Vaccine 37 (2019) A146–A153

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

Cost-effectiveness modelling studies of all preventive measures against rabies: A systematic review

Thunyarat Anothaisintawee [a,b,c], Anne Julienne Genuino [c], Montarat Thavorncharoensap [c,d], Sitaporn Youngkong [c,d], Waranya Rattanavipapong [b], Aronrag Meeyai [c,e], Usa Chaikledkaew [c,d,*]

[a] Department of Family Medicine, Faculty of Medicine, Ramathibodi Hospital, 270 Rama VI Road, Phaya Thai, Ratchathewi, Bangkok 10400, Thailand
[b] Health Intervention and Technology Assessment Program (HITAP), 6th Floor, 6th Building, Department of Health, Ministry of Public Health, Tiwanon Road, Muang, Nonthaburi 11000, Thailand
[c] Health Technology Assessment Postgraduate Program, Mahidol University, 447 Sri-Ayuthaya Road, Phaya Thai, Ratchathewi, Bangkok 10400, Thailand
[d] Social Administrative Pharmacy Excellence Research (SAPER) Unit, Department of Pharmacy, Faculty of Pharmacy, Mahidol University, 447 Sri-Ayuthaya Road, Phaya Thai, Ratchathewi, Bangkok 10400, Thailand
[e] Department of Epidemiology, Faculty of Public Health, Mahidol University, 420/1 Ratchawithi Road, Phaya Thai, Ratchathewi, Bangkok 10400, Thailand

ARTICLE INFO

Article history:
Available online 13 December 2018

Keywords:
Rabies
Vaccine
Prevention and control
Cost-effectiveness model
Economic evaluation
Systematic review

ABSTRACT

Rabies is one of the most feared infectious diseases worldwide, predominantly occurring in Asia and Africa where rabies is endemic in domestic dog populations. Whereas previous studies have demonstrated mass dog vaccination and post-exposure prophylaxis (PEP) as the most effective control strategies, successful rabies elimination has yet to be realized as these recognized effective interventions continue to face challenges of limited accessibility. In the light of new evidence towards improving programmatic feasibility and clinical practice in rabies control especially among endemic countries, a systematic review was undertaken to identify cost-effectiveness modelling studies of rabies preventive measures and to provide a critical review of published evidence through comparative evaluation and model quality assessment, and a synthesis of key findings based thereon. Our search through MEDLINE and SCOPUS identified a total of 17 studies which mostly focused on estimating the impact of increasing PEP and pre-exposure prophylaxis (PrEP) access, human rabies elimination scenarios using mass dog vaccinations only or complemented with PEP strategy. While no significant methodological inconsistency across studies was identified and the extent of reporting is generally high, we note several points for quality and internal validity improvement. Assessment of modelling approach showed that decision tree models had similar pathways. The results of the studies suggest that interventions would be cost-effective at the cost-effectiveness threshold of 1 to 3 times per capita Gross Domestic Product (GDP) as recommended by the Commission on Macroeconomics and Health's GDP based thresholds, compared with no intervention in rabies endemic countries. When compared across studies which reported incremental cost-effectiveness ratio (ICER) as cost per QALY gained or DALY averted in international dollars adjusted by purchasing power parity conversion rate, PEP vaccination yields less cost per DALY averted or QALY gained due to one year-horizon assessment compared to canine vaccination at 4- or 10-year-time horizon.

Contents

* Corresponding author at: Social Administrative Pharmacy Excellence Research (SAPER) Unit, Department of Pharmacy, Faculty of Pharmacy, Mahidol University, 447 Sri-Ayuthaya Road, Phaya Thai, Ratchathewi, Bangkok 10400, Thailand.
E-mail addresses: thunyarat.ano@mahidol.ac.th (T. Anothaisintawee), montharat.tha@mahidol.ac.th (M. Thavorncharoensap), sitaporn.you@mahidol.edu (S. Youngkong), waranya.r@hitap.net (W. Rattanavipapong), aronrag.coo@mahidol.ac.th (A. Meeyai), usa.chi@mahidol.ac.th (U. Chaikledkaew).

https://doi.org/10.1016/j.vaccine.2018.11.071
0264-410X/

1. Introduction

Rabies is one of the most feared infectious diseases and is invariably fatal. The infection spreads through the saliva of the infected hosts and domestic dogs are the most important vectors causing human cases [1,2]. The disease is almost always fatal in both animals and humans. Current estimates suggest that approximately 59,000 human deaths occur each year worldwide [3]. Most of the deaths occur predominantly in Asia and Africa where rabies is endemic in domestic dog populations.

A number of rabies elimination strategies have offered tremendous promise for the eradication of this infection. These include the reduction of dog population density through dog culling; the reduction of rabies incidence through dog bite management such as mass dog vaccination, movement ban, pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) for humans bitten by dogs; and, education of the public and health care providers. Many scholars presented that controlling rabies in dogs is the most cost-effective way to prevent rabies humans [4]. However, successful eradication of canine and human rabies can be achieved with proper condition.

As previous studies have shown that mass vaccination is the most efficacious strategy in reducing diseases in all species, mass dog vaccination is recognized as the most powerful approach in the prevention of rabies at its transmission source if at least 70% of the animal population are vaccinated [5]. However, there has been limited access to dog vaccination campaigns in some underserved communities. Similarly, access to and affordability of life-saving PEP, acknowledged as the best possible way to control rabies in developing nations, is very limited for some reasons in many parts of Africa and Asia, particularly in rural areas where most rabies exposures and deaths occur [2,3,6].

