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Narrative Review

The Checklist and Distribution of Sand Flies (Diptera: Psychodidae) of Guilan Province and Their Medical Importance With a Taxonomic Note on the Name *Sergentomyia murgabiensis sintoni*

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Running Title Sand Flies of Guilan Province

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ABSTRACT

Background: Different forms of leishmaniasis are important infectious diseases in Iran. While Rudbar County of Guilan Province has been introduced as a cutaneous leishmaniasis focus, there are few published data about the phlebotomine sand flies (Diptera: Psychodidae, Phlebotominae) of the province and their medical importance.

Objectives: The present study is going to provide a review of sand fly-borne infections in Guilan Province and a checklist of sand flies of the province. Also, a note is presented on the name *Sergentomyia murgabiensis sintoni*.

Materials & Methods: Using the main databases such as Web of Science, PubMed, Scopus, Google Scholar, Scientific Information Database (SID), IranMedex and Magiran which were searched up to September 2022 and reviewing the literature, the available data about the sand fly-borne diseases of Iran and Guilan Province were extracted and analyzed.

Results: In total, 11 species representing two genera of sand flies, *Phlebotomus* and *Sergentomyia*, are found in Guilan Province. The checklist and distribution of sand flies of the province have been provided. All species of the genus *Phlebotomus* in the province are proven or suspected vectors of leishmaniasis. Sand fly-borne leishmaniasis (cutaneous and visceral), sand fly fever and lizard leishmaniasis, which are among the endemic infections of the province, are discussed. Also, a taxonomic note is presented on the name *Sergentomyia murgabiensis sintoni*.

Conclusion: The prevalence of suspected or proven vectors of sand fly-borne diseases in Guilan Province is noteworthy. The study of the ecology of sand flies and detecting the exact vectors and reservoirs of leishmaniasis and phlebotomine fever by serological or molecular-specific tests in the province are recommended. Moreover, additional samplings of sand flies from localities, where have not been studied, are necessary.

Keywords: *Phlebotomus*, *Sergentomyia*, Cutaneous leishmaniasis, Lizard leishmaniasis, Sand fly fever, Visceral leishmaniasis

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1. Introduction

By now, approximately one thousand sand fly species (Diptera: Psychodidae, Phlebotominae) have been described worldwide [1]. Traditionally, phlebotomines include six genera of the Old World *Chinius*, *Phlebotomus*, *Sergentomyia* and the New World *Brumptomyia, Lutzomyia* and *Warileya* [2, 3]; however, more recent classification has been recognized 31 genera in the subfamily [1].

Among phlebotomine sand flies, at least 98 species of *Phlebotomus* and *Lutzomyia* are proven or suspected vectors of human leishmaniasis, also sand flies play a role in the transmission of viral infections caused by *Phlebovirus* (Phenuiviridae) and *Vesiculovirus* (Rhabdoviridae) and the causal agent of bartonellosis (the bacterium *Bartonella bacilliformis*) [4].

One of the most recent checklists of Iranian sand flies composes 54 species, 31 species of *Phlebotomus* and 23 species of *Sergentomyia* [5]. While at least 62 species of sand flies have been reported from Iran [5-12], there are some controversial debates about the occurrence of some species and the numbers of Iranian species are mentioned from 44 to 50 by different authors [13-16].

The present article is going to provide a comprehensive review of sand fly-borne infections in Guilan Province and a checklist and distribution of sand flies of the province. Also, a taxonomic note is presented on the name *Sergentomyia murgabiensis sintoni*.

