One of the smallest, fiercest biters belongs to the genus *Culicoides* (Diptera: Ceratopogonidae) with amazing ability to transmit 53 arboviruses, 12 species of protozoans and 18 species of filarial nematodes. This genus is distributed on major landmasses of the world with the exceptions of a few regions. In recent years it has assumed worldwide significance due to its role in the transmission of Bluetongue virus in wild and domestic animals. However, the most neglected area is our lack of understanding of the role of *Culicoides* spp. and their ability to transmit pathogens of several human diseases. This article briefly discusses the pathogens vectored by the biting midges and focuses on the neglected and emerging diseases of human. In addition to that they were also presumed to carry other pathogenic parasites. Some of the humanoid pathogens vectored by these midges are *Mansonella ozzardi*, *Mansonella perstans* and *Mansonella streptocerca*. Among viruses, primarily Oropouche virus is transmitted; Vesicular Stomatitis Indiana virus and Rift valley fever virus are also being isolated from the midges however the incidence of such occurrence is rare.

**Keywords:** *Culicoides* spp., Human, *Mansonella ozzardi*, *Mansonella perstans*, *Mansonella streptocerca*, Oropouche Virus, Vesicular Stomatitis Indiana Virus, Rift Valley Fever Virus.

**INTRODUCTION**

The females of *Culicoides* are small hematophagous insects that visit the host intermittently at intervals to obtain the blood meal. These are one of the most significant members of the family Ceratopogonidae owing to their medico–veterinary importance. It shows wide host diversity ranging from invertebrates to vertebrates. In invertebrates, the midges are reported to be ectoparasite on insects (Ma *et al*., 2013), e.g., *Culicoides anophelis* was observed to intake the blood of mosquitoes (Ma *et al*., 2013). Among vertebrates, it shows a wide range of host – preference, the livestock, including cattle, goat, sheep, and birds are well known host; however blood meal analysis indicates mouse, deer (Lassen *et al*., 2012), horse and zebra (Labuschagne, 2007) as their host. Many opportunistic species within the group were also reported to be anthropophilic (Labuschagne, 2007). Most of the species are nocturnal. *Culicoides* are distributed world-wide in all the major land masses except New Zealand and Antarctica. The species ranges from sea level to 4200 m altitude (Tibet) and from tropics to tundra (Kettle, 1995). In the West, they have been generally referred to as punkies, gnats and no-see-ums; in Spanish as jejenes, majes, mimes, and plagas; and as “bigailles” in Haitian French (Arean & Fox, 1955). There has been 1401 extinct and extant species described worldwide (Borkent, 2015) of which 79 species were from India (Nandi, 2014). Several species that were pestiferous to man, e.g., *C. furens* were known to create mayhem along the coastal areas of North America, which otherwise would have been favorable tourist destinations (Wirth & Blanton, 1959). They were also known as bloodsucking pests of man (Arean & Fox, 1955). Regarding transmission of arboviruses in other
animals, the most important one are the Bluetongue Virus (BTV), African Horse Sickness Virus (AHSV), Epizootic Hemorrhagic Disease Virus (EHDV), Oropouche Virus (OROV) and Schmallenberg Virus. Among the human filarioid, *Culicoides* transmits *Mansonella perstans*, *Mansonella ozzardi* and *Mansonella streptocerca* (Linley et al., 1983).

*Culicoides* spp. is identified on the basis of characteristic light and dark patterns on the wings of most of the species (Kettle, 1995). Unlike the colored scales, patterns on the wing could not be removed easily owing to the pigmentation in the membrane of the wing. However, the pattern might fade in case of prolonged preservation in alcohol. The body length of the insects generally does not exceed 3 mm (Mellor et al., 2000). Being a holometabolous insect, the *Culicoides* pass through four physiological stages in its lifecycle, i.e., egg, larva, pupa and adult (Mellor et al., 2000). Besides other factors, the temperature and humidity influences the duration of the life stages. In the tropical region, the midges pass rapidly through all the life stages (Hope, 2013). Usually the eggs of *Culicoides* are cigar-shaped and appear translucent when laid, however in less than an hour it turns brown. *Culicoides* larvae are semi-aquatic, free-swimming and vermiform (Kettle, 1977). Usually *Culicoides* larvae are generalist feeder and they could be classified on the basis of possessing unsclerotized and heavily sclerotized pharyngeal apparatus. Hypothetically it has been inferred that species with sclerotized mouthparts preferred algae as their diet, whereas, those with soft mouthparts shows predatory behavior (Hope, 2013). Larvae passes through four intermediate instars and these phases occupy most of their life span (Mullens & Rutz, 1983). Development of larvae in the afro tropical region is brief, especially in *Culicoides bolitinos* it is 8-10 days (Meiswinkel, 1989). In most of the cases of *Culicoides*, 3rd and 4th instar larvae undergo the phenomena of diapause and successfully overwinter, whereas some species overwinter as egg (Borkent, 2004). *Culicoides* pupee are 3 mm in length and have light or dark brown complexion (Kettle & Lawson, 1952). The pupa is a non feeding stage and usually surfaces in the larval habitat (Kettle, 1977).

