REVIEW ARTICLE

Epidemiology of animal bite in Iran: A Systematic review and meta-analysis

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Background: Despite a lot of efforts made in the rabies health-care system, Iran is still in an endemic region and millions are spent annually to prevent rabies. **Materials and Methods:** Searching in national and international databases has been performed. The preferred reporting items for systematic reviews and meta-analyses protocol were followed. To assess heterogeneity, the I-index was calculated. In addition, sensitivity analysis was performed by the remove-one method. The publication bias was also investigated by Egger's regression test, and the trim and fill method. To perform a meta-analysis, CMA version 2 software was used. **Results:** Totally, 33 studies with 250,980 animal-bite cases were meta-analyzed. A summary estimate of the incidence of 1200 per 100,000 population (95% CI 1000, 1500) with a mean age of 29.97±15.13years (95%CI: 29.33, 30.61) was estimated. The rate in men was higher 76.7% (95%CI 74.7%, 78.8%) than in women and in the rural 49.7% (95%CI: 42.8%, 58.6%) was equal in the urban. Most bites occurred in the spring and summer 20.5% (95%CI: 16.1%, 25.9%). The highest of job-related bites was in students 20.1% (95%CI: 19%, 23%). The highest rate of bite location and the animal type were estimated in the order of lower limbs and by dogs respectively. The rate of complete vaccination 61% (95%CI: 43%, 76%) and immunoglobulin injection 39% (95%CI: 22%, 59%), were estimated respectively. **Conclusion:** Estimates reveal that there has been little change in the animal bites over the years. It is necessary to take special actions to control the disease at the national and international levels.

Key words: Animal bite, epidemiology, incidence, Iran, prevalence, rabies, trend

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INTRODUCTION

The World Health Organization (WHO) reported 59,000 deaths annually from dog-related rabies in its third global report. Most deaths, approximately 59.6%, occur in Asian and African countries because of poor facilities and health-care systems. The reports suggested that "more than 99% of the disability-adjusted life year is due to premature death." However, rabies-related costs vary in different parts of the world.[1]

The total economic burden of dog-related rabies was estimated at $8.6 billion based on the probabilistic decision tree model. More than 55% of all costs are related to premature death and individuals' reduced production and income. Twenty percent of the costs include direct costs of treatment, and 20% include costs of prevention. Other costs include costs related to vaccination and other measures regarding the animals in the region.[1] Rabies is endemic all over the world, except for a few areas. Ninety percent of all deaths occur in low-income areas with inadequate facilities and health-care systems. The increased dog population, urbanization, and lack of sanitation among overcrowded rural communities are considered to be critical risk factors in Asia and African countries. Conversely, European countries have been able to control the disease through compulsory vaccination of animals, especially dogs. Postexposure treatment costs and the costs of the dog rabies control program are the most important determinants of the social costs of rabies in endemic

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countries. In addition to the financial costs of preventing and treating animal bite cases, the psycho-social consequences of animal bites and the remained scars can highly affect the life of the animal-bitten individual and his/her family.[1,2]

Rabies is endemic in Iran and is widespread in many provinces of the country in the forms of wild and urban. Rabies frequently infects domestic animals. The mortality due to this disease in Iran is Two to six deaths per year. In Iran, billions are spent annually to prevent rabies, and this amount is almost spent on all infectious diseases that exist in the country.[2]

The history of rabies health-care system in Iran

The control and health-care program of rabies was established in 1920 by the Pasteur Institute of Iran, and the institute started treating and controlling various infectious diseases, including rabies. Until 1954, only vaccination was performed to treat rabies and animal-bitten individuals whose mortality was also high. In 1954, the Pasteur Institute of Iran reduced mortality with a new treatment and the simultaneous use of the vaccine and immunoglobulin. This experience led to the entrance of the simultaneous use of vaccines and serums to the global guidelines for the treatment of rabid-bitten individuals. For this reason, since 1973, the Pasteur Institute's rabies laboratory has been selected as the reference center of the WHO.[3,4]

The issue of rabies elimination has been seriously raised countrywide since 2015. Among the measures taken until 2016 was to increase the number of health-care centers that implemented caring for and training rabid-bitten individuals, to 700. Vaccination of domestic dogs was also another measure. According to the report by the Iranian Veterinary Organization, there are about 900,000 domestic dogs in Iran, of which only 45% have been vaccinated so far. Based on the WHO, this rate should reach 70%.[1,3]

Despite the long history and efforts made in the rabies health-care system in Iran, there are challenges in disease management, and the animal-bitten cases are still high, and Iran is in the endemic region.

The statistics in some areas for several years, including Sharifi's study in Lorestan province, Vahid By's study in Golestan, Amiri's study in Najafabad, and Saeed Hosseini's study in Bardsir, Kerman province, show an increasing trend.[5,8] A review study by Ebadi *et al*. has recently examined the disease trend from 1993 to 2013. The overall incidence rate was estimated at 13.20/1000 population.[9]

Given the increased cases of animal bites as well as the increased population of stray dogs, the climatic and diverse conditions of the country, on the one hand, and being among the endemic neighboring countries, on the other hand, the control of this disease has become challenging.

The present study was conducted to estimate the prevalence of animal bites to provide up-to-date statistics in the country to improve policy makings and optimal allocation of resources for disease prevention, management, and control on a large scale.

MATERIALS AND METHODS

The current study was performed based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.

Eligibility criteria

We included all observational studies of the original design type, with the research population, consisting of all ages; in Persian or English. Full-text articles of conferences which had obtained the required score in quality evaluation using the strengthening the Reporting of observational studies in epidemiology (STROBE) criteria, were reviewed. The search time was from the beginning of 2016 to 2021.

Information sources and search strategy

The search was conducted in domestic and electronic databases, including PubMed Central, Google Scholar, Scopus, Web of Science, Magiran (Persian), and Scientific Information Database (Persian). Searching was performed through keywords ((Incidence OR prevalence OR epidemiology OR trend OR surveillance) AND (animal bite OR rabies OR rabidity) AND ("IRAN")) as combined and using the relevant Booleans.

((“epidemiology”[Subheading] OR “epidemiology”[All Fields] OR “incidence”[All Fields] OR “incidence”[MeSH Terms]) OR prevalence [All Fields] OR (“epidemiology”[Subheading] OR “epidemiology”[All Fields] OR “epidemiology”[MeSH Terms]) OR trend [All Fields] OR (“epidemiology”[Subheading] OR “epidemiology”[All Fields] OR “surveillance”[All Fields] OR “epidemiology”[MeSH Terms] OR “surveillance”[All Fields])) AND (((“animals”[MeSH Terms: noexp] OR animal [All Fields]) AND (“bites and stings”[MeSH Terms] OR (“bites”[All Fields] AND “stings”[All Fields]) OR “bites and stings”[All Fields] OR “bite”[All Fields])) OR (“rabies”[MeSH Terms] OR “rabies”[All Fields]) OR rabidity [All Fields]) AND “IRAN”[All Fields] AND (“January 1, 2016” [PubDate]:“May 31, 2021” [PubDate]).

Study selection process

The search results were reviewed by two independent researchers in several stages based on the PRISMA

algorithm. In the identification step, the studies were filtered based on relevant and duplicated titles. In the screened step, the abstract of studies was checked for eligibility and finally, full-text relevant articles were assessed preciously, and conflicting cases were resolved. The final studies were selected for quality assessment and meta-analysis.

Quality assessment of studies

To evaluate the quality of the method and ensure the validity of the studies included in the meta-analysis, items of Strengthening the Reporting of Observational Studies in Epidemiology appraisal (STROBE) tool (title and abstract, objectives, statistical methods, study size, participant results, outcome data,.) was used. The maximum score of quality was determined 10 points and the minimum was zero. Three ranges of points for methodology quality were determined by the researchers. A score of 0 to 3 is low quality, 4 to 7 is average, and above 7 is good. Studies with a quality score of average or more were included in the analysis.

Data collection process and data items

A Microsoft Excel spreadsheet was predesigned for beginning the data extraction process. Afterwards, data extraction forms were completed by two independent researchers. Data items included, first author name, area (city/county/province), publication year, sample size, animal bite number, gender, age, occupation, and animal type, and bite location, place of residence, biting season, and history of immunization. To ascertain correctly this process, according to the extraction form, the inputted data were reviewed, revised, and edited several times using two independent researchers.

Statistical analysis

A random effect model was used to estimate the summary incidence of animal bites and the pooled weighted effect size of all subgroup variables (Age, gender, and occupation, type of animal, bite site, residence, bite season, and immunization history).

