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

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

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18 Abstract

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

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

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3 25 Science, and PubMed. After a thorough screening, 7 articles were selected to proceed with
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6 26 quality appraisal using Mixed Method Appraisal Tool.

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8 27 **Results:** A total of 7 articles were included in this analysis. In Vietnam, the incidence of rabies
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10 28 ranged from 1.7 to 117.2 per 100,000 from 2011 to 2015 with higher incidences observed in
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12
13 29 southern Vietnam, particularly in the Mekong River Delta and South-Central Coast. The
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15 30 cumulative incidence in Sibiu, Sarawak was estimated at 1.7 per 100,000 population. In
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17
18 31 Indonesia, 104 human rabies cases were reported in Bali from November 2008 to November
19
20 32 2010 while a total of 46 confirmed and probable cases of human rabies were reported in
21
22
23 33 Thailand from 2010 to 2015. Most cases were male. Increased risk of rabies virus infection
24
25 34 was associated with high population density, illiteracy, seasonal patterns as well as among
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27
28 35 dog butchers. Almost all cases had a history of dog bites. The case-fatality rate was 100%.

29
30 36 **Conclusion:** The presence of rabies cases in Southeast Asia is due to a high number of
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32 37 unvaccinated stray and pet dogs, working hazards (dog butcher in Vietnam), the unavailability
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34
35 38 of rabies vaccine in rural regions, and misinformation about the significance of seeking
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38 39 treatment after dog bites.

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40 40 **Keywords:** Rabies, dog bite, zoonotic disease, epidemiology, Southeast Asia

41 41 **Strengths and limitations**

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43 42 This study only includes research from Southeast Asia, which may not represent rabies
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45 43 infection in other regions or continents. Furthermore, we only used three databases, which
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48 44 may have limited the article's resources. We did not include grey literature or national
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51 45 guidelines, which could have been useful in this study. Our strengths, however, are that we
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54 46 can tailor the control program specifically for Southeast countries, and we are aware of the
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57 47 true burden of rabies infection in our region.

48 Introduction

49 Rabies is a neglected zoonotic disease that is caused by an RNA virus from the family of
50 *Rhabdoviridae*, genus *Lyssavirus* (1). Once clinical symptoms appear, rabies is almost 100%
51 fatal (2). All mammals can be infected with the rabies virus, including humans. More than
52 99% of human rabies cases are transmitted via dogs (3). With the necessary evidence and
53 tools in place for control and elimination of rabies, canine rabies can be eliminated, as
54 demonstrated in Western Europe, Canada, the United States of America (USA), Japan, a few
55 Latin American countries, and many parts in Asia. However, rabies is still widespread,
56 occurring in more than 80 countries, particularly in the developing countries in Africa and Asia
57 (3,4). Furthermore, half of the global population lives in canine rabies-endemic areas hence
58 is at risk of contracting rabies (3).

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

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

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3 72 2015 have relegated Malaysia down from its rabies-free status (7). Even though Thailand and
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6 73 Vietnam have not been able to eliminate rabies, there was a substantial reduction of human
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8 74 rabies deaths through the implementation of dog mass vaccination, intensified post-exposure
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11 75 prophylaxis in humans, and awareness education (8).

12
13 76 Rabies is 100 percent preventable through vaccination in animals and humans (9). The
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15 77 World Health Organization (WHO) recommended pre-exposure prophylaxis (PrEP) for those
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18 78 with continual, frequent, or increased risk of exposure to rabies virus (e.g., veterinarians,
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20 79 animal handlers). If exposed to a rabid animal, the WHO recommended PEP, which consists
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23 80 of immediate wound management, immediate vaccination, as well as administration of rabies
24
25 81 immunoglobulin for high-risk exposure (10). Nevertheless, dog vaccination is considered the
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28 82 most cost-effective strategy for preventing rabies in humans (2).

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30 83 Despite the availability of evidence and guidelines for the control and management of
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33 84 rabies, there are some constraints faced by countries in Southeast Asia in controlling rabies,
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35 85 including inadequate resources, lack of political commitment, lack of consensus on strategy,
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38 86 weak intersectoral coordination, insensitive surveillance systems, limited accessibility to
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40 87 modern rabies vaccine and supply problem, as well as lack of public awareness and
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43 88 cooperation (8). The high estimated burden for rabies more than justifies the need to
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45 89 prioritize rabies control, particularly in Asian countries.

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47 90 Information on rabies epidemiology is a prerequisite for effective planning of rabies
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50 91 control programs. Previous systematic reviews focused on rabies epidemiology in India (11),
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53 92 Nepal (1), and Arab countries (12), while literature synthesizing data regarding rabies
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56 93 epidemiology in Southeast Asia are limited. Hence, this systematic review aims to provide an
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59 94 in-depth assessment of the rabies situation in Southeast Asia countries, based on the
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95 published literature.

96 **Materials and Methods**

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

99 ***Patient and Public involvement***

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

101 ***Research Question Formulation***

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

115 ***Data Source and Search Strategy***

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

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120

121 Table 1: Keywords search used in the screening process

Database	Search string
Scopus	<p>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"))</p> <p>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*"))</p>
Web of Science	<p>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"))</p> <p>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*"))</p>
PubMed	<p>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"))</p>

	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*"))
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123 **Study Selection**

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

129 **Data Extraction and Synthesis**

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

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3 **143 Quality Appraisal**
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6 **144** Quality appraisal was conducted by authors on all 7 studies using the Mixed Method Appraisal
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8 **145** Tool (MMAT) (16). The MMAT is a critical appraisal tool that is developed to appraise studies
9
10 **146** included in systematic mixed study reviews. The methodology quality of five categories of
11
12 **147** studies (qualitative study, randomized control trials, non-randomized studies, quantitative
13
14 **148** descriptive study, and mixed methods study) can be appraised using this tool. For each
15
16 **149** category, five criteria are used to assess the quality of the study. It is advised not to calculate
17
18 **150** an overall score from the rating of each criterion using the latest version of MMAT (2018).
19
20 **151** However, due to problems faced by researchers in reporting the MMAT results, a suggestion
21
22 **152** was provided for reporting an overall score (5*****/100% quality criteria met; 4*****/80%
23
24 **153** quality criteria met; 3*****/60% quality criteria met; 2*****/40% quality criteria met; 1*****/20%
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26 **154** quality criteria met). The details of this assessment are reported in Table 2.
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33 **155** Table 2: The details of mixed method appraisal tool assessment
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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

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157 Results

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

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3 170 ***Background of the Eligible Studies***
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6 171 A total of 7 studies were included in this systematic review in which 4 studies were conducted
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8 172 in Vietnam, and 1 each from Indonesia, Malaysia, and Thailand (Table 3). The theme discussed
9
10 173 by all studies was epidemiology (number of cases, incidence rates, distributions, causes, risk
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13 174 factors) of rabies in Southeast Asia. Among the included studies, 2 studies particularly
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15 175 discussed rabies's impact (mortality).
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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. <i>American Journal of Tropical Medicine and Hygiene</i> 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. <i>Frontiers in Public Health</i> 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. <i>Journal of the</i>	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

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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

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

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%.

178

179 *Epidemiology of Rabies in Southeast Asia Countries*

180 The average monthly number of rabies cases in Vietnam is 429 during the period from 2011
181 to 2015, where the incidences of rabies ranged from 1.7 to 117.2 per 100,000 with higher
182 incidences observed in Red River, South Central Coast (SCC), and the Mekong Delta regions
183 (17). Specific to Southern Vietnam, a total of 94 human rabies cases between 2009 and 2018
184 were reported, with an average of nine cases recorded annually, representing an incidence of
185 2.7 cases per 10 million population (18). The highest number was reported in 2018 (5.5 cases
186 per 10 million population). Most cases were male and those aged 50 years and above.

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

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

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3 202 bite incident (21). Even worse, rabies cases in Sibul, Sarawak did not seek medical attention
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6 203 upon dog bite as well (22). The cumulative incidence in Sibul was estimated at 1.7 per 100,000
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8 204 population. The incubation period varied from 17 days to 2 years.

9
10 205 A total of 46 confirmed and probable cases of human rabies were reported in Thailand
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13 206 from 2010 to 2015, in which 11 were reported from Eastern Thailand (23). Even though rabies
14
15 207 can be prevented by vaccination, more than 90% of rabies deaths in Thailand did not get or
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17
18 208 improperly stopped receiving PEP. In terms of suspected rabies exposures, 6,204 exposures
19
20 209 were reported from eight provinces in Eastern Thailand, resulting in a crude exposure rate of
21
22
23 210 106 reported rabies exposures per 100,000 people. Dogs were the main source of exposure
24
25 211 (77.8%), while children under the age of 15 and the elderly over the age of 60 had the highest
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28 212 overall reported exposure rates (189.7 and 189.2/100,000, respectively).

29 30 213 ***Impact of Rabies in Southeast Asia Countries***

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32 214 The case-fatality rate was 100% as (21,22). Among 6 cases reported in Sibul, 5 cases
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35 215 succumbed to the illness within 2 weeks of symptoms onset.

36 37 216 **Discussion**

38 39 40 217 ***Epidemiology of Rabies in Southeast Asia Countries (Distribution, Causes/Risk Factors of*** 41 42 218 ***Rabies)***

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44 219 Rabies in Asia and Africa contributes to over 99% of human rabies deaths that occur in the
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46
47 220 world today. The vast majority of 60% of these deaths are in Asia (24). Every year, an
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49
50 221 estimated 59,000 people die from rabies worldwide, with the majority (95%) of these deaths
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52 222 occurring in Africa and Asia due to a lack of post-exposure prophylaxis (PEP) services for
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55 223 animal-bite patients and rabies surveillance personnel and facilities (25). This support the
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57 224 result of our study which shows that there is a high number of rabies cases reported in
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59 225 Vietnam, Indonesia, and Thailand, which are medium endemic rabies country (26).
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3 226 Rabies is concentrated in Asia and Southeast Asia region because rabies is frequently
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6 227 neglected when health and agriculture budgets are set although the costs and economic
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8 228 benefits of having rabies prevention programs have been successfully implemented in high-
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10 229 income country (27). The high number of rabies cases in Southeast Asia is also contributed by
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13 230 the high number of unowned, free-roaming dogs that can't be controlled without a lot of
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15 231 effort and thus aren't vaccinated (28). Vaccination programs in dogs can provide herd
16
17 232 immunity and break the rabies transmission cycle in this reservoir species and had been
18
19
20 233 successfully applied in several countries around the world (29).

22
23 234 Another cause of high incidence of rabies in Southeast Asia is due to the working
24
25 235 hazard of dog butchers, especially in a country that legalizes dog consumption such as in
26
27 236 Vietnam (30). Professional dog butchers in northern Vietnam are at a high risk of rabies virus
28
29 237 infection due to exposure during the slaughtering process, which was from the slaughtering
30
31 238 of sick or dead dogs, getting bitten, scratched, or knife cut. (91.9%) professional dog butchers
32
33 239 in Vietnam were not vaccinated against rabies, which maybe because of the fear of side
34
35 240 effects of rabies vaccine, inability to afford vaccination, and incorrect knowledge of rabies
36
37 241 prevention (19).

22 242 ***Impact of Rabies in Southeast Asia Countries (Cases/Outbreak, Morbidity/Mortality)***

243 In this study, rabies had a high fatality rate, with 100 percent of infected cases dying. This is
244 supported by a review done in Africa by Nyasulu et al 2021, who reported that Algeria,
245 Namibia, Eswatini (former Swaziland), Tunisia, Uganda, Zambia, and Zimbabwe had high
246 morbidity and mortality with 563 cases (33.9 percent deaths), 269 cases (94 percent deaths),
247 62 cases (88.7 percent deaths), 91 cases (90 percent deaths), 466 cases (40.9 percent), 207
248 cases (32.8 percent deaths), and 114 (31). Because of the high population of stray dogs in this
249 area, the chances of being bitten by a dog are high. Not only are the chances of being bitten

1
2
3 250 high in these areas, but access to treatment in a timely and adequate manner is also very
4
5
6 251 limited. Rabies vaccines may not be routinely available in rural areas where most exposure
7
8 252 occurs, and rabies immunoglobulins, which are required for category III bites, are always in
9
10
11 253 short supply (32).

