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Where and when to vaccinate? Interdisciplinary design and evaluation of the 2018 Tanzanian anti-rabies campaign

Folorunso O. Fasina[a,*], Niwael Mtui-Malamsha[a], Gladys R. Mahiti[b,c], Raphael Sallu[a], Moses OleNeselle[a], Bachana Rubegwa[a], Yilma J. Makonnen[a], Fred Kafeero[a], Martin Ruheta[d], Hezron E. Nonga[d], Emmanuel Swai[d], Selemani Makungu[d], Japhet Killewo[b,c], Edward G. Otieno[c,e], Athumani M. Lupindu[c,e], Erick Komba[c,e], Robinson Mdegela[c,e], Justine K. Assenga[d,f], Jubilate Bernard[f,g], Mohamed Hussein[b,c], Walter Marandu[h], James Warioba[i], Eliona Kaaya[j], Pius Masanja[j], Gundelinda Francis[j], Violet M. Kessy[k], Janique Savy[l], Hija Choyo[a], Justus Ochieng[m], Almira L. Hoogesteijn[n], Margaret M. Fasina[o], Ariel L. Rivas[p]

[a] *Food and Agriculture Organization of the United Nations, Dar es Salaam, United Republic of Tanzania*
[b] *Muhimbili University of Health and Allied Sciences, United Republic of Tanzania*
[c] *One Health Central and Eastern Africa, Eastern Africa, United Republic of Tanzania*
[d] *Ministry of Livestock and Fisheries, Dodoma, United Republic of Tanzania*
[e] *Sokoine University of Agriculture, Morogoro, United Republic of Tanzania*
[f] *One Health Coordination Desk, Prime Minister's Office, Dodoma, United Republic of Tanzania*
[g] *Ministry of Health, Community Development, Gender, Elderly and Children, Dodoma, United Republic of Tanzania*
[h] *District Veterinary Office, Moshi District, United Republic of Tanzania*
[i] *Zonal Veterinary Center, Arusha, United Republic of Tanzania*
[j] *Tanzania Veterinary Laboratory Agency, Dar es Salaam, United Republic of Tanzania*
[k] *Tanzania National Parks Authority, Same, United Republic of Tanzania*
[l] *Unit of Geoinformation and Mapping, University of Pretoria, Pretoria, South Africa*
[m] *AVRDC – The World Vegetable Center, Eastern and Southern Africa, Arusha, United Republic of Tanzania*
[n] *Human Ecology, Centro de Investigación y de Estudios Avanzados (CINVESTAV), Mérida, Yucatán, Mexico*
[o] *Department of Nursing Science, University of Pretoria, Pretoria, South Africa*
[p] *Center for Global Health, School of Medicine, University of New Mexico, Albuquerque, NM, USA*

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ABSTRACT

Objectives: Hoping to improve health-related effectiveness, a two-phase vaccination against rabies was designed and executed in northern Tanzania in 2018, which included geo-epidemiological and economic perspectives.
Methods: Considering the local bio-geography and attempting to rapidly establish a protective ring around a city at risk, the first phase intervened on sites surrounding that city, where the population density was lower than in the city at risk. The second phase vaccinated a rural area.
Results: No rabies-related case has been reported in the vaccinated areas for over a year post-immunisation; hence, the campaign is viewed as highly cost-effective. Other metrics included: rapid implementation (concluded in half the time spent on other campaigns) and the estimated cost per protected life, which was 3.28 times lower than in similar vaccinations.
Conclusions: The adopted design emphasised local bio-geographical dynamics: it prevented the occurrence of an epidemic in a city with a higher demographic density than its surrounding area and it also achieved greater effectiveness than average interventions. These interdisciplinary, policy-oriented experiences have broad and immediate applications in settings of limited and/or time-sensitive (expertise, personnel, and time available to intervene) resources and conditions.

* Corresponding author at: FAO ECTAD Tanzania & Department of Veterinary Tropical Diseases, University of Pretoria, Pretoria, South Africa.
E-mail address: Folorunso.fasina@fao.org (F.O. Fasina).

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Introduction

Interdisciplinary approaches have been recommended to prevent epidemics (Rushton et al., 2018). The simultaneous consideration of bio-geo-demographic-temporal interactions in the design of epidemiologic policies could improve the bio-economic impact of such policies (Masiira et al., 2018). Furthermore, local geo-referenced and temporal data could unmask dynamic and complex relationships that influence disease dissemination (Rivas et al., 2010, 2012). For instance, investigations of the biogeography associated with rabies could detect factors that promote epidemic spread as well as barriers that prevent dissemination (Smith et al., 2002). Recent studies conducted with wildlife species have identified where vaccinations against rabies are more likely to be beneficial (Resnik et al., 2018). Because delayed interventions tend to be less effective and costlier, estimating when is the optimal (or critical response) time to intervene also requires geographical data (Rivas et al., 2003). Geo-referenced data have been used in rabies-related research since 2005 (Suzuki et al., 2007).

These considerations set the stage to review, propose and evaluate interventions that optimally control rabies outbreaks that affect humans. Rabies is one of the top 13 diseases of worldwide prevalence, causing more than 59,000 annual deaths and up to five times more deaths than Ebola virus (Cleaveland et al., 2017). The mortality induced by rabies may exceed 75% in infected and symptomatic humans and takes place, on average, within 5 days (Hemachudha et al., 2002). While post-exposure treatments are not always effective, some preventive interventions have been highly successful (Cleaveland et al., 2017).

Vaccinations of domestic dogs are, arguably, the best known prevention. They rapidly reduce the number of human deaths attributed to the rabies virus (Cleaveland et al., 2017). In Malawi, the number of rabies-related human deaths reported after vaccination decreased 11-fold between 2012–2015 (22 cases) and 2015–2016 (two cases, Zimmer et al., 2018). In Guangxi, China, the human incidence of rabies after a vaccination declined from 1.08 in 2007 to 0.09 in 2017, that is a 12-fold reduction (Wei et al., 2018). The Chinese success was associated with an explicit analysis of geo-referenced data – particularly case density (Guo et al., 2013).

