OPEN ACCESS Freely available online

Journal of Infectious Diseases & Preventive Medicine

Research Article

Monitoring and Mapping of Insecticide Resistance in Vectors of Visceral leishmaniasis in the World

Mohammad Nasrabadi[1], Amrollah Azarm[1], Maryam Molaeezadeh[1], Fatemeh Shahidi[1], Faramarz Bozorgomid[1], Hassan Vatandoost[1,2*]

[1]Department of Medical Entomology and Vector Control, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran; [2]Department of Environmental Chemical Pollutants and Pesticides, Institute for Environmental Research, Tehran University of Medical Sciences, Tehran, Iran

ABSTRACT

Phlebotominae of sandflies are the vector of leishmaniasis, a disease that spreads to more than 98 countries worldwide. Visceral leshmaniasis is a neglected tropical disease caused by Leishmania spp, a protozoan parasite that can be transmitted by the bite of a sand fly infected *Phlebotomus* spp in the old world and Lutzomyia spp in the new world. Since the introduction of synthetic chemical insecticides in the 1940s, they continue to be an effective tool for controlling insects that carry disease pathogens. Unfortunately, insecticides are used indiscriminately and tremendous selective pressure is applied to resist insecticides. Although most species of sandflies are exposed to all major insecticide groups in the world, further evidence suggests that some Phlebotomine sandflies may be developing insecticide resistance. Some populations of sandflies are tolerant or resistant to insecticides used in the Middle East, South Asia, and South America. Such as DDT, *Phlebotomus* argentipes resistant to Pyrethroids from different regions of India reported. To provide authentic information about this novel, the reliable data on academic resources such as Google Scholar, Scopus, Web of Science, Springer, Pro-Quest, Wiley Online, Science Direct, Research Gate, PubMed, Sage, and SID were used. Different levels of susceptibility to insecticides have been reported around the world. A review of literature on sand fly susceptibility in Southeast Asia shows that P *Phlebotomus* argentipes, the main vector of VL, have shown resistance to DDT. Insecticide resistance has not yet been proven in *Lutzomyia longipalpis* but there are some signs of its occurrence in this species. For up-to-date information on vector susceptibility to insecticides, periodic monitoring of insecticides should be performed for susceptibility testing. Irrational longterm use of insecticides may cause tolerance or resistance to the target insects. To control the resistance to insecticides in sand flies and other VL and CL vectors, the use of rotation, mosaic and insecticide mixtures are possible methods. Furthermore, guidelines are needed for monitoring and evaluation of insecticide susceptibility tests against sand flies.

Keywords: Insecticide resistance; Susceptibility; Vector; Visceral leishmaniasis

Abbreviations: Ad: Adlerius; CL: Cutaneous Leishmaniasis; DL: Diffuse or Dermal Leishmanoid Leishmaniasis; Eu: Eu *Phlebotomus*; L: Leishmania; La: *Larroussius*; Lu: Lutzomyia; Med: Mediterranean; P: *Phlebotomus*; Pa: Para *Phlebotomus*; Pf: Pifanomyia; Sy: Syn *Phlebotomus*; VL: Visceral Leishmaniasis.

INTRODUCTION

Background information

Phlebotominae of sandflies is a vector of leishmaniasis, a disease that spreads to more than 98 countries worldwide. Cutaneous Leishmaniasis (CL), Mucocutaneous Leishmaniasis (MCL), and VL or "kala-azar" are the three main clinical forms of the disease. Leishmaniasis is more common in tropical and temperate regions where sandflies are more common. The disease is endemic in 88 world countries (Figure 1) [1-3].

Visceral leishmaniasis, or kala-azar, is a neglected tropical disease caused by Leishmania spp, a protozoan parasite that can be transmitted by the bite of a sand fly infected *Phlebotomus* spp in the old world and Lutzomyia spp in the new world (Table 1) [4] and dogs are the main reservoir (Figure 2).

Correspondence to: Hassan Vatandoost, Department of Medical Entomology and Vector Control, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran, Tel: 0088954441; E-mail: hvatandoost1@yahoo.com

Received: October 01, 2021; **Accepted:** October 15, 2021; **Published:** October 22, 2021

Citation: Nasarbadi M, Azarm A, Molaeezadeh M, Shahidi F, Bozorgomid F, Vatandoost H (2021) Monitoring and Mapping of Insecticide Resistance in Vectors of Visceral leishmaniasis in the World. J Infect Dis Preve Med. 9: 251.

