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Rabies in Southeast Asia: a systematic review of its epidemiology and impact

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Abstract

Objective: Rabies is a neglected zoonotic disease that can infect all mammals, including humans. We aimed to summarize current knowledge on the epidemiology and impact of rabies in Southeast Asia.

Methods: This systematic review is conducted using PRISMA review protocol and formulation of research questions based on CoCoPop (condition, context, population) and PEO (population, exposure, outcome) concepts. The selected databases included Scopus, Web of

Science, and PubMed. After a thorough screening, 7 articles were selected to proceed with quality appraisal using Mixed Method Appraisal Tool.

Results: A total of 7 articles were included in this analysis. In Vietnam, the incidence of rabies ranged from 1.7 to 117.2 per 100,000 from 2011 to 2015 with higher incidences observed in southern Vietnam, particularly in the Mekong River Delta and South-Central Coast. The cumulative incidence in Sibu, Sarawak was estimated at 1.7 per 100,000 population. In Indonesia, 104 human rabies cases were reported in Bali from November 2008 to November 2010 while a total of 46 confirmed and probable cases of human rabies were reported in Thailand from 2010 to 2015. Most cases were male. Increased risk of rabies virus infection was associated with high population density, illiteracy, seasonal patterns as well as among dog butchers. Almost all cases had a history of dog bites. The case-fatality rate was 100%.

Conclusion: The presence of rabies cases in Southeast Asia is due to a high number of unvaccinated stray and pet dogs, working hazards (dog butcher in Vietnam), the unavailability of rabies vaccine in rural regions, and misinformation about the significance of seeking treatment after dog bites.

Keywords: Rabies, dog bite, zoonotic disease, epidemiology, Southeast Asia

Strengths and limitations

This study only includes research from Southeast Asia, which may not represent rabies infection in other regions or continents. Furthermore, we only used three databases, which may have limited the article's resources. We did not include grey literature or national guidelines, which could have been useful in this study. Our strengths, however, are that we can tailor the control program specifically for Southeast countries, and we are aware of the true burden of rabies infection in our region.

Introduction

Rabies is a neglected zoonotic disease that is caused by an RNA virus from the family of *Rhabdoviridae*, genus *Lyssavirus* (1). Once clinical symptoms appear, rabies is almost 100% fatal (2). All mammals can be infected with the rabies virus, including humans. More than 99% of human rabies cases are transmitted via dogs (3). With the necessary evidence and tools in place for control and elimination of rabies, canine rabies can be eliminated, as demonstrated in Western Europe, Canada, the United States of America (USA), Japan, a few Latin American countries, and many parts in Asia. However, rabies is still widespread, occurring in more than 80 countries, particularly in the developing countries in Africa and Asia (3,4). Furthermore, half of the global population lives in canine rabies-endemic areas hence is at risk of contracting rabies (3).

Globally, canine rabies was estimated to cause approximately 59,000 human deaths annually. Rabies is clearly a major problem in Asia. The number of human deaths due to rabies in Asia is higher than in any other region in the world. Most human rabies deaths occurred in Asia (59.6%), followed by Africa (36.4%), while only less than 0.05% of human rabies deaths occurred in the Americas. Additionally, India alone accounts for 35% of global human rabies deaths, which was higher than any other country (4). In Asia, canine rabies was estimated to cause a loss of 2.2 million Disability-Adjusted Life Years (DALYs) per year, while the annual cost of post-exposure prophylaxis (PEP) was highest in Asia, with estimates up to US$ 1.5 billion (5).

In Southeast Asia, only Singapore has eradicated canine rabies through the implementation of robust national rabies control programs, while other countries in this subregion were not considered to be rabies-free (6). Malaysia was once declared to be rabies-free by the World Animal Health Organisation in July 2013, but several rabies outbreaks since

2015 have relegated Malaysia down from its rabies-free status (7). Even though Thailand and Vietnam have not been able to eliminate rabies, there was a substantial reduction of human rabies deaths through the implementation of dog mass vaccination, intensified post-exposure prophylaxis in humans, and awareness education (8).

Rabies is 100 percent preventable through vaccination in animals and humans (9). The World Health Organization (WHO) recommended pre-exposure prophylaxis (PrEP) for those with continual, frequent, or increased risk of exposure to rabies virus (e.g., veterinarians, animal handlers). If exposed to a rabid animal, the WHO recommended PEP, which consists of immediate wound management, immediate vaccination, as well as administration of rabies immunoglobulin for high-risk exposure (10). Nevertheless, dog vaccination is considered the most cost-effective strategy for preventing rabies in humans (2).

Despite the availability of evidence and guidelines for the control and management of rabies, there are some constraints faced by countries in Southeast Asia in controlling rabies, including inadequate resources, lack of political commitment, lack of consensus on strategy, weak intersectoral coordination, insensitive surveillance systems, limited accessibility to modern rabies vaccine and supply problem, as well as lack of public awareness and cooperation (8). The high estimated burden for rabies more than justifies the need to prioritize rabies control, particularly in Asian countries.

Information on rabies epidemiology is a prerequisite for effective planning of rabies control programs. Previous systematic reviews focused on rabies epidemiology in India (11), Nepal (1), and Arab countries (12), while literature synthesizing data regarding rabies epidemiology in Southeast Asia are limited. Hence, this systematic review aims to provide an in-depth assessment of the rabies situation in Southeast Asia countries, based on the published literature.

Materials and Methods

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (13).

Patient and Public involvement

No patient and/or public involvement in this study (None).

Research Question Formulation

The review question was developed based on the CoCoPop (condition, context, population) and PEO (population, exposure, outcome) concept (14). The PICO (population, intervention, comparison intervention, outcome measures) framework is commonly used in developing focused clinical questions for quantitative reviews (15), while the CoCoPop and PEO concepts are suitable for reviews related to prevalence and aetiology (14). Based on the CoCoPop concept, the condition refers to the epidemiology of rabies, the context refers to Southeast Asia and the population is the general population. Based on the PEO concept, population refers to the general population in Southeast Asia, exposure refers to rabies and the outcome is the impact of rabies. Epidemiology of rabies was defined as the number of outbreaks, cases, and its causes/risk factors, while the impact was defined as rabies mortality. Hence, the main research questions are: (1) What is the epidemiology of rabies among the general population in Southeast Asia countries? and (2) What is the impact (mortality) of rabies among the general population in Southeast Asia countries?

Data Source and Search Strategy

The literature search was conducted in December 2021. For a comprehensive search, we used Scopus, Web of Science, and PubMed databases. The keywords used for the searching of related articles are provided in Table 1.

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121 Table 1: Keywords search used in the screening process

Database	Search string
Scopus	1) TITLE-ABS-KEY((“rabies*” OR “rabies virus*” OR “dog bite*”) AND (“Southeast Asia” OR “Brunei” OR “Myanmar” OR “Cambodia” OR “Timor-Leste” OR “Indonesia” OR “Laos” OR “Malaysia” OR “Philippines” OR “Singapore” OR “Thailand” OR “Vietnam”) AND (“epidemiology” OR “outbreak” OR “case” OR “prevalence” OR “incidence” OR “causes” OR “risk factor”)) 2) TITLE-ABS-KEY((“Rabies*” OR “Rabies virus*” OR “dog bite*”) AND (“Southeast Asia” OR “Brunei” OR “Myanmar” OR “Cambodia” OR “Timor-Leste” OR “Indonesia” OR “Laos” OR “Malaysia” OR “Philippines” OR “Singapore” OR “Thailand” OR “Vietnam”) AND (“mortality*” OR “death*” OR ”fatality*”))
Web of Science	1) (((ALL=("rabies*")) OR ALL=("rabies virus*")) OR ALL=("dog bite*") AND ((((((((((ALL=("Southeast Asia")) OR ALL=("Brunei")) OR ALL=("Myanmar")) OR ALL=("Cambodia")) OR ALL=("Timor-Leste")) OR ALL=("Indonesia")) OR ALL=("Laos")) OR ALL=("Malaysia")) OR ALL=("Philippines")) OR ALL=("Singapore")) OR ALL=("Thailand")) OR ALL=("Vietnam")) AND ((((((ALL=("epidemiology")) OR ALL=("outbreak")) OR ALL=("case")) OR ALL=("prevalence")) OR ALL=("incidence")) OR ALL=("causes")) OR ALL=("risk factor") 2) (((ALL=("rabies*")) OR ALL=("rabies virus*")) OR ALL=("dog bite*") AND ((((((((((ALL=("Southeast Asia")) OR ALL=("Brunei")) OR ALL=("Myanmar")) OR ALL=("Cambodia")) OR ALL=("Timor-Leste")) OR ALL=("Indonesia")) OR ALL=("Laos")) OR ALL=("Malaysia")) OR ALL=("Philippines")) OR ALL=("Singapore")) OR ALL=("Thailand")) OR ALL=("Vietnam")) AND ((ALL=("mortality*")) OR ALL=("death*")) OR ALL=("fatality*")
PubMed	1) ((((("rabies*") OR ("rabies virus*")) OR ("dog bite*")) AND ((((((((((("Southeast Asia") OR ("brunei")) OR ("Myanmar")) OR ("Cambodia")) OR ("Timor-Leste")) OR ("Indonesia")) OR ("Laos")) OR ("Malaysia")) OR ("Philippines")) OR ("Singapore")) OR ("Thailand")) OR ("Vietnam"))) AND (((((("epidemiology") OR ("outbreak")) OR ("case")) OR ("prevalence")) OR ("incidence")) OR ("causes")) OR ("risk factor"))

	2) ((("rabies*") OR ("rabies virus*")) OR ("dog bite*")) AND ((((((((((("Southeast Asia") OR ("brunei")) OR ("Myanmar")) OR ("Cambodia")) OR ("Timor-Leste")) OR ("Indonesia")) OR ("Laos")) OR ("Malaysia")) OR ("Philippines")) OR ("Singapore")) OR ("Thailand")) OR ("Vietnam"))) AND ((("mortality*") OR ("death*")) OR ("fatality*"))

Study Selection

The inclusion criteria were: (1) publication from 2012-2021; (2) original article; (3) publication in the English language. Studies with these characteristics were included in this review: (1) report on the epidemiology of rabies in Southeast Asia; and (2) report on the impact of rabies in Southeast Asia. Non-original articles such as conference proceedings, perspectives, commentary, opinion, reports, systematic reviews, and meta-analyses were excluded.

Data Extraction and Synthesis

Duplicates were deleted, and at least two reviewers re-screened the remaining papers. Before being included in the review, articles were screened in three stages. Any article that did not meet the inclusion criteria from title screening was eliminated in the first phase. The abstracts of the remaining papers were reviewed in the second phase, and any publications that did not fit our inclusion criteria were eliminated from the review. The full-text articles were examined attentively in the last phase to eliminate any papers that did not fulfil our inclusion criteria. Before the data extraction process, both reviewers must agree that the entire publications should be reviewed. Any disagreements were worked out through discussion. All data extraction was conducted independently using a standardized data extraction form which was organized using Microsoft Excel. Information collected in the form included (1) author, (2) publication year, (3) reference, (4) country, (5) study design, (6) statistical analysis, and (7) results.

Quality Appraisal

Quality appraisal was conducted by authors on all 7 studies using the Mixed Method Appraisal Tool (MMAT) (16). The MMAT is a critical appraisal tool that is developed to appraise studies included in systematic mixed study reviews. The methodology quality of five categories of studies (qualitative study, randomized control trials, non-randomized studies, quantitative descriptive study, and mixed methods study) can be appraised using this tool. For each category, five criteria are used to assess the quality of the study. It is advised not to calculate an overall score from the rating of each criterion using the latest version of MMAT (2018). However, due to problems faced by researchers in reporting the MMAT results, a suggestion was provided for reporting an overall score (5*****/100% quality criteria met; 4****/80% quality criteria met; 3***/60% quality criteria met; 2**/40% quality criteria met; 1*/20% quality criteria met). The details of this assessment are reported in Table 2.

Table 2: The details of mixed method appraisal tool assessment

Author	**Type of study**	**Score**	**1.1**	**1.2**	**1.3**	**1.4**	**1.5**
			Is the sampling strategy relevant to address the research question?	Is the sample representative of the target population?	Are the measurements appropriate?	Is the risk of nonresponse bias low?	Is the statistical analysis appropriate to answer the research question?
Nguyen et al. 2021	Quantitative	40%	Can't tell	Can't tell	Yes	Can't tell	Yes

Pham et al. 2021	Quantitative	100 %	Yes	Yes	Yes	Yes	Yes
Sim et al. 2021	Quantitative	60%	Yes	Can't tell	Yes	Can't tell	Yes
Yurachai et al. 2021	Quantitative	80%	Yes	Yes	Yes	Can't tell	Yes
Phung et al. 2018	Quantitative	80%	Yes	Yes	Yes	Can't tell	Yes
Susilawati et al. 2012	Quantitative	80%	Yes	Yes	Yes	Yes	No
Lee et al. 2017	Quantitative	100 %	Yes	Yes	Yes	Yes	Yes

Results

There were 1,366 records identified from the three databases to evaluate the epidemiology of rabies and its impact in Southeast Asia. Using automation tools, 813 records were excluded based on year, publication type, and language. A total of 73 duplicate records were found and removed, leaving 480 records for title screening. We screened the titles and abstracts independently based on the review questions. A total of 462 articles were removed during the screening. For the remaining 18 articles, the full text was retrieved for assessment of eligibility. Disagreements were resolved through discussion to reach a consensus. 11 articles were removed as they were not according to the objective (4), not primary/original research articles (5) and the full article could not be retrieved (2), leaving a total of 7 articles to proceed with a quality appraisal. Our search PRISMA flowchart is presented in Figure 1.

Background of the Eligible Studies

A total of 7 studies were included in this systematic review in which 4 studies were conducted in Vietnam, and 1 each from Indonesia, Malaysia, and Thailand (Table 3). The theme discussed by all studies was epidemiology (number of cases, incidence rates, distributions, causes, risk factors) of rabies in Southeast Asia. Among the included studies, 2 studies particularly discussed rabies's impact (mortality).

