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Optimal frequency of rabies vaccination campaigns in Sub-Saharan Africa

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Rabies causes more than 24 000 human deaths annually in Sub-Saharan Africa. The World Health Organization recommends annual canine vaccination campaigns with at least 70% coverage to control the disease. While previous studies have considered optimal coverage of animal rabies vaccination, variation in the frequency of vaccination campaigns has not been explored. To evaluate the cost-effectiveness of rabies canine vaccination campaigns at varying coverage and frequency, we parametrized a rabies virus transmission model to two districts of northwest Tanzania, Ngorongoro (pastoral) and Serengeti (agro-pastoral). We found that optimal vaccination strategies were every 2 years, at 80% coverage in Ngorongoro and annually at 70% coverage in Serengeti. We further found that the optimality of these strategies was sensitive to the rate of rabies reintroduction from outside the district. Specifically, if a geographically coordinated campaign could reduce reintroduction, vaccination campaigns every 2 years could effectively manage rabies in both districts. Thus, coordinated campaigns may provide monetary savings in addition to public health benefits. Our results indicate that frequency and coverage of canine vaccination campaigns should be evaluated simultaneously and tailored to local canine ecology as well as to the risk of disease reintroduction from surrounding regions.

1. Introduction

Rabies is responsible for the loss of over 600 000 life-years in Sub-Saharan Africa annually, predominantly among children [1]. As more than 99% of human rabies cases arise from exposure to rabid dogs [1], canine vaccination is a highly effective One Health intervention, with veterinary campaigns able to directly avert canine rabies and indirectly prevent rabies transmission to humans [2–4]. Canine rabies virus transmission has been successfully eliminated in all developed countries, with a subsequent dramatic impact upon the human disease burden [1]. However, animal rabies control programmes have not been implemented in many resource-constrained regions, despite high disease burdens in Africa and Asia [1]. Although prompt and appropriate post-exposure prophylaxis (PEP) can prevent human rabies after exposure to a rabid animal, PEP is expensive and often unavailable in Africa, particularly in rural areas that are at highest risk for rabies virus exposure [5,6].

In 2013, the World Health Organization (WHO) called for a renewed focus on rabies control in Sub-Saharan Africa, advocating annual vaccination campaigns to achieve coverage of 70% in canine populations. Previous analyses have been based on relatively closed systems [2,3,7], ignoring the possible impact of rabies reintroduction from unvaccinated regions. However, rabies virus transmission across national and sub-national borders has been documented in Sub-Saharan Africa [8]. In Latin America, reintroduction of rabies from areas with insufficient vaccination coverage into vaccinated regions has hindered elimination efforts [9]. In the face of reintroduction, campaigns may require greater frequency or higher coverage. Alternatively, less frequent campaigns might provide significant monetary savings with minimal adverse consequences in limited-resource settings. Furthermore, previous cost-effectiveness evaluations have focused on annual campaigns [2,10] or one-time campaigns [3], and have not considered the simultaneous optimization of both coverage and frequency, nor even optimization of frequency alone. However, from an implementation standpoint, it is more straightforward to decide how often to conduct vaccination campaigns than to control the coverage achieved.

In our analysis, we evaluated whether alternative frequencies of vaccination campaigns might be equally or more efficient as annual or one-time campaigns. We considered different rates of rabies reintroduction into vaccinated areas by combining transmission modelling of rabies virus in canine and human populations, parametrized to pastoral and agro-pastoral settings, with cost-effectiveness analysis.

2. Methods and materials

We adapted a previously published rabies epidemiological model to examine a range of canine vaccination strategies in two rural settings in Tanzania: Ngorongoro and Serengeti [2]. We compared vaccination campaign frequencies ranging from every six months to every 3 years, and canine vaccination coverage from 0% to 90% in increments of 10%, over a 10 year time horizon. We conducted both a cost-effectiveness analysis and a budget impact analysis from the perspective of a health policymaker. Economic costs were calculated in 2012 United States dollars (purchasing power parity) (USD (PPP)) and health benefits were measured in disability-adjusted life-years (DALYs). We labelled an intervention 'very cost-effective' if its incremental cost-effectiveness ratio (ICER) was less than the Tanzanian *per capita* gross domestic product (GDP) in 2012 ($1 610), and as 'cost-effective' if the ICER was less than three times the GDP per WHO recommendations [11]. For the purpose of cost-effectiveness analysis, we discounted both future costs and health benefits at a rate of 3% annually, also according to WHO guidelines [12]. Costs and health benefits remain undiscounted for the budget impact analysis [13]. We conducted both deterministic and probabilistic sensitivity analysis to evaluate the robustness of our findings in the face of parameter uncertainty.

(a) Study sites

Both Ngorongoro and Serengeti Districts border the Serengeti National Park, but differ in human and canine population density and rabies dynamics [2,14]. Ngorongoro spans an area of 14 036 km^2 with a sparsely distributed human population close to 130 000. In this district, there are approximately 1.5 dogs km^{-2}, and rabies manifests as sporadic outbreaks [2,14]. Serengeti, a smaller district of 3 373 km^2, has both a denser human population of around 200 000 and a denser canine population of approximately 9.5 dogs km^{-2} with endemic canine rabies [2,14].

(b) Model structure

Hosts were stratified into dogs, wildlife, and humans. Canine and wildlife hosts were divided into susceptible, exposed, or infectious classes, as well as into a vaccinated class for dogs. We also incorporated canine and wildlife birth and death demography (electronic supplementary material, table S1). Because rabies is fatal once clinical signs appear, there was no recovered compartment [15]. At the beginning of a year, the specified proportion of dogs corresponding to the vaccination strategy were moved to the vaccinated compartment from the susceptible compartment. For the remainder of year, the epidemiological and demographic processes were modelled in continuous time.

Based on both field data and previous modelling [2,3,16,17], we included three model parameters that together determine mortality rates of dogs and wildlife, respectively: a frequency-dependent term, a density-dependent term, and rabies-related mortality. The frequency-dependent term, μ, was included as a constant rate of removal from each compartment to represent adult canine mortality in Tanzania. It is given by the reciprocal of the empirical life expectancy for adult dogs and parametrized by field data [17]. The density-dependent term is based on logistic population growth models, assuming that increasing mortality rates constrain population growth as the population approaches a defined limit, known as the carrying capacity, K. For dogs, this density-dependent mortality primarily affects puppies, only 30% of whom survive to three months [17]. The density-dependent death rate includes a constant, γ, which is equal to $(b - \mu)/K$, where b is the birth rate. This constant is multiplied by the size of the compartment and total population size (N), because the death rate increases as a second-order effect of increase in population size. This death rate is distributed across all compartments proportionally to the size of the compartment, except for the infectious compartment, as we assume rabies is the primary driver of mortality in rabid animals. Rabid dog survival (i.e. the infectious period $1/\alpha$) is approximately 3 days following onset of active infection [16].

Model outcomes included incidence of rabies in dogs, number of dogs vaccinated, number of canine vaccines used, and incidence of human rabies, which were then linked to economic costs. As wildlife do not maintain rabies independent of dogs in these districts [17,18], they are not a primary target of vaccination intervention, though wildlife virus transmission can impact canine transmission [16]. Most of our model parameters were drawn from previous analyses, where they had been validated from surveillance data (electronic supplementary material, table S1) [2,18]. Specifically, the annual numbers of human deaths in Ngorongoro and Serengeti, at the 15% canine vaccination coverage typically implemented in Tanzania prior to coordinated vaccination campaigns, were consistent with field observations [2,18].

Based on field observations and consistent with other studies [2], we assumed that previously vaccinated dogs who survived to the next campaign were revaccinated, and that a proportion of dogs could not be reached by vaccination campaigns. We did not include vaccine waning, as several commercial domestic animal rabies vaccines have been found to provide complete immunity for at least 3 years [1], the upper interval between campaigns considered. We excluded dogs in the exposed and infectious compartments from vaccination. Although dogs exposed to rabies but not yet infectious may indeed be vaccinated in a campaign, it is unclear whether vaccination would prevent the development of rabies in those dogs. By excluding them from vaccination in our model, we may slightly underestimate the epidemiological benefit of a vaccination campaign, but the number of dogs affected is negligible (less than 0.05% of the canine population).

Because rabies can be reintroduced into vaccinated areas through the migration of unvaccinated dogs from neighbouring regions [8], we incorporated rabies reintroduction parametrized from field studies in Serengeti District [8,19]. This was represented in our model by a low rate of reintroduction of canine rabies. Based on the field observations [8], we considered a range from no reintroduction to 10 rabid dogs entering Serengeti annually, with a base case assumption of five dogs annually. For Ngorongoro, we scaled reintroduction to the relatively lower canine density of the region [18], and used a rate of 3.1 for the base case, with sensitivity analysis ranging from 0 to 6.2 dogs annually reintroduced. Rabid dogs were reintroduced into vaccinated areas as a daily number of dogs per square kilometre.

(c) Economic and health outcomes

The cost of vaccination programmes differed by region and varied nonlinearly, depending on vaccination coverage [2,20]. We parametrized our model based on costs of vaccination campaigns implemented in Tanzanian villages similar to those in Serengeti and Ngorongoro (electronic supplementary material, table S3) [20]. At 70% coverage, vaccination costs an average of $14.02 per dog in Ngorongoro and $8.48 per dog in Serengeti, owing to the less concentrated population of the former and the need for door-to-door campaigns to achieve high coverage (electronic supplementary material, table S2).

