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Cost-Effectiveness of Canine Vaccination to Prevent Human Rabies in Rural Tanzania

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Background: The annual mortality rate of human rabies in rural Africa is 3.6 deaths per 100 000 persons. Rabies can be prevented with prompt postexposure prophylaxis, but this is costly and often inaccessible in rural Africa. Because 99% of human exposures occur through rabid dogs, canine vaccination also prevents transmission of rabies to humans.

Objective: To 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 variables to make probability-based evaluations of cost-effectiveness.

Data Sources: Epidemiologic variables from a contact-tracing study and literature and cost data from ongoing vaccination campaigns.

Target Population: Two districts of rural Tanzania: Ngorongoro and Serengeti.

Time Horizon: 10 years.

Perspective: Health policymaker.

Intervention: Vaccination coverage ranging from 0% to 95% in increments of 5%.

Outcome Measures: Life-years for health outcomes and 2010 U.S. dollars for economic outcomes.

Results of Base-Case Analysis: Annual canine vaccination campaigns were very cost-effective in both districts compared with no canine vaccination. In Serengeti, annual campaigns with as much as 70% coverage were cost-saving.

Results of Sensitivity Analysis: Across a wide range of variable assumptions and levels of societal willingness to pay for life-years, the optimal vaccination coverage for Serengeti was 70%. In Ngorongoro, although optimal coverage depended on willingness to pay, vaccination campaigns were always cost-effective and life-saving and therefore preferred.

Limitation: Canine vaccination was very cost-effective in both districts, but there was greater uncertainty about the optimal coverage in Ngorongoro.

Conclusion: Annual canine rabies vaccination campaigns conferred extraordinary value and dramatically reduced the health burden of rabies.

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Rabies is a viral encephalitic disease of mammals that 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 incidence because more than 99% of all human cases worldwide result from the bite of a domestic dog (4).

Postexposure prophylaxis (PEP), including a series of vaccinations and administration of immunoglobulin, can prevent rabies after a dog bite. Worldwide, more than 7.5 million rabies PEP regimens are delivered annually (5) at an estimated cost of more than $1.5 billion (1). Given that a disproportionate rabies burden occurs in sub-Saharan Africa, these costs often fall to the countries that are 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 (6).

Concerns about program costs and the efficient use of health resources have been identified as major barriers to the implementation of canine vaccination programs (7). One-time canine rabies vaccination campaigns have been evaluated as cost-effective prevention against human rabies in urban Chad (8). However, more than 75% of rabies deaths in Africa occur in rural areas (2), and disease dynamics vary between these 2 settings because of different densities and contact patterns among humans, dogs, and other wildlife (9). Additionally, high birth and death rates in domestic dogs as well as reintroduction of rabies from dogs or wildlife in neighboring, unvaccinated regions make it unlikely that a 1-time vaccination campaign will control canine rabies in rural Africa indefinitely (10). Therefore, we evaluated 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 epidemiologic effects, clinical benefits, economic costs, and cost-effectiveness of canine vaccination coverage strategies ranging from 0% to 95% in

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Context

Human rabies causes many deaths in resource-limited countries, and most are due to dog bites. Administration of postexposure prophylaxis is uncommon because of cost and limited access.

Contribution

Using a model of rabies transmission in 2 rural districts of Tanzania, the authors demonstrated that a campaign of annual rabies vaccination of dogs would be very cost-effective.

Implication

Annual canine rabies vaccination in sub-Saharan Africa could dramatically decrease the occurrence of this disease in humans.

—The Editors

rural Tanzania. No vaccination, which is the status quo in most parts of Tanzania, was considered the baseline for our analysis. Outcome measures included numbers of dogs vaccinated, incidence of human rabies, and economic costs (in 2010 U.S. dollars). 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 were equal to disability-adjusted life-years given that rabies is inevitably fatal. Thus, the entire health burden accrues from deaths rather than illnesses. We assessed economic costs associated with both a canine vaccination campaign and PEP to prevent rabies in exposed persons. In conformity with World Health Organization guidelines (11) and other recommendations for best practices (12), cost-effectiveness outcomes were reported across both 1- and 10-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 1-way sensitivity analysis. We applied World Health Organization recommendations (13, 14) to denote strategies with incremental cost-effectiveness ratios less than the per-capita gross domestic product (GDP) for a life-year saved (GDP, $1430 for Tanzania [15]) as "very cost-effective" and ratios less than 3 times the per-capita GDP ($4290) as "cost-effective."

