# Phlebotomine sand flies and associated pathogens in Algeria: update and comprehensive overview

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#### **Keywords**

Algeria, Leishmania, Phlebotomine, Phlebovirus, Sand flies.

#### **Summary**

Being the only established vectors of the protozoan parasites of the genus *Leishmania*, sand flies have become very important in all countries where leishmaniasis exists. It is caused by a variety of species, each one having specific mammalian reservoir hosts and vectors. *Leishmania* and sand fly classification has always been a controversial matter, and the increasing number of sand fly species described complicates the task. Until recently, sand flies distributed in the Old World were known as vectors for few Phleboviruses including two known species (Sandfly fever Naples virus, and Salehebad virus), and tentative species such as sand fly fever Sicilian virus and Corfou virus. These infections are emerging in the Mediterranean region and will likely spread in forthcoming decades, posing a complex threat to public health. Here, we reviewed the current literature on phlebotomine sand flies fauna and epidemiology of sand fly-borne infections in Algeria.

#### Introduction

Phlebotomine sand flies (Diptera: Psychodidae: Phlebotominae) are blood-feeding insects of great significance for physicians and veterinarians. Indeed, they are vectors of numerous pathogens to humans and animals, including protozoa, bacteria and viruses (Dantas-Torres et al. 2012, Maroli et al. 2013). For instance, species of the genus Phlebotomus are vectors of phleboviruses (e.g., sand fly fever Naples virus, and sand fly fever Sicilian virus) causing the sand fly fever, which is a transient febrile illness that is mainly prevalent in the Mediterranean region (Maroli et al. 2013). Most importantly, phlebotomine sand flies are the biological vectors of Leishmania parasites which still cause disfiguring lesions and claim the lives of thousands of dogs and humans each year in more than 98 endemic countries (Alvar et al. 2012). In Algeria, 25 phlebotomine sand flies species and 3 synonyms were inventoried up to 2018 (Table I), including two genera and seven subgenera (Belazzoug 1991, Berdjane-Brouk et al. 2011, Benallal et al. 2013). Some of them are known to be Leishmania parasite vectors (Boubidi et al. 2011) and phleboviruses vectors (Alkan et al. 2015) (Table II). Knowledge about phlebotomines in Algeria is currently incomplete. Some scientific

contributions provided information but now some reports contain data that need to be updated. With the growing importance of phlebotomine-borne diseases, entomological and epidemiological studies with the inventory of phlebotomine sand flies fauna are the first step to prevent infections and the risk of transmission. Whereas, it is necessary to map the risk areas in relation to the phlebotomine population vector distribution and their pathogens. We propose an updated view of events that have played important roles in the geographical distribution of sand flies (Table I), in relation to both the Leishmania and phleboviruses pathogens associated and circulated in Algeria (Table II). The information gathered in this review was mainly obtained from the online literature using the Pub Med, Google search engines and a personal research of data. A comprehensive literature search using the terms (phlebotomine, sand flies, Leishmania, phlebovirus and Algeria) was conducted.

# Updated inventory of phlebotomine sand fly fauna in Algeria

The name 'sand fly' can be misleading, as it wrongly

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suggests to laypeople that they may be at risk of vector-borne disease while on holiday on the beach. Actually, the English denomination refers to the pale (sandy) color of this small insect. Sand flies belong to the order Diptera, suborder Nematocera, family *Psychodidae*, and subfamily *Phlebotominae*. Phlebotomine sand flies are principally present in the warm zones of Asia, Africa, Australia, southern Europe and the Americas (Killick-Kendrick 1999). Sand flies were identified according to two distinct methods (Akhoundi *et al.* 2016). The analysis of certain

external structures (male genitalia) and descriptions of internal structures such as the spermathecae, cibarium, and the pharynx were employed (Perfil'ev 1968). A distinction must therefore be made for the vectors of the leishmaniases and other diseases of public health concern, which are correctly termed 'phlebotomine sand flies' (Killick-Kendrick 1999). To date, over 800 species have been estimated to exist in different regions of the World. Approximately 464 species are found in the New World and 375 in the Old World (Galati 2003, Seccombe *et al.* 1993).

