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Sandfly-Borne Viruses of Demonstrated/Relevant Medical Importance

Nazli Ayhan and Remi N. Charrel

Abstract

Sandflies show distribution in a vast geographical area from Europe to Asia, Africa, Australia, and Central and South America where they can transmit a large number of viruses. Between these viruses, the most important are grouped into the *Phlebovirus* genus (family *Phenuiviridae*). Among them, several sandfly-borne phleboviruses cause self-limiting febrile disease (sandfly fever) or central and peripheral nervous system infections. Data concerning the geographic distribution of these phleboviruses has drastically increased during the last decade in both the new and the old worlds. The current situation depicts a high viral diversity with taxonomic groups containing human pathogenic and non-pathogenic viruses. This merits to provide insight to address the question of medical and veterinary public health impact of all these viruses, which are poorly studied. To do so, integrated and translational approaches must use ecological, epidemiological, serological and direct clinical evidence. Beside, other viruses transmitted by sandflies and belonging to *Rhabdoviridae* and *Reoviridae* families can also be of veterinary and public health importance. The chapter aims to provide a comprehensive view of the sandfly-borne viral pathogens of the public health impact on humans and other vertebrates in the old and new worlds.

Keywords: sandfly-borne phleboviruses, sandfly fever, phlebovirus, Toscana virus, Sandfly fever Naples virus, Sandfly fever Sicilian virus, Punta Toro virus, Vesiculovirus, Chandipura virus, Changuinola virus

1. Introduction

Sandflies are present in tropical and subtropical, arid and semi-arid areas and temperate zones including southern Europe, Asia, Africa, Australia, Central and South America. Phlebotomine sandflies are tiny diptera insects grouped in the family Psychodidae, subfamily Phlebotominae. To date, over 800 species are estimated to exist in different regions of the world [1]. Two genera (*Phlebotomus* and *Sergentomyia*) of Phlebotominae are mostly recorded in the old world (OW) and the other genus *Lutzomyia* exists in the new world (NW) [2]. Only females are hematophagous and require a blood meal to develop their eggs. Sandflies take blood from a wide range of animals such as cold-blooded vertebrates, mammals and birds; trophic preferences vary depending on the sandfly species.

Of the 800 sandfly species, at least 98 are proven or suspected vectors of microorganisms capable to cause parasitic, viral or bacterial diseases in vertebrates [1].

This chapter will focus essentially on sandfly-borne viruses, which have been proven agents of diseases in humans.

The arthropod-borne diseases including sandfly-borne viral diseases affect urban, peri-urban, and rural population but mostly the communities with poor living conditions. Economic, social and ecological conditions have a huge impact on sandfly-borne viral diseases [3, 4]. The factors that described as associated with arthropod-borne diseases emergence or invasion are (i) competent vector and vertebrate host population repeatedly in contact within an appropriate environment, (ii) vertebrate or vector host species composition changes, (iii) environmental or niche changes and (iv) genetic changes [5].

Although sandflies can transmit a number of arthropod-borne viruses within the families *Phenuiviridae*, *Reoviridae* and *Rhabdoviridae*, they remain neglected vectors of viral diseases in contrast with a high interest for parasitic diseases such as leishmaniasis. The three virus families contain human/animal pathogens. In the *Rhabdoviridae* family, attention will be given to Chandipura virus; in the *Reoviridae* family, we will focus on Changuinola virus [2, 6–8]. In the *Phenuiviridae* family, we will focus on Sandfly fever Sicilian virus, Sandfly fever Naples virus, Toscana virus, Adria virus and Punta Toro virus (PTV).

2. Sandfly-borne phleboviruses

Phleboviruses are enveloped viruses with single-stranded trisegmented RNA. They contain three genomic segments: L (Large) segment encodes the viral RNA polymerase (RdRp), M (medium) segment encodes envelope glycoproteins (Gn and Gc) and non-structural protein m (NSm) and S (small) segment encodes nucleocapsid protein (N) and non-structural protein s (NSs) [9].

Currently, 10 species within the genus *Phlebovirus* are recognized by the International Committee on Taxonomy of Viruses (ICTV): *Sandfly fever Naples virus*, *Salehabad virus*, *Rift Valley fever virus*, *Uukuniemi virus*, *Bujaru virus*, *Candiru virus*, *Chilibre virus*, *Frijoles virus*, *Punta Toro virus*, and *Severe fever with thrombocytopenia syndrome virus*. Of interest, almost 40 phleboviruses are still listed as tentative species for which the ICTV has not officially ruled; interestingly, Sandfly fever Sicilian virus still belongs to this pending group although discovered in 1943 [10].

