Methods for Estimating the Risk of Rabies Transmission to Humans in the Lake Victoria Zone, Tanzania

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SUMMARY

Canine rabies is endemic in Tanzania probably as a result of low dog vaccination coverage which is set between 10 and 20%. By the use of a model, this study aimed to develop methods for estimating risk of rabies transmission to humans, quantify the risks and make recommendations to minimize them. Data obtained from the Lake Victoria Zone were subjected to analysis by running Monte Carlo simulation using 'Simulacion4' for 10 000 iterations. The findings suggested that, at a dog vaccination coverage of 10%, the probability of an individual human being dying from rabies following a bite from a rabid dog was 3.76×10^{-5}. With a human population of 8 509 170 million people found in the Lake zone in 2012, this probability corresponded to an estimated 8921 human dog bite cases and 220 human rabies deaths. This corresponded to an annual bite incidence of 104.8 bites/100 000 and an annual death incidence of 2.6 deaths/100 000 respectively. On the basis of extrapolating these data to the whole country, this probability corresponded to 1163 human rabies deaths per year. At a dog vaccination coverage of 70%, the probability of dying from rabies following a bite from a rabid dog reduced to 1.38×10^{-5}. The percent risk reduction was >60%. Sensitivity analysis showed that post-exposure prophylaxis had a stronger influence on the risk of dying from rabies compared to dog vaccinations. Correlation analysis showed that the correlation of dog vaccinations and the risk of dying from rabies was significant (r^2= 0.95, P=0.0000).

Key words: model, vaccination coverage, simulacion, Monte Carlo

INTRODUCTION

Rabies is a viral zoonotic disease which affects all warm blooded animals and occurs worldwide. The virus that causes rabies is neurotropic and belongs to the genus Lyssavirus, family Rhabdoviridae (Dias *et al.*, 2011). It causes an acute, progressive viral encephalitis with a near 100% case fatality rate. According to the World Health Organisation (WHO, 2005), human mortality from endemic canine rabies was estimated to be 55 000 deaths per year. It was further reported that the majority (84%) of these deaths are estimated to occur in rural Asia (56%) and Africa (44%).

After having started as small foci in the southern highlands of Tanzania, rabies spread northwards and then eastwards, and by the 1990s, it had spread to the rest of the country. By then, although it became endemic, vaccination of dogs against rabies was already being used as a method of controlling the disease (Magembe, 1985; Shayo, 2008). However, the average vaccination coverage through the years has been 10-20% (Shayo, 2008). Domestic dogs are the main host and transmitter of the rabies virus (WHO, 2013). The failure to achieve the minimum WHO recommended vaccination coverage of 70% of dogs in an area in order to break the cycle of transmission of the rabies virus may give grounds to hypothesize that more individuals in human and animal populations may be at risk of contracting the disease. It therefore, emerges as a significant public health concern. Recent disconcerting reports of rabies transmission through contact with infected tissues may complicate the problem (Heiman *et al.*, 2009).

Mathematical epidemiology, through the use of models, has contributed to the understanding of the behavior of infectious diseases, their impacts and possible future predictions about their spread (Bubniakova, 2007). With a near 100% case fatality rate, assessing the risk of rabies transmission to humans would be a critical aspect of developing effective prevention and control programmes. In attempting to add to the knowledge that already exists on rabies, this study sought to address two key concerns- first, that the risk of rabies transmission to human and animal populations exists as a result of the low vaccination rate of the dog population in Tanzania, and second, that there is risk associated with the transmission of the rabies virus to humans following handling of rabies infected tissues and/or saliva. The study aimed to develop methods for estimating risk of rabies transmission to humans by the use of a model, quantify the risks and make recommendations to minimize them. The model will assist in the understanding of the spreading mechanism of rabies, predict its future course and understand how the spread of the disease can be prevented. The tool is envisaged to be pivotal in the process of public health decision making, not only in the control of rabies, but in a variety of situations. In addition, it is envisaged to be a tool in forecasting the long-term epidemiological and economical consequences of intervention strategies.

The main objective of this study was to develop methods for estimating risk of rabies transmission to humans in the Lake Zone, Tanzania and the specific objectives were (i) to develop a model that would be used to quantify the risk associated with an individual developing rabies following a bite from a rabid dog and from handling infective tissues/saliva from rabies infected livestock (cattle), (ii) by the use of the model, to estimate the probability of an individual developing rabies following a bite from a rabid dog and from handling infective tissues from rabies infected livestock, and (iii) to estimate scenarios by carrying out sensitivity analyses on the input variables of the model.

