

The use of immunocontraception to improve rabies eradication in urban dog populations

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Abstract

Context. Rabies causes ~55 000 human deaths each year, primarily as a result of bites from dogs, which are the major rabies reservoir in the developing world. Current rabies control strategies include vaccination, culling and surgical sterilisation of dogs. However, recently developed immunocontraceptives could be used alongside vaccination to apply fertility control to more animals.

Aims. We used a modelling approach to explore (1) whether adding single-dose contraceptives to rabies vaccination would improve effectiveness of rabies eradication, (2) how sensitive control methods are to variation in population parameters and (3) the effects of applying control continuously or in pulses on rabies eradication.

Methods. A continuous time, compartmental model was created to describe canine rabies epidemiology. Parameters were derived from the literature. The following three control methods were applied at varying rates and durations: vaccination, vaccination plus fertility control (v + fc) and culling. Outcomes were classified into the following three categories: rabies persistence, rabies eradication and population extinction.

Key results. When control was applied continuously for up to 24 months, vaccination was least effective; the effort required to eradicate rabies was about twice that required with culling or v + fc. At realistic control rates, only v + fc consistently resulted in rabies eradication. Increasing population growth rate and city size made rabies eradication harder; for vaccination, considerably greater control rates and durations were required, whereas culling and v + fc showed only minor decreases in effectiveness. When control was applied for 1 or 2 months (for one month every 12 months or every 6 months) per year for up to 20 years, vaccination became less effective because of population turnover between control periods; v + fc lost little effectiveness, as decreased birth rates reduced the input of susceptible animals.

Conclusions. Using immunocontraception alongside vaccination could improve rabies control campaigns by reducing the proportion of the population that must be treated, or reducing the necessary duration of the campaign. It could also make control effective under larger population growths, in larger cities and when control is pulsed.

Implications. Immunocontraceptives could become a useful tool in canine rabies control by allowing fertility control to be applied on a large scale. Further work is required to improve understanding of dog ecology and parameterise location-specific models, which could be used to inform management plans.

Introduction

Rabies is a directly transmitted viral infection, affecting the central nervous system of mammals. It is responsible for ~55 000 human deaths each year, with 99% of these occurring in the developing world (WHO 2004). About US\$1bn is spent on rabies prevention each year globally, with over seven million people in Asia alone receiving post-exposure treatment (WHO 2004; Knobel *et al.* 2005). However, these figures underestimate the true burden of rabies, with many cases going unreported by authorities, and many people not seeking treatment because of high costs (Knobel *et al.* 2005).

Over 95% of human rabies cases are caused by bites from domestic dogs (*Canis familiaris*, L.) (Cleaveland *et al.* 2006). As

a result of dog-movement restriction and dog vaccination, canine rabies has been eradicated from much of the developed world, where the disease now persists only in wildlife (Wandeler and Bingham 2000). Canine rabies remains endemic throughout much of the developing world (Wandeler and Bingham 2000). Other species in canine rabies-endemic areas may carry rabies; however, they are not the primary disease reservoir (Bingham 2005). Consequently, attempts to reduce human rabies mortality must focus on controlling canine rabies.

There are three key components to rabies control, namely epidemiological surveillance, dog mass vaccination and population control (WHO 2004). Mass vaccination has been a powerful rabies control tool since the 1920s (Knobel *et al.* 2007).

It is estimated that vaccinating 70% of the population is sufficient to halt rabies transmission (Coleman and Dye 1996). Vaccination campaigns have successfully eradicated rabies in many areas, including Japan, much of Malaysia and many Latin American capital cities (Meslin *et al.* 2000). However, others have failed to reach an adequate proportion of dogs, primarily because of logistical and economic problems (Perry 1993; Cleaveland *et al.* 2006). Furthermore, modelling suggests that inadequate vaccination coverage can reinforce natural disease cycles (Hampson *et al.* 2007) and promote endemic establishment (Kitala *et al.* 2002). Nevertheless, dog vaccination is considerably cheaper than human vaccination or post-exposure treatment, and is considered the only method that can entirely eliminate human rabies mortality (Bögel and Meslin 1990).

Dog population management also plays an important role in rabies control. Enzootic rabies can be sustained only if the host population is above a critical threshold density; population management aims to maintain host populations below this level. Traditionally, culling has been the most common method of population management (Meslin *et al.* 2000). However, the use of culling is controversial, primarily because of the lack of evidence of its effectiveness in controlling populations or disease (WHO 2004). Culling may also promote increased survival and immigration (Leney and Remfry 2000), disrupt social organisation (Matter and Daniels 2000), remove vaccinated individuals (Cleaveland *et al.* 2006) and cause the loss of public support (Beran and Frith 1988), all of which make disease control harder (Massei *et al.* 2008a).

Fertility control, as an alternative to lethal control, is increasingly suggested as a humane means of managing wildlife populations (e.g. Barlow 2000; Massei *et al.* 2008b), and has been used in rabies control programmes in Thailand (Hemachudha 2005) and India (Reece and Chawla 2006). This method has also been evaluated to control overabundant population of free-roaming cats (Schmidt *et al.* 2009) and to assist rabies eradication in stray dogs (Bender *et al.* 2009; Massei *et al.* 2010). In addition, modelling suggests that fertility control could help control rabies in foxes and tuberculosis in koalas (Smith and Cheeseman 2002; Ramsey 2007).

Fertility control aims to reduce population size and growth by decreasing birth rates (Cowan *et al.* 2006). This has several advantages over culling, including the following: treated individuals remain in the population, thus maintaining density-dependent controls on population growth (Merrill *et al.* 2003), there are fewer associated ethical problems (Matter and Daniels 2000) and modelling suggests that fertility control can effectively reduce population numbers in the long term (e.g. Courchamp and Cornell 2000; Cowan and Massei 2008). There are also benefits for disease control, notably that contact rates may be decreased, reducing disease transmission (Ramsey 2007).