Phleboviruses can be detected and isolated from blood-sucking female sandflies and from non-blood-sucking males in equal proportions [11–14]. This suggests that alternative transmission pathways (other than blood-borne from vertebrate reservoir) such as transovarial transmission (female to offsprings) and/or venereal transmission play an important role in the natural cycle [2]. Experimental results done with colonized *P. papatasi* sandflies proved venereal virus transmission and transovarial virus transmission [15]. Viral maintenance during the diapausing period of *Phlebotomus perniciosus* larvae was proved and was not affected by transstadial transmission in laboratory [15]. These routes of virus transmission suggest that phleboviruses can be sustainably transmitted from one generation of sandflies to the next generation. It also raises the question of whether a vertebrate host acting as reservoir is required or not for virus perpetuation. To date, these experiments have been performed primarily with high passage colonies and should be taken with caution because laboratory reared sandflies may behave differently from wild populations. In addition, they have been performed with few species of phlebovirus and with *P. papatasi* and *P. perfiliewi* only. Elucidation of phlebovirus maintenance and transmission is crucial to understand better the natural history of these viruses and to develop adapted method to combat those which are human pathogens [15–17]. Although several sandfly-borne phlebovirus species were isolated from humans, bats and sandflies [18–23], there is no

undisputable evidence that vertebrates play an important role in the natural history of sandfly-borne phleboviruses other than as dead-end hosts.

With recently discovered novel viruses, the geographic distribution of phleboviruses has drastically increased in both the new and the old worlds. The current situation depicts a high viral diversity with taxonomic groups containing pathogenic and non-pathogenic viruses. This merits to provide insight to address the question of medical and veterinary public health impact of all these viruses, which are poorly studied.

2.1 Sandfly-borne phleboviruses in the old world

In the old world (OW), the risk for the infection with sandfly-borne phleboviruses is high depending upon the presence and the density of vectors [24].

Historic and recent epidemics have been caused by sandfly-borne phleboviruses in the OW. In 1937, a massive outbreak occurred in Athens, Greece [25, 26]. During World War II (WWII), outbreaks were described among out-comer soldiers in the Mediterranean basin and Middle East (the Austrian Commission in Balkan countries, British and German troops in the Mediterranean area) [17, 26, 27].

After WWII, sandfly fever epidemics were reported in Belgrade, Serbia, where thousands were sick [28], with subsequent spread into other regions of the Balkans [29–32]. More recently, large epidemics were recorded in Cyprus, Iraq, Turkey and Ethiopia [33–36].

In addition, during the last two decades, an impressive number of novel phleboviruses was either isolated or detected by molecular techniques in France, Italy, Portugal, Greece, Albania, Croatia, Bosnia Herzegovina, Turkey, Iran, Tunisia, Algeria and Morocco [11–14, 23, 37–43]. Accordingly, the Mediterranean area witnesses a very high diversity of phleboviruses transmitted by sandflies [44]. This situation has raised the public health concerns in southern Europe, North Africa and in the Middle East [11, 13, 14, 39, 41, 45, 46].

OW sandfly-borne phleboviruses can be classified into three serological complexes, which are also regarded as taxonomic species, Salehabad species, Sandfly fever Naples species and Sandfly fever Sicilian tentative species.

Sandfly fever Sicilian and Sandfly fever Naples viruses cause fever, also known as “sandfly fever”, “Pappataci fever” or “three-day fever”. It is not possible to distinguish Sandfly fever Sicilian virus infection from Sandfly fever Naples virus infection based on clinical signs, which are virtually identical. They both cause abrupt illness with fever, headache, malaise, photophobia, myalgia and retro-orbital pain usually lasting 2–3 days after 3–5 day incubation [47].

Toscana virus, which belongs to the *Sandfly fever Naples* species, is so far the most pathogenic sandfly-borne phlebovirus due to its propensity to affect the central nervous system (CNS) and cause meningitis and meningoencephalitis [45]. Recently, Adria virus, identified in a case of meningitis, is the first virus belonging to the *Salehabad* species to display human pathogenesis [38].

2.1.1 Sandfly fever

Before WWII, the knowledge on sandfly fever was limited to clinical and epidemiological grounds. It was known that the fever caused by a filterable agent and transmitted by *Phlebotomus papatasi* sandflies [48, 49]. Early assumptions claimed that sandfly fever might be caused by distinct agents or viruses, despite it was impossible to distinguish them from the clinical symptoms [47, 50].