176 Table 3: Table of evidence

Author/year	Country	Reference	Study design	Statistical analysis	Result
Nguyen et al. 2021	Vietnam	Nguyen, A. K. T., Vu, A. H., Nguyen, T. T., Nguyen, D. V., Ngo, G. C., Pham, T. Q., Inoue, S., et al. 2021. Risk factors and protective immunity against rabies in unvaccinated butchers working at dog slaughterhouses in Northern Vietnam. *American Journal of Tropical Medicine and Hygiene* 105(3): 788–793. doi:10.4269/ajtmh.20-1172	Cross-sectional	Pearson correlation Multivariate regression analysis	Study found that 28.3% of butchers were at risk of rabies exposure due to slaughtering sick dog, getting bitten, scratched or knife cut. Only 8.6% had NTA sufficient for protection and only 8.1% of them were vaccinated. Hence dog butchers in Vietnam were at high risk of rabies virus infection.
Pham et al. 2021	Vietnam	Pham, Q. D., Phan, L. T., Nguyen, T. P. T., Doan, Q. M. N., Nguyen, H. D., Luong, Q. C. & Nguyen, T. V. 2021. An Evaluation of the Rabies Surveillance in Southern Vietnam. *Frontiers in Public Health* 9(April): 1–9. doi:10.3389/fpubh.2021.610905	Cross-sectional	Descriptive Chi-square test / Fisher's exact test	94 human rabies cases (2009-2018) were reported in Southern Vietnam, with an average of nine cases recorded annually (2.7 cases per 10 million population). The highest number was reported in 2018. Majority of cases were male and those aged 50 years and above.
Sim et al. 2021	Malaysia	Sim, B. N. H., Liang, B. N. W., Ning, W. S. & Viswanathan, S. 2021. A retrospective analysis of emerging rabies: A neglected tropical disease in Sarawak, Malaysia. *Journal of the*	Cross-sectional	Descriptive	6 cases were identified with a mixture of MN and LMN findings. Most cases did not seek medical attention upon dog bite. The incubation period varied from 17 days to 2 years. All cases died, with 5 cases succumbing to the illness within 2 weeks of symptoms onset. The cumulative

		Royal College of Physicians of Edinburgh 51(2): 133–139. doi:10.4997/JRCPE.2021.207			incidence in Sibu was estimated at 1.7 per 100,000 population.
Yurachai et al. 2021	Thailand	Yurachai, O., Hinjoy, S. & Wallace, R. M. 2020. An epidemiological study of suspected rabies exposures and adherence to rabies post-exposure prophylaxis in Eastern Thailand, 2015. *PLoS Neglected Tropical Diseases* 14(2): 1–17. doi:10.1371/journal.pntd.0007248	Cross-sectional	Descriptive	46 confirmed and probable cases of human rabies were reported in Thailand (2010 – 2015). 11 were reported from Eastern Thailand. 6,204 suspected rabies exposure reported in 8 Eastern Thailand. Children age < 15 years and elderly age > 60 years had the highest suspected reported exposure rate compared to others (189.7/ 100,000 and 189.2/100,000). Overall, the estimated suspected rabies exposure rate was 204/100,000.
Susilawati et al. 2012	Indonesia	Susilawathi, N. M., Darwinata, A. E., Dwija, I. B. N. P., Budayanti, N. S., Wirasandhi, G. A. K., Subrata, K., Susilarini, N. K., et al. 2012. Epidemiological and clinical features of human rabies cases in Bali 2008-2010. *BMC Infectious Diseases* 12(November 2008): 0–7. doi:10.1186/1471-2334-12-81	Cross-sectional	Descriptive	104 human rabies cases reported in Bali during November 2008-November 2010 which all are fatal and the symptom exhibit by all patients. Almost all (92%) cases had a history of dog bite. Only 5.8% had their wounds treated and received an anti-rabies vaccine (ARV) after the bite incident. The case-fatality rate was 100%.

Epidemiology of Rabies in Southeast Asia Countries

The average monthly number of rabies cases in Vietnam is 429 during the period from 2011 to 2015, where the incidences of rabies ranged from 1.7 to 117.2 per 100,000 with higher incidences observed in Red River, South Central Coast (SCC), and the Mekong Delta regions (17). Specific to Southern Vietnam, a total of 94 human rabies cases between 2009 and 2018 were reported, with an average of nine cases recorded annually, representing an incidence of 2.7 cases per 10 million population (18). The highest number was reported in 2018 (5.5 cases per 10 million population). Most cases were male and those aged 50 years and above.

Dog butchers in Vietnam were at high risk of rabies virus infection (19). The study found that 28.3% of butchers were at risk of rabies exposure due to slaughtering sick dogs, getting bitten, scratched, or knife cut. Among 406 participants, 8.6% had rabies neutralizing antibody (NTA) sufficient for protection and only 8.1% of them were vaccinated. In terms of location, rabies cases were limited to specific areas. Hotspots were identified in southern Vietnam, particularly in the Mekong River Delta (MRD) and South-Central Coast (SCC) (20). Seasonal patterns were found in which a strong peak in February/ July and a minor peak in October/ December in the MRD Region. However, a strong peak was detected in the middle of each year in the SCC. Temperature, humidity, and cumulative rainfall are positively associated with an increase in incidences of rabies in Vietnam. In terms of socio-economic factors, increases in population density, as well as the percentages of illiteracy, were sensitive factors for elevated risk of rabies (17).

In Indonesia, 104 human rabies cases were reported in Bali from November 2008 to November 2010. Most of the cases were male. Almost all (92%) cases had a history of a dog bite. Only 5.8% had their wounds treated and received an anti-rabies vaccine (ARV) after the

bite incident (21). Even worse, rabies cases in Sibu, Sarawak did not seek medical attention upon dog bite as well (22). The cumulative incidence in Sibu was estimated at 1.7 per 100,000 population. The incubation period varied from 17 days to 2 years.

A total of 46 confirmed and probable cases of human rabies were reported in Thailand from 2010 to 2015, in which 11 were reported from Eastern Thailand (23). Even though rabies can be prevented by vaccination, more than 90% of rabies deaths in Thailand did not get or improperly stopped receiving PEP. In terms of suspected rabies exposures, 6,204 exposures were reported from eight provinces in Eastern Thailand, resulting in a crude exposure rate of 106 reported rabies exposures per 100,000 people. Dogs were the main source of exposure (77.8%), while children under the age of 15 and the elderly over the age of 60 had the highest overall reported exposure rates (189.7 and 189.2/100,000, respectively).

Impact of Rabies in Southeast Asia Countries

The case-fatality rate was 100% as (21,22). Among 6 cases reported in Sibu, 5 cases succumbed to the illness within 2 weeks of symptoms onset.

Discussion

Epidemiology of Rabies in Southeast Asia Countries (Distribution, Causes/Risk Factors of Rabies)

Rabies in Asia and Africa contributes to over 99% of human rabies deaths that occur in the world today. The vast majority of 60% of these deaths are in Asia (24). Every year, an estimated 59,000 people die from rabies worldwide, with the majority (95%) of these deaths occurring in Africa and Asia due to a lack of post-exposure prophylaxis (PEP) services for animal-bite patients and rabies surveillance personnel and facilities (25). This support the result of our study which shows that there is a high number of rabies cases reported in Vietnam, Indonesia, and Thailand, which are medium endemic rabies country (26).

Rabies is concentrated in Asia and Southeast Asia region because rabies is frequently neglected when health and agriculture budgets are set although the costs and economic benefits of having rabies prevention programs have been successfully implemented in high-income country (27). The high number of rabies cases in Southeast Asia is also contributed by the high number of unowned, free-roaming dogs that can't be controlled without a lot of effort and thus aren't vaccinated (28). Vaccination programs in dogs can provide herd immunity and break the rabies transmission cycle in this reservoir species and had been successfully applied in several countries around the world (29).

Another cause of high incidence of rabies in Southeast Asia is due to the working hazard of dog butchers, especially in a country that legalizes dog consumption such as in Vietnam (30). Professional dog butchers in northern Vietnam are at a high risk of rabies virus infection due to exposure during the slaughtering process, which was from the slaughtering of sick or dead dogs, getting bitten, scratched, or knife cut. (91.9%) professional dog butchers in Vietnam were not vaccinated against rabies, which maybe because of the fear of side effects of rabies vaccine, inability to afford vaccination, and incorrect knowledge of rabies prevention (19).

Impact of Rabies in Southeast Asia Countries (Cases/Outbreak, Morbidity/Mortality)

In this study, rabies had a high fatality rate, with 100 percent of infected cases dying. This is supported by a review done in Africa by Nyasulu et al 2021, who reported that Algeria, Namibia, Eswatini (former Swaziland), Tunisia, Uganda, Zambia, and Zimbabwe had high morbidity and mortality with 563 cases (33.9 percent deaths), 269 cases (94 percent deaths), 62 cases (88.7 percent deaths), 91 cases (90 percent deaths), 466 cases (40.9 percent), 207 cases (32.8 percent deaths), and 114 (31). Because of the high population of stray dogs in this area, the chances of being bitten by a dog are high. Not only are the chances of being bitten

high in these areas, but access to treatment in a timely and adequate manner is also very limited. Rabies vaccines may not be routinely available in rural areas where most exposure occurs, and rabies immunoglobulins, which are required for category III bites, are always in short supply (32).

This significantly contributes to the high mortality rate, as the highly protective rabies vaccine is frequently unavailable in these poor areas. In addition, the public often gets laid back and not aware to get early treatment after having been bitten by dogs (33). According to recent studies, many rabies victims contracted the disease owing to neglect, ignorance, or a lack of primary health care facilities (34). Thus, health promotion and education should be given to the public as knowledge regarding rabies is essential to reduce morbidity and mortality (5).

Compared to high-income countries such as the United States, the mortality caused by rabies is low. In the last decade, there have been only 25 cases of human rabies reported in the United States (2009-2018), with 1 to 3 cases reported each year (6). The low causes of rabies infection are due to successful animal control and vaccination programs, successful outreach programs, public health capacity and laboratory diagnostics, and the availability of modern rabies biologics (35). Even though rabies is avoidable, the exorbitant expense of vaccinations, combined with a lack of education and knowledge about the disease, limits PEP use. According to recent studies, many rabies victims contracted the disease owing to neglect, ignorance, or a lack of primary health care facilities (34).

Recommendation

A successful rabies prevention and control program requires integrating and strengthening intersectoral and transdisciplinary collaboration and cooperation among various society

components (36). The ASEAN Rabies Elimination Strategy places great value on the organizational and One Health frameworks for rabies eradication. The single most significant way to deal with rabies concerns is to eliminate dog-mediated rabies. The requirement for post-exposure human prophylaxis is considerably reduced when dog rabies is eradicated (37). To benefit from synergy and maximization of shared resources, comprehensive rabies control programs should involve the combination of human, financial, and material resources with other interdisciplinary disease programs (24).

Mass canine vaccination campaigns will boost herd immunity and reduce the risk of human rabies exposure, but this will need strong governmental commitment and extensive social mobilization. The veterinary authority's active engagement in animal rabies control at the national level is critical, and it is their social responsibility to prevent human rabies through well-planned dog rabies control programs (26). In 1983, the Pan American Health Organization had initiated an elimination programme for human rabies transmitted by dogs which were mainly based on mass immunization of dogs, and this has led to a 90% reduction of dog rabies in Chile and other Latin American countries (38).

Rabies control and elimination in low endemic rabies countries such as Malaysia and Singapore have been made possible by strong enforcement of dog registration, vaccination, and population management measures. Malaysia shares a border with Thailand, and the notion of an immunological belt has been developed through dog licensing, required vaccination of dogs, and systematic extermination of unvaccinated dogs in a buffer zone to prevent rabies from entering their country (26). Perhaps other middle and high endemic rabies countries could follow the rabies control strategy that had been implemented by their Southeast Asia neighbour.

Public information and education are important to increase awareness and enhance community participation and support in rabies prevention programs. Dissemination of important information such as the high fatality rate of rabies disease, its epidemiology, its prevention and control, the disease control program, in general, is vital for the program implementation and responsible pet ownership. By recognizing rabies' influence on people's daily life and the fact that dogs can be a source of human infection, community and school-based rabies prevention initiatives will be easier to establish (39).

The involvement of stakeholders is crucial and by bringing together key stakeholders from the corporate and public sectors, we can address health security and the need of forming public-private partnerships which are critical in rabies prevention programs (40). National government agencies can maintain standardized ways for rabies management and elimination and advocate on how to begin public-private cooperation to ensure long-term intervention. All stakeholders can benefit from such technical and administrative effort as they provide credibility and quality assurance for the prevention program's effectiveness (24). Various examples of public-private partnerships that aid in implementing public programs, research, and policy formation can be seen in Bali, Indonesia, India, Sri Lanka, Philippines, Thailand, and Vietnam (3).

Conclusion

Rabies had often been neglected and not given priority in terms of funding for prevention programs that resulted in the continued presence of rabies cases in Southeast Asia despite multiple programs being endorsed by WHO. The high number of unvaccinated stray and pet dogs, working hazard (dog butcher in Vietnam), availability of rabies vaccine in rural areas also ignorance regarding the importance of seeking treatment after dog bites are the factors that cause the presence of rabies cases in Southeast Asia.

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The review was not registered, and the protocol was not prepared

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There is no competing interest

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No ethics approval was required for this systematic review

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Not applicable

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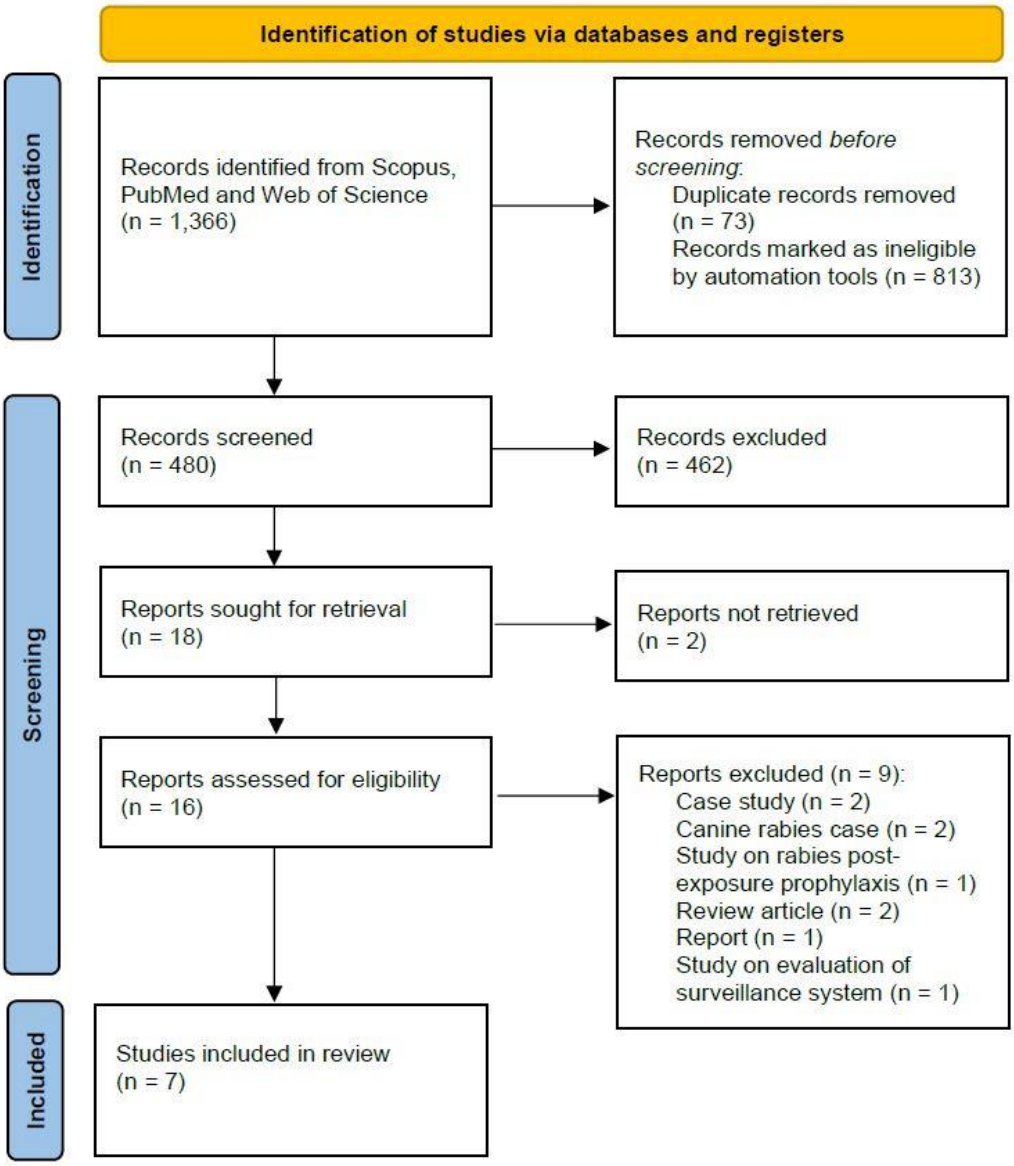
Figures 1: Search PRISMA flowchart for Systematic Review of Rabies in SEA



Reporting checklist for the systematic review of Rabies in South East Asia.

