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A systematic review and meta-analysis of the prevalence of *Leishmania infantum* in sandflies in Iran

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ABSTRACT

Objective: To determine the overall and pooled prevalence of *Leishmania (L.) infantum* in sandfly vectors in Iran.

Methods: The present research conducted a systematic review and meta-analysis and searched regional databases such as PubMed, Scopus, Web of Science (WoS), Embase, PAHO Iris, LILACS, WHO Iris, and local databases named: SID, Magiran, Civilica, and also grey literatures. The current research included studies that were conducted in Iran and examined *L. infantum* in different sandfly vectors. The studies' quality assessment/risk of bias assessment was evaluated by the Joanna Briggs Institute Critical Appraisal Checklist for prevalence data studies, and the data were analyzed by Stata 14 software. In addition, we examined 22 primary studies to estimate the overall prevalence of *L. infantum* among various vectors of visceral leishmaniasis.

Results: According to the meta-analysis, the pooled prevalence of *Phlebotomus (Ph.) tobbi*, *Ph. alexandri*, *Ph. kandelaki*, *Ph. perfiliewi*, *Ph. major*, *Ph. keshishiani* were 5.34%, 4.36%, 2.23%, 1.79%, 4.37% and 1.18%. *Ph. tobbi* has the highest infection rate (25.00%) of *L. infantum* among the sandfly vectors.

Conclusions: Visceral leishmaniasis is widespread in Fars, Ardebil, and East-Azerbaijan provinces, which are the most important endemic regions in Iran.

KEYWORDS: Visceral leishmaniasis; *Leishmania infantum*; Sandfly; Systematic review; Meta-analysis; Iran

1. Introduction

Leishmania is a protozoa parasite that causes various diseases called leishmaniases. More than 20 *Leishmania* species can infect humans through a bite of infected female phlebotomine sandflies. Leishmaniasis has three main forms: (1) visceral leishmaniasis, the most severe type of the disease (VL); (2) cutaneous leishmaniasis,

Significance

This systematic review and meta-analysis addresses the critical question of *Leishmania infantum* prevalence in different sandflies in Iran, highlighting significant findings that reveal the extent of this zoonotic threat. The results showed that *Phlebotomus tobbi*, and *Phlebotomus keshishiani* have the highest and lowest prevalence of *Leishmania infantum* parasite in Iran, respectively. Understanding the prevalence of this parasite in sandfly populations is vital for public health strategies and vector control measures. The study's significance lies in its potential to inform policymakers and researchers about the epidemiological landscape of leishmaniasis, ultimately contributing to more effective prevention and control efforts in the region.

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the most frequent (CL); and (3) mucocutaneous leishmaniasis[1-3]. According to World Health Organization (WHO), leishmaniasis is endemic in 99 out of 200 countries and territories in 2022. This number consists of 71 countries that have both VL and CL forms of the disease, 9 countries that have only VL, and 19 countries that have only CL[4]. VL also known as Kala-azar, is the second deadliest disease in tropical and sub-tropical regions and ranks seventh in causing years of life loss due to disability[5]. Every year, around 50 000 to 90 000 people globally get infected with VL, and the disease also causes around 50 000 fatalities annually[1]. Leishmaniasis is a major health problem in Iran and poses a rising challenge for the society and the community development[6]. Zoonotic visceral leishmaniasis (ZVL) is a form of Kala-azar disease that occurs in Iran. Iran reports 100-300 ZVL cases annually. The disease is not common in most regions of Iran, but it is prevalent in the south and northwest[7-9]. *Leishmania (L.) infantum* causes the disease in these regions, where domestic dogs are the primary hosts and wild canines (jackal, fox, and wolf) may also contribute to the ZVL transmission cycle in the wild. ZVL is transmitted by *Phlebotomus (Ph.) major*, *Ph. kandelaki*, *Ph. keshishiani*, *Ph. perfiliewi*, *Ph. tobbi* and *Ph. alexandri*[10-14]. In Iran, the average rate of ZVL infection among the people was 2%, with the western and northern provinces having the least and the most cases, 0.5% and 3%, respectively[15]. A study summarized previous research, the regions with the most human VL cases were northwest (2.8%) and northeast (0.96%), while the regions with the most dog VL cases were northwest (21.5%) and south (14.4%)[16]. Based on our knowledge, no systematic review and meta-analysis study has been done on the frequency (prevalence) of *L. infantum* in these vectors in Iran. Considering the importance of phlebotomine sandflies in the transmission of ZVL in Iran, this study was conducted to investigate the prevalence of infection of different phlebotomine vectors with *L. infantum* in Iran, using a systematic review and meta-analysis.

2. Materials and methods

The systematic review and meta-analysis followed the Joanna Briggs Institute (JBI) Reviewers' Manual 2014[17]. The PRISMA 2009 flow chart guided the selection of studies and articles in Persian and English for the systematic review of prevalence data[18].

2.1. Data sources and search strategy

Since keyword selection is extremely important for systematic reviews and meta-analyses, the research team first gathered a preliminary list of keywords by consulting subject matter experts and reviewing relevant systematic review studies. The MeSH and Emtree thesauruses were then searched to identify all relevant keywords. About searching internal databases, the Iran-Doc thesaurus was used for identifying synonyms. After the consensus of the authors of this research, the search strategy syntax was compiled and the search keywords/terms are listed in Supplementary Table 1.

This study was performed based on the guidelines of PRISMA-ScR[18]. After finalizing the search syntax, the searches were done in different databases such as Web of Science (WoS), Scopus, PubMed/MEDLINE, Embase, PAHO Iris, LILACS, WHO Iris, and local databases namely: SID, Magiran, Civilica, and also grey literature (conference papers, thesis, and scientific reports). We also checked the references of the primary studies that were included. The search was conducted in 20-31 October, 2022.

Two authors independently selected included documents by rigorously screening the title and abstract of primary studies based on the pre-defined inclusion criteria in the review. The selection process of the included primary studies involved a discussion among the authors or third expert or both, in case of any disagreements. The detailed search strategies for each database can be found in Supplementary Table 2.

2.2. Eligibility criteria

All primary studies that present the prevalence data of *L. infantum* among sandfly vectors in Iran were included. We did not include the comment and letter papers in this systematic review and meta-analysis study.

2.3. Data extraction

After finishing the screening and selection phases, two authors separately read the full-text articles thoroughly and extracted and recorded the following variables such as the year, the first author's name, the study location, the parasite detection method in the vector's body, the vector species, the number of vectors captured, the cases of parasite positivity, the prevalence, the infection rate, and the vector collection site, in the data extraction form.

2.4. Risk of bias assessment (quality assessment)

Two researchers independently did the quality assessment (risk of bias assessment) in this study and used the risk of bias assessment checklist to evaluate and quantify the risk of bias assessment in prevalence studies. We used the tools of Hoy *et al*. to assess the risk of bias assessment. The checklist has 10 questions with a scoring criterion, and it categorizes the articles into 3 groups: low, medium, and high[19]. The two researchers solved any differences by talking and sharing their opinions, and they requested a third expert's opinion when needed.