Quality data from rabies endemic countries is still scarce. The World Health Organization (WHO) and other developmental partners have initiated several work streams to gather available and new evidence, as well as to undertake epidemiological and cost-effectiveness modelling. In the light of new evidence towards improving programmatic feasibility and clinical practice in rabies control especially among endemic countries, a systematic review was undertaken to identify cost-effectiveness modelling studies of all preventive measures for rabies with the objective of appraising the quality of the individual rabies models from previous published studies through comparative evaluation and model quality assessment, and generating a synthesis of key findings based thereon, ultimately towards providing valuable evidence on the effectiveness of rabies control strategies.

2. Methods

2.1. Search strategy

Health economic modelling studies related to all preventive measures for rabies were identified through MEDLINE and SCOPUS. Searches were run since inceptions through 14 June 2017. In addition, published and unpublished studies identified from a meeting of the WHO Expert Consultation on Rabies on 26–28th April 2017 in Bangkok, Thailand were included for review. The search terms "(rabies OR rabid) AND (cost-benefit analysis OR cost OR economic)" were used for MEDLINE, and "(rabies OR rabid) AND (cost-benefit analysis OR cost OR economic OR cost-effectiveness OR cost-benefit OR cost-utility)" for SCOPUS.

2.2. Selection of studies

Two reviewers (WR and TA) independently reviewed each article obtained from databases. Those studies were assessed for relevance based on title and abstract. We then excluded irrelevant studies that did not fulfil the following inclusion criteria: (1) studies examining the economic impact of preventive measures for rabies; (2) interventions targeted on human and/or dog; and, (3) original cost-effectiveness studies. Studies such as articles present of experimental animal models, quantification of rabies virus, genetic analyses, diagnosis of animal and human rabies, immunogenicity studies, vaccine safety, and human attitudes and behaviour were excluded from the review. All records were used to test inter-rater consistency. Percentage agreement between two reviewers was 95%, and after discussions between the two reviewers, a consensus to resolve potential discrepancies was reached for the final inclusion.

2.3. Data extraction and analysis

Data on details about the research question, the interventions, populations, study methods, outcomes, discussion and source of funding were extracted by UC and AJG. We used the frameworks and templates provided by the WHO Immunization and vaccines related implementation research advisory committee (IVR-AC) [7] and Health Intervention and Technology Assessment Program (HITAP) [7] for the evaluation of methodological variations, quality assessment and model comparison. In addition, the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [8] was used to assess the quality and transparency of reporting of the studies. Reviewers independently assessed the assigned modelling studies, extracted the data employing the standard forms, and validated the data extraction tables for accuracy and completeness.

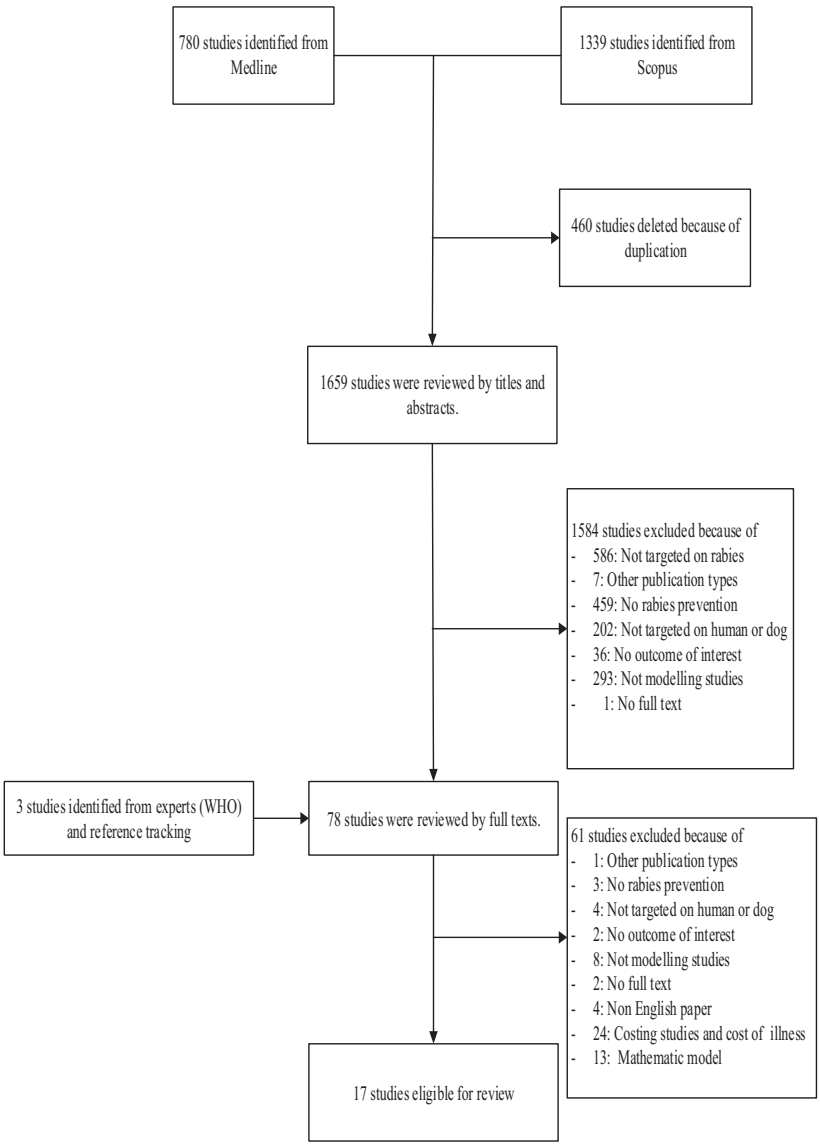

Fig. 1. Flowchart of systematic review.