Surgical sterilisation is time-consuming and expensive, so cannot be used on a large scale (Kutzler and Wood 2006; Massei *et al.* 2008a). Recently developed immunocontraceptives could provide a solution to this problem. These vaccines stimulate the production of antibodies that neutralise proteins or hormones essential for reproduction, thus rendering animals infertile for several years (Miller *et al.* 2008a). Bender *et al.* (2009) found that one of these immunocontraceptives, administered to dogs, did not affect the ability of dogs to seroconvert in response to

the rabies vaccine and suggested using immunocontraception in combination with rabies vaccination to optimise dog population control and rabies eradication. Immunocontraceptives can be administered through single-shot, parenteral injections (Fagerstone *et al.* 2006), so could be applied on a large scale, making them potentially useful in canine rabies control.

We developed a mathematical model of rabies control in urban dog populations to describe the epidemiological cycle of canine rabies, and to explore the effects of different control methods on rabies eradication. The model is based on previous rabies models (e.g. Anderson *et al.* 1981; Smith and Cheeseman 2002), and uses parameters derived from the literature on dog ecology. Our objectives were (1) to determine whether vaccination combined with immunocontraception is more effective in eradicating rabies than vaccination alone or culling, (2) to evaluate how sensitive the control is to variation in dog population parameters and city size and (3) to determine the effects of applying control continuously or in pulses on rabies eradication.

Materials and methods

Model framework

We created a continuous time, compartmental model to investigate the effects of rabies control in dog populations. To achieve this, we adapted the models of Anderson *et al.* (1981), Smith and Cheeseman (2002), and Hampson *et al.* (2007). This is the first model to investigate rabies control in dogs by using a combined vaccine and fertility-control agent. We divided the population into the following three classes: susceptible (*S*) individuals are healthy and susceptible to rabies; exposed (*E*) animals have been infected with rabies and are incubating the disease; infectious (*I*) individuals display clinical symptoms, and can infect susceptible animals. To facilitate a simple model structure, we assumed all dogs to be equally likely to give birth, die, contract rabies and receive rabies control measures. System dynamics were governed by the following differential equations:

$$dS/dt = aS - (b + \gamma N)S - \beta SI, \quad (1)$$

$$dE/dt = \beta SI - (b + \gamma N)E - \sigma E, \quad (2)$$

$$dI/dt = \sigma E - (b + \gamma N + \alpha)I; \quad (3)$$

therefore, overall population behaviour is defined by

$$dN/dt = aS - (b + \gamma N)N - \alpha I, \quad (4)$$

where *S*, *E* and *I* describe densities of each class, so that population density $N = S + E + I$. As the model utilises continuous time, all rates are *per capita*. Susceptible individuals enter the population through births at rate aS , with neither exposed nor infected individuals able to contribute to births. All classes suffer mortality, at a rate composed of constant rate b and density-dependent rate γN (see below). Density-independent population growth therefore occurs at rate $r = a - b$. Susceptible animals become exposed by contact with infectious animals at rate βSI , where β is the transmission coefficient. Exposed individuals become infectious at rate σE , where $1/\sigma$ is the incubation

period. Finally, infectious individuals suffer disease-induced mortality at rate αI , where $1/\alpha$ is the infectious period. It is assumed that no animals recover, and no natural immunity exists.

Density dependence

The model assumes that all density dependence acts through the density-dependent mortality rate γN , where $\gamma = r/K$, and K is the population carrying capacity. Mortality increases until the population reaches carrying capacity, when it becomes equal to birth rate. Consequently, *per capita* growth decreases linearly with increasing population density, reaching zero at carrying capacity. However, as total population growth is the product of *per capita* growth and population size, it reaches a maximum at half carrying capacity.

Barlow (1996) noted that density dependence can act on other processes, and that this can affect disease control. Although previous canine rabies models have utilised density-dependent mortality (e.g. Kitala *et al.* 2002; Hampson *et al.* 2007), it is not yet clear whether this assumption is valid, and whether this could affect control efforts. Because it is important to examine the sensitivity of models to structural uncertainty (Smith *et al.* 2008), we developed two further sets of differential equations to include different forms of density dependence. If birth rate declines with increasing density, all density-dependent population regulation is borne by the susceptible class, and Eqn 4 becomes

$$dN/dt = (a - \gamma N)S - bN - \alpha I. \quad (5)$$

Alternatively, if both birth and mortality rates are affected by density dependence, Eqn 4 becomes

$$dN/dt = [a - (\gamma N/2)]S - [b + (\gamma N/2)]N - \alpha I. \quad (6)$$

Here, to compensate for acting on two processes, γN is divided by two, to ensure that the strength of density dependence remains constant. We used these forms to evaluate how sensitive model behaviour was to the assumption of density-dependent mortality.

Rabies control

To introduce vaccination into the model, a vaccinated (V) class was added. Susceptible individuals are vaccinated at rate vS . If vaccination does not last for an animal's whole lifetime, it is lost at rate δV , where $1/\delta$ is the mean period of protection. Accordingly, the density of vaccinated individuals is described by

$$dV/dt = vS - (b + \gamma N)V - \delta V, \quad (7)$$

where N is redefined as $S + E + I + V$, and Eqn 1 becomes

$$dS/dt = a(S + V) - (b + \gamma N)S - \beta SI - vS + \delta V. \quad (8)$$

If only vaccination is applied, vaccinated animals can contribute to births. To model the addition of fertility control, the aV term is removed from Eqn 8. We assume that if dogs were injected with immunocontraceptives, the opportunity to vaccinate would also be taken; consequently, it is assumed that every individual treated receives both vaccine and fertility control, that both are applied at the same rate, and that the duration of their effects is identical. Further, it is assumed that, although treatment is applied at random to animals in the susceptible class, dogs would be marked once treated, so that retreatment does not occur. The final control strategy examined was culling. We assumed culling to affect all classes equally, and we added a constant culling rate, p , to the death rate. Equation 4 then becomes

$$dN/dt = aS - (b + \gamma N + p)N - \alpha I. \quad (9)$$

Parameterisation

We obtained parameter values from a literature search. Because parameter values vary geographically, we used reported values to inform the selection of generic values (Table 1). Because the rabies incubation period is ~ 1 month, and because control effort can realistically be applied on such a timescale, we converted parameter values to monthly rates where necessary.

