Cost-effectiveness of One Health Interventions for Rabies Elimination - A Systematic Review

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Abstract

The "One Health" (OH) approach is the most promising idea in realising the global goal of eradicating canine-mediated human rabies by 2030. However, taking an OH approach to rabies elimination can mean many different things to different people. We conducted a systematic review scrutinizing economic evaluations (EE), retrieved from MEDLINE OVID, EMBASE OVID, Global Health OVID, CINAHL EBSCO and EONLIT EBSCO that used the OH approach with the intent of identifying cost-effective sets of interventions that can be combined to implement an optimal OH based rabies elimination program and highlight key gaps in the knowledge base.

Our review suggests that an optimal OH program to tackle rabies should incorporate Mass Dog Vaccination and Integrated Bite Case Management in combination with efficient use of Post Exposure Prophylaxis along with a shift to a one-week abbreviated Intra Dermal Rabies Vaccine regimen in humans.

We recommend that future EEs of OH interventions for Rabies Elimination should be performed alongside implementation research to ensure proposed interventions are feasible and adopt a wider societal perspective taking into account costs and outcomes across both the human health and animal welfare sectors.

The systematic review has been registered with PROSPERO.

Keywords: Rabies, Cost measures, Program Evaluation, One Health

Introduction

Rabies is a neglected tropical disease endemic in 150 countries[1] with an estimated 59,000 (95% CI-25,000 to 159,000)[2] people dying of rabies around the world every year. In addition to this loss of life the global cost of treating dog-mediated rabies is estimated at 8.6 billion USD (figure 1). [2] Rabies is currently underreported by a factor of up to 20 times in Asia and 160 times in Africa.[3] Close to 63% of reported global rabies deaths are from Asian regions and 36% are from African regions. [4]

This zoonosis of rabies is unique in that a vaccine exists for almost all the reservoir species, thus making its elimination feasible.[5] Dog mediated rabies has a been eliminated from Western Europe, Canada, the United States of America (USA), and Japan.[6] Great progresses has also been made in reducing human deaths due to rabies in Bangladesh, Philippines, Sri Lanka, Tanzania, Vietnam, and South Africa. [6]

The quadripartite organizations (FAO, UNEP, WHO and WOAH) jointly advocate a global "One Health" framework for the achievable goal of eliminating canine-mediated human rabies by 2030.[1] One Health is defined as "an integrated, unifying approach that aims to sustainably balance and optimize the health of people, animals, and ecosystems."[7] WHO has estimated the cost of vaccinating dogs against rabies at US$ 2.18 and the cost of vaccinating humans at US$ 108.07, i.e. 50 dogs could be vaccinated for the same cost as vaccinating a single human. Furthermore, vaccinating dogs is an upstream intervention in tackling rabies as it is an effective strategy to interrupt transmission, by controlling infection at the source. It can reduce the need for post-exposure prophylaxis (PEP) in humans in the long run. PEP is an expensive strategy. The direct expenditure on PEP estimated at US$ 1.7 billion per year and indirect costs estimated at US$ 1.3 billion.[2] The resulting savings from avoided PEP alone account for nearly 40% of the total costs associated with treating rabies, typically paid for out of pocket (OOP) and potentially resulting in catastrophic health expenditure (see figure 1). Thus, such a one health strategy helping to reduce OOP expenditure is well aligned with the principles of justice and Universal Health Care. However, the current global average spending on dog vaccination and dog population control is only 2% of the total spending on rabies control. There are also challenges in accessing and completing PEP particularly in rural and poor communities, needing them the most. Thus countries need to invest in strategies other than PEP also and identifying the most optimum combinations of approaches is required.

