SYSTEMATIC REVIEW

Incidence of suspected human rabies virus exposure and associated risk factors in Ethiopia: systematic review and meta-analysis

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Abstract

Background Despite the World Health Organization's 2030 goal of zero deaths, rabies disproportionately affects Asia and Africa, causing 55,000 deaths and 8.6 billion monetary losses annually. In Ethiopia, dogs are the primary cause of human rabies virus exposure due to their close interaction with humans and other domestic animals. The results of previous studies on the incidence of suspected human rabies virus exposure were inconsistent and inadequate. This study aimed to measure the pooled incidence of suspected human rabies virus exposure and associated risk factors in Ethiopia.

Methods Published articles without publication date/year restriction were investigated using the guideline Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). We searched PubMed, EMBASE, Science Direct, Google Scholar, and African Journals Online databases. Two independent authors extracted the required data. This meta-analysis was carried out using the program Stata Version 17, the DerSimonian-Laird method, and a randomeffects model. The I2 and Cochrane Q test statistics were used to determine the studies' heterogeneity. Egger's test and funnel plots were used to assess publication bias. Data were displayed using forest plots of incidence and risk ratio (RR) with a 95% confidence interval.

Results Eight articles with 18 data points and 116,484 sample sizes were included. The pooled incidence rate was 54.03 (95% Cl: 43.92–64.13) per 100,000 population. The highest, 107.32 (95% Cl: 80.20-134.45) per 100,000 population, and the lowest, 4.49 (95% CI: 2.00-6.97) per 100,000 incidence rate, were observed in the Oromia and Amhara regions, respectively. Sex was significantly associated with the incidence of human rabies exposure. Being male was (RR = 1.67, 95% Cl; 1.53–1.81) times more likely to be exposed to the human rabies virus than those who were females.

Conclusion The estimated incidence was found to vary by location and was reported as high. One important contributing factor was sex. Human rabies virus exposure prevention, such as dog vaccination, public awareness, and an epidemiological surveillance system, should be improved.

Keywords Incidence, Human, Rabies, Exposure, Review, Ethiopia

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Background

Rabies is a fatal [1, 2] and neglected viral disease [3, 4] that infects the central nervous system of mammals [5, 6]. The cause of the human rabies virus belongs to the Ahabdovirdae family, a genus of lyssavirus with negativestranded RNA genomes [7]. Depending on the site of

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virus entry and viral load, its incubation period is mostly 2–3 months, but it may vary from days to a year [8].

The rabies virus cannot currently be identified clinically unless the symptoms of rabies (hydrophobia or aerophobia) have been detected [9].The early stages of a rabies infection resemble those of the flu. Headaches, fever, nausea, vomiting, agitation, anxiety, confusion, hyperactivity, difficulty swallowing, excessive salivation, difficulty swallowing water, hallucinations, sleeplessness, and partial paralysis are some of the symptoms and signs of the rabies virus [9, 10]. Once rabies symptoms appear, the disease is fatal and incurable [11, 12].

Human rabies virus exposure is a condition where the saliva or nervous system tissue of a potentially infectious animal is entered into open cuts in the skin or mucous membranes [9, 13, 14].

Globally, rabies is reported in more than 150 countries. However, in Asia and Africa, it is the most common and a big public health problem. Although there are safe and effective preventive tools (such as vaccinating domestic dogs, post-exposure prophylaxis, etc.) for the rabies virus in the global market [15], the burden of the disease cannot be reduced in underdeveloped countries [16]. In order to begin the process of achieving zero human rabies deaths by 2030, the World Health Organization (WHO) is leading a worldwide effort against the disease [17]. However, rabies continues to be the global cause of more than 56,000 deaths and 8.6 billion dollars in economic losses annually (4), with Asia and Africa accounting for over 95% of rabies cases. Ethiopia reports over 2700 deaths annually from the rabies virus [18].

Even if any wild and domestic mammals can transmit the rabies virus [19], dogs are the principal source of the human rabies virus, which contributes to more than 99% of human rabies virus transmission [8, 9, 19].