2.5. Data analysis

The meta-analysis method computed the pooled prevalence and Stata software version 14 was utilized to do the data analysis (Stata

Corp LP., College Station, TX). The primary studies reported the prevalence of *L. infantum* parasite in various sandfly vectors for which overall prevalence was computed as a percentage and with a 95% confidence interval. The I^2 index reported and measured the heterogeneity degree of the studies, the random effect model reported and computed the pooled prevalence, and the forest plot showed the meta-analysis results.

3. Results

3.1. Study selection

Following the search syntax and search strategy in worldwide and local databases, 4 059 articles and grey literature were identified, with 2 542 articles from worldwide databases and 1 517 from local databases. After the elimination of duplicates, 1 907 articles remained for checking the title and abstract based on the eligibility criteria. 1 797 Articles were excluded, and 110 articles were selected for full-text review. Totally 89 articles were excluded according to the inclusion and exclusion criteria, ultimately, 22 articles met the inclusion and exclusion criteria and underwent quality assessment and data extraction. Of these, 21 articles were included in the meta-analysis, as the prevalence of the *L. infantum* in *Ph. keshishiani* was reported in only one study conducted in Iran. In addition, the causes for excluding articles in the selection phases are presented in Figure 1.

3.2. Quality assessment (risk of bias assessment) result

In the systematic review and meta-analysis, 15 studies were assigned to the moderate-risk of bias (medium quality) in evaluating the risk of bias assessment[10–13,20–30]. And 7 studies in the group with low risk of bias (high quality)[14,31–36]. All primary studies with varying quality assessment categories from moderate to high were included in the meta-analysis (Figures 2 and 3).

3.3. Study characteristics

The examination of 22 primary studies was performed, and Table 1 displayed the characteristics of the studies, which extended from 1992 to 2020. From all the studies that were included, 5 studies were on the prevalence of *L. infantum* in *Ph. major*[11,12,20,21,24], 7 studies on *Ph. kandelaki*[14,20,22,25–27,31], 10 studies on *Ph. perfiliewi*[13,14,20,22,27–31,34], 6 studies on *Ph. alexandri*[11,12,20,21,23,36], 4 and 2 studies respectively on *Ph. tobbi*[13,32,33,35] and *Ph. keshishiani*[10,20]. A meta-analysis was conducted individually for each sandfly vector. Two methods, leptomonad and molecular

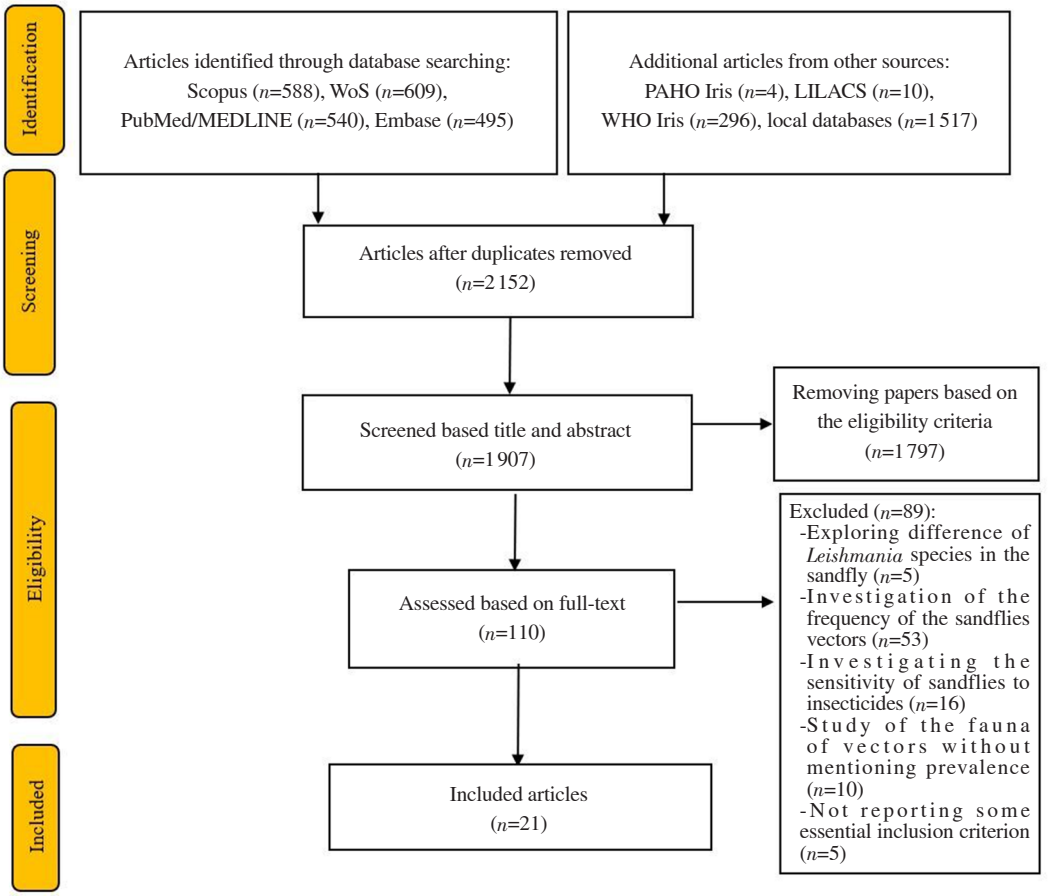

Figure 1. PRISMA flow chart of described study design.

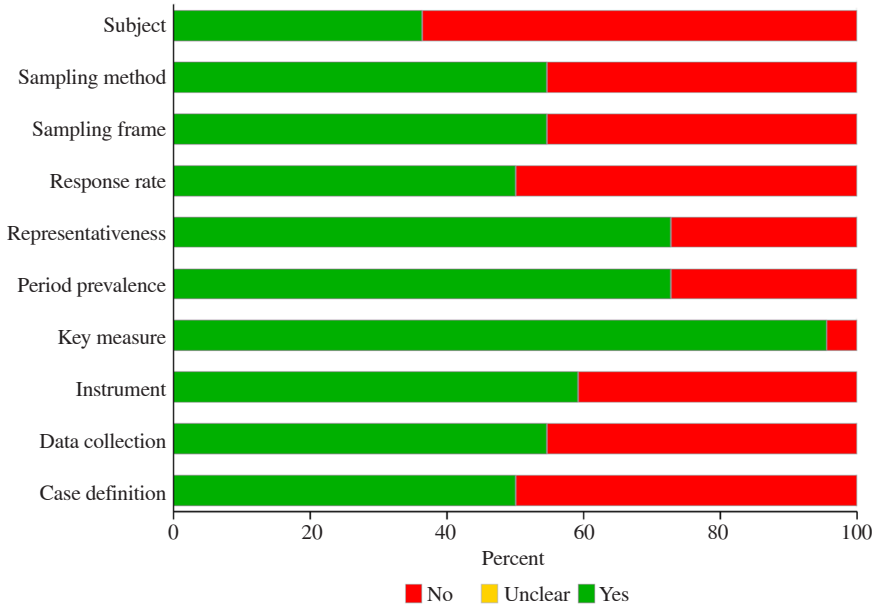

Figure 2. Risk of bias graph: review author's judgement about each risk of bias item presented as percentages across all included studies.

