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Review

Sandfly-borne phleboviruses of Eurasia and Africa: Epidemiology, genetic diversity, geographic range, control measures

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ABSTRACT

Sandfly-borne phleboviruses may cause a transient febrile illness (sandfly fever) or more severe neuroinvasive disease. In the Old World, they are vectored by phlebotomine flies, which are widely distributed in the Mediterranean basin, North Africa, the Indian subcontinent, the Middle East and central Asia. High seroprevalence rates have been recorded in humans and domestic animals in areas where sandflies are present. Most published studies have focused on phlebovirus infections of travelers and of soldiers stationed in endemic areas, but the health impact on local populations should not be underestimated, as seroprevalence studies indicate massive circulation of these viruses, even if disease is seldom documented. Except for Toscana virus, which shows a marked neurotropism and is a leading cause of aseptic meningitis in endemic regions, phlebovirus infections are inadequately considered by physicians and are generally underestimated. However, several properties of these viruses suggest that they will extend their geographic range. First, changes in the areas occupied by sandflies as a result of climate change have a direct impact on the epidemiology of associated human and animal diseases. Second, phleboviruses exhibit a high mutation rate, and their tri-segmented genome is prone to reassortment and recombination. Third, distinct virus strains can be transmitted by the same arthropod species. Recent studies have documented the distribution of sandfly-borne phleboviruses in Western Europe, but data for Eastern Europe, the Middle East and Africa are very limited. With the goal of filling knowledge gaps and planning new research programs, we have examined available information and present it as a comprehensive review, with a specific focus on understudied regions. We also discuss the need to conduct studies aimed at developing new antiviral drugs and vaccines.

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1. Introduction

Sandfly-borne viruses belong to the genera *Phlebovirus* (family *Bunyaviridae*), *Vesiculovirus* (family *Rhabdoviridae*) and *Orbivirus* (family *Reoviridae*). In this review, we focus on phleboviruses transmitted by sandflies in Eurasia and Africa, which are associated with sandfly vectors that belong to the genus *Phlebotomus*. Sandfly-borne phleboviruses are widely distributed in the Mediterranean region, in Africa, the Indian subcontinent, the Middle East and central Asia.

Except for Toscana virus, which has a marked tropism for central and peripheral neurological systems, sandfly fevers cause moderately severe disease, and are often given little attention by physicians. There is also much less scientific interest in sandfly-transmitted viral diseases than in other arboviruses. For instance, a PubMed-based bibliographic search using "Toscana virus", "sandfly virus", and "sandfly fever virus" retrieved 232, 385, and 265 references, respectively, while searches with the keywords "West Nile virus" and "dengue virus" retrieved more than 4500 and 6000 papers. It is therefore difficult to provide accurate

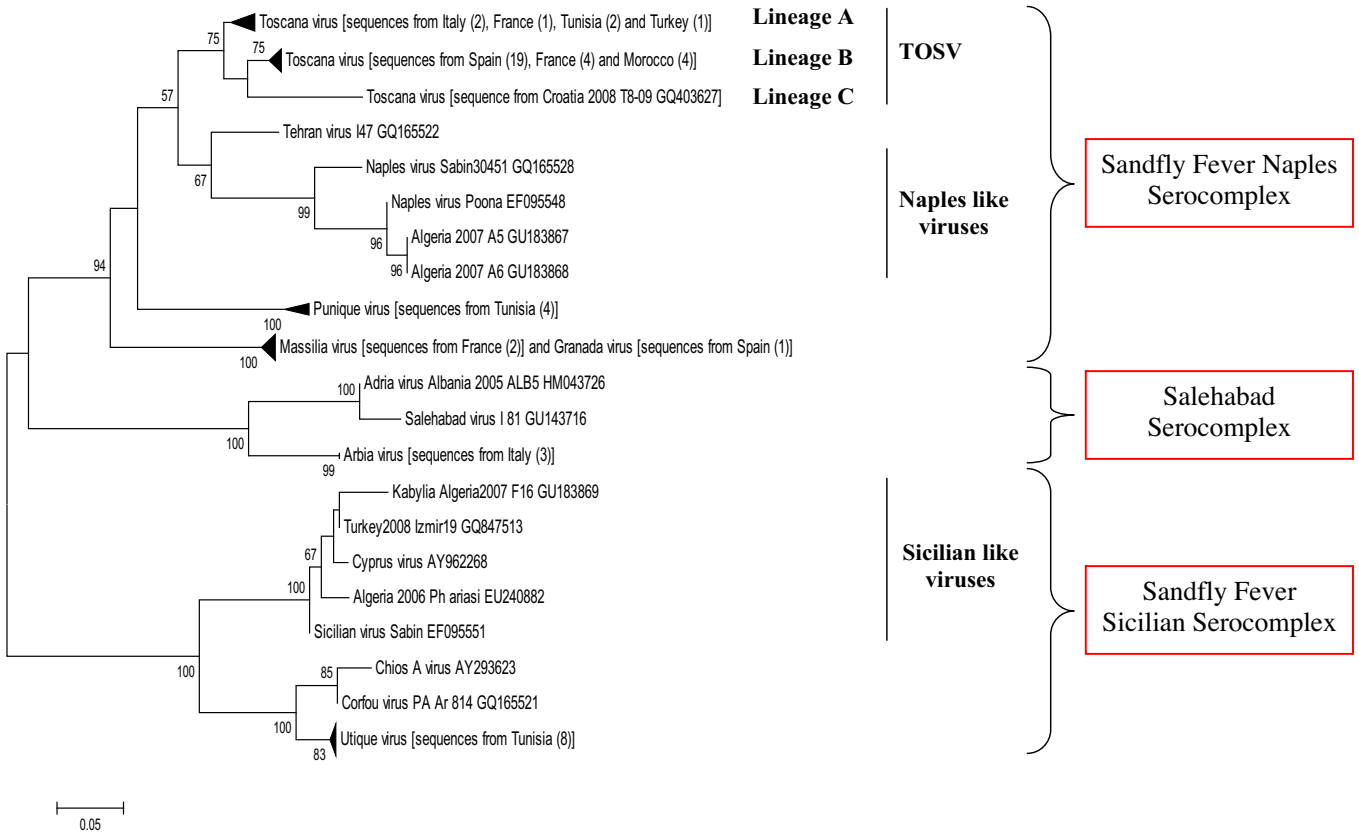


Fig. 1. Neighbour-joining tree of the Old World sandfly-borne phleboviruses (Naples, Sicilian and Salehabad species) based on amino-acid sequences of the L protein. Bootstrap values (%) were calculated with 1000 replicates. For method, see (Moureau et al., 2010).

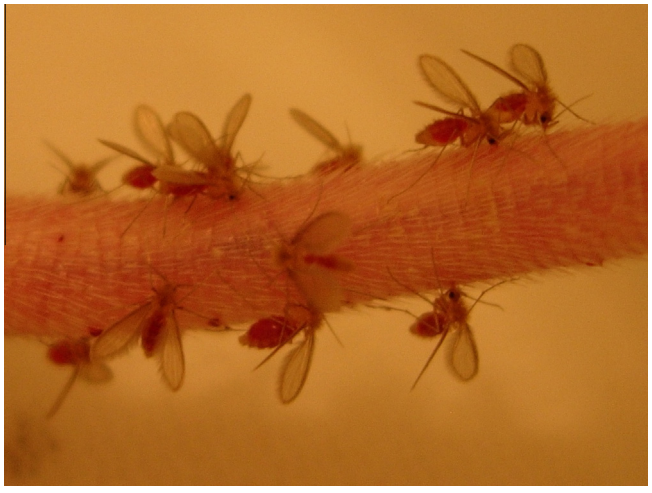


Fig. 2. Female *Phlebotomus papatasi* sandflies taking a blood meal from a mouse tail (Courtesy Filiz Gunay, University of Hacettepe).

estimates of infection rates due to sandfly-transmitted viruses because of the lack of data. However, their significance in terms of public health and human diseases should be underlined and merit increased attention from physicians, public health agencies and diagnostic virology laboratories. In regions where sandflies are present, high seroprevalence rates have been recorded in human populations and in domestic animals. Most published studies have focused on travelers and on soldiers stationed in endemic areas. However, the public health impact of sandfly-borne phleboviruses on populations living in endemic areas should not be disregarded, since seroprevalence studies indicate significant circulation of these viruses, with the potential for emergence as serious human pathogens, even if infections in residents are seldom documented.

A number of recent review articles have addressed the importance of sandfly-borne phleboviruses in Western Europe (Charrel et al., 2005; Cusi et al., 2010; Depaquit et al., 2010; Nicoletti et al., 1996; Maroli et al., 2013). In the present paper, special attention has been given to data from Eastern Europe and from Middle-Eastern and North African (MENA) countries.

2. Phleboviruses and sandflies

2.1. The viruses

The genus *Phlebovirus*, (family *Bunyaviridae*), contains nine viral species (*Sandfly fever Naples, Salehabad, Rift valley fever, Uukuniemi, Bujaru, Candiru, Chilibre, Frijoles, Punta Toro)*, and several tentative species, as defined in the 9th Report of the International Committee for Taxonomy of Viruses (ICTV) (Plyusnin et al., 2011). In the Old World, *Uukuniemi virus* is transmitted by ticks, *Rift valley fever* virus is transmitted by mosquitoes, *Sandfly fever Naples* and *Salehabad viruses* are transmitted by sandflies. Sandfly-borne phleboviruses are transmitted by *Lutzomyia* flies in the New World and by *Phlebotomus* flies in the Old World. The dichotomy is absolute. Considering sandfly-borne phleboviruses of the Old World, the ICTV recognizes at present two viral species (*Sandfly fever Naples, Salehabad*) and two tentative species (Sicilian, Corfu) (Fig. 1).

