

REVIEW ARTICLE

ANIMAL RABIES: A SYSTEMATIC REVIEW

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ABSTRACT

Rabies, a neglected viral zoonosis disease, impose a major public health and veterinary importance. There is limited attention to the role of wild animals as sylvatic reservoirs of the rabies virus. Thus, this systematic review aims to identify various types of animals with rabies infection, determine the prevalence of rabies virus in animals, and identify the high-risk animal that could contribute to human rabies. A systematic search was performed in the PubMed and Web of Science databases for papers on rabies in animals published from 2015 until 2019. The articles were analyzed on the prevalence of rabies infection among the animal which ranges from 0% up to 74.16%. The highest was dogs with 0.02% to 74.16% followed by fox 52.93% up to 70.1%. The other two animals namely camel and sheep/goat revealed more than 50% of rabies prevalence of 59.7% and 57.1% respectively. This study shows that the rabies prevalence in the animal varies, and dogs still have the highest prevalence as the leading causes of rabies transmission to the human. Dog and fox are the most common animal with rabies in our systematic review. Thus, domestic animals that are kept as pets especially dogs should be properly vaccinated against rabies. Meanwhile, avoidance or extra cautious while handling wildlife animals should be of primary importance.

Keywords: Rabies; animals; wildlife; rabies prevalence

INTRODUCTION

Rabies is a neglected viral zoonosis of major global public health and veterinary importance. It is caused by negative stranded ribonucleic acid (RNA) virus of the Lyssavirus genus, of which rabies virus (RABV) is the prototype, transmitted to humans through direct contact with infected saliva from animal scratches or bites, mucous tissue, respiration, placenta, contaminated equipment, and organ transplants¹. Rabies is currently reported in over 100 countries in all continents except Australia and Antarctica. The disease is characterized by neuroencephalitis with 100% case fatality ratio once clinical signs present^{2,3}. The estimated annual mortality of rabies infection estimated was around 59 000 cases which involved more than 150 countries, in which 95% of the mortality cases were from Asia and Africa continents⁴.

There are 2 types of rabies which are i) Urban rabies which is associated with domestic dogs and in a limited number of cases with cats; and ii) Sylvatic rabies which is associated with wildlife include wolves, foxes, weasels, raccoons, and bats¹. In most continents, domestic dogs are the principal reservoir and source of infection for canine RABV. Tens of thousands of human deaths per year are attributed to RABV infections acquired from domestic dogs, particularly *Canis*

familiaris species³. A large multi-centre study in India also reported that dog bites constituted majority of all incidents, while bites from other animals such as monkeys, cats, foxes, bats and rabbits comprised the rest⁵. Rabies in dogs can present as 'furious' or 'paralytic' forms. Rabid cats have been reported to be more violent than rabid dogs⁶. In contrast, the signs in bovine include excessive salivation, behavioural change, vocalization, and pharyngeal paresis³. The disease is untreatable and eventually causes death of the affected animals.

Two main methods used to control rabies are through vaccination and measures aiming to reduce dog population density, usually by culling (i.e., the widespread killing of dogs regardless of infection status) and by sterilization. Vaccinations are often undertaken as annual campaigns that aim to achieve 70% coverage⁷. The disease can be preventable after exposure by initiating as soon as possible the post exposure prophylaxis (PEP). There are few types of PEP vaccination available namely purified chick embryo cell vaccine (PCECV), purified vero cell rabies vaccine (PVRV) and human diploid cell vaccine (HDCV)⁸, administered either via intramuscular or intradermal route, with the suggested regime by the World Health Organization (WHO).

Previous studies have been focusing on the recognized disease effects on domestic dogs, and associated welfare concerns related to dog control strategies⁹. Limited attention has been paid to the role of wild animals as sylvatic reservoirs of RABV. Moreover, due to the vigorous attempt for vaccination among domestic dogs, the enzootic rabies from the wildlife animals may potentially cause spill over effect to human and other domestic animals¹⁰. Thus, to the best of our knowledge, there were limited number of previous systematic reviews conducted in relation to rabies prevalence in animals. The objectives of this systematic review are to identify various types of animals with rabies infection and determine the prevalence of RABV in animal.