Between 1934 and 1939, human sera samples from sandfly fever virus-infected individuals (presumably containing the infectious agent) were inoculated into rhesus monkeys which presented with febrile illness [51]. Inoculation of infectious

human serum (i) into chick embryos showed lesions on the chorioallantoic membrane, whereas (ii) no clinical sign were noticed after inoculation to guinea pigs, rabbits or dogs [47]. Three out of four human volunteers without a previous sandfly fever history developed the typical symptoms and fever after inoculation of 1 ml of the pool of acute sandfly fever serum [47]. Subsequently, *Phlebotomus papatasi*, *Culex pipiens* and *Pulex irritans* fed on sandfly fever acutely infected volunteers, only *P. papatasi* was able to transmit the disease to naïve volunteers [47]. In 1937, a massive outbreak occurred in Athens, Greece [26]. However, most of the outbreaks occurred in non-native persons having entered the endemic area for the first time recently such as soldiers [13]. During WWII, several outbreaks of sandfly fever knocked down battalions of soldiers in both the Allied and Axis troops which were stationed in the Middle East, the Mediterranean and North Africa [17, 52, 53]. The suspected variety of causing agents was shown through isolation of two different viruses names Naples and Sicilian virus from sick soldiers in southern Italy [47, 53]. The antigenic differences between Naples virus and Sicilian virus were confirmed by human cross-immunity test, neutralization and complement fixation test [54].

2.1.2 Sandfly fever Naples virus

Sandfly fever Naples virus was first isolated from blood of a febrile soldier who became ill when stationed in Naples, Italy in 1944 [47]. Afterward, Naples virus was isolated again (i) from febrile patients in Egypt, Turkmenia, Pakistan, Italy, Cyprus and India [55–61] (ii) and from sandflies in Egypt (*P. papatasi*), in Italy (*P. perniciosus*) and Serbia (*P. perfiliewi*) [19, 59, 62]. This was the first clue that Naples virus could be transmitted by distinct vector species. A large and seminal neutralization-based seroprevalence study, performed by Tesh et al. in 1976, showed that Naples virus was likely to have a much wider distribution than initially believed from virus isolation reports [24]; indeed, neutralizing antibodies were detected in human populations from Bangladesh, Ethiopia, Greece, Iraq, Morocco, Saudi Arabia, Sudan, Djibouti, Turkey and former Yugoslavia [24]. Highest rates (55–62%) were observed in Egypt, former Yugoslavia (now Croatia), and Turkey. Another study reported neutralizing antibodies in populations living in Turkmenia, Tajikistan, Uzbekistan, and Moldavia [63]. Clearly, Naples virus circulation has drastically decreased after the 1980s, and the absence of virus isolation or PCR detection, despite an increasing number of studies conducted in previously endemic areas, question whether Naples virus has gone extinct or not [58].

2.1.2.1 Toscana virus

Toscana virus (TOSV) was first isolated from *P. perniciosus* in central Italy in 1971 [17]. It has taken 12 years to recognize that TOSV was capable to infect humans and was able to cause not only sandfly fever, but also more severe infections characterized by central nervous system (CNS) manifestations such as meningitis and encephalitis. The first cases pointing out that Toscana virus causes CNS infections came from two travelers returning from Italy and Portugal to the United States and Sweden, respectively [64, 65]. This underlines the importance of travel-related medicine in the surveillance of infectious diseases, particularly vector-borne infectious diseases. Most of the Toscana virus case records are coming from important or autochthonous human cases from the Mediterranean basin countries [45, 70]. Autochthonous cases in humans have been reported in Italy [71], Greece [72], Cyprus [73], Croatia [74], Turkey [75, 76], Portugal [77] and France [78]. However, these cases account for a minimal proportion of literature-described cases. In most countries, where TOSV is endemic, it is not a notifiable disease; this together with the absence of pathognomonic clinical sign, and the very limited number of

commercially available diagnostic assay may explain why autochthonous cases are drastically under detected, and that most of reported cases have affected travelers, the diagnosis of which is done when returning to their homeland. TOSV cases in travelers have been reported from Italy [66], France [67], Spain [68, 69] and Portugal [64], but also from the Mediterranean islands such as Cyprus [73], Elba [79, 80], Sicily [81] and Sardinia [82].

