Cost-effectiveness of canine vaccination to prevent human rabies in rural Tanzania

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Abstract

Background—The annual mortality rate of human rabies in rural Africa is 3.6 deaths per 100,000 individuals. Rabies can be prevented by prompt post-exposure prophylaxis, but this is costly and often inaccessible in rural Africa. As 99% of human exposures occur through rabid dogs, canine vaccination also prevents transmission of rabies to humans.

Objective—Evaluate the cost-effectiveness of rabies control through annual canine vaccination campaigns in rural sub-Saharan Africa.

Design—We model transmission dynamics in dogs and wildlife and assess empirical uncertainty in the biological parameters to make probability-based evaluations of cost-effectiveness.

Data Sources—Epidemiological parameters from contact tracing study and literature; cost data from ongoing vaccination campaigns

Target Population—Two districts of rural Tanzania, Ngorongoro and Serengeti

Time Horizon—Ten years

Perspective—Health policymaker

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Interventions—Vaccination coverage ranging from 0 to 95% in increments of 5%

Outcome Measures—Life-years for health outcomes and 2010 USD for economic outcomes

Results of Base-Case Analysis—Annual canine vaccination campaigns are very cost-effective in both districts compared with no canine vaccination. In Serengeti, annual campaigns up to 70% coverage are cost-saving.

Results of Sensitivity Analysis—Across a wide range of parameter assumptions and levels of societal willingness-to-pay for life-years, the optimal vaccination coverage for Serengeti is 70%. In Ngorongoro, though optimal coverage depends on willingness-to-pay, vaccination campaigns are always cost-effective and life-saving, and therefore preferred.

Limitations—Canine vaccination is very cost-effective in both districts, but there is greater uncertainty regarding the optimal coverage in Ngorongoro.

Conclusions—Annual canine rabies vaccination campaigns confer extraordinary value and dramatically reduce the health burden of rabies.

Introduction

Rabies is a viral encephalitic disease of mammals which is responsible for an estimated 61,000 human deaths each year (1), nearly one-third of which occur in rural Africa (2). Once symptoms appear, rabies is almost universally fatal (3). Control of the disease in canines is a potential approach to reducing human rabies as more than 99% of all human cases worldwide result from the bite of a domestic dog (4).

Post-exposure prophylaxis (PEP), including a series of vaccinations and administration of immunoglobulin, can prevent rabies following a dog bite. Worldwide, over 7.5 million rabies PEP regimens are delivered annually (5) at an estimated cost of more than US$1.5 billion (6). Given that a disproportionate rabies burden occurs in sub-Saharan Africa, these costs often fall to those countries least able to afford them. In addition, PEP is frequently unavailable in rural areas within the 24-hour period recommended for treatment initiation after exposure to rabies (7).

Concerns about program costs and the efficient use of health resources have been identified as major barriers to the implementation of canine vaccination programs (8). One-time canine rabies vaccination campaigns have been evaluated as cost-effective prevention against human rabies in urban Chad (9). However, over 75% of rabies mortality in Africa occurs in rural areas (2) and disease dynamics vary between these two settings due to different densities and contact patterns among humans, dogs, and other wildlife (10). Additionally, high birth and death rates in domestic dogs as well as re-introduction of rabies from dogs or wildlife in neighboring, unvaccinated regions make it unlikely that a one-time vaccination campaign will control canine rabies in rural Africa indefinitely (11). We therefore evaluate the cost-effectiveness of rabies control in rural Africa through a strategy of annual canine vaccination campaigns.

Methods

We developed a mathematical model of rabies transmission to estimate the epidemiological effects, clinical benefits, economic costs, and cost-effectiveness of canine vaccination coverage strategies ranging from 0 to 95% in rural Tanzania. No vaccination, the status quo in most parts of Tanzania, is considered the baseline for our analysis. Outcome measures included numbers of dogs vaccinated, incidence of human rabies, and economic costs (in 2010 USD). The analysis was conducted from the perspective of a health policymaker, and we therefore considered health burden in terms of life-years, which in this context are equivalent to Disability Adjusted Life Years (DALYs) given that rabies is inevitably fatal and thus the entire health burden accrues from mortality rather than morbidity. We assessed economic costs associated with both a canine vaccination campaign and post-exposure prophylaxis to prevent rabies in exposed people. In conformity with World Health Organization guidelines (12) and other recommendations for best practices (13), cost-effectiveness outcomes are reported across both one-year and ten-year time horizons on a present-value basis with a 3% annual discount rate. We evaluated the robustness of the results to model inputs, using both probabilistic uncertainty analysis and one-way sensitivity analyses. We applied World Health Organization recommendations (14,15) to denote strategies with incremental cost-effectiveness ratios less than the per capita GDP for a life-year saved (GDP, $1430 for Tanzania (16)) as "very cost-effective" and ratios less than three times the per capita GDP ($4290) as "cost-effective."

We compared pastoral (Ngorongoro) and agro-pastoral (Serengeti) districts in rural Tanzania as representative of two major settlement patterns and canine densities in rural Africa. While both are sparsely populated compared to cities, agro-pastoral areas generally consist of larger, more closely located villages than found in pastoral areas. Canine density, measured as dogs per km^2, is nearly seven times higher in Serengeti than in Ngorongoro. Rabies in Serengeti is endemic, with cases continuously observed, while rabies in Ngorongoro is epidemic, with no observed cases between outbreaks (17,18). Additionally, pilot rabies vaccination campaigns in the two districts have required different strategies to achieve high coverage (19). Both districts border Serengeti National Park and are home to abundant and diverse wildlife populations. Although rabies cannot persist solely in wildlife in either district (17), we address concerns that vaccination coverage which has been sufficient for control in some regions might be insufficient in these wildlife-rich areas (8) by explicitly including wildlife hosts and their contribution to transmission in our dynamic model. Additional details and a map of these districts are included in the Appendix.

Model Structure

We developed a compartmental transmission model with two strata, one for domestic dogs and another for wildlife, which includes all other carnivores in the area (Figure 1). Each stratum contains the three disease classes of susceptible, exposed/latent, and infectious, measured in units of animals per km^2. The canine stratum also includes a vaccinated class. As rabies is fatal, there is no recovered class (9,20–22). Canine demography is explicitly considered through birth into the susceptible class, all-cause death (excluding rabies) at constant rates from all classes, and death due to carrying capacity, or the resource

constraints that exist as the population grows and exceeds the limits of the human and geographic environment. We assume that infected animals do not have fecundity because of the typically short incubation period of rabies and the low likelihood that their puppies would survive. To evaluate the impact of uncertainty on our cost-effectiveness assessments, we conducted probabilistic sensitivity analyses and threshold analyses. A full specification of the model equations, parameter values, distributions derived from field and published data, sensitivity analyses, and sources is provided (Appendix, Appendix Tables 1 – 3). We compared our model output to the incidence of canine and human rabies in these two districts before large-scale annual vaccination campaigns began. Due to prior sporadic vaccination efforts, 5 - 10% dogs in these districts had been previously vaccinated when the annual canine incidence was observed to be 1 - 2%. For human rabies, we have previously estimated an incidence of 1.48 - 4.28 deaths per 100,000 people in Ngorongoro prior to large scale implementation of canine vaccination, resulting in 2 - 6 rabies deaths per year for the district (23). From animal bite injury data and availability of PEP, we have estimated that the incidence of human rabies in unvaccinated areas near Serengeti was 4.9 (2.9 - 7.2) deaths annually per 100,000 persons in the late 1990s (24), leading to 5 - 13 human cases of rabies annually.