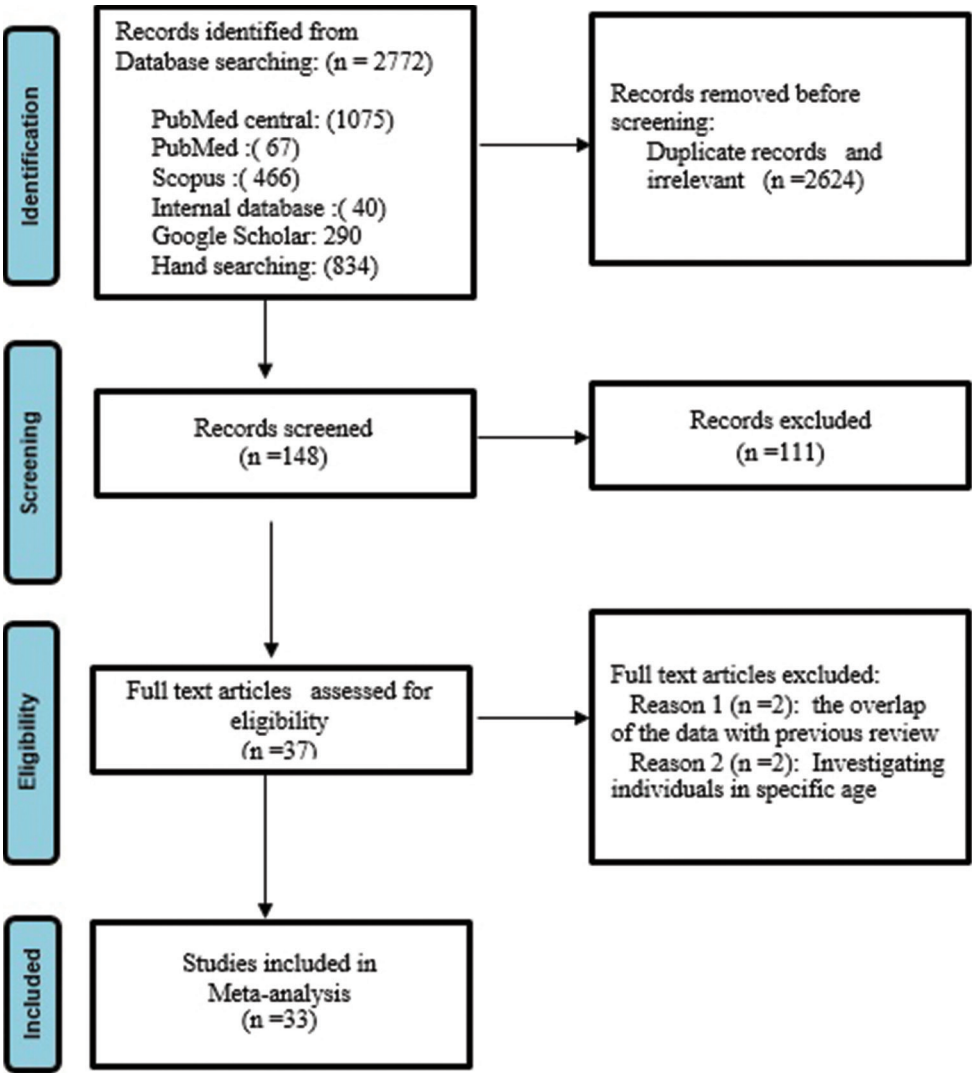

Figure 1: PRISMA flow chart of search and included studies of the review

Table 1: Characteristics of the studies that included in meta-analysis

Author/publication year	City/County	Province	Animal bite cases	Prevalence per 100,000	Ref
By V, 2021	Golestan	Golestan	33996	455	5
Hosseini S, 2017	Bardsir	Kerman	1500	433	8
Sharifi Ac, 2016	Lorestan	Lorestan	43892	223	6
Amiri S, 2020	Najafabad	Isfahan	4104	210	7
Abbasi A,2017	Golestan	Golestan	10810	289	15
Alian D, 2021	Jahrom County	Fars	3913	363	16
Esmaeilzadeh F, 2017	Shiraz university	Fars	7097	154	17
Hatami H, 2017	Shemiranat	Tehran	1875	342	18
Hosseini, SM 2019	Sari	Mazandaran	6560	353	19
Hosseini SA, 2019	Mazandaran	Mazandaran	32469	153	20
Janatolmakan, M 2020	Kermanshah county	Kermanshah	5618	119	21
Karegarian-M, S 2019	Fereydunshahr	Isfahan	2359	448	22
Karimi, A 2019	Abadeh	Fars	1407	190	23
Kassiri H, 2020	Khorramshahr	Khuzestan	733	147	24
Kassiri H, 2017	Abdanan	Illam	309	258	25
Khazaei S, 2018	Nahvand district	Hamedan	1448	265	26
Khazaei S,2016	Khalilabad County	Khorasan Razavi	397	384	27
Moghadami M, 2017	Jahrom city	Fars	2010	237	28
Mohammadzadeh A,2017	Hamedan county	Hamedan	14327	272	29
Mohebbi- N SM,2017	Bandar Abbas County,	Hormozgan	2887	85	30
Roudi K S, 2018	Khaf county	Khorasan Razavi	553	133	31
Sarbishgi- M, M 2016	Sarbisheh County	southern Khorasan	622	285	32
Shamshirgaran SM,2017	Maku County	West Azerbaijan	2232	250	33
Rahmanian V, 2020	Larestan County	Fars	375	170	34
Babazadeh, T 2016	Chaldoran	West Azarbayjan	1724	541	35
Molka A,2017	Galikash	Golestān	1712	540	36
Zohrezad, A 2019	Mashhad & Torbat Heydariyeh	Khorasan Razavi	45735	355	37
Dehghani A, 2019	Yazd county	Yazd	8545	168	38
Ghasemi, M 2016	Kermanshah county	Kermanshah	5031	114	40
Mohammadi, N 2017	Sanandaj	Kurdistan Province	1855	67	41
Amiri, M 2019	Khominishahr	isfahan	2242	302	43
Dehgorji NR, 2019	Bandar Astara city	Gilan	150	291	44
Hamid Kassiri2018	the East of Ahvaz	Khuzestan	2493	123	45

To calculate the incidence per 100,000 population, the census population of the National Statistics Center of Iran in 2016 in each region (city/county/province) was used (10). Given that the reports of most of the studies were provided during a few years, firstly, the calculations were performed for years that did not overlap with previous studies, and secondly, the average annual calculations were performed per 100,000 population [Table1].

The calculations in the subgroups were based on the proportion method. The proportion method is based on writing two ratios. This study for each subgroup was calculated as follows:

(number subgroup: ex; female)/total number animal bite) = (percent/100).

Finally, the summary (pooled) effect size was estimated by a meta-analysis with Logit transformation and the significance level was determined at $p<0.05$. To, outcome number, sample size, and calculation Event rate, Logit event rate, Std Err were used For variables of incidence, gender, occupation, animal type, bite location, place of residence, biting season, and history of immunization, and the mean and standard deviation, sample size, and calculation Std Err were performed for the age variable. The pooled weighted effect size was shown by forest plot with 95% CI for each study subgroup variable.

To evaluate heterogeneity across studies, the I-index was calculated, and analyzes were performed in all subgroups, too. I2 percentage of ≤40% shows low heterogeneity, and ≥75% considers high heterogeneity. Meta-regression analysis was performed to identify sources of heterogeneity. Sample size, publication year, and quality of study score were considered covariates.

Sensitivity analysis was performed for each study, as well as for all variables, by the remove-one model, and the forest plot was drawn for each variable separately.