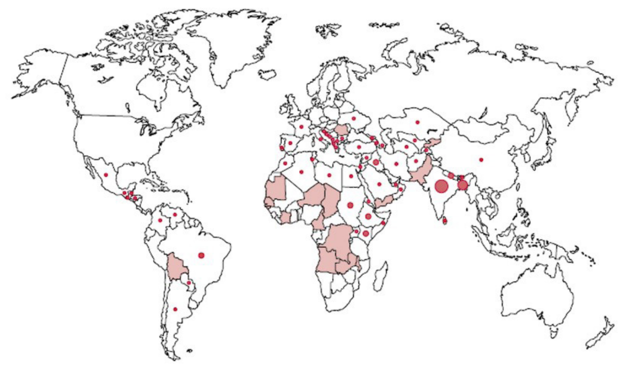

Figure 1: Distribution of Visceral leishmaniasis worldwide.
Note: ( ) < 1000( ) 1000-4999( ) 5000-24999( ) 5000-24999( ) >=25000( )

Table 1: Disease types of Visceral leishmaniasis worldwide.

Parasites	Disease	Countries	Reservoir	Incriminated vector	Suspected vector
L. donovani	VL, DL, CL	Northeast India, Nepal, Bangladesh, (Bhutan), Sri Lanka	Human anthroponosis	*Ph. argentipes*	None
L. donovani	VL	People's Republic of China	Unknown	*None*	Ph. alexandri; P. (Ad.) species
L. donovani	VL, DL	Sudan, Ethiopia, (Chad), (Yemen)	Human anthroponosis; possibly mongoose?	*Ph. orientalis*	None
L. donovani	VL, DL	Sudan, Ethiopia, Kenya, (Uganda)	Human anthroponosis?	*Ph. martini*	Ph. celiae, Ph.vansomerenae
L. infantum	VL, CL	Med Europe, North Africa, Southwest Asia, People's Republic of China	Domestic dog, wild canids, domestic cat	*P. (La.) ariasi, perniciosus*	P. (La.) species; P.(Ad.) species
L. infantum	VL, CL	Latin America: not Peru or Guianas	Domestic dog, wild canids	*Lu. (L.) longipalpis*	Lu. Species; *Lu. evansi*

Figure 2: Infected dog with Visceral leishmaniasis.

After malaria, this disease is the most common cause of death due to parasitic diseases. The disease is mainly distributed in East Africa, South Asia, South America, and the Mediterranean region. It is estimated that about 50,000 to 90,000 new cases of Visceral leishmaniasis occur each year [5]. More than 90% of new cases of Visceral leishmaniasis are reported from six countries: Bangladesh, Brazil, Ethiopia, India, and South Sudan and, Sudan [4].

In Asia, Leishmania donovani is the causative agent. There is no known animal reservoir (human transmission). East India (Bihar) and Bangladesh (Mymensingh District) most endemic areas, followed by Nepal In Southeast Asia, the distribution of VL in Bangladesh, Bhutan, India, Nepal, Sri Lanka, and Thailand is limited [2, 4]. *Ph. argentipes* (Diptera: *Psychodidae*) is a major vector in the Southeast Asia region [6]. *Ph. argentipes* usually rest indoors in cowsheds, human houses, and mixed human-cow houses, while outdoor resting has also been reported in tree holes and underwater.

In Africa, VL occurs in Sudan, South Sudan, Ethiopia, Kenya, Uganda, and Somalia. Here, is Leishmania donovani, but this is very different from that found in Asia. Human-human-animal transmission is mixed, although the exact reservoirs of the animal and its share have not been determined [4]. The *Phlebotomus* (*Larroussius*) orientalis and *Phlebotomus* (Syn *Phlebotomus*) are incriminated vectors in two distinct bioclimatic regions of East Africa [7].