Efficient rabies disease prevention and control could be achieved by establishing strong epidemiological surveillance systems, designing and executing laws for registration, certification, and regular vaccination of owned dogs, creating public awareness, and providing easily accessible, effective, and affordable post-exposure human vaccines [20–22].

Dogs in Ethiopia may be able to spread and maintain the virus among the population because they frequently contact other domestic animals for protection [21]. The main barriers to rabies prevention and control include an increasing number of stray dogs, a lack of post-exposure treatment and vaccine, a lack of diagnostic facilities, a weak surveillance system, a lack of public awareness, a lack of concern, and a lack of government funding [2, 21, 23, 24]. Ethiopia's inadequate dog bite and rabies surveillance system makes it difficult for the country's integrated disease response system to properly respond to the disease in its early stages [25].

In Ethiopia, retrospective studies were conducted on the incidence of suspected human rabies virus exposure [26-29] and risk factors [30-33], but they were inconsistent and unfulfilled [34]. Comprehensive evidence on the incidence of suspected human rabies exposure was required to meet the target of eliminating all human rabies deaths by 2030 [35]. Therefore, this systematic review and meta-analysis aimed to measure the pooled incidence of suspected human rabies exposure and risk factors in Ethiopia by using available published evidence.

Methods

Study design and search strategy

This study applied a systematic review and meta-analysis of published studies. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline was followed during the review and meta-analysis [13]. Before searching terms were developed, the medical-specific headings (Mesh) of incidence, human, rabies, exposure, risk factors, and Ethiopia were identified. Then, searching terms were created by combining keywords, mesh terms, entry terms, and other synonyms (Annex I). From April 1 to August 30/2023, the databases African Journals Online, EMBASE, CINAHL, Science Direct, PubMed, and Google Scholar were searched for published studies. Every published study was considered in this analysis.

Study selection and eligibility criteria

This review included all published studies that were conducted to assess the incidence of human rabies exposure and/or associated risk factors in Ethiopia. All available studies that were observational study designs were included. The reference list from already selected studies was also screened to retrieve additional articles that can be included in the meta-analysis. Studies published only in the English language were included.

Studies on animals without humans or those that were either entirely accessible or abstracted without full text were excluded. Reviews, case reports, and studies that did not explicitly examine the incidence of suspected human rabies exposure and/or associated factors were also excluded.

Outcome of interest

Outcome of interest was suspected human rabies exposure (Annex II).

Quality appraisal

Articles were evaluated using their title, abstract, and a thorough text review before being included in the final meta-analysis. The tool for evaluating quality was the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review [36]. Independently, two authors assessed each full-length publication, looked over the abstracts and titles, and determined which investigations were worthy of inclusion. The team agreed to meet with a third author to ensure candid discussion and thorough evaluation of all possibilities. The quality was evaluated using an eleven-item checklist (Annex III). A quality evaluation was completed prior to data extraction. A quality score was used to assess the included studies' quality, and publications with a score of more than eight out of eleven were deemed high quality.

Data extraction and management

The data extraction tool was adapted by reviewing different kinds of literature (Annex IV). It was developed by two authors independently and revised by another two authors. Before data collection, all authors agreed on the tool. The data extraction tool contained the following information: the name of the author, the year of publication, the study design, the study period, the study setting, the sample size, the incidence of exposure to suspected human rabies virus, the sex-specific incidence per 100,000 population, the age group most affected, the incidence per 100,000 people living in a particular residence, the seasonal incidence of suspected exposure to human rabies, and the risk ratios of being male and living in an urban area.