We compared pastoral (Ngorongoro) and agro-pastoral (Serengeti) districts in rural Tanzania as representative of 2 major settlement patterns and canine densities in rural Africa. Although both are sparsely populated compared with cities, agro-pastoral areas generally consist of larger, more closely located villages than found in pastoral areas. Canine density, measured as dogs per square kilometer, was nearly 7 times higher in Serengeti than Ngorongoro. Rabies in Serengeti was endemic, with cases continuously observed, whereas rabies in Ngorongoro was epidemic, with no observed cases between outbreaks (16, 17). Additionally, pilot rabies vaccination campaigns in the 2 districts have required different strategies to achieve high coverage (18). 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 (16), we addressed concerns that vaccination coverage that had been sufficient for control in some regions may be insufficient in these wildlife-rich areas (7) 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** and **Figure 1** of **Supplement 1** (available at www.annals.org).

Model Structure

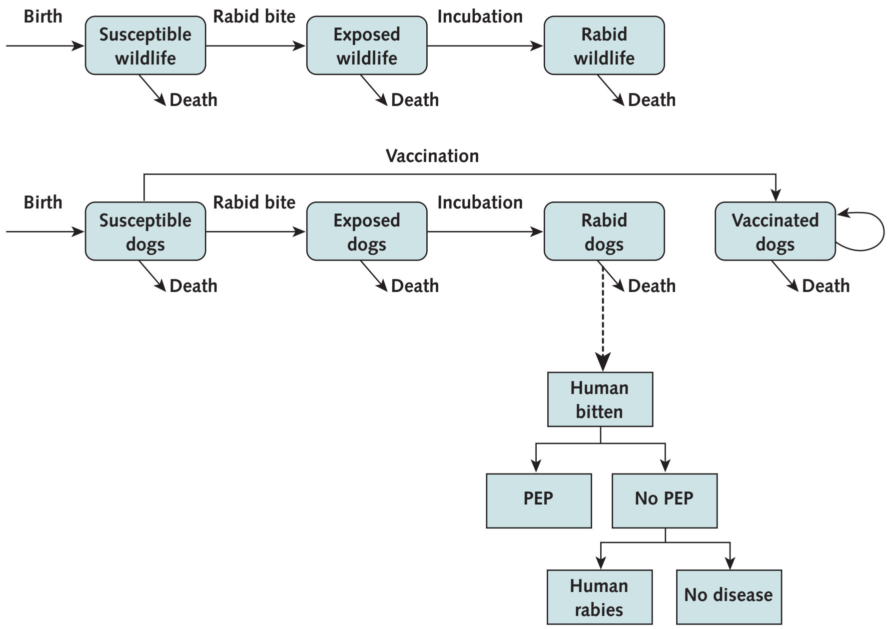
We developed a compartmental transmission model with 2 strata: 1 for domestic dogs and another for wildlife, which included all other carnivores in the area (**Figure 1**). Each stratum contained the 3 disease classes of susceptible, exposed or latent, and infectious, measured in units of animals per square kilometer. The canine stratum also included a vaccinated class. Because rabies is fatal, there was no recovered class (8, 19–21). Canine demography was 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 exceeded the limits of the human and geographic environment. We assumed that infected animals did not have fecundity because of the typically short incubation period of rabies and the low likelihood that their puppies would survive. To evaluate the effect 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 in **Appendix** and Tables 1 to 6 of **Supplement 2** (available at www.annals.org).

We compared our model output with the incidence of canine and human rabies in these 2 districts before large-scale annual vaccination campaigns began. Because of past sporadic vaccination efforts, 5% to 10% of dogs in these districts had been previously vaccinated when the annual canine incidence was 1% to 2%. For human rabies, we had previously estimated an incidence of 1.48 to 4.28 deaths per 100 000 people in Ngorongoro before large-scale implementation of canine vaccination, resulting in 2 to 6 rabies deaths per year for the district (22). From animal-bite injury data and availability of PEP, we had estimated that the incidence of human rabies in unvaccinated areas near Serengeti was 4.9 annual deaths (95% CI, 2.9 to 7.2) per 100 000 persons in the late 1990s (23), leading to 5 to 13 human cases of rabies annually.

Costs of Vaccination

We parameterized the costs in our analysis using field data that we collected during annual vaccination campaigns in Serengeti and Ngorongoro and from published literature (18). We considered only the direct costs of vac-

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 **Table 1** of **Supplement 2** (available at www.annals.org). PEP = postexposure prophylaxis.

cination because dogs are often brought to vaccination stations by children and the average income loss from bringing a dog to the central point was therefore considered to be minimal. We generated functions of cost with increasing vaccination coverage. The costs varied between the 2 districts. In the agro-pastoralist district of Serengeti, central-point vaccination campaigns were 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 to achieve high coverage, increasing the costs per dog vaccinated in Ngorongoro compared with those in Serengeti. We estimated costs as a function of coverage level, taking into account both the fixed costs of program start-up 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 persons with rabies. Monetary losses accrue through the cost of PEP, estimated to be $111.29 per regimen (24), which includes both direct costs of treatment and indirect costs of transportation and lost income for the days on which treatment is administered. We assumed that a full course of PEP was 100% effective, which was both consistent with clinical data (6) and conservative given that this assumption would bias against canine vaccination. When persons who did not receive PEP progressed to rabies, we considered only the health burden because 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 (**Table 2** of **Supplement 2** and **Figure 1**). We did not consider transmission from wildlife to humans because this represented fewer than 1% of human cases (4). However, our previous findings did show that mass vaccination of domestic dogs could concomitantly eliminate disease from wildlife (16), and this would potentially be an additional benefit for conservation (25, 26) as well as human health.