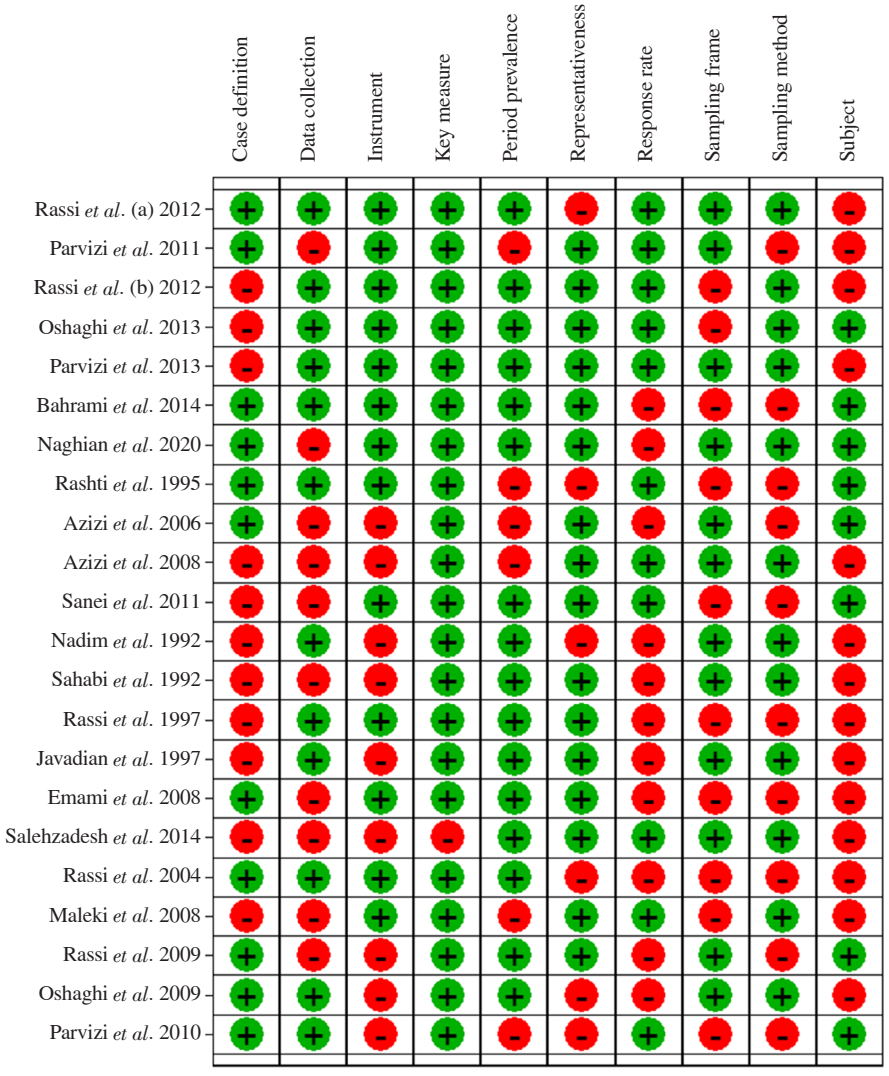

Figure 3. Risk of bias summary: review author's judgement about each risk of bias item for each included study.

Table 1. Description of primary studies included in the study.

ID	Year	Author	Region	Method	Species	No. investigated	No. positive	Infection (%)
1	1992	Nadim *et al*.[20]	Ardebil (Meshkin-shahr)	Leptomonad	*Phlebotomus major*	367	0	0.0
					Phlebotomus kandelaki	649	19	2.9
					Phlebotomus keshishiani	255	0	0
					Phlebotomus perfiliewi	212	4	1.9
					Phlebotomus alexandri	55	0	0.0
2	1992	Shahabi *et al*.[21]	Fars (Ghir-karzin)	Leptomonad	*Phlebotomus major*	150	5	3.3
					Phlebotomus alexandri	27	0	0.0
3	1995	Rashti *et al*.[10]	Fars (Ghir-karzin)	Leptomonad	*Phlebotomus keshishiani*	1 020	12	1.2
4	1997	Javadian *et al*.[23]	Khuzastan	Leptomonad	*Phlebotomus alexandri*	301	5	1.7
5	1997	Rassi *et al*.[22]	Ardebil (Germi)	Leptomonad	*Phlebotomus kandelaki*	882	3	0.35
					Phlebotomus perfiliewi	549	6	1.1
6	2005	Rassi *et al*.[26]	Ardebil	PCR	*Phlebotomus kandelaki*	1 002	11	1.1
7	2006	Azizi *et al*.[11]	Fars (Nourabad)	PCR	*Phlebotomus major*	24	0	0.0
					Phlebotomus alexandri	120	5	4.2
8	2008	Emmami *et al*.[24]	Isfahan (Shahreza)	PCR	*Phlebotomus major*	120	6	5.0
9	2008	Azizi *et al*.[12]	Fars (Ghir-karzin)	PCR	*Phlebotomus major*	45	3	6.7
					Phlebotomus alexandri	39	1	2.6
10	2008	Maleki *et al*.[27]	Ardebil (Germi)	PCR	*Phlebotomus kandelaki*	45	1	2.2
					Phlebotomus perfiliewi	854	9	1.0
11	2009	Rassi *et al*.[28]	Ardebil (Germi)	PCR	*Phlebotomus perfiliewi*	905	10	1.1
12	2009	Oshaghi *et al*.[29]	Ardebil	PCR	*Phlebotomus perfiliewi*	1 569	60	3.4
13	2010	Parvizi *et al*.[30]	East-Azerbaijan (Kalybar)	PCR	*Phlebotomus perfiliewi*	5	1	20.0
14	2011	Sanei *et al*.[13]	Ardebil (Bilesavar)	PCR	*Phlebotomus perfiliewi*	270	6	2.2
					Phlebotomus tobbi	35	0	0.0
15	2011	Parvizi *et al*.[31]	Ardebil	PCR	*Phlebotomus kandelaki*	6	1	16.7
					Phlebotomus perfiliewi	51	4	7.9
16	2012	Rassi *et al*.[14]	North-Khorasan (Shirvan)	PCR	*Phlebotomus kandelaki*	59	2	3.4
17	2012	Rassi *et al*.[32]	Ardebil (Bbilessavar	PCR	*Phlebotomus perfiliewi*	273	4	1.46
					Phlebotomus tobbi	32	2	6.25
18	2013	Oshaghi *et al*.[33]	East-Azerbaijan (Azarshahr)	PCR	*Phlebotomus tobbi*	8	2	25.0
19	2013	Parvizi *et al*.[34]	East-Azerbaijan (Sarab)	PCR	*Phlebotomus perfiliewi*	223	4	1.8
20	2014	Salehzadeh *et al*.[25]	Hamedan	PCR	*Phlebotomus kandelaki*	80	2	2.5
21	2014	Bahrami *et al*.[35]	Alborz (Karaj)	PCR	*Phlebotomus tobbi*	80	1	1.25
22	2020	Naghian *et al*.[36]	Fars	PCR	*Phlebotomus alexandri*	181	17	9.4

(PCR), have been applied in all the primary studies to detect *Leishmania* parasite species.

The meta-analysis for the *Ph. major* showed that the *L. infantum* had a 4.37% prevalence with a 95% *CI* (3.10, 5.63) with estimated predictive interval (0.12, 1.45). A study by Azizi *et al*. (2008) reported the highest prevalence of 6.67%[12] while two studies by Nadim *et al*. and Azizi *et al*. (2006) found no prevalence[11,20]. The meta-analysis revealed that the studies were not homogenous, and the I^2 index was 83.7% (P=0.002) (Figure 4).