Mass Dog Vaccination coverage of 70% is recommended for interrupting the transmission of rabies. The critical threshold of vaccination coverage is estimated at 25-40% using varying levels of basic reproductive number (R_0), for achieving herd immunity. However, since the birth rate and death rate of dogs is high in Low and Middle Income Countries (LMIC), drop in coverage is anticipated and a higher coverage of 70% will be required for sustaining a population immunity between annual vaccination campaigns. Also, economic analyses of vaccination campaigns from rural Tanzania indicate that 70% coverage also represents the optimal scenario in terms of cost effectiveness. Epidemiological and genetic modelling studies show that dogs are the only population that can sustain rabies transmission. The occasional short lived chains of infection in wild life results from spill over from dog population and therefore, interrupting transmission in them also achieves the elimination in wild life.[8]

Cost-effective resource allocations is the right way forward, particularly so for resource poor settings like LMICs. [9] Identifying the most cost- effective interventions are increasingly relevant today given the additional pressures on the national health and pharmaceutical expenditures due to existing resource

constraints driven by population aging and blossoming of NCDs in most of these societies.[10]Several economic evaluations are available that study the usefulness of interventions for rabies elimination. Health policy implications of long-term trends in health spending indicate the need for health technology assessment and matters of cost-effective allocation of limited resources will continue to remain a core challenge in future.[11] Health care policy makers have an uneasy task of striving to achieve universal health coverage [12] and a review of existing economic evaluations will provide insight to make the most efficient choices. We have found only one prior systematic review of economic evaluations of all preventive measures for rabies prevention, published in 2019.[13] This review found human post-exposure prophylaxis to be more cost effective than canine vaccination. However, we were aware of several studies on the cost effectiveness of mass dog vaccination which concluded mass dog vaccination to be the most cost-effective approach to tackling rabies. [14,15]The conflicting results stem from a confusion in what comprises an OH approach to tackling rabies and how various interventions in humans and animals can be combined in order to build such an OH based strategy. It is our aim in this review to carefully review the various components of the OH approach and identify the optimal combination of interventions in humans and dogs that comprise the most cost-effective strategy to eliminate rabies in both humans and dogs whilst highlighting key gaps in the knowledge base requiring further research.

Methods

This review included full economic evaluations which have reported any One Health intervention or combinations of interventions (where at least one is an OH intervention), for rabies prevention in Human and Dog populations, as interventions or comparators. An OH intervention was operationally defined as an intervention in humans or animals which has cross cutting benefits on either. This is depicted in figure 2. Studies which have looked at interventions on the sylvatic cycle of rabies, interventions in Raccoon, Fox and other wild animals were excluded. The review was conducted in accordance with the Cochrane handbook .[16]

Search terms for the concept of Economic Evaluation Models was done using terms as recommended for the various databases. [17-20] The search strategy was developed by one author (ZTN) and validated by another author (MA) using CADTH PRESS 2015 guidelines. An initial search was conducted on MEDLINE OVID and then extended to other databases (EMBASE OVID, Global Health OVID, CINAHL EBSCO and EONLIT EBSCO). The search terms and results are presented in supplementary tables SM1.1 to SM 1.5. The search of other economic databases namely, PEDE (Pediatric Economic Database Evaluation) and

Cost Effectiveness Analysis (CEA) Registry, DARE (Database of Abstracts of Reviews of Effects), NHS Economic Evaluation Database (NHSEED) and NHS Health Technology Assessment (NHS HTA) (via The Centre for Reviews and Dissemination Library- CRD) [21]was done as a supplementary method. Conference proceedings were also searched as supplementary methods, on the websites of Health Technology Assessment International (HTAi), International Society of Pharmacoeconomics and Outcomes Research (ISPOR), International Health Economics Association (iHEA) and Guidelines International Network (GIN). Grey literature sources search was done in IDEAS. Hand-searching using backward and forward hand searching of reference lists and forward citations of papers that cited the included studies, complemented the database searches.

We included the primary publications of full economic evaluations evaluating the cost-effectiveness, cost-benefit or cost-utility of interventions for tackling rabies. Relevant systematic reviews or scoping reviews were included in the first step of screening and then used to complement the primary publications by hand searching of reference lists.

We applied limits on publication year only including papers published after 2010 in this review. We chose 2010 as a cut-off point as this was the year when international agencies including the WHO, WOAH, FAO, CDC, came together to make an implementation roadmap and established a global network for One Health. Only studies published in English language were included.