12
13 254 This significantly contributes to the high mortality rate, as the highly protective rabies
14
15 255 vaccine is frequently unavailable in these poor areas. In addition, the public often gets laid
16
17
18 256 back and not aware to get early treatment after having been bitten by dogs (33). According
19
20
21 257 to recent studies, many rabies victims contracted the disease owing to neglect, ignorance, or
22
23 258 a lack of primary health care facilities (34). Thus, health promotion and education should be
24
25 259 given to the public as knowledge regarding rabies is essential to reduce morbidity and
26
27
28 260 mortality (5).

29
30 261 Compared to high-income countries such as the United States, the mortality caused
31
32
33 262 by rabies is low. In the last decade, there have been only 25 cases of human rabies reported
34
35 263 in the United States (2009-2018), with 1 to 3 cases reported each year (6). The low causes of
36
37 264 rabies infection are due to successful animal control and vaccination programs, successful
38
39
40 265 outreach programs, public health capacity and laboratory diagnostics, and the availability of
41
42 266 modern rabies biologics (35). Even though rabies is avoidable, the exorbitant expense of
43
44
45 267 vaccinations, combined with a lack of education and knowledge about the disease, limits PEP
46
47 268 use. According to recent studies, many rabies victims contracted the disease owing to neglect,
48
49
50 269 ignorance, or a lack of primary health care facilities (34).

51
52 270

53 54 271 **Recommendation**

55
56
57 272 A successful rabies prevention and control program requires integrating and strengthening
58
59 273 intersectoral and transdisciplinary collaboration and cooperation among various society
60

1
2
3 274 components (36). The ASEAN Rabies Elimination Strategy places great value on the
4
5
6 275 organizational and One Health frameworks for rabies eradication. The single most significant
7
8 276 way to deal with rabies concerns is to eliminate dog-mediated rabies. The requirement for
9
10
11 277 post-exposure human prophylaxis is considerably reduced when dog rabies is eradicated (37).
12
13 278 To benefit from synergy and maximization of shared resources, comprehensive rabies control
14
15
16 279 programs should involve the combination of human, financial, and material resources with
17
18 280 other interdisciplinary disease programs (24).

19
20 281 Mass canine vaccination campaigns will boost herd immunity and reduce the risk of
21
22 282 human rabies exposure, but this will need strong governmental commitment and extensive
23
24 283 social mobilization. The veterinary authority's active engagement in animal rabies control at
25
26 284 the national level is critical, and it is their social responsibility to prevent human rabies
27
28 285 through well-planned dog rabies control programs (26). In 1983, the Pan American Health
29
30 286 Organization had initiated an elimination programme for human rabies transmitted by dogs
31
32 287 which were mainly based on mass immunization of dogs, and this has led to a 90% reduction
33
34 288 of dog rabies in Chile and other Latin American countries (38).

35
36
37
38
39 289 Rabies control and elimination in low endemic rabies countries such as Malaysia and
40
41 290 Singapore have been made possible by strong enforcement of dog registration, vaccination,
42
43 291 and population management measures. Malaysia shares a border with Thailand, and the
44
45 292 notion of an immunological belt has been developed through dog licensing, required
46
47 293 vaccination of dogs, and systematic extermination of unvaccinated dogs in a buffer zone to
48
49 294 prevent rabies from entering their country (26). Perhaps other middle and high endemic
50
51 295 rabies countries could follow the rabies control strategy that had been implemented by their
52
53 296 Southeast Asia neighbour.
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1
2
3 297 Public information and education are important to increase awareness and enhance
4
5
6 298 community participation and support in rabies prevention programs. Dissemination of
7
8 299 important information such as the high fatality rate of rabies disease, its epidemiology, its
9
10 300 prevention and control, the disease control program, in general, is vital for the program
11
12
13 301 implementation and responsible pet ownership. By recognizing rabies' influence on people's
14
15 302 daily life and the fact that dogs can be a source of human infection, community and school-
16
17
18 303 based rabies prevention initiatives will be easier to establish (39).

19
20 304 The involvement of stakeholders is crucial and by bringing together key stakeholders
21
22
23 305 from the corporate and public sectors, we can address health security and the need of forming
24
25 306 public-private partnerships which are critical in rabies prevention programs (40). National
26
27
28 307 government agencies can maintain standardized ways for rabies management and
29
30 308 elimination and advocate on how to begin public-private cooperation to ensure long-term
31
32
33 309 intervention. All stakeholders can benefit from such technical and administrative effort as
34
35 310 they provide credibility and quality assurance for the prevention program's effectiveness (24).
36
37
38 311 Various examples of public-private partnerships that aid in implementing public programs,
39
40 312 research, and policy formation can be seen in Bali, Indonesia, India, Sri Lanka, Philippines,
41
42 313 Thailand, and Vietnam (3).

314 **Conclusion**

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

1
2
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4

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12
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14 327 **Author contributions**

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16 328 *Conceptualization: Jewel Bollah, Syed Sharizman Syed Abdul Rahim.*

17
18 329 *Data curation: Jewel Bollah, Noraziah Bakri, Wafaak Esa*

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22 331 *Investigation: Jewel Bollah, Noraziah Bakri, Wafaak Esa.*

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26 333 *Resources: Mohammad Saffree Jeffree, Azman Atil, Mohd Yusof Ibrahim, Mohd Rohaizat*
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29 335 *Writing – original draft: Jewel Bollah, Syed Sharizman Syed Abdul Rahim, Azizan Omar,*
30 336 *Aizuddin Hidrus.*

31
32 337 *Writing – review & editing: Nurul Athirah Naserrudin, Ahmad Hazim Mohammad, Azizan*
33 338 *Omar, Aizuddin Hidrus*

34
35
36 339 **Registration and protocol**

37
38 340 *The review was not registered, and the protocol was not prepared*

39
40 341 **Financial Disclosure**

41
42 342 *The study did not receive any special funding*

43
44 343 **Competing interest**

45
46 344 *There is no competing interest*

47
48 345 **Ethics consideration**

49 346 *No ethics approval was required for this systematic review*

50
51 347 **Data sharing statement**

52
53 348 *Not applicable*
54
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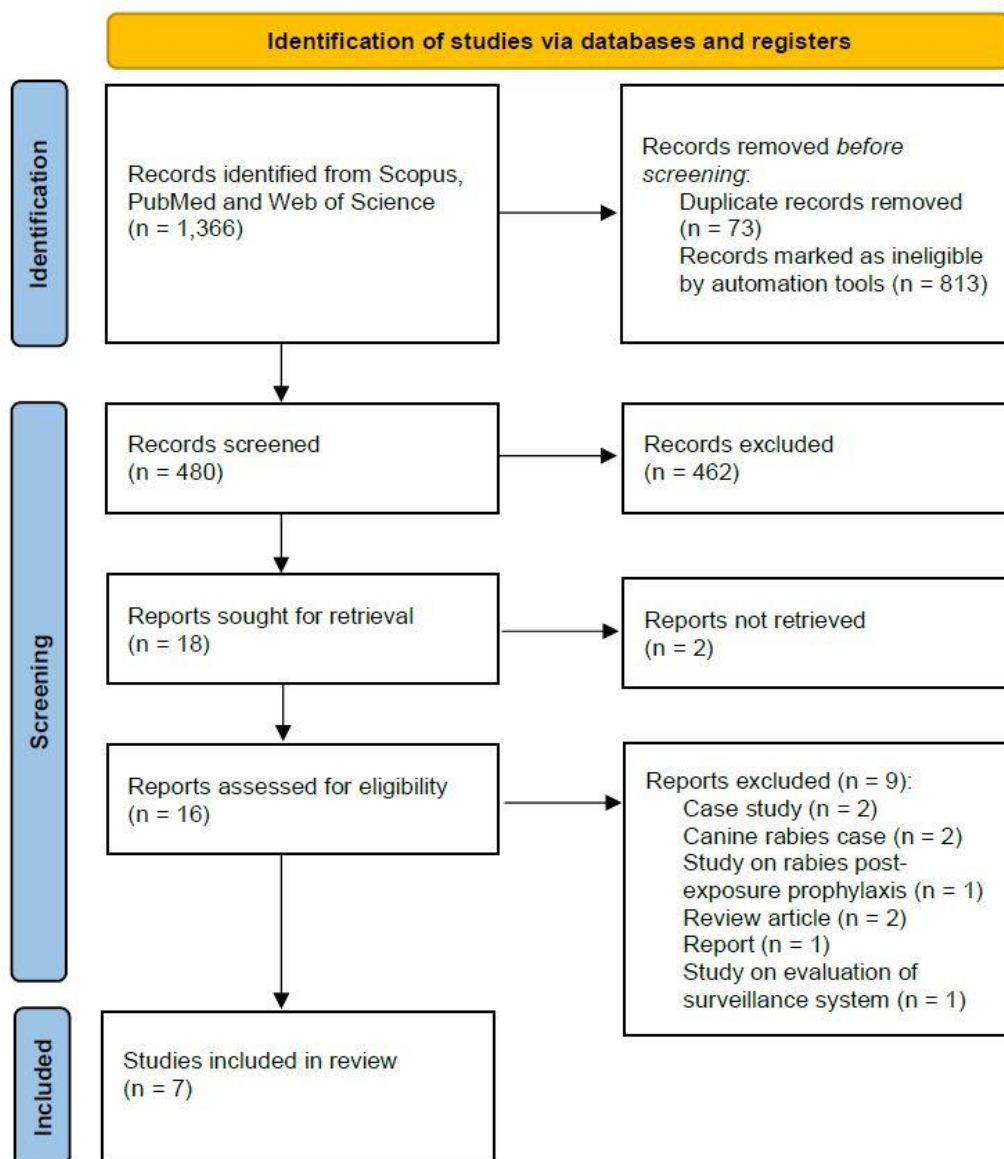
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Figures 1: Search PRISMA flowchart for Systematic Review of Rabies in SEA



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.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA reporting guidelines, and cite them as:

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

Abstract

1	Abstract	#2	Report an abstract addressing each item in the PRISMA	1-2
2				
3			2020 for Abstracts checklist	
4				
5				
6	Introduction			
7				
8				
9				
10	Background/rationale	#3	Describe the rationale for the review in the context of	3
11			existing knowledge	
12				
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14				
15	Objectives	#4	Provide an explicit statement of the objective(s) or	4
16			question(s) the review addresses	
17				
18				
19				
20	Methods			
21				
22				
23	Eligibility criteria	#5	Specify the inclusion and exclusion criteria for the review	6
24			and how studies were grouped for the syntheses	
25				
26				
27				
28				
29	Information sources	#6	Specify all databases, registers, websites, organisations,	5-6
30			reference lists, and other sources searched or consulted to	
31			identify studies. Specify the date when each source was	
32			last searched or consulted	
33				
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38				
39	Search strategy	#7	Present the full search strategies for all databases,	5-6
40			registers, and websites, including any filters and limits used	
41				
42				
43				
44	Selection process	#8	Specify the methods used to decide whether a study met	5-6
45			the inclusion criteria of the review, including how many	
46			reviewers screened each record and each report retrieved,	
47			whether they worked independently, and, if applicable,	
48			details of automation tools used in the process	
49				
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55				
56	Data collection	#9	Specify the methods used to collect data from reports,	5-6
57				
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60				