**IMPACT ON HUMAN HEALTH**

The ability of *Culicoides* midges to vector several pathogens is rarely investigated. Therefore, their role as a potent vector has been considered to be less significant. Compared to the mosquitoes, ticks, lice and fleas, the midges seemed to act as a minor player as vector. However, with recent insight into the investigation related to the epidemiological studies on the species has lead to affirmative conclusions regarding their role as vector species. Arean and Fox (1955) did an extensive study of the altered dermal conditions due to *Culicoides* spp. inflicting bites on human. Hase reported the formation of a bulbous lesion resulted from biting of *C. vexans*. The investigation was performed on a 50 year old woman. She developed a lesion within 24 hours of the attack. Itching and burning were common during the initial phase which subsequently subsided with time. At times, prevalence of anthropophilic species in certain regions made life intolerable for the humans, e.g., *C. furens* adversely affected tourism along the coastal areas. This species was considered to be a pest along the Panama. Women and children residing in the Canal Zone of Fort Kobbe were frequently exposed to the attacks of this species (Wirth & Blanton, 1959). The biting of the midges resulted into secondary infection for which medical treatment was essential. Owing to their small size, the midges could move freely in between and within the houses. One of such species was *C. phlebotomus* which exhibited a significant level of anthropophagy. Conclusion regarding their host preference was drawn after the blood meal analyses of the entrapped midges were performed. The maximum numbers of the flies were caught during dusk. The species has been considered
to be exophilic and a detailed surveillance showed that most of them preferred moonlight for human contact (Nathan, 1981). Several filarial larvae, presumed to be of non-human origin, were isolated from *C. phlebotomus*. The species showed significant level of zoophily in case the human populations were absent. In Japan, Arnaud (1956) reported a case of eczema in man caused by *C. erairai* as well as an incidence of sores formed by the biting of *C. obsoletus* which took several months to be healed. The infection caused by the nematodes to humans has been asymptomatic and the clinical manifestations are mild, so, investigations on the epidemiology regarding the transmission by *Culicoides* is least studied.

**FILARIAL NEMATODE**

*Mansonella ozzardi*

*Mansonella ozzardi* has been an understudied filarial parasite infecting human. The nematode was first described by Patrick Manson (1897). Naturally the filarial nematode was vectored by the members of two Dipteran families, i.e., *Culicoides* (Ceratopogonidae) and *Simulium* (Simulidae) (Linley et al., 1983). The nematode has been indigenous to the Americans and distributed across the Caribbean, Latin America and from Northwestern Argentina to Southern Mexico. Usually in South America it ranges along the Amazon basin, Columbia, Bolivia, Argentina, Venezuela, Surinam and Guyana (Linley et al., 1983; Lima et al., 2016). Irrespective of parasite density, most of the clinical infections caused by *M. ozzardi* do not exhibit a significant pathology (Linley et al., 1983; Lima et al., 2016). As a result, infections due to *M. ozzardi* remained either undetected or untreated. Occasionally the patients complained of arthalgia, fever, headache, itchy cutaneous rashes, and cold extremities in the lower region (Lima et al., 2016). The symptoms were concluded as possible attributions of mansonellosis. Recently, ocular infections related with mansonellosis have fascinated the ophthalmologist (Lima et al., 2016).