All members of the genus *Phlebovirus* have a trisegmented, negative-sense, single-stranded RNA genome. The L, M and S segments encode the RNA-dependent RNA polymerase, the viral envelope

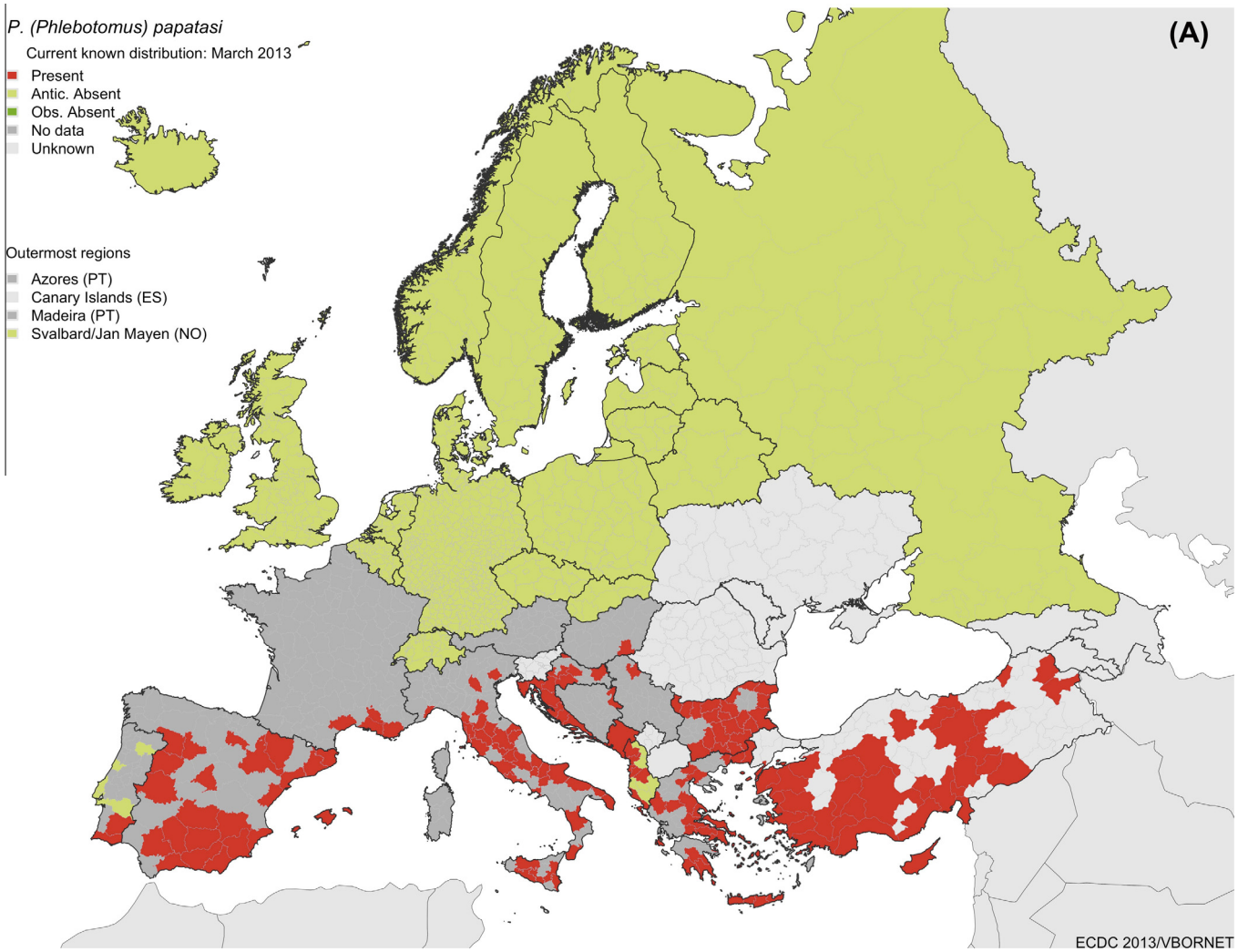


Fig. 3. Distribution of the principal vectors of sandfly-borne phleboviruses in Europe. (A) *Phlebotomus* (*Phlebotomus*) *papatasi*, (B) *Phlebotomus* (*Larroussius*) *perfiliewi*, (C) *Phlebotomus* (*Larroussius*) *perniciosus* (Source: ECDC2013/VBORNET).

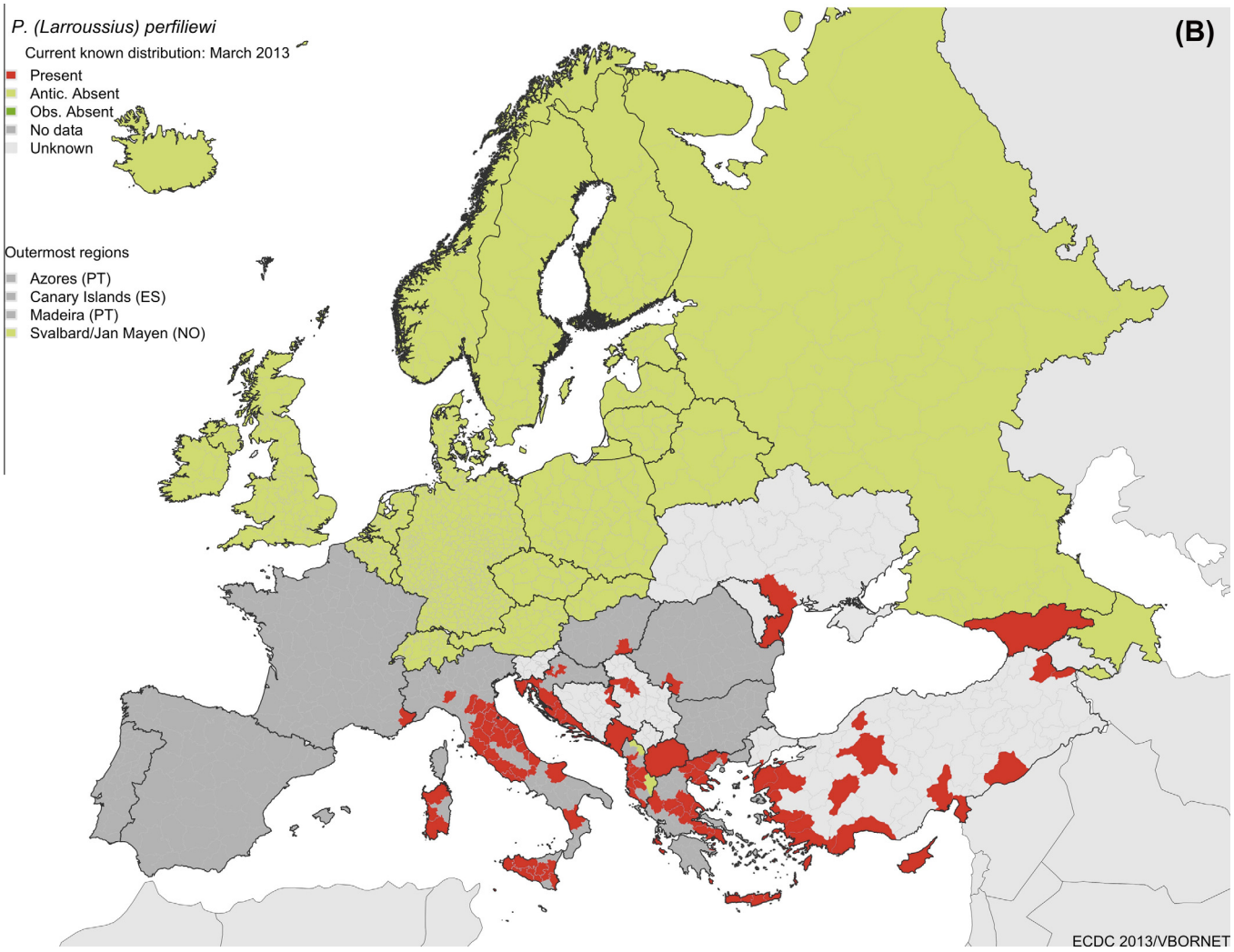
glycoproteins and in the case of the S segment, both the viral nucleocapsid protein (N) and a nonstructural protein (Ns) (Liu et al., 2003; Suzich et al., 1990; Xu et al., 2007). The single stranded RNA segments are known to have high mutation rates due to the lack of proofreading activity of the viral polymerase which may result in genetic drift due to individual accumulated point mutations. RNA viruses are known to replicate as quasispecies populations, a situation favoring development of mutants with modified phenotypic characteristics, and possibly higher virulence and modified properties. Single stranded RNA viruses are known to undergo major evolutionary events due to recombination; this has been demonstrated for many viruses in the *Bunyaviridae* family. The organization of the genome in the form of three segments renders possible genome reassortment (genetic shift), an important evolutionary event characterized by the exchange of genetic material between two distinct virus strains during co-infection of a single eukaryotic cell, resulting in the creation of a chimeric virus potentially exhibiting unique characteristics including virulence potentiation.

2.2. Sandfly vectors

Sandflies in the genera *Phlebotomus*, (Rondani and Berté, 1840); *Sergentomyia*, (França and Parrot, 1920); and *Lutzomyia*, (França, 1924) belong to the order *Diptera*, family *Psychodidae*, and subfamily *Phlebotominae*. The genus *Lutzomyia* is found in the New World and the genera *Phlebotomus* and *Sergentomyia* inhabit the Old World.

The family *Psychodidae*, within which phlebotomines flies are classified, is very old and maintains some of the most ancient dipteran characters. Members of the family are distinguished by a dense covering of narrow scales on head, thorax, legs, and wing veins. Of the five psychodid subfamilies, only the *Phlebotominae* have piercing mouthparts capable of taking blood. Furthermore, the phlebotomines tend to have an elongate and more fragile structure, in contrast to a squatter and more robust appearance of the other psychodid flies. Phlebotomine sandflies are small with a body length seldom exceeding 1.5–3 mm (Fig. 2). Their colour ranges from almost white to almost black.