Table 2: Summary estimate and 95% confidence interval for each variable and subgroups

Variables	Subgroup	Number studies	Effect size and 95% CI			Test of null (two-tail)	
			Point estimate	Lower limit	Upper limit	*Z*	*P*
Prevalence (/100,000)	Total	33	264	227	300	14.251	0.00
Gender	Female	30	0.22	0.21	0.24	−232.59	0.00
	Male	30	0.78	0.76	0.80	235.28	0.00
Age	Female	8	30.48	29.00	31.97	913.43	0.00
	Male	9	29.21	27.63	30.80	808.54	0.00
	Total	15	29.97	29.33	30.61	1525.75	0.00
Residency	Rural	28	0.55	0.48	0.62	90.05	0.00
	Urban	28	0.44	0.38	0.51	−90.48	0.00
Occupation	Child	12	0.10	0.06	0.16	−159.67	0.00
	Employee	24	0.05	0.03	0.08	−233.85	0.00
	Farmer and rancher and Cattleman	28	0.12	0.10	0.14	−263.40	0.00
	Free	23	0.21	0.15	0.29	−115.65	0.00
	Housewife	28	0.14	0.12	0.15	−278.06	0.00
	Other	24	0.12	0.09	0.16	−185.45	0.00
	Student	27	0.21	0.19	0.23	−192.49	0.00
	Worker	17	0.09	0.05	0.14	−124.51	0.00
Season	Fall	21	0.19	0.15	0.23	−156.93	0.00
	Spring	23	0.23	0.18	0.29	−178.82	0.00
	Summer	21	0.21	0.17	0.26	−139.42	0.00
	winter	20	0.18	0.14	0.22	−156.56	0.00
Animal type	Cat	30	0.13	0.11	0.16	−245.82	0.00
	Cow, goats and sheep	12	0.01	0.01	0.01	0.00	357.60
	Dog	32	0.81	0.77	0.84	236.92	0.00
	Horses, ass, camels	14	0.02	0.01	0.04	−118.35	0.00
	Mice (types of mice, guinea pig, rabbit, hamster, squirrels)	13	0.01	0.01	0.02	−132.77	0.00
	Other animals	27	0.02	0.02	0.02	−213.28	0.00
	Reynard, fox, wolf, Jackals	15	0.03	0.01	0.07	−90.26	0.00
Site bite	Chest, abdomen, back	22	0.05	0.04	0.08	−215.02	0.00
	Head, face, and neck	24	0.03	0.02	0.05	−202.71	0.00
	Lower limbs	27	0.49	0.45	0.54	37.45	0.00
	Other organs	5	0.64	0.13	0.95	−53.77	0.00
	Upper and lower limbs	5	0.06	0.00	0.54	−20.98	0.00
	Upper limbs	27	0.36	0.32	0.41	−98.02	0.00
Vaccine history	Complete vaccine	16	0.61	0.43	0.76	−58.36	0.00
	Immunoglobulin	14	0.39	0.22	0.59	65.44	0.00
	Incomplete vaccine: 1 or 2 dose	2	0.80	0.01	1.00	−28.04	0.00
	Incomplete vaccine: 3 dose	4	0.49	0.11	0.88	−57.32	0.00

CI=Confidence interval

Sensitivity analysis was shown the impact of each study on pooled effect size and compared it with the overall pooled estimate.

To perform a meta-analysis, Comprehensive Meta-Analysis (CMA) version3 (Biostat, USA) software was used.

Estimation of bias

The funnel plot was drawn for each variable and was confirmed using Egger's regression test. The sensitive trim and fill method was also used for missing data. The results of the adjusted analysis were compared with the initial summary estimate.

RESULTS

Study selection and its characteristics

Based on the keywords and search strategy described in the method section, the number of 2772 articles were retrieved that based on the steps of the PRISMA model, after eliminating duplicates (2624) and the lack of relevance of the article title and abstract (111), 37 articles were obtained that were examined regarding their full texts. Almost all 37 articles had the minimum quality required for inclusion in the analysis [Figure 1]. After assessing the full-text articles, the following articles (4) were deleted for the reasons presented.

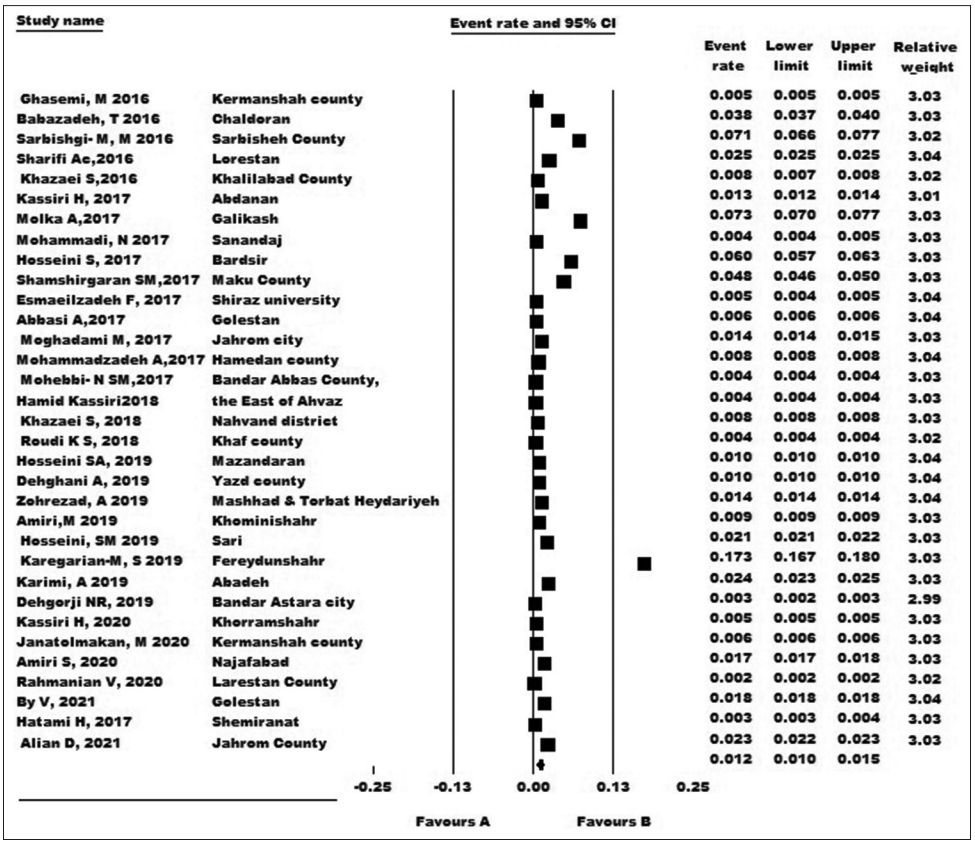

Figure 2: Pool (summary) estimate forest plots of overall incidence

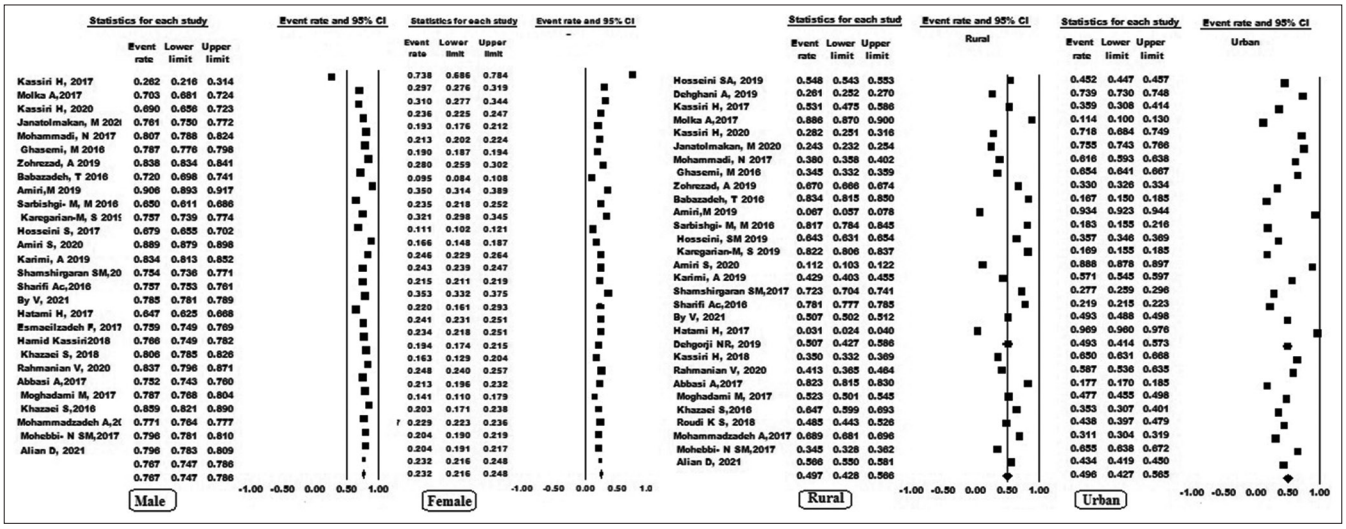

Figure 3: Pool (summary) estimate forest plots of gender, place of residence

- Ghaffari Fam's article (2016) due to the overlap of the data with Hosseini's study (2019) in Mazandaran[11]
- Nikbakht's article due to investigating only individuals under 18 years old[12]
- Barzkar's study (2016) due to investigating only individuals under 10 years old[13]
- Ruhollah Dehghani's study (2016) due to the overlap of the data with the publications in 2013 by the same author[14]
- Case studies and all the conference articles that did not have full text were excluded from the study's final analysis.