3. Results

3.1. Studies included in the analysis

The initial search from MEDLINE and SCOPUS yielded 2119 records. A total of 1584 articles papers were excluded after evaluation of the title and abstract, resulting to 75 short-listed articles. Three articles were additionally identified from a meeting of the WHO Expert Consultation on Rabies on 26–28th April 2017 and by reference tracking. After performing a more detailed full text examination of the 78 papers, 61 were excluded and resulted in 17 articles which were then included in the review -11 studies using cost-effectiveness model without dynamic models and 6 studies using cost-effectiveness with dynamic models. A record of the total number of studies included at each stage of the review is summarized as a flow chart in Fig. 1.

3.2. General study information

Seventeen economic evaluation studies included in this review were dated back as early as 1975 to 2017, with a series of publications starting in 2008 after the release of the WHO recommendation on rabies vaccine in 2007. The primary research objective of the economic evaluations can be classified into 4 groups: (1) the estimation of the impact of increasing access to PEP treatment (7 studies); (2) the assessment of impact or long-term investment for human rabies elimination scenarios using mass dog vaccinations only (5 studies); (3) the estimation of the impact of increasing access to PrEP treatment, (3 studies); and, (4) the evaluation of impact or long-term investment for human rabies elimination scenarios using mass dog vaccinations and PEP strategy (2 studies). As presented in Table 1, majority of the economic evaluation study settings were conducted among the highly rabies-endemic regions in Africa and Asia (10 studies). Among the 14 studies with declared funding support, government agencies were noted to be the common supporting source, while others reported to be funded by research aids or agencies, pharmaceutical industry, academic institution, international non-profit organizations or development partners.

3.3. Study interventions

The most evaluated rabies control intervention among the assessed economic evaluations was PEP treatment of varying implementation strategies and scenarios. Four assessments compared PEP strategies i.e., PEP treatment alone or combined PEP treatment with canine vaccination to no PEP treatment scenario.

Table 1
Summary of study characteristics and different methodologies used in the included economic evaluations.

Study's characteristics	Number of Studies, n	%
Study setting		
Asia	5	29
Africa	4	24
Africa and Asia	1	6
The Americas	4	24
Europe	3	17
First author's affiliation		
Academe	10	59
Government	4	24
University Hospital	1	6
Pharmaceutical industry	1	6
not reported	1	6
Funding source		
Government	5	29
Research aids/agencies	3	18
Pharmaceutical industry	2	12
Academe	1	6
Development partners	1	6
International NGO	1	6
Declared no funding	1	6
not reported	3	18
Economic evaluation method		
CEA	7	41
CUA	6	35
CBA	2	12
CUA and CBA	1	6
CMA	1	6
Main outcome measured		
DALYs	5	31
Life-year gained	3	19
Rabid dog cases averted	2	13
Rabies deaths averted	2	13
QALYs	2	13
Monetary benefit	2	13
Study perspective		
Government or health policy makers	5	28
Societal	4	22
Healthcare	3	17
Payer	1	6
Not specified	5	28
Approach of modelling		100
Decision tree model	6	35
Dynamic transmission model	6	35
Other types of models i.e., spreadsheet, simulation model	2	12
Non modelling i.e., retrospective study	1	6
Not reported	2	12
Time horizon		
1 year	3	18
2 years	1	6
4 years	1	6
10 years	7	41
12 years	1	6
Not reported	4	24
Discounting for costs		
No discount	3	18
3%	6	35
5%	2	12
6%	1	6
3%, 5%, and 10%	1	6
N/A	1	6
Not reported	3	18
Discounting for outcomes		
No discount	4	25
3%	7	44
5%	1	6
3%, 5%, and 10%	1	6
Not reported	3	19
Types of uncertainty analysis		
Univariate analysis alone	5	29
Bivariate analysis alone	1	6
Multivariate analysis alone	2	12
Probabilistic sensitivity analysis alone	1	6
Univariate and Bivariate analysis	1	6
Deterministic and Probabilistic sensitivity analysis	3	18
Not reported	4	24

Moreover, PEP treatment was also assessed within a broader rabies control framework (3 studies). PrEP strategy, on the other hand, was assessed under varying contexts: one paper specifically focused its use among travellers heading to rabies-endemic areas; one study comparing the altered regimens of PrEP; while one study was a comparative assessment of PrEP versus PEP intervention. Five papers focused on the impact of canine vaccination only under varying implementation strategies, coverage scenarios or administration frequency.

3.4. Quality assessment

3.4.1. Methodological variations

The different methodologies used in the economic evaluations are presented in Table 1. Of all 17 studies performing economic evaluation of all preventive measures for rabies using methods i.e., cost-minimization analysis (CMA) (1 study, 6%), cost-benefit analysis (CBA) (2 studies, 12%), cost-effectiveness analysis (CEA) (7 studies, 41%) cost-utility analysis (CUA) (6 studies, 35%) and both CUA and CBA (1 study, 6%). Among the CEA studies, the outcomes were reported as life years gained (3 studies, 19%), rabid dog case averted or rabies death prevented (4 studies, 26%); while CUA studies generally report their outcome measures in terms of i.e., disability adjusted life year (DALY) averted (5 studies, 31%) or quality adjusted life year (QALY) gained (2 studies, 13%). The most commonly applied study's perspective was government or health policy-maker (5 studies, 28%), followed by societal viewpoint (4 studies, 22%). Five studies (28%), however, were not explicit with their evaluation perspective. As regards their modelling technique to estimate the costs and outcomes, a comparable number of studies applied either a static decision-tree modelling (6 studies, 35%) employed by studies which assessed human strategies, or dynamic transmission modelling technique (6 studies, 35%) used in studies which evaluated animal strategies. Further, 7 studies (41%) most commonly applied a 10-year- analytical horizon with a discounting method of 3% both for costs (6 studies, 35%) and outcomes (7 studies, 44%). Among the 14 studies (76%) which performed any form of uncertainty analysis, the most reported performed method was univariate analysis alone (5 studies, 29%) or probabilistic with uni- or bivariate analysis (3 studies, 18%). Studies which have applied and reported explicit cost-effectiveness threshold generally followed the WHO-recommended threshold of 3 times per capita Gross Domestic Product (GDP) to indicate 'cost-effective' interventions, and 1 times per capita GDP for 'very cost-effective' interventions.