Three features of phlebotomines are characteristic to distinguish them from other members of the *Psychodidae*: (1) when at rest, they hold their wings at an angle above the abdomen; (2) they are hairy; and (3) when alighting to engorge, they typically hop around on the host before settling down to bite. The hopping behaviour has given rise to the assumption that they do not disperse far from breeding sites. However, one species (*Phlebotomus ariasi*) has been shown to move further than 2 km, although several studies show that the distance varies with species and habitat and



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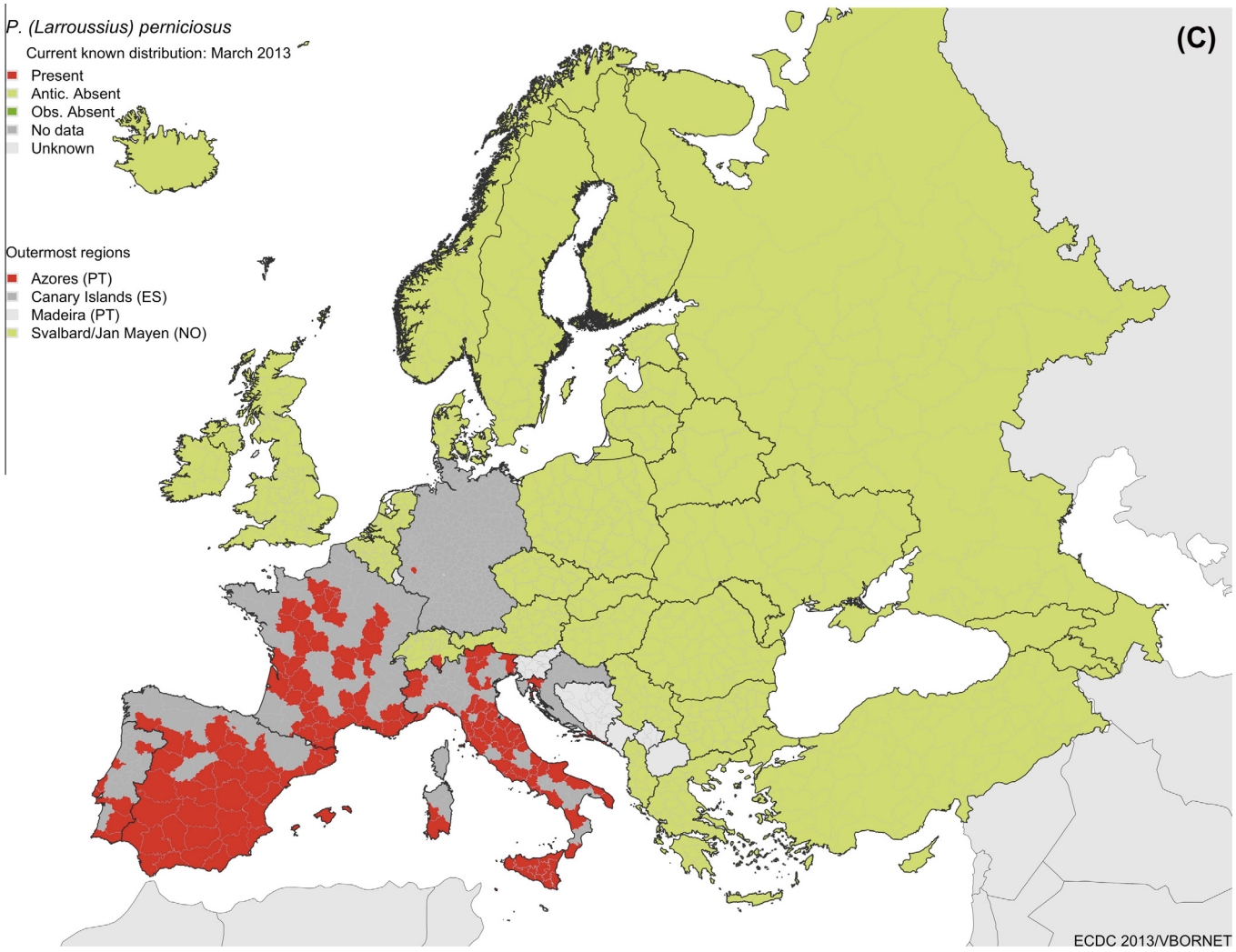
that maximum dispersal seldom exceeds one kilometer. Preliminary studies with a wind tunnel suggest that their maximum flight speed is a little less than 1 m/sec. Unlike mosquitoes, their attack is silent. They are crepuscular-nocturnal but some may bite during daylight. Females of most species are predominantly exophagic (biting outdoors) and exophilic (resting outdoors during the maturation of eggs) and cannot be effectively controlled by house spraying with insecticides. In contrast, species which are endophilic (resting indoors during the maturation of eggs) can be attacked this way (Killick-Kendrick, 1999).

Sandflies are distributed throughout the world in tropical and subtropical, arid and semi-arid areas and temperate zones. Both males and females feed on sugar sources in the wild, but only females take a blood meal prior to laying their eggs in terrestrial microhabitats that are rich in organic matter such as soil and animal burrows, which serves as nutrient for the larvae (Alexander, 2000). Autogeny is also seen (Lewis, 1971). Their life cycle commences with the egg, followed by four larval instars, then pupae and finally the adult stage. Egg and larval dormancy and diapause have been reported for sandflies (Ready, 2013). Diurnal resting places are cool and humid environments (Killick-Kendrick, 1999). They can locate around resting places in large numbers. Possible resting sites include animal barns (inside/outside), houses (inside/outside), poultry houses (inside/outside), caves, tree holes, leaf litter, and spaces between or under rocks, animal burrows, and rock crevices, holes of walls and among vegetation. Animal burrows and rock crevices are used as diurnal resting or breeding sites by many species. For instance, in Mediterranean France, wall holes (barbacanes) near the roads or in the villages are very important resting places for *P. ariasi*. For these types of resting places, a good area to locate is in the vicinity of a hole with a thin layer of moist soil and vegetation (Alexander, 2000; Volf and Volfova, 2011).

Different sandfly species breed and rest in different habitats such as urban and/or rural areas, sheltered and/or open areas. For instance, main resting sites of *Phlebotomus mascittii* include rocks and rock crevices, caves and wall holes. *P. mascittii* is always found at low densities, little is known about its biology. However, previous field surveys give evidence of its anthropophilic nature (Grimm et al., 1993; Pesson et al., 1985). *P. mascittii* is the only European sandfly species which can be found in special ecological niches, such as tunnels, even during winter time (Naucke et al., 2008). In the south of Austria, *P. mascittii* was caught in places situated close to human dwellings. In the northeast of the Iberian Peninsula (only in few locations of Barcelona and Gerona provinces), this species was mostly found in cooler and humid areas. *P. mascittii* is known to be a cavernicolous species, probably autogenous.

As mentioned above, sandflies are small, fragile, nocturnally active insects with weak direct flight capability. Several factors may



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affect the success of their population density, structure, abundance and dispersal activities. In southern Turkey, seasonal sandfly density was related to the amount and distributional pattern of rainfall and humidity according to altitude and that while evenly distributed rainfall was apparently beneficial, heavy rain caused inundation of the forest floor, resulting in death of the immature stages (Simsek et al., 2007). Decreases in population corresponded with peaks in rainfall and humidity, which probably also reduced the amount of suitable diurnal resting sites for the adult insects.

The geographic distribution of sandflies is extensive, including southern and southeastern Europe (Fig. 3), Asia, Africa, Australia, and Central and South America, and quite recently in Central Europe (Farkas et al., 2011; Grimm et al., 1993; Naucke et al., 2011, 2008). Their southernmost distribution is at about latitude 40°S, but they are absent from New Zealand and the Pacific islands. Their distribution also extends northwards to just above latitude 50°N in south west Canada (Young et al., 1984) and just below this latitude in northern France and Mongolia (Lewis, 1982). Their altitudinal distribution is from below sea level (by the Dead Sea) to 3,500 meters above sea level in Afghanistan (*Phlebotomus rupester*) (Artemiev, 1980; Killick-Kendrick, 1999; Lane, 1993). Ongoing field collections and computer modeling scenarios predict the expansion of *Phlebotomus* species to new favorable environments with the influence of climate change (Fischer et al., 2011; Naucke et al., 2008).

3. Maintenance and transmission

To date, sandfly fever viruses have been identified and isolated from humans and sandflies. Only one strain was isolated from a non-human vertebrate animal, a *Pipistrellus kuhli* bat, in Italy (Verani et al., 1988). Other data reported for non-human vertebrates consist of seroprevalence results without evidence for a role in the virus cycle in nature. Virus transmission to humans and animals occurs when female sandflies take a blood meal (May to October). Currently, there are no data to support the hypothesis that humans or large vertebrates are reservoir of these viruses; it is generally believed that they are dead-end hosts, and thus do not play a significant role in the natural virus life cycle. Sandflies take blood from a range of vertebrates; cold-blooded animals, mammals and birds depending on species. Considering the inactive period of the vector species during autumn and winter periods, the underlying mechanism for long-term maintenance of these viruses has not been fully elucidated. It therefore seems reasonable to assume that the primary reservoir host is the sandfly in which the viruses replicate and from which they are transmitted to vertebrate hosts that in most cases do not show clinical evidence of infection.

Identification and isolation of phleboviruses, not only from blood-sucking female sandflies but also from males, indicates that there are likely to be alternative modes of transmission between