Statistical methods and analysis

After being extracted and imported into Microsoft Excel, the data was exported to STATA version 17 in order to do a meta-analysis. The incidence of human rabies exposure, the standard error (SE) from each study, and the total pooled incidence of human rabies virus exposure in Ethiopia and its 95% confidence interval (CI) were calculated using the random effect model and DerSimonian-Laird technique. To display the pooled incidence of human rabies exposure with a 95% confidence interval, forest plots were employed. The forest plot also displayed the odds ratio (OR) with a 95% confidence interval (CI) to indicate the variable linked to human exposure to rabies. Subgroup analysis was performed to investigate potential disparities, accounting for different geography. A random effects model was employed in the meta-analysis to account for the heterogeneity among the included



Fig. 1 PRISMA flow diagram of study selection on incidence and risk factor of suspected human rabies virus exposure in Ethiopia, 2023

studies. We performed a sensitivity analysis using a "leave one out" evaluation approach to verify the stability of the reported effect sizes and the cause of heterogeneity.

Heterogeneity and publication bias

Heterogeneity (I^2) between articles was assessed with Cochrane's Q test. The values of I^2 25, 50, and 75 were assumed to be low, moderate, and high heterogeneity, respectively [37]. Publication bias was evaluated visually by assessing the symmetry of a funnel plot of the included studies. It was also checked statistically using tests such as Egger's test [38]. The publication bias was also detected and adjusted by trim and fill analysis.

Results

Study selection

Using computerized database searching, 359 records in all were examined. About 283 papers were vetted using

their titles, abstracts, and complete article reviews after duplicates were eliminated. As a result, 271 papers in all were eliminated based on their abstract review and title. After twelve papers were assessed for eligibility, four were disqualified due to the absence of the study's desired outcome. Finally, our investigation included eight publications with 18 data points (records) (the authors of the primary studies collected data retrospectively for up to 5 years; these data were not pooled; therefore, we used each observation or data point) (Fig. 1).

Characteristics of included articles

Most of the investigations (5 studies and 13 data points or recordings) were conducted in Ethiopia's northern region, particularly in the Amhara and Tigray regions [26, 30-33]. Three studies totaling eight observations (records) were carried out in the Tigray region based on this research [26, 32, 33]. Only one study was conducted

 Table 1
 Descriptive summary of included studies in the systematic review and meta-analysis of the incidence of suspected human rabies virus exposure and risk factors in Ethiopia, 2023

Authors/year	Study location	Study design	Study period	Sample size	Incidence ^a	Risk factors
Lombamo F.etal, 2020 [28]	Addis Ababa	Retrospective cohort	September 2012 to August 2016	6927	46	
Yibrah and Damtie, 2015 [30]	Amhara	Retrospective cohort	2011 to 2013	140	4.6	Sex and residency: Being
			2011 to 2013	81	2.61	male and living in urban
			2011 to 2013	40	1.27	WEIE HISK FACTORS.
Yizengaw E. et al., 2018 [31]			September 1, 2015 to August 31, 2017	423	6.5	
			September 1, 2015 to August 31, 2017	501	7.5	
Gebru G. et al., 2019 [32]	Tigray	Prospective cohort	01 January 2016 to 31 December 2016	368	42.7	
Mengistu H.T. et al., 2021 [26]		Retrospective cohort	November 2017 to May 2018	14,001	100	
			November 2017 to May 2018	14,001	97	
			November 2017 to May 2018	14,001	8	
Teklu G.G. et al., 2017 [33]		Retrospective cohort	January 1, 2012 to December 31, 2015	288	35.83	Sex: Being male was risk factor.
			January 1, 2012 to December 31, 2015	515	62.96	
			January 1, 2012 to December 31, 2015	747	89.75	
			January 1, 2012 to December 31, 2015	630	79.1	
Beyene T.J. et al., 2018 [29]	Oromia	Retrospective cohort	September 2013 to August 2014	655	135	
			September 2013 to August 2014	655	101	
			September 2013 to August 2014	655	86	
Ramos J.M. et al., 2015 [27]	SPPR	Retrospective cohort	11 September 2006–10 March 2010	91,683	74.5	

^a per 100, 000 population

in each of the Addis Ababa [28] and southern Ethiopia [27] regions, and each study only included one data point. Nevertheless, no studies from Ethiopia's eastern area were published.