2. Materials and Methods

This investigation reviewed the articles indexed in Web of Science, PubMed, Scopus, Google Scholar, Scientific Information Database (SID), IranMedex and Magiran databases which were searched up to September 2022. First, the main textbooks or chapters of textbooks of medical and veterinary entomology pertaining to sand flies [2, 17] were reviewed to extract sand fly-borne diseases. Also, the aforementioned databases were browsed to obtain literature that indicates sand fly-borne diseases, using keywords like “sand fly-borne diseases”, “sand fly-borne infections”, “sand fly-borne pathogens” and “sand fly-borne viruses”. Then, sand fly-borne disease names were extracted from identified literature. Afterward, the databases were browsed to obtain literature reporting the occurrence of sand fly-borne diseases in animals and humans in Guilan Province or Iran. At last, the main keywords were browsed as “extracted sand fly-borne disease names, Iran, Iranian, Guilan, Gilan” and “extracted sand fly-borne pathogen names, Iran, Iranian, Guilan, Gilan”. The main sand fly-borne disease names were ‘bartonellosis, leishmaniasis, sand fly fever’ and the sand fly-borne pathogen generic names were ‘*Bartonella*, *Leishmania*, *Phlebovirus*, and *Vesiculovirus*’. In addition, the references of the selected literature were also reviewed to increase the coverage of the search. With few exceptions, only data from books or peer-reviewed articles were included in the final analysis. Ashford’s article [18] was consulted for the current usage of nomenclature for some parasitic diseases, especially arthropod-borne ones. Also, other names of sand fly-borne diseases (if they were applicable) were extracted and mentioned from the literature. Concerning each disease, data related to infectious agents (pathogens), distribution, reservoir or host (human and animals) and disease prevalence (if there were available) in Guilan Province were extracted and presented from the literature. Also, an updated checklist and distribution of sand flies of Guilan Province was presented. Galati et al. [1] was followed for the phlebotomine name genera and subgenera abbreviations. It is noteworthy that, sand fly-borne Isfahan virus (ISFV) (Rhabdoviridae: *Vesiculovirus*), which was isolated from pools of *Ph. papatasi* for the first time in Isfahan Province of Iran [19, 20], has not been found in Guilan Province. Hence that is not reviewed in the present article.

Checklist and distribution of sand flies in Guilan Province

There are few published documents about the sand flies of Guilan Province. Only four species including *Ph. kandelakii*, *Ph. papatasi*, *Ph. sergenti* and *Ph. tobbi* were recorded in the province up to 1961 by Adler et al. [21] and Mesghali [22]. Surprisingly, Adler et al. [21] described the species *Ph. tobbi* for the first time from Rasht, the capital of Guilan Province. After that, there was no report about the sand fly fauna of the province up to 2020 when Norouzi et al. [23, 24] reported seven species new to the province fauna. In that study, the ecology of some sand flies was studied and the presence of *Ph. neglectus* (*Ph. major krimensis* as a synonym and morphotype) was verified in the province and Iran [23, 24]. During that investigation, sampling was carried out in seven counties (out of 17) of the province and sand flies were collected from five counties [23, 24]. Thus, 11 species representing two genera of sand flies are found in Guilan Province as follows:

1. *Phlebotomus* (*Adlerius*) *halepensis* Theodor, 1958

2. *Ph.* (*Larroussius*) *kandeladii* Shchurenkova, 1929

3. *Ph.* (*Lar.*) *neglectus* Tonnoir, 1921

4. *Ph.* (*Lar.*) *perfiliewi* Parrot, 1930

5. *Ph.* (*Lar.*) *tobbi* Adler & Theodor, 1930

6. *Ph.* (*Paraphlebotomus*) *sergenti* Parrot, 1917

7. *Ph.* (*Phlebotomus*) *papatasi* (Scopoli, 1786)

8. *Sergentomyia* (*Parrotomyia*) *baghdadis* (Adler & Theodor, 1929)

9. *Se.* (*Sergentomyia) dentata* (Sinton, 1933)

10. *Se.* (*Sintonius*) *clydei* (Sinton, 1928)

11. *Se.* (*Sin.*) *tiberiadis* (Adler, Theodor & Lourie, 1930)

The distribution of sand flies in Guilan Province is displayed in Table 1. The exact localities of the sand fly collection in the province have been presented by Norouzi et al. and Norouzi et al. [23, 24]. Among the aforementioned sand flies, *Ph. papatasi* [25-80] and *Ph. sergenti* [25, 26, 29, 44, 55, 67, 71, 81, 82] are known the proven and suspected vectors of zoonotic cutaneous leishmaniasis (ZCL) and anthroponotic cutaneous leishmaniasis (ACL) in Iran, respectively, and four species as the suspected vectors of visceral leishmaniasis (VL) (Kala-azar): *Ph. kandelakii* [83-86], *Ph. neglectus* (as *Ph. major s.l.*) [87-89], *Ph. perfiliewi* [83, 84, 90-93] and *Ph. tobbi* [94]. *Phlebotomus halepensis* is known a suspected vector of VL in other countries of the western Palaearctic Region [4]. It is noteworthy that Yaghoobi-Ershadi [14] only mentioned *Ph. papatasi* proven vector in Iran according to the generally accepted criteria for incriminating *Leishmania* vectors and mentioned other species suspected vectors; however, Maroli et al. [4] also introduced *Ph. neglectus* (as *Ph. major s.l.*), *Ph. segenti*, *Ph. perrfilievi transcaucasicus* (as *Ph. transcaucasicus*) proven vectors in Iran. *Sergentomyia clydei* [25, 29, 95] and *Se. dentata* [84, 96] are assumed to play a role in the transmission of lizard leishmaniasis in Iran. Also, *Ph. papatasi* is considered a potential secondary vector of lizard leishmaniasis [97, 98]. Moreover, *Ph. neglectus* [99], *Ph. papatasi* [19] and *Ph. perfiliewi* [100] are known vec-