Data collected through contact tracing of all rabies cases detected from January 2002 through December 2006 (16, 17) were used to estimate that each rabid dog bites 0.51 humans (**Appendix**). We estimated that each rabid dog led to an average of $36.89 in costs from PEP administration and a loss of 1.07 human life-years (**Table 2** of **Supplement 2**). To estimate the cost of disease for each strategy that we considered, we multiplied each of these measures by the canine rabies incidence predicted through simulation. We calculated the cumulative economic cost of disease and vaccination on 2 time scales, annually and over a decade.

Cost-Effectiveness

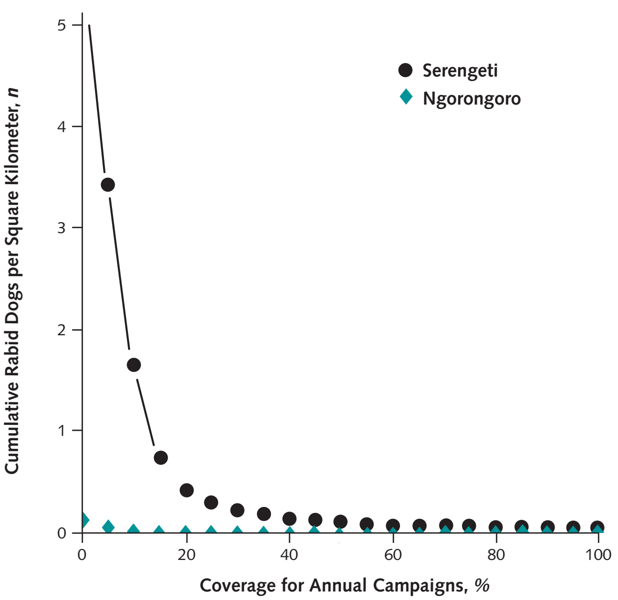
Within each district, any strategy that had both greater monetary cost and more lives lost than some other strategy or combination of strategies was considered to be dominated by the latter strategy. For each nondominated scenario, we calculated the incremental cost-effectiveness ratio as compared with the next-lowest cost scenario. The incremental cost-effectiveness ratio measured 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 (27). 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 (28). This framework yielded a single outcome measure that simplified the identification of the program that provided 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

The study was funded by the National Institutes of Health. The funding source had no role in study design, data collection and analysis, preparation of the manuscript, or the decision to submit the manuscript for publication.

Figure 2. **Cumulative rabies cases after 10 y of annual canine vaccination campaigns at increasing vaccination coverage.**



Cases are undiscounted.

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 vaccination coverage levels. Our results showed that the expected number of rabies cases in both domestic dogs and wildlife hosts decreased monotonically with increasing canine vaccination coverage (**Figure 2** of **Supplement 1** and **Figure 2**). In a scenario with no vaccination, the cumulative burden of rabies after 10 years is estimated to be 0.13 rabid dogs per square kilometer undiscounted in Ngorongoro and 5.43 rabid dogs per square kilometer undiscounted in Serengeti (0.11 and 4.7 rabid dogs per square kilometer, respectively, discounted to present value terms). These values are consistent with our observation that the annual rabies loss is 1% to 2% of the dog population under conditions of very low vaccination coverage. The herd immunity threshold, or the coverage at which rabies would 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 led to humans being exposed to rabies through dog bites, causing death in the absence of prompt PEP. Each death corresponded to a loss of 31.4 life-years (2). Our model projected the loss of 0.14 life-years per square kilometer undiscounted (0.12 life-years discounted) after 10 years in pastoral Ngorongoro when dogs were not vaccinated. In agro-pastoral Serengeti, this estimate was 5.8 life-years per square kilometer 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 0 with increasing canine vaccination coverage.

We compared model predictions of annual human rabies burden for the entirety of each district against data collected before 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 to 6 deaths in Ngorongoro and 5 to 13 deaths in Serengeti during years of low vaccination coverage (22).