3.4.2. Sources of input data

Studies have generally referred to previously published literatures for their input parameters on baseline epidemiological data, vaccine efficacy data and costing data. Regarding clinical effect size of the interventions, none of the studies have applied or referred to systematic reviews or meta-analysis in the estimation of efficacy. It is also noted that five studies assumed 100% vaccine efficacy. Moreover, one study referred to a panel of experts in the estimation of the probabilities of rabies transmission to a human following possible contact with different species of potentially rabid animals, in the absence of data.

3.4.3. Quality of reporting

Among the reporting items in the CHEERS checklist, the background and rationale, setting and location, target population, comparators, and the overall study findings were noted to be the key domains which were explicitly stated by all studies. Not all studies, however, have clearly stated the limitations or potential biases in their assessments. The most unstated information from the studies is the declaration of potential conflict of interests of the authors which were reported by only one-third of all the assessed economic evaluation papers (6 studies, 35%). Other fundamental reporting domains that were noted to be inadequately discussed in some papers included the following: (1) key description of model details (10 studies, 67%) as well their (2) underpinning assumptions (9 studies, 60%); (3) the study parameters with complete information on the values, ranges, probability distributions applied, and references, preferably presented in a tabular format (i.e., 9 studies, 60%); and, (4) the discussion of differences in costs, outcomes or cost-effectiveness that can be likely explained by variations among subgroups in the population with different baseline characteristics or other observed variability in effects that are not reducible by more information (11 studies, 65%). Comparing the extent of reporting across the studies, none was noted to garner a score of less than 50% out of the total key reporting items. The extent of reporting of the studies following the CHEERS checklist is summarized in Table 2.

Table 2
Summary of the Extent of Reporting using CHEERS Checklist.

Reporting Items	Number of studies which reported the corresponding item (N = 17)	%
Title and abstract		
Title	12	71
Abstract	16	94
Introduction		
Background and objectives	17	100
Methods		
Target population and subgroups	17	100
Setting and location	17	100
Study perspective	12	71
Comparators	17	100
Time horizon	13	76
Discount rate	12	71
Choice of health outcomes	14	
Single study-based estimates	0	82
Synthesis-based estimate		0
Measurement and valuation of preference based outcomes	4 out of 6	67
Estimating costs and resources		
Single study-based estimates	14	82
Synthesis-based estimate	2	12
Currency, price date and conversion	14	82
Choice of model	10	67
Assumptions	9	60
Results		
Study parameters	10	63
Incremental costs and outcomes	12	75
Characterising uncertainty		
Single study-based estimates	15	88
Synthesis-based estimate	4 out of 5	80
Characterising heterogeneity	11	65
Discussion		
Study findings, limitations, generalisability, and current knowledge	17	100
Other		
Source of funding	14	82
Conflicts of interest	6	35

3.5. CEA/CUA results

Table 3 demonstrates the results of CEA for rabies preventive measures. Cost-effectiveness results were reported as the ICER in terms of cost per rabid dog prevented or averted (2 studies) [9,10], cost per death prevented or averted (2 studies) [11,12], and cost per life year gained (LYG) or saved (LVS) (2 studies) [13,14]. In addition, the CUA results were presented as incremental cost-effectiveness ratio (ICER) i.e., cost per QALY gained and cost per DALY averted. At the cost-effectiveness threshold of one times GDP per capita recommended by the WHO, compared with no PEP vaccination, PEP vaccination would be more cost-effective based on societal (27 USD per QALY gained) and healthcare perspectives (32 USD per QALY gained) in Tanzania [13], whereas PrEP treatment would be cost-effective compared to PEP vaccination based on healthcare perspective in the Philippines (25,152 PHP) [15]. Furthermore, PEP vaccination would be cost-effective in Iran (233 USD per DALY averted) [16] and Chad (46 USD/DALY averted) compared with no vaccination [17].

In addition, Bilinski et al. (2016) [18] also found that canine vaccination every 2 years with 80% coverage in pastoral area (3,791 USD per DALY averted) or canine vaccination every year with 70% coverage in agro-pastoral areas (2,785 USD per DALY averted) would be cost-effective at the cost-effectiveness threshold of 1–3 times GDP per capita recommended by the WHO. In addition, comprehensive intervention including dog vaccination and culling would cost 1,401 USD to prevent one DALY compared with baseline scenario providing healthcare and PEP vaccine only in Sri Lanka [19]. Similarly, canine vaccination at the target of 100,000 (1,064 USD per DALY averted) and 200,000 dogs (3,694 USD/DALY averted) would be more cost-effective interventions at the cost-effectiveness threshold of 1 to 3 times GDP per capita recommended by the WHO in India [20].