1	process		including how many reviewers collected data from each	
2			report, whether they worked independently, any processes	
3			for obtaining or confirming data from study investigators,	
4			and, if applicable, details of automation tools used in the	
5			process	
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11				
12	Data items	#10a	List and define all outcomes for which data were sought.	5-6
13			Specify whether all results that were compatible with each	
14			outcome domain in each study were sought (for example,	
15			for all measures, time points, analyses), and, if not, the	
16			methods used to decide which results to collect	
17				
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22				
23				
24	Data items	#10b	List and define all other variables for which data were	5-6
25			sought (such as participant and intervention characteristics,	
26			funding sources). Describe any assumptions made about	
27			any missing or unclear information	
28				
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34	Study risk of bias	#11	Specify the methods used to assess risk of bias in the	18
35	assessment		included studies, including details of the tool(s) used, how	
36			many reviewers assessed each study and whether they	
37			worked independently, and, if applicable, details of	
38			automation tools used in the process	
39				
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41				
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46	Effect measures	#12	Specify for each outcome the effect measure(s) (such as	8
47			risk ratio, mean difference) used in the synthesis or	
48			presentation of results	
49				
50				
51				
52				
53				
54	Synthesis methods	#13a	Describe the processes used to decide which studies were	6
55			eligible for each synthesis (such as tabulating the study	
56				
57				
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59				
60				

1		intervention characteristics and comparing against the	
2		planned groups for each synthesis (item #5))	
3			
4			
5			
6	Synthesis methods	#13b Describe any methods required to prepare the data for	6
7		presentation or synthesis, such as handling of missing	
8		summary statistics or data conversions	
9			
10			
11			
12			
13	Synthesis methods	#13c Describe any methods used to tabulate or visually display	6
14		results of individual studies and syntheses	
15			
16			
17			
18			
19	Synthesis methods	#13d Describe any methods used to synthesise results and	6
20		provide a rationale for the choice(s). If meta-analysis was	
21		performed, describe the model(s), method(s) to identify the	
22		presence and extent of statistical heterogeneity, and	
23		software package(s) used	
24			
25			
26			
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29			
30			
31	Synthesis methods	#13e Describe any methods used to explore possible causes of	6
32		heterogeneity among study results (such as subgroup	
33		analysis, meta-regression)	
34			
35			
36			
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38			
39	Synthesis methods	#13f Describe any sensitivity analyses conducted to assess	6
40		robustness of the synthesised results	
41			
42			
43			
44	Reporting bias	#14 Describe any methods used to assess risk of bias due to	18
45		missing results in a synthesis (arising from reporting	
46	assessment	biases)	
47			
48			
49			
50			
51			
52	Certainty assessment	#15 Describe any methods used to assess certainty (or	5
53		confidence) in the body of evidence for an outcome	
54			
55			
56			
57	Results		
58			
59			
60			

1	Study selection	#16a	Describe the results of the search and selection process,	7-10
2			from the number of records identified in the search to the	
3			number of studies included in the review, ideally using a	
4			flow diagram (http://www.prisma-	
5			statement.org/PRISMAStatement/FlowDiagram)	
6				
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13	Study selection	#16b	Cite studies that might appear to meet the inclusion criteria,	7-10
14			but which were excluded, and explain why they were	
15			excluded	
16				
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21	Study characteristics	#17	Cite each included study and present its characteristics	7-10
22				
23				
24	Risk of bias in studies	#18	Present assessments of risk of bias for each included study	18
25				
26				
27	Results of individual	#19	For all outcomes, present for each study (a) summary	16-22
28	studies		statistics for each group (where appropriate) and (b) an	
29			effect estimate and its precision (such as	
30			confidence/credible interval), ideally using structured tables	
31			or plots	
32				
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39	Results of syntheses	#20a	For each synthesis, briefly summarise the characteristics	16-22
40			and risk of bias among contributing studies	
41				
42				
43				
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45	Results of syntheses	#20b	Present results of all statistical syntheses conducted. If	16-22
46			meta-analysis was done, present for each the summary	
47			estimate and its precision (such as confidence/credible	
48			interval) and measures of statistical heterogeneity. If	
49			comparing groups, describe the direction of the effect	
50				
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57	Results of syntheses	#20c	Present results of all investigations of possible causes of	16-22
58				
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heterogeneity among study results

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4	Results of syntheses	#20d	Present results of all sensitivity analyses conducted to 16-22
5			
6			assess the robustness of the synthesised results
7			
8			
9	Risk of reporting	#21	Present assessments of risk of bias due to missing results 16-22
10			
11	biases in syntheses		(arising from reporting biases) for each synthesis assessed
12			
13			
14	Certainty of evidence	#22	Present assessments of certainty (or confidence) in the 16-22
15			
16			body of evidence for each outcome assessed
17			
18			
19	Discussion		
20			
21			
22			
23	Results in context	#23a	Provide a general interpretation of the results in the context 10-12
24			
25			of other evidence
26			
27			
28	Limitations of included	#23b	Discuss any limitations of the evidence included in the 2
29	studies		review
30			
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33	Limitations of the	#23c	Discuss any limitations of the review processes used 2
34			
35	review methods		
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41			future research
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44	Other information		
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47	Registration and	#24a	Provide registration information for the review, including 15
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49	protocol		register name and registration number, or state that the
50			
51			review was not registered
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55	Registration and	#24b	Indicate where the review protocol can be accessed, or 15
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57	protocol		state that a protocol was not prepared
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1	Registration and	#24c	Describe and explain any amendments to information	N/A
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3	protocol		provided at registration or in the protocol	
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6	Support	#25	Describe sources of financial or non-financial support for	15
7			the review, and the role of the funders or sponsors in the	
8			review	
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14	Competing interests	#26	Declare any competing interests of review authors	15
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16				
17	Availability of data,	#27	Report which of the following are publicly available and	16-22
18	code, and other		where they can be found: template data collection forms;	
19			data extracted from included studies; data used for all	
20	materials		analyses; analytic code; any other materials used in the	
21			review	
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BMJ Open

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

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1 Rabies in Southeast Asia: a systematic review of its incidence, risk factors, and 2 mortality

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20 Abstract

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

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3 24 **Design** Systematic review based on the Preferred Reporting Items for Systematic Reviews and
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6 25 Meta Analyses (PRISMA) 2020.

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8 26 **Data sources** Scopus, Web of Science, and PubMed were searched through to 21 February
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10 27 2023.

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13 28 **Eligibility criteria** We included original English language articles published between 2012 and
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15 29 2023.

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18 30 **Data extraction and synthesis** Nine independent reviewers extracted data and assessed the
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20 31 risk of bias. Quality appraisal of included articles was carried out using the Mixed Method
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22 32 Appraisal Tool (MMAT).

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25 33 **Results** A total of 8 articles were included in this analysis. In Vietnam, the incidence of rabies
26
27 34 ranged from 1.7 to 117.2 per 100,000 population. The cumulative incidence in Sarawak was
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29 35 estimated at 1.7 per 100,000 population. In Indonesia, 104 human rabies cases were reported
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31 36 from 2008 to 2010, while a total of 46 rabies cases were reported in Thailand from 2010 to
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33 37 2015. In Philippine, the incidence of rabies ranged between 0.1 to 0.3 per 100,000 population.
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35 38 Increased risk of rabies virus infection was associated with high population density, illiteracy,
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37 39 seasonal patterns as well as among dog butchers. The case-fatality rate was 100%.

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39
40 40 **Conclusion** This study includes research from Southeast Asia, which may not represent rabies
41
42 41 infection on other regions or continents. The role of publication bias should be acknowledged
43
44 42 as we did not include grey literature. The presence of rabies cases in Southeast Asia is due to
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46 43 a high number of unvaccinated stray and pet dogs, working hazards (dog butcher in Vietnam),
47
48 44 the unavailability of rabies vaccine in rural regions, and misinformation about the significance
49
50 45 of seeking treatment after dog bites.

51
52 46 **Keywords** Rabies, dog bite, zoonotic disease, epidemiology, Southeast Asia

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55 47 **Strengths and limitations**

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3 48 • This study only includes research from Southeast Asia, which may not represent rabies
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6 49 infection in other regions or continents.
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8 50 •
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11 51 • We did not include grey literature or national guidelines, which could have been useful
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13 52 in this study.
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16 53 • This systematic review followed the PRISMA 2020 statement for the reporting of
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18 54 systematic reviews to ensure reporting quality.
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55 Introduction

56 Rabies is a neglected zoonotic disease that is caused by an RNA virus from the family of
57 *Rhabdoviridae*, genus *Lyssavirus*[1]. Once clinical symptoms appear, rabies is almost 100%
58 fatal [2]. All mammals can be infected with the rabies virus, including humans. More than
59 99% of human rabies cases are transmitted via dogs [3]. With the necessary evidence and
60 tools in place for control and elimination of rabies, canine rabies can be eliminated, as
61 demonstrated in Western Europe, Canada, the United States of America (USA), Japan, a few
62 Latin American countries, and many parts in Asia. However, rabies is still widespread,
63 occurring in more than 80 countries, particularly in the developing countries in Africa and Asia
64 [3, 4]. Furthermore, half of the global population lives in canine rabies-endemic areas hence
65 is at risk of contracting rabies [3].

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

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

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3 79 2015 have relegated Malaysia down from its rabies-free status [7]. Even though Thailand and
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6 80 Vietnam have not been able to eliminate rabies, there was a substantial reduction of human
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8 81 rabies deaths through the implementation of dog mass vaccination, intensified post-exposure
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10 82 prophylaxis in humans, and awareness education [8].

13 83 Rabies is 100 percent preventable through vaccination in animals and humans [9]. The
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15 84 World Health Organization (WHO) recommended pre-exposure prophylaxis (PrEP) for those
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17 85 with continual, frequent, or increased risk of exposure to rabies virus (e.g., veterinarians,
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19 86 animal handlers). If exposed to a rabid animal, the WHO recommended PEP, which consists
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21 87 of immediate wound management, immediate vaccination, as well as administration of rabies
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23 88 immunoglobulin for high-risk exposure [10]. Nevertheless, dog vaccination is considered the
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25 89 most cost-effective strategy for preventing rabies in humans [2].

30 90 Despite the availability of evidence and guidelines for the control and management of
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32 91 rabies, there are some constraints faced by countries in Southeast Asia in controlling rabies,
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34 92 including inadequate resources, lack of political commitment, lack of consensus on strategy,
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36 93 weak intersectoral coordination, insensitive surveillance systems, limited accessibility to
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38 94 modern rabies vaccine and supply problem, as well as lack of public awareness and
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40 95 cooperation [8]. The high estimated burden for rabies more than justifies the need to
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42 96 prioritize rabies control, particularly in Asian countries.

47 97 Information on rabies epidemiology is a prerequisite for effective planning of rabies
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49 98 control programs. Previous systematic reviews focused on rabies epidemiology in India [11],
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51 99 Nepal [1], and Arab countries [12], while literature synthesizing data regarding rabies
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53 100 epidemiology in Southeast Asia are limited. Hence, this systematic review aims to provide an
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55 101 in-depth assessment of the incidence, risk factors, and mortality of rabies in Southeast Asia
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57 102 countries, based on the published literature.

103 **Materials and Methods**

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

106 ***Patient and Public involvement***

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

108 ***Research Question Formulation***

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

121 ***Data Source and Search Strategy***

122 PubMed, Web of Science and Scopus were searched from 1 January 2012 through to 21
123 February 2023. The keywords used for the searching of related articles are provided in Table
124 1.

125
126 Table 1: Keywords search used in the screening process.