METHODS

Search Method

Systematic search was performed for the relevant titles, abstracts and keywords in the journal databases of PubMed and Web of Science from September 2015 until 2019, based on the PICO (population/problem, intervention, comparison and outcomes) strategy. However, only population/problem and outcome components were included in the search strategy as to answer this review's objectives. The target population of this search was the animal population with rabies and the outcome are either prevalence or incidence. Hence, the keywords and terms entered were "rabies" OR "rabid" AND "animal reservoir" OR "dog" OR "dogs" OR "cat" OR "cats" OR "bat" OR "bats" OR "raccoon" OR "raccoons" OR "fox" OR "foxes" AND "prevalence" OR "incidence".

Selection criteria

The inclusion criteria from the database searches were (a) Original articles that fulfil the keywords and terms searched, (b) Availability of full text article, (c) English-language articles. The exclusion criteria in this search were article on human rabies.

Data extraction tool

All researchers independently extract the information for each article into an excel sheet. The data was customized into (a) Number (b) Author, title and journal (c) Method and (d)

Result. A second reviewer cross-checked the articles assigned for them.

RESULTS

Study Selection

The selection process is illustrated in the Preferred Reporting Items for a Systematic Review (PRISMA) flow chart in Figure 1. A total of 293 studies were identified in the initial searches in databases and through references lists. After removal of duplicates, titles and abstracts were screened, producing a selection of 28 articles. However, only 10 articles were accepted after screening of the full text. The reasons for excluding the studies were based on the full text in view of non-English article (n=2), and irrelevant studies (n=16).

Characteristic of the Study

In this systematic review, a total of 10 articles were included to discuss on the prevalence of rabies in the animal population worldwide (Table 1). The studies were conducted in India (3), Chile (1), Oman (1), Cameroon (1), Zambia (1), China (1), Ukraine (1), and Tanzania (1). The samples were ranging from minimal of 7 up to 257 435 samples. The animals been studied were bat, fox, dog, cat, camel, sheep/goat, cattle, buffalo, equine and others. Most of the studies used the method of detecting DFAT (7), ELISA (2), and Seller's stain for Negri bodies (1).

Types of Animals

Seven studies only focused on one type of animals while the others investigated multiple animals for the rabies prevalence. Most (7) of the studies focus on dog which is the commonest source of transmission to human accounted for 99% of the infection¹¹. Out of these seven studies, two studies included other animals in their research namely cat, camel, buffalo, fox, sheep/goat, equine, cattle and others. The samples for dog ranged from 7 up to 59 496. On the other hand, another two types of animals which are bat and fox are being respectively included in each two studies in this systematic review. A total of minimum samples of 61 till maximum sample of 25 498 were studies for the two types of animals which are the second commonest after dog.

Table 1: Articles included in the systematic review

No	First Author	Year	Study design	Setting	Country	Method detecting	Type animal	No. sample	No. positive samples	Proportion positive
1	Escobar L.E et al ²⁶	2014	Cross- sectional	Surveillance data	Chile	DFAT	Bat	25498	1339	5.25%
2	Al Abaidani I. et al ²⁷	2015	Cross- sectional	Surveillance data	Oman	DFAT	Fox	61	47	70.10%
							Dog	7	2	28.50%
							Cat	8	0	0.00%
							Camel	67	40	59.70%
							Sheep/ goat	546	312	57.10%
							Other	66	22	33.30%
3	Gill G.S et al ²⁸	2019	Cross- sectional	Surveillance data	Punjab, India	DFAT	Dog	59496	14	0.02%
							Cattle	132991	9	0.07%
							Buffalo	257435	5	0.02%
							Equine	1741	5	0.29%
4	Sadeuh-Mba S.A et al ²⁹	2014	Cross- sectional	Surveillance data	Southern Cameroon	DFAT	Dog	89	66	74.16%
5	Babaniyi et al ³⁰	2016	Cross- sectional	Surveillance data	Zambia	DFAT	Dog	2938-8242	1 to 8	2.40-17.50%
6	Zhang J.M et al ³¹	2017	Cross- sectional	9 randomly selected villages from each city	China	ELISA	Dog	3500	171	4.89%
7	Mani R.S et al ³²	2017	Cross- sectional	5 locations in Nagaland	India	DFAT	Bat	164	0	0.00%
8	Bharathy S et al ³³	2016	Cross- sectional	Surveillance data	India	Seller's stain for Negri bodies	Dog	169	125	73.97%
9	Polupan I. et al ³⁴	2019	Cross- sectional	3 locations in Ukraine	Ukraine	DFAT	Foxes	8816	226	52.93%
							Domestic carnivores	1454	169	39.58%
							Other wild animal	57	21	4.92%
							Other domestic animal	233	11	2.57%
10	Mtui-Malamsha N. et al ³⁵	2019	Cross-sectional	4 divisions	Tanzania	ELISA	Dogs	278	94	33.00%