Seroepidemiological studies showed the presence of neutralizing antibodies against Toscana virus in several Mediterranean countries, however, the rates vary depending on the region Mediterranean basin considered as endemic region of Toscana virus [45, 71, 74, 78, 83–88].

Special attention must also be brought to the technique used for serology, since results can greatly vary due to different levels of cross-reactivity depending on the assay; for instance, the most stringent technique is based on neutralization assays whereas ELISA or immunofluorescence techniques are more prone to cross-reactivity between phleboviruses within the same antigenic group, but also between antigenically distinct phleboviruses [88–90].

The geographic distribution of sandfly-borne phleboviruses can also be measured by surveillance of non-human vertebrates such as domestic animals: such studies have demonstrated that TOSV was actively circulating in Portugal, Greece, Cyprus and Algeria [83–85] from the study of dog sera, and in Kosovo from studying cow and sheep sera [86]. TOSV was also isolated and/or detected in different phlebotomine species such as *P. perniciosus*, *P. perfiliewi*, *P. longicuspis*, *P. sergenti*, *P. neglectus* and *Sergentomyia minuta* in Italy, France, Spain, Croatia, Morocco, Tunisia, Algeria and Corsica [13, 18, 82, 87, 91–96]. These results tend to suggest that TOSV can be transmitted by species other than *P. perniciosus* and *P. perfiliewi*. Such data are compatible with the fact that TOSV might be more widely dispersed than believed from the early studies. Of course, this merit to be further investigated through experimental studies addressing competence of these species for TOSV. TOSV belongs to the *Sandfly fever Naples* species.

To date, three genetic groups of TOSV have been recognized, and they are called lineages A, B and C. Although only one lineage has been identified in a given country, the co-circulation of two lineages has been shown in France, in Turkey, and in Croatia. It is possible that different lineages are transmitted by the same sandfly species and that sympatry may be frequent [91, 93, 97]. Recent Toscana virus antibody characterization assay performed with 41 patients diagnosed with Toscana virus meningitis of meningoencephalitis found that specific IgM titers were high during acute infection up to day 30, the presence of IgM antibodies lasts up to 6 months after acute infection in 71% of cases, however IgG antibodies against Toscana virus persisted at least 2 years in the patients, which gets in line with the fact that TOSV infection is associated with long-term, maybe lifelong immunity [88]. There is accumulating evidence that TOSV is one important cause of meningitis and encephalitis during the warm season and that it should be included in the panel of microorganisms to be systematically tested in clinical microbiology laboratory for patients presenting with febrile illness, CNS and peripheral nervous system manifestations.

2.1.3 Sandfly fever Sicilian virus

Sandfly fever Sicilian virus (SFSV) was first isolated, characterized and named Sicilian virus, from the serum of a US soldier, presenting with sandfly fever when he was stationed in Palermo (Sicily) after the landing of the Allied army forces in Italy, in 1943 during WWII [47]. Almost simultaneously, it was also described in sick US soldiers stationed in Egypt. Subsequent studies allowed isolation of SFSV in Egypt, India, Iran, Pakistan and Afghanistan [56, 98–100].

Accumulating direct (virus isolation or molecular detection) and indirect (seroprevalence studies) data allowed to list the following countries as areas where SFSV was circulating: Bangladesh, Greece, Cyprus, Iraq, Morocco, Saudi Arabia, Somalia, Ethiopia, Sudan, Tunisia, Turkey, Turkmenia, Tajikistan, Uzbekistan, Azerbaijan, Moldova, Croatia, Kosovo, France and Portugal [24, 33, 34, 61, 63, 83, 86, 101–103]. Beside the outbreaks described in the Allied and Axis forces during WWII, more recent epidemics were reported in Cyprus, in Turkey and in Ethiopia caused by genetic variants [29–36, 104]. Recent seroprevalence studies provided evidence that SFSV and its genetic variants were still actively circulating in Greece, Cyprus, Portugal and Kosovo [83, 84, 86]. Although *Phlebotomus papatasi*, *Phlebotomus ariasi* and *P. major* complex were indisputably identified as SFSV vectors, transmission might also be done by phlebotomies belonging to other species [20, 100].