**Table 1.** Phlebotomine sand flies species of Algeria: current known distribution - December 2018.

Phlebotomine sand flies species	Geographical distribition	
Phlebotomus		
Phlebotomus (Phlebotomus) papatasi (Scopoli, 1786)	Northern steppe fringe (Highland)	
Phlebotomus (Phlebotomus) bergeroti (Parrot, 1934)	Djanet, In Amguel, Tamanrassat	
Phlebotomus (Paraphlebotomus) sergenti (Parrot, 1917)	South, Tell, Saharian steppe	
Phlebotomus (Paraphlebotomus) alexandri (Sinton, 1928)	Pre-Saharian steppes, Atlas	
Phlebotomus (Paraphlebotomus) chabaudi (Croset, Abonnenc et Rioux, 1970), synonym of <i>P. riouxi</i>	Pre-Saharian steppes (arid climatic), Ghardaia, Aures	
Phlebotomus (Paraphlebotomus) kazeruni (Theodor et Mesghali, 1964)	Hoggar	
Phlebotomus (Larroussius) ariasi (Tonnoir, 1921)	Tell	
Phlebotomus (Larroussius) chadlii (Rioux, Juminer et Gibily 1966)	Tell	
Phlebotomus (Larroussius) perniciosus (Newstead, 1911)	All bioclimatic stage	
Phlebotomus (Larroussius) longicuspis (Nitzulescu, 1911)	Tell, Highlands, Saharian steppe, central Sahara	
Phlebotomus (Larroussius) langeroni (Nitzulescu, 1930)	Tell	
Phlebotomus (Larroussius) perfiliewi (Parrot, 1930)	Tell	
Phlebotomus (Transphlebotomus) mascittii (Grassi, 1908)	Kabylie	
Phlebotomus hirtus (Parrot et de Jolinière, 1945)	Hoggar	
Sergenton	nyia	
Sergentomyia (Sergentomyia) minuta parroti (Adler et Theodor, 1927)	All bioclimatic stage	
Sergentomyia (Sergentomyia) fallax (Parrot, 1921)	Pre-Saharian steppes, Atlas	
Sergentomyia (Sergentomyia) antennata (Newstead, 1912), synonym of S. cincta	Pre-Saharian steppes, central Sahara	
Sergentomyia (Sergentomyia) schwetzi (Adler, Theodor et Parrot, 1929)	Tamanrassat	
Sergetomyia (Parrotomyia) eremitis (Parrot et de Jolinière, 1945), synonym of S. africana asiatica	In Amguel, Tamanrassat	
Sergetomyia (Parrotomyia) lewisi (Parrot, 1948), synonym of S. palestinensis	Biskra, Djanet, Iherir, Tamanrassat	
Sergentomyia (Grassomyia) dreyfussi (Parrot, 1933)	Biskra	
Sergentomyia (Sintonius) clydei (Sinton, 1928)	Northern steppe fringe, central Sahara (Hoggar, Tassili)	
Sergentomyia (Sintonius) christophersi (Sinton, 1927)	Northern steppe fringe, central Sahara (Hoggar, Tassili)	
Sergentomyia (Sintonius) hirta (Parrot et de Jolinière, 1945)	Central Sahara	
Sergentomyia (Sintonius) tiberiadis (Adler, Theodor et Louric, 1930)	Djanet	

**Table II.** Associated pathogens detected in phlebotomine sand flies of Algeria up to December 2018.

Phlebotomine sand flies species	Pathogens detected
Phlebotomus (Phlebotomus) papatasi (Scopoli, 1786)	Leishmania major / Novel Phlebovirus related to Sandfly fever Sicilian virus
Phlebotomus (Paraphlebotomus) sergenti (Parrot, 1917)	Leishmania killicki
Phlebotomus (Larroussius) ariasi (Tonnoir, 1921)	Sandfly fever Sicilian virus
Phlebotomus (Larroussius) perniciosus (Newstead, 1911)	Leishmania infantum / Toscana virus
Phlebotomus (Larroussius) longicuspis (Nitzulescu, 1911)	Leishmania infantum / Novel Phlebovirus related to Sandfly fever Naples virus / Toscana virus
Phlebotomus (Larroussius) perfiliewi (Parrot, 1930)	Leishmania infantum / Toscana virus