In addition to medical and geo-referenced considerations, evaluations of vaccination campaigns may consider economic dimensions. Years of life gained (YLG) is an established metric that could assess rabies-related dynamics (Undurraga et al., 2017). If linked to the per capita national gross domestic product (GDP), YLG could estimate the temporal benefits of health policy on the national economy. Disability-adjusted life years (DALYs) is a similar concept. In rabies, life-years coincide with DALYs because, given that rabies is inevitably fatal, the entire health burden accrues from deaths rather than illnesses (Coleman et al., 2004). DALYs saved reflect the reduced burden of disease as a result of a public health intervention. For example, a 100% effective vaccination implemented in Tanzania at a nationwide level is expected to save 42,669 life-years (Coleman et al., 2004). The cost-effectiveness ratio (CER) is a metric that facilitates the economic comparison of health-related interventions between and within countries. The CER estimates the cost of the intervention in reference to (divided by) the national GDP: CERs less than unity are regarded as very cost-effective. When the CER is >1 but lower than the triple of the national GDP per inhabitant, the intervention is deemed 'cost-effective'. The intervention is regarded as 'not cost-effective' when the cost exceeds the triple of the national GDP per person (Hutubessy et al., 2003).

However, GDP-based analyses emphasise costs not benefits and, therefore, such evaluations may undervalue the impact of vaccinations (Bärnighausen et al., 2014). For example, models that assume the force of infection is static will underestimate the temporal benefits of immunisation programs (Wilder-Smith et al., 2017). To compensate such limitations, benefit-cost analyses have been proposed, which capture many and long-term benefits generated by public health such as: improved educational development, economic growth, reduced demographic growth, and reduced crime (Bärnighausen et al., 2014). Contemporary evaluation designs also assess efficacy (direct effects of health outcomes), effectiveness (direct and indirect effects of health outcomes in individuals and communities), and impact (health-related and non-health related effects, Wilder-Smith et al., 2017). Cost-benefit-oriented analyses differ from cost-effectiveness: while cost benefit calculates the monetary gain associated with increased health, cost-effectiveness estimates the cost per unit gained in health (e.g. the cost of quality-adjusted life years) (Black, 2013).

Therefore, at least six types of evaluations can estimate the cost or benefit of vaccinations against rabies: (1) studies that estimate costs without analysing geo-demographical data, epidemiologic theory, and/or benefits (e.g. those previously promoted by WHO-CHOICE) (Hutubessy et al., 2003); (2) those that consider outcomes (e.g. the cost per life protected) (Elser et al., 2018); (3) cost-centered investigations adjusted to case density (Guo et al., 2013); (4) costs measured over time (Zinsstag et al., 2009); (5) studies that estimate benefits (e.g. those that calculate the number of prevented cases) (Zimmer et al., 2018) and those that focus on benefits that exceed health (Undurraga et al., 2017); and (6) geo-temporal investigations of epidemic dynamics (e.g. those aimed at assessing the benefit of earlier interventions when they are implemented at critical geographical sites) (Rivas et al., 2012).

To test whether a highly multidimensional and interdisciplinary approach can induce better benefits (faster implementation, lower monetary cost and greater prevention), this study evaluated the impact of a vaccination against rabies that took place in 2018 in the Moshi Rural District of Tanzania. The intervention considered One Health concepts (Cleaveland et al., 2017), as well as: (i) interactions between wildlife reservoirs of the virus and humans (Smith et al., 2002; Guo et al., 2013); (ii) the biogeographical diversity of the Mt. Kilimanjaro region, inhabited by at least 154 mammal species that may act as reservoirs of the rabies virus (Grimshaw et al., 1995); (iii) the demographic density of the city of Moshi, not yet affected by the outbreak but geographically close to it, which if infected could require almost 10 times more time and other resources before an epidemic was controlled; and (iv) applications of Network Theory – in particular, measures likely to disrupt the epidemic connectivity (Rivas et al., 2010, 2012). To be effective, it was assumed that the policy to be adopted should protect the city of Moshi without a direct intervention within that city. Otherwise, resources could be rapidly depleted and the campaign would fail.

Consequently, the effectiveness of the 2018 Tanzanian vaccination against rabies was evaluated along three dimensions: time, cost and prevention (decreased numbers of rabies-related human cases). While time and cost can be easily determined with classic metrics, prevention is the consequence of theories and goals being integrated into operations. Here, the hypothesis that a geo-referenced approach that considers where an epidemic may be going and how costly it may become (i.e. determining where and when to vaccinate may influence results) was tested.

Material and methods

Chronology on field reports and responses

On 15 March 2018, the Moshi District Veterinary Office informed the Arusha Zonal Veterinary Centre of outbreaks

of rabies in humans and animals located in the Moshi rural district. The next day, the Tanzanian Ministry of Livestock and Fisheries and the Tanzanian Representation of the Food and Agriculture Organization received those reports, and an additional report from the District Medical Office, which revealed a total of 168 humans bitten by rabid-suspected dogs over 15 consecutive months (January 2017–March 2018; median: 11.2 cases/month; Mtui-Malamsha et al., 2019).