To compare the ICER values of all rabies preventive measures with the unit of outcome as cost per DALY averted or cost per QALY gained across studies, all ICER values in each country were adjusted to international dollar values using purchasing power parity (PPP) in 2016. It was suggested that PEP vaccination yields less cost per DALY averted or QALY gained (ICERs ranging from 91 to 754 International Dollars per QALY gained or DALY averted) due to the assessment of a specific time point at one year compared to canine vaccination (ICERs ranging from 4,262–15,880 International Dollars per QALY gained or DALY averted) during time horizon of 4 or 10 years (Table 4).

3.6. Model comparison

3.6.1. Type of cost-effectiveness modelling

Study designs were retrospective study (1 study, 6%) and modelling approach i.e., decision tree model (6 studies, 35%), dynamic model (6 studies, 35%). The 4 studies, however, which indicated the use of deterministic spreadsheet model (2 studies, 12%), simulation model (1 study, 6%), or model (1 study, 6%), did not adequately report details on their modelling approach. Model comparison in this review focused on decision tree and dynamic transmission models.

3.6.2. Model structure

3.6.2.1. Decision tree model. There were 6 studies which used decision tree model structures for CEA (2 study), CUA (3 study), and CMA (1 study). The CMA study [21] compared rabies pre-exposure vaccination and serological test strategies (i.e., booster vaccination was performed at least every 3 years in cases of seroconversion at Day 379 + 3 years) compared with the recommended strategy by the WHO and the Centers for Disease Control and Prevention (CDC) for both persons at continuous and frequent risk [21]. Five CEA and CUA studies (83%) used decision tree models to compare the costs and outcomes of the inventions as follows: (1) pre-exposure prophylaxis (PrEP) vs no PrEP [11] (1 study), (2) PrEP

Table 3
Summary results of cost-effectiveness analysis for rabies preventive measures.

	Study	Country	Perspective	Comparator	Interventions	ICER
	ICER = Cost per rabid dog prevented or averted					
1	Frerichs, R. R. and J. Prawda (1975). [7]	Colombia	Not reported	No dog vaccination	70% initial dog vaccination (entire city)	7.42 USD
					70% initial dog vaccination + 70% revaccination (yr. 5) (entire city)	4.34 USD
					Preferred vaccination policy (VA = 70%)	3.53 USD
2	Wera, E., et al. (2016) [8]	Indonesia	Government	No dog vaccination	Annual campaigns with short-acting vaccine (immunity duration of 52 weeks) with 70% coverage	3 USD
					Annual campaigns with long-acting vaccine (immunity duration of 156 weeks) with 70% coverage	1.81 USD
					Biannual campaigns with shortacting vaccine with 70% coverage	2.31 USD
					Once-in-2-years campaigns with long-acting vaccine with 70% coverage	9.38 USD
	ICER = Cost per death prevented or averted					
1	LeGuerrier, P., et al. (1996) [9].	Canada	Not reported	No PrEP vaccination	PrEP vaccination for travellers	5 billion CAD
2	Hampson, K., et al (2011) [10]	Africa and Asia	Healthcare providers	No PEP vaccination	PEP vaccination	60–200 USD
	ICER = Cost per life year gained or life year saved					
1	Shim, E., et al. (2009) [11]	Tanzania	Societal	No PEP vaccination	PEP vaccination	555 USD[1]
			Healthcare		PEP vaccination	668 USD
2	Fitzpatrick, M. C., et al. (2014) [12]	Saharan Africa	Policymakers	No dog vaccination	In Ngorongoro (pastoral): Canine vaccination with 45% coverage	4227 USD[2]
					In Serengeti (agro-pastoral): Canine vaccination with 90% coverage	3974 USD
					PEP vaccine for CII and CIII	Dominated
					PEP vaccine + RIG only for CIII	Dominated
					PEP vaccine for CII and vaccine + RIG for CIII	Dominated

[1] Willingness to pay (WTP) = 1 GDP per capita (1400 USD).
[2] WTP = 1-3 GDP per capita ($1430 - $4290).

Table 4
Comparison of the incremental cost-effectiveness ratio (ICER) in international dollar values adjusting by purchasing power parity (PPP) for rabies preventive interventions.

	Study	Country	Perspective	Comparator	Interventions	ICER	ICER International $ (PPP) 2016
	ICER = Cost per quality adjusted life year (QALY) gained						
1	Shim, E., et al. (2009) [11]	Tanzania	Societal	No PEP vaccination	PEP vaccination	27 USD[1]	91
			Healthcare		PEP vaccination	32 USD	108
2	Varghese et al (2017) [13]	The Philippines	Healthcare	PEP vaccination	PrEP vaccination	25,152 PHP[2]	N/A
	ICER = Cost per disability adjusted life year (DALY) averted						
1	Zinsstag, J., et al. (2009) [15]	Chad	Not reported	No PEP vaccination	PEP vaccination	46 USD	153
2	Hatam, N., et al. (2014) [14]	Iran	Government	No PEP vaccination	PEP vaccination	233 USD[3]	754
3	Hasler, B., et al. (2014) [16]	Sri Lanka	Societal	No canine vaccination	Comprehensive intervention (Canine vaccination and culling)	1401 USD	4292
4	Fitzpatrick, M. C., et al. (2016) [17]	India	Government	No canine vaccination	Canine vaccination (100,000 dogs)	1064 USD[4]	4262
					Canine vaccination (200,000 dogs)	3964 USD	15,880
					Canine vaccination + sterilization (100,000 dogs)	Dominated	
					Canine vaccination + sterilization (200,000 dogs)	Dominated	
					Canine vaccination + female sterilization (100,000 dogs)	Dominated	
					Canine vaccination + female sterilization (200,000 dogs)	Dominated	
5	Bilinski, A. M., et al. (2016) [16]	Tanzania	Policymakers	No canine vaccination	In Ngorongoro (pastoral) PEP every 2 years with 80% coverage	3791 USD[5]	10,956
					In Serengeti (agro-pastoral) PEP every year with 70% coverage	2785 USD	8048