Costs of Vaccination

We parameterized the costs in our analysis using field data we collected during annual vaccination campaigns in Serengeti and Ngorongoro and from published literature (19). We considered only the direct costs of vaccination, as dogs are often brought to vaccination stations by children and the average income loss from bringing a dog to the central point is therefore considered to be minimal. We generate functions of cost with increasing vaccination coverage. The costs vary between the two districts. In the agro-pastoralist district of Serengeti, central point vaccination campaigns are sufficient to achieve high coverage, whereas in the more sparsely populated pastoral district of Ngorongoro, central point vaccination campaigns must be supplemented with door-to-door vaccinators in order to achieve high coverage, increasing the costs per dog vaccinated for Ngorongoro compared with Serengeti. We estimated costs as a function of coverage level, taking into account both the fixed costs of program startup and the decreasing efficiency associated with searching for additional dogs to vaccinate as coverage levels increase (Appendix).

Costs of Disease

An untreated rabies bite to a human was estimated to result in the loss of 31.4 life-years on average (2), taking into account the typical age-distribution of rabies victims. Monetary losses accrue through the cost of post-exposure prophylaxis (PEP), estimated to be $111.29 per regimen (25), which includes both direct costs of treatment and indirect costs of transportation and lost income for the days on which treatment is administered. We assume a full course of PEP is 100% effective, both consistent with clinical data (7) and conservative given that this assumption would bias against canine vaccination. When victims who do not receive PEP progress to rabies, we consider only the health burden, as medical care is not effective and usually not provided in rural African settings. We constructed a probability tree to model the chain of events leading from a rabid dog to PEP, a case of rabies, or neither (Figure 1, Appendix Table 2). We do not consider transmission from wildlife to humans, as

this represents less than 1% of human cases (4). However, our previous findings do show that mass vaccination of domestic dogs could concomitantly eliminate disease from wildlife (17), and this would potentially be an additional benefit for conservation (26,27) as well as human health.

Data collected through contact tracing of all rabies cases detected from January 2002 through December 2006 (17,18) were used to estimate that each rabid dog bites 0.51 humans (Appendix). We estimated that each rabid dog leads on average to $36.89 in costs from PEP administration and to a loss of 1.07 human life-years (Appendix Table 2). To estimate the cost from disease for each strategy that we considered, we multiplied each of these measures by the canine rabies incidence predicted through simulation. We calculate the cumulative economic cost of disease and vaccination on two time scales, annually and over a decade.

Cost-Effectiveness

Within each district, any strategy which has both greater monetary cost and more lives lost than some other strategy or combination of strategies is considered to be dominated by the latter strategy. For each non-dominated scenario, we found the incremental cost-effectiveness ratio (ICER) as compared to the next-lowest cost scenario. The ICER measures the additional cost per life-year saved of expanding canine vaccination to the next coverage level.

To compare the cost-effectiveness results from our entire range of 10,000 simulations, we used a net benefits framework (28). Net health benefits are defined as the difference between the average health benefit of an intervention (for us, in life-years saved), and the absolute intervention cost divided by the threshold cost-effectiveness ratio (29). This framework yields a single outcome measure that that simplifies the identification of the program that provides the largest health benefit for a given societal willingness-to-pay for life-years. We calculated the net health benefit of each incremental level of coverage from each simulation across a range of cost-effectiveness ratios. From this, we found the probability that a given coverage had the greatest net health benefit across a wide range of alternative cost-effectiveness ratios or levels of willingness-to-pay.

Role of the Funding Source

Results

Rabies Burden

To determine the cost-effectiveness of using annual canine vaccination to prevent human cases of rabies, we modeled rabies in dogs and wildlife using a dynamic transmission model and assessed the costs of vaccination campaigns and expected outcomes across a range of

vaccine coverage levels. Our results show that the expected number of rabies cases in both domestic dogs and wildlife hosts decreases monotonically with increasing canine vaccination coverage (Figure 2, Appendix Figure 2). In a scenario with no vaccination, the cumulative burden of rabies after ten years is estimated to be 0.13 rabid dogs/km^2 undiscounted in Ngorongoro and 5.43 rabid dogs/km^2 undiscounted in Serengeti (0.11 rabid dogs/km^2 and 4.7 rabid dogs/km^2, respectively, discounted to present value terms). These values are consistent with our observation that the per annum rabies loss is 1-2% of the dog population under conditions of very low vaccination coverage. The herd immunity threshold, or the coverage at which rabies will no longer persist in the dog population, is reached at roughly 10% coverage in Ngorongoro and 30% coverage in Serengeti (Figure 2).

Higher densities of rabid dogs lead to humans being exposed to rabies through dog bites, causing mortality in the absence of prompt PEP. Each death corresponds to a loss of 31.4 life-years (2). Our model projects the loss of 0.14 life-years per km^2 undiscounted (0.12 life-years discounted) after ten years in pastoral Ngorongoro when dogs are not vaccinated. In agro-pastoral Serengeti, this estimate is 5.8 life-years per km^2 undiscounted (5.0 life-years discounted), reflecting the higher population density of both dogs and humans in this district. The expected loss of life decreases monotonically to approach zero with increasing canine vaccination coverage. We compared model predictions of annual human rabies burden for the entirety of each district against data collected prior to large-scale vaccination campaigns. Our model predicts 2.0 rabies deaths annually at 5% vaccination coverage and 0.6 deaths annually at 15% coverage in Ngorongoro, as well as 39.3 and 8.3 rabies deaths annually in Serengeti, at 5% and 15% coverage respectively. These model results are consistent with observations of 2 – 6 deaths in Ngorongoro and 5 – 13 deaths in Serengeti during years of low vaccination coverage (23).