MATERIALS AND METHODS

Study area

The Lake Zone was the area of study. It surrounds Lake Victoria in the Northwest of Tanzania. It is made up of Kagera, Mara, Mwanza and Shinyanga regions and more recently Geita region (originally part of Kagera, Mwanza and Shinyanga) and Simiyu region (originally part of Mwanza and Shinyanga) (Fig. 1). The Zone is found between longitudes 30^{o} 15' and 30^{o} 30' E and latitudes 1^{o} and 34^{o}5' S. The Lake Zone is inhabited by 8 509 170 million people (TNBS, 2012), which accounts for approximately 18.9% of Tanzania’s population. It covers an area of 154 685 km^2 (Land area- 138 129 km^2 and water area- 16 556 km^2). The Lake Victoria waters separate the zone from the neighboring countries of Kenya and Uganda.

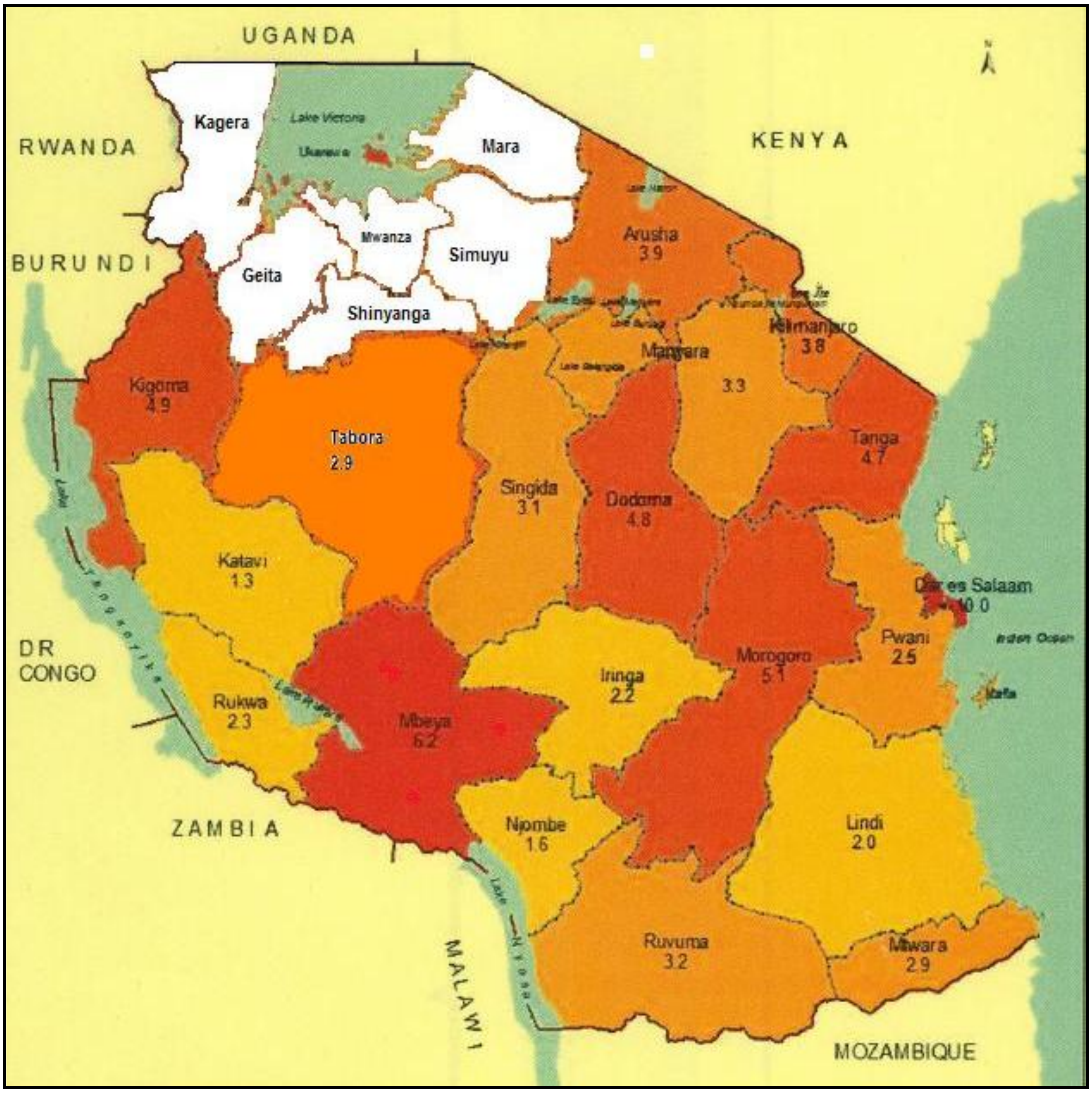

Figure 1. Map of Tanzania showing the Lake Zone (Source: TNBS, 2012)