Prevalence

The rabies prevalence among the animal ranged from 0% till the highest up to 74.16%. However, dog rabies prevalence ranges from 0.02% till 74.16% while the least with 0% are bat and cat in each study individually. Surprisingly, fox had the highest prevalence after dog which ranges 52.93% up to 70.10%. Others two animals namely camel and sheep/ goat revealed more than 50% rabies prevalence of 59.70% and 57.10% respectively. There were few studies on other animals that the prevalence ranges from 2.57% to 39.58%. Thus, in this study, it shows that the rabies prevalence in the

animal varies, and dogs still has the highest prevalence as the leading causes of rabies transmission to the human.

Quality Assessment Tool

By using mixed method assessment tool (MMAT version 2018) the articles were critically appraised for its quality by two independent reviewers. Any discrepancy about the quality was then reviewed by a third person. Overall, all the included studies were good quality and were selected in this systematic review.

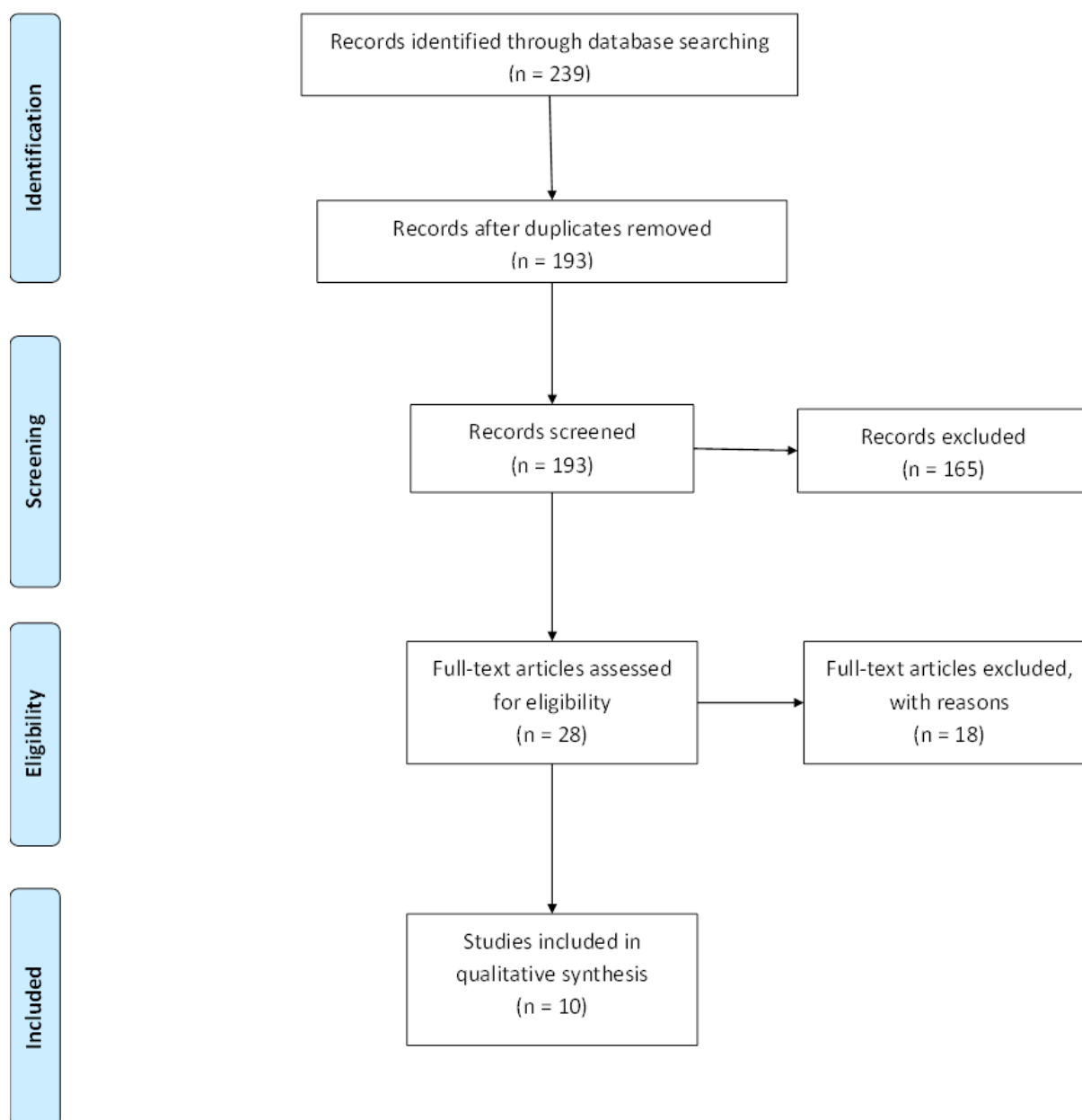


Figure 1: Flow Diagram for Systematic Review of Animal Rabies, adapted from PRISMA 2020 checklist

DISCUSSION

A proper understanding of the epidemiology of rabies in animal such as prevalence and types of animals infected with rabies virus is crucial for planning, implementing and evaluating rabies control programmes. This is because the typical route of transmission of rabies virus to human is through bite of the rabid animal¹². In this systematic review, we have tried to generate the best possible summary of data on prevalence and types of animals infected with rabies virus worldwide.

The exponential growth of the human population has led to major ecologic changes and drastic wildlife habitat reduction. The emergence or re-emergence of rabies are related to human encroachment on wildlife habitats. For instance, deforestation, development of human habitat, and mining activities has been suggested as risk factors associated with the re-emergence of vampire bat rabies in humans in the Amazon Basin¹³. Rabies was reported to kill about 55,000 people and over 1 million