Economic Costs

The expected cumulative cost of providing PEP to victims of rabies bites at current levels for ten years is estimated to be $57,280 ($4.08/km^2) for Ngorongoro and $584,484 ($173.28/km^2) for Serengeti (Table 1) in present-value terms. As the incidence of canine rabies declines, these costs decline simultaneously (Figure 3). Conversely, the cost of canine vaccination increases with increasing coverage. The strategy with lowest total cost in Ngorongoro is no canine vaccination. In Serengeti, the lowest cost strategy is 25% coverage, as the high cost of PEP outweighs the cost of campaigns below that coverage. Regardless of the time horizon, no canine vaccination always remained the lowest cost strategy in Ngorongoro. However, in Serengeti, the costs of vaccination strategies up to 80% coverage break even with the costs of not vaccinating by the end of the first year (Appendix Figures 3 – 4).

Cost-Effectiveness of Vaccination

In Serengeti, vaccination coverage at 25% has lower monetary costs and higher health benefits than coverage below 25% (Table 1, Figure 4). Therefore, strategies with coverage below 25% are considered to be dominated. As coverage increases above 25%, both life-years saved and costs increase. In Ngorongoro, 5 – 15% coverage is dominated. With the thresholds set by per-capita GDP at $1430 and $4290 per life-years saved (16) , canine

vaccination in Ngorongoro is very cost effective for annual campaigns that reach 20% to 30% coverage, and cost effective for campaigns reaching 35% to 50%. In Serengeti, vaccination would be very cost-effective at coverage from 25% to 70%, and cost-effective for coverage ranging from 75% to 85%.

Uncertainty and Sensitivity Analyses

When considering all of the uncertainty in the epidemiological parameters, a cost-effectiveness acceptability curve identifies the optimal strategy as the one having the highest probability of being cost-effective for each willingness-to-pay threshold. At the very cost-effective threshold of $1430 per life-year gained, 80% vaccine coverage is optimal for Ngorongoro with a probability of 0.28 and 70% coverage is optimal for Serengeti with a probability of 0.85 (Figure 5). At the "cost-effective" threshold of $4290, campaigns achieving 90% coverage are most likely to be optimal for both districts. Regardless of willingness-to-pay, canine vaccination is the optimal choice at a probability of at least 0.68 in Ngorongoro and 0.86 in Serengeti. At any level of PEP availability below 98%, canine vaccination remains cost-effective (Appendix Figures 5 – 6). This is true irrespective of the price of PEP (Appendix Figure 6).

It is common in northwest Tanzania to kill, tie, or otherwise restrain rabid dogs. Our baseline analysis includes consideration of these practices. Given the possibility that these practices might change in the future or across different settings, we consider the impact that a change in these practices would have on the cost-effectiveness of the system. Without rabid dog removal, rabies transmission increases dramatically. Consequently, canine vaccination would be cost-saving in Ngorongoro as well as Serengeti, and would be cost-effective at up to 90% coverage in Ngorongoro and 95% coverage in Serengeti (Appendix Table 5).

Vaccination campaign costs are lower in both districts if dogs are not repeatedly vaccinated every year, by approximately 15% regardless of district or coverage acheived (Appendix Table 6). The cost differences represent the largest additional expenditure that a program should be willing to spend on education, tagging, or other methods to avoid revaccinating the same dogs.

Discussion

We found that canine vaccination against rabies is a very cost-effective approach to prevent human rabies in two distinct settings of rural Africa. In an agro-pastoral region such as Serengeti, canine vaccination is even cost-saving relative to PEP alone. Yet throughout most of sub-Saharan Africa, canine vaccination is exceedingly limited and rarely implemented with sufficient coverage to achieve these benefits. In Serengeti, the health burden and economic cost of maintaining the status quo of no canine vaccination is higher than the cost of establishing canine vaccination programs, even at high levels of coverage (85%). Coverage below 25% in Serengeti generates both higher spending and more deaths than coverage at 25%. In pastoral Ngorongoro, lives could be saved both efficiently and inexpensively by achieving up to 50% coverage. Even the highest-cost strategy, 95% coverage in Ngorongoro, would consume less than 0.2% of the overall health budget for

Tanzania (30). These results are robust to empirical uncertainty, and we find that the optimal strategy to prevent human rabies under any assumption about societal willingness-to-pay is one that includes annual canine vaccination campaigns.

While Serengeti and Ngorongoro are representative of agro-pastoral and pastoral communities in sub-Saharan Africa, they differ from each other with regard to dog and human density, to wildlife transmission dynamics, and, consequently, to the most suitable approach for program implementation. Nonetheless, annual canine rabies vaccination is broadly cost-effective in both regions, suggesting that this finding is applicable across different rural settings. Specifically, Ngorongoro is more sparsely populated by both humans and dogs, requiring a more expensive house-to-house approach to achieve the same coverage that central-point campaigns would yield in Serengeti. Additionally, the rabies burden is lower in Ngorongoro than in Serengeti, so the potential health impact is less dramatic. These differences suggest that the optimal level of coverage for an annual campaign might differ across rural Africa, with higher coverage potentially both more necessary and more efficient in rural areas of higher human and dog density.

Our base case analysis recommends lower coverage for Ngorongoro than for Serengeti across all levels of societal willingness-to-pay. However, our uncertainty analysis suggests that commensurately high coverage might be optimal for Ngorongoro. The difference between the central-point estimate and the uncertainty analysis may be attributed to the threshold behavior of the transmission dynamics, i.e., that the R_0 of rabies is close to 1 in Ngorongoro. Consequently, near this threshold even small shifts in the transmission parameters that we draw from the parameter distributions in our probabilistic analysis can significantly impact the coverage necessary to curtail transmission. Alternatively, the discrepancy between the probabilistic and deterministic results could be related to the exclusion of combinations of parameters that lead to R_0 values below one. Their exclusion may lead to an average R_0 in the uncertainty analysis that would be higher than that used in the base case and hence make high coverage vaccination campaigns more likely to be optimal in the uncertainty analysis. Additionally, the empirical distributions of the transmission parameters from which we draw are wider for Ngorongoro than for Serengeti, a result of the smaller sample size of rabies in Ngorongoro (10). Therefore, there is less certainty in choosing a particular coverage as optimal for Ngorongoro, although it is clear that the status quo of no vaccination is unlikely to be the best choice from neither economic nor public health perspectives.

Our model estimates the costs of vaccination campaigns along a wide range of coverage, but the original data was collected in association with a few specific coverage levels for each district. We assumed the most likely scenario that costs accumulate linearly between start-up costs and the observed coverage of central-point campaigns, but this may not be the case. Should the cost structure be different for vaccination campaigns achieving coverage below what we have observed, the optimal coverage levels might be different than what is reported here for low willingness-to-pay values. Similarly, the cost structure at very high coverage might change, as these costs were also estimated but not actually observed. However, neither limitation changes the general conclusion of our results, which is that canine

vaccination campaigns achieving 70% coverage or higher are very cost-effective for both districts.