We set maximum *per capita* population growth at 0.2 year^{-1} , similar to that reported by Acosta-Jamett *et al.* (2010). Therefore, at half carrying capacity, the population grew at 0.1 year^{-1} , which is close to reported values and is a realistic assumption (E. Hiby, WSPA, pers. comm.). This was modelled by setting mortality as $5\% \text{ month}^{-1}$ and adding the desired growth rate; this produced a relative birth rate of $6.67\% \text{ month}^{-1}$. Although these values were not taken directly from the literature, they are similar to those reported by Cleaveland and Dye (1995), namely mortality of $1\% \text{ week}^{-1}$ and birth rate of $1.1\% \text{ week}^{-1}$. Population densities vary considerably among areas, making a widely applicable value hard to find. Therefore, we used an initial value of 750 dogs km^{-2} , because this was in the range reported by several studies (Beran and Frith 1988; Daniels and Bekoff 1989; Wandeler *et al.* 1993). Difficulties in estimating carrying capacity from field studies mean it is rarely reported, so we

Table 1. Parameter definitions, default values and extreme published values (for the sensitivity analysis) used in modelling

Symbol	Parameter	Value	Extremes
r	Average <i>per capita</i> growth rate	$0.0167 \text{ month}^{-1}$	$0.004^A - 0.017^B \text{ month}^{-1}$
a	Average <i>per capita</i> birth rate	$0.0667 \text{ month}^{-1}$	Not changed independently
b	Average <i>per capita</i> mortality rate	0.05 month^{-1}	Not changed independently
β	Transmission rate	0.0085	Fixed to maintain required dynamics
σ	Rate of transfer from exposed to infected	1.04 month^{-1}	$0.90^C - 1.36^D \text{ month}^{-1}$
α	Disease-induced mortality rate	5.35 month^{-1}	$5.33^E - 9.81^D \text{ month}^{-1}$
K	Carrying capacity	$1000 \text{ dogs km}^{-2}$	$1.0^B - 2930^F \text{ km}^{-2}$
S	Initial susceptible density	750 dogs km^{-2}	Not changed
E	Initial exposed density	0 dog km^{-2}	Not changed
I	Initial infected density	1 dog km^{-2}	Not changed

^ABrooks (1990); ^BAcosta-Jamett *et al.* (2010); ^CColeman and Dye (1996); ^DHampson *et al.* (2009); ^EHampson *et al.* (2007); ^FKato *et al.* (2003).

assumed this to be $1000 \text{ dogs km}^{-2}$. Because of the uncertainty associated with population size-related parameter estimates, we used sensitivity analysis.

We derived incubation- and infectious-period parameters from Foggin (1988), reported in Coleman and Dye (1996). These are derived from natural rabies infections, so provide more realistic estimates than values obtained from experimental infection (Coleman and Dye 1996). Because β is location-specific (Anderson 1982), various values were tested. When <0.0067 , rabies could not establish, whereas when >0.0098 , an intense epidemic occurred, which burnt itself out. Consequently, we chose 0.0085 , because it produced damped oscillations with periodicity similar to, if slightly slower than, the observed periodicity of dog rabies (Hampson *et al.* 2007).

Applying control

To implement control measures, we defined *per capita* control rates for vaccination (v in Eqn 7) and culling (p in Eqn 9). These could vary from 0 to 1, and described the number of animals treated within 1 month; a control rate of 0.5 would treat $0.5 \times$ density animals each month. However, because density is recalculated continuously because of births, deaths and disease, a constant rate does not treat a constant number of animals. *Per capita* rates could take values >1 , with which the population could be treated in <1 month, but initial evaluations suggested dominant system dynamics were covered in the range 0–1. For vaccination and vaccination with fertility control, there were two further options; treatment could remain effective permanently, or could be lost over time. We assumed that if temporary, vaccination and fertility control would both last 3–3.5 years, giving a loss rate of $\delta = 0.025 \text{ month}^{-1}$ (giving a duration of 3.33 years) (Sallum *et al.* 2000; Miller *et al.* 2008a).

We also modelled the impact of city size and different rates of dog population growth on rabies eradication carried out through different control methods. Variation in the city-size parameter could affect control success, because as city size increases, the absolute number of dogs increases (even if population density is equal). Thus, disease eradication becomes harder to achieve. Control was modelled for cities of 500 km^2 and 1000 km^2 , and results were compared with those described above from a 100 km^2 city. We set population growth at 10%, 20% and 30%.

In rabies control campaigns, control effort is likely to be applied in short, regular pulses. This could, however, reduce control efficacy, because normal disease dynamics can re-establish between control periods. Thus, we used the model to simulate two control-application strategies. The first was to apply control continuously, lasting from 1 to 24 months. The second was to apply control in yearly or twice-yearly pulses of 1 month, lasting 1–20 years.

We recorded the final status of the system for each combination of control rate and duration, to determine whether control was successful; rabies eradication occurred when infected density reached less than $(1/\text{city area}) \text{ km}^{-2}$; extinction of the dog population occurred when the density of susceptible and vaccinated reached less than $(1/\text{city area}) \text{ km}^{-2}$ (when fertility control was applied with vaccination, only susceptible density

was evaluated). We then compared this to the maximum known cull of 15% and target vaccination coverage of 70% (WHO 2004) to understand whether realistic treatment rates would be successful. We performed all modelling in STELLA[®] version 9.0 (iSee Systems Inc., Lebanon, NH), and analysis in R version 2.7.1 (R Development Core Team 2008).