Database	Search string
Scopus	<p>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"))</p> <p>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*"))</p>
Web of Science	<p>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"))</p> <p>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*"))</p>
PubMed	<p>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"))</p> <p>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*"))</p>

128 **Study Selection**

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

135 **Data Extraction and Synthesis**

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

149 **Quality Appraisal**

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

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3 152 included in systematic mixed study reviews. The methodology quality of five categories of
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6 153 studies (qualitative study, randomized control trials, non-randomized studies, quantitative
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8 154 descriptive study, and mixed methods study) can be appraised using this tool. For each
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10 155 category, five criteria are used to assess the quality of the study. It is advised not to calculate
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13 156 an overall score from the rating of each criterion using the latest version of MMAT (2018).
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15 157 However, due to problems faced by researchers in reporting the MMAT results, a suggestion
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18 158 was provided for reporting an overall score (5*****/100% quality criteria met; 4*****/80%
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20 159 quality criteria met; 3****/60% quality criteria met; 2***/40% quality criteria met; 1*/20%
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23 160 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

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6 165 **Results**
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8 166 There were 1,437 records identified from the three databases to evaluate the incidence, risk
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10 167 factors and mortality rate of rabies in Southeast Asia. Using automation tools, 829 records
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12 168 were excluded based on year, publication type, and language. A total of 98 duplicate records
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14 169 were found and removed, leaving 510 records for title screening. We screened the titles and
15
16 170 abstracts independently based on the review questions. A total of 491 articles were removed
17
18 171 during the screening. For the remaining 19 articles, the full text was retrieved for assessment
19
20 172 of eligibility. Disagreements were resolved through discussion to reach a consensus. 11
21
22 173 articles were removed as they were not according to the objective (4), not primary/original
23
24 174 research articles (5) and the full article could not be retrieved (2), leaving a total of 8 articles
25
26 175 to proceed with a quality appraisal. The PRISMA flowchart is presented in Figure 1.
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35 177 ***Background of the Eligible Studies***
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37 178 A total of 8 studies were included in this systematic review in which 4 studies were conducted
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39 179 in Vietnam, and 1 each from Indonesia, Malaysia, Thailand, and Philippine (Table 3). The
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41 180 theme discussed by all studies was incidence rates, number of cases, and risk factors of rabies
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43 181 in Southeast Asia. Among the included studies, 3 studies particularly discussed rabies's
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45 182 mortality.
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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. <i>American Journal of Tropical Medicine and Hygiene</i> 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. <i>Frontiers in Public Health</i> 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. <i>Journal of the</i>	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

		<i>Royal College of Physicians of Edinburgh</i> 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. <i>PLoS Neglected Tropical Diseases</i> 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. <i>PLoS ONE</i> 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. <i>BMC Infectious Diseases</i> 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. <i>PloS ONE</i> 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. <i>PLoS Negl Trop Dis</i> 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.

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6 186 ***Incidence and Risk Factors of Rabies in Southeast Asia Countries***

7
8 187 Overall, the incidence of rabies ranged between 0.1 per 100,000 population in Philippine
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10 188 [17]to 117.2 per 100,000 population in Vietnam [18]. The average monthly number of rabies
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12 189 cases in Vietnam is 429 during the period from 2011 to 2015, where the incidences of rabies
13
14 190 ranged from 1.7 to 117.2 per 100,000 with higher incidences observed in Red River, South
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16 191 Central Coast (SCC), and the Mekong Delta regions [18]. Specific to Southern Vietnam, a total
17
18 192 of 94 human rabies cases between 2009 and 2018 were reported, with an average of nine
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20 193 cases recorded annually, representing an incidence of 2.7 cases per 10 million population [19].
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22 194 The highest number was reported in 2018 (5.5 cases per 10 million population). Most cases
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24 195 were among males and those aged 50 years and above.

25
26 196 Dog butchers in Vietnam were at high risk of rabies virus infection [20]. The study
27
28 197 found that 28.3% of butchers were at risk of rabies exposure due to slaughtering of sick dogs,
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30 198 getting bitten, scratched, or knife cut. Among 406 participants, 8.6% had rabies neutralizing
31
32 199 antibody (NTA) sufficient for protection and only 8.1% of them were vaccinated. In terms of
33
34 200 location, rabies cases were limited to specific areas. Hotspots were identified in southern
35
36 201 Vietnam, particularly in the Mekong River Delta (MRD) and South-Central Coast (SCC) [21].
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38 202 Seasonal patterns were found in which a strong peak in February/ July and a minor peak in
39
40 203 October/ December in the MRD Region. However, a strong peak was detected in the middle
41
42 204 of each year in the SCC. Temperature, humidity, and cumulative rainfall are positively
43
44 205 associated with an increase in incidences of rabies in Vietnam. In terms of socio-economic
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46 206 factors, increases in population density, as well as the percentages of illiteracy, were sensitive
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48 207 factors for elevated risk of rabies [18].
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3 208 In Indonesia, 104 human rabies cases were reported in Bali from November 2008 to
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6 209 November 2010. Most of the cases were among males. Almost all (92%) cases had a history
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8 210 of a dog bite. Only 5.8% had their wounds treated and received an anti-rabies vaccine (ARV)
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10
11 211 after the bite incident [22]. Even worse, rabies cases in Sibu, Sarawak did not seek medical
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13 212 attention upon dog bite as well [23]. The cumulative incidence in Sibu was estimated at 1.7
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15 213 per 100,000 population. The incubation period varied from 17 days to 2 years.

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17
18 214 A total of 46 confirmed and probable cases of human rabies were reported in Thailand
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20 215 from 2010 to 2015, in which 11 were reported from Eastern Thailand [24]. Even though rabies
21
22 216 can be prevented by vaccination, more than 90% of rabies death cases in Thailand did not get
23
24 217 or improperly stopped receiving PEP. In terms of suspected rabies exposures, 6,204 exposures
25
26 218 were reported from eight provinces in Eastern Thailand, resulting in a crude exposure rate of
27
28 219 106 reported rabies exposures per 100,000 people. Dogs were the main source of exposure
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30 220 (77.8%), while children under the age of 15 and the elderly over the age of 60 had the highest
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32 221 overall reported exposure rates (189.7 and 189.2/100,000, respectively).

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34
35 222 In Philippines, there were 575 rabies cases from 2006 to 2015. 70% from the rabies
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37 223 cases were among males. Nearly 34% from the patients aged 41 to 60 years. The incidence
38
39 224 rate of human rabies per 100,000 population in 2007, 2010, and 2015 were 0.1305, 0.1356,
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41 225 and 0.1708 in the National Capital Region; 0.2890, 0.2965, and 0.1961 in Region III; and 0.1449,
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43 226 0.1272, and 0.1041 in Region IV-A, respectively [17].
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53 227 54 228 ***Mortality of Rabies in Southeast Asia Countries***

55 229 The case-fatality rate was 100% as mentioned in 2 studies [22, 23]. Among 6 deaths reported
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57 230 in Sibu, 5 succumbed to the illness within 2 weeks of symptoms onset, with total of 5 out of
58
59 231 6 cases reported dog bite history [23]. In Indonesia, Susilawati et al. reported that there were

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3 232 104 fatalities due to rabies, of which 96 cases had history of dog bite [22]. In Philippine, 463
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6 233 people died from rabies infection [17].
7

8 234 **Discussion**

9 10 235 ***Incidence and Risk factor of Rabies in Southeast Asia Countries.***

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13 236 Rabies in Asia and Africa contributes to over 99% of human rabies deaths that occur in the
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15 237 world today. The vast majority of 60% of these deaths are in Asia [25]. Every year, an
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18 238 estimated 59,000 people die from rabies worldwide, with the majority (95%) of these deaths
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20 239 occurring in Africa and Asia due to a lack of post-exposure prophylaxis (PEP) services for
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23 240 animal-bite patients and rabies surveillance personnel and facilities [26]. This support the
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25 241 result of our study which shows that there is a high number of rabies cases reported in
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28 242 Vietnam, Indonesia, and Thailand, which are medium endemic rabies country [27].
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30 243 Rabies is concentrated in Asia and Southeast Asia region because rabies is frequently
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32 244 neglected when health and agriculture budgets are set although the costs and economic
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35 245 benefits of having rabies prevention programs have been successfully implemented in high-
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37 246 income country [28]. The high number of rabies cases in Southeast Asia is also contributed by
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39
40 247 the high number of unowned, free-roaming dogs that can't be controlled without a lot of
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42 248 effort and thus aren't vaccinated [29]. Vaccination programs in dogs can provide herd
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45 249 immunity and break the rabies transmission cycle in this reservoir species and had been
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47 250 successfully applied in several countries around the world [30].
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50 251 Another cause of high incidence of rabies in Southeast Asia is due to the working
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52 252 hazard of dog butchers, especially in a country that legalizes dog consumption such as in
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54 253 Vietnam [31]. It was also reported by the Centers for Disease Control and Prevention (CDC)
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56
57 254 that there is illegal trafficking of dogs for human consumption occurring in Vietnam
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59 255 (https://www.cdc.gov/globalhealth/stories/rabies_southeast_asia.htm) which could possibly
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3 256 contributes to the high incidence of rabies in Vietnam. Professional dog butchers in northern
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6 257 Vietnam are at a high risk of rabies virus infection due to exposure during the slaughtering
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8 258 process, which was from the slaughtering of sick or dead dogs, getting bitten, scratched, or
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10
11 259 knife cut. Study reported that 91.9% of professional dog butchers in Vietnam were not
12
13 260 vaccinated against rabies, which may be because of the fear of side effects of rabies vaccine,
14
15 261 inability to afford vaccination, and incorrect knowledge of rabies prevention [20].

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18 262 The rabies incidence of 0.1 per 100,000 population in Philippine is similar to that
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20 263 reported in China in 2016 [32]. The lower rabies incidence in Philippine compared to other
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22 264 Southeast Asia countries may be due to the implementation of Anti-Rabies Act of 2007 to
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24 265 prevent and control human rabies [33]. Additionally, the consumption of dog meat was
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26 266 banned in 1998 with the implementation of Animal Welfare Act which may contribute to the
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28 267 lower incidence of rabies in Philippine [34].

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32 268 In comparison to females, males are more likely to contract rabies infection [19].
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34 269 Similar finding was found in Iraq, where more than 89% of the cases were among males
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36 270 [35]. This can be attributed to the fact that most females are housewives, while males are
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38 271 engaged in outdoor activities [36]. Another study in Ethiopia also stated that males are more
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40 272 likely to do nightly and outdoor activities while females are more likely to remain indoors due
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42 273 to cultural and religious reasons [37], which could explain the increase incidence of rabies in
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44 274 males.

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49 275 According to study by Yurachai et al, rabies infection affects children more compared
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51 276 to other age group [24]. This corresponds to the WHO report, which states that 40% of rabies
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53 277 victims are children ages 4 to 15 (<https://www.who.int/news-room/fact-sheets/detail/rabies>).
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55 278 Similar finding was found in other studies in Yemen and Iran where nearly 40% of individual
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57 279 exposed to rabies infection fall in this age group [35, 38]. Children in this age group are
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3 280 probably more likely to play with, annoy, or approach the biting animals, which contributes
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6 281 to the higher rate of bites in this age group [35]. In contrast, according to a study from Pham
7
8 282 et al, older people are more likely to become infected with rabies [19].
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10 283 In several studies included in this systematic review, the diagnosis of most rabies cases
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13 284 was based only on detailed history and clinical diagnosis [17, 19, 21]. To diagnose rabies in
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15 285 humans, multiple tests are required such as saliva, serum, spinal fluid, and skin biopsies of
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18 286 hair follicles from the nape of the neck are analysed. Viral isolation or reverse transcription
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20 287 followed by polymerase chain reaction can be used to analyse saliva (RT-PCR). Serum and
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22
23 288 spinal fluid are tested for rabies virus antibodies. Skin biopsies can be used to detect rabies
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25 289 antigen in the cutaneous nerves at the base of the hair follicles
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27
28 290 (<https://www.cdc.gov/rabies/diagnosis/animals-humans.html>). In the future, there is a need
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30 291 for developing country to standardize the diagnosis of rabies based on the laboratory test as
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32
33 292 mentioned above for accuracy of the diagnosis and to enable comparison with other studies
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35 293 done in developed country.