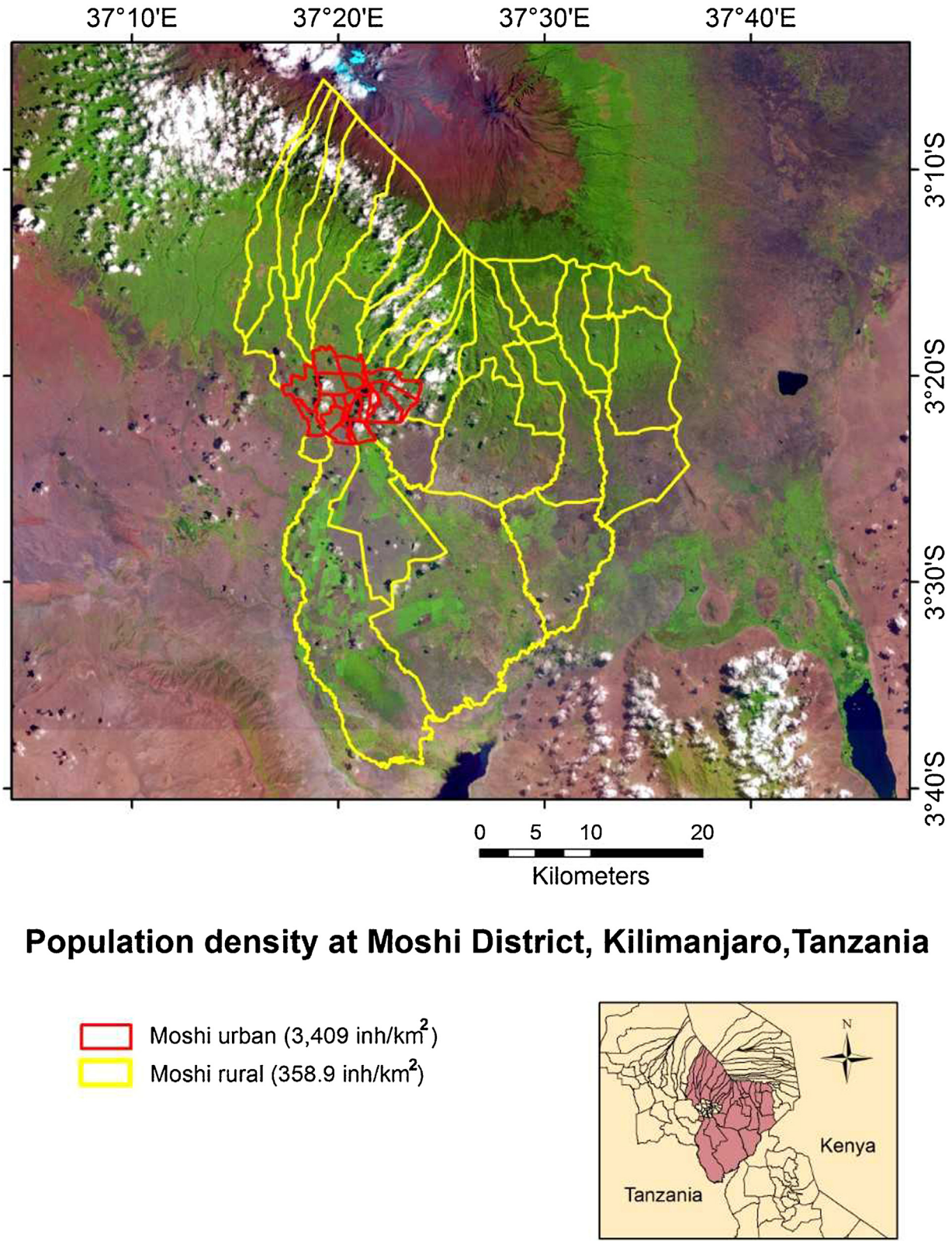

Figure 1. The bio-geo-demographic context. A map of the Moshi region in northern Tanzania is displayed. It includes an underlying satellite photo of Mt. Kilimanjaro, on the northern edge. A red contour identifies the city of Moshi. The rabies outbreak was reported at and controlled within the rural area of the Moshi district, identified by a yellow contour.

The bio-geographical context

Located within the Kilimanjaro Region, the Moshi rural district was inhabited by 509,431 people in 2017. It is geographically contiguous to the city of Moshi, which was inhabited by 201,150 people in 2017 (Tanzania National Bureau of Statistics, Tanzania Total Population by District – Regions – 2016–2017, http://www.nbs.go.tz/; accessed 5 December 2018). Dogs suspected to be rabid