In early 1930, *C. furens* has been identified as vectors of *M. ozzardi* in St. Vincent Island (Buckley, 1934). Initially they were found to transmit this parasites in Mexico and several Caribbean Islands, whereas, *Simulium* spp. vectored the nematode in South and Central America. Thus, Nathan et al. (1979) reported that in Las Cuevas, seventy five percent of the fisherman possessed *M. ozzardi* larvae, which was relatively higher compared to the entire population of that region. The fact was correlated with the fisherman’s highest exposure to the *C. phlebotomus* inflicting bites at the foreshore (Nathan, 1981). The prevalence of the *C. phlebotomus* in truck-trap and man-baited trap collections, along with the greater incidence of isolation of *M. ozzardi* third instars larva from 0.1 % of the entrapped population led to a conclusion that *C. phlebotomus* might be the most important vector of this filarial nematodes in that region (Nathan, 1981). In Columbia, *C. insiniatus* has been described as vectors of *M. ozzardi* (Tidwell & Tidwell, 1982.). *C. phlebotomus* were reported as vectors in Trinidad and Haiti. Moreover, a year round transmission of the *M. ozzardi* larvae by *C. phlebotomus* were suggested, since the collections all over the year sans few months showed the prevalence of the filarial larvae within the midge population. Similarly in Africa *C. grahamii* was found to vector *M. ozzardi* in Congo (Noireau et al., 1990). *C. lahillei* were the main vectors in Jujuy province of Argentina whereas *C. paraensis* were the secondary vector (Shelley & Coscaron, 2001). In recent times, *C. debilipalpis, C. paraensis* and *C. lahillei* have been reported as the chief vector of *M. ozzardi* in southwest Bolivia and northwestern Argentina (Veggiani-Aybar et al., 2016).

*Mansonella persans*

There have been two reports of fatalities due to *Mansonella persans* infection (Foster, 1956) in which the filarial larva was found in human cerebrospinal fluid (Dukes et al., 1968). Holmes et
al. (1969) found the symptoms in Rhodesian population to be mild. Hawking (1977) reviewed the Rhodesian populations for mansonellosis. The nematode has been distributed widely throughout the central region of the continent and the sub Saharan countries, ranging from Mozambique and Kenya in the east to Angola and Gabon in the west. Southern Africa was observed to be free of *M. perstans*. In the light of slave trade, the filarial nematode made its incursions into the America, dominating along northern province of South America, i.e., Guyana, French Guiana, Surinam and Venezuela. The parasite was also abundant in Trinidad, some Caribbean Islands and Mexico (Linley et al., 1983). *M. perstans* was known to infect humans (Downess & Jacobsen, 2010) and has been reported as indigenous in Africa. However, no incidence of mansonellosis due to *M. perstans* has been reported from Asia or Pacific area. Even though several people were affected by *M. perstans*, yet they have been reported to be non-pathogenic. The observations were so concluded because the symptoms observed were highly non-specific and ill-defined to be associated with clinical episodes of mansonellosis by *M. perstans*. The foremost symptoms were eosinophilia, transient swelling, pruritis, arthalgia, liver pain and febrile manifestations.

Buckley (1934) enthused the research on *Culicoides* as vector to nematodes with the discovery of *C. austeni* as a vector to *M. perstans*. *Culicoides inornatipennis, C. austeni* and *C. grahamii* showed a positive vector competence as all of the species were capable supporting the development of larva till the 3rd stage. To support with the study on competence, Nicholas (1953) worked on the dispersal of *C. austeni* and *C. grahamii* from the larval habitats. Initially specific identification of the vectors of *M. perstans* were not done from the New World, however, Wirth and Blanton (1973), identified 17 species of *Culicoides* collected using human as bait in the Amazon region.

These filarial worms of human were reported from Africa and British Guiana. In spite of their abundance, the study on the vector of *M. perstans* in Ethiopia was inconclusive. *C. fulvithorax* and *C. grahamii* were the most dominating species of the biting midges in the lowland. Complications coming up from a partial understanding of the vectors have lead to a conclusion that *M. perstans* itself were possibly a complex of several species (Hawking, 1977). Anthropophily in either species has been well established. In Nigeria, *M. perstans* was vectored by the *C. fulvithorax* (Agbolade et al., 2006). The midges were found to be prevalent and endemic in certain regions along the rural communities of the western Nigeria. Hence, in Africa, it was concluded that *C. grahamii, C. inornatipennis* and may be *C. hortensis, C. milnei, C. vitshubiensis* and *C. krameri* were the vectors of *M. perstans*. *Culicoides pycnostictus* and *C. ravus* were considered to be probable vectors but with significant equivocality.