Based on the PRISMA guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Title			
Title	#1	Identify the report as a systematic review	1
Abstract			

Abstract	#2	Report an abstract addressing each item in the PRISMA 2020 for Abstracts checklist	1-2
Introduction			
Background/rationale	#3	Describe the rationale for the review in the context of existing knowledge	3
Objectives	#4	Provide an explicit statement of the objective(s) or question(s) the review addresses	4
Methods			
Eligibility criteria	#5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses	6
Information sources	#6	Specify all databases, registers, websites, organisations, reference lists, and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted	5-6
Search strategy	#7	Present the full search strategies for all databases, registers, and websites, including any filters and limits used	5-6
Selection process	#8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and, if applicable, details of automation tools used in the process	5-6
Data collection	#9	Specify the methods used to collect data from reports,	5-6

process		including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and, if applicable, details of automation tools used in the process	
Data items	#10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (for example, for all measures, time points, analyses), and, if not, the methods used to decide which results to collect	5-6
Data items	#10b	List and define all other variables for which data were sought (such as participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information	5-6
Study risk of bias assessment	#11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and, if applicable, details of automation tools used in the process	18
Effect measures	#12	Specify for each outcome the effect measure(s) (such as risk ratio, mean difference) used in the synthesis or presentation of results	8
Synthesis methods	#13a	Describe the processes used to decide which studies were eligible for each synthesis (such as tabulating the study	6

		intervention characteristics and comparing against the planned groups for each synthesis (item #5))	
Synthesis methods	#13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics or data conversions	6
Synthesis methods	#13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses	6
Synthesis methods	#13d	Describe any methods used to synthesise results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used	6
Synthesis methods	#13e	Describe any methods used to explore possible causes of heterogeneity among study results (such as subgroup analysis, meta-regression)	6
Synthesis methods	#13f	Describe any sensitivity analyses conducted to assess robustness of the synthesised results	6
Reporting bias assessment	#14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases)	18
Certainty assessment	#15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome	5

Results

Study selection	#16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram (http://www.prisma-statement.org/PRISMAStatement/FlowDiagram)	7-10
Study selection	#16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded	7-10
Study characteristics	#17	Cite each included study and present its characteristics	7-10
Risk of bias in studies	#18	Present assessments of risk of bias for each included study	18
Results of individual studies	#19	For all outcomes, present for each study (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (such as confidence/credible interval), ideally using structured tables or plots	16-22
Results of syntheses	#20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies	16-22
Results of syntheses	#20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (such as confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect	16-22
Results of syntheses	#20c	Present results of all investigations of possible causes of	16-22

		heterogeneity among study results	
Results of syntheses	#20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesised results	16-22
Risk of reporting biases in syntheses	#21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed	16-22
Certainty of evidence	#22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed	16-22
Discussion			
Results in context	#23a	Provide a general interpretation of the results in the context of other evidence	10-12
Limitations of included studies	#23b	Discuss any limitations of the evidence included in the review	2
Limitations of the review methods	#23c	Discuss any limitations of the review processes used	2
Implications	#23d	Discuss implications of the results for practice, policy, and future research	13-15
Other information			
Registration and protocol	#24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered	15
Registration and protocol	#24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared	15

Registration and protocol	#24c	Describe and explain any amendments to information provided at registration or in the protocol	N/A
Support	#25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review	15
Competing interests	#26	Declare any competing interests of review authors	15
Availability of data, code, and other materials	#27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review	16-22

BMJ Open

Rabies in Southeast Asia: a systematic review of its incidence, risk factors, and mortality

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Rabies in Southeast Asia: a systematic review of its incidence, risk factors, and mortality

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Abstract

Objective Rabies is a neglected zoonotic disease that can infect all mammals, including humans. We aimed to summarize current knowledge on the incidence, risk factors, and mortality of rabies in Southeast Asia.

Design Systematic review based on the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) 2020.

Data sources Scopus, Web of Science, and PubMed were searched through to 21 February 2023.

Eligibility criteria We included original English language articles published between 2012 and 2023.

Data extraction and synthesis Nine independent reviewers extracted data and assessed the risk of bias. Quality appraisal of included articles was carried out using the Mixed Method Appraisal Tool (MMAT).

Results A total of 8 articles were included in this analysis. In Vietnam, the incidence of rabies ranged from 1.7 to 117.2 per 100,000 population. The cumulative incidence in SSarawak was estimated at 1.7 per 100,000 population. In Indonesia, 104 human rabies cases were reported from 2008 to 2010, while a total of 46 rabies cases were reported in Thailand from 2010 to 2015. In Philippine, the incidence of rabies ranged between 0.1 to 0.3 per 100,000 population. Increased risk of rabies virus infection was associated with high population density, illiteracy, seasonal patterns as well as among dog butchers. The case-fatality rate was 100%.

Conclusion This study includes research from Southeast Asia, which may not represent rabies infection on other regions or continents. The role of publication bias should be acknowledged as we did not include grey literature. The presence of rabies cases in Southeast Asia is due to a high number of unvaccinated stray and pet dogs, working hazards (dog butcher in Vietnam), the unavailability of rabies vaccine in rural regions, and misinformation about the significance of seeking treatment after dog bites.

Keywords Rabies, dog bite, zoonotic disease, epidemiology, Southeast Asia

Strengths and limitations

- This study only includes research from Southeast Asia, which may not represent rabies infection in other regions or continents.
-
- We did not include grey literature or national guidelines, which could have been useful in this study.
- This systematic review followed the PRISMA 2020 statement for the reporting of systematic reviews to ensure reporting quality.

Introduction

Rabies is a neglected zoonotic disease that is caused by an RNA virus from the family of *Rhabdoviridae*, genus *Lyssavirus*[1]. Once clinical symptoms appear, rabies is almost 100% fatal [2]. All mammals can be infected with the rabies virus, including humans. More than 99% of human rabies cases are transmitted via dogs [3]. With the necessary evidence and tools in place for control and elimination of rabies, canine rabies can be eliminated, as demonstrated in Western Europe, Canada, the United States of America (USA), Japan, a few Latin American countries, and many parts in Asia. However, rabies is still widespread, occurring in more than 80 countries, particularly in the developing countries in Africa and Asia [3, 4]. Furthermore, half of the global population lives in canine rabies-endemic areas hence is at risk of contracting rabies [3].

Globally, canine rabies was estimated to cause approximately 59,000 human deaths annually. Rabies is clearly a major problem in Asia. The number of human deaths due to rabies in Asia is higher than in any other region in the world. Most human rabies deaths occurred in Asia (59.6%), followed by Africa (36.4%), while only less than 0.05% of human rabies deaths occurred in the Americas. Additionally, India alone accounts for 35% of global human rabies deaths, which was higher than any other country ([4]. In Asia, canine rabies was estimated to cause a loss of 2.2 million Disability-Adjusted Life Years (DALYs) per year, while the annual cost of post-exposure prophylaxis (PEP) was highest in Asia, with estimates up to US$ 1.5 billion[5].

In Southeast Asia, only Singapore has eradicated canine rabies through the implementation of robust national rabies control programs, while other countries in this subregion were not considered to be rabies-free [6]. Malaysia was once declared to be rabies-free by the World Animal Health Organisation in July 2013, but several rabies outbreaks since

2015 have relegated Malaysia down from its rabies-free status [7]. Even though Thailand and Vietnam have not been able to eliminate rabies, there was a substantial reduction of human rabies deaths through the implementation of dog mass vaccination, intensified post-exposure prophylaxis in humans, and awareness education [8].

Rabies is 100 percent preventable through vaccination in animals and humans [9]. The World Health Organization (WHO) recommended pre-exposure prophylaxis (PrEP) for those with continual, frequent, or increased risk of exposure to rabies virus (e.g., veterinarians, animal handlers). If exposed to a rabid animal, the WHO recommended PEP, which consists of immediate wound management, immediate vaccination, as well as administration of rabies immunoglobulin for high-risk exposure [10]. Nevertheless, dog vaccination is considered the most cost-effective strategy for preventing rabies in humans [2].

Despite the availability of evidence and guidelines for the control and management of rabies, there are some constraints faced by countries in Southeast Asia in controlling rabies, including inadequate resources, lack of political commitment, lack of consensus on strategy, weak intersectoral coordination, insensitive surveillance systems, limited accessibility to modern rabies vaccine and supply problem, as well as lack of public awareness and cooperation [8]. The high estimated burden for rabies more than justifies the need to prioritize rabies control, particularly in Asian countries.

Information on rabies epidemiology is a prerequisite for effective planning of rabies control programs. Previous systematic reviews focused on rabies epidemiology in India [11], Nepal [1], and Arab countries [12], while literature synthesizing data regarding rabies epidemiology in Southeast Asia are limited. Hence, this systematic review aims to provide an in-depth assessment of the incidence, risk factors, and mortality of rabies in Southeast Asia countries, based on the published literature.

Materials and Methods

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [13].

Patient and Public involvement

No patient and/or public involvement in this study (None).

Research Question Formulation

The review question was developed based on the CoCoPop (condition, context, population) and PEO (population, exposure, outcome) concept [14]. The PICO (population, intervention, comparison intervention, outcome measures) framework is commonly used in developing focused clinical questions for quantitative reviews [15], while the CoCoPop and PEO concepts are suitable for reviews related to prevalence and aetiology [14]. Based on the CoCoPop concept, the condition refers to the incidence of rabies, the context refers to Southeast Asia and the population is the general population. Based on the PEO concept, population refers to the general population in Southeast Asia, exposure refers to rabies and the outcome is the mortality of rabies. Hence, the main research questions are: (1) What is the incidence of rabies among the general population in Southeast Asia countries? and (2) What is the risk factors of rabies among the general population in Southeast Asia countries? (3) What is the mortality rate of rabies among the general population in Southeast Asia countries?

Data Source and Search Strategy

PubMed, Web of Science and Scopus were searched from 1 January 2012 through to 21 February 2023. The keywords used for the searching of related articles are provided in Table 1.

Table 1: Keywords search used in the screening process.

Database	Search string
Scopus	1) TITLE-ABS-KEY((“rabies*” OR “rabies virus*” OR “dog bite*”) AND (“Southeast Asia” OR “Brunei” OR “Myanmar” OR “Cambodia” OR “Timor-Leste” OR “Indonesia” OR “Laos” OR “Malaysia” OR “Philippines” OR “Singapore” OR “Thailand” OR “Vietnam”) AND (“epidemiology” OR “outbreak” OR “case” OR “prevalence” OR “incidence” OR “causes” OR “risk factor”)) 2) TITLE-ABS-KEY((“Rabies*” OR “Rabies virus*” OR “dog bite*”) AND (“Southeast Asia” OR “Brunei” OR “Myanmar” OR “Cambodia” OR “Timor-Leste” OR “Indonesia” OR “Laos” OR “Malaysia” OR “Philippines” OR “Singapore” OR “Thailand” OR “Vietnam”) AND (“mortality*” OR “death*” OR ”fatality*”))
Web of Science	1) (((ALL=("rabies*")) OR ALL=("rabies virus*")) OR ALL=("dog bite*") AND ((((((((((ALL=("Southeast Asia")) OR ALL=("Brunei")) OR ALL=("Myanmar")) OR ALL=("Cambodia")) OR ALL=("Timor-Leste")) OR ALL=("Indonesia")) OR ALL=("Laos")) OR ALL=("Malaysia")) OR ALL=("Philippines")) OR ALL=("Singapore")) OR ALL=("Thailand")) OR ALL=("Vietnam")) AND ((((((ALL=("epidemiology")) OR ALL=("outbreak")) OR ALL=("case")) OR ALL=("prevalence")) OR ALL=("incidence")) OR ALL=("causes")) OR ALL=("risk factor") 2) (((ALL=("rabies*")) OR ALL=("rabies virus*")) OR ALL=("dog bite*") AND ((((((((((ALL=("Southeast Asia")) OR ALL=("Brunei")) OR ALL=("Myanmar")) OR ALL=("Cambodia")) OR ALL=("Timor-Leste")) OR ALL=("Indonesia")) OR ALL=("Laos")) OR ALL=("Malaysia")) OR ALL=("Philippines")) OR ALL=("Singapore")) OR ALL=("Thailand")) OR ALL=("Vietnam")) AND ((ALL=("mortality*")) OR ALL=("death*")) OR ALL=("fatality*")
PubMed	1) ((((("rabies*") OR ("rabies virus*")) OR ("dog bite*")) AND ((((((((((("Southeast Asia") OR ("Brunei")) OR ("Myanmar")) OR ("Cambodia")) OR ("Timor-Leste")) OR ("Indonesia")) OR ("Laos")) OR ("Malaysia")) OR ("Philippines")) OR ("Singapore")) OR ("Thailand")) OR ("Vietnam"))) AND (((((("epidemiology") OR ("outbreak")) OR ("case")) OR ("prevalence")) OR ("incidence")) OR ("causes")) OR ("risk factor")) 2) ((((("rabies*") OR ("rabies virus*")) OR ("dog bite*")) AND ((((((((((("Southeast Asia") OR ("Brunei")) OR ("Myanmar")) OR ("Cambodia")) OR ("Timor-Leste")) OR ("Indonesia")) OR ("Laos")) OR ("Malaysia")) OR ("Philippines")) OR ("Singapore")) OR ("Thailand")) OR ("Vietnam"))) AND (((("mortality*") OR ("death*")) OR ("fatality*"))

Study Selection

The inclusion criteria were: (1) publication from 2012-2023; (2) original article; (3) publication in the English language. Studies with these characteristics were included in this review: (1) report on the incidence and risk factors of rabies in Southeast Asia; and (2) report on the mortality rate of rabies in Southeast Asia. Non-original articles such as conference proceedings, perspectives, commentary, opinion, reports, systematic reviews, and meta-analyses were excluded.