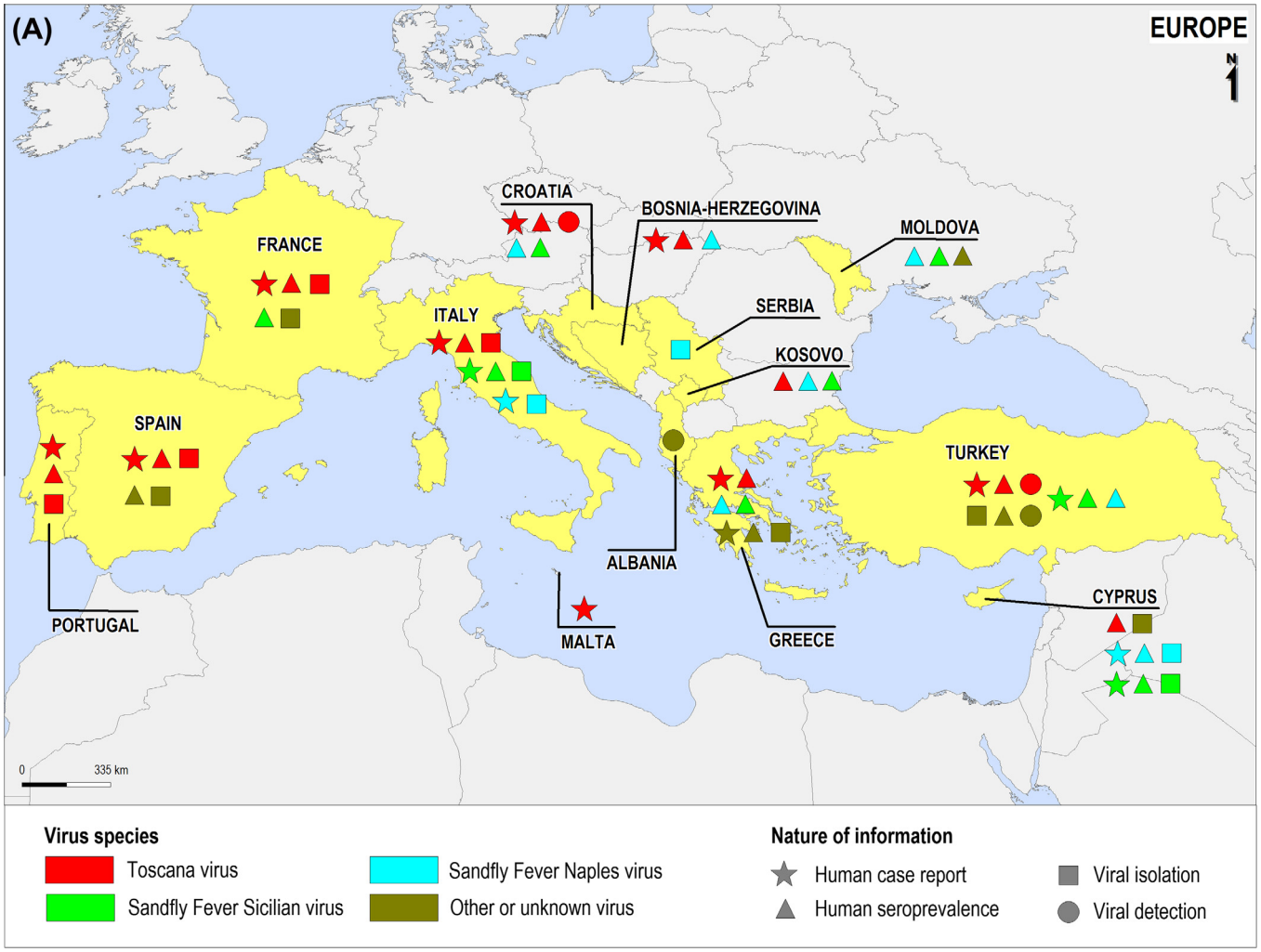


Fig. 4. Distribution of the sandfly-borne phleboviruses in the Old World. (A) Europe, (B) the Middle East, (C) Africa.

sandflies. For example, if transovarial (vertical) transmission occurs in natural habitats, it is not yet known how significant or efficient this mechanism of transmission is, in terms of virus survival. However, it has been experimentally demonstrated (Ciufolini et al., 1991, 1989, 1985; Maroli et al., 1993; Tesh and Modi, 1987). Since the rates of offspring infection are low and show decline from the first generation to ongoing generations during laboratory experiments, phleboviruses are likely to have evolved other mechanisms of transmission in nature (Tesh, 1988). Venereal (horizontal) transmission from infected males to uninfected females by mating has been reported (Ciufolini et al., 1989; Tesh et al., 1992). Toscana virus was shown to maintain in diapausing *Phlebotomus perniciosus* larvae and transstadial transmission was not effected during and after diapause. This can be a way of virus for overwintering (Tesh et al., 1992). Transstadial transmission was reported also for bacteria such as *Bacillus cereus* and *Lysinibacillus fusiformis* in *Phlebotomus argentipes* flies (Hurwitz et al., 2011).

Currently, maintenance and transmission of sandfly-borne phleboviruses appears to depend on the availability of appropriate vector species and their abundance since there is no defined reservoir. This lack of available knowledge of virus transmission and the maintenance mechanisms clearly need to be investigated both in natural habitats and under experimental conditions since new methods for virus control could be beneficial both for public health and for predicting their potential to spread into new regions.

4. Discovery of the sandfly-borne phleboviruses

4.1. First identification of sandfly fever and early studies

Sandfly-borne phleboviral infections have been a significant cause of febrile illness among military forces as exemplified during the Napoleonic Wars, the Austrian Commission in the Balkans, and the British colonization in India and Pakistan (Tesh, 1988). Sandfly fever was first clinically described by Alois Pick in 1886, in the Balkans region where the disease was prevalent in an endemic form within the local population and presented a high risk to visitors to the area (Pick, 1887; 1886). The presence of sandflies was observed in Herzegovina in the military barracks (Taussig, 1905) and it was subsequently discovered that the agent causing sandfly fever was a filterable agent transmitted by infected sandflies (Doerr et al., 1909), hence the disease was named "papataci fever" or "phlebotomus fever" or "three-day fever". After the discovery and description of the disease, outbreaks were recognized among soldiers who had recently arrived in endemic regions, and most of the literature on sandfly fever has been published in military journals or reports (Anderson, 1941; Niklasson and Eitrem, 1985; Oldfield et al., 1991; Sabin, 1951; Tesh and Papaevangelou, 1977). During World War II, sandfly fever affected large numbers of British and German-allied troops, in the Mediterranean, the Middle East and North Africa (Hertig and Sabin, 1964; Sabin, 1951). Human cases of sandfly fever occur each year during the season

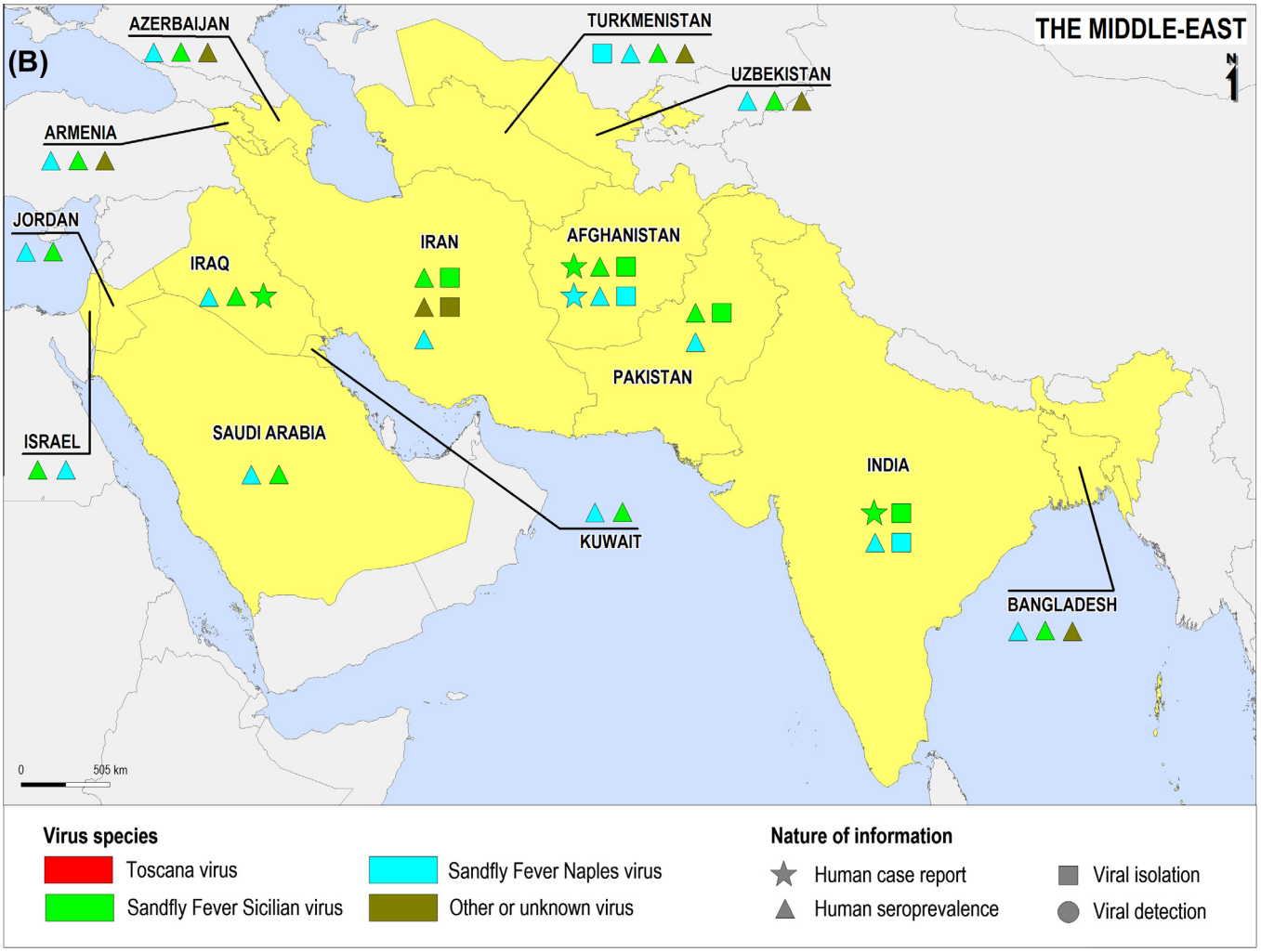


Fig. 4 (*continued*)

of sandfly activity (from May to October) in regions where they circulate (Fig. 4).

4.2. Discovery of Sicilian virus

Sicilian virus is endemic in the Mediterranean basin, the Middle East, Central Asia and Europe. Sicilian virus was first isolated from the sera of sick soldiers in Egypt in 1943 during World War II by Albert Sabin. Later, he isolated it again in Sicily during an outbreak of febrile illness among USA army troops and it was shown that the two aetiological agents were identical based on cross-immunity tests in volunteers (Sabin, 1951). *Phlebotomus papatasi* was identified as the vector.