36
37 294 Of the included studies, only one study was conducted among butchers who were at
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40 295 higher risk of contracting rabies [20]. Apart from butchers, individuals working as
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43 296 veterinarians, veterinary technicians, animal control workers, and wildlife rehabilitators were
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45 297 also considered to have higher risk of contracting rabies than the general population [39]. This
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47 298 calls for more studies that incorporate individuals involved in occupations identified as high
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50 299 risk for rabies exposure and infection.

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52 300 In this study, climate factor was postulated to be one of the risk factors for rabies
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54
55 301 infection. This was echoed by a study in China, where the incidence of rabies increases
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57 302 alongside the ambient temperature. A warmer climate causes animals to be more active in
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59 303 their environment and to travel greater distances when tracking, which contributes to the
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3 304 spread of rabies. In addition, as temperatures rise, people tend to wear lighter clothing and
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6 305 expose more skin, which increases the likelihood of being bitten by a dog [40]. In South Korea,
7
8 306 it had been demonstrated that the seasonality of wildlife rabies were attributed to behaviours
9
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11 307 such as searching for food during the winter or early spring. Dogs may have had more
12
13 308 opportunities to come into contact with the rabid animals during this time due to greater
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15 309 animal movement, which could have contributed to seasonal patterns in the occurrence of
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17
18 310 rabies in humans [41].

311 ***Mortality of Rabies in Southeast Asia Countries***

312 In this study, rabies had a high fatality rate, with 100 percent of infected cases dying. This is
313 supported by a review done in Africa by Nyasulu et al, who reported that Algeria, Namibia,
314 Eswatini (former Swaziland), Tunisia, Uganda, Zambia, and Zimbabwe had high morbidity and
315 mortality with 563 cases (33.9 percent deaths), 269 cases (94 percent deaths), 62 cases (88.7
316 percent deaths), 91 cases (90 percent deaths), 466 cases (40.9 percent), 207 cases (32.8
317 percent deaths), and 114 cases [42]. Because of the high population of stray dogs in this area,
318 the chances of being bitten by a dog are high. Not only are the chances of being bitten high
319 in these areas, but access to treatment in a timely and adequate manner is also very limited.
320 Rabies vaccines may not be routinely available in rural areas where most exposure occur, and
321 rabies immunoglobulins, which are required for category III bites, are always in short supply
322 [43].

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

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3 328 given to the public as knowledge regarding rabies is essential to reduce morbidity and
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6 329 mortality [5].
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8 330 In high-income countries such as the United States, the incidence and mortality caused
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10 331 by rabies is low. In the last decade, there have been only 25 cases of human rabies reported
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12 332 in the United States (2009-2018), with 23 deaths reported [6]. The low cases of rabies
13
14 333 infection are due to successful animal control and vaccination programs, successful outreach
15
16 334 programs, public health capacity and laboratory diagnostics, and the availability of modern
17
18 335 rabies biologics [46]. Even though rabies is avoidable, the exorbitant expense of vaccinations,
19
20 336 combined with a lack of education and knowledge about the disease, limits PEP use.
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22 337 According to recent studies, many rabies victims contracted the disease owing to neglect,
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24 338 ignorance, or a lack of primary health care facilities [45].
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30 339 ***Strengths and Limitations***

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32 340 In this study, we only include research from Southeast Asia, which may not represent rabies
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34 341 infection in other regions or continents. We did not include grey literature or national
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36 342 guidelines, which could have been useful in this study. Our strengths, however, are that we
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38 343 can tailor the control programme specifically for Southeast Asia countries, and we are aware
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40 344 of the true burden of rabies infection in our region.
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45 345 ***Recommendation***

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47 346 A successful rabies prevention and control program requires integrating and strengthening
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49 347 intersectoral and transdisciplinary collaboration and cooperation among various society
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51 348 components [47]. The ASEAN Rabies Elimination Strategy places great value on the
52
53 349 organizational and One Health frameworks for rabies eradication. The single most significant
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55 350 way to deal with rabies concerns is to eliminate dog-mediated rabies. The requirement for
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57 351 post-exposure human prophylaxis is considerably reduced when dog rabies is eradicated [48].
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3 352 To benefit from synergy and maximization of shared resources, comprehensive rabies control
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6 353 programs should involve the combination of human, financial, and material resources with
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8 354 other interdisciplinary disease programs [25].
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10 355 Mass canine vaccination campaigns will boost herd immunity and reduce the risk of
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13 356 human rabies exposure, but this will need strong governmental commitment and extensive
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15 357 social mobilization. The veterinary authority's active engagement in animal rabies control at
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17
18 358 the national level is critical, and it is their social responsibility to prevent human rabies
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20 359 through well-planned dog rabies control programs [27]. In 1983, the Pan American Health
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23 360 Organization had initiated an elimination programme for human rabies transmitted by dogs
24
25 361 which were mainly based on mass immunization of dogs, and this has led to a 90% reduction
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27 362 of dog rabies in Chile and other Latin American countries [49].
28
29

30 363 Rabies control and elimination in low endemic rabies countries such as Malaysia and
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32
33 364 Singapore have been made possible by strong enforcement of dog registration, vaccination,
34
35 365 and population management measures. Malaysia shares a border with Thailand, and the
36
37 366 notion of an immunological belt has been developed through dog licensing, required
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40 367 vaccination of dogs, and systematic extermination of unvaccinated dogs in a buffer zone to
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42 368 prevent rabies from entering their country [27]. Perhaps other middle and high endemic
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45 369 rabies countries could follow the rabies control strategy that had been implemented by their
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47 370 Southeast Asia neighbour.
48

49 371 Public information and education are important to increase awareness and enhance
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52 372 community participation and support in rabies prevention programs. Dissemination of
53
54 373 important information such as the high fatality rate of rabies disease, its epidemiology, its
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56
57 374 prevention and control, the disease control program, in general, is vital for the program
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59 375 implementation and responsible pet ownership. By recognizing rabies' influence on people's
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3 376 daily life and the fact that dogs can be a source of human infection, community and school-
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6 377 based rabies prevention initiatives will be easier to establish [50].
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8 378 The involvement of stakeholders is crucial and by bringing together key stakeholders
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10 379 from the corporate and public sectors, we can address health security and the need of forming
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12
13 380 public-private partnerships which are critical in rabies prevention programs [51]. National
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15 381 government agencies can maintain standardized ways for rabies management and
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18 382 elimination and advocate on how to begin public-private cooperation to ensure long-term
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20 383 intervention. All stakeholders can benefit from such technical and administrative effort as
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23 384 they provide credibility and quality assurance for the prevention program's effectiveness [25].
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25 385 Various examples of public-private partnerships that aid in implementing public programs,
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28 386 research, and policy formation can be seen in Bali, Indonesia, India, Sri Lanka, Philippines,
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30 387 Thailand, and Vietnam [3].
31

32 388 **Conclusion**

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35 389 Rabies had often been neglected and not given priority in terms of funding for prevention
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38 390 programs that resulted in the continued presence of rabies cases in Southeast Asia despite
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40 391 multiple programs being endorsed by WHO. The high number of unvaccinated stray and pet
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42 392 dogs, working hazard (dog butcher in Vietnam), unavailability of rabies vaccine in rural areas,
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44
45 393 as well as ignorance regarding the importance of seeking treatment after dog bites are among
46
47 394 the factors that contribute to rabies cases in Southeast Asia.
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49 395

50 396 **Author Contributions**

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54 397 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
55
56
57 398 involved in conceptualisation, methodology, extensive search of articles, critical review of
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2
3 399 articles, results synthesis and original draft write up. M.R.H. supervised the manuscript
4
5 400 preparation. All authors have read and agreed to the final draft of the manuscript.
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8
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10
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15 403 **Competing interests**

16
17 404 The authors declare no conflict of interest.
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21 405 **Patient consent for publication**

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23 406 Not applicable.
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27 407 **Ethics approval**

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29 408 Not applicable.
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33 409 **Data availability statement**

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35 410 Data are available upon reasonable request.
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38
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40
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42
43 413 University of Malaysia, for the technical support.
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47 414 **Figure:** PRISMA 2020 flow diagram for new systematic reviews which included searches of
48
49 415 databases and registers only
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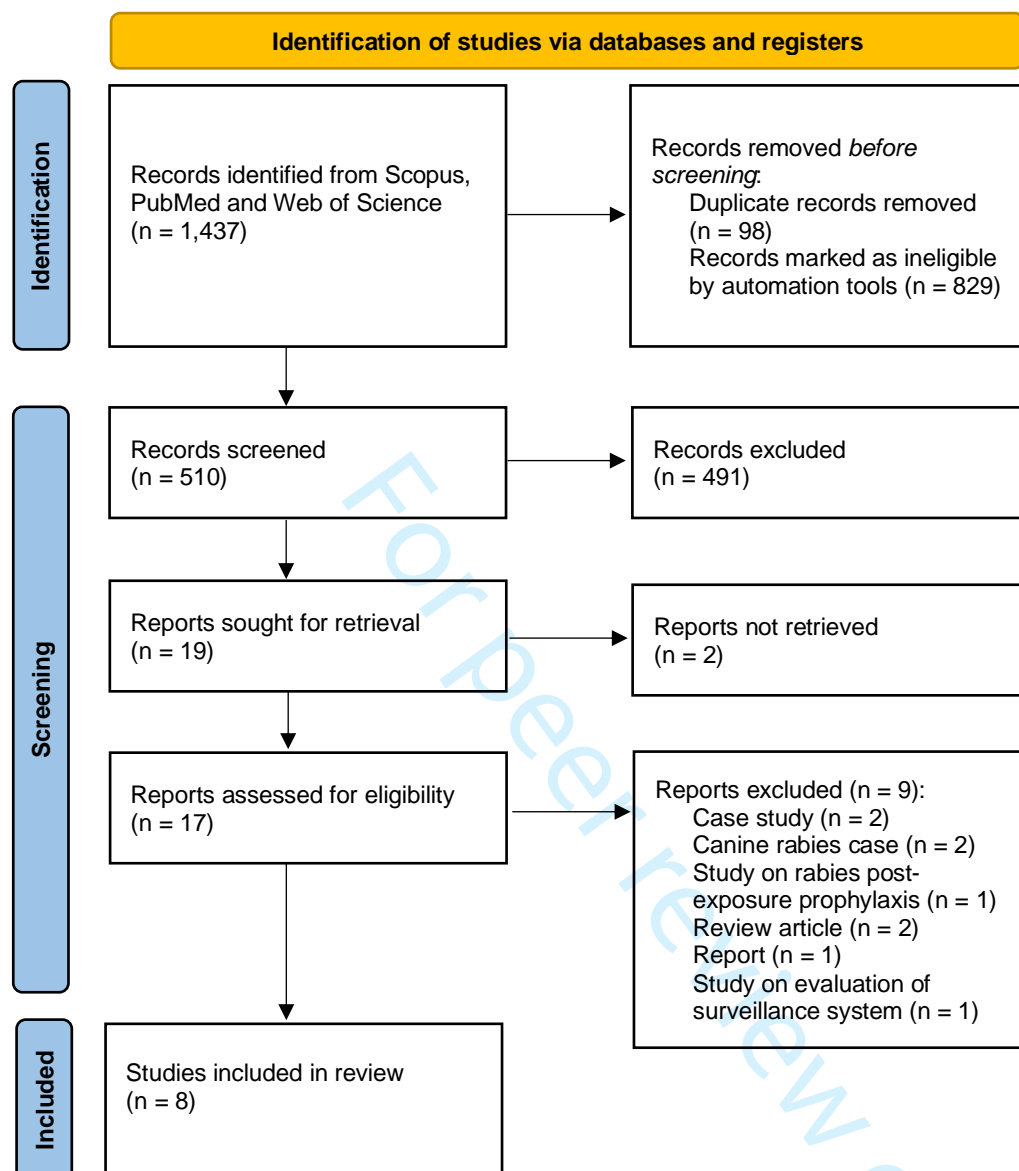
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PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