Finally, 33 studies were entered into quantitative evaluation and meta-analysis.[5-7,15-45] Findings of studies characteristics in each province/county/city, separately, are shown in Table 1.

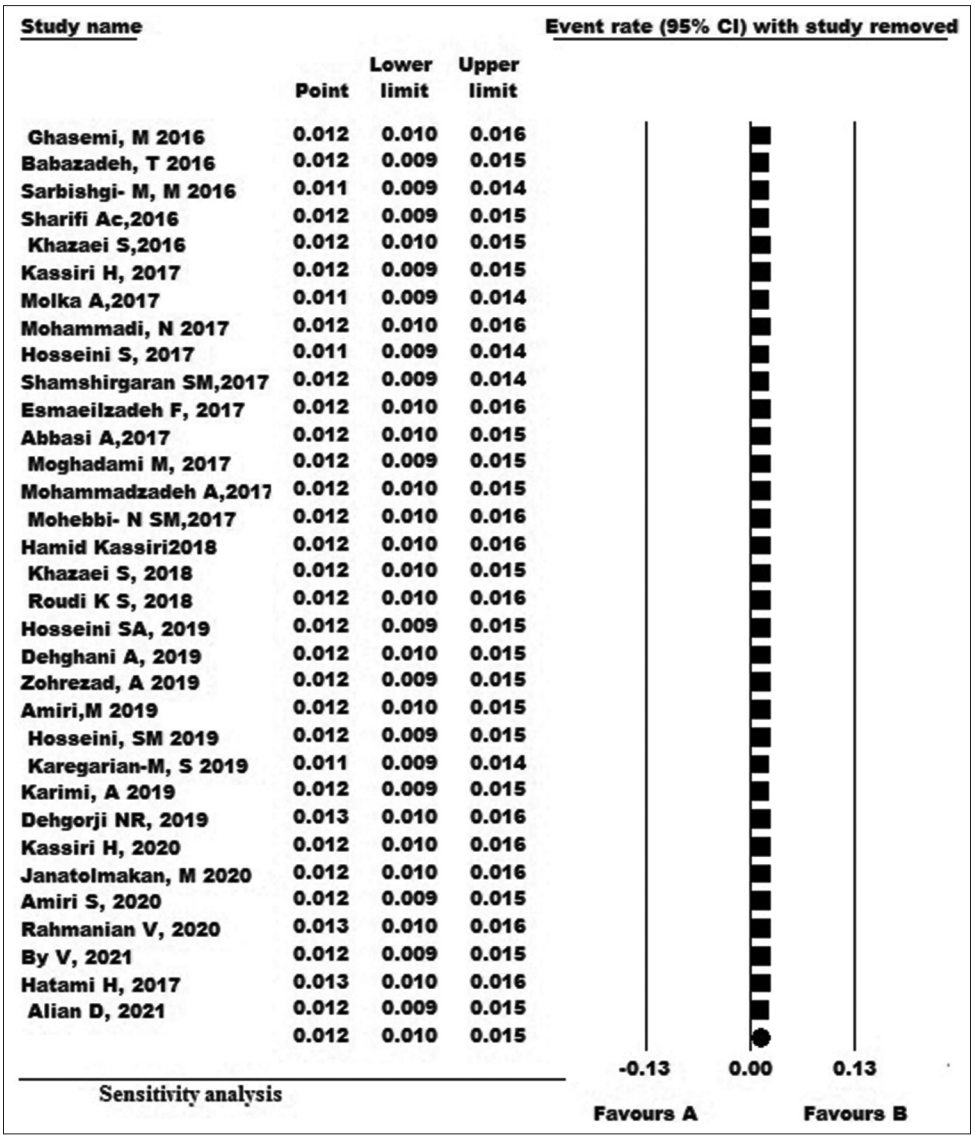

Figure 4: Sensitivity analysis of the meta-analysis for each of the included studies for each variable

The results of the summary estimate of variables in a 95% confidence interval were shown in Table 2. A Forest plot was drawn to show a summary estimate in a 95% confidence interval and heterogeneity of each study.

Quality assessment of studies

In evaluating the quality of studies with the STROBE checklist, out of 33 articles, 2 articles with a score of 9, 5 articles with a score of 7, and 2 articles with a score of 8 were classified as high quality. 10 articles with a score of 6 and 2 articles with a score of 5 were classified in the medium quality range. The quality score of the articles was crosschecked by two researchers. No articles were classified as low quality and were not excluded from the meta-analysis.

Meta-analysis results: Summary estimate of variables

The present study was performed by entering and analyzing 33 studies and 250,980 cases of animal bites. Studies included all parts and climates of the country. Forest plots for each variable and its subgroups were also shown. The summary estimate of incidence in the adjusted values was estimated at 1200 per 100,000 population (95%CI: 1000, 1500) [Figure 2].

The summary estimate of the mean age in the total population included 30 years (95%CI: 29.33, 30.61). The mean age of the bite was higher in women 30.84years (95%CI: 29, 31.97) than in men 29.21 years (95%CI: 27.63, 30.79) [Supplementary Figure 1].

Findings regarding the subgroup of gender in the analysis of 30 studies showed that the summary estimate in men was to be 76.7% (95%CI: 74.7%, 78.8%) higher than in women 23.2% (95%CI: 21.6%, 24.8%) [Figure 3].

Findings regarding the subgroup of the place of residence in the random effect model with the analysis of 30 studies

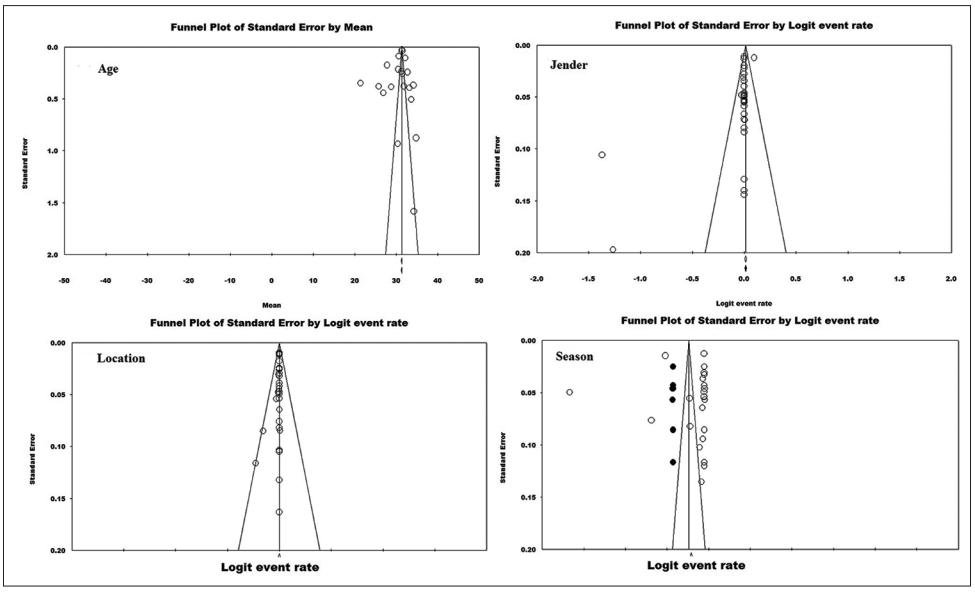

Figure 5: Funnel plots for observed studies and imputed studies of age, sex, location, and season variables (trim and fill test)