In the Mediterranean, VL is caused by *L. infantum* and all the countries of the Mediterranean are endemic. Dogs are known reservoirs. Other indigenous regions include China, Sri Lanka, Thailand, Bhutan, various Central Asian countries, Iran, Iraq, and Saudi Arabia. The *L. infantum* and *L. donovani* are found, and dogs, jackals, and foxes are reservoirs. In Central and South America, VL is caused by *L. infantum* and dogs are the main reservoirs [4]. The *Lutzomyia longipalpis* (Diptera: *Psychodidae*) is the most important vector of *L. infantum*, a parasite that causes common human-animal Visceral leishmaniasis in the Americas [8]. Since the introduction of synthetic chemical insecticides in the 1940s, they continue to be an effective tool for controlling insects that carry disease pathogens. Unfortunately, insecticides are used indiscriminately and tremendous selective pressure is applied to resist insecticides [9]. Leishmaniasis control can be achieved by interrupting the transmission cycle. The most widely used methods of early detection and treatment of illnesses and infection control vectors and hosts its repository. Although it is often used as a strategy to control the disease leishmaniasis, because of the difficulty of locating terrestrial habitat for mosquito larvae, it is limited. Therefore, vector control further relies on the control of adult mosquitoes, often through the use of chemical insecticides [3]. Sandflies are insects that need to be monitored because they are actively targeted by insecticides [9]. To control sandflies, their populations around the world have been exposed to four main groups of insecticides: Organochlorines, Organophosphates, Carbamates, and Pyrethroids by residual spraying, ultra-low volume spraying, insecticide-treated clothing, and insecticide-treated nets. This exposure is directed either in an attempt to control the vector or as part of the effort to control vectors against other insect vectors; it is inadvertent [4]. Although most species of sandflies are exposed to all major insecticide groups in the world, further evidence suggests that some phlebotomine sandflies may be developing insecticide resistance [10]. Some populations of sandflies are tolerant or resistant to insecticides used in the Middle East, South Asia, and South America [9]. In Montes Claros, Brazil, 29 of 80 (36.3%) *Lu longipalpis* survived against Deltamethrin 0.05 [11]. 11 of 80 *Ph. argentipes* (14%) in the Delft Island population of Sri Lanka, had insensitive acetyl cholinesterase and 20 (25%) had high esterase's, that both these results linking resistance to Malathion [4]. Historically, sandflies phlebotomine in India were susceptible to all insecticides before 1976. However, from 1976 to oversee spraying Dichlorodiphenyltrichloroethane (DDT) to control Kalar-azar in Bihar said the problem has provoked resistance among them. During 1979, cases with the highest degree of DDT resistance were reported in *Ph. papatasi* from northern Bihar, while DDT resistance in *Ph. argentipes* was first reported from the village of Samastipur region [12]. Until 1978, sandflies were known to be sensitive to insecticides, but resistance to DDT was reported in *Ph. papatasi* and *Ph. argentipes* in 1979 and 1990 [2]. The *Ph. argentipes* in all areas of Muzaffarpur, Vaishali, and Patna in the Bihar state of India and in the village of amahibelha in Sunsari, Nepal are resistant to DDT, respectively 43 and 62% of the population as a result of exposure to DDT died [9]. Such as DDT, *Ph. argentipes* resistant to Pyrethroids from different regions of India reported [13]. In many vector species, such as sand flies Neotropical phlebotomine, the existence of insecticide resistance has not yet been well studied. Insecticide resistance has not yet been proven in *Lu longipalpis* but there are some signs of its occurrence in this species [10]. Although in some parts of Brazil and Venezuela development of *Lu longipalpis* resistance to insecticides in agriculture and mosquito control has been reported. The current action of the IRS in response to human VL cases is geographically discontinuous, temporarily dispersed, and a stable variable, and is unlikely to lead to insecticide resistance due to its detrimental effect on *Lu longipalpis* accumulation behavior [8].

RESULTS AND METHODS

To provide valid information about these new results, we use reliable data from academic sources such as Google Scholar, Scopus, Web of Science, Springer, Pro-Quest, Wiley Online, Science Direct, Research Gate, PubMed, Sage, and SID we did.

Studies on susceptibility of *Visceral leishmaniasis* mosquitoes vector to insecticides

Studies on susceptibility of Visceral leishmaniasis mosquito's vector to insecticides and their findings are summarized in Table 2. Kala-azar has been endemic to the Indian continent since 1824 and has caused an epidemic. During the early years of the malaria campaign in India (1953–1958), the incidence of Kala-azar also declined significantly due to the benefit of IRS bail with DDT. Geographical locations Studies on the susceptibility of sandflies to DDT or other insecticides are shown in Figure 3 [2].

Table 2: Status of insecticide susceptibility status in Visceral leishmaniasis sandflies vector in the world.

Species	Country	Insecticides	Susceptibility	Source
Ph. argentipes	India	DDT	Susceptible	[2]
Ph. argentipes	India	DDT, Dieldrin	Susceptible	[14]
Ph. argentipes	India	DDT, Dieldrin	Susceptible	[15]
Ph. argentipes	India	DDT	Tolerant	[17]
Ph. argentipes	India	DDT, Dieldrin	Resistant to DDT and susceptible to Dieldrin	[2]
Lu. longipalpis	Brazil	DDT	Studies on the baseline activity of possible DDT-resistance mechanisms	[18]
Ph. argentipes	India	DDT	Resistant	[18]
Ph. argentipes	India	DDT	Resistant	[19]
Ph. argentipes	India	DDT	Resistant	[20]
Lu. longipalpis	Brazil	DDT, Chlorpyriphos, Malathion, Propoxur, Deltamethrin	Susceptible to all insecticides studied	[14]
Ph. argentipes	India	DDT	Resistant	[21]
Ph. argentipes	India	DDT	Susceptible	[22]
Ph. argentipes	India	DDT	Susceptible	[23]

