

Review Article

Control of Phlebotomine Sand Flies in Iran: A Review Article

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Abstract

Leishmaniasis has long been known as a significant public health challenge in many parts of Iran. *Phlebotomus papatasi* and *P. sergenti* are the vectors of Zoonotic Cutaneous Leishmaniasis and Anthroponotic Cutaneous Leishmaniasis respectively, and 5 species of sand flies including *P. kandelakii*, *P. neglectus*, *P. perfilliewi*, *P. keshishiani* and *P. alexandri* are considered as probable vectors of Zoonotic visceral leishmaniasis. A literature search was performed of the relevant multiple databases from 1966 to 2013 to include studies on sand flies, vector control, leishmaniasis, *Phlebotomus*. Sand fly control in Iran began in 1966 by Iranian researchers, and long-term evaluation of its effects was completed in the study areas of the country. Herein, a review of vector control strategies in Iran to combat leishmaniasis including indoor residual spraying, application of chemicals in rodent burrows, impregnation of bed nets and curtains with insecticides, the use of insect repellents, impregnation of dog collars and the susceptibility of sand fly vectors to various insecticides has been summarized thus far. The investigation of the behavioral patterns of the adults of different sand fly species, introduction of biological insecticide agents, the use of insecticidal plants and other novel strategies for the control of sand fly populations have received much attention in the areas of studies, hence should be recommended and improved since they provide optimistic results.

Keywords: Leishmaniasis, *Phlebotomus*, Sand flies, Vector control, Iran

Introduction

Leishmaniasis remains a significant public health problem over a wide geographical area in Iran. Cutaneous and visceral leishmaniasis is historical endemic disease in the country. Cutaneous leishmaniasis (CL) occurs in two forms, Anthroponotic Cutaneous Leishmaniasis (ACL) and Zoonotic Cutaneous Leishmaniasis (ZCL). *Leishmania major*, the causative agent of ZCL, is endemic in many rural areas of 17 out of the 31 provinces of Iran. The principal vector of ZCL has been identified as *Phlebotomus papatasi* which has a wide range of distribution, and four species of rodents belonging to the family Cricetidae involving *Rhombomys opimus*, *Meriones libycus*, *Tatera indica* and *M. hurrianae* are considered as the main reservoir hosts in different parts of Iran. Over the last three decades,

the increasing number of ZCL cases in the traditional foci and their transmission to new foci in the western, southern, southwestern (near the central desert), and northeastern regions of Iran has been of major concern to the health authorities (Yaghoobi-Ershadi and Javadian 1995, Yaghoobi-Ershadi et al. 2001, 2003, Akhavan et al. 2007).

Anthroponotic Cutaneous Leishmaniasis has been a very old endemic disease in many parts of Iran. The burden of the disease was greatly reduced in many foci following the introduction of antimalarial measures in Iran, however, its foci remained active in some large and medium-sized cities such as Tehran, Mashhad, Neishabur, and Sabzvar in the northeast, Shiraz in the south, Kerman and Bam in the southeast (Nadim and Tahvildari-Bidruni 1977,

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Yaghoobi-Ershadi et al. 2002). *Leishmania tropica*, recognized as the agent of ACL, is currently prevalent in 14 foci located in 8 provinces. The vector responsible for the maintenance of *L. tropica* is *P. sergenti*, and human serve as the main reservoir host of the disease, however infected dogs play a crucial role as animal reservoir host of the parasite (Yaghoobi-Ershadi et al. 2002, 2008).

Leishmania infantum, the causative agent of Zoonotic Visceral Leishmaniasis (ZVL), has been reported sporadically from all areas of the country, however, seven endemic foci are located in the southern, southwestern, western, northwestern and northeastern regions of the country (Nadim et al. 1978, Nadim 2008). *Leishmania tropica* has also been known to cause the disease in immunosuppressed patients (Mohebali 2013). Five species of sand flies including *P. kandelakii*, *P. neglectus*, *P. perfiliewi*, *P. keshishiani*, *P. alexandri* (Yaghoobi-Ershadi 2012) are considered as probable vectors of ZVL. Dogs, foxes, jackals and wolves have been found infected in different parts, but dogs are the main reservoir host (Navid-Hamidi et al. 1982, Nadim 2008). The mean annual number of leishmaniasis cases has been projected as almost 20,000 in Iran during 1983–2014. Nearly eighty percent of these cases are of the ZCL form, 0.5% classified as ZVL, and the rest are ACL (Yaghoobi-Ershadi and Javadian 1995, Yaghoobi-Ershadi et al. 2001, Akhavan et al. 2007). Based on proven epidemiological studies, the provinces of Ilam in the west, Fars in the south and Khorassane-Razavi in the northeast have recorded the highest incidence of CL, ranging between 59.9–98.8 cases per 100,000 inhabitants (Shirzadi et al. 2015).