Livestock keeping in the region is dominated by multi-ethnic groups that are agro-pastoralists, such as the Wasukuma of Mwanza, Geita, Simiyu and Shinyanga, the Wahaya of Kagera, and the Kurya, the Jita and Luo of Mara. They keep cattle, goats, sheep, donkeys and poultry and to a smaller extent, pigs in urban and peri-urban areas. Apart from livestock, livestock keepers also keep dogs for security and for hunting purposes (TNBS, 1998; TNBS, 2006; TNBS, 2007; TNBS, 2010).

Development of the risk model

Development of a rabies scenario tree

To work out the probability of an individual human being dying of rabies following a bite from a rabid animal and/or human contact with rabies virus infected tissues, two probability decision-tree models which considered the key stages in the transmission of the rabies virus in the two scenarios were constructed (Figs. 2 and 3).

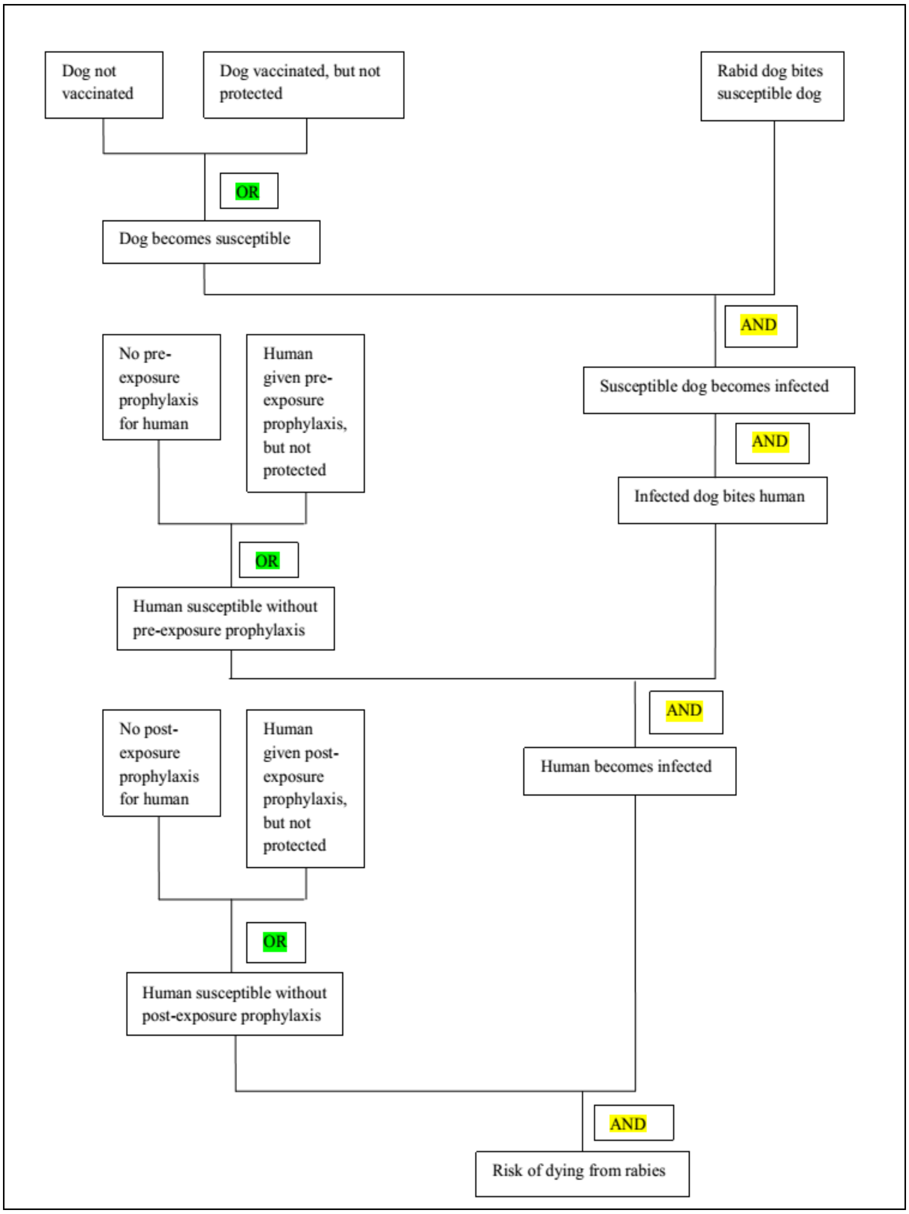

Figure 2. Rabies virus pathway through the dog-human route

Assumptions of the model and input data

i. The probability of a rabid dog biting another dog, human or cattle was computed from dog, human and cattle rabies prevalence, incidence and mean bites per rabid dog from the study area, respectively. The mean bites per rabid dog, 2.15 (Hampson *et al.*, 2009), were assumed to be the same for dogs, humans and cattle.

ii. The number of dogs in the area was estimated from the human population using a human: dog ratio of 14: 1 (Gsell *et al.*, 2012) (Table 1a and 1b).

iii. The mean probabilities of receiving pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PoEP) were assumed to be 0.01±0.002 and 0.5±0.1 respectively. The probabilities for PrEP were based on the assumption that only professionals and law enforcement officers (Expert opinion) are likely to be vaccinated prior to exposure. These probabilities remained constant throughout the computations.
iv. The probability for not being protected post vaccination for dogs, 0.38, was obtained from a study that was conducted by Mpelumbe-Ngeleja (2005), and it was assumed to be the same for humans and cattle.