Results

Model behaviour and sensitivity

Modelled population density showed damped oscillations. Mean periodicity, measured as the time between peaks, varied only slightly between forms of density dependence (mortality, 90.5 months; birth, 90.2 months; both, 89.7 months). Density-dependent mortality produced the highest population densities, and density-dependent birth produced the lowest, with a mean difference of $8.23 \text{ dogs km}^{-2}$. Consequently, results hereafter refer to the density-dependent mortality model, which is preferred because of its more conservative impact on population density and its wide use in previous rabies models.

When we examined the model for sensitivity to variation in parameter values, initial densities of $>850 \text{ dogs km}^{-2}$ produced a strong initial epidemic, which burnt itself out. At initial densities $<550 \text{ dogs km}^{-2}$, rabies transmission could not be maintained because of a lack of susceptible individuals. Within these bounds, damped oscillations were produced, reaching an equilibrium population density of $670\text{--}680 \text{ dogs km}^{-2}$. When carrying capacity was $<710 \text{ dogs km}^{-2}$, density-dependent mortality reduced susceptible density, leading to rabies eradication after an initial epidemic. Above this, however, increasing carrying capacity caused faster, larger-amplitude cycles; when $K = 1500 \text{ dogs km}^{-2}$, cycles had a mean periodicity of 71.3 months. Likewise, as growth increased, cycles occurred faster, and cycle damping occurred sooner; when $r = 1.0 \text{ year}^{-1}$, cycles had a mean periodicity of 43.4 months. Sensitivity analysis of the other parameters (see Table 1) did not qualitatively affect the disease dynamics or control, with the exception of the disease-induced mortality rate. When set to the shortest period reported (3.3 days: Hampson *et al.* 2009), an epidemic occurred only if the transmission rate was increased.

Continuous rabies control

The model was used to explore the impacts of culling, vaccination, and vaccination with fertility control ($v + fc$) when applied at varying rates and durations (Fig. 1); these results are compared to the rates required to achieve target vaccination coverage (70% coverage) and maximum reported cull (15%) (WHO 2004). By calculating the proportion of the population treated by the end of each month when different control rates and durations were applied, we could identify the appropriate *per capita* rates that generate the 70% and 15% thresholds. We assumed that vaccines and immunocontraceptives are applied via injection, so treated dogs can be marked to avoid retreatment. Although various combinations of control rate and control duration resulted in rabies eradication, comparisons among methods were most revealing with respect to the *per capita* rate required for disease eradication with a duration of only 1 month (hereafter referred to as the maximum control rate)