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.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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

Abstract

1	Abstract	#2	Report an abstract addressing each item in the PRISMA	1-2
2				
3			2020 for Abstracts checklist	
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6	Introduction			
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10	Background/rationale	#3	Describe the rationale for the review in the context of	3
11			existing knowledge	
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15	Objectives	#4	Provide an explicit statement of the objective(s) or	4
16			question(s) the review addresses	
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20	Methods			
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23	Eligibility criteria	#5	Specify the inclusion and exclusion criteria for the review	6
24			and how studies were grouped for the syntheses	
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29	Information sources	#6	Specify all databases, registers, websites, organisations,	5-6
30			reference lists, and other sources searched or consulted to	
31			identify studies. Specify the date when each source was	
32			last searched or consulted	
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39	Search strategy	#7	Present the full search strategies for all databases,	5-6
40			registers, and websites, including any filters and limits used	
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44	Selection process	#8	Specify the methods used to decide whether a study met	5-6
45			the inclusion criteria of the review, including how many	
46			reviewers screened each record and each report retrieved,	
47			whether they worked independently, and, if applicable,	
48			details of automation tools used in the process	
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56	Data collection	#9	Specify the methods used to collect data from reports,	5-6
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1	process		including how many reviewers collected data from each	
2			report, whether they worked independently, any processes	
3			for obtaining or confirming data from study investigators,	
4			and, if applicable, details of automation tools used in the	
5			process	
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12	Data items	#10a	List and define all outcomes for which data were sought.	5-6
13			Specify whether all results that were compatible with each	
14			outcome domain in each study were sought (for example,	
15			for all measures, time points, analyses), and, if not, the	
16			methods used to decide which results to collect	
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24	Data items	#10b	List and define all other variables for which data were	5-6
25			sought (such as participant and intervention characteristics,	
26			funding sources). Describe any assumptions made about	
27			any missing or unclear information	
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34	Study risk of bias	#11	Specify the methods used to assess risk of bias in the	18
35	assessment		included studies, including details of the tool(s) used, how	
36			many reviewers assessed each study and whether they	
37			worked independently, and, if applicable, details of	
38			automation tools used in the process	
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46	Effect measures	#12	Specify for each outcome the effect measure(s) (such as	8
47			risk ratio, mean difference) used in the synthesis or	
48			presentation of results	
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54	Synthesis methods	#13a	Describe the processes used to decide which studies were	6
55			eligible for each synthesis (such as tabulating the study	
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1		intervention characteristics and comparing against the	
2		planned groups for each synthesis (item #5))	
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6	Synthesis methods	#13b Describe any methods required to prepare the data for	6
7		presentation or synthesis, such as handling of missing	
8		summary statistics or data conversions	
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13	Synthesis methods	#13c Describe any methods used to tabulate or visually display	6
14		results of individual studies and syntheses	
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19	Synthesis methods	#13d Describe any methods used to synthesise results and	6
20		provide a rationale for the choice(s). If meta-analysis was	
21		performed, describe the model(s), method(s) to identify the	
22		presence and extent of statistical heterogeneity, and	
23		software package(s) used	
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31	Synthesis methods	#13e Describe any methods used to explore possible causes of	6
32		heterogeneity among study results (such as subgroup	
33		analysis, meta-regression)	
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39	Synthesis methods	#13f Describe any sensitivity analyses conducted to assess	6
40		robustness of the synthesised results	
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44	Reporting bias	#14 Describe any methods used to assess risk of bias due to	18
45	assessment	missing results in a synthesis (arising from reporting	
46		biases)	
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51	Certainty assessment	#15 Describe any methods used to assess certainty (or	N/A5
52		confidence) in the body of evidence for an outcome	
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57	Results		
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1	Study selection	#16a	Describe the results of the search and selection process,	7-10
2			from the number of records identified in the search to the	
3			number of studies included in the review, ideally using a	
4			flow diagram (http://www.prisma-	
5			statement.org/PRISMAStatement/FlowDiagram)	
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13	Study selection	#16b	Cite studies that might appear to meet the inclusion criteria,	7-10
14			but which were excluded, and explain why they were	
15			excluded	
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21	Study characteristics	#17	Cite each included study and present its characteristics	7-10
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24	Risk of bias in studies	#18	Present assessments of risk of bias for each included study	18
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27	Results of individual	#19	For all outcomes, present for each study (a) summary	16-22
28	studies		statistics for each group (where appropriate) and (b) an	
29			effect estimate and its precision (such as	
30			confidence/credible interval), ideally using structured tables	
31			or plots	
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39	Results of syntheses	#20a	For each synthesis, briefly summarise the characteristics	16-22
40			and risk of bias among contributing studies	
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45	Results of syntheses	#20b	Present results of all statistical syntheses conducted. If	16-22
46			meta-analysis was done, present for each the summary	
47			estimate and its precision (such as confidence/credible	
48			interval) and measures of statistical heterogeneity. If	
49			comparing groups, describe the direction of the effect	
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57	Results of syntheses	#20c	Present results of all investigations of possible causes of	16-22
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heterogeneity among study results

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4 Results of syntheses [#20d](#) Present results of all sensitivity analyses conducted to 16-22
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6 assess the robustness of the synthesised results
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9 Risk of reporting [#21](#) Present assessments of risk of bias due to missing results 16-22
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11 biases in syntheses (arising from reporting biases) for each synthesis assessed
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14 Certainty of evidence [#22](#) Present assessments of certainty (or confidence) in the 16-22
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16 body of evidence for each outcome assessed
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19 Discussion

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23 Results in context [#23a](#) Provide a general interpretation of the results in the context 10-12
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25 of other evidence
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28 Limitations of included [#23b](#) Discuss any limitations of the evidence included in the 2
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33 Limitations of the [#23c](#) Discuss any limitations of the review processes used 2
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39 Implications [#23d](#) Discuss implications of the results for practice, policy, and 13-15
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41 future research
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44 Other information

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47 Registration and [#24a](#) Provide registration information for the review, including 15
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49 protocol register name and registration number, or state that the
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55 Registration and [#24b](#) Indicate where the review protocol can be accessed, or 15
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57 protocol state that a protocol was not prepared
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1	Registration and	#24c	Describe and explain any amendments to information	N/A
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3	protocol		provided at registration or in the protocol	
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6	Support	#25	Describe sources of financial or non-financial support for	15
7			the review, and the role of the funders or sponsors in the	
8			review	
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14	Competing interests	#26	Declare any competing interests of review authors	15
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17	Availability of data,	#27	Report which of the following are publicly available and	16-22
18	code, and other		where they can be found: template data collection forms;	
19			data extracted from included studies; data used for all	
20	materials		analyses; analytic code; any other materials used in the	
21			review	
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31 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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BMJ Open

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

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1 Rabies in Southeast Asia: a systematic review of its incidence, risk factors and 2 mortality

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20 ABSTRACT

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

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3 24 **Design** Systematic review based on the Preferred Reporting Items for Systematic Reviews and
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6 25 Meta-Analyses (PRISMA) 2020.

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8 26 **Data sources** Scopus, Web of Science and PubMed were searched from 1 January 2012 to 21
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11 27 February 2023.

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13 28 **Eligibility criteria** Original English language articles published between 2012 and 2023 were
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16 29 included.

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18 30 **Data extraction and synthesis** Nine independent reviewers extracted data and assessed the
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21 31 risk of bias. The quality appraisal of included articles was carried out using the Mixed Methods
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23 32 Appraisal Tool (MMAT).

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25 33 **Results** A total of eight articles were included in this analysis. In Vietnam, the incidence of
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28 34 rabies ranged from 1.7 to 117.2 per 100,000 population. The cumulative incidence in Sarawak
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31 35 was estimated at 1.7 per 100,000 population. In Indonesia, 104 human rabies cases were
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33 36 reported from 2008 to 2010, while in Thailand, a total of 46 rabies cases were reported in
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35 37 Thailand from 2010 to 2015. In the Philippines, the incidence of rabies ranged from 0.1 to 0.3
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38 38 per 100,000 population. An increased risk of rabies virus infection was associated with a high
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41 39 population density, illiteracy, seasonal patterns and dog butchers. The case-fatality rate was
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43 40 100%.

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45 41 **Conclusion** This study included research from Southeast Asia, which may not represent rabies
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48 42 infection in other regions or continents. Additionally, the role of publication bias should be
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51 43 acknowledged as grey literature was not included. The occurrence of rabies in Southeast Asia
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53 44 is due to the high number of unvaccinated stray and pet dogs, working hazards (dog butchers
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55 45 in Vietnam), the unavailability of the rabies vaccine in rural regions, and misinformation about
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57 46 the significance of seeking treatment after dog bites.

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59 47 **PROSPERO registration number** CRD42022311654.
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3 48 **Keywords** Rabies, dog bite, zoonotic disease, epidemiology, Southeast Asia
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6 49 **Strengths and limitations**
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- 8 50 • This review only includes research from Southeast Asia, which may not represent
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10 51 rabies infection in other regions or continents.
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13 52 • We did not include grey literature or national guidelines, which could have been useful
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15 53 in this study.
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18 54 • The inclusion of studies that defined or diagnosed rabies based on clinical signs or
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20 55 laboratory tests increased the chances of identifying rabies cases in Southeast Asian
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57 INTRODUCTION

58 Rabies is a neglected zoonotic disease caused by an RNA virus from the family *Rhabdoviridae*,
59 genus *Lyssavirus* (1). Once clinical symptoms appear, rabies is almost 100% fatal (2). All
60 mammals can be infected with the rabies virus, including humans. More than 99% of human
61 rabies cases are transmitted via dogs (3). With the necessary evidence and tools in place for
62 the control and elimination of rabies, canine rabies can be eliminated, as demonstrated in
63 Western Europe, Canada, the United States of America (USA), Japan, a few Latin American
64 countries and many parts of Asia. However, rabies is still widespread, occurring in more than
65 80 countries, particularly developing countries in Africa and Asia (3,4). Furthermore, half of
66 the global population lives in canine rabies-endemic areas and hence is at risk of contracting
67 rabies (3).

68 Globally, canine rabies is estimated to cause approximately 59,000 human deaths
69 annually. In Asia, rabies is clearly a major problem: the number of human deaths due to rabies
70 in Asia is higher than in any other region in the world. Most human rabies deaths occur in Asia
71 (59.6%), followed by Africa (36.4%), while only less than 0.05% of human rabies deaths occur
72 in the Americas. Additionally, India alone accounts for 35% of global human rabies deaths,
73 higher than any other country (4). In Asia, canine rabies is estimated to cause a loss of 2.2
74 million Disability-Adjusted Life Years (DALYs) per year, while the annual cost of post-exposure
75 prophylaxis (PEP) is highest in Asia, estimated at up to US\$ 1.5 billion (5).

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

1
2
3 81 been able to eliminate rabies, there has been a substantial reduction in human rabies deaths
4
5
6 82 through the implementation of dog mass vaccination, intensified PEP in humans and
7
8 83 awareness education (8).

9
10 84 Rabies is 100% preventable through vaccination in animals and humans (9). The World
11
12
13 85 Health Organization (WHO) has recommended pre-exposure prophylaxis (PrEP) for those with
14
15 86 continual, frequent or increased risk of exposure to rabies virus (e.g. veterinarians and animal
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17
18 87 handlers). If exposed to a rabid animal, the WHO recommends PEP, which consists of
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20 88 immediate wound management, immediate vaccination and the administration of rabies
21
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23 89 immunoglobulin for high-risk exposures (10). Nevertheless, dog vaccination is considered the
24
25 90 most cost-effective strategy for preventing rabies in humans (2).