Data Extraction and Synthesis

Duplicates were deleted, and at least two reviewers re-screened the remaining papers. Before being included in the review, articles were screened in three stages. Any article that did not meet the inclusion criteria from title screening was eliminated in the first phase. The abstracts of the remaining papers were reviewed in the second phase, and any publications that did not fit our inclusion criteria were eliminated from the review. The full-text articles were examined attentively in the last phase to eliminate any papers that did not fulfil our inclusion criteria. Before the data extraction process, both reviewers must agree that the entire publications should be reviewed. Any disagreements were worked out through discussion. All data extraction was conducted independently using a standardized data extraction form which was organized using Microsoft Excel. Information collected in the form included (1) author, (2) publication year, (3) reference, (4) country, (5) study design, (6) statistical analysis, and (7) results.

Quality Appraisal

Quality appraisal was conducted by authors on all 8 studies using the Mixed Method Appraisal Tool (MMAT) [16]. The MMAT is a critical appraisal tool that is developed to appraise studies

included in systematic mixed study reviews. The methodology quality of five categories of studies (qualitative study, randomized control trials, non-randomized studies, quantitative descriptive study, and mixed methods study) can be appraised using this tool. For each category, five criteria are used to assess the quality of the study. It is advised not to calculate an overall score from the rating of each criterion using the latest version of MMAT (2018). However, due to problems faced by researchers in reporting the MMAT results, a suggestion was provided for reporting an overall score (5*****/100% quality criteria met; 4****/80% quality criteria met; 3***/60% quality criteria met; 2**/40% quality criteria met; 1*/20% quality criteria met). The details of this assessment are reported in Table 2.

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162 Table 2: The details of mixed method appraisal tool assessment

Author	Type of study	Score	1.1	1.2	1.3	1.4	1.5
			Is the sampling strategy relevant to address the research question?	Is the sample representative of the target population?	Are the measurements appropriate?	Is the risk of nonresponse bias low?	Is the statistical analysis appropriate to answer the research question?
Nguyen et al. 2021	Quantitative	40%	Can't tell	Can't tell	Yes	Can't tell	Yes
Pham et al. 2021	Quantitative	100%	Yes	Yes	Yes	Yes	Yes
Sim et al. 2021	Quantitative	60%	Yes	Can't tell	Yes	Can't tell	Yes
Yurachai et al. 2021	Quantitative	80%	Yes	Yes	Yes	Can't tell	Yes
Phung et al. 2018	Quantitative	80%	Yes	Yes	Yes	Can't tell	Yes
Susilawati et al. 2012	Quantitative	80%	Yes	Yes	Yes	Yes	No
Lee et al. 2017	Quantitative	100%	Yes	Yes	Yes	Yes	Yes
Guzman et al.2021	Quantitative	80%	Yes	Yes	Yes	No	Yes

Results

There were 1,437 records identified from the three databases to evaluate the incidence, risk factors and mortality rate of rabies in Southeast Asia. Using automation tools, 829 records were excluded based on year, publication type, and language. A total of 98 duplicate records were found and removed, leaving 510 records for title screening. We screened the titles and abstracts independently based on the review questions. A total of 491 articles were removed during the screening. For the remaining 19 articles, the full text was retrieved for assessment of eligibility. Disagreements were resolved through discussion to reach a consensus. 11 articles were removed as they were not according to the objective (4), not primary/original research articles (5) and the full article could not be retrieved (2), leaving a total of 8 articles to proceed with a quality appraisal. The PRISMA flowchart is presented in Figure 1.

Background of the Eligible Studies

A total of 8 studies were included in this systematic review in which 4 studies were conducted in Vietnam, and 1 each from Indonesia, Malaysia, Thailand, and Philippine (Table 3). The theme discussed by all studies was incidence rates, number of cases, and risk factors of rabies in Southeast Asia. Among the included studies, 3 studies particularly discussed rabies's mortality.

183 Table 3: Table of evidence

Author/year	Country	Reference	Study design	Statistical analysis	Result
Nguyen et al. 2021	Vietnam	Nguyen, A. K. T., Vu, A. H., Nguyen, T. T., Nguyen, D. V., Ngo, G. C., Pham, T. Q., Inoue, S., et al. 2021. Risk factors and protective immunity against rabies in unvaccinated butchers working at dog slaughterhouses in Northern Vietnam. *American Journal of Tropical Medicine and Hygiene* 105(3): 788–793. doi:10.4269/ajtmh.20-1172	Cross-sectional	Pearson correlation Multivariate regression analysis	Study found that 28.3% of butchers were at risk of rabies exposure due to slaughtering sick dog, getting bitten, scratched or knife cut. Only 8.6% had NTA sufficient for protection and only 8.1% of them were vaccinated. Hence dog butchers in Vietnam were at high risk of rabies virus infection.
Pham et al. 2021	Vietnam	Pham, Q. D., Phan, L. T., Nguyen, T. P. T., Doan, Q. M. N., Nguyen, H. D., Luong, Q. C. & Nguyen, T. V. 2021. An Evaluation of the Rabies Surveillance in Southern Vietnam. *Frontiers in Public Health* 9(April): 1–9. doi:10.3389/fpubh.2021.610905	Cross-sectional	Descriptive Chi-square test / Fisher's exact test	94 human rabies cases (2009-2018) were reported in Southern Vietnam, with an average of nine cases recorded annually (2.7 cases per 10 million population). The highest number was reported in 2018. Majority of cases were male and those aged 50 years and above.
Sim et al. 2021	Malaysia	Sim, B. N. H., Liang, B. N. W., Ning, W. S. & Viswanathan, S. 2021. A retrospective analysis of emerging rabies: A neglected tropical disease in Sarawak, Malaysia. *Journal of the*	Cross-sectional	Descriptive	6 cases were identified with a mixture of MN and LMN findings. Most cases did not seek medical attention upon dog bite. The incubation period varied from 17 days to 2 years. All cases died, with 5 cases succumbing to the illness within 2 weeks of symptoms onset. The cumulative

		Royal College of Physicians of Edinburgh 51(2): 133–139. doi:10.4997/JRCPE.2021.207			incidence in Sibu was estimated at 1.7 per 100,000 population.
Yurachai et al. 2021	Thailand	Yurachai, O., Hinjoy, S. & Wallace, R. M. 2020. An epidemiological study of suspected rabies exposures and adherence to rabies post-exposure prophylaxis in Eastern Thailand, 2015. *PLoS Neglected Tropical Diseases* 14(2): 1–17. doi:10.1371/journal.pntd.0007248	Cross-sectional	Descriptive	46 confirmed and probable cases of human rabies were reported in Thailand (2010 – 2015). 11 were reported from Eastern Thailand. 6,204 suspected rabies exposure reported in 8 Eastern Thailand. Children age < 15 years and elderly age > 60 years had the highest suspected reported exposure rate compared to others (189.7/ 100,000 and 189.2/100,000). Overall, the estimated suspected rabies exposure rate was 204/100,000.
Phung et al. 2018	Vietnam	Phung, D., Nguyen, H. X., Thi Nguyen, H. L., Luong, A. M., Do, C. M., Tran, Q. D. & Chu, C. 2018. The effects of socioecological factors on variation of communicable diseases: A multiple-disease study at the national scale of Vietnam. PLoS ONE 13(3): 1–14. doi:10.1371/journal.pone.0193246	Ecological	Moran's I tests Multilevel negative binomial regression model / zero-inflated negative binomial regression	The average monthly number of rabies cases is 429 from 2011 to 2015. The incidences of rabies ranged from 1.7 to 117.2 per 100,000 with higher incidences observed in Red River, South Central Coast (SCC), and the Mekong Delta regions Climate factors: temperature, humidity and cumulative rainfall were associated with increase in rabies incidence in Vietnam. Socio-economic factors: population density and illiteracy were sensitive factor increased risk of rabies.
Susilawati et al. 2012	Indonesia	Susilawathi, N. M., Darwinata, A. E., Dwija, I. B. N. P., Budayanti, N. S., Wirasandhi, G. A. K., Subrata, K.,	Cross-sectional	Descriptive	104 human rabies cases reported in Bali during November 2008-November 2010 which all are fatal and the symptom exhibit by all patients. Almost all (92%) cases had a history

		Susilarini, N. K., et al. 2012. Epidemiological and clinical features of human rabies cases in Bali 2008-2010. *BMC Infectious Diseases* 12(November 2008): 0–7. Doi:10.1186/1471-2334-12-81			of dog bite. Only 5.8% had their wounds treated and received an anti-rabies vaccine (ARV) after the bite incident. The case-fatality rate was 100%.
Lee et al. 2017	Vietnam	Lee, H. S., Thiem, V. D., Anh, D. D., Duong, T. N., Lee, M., Grace, D. & Nguyen-Viet, H. 2018. Geographical and temporal patterns of rabies post exposure prophylaxis (PEP) incidence in humans in the Mekong River Delta and Southeast Central Coast regions in Vietnam from 2005 to 2015. PloS ONE 13(4): 1–12. Doi:10.1371/journal.pone.0194943	Ecological	Univariate negative binomial regression	Hotspot localities were identified in Southern Vietnam (mainly at Mekong River Delta and South-Central Coast) MRD: strong peak in February / July SCC: middle of the year
Guzman et al.2021	Philippines	Guzman FD, Iwamoto Y, Saito N, Salva EP, Dimaano EM, Nishizono A, et al. (2022) Clinical, epidemiological, and spatial features of human rabies cases in Metro Manila, the Philippines from 2006 to 2015. PLoS Negl Trop Dis 16(7): e0010595. https://doi.org/10.1371/journal.pntd.0010595	Cross-sectional	Descriptive	575 rabies cases from 2006 to 2015. Most patients were male (70.3%) and aged 41 to 60 years (34.1%). The incidence rate of human rabies per 100,000 population in 2007, 2010, and 2015 were 0.1305, 0.1356, and 0.1708 in the National Capital Region; 0.2890, 0.2965, and 0.1961 in Region III; and 0.1449, 0.1272, and 0.1041 in Region IV-A, respectively. 463 people died of rabies.

Incidence and Risk Factors of Rabies in Southeast Asia Countries

Overall, the incidence of rabies ranged between 0.1 per 100,000 population in Philippine [17]to 117.2 per 100,000 population in Vietnam [18]. The average monthly number of rabies cases in Vietnam is 429 during the period from 2011 to 2015, where the incidences of rabies ranged from 1.7 to 117.2 per 100,000 with higher incidences observed in Red River, South Central Coast (SCC), and the Mekong Delta regions [18]. Specific to Southern Vietnam, a total of 94 human rabies cases between 2009 and 2018 were reported, with an average of nine cases recorded annually, representing an incidence of 2.7 cases per 10 million population [19]. The highest number was reported in 2018 (5.5 cases per 10 million population). Most cases were among males and those aged 50 years and above.

Dog butchers in Vietnam were at high risk of rabies virus infection [20]. The study found that 28.3% of butchers were at risk of rabies exposure due to slaughtering of sick dogs, getting bitten, scratched, or knife cut. Among 406 participants, 8.6% had rabies neutralizing antibody (NTA) sufficient for protection and only 8.1% of them were vaccinated. In terms of location, rabies cases were limited to specific areas. Hotspots were identified in southern Vietnam, particularly in the Mekong River Delta (MRD) and South-Central Coast (SCC) [21]. Seasonal patterns were found in which a strong peak in February/ July and a minor peak in October/ December in the MRD Region. However, a strong peak was detected in the middle of each year in the SCC. Temperature, humidity, and cumulative rainfall are positively associated with an increase in incidences of rabies in Vietnam. In terms of socio-economic factors, increases in population density, as well as the percentages of illiteracy, were sensitive factors for elevated risk of rabies [18].

In Indonesia, 104 human rabies cases were reported in Bali from November 2008 to November 2010. Most of the cases were among males. Almost all (92%) cases had a history of a dog bite. Only 5.8% had their wounds treated and received an anti-rabies vaccine (ARV) after the bite incident [22]. Even worse, rabies cases in Sibu, Sarawak did not seek medical attention upon dog bite as well [23]. The cumulative incidence in Sibu was estimated at 1.7 per 100,000 population. The incubation period varied from 17 days to 2 years.

A total of 46 confirmed and probable cases of human rabies were reported in Thailand from 2010 to 2015, in which 11 were reported from Eastern Thailand [24]. Even though rabies can be prevented by vaccination, more than 90% of rabies death cases in Thailand did not get or improperly stopped receiving PEP. In terms of suspected rabies exposures, 6,204 exposures were reported from eight provinces in Eastern Thailand, resulting in a crude exposure rate of 106 reported rabies exposures per 100,000 people. Dogs were the main source of exposure (77.8%), while children under the age of 15 and the elderly over the age of 60 had the highest overall reported exposure rates (189.7 and 189.2/100,000, respectively).

In Philippines, there were 575 rabies cases from 2006 to 2015. 70% from the rabies cases were among males. Nearly 34% from the patients aged 41 to 60 years. The incidence rate of human rabies per 100,000 population in 2007, 2010, and 2015 were 0.1305, 0.1356, and 0.1708 in the National Capital Region; 0.2890, 0.2965, and 0.1961 in Region III; and 0.1449, 0.1272, and 0.1041 in Region IV-A, respectively [17].

Mortality of Rabies in Southeast Asia Countries

The case-fatality rate was 100% as mentioned in 2 studies [22, 23]. Among 6 deaths reported in Sibu, 5 succumbed to the illness within 2 weeks of symptoms onset, with total of 5 out of 6 cases reported dog bite history [23]. In Indonesia, Susilawati et al. reported that there were

104 fatalities due to rabies, of which 96 cases had history of dog bite [22]. In Philippine, 463 people died from rabies infection [17].