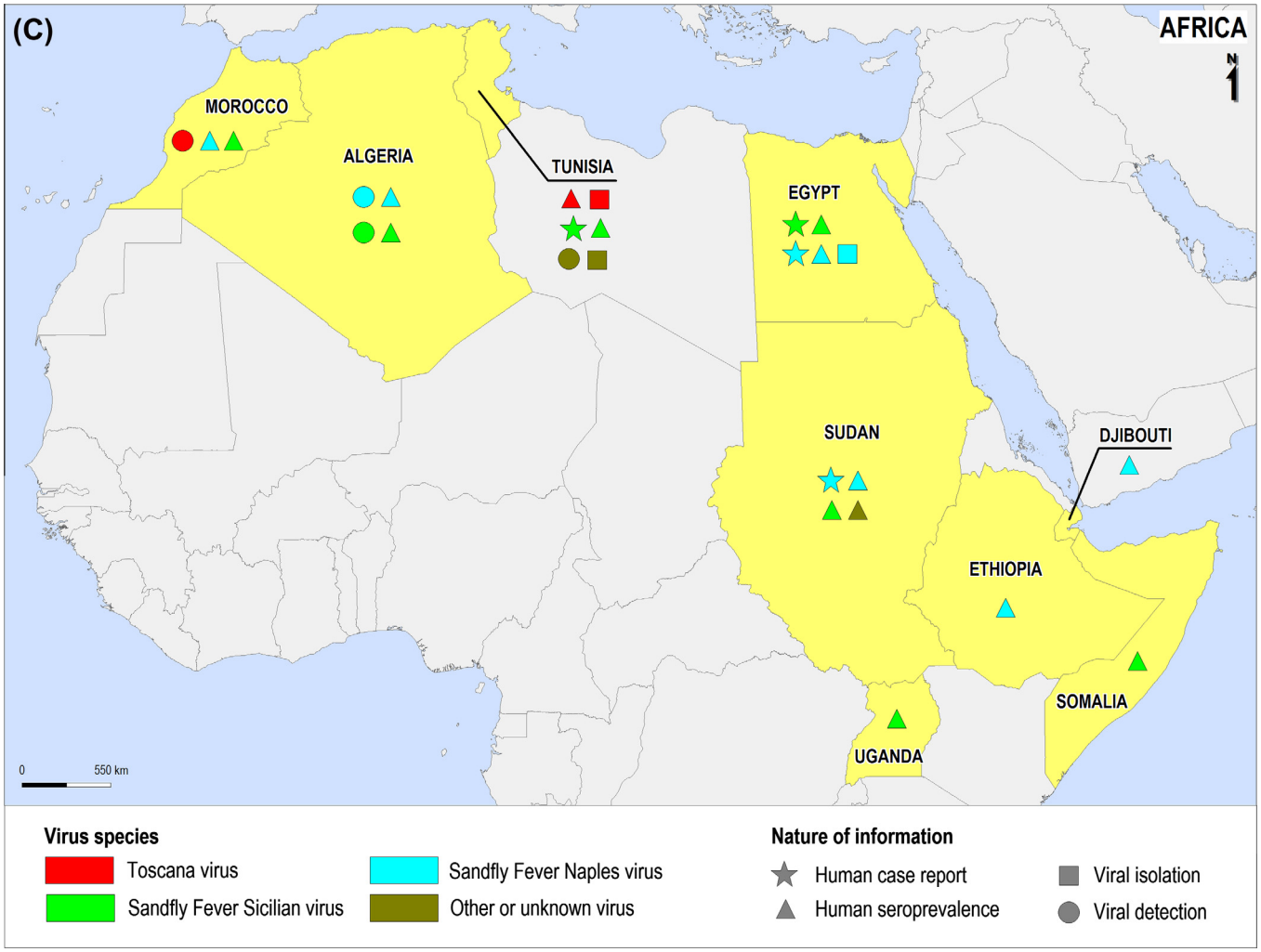
4.3. Discovery of Naples virus

Naples virus was first isolated from the blood of a sick soldier in Naples in 1944 during World War II (Sabin, 1951). The absence of immunologic relationships between Sicilian and Naples viruses was first demonstrated in human cross-immunity tests and subsequently confirmed in neutralization and complement fixation test (Sabin, 1955). Because Naples and Sicilian viruses were significantly different in terms of antigenic properties, no cross-protection was observed and patients could therefore be successively infected with the two viruses.

Naples virus was endemic in the Mediterranean basin, the Middle East, Central Asia and Europe. However, the most recent detection of Naples virus was reported in Cyprus (Eitrem et al., 1990) and Afghanistan (Gaidamovich et al., 1990) but not in the mentioned endemic regions suggesting that circulation has significantly decreased in previously endemic regions. Other than *P. papatasi*, Naples virus was isolated from *P. perniciosus* in Italy (Verani et al., 1980) and from *Phlebotomus perfiliewi* in Serbia (Gligic et al., 1982).

4.4. Discovery of Toscana virus

Toscana virus, which is a close relative of Naples virus, was first isolated from *P. perniciosus* in central Italy, in 1971 (Verani et al., 1980). The first evidence of human pathogenicity followed the demonstration of its involvement in CNS infection of Swedish and US citizens returning home after visiting Portugal and Italy, respectively (Calisher et al., 1987; Ehrnst et al., 1985). Subsequently, the isolation of Toscana virus from a woman with aseptic meningitis confirmed it as a major cause of CNS infections in Central Italy (Nicoletti et al., 1991). Other strains of Toscana virus were isolated in Italy from *P. perfiliewi* (Verani et al., 1988). There is also one study which reports Toscana virus in *Sergentomyia minuta* (known to feed on reptiles) sandflies collected from Marseille,



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France (Charrel et al., 2006), but the relevance of *Sergentomyia* in the life cycle of Toscana virus remains unknown.

Following its discovery in Central Italy, it was shown to be endemic in several other regions of Italy, where it causes neuroinvasive infections during summertime (Cusi et al., 2010; Nicoletti et al., 1991; Valassina et al., 2000, 1998, 1996). In addition to Italy and Spain, other Mediterranean countries including France, Portugal, Cyprus, Greece and Turkey have been included in the endemic regions of Toscana virus. To date, Toscana virus is the only sandfly-borne phlebovirus to be unambiguously associated with central nervous system manifestations.

4.5. Other sandfly-borne phleboviruses

Corfu virus, isolated from sandflies belonging to *Phlebotomus major* complex (Rodhain et al., 1985) on Corfu Island, which is genetically- and antigenically-closely related to but distinct from Sicilian virus. Similarly, other Sicilian-like viruses were isolated or detected in many Mediterranean countries, and may be proposed to be included in a sandfly fever Sicilian species in the next ICTV classification. Such Sicilian-like viruses were described in Algeria from *P. ariasi* (Izri et al., 2008), in Tunisia from *Phlebotomus longicuspis*, *P. perniciosus* and *Sergentomyia minuta* (Zhioua et al., 2010). Another Sicilian-like virus, provisionally named Sandfly fever Cyprus virus (SFCV), was isolated from a human serum (Konstantinou et al., 2007; Papa et al., 2006), whereas Sandfly fever Turkey virus (SFTV) was isolated from the serum of a patient (Carhan et al., 2010) and detected in sandflies belonging to *Phlebotomus major* complex (Ergunay et al., 2012d). All these Sicilian-like viruses exhibit close antigenic relationships, thus making them impossible to be distinguished using indirect immunofluorescence (IIF), enzyme-linked immunosorbent assay (ELISA), hemagglutination inhibition (HI) or complement fixation tests (CFT).

In France and Spain, Massilia and Granada viruses were isolated from*P. perniciosus* (Charrel et al., 2009) and *Phlebotomus* spp. (Collao et al., 2010), respectively. In Tunisia, Punique virus was isolated from *P. longicuspis* and *P. perniciosus* (Zhioua et al., 2010). All these viruses are genetically- and antigenically-closely related to but distinct from Naples and Toscana virus. The same problems of antigenic cross-reactivity apply to these Naples-like and Toscana-like viruses that are to be proposed for inclusion in the Sandfly fever Naples virus species (or serocomplex) in the next ICTV classification.

5. Clinical syndromes

Infections with Naples and Sicilian viruses are clinically indistinguishable. After a 3–5 day incubation period, the onset is abrupt and severe with fever, headache, malaise, photophobia, myalgia, and retro-orbital pain. The duration of fever is 2–3 days. Leuco-

penia can be observed during the onset of the disease (Sabin, 1951; Bartelloni and Tesh, 1976).

Toscana virus clinical infection starts as a mild febrile illness, following an incubation period of 3–7 days, without involvement of the central nervous system (CNS) (Charrel et al., 2005). Neuroinvasive infections usually begin with headache, fever, nausea, vomiting, and myalgia. Physical examination may show neck rigidity, Kernig sign, and in some cases unconsciousness, tremors, paresis and nystagmus. In most cases the CSF contains more than 5–10 cells/mL with normal levels of glucose and proteins. Leucopenia or leucocytosis can be observed. The outcome is usually favorable without sequelae. Other neurological manifestations have been reported such as encephalitis (Dionisio et al., 2001), severe meningoencephalitis (Baldelli et al., 2004), deafness (Martinez-Garcia et al., 2008; Pauli et al., 1995), persistent personality alterations (Serata et al., 2011), long-lasting unconsciousness with seizures, prolonged convalescence (Kuhn et al., 2005), and even fatal encephalitis (Bartels et al., 2012). Speech disorders and paresis have been reported to persist for months after the acute phase (Sanbonmatsu-Gamez et al., 2009).

6. Experimental studies

6.1. Replication in cell culture

Sicilian and Naples viruses replicate in Vero, BHK-21 and LLC-MK-2 cells but not in mosquito cells (Karabatos, 1985). Toscana virus also replicates in CV-1 and RD cells (Verani et al., 1984).

6.2. Infection of laboratory animals

Most of the recent phlebovirus studies on laboratory animals were performed with Rift valley fever virus and Punta Toro virus rather than viruses transmitted by Old World sandflies (Bird et al., 2011; Dodd et al., 2012; Moser et al., 2012; Scott et al., 2012; Sidwell and Smee, 2003), most likely due to the availability of animal models for these two viruses.

In earlier studies, serum from sick soldiers (containing Sicilian or Naples virus) was inoculated into monkeys (*Macaca mulatta, Cercopithecus griseoviridis, Cercopithecus aethiops centralis, Cercopithecus erythrocebus patas, Macaca radiate, Papio hamadryas*), hamsters, albino mice, wild grey mice, desert rats, rabbits and guinea pigs by a variety of routes: clinical disease was not observed in those animals (Sabin, 1951, 1955). Sicilian and Naples viruses were successfully adapted to suckling mice through sequential passages (Sabin, 1955). Cynomolygus monkeys, as well as other nonhuman primates, that were inoculated with Sicilian virus did not show any clinical manifestations (McClain et al., 1997). A mouse model was developed for Toscana virus using a neurovirulent strain (Cusi et al., 2005).

6.3. Human volunteer studies

When sandfly fever was seen among British and American troops in Egypt, sera of sick soldiers suspected of being infected by sandfly fever virus were collected. After being inoculated with these sera, volunteers presented with manifestations suggestive of sandfly fever, and virus was recovered from these sick volunteers. Other naive volunteers agreed to be fed upon by *P. papatasi* flies that had previously engorged on febrile soldiers. The purpose of these experiments was to demonstrate the vectorial capacity of these infected flies (Sabin, 1951). Biological material obtained from soldiers in Egypt and Italy was transferred to the United States where studies were conducted to show that two distinct viruses were able to cause a similar febrile syndrome, known as sandfly fever, and that these two viruses did not confer cross-protective immunity with possible successive infections, i.e. Naples then Sicilian, or Sicilian then Naples. From successive challenges in volunteers using Naples, Sicilian and Egypt virus, it was concluded that Sicilian and Egypt viruses were in fact two strains of the same virus, but were distinct from Naples virus (Sabin, 1951).