animals annually. Direct losses from rabies amount to over 4 billion Euro each year³. However, these estimates very likely represent serious underestimations of the true rabies burden. Indeed, underreporting is very likely to occur in both the animal and human passive surveillance systems¹⁴, and a proper understanding and quantification of the various reporting biases is a major research gap. The reporting of animal rabies cases may depend on the economic value of the affected species, the remoteness of the area, and the motivation of the practitioner¹⁵.

Rabies prevalence in animals depends on which animals being sampled and tested using different types of detection methods in the laboratory. Even sampled animals that humans were bitten by may not be randomly chosen, so the interpretation of prevalence data is often very difficult¹⁶. In this systematic review, there are wide range of animal rabies prevalence being reported, ranging from 0% (cats' population in Oman) up to 74.17% (dogs' population in Cameroon). However, seven out of eleven studies in this systematic review were using surveillance data to capture the prevalence. Thus, it might not be a true prevalence due to underreporting of passive surveillance system since it relies on people reporting to the authority of bites episode by animal and abnormal behaviour of animals. Moreover, once cases being reported, the affected animals especially in cases involved wild type of animals are difficult to catch and there is resistance from the animal's right people. In rabies, sample from the animal's brain is needed to test and diagnose the presence of rabies virus. Besides, there are other factors that will affect the surveillance system such as lack of financial capital investment for the system, and limited enforcement on the legislation and guidance¹⁷. Rabies cases are endemic in Iran and the incidence of animal and human rabies is increasing over years. Rabies is the most important

zoonotic disease in Iran. In 2006, more than 130,000 people and animals respectively received rabies post-exposure prophylaxis. Majority of human exposures were due to biting episodes caused by dogs¹⁸.