Official publications have revealed the existence of 48 species of sand flies in the country, 30 species belonging to the genus *Phlebotomus*, and 18 species of the genus *Sergentomyia* (Yaghoobi-Ershadi 2012, Zahraei-Ramazani et al. 2013, 2015).

The practical application of sand fly control measures has been appraised in most Old World situations (Alexander and Maroli 2003). Indoor Residual Spraying (IRS) with DDT (dichlorodiphenyltrichloroethane) against malaria vectors in India during the 1950s and again in the 1970s was effective in reducing the density of *P. argentipes* and Visceral Leishmaniasis (VL) cases, but after the cessation of IRS, sand fly population and incidence of VL increased (Kishore et al. 2006, Thakur 2007). Indications of the impact of DDT spraying on sand flies were obtained from a trial conducted in a few coastal villages in Ramanathapuram district, Tamil Nadu of India during 1953–1954. No sand flies could be collected from villages sprayed with DDT at a rate of 1g/m² and 2g/m² for seven and 21 months respectively (WHO 1980).

DDT and BHC (Benzene hexachloride) have been used extensively in the former Soviet Union for sand fly control (Perfiliev 1966). In a field trial in China, a village sprayed at a dosage of 1.58gr DDT/m² against *P. chinensis* in 1951 was protected by a subsequent reduction of sand fly up to eight years, while in another village sprayed in the same year at a dosage of 0.128gr gamma HCH/m², the sand fly density showed an annual increase until it reached the level of density recorded in an unsprayed area in 1956. In a further trial a mixture of both insecticides was applied in a village in 1953, and very few sand flies were observed for six years after spraying (Wang and Wu 1959).

In Palestine, IRS with DDT provided more than 50 days of protection against sand flies (Jacusiel 1947). During 2003–2004, a residual spraying program combined with the distribution of permethrin-treated bed nets in the Thi Qar Governate of Iraq resulted in a significant reduction in VL cases, however, no information was reported on the insecticides used or any impact of treatment on the density of sand flies (Jassim et al. 2006).

Methods

The electronic databases including Pub-Med, Web of Science, Literature retrieval System of the Armed Forces Pest Management Board, Google Scholar and MEDLINE were searched from 1966 to 2013 using the term Iran in combination with the keywords: Sand flies, Vector control, Leishmaniasis, *Phlebotomus*. A special emphasis was performed to refer to published original articles within the last 3 decades in international scientific journals that deal with vector control of sand flies in Iran.

Control Strategies

Indoor Residual Spraying

Leishmaniasis control has been a matter of interest by different researchers at the Institute of Public Health, University of Tehran, in coincidence with the beginning of epidemiological studies on CL in 1965. Table 1 summarizes the comparison results for the intervention against leishmaniasis vectors in Iran during 1966–2010. The effect of anti-malarial spraying on sand fly populations and the incidence of ZCL has been evaluated in Esfahan Province by Nadim and Amini in 1970. They found that DDT spraying applied at a dosage of 2g/m² in April in both 1966 and 1967 reduced ZCL incidence, but the transmission of the disease was not interrupted. As the incidence in 19 sprayed villages was 3.8 per 1000 in the first year, the incidence in the second year was calculated to be 2.7 per 1000. In the control villages, the corresponding incidence was highlighted as 14.4 and 10.6 per 1000 respectively. Collection of sand flies in sprayed rooms, with the exception of the ones collected which gave negative results, while sticky paper traps placed in the same rooms gave positive results from June to the end of season, indicated that *P. papatasi* has invaded the sprayed rooms. Additional evidence was collated from

another group of sprayed villages, which showed that the number of sand flies collected from nearby rodent burrows was similar to that recorded before spraying. The abundance of sand flies, and the consequent exposure of people to their bites as they sleep on roofs, could explain how transmission persisted despite house spraying.

Long-term evaluation of the effect of anti-malarial DDT house spraying on the incidence of ZCL was completed during 1966–1971 in Esfahan, central Iran, the results of which were summarized by Seyedi-Rashti and Nadim (1973) and given in more details by the same authors in 1975. The following groups of villages were kept under surveillance (monthly or every three months) since 1963 for the detection of ZCL cases from which the annual incidence was calculated: Group I, 16 villages sprayed annually with DDT throughout 1966–1969, Group II, three villages also sprayed annually with DDT during 1966–1967, and Group III, four villages kept without spraying for comparison.