2.1.4 *Adria virus*

Adria virus was first detected in 2005 from field-collected sandflies in Albania [39]. Genetic data consisting of partial sequence in the polymerase gene showed that Adria virus is much closely related with viruses belonging to the *Salehabad* species than with other phleboviruses belonging to the *Sandfly fever Naples* or to the *Sandfly fever Sicilian* species. In 2009, a 30-month-old patient was admitted to hospital in Greece for fever and seizure during summertime; his blood was tested positive for the presence of phlebovirus RNA, whose sequence was most closely related with Adria virus sequence [23]. Adria virus is the first, and so far the only member of the *Salehabad* species to be associated with human disease. Interestingly, the number of viruses identified in this species has drastically increased during the last decade. Thus efforts should now be deployed to investigate to what extent, Adria virus in particular but also other newly recognized *Salehabad* viruses have a medical impact.

2.1.5 *Other phleboviruses*

The last decade has been marked by discovery of an unprecedented number of sandfly-borne phleboviruses in old world phlebotomies. Although most of the remains to be classified or listed by the ICTV, they each belong to one of the three species aforementioned: *Sandfly fever Naples*, *Sandfly fever Sicilian* or *Salehabad*. Accordingly, they have drastically increased the genetic diversity within each of these species. Since several of these viruses were discovered in sandflies trapped in countries where phleboviruses had never been described before, the geographic range of circulation of the phleboviruses transmitted by sandflies has dramatically expanded.

Sandfly fever Naples species shows an important genetic diversity which has motivated a proposed subdelineation into four groups [42]: subgroup I includes Tehran virus (Iran), Zerdali virus (Turkey) and Sandfly fever Naples virus strain YU 8–76 (Serbia); subgroup II contains the three genotypes of Toscana virus; subgroup III includes Sandfly fever Naples virus and subgroup IV comprises Massilia virus (France), Arrabiata virus (Portugal), Granada virus (Spain) and Punique virus (Tunisia) [11, 18, 37, 42, 46, 47, 105]. Whether viruses belonging to subgroup I and IV can infect humans and may cause disease is currently unknown.

Genetic and phylogenetic analyses show that viruses that can be grouped into the Sandfly fever Sicilian/Corfou virus group or tentative species can be subdivided into two clusters: (i) lineage I contains Sandfly fever Sicilian viruses together with the newly isolated Dashli virus [43] and (ii) lineage II includes Corfou virus together with Toros virus which were isolated from Greece and Turkey, respectively [42, 89].

During the last decade, the *Salehabad virus species* which contained initially only Salehabad and Arbia viruses has greatly increased by addition of newly discovered

viruses such as Adana virus, Alcube virus and Medjerda Valley virus, respectively, isolated from sandflies collected in Turkey, Portugal and Tunisia [37–40, 106]. Several other viruses were not isolated but discovered through sequencing a part of their genome such as Adria virus (Albania and Greece), Edirne virus (Turkey) and Olbia virus (France) [23, 39, 107, 108]. To date, Adria virus is the only virus belonging to the *Salehabad species* that was associated with a case of human disease.

Although a large number of these viruses have not been associated with cases of human or veterinarian diseases, it must be remembered that 12 years have passed between the discovery of Toscana virus and the first evidence that it was pathogenic for humans. It is, therefore, crucial to address the public health impacts of these newly described phleboviruses via seroprevalence studies and molecular virological investigations of clinical cases of fever of unknown origin and infections of the central nervous system during summer.

2.2 Sandfly-borne phleboviruses in the new world

2.2.1 *Punta Toro virus*

Medically speaking, it is the most important phlebovirus in the Americas. Punta Toro virus (PTV) was first identified in the blood of a febrile soldier who participated in military training in the jungle of the Panama Canal Zone, in 1966 [109]. PTV was isolated for the second time in the blood of an entomologist who was doing field collection of insects in the forested area of Darien Province in Panama [108]. Fever, headache, weakness, back, and retro-orbital pain were the common symptoms in both cases with 3–4 days duration. Several Punta Toro virus strains were isolated from sandflies and wild sentinel hamsters in Bayano district of Panama between 1975 and 1976 [109]. To date, PTV has been described only in Central America where several strains of the virus isolated from *Lutzomyia (Nyssomyia) trapidoi* and *L. (Ny.) ylephiletor* [16]. One strain was isolated from the blood of an apparently healthy wild-caught sloth in central Panama [110]. In 1974, a seroprevalence study showed that 5% of the children under the age of 20 and 27–40% of adults in Panama had specific antibodies [111]. In 2009, during the dengue surveillance programme in Panama, dengue virus-negative human samples were found to contain PTV RNA strains. Of the 201 tested sera from febrile patients, 27 (13.4%) were positive for PTV [112].