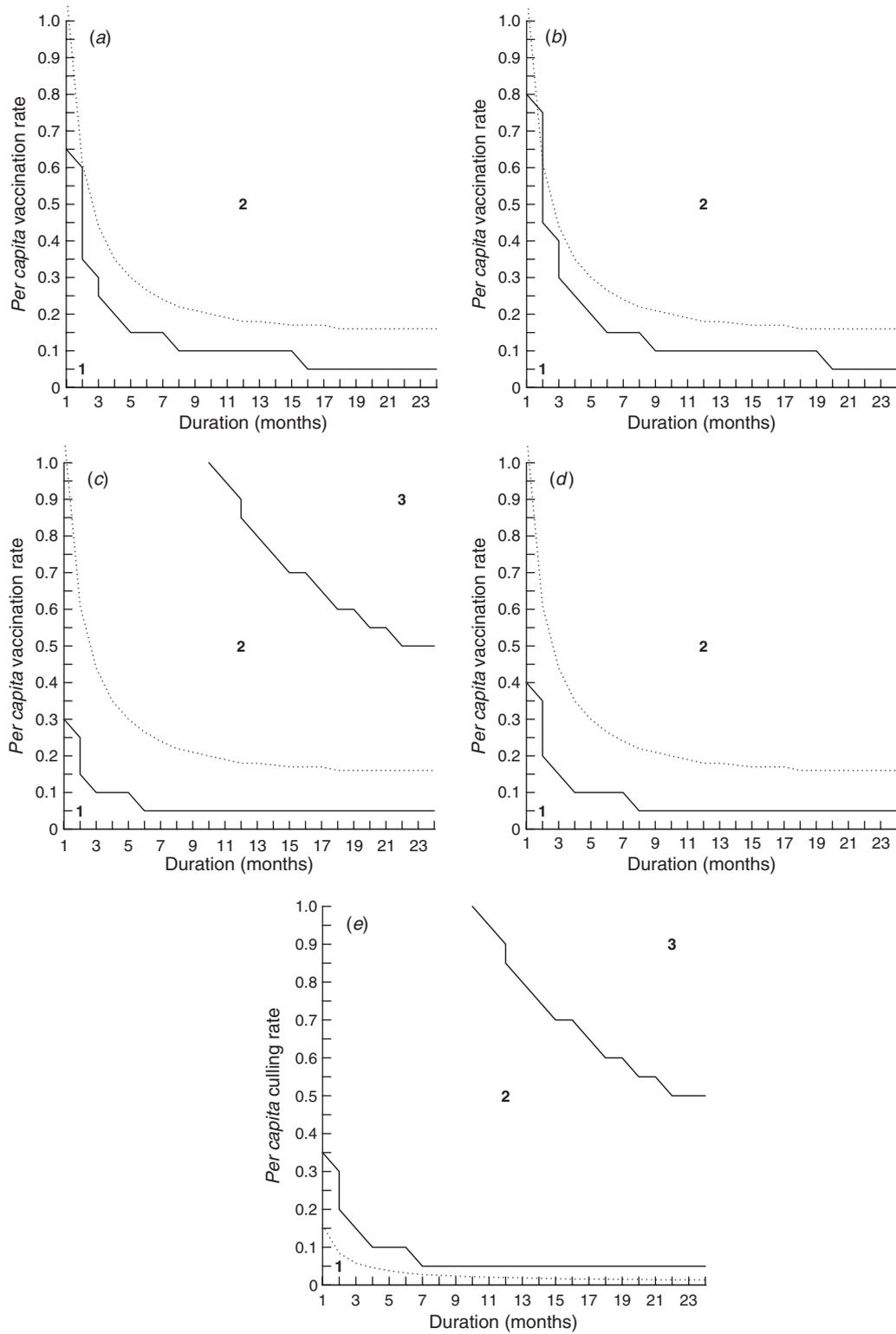


Fig. 1. Outcomes of continuous application of different rabies control methods over varying durations and rates, as follows: (a) vaccination effective for life, (b) vaccination effective for 3.33 years, (c) vaccination and fertility control effective for life, (d) vaccination and fertility control effective for 3.33 years and (e) culling. Solid lines indicate boundaries between different outcomes. Area 1 indicates that rabies is not eradicated; Area 2 indicates rabies eradication; and Area 3 indicates population extinction. Dotted lines indicate control rates required to achieve vaccination target of 70% or maximum known cull of 15%.

and the duration of control required for disease eradication when controlling at a *per capita* rate of 0.05 (hereafter referred to as the maximum control duration).

Vaccination was the least efficient method; the model predicted that rabies could be eradicated with a maximum control rate of 0.65–0.8, or a maximum control duration of 16–20 months. Culling and $v+fc$ required approximately half of this effort, with a maximum control rate of 0.3–0.4 or a maximum control duration of 7–8 months. Culling and $v+fc$ could cause population extinction, although this involved high-intensity, long-duration control. When the effects of vaccination and $v+fc$ were temporary, the maximum control rate increased by 0.1–0.15 and the maximum control duration increased by 2–4 months. However, this also removed the risk of causing population extinction.

Predicted outcomes were compared with the maximum achievable cull and target vaccination rates. For vaccination, we found this target rate to lie in the region of rabies eradication, but close to the persistence–eradication threshold, indicating that vaccination coverage of 70% should eradicate rabies, whereas failure to reach 70% of the population, or underestimating the true population, would probably lead to rabies persistence. For $v+fc$, the reduced control rates and durations required meant that 70% coverage would be more than adequate for disease eradication. Although culling was as efficient as $v+fc$, the maximum known culling rate of 15% fell under the disease-eradication threshold, suggesting that rabies would not be eradicated.

When density-dependent births were simulated, the rates required to achieve rabies eradication showed very little variation. With density-dependent births only, the rate required to achieve eradication with 1 month's control was identical to the density-dependent mortality model for $v+fc$ and culling, but was 0.05 lower for vaccination. Durations required for eradication when controlling at 0.05 were 1 month shorter for vaccination, 1 month longer for $v+fc$, and identical for culling. When both births and deaths were density-dependent, the maximum rate required for disease eradication was identical to that from the density-dependent mortality model for all control methods; the duration required for eradication at a control rate of 0.05 was 1 month shorter for vaccination, 1 month longer for $v+fc$ and identical for culling. Therefore, the qualitative difference between the methods remained, so that $v+fc$ was better than, or at least as good as, culling in all circumstances.

When we used the model to predict the time taken within the model for rabies to reach eradication (Fig. 2), we found that, for all methods, the maximum time to eradication was ~3 years. However, these times should be used only to compare among methods and are not definitive predictions of time to eradication. Figure 2 indicates that, for a given combination of control rate and duration, culling eradicated rabies several months earlier than did other methods. $V+fc$ eradicated rabies quicker than vaccination only, although the differences were small. If vaccination or infertility effects were temporary, it took longer for rabies to vanish from the system than if protection was permanent. For all methods, increasing control duration up to ~5 months could accelerate eradication. After 5 months, substantial benefits could be gained only by increasing the control rate.

Impacts of population growth and city-size variation

Under increased growth rates, rabies eradication required control for longer durations and at higher rates (Table 2). Increasing growth rate affected mostly vaccination, with increases in maximum control rate of up to 0.35, and in maximum duration of up to 13 months. Culling and $v+fc$ were again more efficient than vaccination and were less strongly affected by growth-rate variation, with increases in maximum control rate up to 0.1, and in maximum duration of up to 3 months.

Increasing city size had the largest effect on vaccination (Table 3). When city size increased beyond 100 km², rabies could not be eradicated with control rates of 0.05 or with a control duration of 1 month. Culling and $v+fc$ required greater effort for disease eradication, but showed increases in the maximum control rate of only up to 0.1, and in the maximum duration of up to 3 months.

Impacts of pulsing control effort

Achieving rabies eradication with pulsed control required higher control rates than did continuous control. For instance, rabies eradication required a minimum control rate of 0.15 twice-yearly for at least 6 years, or 0.25–0.3 yearly for at least 4 years, depending on whether the vaccine generated lifetime protection (Fig. 3). Indeed, only twice-yearly vaccination was likely to eradicate rabies when controlling at a rate to achieve 70% coverage. Furthermore, vaccination with temporary protection introduced a new dynamic when controlling at a rate of 0.15 twice-yearly or at a rate of 0.3 yearly; when control stopped after 5–8 years, a strong epidemic occurred that burnt itself out, eradicating rabies; when control lasted >8 years, a small epidemic occurred before control stopped, which caused the subsequent epidemic to be weaker, preventing burnout and allowing rabies to persist.

The impact of pulsing control was less evident for culling and $v+fc$, although effectiveness did decrease a little. Indeed, culling and $v+fc$ with temporary effects could no longer eradicate rabies when applied at a rate of 0.05 yearly. A population coverage of 70% with $v+fc$ was predicted to eradicate rabies, for both yearly and twice-yearly control. However, a 15% cull fell under the disease eradication threshold for both control frequencies, indicating it would again be ineffective. Population extinction became considerably easier when controlling twice-yearly, although high control rates and durations were still required, making it an unlikely outcome. Therefore, $v+fc$ remained effective even when control was pulsed, whereas vaccination became considerably less effective.