[1] Willingness to pay (WTP) = 1 GDP per capita (1400 USD).
[2] WTP = 1 GDP per capita (118,295 PHP).
[3] WTP = 1 GDP per capita (12,258 USD).
[4] Willingness to pay (WTP) = 1–3 GDP per capita (1582 – 4746 USD).
[5] WTP = 1–3 GDP per capita (1610–4830 USD); N/A = not applicable.

vs post-exposure rabies prophylaxis (PEP) [15] (1 study), and (3) PEP vs no PEP (3 studies) [13,16,22]. Decision tree model was performed within time horizons of either 1 year (2 studies) or 10 years (2 studies); however, 2 studies did not report. All 5 studies developed different decision tree model structures to imitate the progression of rabies and treatment pattern according to preventive measures for rabies.

3.6.2.2. Transmission dynamic model for cost-effectiveness analysis. There were 6 studies which used transmission dynamic model to compare cost-effectiveness of rabies preventive interventions i.e., canine and wildlife vaccination (5 studies) as well as human PEP (1 study) in rabies endemic regions i.e., Africa (Chad, Tanzania), Asia (India, Indonesia) and Colombia (Latin America). Fitzpatrick et al conducted 2 studies in Tanzania [14] and India [20] using the

compartmental dynamic models. Mostly transmission dynamic models were consisted of 5 states i.e., susceptible (S), infectious (I), vaccinated (V) and immune (R) to simulate the dynamics of dog or wildlife population and rabies virus transmission. Similarly, Billinski et al (2016) also applied the transmission model adapted from a dynamic transmission model used in the published study of Fitzpatrick et al (2014). The study of Wera et al (2016) applied a deterministic simulation model incorporating the dynamics of a dog population and rabies virus transmission following the principles obtained from Hampson et al (2007) and Zinsstag et al (2009). In addition, another study of Zinsstag et al (2009) conducted in Chad, Africa also used the dynamic transmission models with 4 compartments of the models for dogs and humans.

4. Discussion

This review detected a reasonable number of economic evaluations of different preventive strategies for rabies elimination, with majority of the studies focused on the country assessment of the impact of PEP access after the release of the WHO recommendation on rabies vaccine in 2007. Given the endemicity of rabies, the quantity of studies identified was not expected to be high (only 17 studies), and most studies (65%) has been performed in Africa and Asia where human death due to rabies were the highest compared to other regions of the world. Economic evaluation studies of a variety of rabies preventive interventions were performed and compared interventions which mostly focused on PEP treatment of varying implementation strategies and scenarios, while transmission dynamic modelling primarily focused on dog vaccination and other dog management strategies. The main research objectives were related to (1) the estimation of the impact of increasing access to PEP treatment, (2) the assessment of impact or long-term investment for human rabies elimination scenarios using mass dog vaccinations only, (3) the estimation of the impact of increasing access to PrEP treatment, and (4) the evaluation of impact or long-term investment for human rabies elimination scenarios using mass dog vaccinations and PEP strategy.

Until now, human rabies deaths have been still occurred especially in the low resource setting such as countries in Africa and Asia. These may be resulted from the lack of PEP, reduced vaccination coverage, and lack of people knowledge and awareness of the importance of PEP vaccination [23,24]. Results from our review suggest that PEP vaccination was the most cost-effective strategy to prevent human death from rabies. This finding was also complied with WHO strategies that recommend post-exposure treatment for human rabies prevention. Therefore, increase availability and accessibility of PEP vaccination, as well as emphasize health education and public awareness about the importance of post exposure treatment are the significant issues to minimize the human death from rabies.

Overall, the quality of methods employed by the economic evaluations is relatively good. Most studies applied CEA or CUA methods - the recommended economic evaluation methods to compare costs and outcomes of rabies preventive measures to inform policy decision-making [25]. No significant inconsistency across their methods was identified and the extent of reporting based on the CHEERS checklist is generally high either across individual studies or across the reporting domains. This may be on account of the fact that while most studies were focused on low-income country settings where rabies is endemic, it was noted that the first authors were mostly affiliated with the academe and institutions from high-income countries where health economics are relatively well-established.

Nevertheless, there remains to be room for improvement on the following fundamental economic evaluation domains. First, while many studies have been found to have considered the efficacy of the human rabies vaccine [26] in the evaluations, it was noticed that none has conducted or referred to systematic reviews or meta-analyses in the estimation of vaccine efficacy. It was also highlighted that five studies assumed 100% vaccine efficacy of human vaccines, as the efficacy of human rabies vaccine is very high and true vaccine failures are very rare and mostly related to non-compliance with recommended procedures of PEP. Second, model specifics and underpinning assumptions, as well as complete study parameters and necessary details (i.e., ranges, distribution and references) should be clearly and completely discussed, as these were not sufficiently reported by all studies. Third, we have noted that only two papers have reported clear information on the fitting of the model (i.e., Fitzpatrick et al, 2016 [20] and Zinsstag et al, 2009 [15]). Albeit not covered in the CHEERS checklist, the internal validity of these assessments may be improved by discussing methods on model calibration or validation, as these methods are crucial steps in understanding whether the obtained results would be reliable to inform policy decision-making towards efficiently implementing rabies preventive measures. Lastly, the failure to adequately stipulate the study limitations and potential biases along with the discussion of key findings of the assessed economic evaluations and conflicts of interest was noted as common gaps and point for improvement for the reporting quality. Although one-third of all studies did not report the conflicts of interest statements, we included these studies for the reason that our systematic review aimed to identify all existing cost-effectiveness modelling studies of all preventive measures for rabies, assess the quality of individual rabies models as well as generate a synthesis of key findings. However, it was noticed that no conflict of interest statements from such studies might not have the impact on the outcome of the review, in particularly economic evaluation results, since these papers were conducted from the researchers in academic institutions where usually had clear guidelines to manage conflicts of interest [11,13,14].