The annual incidence per 1000 population in Group I which was 8.2 and 4.6 respectively in 1964 and 1965 before spraying decreased to 0.7 in 1969 i.e. after four years of spraying; following the cessation of spraying in 1970, the incidence increased sharply to 15, after which a further increase was recorded in 1971. In Group II, which was surveyed under IRS for two consecutive years, the incidence decreased from 15.9 in 1965 to 2.9 and 5.7 in 1966 and 1967 respectively, but steadily increased after the discontinuation of spraying, reaching 17.5–19.7 during 1969–1971. In Group III (Comparison group) the annual incidence per 1000 ranged between 9–21 during 1964–1970 reaching 46.3 in 1971 when an epidemic of ZCL broke in one of the villages. Analysis of the age distribution of children's cases in previously sprayed and comparison villages indicated that once spraying was stopped, transmission was vigorously resumed through the abun-

dance of rodent reservoirs and sand flies in the vicinity of villages, striking the children who were protected during the years of spraying. From these observations, it was concluded that house spraying cannot be considered a permanent measure for the control of ZCL in an endemic area, and the feasibility of alternative control measures involving reservoir hosts and immunization should be sought.

Nadim et al. (1977) indicated that two rounds of antimalaria spraying with malathion ($2\text{g}/\text{m}^2$) reduced the level of endemicity of ZCL greatly in Khuzestan Province, southwest of Iran, thus epidemiological studies have become difficult.

The absence or scarcity of sand flies resting in sprayed rooms was taken as an indication of their susceptibility to insecticides as noted by Nadim and Amini in 1970. From his previous fauna survey in Bandar Abbas and Jask areas in southern Iran under the application of DDT, dieldrin and later malathion spraying, Mesghali (1965) inferred that *P. papatasi* hitherto has not shown any insecticide resistance, but the LC50 became higher. Although they were absent in premises freshly sprayed with malathion, they were present outdoors. Almost the same remarks were repeated in a paper dealing with *P. salehi* in Baluchestan, southeast of Iran by Mesghali and Seyedi-Rashti in 1968.

In Neishabur, Nadim and Tahvildar-e-Bidruni (1977) showed that DDT spraying at a rate of $2\text{gr}/\text{m}^2$ in and around houses of acute cases was highly effective on the control of *P. sergenti* but the endemicity remained at a little bit higher level than in the period before the outbreak.

In 1970 during an epidemic of ACL at Janatabad district, northwest of Tehran, the population of *P. sergenti* was effectively suppressed by house spraying with DDT 75% WP, at a rate of $2\text{g}/\text{m}^2$ and the transmission of the disease was halted (West Health Center of Tehran, 1970).

As the result of an earthquake (6.6 on the Richter scale) in the city of Bam (Kerman Province, southeastern Iran) on December 26, 2003, nearly all buildings were destroyed and a suitable condition was obtained for the breeding of *P. sergenti*, and there was the danger of an outbreak of ACL in this old endemic focus due to the: extent of the destruction, premature warning, raining in several times after the earthquake, movement of a large number of non-immune individuals from neighboring and other areas into the affected area and the destruction of all health facilities. According to the suggestions of Leishmaniasis Committee of Iranian Ministry of Health, residual spraying with deltamethrin at a rate of $25\text{mg}/\text{m}^2$ was applied on tents and in the remaining indoors twice, the first in May and the second in late August, 2004. Space spraying with Symprator (a combination of Cypermethrin+ Tetramethrin and Piperonyl butoxide) was also applied in different parts of the city once a week. Interestingly, the comparison of the density of *P. sergenti* before and after the occurrence of the earthquake showed that IRS with deltamethrin and space spraying with Symprator had reduced the density of the main vector significantly. In early July coincident with the first peak, the density of this species was zero. In late August coincident with second peak of the species, the density had reduced more than 8 fold in outdoors and 14 fold in indoors (Institute of Public Health, unpublished data). Susceptibility tests by WHO standard method on *P. sergenti*, collected in the city showed that the mortality for diagnostic doses of DDT 4% and deltamethrin 0.025% were 100%, which indicates that the field population of the species is susceptible to both insecticides. According to the reports of the Disease Management Center, the cases of leishmaniasis had reduced sharply in comparison with the cases of the previous year (2003) from April to October. Although we were expecting to have a serious epidemic of ACL in the city.

In 2005, IRS was applied with deltamethrin, 0.025g/m² against *P. sergenti* in the houses with ulcers and their neighboring houses in the city of Yazd, central Iran. The operations discontinued the transmission of ACL (Health Center of Yazd Province, 2005).

In order to control ACL in the endemic focus of Dehbakri, a village of Kerman Province, southeastern Iran, IRS with deltamethrin WP 50% was applied at 25mg/m² against *P. sergenti* in April 2010. The reduction of the density of the species, the percent of blood-fed and gravid sand flies and also the incidence of the disease were significant in the treated area (Aghaei-Afshar et al. 2013).