v. The probability of animal tissue (for purposes of this study, cattle brain and salivary glands) to be infected with the rabies virus, 0.8, was estimated from a study conducted by Pepin *et al*. (1984).

Data collection for model validation

Dog rabies data were obtained from the Tanzania Veterinary Laboratory Agency (TVLA) and Zonal Veterinary Centre (ZVCs) located in Mwanza. These departments are concerned with the diagnosis of veterinary diseases and implementation of surveillance activities respectively. Data for human animal-bite injuries for the study area were obtained from the Ministry of Health and Social Welfare (MoHSW). Data were collected for the period 2007-2012.

Analysis of risk scenarios

Input and output variables

Input variables: (i) Dog not vaccinated, (ii) Dog vaccinated, not protected, (iii) Human not vaccinated- PrEP, (iv) Human vaccinated, not protected- PrEP , (v) Human not vaccinated- PoEP, (vi) Human vaccinated, not protected- PoEP.
Output variable: Risk of dying from rabies

Model Distributions

Prominent probability distribution functions (PDF) used in the model included the Normal, Uniform, Triangular, Beta, Binomial and Poisson distributions depending on the nature of the variable/s (Table 2).

Monte Carlo simulation

The simulations were run using the Simulacion4.0 (Copyright (c) 2003) software [http://www.ucema.edu.ar/u/jvarela/index_eng.htm]. In order to yield reliable results, simulation with the Monte Carlo method were performed at 10 000 iterations.

Correlation Analysis

Applying Epi Info™ 7, a data collection, management, analysis, visualization, and reporting software for public health professionals developed by the Centers for Disease Control and Prevention (CDC) in the United States of America, the association of dog rabies vaccinations (independent variable) and percent rabies risk reduction in humans (dependent variable) was analysed.