We calculated the impact of rabid dogs in terms of health and economic costs by considering the number of humans bitten per rabid dog and the probabilities of and costs associated with three possible human outcomes: PEP administration, death due to human rabies, or neither (electronic supplementary material, table S2). Based on field data, the average dog-to-human bite rate is 0.51 persons bitten per rabid dog [2]. Based on data from the implementation of rabies vaccination programmes in Tanzania, the economic cost of a single PEP delivery was estimated at $318 per regimen [2].

The health burden of a single human rabies case in rural Tanzania was estimated at 42.55 DALYs [21], and because there is no morbidity associated with rabies, this corresponds directly to years of life lost. To estimate the cost per rabid dog, we multiplied this health burden by the number of humans bitten per dog and the probability that each bitten human developed rabies, an average cost of 1.44 DALYs/rabid dog. To be conservative in our assessment of the benefits of vaccination, we did not include the indirect time and productivity costs associated with travel to obtain PEP and bite-related care. We assumed neither health nor economic costs were associated with individuals who did not seek care and did not develop rabies.

Costs were converted from pre-2012 non-PPP USD by adjusting for inflation [22], the change in exchange rates between USD and Tanzanian shillings (Tsh) between the year from which costs were derived and 2012 [23], and the 2012 PPP adjustment factor for Tsh (2.63) [24].

(d) Cost-effectiveness analysis

We first conducted a series of deterministic analyses varying frequency and coverage for each location. We calculated the monetary cost and the DALYs averted of each combination of canine vaccination coverage and frequency, compared to the *status quo* of no vaccination. The cost of PEP for bite victims of rabid dogs was included in all scenarios. We assumed that the proportion of rabid bite victims treated with PEP would remain constant at 0.86 [21], regardless of canine vaccination level, as access to PEP is unlikely to be affected by a canine-focused intervention. We then identified the 'efficient frontier' in each location as follows: we first found the least expensive strategy that was not strictly dominated, that is, for which there was no alternative strategy that was both less expensive and averted more DALYs. We then identified each subsequent strategy with the lowest ICER, which is the cost per DALY of a marginal gain over an alternative strategy [25]. For each location, we highlighted the strategies that averted the greatest number of DALYs with ICERs below the cost-effective and very cost-effective thresholds.

(e) Uncertainty and sensitivity analyses

To assess the impact of parameter uncertainty on our epidemiological outcomes, we next generated 10 000 sets of parameters, sampled from their empirical distributions (electronic supplementary material, table S1), and estimated the epidemiological and economic outcomes across all combinations of frequency and coverage for each set of parameters. We determined the net benefit [26] of every vaccination strategy at each $10 increment of willingness to pay (WTP) per DALY ranging from $1 to $5 000, dividing the cost of each strategy by the WTP and subtracting this value from the DALYs averted. We defined the optimal strategies as those with the highest probability of providing the largest net benefit at the very cost-effective and cost-effective thresholds. We repeated this uncertainty analysis across the range of rabies reintroduction rates and performed one-way sensitivity analyses for parameters that lacked well-defined empirical distributions.

We also examined the possibility that longer intervals between campaigns may increase the probability of a catastrophic rabies outbreak. As a deterministic model does not capture the potential for large stochastic outbreaks, we considered 'control thresholds' below which we assumed such outbreaks were unlikely. As any single threshold would be arbitrary, we evaluated the probability that annual human cases exceeded 'control thresholds' between 1 and 10 in the district.

(f) Budget impact analysis

To provide a fiscal planner with an estimate of the total cost of programme implementation, we calculated the undiscounted cost of different rabies control programmes over the same 10 year time horizon [13]. We incorporated the costs associated with both canine vaccination campaigns and PEP delivery; after PEP or death, there are no follow-up treatment costs associated with rabies. We present budgetary resources required for both the WHO recommended annual campaign with 70% coverage strategy [1] and the strategies we found optimal in our analysis for each district. While we restricted ourselves to the likely costs of implementing a rabies vaccination campaign, we recognize that a comprehensive fiscal plan would consider non-rabies health costs triggered by vaccination. An assessment of the costs associated with these competing risks is beyond the scope of the present analysis.

3. Results

(a) Rabies occurrence and health burden

Without vaccination, we predicted 0.2 canine cases per km^2 in Ngorongoro and 6.8 cases per km^2 in Serengeti over a 10 year

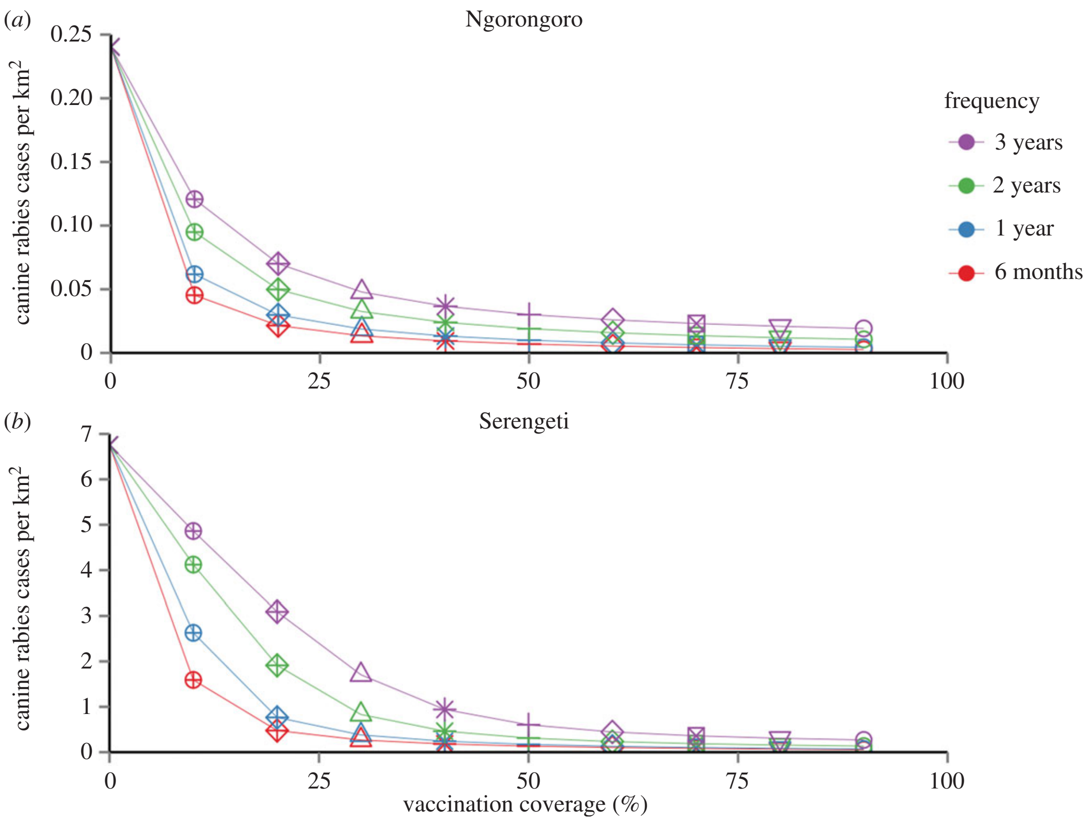

Figure 1. Rabies cases. Canine rabies cases per square kilometre over 10 years of vaccination campaigns at varying frequency and coverage. Scale of the *y*-axes differs between the two districts. (*a*) Ngorongoro and (*b*) Serengeti.

period (figure 1). This corresponded to a human health burden of rabies of 0.2 DALYs per km^2 compared to 6.2 DALYs per km^2 over the decade. More frequent vaccination resulted in fewer rabies cases, although at high levels of coverage we observed rapidly diminishing marginal returns to increased investment. Low frequency, low coverage campaigns had a greater impact on rabies cases in Ngorongoro than in Serengeti.

(b) Cost-effectiveness analysis

In Ngorongoro, the lowest-cost non-dominated strategy was that of no vaccination with a cost of $22 per km^2 (table 1). Biennial vaccination of 50% of the canine population had the highest ICER below the 'very cost-effective' threshold (ICER: $1 222/DALY), and vaccinating 80% of the canine population biennially had the highest ICER below the 'cost-effective' threshold (ICER: $3 791/DALY).

For Serengeti, we found that vaccination at low coverage and frequency was more expensive and averted fewer DALYs than vaccination at intermediate to high rates and frequencies (figure 2), as a consequence of the high cost of PEP and the even higher human health cost incurred by the greater number of rabies cases in this district. The lowest-cost, non-dominated strategy was vaccination every 3 years to achieve coverage of 60%, with a cost of $236 per square kilometre and 7.8 DALYs averted per square kilometre, compared to no vaccination. Therefore, canine vaccination is cost saving relative to a strategy of no vaccination. Biennial vaccination with a coverage of 70% had the highest ICER below the 'very cost-effective' threshold for Tanzania (ICER: $191/DALY). Annual vaccination at 70% (ICER: $2 785/DALY) had the highest ICER below the 'cost-effective' threshold.