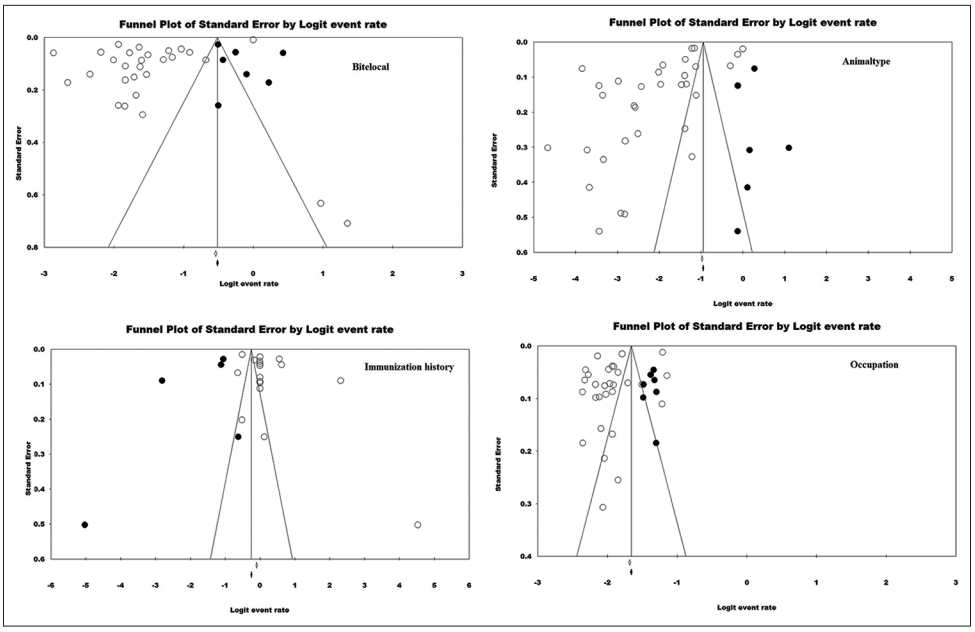

Figure 6: Funnel plots for observed studies and imputed studies of occupation, animal type, site bite, and vaccine history variables (trim and fill test)

showed that the proportion was equal in the rural and urban 49.7% (95%CI: 42.8%, 58.8%) [Figure 3]. Based on the findings regarding the proportion of the biting season variable in 23 studies, most of the bites with a summary estimate of 23% (95%CI: 18%, 29%) occurred in the spring [Supplementary Figure 2].

Findings regarding the subgroup of occupation-related bites with the analysis of 28 studies were highest in students with a summary estimate of 21% (95%CI: 19%, 23%), freelancers 21% (95% CI: 15%, 29%), and then housewives, respectively [Supplementary Figure 3].

The highest proportion of bite location was calculated by reports in 27 studies with a summary estimate of 49% (95%CI: 45%, 54%), in the lower limbs [Supplementary Figure 4]. According to the reports in 32 studies, the highest of bites in terms of animal type had occurred by dogs with a summary estimate of 80.7% (95%CI: 77.3%, 83.7%) [Supplementary Figure 5].

In the investigation of the history of immunization, 16 studies with a summary estimate of 61% (95%CI: 43%, 76%), reported a complete history of vaccination. The investigation estimated the proportion of immunoglobulin

injections in 14 studies is 39% (95%CI: 22%, 59%). The reports on treatment history were not provided completely in most studies, and the reports were incomplete [Supplementary Figure 1].

Sensitivity analysis

The forest plot of sensitivity analysis of the variables was shown by estimating the combined effect The results of sensitivity analysis with the omission of each study(the remove-one model) did not show any significant changes in the final effect size of most variables, indicating the reliability of the meta-analysis [Figure 4]. The variables of history of vaccination and animal type with the omission of some studies showed slight changes in the combined effect estimate.

There was a change in the combined effect of the history of vaccination variable 47% (95%CI: 47%, 48%), with the omission of Vahid By's study (2021) in Golestan to 53% (95%CI: 52%, 54%), and in the animal type variable 27% (95%CI: 27%, 28%) with the removal of Mohammadzadeh's study (2017) to 22% (95%CI: 21, 23%) (5, 29)

Heterogeneity and meta-regression

The heterogeneity in the study variables ranged from I2=0 in the place of residence variable to I2 = 86% in the gender variable. Meta-regression was performed to identify sources of heterogeneity using possible moderator variables. Census sample, quality study score and publication year considered as the moderator. R2 was estimated for the effect of the moderators on heterogeneity. The model was significant for the census sample and quality study score (p-value≤ 0.05). 33% between study variance was explained by the model (R2 = 0.32, p-value =0.0001) [Supplementary Figure 6].

Publication Bias and missing result

Funnel plots depict the results of publication bias in both initial and adjusted modes by the trim and fill method [Figures 5 and 6].

The funnel plot is almost symmetrical in two initial and adjusted modes by the trim and fills method for the overall incidence of an animal bite, Age, place of residency, and gender.

The results of the Egger's regression test at the level of 0.05 in random and fixed mode (p-value = 0.461) for overall incidence, (p-value = 0.214) for age, (p-value = 0.088) for the place of residence, and (p-value=0.126) for gender was not significant, which indicates no bias.

The summary estimate was calculated at 1200 per100000 (95%CI: 1200, 1500) in the overall estimate and was 1500 per100000 (95%CI: 1200, 1800) in the adjusted variable with 4 missed studies. Egger's test not confirmed bias.

A funnel plot is not symmetrical for a history of immunization, Animal type, local bite, occupation and season, and it is also confirmed bias by regression test (p-value≤ 0.05). Egger's regression test did not confirm bias in the season (p-value=0.088). The summary estimate of the missed studies was the same in initial and adjusted modes or was slightly different in the random effects the combined estimate was calculated at 13% (95%CI: 11%, 15%) in the occupation variable and was 14% (95%CI: 12%, 16%) in the adjusted variable with 7 missed studies.

The combined estimate was calculated at 56% (95%CI: 50%, 62%) in the history of immunization variable and 64% (95%CI: 54%, 71%) in the adjusted variable with 5 missed studies. Egger's test was estimated at p-value = 0.051.

The combined estimate was calculated at 49% (95%CI: 42%, 56%) in the local bite variable and 39% (95%CI: 31%, 49%) in the adjusted variable with 7 missed studies. This was estimated at 10% (95%CI: 7%, 13%) in the animal type variable and was 14% (95%CI: 11%, 18%) in the adjusted variable with 6 missed studies.

DISCUSSION

Despite the efforts made to promote the rabies healthcare system in Iran, there is still an important and costly healthcare challenge in the country and Iran is still in the endemic region.

This systematic review and meta-analysis aimed to calculate the pooled incidence of animal bites to provide information to decision-makers for effective interventions.

The overall summary incidence per 100,000 population using the analysis by the random method in 33 studies was estimated at 1200 per100000 (95%CI: 1200, 1500) population. Compared to previous studies, this rate did not show a noticeable decrease in recent years despite the great efforts of the country's health system and budg*et al*location to control it. Although there is a possibility of underestimation in some parts of the country.

Relying on both summary and point estimates, most of the studies entered into the analysis of the present study showed that, in the most optimistic case, little change has occurred in the prevalence of animal bites in the country over the years. In many parts of the country, such as Golestan and Isfahan and West Azerbaijan provinces, the prevalence is much more than the summary estimate and requires local attention and care.[5,7,22,33]

Also, looking at the statistics of several years, it is found that there has been an increasing trend in most provinces, as Sharifi's study in Lorestan province in 2009 reported a prevalence of 208 and another research by the same author in 2013 and 2014 reporting the prevalence of 239 and 260 per 100,000 population.[6] In Vahid By's study in Golestan, the values showed an increase from 570 in 2017 to 652 in 2020(5). Also, Amiri's study (2012) in Najafabad increased by 206 in 2016 and by 214 per 100,000 individuals.[7] There was also an increase in Bardsir, Kerman province.[39] In some areas such as Isfahan, and Mazandaran, these values were variable, but there was no significant decrease.[19,20,22]

We had an increase in the age of bite in the present study.[9] The mean age of bite was higher in women than in men. The study of Babazadeh in Chaldoran and the study of Shamshirgaran in Mako, West Azerbaijan province, showed lower ages of bite compared to the national estimate.[33,35]

The prevalence was higher in men than in women. The findings were consistent with Ebadi's review study. In Ebadi's study, the prevalence was three times higher in men than in women.[9] Regarding the comparison of the different parts of the country, in a few parts such as Sarbishegi's study in Sarbisheh, North Khorasan province, this rate was lower in men.[32]

In investigating the place of residence in the reports of 30 studies, 12 studies reported the rates in the city more than in the village. It was shown that the rate in rural areas was nearly equal in urban areas. Although, given that in most previous studies the number of reports in the villages was many times higher than in the cities. In the present study, the findings showed that the distance between events decreased in the village and the city.[9] there is a clear question in Iranian society "Is this change related to the conditions and the interest of urban residents in keeping domestic animals in recent years or due to a lack of reporting in some rural areas?" In response to this question, a study should be conducted to determine the dimensions of the issue.