PTV has been used in several experimental studies [113–115]. Interestingly, when Syrian golden hamsters are inoculated with the Adames strain (PTV-A), they develop a fatal disease; in contrast, hamsters infected with the Baillet strain (PTV-B) do develop a disease but all survive the challenge [113].

2.2.2 *Other phleboviruses*

A large number of phleboviruses have been isolated from sandflies in Brazil, Panama and Peru [116, 117]. Several viruses have been classified into one the five following groups or species: *Punta Toro*, *Candiru*, *Bujaru*, *Tapara* and *Frijoles species*. However, those which were not classified were included in the tentative species category.

Cocle virus (*Punta Toro species*) was isolated from the serum of a febrile patient in Cocle province, Panama in 2009 [109]. Although it appears that Cocle virus belongs to a species which contains viruses transmitted by sandflies, the absence of entomological data does not allow to conclude about the vector involved in the natural cycle.

Oriximina, Turuna, and Ariquemes viruses (*Candiru species*) were isolated from *Lutzomyia sp.* sandflies in Brazil and Nique virus was isolated from *Lutzomyia panamensis* in Madre de Dios, Peru [116]. Although several viruses belonging to the *Candiru virus species* were identified from febrile patients, there is limited knowledge about the nature of the insect species that transmit these viruses.

3. Other pathogenic sandfly-borne viruses

3.1 *Rhabdoviridae* family

The *Rhabdoviridae* family includes 18 genera and 134 species with negative-sense, single-stranded RNA genomes [118]. In this family, members of the *Vesiculovirus* genus are able to infect at least 28 invertebrates and vertebrates including human [27, 119]. They cause vesicular stomatitis in human and domestic animals and they show a worldwide distribution both in the new and old worlds.

The disease manifests itself into two different forms in the United States; either as sporadic outbreaks with a 10-year intervals in the southwestern states (New Mexico, Arizona, Utah and Colorado) [120]. However, in some other states as Georgia, Alabama, North and South Carolina, the disease occurred yearly with clinical signs in cattle, pig and horses. Since 1970, viral activity has been focal and limited to isolated wildlife populations. [120]. In addition, the virus is considered as endemic in Colombia, Venezuela, Ecuador, Peru and Mexico, where outbreaks occur every year [121, 122].

In the old world, another vesiculovirus, Chandipura virus has recently emerged and caused severe encephalitis in human in different parts of India [6, 123]. The first isolation of Chandipura virus was from two patients with febrile illness in 1965 [6]. In 2003, the virus caused the first outbreak of acute encephalitis in children with high fatality rate (183 deaths out of 329 cases, 55.6%) in Andhra Pradesh, India [124]. The second outbreak has occurred in the eastern state of Gujarat with higher fatality rate in 2004 (>75%) [123]. Recently, an outbreak of acute encephalitis syndrome was recorded in Maharashtra, India with 43.6% fatality rate in children younger than 15-year-old [125].

Chandipura virus has been isolated from field-collected *Phlebotomus spp.* sandflies [7]. The virus was also detected in sandflies belonging to the genus *Sergentomyia* in India [126]. This virus has not only been detected in India but also in Senegal and Nigeria, respectively, from phlebotomine sandflies and hedgehog (*Atelerix spiculus*) [127]. This suggests that Chandipura virus is widely distributed and should be investigated in a more detailed manner.

3.2 *Reoviridae* family

Changuinola virus was first isolated from *Lutzomyia sp.* sandflies in 1960 in Panama [128]. Since then 12 isolates were described from phlebotomine flies [129]. Another, seven strains were isolated from 80 wild-trapped sloths (*Bradypus variegatus* and *Choloepus hoffmanni*) from Central Panamá [109]. Neutralizing antibody were detected in these two sloth species, despite they were virtually absent from other wild vertebrate species tested. Several strains were associated with prolonged or recrudescing viremias in sloths [130]. Besides, one strain of Changuinola virus was identified from a febrile patient [8]. Changuinola virus can replicate in mosquito cell lines (C6/36 [*Aedes albopictus* cells]), *Culicoides sonorensis* KC and African green monkey kidney Vero cells [131].

4. Conclusions

Sandfly-borne viral pathogens are widespread in both old and new worlds particularly in tropical/subtropical areas, and temperate zones including southern Europe, Asia, Africa, Australia and Central and South America [24]. Due to vector sandfly species activity, the sandfly-borne viral diseases peaks during summer which affect both urban, peri-urban and rural population, but mostly the communities with poor living conditions [3, 4] (**Figure 1, Table 1**).