Discussion

Incidence and Risk factor of Rabies in Southeast Asia Countries.

Rabies in Asia and Africa contributes to over 99% of human rabies deaths that occur in the world today. The vast majority of 60% of these deaths are in Asia [25]. Every year, an estimated 59,000 people die from rabies worldwide, with the majority (95%) of these deaths occurring in Africa and Asia due to a lack of post-exposure prophylaxis (PEP) services for animal-bite patients and rabies surveillance personnel and facilities [26]. This support the result of our study which shows that there is a high number of rabies cases reported in Vietnam, Indonesia, and Thailand, which are medium endemic rabies country [27].

Rabies is concentrated in Asia and Southeast Asia region because rabies is frequently neglected when health and agriculture budgets are set although the costs and economic benefits of having rabies prevention programs have been successfully implemented in high-income country [28]. The high number of rabies cases in Southeast Asia is also contributed by the high number of unowned, free-roaming dogs that can't be controlled without a lot of effort and thus aren't vaccinated [29]. Vaccination programs in dogs can provide herd immunity and break the rabies transmission cycle in this reservoir species and had been successfully applied in several countries around the world [30].

Another cause of high incidence of rabies in Southeast Asia is due to the working hazard of dog butchers, especially in a country that legalizes dog consumption such as in Vietnam [31]. It was also reported by the Centers for Disease Control and Prevention (CDC) that there is illegal trafficking of dogs for human consumption occurring in Vietnam (https://www.cdc.gov/globalhealth/stories/rabies_southeast_asia.htm) which could possibly

contributes to the high incidence of rabies in Vietnam. Professional dog butchers in northern Vietnam are at a high risk of rabies virus infection due to exposure during the slaughtering process, which was from the slaughtering of sick or dead dogs, getting bitten, scratched, or knife cut. Study reported that 91.9% of professional dog butchers in Vietnam were not vaccinated against rabies, which may be because of the fear of side effects of rabies vaccine, inability to afford vaccination, and incorrect knowledge of rabies prevention [20].

The rabies incidence of 0.1 per 100,000 population in Philippine is similar to that reported in China in 2016 [32]. The lower rabies incidence in Philippine compared to other Southeast Asia countries may be due to the implementation of Anti-Rabies Act of 2007 to prevent and control human rabies [33]. Additionally, the consumption of dog meat was banned in 1998 with the implementation of Animal Welfare Act which may contribute to the lower incidence of rabies in Philippine [34].

In comparison to females, males are more likely to contract rabies infection [19]. Similar finding was found in Iraq, where more than 89% of the cases were among males [35].This can be attributed to the fact that most females are housewives, while males are engaged in outdoor activities [36]. Another study in Ethiopia also stated that males are more likely to do nightly and outdoor activities while females are more likely to remain indoors due to cultural and religious reasons [37], which could explain the increase incidence of rabies in males.

According to study by Yurachai et al, rabies infection affects children more compared to other age group [24]. This corresponds to the WHO report, which states that 40% of rabies victims are children ages 4 to 15 (https://www.who.int/news-room/fact-sheets/detail/rabies). Similar finding was found in other studies in Yemen and Iran where nearly 40% of individual exposed to rabies infection fall in this age group [35, 38]. Children in this age group are

probably more likely to play with, annoy, or approach the biting animals, which contributes to the higher rate of bites in this age group [35]. In contrast, according to a study from Pham et al, older people are more likely to become infected with rabies [19].

In several studies included in this systematic review, the diagnosis of most rabies cases was based only on detailed history and clinical diagnosis [17, 19, 21]. To diagnose rabies in humans, multiple tests are required such as saliva, serum, spinal fluid, and skin biopsies of hair follicles from the nape of the neck are analysed. Viral isolation or reverse transcription followed by polymerase chain reaction can be used to analyse saliva (RT-PCR). Serum and spinal fluid are tested for rabies virus antibodies. Skin biopsies can be used to detect rabies antigen in the cutaneous nerves at the base of the hair follicles (https://www.cdc.gov/rabies/diagnosis/animals-humans.html). In the future, there is a need for developing country to standardize the diagnosis of rabies based on the laboratory test as mentioned above for accuracy of the diagnosis and to enable comparison with other studies done in developed country.

Of the included studies, only one study was conducted among butchers who were at higher risk of contracting rabies [20]. Apart from butchers, individuals working as veterinarians, veterinary technicians, animal control workers, and wildlife rehabilitators were also considered to have higher risk of contracting rabies than the general population [39]. This calls for more studies that incorporate individuals involved in occupations identified as high risk for rabies exposure and infection.

In this study, climate factor was postulated to be one of the risk factors for rabies infection. This was echoed by a study in China, where the incidence of rabies increases alongside the ambient temperature. A warmer climate causes animals to be more active in their environment and to travel greater distances when tracking, which contributes to the

spread of rabies. In addition, as temperatures rise, people tend to wear lighter clothing and expose more skin, which increases the likelihood of being bitten by a dog [40]. In South Korea, it had been demonstrated that the seasonality of wildlife rabies were attributed to behaviours such as searching for food during the winter or early spring. Dogs may have had more opportunities to come into contact with the rabid animals during this time due to greater animal movement, which could have contributed to seasonal patterns in the occurrence of rabies in humans [41].

Mortality of Rabies in Southeast Asia Countries

In this study, rabies had a high fatality rate, with 100 percent of infected cases dying. This is supported by a review done in Africa by Nyasulu et al, who reported that Algeria, Namibia, Eswatini (former Swaziland), Tunisia, Uganda, Zambia, and Zimbabwe had high morbidity and mortality with 563 cases (33.9 percent deaths), 269 cases (94 percent deaths), 62 cases (88.7 percent deaths), 91 cases (90 percent deaths), 466 cases (40.9 percent), 207 cases (32.8 percent deaths), and 114 cases [42]. Because of the high population of stray dogs in this area, the chances of being bitten by a dog are high. Not only are the chances of being bitten high in these areas, but access to treatment in a timely and adequate manner is also very limited. Rabies vaccines may not be routinely available in rural areas where most exposure occur, and rabies immunoglobulins, which are required for category III bites, are always in short supply [43].

This significantly contributes to the high mortality rate, as the highly protective rabies vaccine is frequently unavailable in these poor areas. In addition, the public often gets laid back and not aware to get early treatment after having been bitten by dogs [44]. According to recent studies, many rabies victims contracted the disease owing to neglect, ignorance, or a lack of primary health care facilities [45]. Thus, health promotion and education should be

given to the public as knowledge regarding rabies is essential to reduce morbidity and mortality [5].

In high-income countries such as the United States, the incidence and mortality caused by rabies is low. In the last decade, there have been only 25 cases of human rabies reported in the United States (2009-2018), with 23 deaths reported [6]. The low cases of rabies infection are due to successful animal control and vaccination programs, successful outreach programs, public health capacity and laboratory diagnostics, and the availability of modern rabies biologics [46]. Even though rabies is avoidable, the exorbitant expense of vaccinations, combined with a lack of education and knowledge about the disease, limits PEP use. According to recent studies, many rabies victims contracted the disease owing to neglect, ignorance, or a lack of primary health care facilities [45].

Strengths and Limitations

In this study, we only include research from Southeast Asia, which may not represent rabies infection in other regions or continents. We did not include grey literature or national guidelines, which could have been useful in this study. Our strengths, however, are that we can tailor the control programme specifically for Southeast Asia countries, and we are aware of the true burden of rabies infection in our region.

Recommendation

A successful rabies prevention and control program requires integrating and strengthening intersectoral and transdisciplinary collaboration and cooperation among various society components [47]. The ASEAN Rabies Elimination Strategy places great value on the organizational and One Health frameworks for rabies eradication. The single most significant way to deal with rabies concerns is to eliminate dog-mediated rabies. The requirement for post-exposure human prophylaxis is considerably reduced when dog rabies is eradicated [48].

To benefit from synergy and maximization of shared resources, comprehensive rabies control programs should involve the combination of human, financial, and material resources with other interdisciplinary disease programs [25].

Mass canine vaccination campaigns will boost herd immunity and reduce the risk of human rabies exposure, but this will need strong governmental commitment and extensive social mobilization. The veterinary authority's active engagement in animal rabies control at the national level is critical, and it is their social responsibility to prevent human rabies through well-planned dog rabies control programs [27]. In 1983, the Pan American Health Organization had initiated an elimination programme for human rabies transmitted by dogs which were mainly based on mass immunization of dogs, and this has led to a 90% reduction of dog rabies in Chile and other Latin American countries [49].

Rabies control and elimination in low endemic rabies countries such as Malaysia and Singapore have been made possible by strong enforcement of dog registration, vaccination, and population management measures. Malaysia shares a border with Thailand, and the notion of an immunological belt has been developed through dog licensing, required vaccination of dogs, and systematic extermination of unvaccinated dogs in a buffer zone to prevent rabies from entering their country [27]. Perhaps other middle and high endemic rabies countries could follow the rabies control strategy that had been implemented by their Southeast Asia neighbour.

Public information and education are important to increase awareness and enhance community participation and support in rabies prevention programs. Dissemination of important information such as the high fatality rate of rabies disease, its epidemiology, its prevention and control, the disease control program, in general, is vital for the program implementation and responsible pet ownership. By recognizing rabies' influence on people's

daily life and the fact that dogs can be a source of human infection, community and school-based rabies prevention initiatives will be easier to establish [50].

The involvement of stakeholders is crucial and by bringing together key stakeholders from the corporate and public sectors, we can address health security and the need of forming public-private partnerships which are critical in rabies prevention programs [51]. National government agencies can maintain standardized ways for rabies management and elimination and advocate on how to begin public-private cooperation to ensure long-term intervention. All stakeholders can benefit from such technical and administrative effort as they provide credibility and quality assurance for the prevention program's effectiveness [25]. Various examples of public-private partnerships that aid in implementing public programs, research, and policy formation can be seen in Bali, Indonesia, India, Sri Lanka, Philippines, Thailand, and Vietnam [3].

Conclusion

Rabies had often been neglected and not given priority in terms of funding for prevention programs that resulted in the continued presence of rabies cases in Southeast Asia despite multiple programs being endorsed by WHO. The high number of unvaccinated stray and pet dogs, working hazard (dog butcher in Vietnam), unavailability of rabies vaccine in rural areas, as well as ignorance regarding the importance of seeking treatment after dog bites are among the factors that contribute to rabies cases in Southeast Asia.

Author Contributions

All authors, J.L.M.Y., A.F.N.A.H., D.A., N.R., M.R.H., S.S.S.A.R., M.S.J., A.O., and A.H. were involved in conceptualisation, methodology, extensive search of articles, critical review of

articles, results synthesis and original draft write up. M.R.H. supervised the manuscript preparation. All authors have read and agreed to the final draft of the manuscript.

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Competing interests

The authors declare no conflict of interest.

Patient consent for publication

Not applicable.

Ethics approval

Not applicable.

Data availability statement

Data are available upon reasonable request.

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Figure: PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only

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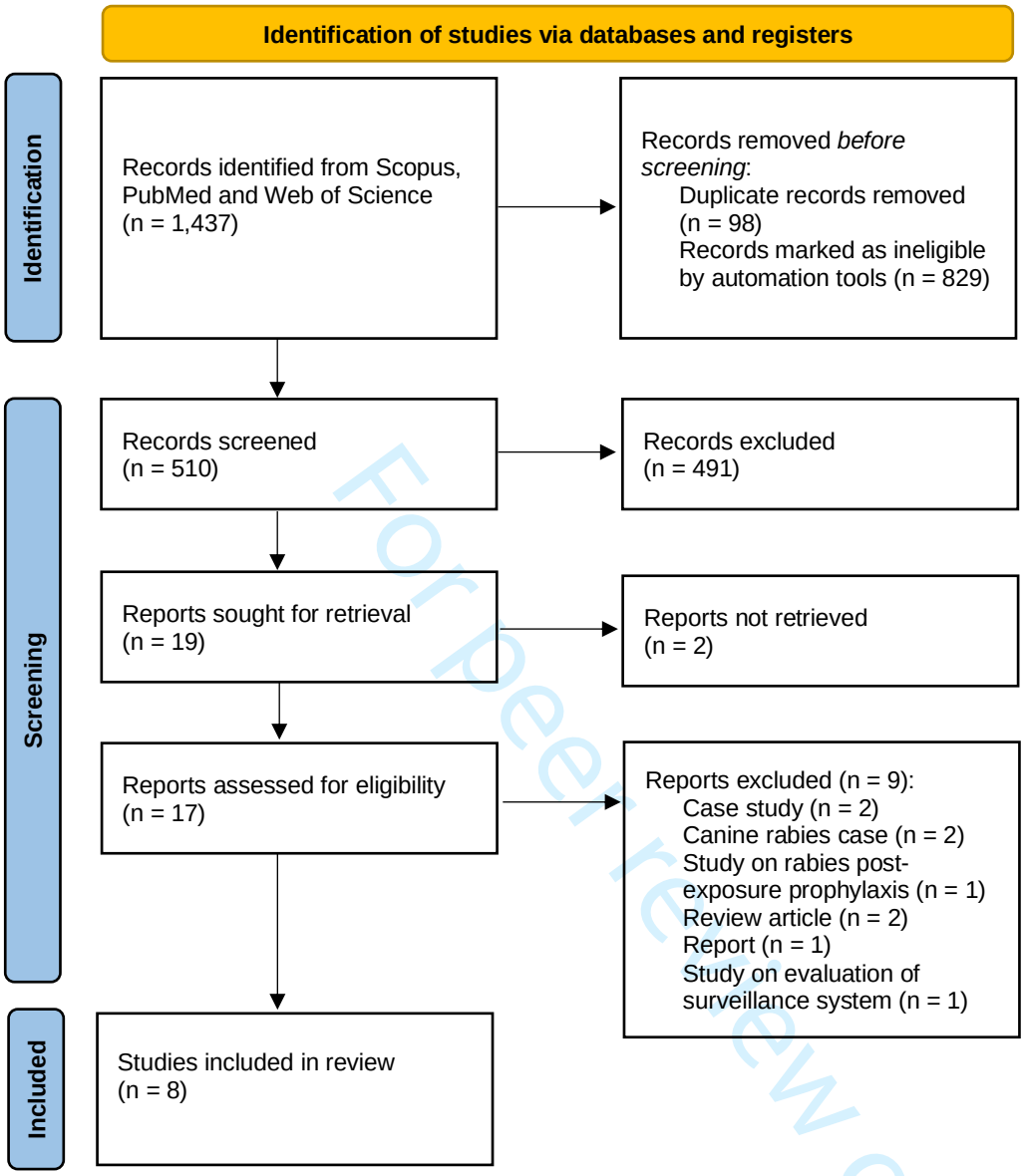
PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



Reporting checklist for the systematic review of Rabies in South East Asia.