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In Algeria, phlebotomine sand flies were reported for the first time in 1912 (Foley and Leduc 1912). Sand flies have been the subject of very important work carried out in Pasteur Institute of Algeria, under the direction of Parrot and the Sergent brothers, with description of several new species (Phlebotomus sergenti in 1917, Sergentomyia fallax in 1921, *S. dreyfussi* in 1933 and *P. bergeroti* in 1934) In 1980 and 1981 respectively, phlebotomine sand flies population of Tassili n'Ajjer and Hoggar from the Southern part of Algeria was described (Belazzoug et al. 1980, Belazzoug et al. 1981). After that, the same team reported for the first time the presence of S. minuta (Belazzoug et al. 1982). Later in literature, after an epidemiological survey on leishmaniases conducted in Algeria between 1972 and 1976, Dedet and colleagues reported the result of their entomological investigations with special reference to taxonomy, distribution, ecology and pathogenic role of the 15 species found. The check-list of sand flies was then actualized to 21 species and a key was provided to aid identification of Algerian sand flies (Dedet et al. 1984). In 1991, Belazzoug established a new status of Algerian sand flies fauna with 22 species recorded (Belazzoug 1991). Some studies in the Northeast of the country have been realized in concern of ecological status of phlebotomine sand flies (Kabbout et al. 2016), and morphological distinction between two sympatric species: P. perniciosus and P. longicuspis (Berchi et al. 2007). In 2011, P. mascittii was reported for the first time in Algeria during an entomological study conducted in endemic visceral leishmaniasis (VL) focus from the north part of the country (Kabylia) (Berdjane-Brouk et al. 2011). Another entomological survey carried out in Tamanrasset enabled us to identify a new location for P. kazeruni in Algeria (Benallal et al. 2013), which lead to enlarge phlebotomine fauna into 25 species. Recently, Lafri and colleagues established the application of MALDI-TOF MS for monitoring and identification of field caught sand flies (Lafri et al. 2016). More recently, an entomological study provided for the first time the presence of atypical form of P. perniciosus in Algeria (Benallal et al. 2017).

## Phlebotomine sand flies pathogens reported in Algeria

#### Leishmaniases

Among the over 800 phlebotomine sand fly species estimated to exist, only 98 species of *Phlebotomus* and *Lutzomyia* genera are currently proven or suspected vectors of human leishmaniases (Maroli *et al.* 2013). Leishmaniases are vector-borne diseases caused by obligate protozoan parasites