In relation to the comparative assessment of the economic evaluation studies on rabies preventive interventions (17 studies) which applied the modelling approach (12 studies), we found that decision tree (6 studies) and transmission dynamic (6 studies) models were used to evaluate costs and outcomes of PEP vaccination and canine or wildlife related interventions, respectively. Decision tree models had similar pathways and dynamic transmission models were similarly demonstrated as a compartmental model with 5 states i.e., susceptible (S), infectious (I), vaccinated (V) and immune (R) to simulate the dynamics of dog or wildlife population and rabies virus transmission.

According to the results of CEA or CUA studies, it was suggested that rabies preventive interventions would be cost-effective at the cost-effectiveness threshold of 1 to 3 times per capita GDP as recommended by the WHO, compared with no intervention in rabies endemic countries. Most studies referred the cost-effectiveness threshold from the Commission on Macroeconomics and Health's GDP based thresholds [27]; however, it should be interpreted with caution that the cost-effectiveness threshold should not be used as the only criteria for policy decision-making and other criteria such as affordability, budget impact, fairness, and other important considerations in the local context should also be accounted in a country-specific process for decision-making [28]. Nevertheless, it was noted that there were still controversies and limitations in using the cost-effectiveness threshold recommended by the Commission on Macroeconomics and Health's GDP based thresholds which could result in failing to assess and rank interventions within countries and ignore budget limitations and possibly misleading decision makers [29]. Therefore, it was suggested that WHO should develop a new framework for guiding cost-effectiveness threshold especially low and middle income countries[29].

When compared across studies which reported ICER as cost per QALY gained or DALY averted in international dollars adjusted by purchasing power parity conversion rate, it was demonstrated that PEP vaccination yields less cost per DALY averted or QALY gained due to the assessment of a specific time point at one year com-

pared to canine vaccination during time horizon of 4 or 10 years. This could be explained by the targeted provision of PEP vaccination administered only to patients who were suspected to be exposed with rabid animals; whereas higher budget would be required to invest in canine related rabies preventive measures such as mass canine vaccination, sterilization, culling, etc.

It is important to address the limitation that this review included published studies in English language only, thereby eliminating other possibly available data published as local reports or grey literature, except one included unpublished report from the GSK vaccine [15] which was submitted to the WHO Immunization and vaccines related implementation research advisory committee (IVR-AC).

5. Conclusion

Our review found 17 economic evaluation studies comparing interventions for rabies elimination. These interventions would depend from country to country. Most of the interventions focused on PEP treatment. However, the implementation strategies and scenarios of PEP treatment were varied in African and Asian countries. The overall quality of reporting and methods used in economic evaluation studies is relatively good. Decision tree models and dynamic transmission models were applied to evaluate costs and outcomes of PEP vaccination and canine or wildlife related interventions, respectively. Generally, rabies preventive interventions would be cost-effective at the cost-effectiveness threshold of 1 to 3 times per capita GDP as recommended by the WHO, compared with no intervention in rabies endemic countries. In addition, PEP vaccination was the most cost-effectiveness strategy to prevent rabies human death, when compared with other interventions. However, it should be interpreted with caution that the cost-effectiveness threshold should not be used as the only criteria for policy decision-making and there were still controversies and limitations in using the cost-effectiveness threshold recommended by the Commission on Macroeconomics and Health's GDP based thresholds which could result in failing to assess and rank interventions within countries and ignore budget limitations and possibly misleading decision makers.

Conflict of interest declaration

All authors have no conflict of interest.

Acknowledgements

This work was supported by grants from the World Health Organization (WHO) and Health Intervention and Technology Assessment Program (HITAP), Department of Health, Ministry of Public Health, Nonthaburi, Thailand. HITAP is funded by the Thailand Research Fund under the senior research scholar on Health Technology Assessment [grant numbers RTA5980011] and the Bureau of Health Policy and Strategy, Ministry of Public Health. HITAP's International Unit is part of the iDSI to provide technical assistance on health intervention and technology assessment to governments in low- and middle-income countries. The iDSI is funded by the Bill & Melinda Gates Foundation; the UK's Department for International Development and the Rockefeller Foundation [grant numbers OPP124589]. The findings, interpretations and conclusions expressed in this article do not necessarily reflect the views of the aforementioned funding agencies. We would like to thank Professor Ben Cooper for providing useful comments and suggestions on this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2018.11.071.