Economic Costs

The expected cumulative cost of providing PEP to victims of rabid dog bites at current levels for 10 years was estimated to be \$57 280 (\$4.08/km^2) for Ngorongoro and \$584 484 (\$173.28/km^2) for Serengeti (**Table**) in present-value terms. As the incidence of canine rabies declined, these costs declined simultaneously (**Figure 3**). Conversely, the cost of canine vaccination increased with increasing coverage. The strategy with the lowest total cost in Ngorongoro was no canine vaccination. In Serengeti, the

Table. **Costs, Benefits, and ICERs for Control Strategies***

Vaccination Coverage, %	Cost, $/km²	LYs Saved Per Square Kilometer, *n*	District Cost, $	District LYs Saved, *n*	ICER, $/LY
Ngorongoro district					
0	4.08	0.000	57 280	0	Minimum cost
5	*14.66*	*0.078*	*205 816*	*1098*	*Dominated*
10	*14.41*	*0.098*	*202 248*	*1382*	*Dominated*
15	*14.59*	*0.106*	*204 718*	*1484*	*Dominated*
20	14.90	0.109	209 105	1535	98.90
25	17.19	0.112	241 305	1565	1070.10
30	19.51	0.113	273 856	1585	1644.92
35	21.87	0.114	306 976	1599	2382.42
40	24.21	0.115	339 853	1609	3215.87
45	26.55	0.115	372 719	1617	4227.39
50	28.95	0.116	406 383	1623	5547.53
55	31.32	0.116	439 627	1628	6874.51
60	33.68	0.116	472 716	1632	8439.08
65	36.04	0.116	505 922	1635	10 290.46
70	38.44	0.117	539 515	1638	12 486.69
75	40.78	0.117	572 383	1640	14 485.27
80	43.17	0.117	606 001	1642	17 382.35
85	45.53	0.117	639 075	1644	19 872.75
90	52.11	0.117	731 397	1645	63 903.77
95	65.24	0.117	915 727	1646	145 801.16
Serengeti district					
0	*173.28*	*0.000*	*584 484*	*0*	*Dominated*
5	*180.71*	*1.842*	*609 533*	*6213*	*Dominated*
10	*129.16*	*3.449*	*435 646*	*11 635*	*Dominated*
15	*103.32*	*4.299*	*348 494*	*14 499*	*Dominated*
20	*96.00*	*4.598*	*323 807*	*15 510*	*Dominated*
25	94.44	4.727	318 535	15 945	Minimum cost
30	94.79	4.799	319 737	16 188	4.95
35	96.19	4.846	324 446	16 344	30.11
40	97.88	4.878	330 165	16 453	52.50
45	100.09	4.902	337 595	16 533	92.98
50	102.31	4.920	345 084	16 594	123.25
55	104.53	4.934	352 580	16 641	157.93
60	107.11	4.945	361 279	16 679	229.58
65	109.28	4.954	368 603	16 710	237.95
70	111.77	4.962	376 989	16 735	330.27
75	129.16	4.968	435 662	16 757	2764.60
80	146.50	4.973	494 157	16 775	3258.65
85	162.79	4.978	549 076	16 790	3578.78
90	178.39	4.982	601 723	16 803	3974.04
95	217.85	4.985	734 792	16 815	11 532.80

ICER = incremental cost-effectiveness ratio; LY = life-year.
* Costs are in 2010 U.S. dollars, and both costs and life-years saved are cumulative over 10 y and discounted to present-value terms with a 3% discount rate. Dominated strategies, which are italicized, are more expensive and provide less benefit than another strategy or combination of strategies.

lowest-cost strategy is 25% coverage because 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 broke even with the costs of not vaccinating by the end of the first year (**Figures 3** and **4** of **Supplement 1**).

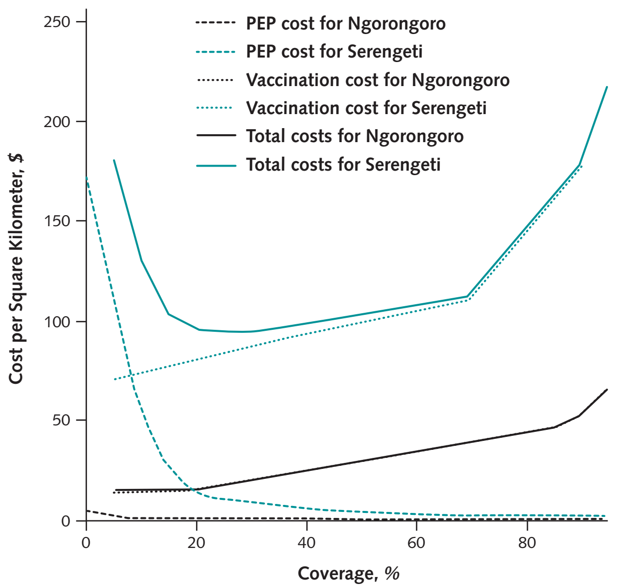
Cost-Effectiveness of Vaccination

In Serengeti, vaccination coverage at 25% had lower monetary costs and higher health benefits than coverage less than 25% (**Table** and **Figure 4**). Therefore, strategies with coverage less than 25% were considered to be dominated. As coverage increased to more than 25%, both life-years saved and costs increased. In Ngorongoro, 5% to 15% coverage was dominated. With the thresholds set by per-capita GDP at $1430 and $4290 per life-years saved (15), canine vaccination in Ngorongoro was very cost-effective for annual campaigns that reached 20% to 30% coverage and cost-effective for campaigns that reached 35% to 50%. In Serengeti, vaccination was very cost-effective at coverage from 25% to 70% and cost-effective for coverage between 75% and 85%.