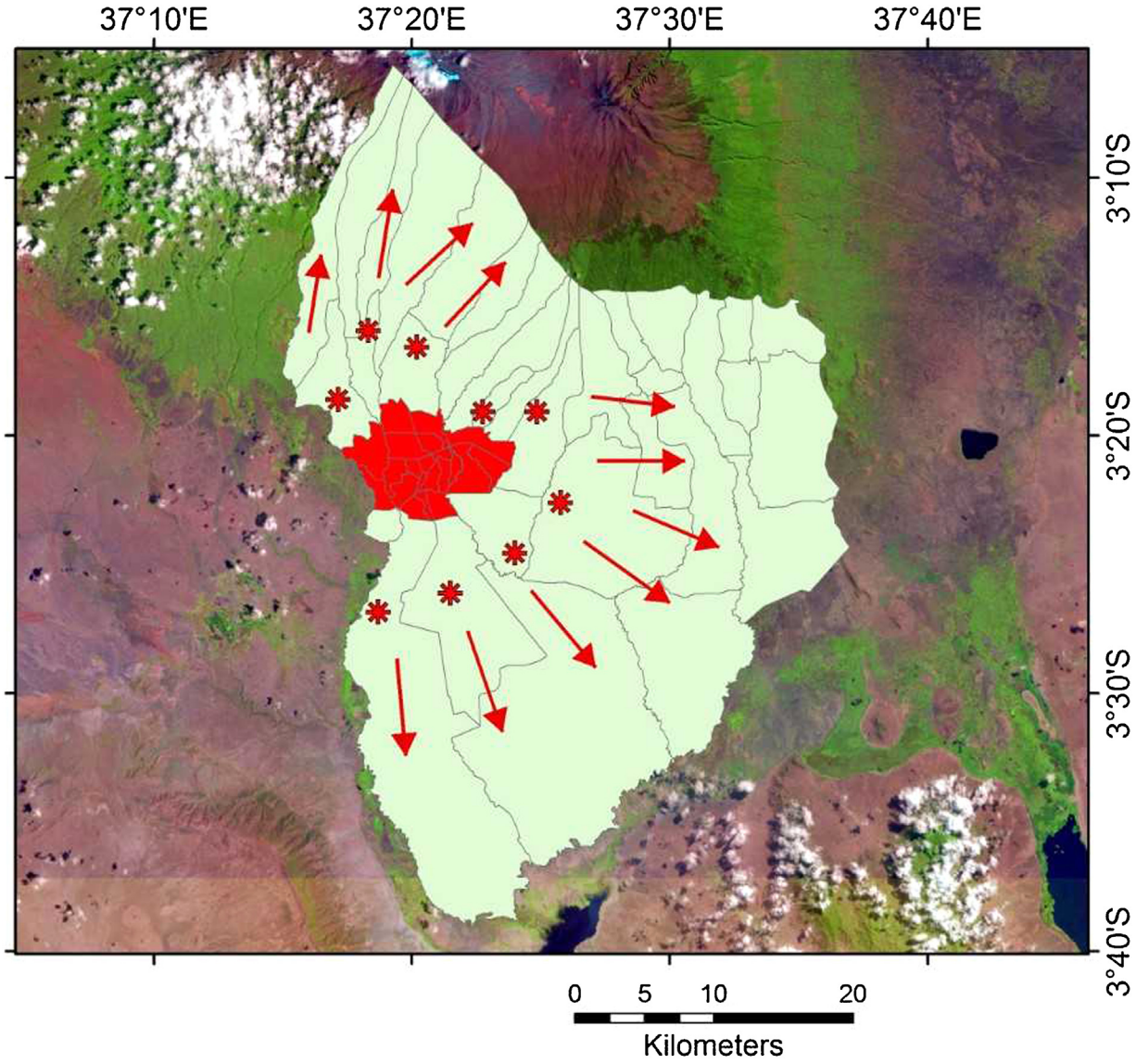

Figure 2. A two-step vaccination policy. A two-phase vaccination program was meant to: rapidly and at a low cost establish an immune ring around urban Moshi (red circles). The second vaccination phase was implemented later in more than 150 small villages located along the direction indicated by arrows.

Table 1
Intervention cost.

Intervention	Humans at risk	Immunised animals (dogs and cats)	Total cost of intervention	Cost/immunised animal	Cost/protected person
Tanzania, 2018	710,581	28,885	US$48,000	US$1.61	US$0.067
Tanzania, 2016[a]	10,224,015	–	US$2,271,668	–	US$0.222
Serengeti Tanzania	–	–	–	US$2.16[b]	
South Eastern Tanzania	–	–		US$5.40[c]	

[a] Elser et al. (2018).
[b] Kaare et al. (2009).
[c] Hatch et al. (2016).

were tested with the direct fluorescent antibody technique described elsewhere (OIE, 2018). The dog and cat populations in the rural Moshi districts were estimated at 26,712 and 13,390 animals, respectively (Department of Veterinary [Livestock] Development and Fisheries of the Moshi Rural District, Tanzania, personal communication).[1] Because mass dog and cat vaccination with a coverage ≥70% has been recommended to control rabies in human and non-human animals (Cleaveland et al., 2003), vaccine doses to reach a 80% vaccination coverage (or 32,082 of all 40,102 dogs and cats) were requested.

Personnel

All persons involved in the campaign had an updated rabies pre-exposure immunisation status, which met the 2014 *WHO Guide for Rabies Pre and Post Exposure Prophylaxis in Humans* (https://www.who.int/rabies/PEP_Prophylaxis_guideline_15_12_2014.pdf).

Logistics and funding

Economic support (US$48,000) was provided by USAID and managed by FAO, through the Global Health Security Agenda – Zoonotic Disease and Animal Health in Africa. Using the OIE Vaccine Bank (Boehinger Ingelheim, Lyon, France), 33,700 doses of canine rabies vaccine with expected potency over 104 weeks arrived in Tanzania 41 days after the initial report was made. To develop a context-specific intervention, several meetings were held in three Tanzanian cities, over 6 weeks (15 March–26 April 2018), which involved many national and international agencies.

Disease mapping

Bio-geo-referenced maps were built using a geographical software package (ArcGIS 10.1, ESRI, Redlands, CA, USA), as well as satellite pictures collected from a public source (http://landsatlook.usgs.gov/, accessed 02 July 2019) and shapefiles created by the Tanzanian National Bureau of Statistics (http://www.nbs.go.tz/, accessed 04 July 2019). All bio-geo-referenced maps were built at CINVESTAV (Mérida, México). Maps included natural barriers (e.g. the location of Mt. Kilimanjaro, seen on the northern edge of the map, Figure 1) and an urban area (the city of Moshi, indicated by a red contour, located on the centre of the map, Figure 1). Mt. Kilimanjaro provides abundant water to its surrounding area, generating a densely vegetated region occupied by about 200 mammalian species that may carry the rabies virus. Over 200 villages exist on the southern edge of the area. The area closer to Mt. Kilimanjaro and outside the city of Moshi (yellow contour, Figure 1) has a demographic density 9.5 times lower than the city of Moshi (3409 vs. 358.9 inhabitants/km^2, respectively).

Policy mapping

A two-phase vaccination program was created. The first vaccination phase took place over 5 days (29 April–04 May 2018) in a few sites of the Moshi rural district, where 7758 animals (6701 dogs and 1057 cats) were vaccinated. The vaccination was implemented in a 'ring' or 'containment wall' established around urban Moshi (red circles, Figure 2). By vaccinating around but outside the city of Moshi, dissemination of the virus was disrupted. Then, after the vaccination ring was completed, further vaccinations were implemented in >150 small villages located along the direction indicated by the arrows shown in Figure 2.

Scenario analysis

Two scenarios were compared. The first one assumed no delayed or false-negative reporting (i.e. a high-impact vaccination, which prevented 11.2 (168/15) human cases/month after the intervention). The second scenario assumed a lower impact: one case prevented/month after the vaccination.

Variables used in cost-effectiveness and impact analyses

Years of life gained (YLG (Undurraga et al., 2017)) were calculated by subtracting the median age from life expectancy. Disability-adjusted life years (DALYs) was estimated as described elsewhere (Coleman et al., 2004).

Results

The two phases of the emergency vaccination were implemented over 4 months (30 April–31 August 2018) – a period in which 74.5% of domestic dogs and cats (29,885 animals) were vaccinated at a total cost of US$48,000. No rabies-related human, dog or cat cases were reported in Moshi in the first year after this intervention was completed.