(c) Uncertainty analysis: optimal strategies

We used Monte Carlo sampling to examine the impact of parameter uncertainty and identify the optimal strategy for each district (figure 3). We found that in Ngorongoro, the optimal strategy at a WTP of $1 610 per DALY, the 'very cost-effective' threshold for Tanzania, was biennial campaigns with 80% coverage, conferring the largest net benefits with higher probability than any other strategy. Biennial campaigns at 90% coverage were most likely to be optimal at a WTP of $4 830 per DALY, the 'cost-effective' threshold. Annual vaccination in Ngorongoro District was only optimal for WTP thresholds over $6 701. In Serengeti, the strategy most likely to be optimal at a WTP of $1 610 was biennial vaccination at 70% coverage. At a WTP of $4 830, annual campaigns with 70% coverage were optimal.

To consider the risk of a catastrophic rabies outbreak under optimal strategies in the deterministic model, we examined the percentage of simulations in which human rabies cases exceeded different 'control thresholds.' We found that annual human rabies remained below 5 cases in more than 97% of simulations for all strategies found to be optimal in both districts (electronic supplementary material, figure S6).

(d) Uncertainty analysis: reintroduction

To assess sensitivity to reintroduction rates, we identified the optimal strategy at varied levels of reintroduction at the 'cost-effective' threshold of $4 830 (figure 4). We found that biennial vaccination campaigns at 90% coverage were optimal in Ngorongoro when rabies reintroduction was below 4.6 dogs per year in the district. Once reintroduction

Table 1. Vaccination strategies on the efficient frontier for each district at baseline rates of reintroduction. Italicized strategies indicate the optimal strategy at the WHO criteria for 'very cost-effective', and those in bold are the optimal strategies that meet criteria for 'cost-effective'. Costs and DALYs averted are cumulative over 10 years, discounted at 3% annually, and estimated for the entirety of each district. A strategy's ICER is calculated by dividing the difference between its cost and the cost of the strategy above it by the difference in DALYs averted. Due to rounding, ICERs in the table may not directly correspond to costs and DALYs presented.

campaign frequency	coverage (%)	cost ($)	DALYs averted	ICER ($/DALY)
Ngorongoro				
no vaccination	no vaccination	22	0.00	n.a.
3 years	20	26	0.21	21
2 years	20	29	0.23	140
3 years	30	30	0.24	293
2 years	30	36	0.25	297
2 years	40	43	0.27	675
2 years	*50*	*51*	*0.27*	*1222*
2 years	60	59	0.28	1930
2 years	70	67	0.28	2790
2 years	**80**	**75**	**0.28**	**3791**
1 year	60	114	0.29	8093
1 year	70	130	0.29	8278
1 year	80	146	0.29	11 245
1 year	90	176	0.29	27 566
6 months	90	333	0.29	73 263
Serengeti				
3 years	60	236	7.84	n.a.
3 years	70	238	7.95	17
2 years	*70*	*278*	*8.17*	*191*
2 years	80	358	8.21	1994
2 years	90	433	8.23	2596
1 year	**70**	**526**	**8.27**	**2785**
1 year	80	689	8.29	6337
1 year	90	839	8.31	7940
6 months	90	1590	8.33	41 025

exceeded 4.6 dogs per year, annual vaccination at 80 or 90% coverage was optimal.

In Serengeti, when reintroduction was between 0.5 dogs per year and 4.2 dogs per year, the optimal vaccination strategy was biennial vaccination at 90% coverage. When reintroduction was greater than 4.2 dogs per year, the optimal strategies were annual campaigns at 70% coverage.

Reducing reintroduction also reduced the risk of uncontrolled rabies at lower frequencies of vaccination, particularly in Ngorongoro in which a greater number of human cases was observed. For example, when reintroduction into Ngorongoro was reduced from 3.1 dogs per year to 1 dog per year, the probability of observing three or more human cases per year fell from 6.7 to 2.1% of simulations under biennial vaccination with 80% coverage and from 3.2 to 0.5% of simulations under biennial vaccination with 90% coverage.

(e) Other sensitivity analyses

We conducted sensitivity analyses with regard to canine demography, specifically canine lifespan, and carrying capacity. The optimal campaign frequency was insensitive to variations in canine lifespan and canine carrying capacity, which affect the estimate of DALYs saved but do not shift the optimal strategy (electronic supplementary material, figure S2). Our results were also robust to variations in a PEP cost, DALYs averted, and dog–human bite rate (electronic supplementary material, figures S3 and S4). Results for Ngorongoro were robust to variation in wildlife birth and death rates, but in Serengeti, the optimal strategy shifts from annual to biennial as the birth rate decreases and the frequency-dependent death rate increases (electronic supplementary material, figure S5).

(f) Budget impact

In Ngorongoro, the current WHO recommendation of annual campaigns at 70% coverage would cost $1 821 353 to implement over 10 years, including $1 811 895 in dog vaccination costs and $9 458 in PEP costs. Biennial campaigns at 80% coverage would cost $1 049 881, comprised of $1 032 170 for dog vaccination costs and $17 711 in PEP costs. In Serengeti, campaigns at the current WHO recommendation of 70% annual coverage would cost $1 776 922 over 10 years, including $1 740 136 for dog vaccination and $36 787 for PEP, while biennial campaigns at 80% coverage would cost $1 213 584, comprised of $1 157 989 for dog vaccination and $55 595 for PEP. A shift from annual to biennial campaigns therefore represents a 42% cost reduction in Ngorongoro, saving $656 101 over 10 years and a 32% cost reduction in Serengeti, saving $333 030 over 10 years. Though the percentage of the budget dedicated to PEP increases for biennial strategies, it remains less than 2% of the total budget in all of these strategies.

Overall, the direct economic benefit of reducing reintroduction would be low if the vaccination strategy remained unchanged, as lower reintroduction would mainly reduce PEP expenditures, a small percentage of the overall budget. Nevertheless, concerted vaccination campaigns that covered wide geographical regions and reduced reintroduction would also allow for a safe shift from annual to biennial campaigns, with more substantial financial savings.

4. Discussion

Our cost-effectiveness analysis of canine rabies vaccination campaigns is the first to examine the impact of campaign frequency and to consider reintroduction of rabies from unvaccinated areas rather than focus entirely on closed systems. Previous work has focused primarily on the cost-effectiveness of the WHO recommended strategy of annual campaigns covering at least 70% of the canine population [1–3]. By contrast, we explored the role that campaign frequency, an easily modifiable aspect of vaccination programmes, plays in rabies control. Our analysis indicates the optimal strategy depends on the local canine population dynamics and human demography.

As Ngorongoro is a sparsely populated district with a lower dog carrying capacity than Serengeti, rabies in the former can be

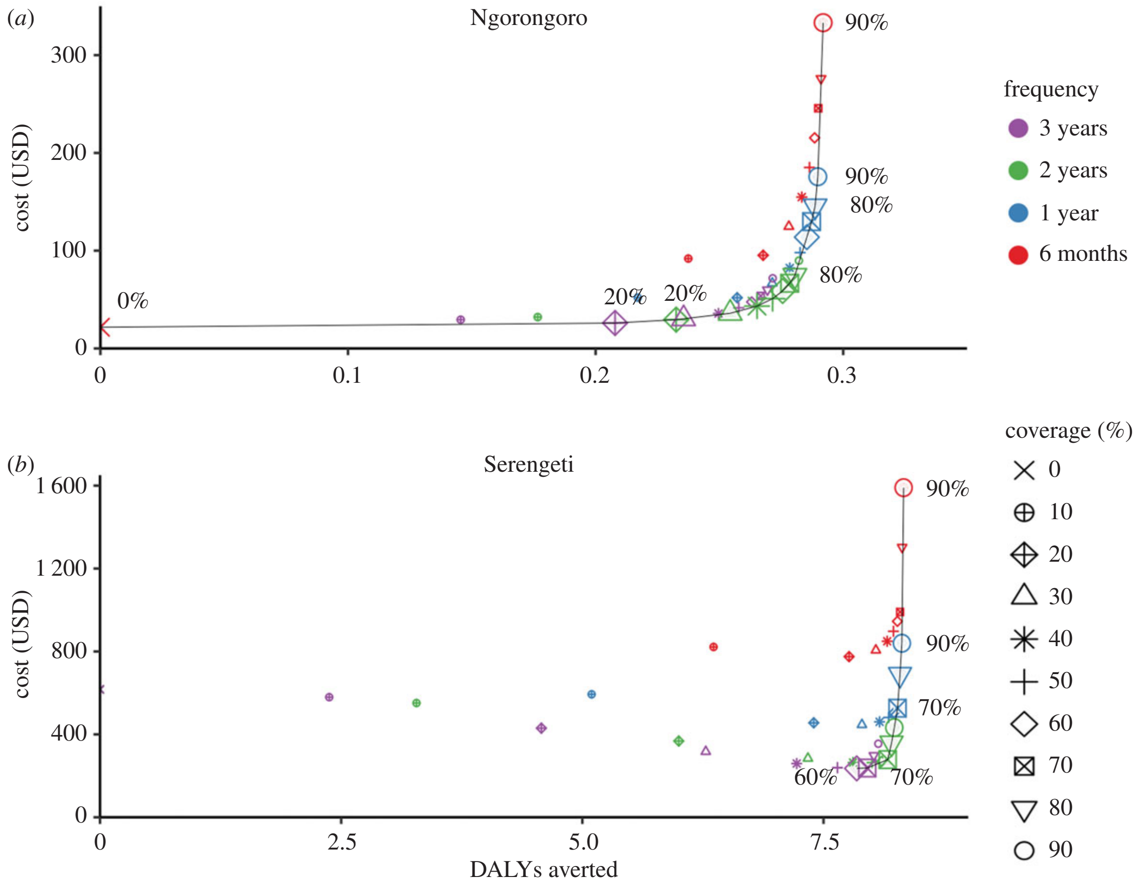

Figure 2. Cost versus DALYs averted of vaccination strategies per km^2. Costs and DALYs are cumulative over 10 years and discounted at 3% annually. Non-dominated strategies are shown with large points and connected by a solid black line, representing the efficient frontier. (*a*) Ngorongoro and (*b*) Serengeti.