Following the search, all identified citations were collated and uploaded into EndNote version 20 (Clarivate Analytics, PA, USA) and duplicates removed. Titles and abstracts were screened by two independent reviewers (ZTN, KKK) using the Rayyan software. At the stage of screening of title and abstracts economic evaluations of all interventions for rabies elimination were included. Relevant studies were retrieved in full and their citation details imported into EndNote. The full text of selected citations was assessed in detail against the inclusion criteria by two independent reviewers (ZTN, KKK). Reasons for exclusion of full-text studies were recorded and reported. At this stage, only studies on One Health interventions were included. Any disagreements that arose between the reviewers at each stage of the study selection process were resolved through discussion with a third reviewer (MA). The results of the search are presented in a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram shown in figure 3.[22]

For the assessment of quality of economic evaluations, we used the Drummond checklist (see table S1). The assessment of methodological quality was conducted by two independent reviewers (ZTN, MA). Any

disagreements that arose between the reviewers were resolved through discussion. Following critical appraisal, studies that did not meet a certain quality threshold (score less than 6) were excluded. (Table 1)

We prepared a data extraction form and it was pilot tested using some included studies. The data extraction form was completed by the first reviewer (ZTN). A second reviewer (MA) reviewed the completed forms for quality. Any disparity was resolved through discussion. The evidence from studies is presented as a brief narrative commentary to summarize the findings of identified economic evaluations with appropriate caveats. We registered the study on the PROSPERO platform (www.crd.york.ac.uk/prospero, CRD42023410651).

Results

Our initial searches identified 2,192 studies of which 793 were duplicates. After removing duplicates, and reviewing titles and abstracts and excluding irrelevant and low quality studies,[22-30] 24 studies remained (Figure 3). The details of excluded studies are provided in supplementary Table S4. The year-wise distribution of included studies is given in Figure 4.

Study Characteristics

All the included economic evaluations were from Low and middle-income countries (95.8%), except one which was from Japan. The perspective was explicitly stated as societal only in two studies. Discounting was done in most studies. The most commonly used discount rate for the base case analysis was 3%, one study each had used 4% and 6%. Sensitivity analysis was not conducted in 8 (33.3%) of the 24 studies. (Table 2.)

Seventeen studies (17/24; 70.8%) used a transmission model, to inform the economic model on the burden of rabies. A Deterministic Compartmental model was the most frequently used (9/17), of which the RabiesEcon Model produced by the CDC was the most commonly used (5/9). Individual Based Stochastic (IBS) models were used in the WHO Consortium study[31] and a bio-economic model was used in the remaining study. [32]The earliest use of a transmission model was developed by Zinstag et al in 2011.[33] The other evaluations were done alongside implementation of programmes or using the data of already implemented programmes. Such evaluations were judged to be of lesser quality compared to those done using models. The mean quality score of economic evaluations using programme data was 7, while that of studies using model was 9.2. Decision tree models were most frequently used for the

economic evaluation. Cost - effectiveness analysis (CEA) was the most common type of economic evaluation (16/24).

The OH interventions evaluated in the selected studies included, Mass Dog Vaccination (MDV)[31-39], Integrated Bite Case Management (IBCM)[31,34], and Human Animal Rabies Surveillance Programme (HARSP).[40] The comparators were no intervention (counterfactual), PEP alone (current status), MDV coverage of zero (where higher coverage were considered as intervention), and implementation programs prior to the ones being evaluated. The WHO Consortium study[31] mainly assessed the cost-effectiveness of improved PEP along with a shift to an abridged 1-week PEP. Other interventions assessed for cost-effectiveness included the strategies of MDV [administering the vaccine as mobile single point (MSP), Catch Vaccinate and Release (CVR), Door to Door vaccination (DDV)and Oral Rabies Vaccine (ORV)[41]], dog vaccination administration frequency (semi-annual, annual, biennial to once in three years) along with the duration of immunity [42,43] and vaccinating puppies.[32] The different MDV coverage ranging from zero/status quo to 95 % have been assessed in several studies. [42-46](Table S5)