Discussion

Model success

The model we created to examine the effects of canine rabies control methods was based on generic population parameters derived from published estimates, so results were not site-specific. The turnover rate was higher than published estimates for rural populations, but this is a well known feature of urban populations (Matter and Daniels 2000). The most variable parameter was dog density, and the value we used adequately represented densities reported for Tunisia (Wandeler *et al.* 1993),

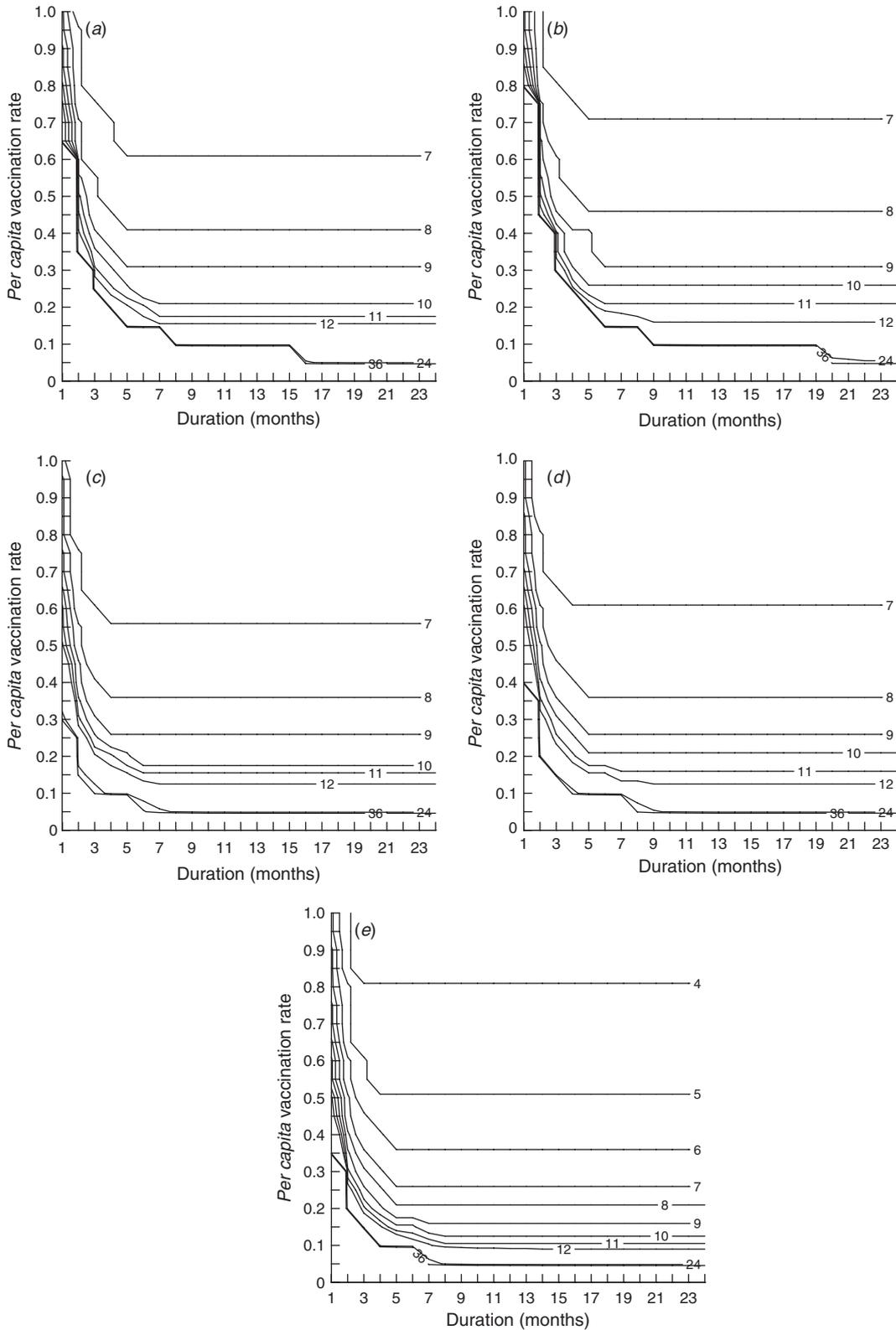


Fig. 2. Contours for the time to eradication (in months) for continuous application of different rabies control methods in relation to varying control durations and rates, as follows: (a) vaccination effective for life, (b) vaccination effective for 3.33 years, (c) vaccination and fertility control effective for life, (d) vaccination and fertility control effective for 3.33 years and (e) culling.

Table 2. Comparison of the maximum control rate and maximum control duration necessary for rabies eradication, for different rabies control methods, under varying population growth

Parameter	10% yearly growth	20% yearly growth	30% yearly growth	Increase
Maximum control rate				
Culling	0.25	0.35	0.35	0.1
V + fc, temporary effects	0.35	0.4	0.4	0.05
V + fc, permanent effects	0.25	0.3	0.35	0.1
Vaccination, temporary effects	0.5	0.8	0.85	0.35
Vaccination, permanent effects	0.45	0.6	0.7	0.25
Maximum duration (months)				
Culling	5	7	8	3
V + fc, temporary effects	7	8	9	2
V + fc, permanent effects	5	6	7	2
Vaccination, temporary effects	11	20	24	13
Vaccination, permanent effects	10	16	18	8

Table 3. Comparison of the maximum control rate and maximum control duration necessary for rabies eradication, for different rabies control methods, under varying city size

'>' indicates that rabies eradication was not achieved within the range of control rates or control durations modelled

Parameter	100 km ²	500 km ²	1000 km ²	Increase
Maximum control rate				
Culling	0.35	0.4	0.4	0.05
V + fc, temporary effects	0.4	0.45	0.5	0.1
V + fc, permanent effects	0.3	0.35	0.35	0.05
Vaccination, temporary effects	0.8	>1.0	>1.0	>0.2
Vaccination, permanent effects	0.65	0.9	1.0	0.35
Maximum control duration (months)				
Culling	7	8	9	2
V + fc, temporary effects	8	10	11	3
V + fc, permanent effects	6	7	8	2
Vaccination, temporary effects	20	>24	>24	>4
Vaccination, permanent effects	16	21	24	8

Ecuador (Beran and Frith 1988) and Mexico (Daniels and Bekoff 1989). Moreover, initial density could vary between 550 and 850 dogs km⁻² without changing model dynamics.