Uncertainty and Sensitivity Analyses

When considering all of the uncertainty in the epidemiologic variables, a cost-effectiveness acceptability curve identifies the optimal strategy as the one having the highest probability of being cost-effective for each willingness-to-

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



All costs are cumulative over 10 y. PEP = postexposure prophylaxis.

pay threshold. At the very cost-effective threshold of $1430 per life-year gained, 80% vaccine coverage was optimal for Ngorongoro with a probability of 0.28, and 70% coverage was optimal for Serengeti with a probability of 0.85 (**Figure 5**). At the "cost-effective" threshold of $4290, campaigns achieving 90% coverage were most likely to be optimal for both districts. Regardless of willingness to pay, canine vaccination was 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 remained cost-effective (**Figures 5** and **6** of **Supplement 1**). This was true regardless of the price of PEP (**Figure 6** of **Supplement 1**).

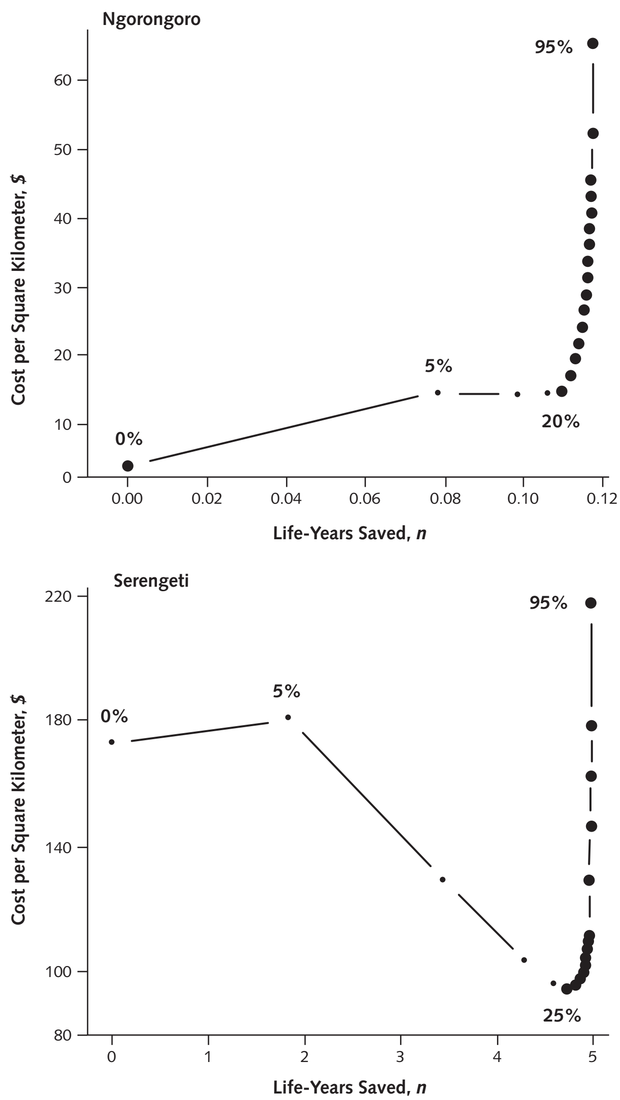
It is common in northwest Tanzania to kill, tie, or otherwise restrain rabid dogs. Our baseline analysis included consideration of these practices. Given the possibility that these practices may change in the future or across different settings, we considered the effect that a change in these practices would have on the cost-effectiveness of the system. Without rabid dog removal, rabies transmission increased dramatically (**Table 4** of **Supplement 2**). 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 (**Table 5** of **Supplement 2**).

Vaccination campaign costs were lower in both districts if dogs were not repeatedly vaccinated every year by approximately 15% regardless of district or coverage achieved (**Table 6** of **Supplement 2**). 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