Cost-effectiveness of strategies

Mass Dog Vaccination was found to be a cost-effective strategy alone and in combination with other strategies.[35,38] Economic evaluation done alongside implementation programmes (Mission Rabies, Goa) show that it is possible to sustain an MDV coverage of 70%.[38]Disruption of MDV during COVID times was found to have adverse outcomes and restarting it early was found to save substantial human lives cost-effectively.[47] Increasing coverage above 40% increases the cost substantially but achieving coverage of up to 85% was deemed to be cost-effective.[45] Biennial vaccinations of 50% of the canine population had the highest incremental cost-effectiveness ratio (ICER) below the 'very cost-effective' threshold and vaccinating 80% of the canine population biennially had the highest ICER below the 'cost-effective' threshold.[45] A shift from annual to biennial campaigns represents a 32- 42% cost reduction over 10 years. Though the percentage of the budget for PEP increases in a biennial strategy, it remained less than 2% in all strategies.[46] Mass vaccination of 70% of the dog population was found to be the most profitable and cost-effective intervention, sufficient to interrupt rabies virus transmission for at least 6 years.[33] Highly feasible strategies focused on stray dogs, vaccinating as few as 7% of dogs annually, could very cost-effectively reduce human rabies deaths by 70% within 5 years, and a modest expansion to vaccinating 13% of stray dogs could cost-effectively reduce human rabies by almost 90%.[48] Post-elimination, sustaining vaccination coverage of 38-56% was found to be cost-effective.[49] There is also evidence on the cost-effectiveness of vaccinating puppies. [32]

Various strategies for vaccinating dogs have been evaluated. Combining Door to Door Vaccination with Oral Rabies Vaccine (DDV+ORV) was more cost-effective compared to Mobile Single Point (MSP), although oral vaccines are more costly. ORV helps to reach inaccessible dog population groups and help achieve the required coverage faster. [38, 41, 50]The duration of immunity required has also been evaluated in cost-effectiveness studies. Annual vaccination campaigns with a vaccine with long lasting immunity (152 weeks) and covering 70% of dogs were found to be more cost-effective than a strategy of 50% coverage with a vaccine with short lasting immunity (52 weeks). [42]One study used an innovative approach using a linear programing model to guide the use of resources cost-effectively, diverting them from districts that have already attained coverage of 70% to less covered districts, since increasing the coverage beyond 70% was deemed unecessary.[51] Economic evaluation of dog vaccination programmes in a country free of rabies (Japan) was conducted to inform policy on whether to continue the current mandatory dog vaccination policy and found this continued vaccination policy not to be cost-effective. [52]

Sterilization of dogs was not found to have an additional benefit over vaccination in terms of cost-effectiveness. The Help in Suffering (HIS) programme in Goa India compared cost-effectiveness of Dog vaccination alone (Catch Vaccinate release -CVR) to combining it with sterilisation (Catch Vaccinate Sterilise and Release -CVSR), using the programmatic data from the periods in which these interventions were given. Sterilisation was 10 times more costly than vaccination (CSVR -10.7, CVR-1.8 USD). HIS could only vaccinate 9% of dogs over a 12 year period when the strategy was CVSR but with CVR they could vaccinate 40% dogs in 2 years.[53] Another, study showed that adding female sterilization was not cost-effective.[46] Euthanasia and chemo contraception were rarely studied and not found to be feasible. [32, 54]