7. Geographic distribution of the sandfly-borne phleboviruses

Before reading the following sections, it is important to underline that most of the seroprevalence studies based on IIF, ELISA, HI or CF methods cannot distinguish between antigenically related viruses included in the sandfly fever Naples species (Naples, Toscana, Tehran, Massilia, Granada, Punique) and viruses closely related to Sandfly fever Sicilian virus (such as Corfu, Utique, sandfly fever Cyprus, and sandfly fever Turkey viruses). Only studies using neutralization tests and a variety of closely related strains are capable of specifically distinguishing these closely related viruses.

The following sections summarize what is known about the prevalence of sandfly-borne phleboviruses in countries of Europe, Africa and Asia (Fig. 4). When a section contains no information about the identification or isolation of Sicilian virus, Naples virus or Toscana virus, the reader should assume that no research on the agent has been reported.

7.1. Western Europe

7.1.1. Italy

Naples, Sicilian and Toscana viruses were isolated for the first time in Italy. Toscana virus has been reported as the leading cause of summertime CNS infections in Italy in the 1990's. For Toscana virus, isolation and high seroprevalence rates (30–50%) were reported from several regions of Italy, largely expanding the geographic area of central Italy defined in earlier studies: Tuscany (Braito et al., 1998; Nicoletti et al., 1991; Terrosi et al., 2009; Valassina et al., 2003), Marches (Nicoletti et al., 1991), Siena (Braito et al., 1998; Cusi et al., 2010; Valassina et al., 1996), Sicily (Amodio et al., 2012; Calamusa et al., 2012; Colomba et al., 2012; Valassina et al., 1996), Emilia Romagna (Portolani et al., 2002; Vocale et al., 2012), Piedmont (Valassina et al., 2003), Umbria (Baldelli et al., 2004; Francisci et al., 2003), Naples (Di Nicuolo et al., 2005), Sardinia island (Venturi et al., 2007), Elba island (Gabriel et al., 2010; Sonderegger et al., 2009), and Calabria (Greco et al., 2012).

Seroprevalence studies conducted among voluntary subjects registered at the National Health Laboratories in Sicily, provided evidence of the circulation of Sicilian or Sicilian-like viruses (Calamusa et al., 2012) which had also previously been implicated in an earlier study among ovine species (Castro et al., 1976). Sicilian virus was reported not to be circulating in Tuscany where Toscana virus is the main cause of sandfly fever (Cusi et al., 2013).

Arbia virus which was isolated from *P. perniciosus* in Tuscany was considered to be a strain or subtype of Salehebad virus (Verani et al., 1988). Subsequently another virus, Adria virus was added. There are no data suggesting that Arbia virus is capable of infecting humans, and causing disease.

7.1.2. France

The first case of Toscana virus infection in France was reported in a German tourist (Dobler et al., 1997) and cases with and without meningitis were subsequently reported (Hemmersbach-Miller et al., 2004; Peyrefitte et al., 2005). One case of encephalitis was reported (Doudier et al., 2011). Virus isolation was achieved from human samples and from *P. perniciosus* sandflies in Marseille (Charrel et al., 2007). Detection of Toscana virus RNA from *Sergentomyia*

minuta was also reported (Charrel et al., 2006). Two seroprevalence studies conducted on blood donors from Marseille and southeastern France, respectively, provided similar results and demonstrated that Toscana virus circulates actively in southeastern France (12–14% of blood donors possessed anti-Toscana virus IgG) (Brisbarre et al., 2011; De Lamballerie et al., 2007). In the latter study, 8.7% of sera collected in Corsican blood donors were anti Toscana virus IgG-positive.

Low seroprevalence rates of Sicilian virus antibodies were reported in the southwestern France (2%) and in Marseille (1%) among blood donors (Bichaud et al., 2011; Enjalbert et al., 1969). Moreover, a serosurvey in wild mammals reported 0.3% seropositivity for Sicilian virus antibodies (Le Lay-Rogues et al., 1987).

Massilia virus, which is most closely related to viruses in the SFNV species, was isolated from *P. perniciosus* in Marseille and Nice and reported to circulate in southeastern France (Charrel et al., 2009).

7.1.3. Spain

The first case of Toscana virus infection in Spain was reported from Catalonia in a Swedish tourist (Eitrem et al., 1991a). Positive results obtained from seroprevalence studies were reported in Granada (Mendoza-Montero et al., 1998; Sanbonmatsu-Gámez et al., 2005), Madrid (Echevarria et al., 2003), Murcia (Martinez-Garcia et al., 2007), Majorca (Leyes et al., 2011), and Catalonia (Cardeñosa et al., 2013). Virus isolation was obtained from human clinical specimens in Granada (Mendoza-Montero et al., 1998; Sanbonmatsu-Gamez et al., 2005) and sandflies (Sanbonmatsu-Gamez et al., 2005). Seropositivity rates were lower (5–26%) than those reported in Italy. IFA-based seroprevalence studies conducted in domestic animals in Granada showed evidence that they were frequently bitten by infected sandflies (17.7% in goats, 17.9% in cows, 22% in pigs, 32.3% in sheep, 48.3% in dogs, 59.6% in cats and 64.3% in horses). The absence of virus isolation and a single goat sample positive for Toscana virus RNA suggest that domestic animals are not reservoirs for Toscana virus (Navarro-Mari et al., 2011).

Granada virus which is most closely related with Massilia virus was isolated from *Phlebotomus spp*. in southeastern Spain (Collao et al., 2010). Low seroprevalence of Granada virus was detected in healthy humans but its potential for causing human disease is unknown (Navarro-Mari et al., 2013).

7.1.4. Portugal

In Portugal, two cases, one of which was confirmed by virus isolation, were reported in travelers (Ehrnst et al., 1985; Schwarz et al., 1995). Among 106 cerebrospinal fluid samples from the patients with meningitis, 5.6% were positive for Toscana virus infection (Santos et al., 2007). Another study reported 4.2% and 1.3% in patients with neurological symptoms (5 patients had recent infections) and without neurological symptoms, respectively (Amaro et al., 2012). In addition, *P. perniciosus*, *P. papatasi*, *P. ariasi*, and *S. minuta* were identified with some other species in Portugal (Afonso et al., 2005; Maia et al., 2009).

7.1.5. Greece

The massive outbreak of sandfly fever that affected the residents of Athens in 1937 suggests either particularly favorable environmental conditions or the introduction of a novel virus (against which indigenous populations were not immune). During World War II, epidemics of sandfly fever were prominent amongst American, British and German troops stationed successively in Athens (Tesh and Papaevangelou, 1977). Following the malaria control programme of insecticide spraying in 1946, the density of *P. papatasi* and related sandfly diseases showed noticeable decreases among humans $\leqslant$ 29 years (Tesh and Papaevangelou, 1977).

Using the plaque reduction neutralization test (PRNT (80)), positivity (sera producing $\geqslant$ 80% plaque inhibition) rates were 13.1% for Naples virus in the island of Crete 24.7% and 8.5% for Naples and Sicilian virus respectively in Athens in the 1970's (Tesh et al., 1976). A study conducted with sera collected from 1981 to 1988 from healthy residents using PRNT (80) showed neutralizing activity against Naples and Sicilian virus in 16.7% and 2% of 245 sera (all of these sera were obtained from farmers), respectively in Northern Greece (Trace and Macedonia), Central Greece (Magnesia) and Crete (Antoniadis et al., 1990).

The first Toscana virus infection was reported in the vicinity of Athens in 1993 based on seroconversion revealed by IIF (Dobler et al., 1997). In Corfu and Cephalonia Islands, Toscana virus IgG antibodies were detected using IIF or ELISA in 51.7% and 39%, respectively (Papa et al., 2010). More recently IgG rates against Toscana virus of 11% and 21%were reported in north-eastern/north-central Greece and 7 islands in the Aegean Sea, Greece (Anagnostou and Papa, 2013, 2012).

Corfu virus which is closely related to Sicilian virus was isolated from sandflies belonging to *Phlebotomus major* complex on the island of Corfu. In serological tests, these viruses can only be distinguished by PRNT (Rodhain et al., 1985). Antibodies, in humans, against Corfu virus/Sicilian virus were detected using IFA in Northern Greece (Macedonia), Central Greece (Evritania and Larisa), North–Western Greece (Epirus), and Corfu Island in 4% of 826 healthy residents (Antoniadis et al., 1990).

Recently, a 2-year-old boy was hospitalized for febrile seizure, and virological investigations revealed that the CSF contained viral RNA corresponding to a new phlebovirus, provisionally named Adria virus, which is closely related to but distinct from Arbia and Salehabad viruses (both included in the Salehabad virus group), none of them having been incriminated as human pathogens before. Additional studies are necessary to isolate this virus from clinical cases or sandflies, and to characterize it by complete genome sequencing (Anagnostou et al., 2011).

7.2. Eastern Europe and the Balkans

Sandfly fever has been recorded in the Balkan region, in Macedonia, Montenegro and Slovenia (Guelmino and Jevtič, 1955; Hukić et al., 2010; Hukić and Salimović-Besić, 2009). However, there are no recent data.

7.2.1. Croatia

Earlier studies reported seroprevalence rates of 15.6% and 57.6% in the Dalmatian region for Sicilian and Naples virus, respectively, using the PRNT (80) (Tesh et al., 1976). Ten years later, 23.6% of the residents of the coastal region (including Dubrovnik and the Island of Korčula) were shown to be positive for Naples by HI (Borčič and Punda, 1987). On the Island of Mljet in the Adriatic Sea, 51.4% of the 216 healthy residents had antibodies (PRNT (90)) against Naples virus (Punda-Polic et al., 1990). In a study, IgG antibodies to Toscana virus were recorded in 755 (37.5%) of 2016 healthy residents from the islands, the coastal area and the mainland using an enzyme immunoassay (Punda-Polic et al., 2012a). The first direct evidence for the presence of Toscana virus was recently reported through the detection of Toscana virus RNA in the CSF of two patients; sequence analysis suggested the existence in Croatia of a third genetic lineage of Toscana virus. This needs to be complemented by virus isolation and complete sequence analysis (Punda-Polic et al., 2012b).

7.2.2. Bosnia-Herzegovina

Bosnia-Herzegovina is the country where sandfly fever disease was first clinically described towards the end of the 19th century (Pick, 1887, 1886). After WWII, antibodies against Naples virus

were reported but technical details were not accessible (Terzin et al., 1962; Vesenjak-Hirjan et al., 1980). In a single recent study patients with fever of unknown origin (FUO) were for Toscana virus IgM and IgG using an immuno-line assay. Acute Toscana virus infection was detected in 10.3% of cases (Hukić and Salimović-Besić, 2009).