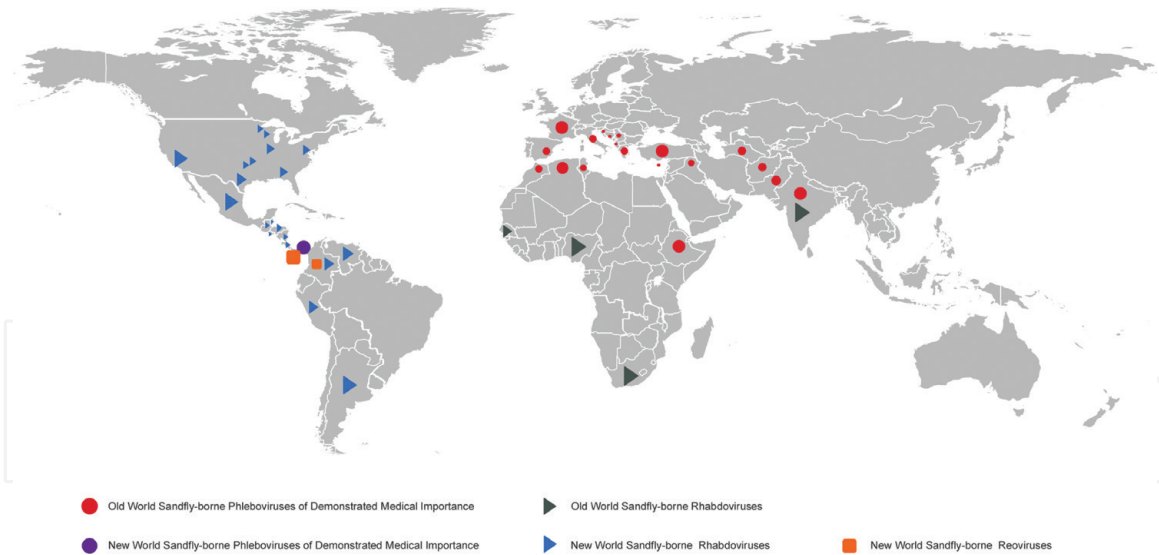


Figure 1.
 Schematic overview of the sandfly-brone viruses, according to geographical regions.

Group	Virus	Virus origin	Country
Sandfly-borne phleboviruses of demonstrated medical importance			
Old World Sandfly-borne phleboviruses of demonstrated medical importance			
Sandfly fever Naples Species	Sandfly fever Naples virus	Blood sample	Italy
	Sandfly fever Naples virus Sabin		
	Sandfly fever Naples virus R-3	Human sera	Cyprus
	Sandfly fever Naples virus Namru	<i>Phlebotomus papatasi</i>	Egypt
	Sandfly fever Naples virus	Human	Turkmenistan
	Sandfly fever Naples virus	Human	Afghanistan
	Sandfly fever Naples virus	<i>Phlebotomus longicuspis</i>	Algeria
	Sandfly fever Naples virus	<i>Phlebotomus spp.</i> and humans	India
	Sandfly fever Naples virus YU 8-76	<i>Phlebotomus perfiliewi</i>	Serbia
	Toscana virus	<i>Phlebotomus perniciosus</i>	Italy
	Toscana virus	Human CSF	Italy
	Toscana virus	<i>Pipistrellus kuhli</i> brain	Italy
	Toscana virus	<i>Phlebotomus spp.</i>	Italy
	Toscana virus	<i>Phlebotomus perniciosus</i>	France
	Toscana virus	<i>Sergentomyia minuta</i>	France
	Toscana virus	human CSF	Croatia
	Toscana virus	<i>Phlebotomus neglectus</i>	Croatia
	Toscana virus	<i>Phlebotomus spp.</i>	Cyprus
	Toscana virus	Human sera, urine	Turkey
	Toscana virus	<i>Phoenicopterus roseus</i> , <i>Pelecanus onocrotalus</i> , <i>Ciconia nigra</i>	Turkey
	Toscana virus	<i>Phlebotomus perniciosus</i>	Morocco
	Toscana virus	<i>P. longicuspis</i> , <i>P. sergenti</i>	Morocco