26
27
28 91 Despite the availability of evidence and guidelines for the control and management of
29
30 92 rabies, countries in Southeast Asia face some constraints in controlling rabies, including
31
32 93 inadequate resources, lack of political commitment, lack of consensus on strategy, weak
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34
35 94 intersectoral coordination, insensitive surveillance systems, limited accessibility to modern
36
37 95 rabies vaccines and supply problems, as well as a lack of public awareness and cooperation
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40 96 (8). However, the high estimated burden of rabies more than justifies the need to prioritise
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42 97 rabies control, particularly in Asian countries.

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45 98 Information on rabies epidemiology is a prerequisite for the effective planning of
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47 99 rabies control programs. Previous systematic reviews focused on rabies epidemiology in India
48
49
50 100 (11), Nepal (1), and Arab countries (12), while literature synthesising data on rabies
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52 101 epidemiology in Southeast Asia is limited. Hence, this systematic review aims to provide an
53
54 102 in-depth assessment of the incidence, risk factors, and mortality of rabies in Southeast Asian
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56
57 103 countries, based on the published literature.

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59 104
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105 **MATERIALS AND METHODS**

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

113 **Patient and public involvement**

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

116 **Research question formulation**

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

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2
3 128 What is the mortality rate of rabies among the general population in Southeast Asian
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6 129 countries?
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8 130 **Data source and search strategy**
9

10 131 PubMed, Web of Science and Scopus were searched from 1 January 2012 to 21 February 2023.
11
12

13 132 The keywords used to search for related articles are provided in Table 1.
14
15

16 133
17

18 134 Table 1: Keywords search used in the screening process.
19

Database	Search string
Scopus	<p>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"))</p> <p>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*"))</p>
Web of Science	<p>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"))</p> <p>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*"))</p>

PubMed	<p>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"))</p> <p>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*"))</p>

135

136 Study selection

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

144

145 Data extraction and synthesis

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

1
2
3 152 inclusion criteria. Before the data extraction process, both reviewers needed to agree that
4
5
6 153 the entire publication should be reviewed. Any disagreements were worked out through
7
8 154 discussion. All data extraction was conducted independently using a standardised data
9
10
11 155 extraction form that was organised using Microsoft Excel. Information collected in the form
12
13 156 included (1) author, (2) publication year, (3) reference, (4) country, (5) study design, (6)
14
15 157 statistical analysis and (7) results, which included incidence, risk factors and mortality. Due to
16
17
18 158 the heterogeneity of the included studies, narrative synthesis was performed.
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22 23 160 **Quality assessment**

24
25 161 Quality assessment was conducted by the authors on all eight studies using the Mixed
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27 162 Methods Appraisal Tool (MMAT) (16). The MMAT is a critical appraisal tool that was
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29
30 163 developed to appraise studies included in systematic mixed study reviews. The quality of the
31
32 164 methodology of five categories of studies (qualitative studies, randomized controlled trials,
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34
35 165 non-randomised studies, quantitative descriptive studies, and mixed methods studies) can be
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37 166 appraised using this tool. For each category, five criteria are used to assess the quality of the
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39
40 167 study. It is advised not to calculate an overall score from the rating of each criterion using the
41
42 168 latest version of MMAT (2018). However, due to problems faced by researchers in reporting
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44
45 169 the MMAT results, a suggestion was provided for reporting an overall score (5*****/100% of
46
47 170 the quality criteria met, 4*****/80% of the quality criteria met; 3*****/60% of the quality
48
49
50 171 criteria met; 2*****/40% of the quality criteria met; 1*****/20% of the quality criteria met). The
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52 172 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

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3 factors of rabies in Southeast Asia. Among the included studies, three studies particularly
4
5 discussed rabies mortality.
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10 **Incidence and risk factors of rabies in Southeast Asian countries**

11
12 Overall, the incidence of rabies ranged between 0.1 per 100,000 population in the Philippines
13
14 (28) 117.2 per 100,000 population in Vietnam [18]. The average monthly number of rabies
15
16 cases in Vietnam was 429 during the period from 2011 to 2015, with the incidence ranging
17
18 from 1.7 to 117.2 per 100,000, with higher incidences observed in the Red River, South Central
19
20 Coast (SCC) and Mekong River Delta (MRD) regions (29). Specific to Southern Vietnam, a total
21
22 of 94 human rabies cases were reported between 2009 and 2018, with an average of nine
23
24 cases recorded annually, representing an incidence of 2.7 cases per 10 million population (30).
25
26 The highest number was reported in 2018 (5.5 cases per 10 million population). Most cases
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28 were among men and individuals aged 50 years and above.
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35 Dog butchers in Vietnam were at high risk of rabies virus infection (31). The study
36
37 found that 28.3% of butchers were at risk of rabies exposure due to the slaughtering of sick
38
39 dogs and getting bites, scratches or knife cuts. Of 406 participants, 8.6% had sufficient levels
40
41 of rabies neutralising antibody (NTA) for protection and only 8.1% were vaccinated. In terms
42
43 of location, rabies cases were limited to specific areas. Hotspots were identified in southern
44
45 Vietnam, particularly in the MRD and SCC (32). Seasonal patterns were observed, with a
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47 strong peak in February/July and a minor peak in October/December in the MRD region.
48
49 However, a strong peak was detected in the middle of each year in the SCC. Temperature,
50
51 humidity and cumulative rainfall are positively associated with an increased incidence of
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53 rabies in Vietnam. In terms of socio-economic factors, increases in population density, as well
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55 as the percentage of illiteracy, elevated the risk of rabies (29).
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3 In Indonesia, 104 human rabies cases were reported in Bali from November 2008 to
4 November 2010. Most of the cases were among men. Almost all (92%) cases had a history of
5 a dog bite. Only 5.8% had their wounds treated and received an anti-rabies vaccine (ARV)
6 after the bite incident (33). Even worse, rabies cases in Sibu, Sarawak, also did not seek
7 medical attention following a dog bite (34). The cumulative incidence in Sibu was estimated
8 at 1.7 per 100,000 population. The incubation period varied from 17 days to 2 years.
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18 A total of 46 confirmed and probable cases of human rabies were reported in Thailand
19 from 2010 to 2015, of which 11 were reported in Eastern Thailand (35). Even though rabies
20 can be prevented by vaccination, more than 90% of rabies death cases in Thailand did not
21 receive or improperly stopped receiving PEP. In terms of suspected rabies exposures, 6,204
22 exposures were reported from eight provinces in Eastern Thailand, resulting in a crude
23 exposure rate of 106 reported rabies exposures per 100,000 people. Dogs were the main
24 source of exposure (77.8%), while children under the age of 15 and older persons over the
25 age of 60 had the highest overall reported exposure rates (189.7 and 189.2/100,000,
26 respectively).
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40 In the Philippines, there were 575 rabies cases from 2006 to 2015, of which 70% were
41 among men. Nearly 34% of the patients were aged 41 to 60 years. The incidence rate of
42 human rabies per 100,000 population in 2007, 2010 and 2015 was 0.1305, 0.1356 and 0.1708
43 in the National Capital Region; 0.2890, 0.2965 and 0.1961 in Region III; and 0.1449, 0.1272
44 and 0.1041 in Region IV-A, respectively (28).
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55 **Rabies mortality in Southeast Asian countries**

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57 The case fatality rate was 100% as mentioned in two studies (33,34). Of the six deaths
58 reported in Sibu, five patients succumbed to the illness within 2 weeks of symptom onset,
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3 with five out of the six cases reporting a dog bite history [23]. In Indonesia, Susilawati et al.
4 reported 104 fatalities due to rabies, of which 96 cases had a history of dog bites [22]. In the
5
6 Philippines, 463 people died from rabies infection (28).
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10 11 12 13 **DISCUSSION**

14 15 **Incidence and risk factors of rabies in Southeast Asian countries**

16
17 Rabies in Asia and Africa contributes to over 99% of the human rabies deaths that occur in
18 the world today. The vast majority (60%) of these deaths occur in Asia (36). Every year, an
19 estimated 59,000 people die from rabies worldwide, with the majority (95%) of these deaths
20 occurring in Africa and Asia due to a lack of PEP services for animal-bite patients and rabies
21 surveillance personnel and facilities (37). These statistics support the results of our study,
22 which shows the reporting of a high number of rabies cases in Vietnam, Indonesia and
23 Thailand, which are endemic for rabies (38).
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35 Rabies is concentrated in Asia and Southeast Asia because it is frequently neglected
36 when health and agriculture budgets are set, although the costs and economic benefits of
37 implementing rabies prevention programs have been successfully established in high-income
38 countries (39). The high number of rabies cases in Southeast Asia can also be attributed to
39 the high number of unowned, free-roaming dogs that cannot be controlled without
40 considerable effort and thus are not vaccinated (40). Vaccination programs for dogs can
41 provide herd immunity and break the rabies transmission cycle in this reservoir species and
42 have been successfully applied in several countries around the world (41).
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55 Another cause of the high incidence of rabies in Southeast Asia is the working hazards
56 of dog butchers, especially in countries that have legalised dog consumption, such as Vietnam
57 (42). The Centers for Disease Control and Prevention (CDC) also reported the illegal trafficking
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2
3 of dogs for human consumption in Vietnam
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5 (https://www.cdc.gov/globalhealth/stories/rabies_southeast_asia.htm), which could
6
7 possibly contribute to the high incidence of rabies in Vietnam. Professional dog butchers in
8
9 northern Vietnam are at a high risk of rabies virus infection due to exposure during the
10
11 slaughtering process from the handling of sick or dead dogs and getting bitten, scratched, or
12
13 cut with knives. A study reported that 91.9% of professional dog butchers in Vietnam were
14
15 not vaccinated against rabies, which may be because of fear of the side effects of the rabies
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17 vaccine, inability to afford vaccination, and incorrect knowledge of rabies prevention (31).
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23 The rabies incidence of 0.1 per 100,000 population in the Philippines is similar to that
24
25 reported in China in 2016 (43). The lower rabies incidence in the Philippines compared to
26
27 other Southeast Asian countries may be due to the implementation of the Anti-Rabies Act of
28
29 2007 to prevent and control human rabies (44). Additionally, the consumption of dog meat
30
31 was banned in 1998 with the implementation of the Animal Welfare Act which may contribute
32
33 to the lower incidence of rabies in the Philippines (45).
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37 Men are more likely to contract rabies infection than women [19]. Similar findings
38
39 were reported in Iraq, where more than 89% of rabies cases were among men (46). This can
40
41 be attributed to the fact that most women are housewives, while men are engaged in outdoor
42
43 activities (47). Another study in Ethiopia also stated that men are more likely to perform
44
45 nightly and outdoor activities, while women are more likely to remain indoors for cultural and
46
47 religious reasons (48), which could explain the increased incidence of rabies in men.
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51 According to study a by Yurachai et al., rabies infection affects children more
52
53 compared to other age groups [24]. This corresponds to a WHO report, stating that 40% of
54
55 rabies victims are children ages 4 to 15 ([https://www.who.int/news-room/fact-](https://www.who.int/news-room/fact-sheets/detail/rabies)
56
57 [sheets/detail/rabies](https://www.who.int/news-room/fact-sheets/detail/rabies)). Other studies in Yemen and Iran reported similar findings, with nearly
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2
3 40% of the individuals exposed to rabies infection falling in this age group (46,49). Children in
4
5 this age group are probably more likely to play with, annoy or approach biting animals, which
6
7 contributes to the higher rate of bites in this age group (46). In contrast, according to a study
8
9 by Pham et al., older people are more likely to become infected with rabies [19].
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12
13 In several studies included in this systematic review, the diagnosis of most rabies cases
14
15 was based only on detailed history and clinical diagnosis [17, 19, 21]. To diagnose rabies in
16
17 humans, multiple samples such as saliva, serum, spinal fluid and skin biopsies of hair follicles
18
19 from the nape of the neck are analysed. Viral isolation or reverse transcription followed by
20
21 polymerase chain reaction (RT-PCR) can be used to analyse saliva. Serum and spinal fluid are
22
23 tested for rabies virus antibodies. Skin biopsies can be used to detect rabies antigens in the
24
25 cutaneous nerves at the base of the hair follicles
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27 (<https://www.cdc.gov/rabies/diagnosis/animals-humans.html>). In the future, developing
28
29 countries need to standardise the diagnosis of rabies based on the laboratory tests mentioned
30
31 above for the accuracy of the diagnosis and to enable comparison with other studies in
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33 developed countries.
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40 Of the included studies, only one was conducted among butchers, who were at higher
41
42 risk of contracting rabies [20]. Apart from butchers, individuals working as veterinarians,
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44 veterinary technicians, animal control workers, and wildlife rehabilitators were also
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46 considered to have a higher risk of contracting rabies than the general population (50). This
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48 calls for more studies incorporating individuals involved in occupations identified as high risk
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50 for rabies exposure and infection.
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54 In this study, climate was postulated to be one of the risk factors for rabies infection.
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56 This was echoed by a study in China showing that the incidence of rabies increases with the
57
58 ambient temperature. A warmer climate causes animals to be more active in their
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3 environment and to travel greater distances when tracking, which contributes to the spread
4 of rabies. In addition, as temperatures rise, people tend to wear lighter clothing and expose
5 more skin, which increases the likelihood of being bitten by a dog (51). In South Korea, the
6 seasonality of wildlife rabies was attributed to behaviours such as searching for food during
7 the winter or early spring. Dogs may thus have more opportunities to come into contact with
8 rabid animals during this period due to greater animal movement, which could contribute to
9 seasonal patterns in the occurrence of rabies in humans (52).
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23 **Rabies mortality in Southeast Asian countries**