Lu. longipalpis	Venezuela	DDT=2%, Propoxur=0.01%, Malathion=2%, Fenitrothion=1%, Pirimiphos methyl=1%, Deltamethrin=0.06%, Lambda-cyhalothrin=0.06%, Permethrin=0.2%	Susceptible to all insecticides studied	[16]
Ph. kandelakii and Ph. perfiliewi	Iran	DDT	Susceptible	[24]
Ph. argentipes	India	DDT, BHC, Malathion, Deltamethrin, Permethrin, Bendiocarb	DDT and BHC=Tolerant, Malathion, Deltamethrin, Permethrin=Resistant Bendiocarb=susceptible	[25]
Ph. argentipes	Bangladesh	DDT	Susceptible	[2]
Ph. argentipes	Nepal	DDT	Susceptible	[2]
Ph. argentipes	Nepal	Malathion, Bendiocarb,	Susceptible to all insecticides	Environmental health
		Deltamethrin and Lambda-cyhalothrin	Studied	
Ph. argentipes	India	DDT	Resistant and Susceptible	[26]
Ph. argentipes	India	DDT and Deltamethrin	DDT=Resistant Deltamethrin=susceptible	[27]
Ph. argentipes	Sri Lanka	Malathion	Biochemical evidence of resistance	[28]
Lu. longipalpis	Brazil	Malathion, Fenitrothion, λ-cyhalothrin, Permethrin and Deltamethrin	Susceptible	[11]
Ph. argentipes	India	DDT and Deltamethrin	DDT=Resistant Deltamethrin=Susceptible	[29]
Ph. argentipes	Nepal	DDT and Deltamethrin	DDT=Resistant Deltamethrin=Susceptible	[29]
Ph. argentipes	India	DDT, Deltamethrin and Malathion	DDT=Resistant, Deltamethrin and Malathion=Susceptible	[30]
Lu. longipalpis	United States	Cypermethrin, Deltamethrin, lambda(λ)-cyhalothrin, Permethrin, chlorpyriphos, Fenitrothion, Malathion, Bendiocarb, Propoxur, DDT	Susceptible	[9]
Lu. longipalpis	Brazil	Alpha-cypermethrin	Susceptible	[10]
Ph. argentipes	India	DDT	Resistant	[31]
Ph. argentipes	India	DDT	Resistant	[32]
Ph. argentipes	India	DDT	resistant	[12]
Ph. argentipes	India	DDT, Deltamethrin and Malathion	DDT=Resistant Deltamethrin and Malathion=susceptible	[13]
Ph. argentipes	Sri Lanka	DDT, Malathion, Propoxur, and Deltamethrin	susceptible	[3]
Ph. kandelakii and Ph. perfiliewi	Iran	DDT, Malathion, Propoxur, Lambda-cyhalothrin	Lambda-cyhalothrin=Susceptible Propoxur, Malathion, and DDT= possible resistance	[33]

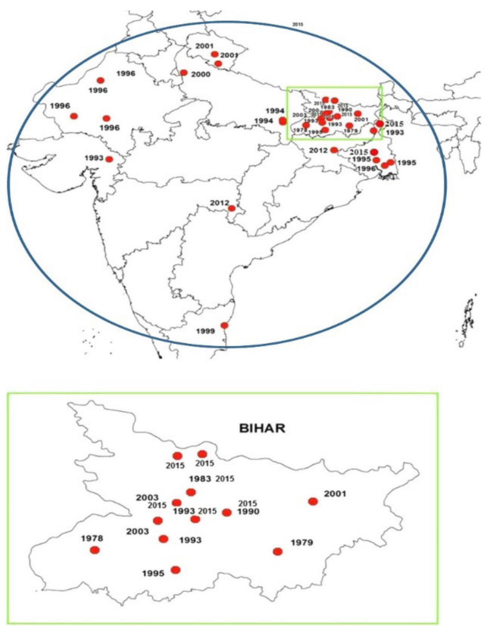

Figure 3: Locations in India (top) and Bihar state (bottom) where susceptibility tests against sandflies have been reported since 1978.