A field trial which was carried out during 1991–1993 in 80 villages of Meshkinshahr county, Ardebil Province, northwest of Iran, reduced the incidence of ZVL due to the combined application of IRS with DDT 75% WP 2g/m² in houses with human or canine cases against *P. kandelakii*, along with the culling infected dog and the introduction of

health education. The incidence was 190/100000 in 1991 which dropped to 123/100000 in 1992. The difference was statistically significant (P = 0.05). Taking into consideration that 75% of cases in the area were children between 1–4 age group, the incidence in this age group was compared before and after intervention. The incidence before intervention was 440/100000 which was reduced to 71/100000 at the end of the study (P = 0.05) (Bokaei 1994).

Indoor residual spraying is a cost effective method of controlling of *P. sergenti* in ACL foci during epidemic scenarios in Iran. In temperate regions one round of spraying with one of available insecticides is needed but in tropical areas the second round of spraying should be carried out in mid or late August in urban areas. Although spraying of houses and shelters is unlikely to be effective in ZCL and ZVL foci but one round of IRS is recommended in epidemic conditions.

Table1. Comparison results for the intervention against leishmaniasis vectors by indoor residual spraying in Iran, 1966–2010

Locality	Year	Insecticide	Dosage (gai/m ²)	Main Vector	Impact Measurement	Results	Reference
Esfahan	1966–1967	DDT (one round)	2	<i>P. papatasi</i>	Reduced ZCL incidence	With discontinuation of spraying incidence increased	Nadim and Amini 1970, Seyedi-Rashti and Nadim 1973
Khuzestan	1976	Malathion (2 rounds)	2	<i>P. papatasi</i>	As above	Long term studies did not carry out	Nadim et al. 1977
Bandar-Abbas and Jask	1965	Malathion	2	<i>P. papatasi</i>	As above	As above	Mesghali 1965
Neishabur	1976	DDT	2	<i>P. sergenti</i>	Reduced ACL incidence	Endemicity remained at a low level	Nadim and Tahvildare-Bidruni 1977
Yazd	2005	Deltamethrin	0.025 mg/m ²	<i>P. sergenti</i>	Transmission of ACL reduced sharply	As above	Health Center of Yazd Province 2005

Table 1. Continued...

Janatabad (Tehran)	1970	DDT	2	<i>P. sergenti</i>	Transmission of ACL discontinued	ACL cases disappeared	West Health Center of Tehran 1970
Bam	2004	Deltamethrin	25 mg/m ²	<i>P. sergenti</i>	Reduced density of sand fly vector	Reduced ACL incidence sharply	Institute of Public Health 2004
Dehbakri	2010	Deltamethrin	25 mg/m ²	<i>P. sergenti</i>	Reduced density, percent of blood fed and gravid sand flies	Endemicity remained at a low level	Aghaei-Afshar et al. 2013
Meshkinshahr	1991	DDT	2	<i>P. kandelakii</i>	Reduced density of the vector	Incidence of VL reduced	Bokaie 1994

Applying chemicals in rodent burrows

In 1972, in five villages with a total population of 1471 in the infected area of Esfahan, central Iran rodent burrows were dusted with 75% DDT powder within a radius of 300 meters around the villages, once every month (June, July, August and September) at a rate of 0.5g/m² in each burrow with a hand dusting equipment. Dusting of the burrows had no effect on the density of *P. papatasi*, the main vector of *L. major* in the area. This could be due to the loose nature of the soil within the area such that the insecticide dust is quickly buried under soil upon falling to the ground, having no effect on sand flies coming out from the depth of the burrows (Seyedi-Rashti and Nadim 1974).

During 1972–1973 coincident with the active season of sand flies, rodent control operations within 300 meters of the houses using poisoned bait consisting of 12–15 grams wheat containing 2.5% zinc phosphide was carried out against ZCL once every month from early June through September in 5 villages of Borkhar county, Esfahan Province, central Iran. The method was very effective in destroying the rodent reservoirs, but it was ineffective in the reduction of the incidence of the disease. Its effect on the sand flies was not evaluated in the area (Seyedi-Rashti and Nadim 1974).

In 1974, rodent control by carbon monoxide (CO) was carried out against ZCL at an area of 25 hectare in the village of Adermanabad, Borkhar County, Esfahan Province. Although it was very effective on the control of the population of great gerbil, *Rhombomys opimus*, its effect on the reduction of the density of *P. papatasi* and incidence of the disease was not evaluated (Deputy of Health, Esfahan University of Medical Sciences, 1974).