**Mansonella streptocerca**

The parasite was highly considered to be asymptomatic with symptoms frequently observed on the skin (Colbourne et al., 1950). The distribution of *Mansonella streptocerca*, a human filarioid (Downess & Jacobsen, 2010), has been constrained to Africa where its distribution was restricted to Nigeria, Ghana and Zaire (Hawking, 1977). *M. streptocerca* were known to make infestations in the skin, however its prevalence was relatively less intense than *M. perstans*.

*Mansonella streptocerca* has been found in *C. grahamii* (Chardome & Peel, 1949). Besides vectoring *M. Streptocerca*, *C. grahamii* also supports the development of the larva of *M. perstans* (Duke, 1954). White (1977) performed a detailed investigation of Ceratopogonids in Ethiopia. *C. fulvithorax, C. kingi, C. grahamii* and *C. milnei* has been reported as the man-biting species in that region. *Culicoides milnei* was the most abundant species at higher altitude. It was an
endophilic species with higher biting rates on man as well as livestock. Usually the species are nocturnal; however, often there have been reports of the C. milnei attack during the day hours. The higher abundance of C. milnei was established following the observations made from the light trap collections, which collected 35000 C. milnei per trap night. Culicoides showed a significant competence in vectoring M. streptocerca (Heyneman, 2004).

**VIRUS**

**OROPOUCHE VIRUS**

Undoubtedly the most vital role of Culicoides in human health was due to their able competence in transmitting the pathogen causing Oropouche fever, i.e., Oropouche virus (OROV) (Linley et al., 1983; Mellor et al., 2000). Isolation of OROV was first done in Trinidad (1955), from a charcoal worker with febrile symptoms recurring every 48 hours. The clinical manifestations of the Oropouche virus have been characterized by joint pain, fever, anorexia, headache and seldom cases of meningitis were witnessed (Pinheiro et al., 1981). OROV was distributed in Peru, Brazil, Panama, Trinidad and Columbia (Saeed et al., 2000). However, incidence of Oropouche Virus has not been reported in Venezuela, Costa Rica and some parts of Caribbean. Outbreaks of Oropouche Virus epidemics have been reported from various parts of Brazil between 1961 and 1978 (Nunes et al., 2005). In a year, clinical cases reported from Oropouche virus have been well beyond thousands which were surpassed only by the pathogenicity of the Dengue virus. Acute reporting of the disease was hampered greatly due to the absence of specific symptoms and the incidence being further complicated with a background of febrile manifestations. Recently with the incidence of Iquitos virus in Peru, the endemicity of OROV was highly reviewed, since both of the disease exhibit similar symptoms (Aguilar et al., 2011). Even though research on identification of the pathogen’s vector has been carried out with Aedes serratus, Culex quinquefasciatus and Coquillettidia venezuelensis (Anderson et al., 1961; Pinheiro et al., 1981), but the isolates of OROV made from the mosquitoes has been very less. In the light of identification of the reservoir host of OROV, various research works were done, however with little effect as the outcome remains inconclusive (Carpenter et al., 2013). Regarding the notion of anthroponosis of OROV as seen within human, C. paraensis was thought to be the key player as the candidate vector. Subsequently their role in the transmission was well-established under laboratory conditions (Pinheiro et al., 1981) as well as in the field (Roberts et al., 1981). The immatures of C. paraensis develop in rotten banana stump, plantain stalks and cacao hulls (Hoch et al., 1986). In contrast to most of the species of Culicoides, which are nocturnal (Kettle et al., 1977; Mellor et al., 2000), C. paraensis is diurnal as they follow a dawn-dusk periodicity with maximum activity between 1700-1800 hours (Roberts et al., 1981; Hoch et al., 1990). Besides OROV, other globally important zoonotic arboviruses were also thought to be transmitted by the Culicoides species; however their role in such activity has been ill-defined and restricted.