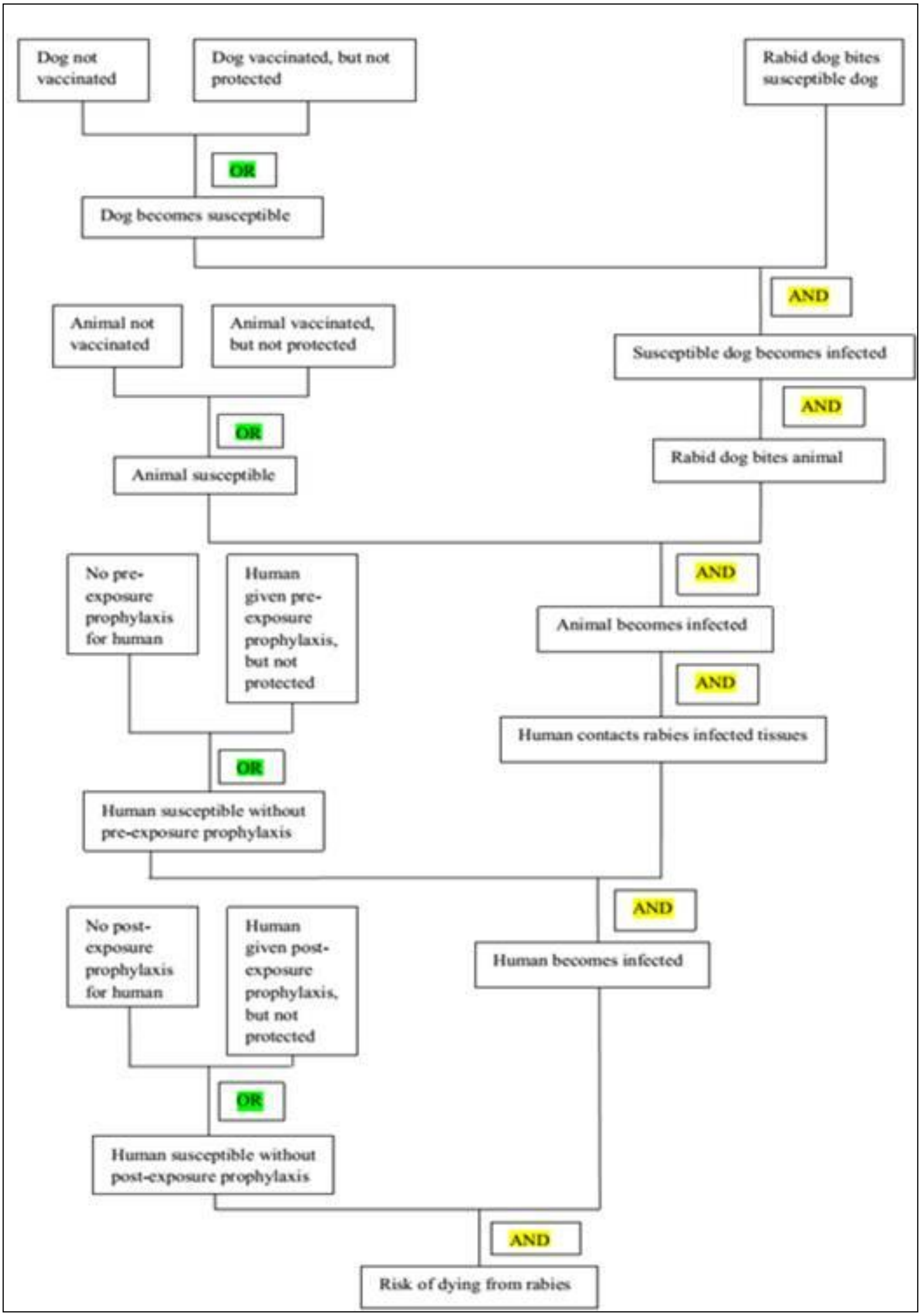

Figure 3. Rabies virus pathway through the dog-cattle-human route

Table 1a. Estimates of retrospective human populations from 2012-2007 in the Lake Zone

2012	ADR	AGR multi fat	2011	2010	2009	2008	2007
2 772 509	3	10.03	2 764 216	2 755 949	2 747 705	2 739 487	2 731 293
2 458 023	3.2	10.032	2 450 182	2 442 367	2 434 576	2 426 810	2 419 069
1 743 830	2.5	10.025	1 739 481	1 735 143	1 730 816	1 726 500	1 722 195
1 534 808	2.1	10.021	1 531 592	1 528 382	1 525 179	1 521 983	1 518 794
8 509 170			8 485 472	8 461 841	8 438 277	8 414 780	8 391 351

AGR- Annual growth rate.

AGR- Multi fct- Annual growth rate multiplication factor

Table 1b. Estimates of retrospective dog populations from 2012-2007 in the Lake Zone

YEAR	Human population (TNBS, 2012)	Estimated Dog Population	Actual Number of vaccinations	Percentage vaccinations
2012	8 509 170	607 798	84 950	13.98
2011	8 485 471	606 105	52 031	8.58
2010	8 461 841	604 417	47 287	7.82
2009	8 438 276	602 734	65 137	10.81
2008	8 414 780	601056	45 981	7.65
2007	8 391 351	599 382	47 169	7.87

Note: For the period under study, the number of cattle rabies was 178 and the cattle population was 6 069 304

RESULTS

By the use of a model, the present study predicted the risk of dying from rabies for an individual human being. The findings from the model suggest that at a dog vaccination rate of 10% and when the rates of receiving PrEP and PoEP were kept constant at 1% and 50% respectively, the probability of dying from rabies for an individual human being in the Lake Zone following a bite from a rabid dog was 3.76×10^{-5}. When the WHO recommended minimum rabies vaccination rate of 70% of the total dog population in an area was simulated and the rates of receiving PrEP and PoEP were kept constant at 1% and 50% respectively, the probability of dying from rabies following a bite from a rabid dog was reduced to 1.38×10^{-5} (Table 3). At the same vaccination rates of 10% and70%, the probability of dying from rabies for an individual human being in the same area following exposure to rabies virus infected animal tissues was reduced from 2.7×10^{-7} to 3.5×10^{-8}.