The susceptibility of *Ph. argentipes* to DDT was also studied in West Bengal in 1959. All sand flies were 95 to 100% susceptible [2]. Kaul published preliminary results on the susceptibility of *Ph. argentipes* and *Ph. papatasi* collected from Bihar [14]. In 1979, more accurate results were published by Joshi. This confirmed susceptibility in Ph. Argentipes, and resistance in *Ph. papatasi* [15]. Following indoor residual spraying with DDT, Mukhopadhyay observed rehabilitation of *Ph. argentipes* in northern Bihar and provided a clue to the possible development of sandfly resistance [16]. Later, Mukhopadhyay first reported the development of tolerance in *Ph. argentipes* from the Samastipur region of Bihar [17]. In 1991, the National Malaria Eradication Program in India reported a mortality rate of 82-100% in *Ph. argentipes* collected from the Sahibganj area against DDT test paper [2]. DDT resistance was first observed in Ph. argentipes, a VL vector, from endemic areas of India [18]. After reporting tolerance to DDT in Ph. argentipes, studies on the effect of house spraying DDT on field populations of vector species in Bihar, Uttar Pradesh, and West Bengal in India and Bangladesh and Nepal [2]. In Kaul study, the effect of DDT spraying on field populations of *Ph. argentipes* in Aishali and Patna districts was investigated. Susceptibility experiments using 4% DDT showed only 15.4% mortality of Ph. argentipes. This study provides field evidence for the development of *Ph. argentipes* resistance to DDT in Bihar [19]. Joshi and Rai studied the effect of DDT spraying on field populations of *Ph. argentipes* in Varanasi district, India, and found that *Ph. argentipes* is susceptible to DDT [20]. In a 1994 study by Oliveira Filho and Melo, the *Lu longipalpis* field population showed susceptibility to the insecticides tested and showed Lethal Time (LT) values similar to the reference strain [18]. Basak and Tandon [21] and Chandra [22] found resistance in *Ph. argentipes* from 24 Parganas (West Bengal), India while from the Hoogly region of West Bengal were 100% susceptible. In a study by Mukhopadhyay (1996) in West Bengal, *Ph. argentipes* was found to be susceptible to DDT [23]. The field population of *Lu longipalpis* from La Rinconada, Lara State, an endemic focus of Visceral leishmaniasis in Venezuela, was studied for susceptibility to Organochlorines (DDT 2%), Carbamates (Propoxur 0.02%), Organophosphate (Malathion 2%, Fenitrothion 1%, and Pirimiphos-methyl 1%), and pyrethroids (Deltamethrin 0.06%, lambda-cyhalothrin 0.06%, and Permethrin 0.2%) insecticides and compared with a laboratory reference strain. *Lu longipalpis* field population showed susceptibility to tested insecticides and showed LT values similar to the reference strain [18]. In a 1994 study by Rassi in Iran, the susceptibility of two vectors of Visceral leishmaniasis, Ph. kandelakii and Ph. perfiliewi were tested for DDT 4% insecticide in Ardabil province (northeast) of Iran. The results showed that both species were completely sensitive to DDT after 60 minutes of exposure with a 100% mortality rate [24]. Amalraj reported tolerance in *Ph. argentipes* from Pondicherry, southern India against DDT and Malathion but resistance to Permethrin. The study also showed that Bendiocarb, a Carbamates insecticide, may be effective against populations of *Ph. argentipes* resistant to Organophosphates and pyrethroids [25]. A study by Choudhury in Bangladesh reported *Ph. argentipes* sandflies susceptible to DDT [2]. In Nepal, according to studies by Anonymous and Project Environmental Health, the same vector in Dhansua was susceptible to DDT [2]. In 2001, varying levels of DDT susceptibility from susceptible to resistant species of *Ph. argentipes* were reported by Singh [26]. Dhiman also reported resistance to *Ph. argentipes* from the Vaishali area of Bihar to DDT while being susceptible to Deltamethrin [27]. In Sri Lanka Surendran provided biochemical evidence of increased esterase levels for resistance in *Ph. argentipes* to Malathion [28] and another study in 2009 by Alexander. On susceptibility to insecticides in two Brazilian populations of Lulongipalpis (Lapinha and Montes Claros) vector of Visceral leishmaniasis. Survival analysis showed that while there was no significant overall difference in the susceptibility of both populations to organophosphates, Lapinha sandflies were significantly more susceptible to Pyrethroids than those from Montes Claros [11]. Dinesh in its study reported 43% mortality with 4% DDT in *Ph. argentipes* collected from three Bihar regions, and also reported only 62% mortality in one of the villages of the Sunsari region in Nepal [29]. In another study, Singh reported DDT resistance (89.5% mortality) in *Ph. argentipes* and complete susceptibility to Malathion and Deltamethrin in some parts of India [30]. Denlinger, Lozano-Fuentes in 2015 tested the laboratory susceptibility of *Lu longipalpis* to 10 insecticides. Despite differences in the killing rates of Carbamates and Organophosphates, *Lu longipalpis* is most susceptible to Bendiocarb, Propoxur, and Fenitrothion. Conversely, of the 10 insecticides tested, the least susceptible are to DDT [9]. Another study conducted in Brazil by Grasielle Caldas DÁvila Pessoa in 2015 examined the susceptibility of alpha-Cypermethrin in *Lu longipalpis*. The field assay method showed that the test population at all treated levels was highly susceptible to alpha-Cypermethrin[10]. In 2015, Vijay Kumar tested insecticide susceptibility in *Ph. argentipes* in two areas in West Bengal, India. Susceptibility status *Ph. argentipes* to DDT ranged from 40 to 61.54% [31]. Aarti Rama In their study to monitor the susceptibility status for the preparation of resistant sandfly colonies after examining the susceptibility characteristics of *Ph. argentipes* to DDT for Bihar regions performed DDT susceptibility testing in seven regions of Bihar (India). The Vaishali area was subsequently selected as a "suitable place for collecting resistant sandflies". Here Percentage Mortality Range (PMR) and Corrected Mortality Rate are 41.00-52.73 and 44.83%, respectively, the lowest recorded rates of highly resistant DDT sandflies [32]. In 2017, Aarti Rama conducted a study to evaluate the maximum exposure time that DDT-resistant *Ph. argentipes* can tolerate the effect of DDT for survival. The mortality rate of laboratory-reared DDT-resistant *Ph. argentipes* strains exposed to DDT was studied at 60-min intervals, and it was concluded that highly resistant sandflies can withstand this insecticide for up to 420 min. Finally, in 480 minutes of exposure to insecticides, they achieved absolute mortality. Also, LT was observed for female *Ph. argentipes* more than males, indicating that they are highly resistant to DDT toxicity [12]. The values of LT-50, LT-90, and LT-95 for *Ph. argentipes* tested were observed with 95% confidence intervals at 280 min, 370 min and 400 min, respectively (Table 3) [12].