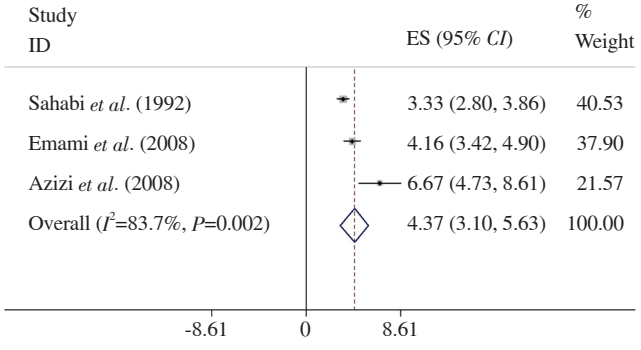

Figure 4. Forest plot of pooled prevalence of *Leishmania infantum* in *Phlebotomus major* sandfly vectors in Iran (*CI*=confidence interval). Weights are from random effects analysis.

Based on the meta-analysis results, the overall prevalence of *L. infantum* was 1.79% for the *Ph. perfiliewi* with a 95% confidence interval of (1.42, 2.16) with estimated predictive interval (0.49, 3.09). A study by Parvizi *et al*. (2010) reported the highest prevalence of 20.00%[30], and a study by Rassi *et al*. (2012) described the lowest prevalence of 1.05% (Figure 5)[32]. It was determined by the meta-analysis that the studies were heterogeneous, and 98.7% (P<0.001) was the I^2 index.

The *L. infantum* had a 2.23% prevalence with a 95% confidence interval of (0.85, 3.60) with estimated predictive interval (-2.50, 6.96) according to the meta-analysis for the *Ph. kandelaki*. The maximum prevalence of 16.66% was found in a study by Parvizi *et al*. (2011)[31], and the minimum prevalence of 0.34% was found in a study by Rassi *et al*. (1997) (Figure 6)[22]. The meta-analysis showed that the studies lacked homogeneity and that the I^2 index was 99.1% (P<0.001).

Meta-analysis could not be performed for *Ph. keshishiani* with only two primary studies, so the pooled prevalence is not reportable. A prevalence with a 95% confidence interval of 1.18 (1.12, 1.24) was reported for *L. infantum* in the *Ph. keshishiani* in one study[10], while no infection was found in another study[20].

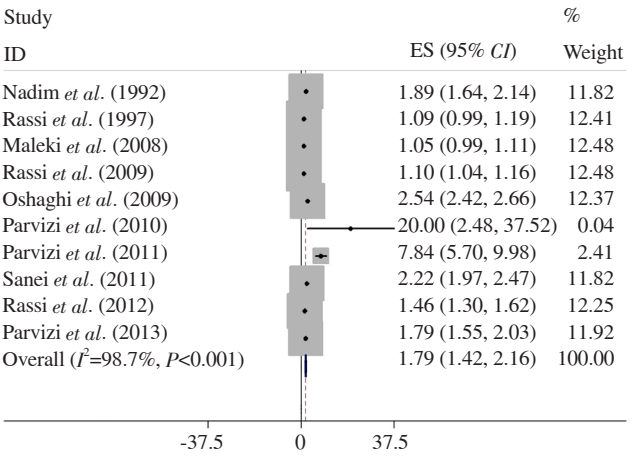

Figure 5. Forest plot of pooled prevalence of *Leishmania infantum* in *Phlebotomus perfiliewi* sandfly vectors in Iran. Weights are from random effects analysis.

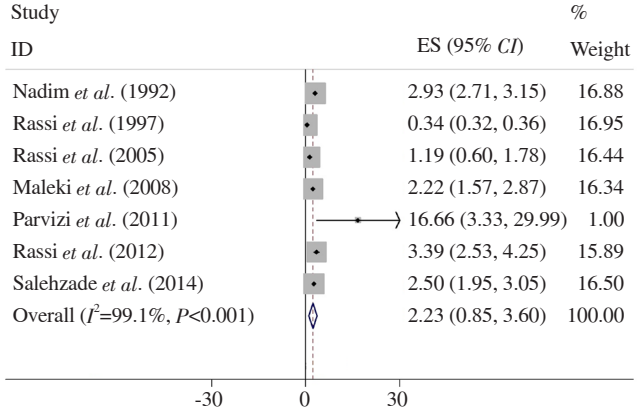

Figure 6. Forest plot of pooled prevalence of *Leishmania infantum* in *Phlebotomus kandelaki* sandfly vectors in Iran. Weights are from random effects analysis.

According to the meta-analysis for the *Ph. tobbi*, the prevalence of *L. infantum* varied from 0[13] to 25%[33] with an overall prevalence of 5.34% and a 95% confidence interval of (0.02, 10.67) with estimated predictive interval (-3.53, 7.24). The meta-analysis also revealed a high degree of heterogeneity among the primary studies, as indicated by the I^2 index of 92.7% (P<0.001) (Figure 7).

The meta-analysis demonstrated that the *L. infantum* had a pooled prevalence of 4.36% with a 95% confidence interval (1.98, 6.74) with estimated predictive interval (1.54, 7.02) in the *Ph. alexandri*. The prevalence varied from 0[20,21] to 9.39%[36], and the homogeneity was very low, as indicated by the I^2 index of 98.1% (P<0.001) (Figure 8).

A sensitivity analysis was conducted to assess the robustness of our findings regarding the prevalence of *L. infantum* in different phlebotomine sandflies. In our sensitivity analysis, two studies[30,31] were excluded, demonstrating an insignificant influence on the overall prevalence estimates of *L. infantum*. Following this exclusion, the pooled prevalence of *Ph. perfiliewi* shifted from 1.79% (95% *CI* 1.42, 2.16) to 1.78% (95% *CI* 1.42, 2.15), and for *Ph. kandelaki* shifted from 2.23% (95% *CI* 0.85, 3.60) to 2.08% (95% *CI* 0.71, 3.46). However, after the removal of one study[33], the pooled prevalence of *Ph. tobbi* shifted from 5.34% (95% *CI* 0.02, 10.67) to 3.63% (95% *CI* -1.26, 8.53). The related forest plots are provided in Supplementary Figures 1-3.

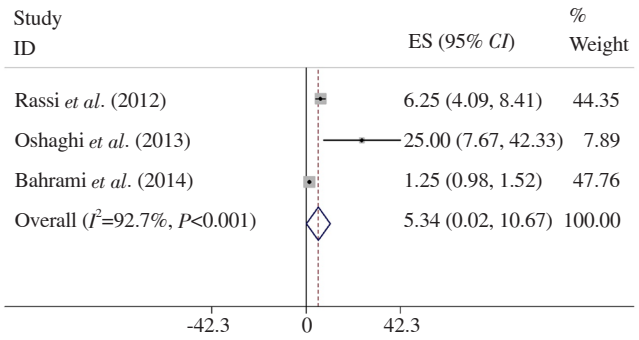

Figure 7. Forest plot of pooled prevalence of *Leishmania infantum* in *Phlebotomus tobbi* sandfly vectors in Iran. Weights are from random effects analysis.