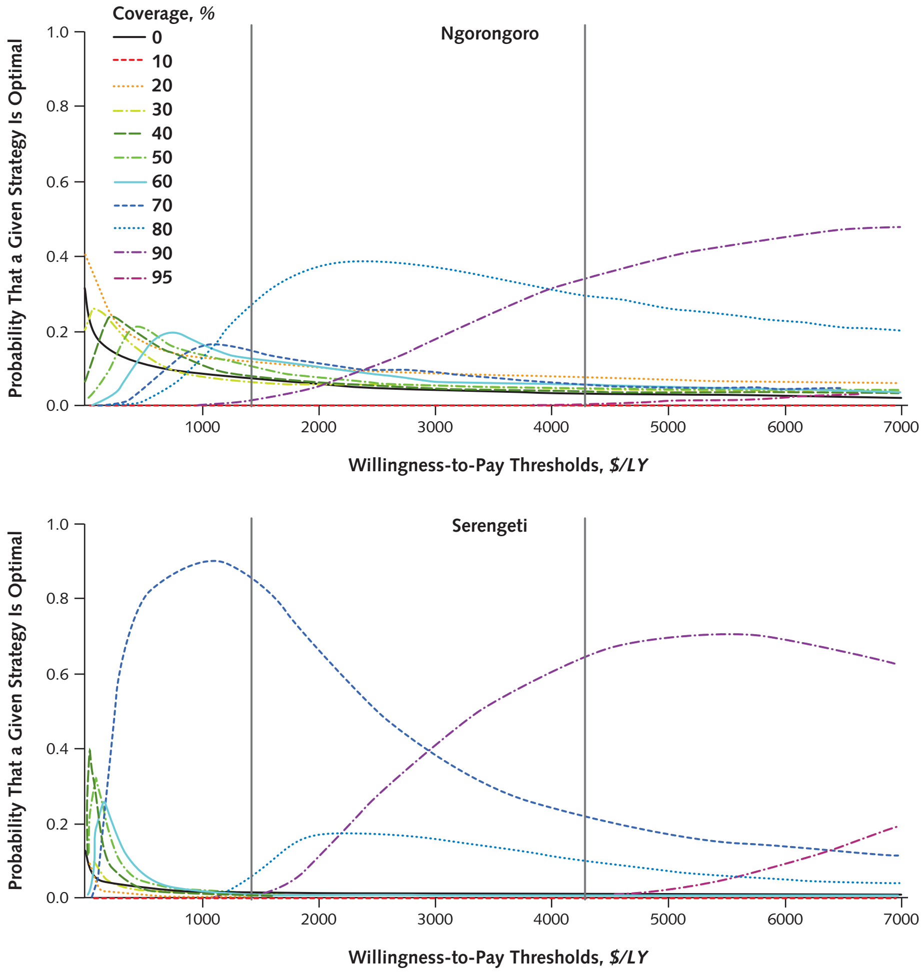
We found that canine vaccination against rabies is a very cost-effective approach to prevent human rabies in 2 distinct settings of rural Africa. In an agro-pastoral region, such as Serengeti, canine vaccination is even cost-saving relative to PEP alone. However, throughout most of sub-Saharan Africa, canine vaccination is exceedingly limited and rarely implemented with sufficient coverage to achieve these benefits. In Serengeti, the health burden and eco-

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 10 y. Note that the 2 districts are represented on different scales.

Figure 5. **Cost-effectiveness acceptability curves.**



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

nomic cost of maintaining the status quo of no canine vaccination is greater than the cost of establishing canine vaccination programs, even at high levels of coverage (85%). Coverage less than 25% in Serengeti generated both greater spending and more deaths than coverage at 25%. In pastoral Ngorongoro, lives can 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 (29). These results were robust to empirical uncertainty, and we found that the optimal strategy to prevent human rabies under any assumption about societal willingness to pay was one that included annual canine vaccination campaigns.

Although 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, wildlife transmission dynamics, and consequently 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. In particular, 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. In addition, the rabies burden is lower in Ngorongoro than in Serengeti, so the potential health effect is less dramatic. These differences suggest that the optimal level of coverage for an annual campaign may differ across rural Africa, with higher coverage potentially both more necessary and more efficient in rural areas of greater human and dog density.

Our base-case analysis recommended lower coverage for Ngorongoro than for Serengeti across all levels of societal willingness to pay. However, our uncertainty analysis suggested that commensurately high coverage may 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 (that is, that the R_0 of rabies was close to 1 in Ngorongoro). Near this threshold, even small shifts in the transmission variables that we drew from the variable distributions in our probabilistic analysis could significantly impact the coverage necessary to curtail transmission. However, the discrepancy between the probabilistic and deterministic results could be related to the exclusion of variable combinations that led to R_0 values less than 1. Their exclusion may have generated an average R_0 in the uncertainty analysis that would be greater than the value used in the base case and hence may elevate predictions of optimal-coverage vaccination campaigns in the uncertainty analysis. In addition, the empirical distributions of the transmission variables from which we drew were wider for Ngorongoro than for Serengeti, a result of the smaller sample size of rabies in Ngorongoro (9). Therefore, there was 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 economic and public health perspectives.

Our model estimated the costs of vaccination campaigns over a wide range of coverage, but the original data were collected in association with a few specific coverage levels for each district. We assumed the most likely scenario that costs accumulated linearly between start-up and the observed coverage achieved by central-point campaigns, but many factors could have affected the assumption of linearity. For example, if the cost structure varied for vaccination campaigns achieving coverage less than what we saw, the optimal coverage may have differed from our predictions for low willingness-to-pay values. Likewise, the cost structure at very high coverage was unknown empirically because these costs were also estimated but not actually observed. However, neither limitation affects the general conclusion of our results, which was that canine vaccination campaigns achieving 70% coverage or higher were very cost-effective for both districts.