The inputs "human not vaccinated-PoEP" and "human vaccinated, not protected-PoEP" showed higher influence on the output variable than did the other inputs. The correlation coefficients of these input variables, at a dog vaccination rate of 10% were 0.6087 and 0.7353 respectively. At the same dog vaccination rate, the inputs "dog not vaccinated", "dog vaccinated, not protected" had weaker influence on the output variable with correlation coefficients of 0.1593 and 0.2482 respectively. However, every 10% increase in dog vaccinations reduced the influence of PoEP on the risk of dying from rabies for an individual human being. The inputs "human not vaccinated-PrEP" and "human vaccinated, not protected-PrEP" showed very low influence on the output variable (Table 3). The correlation analysis showed that the correlation of dog vaccinations and the risk of dying from rabies was significant (r^2= 0.95, P= 0.000).

DISCUSSION

Vaccination of dogs against rabies clearly emerges as a crucial step in the strategy to combat this deadly disease in dogs and humans. Furthermore, dog bite and human bite records provide an accessible and valuable source of epidemiological data that have generally been under-exploited. To better appreciate the probabilities in the results obtained from the model, at a human population of 8 509 170 million people in the Lake Zone in 2012 (TNBS, 2012), and at a dog vaccination coverage of 10%, the probability corresponded to an estimated 8921 human dog bite cases and 220 human deaths from rabies following a bite from a rabid dog. This corresponded to an annual rabies death incidence of 2.6 deaths/100 000 and an annual bite incidence of 104.8 bites/100 000. Assuming that the prevalence and incidence of rabies infection in dogs and humans were the same across the country, with a population of approximately 45 million people in 2012 (TNBS, 2012), 1163 human rabies deaths were predicted per year. The validity of this indirect estimate of human rabies mortality depended on one key assumption, that data from the Lake Zone are representative of Tanzania as a whole.

Records from the MoHSW in the study area indicated that 2709 human animal bite/rabies cases were reported, while 42 people were reported to have died of rabies in 2012. This translated to a bite incidence of 31.8 bites/100 000 and death incidence of 0.49 deaths/100 000 respectively.

Table 2. Model set-up (summary of model elements- showing results for dog-human pathway)

S/N	Model	Parameters	Distribution	Minimum	Mean	Maximum
A1	P(dog not vaccinated)	0.9	Beta	0.88	0.9	0.92
A2	P(dog vaccinated, but not protected)	0.038	Beta	0.08	0.1	0.12
A3	P(dog susceptible)	0.938		0.018	0.038	0.058
A4	P(rabid dog bites susceptible dog)	0.0559				
A5	P(susceptible dog infected)	0.0524342				
A6	P(infected dog bites human)	0.0010484				
C1	Infected dog bites animal	9.337×10^{-6}				
C2	Animal not vaccinated	1	Poisson	0	0.999	0.9991
C3	Animal vaccinated, but not protected	0	Poisson	0.0009	0.001	1
C4	Animal susceptible	1		0.00028	0.00038	0.00048
C5	Animal infected	4.715×10^{-7}				
C6	Human contacts rabies infected tissues	0.8				
A7	P(human not vaccinated with PrEP)	0.99	Beta	0.988	0.99	0.992
A8	P(human vaccinated with PrEP, but not protected)	0.0038	Beta	0.008	0.01	0.012
A9	P(human susceptible without PrEP)	0.9938		0.0018	0.0038	0.0058
A10	P(human infected)	5.463×10^{-5}				
A11	P(human not vaccinated with PoEP)	0.5	Beta	0.4	0.5	0.6
A12	P(human vaccinated with PoEP, but not protected)	0.19	Beta	0.4	0.5	0.6
A13	P(human susceptible without PoEP)	0.69		0.09	0.19	0.29
A14	P(risk of dying from rabies)	3.770×10^{-5}				

The minimum, mean and maximum are the vaccination parameters. The figures in yellow are the mean vaccination rates that can be varied depending on the situation. In blue, is the cattle component of the model.