Animal rabies surveillance and human health interventions post exposure are usually the realms of two separate government sectors and are rarely coordinated. There is a scope for the better efficiency of PEP use if this is done. The Haiti HARSP brought together these efforts and it was found to be cost-effective.[40] The same concept is adopted in the IBCM strategy which was cost-effective in all scenarios, since it reduced the requirement of PEP. [31]One study combined One Health Communication with PEP and MDV and found it to be cost- effective.[37] Combinations of interventions have been assessed for cost- effectiveness, along with analyzing individual interventions. We identified conflicting evidence on the cost-effectiveness of combining improved PEP access to MDV and IBCM from two studies. The WHO consortium study which modelled rabies in 67 GAVI countries found that improving PEP access alone [31]was highly cost-effective compared to the current status of PEP access in these countries and

combining it with other OH interventions. A similar study was done in China using the same model but found that improving PEP access alone was not cost-effective. It found that combining IBCM with Mass Dog vaccination was the most cost effective and dominant strategy. We believe the use of an abbreviated one week intradermal regimen and the proportion of those being administered Rabies Immunoglobulin (RIG) would have made the difference. Also, access to PEP in China is adequate already. [34]These studies did not identify and measure the indirect costs of resources used.

Outcomes of interventions studied were mostly human deaths averted [31,34,35,44, 47, 49]and DALYs averted. [31,37,38, 43, 46, 48, 53, 54] Some studies used dog deaths averted due to rabies[335,42,47], life years gained, [49,54] and intermediate outcomes like the cost of dogs vaccinated[41,50]. Only one study accounted for cattle /livestock- related losses[43]. It is important to look at livestock losses in relevant areas and the coverages of MDV required would be higher if this were also considered. The importance of looking at outcomes like impact of interventions on animal welfare, social acceptability, and ethical approaches to assessment has been modelled in Sri Lanka where OH interventions were seen to result in statistically significant improvements in social acceptance of dogs and animal welfare, besides being cost-effective. [54]**Discussion**

We evaluated 24 studies in this systematic review of economic evaluations to identify cost-effective approaches that would fit the One Health Paradigm for Rabies elimination, and find the knowledge gaps in the area.

Based on this review, the optimum combination of strategies that would be a recommended for a One Health program would include MDV & IBCM with efficient PEP use, along with a shift to the one week abbreviated IDRV regime, mostly arrived at from modelling studies. Modeling plays a pivotal role in designing and evaluating strategies for the elimination of rabies, a deadly zoonotic disease. These models integrate data on disease dynamics, animal demographics, and vaccination efforts into a single framework to simulate and predict the impact of control measures. [55]Preemptive MDV offers the advantage of the most cost-effective strategy for infection control at source. In the biology of rabies vaccination. Post-exposure prophylaxis (PEP) against rabies infection consists of a combination of passive immunisation with plasma-derived human or equine immune globulins and active immunisation with vaccine delivered shortly after exposure. This induces an immune response that prevents the virus from establishing an infection by gaining entry into the nerve endings.

The use of oral vaccination typically presented as bait, as a strategy for MDV, provide several advantages and needs to be considered. They are efficient in covering a large population, including free-roaming and difficult-to-reach dogs; they reduce the need for capture and handling of animals; and they can create a barrier of immunity within the dog population, hindering virus transmission to humans and other animals. It is mostly used now for controlling rabies in wildlife reservoirs like raccoons and foxes, but if cheaper oral vaccines are made available, it can be effectively used in MDV.[38,41,50]

The recommendation of the abridged one week regime for PEP by the WHO is based on several studies showing that the fourth dose of IDRV on day 28 offers no additional benefits. The regimen makes PEP more affordable by reducing the direct cost of vaccines and logistics and indirect costs of clinic visit. It offers an opportunity for more people to get PEP, especially in regions where the vaccine is in short supply. The chances of compliance and completing PEP increases. Furthermore it is more convenient for specific groups like travelers and people in remote areas with less access to PEP. All these are benefits of the shorter regime with no compromise on safety or efficacy. [56,57]

Most studies included used modelling for economic evaluation. Mathematical models are simple, easy to comprehend and crucial for analyzing disease dynamics and understanding the impact of control measures. However, they fail to capture the implementation challenges, societal attitudes and do not address larger ethical or animal welfare issues.[54] The studies that have used data from implementation have used the data from years prior to the implementation for comparison. Making causal claims from such before and after studies is challenging. The methodological quality of economic evaluations conducted using data from implementation programs was also found to be lower than those studies that relied on mathematical models. It would be ideal for researchers to conduct implementation research like a cluster randomised controlled trial (RCT) with an intervention and a control arm, similar to an economic evaluation alongside a clinical trial for more robust real- world feasibility informed economic evaluations.