Regarding the animal type, most cases of bites (81%) were reported related to dogs; then, followed by cats and domestic animals, including horses, donkeys, and camels, which was in line with Ebadi's study.[9] Numerous studies, such as Ebadi's study have recently shown that most bites occur by dogs and domestic animals, and given that having animals at home in urban areas in Iranian society is increasing.

Regarding the occupation, the highest value was reported in students and freelancers, and then in housewives. According to Ebadi's study, students were the most injured, followed by housewives and farmers. Comparing the rates of different parts of the country as with national estimates indicated that the prevalence in the studies of Babazadeh in Chaldoran, Rahmanin in Larestan, and Kargarian in Fereydunshahr in farmers was several times the summary amount.[22,34,35]

In the assessment of bite location, the most bite location was the lower limbs (45%), which is consistent with the results of Ebadi's study as well as that of most parts of the country.[9] In investigating the biting season, the highest prevalence in spring was 23%, which was consistent with the results of Ebadi's study. Rudi, Rahmanian, Mohebbi, and Kasiri recorded the highest values in winter.[25,30,34]

The results of the present study were also consistent with the results in this endemic neighbouring country. To this end, we take a look at neighbouring countries.

Findings from Oztoprak's study in southwestern Turkey showed that the mean age of suspected rabies cases was 30.04 ± 19.63 years. The highest prevalence was reported in men. Ninety-one per cent of suspected rabies cases occurred in cities. Dogs were the main source. 79.7% received prophylaxis after exposure. The results of the present study were also consistent with the results in this endemic neighboring country.[46]

The results of the review study by Taghreed Alaifan in Arab countries of the region showed that dogs were the main source in most Arab countries studied, except for Oman, where most rabies cases occurred in foxes, and most cases of human rabies have been reported in children less than 15 years of age.[47] Algeria had the highest prevalence of 131 cases per year. However, the author claimed that according to the findings of Samy Kasema's study rabies was still a public healthcare problem in Saudi Arabia and that dogs and camels were the main sources.[48]

The results of a review study by Farida Bibi Mughal1 in Pakistan, another endemic neighbouring country, showed that rabies was a common disease increasing daily. Also, there were many obstacles to controlling rabies in Pakistan. Lack of awareness and improper vaccination of dogs were among the most important obstacles.[49]

The findings of Thane Muhsen's study in Iraq showed that there were 11,600 cases of animal bites. Most bites by stray dogs were 11577 cases (99.8%), and men were more affected than women. The bite location was mostly the lower limbs.[50]

In a review study in developing countries, Bayu Begashaw pointed to unrealistic and less realistic records due to poor information systems in these regions. He showed that 60%

of the age distribution of animal-bitten individuals deviated to young ages (mean age = 9 years).[51]

Findings of a study by Farah Asad Mansuri1 at Karachi Hospital showed that 83% of the victims were male and 52.4% were under 15 years old. Individuals' knowledge regarding rabies was very poor and 91% of people were unaware that rabies could result after a dog biting.[52]

Kumar in Tamilnadu in rural areas of India showed that the prevalence of dog bites in the general population occurred at 31.1 per 1000 population. Children under 15 years old (RR = 1.86) and those with low socioeconomic status (SES) (RR = 2.54) were more vulnerable to dog bites. The results of the study also showed that there was very little awareness regarding the method of caring for rabies caused by domestic animals.[53]

Based on the findings of Ngugi's analysis conducted on 7,307 cases of rabies for 6 years in Kenya, the mean age was 22 years. Fifty-five per cent were men. Ninety-three percent of bites were caused by dogs. Forty percent of people received at least three doses of the vaccine. The incidence rate was reported at 289 percent per 100,000 individuals.[54]

The rates are almost consistent in different countries, and all cases suffer from ineffective disease control for reasons such as lack of awareness, poor disease management, dysfunctional healthcare systems, and poor infrastructure.

Given the findings and evidence, the disease mostly occurs in adolescence and youth, and its lethality is high. It also imposes a psychological and economic burden on society. On the other hand, the costs of animal vaccination are much lower than the costs of treatment and prevention. Therefore, controlling measures in animals and also rabies-related hygiene education in high-risk areas can prevent disease incidence and mortality, as well as impose a double economic burden. Due to the critical role of dogs in disease transmission, the recommendation of the WHO for the effective control of the disease in endemic areas is to vaccinate dogs up to at least 70%.[1]

Also, to continue effective measures, we can point to conducting systematic studies[55] in different regions of the country at short intervals to control and monitor the results of policies implemented and also establish new policies appropriate to each region to prevent and control the disease.

Limitations

One of the limitations of the present study is the omission of non-English articles and also the conference papers that did not have full text, which may lead to the loss of several disease cases.

One of the methodological limitations in the study was the high heterogeneity of the analyzed articles, whose origin seems to be the very different sample size of the analyzed articles.

However, by performing sensitivity analysis and the analysis in subgroups, an attempt was made to identify heterogeneity sources. The results should be described and interpreted cautiously.

The discrepancy between the year of publication and the years of performing the study, and sometimes their several-year distance, may be among the sources of heterogeneity in the studies. Thus, we tried to calculate the average of the recent years.

Given that the incidence/100000 individuals has been calculated based on the population in 2016 reported by the last census in the National Statistics Portal, and considering the increased population in recent years and several studies conducted in the same years, estimates may be slightly different from the actual rates.

Another limitation includes cases of reports in provinces that did not exactly specify from which areas of the province they were. It is somehow difficult to make sure that the reports completely covered all areas. In such cases, there is a probability of undercounting.

CONCLUSION

Findings show that the cases of animal bites in some parts of the country are still high; of course, it may be due to the increase in healthcare centres, the increased visits to these centres, and the increased level of public awareness in some areas. Also, another important challenge is the low sensitivity of the healthcare system in identifying animal bites in some other areas. Reports in some areas show very lower statistics than expected which may be due to a lack of referral or disease records. In this regard, and given the proven findings of studies and the relationship between rabid bites and awareness, it is necessary to increase the awareness of people in high-risk communities of referring and getting prophylaxis. In this regard, considering the diverse climatic conditions and different cultures and the hygiene of the people in different regions, special actions are required to control the disease in each region. In addition, the cost of the most effective way to reduce the disease burden, i.e. vaccinating dogs and domestic animals, should be seriously followed in the agenda. Another problem is that Iran is located among the endemic neighbouring countries, which facilitates the transmission of the virus.

Finally, national, regional, and international cooperation is needed to effectively control the disease due to the disease conditions.

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Conflicts of interest
There are no conflicts of interest.