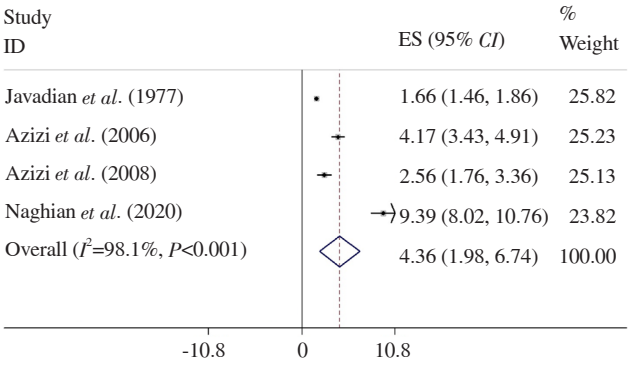

Figure 8. Forest plot of pooled prevalence of *Leishmania infantum* in *Phlebotomus alexandri* sandfly vectors in Iran. Weights are from random effects analysis.

Funnel plots for *L. infantum* prevalence studies are shown in Figure 7. The outer dashed lines indicate the triangular region within which 95% of studies are expected to lie in the absence of both biases and heterogeneity. All of them are asymmetrical, and some studies are located outside the dashed lines (Figure 9).

4. Discussion

To the best of our knowledge, the present study is the first systematic review and meta-analysis of the field of investigation of the overall prevalence of *L. infantum* infection in different species of sandflies in Iran. A diverse range of prevalence values for *L. infantum*

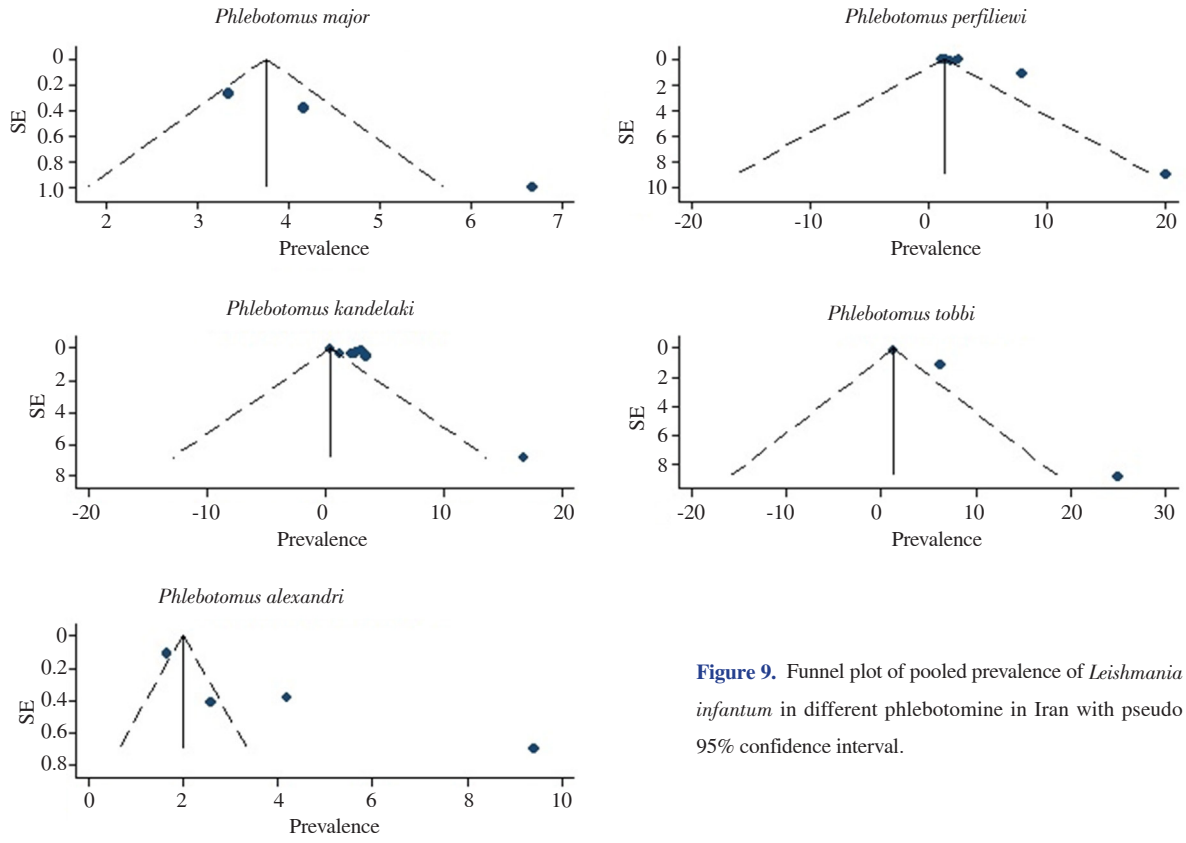

Figure 9. Funnel plot of pooled prevalence of *Leishmania infantum* in different phlebotomine in Iran with pseudo 95% confidence interval.

in different sandfly vectors, from 0 to 25.00%, were reported in the primary studies of the present systematic review and meta-analysis.

One of the key findings in meta-analysis of prevalence studies is the identification of heterogeneity sources. These studies reveal that the sources of heterogeneity are highly diverse, significantly impacting the overall prevalence rate. However, precisely pinpointing this impact remains challenging. The study results highlight several potential sources of heterogeneity, including varied methods of sampling or catching leishmaniasis vectors, distinct approaches to detecting *Leishmania* parasites in vectors (using both microscopic and molecular methods), and different sampling environments (both outdoors and indoors in human habitats). Therefore, it is advisable that all studies adhere to specific standardized forms and formats to ascertain the accurate pooled prevalence of sandfly infection.

The pooled prevalence of *Leishmania* parasite infection in sandfly vectors is very hard to determine accurately, as different factors are involved in this process. Some of the most important factors that affect the rate of infection of sandfly vectors are the region, the disease endemicity, the time of sandflies sampling, the locations, the abdominal status of the vectors, and the laboratory methods of testing the vectors[6,37].

The meta-analysis of this study in Iran revealed that *Ph. tobbi* had the highest overall prevalence of *L. infantum* at 5.34% and *Ph. major* had 4.37%, while *Ph. keshishiani* had the lowest overall prevalence at 1.18%.

Ph. major is widely distributed in Iran and many provinces have reported it. According to the meta-analysis results, the prevalence of *Leishmania* infection for *Ph. major* ranged from 0 to 6.67%. In addition, only Fars province (Ghir-Karzin) with 3.3% to 6.7%[12,21], and Isfahan with 5.0% prevalence have confirmed the natural infection of *Ph. major* with *L. infantum* promastigotes[24]. Based on the high overall prevalence, the confirmation of natural infection of *Ph. major* with *Leishmania* promastigotes and its relative frequency in the region (11.2%)[12], *Ph. major* is the vector of visceral leishmaniasis (Kala-azar) in southern Iran.

The meta-analysis results show that the pooled prevalence of *L. infantum* in *Ph. alexandri* is 4.36% and it ranges from 0 to 9.39%. Many parts of Iran have *Ph. alexandri*, but Ardebil, Fars, and Khuzestan provinces are endemic areas of visceral leishmaniasis. This vector had a 1.7% infection rate with *L. infantum* in Khuzestan province[23] and Fars province, from 2.6% in Ghir-Karzin to 9.4% in Nourabad[12,36], and it has been introduced as the primary vector of visceral leishmaniasis in Fars province.