Seven retrospective studies [18, 26, 27, 29–31, 33] and one prospective study [32] were included in the systematic review and meta-analysis. A total of 116,484 sample sizes are included in this investigation. The samples ranged from 40 [30] to 14,001 [26]. There were 1.27 [30] to 101 [29] cases of human rabies virus exposure for every 100,000 individuals, according to reports. All studies collected data between 2006 and 2018 using a facilitybased rabies virus exposure registration book (Table 1).

Incidence of suspected human rabies virus exposure

The pooled incidence of human rabies virus exposure was 54.03 (95% CI: 43.92–64.13) per 100,000 populations. High and significant heterogeneity was observed (I^2 =99.93%, *P*=0.000). The funnel plot (Fig. 2) and Egger's regression asymmetry coefficient [b: 12.57] (95% CI: 8.54–16.59, P-value=0.000) indicated publication bias. Studies were almost weighted approximately equal, with an individual weight ranging from 4.92 to 5.51% (Fig. 3).

Nonparametric trim-and-fill analysis

The incidence of suspected human rabies virus exposure, both unadjusted (observed) and adjusted (observed + imputation), was 54.03 (95 CI: 43.92–64.13) per 100,000 people (Table 2). Symmetry was visible in the funnel plot (Fig. 4).

Sensitivity analysis results

The results of the sensitivity analysis demonstrated that the meta-analysis's conclusion was unrelated to any specific trial and that the effect size remained constant. All of the studies' reported effect sizes matched the overall effect size discovered in a meta-analysis that did not include that particular study. The leave-one-out forest plot was another approach that was used to identify outlier studies. The overall effect size derived from all available studies (none excluded) was shown in this graphic as a vertical line. A shift from 48.99 (95% CL 40.42–57.55) per 100,000 population to 57.30 (44.77–69.84) per population was seen in the pooled estimate of probable human rabies exposure (Fig. 5).

Subgroup analysis

According to a subgroup analysis of the incidence rate by region, the Oromia region had the highest incidence rate, at 107.32 per 100,000 population (95% CI:80.20–134.45 per 100,000 population), while the Amhara region had the lowest, at 4.49 per 100,000 population (95% CI: 2.00–6.97 per 100,000 population) (Table 3).

Associated risk factors for incidence of suspected human rabies virus exposure

Sex and the incidence of human rabies virus exposure had a significant association in the included studies. Males were 1.67 (95% CI: 1.53–1.81) times more likely than females to have been exposed to the human rabies virus (Fig. 6).



Fig. 2 Forest plot of incidence of suspected human rabies virus exposure in Ethiopia, 2023



Fig. 3 Funnel plot for assessing the presence of publication bias on incidence of suspected human rabies virus exposure in Ethiopia, 2023



Fig. 4 The funnel plot of nonparametric trim and fill analysis on incidence of suspected human rabies virus exposure in Ethiopia, 2023

There was no publication bias in this meta-analysis, as seen by the funnel plot (Fig. 7) and Egger's regression asymmetry coefficient [b:-0.74] (95%:-3.10-1.59, P=0.533), which also showed no heterogeneity (I²=0.0%, P=0.94).

Residence

The incidence of probable human rabies exposure did not significantly correlate with residence. Significant heterogeneity was seen (I2=70.26% and P=0.03) in Fig. 8; however, publication bias was absent (Egger's test=0.5466) in Fig. 9.

Discussion

By extracting published articles, a systematic review and meta-analysis were conducted to determine the pooled incidence and identify risk factors for suspected human rabies virus exposure in Ethiopia.

The world's poorest regions are at the highest risk of contracting rabies due to limited access to post-exposure prophylaxis (PEP) and a lack of widespread adoption of domestic dog vaccination programs [36].