References

[1] Frey J, Mindekem R, Kessely H, Doumagoum Moto D, Naissengar S, et al. Survey of animal bit injuries and their management for an estimate of human rabies deaths in N'Djamena. Chad. Trop Med Int Health 2013;18:1555–62.
[2] Knobel DL, Cleaveland S, Coleman PG, Fevre EM, Meltzer MI, et al. Re-evaluating the burden of rabies in Africa and Asia. Bull World Health Organ 2005;83.
[3] Hampson K, Coudeville L, Lembo T, Sambo M, Kieffer A, Attlan M, et al. Estimating the global burden of endemic canine rabies. PLoS Negl Trop Dis. 2015;9:e0003709.
[4] Coleman PG, Dye C. Immunization coverage required to prevent outbreaks of dog rabies. Vaccine 1996;14:185–6.
[5] Kasempimolporn S, Sichanasai B, Saengseesom W, Puempumpanich S, Sitprija V. Stray dogs in Bangkok, Thailand: rabies virus infection and rabies antibody prevalence. Dev Biol (Basel) 2008;131:137–43.
[6] Kayali U, Mindekem R, Yemadji N, Vounatsou P, Kaninga Y, Ndoutamia A, et al. Coverage of pilot parenteral vaccination campaign against canine rabies in N'Djamena. Chad. Bull World Health Organ 2003;81:739–44.
[7] Chaikledkaew U, Thavorncharoen M, Thunyarat A, Youngkong S, Meeyai AC, Rattanavipapong W, et al. Report of Epidemiological, Cost-effectiveness and Impact Modelling for Rabies. Bangkok: Mahidol University; 2017.
[8] Husereau D, Drummond M, Petrou S, Moher D, Greenberg D, Augustovski F, et al. Consolidated health economic evaluation reporting standards (CHEERS) statement. BMJ 2013;346:f1049.
[9] Frerichs RR, Prawda J. Computer simulation model for the control of rabies in an urban area of colombia. Manage Sci 1975;22:411–21.
[10] Wera E, Mourits MC, Siko MM, Hogeveen H. Cost-effectiveness of mass dog vaccination campaigns against rabies in Flores Island, Indonesia. Transbound Emerg Dis. 2016.
[11] LeGuerrier P, Pilon PA, Deshaies D, Allard R. Pre-exposure rabies prophylaxis for the international traveller: a decision analysis. Vaccine 1996;14:167–76.
[12] Hampson K, Cleaveland S, Briggs D. Evaluation of cost-effective strategies for rabies post-exposure vaccination in low-income countries. PLoS Negl Trop Dis 2011;5:e982.
[13] Shim E, Hampson K, Cleaveland S, Galvani AP. Evaluating the cost-effectiveness of rabies post-exposure prophylaxis: a case study in Tanzania. Vaccine 2009;27:7167–72.
[14] Fitzpatrick MC, Hampson K, Cleaveland S, Mzimbiri I, Lankester F, Lembo T, et al. Cost-effectiveness of canine vaccination to prevent human rabies in rural Tanzania. Ann Intern Med 2014;160:91–100.
[15] Varghese L, Demarteau N, Preiss S, Mukherjee P. A health economic model for a rabies pre-exposure prophylaxis program in high-risk age groups. GlaxoSmithKline (GSK) 2017.
[16] Hatam N, Esmaelzade F, Mirahmadizadeh A, Keshavarz K, Rajabi A, Afsar Kazerooni P, et al. Cost-effectiveness of rabies post exposure prophylaxis in Iran. J Res Health Sci. 2014;14:122–7.
[17] Zinsstag J, Durr S, Penny MA, Mindekem R, Roth F, Menendez Gonzalez S, et al. Transmission dynamics and economics of rabies control in dogs and humans in an African city. Proc Natl Acad Sci USA. 2009;106:14996–5001.
[18] Bilinski AM, Fitzpatrick MC, Rupprecht CE, Paltiel AD, Galvani AP. Optimal frequency of rabies vaccination campaigns in Sub-Saharan Africa. Proc Biol Sci 2016;283.
[19] Hasler B, Hiby E, Gilbert W, Obeyesekere N, Bennani H, Rushton J. A one health framework for the evaluation of rabies control programmes: a case study from Colombo CitySri Lanka. PLoS Negl Trop Dis. 2014;8:e3270.
[20] Fitzpatrick MC, Shah HA, Pandey A, Bilinski AM, Kakkar M, Clark AD, et al. One Health approach to cost-effective rabies control in India. Proc Natl Acad Sci USA. 2016;113:14574–81.
[21] Strady C, Hung Nguyen V, Jaussaud R, Lang J, Lienard M, Strady A. Pre-exposure rabies vaccination: strategies and cost-minimization study. Vaccine 2001;19:1416–24.
[22] Ribadeau Dumas F, N'Diaye DS, Paireau J, Gautret P, Bourhy H, Le Pen C, et al. Cost-effectiveness of rabies post-exposure prophylaxis in the context of very low rabies risk: a decision-tree model based on the experience of France. Vaccine 2015;33:2367–78.
[23] Barbosa Costa G, Gilbert A, Monroe B, Blanton J, Ngam Ngam S, Recuenco S, et al. The influence of poverty and rabies knowledge on healthcare seeking behaviors and dog ownership Cameroon. PloS one 2018;13:e0197330.
[24] Knobel DL, Cleaveland S, Coleman PG, Fevre EM, Meltzer MI, Miranda ME, et al. Re-evaluating the burden of rabies in Africa and Asia. Bull World Health Organ 2005;83:360–8.
[25] Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. Methods for the economic evaluation of health care programme. Third ed. Oxford: Oxford University Press; 2005.
[26] World Health Organization. Rabies vaccines: WHO position paper. Geneva: World Health Organization; 2010.
[27] World Health Organization. Macroeconomics and health: investing in health for economic development. Report of the Commission on Macroeconomics and Health. Geneva: World Health Organization; 2001.
[28] Bertram MY, Lauer JA, Joncheere KD, Edejer T, Hutubessy R, Kienya MP, et al. Cost–effectiveness thresholds: pros and cons. Bull World Health Organ 2016;94:925–30.
[29] Marseille E, Larson B, Kazi D, Kahn J, Rosen S. Thresholds for the cost–effectiveness of interventions: alternative approaches. Bull World Health Organ 2015;93. 118-24.