Table 1. Distribution of sand flies in Guilan Province based on counties

County / Species	Amlash	Anzali	Astaneashrafieh	Astara	Fuman	Khomam	Lahijan	Langroud	Masal	Rasht	Rezvanshahr	Rudbar	Rudsar	Shaft	Siahkal	Soomesara	Talish
Ph. halepensis	-	-	-	-	-	-	-	-	-	-	-	*	-	-	-	-	-
Ph. kandeladii	-	-	-	-	-	-	-	-	-	*	-	*	-	-	-	-	-
Ph. neglectus	-	-	-	-	-	-	-	-	-	-	-	*	-	-	-	-	-
Ph. perfiliewi	-	-	-	*	-	-	-	-	-	-	-	*	-	-	-	-	-
Ph. tobbi	-	-	-	-	-	-	-	-	-	*	-	*	*	-	*	-	-
Ph. sergenti	-	-	-	*	-	-	-	-	-	-	-	*	-	-	-	-	-
Ph. papatasi	-	-	-	-	-	-	-	-	-	*[1]	-	*	-	-	-	-	-
Se. baghdadis	-	-	-	-	-	-	-	-	-	-	-	*	-	-	-	-	-
Se. dentata	-	-	-	-	-	-	-	-	-	-	-	*	-	-	-	-	-
Se. clydei	-	-	-	-	-	-	-	-	-	-	-	*	-	-	-	-	-
Se. tiberiadis	-	-	-	-	-	-	-	-	-	-	-	*	-	-	-	-	-

[1] Based on Adler et al. [21]

Ph: *Phlebotomus*; *Se*: *Sergentomyia*

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tors of sand fly fever. There is no information about the vector potential of the aforementioned species in Guilan Province. Also, many localities (counties) of the province have not been investigated for the sand fly fauna yet.

Medical importance of sand flies in Guilan Province

Leishmaniasis or leishmaniosis

Human leishmaniasis or leishmaniosis caused by different species of the obligate protozoan parasites of the genus *Leishmania* (Trypanosomatida: Trypanosomatidae) biologically and exclusively are vectored by the bite of sand flies. Different forms of the disease are cutaneous (including anthroponotic, zoonotic and diffuse), visceral and muco-cutaneous (espundia). The infection is considered a vector-borne, neglected and mainly zoonotic disease. Different mammal species, especially canines and rodents, play a role as animal reservoir hosts for zoonotic forms of leishmaniasis [14, 97]. Currently, the genus *Leishmania* includes at least 53 species [97]. The species that cause disease in humans develop in the hindgut and midgut (prepylarian) of sand flies, the New World subgenus *Viannia*, or just in the midgut (suprapylarian), the subgenus *Leishmania* [97, 101].

More than 20000 human cases of CL and VL are annually reported from Iran [41] with about 80% of the cases being ZCL [14, 102]. The average annual incidence of CL is 30.9 per hundred thousand people [103]. The incidence and burden of CL have not decreased in recent years [104]. The indigenous transmission of CL is found in at least 19 provinces (out of 31) of the country [105] and the present article). The animal reservoir hosts of ZCL are different rodent species, especially the great gerbil *Rhombomys opimus* [14]. Visceral leishmaniasis is sporadically reported from all provinces with four main endemic foci in northwestern (Ardebil and East Azerbaijan Provinces) and southern (Fars and Bushehr Provinces) Iran. There are 100-300 new cases of VL annually in the country [106]. The main reservoir host is human; however, domestic dogs have also a role as animal reservoir hosts [14, 106].