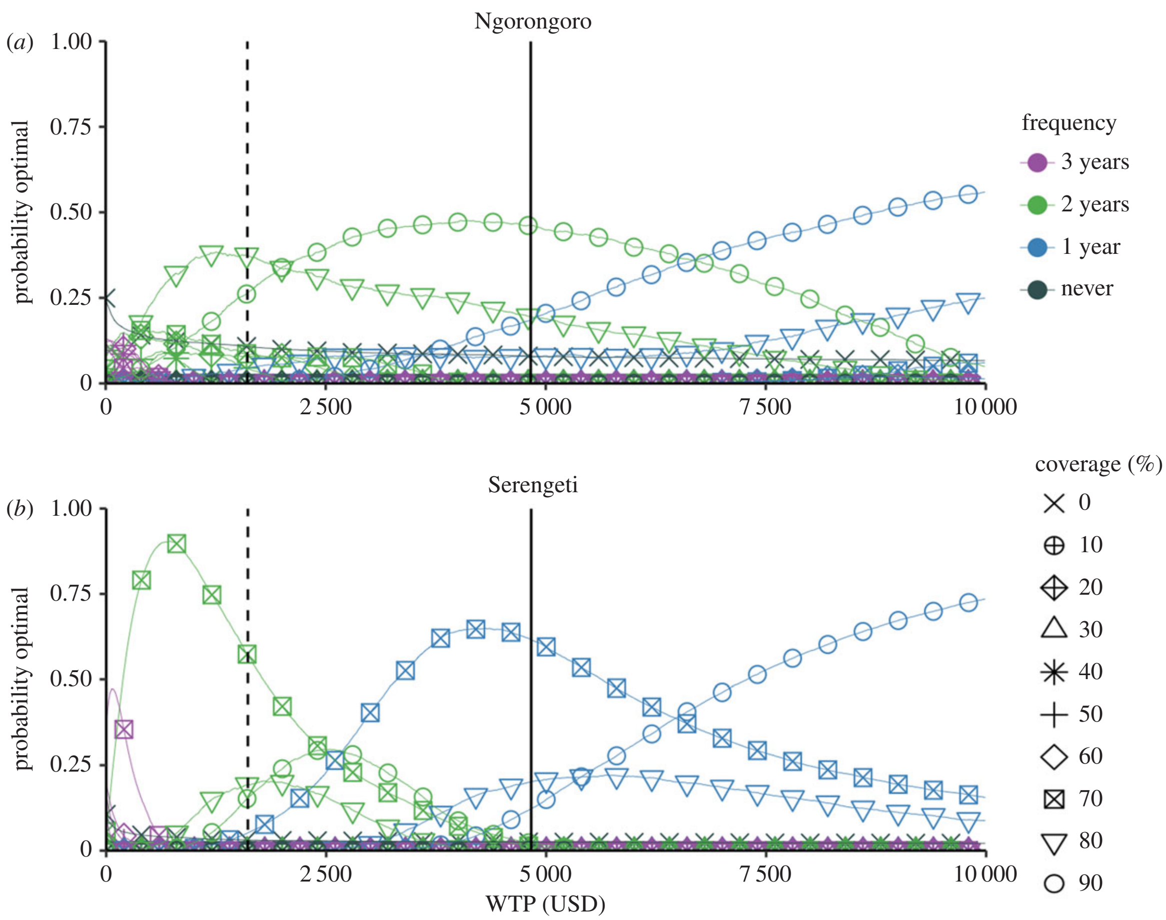

Figure 3. Global uncertainty analysis of rabies vaccination strategies. Probabilities represent the proportion of simulations for which each strategy was optimal, where 'optimal' is defined as conferring the largest net benefit at a given value of willingness-to-pay per DALY averted. Each simulation draws a set of parameters from their empirical distributions. Vertical lines indicate the WHO thresholds for 'cost-effective' (dashed) and 'very cost-effective' (solid) interventions. No strategies with a six month frequency were optimal. (*a*) Ngorongoro and (*b*) Serengeti.

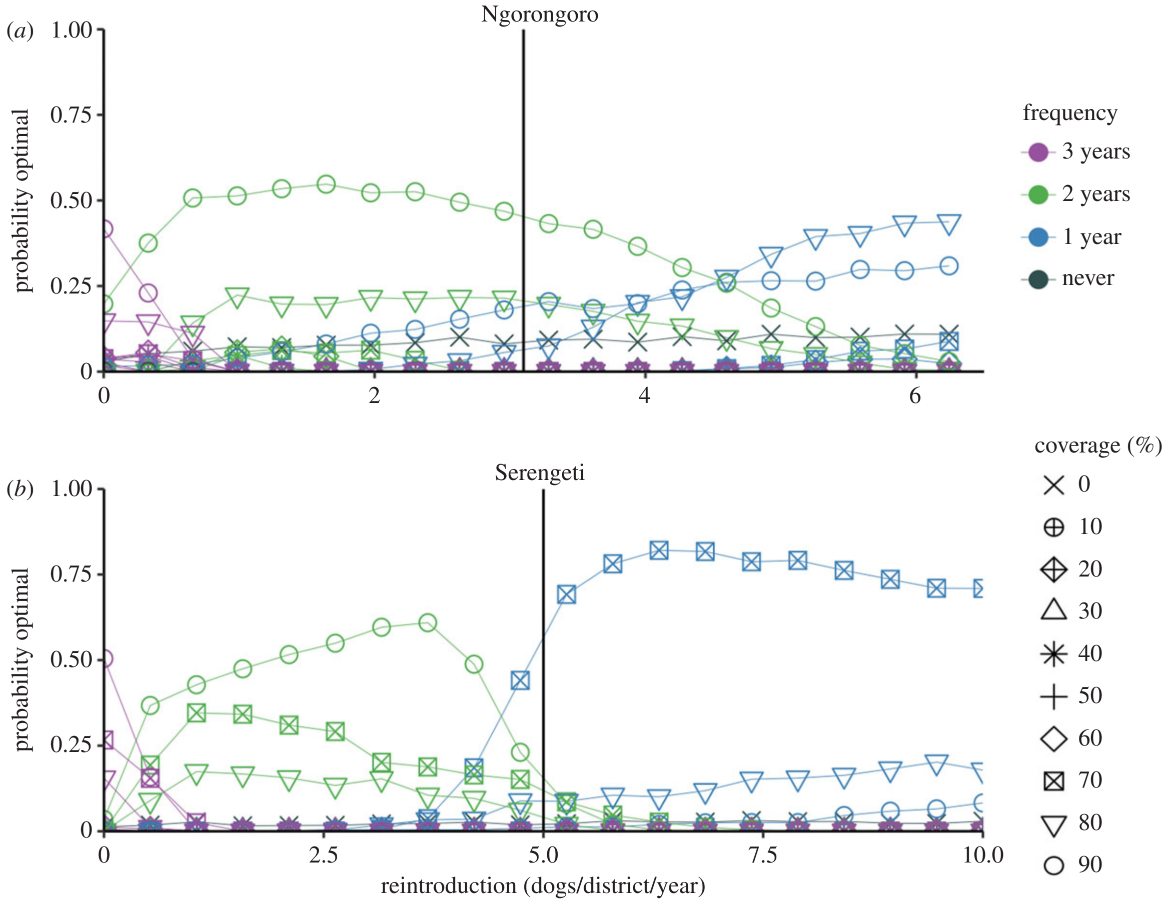

Figure 4. Optimal vaccination strategy varies by reintroduction level. An 'optimal' strategy is that which confers the largest net benefit at each level of reintroduction, for a willingness-to-pay of $4 830 per DALY. Probabilities represent the proportion of simulations for which each strategy was optimal, with each simulation drawing a set of parameters from their empirical distributions. Vertical lines indicate the baseline level of reintroduction for each district. (*a*) Ngorongoro and (*b*) Serengeti.

controlled with less frequent vaccination. In Ngorongoro, our predictions indicate that high levels of canine coverage achieved during campaigns every 2 years would be the optimal approach to combating rabies. By contrast, in Serengeti, with higher circulation of rabies virus and lower costs of vaccination than Ngorongoro, the WHO recommendation is optimal at the threshold for cost-effectiveness.

Our analysis is also the first to consider rabies reintroduction in an economic, rather than ecological, framework. In both districts, reintroduction of rabies from non-vaccinated areas is a major threat to rabies control, and the effectiveness of vaccination strategies could be reinforced through regionally coordinated vaccination campaigns that reduce this risk. If reintroduction could be substantially reduced, campaign frequency could be reduced to biennial campaigns in both districts, and resources saved from less frequent campaigns could be allocated to expanding campaigns geographically. Cross-national coordination of rabies vaccination campaigns has been highly effective in Latin America, reducing human rabies by 97%, from 350 cases in 1980 to less than 10 in 2010 [9]. Research regarding the movement of rabid dogs and the rates of reintroduction after a vaccination campaign would facilitate validation of the likely benefits of such international coordination.