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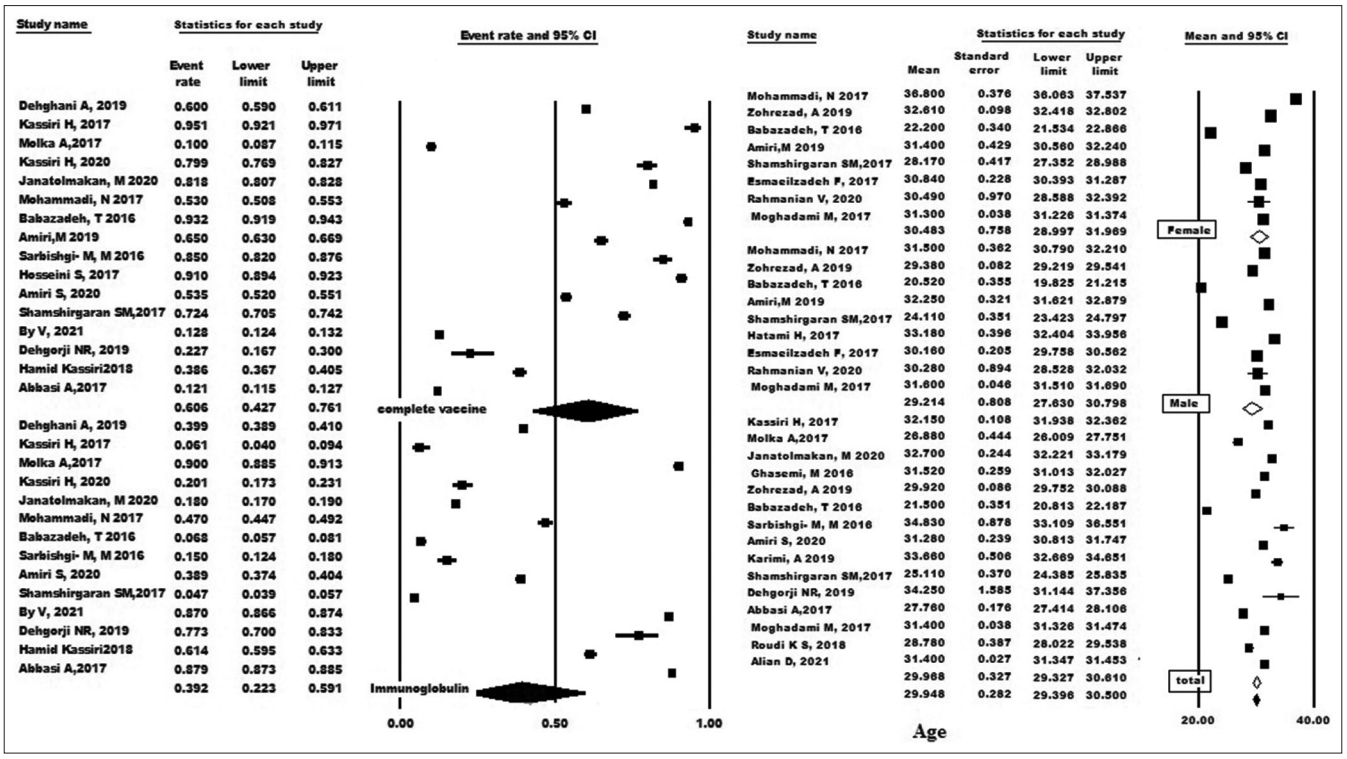
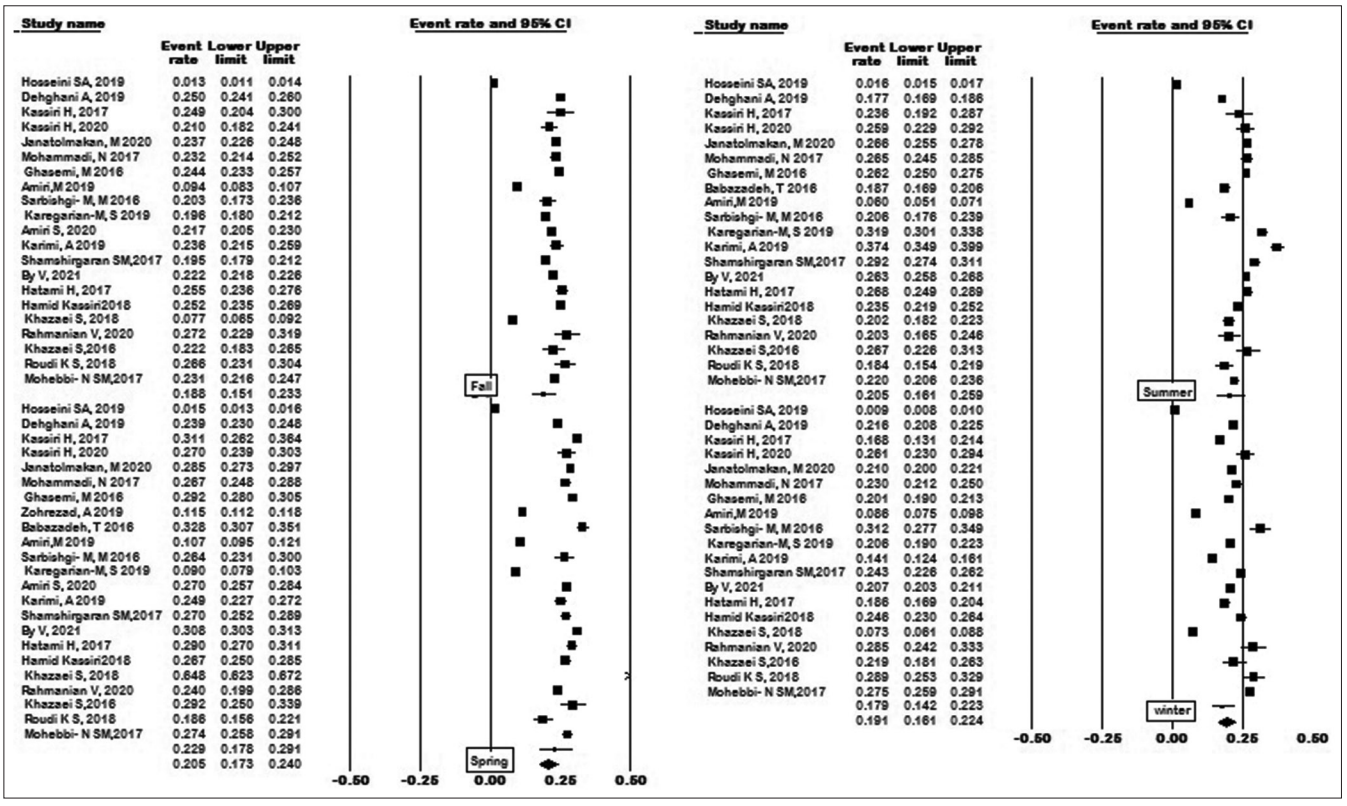
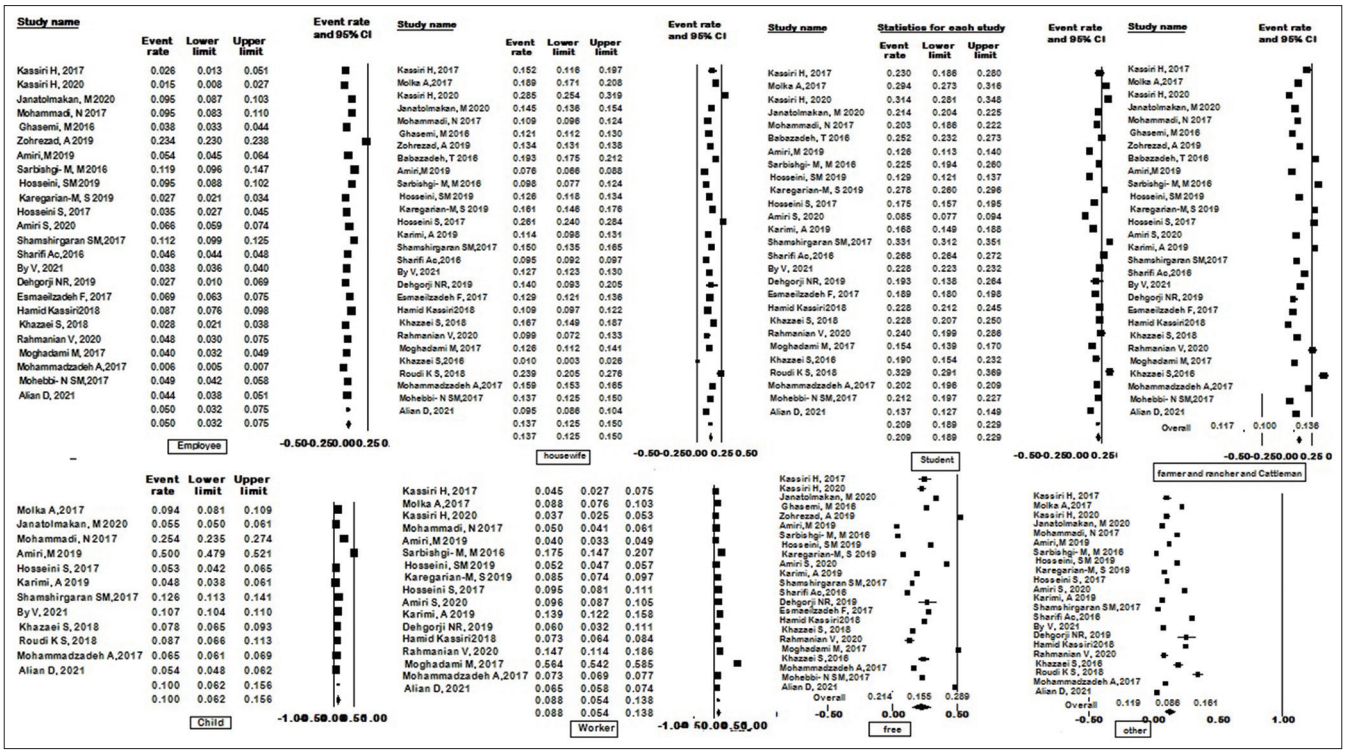