Most provinces of Iran have reported *Ph. tobbi*, but only Ardebil (Bilesavar) with 6.25%, East-Azerbaijan (Azarshahr) with 25.00%, and Alborz province 1.25% have confirmed its *Leishmania* promastigotes infection[32,33,35]. The meta-analysis results indicate that the overall prevalence of *L. infantum* in *Ph. tobbi* was 5.34% and the prevalence rates ranged from 0 to 25.00%. The results also show that this species is the main vector of visceral leishmaniasis in East-

Azerbaijan, Ardebil, and Alborz provinces.

Ph. perfiliewi has been found in Iran from West-Azerbaijan, East-Azerbaijan, Ardebil, Ilam, Tehran, Zanjan, Kurdistan, and Kermanshah provinces. The Provinces of Ardebil and East-Azerbaijan have reported and confirmed leptomonad infection with *L. infantum*, with a prevalence ranging from 1.0% to 7.9% in Ardebil[27,31] and from 1.8% to 20.0% in East-Azerbaijan[30,34]. According to the meta-analysis, the pooled prevalence of *L. infantum* in *Ph. perfiliewi* is 1.79%, with the highest prevalence in East-Azerbaijan province (Kalybar) and the lowest prevalence in Ardebil province (Germi). Based on the confirmation of leptomonad infection, *Ph. perfiliewi* is the primary vector of visceral leishmaniasis in Ardebil and East-Azerbaijan.

Ph. kandelaki is widely distributed in Iran. Two provinces of North-Khorasan (Shirvan) and Ardebil province (Meshkin-shahr) have confirmed leptomonad infection of this species, with a prevalence of 3.4% to 16.7% respectively[14,31]. The meta-analysis results show that the overall prevalence of *L. infantum* in *Ph. kandelaki* was 2.23%, ranging from 0.35% to 16.7%. Therefore, *Ph. kandelaki* is the primary vector of visceral leishmaniasis in the Ardebil and North Khorasan provinces.

Many provinces in Iran have reported *Ph. keshishiani*. The sole documented case of *Ph. keshishiani* infection in the promastigote form of the *Leishmania* parasite originated from the endemic region of visceral leishmaniasis in Ghir-Karzin, Fars province. The results of the study conducted in 1995 show that only 12 samples (1.18%) out of 1 020 dissected females had the *Leishmania* parasite. *Ph. keshishiani* is a potential vector of visceral leishmaniasis in Ghir-Karzin region[10]. However, meta-analysis is not feasible due to the scarcity of research on this species' *Leishmania* infection.

Meta-analysis results show that the primary vectors of *L. infantum* have the highest infection rates in these provinces: *Ph. perfiliewi* (20.0%) in East-Azerbaijan, *Ph. kendelaki* (16.7%) and *Ph. tobbi* (6.25%) in Ardebil, *Ph. alexandri* (9.4%), *Ph. major* (6.7%) and *Ph. keshishiani* (1.2%) in Fars. Moreover, these findings indicate that the region's visceral leishmaniasis and sandfly vectors have the same spatial pattern. Visceral leishmaniasis is common in these parts of Iran: Fars (Qirkarzin, Nourabad), Ardebil (Germi, Bilesavar, Meshkin-shahr), East-Azerbaijan (Sarab, Kalybar, Azarshahr), Saveh and Qom, Khuzestan, and North-Khorasan (Shirvan)[38–42].

Based on the meta-analysis, *Ph. major* is the primary vector of VL in the southern regions of Iran, with an overall prevalence of 4.37% and a relative frequency of 11.2%. *Ph. alexandri* exhibited the highest pooled prevalence of the *L. infantum* parasite, with an overall prevalence of 4.36%, in Fars province. *Ph. tobbi*, a vector of VL that likes to feed on humans, has a 5.34% pooled prevalence in East-Azerbaijan, Ardebil, and Alborz provinces. The *L. infantum* is mostly transmitted by *Ph. perfiliewi* in the Ardebil and East-Azerbaijan provinces, which has a 1.79% pooled prevalence and a 45.0% relative frequency. Its blood-feeding index is about 39.3%[28]. In Ardebil, North-Khorasan, and Hamedan provinces, *Ph. kandelaki* is the probable vector of the VL, with 2.23% pooled prevalence. In Ardebil province, it has a 40.0% relative frequency and blood-feeding index is 32.8%[26]. *Ph. keshishiani*, which has a 1.18% overall prevalence, a high frequency, and a 28.5% blood-feeding index[10], is a potential vector of VL in Fars province.

Based on the examination of the initial studies included in this systematic review and meta-analysis, 5 primary studies used the microscopy method (Leptomonad)[10,20–23] and 17 primary studies used the molecular method (PCR) to identify *Leishmania* parasite infection in different sandfly vectors[11–14,24–36].

According to the meta-analysis, *Ph. tobbi* is the most infected with *L. infantum* among the sandfly vectors. *Ph. perfiliewi* and *Ph. kandelaki* are the key and primary vectors of VL disease in Iran. Fars, Ardebil, and East-Azerbaijan provinces are the most important endemic areas of VL disease in Iran, where it is widespread.

One of the limitations in systematic review and meta-analysis of prevalence is the difficulty of estimating accurate pooled prevalence. Various factors influence the overall prevalence, and some of these factors are unknown. In this study, one of the key limitations that can cause heterogeneity is the lack of separate prevalence data for outdoor and indoor sampling, and monthly activity of sandflies vectors of the year, in the primary studies.

In conclusion, this study is a systematic review and meta-analysis, and its results can serve as an index to compare the prevalence of *L. infantum* in sandfly vectors in different endemic regions in Iran. Among the sandfly vectors, *Ph. tobbi* has the highest infection rate of *L. infantum*. Based on the results of the meta-analysis, the two species *Ph. perfiliewi* and *Ph. kandalaki* exhibit the highest pooled prevalence of the *L. infantum* parasite in Iran. VL disease is prevalent in Fars, Ardebil, and East-Azerbaijan provinces, which are the most significant endemic areas in Iran.

Conflict of interest statement

The authors declare that there are no competing interests.

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Authors' contributions

SR, HA, and AL performed initial searches, screened, and selected eligible studies. SR, and H.R SH conducted the risk of bias assessment and quality control of included studies. SR, AL, and AS extracted the data. H.R SH and AS analyzed and interpreted the data. SR and HA drafted the manuscript. Al, H.R SH, and AS performed revision.