7.2.3. Serbia

The first outbreak of sandfly fever was recorded in 1946. The disease was reported in several large cities in different provinces (Guelmino and Jevtič, 1955; Hukić and Salimović-Besić, 2009; Simić, 1951). Thousands of people are believed to have been infected, and hundreds of sandflies were collected. In 1982, Naples virus was isolated from *P. perfiliewi* in Dobrič, Southeast Serbia (Gligic et al., 1982).

7.2.4. Kosovo

In the 1970's, 9.6% and 27.9% of tested sera contained neutralizing antibodies (PRNT (80)) against Sicilian and Naples virus, respectively (Tesh et al., 1976). Recently in North-Western Kosovo, 200 blood donors were screened for Toscana virus and Naples virus through ELISA and confirmed via PRNT (80) with Naples virus and Toscana virus (Venturi et al., 2011): 11 sera were positive in the screening step (5.5%), and 2 were confirmed with Naples virus and 1 with Toscana virus.

7.2.5. Albania

There are no records of studies that report Toscana virus, Naples or Sicilian virus in Albania. From 438 sandflies collected in 2005 from the Kruje and Lezhe regions (Northern Albania), known to be endemic for leishmaniasis (Papa et al., 2011), two pools originating from Lezhe were positive for phlebovirus RNA: the 201-nt sequence in the polymerase gene was clearly distinct from all Naples and Sicilian virus for which sequence are available, and most closely related to Arbia virus (within the *Salehebad virus* species). Based on sequence data, this new virus was provisionally named Adria virus, but virus isolation was not obtained (Papa et al., 2011).

7.3. Central Asia and other countries in Eastern Europe

Just after WWII, sandfly fever outbreaks were recorded in Armenia, Moldova, Turkmenistan, Uzbekistan, Crimea and Romania (Gaidamovich et al., 1974; Hertig and Sabin, 1964). Antibodies against Sicilian, Naples and Karimabad virus were detected in Moldova, Azerbaijan, Uzbekistan, Tajikistan, and Turkmenistan by PRNT (80) (Gaidamovich et al., 1978; Tesh et al., 1976). A strain of Naples virus was isolated in 1950 in Turkmenistan and identified later (Gaidamovich et al., 1974).

7.4. Mediterranean islands

7.4.1. Malta

The single evidence for the presence of sandfly fever in Malta is based on a case of infection that was documented in a Swiss traveler after returning from a two-week vacational stay on the island. After his hospitalization with common symptoms of sandfly fever (without meningitis), he was detected positive for Naples virus and Toscana virus antibodies by IIFT. Immunoblot (IB) for bunyaviruses also showed positivity for Toscana virus. His wife also had IgM antibodies against Naples virus and Toscana virus with milder symptoms. After approximately 2 months of onset of illness, they both had anti-Toscana virus IgM and IgG with increased levels (Schultze et al., 2012).

P. perniciosus is present in Malta, and recognized as the vector of *Leishmania infantum* (Pace et al., 2011).

7.4.2. Cyprus

In 1984, sandfly fever was first reported in Cyprus during an outbreak of febrile illness in Swedish soldiers, serving in the United Nations forces (Niklasson and Eitrem, 1985). Neutralisation tests revealed that Naples, Toscana virus and Sicilian virus were co-circulating and caused acute infections demonstrated through seroconversion. Naples and Sicilian virus strains were isolated (Eitrem et al., 1990). Three years later, 35 of 72 Swedish tourists were found to have antibodies against Sicilian virus after visiting different hotels in Cyprus (Eitrem et al., 1991a). Seroprevalence in Cypriot residents showed high rates of neutralizing antibodies ($\geqslant$1:80) against Naples (57%), Sicilian (32%) and Toscana virus (20%) (Eitrem et al., 1991b).

In 2002, a sandfly fever epidemic occurred in Greek soldiers stationed close to the capital Nicosia. Fifteen blood samples were RT-PCR positive. Virus isolation was obtained from blood specimens, and genetic analysis showed that this strain was related to but clearly distinct from Sicilian virus. This virus was named Sandfly fever Cyprus virus (Konstantinou et al., 2007; Papa et al., 2006).

7.5. Turkey and the near East

7.5.1. Turkey

In early studies, seroprevalence rates of 22% and 62% were found for Sicilian and Naples virus, respectively (PRNT (80)) in the Mediterranean Region (Tesh et al., 1976). In the Aegean Region, Sicilian and Naples virus neutralizing antibodies were detected in 0.8% and 13.9% sera, respectively among 1074 healthy residents (Serter, 1980).

Sandfly fever was first diagnosed in one case of meningitis in a patient returning to Germany (Becker et al., 1997). Sicilian virus was suspected based on ELISA and immunoblot results. According to CDC criteria for the diagnosis of arboviral diseases (2012 Case Definitions: Nationally Notifiable Conditions Infectious and Non-Infectious Case), this case should be considered as probable, but not confirmed. Moreover, CNS manifestations were reported seldom with Sicilian virus and direct evidence (RT-PCR, virus isolation) remains to be provided.

Extensive investigations have been initiated during the last decade, especially in the regions where outbreaks have occurred: in the Mediterranean region in 2008, in the Aegean region in 2004-8), and in Central Anatolia in 2007-8). IgM antibodies to Sicilian virus, Sicilian or Cyprus virus, and Cyprus virus were detected by immunofluorescence assay in 36%, 12%, and 4% of acute patient sera, respectively. The recurrent problem of cross reactivity between these antigenically related viruses is exemplified here. No serological technique other than neutralization is currently capable of resolving this issue. A new serotype of Sicilian virus was also isolated from the serum of a patient and named Sandfly fever Turkey virus (SFTV) (Carhan et al., 2010). IgM antibodies to Naples or Sicilian virus were detected in 45.45% and 27.27% of sera, respectively, using a commercial mosaic IFA test, during an outbreak in 2009 in a region of Central Anatolia (Torun Edis et al., 2010) suggesting that viruses very closely related to Naples and Sicilian viruses were still circulating 30 years after the first reported study of Tesh et al. (1976). Another outbreak due to Sicilian virus was detected using a commercial mosaic IFA test and confirmed by a real time PCR in a region of East Mediterranean (Guler et al., 2012).

The first acute Toscana virus infection was reported in Ergunay et al. (2011). In 15.7% of 102 sera, Toscana virus-specific RNA was detected by real time RT-PCR and sequence confirmation. Interestingly RT-PCR was positive on blood samples, in these patients who presented with acute meningitis, which is not commonly observed. Neutralizing antibodies to Toscana virus, SFTV, Sicilian and Naples viruses were also found in 13.7%, 12.1%, 14.7% and 5.2% sera from

blood donors, respectively by virus neutralization test (VNT) in Central Anatolia.

Toscana virus IgM antibodies were detected in 11.2% of the sera and in 1.76% of the CSF samples in the Central Anatolia and the Aegean regions, respectively, whereas IgG antibodies were detected in 8% of the sera and 3% of the CSF samples in Central Anatolia, respectively and in 2.7% of the CSF samples in the Aegean regions by commercial IFA, (Ergunay et al., 2012d). Sandflies belonging to *Phlebotomus major* complex collected in Central Anatolia were positive for SFTV RNA (Ergunay et al., 2012b). Subsequently, VNT for Toscana virus seroreactivity were carried out among 1115 healthy blood donors from 4 geographical regions and IgG and IgM antibodies were detected in 56% and 43.6% sera, respectively (Ergunay et al., 2012a).

Recent studies suggest that SFTV may be neurotropic in some human cases, a property previously considered to be confined to Toscana virus; a case of encephalitis due to SFTV was documented in South-Eastern Anatolia through RT-PCR and sequencing (Ergunay et al., 2012c).

The sandfly fever viruses appear to be widespread throughout the country. This situation needs to be investigated in more depth taking into account the recent data about co-circulation of distinct sandfly-borne phleboviruses in defined regions such as Central Anatolia.

7.5.2. Israel

Anti-Sicilian IgG and anti-Naples IgG were reported in 7.9% and 11.7% of 1017 sera using ELISA (Cohen et al., 1999).

7.5.3. Jordan

In 1998, 47.1% and 29.5% of 261 human sera were found positive for Sicilian and Naples virus IgG, respectively, using ELISA (Batieha et al., 2000).

7.5.4. Saudi Arabia

A single study reports that Sicilian and Naples viruses were circulating in the country (Tesh et al., 1976).

7.5.5. Kuwait

In the late 1960's, investigations conducted in northern, central and southern districts on 620 human sera indicated seroprevalence rates of 24.2% and 48.8% for Sicilian and Naples viruses, respectively, using HI test (Ibrahim et al., 1974). In contrast, sera tested more recently did not provide any positive results for IgG using an ELISA test (Pacsa et al., 2003). Clearly, more detailed investigations are required.

7.6. North and Central Africa

7.6.1. Morocco

In central Morocco, 5.7% and 2.9% of sera contained neutralizing antibodies (PRNT (80)) against Sicilian and Naples virus, respectively (Tesh et al., 1976). Another study reported anti-Sicilian virus antibodies in rodents and insectivores based on HI (Chastel et al., 1982). Recently, Toscana virus RNA was detected in sandflies collected in the Sefrou province (Es-Sette et al., 2012).

7.6.2. Algeria

In 1976, neutralizing antibodies against Sicilian and Naples virus were not found in southeastern Algeria (Tesh et al., 1976). In 2006, one of 460 sandflies (mostly *P perniciosus*) contained Sicilian-like virus RNA: interestingly, this was a *P. ariasi*. In 2007, a sandfly collection organized in the Kabylia and Algiers regions, provided two positive, one for Naples-like virus RNA (*P. longicuspis*) and the second was positive for Sicilian-like virus RNA (*P. papatasi*). Seroprevalence studies conducted in Northern Algeria reported antibodies against Sicilian and Naples virus at respective rates of 5% and 10.6–21.6% using IIF and ELISA tests (Izri et al., 2008; Moureau et al., 2010).

7.6.3. Tunisia

In Tunisia, neutralizing antibodies (PRNT (80)) against Sicilian virus were detected in 1.3% of sera (Tesh et al., 1976). Using HI, 31% of sera collected from rodents, insectivores and chiropters were positive for Sicilian antibodies (Chastel et al., 1983). A case of Sicilian virus infection in a German traveler returning from Tunisia was reported (Pauli et al., 1995). In North eastern regions, sandfly trapping campaigns were organized and a new virus, named Punique virus, was repeatedly isolated. This virus is most closely related to Toscana virus although it is clearly distinct. Punique virus has been isolated in *Laroussius* sandflies (mostly *P. perniciosus* and *P. longicuspis*) (Zhioua et al., 2010). In addition, a new Sicilian-like virus (provisionally named Utique virus although no isolation was obtained) was also repeatedly detected in *Laroussius* flies from the same region (Zhioua et al., 2010). Anti-Toscana virus IgM and IgG were detected in 10% and 7% of the 167 sera and 178 CSF samples from patients, respectively by ELISA (Bahri et al., 2011).