In this study, the pooled incidence of suspected human rabies virus exposure was 54.03 (95% CI: 15.24–31.65) per 100,000 populations. This is congruent with the studies

 Table 2
 Results of trim and fill analysis of incidence of suspected human rabies virus exposure in Ethiopia, 2023

Number of data points = 18	Studies	Incidence per 100,000	95% CI
Observed = 18	Observed	54.03	43.92-64.13
Imputed = 0	Observed + Imputed	54.03	43.92-64.13

conducted in Colombia (40.9/100,000 to 234.9/100,000 population) [39], Madagascar (42/100,000 to 110/100,000 population) [40] and Tanzania (58 per 100,000 population) [41], whereas this finding was higher than the study conducted in Yemen (14 per 100,000 population) [42]. Although rabies is a serious illness in Yemen, there is little data on the country's human rabies case count because of inadequate surveillance [43]. This could be underestimating the incidence of suspected human rabies virus exposure in Yemen.

In the trim and fill analysis of publication bias, there were similar incidences of suspected human rabies virus exposure for the adjusted (observed+imputation) and unadjusted (observed) cases. This similarity points to a low level of publication bias, which might be attributable to fewer missing studies that wouldn't significantly influence the effect size or, in the case of small effect sizes or low study variability, to imputation that might not substantially affect the total effect size [44].

The highest rate of suspected human rabies virus exposure (30.5%) in a single publication with a single data point was seen in the age range of 5-14 years [31]. According to four data points in a single publication, the age group over 15 years had the highest percentage of suspected human rabies virus exposure (57.6%, 62.5%, 65.0%, and 65.9%) [33]. This could be due to the fact that kids over five might spend the majority of their time outside the home. Because of this, they may be more susceptible to dog bites.

Dogs may mate more frequently in the fall and winter; therefore, dog bits may be at their peak during these seasons [45]. The seasonal variation in the incidence of suspected human rabies virus exposure was not documented, with the exception of one paper and two data points. With 30.2% of cases of suspected human rabies exposure in each of the two seasons under review, Autumn and Winter had the greatest incidence [31].

In subgroup analysis, the incidence rate approximately differs significantly between regions, which might be influenced by different observations. Even though the smallest sample size was reported from the Oromia region, the highest incidence rate was recorded in this region (107.32

				1	ncidence per 100000	
Omitted study					(95% CI)	p-value
Lombamo F.et al, 2020			-		54.50 [44.13, 64.87]	0.000
Yibrah and Damtie, 2015	5		•		57.03 [45.84, 68.23]	0.000
Yibrah and Damtie, 2015	5	-	•	_	57.19 [45.39, 68.98]	0.000
Yibrah and Damtie, 2015	5		•	-	57.30 [44.77, 69.84]	0.000
Yizengaw E. et al, 2018			•		56.95 [45.25, 68.65]	0.000
Yizengaw E. et al, 2018			•		56.88 [45.38, 68.38]	0.000
Gebru G. et al, 2019			•	-	54.69 [44.32, 65.07]	0.000
Mengistu H.T. et al, 202	1 —	•			51.30 [41.15, 61.45]	0.000
Mengistu H.T. et al, 2021	1 —	•			51.80 [41.46, 62.14]	0.000
Mengistu H.T. et al, 202	1	-			56.79 [46.18, 67.40]	0.000
Teklu G.G. et al, 2017			•	-	55.10 [44.71, 65.49]	0.000
Teklu G.G. et al, 2017	-	•			53.50 [43.17, 63.83]	0.000
Teklu G.G. et al, 2017	-	•			51.93 [41.66, 62.21]	0.000
Teklu G.G. et al, 2017	10	•			52.55 [42.26, 62.84]	0.000
Beyene T.J. et al, 2018		•			48.99 [40.42, 57.55]	0.000
Beyene T.J. et al, 2018	_	•			51.09 [41.97, 60.22]	0.000
Beyene T.J. et al, 2018	-	•			52.02 [42.65, 61.39]	0.000
Ramos J.M. et al, 2015	-	•			52.82 [42.52, 63.11]	0.000
	40	50	60	70		

Note: Leave one-out sensitivity analysis was from Random-effects model

Fig. 5 A forest plot depicting leave-one-out sensitivity analysis to estimate pooled incidence of suspected human rabies virus exposure in Ethiopia, 2023