Because of the lowest incidence of CL in Guilan Province among 31 provinces of Iran [103] and very rare cases of VL in the province [102], leishmaniasis has not been considered an important infectious disease there. However, a few indigenous cases of the disease (especially CL) always have been yearly reported in Guilan Province, especially in Rudbar County [102]. Adler et al. [21] have noted “a few” autochthonous cases of human leishmaniasis in Rasht, capital of Guilan Province. Golchay et al. [107] have reported three cases of CL in the province and introduced CL as an endemic disease in Guilan Province. Nadim et al. [108] have mentioned that Rudsar, located in the east of Guilan Province, could be considered a less important focus of CL. Majidi-Shad et al. [109] have introduced Rudbar County of the province as a new focus of CL. During the 20-year period of 2002–2021, up to 21 autochthonous cases of CL and/or VL have been recorded in Guilan Province yearly, especially in Rudbar County [102] (Figure 1). Recently, Amir Niaye Shad et al. [110] found that 1.52% of children under 12 years old are serologically positive against *Leishmania infantum* antigen using direct agglutination test (DAT) in Rudbar County. Although, all *Phlebotomus* species collected from Guilan Province are suspected or proven vectors of VL or CL, there is no information about their vector potential in the province. Also, there is no information about the reservoirs of leishmaniasis in the region.

Sand fly fever, papatasi fever, phlebotomine fever, *Phlebotomus* fever or three-day fever

Sand fly fever, is caused by different sand fly-borne phleboviruses (SFN-SV) (Phenuiviridae: *Phlebovirus*), which are transmitted in the Old World by species of the genus *Phlebotomus*, and probably also the genus *Sergentomyia*, and in the New World by species of the genus *Lutzomyia*. Different vertebrates including bats, carnivora, insectivora, rodents and sheep, may serve as hosts in nature. Sand fly fever caused by most of the sand fly-borne phleboviruses is a self-limiting influenza-like disease without mortality, however, acute meningitis or meningo-encephalitis has been reported for Toscana virus (TOSV) in several European countries [3, 100, 111-114]. The main vector is *Ph. papatasi*, the distribution of which coincides closely with the distribution of the disease. Dashli virus (DASHV), Karimabad virus (KARV), sand fly fever Naples virus (SFNV), sand fly fever Sicilian virus (SFSV) and Tehran virus (THEV) have been isolated from *Ph. papatasi* [19, 100, 113, 115]. Also, SFSV was isolated from *Ph. ariasi* in Algeria [116]. Corfou virus (CFUV), closely related to SFSV, was isolated from *Ph. neglectus* (as *Ph. major*) in Greece [99]. In Europe, Arbia virus (ARBV), closely related to Salehabad virus (SALV), SFNV and TOSV were isolated from *Ph. perfiliewi* [100] and *Ph. perniciosus* [100, 117]. TOSV has been isolated from *Se. minuta* [118] and Massilia virus (MASV), closely related to SFNV, has been isolated from *Ph. perniciosus* [119].

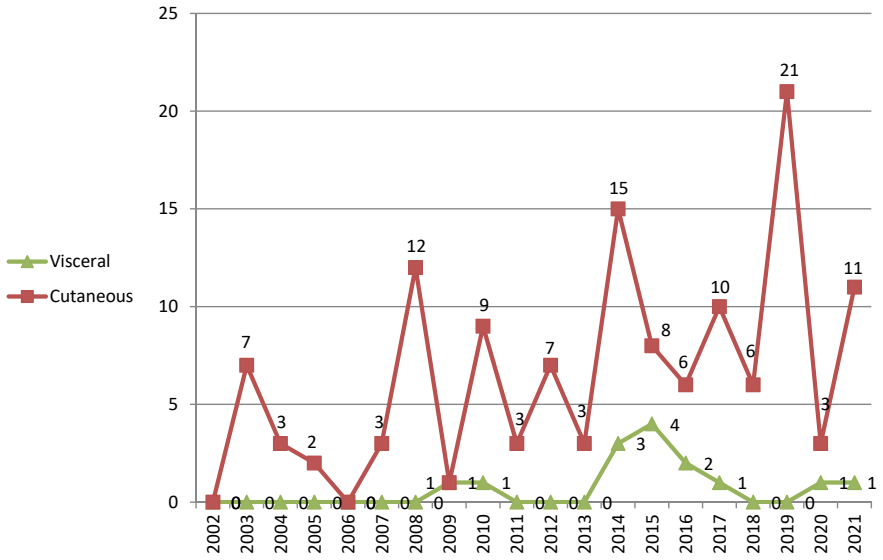

Figure 1. Trend of the indigenous human leishmaniasis cases (cutaneous and visceral) in Guilan Province during 2002–2021
Center of Disease Control, Health Vice-Chancellorship, Guilan University of Medical Sciences.