In 1978, the effect of insecticide spraying inside the rodent burrows against *P. papatasi* was evaluated in Borkhar area, Esfahan Province, central Iran. About 8000 rodent holes in an area of 38 hectare were sprayed by DDT 75% WP (4.3gr in each hole), in two rounds, the first in late June and the second round in early August. Monitoring the density of sand flies before and after the spraying showed that although the operations could reduce the population of sand flies, the density returned to its normal level after about a week. This could be due to the curving nature of rodent burrows and the resulting lack of access to the depth of holes which are considered the best resting place and oviposition of sand flies. Hence, this method has no robust effect in the reduction of sand fly population for a longer time (Moosavi 1979).

Yaghoobi-Ershadi et al. (2000) conducted

a field trial for the control of ZCL during 1997–1999 in the rural district of Badrood, Esfahan Province. Rodent control operations were carried out within a radius of 500 meters from the houses baited with 12–15 grams of wheat containing 2.5% zinc phosphide in each burrow. The evaluation showed that the control program reduced the incidence of ZCL 12 fold in the treated village compared to the control at the end of the first year of operation. Comparison of the density of *P. papatasi*, in the treated and the control area indicated that the program was effective in the reduction of the density of this species in rodent burrows of the treated area. At the end of July, coincident with the first peak of *P. papatasi* its density was 261 per 30 traps in the control area which reduced to 75/30 traps in the treated area. In the second peak (end of September) the density was 717/30 traps and 199/30 traps in the control and treated areas respectively. The operation was also effective in disturbing the sex ratio of the species which was 172 and 21.9 in the control and treated areas respectively. There was also significant difference between fed and unfed *P. papatasi*. It means that in the intervention village the ratio decreased to one-third in comparison with the control area. The method was ineffective on the density of *P. papatasi* in indoors in the study area (Motavalli-Emami 1998).

A comparative study was carried out on the effectiveness of Comavec and zinc phosphide against the great gerbil, *R. opimus* in a hyperendemic focus of ZCL in central Iran during 2011–2012. The reduction rate of rodent holes in intervention areas with Comavec and zinc phosphide was calculated to be 48.5% and 58.2% respectively and the incidence of ZCL reduced significantly in the treated areas. Comavec seems to be effective on the outdoor density of *P. papatasi*, the main vector of *L. major* (Veisi et al. 2012). In another study at the same time, a field evaluation of phostoxin and zinc phosphide was

also conducted against ZCL in four villages around the city of Esfahan, central Iran. The incidence of the disease decreased to 19.2 and 11.4 per thousand in areas treated with phostoxin and zinc phosphide respectively and the density of *P. papatasi* in outdoors of the village treated with phostoxin was lower than indoors but its density in the village treated with zinc phosphide was higher in outdoors (Akhavan et al. 2014).

Impregnated Bed nets and Curtains

Nadim et al. (1995) evaluated the use of deltamethrin (K-othrin) impregnated bed nets, 25mg per ml for the control of ACL in a restricted area in the city of Bam, Kerman Province southeast of Iran where, it was very hot during the day in summer but rather good weather at night. The results showed that the number of active cases decreased 2.6 fold in the intervention area but the transmission was not interrupted. Non-significant difference was observed between the density of *P. sergenti* in indoors of the intervention and control areas.

During 2003–2004 in a study which was conducted in the hyperendemic area of CL due to *L. major* (Borkhar, Esfahan Province, Iran) efficacy of deltamethrin impregnated bed nets and curtains, 25mg a.i/m² polyester mesh size 156 holes inch² combination with a health education program were assessed in relation to ZCL control (Yaghoobi-Ershadi et al. 2006a). The results indicated that the nets could afford a definite personal defence against sand fly bites and interrupted the transmission of ZCL in the intervention area. Non-impregnated bed nets and curtains did not give any protection against the disease. There was no significant difference in monthly density of *P. papatasi* in indoors and outdoors among the villages ($P > 0.05$).

Moosa-Kazemi et al. (2007) carried out a field evaluation of deltamethrin-impregnated bed nets and curtains with 25mg/m², in combination with a health education program against

ACL in the city of Mashhad, northeastern Iran. The area has a cooler climate in summer where people sleep in rooms at night. These nets provided very good protection against sand fly bites and subsequently reduced the transmission of ACL (4.5 fold) but there was non-significant differences in the reduction of the density of *P. sergenti* among different months. Non-impregnated bed nets and curtains did not provide any protection against the disease. Bioassays confirmed that the nets treated with deltamethrin remained effective for more than 3 months. High Performance Thin Layer Chromatography (HPTLC) analysis of deltamethrin residue on the impregnated bed nets showed that the residue of the insecticide persisted well on impregnated nets at least 15 weeks after impregnation (Moosa-Kazemi et al. 2009).