The World Health Organization Commission on Macroeconomics and Health recommends that interventions which confer DALYs (life-years, in the case of rabies) at an incremental cost less than the national per capita GDP ($1430 for Tanzania) or three times that GDP ($4290) be considered "very cost-effective" or "cost-effective," respectively (14). Although these guidelines are considered simplistic (31), they are among the more stringent criteria and most typically used. The World Health Organization's Choosing Interventions that are Cost-Effective program (WHO-CHOICE) recommends threshold criteria at $2154 and $6461 per DALY, respectively, for Africa Region E, of which Tanzania is a part (15). Our analysis provides the incremental cost-effectiveness ratios across a large range of feasible coverage scenarios, including all these thresholds, equipping policymakers with the information necessary to select among these criteria based on their priorities and on the incremental benefits of competing health programs.

Our study is the first to reveal that repeated annual canine vaccination against rabies may be cost-saving. We find that even high-coverage annual vaccination campaigns in Serengeti are cost-saving relative to PEP alone within the first year. This is a more rapid recouping of expenditure than predicted in an urban setting (9) or from static models that do not incorporate transmission (32). In N'Djaména, Chad, the canine density is three times that in Serengeti and more than ten times that in Ngorongoro (9), elevating the total costs of canine vaccination programs in cities relative to those in agro-pastoral areas, and extending the time required to recoup costs.

Compared with a one-time campaign, annual vaccination protects better against the threat of rabies reintroduction from bordering unvaccinated populations. True elimination of rabies in any country would rely on a coordinated effort across political boundaries (33,34). Without such international cooperation in East Africa, permanent elimination of rabies in northwest Tanzania is not a feasible goal and sustained vaccination efforts will be required for control.

When access to the relatively expensive PEP is limited, as is usually the case in rural Africa, canine vaccination is imperative to prevent human death. A study in northwest Tanzania traced 699 victims of confirmed rabid dogs and found that only 456 (65%) of these victims received PEP (23). Without PEP, 19% of bite victims die of rabies (25). Lack of education about rabies, distance from the nearest clinic, or an inability to afford the fees contribute to imperfect rates of PEP administration (23). In addition, clinics do not always have PEP in stock, immunoglobulin is almost inevitably absent (23,35), and dog owners may be mistaken about the vaccination status of their dog (23). Although improved access to PEP is itself cost-effective (25,36), we found that canine vaccination would remain cost-effective even if PEP were more accessible (Appendix Figures 5 – 6).

Vaccination up to the coverage of herd immunity ensures the eventual control of the disease, but vaccinating beyond herd immunity continues to be cost-effective and even cost-saving. While herd immunity indicates the coverage at which vaccination will ultimately control rabies, higher coverage controls rabies even faster and likewise averts further human cases

earlier. Additional coverage is inexpensive relative to the cost of PEP and the willingness-to-pay thresholds. Therefore, optimal coverage even at the lowest willingness-to-pay threshold is higher than herd immunity alone might suggest.

In our current vaccination trials in Tanzania, every dog brought to the vaccination site is vaccinated, regardless of whether the dog has been previously vaccinated. This current practice is implemented to reduce confusion about which dogs should be brought in a given year, because vaccination certificates are often lost and veterinary registers incomplete. However, our household surveys suggest that, once vaccinated, dogs will usually be brought each subsequent year for revaccination. We found that the cost of annual campaigns could be reduced by about 15% over a decade in both districts by eliminating these repeat vaccinations. This suggests that a vaccination campaign might achieve significant savings by investing in record-keeping practices, marking dogs, and/or discouraging serial canine vaccination. In addition, the implications of relatively less straight-forward promotion and the practicalities of such changes to campaigns would also require further consideration.

A challenge for any vaccination program is the integration of canine vaccination into existing infrastructure and ongoing health programs. Health authorities must balance the investment of scarce resources, and veterinary programs are often perceived as low priority. However, our results demonstrate the tremendous human health benefits of canine rabies vaccination and that annual canine vaccination may actually release resources currently being used for rabies post-exposure prevention, so that other health goals may be pursued. Ongoing campaigns in Tanzania may serve as a model for implementation of such programs in other parts of sub-Saharan Africa. Efforts in Tanzania demonstrate that necessary levels of coverage are achievable, but they do require considerably more effort in terms of organization than is typically allocated to canine vaccination in sub-Saharan Africa. During the initial phase of vaccination program scale-up in areas without prior experience in canine vaccination, coverage lower than the targets are likely to be achieved, but even these lower levels are likely to be beneficial and cost-effective.