The World Health Organization Commission on Macroeconomics and Health recommends that interventions that confer disability-adjusted life-years (life-years, in the case of rabies) at an incremental cost less than the national per capita GDP ($1430 for Tanzania) or 3 times that GDP ($4290) be considered "very cost-effective" or "cost-effective," respectively (13). Although these guidelines are considered simplistic (30), they are among the more stringent criteria and most typically used. The World Health Organization's Choosing Interventions That Are Cost-Effective program recommends threshold criteria at $2154 and $6461 per disability-adjusted life-year for very cost-effective and cost-effective interventions, respectively, for Africa Region E, of which Tanzania is a part (14). Our analysis provides the incremental cost-effectiveness ratios across a large range of feasible coverage scenarios, including all of these thresholds, equipping policymakers with the information necessary to select among these criteria on the basis of their priorities and the incremental benefits of competing health programs.

To our knowledge, our study is the first to reveal that repeated annual canine vaccination against rabies may be cost-saving. We found that even high-coverage annual vaccination campaigns in Serengeti were cost-saving relative to PEP alone within the first year. This is a more rapid recouping of expenditure than predicted in an urban setting (8) or from static models that do not incorporate transmission (31). In N'Djaména, Chad, the canine density is 3 times that in Serengeti and more than 10 times that in Ngorongoro (8), 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 1-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 (32, 33). 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 persons who had been bitten by confirmed rabid dogs and found that only 456 (65%) of them received PEP (22). Without PEP, 19% of persons who are bitten die of rabies (24). Lack of education about rabies, distance from the nearest clinic, and an inability to afford the fees contribute to imperfect rates of PEP administration (22). In addition, clinics do not always have PEP in stock, immunoglobulin is nearly inevitably absent (22, 34), and dog owners may be mistaken about the vaccination status of their dog (22). Although improved access to PEP is itself cost-effective (24, 35), we found that canine vaccination would remain cost-effective even if PEP were more accessible (**Figures 5** and **6** of **Supplement 1**).

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. Although herd immunity indicates the coverage at which vaccination will ultimately control rabies, greater coverage controls rabies even faster and likewise averts further human cases earlier. Additional coverage is inexpensive relative to the cost of PEP and willingness-to-pay thresholds. Therefore, optimal coverage even at the lowest willingness-to-pay threshold is greater than herd immunity alone may suggest.

In our current vaccination trials in Tanzania, every dog that is 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 approximately 15% over a decade in both districts by eliminating these repeated vaccinations. This suggests that a vaccination campaign may achieve significant savings by investing in record-keeping practices, marking dogs, 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 PEP postexposure 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 previous 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.

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Appendix: Site Description

Ngorongoro District is 14 036 km^2, with 39 villages and a human population of 174 273. The inhabited area of Serengeti District (excluding Serengeti National Park and Game Reserves) is 3373 km^2 (**Figure 1** of **Supplement 1**), with 40 villages and a human population of 249 420. The ethnic diversity in Serengeti and Ngorongoro is representative of agro-pastoral and pastoral communities in sub-Saharan Africa. There are broad similarities among traditional rural African communities in terms of dog ownership (36), rabies infection dynamics (17), and health-seeking behaviors.

The basic reproduction number for rabies, R_0, was estimated in a previous study to be 1.24 for Ngorongoro and 1.18 for Serengeti, with a greater contribution to transmission from wildlife in Ngorongoro compared with Serengeti (9). Canine densities are 1.5 and 9.5 dogs per square kilometer for Ngorongoro and Serengeti Districts, respectively (17), which are similar to other regions of rural sub-Saharan Africa (20, 37).

Model Parameterization

The values and distributions of model variables were derived from our field data and published literature (**Table 2** of **Supplement 2**). Because rabies transmission is not sensitive to demography of wild carnivores (**Table 3** of **Supplement 2**), we used rates equal to those for dogs as a plausible range. Carrying capacity (K) for dogs was governed by human ownership preferences. Thus, we assigned K as the measured densities in the region, noted previously. On the basis of night transects, the estimated density in Ngorongoro was 4.5 wild carnivores per square kilometer and 3.0 wild carnivores per square kilometer in Serengeti.

Rabies transmission rates between and among dogs and wild carnivores were estimated previously (9). These rates were estimated for a "worst-case" vaccination scenario, in which the killing or restraint of rabid dogs is not practiced. However, such rabid dog removal practices are common in Tanzania and are part of the environment in which we were evaluating canine vaccination. Therefore, we have recalculated rabies transmission rates to take rabid dog removal into consideration for our baseline analysis (**Table 4** of **Supplement 2**). As the practices of rabid dog removal may change over time, we also examined the effectiveness and cost-effectiveness of canine vaccination in a situation where humans did not remove rabid dogs from the transmission cycle. The term β_{ij} describes the effective contact rate between host types in our transmission model and is calculated from the rates in **Table 4** of **Supplement 2** using $\beta_{ij} = k_{ij}{}^{*}\alpha/d_i$, where $1/\alpha$ is the infectious period of rabies and d_i indicates the density of host i.