Subgroup	Number of observations	Sample size	Incidence Per 100,000 (95% Cl)	Heterogeneit statistics	y
Region				²	P-value
Tigray	8	16,181	64.24 (35.07–93.42)	99.71%	0.000
Amhara	5	1185	4.49 (2.00–6.97)	98.94%	0.000
Oromia	3	655	107.32 (80.20–134.45)	99.74%	0.000
Addis Ababa	1	6927	46 (40.90–51.10)	-	-
Southern Ethiopia	1	91,683	74.50 (69.01–79.99)	-	-

Table 3 Subgroup analysis for incidence of human rabies virus exposure in Ethiopia



Note: Weights were from Random-effects model analysis

Fig. 6 Forest plot of being male as a risk factor for human rabies virus exposure in Ethiopia, 2006-2018



Fig. 7 Funnel plot for assessing the presence publication bias



Fig. 8 Pooled risk ratio between residence and incidence of suspected human rabies virus exposure in Ethiopia, 2023



Fig. 9 Funnel plot to assess publication bias of risk ratio between residence and incidence of suspected human rabies virus exposure in Ethiopia, 2023

per 100,000 population), whereas the lowest incidence rate was observed in the Amhara region (4.49 per 100,000 population). This might be due to a difference in the number of dogs, dog handling, or surveillance system. There could be variations in the surveillance of animal diseases because of incomplete, sensitive, and limited information exchange, which is mostly caused by the country's weak One Health [46]. This is also because of variations in both geography and culture. For example, due to cultural differences, lack of knowledge, or difficulty accessing medical care, people in rural Ethiopia who have been exposed to rabies frequently choose to consult traditional healers for the disease's diagnosis and treatment. There is a possibility that the prevalent customs surrounding the management of human rabies exposure may hinder the process of seeking medical attention [34], leading to an underestimation of the true number of exposures in the Amhara region.

Two articles with five data points each show that males had the highest sex-specific incidence rates: 8.1 per 10,000 population [31], 43.8, 80, 89.2, and 114.4 per 100,000 population [33]. Sex was also statistically significantly associated with the incidence of suspected human rabies virus exposure. Being male was almost two times more risky to be exposed to the human rabies virus as compared to being female. This is consistent with the studies conducted in the Netherlands [39] and Zimbabwe [40]. This might be justified as: most of the time, males spend their time in the field, whereas, due to religious and cultural perspectives, females spend their time indoors.

In developing nations, rabies is a problem for urban populations due to the large number of stray dogs [34]. In one article with two data points, living in urban areas had the highest residence-specific incidence rates: 10.5 and 12.2 per 100,000 population [31], whereas residence was not statistically significant.

Limitations

This study tried to calculate the pooled incidence of suspected human rabies exposure. However, the results might be underestimated because all of the included studies were conducted at health facilities. Facility-based studies may not accurately represent community-level factors like public health efforts and local culture and may overlook vaccination rates and stray dog numbers due to smaller sample sizes.

Conclusions

The estimated pooled incidence rate showed regional variations and was reported as high. In Ethiopia's north, a comparatively greater number of studies were carried out. Exposure to the suspected human rabies virus and sex were significantly associated. Enhancements should be made to measures that prevent human exposure to the rabies virus, such as dog vaccination, dog population control, rabies control implementation, public awareness campaigns, and epidemiological surveillance systems.

Abbreviations

CI Confidence interval

- RR Risk ratio
- S.E Standard error
- WHO World health organization

Supplementary Information

The online version contains supplementary material available at https://doi. org/10.1186/s12879-024-10389-x.

Supplementary Material 1: Annex I. Searching strategy. Annex II. Annex III. Annex IV. Data extraction Tool.

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Authors' contributions

All authors reviewed the manuscript. M.K. and S.W. wrote the main manuscript text. A.H. prepared all Figs. 1, 2, 3, 4 and 5. D.T. prepared Tables 1, 2 and 3 and and abstract.

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Data availability

The data sets generated during the current study are available from the all authors upon reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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