Based on the PRISMA guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Title			
Title	#1	Identify the report as a systematic review	1
Abstract			

Abstract	#2	Report an abstract addressing each item in the PRISMA 2020 for Abstracts checklist	1-2
Introduction			
Background/rationale	#3	Describe the rationale for the review in the context of existing knowledge	3
Objectives	#4	Provide an explicit statement of the objective(s) or question(s) the review addresses	4
Methods			
Eligibility criteria	#5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses	6
Information sources	#6	Specify all databases, registers, websites, organisations, reference lists, and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted	5-6
Search strategy	#7	Present the full search strategies for all databases, registers, and websites, including any filters and limits used	5-6
Selection process	#8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and, if applicable, details of automation tools used in the process	5-6
Data collection	#9	Specify the methods used to collect data from reports,	5-6

process		including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and, if applicable, details of automation tools used in the process	
Data items	#10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (for example, for all measures, time points, analyses), and, if not, the methods used to decide which results to collect	5-6
Data items	#10b	List and define all other variables for which data were sought (such as participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information	5-6
Study risk of bias assessment	#11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and, if applicable, details of automation tools used in the process	18
Effect measures	#12	Specify for each outcome the effect measure(s) (such as risk ratio, mean difference) used in the synthesis or presentation of results	8
Synthesis methods	#13a	Describe the processes used to decide which studies were eligible for each synthesis (such as tabulating the study	6

		intervention characteristics and comparing against the planned groups for each synthesis (item #5))	
Synthesis methods	#13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics or data conversions	6
Synthesis methods	#13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses	6
Synthesis methods	#13d	Describe any methods used to synthesise results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used	6
Synthesis methods	#13e	Describe any methods used to explore possible causes of heterogeneity among study results (such as subgroup analysis, meta-regression)	6
Synthesis methods	#13f	Describe any sensitivity analyses conducted to assess robustness of the synthesised results	6
Reporting bias assessment	#14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases)	18
Certainty assessment	#15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome	N/A~~5~~

Results

Study selection	#16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram (http://www.prisma-statement.org/PRISMAStatement/FlowDiagram)	7-10
Study selection	#16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded	7-10
Study characteristics	#17	Cite each included study and present its characteristics	7-10
Risk of bias in studies	#18	Present assessments of risk of bias for each included study	18
Results of individual studies	#19	For all outcomes, present for each study (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (such as confidence/credible interval), ideally using structured tables or plots	16-22
Results of syntheses	#20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies	16-22
Results of syntheses	#20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (such as confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect	16-22
Results of syntheses	#20c	Present results of all investigations of possible causes of	16-22

		heterogeneity among study results	
Results of syntheses	#20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesised results	16-22
Risk of reporting biases in syntheses	#21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed	16-22
Certainty of evidence	#22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed	16-22
Discussion			
Results in context	#23a	Provide a general interpretation of the results in the context of other evidence	10-12
Limitations of included studies	#23b	Discuss any limitations of the evidence included in the review	2
Limitations of the review methods	#23c	Discuss any limitations of the review processes used	2
Implications	#23d	Discuss implications of the results for practice, policy, and future research	13-15
Other information			
Registration and protocol	#24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered	15
Registration and protocol	#24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared	15

Registration and protocol	#24c	Describe and explain any amendments to information provided at registration or in the protocol	N/A
Support	#25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review	15
Competing interests	#26	Declare any competing interests of review authors	15
Availability of data, code, and other materials	#27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review	16-22

BMJ Open

Rabies in Southeast Asia: a systematic review of its incidence, risk factors, and mortality

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Rabies in Southeast Asia: a systematic review of its incidence, risk factors and mortality

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ABSTRACT

Objective Rabies is a neglected zoonotic disease that can infect all mammals, including humans. We aimed to summarise the current knowledge of the incidence, risk factors and mortality of rabies in Southeast Asia.

Design Systematic review based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020.

Data sources Scopus, Web of Science and PubMed were searched from 1 January 2012 to 21 February 2023.

Eligibility criteria Original English language articles published between 2012 and 2023 were included.

Data extraction and synthesis Nine independent reviewers extracted data and assessed the risk of bias. The quality appraisal of included articles was carried out using the Mixed Methods Appraisal Tool (MMAT).

Results A total of eight articles were included in this analysis. In Vietnam, the incidence of rabies ranged from 1.7 to 117.2 per 100,000 population. The cumulative incidence in Sarawak was estimated at 1.7 per 100,000 population. In Indonesia, 104 human rabies cases were reported from 2008 to 2010, while in Thailand, a total of 46 rabies cases were reported in Thailand from 2010 to 2015. In the Philippines, the incidence of rabies ranged from 0.1 to 0.3 per 100,000 population. An increased risk of rabies virus infection was associated with a high population density, illiteracy, seasonal patterns and dog butchers. The case-fatality rate was 100%.

Conclusion This study included research from Southeast Asia, which may not represent rabies infection in other regions or continents. Additionally, the role of publication bias should be acknowledged as grey literature was not included. The occurrence of rabies in Southeast Asia is due to the high number of unvaccinated stray and pet dogs, working hazards (dog butchers in Vietnam), the unavailability of the rabies vaccine in rural regions, and misinformation about the significance of seeking treatment after dog bites.

PROSPERO registration number CRD42022311654.

Keywords Rabies, dog bite, zoonotic disease, epidemiology, Southeast Asia

Strengths and limitations

- This review only includes research from Southeast Asia, which may not represent rabies infection in other regions or continents.
- We did not include grey literature or national guidelines, which could have been useful in this study.
- The inclusion of studies that defined or diagnosed rabies based on clinical signs or laboratory tests increased the chances of identifying rabies cases in Southeast Asian countries.

INTRODUCTION

Rabies is a neglected zoonotic disease caused by an RNA virus from the family *Rhabdoviridae*, genus *Lyssavirus* (1). Once clinical symptoms appear, rabies is almost 100% fatal (2). All mammals can be infected with the rabies virus, including humans. More than 99% of human rabies cases are transmitted via dogs (3). With the necessary evidence and tools in place for the control and elimination of rabies, canine rabies can be eliminated, as demonstrated in Western Europe, Canada, the United States of America (USA), Japan, a few Latin American countries and many parts of Asia. However, rabies is still widespread, occurring in more than 80 countries, particularly developing countries in Africa and Asia (3,4). Furthermore, half of the global population lives in canine rabies-endemic areas and hence is at risk of contracting rabies (3).

Globally, canine rabies is estimated to cause approximately 59,000 human deaths annually. In Asia, rabies is clearly a major problem: the number of human deaths due to rabies in Asia is higher than in any other region in the world. Most human rabies deaths occur in Asia (59.6%), followed by Africa (36.4%), while only less than 0.05% of human rabies deaths occur in the Americas. Additionally, India alone accounts for 35% of global human rabies deaths, higher than any other country 4)4). In Asia, canine rabies is estimated to cause a loss of 2.2 million Disability-Adjusted Life Years (DALYs) per year, while the annual cost of post-exposure prophylaxis (PEP) is highest in Asia, estimated at up to US$ 1.5 billion (5).

In Southeast Asia, only Singapore has eradicated canine rabies through the implementation of robust national rabies control programs, while other countries in this subregion are not considered rabies-free (6). Malaysia was declared rabies-free by the World Organization for Animal Health in July 2013, but several rabies outbreaks since 2015 have caused Malaysia to lose its rabies-free status (7). Even though Thailand and Vietnam have not

been able to eliminate rabies, there has been a substantial reduction in human rabies deaths through the implementation of dog mass vaccination, intensified PEP in humans and awareness education (8).

Rabies is 100% preventable through vaccination in animals and humans (9). The World Health Organization (WHO) has recommended pre-exposure prophylaxis (PrEP) for those with continual, frequent or increased risk of exposure to rabies virus (e.g. veterinarians and animal handlers). If exposed to a rabid animal, the WHO recommends PEP, which consists of immediate wound management, immediate vaccination and the administration of rabies immunoglobulin for high-risk exposures (10). Nevertheless, dog vaccination is considered the most cost-effective strategy for preventing rabies in humans (2).

Despite the availability of evidence and guidelines for the control and management of rabies, countries in Southeast Asia face some constraints in controlling rabies, including inadequate resources, lack of political commitment, lack of consensus on strategy, weak intersectoral coordination, insensitive surveillance systems, limited accessibility to modern rabies vaccines and supply problems, as well as a lack of public awareness and cooperation (8). However, the high estimated burden of rabies more than justifies the need to prioritise rabies control, particularly in Asian countries.

Information on rabies epidemiology is a prerequisite for the effective planning of rabies control programs. Previous systematic reviews focused on rabies epidemiology in India (11), Nepal (1), and Arab countries (12), while literature synthesising data on rabies epidemiology in Southeast Asia is limited. Hence, this systematic review aims to provide an in-depth assessment of the incidence, risk factors, and mortality of rabies in Southeast Asian countries, based on the published literature.

MATERIALS AND METHODS

This systematic review was registered with the PROSPERO database (CRD42022311654) and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (13). A meta-analysis was not carried out as the included studies differed in terms of methodology, settings, participants, interventions, and outcomes, suggesting heterogeneity. An internal protocol was developed to document the criteria for conducting this systematic review, but this is not published.

Patient and public involvement

There was no patient and/or public involvement in this study (None).

Research question formulation

The review question was developed based on the CoCoPop (condition, context, population) and PEO (population, exposure, outcome) concepts (14). The PICO (population, intervention, comparison intervention, outcome measures) framework is commonly used to develop focused clinical questions for quantitative reviews (15), while the CoCoPop and PEO concepts are suitable for reviews related to prevalence and aetiology (14). Based on the CoCoPop concept, the condition refers to the incidence of rabies, the context refers to Southeast Asia and the population is the general population. Based on the PEO concept, the population refers to the general population in Southeast Asia, the exposure refers to rabies and the outcome is the mortality caused by rabies. Hence, the main research questions are (1) What is the incidence of rabies among the general population in Southeast Asian countries? (2) What are the risk factors of rabies among the general population in Southeast Asian countries? and (3)

What is the mortality rate of rabies among the general population in Southeast Asian countries?

Data source and search strategy

PubMed, Web of Science and Scopus were searched from 1 January 2012 to 21 February 2023. The keywords used to search for related articles are provided in Table 1.

Table 1: Keywords search used in the screening process.

Database	Search string
Scopus	1) TITLE-ABS-KEY((“rabies*” OR “rabies virus*” OR “dog bite*”) AND (“Southeast Asia” OR “Brunei” OR “Myanmar” OR “Cambodia” OR “Timor-Leste” OR “Indonesia” OR “Laos” OR “Malaysia” OR “Philippines” OR “Singapore” OR “Thailand” OR “Vietnam”) AND (“epidemiology” OR “outbreak” OR “case” OR “prevalence” OR “incidence” OR “causes” OR “risk factor”)) 2) TITLE-ABS-KEY((“Rabies*” OR “Rabies virus*” OR “dog bite*”) AND (“Southeast Asia” OR “Brunei” OR “Myanmar” OR “Cambodia” OR “Timor-Leste” OR “Indonesia” OR “Laos” OR “Malaysia” OR “Philippines” OR “Singapore” OR “Thailand” OR “Vietnam”) AND (“mortality*” OR “death*” OR ”fatality*”))
Web of Science	1) (((ALL=("rabies*")) OR ALL=("rabies virus*")) OR ALL=("dog bite*") AND ((((((((((ALL=("Southeast Asia")) OR ALL=("Brunei")) OR ALL=("Myanmar")) OR ALL=("Cambodia")) OR ALL=("Timor-Leste")) OR ALL=("Indonesia")) OR ALL=("Laos")) OR ALL=("Malaysia")) OR ALL=("Philippines")) OR ALL=("Singapore")) OR ALL=("Thailand")) OR ALL=("Vietnam")) AND ((((((ALL=("epidemiology")) OR ALL=("outbreak")) OR ALL=("case")) OR ALL=("prevalence")) OR ALL=("incidence")) OR ALL=("causes")) OR ALL=("risk factor") 2) (((ALL=("rabies*")) OR ALL=("rabies virus*")) OR ALL=("dog bite*") AND ((((((((((ALL=("Southeast Asia")) OR ALL=("Brunei")) OR ALL=("Myanmar")) OR ALL=("Cambodia")) OR ALL=("Timor-Leste")) OR ALL=("Indonesia")) OR ALL=("Laos")) OR ALL=("Malaysia")) OR ALL=("Philippines")) OR ALL=("Singapore")) OR ALL=("Thailand")) OR ALL=("Vietnam")) AND ((ALL=("mortality*")) OR ALL=("death*")) OR ALL=("fatality*")

PubMed	1) ((((("rabies*") OR ("rabies virus*")) OR ("dog bite*")) AND ((((((((((("Southeast Asia") OR ("Brunei")) OR ("Myanmar")) OR ("Cambodia")) OR ("Timor-Leste")) OR ("Indonesia")) OR ("Laos")) OR ("Malaysia")) OR ("Philippines")) OR ("Singapore")) OR ("Thailand")) OR ("Vietnam"))) AND (((((("epidemiology") OR ("outbreak")) OR ("case")) OR ("prevalence")) OR ("incidence")) OR ("causes")) OR ("risk factor")) 2) ((((("rabies*") OR ("rabies virus*")) OR ("dog bite*")) AND ((((((((((("Southeast Asia") OR ("Brunei")) OR ("Myanmar")) OR ("Cambodia")) OR ("Timor-Leste")) OR ("Indonesia")) OR ("Laos")) OR ("Malaysia")) OR ("Philippines")) OR ("Singapore")) OR ("Thailand")) OR ("Vietnam"))) AND ((("mortality*") OR ("death*")) OR ("fatality*"))

Study selection

The inclusion criteria were (1) publications from 2012 to 2023, (2) original articles and (3) publications in the English language. The following types of studies were included in this review: (1) reports on the incidence and risk factors of rabies in Southeast Asia and (2) reports on the mortality rate of rabies in Southeast Asia. Non-original articles such as conference proceedings, perspectives, commentaries, opinions, reports, systematic reviews and meta-analyses were excluded. The publication period was limited to 2012–2023 so that the systematic review could be built on recent literature.