Dog owners often bring the same dog to be vaccinated year after year. In the field, we routinely vaccinate all dogs that attend a vaccination station because it is difficult and time-consuming to distinguish between naive and previously vaccinated dogs. This practice also ensures that a simple message can be communicated during advertising campaigns. In the model, we assumed that all dogs in the vaccinated class received a "repeated" vaccine and that an additional proportion of unvaccinated dogs received their first vaccine to achieve the target coverage. This representation was conservative and, if anything, imposed additional costs on the vaccination programs without providing additional population coverage. A more efficient program may include a system to encourage owners to bring a dog for vaccination only once every 3 years. To explore the potential benefits of such a program, we compared the costs of the current programs in Tanzania with those of a program only vaccinating previously unvaccinated dogs.

Given the status quo that dogs are revaccinated annually and that clinical trials have shown that complete vaccine efficacy lasts for at least 3 years (38), we assumed that vaccine efficacy did not wane between campaigns. We considered 10 years of annual vaccination campaigns and coverage in 5% increments ranging from no canine vaccination to 95% coverage. We did not consider complete coverage, given that a very small percentage of dogs (less than 5%) are considered feral or inaccessible (18, 39). Although these dogs are theoretically able to be vaccinated using oral baits or more expensive traps, these methods are unlikely to be employed in rural Africa in the near future. Given that mass canine vaccination is not currently standard practice in this region, our baseline for comparison is no vaccination.

Model Analysis and Uncertainty

Model development and uncertainty analysis were coded in R (R Foundation for Statistical Computing, Vienna, Austria). In our base-case analysis, we used the central estimates for each variable. To define initial conditions, we ran the model scenario without vaccination to steady state. To evaluate uncertainty and make probabilistic predictions of cost-effectiveness according to different levels of willingness to pay, we made 10 000 random draws from the distribution for each epidemiologic and demographic variable, as determined from empirical data we have previously published or analyzed in the Methods section (**Table 2** of **Supplement 2**). We then ran the deterministic model with each set of variables, generating 20 vaccination scenarios (0% to 95% in 5% increments) for each of the 10 000 variable combinations.

In some cases, the combination of transmission variables drawn led to an R_0 less than 1, such that rabies would not persist even in the absence of intervention. However, given that rabies has persisted in the region for several decades, these combinations of variables were taken to be unrealistic and excluded from the cost-effectiveness analysis. In total, 3859 combinations were discarded for Ngorongoro and 14 combinations for Serengeti. The wider CIs for the Ngorongoro variables, the result of a smaller sample size, are largely responsible for this difference between districts (9).

Costs of Vaccination

Both total costs and costs per dog increase nonlinearly with increasing vaccination coverage. Start-up expenses of vaccination campaigns increase the per-dog costs for low vaccination coverage. Conversely, if a high coverage has been achieved through a central-point strategy, it is very costly to reach even higher levels through supplementary vaccination efforts. The average startup cost (transportation and personnel) for a central-point campaign was estimated at $187.50 per village. Then, the cost per dog was estimated to be that of consumables, $0.65 per dog, up to the coverage shown to be achieved by the central-point campaign, which was 80% for Serengeti and 20% for Ngorongoro (18). Therefore, in Serengeti, the average cost per dog was $1.73 at a coverage of 70% (18). The marginal cost of vaccinating additional dogs increased linearly to a maximum of $9.50 per dog in the interval between 90% and 95%. These search costs were the estimated costs from transport and personnel of traveling house-to-house between homesteads on the outskirts of a village. For Ngorongoro, central-point vaccination alone achieved 20% coverage at an average cost of $5.55 per dog (18). As effort was made to expand coverage, the addition of the more expensive door-to-door vaccination strategy was required, costing approximately $3.40 per dog up to 85% coverage. At 85% coverage, these factors combined to give an overall cost of $4.07 per dog (18). Additional search costs to achieve coverage greater than 85% were then estimated as for Serengeti.

Estimation of Human Biting Rate

Data collected through contact tracing of all rabies cases detected from January 2002 through December 2006 (16, 17) were used to estimate the average number of humans bitten by each rabid dog. All animal-bite injuries reported in hospitals and clinics in the region, as well as suspect rabid animals reported at livestock offices or through community-based surveillance, were investigated. Surveys were conducted to identify the source of exposure and subsequent contacts with animals and humans. Cases were diagnosed through epidemiologic and clinical criteria, and brain samples were collected whenever possible. Brain samples were not collected in most cases, but more than 75% of tested samples were confirmed positive, indicating the robustness of the clinical and epidemiologic criteria (16). From these data, we estimated that a single rabid dog bit an average of 0.51 humans.

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