$ and the estimated values from numerical simulations were $P^* = 0.26$ and $\varphi^* = 0.00023$. In contrast for $R_0 = 2.626$ the estimated values were very close to those expected: the expected values were $P^* = 0.62$ and $\varphi^* = 0.0022$ and the estimated values were $P^* = 0.65$; $\varphi^* = 0.0025$. A higher level of security was achieved when we considered the 95th percentile for eradication. That was obtained at 42% of coverage for $R_0 = 1.576$ and 75% for $R_0 = 2.626$. For dogs and wild reservoir R_0 between 1.05 and 1.72 (Hampson et al. 2009), $R_0 = 1.2$ in Bali (Townsend et al. 2013), $R_0 = 2$ in China (Zhang et al. 2011) and the highest value $R_0 = 2.334$ in the USA in 1948 (Coleman & Dye 1996, Uhaa et al. 1992) have been reported. With these values a 70% coverage was recommended by WHO in 2004 (Morters et al. 2013), consistent with values obtained for R_0 greater than 2, which in light of the recent literature reports are very improbable. Our value of 42% obtained for the realistic value $R_0 = 1.576$ can be compared with those obtained by Fitzpatrick et al (2012) in Serengeti and Ngorongoro, $R_0 = 1.18$ and $R_0 = 1.24$ respectively. These authors obtained 25% and 39% of coverage for 95th percentile of eradication, values that are similar to those obtained in our study.

Our sensitivity analysis showed that the two main positive parameters affecting R_0 were the birth rate (a) and the transmission coefficient (β) and the two negative parameters were the mortality rate (b) and the vaccination rate (φ), without considering the specific mortality of rabies that in this study was considered to be $\alpha = 100b$. These results suggest that an effective control strategy must include reducing the birth rate (a) and the contact rate in the reservoir and between the reservoir and humans (β) and also vaccination campaigns (φ). Culling of dogs or of wild reservoir (b) have been proved to be inefficient because of the absence of correlation between R_0 and dog density (Morters et al. 2013). Among these relevant parameters, reducing birth rate and

increasing reservoir immunity coverage have been reported recently as the main strategies of control in China (Zhang et al. 2011), agreeing with our results.

In summary, our results suggest i) that both strategies may be equally efficient to eradicate rabies epidemics, being constant rates of vaccination more applicable for dog population in cities and massive campaigns for wild reservoir; ii) that the 70% coverage proposed by WHO is considerably greater than the coverage necessary to interrupt the transmission chain for the R_0 values reported today (between 1 and 2) and iii) that birth rate (a), transmission coefficient (β) and reservoir immunity coverage (φ or P) are the key factors for rabies control.

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Figure legends

Figure 1.- Transmission diagram of rabies: a is the birth rate and b is the mortality rate of the population, γ is the density-dependent effect, β is the transmissibility, σ is the transfer rate from latent to infectious, α is the specific death rate from rabies, φ is the vaccination rate and δ the rate of immunity loss.

Figure 2.- Numerical simulations of the progression of the cases of rabies without vaccination with their confidence limits for $R_0 = 1.576$ (top) and $R_0 = 2.626$ (bottom).

Figure 3.- Numerical simulations of the progression of the cases of rabies for several vaccination rates (φ) for $R_0 = 1.576$ (top) and $R_0 = 2.626$ (bottom).

Figure 4.- Numerical simulations of the progression of the cases of rabies for several covertures of vaccination at 120 days for $R_0 = 1.576$ (top) and $R_0 = 2.626$ (bottom).

Figure 5.- Probabilities of rabies epidemics (PE) as function of vaccination rates (φ) (top) and as a function of the proportion of vaccinated (P) (bottom) for two different values of R_0 . Stars indicates the position of the 95th percentile for eradication (φ^{*95} and P^{*95})