Data extraction and synthesis

Duplicates were deleted, and at least two reviewers re-screened the remaining papers. Before their inclusion in the review, articles were screened in three stages. Any article that did not meet the inclusion criteria based on title screening was eliminated in the first phase. The abstracts of the remaining papers were reviewed in the second phase, and any publications that did not fit the inclusion criteria were eliminated from the review. The full-text articles were examined attentively in the last phase to eliminate any papers that did not fulfil the

inclusion criteria. Before the data extraction process, both reviewers needed to agree that the entire publication should be reviewed. Any disagreements were worked out through discussion. All data extraction was conducted independently using a standardised data extraction form that was organised using Microsoft Excel. Information collected in the form included (1) author, (2) publication year, (3) reference, (4) country, (5) study design, (6) statistical analysis and (7) results, which included incidence, risk factors and mortality. Due to the heterogeneity of the included studies, narrative synthesis was performed.

Quality assessment

Quality assessment was conducted by the authors on all eight studies using the Mixed Methods Appraisal Tool (MMAT) (16). The MMAT is a critical appraisal tool that was developed to appraise studies included in systematic mixed study reviews. The quality of the methodology of five categories of studies (qualitative studies, randomized controlled trials, non-randomised studies, quantitative descriptive studies, and mixed methods studies) can be appraised using this tool. For each category, five criteria are used to assess the quality of the study. It is advised not to calculate an overall score from the rating of each criterion using the latest version of MMAT (2018). However, due to problems faced by researchers in reporting the MMAT results, a suggestion was provided for reporting an overall score (5*****/100% of the quality criteria met, 4****/80% of the quality criteria met; 3***/60% of the quality criteria met; 2**/40% of the quality criteria met; 1*/20% of the quality criteria met). The details of this assessment are reported in Table 2.

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174 Table 2: The details of mixed method appraisal tool assessment

Author	Type of study	Score	1.1	1.2	1.3	1.4	1.5
			Is the sampling strategy relevant to address the research question?	Is the sample representative of the target population?	Are the measurements appropriate?	Is the risk of nonresponse bias low?	Is the statistical analysis appropriate to answer the research question?
Nguyen et al. 2021	Quantitative	40%	Can't tell	Can't tell	Yes	Can't tell	Yes
Pham et al. 2021	Quantitative	100%	Yes	Yes	Yes	Yes	Yes
Sim et al. 2021	Quantitative	60%	Yes	Can't tell	Yes	Can't tell	Yes
Yurachai et al. 2021	Quantitative	80%	Yes	Yes	Yes	Can't tell	Yes
Phung et al. 2018	Quantitative	80%	Yes	Yes	Yes	Can't tell	Yes
Susilawati et al. 2012	Quantitative	80%	Yes	Yes	Yes	Yes	No
Lee et al. 2017	Quantitative	100%	Yes	Yes	Yes	Yes	Yes
Guzman et al.2021	Quantitative	80%	Yes	Yes	Yes	No	Yes

RESULTS

A total of 1,437 records were identified from the three databases to evaluate the incidence, risk factors and mortality rate of rabies in Southeast Asia. Using automation tools, 829 records were excluded based on year, publication type and language. A total of 98 duplicate records were found and removed, leaving 510 records for title screening. The titles and abstracts were screened independently based on the review questions. A total of 491 articles were removed during the screening. For the remaining 19 articles, the full text was retrieved for assessment of eligibility. Disagreements were resolved through discussion to reach a consensus. Eleven articles were removed for the following reasons: they did not meet the objective (*n* = 4) (17–20), they were not primary/original research articles (*n* = 4) (21–24), the full article could not be retrieved (*n* = 2) (25,26) and they were duplicates (*n* = 1) (27), leaving a total of eight articles for proceeding with the quality appraisal. The PRISMA flowchart is presented in Figure 1.

Quality appraisal

According to the MMAT evaluation criteria, 75% of the articles (*n* = 6) met 75–100% of the MMAT checklist, representing high quality. Of the articles, 12.5% (*n* = 1) met 50–75% of the evaluated criteria, representing moderate quality, while 12.5% of the articles (*n* = 1) met less than 50% of the evaluated criteria, representing low quality.

Background of the eligible studies

A total of eight studies were included in this systematic review, of which four were conducted in Vietnam, and 1 each in Indonesia, Malaysia, Thailand and the Philippines (Supplementary table). The themes covered by all studies included incidence rates, case numbers and risk

factors of rabies in Southeast Asia. Among the included studies, three studies particularly discussed rabies mortality.

Incidence and risk factors of rabies in Southeast Asian countries

Overall, the incidence of rabies ranged between 0.1 per 100,000 population in the Philippines (28) 117.2 per 100,000 population in Vietnam [18]. The average monthly number of rabies cases in Vietnam was 429 during the period from 2011 to 2015, with the incidence ranging from 1.7 to 117.2 per 100,000, with higher incidences observed in the Red River, South Central Coast (SCC) and Mekong River Delta (MRD) regions (29). Specific to Southern Vietnam, a total of 94 human rabies cases were reported between 2009 and 2018, with an average of nine cases recorded annually, representing an incidence of 2.7 cases per 10 million population (30). The highest number was reported in 2018 (5.5 cases per 10 million population). Most cases were among men and individuals aged 50 years and above.

Dog butchers in Vietnam were at high risk of rabies virus infection (31). The study found that 28.3% of butchers were at risk of rabies exposure due to the slaughtering of sick dogs and getting bites, scratches or knife cuts. Of 406 participants, 8.6% had sufficient levels of rabies neutralising antibody (NTA) for protection and only 8.1% were vaccinated. In terms of location, rabies cases were limited to specific areas. Hotspots were identified in southern Vietnam, particularly in the MRD and SCC (32). Seasonal patterns were observed, with a strong peak in February/July and a minor peak in October/December in the MRD region. However, a strong peak was detected in the middle of each year in the SCC. Temperature, humidity and cumulative rainfall are positively associated with an increased incidence of rabies in Vietnam. In terms of socio-economic factors, increases in population density, as well as the percentage of illiteracy, elevated the risk of rabies (29).

In Indonesia, 104 human rabies cases were reported in Bali from November 2008 to November 2010. Most of the cases were among men. Almost all (92%) cases had a history of a dog bite. Only 5.8% had their wounds treated and received an anti-rabies vaccine (ARV) after the bite incident (33). Even worse, rabies cases in Sibu, Sarawak, also did not seek medical attention following a dog bite (34). The cumulative incidence in Sibu was estimated at 1.7 per 100,000 population. The incubation period varied from 17 days to 2 years.

A total of 46 confirmed and probable cases of human rabies were reported in Thailand from 2010 to 2015, of which 11 were reported in Eastern Thailand (35). Even though rabies can be prevented by vaccination, more than 90% of rabies death cases in Thailand did not receive or improperly stopped receiving PEP. In terms of suspected rabies exposures, 6,204 exposures were reported from eight provinces in Eastern Thailand, resulting in a crude exposure rate of 106 reported rabies exposures per 100,000 people. Dogs were the main source of exposure (77.8%), while children under the age of 15 and older persons over the age of 60 had the highest overall reported exposure rates (189.7 and 189.2/100,000, respectively).

In the Philippines, there were 575 rabies cases from 2006 to 2015, of which 70% were among men. Nearly 34% of the patients were aged 41 to 60 years. The incidence rate of human rabies per 100,000 population in 2007, 2010 and 2015 was 0.1305, 0.1356 and 0.1708 in the National Capital Region; 0.2890, 0.2965 and 0.1961 in Region III; and 0.1449, 0.1272 and 0.1041 in Region IV-A, respectively (28).

Rabies mortality in Southeast Asian countries

The case fatality rate was 100% as mentioned in two studies (33,34). Of the six deaths reported in Sibu, five patients succumbed to the illness within 2 weeks of symptom onset,

with five out of the six cases reporting a dog bite history [23]. In Indonesia, Susilawati et al. reported 104 fatalities due to rabies, of which 96 cases had a history of dog bites [22]. In the Philippines, 463 people died from rabies infection (28).

DISCUSSION

Incidence and risk factors of rabies in Southeast Asian countries

Rabies in Asia and Africa contributes to over 99% of the human rabies deaths that occur in the world today. The vast majority (60%) of these deaths occur in Asia (36). Every year, an estimated 59,000 people die from rabies worldwide, with the majority (95%) of these deaths occurring in Africa and Asia due to a lack of PEP services for animal-bite patients and rabies surveillance personnel and facilities (37). These statistics support the results of our study, which shows the reporting of a high number of rabies cases in Vietnam, Indonesia and Thailand, which are endemic for rabies (38).

Rabies is concentrated in Asia and Southeast Asia because it is frequently neglected when health and agriculture budgets are set, although the costs and economic benefits of implementing rabies prevention programs have been successfully established in high-income countries (39). The high number of rabies cases in Southeast Asia can also be attributed to the high number of unowned, free-roaming dogs that cannot be controlled without considerable effort and thus are not vaccinated (40). Vaccination programs for dogs can provide herd immunity and break the rabies transmission cycle in this reservoir species and have been successfully applied in several countries around the world (41).

Another cause of the high incidence of rabies in Southeast Asia is the working hazards of dog butchers, especially in countries that have legalised dog consumption, such as Vietnam (42). The Centers for Disease Control and Prevention (CDC) also reported the illegal trafficking

of dogs for human consumption in Vietnam (https://www.cdc.gov/globalhealth/stories/rabies_southeast_asia.htm), which could possibly contribute to the high incidence of rabies in Vietnam. Professional dog butchers in northern Vietnam are at a high risk of rabies virus infection due to exposure during the slaughtering process from the handling of sick or dead dogs and getting bitten, scratched, or cut with knives. A study reported that 91.9% of professional dog butchers in Vietnam were not vaccinated against rabies, which may be because of fear of the side effects of the rabies vaccine, inability to afford vaccination, and incorrect knowledge of rabies prevention (31).

The rabies incidence of 0.1 per 100,000 population in the Philippines is similar to that reported in China in 2016 (43). The lower rabies incidence in the Philippines compared to other Southeast Asian countries may be due to the implementation of the Anti-Rabies Act of 2007 to prevent and control human rabies (44). Additionally, the consumption of dog meat was banned in 1998 with the implementation of the Animal Welfare Act which may contribute to the lower incidence of rabies in the Philippines (45).

Men are more likely to contract rabies infection than women [19]. Similar findings were reported in Iraq, where more than 89% of rabies cases were among men (46). This can be attributed to the fact that most women are housewives, while men are engaged in outdoor activities (47). Another study in Ethiopia also stated that men are more likely to perform nightly and outdoor activities, while women are more likely to remain indoors for cultural and religious reasons (48), which could explain the increased incidence of rabies in men.

According to study a by Yurachai et al., rabies infection affects children more compared to other age groups [24]. This corresponds to a WHO report, stating that 40% of rabies victims are children ages 4 to 15 (https://www.who.int/news-room/fact-sheets/detail/rabies). Other studies in Yemen and Iran reported similar findings, with nearly

40% of the individuals exposed to rabies infection falling in this age group (46,49). Children in this age group are probably more likely to play with, annoy or approach biting animals, which contributes to the higher rate of bites in this age group (46). In contrast, according to a study by Pham et al., older people are more likely to become infected with rabies [19].

In several studies included in this systematic review, the diagnosis of most rabies cases was based only on detailed history and clinical diagnosis [17, 19, 21]. To diagnose rabies in humans, multiple samples such as saliva, serum, spinal fluid and skin biopsies of hair follicles from the nape of the neck are analysed. Viral isolation or reverse transcription followed by polymerase chain reaction (RT-PCR) can be used to analyse saliva. Serum and spinal fluid are tested for rabies virus antibodies. Skin biopsies can be used to detect rabies antigens in the cutaneous nerves at the base of the hair follicles (https://www.cdc.gov/rabies/diagnosis/animals-humans.html). In the future, developing countries need to standardise the diagnosis of rabies based on the laboratory tests mentioned above for the accuracy of the diagnosis and to enable comparison with other studies in developed countries.

Of the included studies, only one was conducted among butchers, who were at higher risk of contracting rabies [20]. Apart from butchers, individuals working as veterinarians, veterinary technicians, animal control workers, and wildlife rehabilitators were also considered to have a higher risk of contracting rabies than the general population (50). This calls for more studies incorporating individuals involved in occupations identified as high risk for rabies exposure and infection.

In this study, climate was postulated to be one of the risk factors for rabies infection. This was echoed by a study in China showing that the incidence of rabies increases with the ambient temperature. A warmer climate causes animals to be more active in their

environment and to travel greater distances when tracking, which contributes to the spread of rabies. In addition, as temperatures rise, people tend to wear lighter clothing and expose more skin, which increases the likelihood of being bitten by a dog (51). In South Korea, the seasonality of wildlife rabies was attributed to behaviours such as searching for food during the winter or early spring. Dogs may thus have more opportunities to come into contact with rabid animals during this period due to greater animal movement, which could contribute to seasonal patterns in the occurrence of rabies in humans (52).

Rabies mortality in Southeast Asian countries

In this study, rabies had a high fatality rate, with 100% of the infected cases dying. This is supported by a review in Africa by Nyasulu et al., who reported that Algeria, Namibia, Eswatini (formerly Swaziland), Tunisia, Uganda, Zambia, and Zimbabwe had high morbidity and mortality due to rabies, with 563 cases (33.9% deaths), 269 cases (94% deaths), 62 cases (88.7% deaths), 91 cases (90% deaths), 466 cases (40.9% deaths), 207 cases (32.8% deaths), and 114 cases (80.7% deaths), respectively (53). Because of the large population of stray dogs in this area, the chances of being bitten by a dog are high. Not only are the chances of being bitten high in these areas, but access to treatment in a timely and adequate manner is also very limited. Rabies vaccines may not be routinely available in rural areas where most exposures occur, and rabies immunoglobulins, which are required for category III bites, are always in short supply (54).

These factors significantly contribute to the high mortality rate, as the highly protective rabies vaccine is frequently unavailable in these poor areas. In addition, the public is often unconcerned and unaware of the need for early treatment after being bitten by dogs (55). According to recent studies, many rabies victims contracted the disease owing to neglect,

ignorance, or a lack of primary healthcare facilities (56). Thus, health promotion and education should be given to the public as knowledge regarding rabies is essential to reduce morbidity and mortality (5).

In high-income countries such as the USA, the incidence of rabies and associated mortality is low. In the last decade, there have been only 25 cases of human rabies reported in the USA (2009–2018), with 23 deaths (6). The low number of cases of rabies infection is due to successful animal control and vaccination programs, successful outreach programs, public health capacity and laboratory diagnostics, and the availability of modern rabies biologics (57). Even though rabies is preventable, the exorbitant cost of vaccinations, combined with a lack of education and knowledge about the disease, limits PEP use. (56)

Strengths and limitations

In this study, we only included research from Southeast Asia, which may not represent rabies infection in other regions or continents. We did not include grey literature or national guidelines, which could have been useful in this study. Nevertheless, the strength of this review lies in its inclusion of studies that defined or diagnosed rabies based on either clinical signs or laboratory testing. Given that rabies is often diagnosed clinically, especially in developing countries (58), this process increased the chances of identifying rabies cases in Southeast Asian countries.