In summary, canine vaccination is a highly cost-effective approach to reducing human rabies fatalities in rural Tanzania. In some settings, canine vaccination is even cost-saving relative to the current status quo of providing PEP without vaccination of the canine reservoir. These results, modeled both in pastoral and agro-pastoral areas, are likely to be applicable across a wide range of rural African settings. We recommend the continuation of annual canine vaccination in rural Tanzania, and the immediate implementation of campaigns in other areas of rural Africa. This is particularly imperative in regions where PEP is expensive or unavailable, and it is important for policymakers and the medical community to recognize that this basic veterinary measure can prevent human death from a devastating disease. Although the precise quantitative recommendations of optimal coverage may be specific to a region, it is clear from our results that high coverage campaigns confer extraordinary value. An investment in canine vaccination throughout Tanzania specifically and sub-Saharan Africa generally will be repaid both in dollars and in lives.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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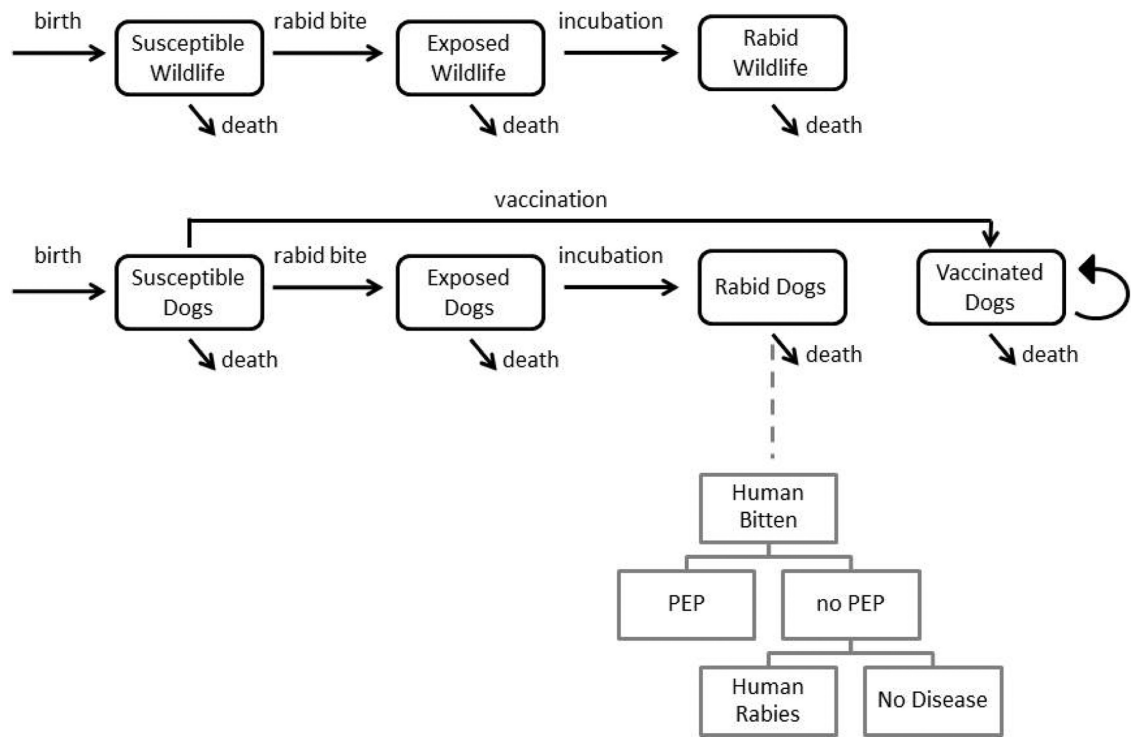
Figure 1. Rabies transmission model
Our dynamic compartmental model is stratified by host type. Rabid dogs are linked to human deaths through a probability tree of human health outcomes. The equations governing the movement between classes are given in the Appendix.
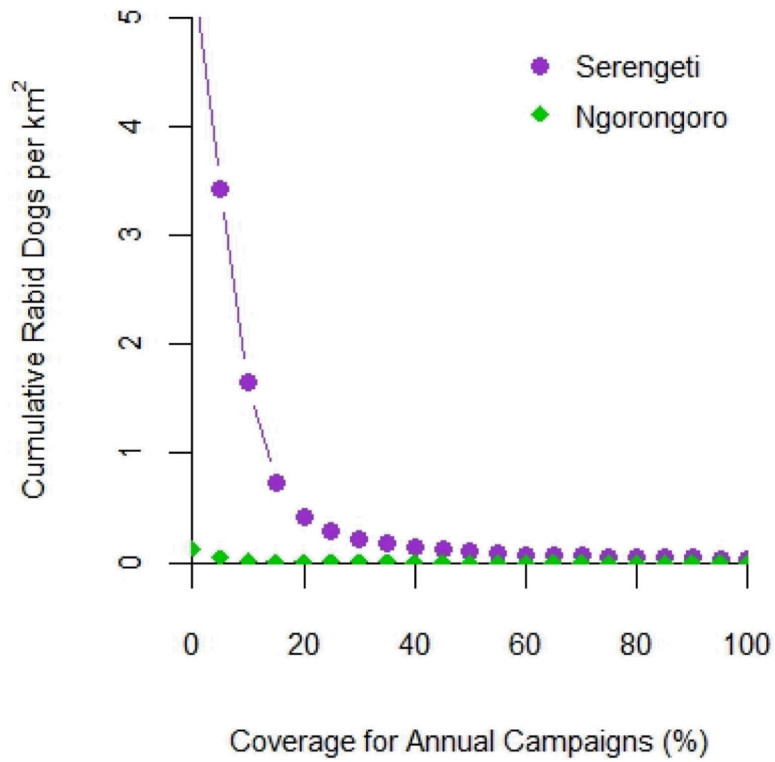
Figure 2. Cumulative rabies cases after ten years of annual canine vaccination campaigns at increasing vaccination coverage
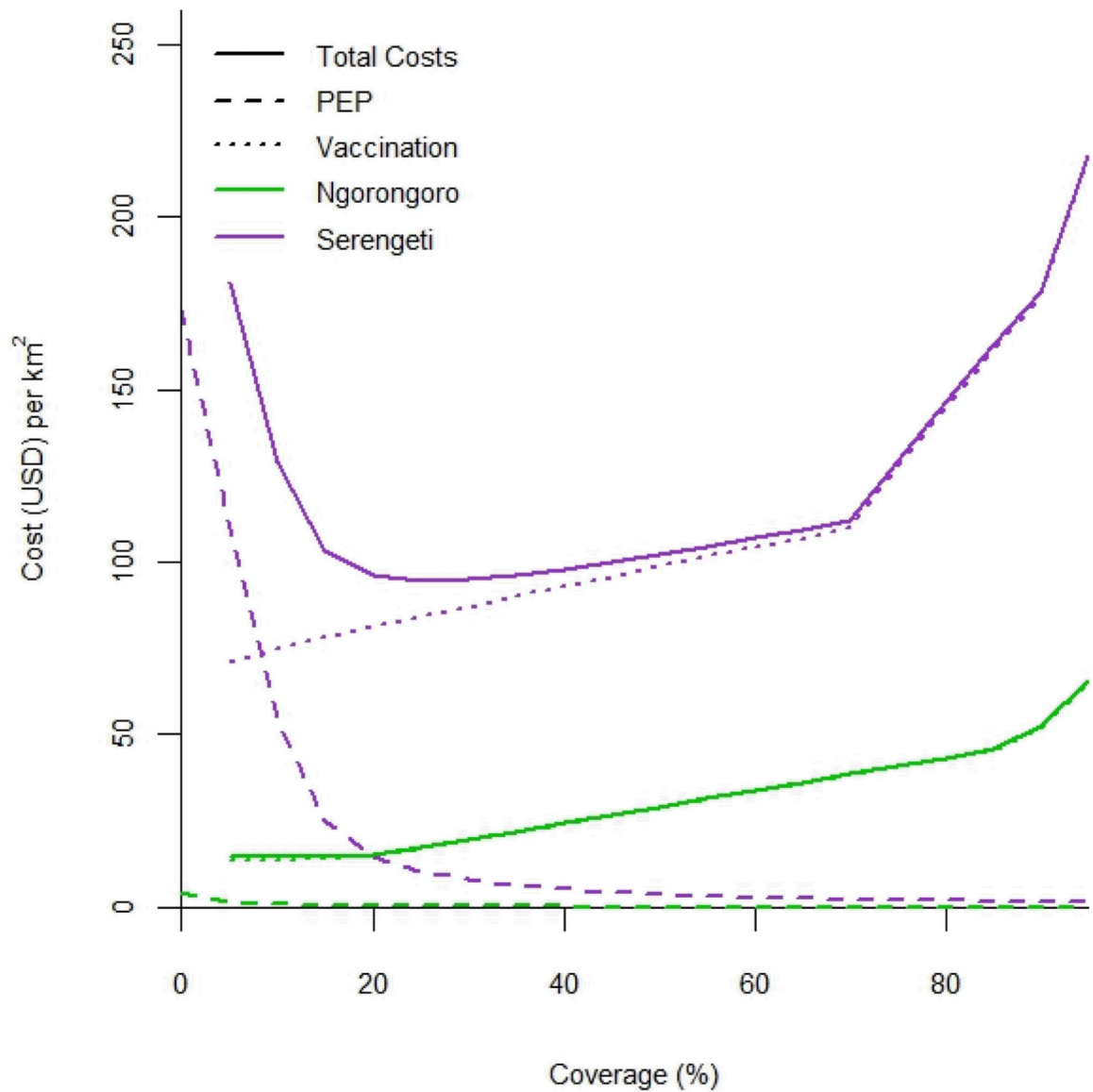Cases are undiscounted.