Table 3: Susceptibility test result for estimating LT-50, LT-90, and LT-95 for resistant Ph. argentipes responded towards the prolonged exposure of DDT at discriminating time intervals of 60 min.

Insecticide exposure time (in min)								
Observed Parameter	60	120	180	240	300	360	420	480
Control								
No. of sand flies Tested (NT)	(15 Female, 25 Male); Total=40							

Alive	40	40	40	40	40	40	40	40
Mortality %	0	0	0	0	0	0	0	0
Experiment								
No. of sand flies Tested (NT)	(60 Female, 50 Male); Total=110							
No. of Alive (NA) ± %	109 ± 99.09%	106 ± 96.36%	82 ± 74.54%	56 ± 50.90%	32 ± 29.09%	3 ± 2.72%	0 ± 0%	0 ± 0%
No. of Senseless (NS) ± %	1 ± 0.90%	3 ± 2.72%	15 ± 13.63%	22 ± 20%	13 ± 11.81%	10 ± 9.09%	1 ± 0.90%	0 ± 0%
No. of Dead (ND) ± %	0 ± 0%	1 ± 0.90%	13 ± 11.81%	32 ± 29.09%	65 ± 59.09%	97 ± 88.18%	109 ± 99.09%	110 ± 100%
Observed Mortality=ND/NT*100	0	0.90	11.81	29.09	59.09	88.18	99.09	100
LT-50 tested Ph. *argentipes* against DDT (4%)	280 min; at CI of 95%							
LT-90 tested Ph. *argentipes* against DDT (4%)	370 min; at CI of 95%							
LT-95 tested Ph. *argentipes* against DDT (4%)	400 min; at CI of 95%							

Sardar a study to evaluate the susceptibility of carrier sand fly species (Ph. argentipes) to Deltamethrin (type II Pyrethroids), DDT (Organochlorines), and Malathion (Organophosphate) and to detect polymorphisms in the voltage-gated sodium channel gene (VGC) and They examined their association with susceptibility to pyrethroids type II and DDT in three endemic areas of Kala-azar in West Bengal, India. Polymorphisms were detected in the second domain of segment 6 VGSC gene of pyrethroids and DDT susceptible and tolerant *Ph. argentipes* by DNA sequencing. It was found that the population of *Ph. argentipes* in the study area is between 98.02% to 98.80% and 98.81% to 100% susceptible to Deltamethrin and Malathion respectively, but resistant to DDT [13]. In a recent study by Pathirage, patterns of *Ph. argentipes* insecticide susceptibility were investigated by exploring possible underlying resistance mechanisms. Adult offspring of *Ph. argentipes* collected from four different regions of Sri Lanka (Mirigama, Pannala, Thalawa, and Mamadala) were exposed to different concentrations of DDT, Malathion, Deltamethrin, and Propoxur using WHO bioassay susceptibility kits [3]. The lowest susceptibility (excluding Deltamethrin) was observed in the Mamadala population, while the highest was observed in the Mirigama population. Increased levels of glutathione S-transferase and esterase activity were observed in sandflies originating from Mirigama, Panala, Talawa, and Medala, respectively [3].

In another study by Rassi 2020 to evaluate susceptibility to insecticides DDT (4%), Malathion (5%), Propoxur (0.1%), and Lambda-cyhalothrin (0.05%) in two vectors of Visceral leishmaniasis in Iran Ph. kandelakii and Ph. perfiliewi collected from the endemic focus of Visceral leishmaniasis region. These species were sensitive to Lambda-cyhalothrin but despite this, they have potential resistance to three other insecticides [33].