We furthermore conducted a budget impact analysis, which calculates the total cost of implementing various vaccination strategies, to provide information about the affordability of rabies control. Such analysis may be useful to a policymaker seeking to add canine rabies vaccination to an immunization budget and wanting to understand the breakdown of canine preventative vaccination costs and human PEP costs, which may be financed through different funding mechanisms [27]. Though we do not consider downstream costs of competing risks increased by rabies vaccination, a limitation of our analysis, we provide an estimate of the capital resources required to implement a vaccination programme in the district and to provide PEP to those exposed to rabid dogs.

We assume that the number of people treated with PEP for bites from non-rabid dogs is unaffected by canine vaccination campaigns. It is possible that increased awareness of rabies may increase demand for PEP among bite victims of non-rabid dogs, although it is also possible that a lowered perception of risk may decrease demand. In either case, it is likely that the use of PEP to treat victims of non-rabid dog bites will continue until regional rabies elimination is achieved, a possibility not considered here.

Less frequent vaccination campaigns may be preferable in some settings not only because of the overall cost saving, but also because a vaccination campaign that targets a large portion of the canine population can prevent rabies outbreaks for several years [3]. At the threshold for cost-effectiveness in Ngorongoro, the optimal strategy would involve vaccinating 90% of the canine population every 2 years. Although 90% coverage is challenging to achieve, our model incorporated the cost of a comprehensive house-by-house search for unvaccinated dogs to reach this threshold. Such visits, albeit time-consuming, would cost less than a full additional campaign in the subsequent year. Alternatively, vaccination campaigns with 70 or 80% coverage typically have similar epidemiological impact as those at 90% coverage for a given frequency of vaccination, meaning that it is not crucial to meet exact coverage targets.

Our emphasis on campaign frequency, rather than coverage provides a pragmatic guideline: if reintroduction is low, biennial campaigns are cost-effective and sufficient to manage the disease. However, certainty of our model predictions is limited by empirical estimation of rabies virus reintroduction rates. The rate of reintroduction we used for the Serengeti District, five dogs per year, was based on estimates of reintroduction from a metapopulation model, and probably represents a high estimate of this parameter [2,8]. There was no literature available on the Ngorongoro District, and we estimated this value by scaling the reintroduction rate for Serengeti District by the ratio of the canine carrying capacity in the two districts [8,19]. While we performed sensitivity analysis with regard to this parameter, our finding that optimal vaccination strategies can be sensitive to reintroduction rates indicate that field research regarding the movement of rabid dogs and the risk of importation from neighbouring and non-neighbouring areas would be useful in more precisely estimating these risks. Nevertheless, our results suggest that substantial benefits could result from steps to reduce the reintroduction of disease to a given area.

5. Conclusion

We found that consideration of the frequency of canine rabies vaccination campaigns, as well as their coverage, is an important component in a One Health stewardship of limited resources in Sub-Saharan Africa. Optimal campaign frequencies can differ between regions within countries as a result of variation in canine ecology and human population density. Specifically, we found that the WHO recommendation for annual canine vaccination at 70% coverage was optimal for Serengeti, but not for Ngorongoro. In Ngorongoro, significant efficiency could be gained by switching to biennial vaccination at higher coverage, particularly if rates of rabies reintroduction are low. In either case, a geographically coordinated strategy that reduces cross-border rabies reintroduction could allow for a safe move to biennial campaigns and result in substantial savings of costs and lives to both districts. Such comparative analyses should be extended to other areas in Africa and Asia for consideration in the global effort to eliminate canine rabies virus transmission and minimize the human rabies burden.

Ethics. This study used secondary data and no human subjects were involved.

Data accessibility. Model code data available from the Dryad Digital Repository: http://dx.doi.org/10.5061/dryad.3cn95 [28]. No primary data were collected for this study.

Authors' contributions. A.B. assisted with study design, conducted analyses and drafted the manuscript. M.C.F. and A.P.G. conceived and designed the study. A.D.P. assisted with economic analyses. All authors critically revised the manuscript and gave approval for final publication.

Competing interests. We have no competing interests.

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Optimal Frequency of Rabies Vaccination Campaigns in Sub-Saharan Africa

Supplemental Information

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Transmission Models

The transmission models incorporated both canine transmission (d) and other carnivore transmission, grouped into the category of wildlife (w) (1). Models were run separately for Ngorongoro and Serengeti Districts.

Dogs

$$\frac{dS_d}{dt} = b_d * (S_d + V_d) - \beta_{11} * I_d * S_d - \beta_{12} * I_w * S_d - v * (N_d - V_d) - (\mu_d + \gamma_d * N_d) * S_d$$

$$\frac{dE_d}{dt} = \beta_{11} * I_d * S_d + \beta_{12} * I_w * S_d - (\mu_d + \sigma + \gamma_d * N_d) * E_d$$

$$\frac{dI_d}{dt} = \sigma * E_d - (\mu_d + \alpha) * I_d + \tau$$

$$\frac{dR_d}{dt} = v * (N_d - V_d) - (\mu + \gamma_d * N_d) * V_d$$

$$N_d = S_d + E_d + I_d + V_d$$

Wildlife

$$\frac{dS_w}{dt} = (b_w - u_w) * S_w - \beta_{22} * I_w * S_w - \beta_{21} * I_d * S_w - \gamma_w * S_w * N_w$$

$$\frac{dE_w}{dt} = \beta_{22} * I_w * S_w + \beta_{21} * I_d * S_w - (\mu_w + \sigma + \gamma_w * N_w) * E_w$$

$$\frac{dI_w}{dt} = \sigma * E_w - (\mu_w + \alpha) * I_w$$

$$N_w = S_w + E_w + I_w$$

Table S1. Transmission Model Parameters

Parameter	Estimate	Description	Distribution	Reference
b_d	1.72/year	Birth rate, domestic dogs	Normal (1.72, 0.11)	(2)
μ_d	.45/year	Death rate, adult dogs	Normal (0.45, 0.02)	(2)
b_w, μ_w	unknown	Birth/death rate, wildlife	same as for dogs	(2)
$K_{d,N}$	1.5/km^2	Carrying capacity, dogs, Ngorongoro		(2)
$K_{d,S}$	10/km^2	Carrying capacity, dogs, Serengeti		(2)
$K_{w,N}$	4.5/km^2	Carrying capacity, wildlife, Ngorongoro		(3)
$K_{w,S}$	3.0/km^2	Carrying capacity, wildlife, Serengeti		(3)
γ_d	$(b_d - \mu_d)/K_d$	Dog death from carrying capacity limits		
γ_w	$(b_w - \mu_w)/K_w$	Wildlife death from carrying capacity limits		
$1/\sigma$	22.3 days	Incubation period of rabies	Normal (22.3, 1.28)	(2)
$1/\alpha$	3.1 days	Infectious period of rabies	Normal (3.10, 0.13)	(2)
v	varies	Vaccination coverage	0 - 1	
$k_{11,N}$	0.93	Dog to dog transmission, Ngorongoro[1]	Normal (0.93, 0.092)	(1)
$k_{12,N}$	0.49	Wildlife to dog transmission, Ngorongoro[1]	Normal (0.49, 0.16)	(1)
$k_{21,N}$	0.13	Dog to wildlife transmission, Ngorongoro[1]	Normal (0.13, 0.032)	(1)
$k_{22,N}$	0.40	Wildlife to wildlife transmission, Ngorongoro[1]	Normal (0.40, 0.13)	(1)
$k_{11,S}$	1.01	Dog to dog transmission, Serengeti	Normal (1.09, 0.060)	(1)
$k_{12,S}$	0.95	Wildlife to dog transmission, Serengeti	Normal (0.95, 0.12)	(1)
$k_{21,S}$	0.09	Dog to wildlife transmission, Serengeti	Normal (0.09, 0.010)	(1)
$k_{22,S}$	0.23	Wildlife to wildlife transmission, Serengeti	Normal (0.23, 0.057)	(1)
τ_N	0.00022/ (year*km^2)	Reintroduction of rabid dogs through migration, Ngorongoro[2]		See note 2
τ_S	0.0015/ (year*km^2)	Reintroduction of rabid dogs through migration, Serengeti[2]		(4)
S_{dN}	1.485 dogs/km^2	Initial susceptible dog density in Ngorongoro District		See note 3
S_{wN}	4.497 dogs/km^2	Initial susceptible wildlife density in Ngorongoro District		See note 3

E_{dN}	0.000852 dogs/km^2	Initial exposed dog density in Ngorongoro District	See note 3
E_{wN}	0.000151 dogs/km^2	Initial exposed wildlife density in Ngorongoro District	See note 3
I_{dN}	0.000118 dogs/km^2	Initial infected dog density in Ngorongoro District	See note 3
I_{wN}	0.0000208 dogs/km^2	Initial infected wildlife density in Ngorongoro District	See note 3
V_{dN}	0 dogs/km^2	Initial vaccinated wildlife density in Ngorongoro district	See note 3
S_{dS}	9.36 dogs/km^2	Initial susceptible dog density in Serengeti District	See note 3
S_{wS}	2.94 dogs/km^2	Initial susceptible wildlife density in Serengeti District	See note 3
E_{dS}	0.0351 dogs/km^2	Initial exposed dog density in Serengeti District	See note 3
E_{wS}	0.00357 dogs/km^2	Initial exposed wildlife density in Serengeti District	See note 3
I_{dS}	0.00486 dogs/km^2	Initial infected dog density in Serengeti District	See note 3
I_{wS}	0.000493 dogs/km^2	Initial infected wildlife density in Serengeti District	See note 3
V_{dS}	0 dogs/km^2	Initial vaccinated wildlife density in Serengeti district	See note 3

[1] We calculated β_{ij} using $k_{ij}/(\alpha^* d_i)$, where k_{ij} is the average number of animals of host-type i infected by a single animal of host-type j, $1/\alpha$ is the infectious period of rabies, and d_i indicates the density of host i. [2]

[2] We assumed that 5 rabid dogs entered Serengeti through migration per year (4) and 3.1 rabid dogs entered Ngorongoro through migration per year (based on scaling the Serengeti estimate to Ngorongoro area and dog carrying capacity). For each location, we divided the number of rabid dogs by the area of the district to calculate dogs/(year*km^2).