Historically, the first reports of sand fly fever infection in Iran were by foreign investigators in the 1940s and 1950s [112, 120, 121]. Eight sand fly fever viruses have been found in Iran: DASHV, KARV, SFNV, SALV, SFSV, THEV, TOSV and sand fly fever Cyprus virus (SFCV). They are reported from at least ten provinces: East Azerbaijan, Golestan, Guilan, Ilam, Isfahan, Kermanshah, Khuzistan, Mazandaran, Razavi Khorasan and Tehran. It seems that while Naples and Sicilian viruses are the most prevalent viruses in most studied areas, Karimabad virus is most abundant in Isfahan Province, in central Iran, and is also very common in Razavi Khorasan Province, in north-eastern Iran, according to seroepidemiological studies [19, 115, 122-133]. There is doubt about the occurrence of SFCV and TOSV in Iran because of the rarity of cases and probable cross-reaction between viral serotypes [132]. In addition to humans, sand fly-borne phleboviruses have been isolated from *Ph. papatasi*, possibly *Ph. caucasicus*, *Sergentomyia* species, sheep and the gerbil *Rhombomys opimus* in Iran [19, 115, 126].

Saidi [133] found seropositive antibodies for KARV in 3% of preschool children in the Caspian area, including Guilan Province, using hemagglutination inhibition (HI) tests. Tesh et al. [123, 124] reported positive neutralization tests for humans in different urban areas of Rasht in Guilan Province: SFSV (12.9%) and SFNV (21.5%). Although, sand fly fever infection and its main vector, *Ph. papatasi*, and also *Ph. neglectus* and *Ph. perfiliewi* [19, 99, 100] are known in Guilan Province, there is no information about its exact vector and reservoir in the province.

Lizard leishmaniasis

Lizard leishmaniasis, caused by the subgenus *Sauroleishmania* of the genus *Leishmania* which is not pathogenic for mammals, is found in reptiles. Currently, the subgenus includes 21 species. They infect many different reptile species mainly lizards of the families Agamidae, Gekkonidae, Iguanidae, Lacertidae and Scincidae. However, there are some reports of the detection of this subgenus species in the blood of some mammals such as rodents, canines and humans. In general, it is considered that reptiles are infected by the bite and/or ingestion of reptile-biting sand flies of the genus *Sergentomyia*, although some *Phlebotomus* species, such as *Ph. caucasicus*, *Ph. papatasi* and *Ph. perniciosus*, are introduced potential secondary vectors. The parasites develop in the hindgut of sand flies (hypopylarian) [97, 98].

In Iran, the infections of lizard leishmaniasis are found in five lizard species: *Laudakia melanura* (as *Agama melanura*), *Mesalina watsonana* (as *Eremias guttulata watsonana*), *Paralaudakia caucasia* (as *Agama caucasia*), *Tenuidactylus caspius* (as *Cyrtopodion caspius*) and *Trapelus agilis* (as *Agama agilis*) in at least four provinces: Golestan, Guilan, Khuzistan and Razavi Khorasan [134-137]. Also, *Sauroleishmania* promastigotes are isolated from three *Sergentomyia* species: *Se. clydei* [25, 29, 95] , *Se. dentata* [84,

96] and *Se. murgabiensis sintoni* (as *Se. sintoni*) [27, 29-31, 36, 38, 39, 95, 136-139]. Also, *L. major* and *L. near gerbilli* have been detected in *Se. murgabiensis sintoni* (as *Se. sintoni*) by PCR [55, 140].

The promastigotes of *Sauroleishmania* are reported in the lizard Caucasian agama *Paralaudakia caucasia* (as *Agama caucasia*) in Manjil of Guilan Province [135]. Two species *Se. clydei* and *Se. dentata* collected from Guilan Province are known vectors of the lizard leishmaniasis and *Ph. papatasi* is introduced potential secondary vector [25, 29, 84, 95, 96, 98]. However, there is no information about the vector potential of the aforementioned sand flies in the province.