DISCUSSION

Insecticides, in fact under the control of integrated disease management (IDM), play an important role in controlling carrier disturbance to reduce disease burden. For many years, DDT has been used worldwide to control sand flies [9]. Previous reports confirm the decline in VL cases during the 1970s and 1970s, as an advantage of DDT spraying collateral for malaria control programs under the National Malaria Control Program and the National Malaria Eradication Program, launched in 1953 and 1958, respectively and hence populations of *Ph. argentipes* were also effectively suppressed due to higher levels of DDT susceptibility [25, 32]. Laboratory colonies of insecticide-susceptible sandflies are not very sensitive to DDT. Despite reports of sand flight tolerance and DDT resistance in India, Iran, Nepal, and Turkey, the use of DDT for residual indoor spraying is still permitted. Large doses of DDT are required, which, if not applied properly or at the right time, can create strong pressure for resistance. With years of DDT use and the potential for low tolerability, sandfly populations may develop DDT resistance faster than other insecticides [9]. To date, resistance to DDT has been reported in 2 species of phlebotomine sand fly carriers. For the first time, resistance to *Ph. papatasi* from northeastern India and more recently from Iran was described. Similarly, DDT resistance was detected in *Ph. argentipes* (carriers of Visceral leishmaniasis) from endemic areas in India [18]. A review of the literature on sandfly susceptibility in Southeast Asia shows that *Ph. Argentipes* the main vector of VL has developed DDT resistance in previously used areas such as Bihar, Jharkhand, and Maharashtra, and parts of West Bengal. However, *Ph. argentipes* is resistant to DDT in important endemic areas of kala-azar in India where pyrethroids insecticides have not previously been used. These insecticides should be used as part of a kala-azar vector resistance management strategy [2]. The development of resistance in the VL vector against DDT is a major concern for the kala-azar control program. To have appropriate vector control strategies, regular evaluation of insecticide vulnerability in the kala-azar vector is desirable. The current strategy for controlling Leishmania transmission based on IRS with DDT should be clarified regarding the development of resistance in target species to DDT and other insecticides. DDT is no longer as effective as it was in the 1970s, so it is worrying that the situation may worsen after the development of 100% resistance to DDT in *Ph. argentipes* [31].

Need to conduct a comprehensive study on the distribution and type of insecticide resistance mechanisms in sandflies, strengthen public health entomology capacity including field resistance data collection system, GIS-based resistance monitoring, and mapping, funding of susceptibility testing kits and supplies, and training of program managers in the field of insecticide resistance management. To control the resistance to insecticides in sand flies and other VL and CL vectors, the use of rotation, mosaic and insecticide mixtures are possible methods [2].

CONCLUSION

For up-to-date information on vector susceptibility to insecticides, periodic monitoring of insecticides should be performed for susceptibility testing. Irrational long-term use of insecticides may cause tolerance or resistance to the target insects. Studies on the molecular mechanisms of insecticide resistance, such as the identification of molecular markers and biochemical experiments, are also needed. There is a need to establish surveillance in disease-free areas in pre-endemic countries or countries.

REFERENCES

1. Karimi A, Alborzi A, Amanati A. Visceral leishmaniasis: An update and literature review. Arch Pediatr Infect Dis. 2016;4(3):1-10.

2. Dhiman RC, Yadav RS. Insecticide resistance in phlebotomine sandflies in Southeast Asia with emphasis on the Indian subcontinent. Infect Dis Poverty. 2016;5(1):1-10.

3. Pathirage DR. Insecticide susceptibility of the sand fly leishmaniasis vector *phlebotomus* argentipes in Sri Lanka. Parasit Vectors. 2020;13:1-12.

4. Zijlstra EE. Visceral leishmaniasis: A forgotten epidemic. Arch Dis Child. 2016;101(6):561-567.

5. Bi K, Chen Y, Zhao S, Kuang Y, John WU. Current Visceral leishmaniasis research: A research review to inspire future study. BioMed Res Int. 2018;(5):1-13.

6. Chowdhury R, Lal Das K, Chowdhury V, Roy L, Faria S, Priyanka J, et al. Susceptibility of field-collected *Phlebotomus* argentipes (Diptera: *Psychodidae*) sand flies from Bangladesh and Nepal to different insecticides. Parasit Vectors. 2018;11(1):1-11.

7. Ready PD. Epidemiology of Visceral leishmaniasis. Clin Epidemiol. 2014;6:147-154.

8. González MA, Bell MJ, Bernhardt SA, Brazil RP, Dilger E, Courtenay O, et al. Susceptibility of wild-caught *Lutzomyia longipalpis* (Diptera: *Psychodidae*) sand flies to insecticide after an extended period of exposure in western São Paulo, Brazil. Parasit Vectors. 2019;12(1):1-9.

9. Denlinger DS. Assessing insecticide susceptibility of laboratory *Lutzomyia longipalpis* and *phlebotomus* papatasi sand flies (Diptera: *Psychodidae*: *Phlebotominae*). J Med Entomol. 2015;52(5):1003-1012.

10. Pessoa GCD, Lopes JV, Rocha MF, Pinheiro LC, e Luiz Rosa AC, Michalsky EM, et al. Baseline susceptibility to alpha-cypermethrin in *Lutzomyia longipalpis* (Lutz & Neiva, 1912) from Lapinha Cave (Brazil). Parasit Vectors. 2015;8(1):1-6.

11. Alexander B, Barros VC, De Souza SF, Barros SS, Teodoro LP, Soares ZR, et al. Susceptibility to chemical insecticides of two Brazilian populations of the visceral leishmaniasis vector *Lutzomyia longipalpis* (Diptera: *Psychodidae*). Trop Med Inter Health. 2009;14(10):1272-1277.

12. Rama A , Kesari S, Sushmita D, Kumar D. Studying DDT susceptibility at discriminating time interval focusing maximum limit of exposure time survived by DDT resistant *Phlebotomus* argentipes (Diptera: *Psychodidae*)-an investigatory report. Jpn J Infect Dis. 2017:1-16.