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25 In this study, rabies had a high fatality rate, with 100% of the infected cases dying. This is
26 supported by a review in Africa by Nyasulu et al., who reported that Algeria, Namibia, Eswatini
27 (formerly Swaziland), Tunisia, Uganda, Zambia, and Zimbabwe had high morbidity and
28 mortality due to rabies, with 563 cases (33.9% deaths), 269 cases (94% deaths), 62 cases (88.7%
29 deaths), 91 cases (90% deaths), 466 cases (40.9% deaths), 207 cases (32.8% deaths), and 114
30 cases (80.7% deaths), respectively (53). Because of the large population of stray dogs in this
31 area, the chances of being bitten by a dog are high. Not only are the chances of being bitten
32 high in these areas, but access to treatment in a timely and adequate manner is also very
33 limited. Rabies vaccines may not be routinely available in rural areas where most exposures
34 occur, and rabies immunoglobulins, which are required for category III bites, are always in
35 short supply (54).
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52 These factors significantly contribute to the high mortality rate, as the highly
53 protective rabies vaccine is frequently unavailable in these poor areas. In addition, the public
54 is often unconcerned and unaware of the need for early treatment after being bitten by dogs
55 (55). According to recent studies, many rabies victims contracted the disease owing to neglect,
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3 ignorance, or a lack of primary healthcare facilities (56). Thus, health promotion and
4
5 education should be given to the public as knowledge regarding rabies is essential to reduce
6
7 morbidity and mortality (5).
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10
11 In high-income countries such as the USA, the incidence of rabies and associated
12
13 mortality is low. In the last decade, there have been only 25 cases of human rabies reported
14
15 in the USA (2009–2018), with 23 deaths (6). The low number of cases of rabies infection is
16
17 due to successful animal control and vaccination programs, successful outreach programs,
18
19 public health capacity and laboratory diagnostics, and the availability of modern rabies
20
21 biologics (57). Even though rabies is preventable, the exorbitant cost of vaccinations,
22
23 combined with a lack of education and knowledge about the disease, limits PEP use. (56)
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30 **Strengths and limitations**

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32 In this study, we only included research from Southeast Asia, which may not represent rabies
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34 infection in other regions or continents. We did not include grey literature or national
35
36 guidelines, which could have been useful in this study. Nevertheless, the strength of this
37
38 review lies in its inclusion of studies that defined or diagnosed rabies based on either clinical
39
40 signs or laboratory testing. Given that rabies is often diagnosed clinically, especially in
41
42 developing countries (58), this process increased the chances of identifying rabies cases in
43
44 Southeast Asian countries.
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51 **Recommendations**

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53 A successful rabies prevention and control program requires integrating and strengthening
54
55 intersectoral and transdisciplinary collaboration and cooperation among various societal
56
57 components (59). The Association of Southeast Asian Nations (ASEAN) Rabies Elimination
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3 Strategy places great value on the organisational and One Health frameworks for rabies
4 eradication. The single most significant way to deal with rabies concerns is to eliminate dog-
5 mediated rabies. The requirement for PEP is considerably reduced when dog rabies is
6 eradicated (60). To benefit from the synergy and maximisation of shared resources,
7 comprehensive rabies control programs should involve the combination of human, financial,
8 and material resources with other disease programs (36).
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18 Mass canine vaccination campaigns will boost herd immunity and reduce the risk of
19 human rabies exposure, but this will need strong governmental commitment and extensive
20 social mobilisation. The veterinary authority's active engagement in animal rabies control at
21 the national level is critical, and it is their social responsibility to prevent human rabies
22 through well-planned dog rabies control programs (38). In 1983, the Pan American Health
23 Organization initiated an elimination programme for human rabies transmitted by dogs that
24 was mainly based on the mass immunisation of dogs; this has led to a 90% reduction in dog
25 rabies in Chile and other Latin American countries (61).
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37 Rabies control and elimination in low endemic rabies countries such as Malaysia and
38 Singapore have been made possible by the strict enforcement of dog registration, vaccination,
39 and population management measures. Malaysia shares a border with Thailand, and the
40 notion of an immunological belt has been developed through dog licensing, required
41 vaccination of dogs and the systematic extermination of unvaccinated dogs in a buffer zone
42 to prevent rabies from entering the country (38). Perhaps other middle and high endemic
43 rabies countries could follow this rabies control strategy implemented by their Southeast
44 Asian neighbour.
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57 Public information and education are important to increase awareness and enhance
58 community participation and support in rabies prevention programs. Dissemination of
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3 important information such as the high fatality rate of rabies, its epidemiology, its prevention
4 and control, and the disease control program, in general, is vital for program implementation
5 and responsible pet ownership. By recognising rabies' influence on people's daily lives and
6 the fact that dogs can be a source of human infection, community and school-based rabies
7 prevention initiatives will be easier to establish (62).

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

41 42 **CONCLUSION**

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44 Rabies has often been neglected and not given priority in terms of funding for prevention
45 programs, resulting in the continued presence of rabies cases in Southeast Asia despite the
46 endorsement of multiple programs by the WHO. The high number of unvaccinated stray and
47 pet dogs, working hazards (dog butchers in Vietnam), unavailability of the rabies vaccine in
48 rural areas, as well as ignorance regarding the importance of seeking treatment after dog
49 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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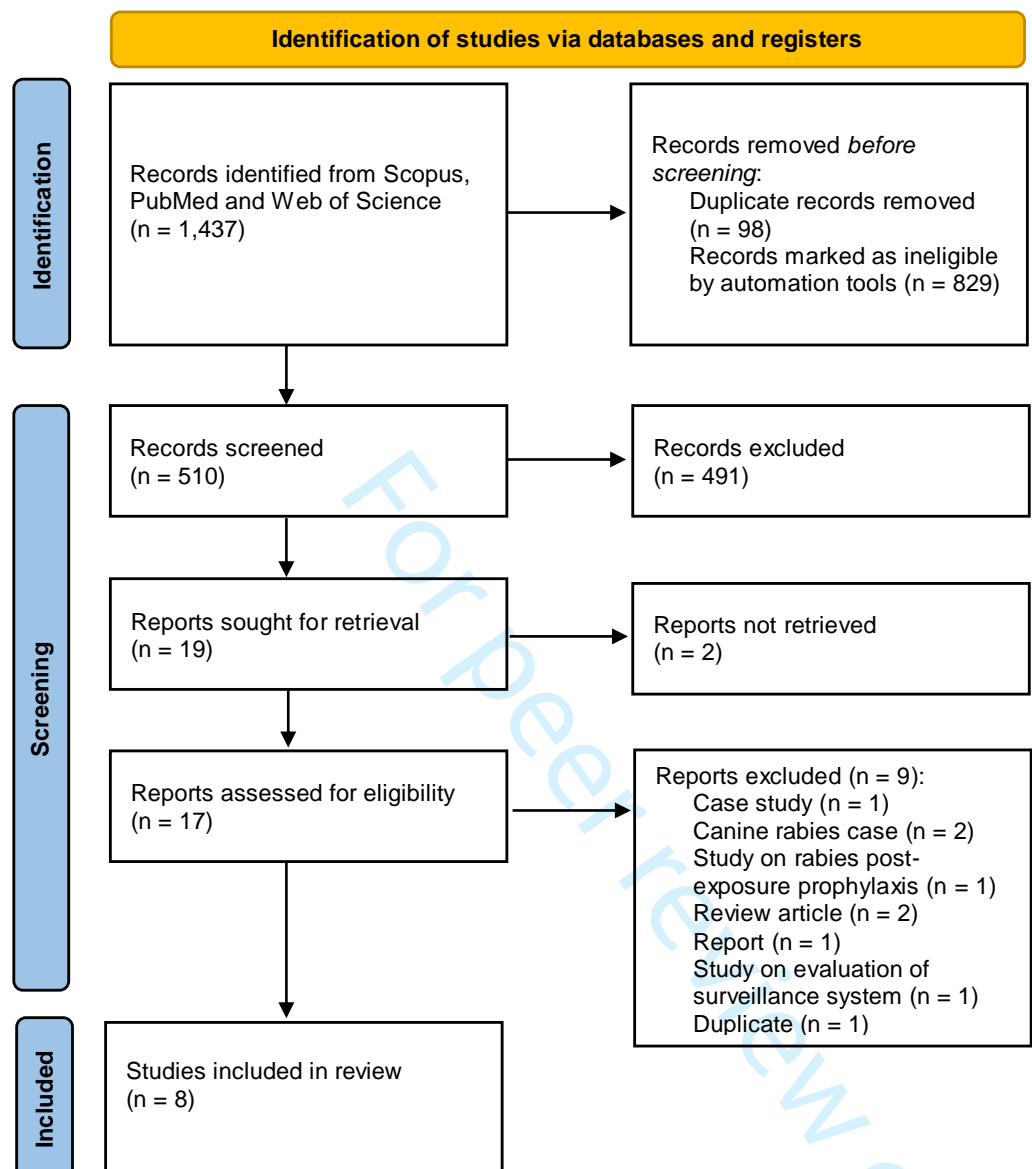
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PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



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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. <i>American Journal of Tropical Medicine and Hygiene</i> 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. <i>Frontiers in Public Health</i> 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. <i>Journal of the</i>	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

		<i>Royal College of Physicians of Edinburgh</i> 51(2): 133–139. doi:10.4997/JRCPE.2021.207			incidence in Sibuh 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. <i>PLoS Neglected Tropical Diseases</i> 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. <i>PLoS ONE</i> 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. <i>BMC Infectious Diseases</i> 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. <i>PloS ONE</i> 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. <i>PLoS Negl Trop Dis</i> 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.

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For peer review only



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

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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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