This campaign was initiated 6 weeks (42 days) after the initial report was received by the national authorities. In contrast, a simulation on a similar campaign estimated that vaccinations start 13 weeks after the disease was recognised (Wera et al., 2017). When the cost/immunised dog was considered, the 2018 campaign showed a 23–69% lower cost/vaccinated animal than previous interventions conducted in Tanzania (Table 1).

Because 710,581 people (509,431 inhabiting the rural and 201,150 living in the urban Moshi districts) were at risk and the total monetary cost of the intervention was US$48,000, the cost per protected person (CPPP) was 6.7 cents of a US dollar (48,800/710,581). Thus, the 2018 strategy was 3.28 times less costly than a previous vaccination conducted in Tanzania, which resulted in a CPPP equal to 22 cents (2,271,668/10,224,015, Table 1). However,

[1] As a result of this study, the Ministry of Livestock and Fisheries (MoLF) is currently developing a dedicated website site that will include all rabies and dog bite-related data reported in Tanzania.

Table 2
Case density before and after the intervention.

Region	Area (km^2)	Cases before intervention	Pre-intervention cases/km^2	Cases after intervention	Post-intervention cases/km^2	Pre-intervention/ post-intervention ratio
Moshi	1713	134	0.07823	0	0	∞
Malawi[a]	118,000	10	0.0000847	1	0.00000847	10
Guangxi[b]	236,700	602	0.00254	41	0.000173	14.68

[a] Zimmer et al. (2018).
[b] Guo et al. (2013).

Table 3
Benefit-cost analysis (high-impact scenario).

Date	Benefit (A) Cases prevented by vaccination	Benefit (B) Median years of healthy life gained (YLG) or 44.9* cases prevented by vaccination	Monthly cost (C) (US$48,000/cases prevented by vaccination)	Net long-term benefit (D) YLG-related per capita GDP ([US$936*B] minus cost (US$48,000)
May 2018	11.2*	502.88 YLG	US$4285.71	US$422,695.68
June 2018	22.4	1005.76 YLG	US$2142.85	US$ 941,391.36
July 2018	33.6	1508.64 YLG	US$1428.57	US$1,364,087.04
August 2018	44.8	2011.52 YLG	US$1071.42	US$1,834,782.72
September 2018	56	2514.4 YLG	US$857.14	US$2,305,478.40
October 2018	67.2	3017.28 YLG	US$714.28	US$2,776,174.08
November 2018	78.4	3520.16 YLG	US$612.24	US$3,246,869.76
December 2018	89.6	4023.04 YLG	US$535.71	US$3,717,565.44
January 2019	100.8	4525.92 YLG	US$476.19	US$4,188,261.12
February 2019	112	5028.8 YLG	US$428.57	US$4,658,208.00
March 2019	123.2	5531.68 YLG	US$389.61	US$5,129,652.48
April 2019	134.4	6034.56 YLG	US$357.14	US$5,600,348.16

* Based on records from the previous 15 months, it was estimated that 11.2 human cases were prevented per month after the vaccination.

the cost per protected person does not inform on the size of the challenge being addressed by the intervention. An alternative indicator is the case density ratio, which describes the number of cases reported before and after an intervention, as shown in Table 2.

Temporal data can also improve the metrics used in evaluations. Because no rabies-related case has been reported since completion of the first phase of the vaccination and in the previous 15 months an average of 11.2 monthly human cases were reported, the monthly adjusted cost per prevented case has diminished from US $4285 (May 2018) to US$357 (April 2019, Table 3).

Because the benefit already achieved (April 2019) is estimated at 134.4 prevented cases (11.2 cases/month × 12 months) and the median age in Tanzania is 17.7 years, while life expectancy is 62.6 years (http://worldpopulationreview.com/countries/tanzania-population/, accessed 02 December 2018), it may be concluded that 6034 years of healthy and productive life (44.9 years [62.6–17.7] × 134.4 healthy lives) have already been saved (Table 3). Considering that Tanzania's national GDP per capita, in current US$, is $936, the net societal gains associated with 134.4 people expected to live 44.9 more years of a healthy life were estimated (as of April 2019) at US $5,600,348.16 (Table 3). Therefore, the geo-referenced and dynamic assessment revealed that the cost diminished exponentially over time, while benefits increased linearly (Figure 3). If, instead, a lower impact was assumed – a policy that would prevent one case/month – the overall benefit for society would represent US$456,316 over 44.9 years (Table 4).

With the exception of the first month after completion of the vaccination (when the cost exceeded the long-term benefits), even a low-impact policy would be beneficial. Yet, this assessment is conservative: it assumes that no new cases will be prevented after April 2019 when, in fact, the vaccine administered in 2018 may protect for up to 24 months.

As a comparison, the cost-effectiveness ratio (CER) of a nationwide campaign was calculated. To that end, the cost per

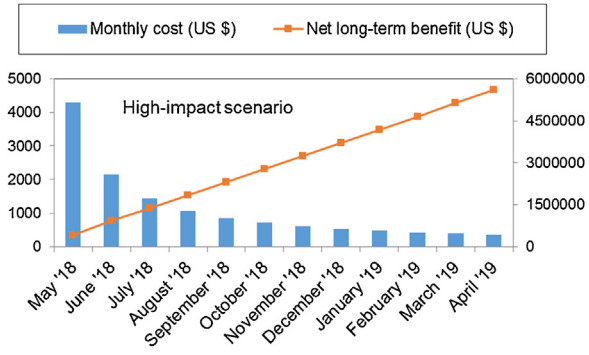

Figure 3. Benefit-cost analysis under a high-impact assumption. Costs were estimated by dividing the total cost of the intervention (US$48,000) by the number of cases prevented at a specific time point. Long-term net benefits were estimated by multiplying the national GDP per capita (US$936, in this case) times the number of years gained by preventing rabies cases and then subtracting the total cost of the intervention. Here it was assumed that 11.2 human cases would be prevented each month by the vaccination. This was a high-impact assumption, which presupposed that no case or rabies-related death was unaccounted for. It is shown that the costs decreased exponentially, while the gains increased linearly. Benefits, at all times, exceeded the cost of the intervention.