Findings from the model are similar to those from other studies (albeit using methods different from this study) conducted in Tanzania (Cleaveland *et al.*, 2002; Lembo *et al.,* 2010). These studies estimated human rabies deaths to be 891-2238 and 389-1900 respectively. The incidence of rabies bites were reported to be 103.9 bites/100 000 and 140 bites/100 000 respectively, while the incidence of rabies deaths were reported to be 4.9 deaths/100 000 and 1~5 deaths/100 000 respectively. Comparing findings from the model and findings from these studies with records of the study area from the MoHSW, there is strong evidence that rabies is under-reported. Furthermore, the results from the model showed that every 10% increase in dog vaccinations, reduced the influence of PoEP on the risk of a human being dying from rabies (Table 3). This demonstrated that if dog vaccinations were carried out at the recommended coverage of 70% to break the cycle of transmission of the virus, the use of PoEP could be minimized. This would be desirable as it would reduce the cost of treating dog bite victims. More often, PoEP is administered indiscriminately to patients reporting with animal-bite injuries, including to those with little or no possibility of genuine exposure to the virus (Shim *et al.,* 2009). Since 1970, five people have been reported to have suffered from rabies after receiving PoEP. None of the patients had received rabies immunoglobulin (RIG). The victims survived, albeit with profound residual neurological deficits (Warrell and Warrell, 2004). The report from this study indicates that there may be treatment failure or some other uncertainties with PoEP. At present in Tanzania, RIG is not provided to bite victims because of its rarity (Shim *et al.*, 2009). Recent advancements in medicine have reported of an unvaccinated adolescent survivor of rabies following the use of a novel therapy dubbed the Milwaukee Protocol (MP). Unfortunately, after implementation of this same therapeutic protocol, another rabies victim succumbed to the disease. There are still uncertainties surrounding the treatment and medical breakthrough is still being awaited (Aramburo *et al.,* 2011). With this present scenario, hope lies in eliminating the virus through vaccination of the reservoir host.

The domestic dog is the primary reservoir of the rabies virus in Tanzania. To be effective, the disease has to be managed from the level of the host animal. According to Blancou (1985), the primary objective of vaccinating animals against rabies, whether domestic or wild, is to protect the human population. This objective may be achieved at three levels. In the Tanzanian context, these levels may be adapted to include vaccination of dogs, vaccination of wild animals and vaccination of human beings. The latter is a purely defensive measure and applicable in smaller high risk groups and therefore impractical for population intervention. Intervention in the wild populations, by the use of vaccine laden baits, was successful in the elimination of rabies in Western Europe and North America (Rupprecht *et al.*, 2004), but it is doubtful if this approach is practical in Africa. However, a study that was conducted in the Ngorongoro and Serengeti districts of Tanzania by Fitzpatrick *et al.* (2012) demonstrated that a programme of domestic canine vaccination, at the coverage levels recommended by the WHO, has the indirect benefit of controlling rabies in wildlife. Prager *et al.* (2012) suggested that rabies virus risks to people and wild carnivores might be controlled by domestic dog vaccination. From these studies, it is evident that vaccination of dogs could successfully minimize the transmission of the virus from dogs to other hosts susceptible to the virus. Control should, therefore, be focussed on vaccinating the domestic dog population with the objective of minimizing and ultimately eliminating the rabies virus in dogs and consequently in other susceptible populations.

Sambo (2012) calculated the costs that an animal bite victim would incur during their course of receiving PoEP. It was found that it would cost approximately $158.00 to receive PoEP. This was broken down into direct costs of $112.70 incurred for one animal-bite victim to receive an unsubsidized full WHO recommended 5-dose PoEP regimen and indirect costs of $44.79 incurred from transportation, accommodation, income loss and other costs incurred while obtaining PoEP. Kaare *et al.* (2009) estimated the costs of vaccinating dogs in rural Tanzania using different strategies. Considering the dog population of the Lake Zone in 2012 (Table 1b), and using cost estimates from these two studies, it would cost approximately between $851,000.00 and $1,732,000.00 to vaccinate 70% of the dog population in the area. At a dog vaccination coverage of 70%, the number of bite victims would be reduced from 8921 to 5383 (a 60% reduction in human bite cases), reducing the cost of providing PoEP from approximately $1,410,000.00 to $851,000.00. It would therefore, be tempting to take the alternative of providing PoEP to reduce costs. However, this alternative cannot be achieved for as long as dog vaccination rates remain low. If the more economical dog vaccinations are increased to 70% or more from the current 10-20%, the provision of the more costly PoEP would be minimized. Effective and consistent vaccinations are key to minimizing the rabies virus in dogs, otherwise costs associated with the provision of PoEP would be incurred year after year for as long as there is sustained transmission of the virus from the reservoir host. Nonetheless, the two strategies, that is, vaccination of dogs and the provision of PoEP, should be implemented in tandem in order to accommodate bite victims, ideally to those actually exposed to the rabies virus in order to ensure judicious use of the treatment. This approach minimizes unnecessary administration of PoEP and curbs shortages so that the treatment can be available for those in genuine and urgent need. Eventually, costs associated with rabies treatment would essentially be incurred during vaccination of dogs which are much lower (Kaare *et al.,* 2009).