A quantitative synthesis across the studies done in different parts of the world may not be meaningful since thresholds related to cost-effectiveness measures vary according to the evaluation context.[58] Analyzing incremental cost-effectiveness ratios, through meta-analysis can be challenging due to significant variations in methodologies, as well as practical difficulties. [59]Hence it was not attempted in this review.

In the context of One Health, animal welfare should be given some importance alongside human health. However, only few of the studies we reviewed considered animal welfare at all.[54, 58, 59] It is important to differentiate our ethical judgments from animal welfare, and the impact of our interventions on animal welfare must be assessed objectively. [60-63]Accounting for the loss of livestock and companion animals was generally overlooked in the literature and including such considerations would broaden the outlook in the perspective of One Health.

We did not find any studies comparing the cost-effectiveness of human pre-exposure prophylaxis (PrePH) to OH interventions. Such evaluations could be helpful in regions where the use of rabies immunoglobulin is high and in regions where access to timely PEP is difficult. There are studies showing that PrePH is cost-effective, [64]but in these studies the comparison is with existing regimes of post exposure prophylaxis and the estimates used in the study are debated.[65] Environmental measures like waste management have not been assessed as a One health intervention, for rabies prevention. Dog culling as a strategy has been rarely studied.

Rabies has been confirmed by laboratory examination in several puppies less than three months old, indicating the need for vaccinating dams.[66] Dogs are usually vaccinated after three months. In this review one study showed clearly that vaccinating puppies is cost-effective but most programmes avoid it because of the belief that puppies may not reliably respond to vaccination due to immature immune mechanisms and a higher probability of mortality compared to adults. [32]

The assessment of multiple outcomes across different government sectors is required when conducting thorough economic evaluations of One Health interventions as costs and benefits accrue to different sectors of the economy and fall under the purview of different decision makers who need to be able to collaborate to implement and evaluate such complex interventions. [67,68]

Conclusion and Recommendation

While there exists economic evaluations of high quality that provide evidence on the cost - effectiveness of One Health Interventions for Rabies prevention using modelling approaches, there is need for better quality economic evaluations to be done particularly in alongside implementation research to inform policy makers regarding interventions in a feasible real-world context. Our review suggests that combining One Health approaches like MDV & IBCM with efficient PEP use, along with a shift to the one week abbreviated IDRV regime will form the optimal set of strategies for a One Health program. The availability of cheaper oral rabies vaccination for dogs will make MDV a more cost-effective strategy in

the long term for vaccinating dogs and reaching a higher vaccine coverage rate, especially in the most inaccessible dogs.

Cost-effectiveness of interventions like PreP in humans, environmental measures like waste management also needs to be assessed in combination with One Health interventions. Standardized methods for assessing animal welfare outcomes, the aggregation of outcomes from different sectors and the adoption of broader societal perspective can enrich the economic evaluation of One Health interventions for Rabies Elimination.

Author contributions

ZTN, MA, KKK, MM, SM, MD and HT have been involved in the conceptualization of this review, writing the paper & have seen and approved the final version of the paper. ZTN and KKK will be involved in the preliminary search and screening of titles and abstracts. For full text review, ZTN was first reviewer KKK and MA were second and third reviewers respectively. MM, SM, MD and HT provided inputs throughout the process. Data extraction and synthesis was done by ZTN and reviewed and finalized by MA.

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Conflicts of interest

The authors declare that there are no conflict of interests.

Ethical Approval

None required

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Figure 1: Economic cost of dog mediated rabies (recreated from WHO Open course on Rabies and One Health)

Figure 2: Framework of interventions for canine rabies elimination in humans

Figure 3: Flowchart on systematic identification of studies for inclusion in systematic review

Figure 4: Year wise publications of Economic Evaluation of One Health interventions after 2010