DALY saved was estimated under two hypotheses of vaccination efficacy and divided over the Tanzanian per capita GDP (US$936). While the 100% vaccination efficacy hypothesis (100% reduction in the number of cases reported) resulted in a CER equal to 0.01, a vaccination assumed to be 1% efficacious was still below unity (CER: 0.75, Table 5) (Figure 4).

Discussion

In the Philippines, the cost of preventing a human case has been reported to be between 1498 and 1621 US$ (Miranda et al., 2017).

Table 4
Benefit-cost analysis (low-impact scenario).

Post-vaccination month	Benefit (A)	Benefit (B) (44.9 years*A)	Monthly cost (C) (US$48,000/A	Net long-term benefit (D) (US$936)*B minus cost [US$48,000])
May 2018	1	44.9	US$48,000	– US$5,973.6
June 2018	2	89.8	US$24,000	US$36,052.8
July 2018	3	134.7	US$16,000	US$78,079.2
August 2018	4	179.6	US$12,000	US$120,105.6
September 2018	5	224.5	US$9600	US$162,132.0
October 2018	6	269.4	US$8000	US$204,158.4
November 2018	7	314.3	US$6857	US$246,184.8
December 2018	8	359.2	US$6000	US$288,211.2
January 2019	9	404.1	US$5333	US$330,237.6
February 2019	10	449	US$4800	US$372,264.0
March 2019	11	493.9	US$4363	US$414,290.4
April 2019	12	538.8	US$4000	US$456,316.8

Table 5
Estimated cost-effectiveness of a nationwide Tanzanian rabies vaccination.

DALYs lost per year[a]	42,669 lives
DALYs saved due to a 100% effective vaccination	42,669 lives
DALYs saved due to a 1% effective vaccination, nationwide	426.69 lives
Cost per DALY saved per year, with a 100% effective vaccination (US$)[b]	$7.07
Cost per DALY saved per year, with a 1% effective vaccination (US$)[b]	$706.56
Cost-effectiveness ratio (CER) with a 100% effective vaccination[c]	0.01 (1% of the annual Tanzanian GDP per capita)
Cost-effectiveness ratio (CER) with a 1% effective vaccination[c]	0.75 (3/4 of the annual Tanzanian GDP per capita)

[a] Disability-adjusted life years (DALYs) corresponding to Tanzania, as estimated by Coleman et al. (2004).
[b] The annual cost per DALYs saved is determined by dividing the cost of a vaccination campaign over the number of DALYs saved. The numerator (cost of a nationwide campaign) is estimated as the cost of reaching 2% of the 9,362,758 Tanzanian households assumed to be affected by rabid dogs, when the total cost/vaccination (including administration costs) is US$1.61 or $301,481(9,362,758*2%*1.61). When a vaccination is 100% effective over a year, 42,669 could be saved in Tanzania (i.e. the cost per saved life is $7.07 (301,481/42,669).
[c] The cost-effectiveness ratio (CER) of such an intervention is determined by dividing the annual cost per DALY saved over the Tanzanian Gross Domestic Product (GDP) per capita (US$936 in 2018 (World Bank, 2018)). The CER is 0.01 (7.07/936) or 0.75 (706.56/936), depending on whether 100% or 1% vaccine efficacy is considered. In both scenarios, the CER is very cost-effective: it is below unity. Because it is less costly to save a life potentially lost due to rabies than the (smallest) economic product that person is expected to generate, it is not only morally and socially needed but also economically justified. Because, over time, the economic product a person generates tends to increase, the actual benefit is much larger and more multidimensional than portrayed by this ratio. Even if the geo-referenced and dynamic considerations were not applied and a vaccination applied to cover the entire country, it would still be very cost-effective.

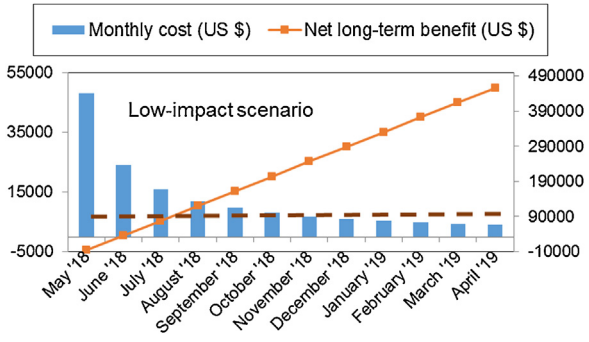

Figure 4. Benefit-cost analysis under a low-impact assumption. Impacts were also estimated assuming that one human case would be prevented each month by the vaccination. It is shown that the costs decreased exponentially, while the gains increased linearly. The horizontal line shows the breakeven point (no net gain). With the exception of the first month after completion of the vaccination (May, 2018), benefits exceeded the cost of the intervention.

In Haiti, the corresponding cost has been $3534–7171 (Undurraga et al., 2017). While not considering bio-geo-temporal conditions, econometric studies on cost-effectiveness have predicted that with a 50% vaccination coverage, the cost/life saved may be as low as $385–451 (Borse et al., 2018). In contrast, in the intervention conducted in northern Tanzania with a higher (70%) vaccination coverage, the cost per averted case, as of April 2019, was US$357 (Table 3). Yet, this cost is likely to experience a further decrease because the vaccine utilized in 2018 may protect for up to 2 years. Findings also appeared to be less costly or more beneficial than those of previous campaigns or simulations (Zinsstag et al., 2009; Kaare et al., 2009; Hatch et al., 2016; Elser et al., 2018). Even if its coverage was 1%, a hypothetical nationwide vaccination with a similar cost would be regarded as 'very cost-effective' (Table 5).