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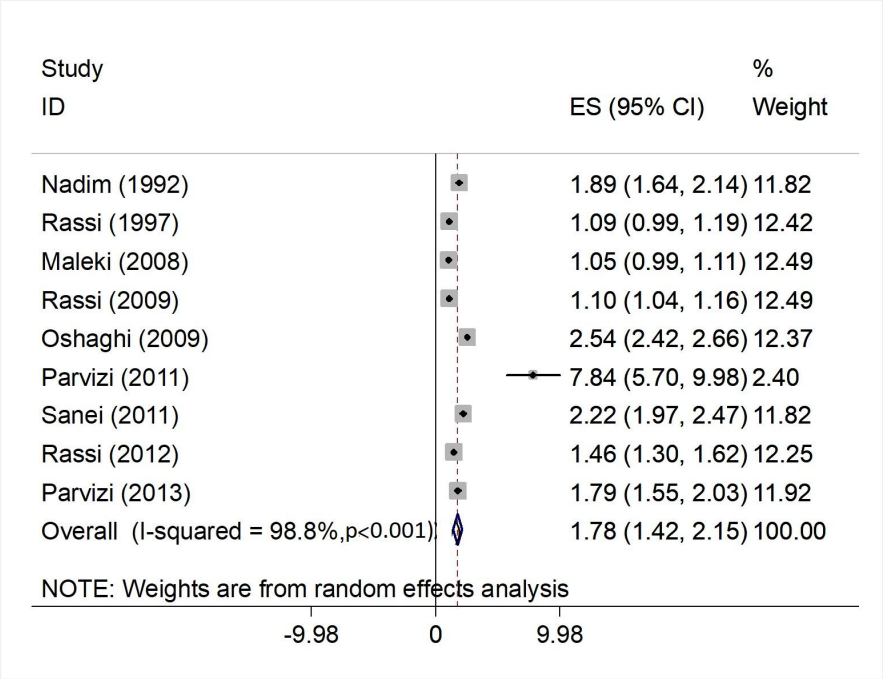
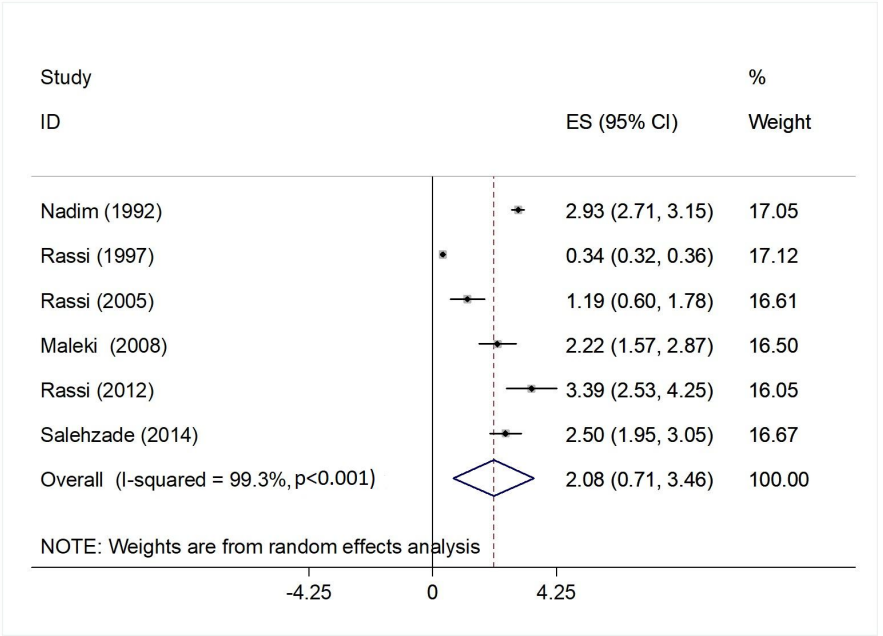
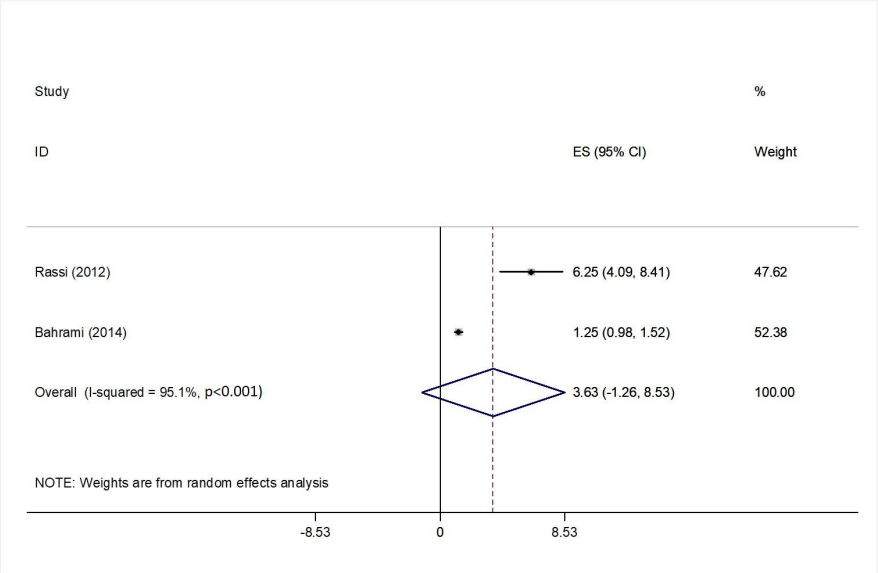


Supplementary Figure 1. Forest plot of pooled prevalence of *Leishmania infantum* in *Phlebotomus perfiliewi:* reference[30] is excluded.



Supplementary Figure 2. Forest plot of pooled prevalence of *Leishmania infantum* in *Phlebotomus kandelaki:* reference[31] is excluded.



Supplementary Figure 3. Forest plot of pooled prevalence of *Leishmania infantum* in *Phlebotomus tobbi:* reference[33] is excluded.

Supplementary Table 1. All search terms/keywords.

(Leishmania AND infantum)	"kala-azar"	(Phlebotomus AND kandelaki)
"Leishmania infantum"	kalaazar	(Phlebotomus AND major)
leishmania mediterranea		
"Leishmania donovani infantum"	"Kala Azar"	"P. major"
("donovani infantum" AND Leishmania)	(Leishmaniasis AND Visceral)	"Phlebotomus perfiliewi"
(infantum AND "Leishmania donovani")	(Fever AND Black)	"P. perfiliewi"
"Leishmania chagasi"		"Phlebotomus keshishiani"
(chagasi AND Leishmania)	“Visceral Leishmaniasis”	"P. keshishiani"
"Leishmania donovani chagasi"	“Black Fever”	"Phlebotomus tobbi"
("donovani chagasi" AND Leishmania)		"P. tobbi"
(chagasi AND "Leishmania chagasi")		"Phlebotomus alexandri"
"Leishmania infantum chagasi"		"Ph. Alexandri"
(chagasi AND "Leishmania infantum")		"P. alexandri"
("infantum chagasi" AND Leishmania)		

Supplementary Table 2. Detailed search strategies for each database.