Most of the studies included in this systematic review were using direct fluorescent antibody testing (DFAT) to detect RABV in animals. DFAT is the main assay used worldwide as it is recommended by WHO and World Organization for Animal Health (OIE) as gold standard for the diagnosis of rabies in fresh or frozen brain samples. The frozen brain samples are important in tropical countries as preserving fresh samples at 4°C is often a challenge¹⁹. It is based on attaching fluorescein isothiocyanate to polyclonal antibodies targeting the RABV ribonucleocapsid or monoclonal antibodies targeting the RABV nucleoprotein (N). If the targeted RABV antigen is present in the sample fixed on a slide, antibodies attach to it, remain attached despite lavage and can be observed using a fluorescence microscope²⁰. Results are available within 1-2 hours and results are expressed as positive or negative. The sensitivity and specificity of DFAT nears 99% in an experienced laboratory but is extremely observer-dependent²¹. At least two observers must spend enough time on each slide once the quality of the sample has been ensured. Inadequate training of the laboratory personnel could affect the detection rate of the disease¹⁶.

As for controlling rabies in dogs, there is no evidence that removal of dogs alone has ever had a significant impact on dog population densities or the spread of rabies. In addition, dog removal may be unacceptable to certain local communities. However, the targeted removal of unvaccinated, ownerless dogs may be effective when used as a supplementary measure to mass vaccination. Mass dog vaccination campaigns have been the most effective measure for controlling dog rabies. High vaccination coverage can be achieved by comprehensive strategies consisting of educational campaigns, intersectoral collaboration, and community participation in planning and execution. Surveillance of rabies is the basis for any programme of rabies control. Unfortunately, surveillance system in many dogs' rabies endemic countries is relatively very poor, with few labs, small numbers of samples tested, and variant typing usually not possible locally¹⁶. Besides dogs, the common vampire bat, *Desmodus rotundus*, has emerged as the principle RABV reservoir host along the species natural range from Mexico to South America. *D. rotundus* was correlated with the vampire bat RABV variants which is more prevalent than the dog RABV variants in Peru²². Veterinary surveillance of rabies and laboratory submission of reports of suspected cases is crucial for management of potential human exposures and for veterinarians to adopt appropriate measures towards animals in contact with a suspected animal case⁴. In the European Union (EU), the elimination of rabies transmitted by RABV is now

in sight. The key elements of the rabies eradication programs in EU are oral rabies vaccination (ORV), quality control of vaccines and control of their distribution, rabies surveillance and monitoring of the vaccination effectiveness²³. Post-exposure prophylaxis against rabies was proven to be almost 100% effective and serve as one of the public health controls to reduce mortality²⁴. However, the cost-effectiveness and the availability of this service is still questionable in most of the developing countries²⁵.

The limitation of this systematic review is most of the studies included only come from countries which are underdeveloped and developing countries due to the selection criteria of latest five years period. Thus, it may not show the true picture of rabies situation in the animal's population. Most of the developed countries rarely have rabies cases nowadays, likely due to their effective preventive and control measures. There is also limitation on the types of animals found in this review as most of the animals are considered as domestic or peri domestic and very low coverage for wild animals. Another limitation of this review is there are limited published data available, although, most of the countries do have surveillance system and monitoring of the rabies disease, including Malaysia.

CONCLUSION

Dog and fox are the most common animal with rabies in our systematic review. Thus, human contact with these wild types of animals especially in endemic area should be treated cautiously and since they are usually kept as pets, therefore the pets should be properly vaccinated against rabies. Limited data indicate that rabies probably still is a major zoonosis in most endemic countries. However, more and better data are needed, especially from rural areas, to estimate the true burden of animal rabies and to plan, implement and evaluate rabies control programmes. The way forward for effective rabies control programmes lies in more collaboration, both within the country and within the region. Efforts should be made to fully incorporate rabies control activities in all levels of the health services, aligning them with other public health programmes. Synergies between programmes hopefully will improve logistical use of human, material and financial resources.

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Conflicts Of Interest

The authors declare that the study was conducted in the absence of any commercial or financial

relationships that could be construed as a potential conflict of interest.

Ethical Statement

This is a systematic review article which does not require approval from the ethical committee or the Institutional Review Board (IRB).

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