Taxonomic note on the name *Sergentomyia murgabiensis sintoni*

Iranian researchers use the name '*Se. sintoni* Pringle, 1953', as a species rank, without any specified taxonomic evidence [5, 6, 14, 27, 29-31, 36, 38, 39, 55, 95, 136-139], while that name is internationally considered a subspecies or even synonym of the valid species name *Se. murgabiensis* (Perfil'ev, 1939) [8, 141]. Pringle [142] described '*Se. sintoni*' as a species, however Perfil'ev [143] treated it as a synonym of *Se. arpaklensis* (Perfil'ev, 1933). Also, Artemiev [7] considered it a synonym of *Se. murgabiensis* and later as a subspecies of *Se. murgabiensis* [144]. The subspecies rank of *Se. murgabienisis sintoni* was adopted in "A Catalogue of Old World Phlebotomine Sandflies (Diptera: Psychodidae, Phlebotominae)" [8]. *Sergentomyia murgabiensis* consists of three valid subspecies: *murgabiensis murgabiensis*, *murgabiensis pashtunica* Artemiev, 1974 and *murgabiensis sintoni* [8]. Krüger et al. [141] reported that a specimen of *Se. murgabiensis* from Afghanistan was found to share 97%-99% nucleotide identity with Iranian '*Se. sintoni*' in its cyt b gene, indicating possible conspecificity. They concluded that if the synonymy of '*Se. sintoni*' with *Se. murgabiensis* was proven, '*Se. sintoni*' would become a junior synonym.

Also, Sinton [145] suggested that *Se. arpaklensis* is apparently identical to *Se. dentata*. Artemiev [144] treated *Se. arpaklensis* as a synonym of *Se. murgabiensis*. However, the type series of *Se. arpaklensis* consists of at least two morphological forms including *Se. dentata* and *Se. arpaklensis* [8, 143]. Theodor and-Mesghali [146] treated *Se. arpaklensis* as a subspecies of *Se. dentata*, however, Perfil'ev [143] disagreed with that and considered *Se. arpaklensis* as a valid species. It seems that the type series of *Se. arpaklensis* have become associated with three taxa namely *Se. arpaklensis*, *Se. dentata* and *Se. murgabiensis* and the taxonomic status of *Se. arpaklensis* awaits the designation of a lectotype. Thus, if *Se. arpaklensis* becomes a valid species, *Se. murgabiensis* will be a junior synonym [8].

Moreover, Theodor and Mesghali [146] mentioned a form of '*sintoni*' from northern Iran which was not differentiated from *Se. arpaklensis* and/or '*Se. dentata arpaklensis*' and a southern form that was similar to *Se. antennata*. They suggested this southern form as a subspecies of '*sintoni*'. However, Lewis & Büttiker [147], based on the comparison of the specimens of *Se. antennata* from Saudi Arabia with the form of '*sintoni*' from southern Iran, concluded that the southern form of '*sintoni*' from Iran is a synonym of *Se. antennata*. Hence, they were in doubt about the specific distinction between *Se. murgabiensis* and *Se. antennata*, because Artemiev [7] treated '*sintoni*' as a synonym of *Se. murgabiensis* and later as a subspecies of *Se. murgabiensis* [144].

At present time, *Se. murgabiensis* is a valid species and '*sintoni*' is one of its subspecies or possibly synonym [8, 141]. Whether *Se. murgabiensis* is a synonym of *Se. arpaklensis* or not, the use of '*Se. sintoni*' as a valid species by Iranian researchers does not seem to be accurate. Because, if *Se. murgabiensis* becomes a synonym of *Se. arpaklensis*, then '*sintoni*' will be a subspecies or possible synonym of *Se. arpaklensis*. Hence, it is suggested using the name *Se. murgabiensis* or *Se. murgabiensis sintoni* in the literature instead of '*Se. sintoni*', up to that time when new morphological or molecular taxonomic evidence or the designation of new type is presented.

3. Conclusion

All collected *Phlebotomus* species in Guilan Province are suspected or proven vectors of CL, VL and/or sand fly fever in Iran or adjoining countries. Also, two species of *Sergentomyia* are assumed to play a role in the transmission of lizard leishmaniasis. The investigation of bionomics of suspected or proven vectors and detecting the exact vectors and reservoirs of leishmaniasis and three-day fever by means of serological or molecular-specific tests in Guilan Province should be the subject of future studies. Also, additional samplings of sand flies from localities, where have not been studied, are necessary.

Ethical Considerations

Compliance with ethical guidelines

This article is a narrative review with no human or animal sample.

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Authors' contributions

Conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing–original draft, preparation, writing–review & editing, supervision: Shahyad Azari-Hamidian; Visualization: Behzad Norouzi and Shahyad Azari-Hamidian; Rerview: Shahyad Azari-Hamidian , Behzad Norouzi and Hannaneh Maleki.

Conflict of interest

The authors declare no conflict of interest.

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