A large scale installation of deltamethrin impregnated screens and curtains, 25mg/m², combination with passive and active case surveillance and treatment was assessed in the southeastern Iranian city of Bam during 2008–2010. The city which was devastated in 2003 earthquake is known historically as a major endemic focus of ACL in the country. Comparison of cumulative incidence between the intervention and control areas before and after installation indicated a significant differential reduction in the cumulative ACL incidence in the intervention area. The authors believed that the use of impregnated screens and curtains provided a good barrier in the way of sand flies entering the buildings (Noazin et al. 2013).

Insect repellents

During the Iran-Iraq war (1980–1988) CL due to *L. major* was prevalent among the soldiers, inhabitants and emigrants in the west of the country especially in the provinces of Khuzestan, Ilam, Kermanshah, and some parts of Kurdistan (Marivan). Every year more than 10 thousand cases were reported among the

soldiers and emigrants. Based on official reports in 1982 more than 3000 military personnel referred to provincial health center of Khuzestan for treatment. The density of *P. papatasi* was in a high level, as in a study on hourly activity of sand flies, the number of biting was reported 120 in each hour during the night around the city of Dezful, Khuzestan Province. The available repellents such as Odomos (12% N, N-diethyl-benzamide) and Autan (DEET 25%) were used as topical application on face and hands by military personnel to protect them from sand fly bites. At the same time, a kind of insect repellent called "Trench Pomade" which was a mixture of diethyl-toluamide (DEET 25%) and dimethyl-phthalate (DMP 5%) in the ratio of 5:1 respectively and had been produced at the School of Pharmacy, Tehran University of Medical Sciences was widely used by soldiers which provided 11h protection against the bites of *P. papatasi*. About one million tubes of Trench pomade was produced monthly and 4000 tubes were distributed every day among the personnel. Each soldier was delivering one tube of the pomade twice in each month (Javadian E, School of Public Health, TUMS, personal communication). The vehicle of this cream is Propylene glycol and is still used by military personnel in the borderlines of the country.

Repellency effect of the plant Myrtle, *Myrtus communis* essential oil and DEET against *P. papatasi*, the main vector of ZCL was evaluated under laboratory and field conditions during 2004–2005. The modified K&D (Klun and Debboun) apparatus with Wirtex method was employed in dose-response tests (calculation of ED50 and ED90 values). Significant difference was observed between ED50 of DEET and Myrtle essential oil (P 0.05). DEET was found to be more effective as a repellent than Myrtle essential oil against *P. papatasi* (Yaghoobi-Ershadi et al. 2006b). To determine the protection time of Myrtle essential oil and DEET at the laboratory, tests

were carried out on 9 volunteers for 10 hours in 18 days. The mean protection time for Myrtel essential oil and DEET on *P. papatasi* was calculated to be 51min and 10h respectively. Significant difference was observed between the protection time of them ($P = 0.0001$). To find out the protection time of the repellency in the field, tests were carried out on 9 volunteers in the village of Matinabad, Natanz (Esfahan province) during 18 nights. The mean protection time of Myrtle essential oil 20% and DEET 20% were calculated to be 110 minutes, 28 seconds and 10 hours respectively. Significant difference was observed between the protection time of them ($P = 0.0001$).

To calculate the protection percent of Myrtle essential oil 20% and DEET 20% a total of 3981 female *P. papatasi* were collected on the treated volunteers by Myrtel essential oil (1381 flies) and control (2600 flies). No flies were collected on volunteers against *P. papatasi* for 1h following application to human volunteers but it decreased to 50% after 4h. The percentage of protection of Myrtel essential oil 20% and DEET 20% were calculated 46.41% and 100% correspondingly after 10h during 18 nights. The mean number of bites on the treated legs with Myrtel essential oil was 7.69 ± 4.51 bites human-h, whereas those figures on the control were 14.33 ± 3.95 bites/human-h. A significant difference was observed between the protection percent of Myrtel essential oil and DEET ($P = 0.0001$) (Jahanifard 2006).

Saberi et al. (2011) studied the efficacy of DEET repellent pen against ZCL in a military area in Esfahan, central Iran. The trial was carried out on 430 high school students. The results showed non-significant efficacy on the prevention of ZCL.

Asilian et al. (2003) evaluated the efficacy of permethrin-impregnated uniforms for the prevention of ZCL among 324 Iranian soldiers in the hyperendemic area of Esfahan. The uniforms were impregnated with per-

methrin and its concentration was $850\text{mg}/\text{m}^2$. Statistical analysis showed non-significant difference between the incidence of ZCL in the permethrin group and that in the control group ($P = 0.05$) and did not protect volunteers from sand fly bites.