To ensure judicious use of PoEP, it would be imperative, therefore, to identify and diagnose the offending animal by using either the six step method (Tepsumethanon *et al.,* 2005) when it is still alive or by employing the use of the direct rapid immunohistochemical test (dRIT) when the animal is dead or by the use of both methods. However, consideration to save costs should not outweigh the decision to provide PoEP. When in doubt about the rabies status of the suspect animal, PoEP should be administered without delay.

Both inputs on PrEP showed very weak influence on the output variable (Table 3). Despite these findings, people who are at a higher risk of coming into contact with rabid animals should receive PrEP. Expert opinion states that in Tanzania, professionals, who may include veterinarians and laboratory personnel, and personnel in law enforcement such as in the police service, are likely to receive PrEP. To strengthen this claim, during the World Rabies Day celebrations in Dar es Salaam in 2010, police officers who managed the dog platoon were vaccinated against rabies.

The risk of humans dying from rabies after contact with rabies infected tissues from cattle in Tanzania was very low. At a dog vaccination coverage of 10%, the risk of dying from rabies following contact with rabies infected tissues was 2.7×10^{-7}, corresponding to 0.17 human rabies deaths. However, Lembo *et al.* (2010) reported that the incidence of cattle rabies in Tanzania is higher than is reported, 12–25 cases/100,000 as opposed to the reported 5 deaths/100 000. Therefore, with these statistics and despite the low risk found in this study, caution is critical when in doubt of any neurological condition in cattle.

The correlation analysis showed that the correlation of dog vaccinations and the risk of dying from rabies was significant (r^2= 0.95, P= 0.000). The model thus demonstrated that increasing dog rabies vaccinations resulted in a corresponding decrease in the risk of an individual human being dying from rabies. This shows that the focus should be on vaccination of dogs. It has been demonstrated that if two or three further consecutive vaccinations were carried out in the same area, most dogs would have protective antibody titres, up to or greater than 0.5I U/ml (Mpelumbe-Ngeleja, 2005; World Organization for Animal Health [OIE], 2013). The percentage of those dogs that are vaccinated and not protected would be reduced so that the dog population in the area would not only be vaccinated against rabies, but would also be adequately protected against infection. Rabies-related animal bites would reduce, consequently reducing the threat of the disease to humans and in the domestic dog population.

In the due process of implementing the model however, major challenges encountered included; the model relied on vaccination rates and bite cases. Since not all bite cases are reported (Shim *et al.*, 2009) and vaccination rates are reported in terms of target populations and not total populations of the area, the outcome would be affected, mostly by under-estimating the risk and consequently the number of subjects expected to be affected at each stage of the model. This would affect planning of control strategies. Nonetheless, the model is a tool that can be used to give a broader view of the rabies situation in an area; a view that usually is hidden as a result of under reporting.

Because intervention methods work well in conjunction with others, it is recommended that**,** in tandem with the findings of this study, efforts should be made to ensure that dog census reports are up-dated timely. Dog bite cases should be reported routinely. All vaccinated animals should be identified by a collar. The media should be involved in rabies campaigns and messages should include emphasis on early presentation of cases. For effective human rabies post exposure management, communication between veterinary and human health services should be strengthened. Results of the status of the biting animal should be communicated at the earliest so that the decision to commence PoEP is not delayed.

In conclusion, the study achieved its objectives of developing methods for estimating the risk of rabies transmission to humans, quantifying the risks and making recommendations to minimize them. The model has demonstrated the association between vaccination of dogs against rabies and the risk of a human being dying from rabies. It has shown that increasing dog rabies vaccinations minimizes the risk of an individual human being dying from rabies. Thus, the findings of this study can assist to make decisions. During the process of decision making however, it is imperative that an inter-sectoral approach is considered so that crucial efforts that are sustained, committed and concerted among all players are employed if the fight against this deadly disease is to be realized.

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