Figure 3. Component and total costs of rabies control with increasing canine vaccination coverage

Dotted lines, costs due to canine vaccination programs achieving a given coverage level; dashed lines, costs due to human post-exposure prophylaxis in the presence of canine vaccination at a given coverage level; and solid lines, sum of these two costs. All costs are cumulative over ten years.
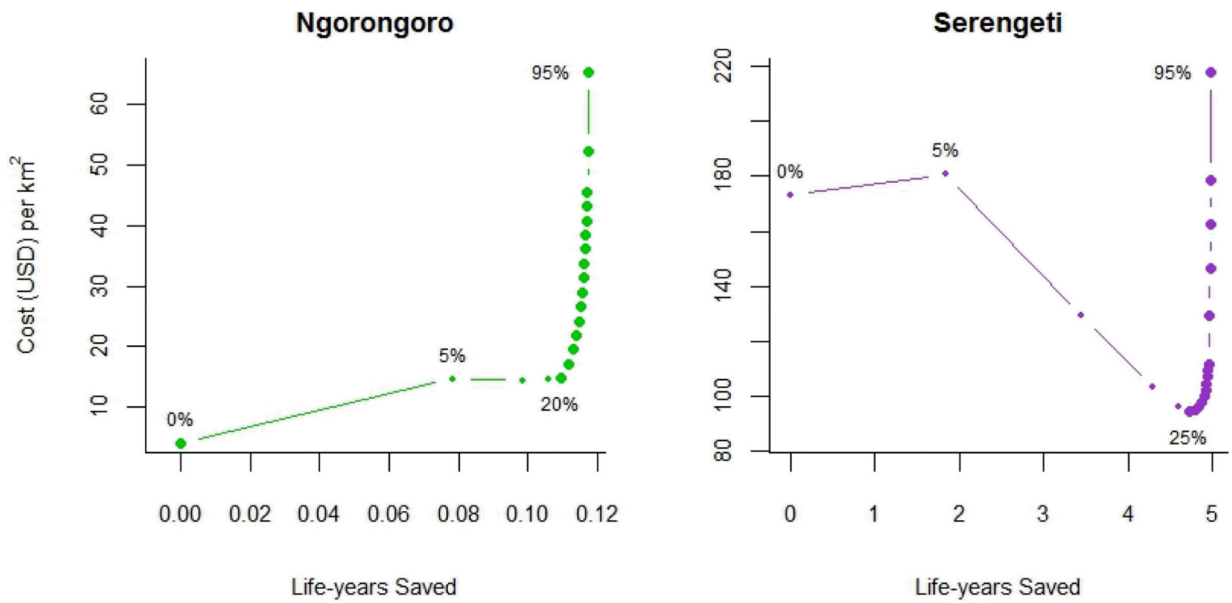
Figure 4. Cost of vaccination coverage and life-years saved

Points indicate increasing canine vaccination coverage. Smaller points indicate dominated strategies, which achieve fewer health benefits than other strategies of equal or lesser cost. Costs and life-years saved are cumulative over ten years. Please note that the two districts are represented on different scales.
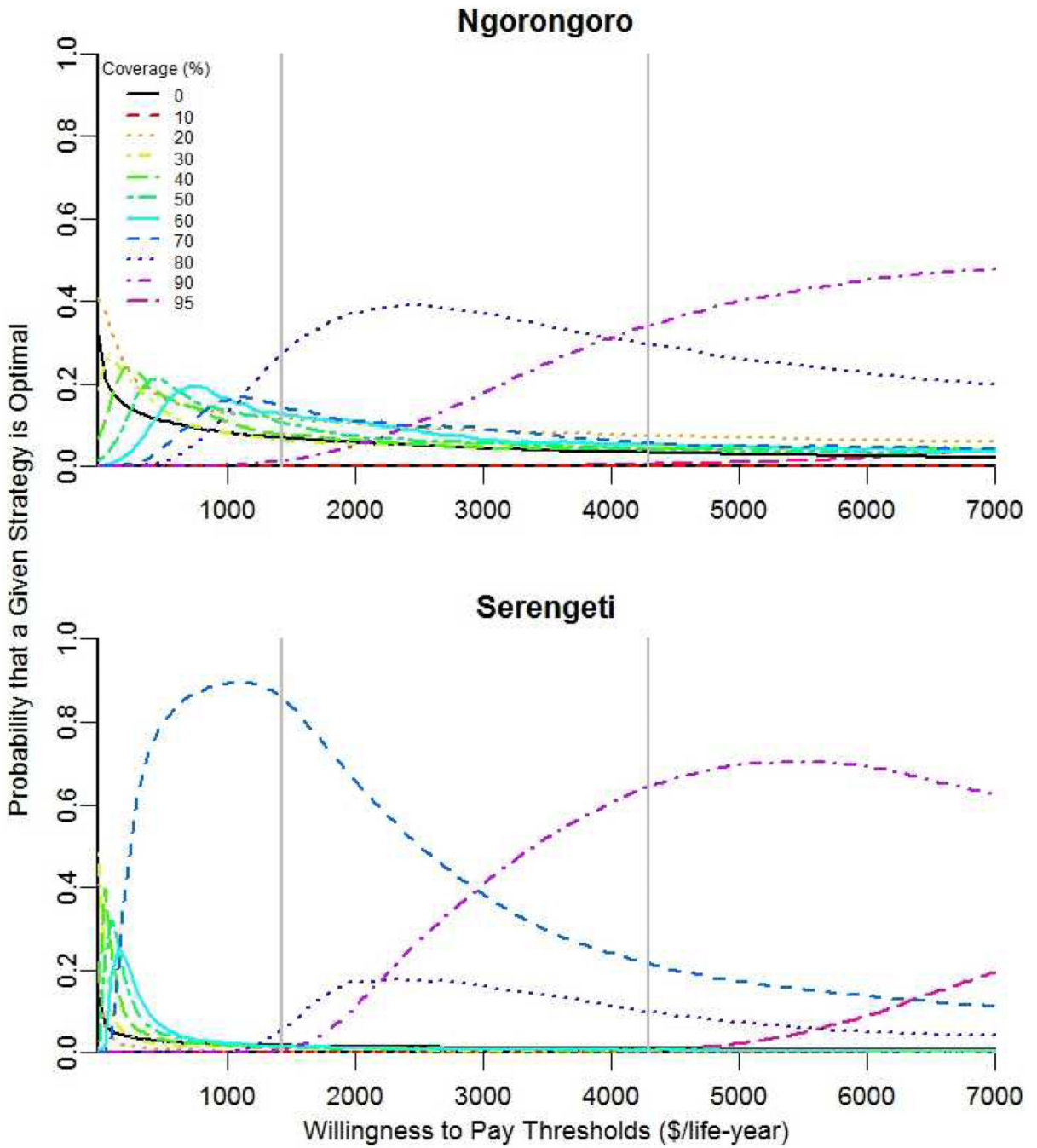
Figure 5. Cost-effectiveness acceptability curves