Recommendations

A successful rabies prevention and control program requires integrating and strengthening intersectoral and transdisciplinary collaboration and cooperation among various societal components (59). The Association of Southeast Asian Nations (ASEAN) Rabies Elimination

Strategy places great value on the organisational and One Health frameworks for rabies eradication. The single most significant way to deal with rabies concerns is to eliminate dog-mediated rabies. The requirement for PEP is considerably reduced when dog rabies is eradicated (60). To benefit from the synergy and maximisation of shared resources, comprehensive rabies control programs should involve the combination of human, financial, and material resources with other disease programs (36).

Mass canine vaccination campaigns will boost herd immunity and reduce the risk of human rabies exposure, but this will need strong governmental commitment and extensive social mobilisation. The veterinary authority's active engagement in animal rabies control at the national level is critical, and it is their social responsibility to prevent human rabies through well-planned dog rabies control programs (38). In 1983, the Pan American Health Organization initiated an elimination programme for human rabies transmitted by dogs that was mainly based on the mass immunisation of dogs; this has led to a 90% reduction in dog rabies in Chile and other Latin American countries (61).

Rabies control and elimination in low endemic rabies countries such as Malaysia and Singapore have been made possible by the strict enforcement of dog registration, vaccination, and population management measures. Malaysia shares a border with Thailand, and the notion of an immunological belt has been developed through dog licensing, required vaccination of dogs and the systematic extermination of unvaccinated dogs in a buffer zone to prevent rabies from entering the country (38). Perhaps other middle and high endemic rabies countries could follow this rabies control strategy implemented by their Southeast Asian neighbour.

Public information and education are important to increase awareness and enhance community participation and support in rabies prevention programs. Dissemination of

important information such as the high fatality rate of rabies, its epidemiology, its prevention and control, and the disease control program, in general, is vital for program implementation and responsible pet ownership. By recognising rabies' influence on people's daily lives and the fact that dogs can be a source of human infection, community and school-based rabies prevention initiatives will be easier to establish (62).

The involvement of stakeholders is crucial, and by bringing together key stakeholders from the corporate and public sectors, health security and the need to form public-private partnerships, which are critical in rabies prevention programs, can be addressed (63). National government agencies can maintain standardised approaches for rabies management and elimination and advocate on how to begin public-private cooperation to ensure long-term intervention. All stakeholders can benefit from such technical and administrative effort as they provide credibility and quality assurance to the prevention program's effectiveness (36). Various examples of public-private partnerships that aid in implementing public programs, research, and policy formation can be seen in Indonesia, India, Sri Lanka, the Philippines, Thailand, and Vietnam (3).

CONCLUSION

Rabies has often been neglected and not given priority in terms of funding for prevention programs, resulting in the continued presence of rabies cases in Southeast Asia despite the endorsement of multiple programs by the WHO. The high number of unvaccinated stray and pet dogs, working hazards (dog butchers in Vietnam), unavailability of the rabies vaccine in rural areas, as well as ignorance regarding the importance of seeking treatment after dog bites, are among the factors that contribute to rabies cases in Southeast Asia.

Author contributions

All authors, J.L.M.Y., A.F.N.A.H., D.A., N.R., M.R.H., S.S.S.A.R., M.S.J., A.O., and A.H. were involved in the conceptualisation, methodology, extensive search for articles, critical review of articles, synthesis of results and original draft write-up. M.R.H. supervised the manuscript preparation. All authors have read and agreed to the final draft of the manuscript.

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Competing interests

The authors declare no conflicts of interest.

Patient consent for publication

Not applicable.

Ethics approval

Not applicable.

Data availability statement

Data are available upon reasonable request.

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Figure: PRISMA 2020 flow diagram for new systematic reviews that included searches of databases

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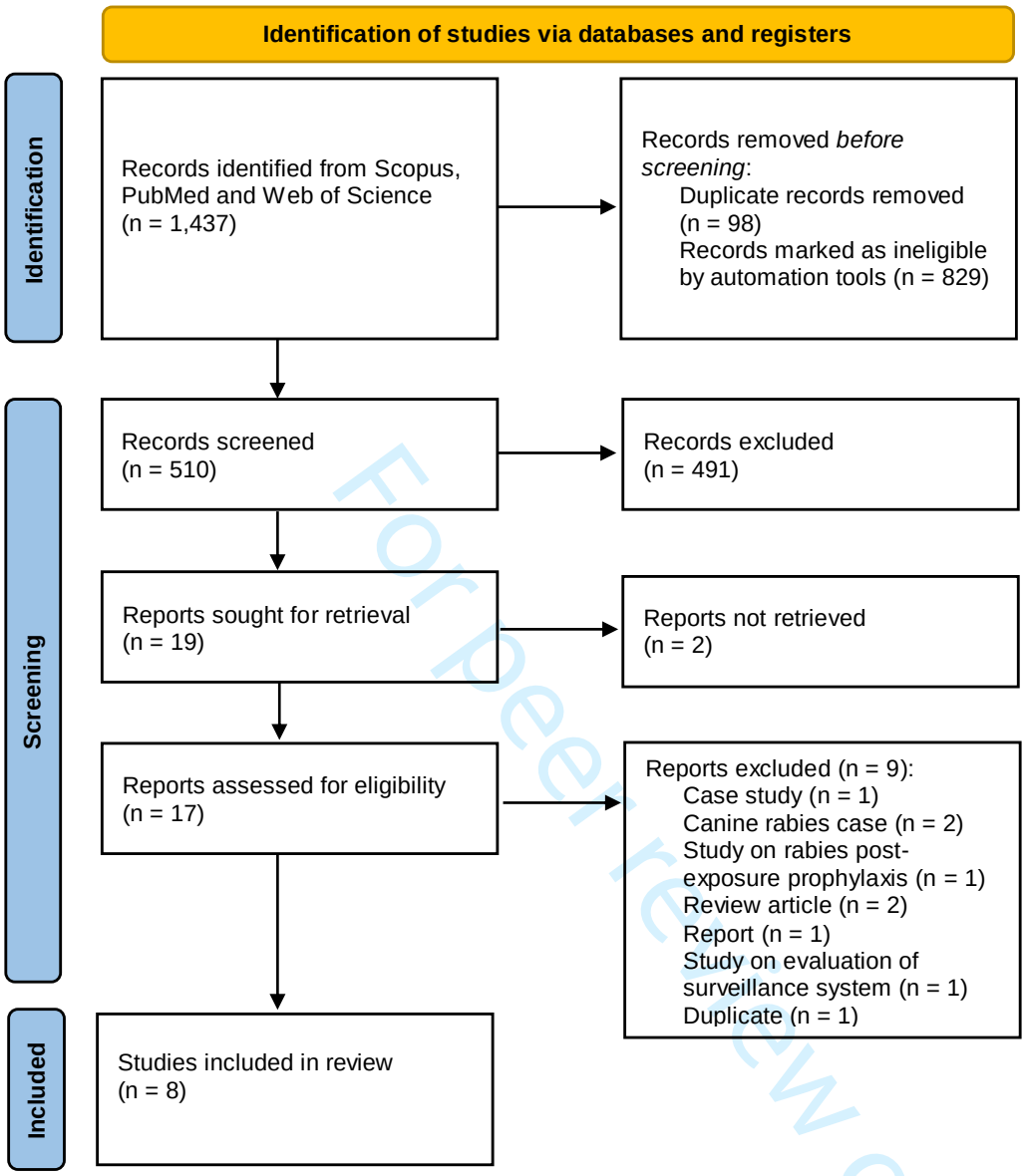
PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



Supplementary table: Table of evidence

Author/year	Country	Reference	Study design	Statistical analysis	Result
Nguyen et al. 2021	Vietnam	Nguyen, A. K. T., Vu, A. H., Nguyen, T. T., Nguyen, D. V., Ngo, G. C., Pham, T. Q., Inoue, S., et al. 2021. Risk factors and protective immunity against rabies in unvaccinated butchers working at dog slaughterhouses in Northern Vietnam. *American Journal of Tropical Medicine and Hygiene* 105(3): 788–793. doi:10.4269/ajtmh.20-1172	Cross-sectional	Pearson correlation Multivariate regression analysis	Study found that 28.3% of butchers were at risk of rabies exposure due to slaughtering sick dog, getting bitten, scratched or knife cut. Only 8.6% had NTA sufficient for protection and only 8.1% of them were vaccinated. Hence dog butchers in Vietnam were at high risk of rabies virus infection.
Pham et al. 2021	Vietnam	Pham, Q. D., Phan, L. T., Nguyen, T. P. T., Doan, Q. M. N., Nguyen, H. D., Luong, Q. C. & Nguyen, T. V. 2021. An Evaluation of the Rabies Surveillance in Southern Vietnam. *Frontiers in Public Health* 9(April): 1–9. doi:10.3389/fpubh.2021.610905	Cross-sectional	Descriptive Chi-square test / Fisher's exact test	94 human rabies cases (2009-2018) were reported in Southern Vietnam, with an average of nine cases recorded annually (2.7 cases per 10 million population). The highest number was reported in 2018. Majority of cases were male and those aged 50 years and above.
Sim et al. 2021	Malaysia	Sim, B. N. H., Liang, B. N. W., Ning, W. S. & Viswanathan, S. 2021. A retrospective analysis of emerging rabies: A neglected tropical disease in Sarawak, Malaysia. *Journal of the*	Cross-sectional	Descriptive	6 cases were identified with a mixture of MN and LMN findings. Most cases did not seek medical attention upon dog bite. The incubation period varied from 17 days to 2 years. All cases died, with 5 cases succumbing to the illness within 2 weeks of symptoms onset. The cumulative

		Royal College of Physicians of Edinburgh 51(2): 133–139. doi:10.4997/JRCPE.2021.207			incidence in Sibu was estimated at 1.7 per 100,000 population.
Yurachai et al. 2021	Thailand	Yurachai, O., Hinjoy, S. & Wallace, R. M. 2020. An epidemiological study of suspected rabies exposures and adherence to rabies post-exposure prophylaxis in Eastern Thailand, 2015. *PLoS Neglected Tropical Diseases* 14(2): 1–17. doi:10.1371/journal.pntd.0007248	Cross-sectional	Descriptive	46 confirmed and probable cases of human rabies were reported in Thailand (2010 – 2015). 11 were reported from Eastern Thailand. 6,204 suspected rabies exposure reported in 8 Eastern Thailand. Children age < 15 years and elderly age > 60 years had the highest suspected reported exposure rate compared to others (189.7/ 100,000 and 189.2/100,000). Overall, the estimated suspected rabies exposure rate was 204/100,000.
Phung et al. 2018	Vietnam	Phung, D., Nguyen, H. X., Thi Nguyen, H. L., Luong, A. M., Do, C. M., Tran, Q. D. & Chu, C. 2018. The effects of socioecological factors on variation of communicable diseases: A multiple-disease study at the national scale of Vietnam. PLoS ONE 13(3): 1–14. doi:10.1371/journal.pone.0193246	Ecological	Moran's I tests Multilevel negative binomial regression model / zero-inflated negative binomial regression	The average monthly number of rabies cases is 429 from 2011 to 2015. The incidences of rabies ranged from 1.7 to 117.2 per 100,000 with higher incidences observed in Red River, South Central Coast (SCC), and the Mekong Delta regions Climate factors: temperature, humidity and cumulative rainfall were associated with increase in rabies incidence in Vietnam. Socio-economic factors: population density and illiteracy were sensitive factor increased risk of rabies.
Susilawati et al. 2012	Indonesia	Susilawathi, N. M., Darwinata, A. E., Dwija, I. B. N. P., Budayanti, N. S., Wirasandhi, G. A. K., Subrata, K.,	Cross-sectional	Descriptive	104 human rabies cases reported in Bali during November 2008-November 2010 which all are fatal and the symptom exhibit by all patients. Almost all (92%) cases had a history

		Susilarini, N. K., et al. 2012. Epidemiological and clinical features of human rabies cases in Bali 2008-2010. *BMC Infectious Diseases* 12(November 2008): 0–7. Doi:10.1186/1471-2334-12-81			of dog bite. Only 5.8% had their wounds treated and received an anti-rabies vaccine (ARV) after the bite incident. The case-fatality rate was 100%.
Lee et al. 2017	Vietnam	Lee, H. S., Thiem, V. D., Anh, D. D., Duong, T. N., Lee, M., Grace, D. & Nguyen-Viet, H. 2018. Geographical and temporal patterns of rabies post exposure prophylaxis (PEP) incidence in humans in the Mekong River Delta and Southeast Central Coast regions in Vietnam from 2005 to 2015. PloS ONE 13(4): 1–12. Doi:10.1371/journal.pone.0194943	Ecological	Univariate negative binomial regression	Hotspot localities were identified in Southern Vietnam (mainly at Mekong River Delta and South-Central Coast) MRD: strong peak in February / July SCC: middle of the year
Guzman et al.2021	Philippines	Guzman FD, Iwamoto Y, Saito N, Salva EP, Dimaano EM, Nishizono A, et al. (2022) Clinical, epidemiological, and spatial features of human rabies cases in Metro Manila, the Philippines from 2006 to 2015. PLoS Negl Trop Dis 16(7): e0010595. https://doi.org/10.1371/journal.pntd.0010595	Cross-sectional	Descriptive	575 rabies cases from 2006 to 2015. Most patients were male (70.3%) and aged 41 to 60 years (34.1%). The incidence rate of human rabies per 100,000 population in 2007, 2010, and 2015 were 0.1305, 0.1356, and 0.1708 in the National Capital Region; 0.2890, 0.2965, and 0.1961 in Region III; and 0.1449, 0.1272, and 0.1041 in Region IV-A, respectively. 463 people died of rabies.

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1 - 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4 - 5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	8
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	7
Search strategy	7	Present the full search strategies for all databases, registers, and websites, including any filters and limits used.	7 – 8
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	8 – 9
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	8 – 9
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	9
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	-
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	9
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	-
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	9
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	9
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	9
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	9
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	-
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	-
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	-
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	9

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	11
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	11
Study characteristics	17	Cite each included study and present its characteristics.	12 - 14
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	10
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	12 - 14
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	15 - 16
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	-
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	-
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	-
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	-
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	-
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	17 - 21
	23b	Discuss any limitations of the evidence included in the review.	19
	23c	Discuss any limitations of the review processes used.	21
	23d	Discuss implications of the results for practice, policy, and future research.	21 – 23
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	6
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	6
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	24
Competing interests	26	Declare any competing interests of review authors.	24
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	24

PRISMA 2020 Checklist

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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