Search syntax in PubMed/MEDLINE

	Search terms/keywords	*N*
#1	((Leishmania[Title/Abstract] AND infantum[Title/Abstract]) OR "Leishmania infantum"[Title/Abstract] OR "Leishmania donovani infantum"[Title/Abstract] OR ("donovani infantum"[Title/Abstract] AND Leishmania[Title/Abstract]) OR (infantum[Title/Abstract] AND "Leishmania donovani"[Title/Abstract]) OR "Leishmania chagasi"[Title/Abstract] OR (chagasi[Title/Abstract] AND Leishmania[Title/Abstract]) OR "Leishmania donovani chagasi"[Title/Abstract] OR ("donovani chagasi"[Title/Abstract] AND Leishmania[Title/Abstract]) OR (chagasi[Title/Abstract] AND "Leishmania chagasi"[Title/Abstract]) OR "Leishmania infantum chagasi"[Title/Abstract] OR"leishmania mediterranea"[Title/Abstract] OR (chagasi[Title/Abstract] AND "Leishmania infantum"[Title/Abstract]) OR ("infantum chagasi"[Title/Abstract] AND Leishmania[Title/Abstract])) AND (IRAN)	314
#2	("kala-azar"[Title/Abstract] OR kalaazar [Title/Abstract] OR "Kala Azar"[Title/Abstract] OR (Leishmaniasis[Title/Abstract] AND Visceral[Title/Abstract]) OR (Fever[Title/Abstract] AND Black[Title/Abstract]) AND IRAN[Title/Abstract])	284
#3	((Phlebotomus[Title/Abstract] AND kandelaki[Title/Abstract]) OR (Phlebotomus[Title/Abstract] AND major[Title/Abstract]) OR "P. major"[Title/Abstract] OR "Phlebotomus perfiliewi"[Title/Abstract] OR "P. perfiliewi"[Title/Abstract] OR "Phlebotomus keshishiani"[Title/Abstract] OR "P. keshishiani"[Title/Abstract] OR "Phlebotomus tobbi"[Title/Abstract] OR "P. tobbi"[Title/Abstract] OR "Phlebotomus alexandri"[Title/Abstract] OR "Ph. Alexandri"[Title/Abstract] OR "P. alexandri"[Title/Abstract] AND IRAN[Title/Abstract])	119
	#1 OR #2 OR #3	**540**

Search syntax in WoS

(http://webofscience.com/)

	Search terms/keywords	*N*
#1	((((((((((((((TS=((Leishmania AND infantum))) OR TS=("Leishmania infantum")) OR TS=("Leishmania donovani infantum")) OR TS=(("donovani infantum" AND Leishmania))) OR TS=((infantum AND "Leishmania donovani"))) OR TS=("Leishmania chagasi")) OR TS=((chagasi AND Leishmania))) OR TS=("Leishmania donovani chagasi")) OR TS=(("donovani chagasi" AND Leishmania))) OR TS=((chagasi AND "Leishmania chagasi"))) OR TS=("Leishmania infantum chagasi")) OR TS=((chagasi AND "Leishmania infantum"))) OR TS=(("infantum chagasi" AND Leishmania))) AND TS=(IRAN)) AND TS=(IRAN)	250
#2	(((((TS=("kala-azar")) OR TS=(kalaazar)) OR TS=("Kala Azar")) OR TS=((Leishmaniasis AND Visceral))) OR TS=((Fever AND Black))) AND TS=(IRAN)	480
#3	((((((((((((TS=((Phlebotomus AND kandelaki))) OR TS=((Phlebotomus AND major))) OR TS=("Phlebotomus perfiliewi")) OR TS=("P. perfiliewi")) OR TS=("Phlebotomus keshishiani")) OR TS=("P. keshishiani")) OR TS=("Phlebotomus tobbi")) OR TS=("P. tobbi")) OR TS=("Phlebotomus alexandri")) OR TS=("Ph. Alexandri")) OR TS=("P. alexandri"))) OR TS=("p. major")) AND TS=(IRAN)	140
	#1 OR #2 OR #3	**609**

Search syntax in Embase

(https://www.embase.com/)

	Search terms/keywords	*N*
#1	(leishmania:ti,ab,kw AND infantum:ti,ab,kw) OR 'leishmania infantum':ti,ab,kw OR 'leishmania donovani infantum':ti,ab,kw OR ('donovani infantum':ti,ab,kw AND leishmania:ti,ab,kw) OR (infantum:ti,ab,kw AND 'leishmania donovani':ti,ab,kw) OR 'leishmania chagasi':ti,ab,kw OR (chagasi:ti,ab,kw AND leishmania:ti,ab,kw) OR 'leishmania donovani chagasi':ti,ab,kw OR ('donovani chagasi':ti,ab,kw AND leishmania:ti,ab,kw) OR (chagasi:ti,ab,kw AND 'leishmania chagasi':ti,ab,kw) OR 'leishmania infantum chagasi':ti,ab,kw OR (chagasi:ti,ab,kw AND 'leishmania infantum':ti,ab,kw) OR 'leishmania mediterranea':ti,ab,kw OR ('infantum chagasi':ti,ab,kw AND leishmania:ti,ab,kw)) AND iran:ti,ab,kw	219
#2	('kala-azar':ti,ab,kw OR kalaazar:ti,ab,kw OR 'kala azar':ti,ab,kw OR (leishmaniasis:ti,ab,kw AND visceral:ti,ab,kw) OR (fever:ti,ab,kw AND black:ti,ab,kw)) AND iran:ti,ab,kw	359
#3	(phlebotomus:ti,ab,kw AND kandelaki:ti,ab,kw OR (phlebotomus:ti,ab,kw AND major:ti,ab,kw) OR 'p. major':ti,ab,kw OR 'phlebotomus perfiliewi':ti,ab,kw OR 'p. perfiliewi':ti,ab,kw OR 'phlebotomus keshishiani':ti,ab,kw OR 'p. keshishiani':ti,ab,kw OR 'phlebotomus tobbi':ti,ab,kw OR 'p. tobbi':ti,ab,kw OR 'phlebotomus alexandri':ti,ab,kw OR 'ph. alexandri':ti,ab,kw OR 'p. alexandri':ti,ab,kw) AND iran:ti,ab,kw	136
	#1 OR #2 OR #3	**495**

Search syntax in Scopus

(scopus.com)

	Search terms/keywords	*N*
#1	(TITLE-ABS-KEY ((leishmania AND infantum) OR "leishmania infantum" OR **"leishmania mediterranea" OR** "leishmania donovani infantum" OR ("donovani infantum" AND leishmania) OR (infantum AND "leishmania donovani") OR "leishmania chagasi" OR (chagasi AND leishmania) OR "leishmania donovani chagasi" OR ("donovani chagasi" AND leishmania) OR (chagasi AND "leishmania chagasi") OR "leishmania infantum chagasi" OR (chagasi AND "leishmania infantum") OR ("infantum chagasi" AND leishmania)) AND TITLE-ABS-KEY (iran))	259
#2	(TITLE-ABS-KEY ("kala-azar" OR kalaazar OR "Kala Azar" OR (leishmaniasis AND visceral) OR (fever AND black)) AND TITLE-ABS-KEY (iran))	407
#3	(TITLE-ABS-KEY ((phlebotomus AND kandelaki) OR (phlebotomus AND major) OR "P. major" OR "Phlebotomus perfiliewi" OR "P. perfiliewi" OR "Phlebotomus keshishiani" OR "P. keshishiani" OR "Phlebotomus tobbi" OR "P. tobbi" OR "Phlebotomus alexandri" OR "Ph. Alexandri" OR "P. alexandri") AND TITLE-ABS-KEY (iran))	172
	#1 OR #2 OR #3	**588**

	Other databases	*N*
1	**WHO Iris:** http://apps.who.int/iris/simple-search	296
2	**Lilacs:** https://lilacs.bvsalud.org/en/	10
3	**PAHO Iris:** https://iris.paho.org/	4