One possible reason for the high cost-effectiveness of the 2018 Tanzanian policy is that its vaccination did not take place within the area with the highest demographic density. While it is factually correct that vaccination costs tend to be lower in areas of higher demographic density (Elser et al., 2018), that is only so when the data are constant or static. When the data changes over time – as in actual epidemics – the local bio-geography influences dynamics (Rivas et al., 2010, 2012). When, instead of conducting interventions only within the area that displays the highest demographic density, vaccinations create an immunological barrier around – but not within – an urban area, the control strategy increases the demographic denominator (the number of people potentially protected) without increasing the numerator of the cost/protected population ratio (i.e. such a design may protect more people at a lower cost). By increasing the number of people to be protected with an intervention that initially only involved a few sites (the early vaccination ring), the 2018 policy created a 'containment wall' around the city of Moshi, which increased the demographic denominator in 39% (it added 201,150 people to the 509,431 people already identified at risk) and, consequently, reduced the cost of the intervention in a similar percentage. This is equal to, say, that intervening where the problem is observed, while apparently reasonable, is not necessarily the best

strategy: preventing where a larger problem might soon occur (creating a protective 'ring') may be even better.

However, economic considerations are only one way to estimate health-induced benefits. Estimations on the value of reducing threats to human and non-human life can also be conducted without a cost analysis (Ozawa et al., 2011). Other evaluation strategies compare case density before and after an intervention. For example, considering the area of the Guangxi province, in China (236,700/km^2), the number of deaths attributed to rabies in 2004 was 604 (Guo et al., 2013). Therefore, the Guangxi pre-vaccination case density was 0.00254 cases/km^2. In Malawi (118,000 km^2), 10 cases were reported in 2012 (or 0.0000847 cases/km^2, Zimmer et al., 2018). In Tanzania, 134 cases likely associated with rabies occurred in 2017 in the Moshi Rural District (1713 km^2), which corresponded to a pre-vaccination density equal to 0.07823 cases/km^2 (Table 2). Given these figures, it can be inferred that the 2018 Tanzanian campaign addressed a larger risk. Because it assessed the same environment, the pre-intervention/post-intervention indicator eliminated group-related variability. While the numbers shown in Table 2 should not be used to compare different campaigns – because the term 'case' may have different meanings in different places – they illustrate how future evaluations could simultaneously assess the cost and pre-intervention/post-intervention case density, providing more information than classic approaches.

Some evaluations of vaccinations against rabies have followed the Kermack and McKendrick (K & McK) model, which assumes that closed populations can be classified into three non-overlapping categories: (i) susceptible individuals, that is: those neither infected nor recovered (*S* category); (ii) infected and infectious individuals (i.e. those capable of transmitting the disease (*I* category)); and (iii) those previously infected and currently recovered, which do not disseminate the disease anymore (*R* category). The K & McK (also known as the SIR) model is known as SEIR when exposed (infected but not yet infectious) individuals are also considered (Zinsstag et al., 2009). When, in addition, vaccinated individuals are considered, the K & McK model includes five (*SEIVR*) classes (Wera et al., 2017).

The K & McK model is not geographically explicit and, therefore, it is not adjusted to the local biogeography. While the K & McK model assumes that populations are constant in number and homogeneously distributed in space, the geo-temporal distribution of canine rabies is heterogeneous (Suzuki et al., 2007). The geo-epidemiological-econometric model used here prevented those shortcomings (it captured the spatial heterogeneity of the population) and it was also compatible with economic evaluations based on the K & McK model. This study supports the view that nationwide vaccinations against the rabies virus can be very cost-effective (Hutubessy et al., 2003).

It is suggested that designs and evaluations that use biogeographic data may require interdisciplinary integration. It is argued that the first step toward less costly and more effective vaccination strategies is the creation of a novel academic program in Sub-Saharan Africa, which could include, at least, four groups of disciplines: (i) geographical information systems; (ii) One Health (human and veterinary medical approaches); (iii) economics; and (iv) computational skills relevant for the analysis of epidemic networks. By developing the skills and maps required to both make epidemiologic decisions and validate any technique or theory used in epidemiology, this interdisciplinary academic program could rapidly ameliorate major threats to public health such as rabies.

Disclaimer

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Author contributions

Conceptualization: FOF, NMM, WM, JW, HC, MR; Data curation: NMM, GRM, RS, ES, SM, EGO, AML, EK, JAA, JB, MH, WM, JW, ALH, MMF, ALR, FOF; Formal analysis: FOF, NMM, ALR, ALH, EK, PM, GF, VMK, JS, MO, BR, JO; Investigation: WM, JW, ES, SM, JAA, JB, PM, GF, VMK, JS, MO, BR, JO, GRM, RS, NMM, FOF, MO; Methodology: All authors; Project administration: FOF, YM, FK, MH, HEN, JK, RM, WM, JW, ALH, ALR; Resources: YJM, FK, FOF, JK, MR, HEN; Software: FOF, NMM, GRM, JS, ALH, ALR; Supervision: YJM, FK, FOF, MR, HEN, JW, WM; Validation and visualisation: JS, ALR, FOF, ALH, NMM, SM; Writing original draft: NMM, FOF; Writing review and editing: all authors.

Conflict of interest

None of the authors have any conflict of interest that should prevent the review or publication of this manuscript.

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Ethical clearance

Written consent forms were provided to all participants and only those who signed the consent form participated in the interviews. Interviewed participants were informed that they reserved the right to discontinue participation if they so wish. The Moshi District Council and the Directorate of Veterinary Services, Ministry of Livestock and Fisheries, United Republic of Tanzania provided permission to obtain and process samples and ethical clearance through the approval numbers: MDC/V/10/3/84 and PA.116/340/01 respectively.

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References

Bärnighausen T, et al. Valuing vaccination. PNAS USA 2014;111:12313–9, doi:http://dx.doi.org/10.1073/pnas.1400475111.

Black S. The role of health economic analyses in vaccine decision making. Vaccine 2013;31:6046–9, doi:http://dx.doi.org/10.1016/j.vaccine.2013.08.008.

Borse RH, et al. Cost-effectiveness of dog rabies vaccination programs in East Africa. PLoS Negl Trop Dis 2018;12(5):e0006490, doi:http://dx.doi.org/10.1371/journal.pntd.0006490.

Cleaveland S, et al. A dog rabies vaccination campaign in rural Africa: impact on the incidence of dog rabies and human dog-bite injuries. Vaccine 2003;21:1965–73, doi:http://dx.doi.org/10.1016/S0264-410X(02)00778-8.