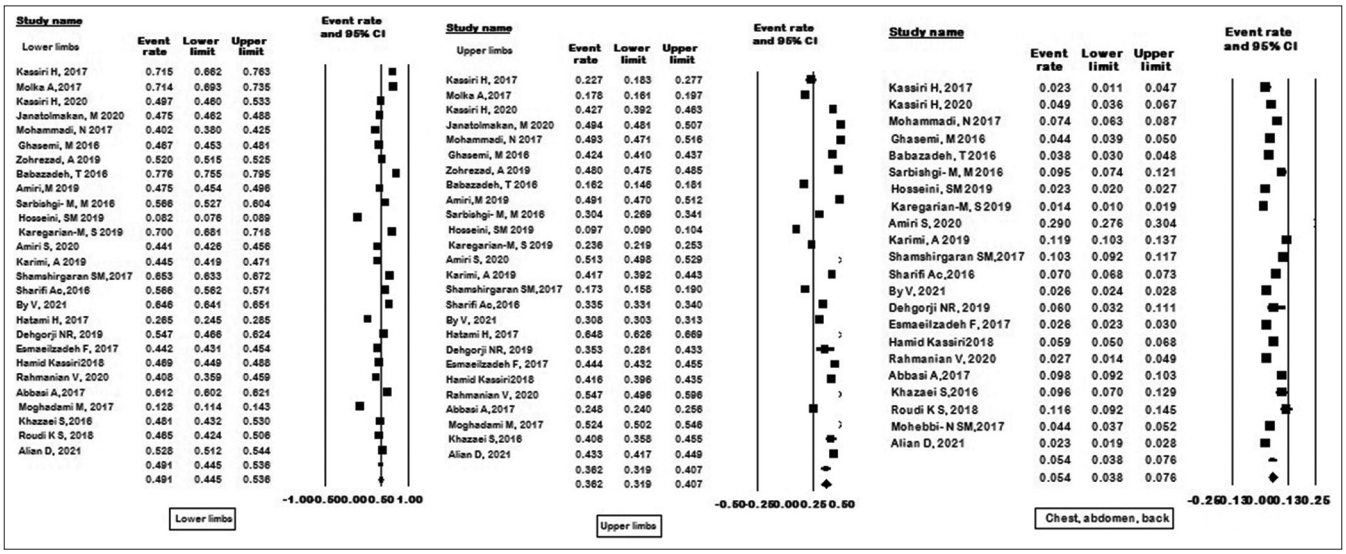
Supplementary Figure 1: Pool estimate forest plots of history of vaccination and age



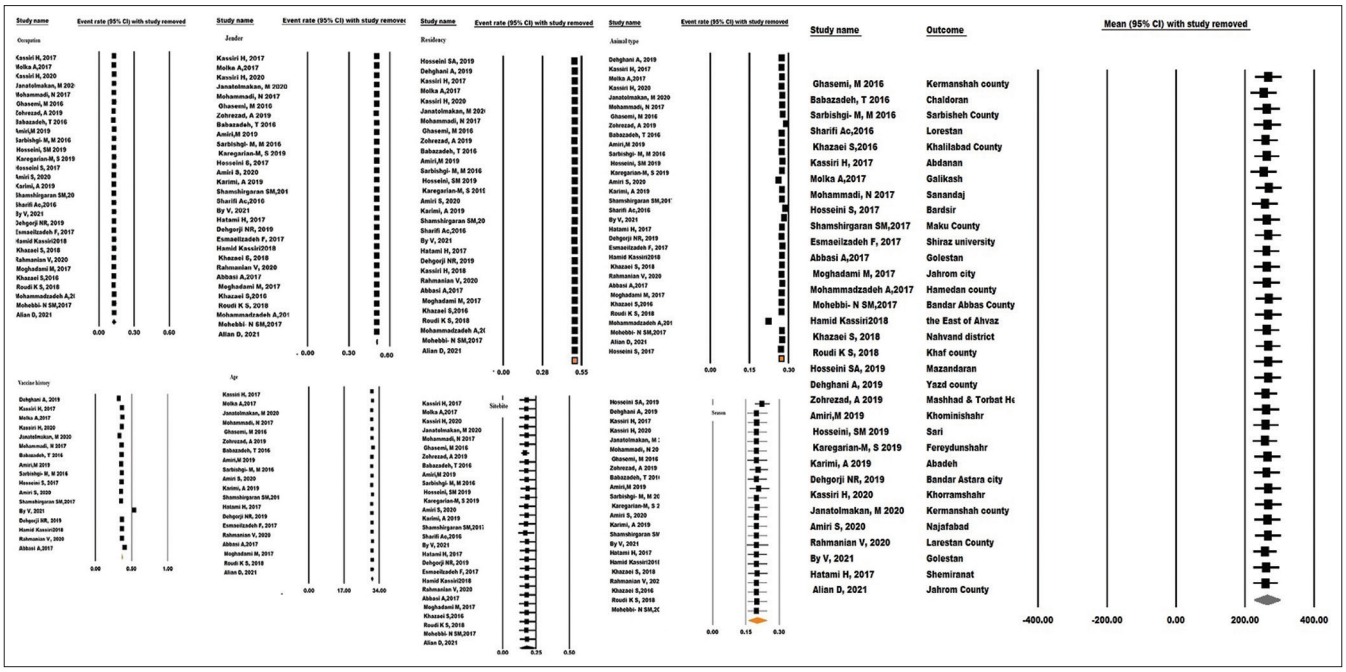
Supplementary Figure 2: Pool estimate forest plots of biting season



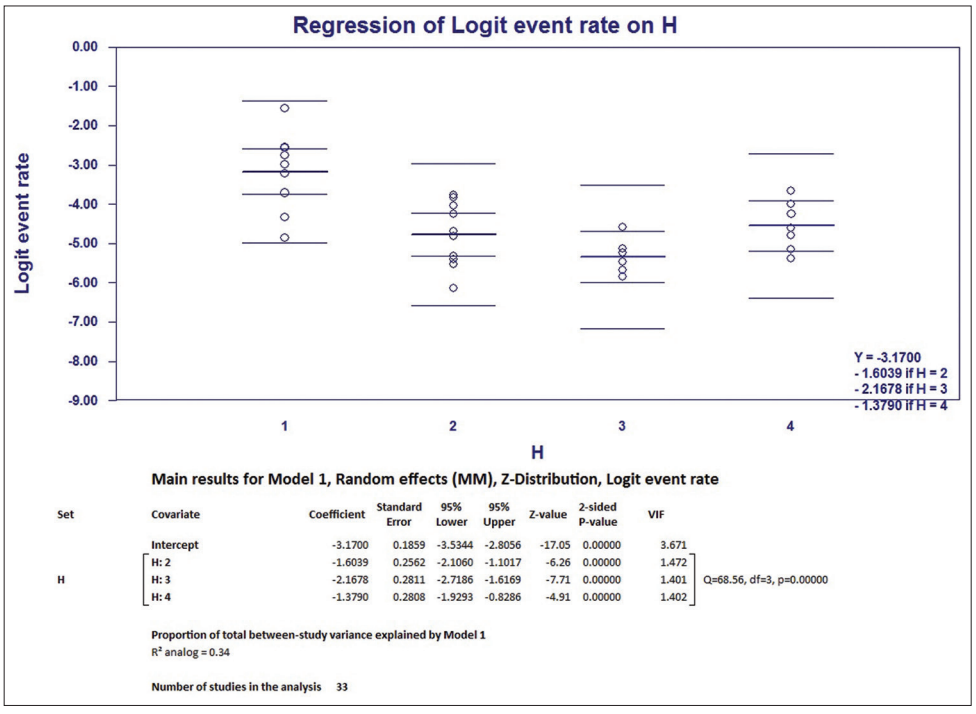
Supplementary Figure 3: Pool estimate forest plots of occupation



Supplementary Figure 4: Pool estimate forest plots of bite location and prevalence animal bite



Supplementary Figure 5: Pool estimate forest plots of animal type



Main results for Model 1, Random effects (MM), Z-Distribution, Logit event rate

Set	Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided P-value	VIF	
	Intercept	-3.1700	0.1859	-3.5344	-2.8056	-17.05	0.00000	3.671	
H	H: 2	-1.6039	0.2562	-2.1060	-1.1017	-6.26	0.00000	1.472	
	H: 3	-2.1678	0.2811	-2.7186	-1.6169	-7.71	0.00000	1.401	Q=68.56, df=3, p=0.00000
	H: 4	-1.3790	0.2808	-1.9293	-0.8286	-4.91	0.00000	1.402	

Proportion of total between-study variance explained by Model 1

R^2 analog = 0.34

Number of studies in the analysis 33

Supplementary Figure 6: Meta-regression analysis for census sample