When run without rabies control, the model generated damped epidemic oscillations, describing the epidemiology of canine rabies relatively well. Cycles lasted slightly longer than the observed 3–6 years, although this is a common feature of canine rabies models, and has been attributed to reactive vaccination campaigns forcing faster cycling (Hampson *et al.* 2007). Our model, however, indicated that increasing population growth rate or carrying capacity increased the cycle speed. This could suggest, therefore, that previous canine rabies models underestimated either of these parameters.

Model assumptions deviated from real populations in several ways. First, the assumption of homogeneous, non-spatial population mixing is inherent in models of this type (Anderson 1982). However, food sources and shelter influence dog-population interactions, and consequently the disease-

transmission risk (Matter and Daniels 2000). The lack of age and sex structure could also have affected results, as these too can influence disease transmission (Anderson 1982). Current immunocontraceptives are more effective on females and sexually mature animals (Killian *et al.* 2006; Miller *et al.* 2008b), so the assumption of perfect efficacy may slightly overestimate effectiveness. Finally, humans cause city-specific variation in factors such as birth and death rates, and more importantly, in the accessibility of dogs (Matter and Daniels 2000). Parameter estimates relating to this variation are rare, so we could not quantify this variation. Some of these concerns have been addressed for fox rabies (e.g. Smith and Harris 1991); however, they have yet to be addressed for dogs, making this a priority for future studies.

Rabies control

The results of the model suggested that applying fertility control in conjunction with vaccination can improve the success of rabies control. Rabies vaccination repeatedly proved the least effective of the rabies control methods we modelled. Although vaccinating 70% of the dog population can eradicate rabies (Cleaveland *et al.* 2006), the model suggested that this was close to the minimum control rate required for rabies eradication. Therefore, a relatively small change in coverage could determine whether control succeeds or fails. Because many campaigns fail to reach 70% (Cleaveland 1998), rabies eradication may be unlikely when using vaccination alone.

Vaccination campaigns often focus control into 1 month of every year (e.g. Sallum *et al.* 2000). The model indicated that this reduces effectiveness, because high population turnover between control periods reduces herd immunity. Furthermore, at low control rates, rabies could be eradicated only by forcing an intense epidemic that burnt itself out. Longer control allowed a small epidemic to occur before control ceased, which inhibited epidemic burnout, allowing rabies to persist. The exact conditions required to generate this effect remain unclear, although similar effects are also seen in fox rabies models, where inadequate removal of susceptible individuals increases epizootic duration (Smith and Harris 1989).

Control through culling was found to be more effective than vaccination for a given level of control. This supports model results for other diseases (e.g. Barlow 1996), but contradicts suggestions that culling is ineffective for canine rabies control (e.g. WHO 2004). The model predicted that culling 35% of the population in 1 month could eradicate rabies. Given initial parameter values of 750 dogs km⁻² and a 100 km² city, this would equate to culling ~26 000 dogs, which would be extremely difficult to achieve. The highest recorded culling rate of ~15% (WHO 2004) always fell below the rabies eradication threshold. Therefore, although culling appeared more effective, it is unlikely that the necessary rate could be achieved. Furthermore, if culling is used alongside mass vaccination, vaccinated animals may be eliminated (Beran and Frith 1988).

When fertility control was added to vaccination, the control rate and duration required for rabies eradication were reduced by about half, supporting similar predictions from fox rabies models (e.g. Smith and Wilkinson 2003). Rabies eradication was