Impregnated dog-collars

A pilot field study was implemented on the effects of deltamethrin-impregnated dog collars against sand fly bites in Azar-Shahr District, an endemic focus of ZVL in Eastern Azarbaijan Province, north-west Iran in 1999. Each dog was fitted with a plastic collar (length 48cm, weigh 20g) containing deltamethrin 40mg/g and the protective value of collars were tested against wild caught *P. papatasi*. For each test, the dog was caged in a net with 70–100 wild caught sand flies overnight. The results showed that the successful blood-feeding by *P. papatasi* was significantly reduced about 80% (Halbig et al. 2000).

A matched community-based trial undertook to investigate the epidemiological impact of applying collars to all domestic dogs in the counties of Kalaybar and Meshkin-Shahr in north-west Iran during 2000–2001. The area is considered as the main focus of ZVL in the country. Eighteen villages including nine treated and nine as control were selected. *Leishmania infantum* zymodeme MON-1 is the causative agent of the disease and the probable sand fly vector is *P. kandelakii* in the area. Dog collars consisted of 65cm strip of white polyvinyl chloride weighing 25g, impregnated with deltamethrin 40mg/g. The authors reported that seroconversion rate in children was 1.49% in the intervention villages and 2.4% in control villages. Leishmanian skin test conversion was also lowered but not significantly. The seroconversion rate in dogs of the intervention villages was also significantly reduced (Mazloumi-Gavgani et al. 2002).

The efficacy of deltamethrin-impregnated

dog collars (Scalibor) was evaluated against *P. papatasi* in an endemic focus of ZVL in Bojnord County, north Khorasan Province, northeastern Iran during 2006–2007. In this experiment 6 healthy dogs with similar age, sex, weight and race were selected and randomly classified in two groups as treated and untreated. At the beginning of the transmission season, 3 dogs received collars and the other group was considered as control group. Two weeks after fitting the collars, one of the treated and untreated dogs were exposed to the bites of wild caught *P. papatasi* in the evening for 2h under the bed net biweekly. In order to assess the mortality of sand flies, they were recaptured at the end of the exposure time and transferred into cups and maintained at optimal condition for 24h. Data analysis revealed that the blood-feeding index of *P. papatasi* was between 13.4–27.6% for dogs with collars and 54.2–59.3% for the dogs of control group which showed significant difference ($P = 0.005$). The index of blood-feeding inhibition were calculated to be between 51.3–66.2% and 37%–44.8% for collared and collarless dogs respectively and showed a significant difference ($P = 0.01$). The range of combined effects (inhibition of blood-feeding and mortality of *P. papatasi*) was between 72.37–86.62% for collared dogs and 40.74–45.83% for control dogs (Ramazani Awal et al. 2009).

In 2013, the pour-on formulation of flumethrin on dog (with same race, sex and age) was evaluated against blood-feeding and mortality of sand flies in endemic focus of ZVL in Meshkinshahr, northwest of Iran. Before the application of flumethrin, direct agglutination test (DAT) was used for determining the positive or negative cases of dogs. The treated and control dogs were exposed with wild sand flies for 2h under the bed net (2x2x2 meters) once every 20 days during May–September. Both alive and dead sand flies were transferred in netted cups to the laboratory and their mortality was assessed

after 24h. The blood-fed or unfed conditions of sand flies were determined 2h after exposure to the dogs under stereomicroscope. The results showed that the feeding rate of sand flies on treated dogs was 3.3 fold lower than control and the inhibition of feeding rate on treated dogs was 1.8 fold higher than control. The difference between total mortality of treated and control groups was highly significant ($P = 0.0001$) (Jalilnavaz et al. 2016).

Susceptibility of sand flies to insecticides

Studies on the susceptibility level of *P. papatasi* to insecticides started in 1970 and continuing in some foci of ZCL in the country. Seyedi-Rashti et al. (1970) evaluated the susceptibility of field population of *P. papatasi* strain from unsprayed area of Mashhad by WHO standard method in northeastern Iran in August 1970. The baseline LC50 value for DDT and dieldrin was calculated to be 0.47% and 0.54% respectively (Seyedi-Rashti 1971). In susceptibility tests carried out on this species from the Esfahan area, central Iran the LC50 for DDT was 0.47% in September 1976 (Soltani 1977), indicating no development of resistance. Another survey was performed by WHO standard method on wild caught *P. papatasi* from human dwellings in Mashhad (northeast), Esfahan (central Iran) and Khuzestan (southwest) during 1985–1986. The results showed that the LC50 value for DDT had increased to 2.3% and 3% in Mashhad and Esfahan respectively, disclosing the existence of selection pressure in the lack of public health insecticide use (Seyedi-Rashti et al. 1992).