Cleaveland S, et al. One Health contributions towards more effective and equitable approaches to health in low- and middle-income countries. Philos Trans R Soc B Biol Sci 2017;372(1725), doi:http://dx.doi.org/10.1098/rstb.2016.0168 pii 20160168.

Coleman PG, et al. Estimating the public health impact of rabies. Emerg Infect Dis 2004;10(1):140–2, doi:http://dx.doi.org/10.3201/eid1001.020744.

Elser JL, et al. Towards canine rabies elimination: economic comparisons of three project sites. Transbound Emerg Dis 2018;65:135–45, doi:http://dx.doi.org/10.1111/tbed.12637.

Grimshaw JM, et al. The Mammals of Kilimanjaro. J East Afr Nat Hist 1995;84(2)105–39 doi: 10.2982/0012-8317(1995)84[105:TMOK]2.0.CO;2.

Guo D, et al. Geographical analysis of the distribution and spread of human rabies in China from 2005 to 2011. PLoS ONE 2013;8(8):e72352, doi:http://dx.doi.org/10.1371/journal.pone.0072352.

Hatch B, et al. Towards canine rabies elimination in South-Eastern Tanzania: assessment of health economic data. Transbound Emerg Dis 2016;64(3):951–8, doi:http://dx.doi.org/10.1111/tbed.12463.

Hemachudha T, et al. Human rabies: a disease of complex neuropathogenetic mechanisms and diagnostic challenges. Lancet Neurol 2002;1:101–9.

Hutubessy R, et al. Generalized cost-effectiveness analysis for national-level priority-setting in the health sector. Cost Effect Resour Alloc 2003;1:8, doi:http://dx.doi.org/10.1186/1478-7547-1-8.

Kaare M, et al. Rabies control in rural Africa: evaluating strategies for effective domestic dog vaccination. Vaccine 2009;27:152–60, doi:http://dx.doi.org/10.1016/j.vaccine.2008.09.054.

Masiira B, et al. Longterm trends and spatial distribution of animal bite injuries and deaths due to human rabies infection in Uganda, 2001–2015. PLoS ONE 2018;13(8):e0198568, doi:http://dx.doi.org/10.1371/journal.pone.0198568.

Miranda LM, et al. Towards canine rabies elimination in Cebu, Philippines: assessment of health economic data. Transbound Emerg Dis 2017;64:121–9, doi:http://dx.doi.org/10.1111/tbed.1235.

Mtui-Malamsha N, et al. Ecological and epidemiological findings associated with Zoonotic Rabies Outbreaks and Control in Moshi, Tanzania, 2017–2018. Int J Environ Res Public Health 2019;16(16):2816, doi:http://dx.doi.org/10.3390/ijerph16162816.

World Organization for Animal Health (OIE). Rabies (infection with rabies virus) and other Lyssaviruses, Chapter 2.1.17. 2018. Manual of diagnostic tests and vaccines for terrestrial animals. http://www.oie.int/fileadmin/Home/eng/Health_standards/tahm/2.01.17_RABIES.pdf.

Ozawa S, et al. During The 'Decade Of Vaccines,' the lives of 6.4 million children valued at $231 billion could be saved. Health Aff (Millwood) 2011;30:1010–20, doi:http://dx.doi.org/10.1377/hlthaff.2011.0381.

Resnik JR, et al. Island fox spatial ecology and implications for management of diseases. J Wildlife Manag 2018;82:1185–98, doi:http://dx.doi.org/10.1002/jwmg.214641198.

Rivas AL, et al. Critical Response Time (time available to implement effective measures for epidemic control): model building and evaluation. Can J Vet Res [314_TD$DIFF]2003;67:307–15.

Rivas AL, et al. Lessons from Nigeria: the role of roads in the geo-temporal progression of the avian influenza (H5N1). Epidemiol Infect 2010;138:192–8, doi:http://dx.doi.org/10.1017/S0950268809990495.

Rivas AL, et al. Connecting network properties of rapidly disseminating epizoonotics. PLoS ONE 2012;7:e39778, doi:http://dx.doi.org/10.1371/journal.pone.0039778.

Rushton J, et al. An interdisciplinary approach to the economics of animal health: Introduction. J Agric Econs 2018;69:199–200, doi:http://dx.doi.org/10.1111/1477-9552.12265.

Smith DL, et al. Predicting the spatial dynamics of rabies epidemics on heterogeneous landscapes. PNAS USA 2002;99:3668–72, doi:http://dx.doi.org/10.1073/pnas.042400799.

Suzuki K, et al. Descriptive spatial and spatio-temporal analysis of the 2000–2005 canine rabies endemic in Santa Cruz de la Sierra, Bolivia. Acta Trop 2007;103:157–62.

Undurraga EA, et al. Cost-effectiveness evaluation of a novel integrated bite case management program for the control of human rabies, Haiti 2014–2015. Am J Trop Med Hyg 2017;96:1307–17, doi:http://dx.doi.org/10.4269/ajtmh.16-0785.

Wei XK, et al. Vaccination demonstration zone successfully controls rabies in Guangxi Province, China. BMC Infect Dis 2018;18:386, doi:http://dx.doi.org/10.1186/s12879-018-3301-8.

Wera M, et al. Cost-effectiveness of mass dog vaccination campaigns against rabies in Flores Island, Indonesia. Transbound Emerg Dis 2017;64(6):1918–28, doi:http://dx.doi.org/10.1111/tbed.12590.

Wilder-Smith A, et al. The public health value of vaccines beyond efficacy: methods, measures and outcomes. BMC Med 2017;15:138, doi:http://dx.doi.org/10.1186/s12916-017-0911-8.

Zimmer BL, et al. Canine rabies vaccination reduces child rabies cases in Malawi. Lancet 2018;392:1115–6, doi:http://dx.doi.org/10.1016/S0140-6736(18)32175-5.

Zinsstag J, et al. Transmission dynamics and economics of rabies control in dogs and humans in an African city. PNAS USA 2009;106(35):14996–5001, doi:http://dx.doi.org/10.1073/pnas.0904740106.