[3] For each simulation, we started the model with these initial conditions and then solved for 8 years, establishing equilibrium before beginning canine interventions

Table S2. Economic and health costs of rabies

Parameter/Outcome	Description	Value	Reference
P1	Number of humans bitten per rabid dog	.51	(1)
P2	That a bite victim of an unvaccinated rabid dog goes to the hospital (.76) and receives PEP (.86)	.65	(5)
P3	That a bite victim of an unvaccinated rabid dog who does not receive PEP will contract	.19	(5)
No Bites, No Disease	n/a	$0, 0 DALY	
Cost of PEP per rabid dog[1]	P1*P2*$318	$105	(1)
Human health burden per rabid dog[2]	P1*(1-P2)*P3*42.55 DALY	1.44 DALY	(1,5)

[1] Costs were updated to 2012 PPP USD PPP calculated based on from reported costs in 2010 non-PPP USD (1). The cost of PEP per rabid dog includes: 1) the number of humans bitten per rabid dog, 2) the probability that each bitten human received PEP (assumed to be independent because the average rabid dog bites < 1), and 3) the cost of PEP per regimen.

[2] The human health burden per rabid dog includes 1) the number of humans bitten per rabid dog, 2) the probability that each bitten human develops rabies (assumed to be independent because the average rabid dog bites < 1), and 3) the average DALYs in Tanzania per rabies case.

Table S3. Vaccination costs[1]

Serengeti[2]	
Disposables cost per dog	2.19
Fixed cost of central point campaign (staff, vehicles, supplies)	631.02
Dog search cost above 80% coverage (HH search)	11.28
Ngorongoro[3]	
Disposables cost per dog	2.19
Fixed cost of central point campaign (staff, vehicles, supplies)	631.02
Dog search cost above 20% coverage (HH search)	20.20

[1] Costs were updated to 2012 PPP USD from reported costs in 2003 non-PPP USD (6). More detailed itemization for each district is available in Kaare (2009).

[2] As in Fitzpatrick (2014), costs are from a representative village in Serengeti District (Manyamanyama) based on Kaare (2009).

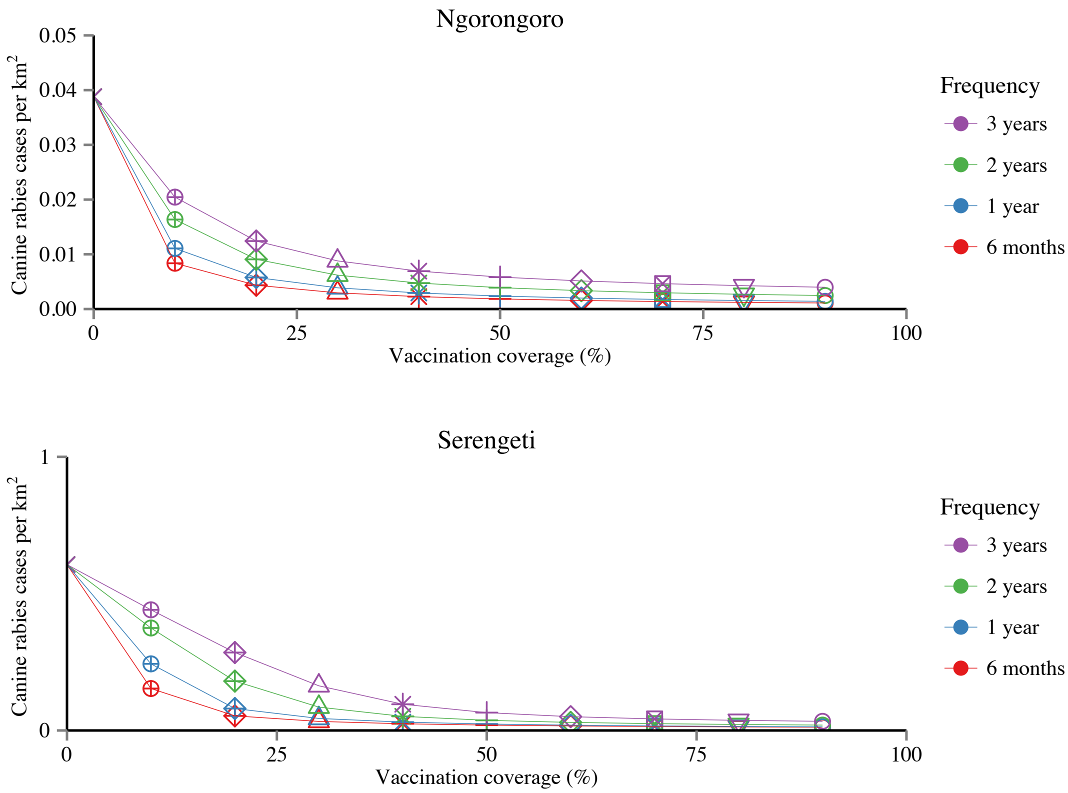
[3] In Ngorongoro, we used costs reported for this district in Kaare (2009). We assumed identical disposable costs as in Serengeti, and a constant marginal cost per dog during the community animal health worker (CAHW) component, from 20-85% coverage. Above 85% coverage, search costs approximately double with each 10% increase in coverage, as in Fitzpatrick (2014).

Table S4. Per-dog vaccination cost for a single campaign at varying coverage levels[1]

Percent coverage	Ngorongoro	Serengeti
0	0	0
10	35.15	41.11
20	18.67	22.08
30	16.48	15.73
40	15.4	12.57
50	14.76	10.69
60	14.33	9.42
70	14.02	8.48
80	13.79	9.79
90	14.8	10.64

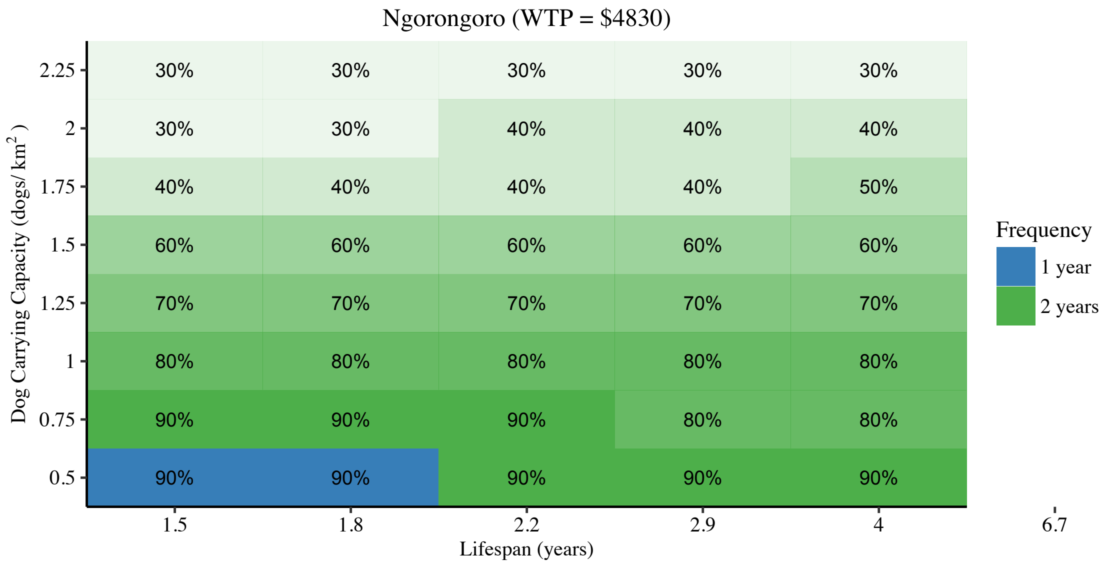
[1] These were calculated based on the costs in Table S3.

Figure S1. Wildlife rabies after 10 years. Wildlife rabies cases per square kilometer over 10 years of canine vaccination campaigns at varying frequency and coverage. Scale of the y-axes differs between the two districts.