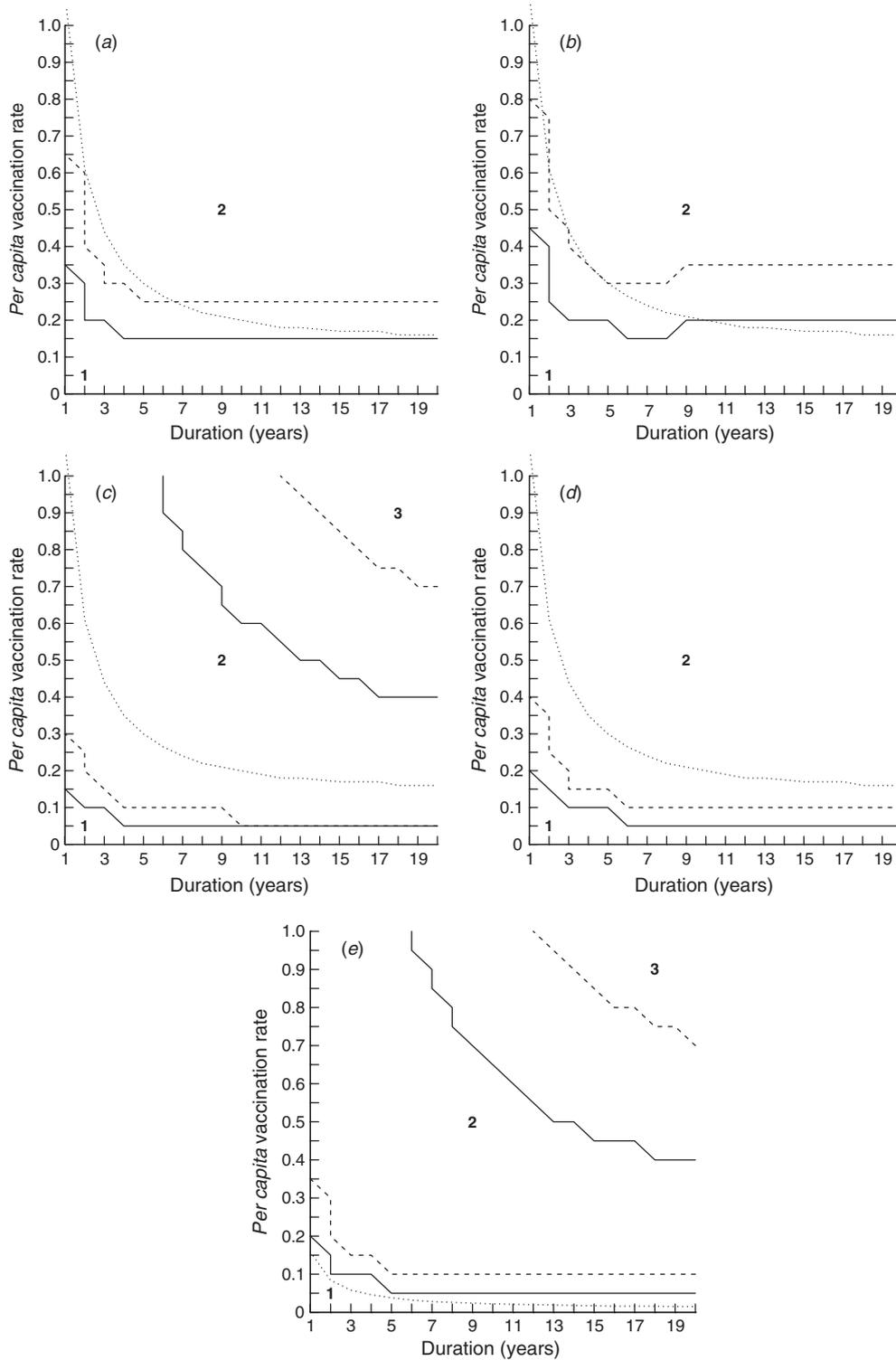


Fig. 3. Long-term outcome of rabies control when control is pulsed, in relation to varying control durations and rates, as follows: (a) vaccination effective for life, (b) vaccination effective for 3–3.5 years, (c) vaccination and fertility control effective for life, (d) vaccination and fertility control effective for 3–3.5 years and (e) culling. Solid lines indicate one pulse every 6 months; dashed lines indicate one pulse every 12 months. Area 1 indicates that rabies remained in the population, Area 2 indicates that rabies was eradicated, and Area 3 indicates that the dog population became extinct. Dotted lines indicate control rates required to achieve vaccination target of 70% coverage or maximum known cull of 15%.

therefore predicted to be possible with as little as 30% population coverage. Fertility control aids rabies eradication by lowering birth rates, so that fewer susceptible animals are added to the population. This provides two benefits, namely the proportion of vaccinated animals remains high, and the population is maintained at a lower density, reducing the risk of reinfection (Smith and Cheeseman 2002). However, mortality rates are unchanged in the short term, so density-dependent population regulation remains in place (Cowan *et al.* 2006). Applying fertility control may even enhance density-dependent population regulation by increasing life expectancy (Williams *et al.* 2007). These results are not changed by the inclusion of density-dependent births into the model.

An important result was that vaccination with fertility control became only marginally less effective when city size and population growth increased, and when control was pulsed. This contrasted sharply with vaccination alone, which became considerably less effective. The result is again linked to the effects fertility control has on the population turnover; in smaller populations with lower birth rates and lower density-dependent mortality, vaccination coverage remains high for longer. However, as the city size increases, control at a given rate means that proportionally more animals must be treated. It is therefore encouraging that treating a maximum of ~50% of the population was sufficient to eradicate rabies when fertility control was used. Because fertility control may be less effective for species with high reproductive rates (Cowan *et al.* 2006), further population monitoring is required to ensure the accuracy of growth estimates and the population turnover. Finally, pulsing control may prove more efficient in the long-term, and could have benefits over continuous control in a spatial model (Earn *et al.* 1998). Further work is required to find the optimum control frequency.

The model indicated that culling achieved eradication quickest by directly reducing population density, and hence causing transmission rate to decline. However, culling might actually increase disease transmission, as contact rates between the remaining animals increase, making disease eradication harder. This effect has been shown to occur in European badgers (*Meles meles*) involved in transmission of bovine tuberculosis (Woodroffe *et al.* 2006; Carter *et al.* 2007) and should be investigated in dogs. With such effects taken into account, vaccination and fertility control may still improve the speed of disease eradication, because fertility control can reduce contact rates through reduced reproduction-related behaviour (Ramsey 2007). Fertility control could also be used as a complementary method to culling; for instance, the model by White *et al.* (1997) suggested that fertility control integrated with culling could be effective in controlling bovine tuberculosis in badgers.

The results of this work support previous reports of successful rabies eradication through combining vaccination with surgical sterilisation (e.g. Reece and Chawla 2006). It is evident though, that large-scale use of surgical sterilisation is impractical because of high cost and time requirements (Massei *et al.* 2010). Single-shot immunocontraceptives provide a potential solution, allowing fertility control to be applied at the same rate as vaccination, and for a lower cost than that of surgery (Massei *et al.* 2008b, Bender *et al.* 2009). However, results from this model provide only preliminary indications of the possible

success of immunocontraceptives. Further work, in both dog population studies and in epidemiological modelling, is required to confirm these findings.

Long-term monitoring is also required to gain detailed estimates of population growth, and birth and death rates in specific contexts. This would aid model parameterisation, enhance the accuracy of predictions and provide a better understanding of density dependence in dog populations. Importantly, this would also clarify whether observed rabies periodicity is caused by reactive vaccination or whether population growth has previously been underestimated. Site-specific spatial models would help identify human influences on the transmission of canine rabies, allow more accurate management decisions to be made (Smith and Cheeseman 2002) and may provide more accurate estimates of the required control rates, as has been suggested for rabies control in the fox (Thulke and Eisinger 2008).

Although more detailed models could strengthen predictions, results presented here offer an initial indication that immunocontraceptives could become a valuable addition to canine rabies control.

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