from the genus *Leishmania* (Trypanosomatida: Trypanosomatidae). Leishmaniases are endemic in large areas of the tropics, subtropics, and the Mediterranean basin, where there are a total of 350 million people at risk and 12 million cases of infection (Moreno and Alvar 2002, Alvar et al. 2012) with few exceptions; phlebotomine sand flies are the unique haematophagous insects proven to transmit leishmaniases through the bite of infected female that have previously fed on an infected mammal. After Afghanistan, Algeria is the second largest focus of cutaneous leishmaniasis (CL) in the world. In Algeria, the first report dates back to the time of Sergent who succeeded to produce an experimental lesion of CL to a volunteer by filing on a scarification dermal seven specimens of P. papatasi captured in Biskra (Sergent et al. 1921); It was the first evidence of the role vector of leishmaniasis played by a sand fly. After that, Parrot and colleagues, recorded the infection of four females of P. perniciosus out of 53 induced to feed on a dog with VL in Algiers (Parrot et al. 1930). In 1931, Parrot and colleagues, observed the spontaneous infection of P. perniciosus by promastigotes of L. infantum in 14 of 58 females gorged from dog having leishmaniosis (Parrot et al. 1931); this experience continued for several consecutive years (Parrot et al. 1941). It was the first evidence of L. infantum in Algeria. In 1941, Parrot observed a natural infection in 16.5% of *P. longicuspis* females gorged from dogs affected by leishmaniosis (Parrot et al. 1941). This fact suggested to consider P. longicuspis as possible vector of VL, associated to P. perniciosus. A very interesting investigation done in Kabylia by Izri and colleagues lead to isolate L. infantum MON-1 from P. perniciosus (Izri et al. 1990), to confirm its role vector of VL in Algeria. After this work, the same team isolated L. major in P. papatasi in Biskra (Izri et al. 1992); this supports classical observations of Sergent, that P. papatasi is the main vector in this focus in 1921 (Sergent et al. 1921). During these epidemiological series in concern to Phlebotomine-associated pathogens of Algeria, this team realized another record and proved that P. perfiliewi was found naturally infected with dermotropic L. infantum at Tenes (Izri and Bellazoug 1993). In the last decade, some researcher have adopted molecular tools to control phlebotomine sand flies in Algeria. In 2011, a team of Pasteur Institute of Algeria suggested that CL caused by L. killicki could be a zoonotic disease, with P. sergenti sand flies acting as hosts and vectors and gundi rodents as reservoirs in Ghardaia, from the South (Boubidi et al. 2011). Going back in time, Parrot's hypothesis raised in 1941 (Parrot et al. 1941) concerning the role of P. longicuspis in the transmission of L. infantum was strongly supported by the detection of *L. infantum* DNA in P. longicuspis from VL endemic focus in Kabylia (Berdjane-Brouk et al. 2012).

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#### Viral diseases

Phlebotomine sand flies are involved in the transmission of several viral agents, among which the most important are grouped into the *Phlebovirus* genus (family Bunyaviridae), which includes the sand fly fever Sicilian virus and Toscana virus, and the Vesiculovirus genus (family Rhabdoviridae), which encompasses vesicular stomatitis, Chandipura and Isfahan viruses (Maroli et al. 2013). The risk for infection with sand fly-transmitted phleboviruses has been shown to pertain to very large areas of the Old World in association with the presence of sand fly vectors (Tesh et al. 1976). In Algeria, Phleboviruses have also been highlighted and detected in humans (Izri et al. 2008), dogs (Tahir et al. 2016), and sand flies (Alkan et al. 2015). A molecular evidence for the presence of a phlebovirus closely related to sand fly fever Sicilian virus was detected in a P. ariasi (Izri et al. 2008). After that, another investigation conducted by the same team in the North of Algeria indicated that a viral sequence from P. papatasi was closely related to, but distinct from, a sequence obtained from P. ariasi (Izri et al. 2008), and that two viral sequences from *P. longicuspis* were genetically distantly related to sequences corresponding to virus members of the sand fly fever Naples virus species, although falling within the same group (Moureau et al. 2010). This clearly represents a distinct novel lineages of Phleboviruses detected in Algeria. Recently, one strain of Toscana virus was isolated from a total of almost 23,000 sand flies collected in Kabylia (Alkan et al. 2015) (Table II).

### **Conclusions**

Regrettably, field biology research worldwide

is limited to the work of relatively few groups of entomologists experienced in phlebotomine research. If this trend continues, aspects of sand fly behaviour that might be relevant to target control may remain unknown or neglected. Leishmaniases and other tropical infectious diseases, are generally regarded as neglected diseases because of the lack of effective, affordable and easy-to-use drug treatments. Otherwise, as most affected patients live in developing countries, the pharmaceutical industry has ignored these diseases. Understanding these evolutionary relationships between phlebotomine and associated pathogens is of epidemiological importance for the future prediction of *Leishmania* transmission patterns in the first instance and other phlebotomine-associated pathogens. We have expanded the understanding and updated the phlebotomine sand flies repertoire and associated pathogens reported in Algeria. This review will help researcher, human and veterinary clinicians to enlarge the spectrum of pathogens to be considered in differential diagnoses. Further work is needed to map phlebotomine-associated pathogens distribution in relation to environmental and climatic characteristics. Educational health programmes seem to have been neglected, when they have been implemented, they have been poorly evaluated in many countries. This fact should be taken into consideration by all public health actors institutions in Algeria.

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