Figures S2-5. One-way sensitivity analyses

Figure S2: Sensitivity analysis of rabies vaccination strategies by lifespan and dog carrying capacity. Color indicates the optimal campaign frequency and shade and text indicate optimal coverage level at a willingness-to-pay for $4830 per DALY averted. In the base case, canine lifespan was 2.2 years, and canine carrying capacity was 1.5 dogs/km^2 in Ngorongoro and 10 dogs/km^2 in Serengeti.(1)



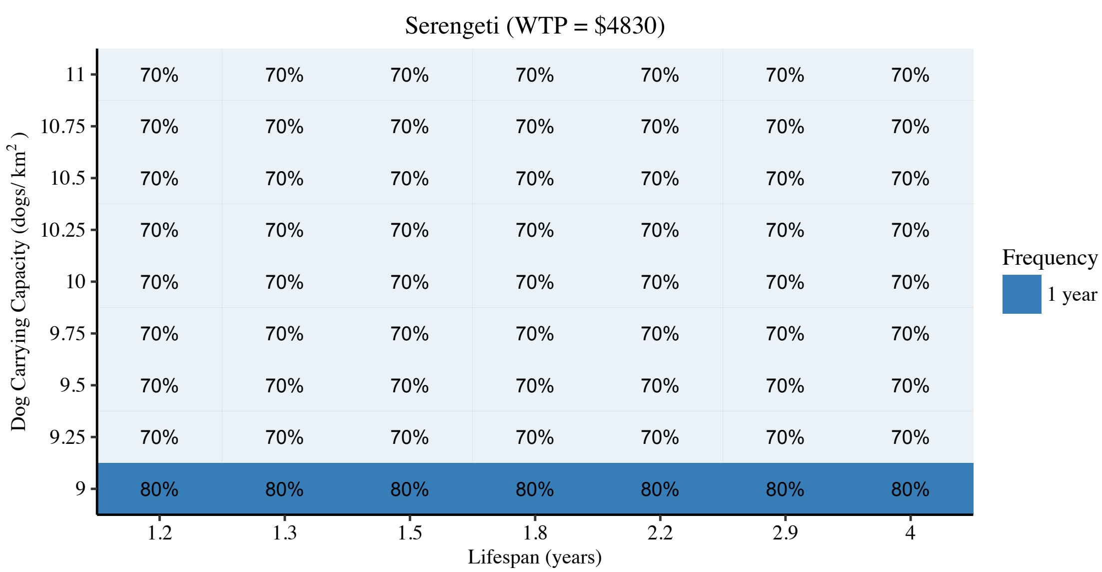
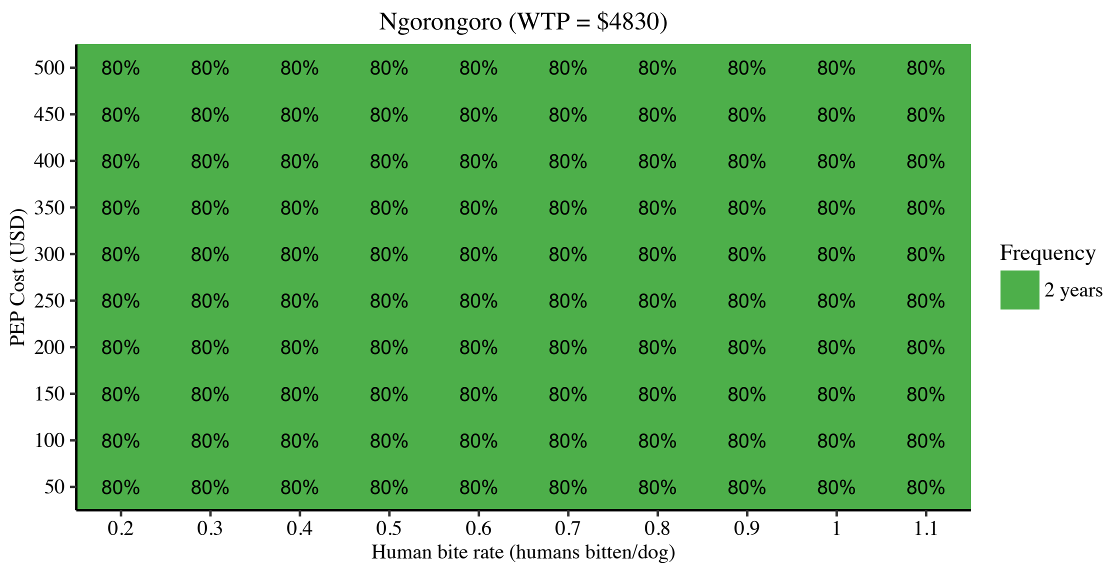


Figure S3: Sensitivity analysis of rabies vaccination strategies by PEP cost and human bite rate. Color indicates the optimal campaign frequency and shade (and text) indicate optimal coverage level at a willingness-to-pay for $4830 per DALY averted. In the base case, PEP cost was $318, and human bite rate was 0.51 people bitten by each rabid dog (1).



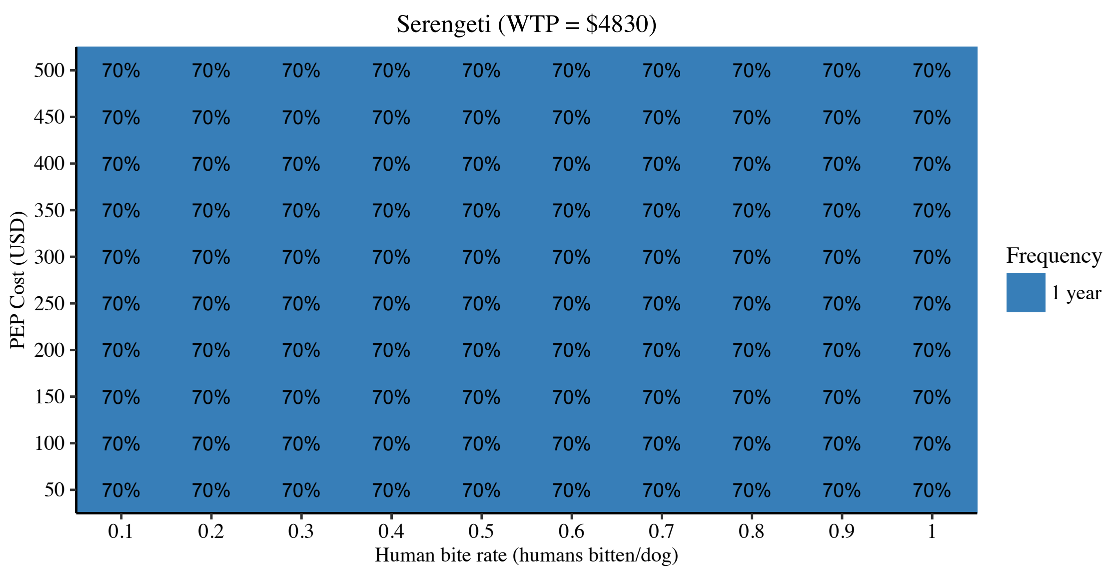


Figure S4: Sensitivity analysis of rabies vaccination strategies by PEP cost and health burden per human case. Color indicates the optimal campaign frequency and shade (and text) indicate optimal coverage level at a willingness-to-pay for $4830 per DALY averted. In the base case, PEP cost was $318, and DALY cost per human rabies case was 1.07 (1).