Yaghoobi-Ershadi (1993) provided evidence of tolerance of *P. papatasi* to 4.0% DDT following a standard WHO technique in Esfahan. In this program 40 series of susceptibility tests were carried out on a total of 1248 fed *P. papatasi* from 4 villages in the rural district of Borkhar. Lt50 and Lt90 values were calcu-

lated to be 18.12 and 63.31min respectively. The mortality rate after one hour exposure to 4.0% DDT and the 24h recovery period was 88.8%. When the exposure time increased to 90 and 120min, the mortality rate was 95.2% and 98.8% respectively. Appearance of tolerance on *P. papatasi* in the area was due to the irregular and excess use of Chlorinated insecticides in agriculture. The mortality rate of this species after one hour exposure to 4.0% dieldrin was 100%. At the same time 32 series of tests were conducted on 1112 *P. papatasi* against DDT 4.0% in two villages located in the rural district of Varzaneh (73–98km, southeast of Esfahan). Lt50 and Lt90 values was calculated to be 20.51 and 43min respectively and the mortality rate after one hour exposure and 24h recovery period was 98.61% so it was found to be susceptible to DDT 4.0% (Yaghoobi-Ershadi and Javadian 1993).

In 2001, the tests with WHO technique which was performed in the rural district of Borkhar (Esfahan) showed that the susceptibility of *P. papatasi* to DDT 4.0% has been returned because the mortality rate after one hour exposure was calculated to be 100%. This was achieved due to the low use of Chlorinated insecticides in agriculture, during the last 9 years in the area (Yaghoobi-Ershadi, Tehran University of Medical Sciences, unpublished data). During 1993–2001 the same study was carried out in the provinces of Fars (southwest), Kerman (southeast) and Badrood area in Esfahan and Lt50 ranged between 5.5–29.7 minutes and Lt90 between 18.5–58 minutes respectively. *Phlebotomus papatasi* was found to be susceptible to DDT in all of these areas (Aghasi 1996, Yaghoobi-Ershadi and Akhavan 1999, Rassi et al. 2000).

Susceptibility tests which were performed again during 2002–2013 on *P. papatasi* against DDT 4%, deltamethrin 0.05% and 0.025% and propoxur 0.1% by WHO standard method in Sabzevar (northeast), Esfahan (Central), Bam, Baft and Dehbakri (southeast) showed that the field population of the species was still sus-

ceptible to these insecticides in different studied areas (Yaghoobi-Ershadi et al. 2003, 2007, Akhavan et al. 2007, Aghaei et al. 2011, Saeidi et al. 2011).

Several susceptibility tests which have been undertaken on *P. sergenti*, the main vector of *leishmania tropica* in the cities of Mashhad (northeast), Kerman and Bam (southeast) during 1970–2010 showed that it was susceptible to DDT, dieldrin and deltamethrin (Aghasi 1996, Yaghoobi-Ershadi and Akhavan 1999).

In 1994, susceptibility tests were conducted on *P. kandelakii* and *P. perfiliewi*, the probable vectors of ZVL in Meshkinshahr and Germi counties, Ardebil province (northwest), Iran. The results revealed that the both species were susceptible to the insecticides (Rassi and Javadian 1998).

Concluding remarks

The national strategy arranged by the Iranian government emphasizes case detection and treatment for ACL and ZVL. Results of many scientific works in the country state that, whether integrated vector management is needed, IRS remains the main support for vector control in epidemics which provides a cheaper and more practical solution to prevent cases of leishmaniasis. House spraying with insecticides, although being able to combat an outbreak, cannot be used on a long-term basis in urban areas to maintain transmission at a low level. Well organized town planning expansions based on environmental protection measures such as a lack of waste management or open sewage, the presence of idle land among the new construction homes, inadequate garbage collection and sanitation, crowded suburban areas with residents of low socio-economic levels and with existence with domestic animals are the key to prevention of leishmaniasis in urban areas. As they provide a good source for high phlebotomine density and favorable conditions for disease transmission.

Impregnated bed nets and curtains may

provide the best way out in rural areas where transmission is largely occurs outdoors. The critical studies such as biting behavior of different sand fly species, their resting and breeding places, the type of plants which provide sugar meal, potential reservoir hosts along with community participation and education should be studied in leishmaniasis foci which will help in the battle against sand fly vectors and reduce the cost of intervention. New methodological advances, such as geographical information systems and remote sensing can make a positive contribution to these efforts. Increasing the awareness of physicians and medical staff on the ecology and control of sand flies and close collaboration between health authorities and researchers are required to achieve the best control measures. Health education activities focused on sand fly control among inhabitants living in foci of leishmaniasis, early reporting of active cases by individuals, disease mapping of ZCL, ACL, ZVL and qualified staff for vector control are critical points in effective prevention and control of leishmaniasis.

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