13. Sardar AA. Insecticide susceptibility status of *Phlebotomus* argentipes and polymorphisms in voltage-gated sodium channel (vgsc) gene in Kala-azar endemic areas of West Bengal, India. Acta Tropica. 2018;185:285-293.

14. Kaul S. Preliminary observations on the susceptibility status of *Phlebotomus argentipes and P. papatasi* to DDT in two districts of North Bihar (India). J Comm Dis. 1978;10(4):208-211.

15. Joshi G, Kaul S, Wattal B. Susceptibility of sandflies to organochlorine insecticides in Bihar (India)-further reports. J Comm Dis. 1979;11(4):209-213.

16. Mukhopadhyay A. Resurgence of *Phlebotomus* argentipes and *Ph. papatasi* in parts of Bihar (India) after DDT spraying. Indian J Med Res. 1987;85:158-160.

17. Mukhopadhyay A, Saxena N, Narasimham M. Susceptibility of *Phlebotomus* argentipes to DDT in some kale-Azar-endemic districts of Bihar, India. Geneva: WHO. 1992.

18. Bravg A. Susceptibility of *Lutzomyia longipalpis* (Diptera: *Psychodidae*) to selected insecticides in an endemic focus of Visceral leishmaniasis in Venezuela. J Am Mosq Control Assoc. 1997;13(4):335-341.

19. Kaul S. Entomological monitoring of kala-azar control in Bihar State, India: observations in Vaishali and Patna districts. J Commun Dis. 1993;25:101-111.

20. Joshi R, Rai R. Impact of DDT spraying on populations of *Ph. argentipes* and *Ph. papatasi* in Varanasi district, Uttar Pradesh. J Commun Dis. 1994;26(1):56-58.

21. Basak B, Tandon N. Observations on susceptibility status of Phlebotomus argentipes to DDT in district South 24-Parganas, West Bengal. J Commun Dis. 1995;27(3):196-197.

22. Chandra G, Bhattacharya J, Hati Ak. Susceptibility status of *Phlebotomus* argentipes to DDT, Dieldrin, and malathion in Hoogly, West Bengal. J Commun Dis. 1995;27(4):247-249.

23. Mukhopadhyay A, Hati AK, Chakraborty S, Saxena NB. Effect of DDT on *Phlebotomus* sandflies in Kala-Azar endemic foci in West Bengal. J Commun Dis. 1996;28(3):171-175.

24. Rassi Y, Javadian E. The susceptibility to 4% DDT and host preference of the probable vectors of Visceral leishmaniasis in the northwest of Iran. Iran J Public Health. 1998;27(1):47-54.

25. Amalraj D, Sivagnaname N, Srinivasan R. Susceptibility of *Phlebotomus* argentipes and *Ph. papatasi* (Diptera: *Psychodidae*) to insecticides. J Commun Dis. 1999;31(3):177-180.

26. Singh R, Das R, Sharma S. Resistance of sandflies to DDT in Kala-azar endemic districts of Bihar, India. Bull World Health Org. 2001;79:793-793.

27. Dhiman R. Susceptibility status of *Phlebotomus* argentipes to insecticides in districts Vaishali and Patna (Bihar). J Commun Dis. 2003;35(1):49-51.

28. Surendran NS, Karunaratne SHPP, Adamas ZJO. Molecular and biochemical characterization of sand fly population from Sri Lanka: evidence for insecticide resistance due to altered esterases and insensitive acetylcholinesterase. Bull Entomol Res. 2005;95(4):371-380.

29. Dinesh DS, Das M, Picado A, Roy L, Rijal S, Singh SP, et al. Insecticide susceptibility of *Phlebotomus* argentipes in Visceral leishmaniasis endemic districts in India and Nepal. PLoS Negl Trop Dis. 2010;4(10): e859.

30. Singh R, Mittal P, Dhiman R. Insecticide susceptibility status of *Phlebotomus* argentipes, a vector of Visceral leishmaniasis in different foci in three states of India. J vector-borne Dis. 2012;49(4):254-261.

31. Kumar V, Shankar L, Kesari S, Bhunia SS, Dinesh DS, Mandal R, et al . Insecticide susceptibility of *Phlebotomus* argentipes and assessment of vector control in two districts of West Bengal, India. Indian J Med Res. 2015;142(2):211-215.

32. Rama A, Kumar V, Kesari S, Singh VP, Das P. Monitoring susceptibility status of *Phlebotomus* argentipes (Diptera: *Psychodidae*) at Bihar (India) for the procurement of homozygous DDT resistant colony. J Trop Dis Public Health. 2015;3(4):1-7.

33. Rassi Y, Moradi-Asl E, Vatandoost H, Abazari M, Saghafipour A. Insecticide susceptibility status of the wild population of *Phlebotomus* kandelakii and *Phlebotomus* perfiliewi Transcaucasus collected from Visceral leishmaniasis endemic foci in northwestern Iran. J Arthropod-Borne Dis. 2020;14(3):277-285.