Group	Virus	Virus origin	Country
	Toscana virus	<i>Phlebotomus spp.</i>	Algeria
	Toscana virus	<i>Phlebotomus spp.</i>	Tunisia
	Toscana virus	Human CSF	Greece
Sandfly Fever Sicilian Species	Sandfly fever Sicilian virus Sabin	Human sera	Italy
	Sandfly fever Sicilian virus	<i>Phlebotomus spp.</i>	Iran
	Sandfly fever Sicilian virus	Human sera	Cyprus
	Sandfly fever Sicilian virus	<i>Phlebotomus papatasi</i>	Pakistan
	Sandfly fever Sicilian virus	<i>Phlebotomus ariasi</i>	Algeria
	Sandfly fever Sicilian virus	<i>Phlebotomus papatasi</i>	Algeria
	Sandfly fever Sicilian virus	Human	Afghanistan
	Sandfly fever Sicilian virus	<i>Phlebotomus spp.</i>	India
	Sandfly fever Sicilian virus	Human	Ethiopia
	Sandfly fever Cyprus virus	Human sera	Cyprus
	Sandfly fever Turkey virus	Human sera	Turkey
	Sandfly fever Turkey virus	<i>Phlebotomus major</i> complex	Turkey
	Dashli virus	<i>Phlebotomus spp./</i> <i>Sergentomyia spp.</i>	Iran
Salehabad Species	Adria virus	Human blood	Greece
	Adria virus	<i>Phlebotomus spp.</i>	Albania
New World Sandfly-borne phleboviruses of demonstrated medical importance			
Punta Toro Species	Punta Toro virus Adames	Human	Panama
	Punta Toro virus Balliet	Human	Panama
	Punta Toro virus	Human	Panama
	Punta Toro virus	Human	Panama
	Punta Toro virus	Sentinel hamster	Panama
	Punta Toro virus	Sentinel hamster	Panama
	Punta Toro virus	<i>Lutzomyia spp.</i>	Panama
	Punta Toro virus	Human	Panama
	Punta Toro virus	Human	Panama
	Punta Toro virus	Human	Panama
	Punta Toro virus	Human	Panama
Sandfly-borne Rhabdoviruses			
Vesiculovirus Species	Vesiculovirus	Horse	South Africa
	Vesiculovirus	Bovine	Indiana, USA
	Vesiculovirus	Bovine, equine	New Jersey
	Vesiculovirus	Cattle, horse	Wisconsin, Minnesota, Dakota
	Vesiculovirus	Cattle, horse	Argentina
	Vesiculovirus	Cow, horse, pig	Venezuela
	Vesiculovirus	Horse	Texas, Louisiana
	Vesiculovirus	Horse	Kansas
	Vesiculovirus	Horse	Colorado
	Vesiculovirus	Swine	Colombia

Group	Virus	Virus origin	Country
	Vesiculovirus	Swine	Venezuela
	Vesiculovirus	Swine	Missouri
	Vesiculovirus	Swine	Colorado
	Vesiculovirus	Cattle	California
	Vesiculovirus	Horse	Arizona
	Vesiculovirus	Cattle	Mexico
	Vesiculovirus	Horse	Alabama
	Vesiculovirus	Horse	Mississippi, Georgia, Tennessee, Florida
	Vesiculovirus	Bovine, porcine	Guatemala
	Vesiculovirus	Equine	Belize
	Vesiculovirus	Bovine	Honduras
	Vesiculovirus	Bovine	El Salvador
	Vesiculovirus	Bovine, porcine	Nicaragua
	Vesiculovirus	Bovine	Costa Rica
	Vesiculovirus	Bovine	Peru
	Chandipura virus	Human	India
	Chandipura virus	Sandfly	India
	Chandipura virus	Sandfly	Senegal
	Chandipura virus	Sandfly	Nigeria
Sandfly-borne Reoviruses			
Changuinola virus Species	Changuinola virus	<i>Lutzomyia sp.</i>	Panama
	Changuinola virus	Rice rat, armadillo, sloth	Panama
	Changuinola virus	Human	Panama
	Changuinola virus	<i>Lutzomyia sp.</i>	Colombia
	Changuinola virus	<i>Bradypus variegatus,</i> <i>Choloepus hoffmanni</i>	Panama

Table 1.
 Features of the medically important sandfly-borne viruses.

Both molecular characterization and seroepidemiological studies demonstrated broad distribution of sandfly-borne phleboviruses in the old world in the Mediterranean region, in the African continent, in the Indian subcontinent, in the Middle East and in Central Asia. However, the pathogen sandfly-borne phleboviruses were recorded in the limited geographical area (Panama) in the new world with sporadic human cases. This must be due to (i) limited investigations in the new world; (ii) vector competence of phlebovirus in the new world; (iii) small-sized human population and (iv) lack of case report.

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