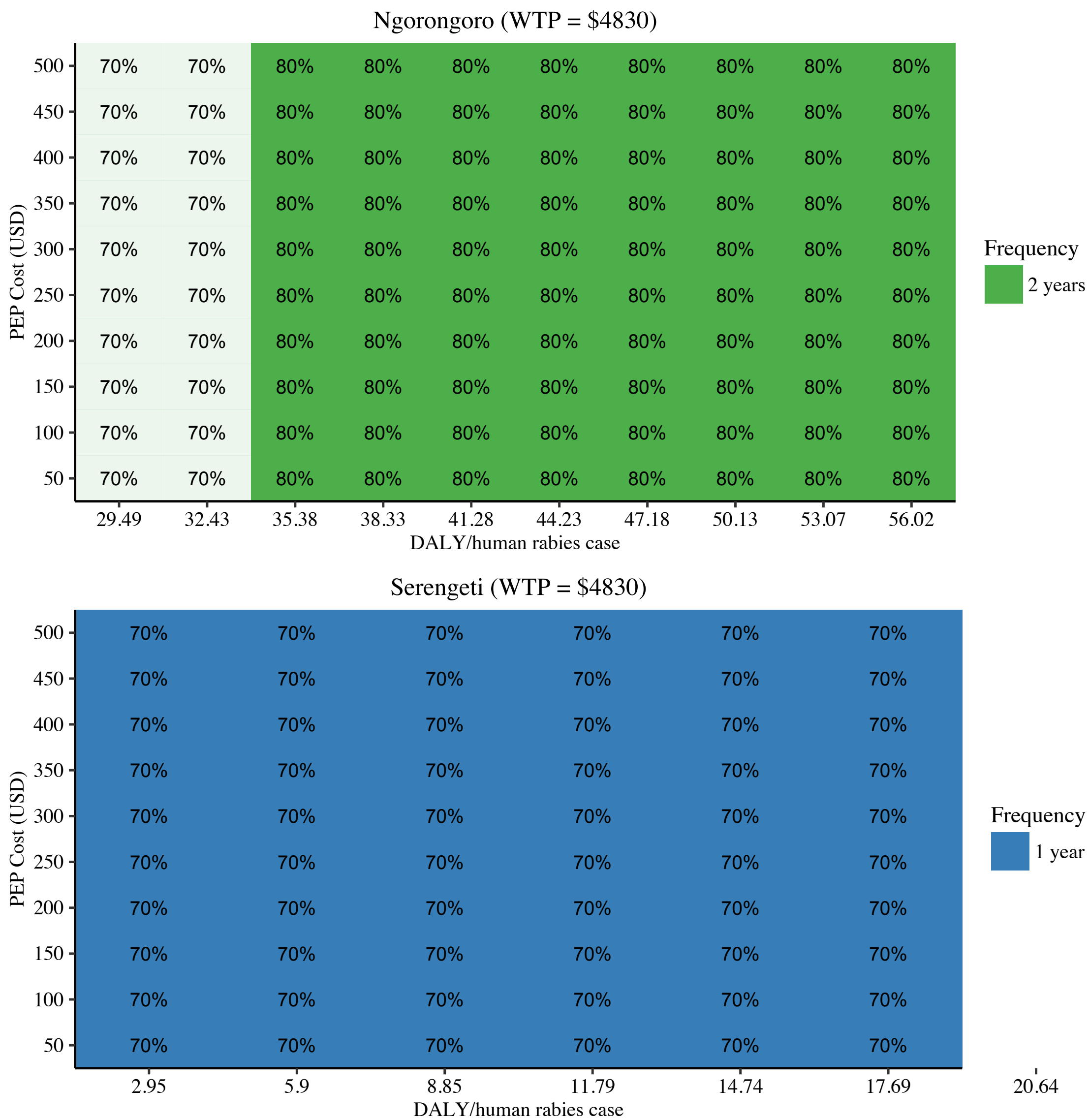


Figure S5: Sensitivity analysis of rabies vaccination strategies to wildlife birth rate and frequency-dependent death rate. Color indicates the optimal campaign frequency and shade (and text) indicate optimal coverage level at a willingness-to-pay for $4830 per DALY averted. Combinations in which the frequency-dependent death rate exceeds the birth rate lead to local extinction of wildlife hosts, and and are excluded (gray areas). In the base case, birth rate was 0.0047 births per animal per day, and death rate was 0.0017 births per animal per day (1). We used Watts and Holekamp (2009) (Figure 5) to develop approximate ranges for birth and death rates (7).

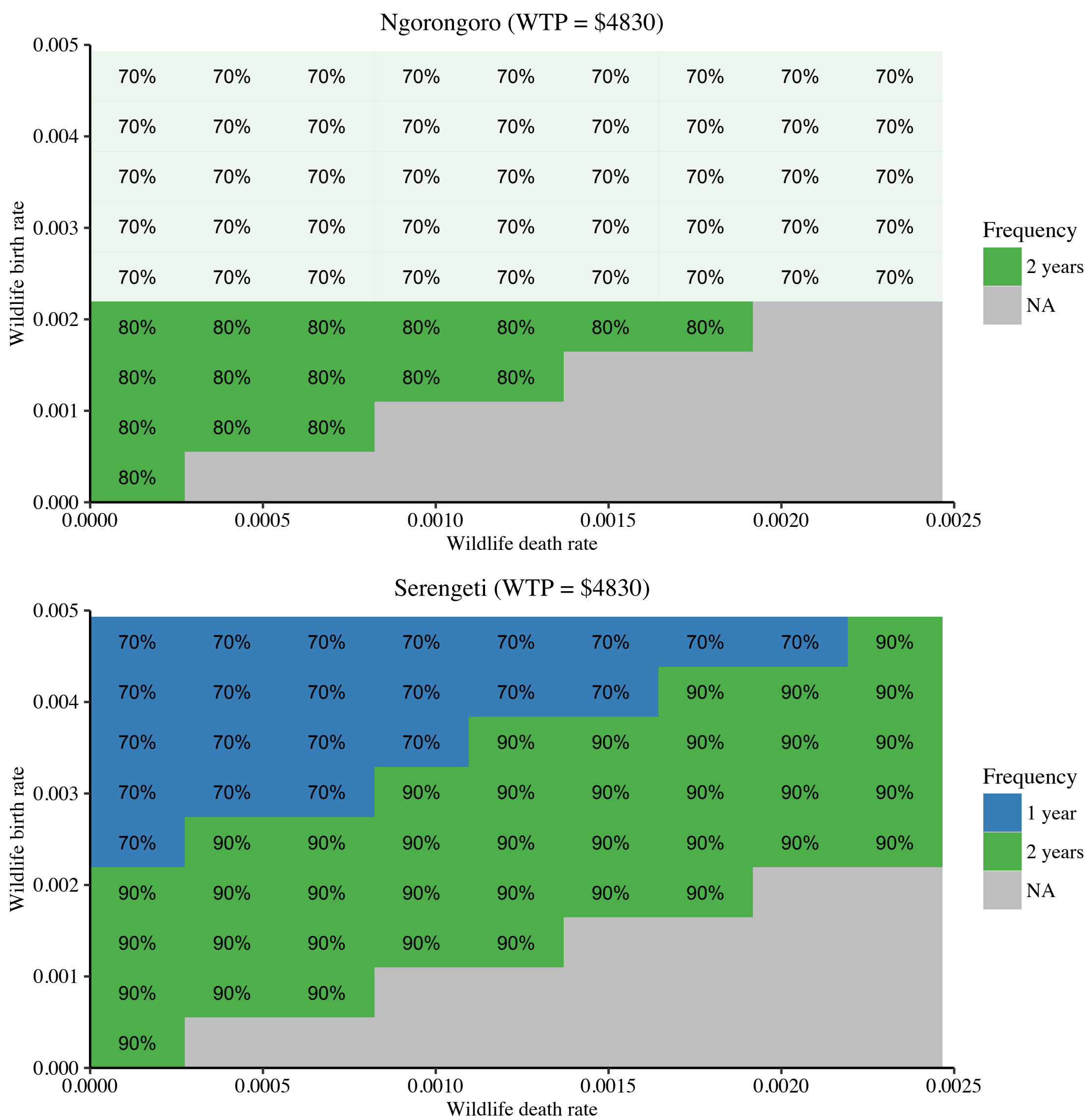
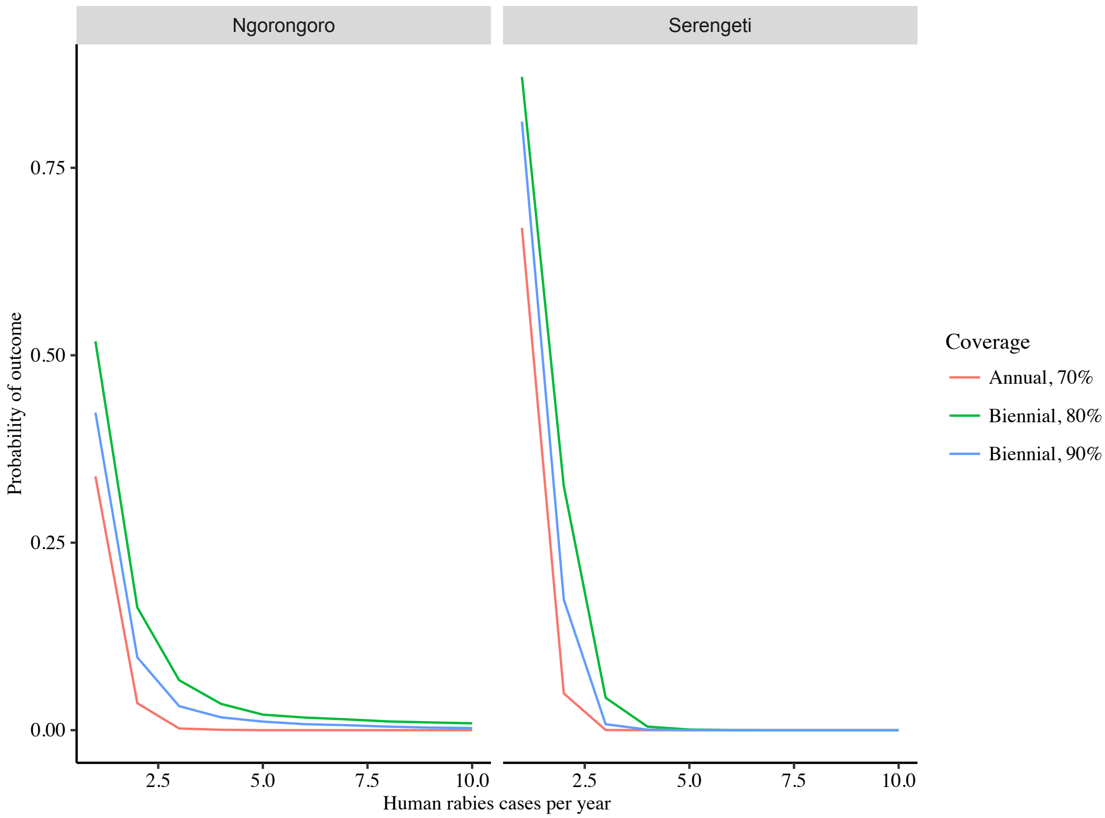


Figure S6. Sensitivity of "uncontrolled rabies" outcome to threshold of control. Lines indicate the probability that human rabies cases remain above a given threshold defining human rabies control (x-axis) under annual canine campaigns at 70% coverage (red), biennial campaigns at 80% coverage (green), or biennial campaigns at 90% coverage (blue).



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