Curves show the probability that a given canine vaccination coverage is optimal, *i.e.* providing the largest net health benefit at a given willingness-to-pay threshold. At willingness-to-pay thresholds of $1430/life-year and $4290/life-year, the World Health Organization thresholds for "very cost-effective" and "cost-effective" interventions in Tanzania, optimal annual coverage ranges between 70 - 90% in both districts. These thresholds are indicated by solid vertical lines.

Table 1

Costs, benefits, and incremental cost-effectiveness ratios for control strategies. Costs are in 2010 USD, and both costs and life-years saved are cumulative over ten years and discounted to present-value terms with a 3% discount rate. Dominated strategies, which are italicized, are those which are more expensive and which provide less benefit than another strategy orcombination of strategies.

Vaccination Coverage (%)	Ngorongoro District					Serengeti District				
	Cost ($/km²)	Life-years saved (/km²)	District Cost ($)	District life- years saved	ICER[1]ᵐ($/life-year)	Cost ($/km²)	Life-years saved (/km²)	District Cost ($)	District life- years saved	ICER[1] ($/life-year)
0	4.08	0.000	57 280	0	minimum cost	173.28	0.000	584 484	0	dominated
5	14.66	0.078	205 816	1 098	dominated	180.71	1.842	609 533	6 213	dominated
10	14.41	0.098	202 248	1 382	dominated	129.16	3.449	435 646	11 635	dominated
15	14.59	0.106	204 718	1 484	dominated	103.32	4.299	348 494	14 499	dominated
20	14.90	0.109	209 105	1 535	98.90	96.00	4.598	323 807	15 510	dominated
25	17.19	0.112	241 305	1 565	1 070.10	94.44	4.727	318 535	15 945	minimum cost
30	19.51	0.113	273 856	1 585	1 644.92	94.79	4.799	319 737	16 188	4.95
35	21.87	0.114	306 976	1 599	2 382.42	96.19	4.846	324 446	16 344	30.11
40	24.21	0.115	339 853	1 609	3 215.87	97.88	4.878	330 165	16 453	52.50
45	26.55	0.115	372 719	1 617	4 227.39	100.09	4.902	337 595	16 533	92.98
50	28.95	0.116	406 383	1 623	5 547.53	102.31	4.920	345 084	16 594	123.25
55	31.32	0.116	439 627	1 628	6 874.51	104.53	4.934	352 580	16 641	157.93
60	33.68	0.116	472 716	1 632	8 439.08	107.11	4.945	361 279	16 679	229.58
65	36.04	0.116	505 922	1 635	10 290.46	109.28	4.954	368 603	16 710	237.95
70	38.44	0.117	539 515	1 638	12 486.69	111.77	4.962	376 989	16 735	330.27
75	40.78	0.117	572 383	1 640	14 485.27	129.16	4.968	435 662	16 757	2 764.60
80	43.17	0.117	606 001	1 642	17 382.35	146.50	4.973	494 157	16 775	3 258.65
85	45.53	0.117	639 075	1 644	19 872.75	162.79	4.978	549 076	16 790	3 578.78
90	52.11	0.117	731 397	1 645	63 903.77	178.39	4.982	601 723	16 803	3 974.04
95	65.24	0.117	915 727	1 646	145 801.16	217.85	4.985	734 792	16 815	11 532.80

[1]Incremental Cost-Effectiveness Ratio

Appendix Table 1 Transmission model equations

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

$dS_d/dt = \beta_{11}*I_d* S_d + \beta_{12}*I_w* S_d - \mu_d*E_d - \gamma*E_d*N_d - \sigma*E_d$

$dI_d/dt = \sigma*E_d - \mu_d*I_d - \gamma*I_d*N_d - \alpha*I_d$

$dV_d/dt = (v*N_d - V_d) - \mu_d*V_d - \gamma*V_d*N_d$

$dS_w/dt = (b_{w-\mu w})* S_w - \gamma_w*S_w*N_w - \beta_{22}*I_w*S_w - \beta_{21}*I_d*S_w$

$dE_w/dt = \beta_{22}*I_w*S_w + \beta_{21}*I_d*S_w - \mu_w*E_w - \gamma*E_w*N_w - \sigma*E_w$

$dI_w/dt = \sigma*E_w - \mu_w*I_w - \gamma*I_w*N_w - \alpha*I_w$

$N_d = S_d + E_d + I_d + V_d$

$N_w = S_w + E_w + I_d$

Blue portions are active only during vaccination campaigns.

Appendix Table 2 Parameters for transmission model, cost, and decision model. Estimates were used for the base-case analysis, and the full distribution was sampled for the uncertainty analysis.