**VESICULAR STOMATITIS INDIANA VIRUS**

Till then, one of the most important humanoid arboviruses is Vesicular Stomatitis Indiana virus (VSIV) (Carpenter et al., 2013). Most of the research concentrated on identification of the host largely centered on the ruminants, because incidence of disease in human arising from the transmission of VISV by the arthropod was extremely rare (De Leon & Tabachnick, 2006; Drolet et al., 2005; Nunamaker et al., 2000). Vesicular stomatitis was a disease primarily affecting the livestock. The causative agents belong to the Rhabdoviridae family. The disease has been reported to be highly infectious to human (Bhatt & Rodrigues, 1967; Letchworth et al., 1999). The symptoms are severe ulceration of oral tissues, tongue, teats and feet (Letchworth et
al., 1999). Seasonal prevalence of the disease was observed in Central America, southeastern parts of USA, southern Mexico and northern regions of South America. Africa and India (Bhatt & Rodrigues, 1967) were known to be endemic to certain Vesicular Stomatitis Virus strains (Letchworth et al., 1999). The transmission of VSIV by Culicoides was poorly understood. Laboratory transmission of VSIV by S. vittatum (Mead et al., 1999, 2000) and C. sonorensis were investigated (Drolet et al., 2005).

**RIFT VALLEY FEVER VIRUS**

Sylvian cycle of Rift valley Fever virus has been investigated extensively in female Culicoides midges. In this study Culicoides sonorensis colony line obtained from colonized population maintained in the USA were treated to observe the vector competence, however RVFV failed to replicate beyond 135 individuals of the midges (Jennings et al., 1982).

**DISCUSSION**

Worldwide the Culicoides spp. are considered to be one of the most abundant biting midges to vector arboviruses (Mellor et al., 2000), however their overall effect on the health of human are restricted to incidences of mild cases of mansoonellosis, oropouche fever and biting nuisance. The role of the Culicoides midges as a vector of humanoid arboviruses has been poorly understood and was inferred to be limited. However, the report of isolation of VSIV and RVFV from the midges should not be discounted, rather these reports should be considered for future assessment of risk (Carpenter et al., 2013). Recently in Europe, the impact of Culicoides midges on public health was constrained to inconvenience caused by the biting activity of C. impunctatus due to its high abundance. The midge has been distributed widely in Northern Europe, whereas most of the studies regarding the impact of C. impunctatus on human population were focused around Scottish Highlands (Blackwell, 2001; Stuart et al., 1996). The biting rate of C. impunctatus reported in this region exceeds that of other hematophagous Dipterans distributed worldwide. Maximum biting activity of C. impunctatus was reported from Ormsary, UK, as 635 midges were collected per minute using human bait (Carpenter et al., 2005). Unlike C. paraensis, C. impunctatus was reported to be a crepuscular species (Blackwell, 1997), however most of the incidences of biting were recorded under cloudy conditions during the daytime (Hendry, 2011). Most of the common mammalophilic species of Culicoides were reported to be intermittently inflicting bites on human and such investigations have been further enriched with the usage of PCR for identification of the host (Garros et al., 2011; Santiago-Alarcon et al., 2012). In Europe, these species consisted of the vectors inferred to be associated with the transmission of arboviruses in livestock: C. scotius, C. chiopterus, C. punctatus, C. obsoletus, C. dewulfi and C. pulicaris (Dzhafarov, 1962; Overgaard Nielsen, 1964; Service, 1971; Szadziewski & Kubica, 1988; Santiago-Alarcon et al., 2012). In the Afro-tropical region, C. imicola has been the most prevalent species considered to be the primary vector of the livestock, however episodes of this species inflicting bites on human has been rare or absent. In Asia, the role of Culicoides on transmitting the anthropophilic pathogens were least studied except the case of eczema caused by C. erairai (Arnaud, 1956). Of the 1401 species (Borkent, 2015) reported worldwide, India houses 79 of the species (Nandi, 2014), amongst which most of them are reported to be potent vector of arboviruses of economic importance worldwide (Borkent, 2004). Even though C. oxystoma was the Bluetongue Virus vector with significant potency prevalent in entire regions of the south East Asia including India (Dadawala et al., 2013), its role in vectoring pathogens between human was least investigated in this part of the world.
REFERENCES