Parameter	Description	Estimate	Distribution	Reference
Transmission Model Parameters				
b_d	Birth rate (domestic dogs)	1.72/year	normal (1.72, 0.11)	(18)
μ_a	Death rate (adult dogs)	.45/year	normal (0.45, 0.02)	(18)
b_w, μ_w	Birth/death rate (wildlife)	same as for dogs	same as for dogs	
$K_{d,N}$	Carrying capacity (Ngorongoro, dogs)	1.5		(18)
$K_{d,S}$	Carrying capacity (Serengeti, dogs)	10		(18)
$K_{w,N}$	Carrying capacity (Ngorongoro, wildlife)	4.5		Field data
$K_{w,S}$	Carrying capacity (Serengeti, wildlife)	3.0		Field data
γ	Death from carrying capacity limits	$(b-\mu)/K$		
$1/\sigma$	Incubation period of rabies	22.3 days	normal (22.3, 1.28)	(18)
$1/\alpha$	Infectious period of rabies	3.1 days	normal (3.10, 0.13)	(18)
V	Vaccination coverage	varies	0 – 1	
$\beta_{11,N}$	Dog to dog transmission (Ngorongoro)	0.20	tnorm[1] (0.20, 0.020)	(10)
$\beta_{12,N}$	Wildlife to dog transmission (Ngorongoro)	0.11	tnorm[1] (0.11, 0.035)	(10)
$\beta_{21,N}$	Dog to wildlife transmission (Ngorongoro)	0.01	tnorm[1] (0.01, 0.002)	(10)
$\beta_{22,N}$	Wildlife to wildlife transmission (Ngorongoro)	0.03	tnorm[1] (0.03, 0.009)	(10)
$\beta_{11,S}$	Dog to dog transmission (Serengeti)	0.03	tnorm[1] (0.03, 0.001)	(10)
$\beta_{12,S}$	Wildlife to dog transmission (Serengeti)	0.03	tnorm[1] (0.03, 0.004)	(10)
$\beta_{21,S}$	Dog to wildlife transmission (Serengeti)	0.01	tnorm[1] (0.01, 0.001)	(10)
$\beta_{22,S}$	Wildlife to wildlife transmission (Serengeti)	0.02	tnorm[1] (0.02, 0.006)	(10)
Cost Parameters				
	Dog vaccination, Ngorongoro, per dog	$4.07	uniform (3.41 –4.77)	(19)
	Dog vaccination, Serengeti, per dog	$2.05	uniform (1.00 –3.19)	(19)
	PEP[2] administration, per regimen	$111.29		(25)
	Life-year cost per human case	31.426		(2)
Decision Tree Parameters				
P1	Number of humans bitten by a single rabid dog	.51		Field data
P2	That a bite victim of a rabid dog goes to the hospital (.76) and receives PEP[2] (.86)	.65		(25)
P3	That a bite victim of a rabid dog who does not seek PEP[2] will contract rabies	.19		(25)
	PEP[2] cost per bite (P1*P2*$111.29)	$36.89		
	Human rabies health burden per bite (P1*(1-P2)*P3*31.426 life-years)	1.07 life-years		

[1] Truncated normal distribution

[2] Post-exposure prophylaxis

Table 3

Appendix Model sensitivity to variation in wildlife density. Health and economic outcomes associated with varying wildlife density are listed for Ngorongoro. K_w indicates the carrying capacity of wild carnivores (per km^2). For central-point implementation, $K_w = 4.5$ carnivores per km^2. Health and economic outcomes are cumulative over ten years and discounted at 3% annually.

Vaccination Coverage (%)		$K_w = 3$	$K_w = 4.5$	$K_w = 6$
30	Life-years saved per km2	0.113	0.113	0.113
60		0.116	0.116	0.116
90		0.117	0.117	0.117
30	Cost per km2	$19.51	$19.51	$19.51
60		$33.68	$33.68	$33.68
90		$52.11	$52.11	$52.11

Table 4

Appendix Estimates of rabies epidemiological parameters. The parameter k_{ij} indicates the number of animals of type i that a single rabid animal of type j is likely to infect. Values are reported both for the scenario in which rabid dogs are killed or restrained ("w/ removal") and for that in which they are not ("w/o removal"). The 95% confidence interval is given in parentheses. We previously reported estimates of transmission parameters for the scenario without rabid canine removal (10).

	Description		Ngorongoro District		Serengeti District	
	1° Infection	2° Infection	w/o removal	w/ removal	w/o removal	w/removal
k_{11}	dog	dog	1.16 (0.85 – 1.54)	0.92 (0.75 – 1.11)	1.09 (0.98 – 1.21)	1.01 (0.94 – 1.07)
k_{21}	dog	other	0.13 (0.05 – 0.27)	0.12 (0.07 – 0.19)	0.09 (0.06 – 0.13)	0.09 (0.07 – 0.11)
k_{12}	other	dog	0.49 (0.23 – 0.84)	0.48 (0.23 – 0.86)	0.95 (0.71 – 1.21)	0.95 (0.71 – 1.20)
k_{22}	other	other	0.39 (0.20 - 0.67)	0.39 (0.19 – 0.67)	0.23 (0.13 – 0.35)	0.23 (0.12 – 0.35)
R_0	basic reproduction number		1.24	1.02	1.18	1.11

Table 5

Appendix Costs, benefits, and incremental cost-effectiveness ratios for control strategies when canine removal is not practiced. Costs are in 2010 USD, and both costs and life-years saved are cumulative over ten years and discounted to present-value terms with a 3% discount rate. Dominated strategies, which are italicized, are those which are more expensive and which provide less benefit than another strategy or combination of strategies.

Vaccination Coverage (%)	Ngorongoro District			Serengeti District		
	Total Cost ($/km²)	Life-years saved	ICER[1] ($/life-year)	Total Cost ($/km²)	Life-years saved	ICER[1] ($/life-year)
0	*61.87*	*0.000*	*dominated*	*240.02*	*0.000*	*dominated*
5	*64.65*	*0.182*	*dominated*	*246.09*	*1.440*	*dominated*
10	*58.32*	*0.381*	*dominated*	*198.05*	*2.929*	*dominated*
15	*51.44*	*0.596*	*dominated*	*151.45*	*4.376*	*dominated*
20	*44.12*	*0.824*	*dominated*	*115.72*	*5.499*	*dominated*
25	*37.87*	*1.063*	*dominated*	*97.34*	*6.111*	*dominated*
30	*31.25*	*1.316*	*dominated*	*90.09*	*6.393*	*dominated*
35	*25.09*	*1.556*	*dominated*	*87.59*	*6.539*	*dominated*
40	22.69	1.683	minimum cost	86.87	6.628	minimum cost
45	23.27	1.722	14.84	87.28	6.688	6.76
50	24.65	1.738	86.63	88.10	6.732	18.67
55	26.21	1.748	163.26	89.17	6.766	31.99
60	27.86	1.754	243.12	90.69	6.792	58.15
65	29.56	1.760	332.10	92.01	6.813	62.33
70	31.33	1.764	435.01	93.66	6.830	96.20
75	33.07	1.767	532.34	107.51	6.844	972.03
80	34.88	1.770	666.88	121.37	6.856	1158.79
85	36.67	1.772	787.46	134.40	6.867	1284.46
90	41.80	1.774	2654.69	146.93	6.875	1439.37
95	52.11	1.776	6201.99	178.88	6.883	4247.69

[1] Incremental Cost-Effectiveness Ratio

Table 6

Appendix Comparative cost of revaccination. The estimated cost per km^2 of a vaccination campaign is listed for scenarios where dogs are vaccinated every year regardless of vaccine history compared with scenarios where dogs are never revaccinated. Costs are in 2010 USD, discounted, and cumulative over ten years.

	Ngorongoro		Serengeti	
	standard	no repeat vaccination	standard	no repeat vaccination
30%	$19.32	$16.24	$86.97	$72.97
60%	$33.61	$28.24	$104.31	$87.57
90%	$52.07	$43.75	$176.86	$148.48