From 2003 to 2009, a total of 1071 patients with CNS infections were tested; a virus was incriminated in 17.5% with 58% caused by West Nile virus and enteroviruses, 23.5% caused by enteroviruses, 10% caused by Toscana virus and 8.5% caused by herpesviruses (Sghaier et al., 2013). Very recently, 2 strains of Toscana virus were isolated from *P. perniciosus* collected in northern regions (Bichaud et al., 2013).

7.6.4. Egypt

Two strains of Naples virus were isolated from febrile patients in the early 1950's (Feinsod et al., 1987). In 1959, Naples virus was isolated from *P. papatasi* (Schmidt et al., 1971). Using PRNT (80) seropositive results for Sicilian virus (2–59.4%) and Naples virus (3.9–56.3%) were reported from 11 geographically widespread regions of Egypt (Tesh et al., 1976). Naples virus was isolated from one acutely ill patient from northern Egypt (Darwish et al., 1987; Feinsod et al., 1987). One acute case of Sicilian virus infection was also reported in the study. In 1989, sera were collected from children (8–14 years-old) from four villages in the Bilbeis area of the Nile river delta (60 km northeast of Cairo). IgG antibodies to Sicilian virus were detected in 9% of the 223 tested sera by enzyme immunoassay (Corwin et al., 1992). In 1991, in the northeast of Cairo, seroprevalence rates of 4% for Sicilian virus and 2% for Naples virus were reported (Corwin et al., 1993). During an epidemic of 79 cases of encephalitis, one was diagnosed as probable Sicilian virus infection through detection of IgM in the serum. The virus was neither isolated nor sequenced. The case remains as a probable infection with Sicilian virus, and would be the first case of Sicilian virus to cause CNS infection with a fatal outcome (Selim et al., 2007).

7.6.5. Sudan

Neutralizing antibodies to Sicilian virus (6.6–20%), Naples virus (14–33%), and Karimabad virus (1.3–11%) were detected (PRNT (80)) from six provinces over a wide geograghical range (Tesh et al., 1976). In 1988, in Khartoum, sera from patients with febrile illness were tested via ELISA for Sicilian and Naples virus (McCarthy et al., 1996): IgGs against Sicilian and Naples were detected in 54% and 34% of sera, respectively. Less than 10% of sera were positive for IgM against either of these two viruses. However, 5% and 7% of the controls were also positive for Sicilian and Naples virus IgM thus questioning the specificity of the IgM detection in this population. During August and September 1989 an outbreak of

febrile illness occurred in Northern Province of which the causative agent was probably Naples virus or an antigenically related virus since IgM specific for Naples virus was detected in 24% of 185 sera tested by ELISA (Watts et al., 1994). IgG antibody prevalence to Sicilian virus was 53% (98 samples) and to Naples virus was 32% (60 samples) among 185 febrile patients which were detected using an indirect ELISA assay.

7.6.6. Uganda

A single study was done based on HI test in 1984: one of 132 sera was found to contain anti-Sicilian virus antibodies (Rodhain et al., 1989).

7.7. Other African countries

Tesh et al. (1976) also reported Sicilian virus neutralizing antibodies in Somalia, and Naples virus neutralizing antibodies in Djibouti and Ethiopia. But they did not find neutralizing antibodies in Senegal, Liberia, Ghana, Nigeria and Kenya. However, these results were obtained almost 40 years ago, and new studies are necessary since the local and regional situation has probably changed significantly meantime.

7.8. The Middle East

7.8.1. Iraq

During World War II, cases of sandfly fever were reported with a high incidence in the Middle East including Iraq and Iran (Oldfield et al., 1991). In the early 1970's, neutralizing antibodies against Sicilian virus (2.5%) and Naples virus (7.5%) were reported in human sera (Tesh et al., 1976). During an outbreak in US Army troops in 2007, 13 of 14 convalescent sera contained IgM specific for Sicilian virus using ELISA (Ellis et al., 2008). IgG specific for Sicilian virus was also found in marines after self-reporting of febrile illness using ELISA (Riddle et al., 2008).

7.8.2. Iran

Extensive studies were conducted in Iran. Hitherto, five different sandfly fever viruses were reported to be present in Iran with virus isolation representing of Sicilian virus, Salehabad, Karimabad, and Tehran but only indirect evidence for Naples virus. Salehebad virus was isolated from *P. papatasi* in 1959, Tehran virus was isolated in 1959 from unidentified sandflies, and Karimabad virus was first isolated from an unidentified pool of sandflies as well as from *P. papatasi* (Tesh et al., 1977, 1976). Although the pathogenicity of Karimabad virus is unknown, specific antibodies were found in humans and other vertebrates (Darwish et al., 1983; Gaidamovich et al., 1984; 1978; Saidi et al., 1977; Tesh et al., 1976). The presence of neutralizing antibodies in human sera collected from seven provinces of Iran over a wide geographical range demonstrates that Sicilian virus (9.4–21.8%), Naples virus (13.2–30.4%), and Karimabad virus (0.2–62.1%) were highly prevalent throughout the country before the 1970's (Tesh et al., 1976). In contrast, Salehebad neutralizing antibodies were not detected in humans (Tesh et al., 1976). Karimabad virus and Sicilian virus can also infect gerbils as shown by respective rates of 31.6% and 34.2%, using PRNT (80) (Saidi et al., 1977).

From *P. papatasi* flies, 49 strains of Sicilian virus and 11 strains of Karimabad virus were isolated (Tesh et al., 1977). Although seroprevalence rates of antibodies against Naples virus were significant, the virus was not isolated in Iran.

7.8.3. Afghanistan

In 1986–1987, three strains of Naples virus and two strains of Sicilian virus were isolated from febrile Soviet troops (Gaidamovich et al., 1990). However, a very low prevalence of HI antibodies was reported Bryan et al. (1996). Microbiological investigations of 26 cases of unexplained febrile illness that occurred in British troops stationed in Helmand district during summer 2008 revealed that 12 cases were associated with sandfly fever although the status " probable" or "confirmed" and the method used for diagnosis were not detailed (Bailey et al., 2011).

7.8.4. Southern Asia

The studies of Tesh et al. (1976) did not lead to the discovery of neutralizing antibodies in Burma, Vietnam, Malaysia or China.

7.8.5. Pakistan

In Western provinces of Pakistan, a strain of Sicilian virus was isolated from *P. papatasi* (George, 1970). In Karachi, 2.7% and 9.3% of sera tested positive for neutralizing antibodies against Sicilian and Naples virus, respectively (Tesh et al., 1976). Additionally, antibodies against Sicilian virus, Naples virus, Karimabad virus and Salehebad virus were detected in 2.5%, 9.5%, 3.8%, and 3.2% of the tested rodents, and in 5.8%, 1.7%, 0.6%, and 1.2% of the domestic animals (Darwish et al., 1983). Antibodies specific for Sicilian and Naples viruses were detected in 27% to 70% of Pakistani military personnel by ELISA (Bryan et al., 1996).

7.8.6. India

In 1936, a viral strain was isolated from a patient presenting with a syndrome compatible with sandfly fever (Shortt, 1936). However this strain was not characterized, either antigenically or genetically, and was finally lost (Bhatt et al., 1971). Sicilian virus was isolated in Maharastra state during an epidemic of febrile illness (Bhatt et al., 1971). In addition, nine strains of Sicilian virus and 11 strains of Naples virus were isolated from *Phlebotomus spp*., while neutralizing antibodies against Naples virus were detected in human sera (Goverdhan et al., 1976).

7.8.7. Bangladesh

Two seroprevalence studies conducted in 1976 and 1984 described the presence of antibodies against Sicilian and Naples virus at rates ranging from 2.7–6.25% and 1.25–12%, respectively using either PRNT (80) or HI tests (Gaidamovich et al., 1984; Tesh et al., 1976). HI-based antibodies against Karimabad were reported in 11.25% of human sera.

7.9. Potential for further geographic spread

The geographic spread of sandfly-borne phleboviruses depends on the geographic distribution of *Phlebotomus* species, which are considerably influenced by climatic changes and environmental modifications (Weaver and Reisen, 2010). Even under conservative and optimistic scenarios, future climate change is likely to increase air temperatures. At the end of this century, the number of hot days in central Europe is projected to reach conditions that are currently experienced in southern Europe. While heavy summer precipitation is expected to increase in northeastern parts of Europe, it is likely to decrease in the south (Beniston et al., 2007). In addition, changes in annual cold extremes are projected, whereby the largest relative warming is expected for northeastern Europe (Goubanova and Li, 2007). These climatic changes may support a range shift and further regional establishment of certain sandfly species, including *P. mascittii*.

As an ectothermal arthropod, like other sandfly species, *P. papatasi* is unable to regulate its body temperature. Hence the species directly depends on the thermal conditions of its environment. Under laboratory conditions, changes in temperature and humidity affect the population dynamics of this species, which suggests that climate change is likely to extend the limits of its northern distribution (Kasap and Alten, 2005). Regarding a northward shift, espe-

cially temperature constraints in the cold period and decreasing photoperiod are of main interest, as factors determine diapause of eggs and thus the survival of sandfly species. The 10 °C coldest-month isotherm coincides with the separation between continuously breeding populations and those that must undergo a period of dormancy to survive cold periods in winter (Mitchell, 1988). Nawrocki and Hawley, (1987) stated that the 5 °C coldest-month isotherm describes the maximum northward expansion of some vector species including sandflies in continental Asia and, presumably, also in North America.

Low temperatures are not the only climatic factor that has to be considered; warm temperatures also play an important role for many vector species. Sufficient precipitation, or perhaps more generally a suitable local moisture regime, is an additional prerequisite for the occurrence of sandfly species. Moisture directly controls the availability of breeding sites and the relative humidity is an important factor for egg survival (Kasap and Alten, 2005).

There are evidences of an increasing risk of establishment of sandfly species, especially in the Atlantic Coast and inland parts of Germany, Switzerland, Hungary and Austria (Depaquit et al., 2005; Farkas et al., 2011; Naucke et al., 2011; Naucke and Schmitt, 2004). In addition to the detection of already appropriate areas, the findings show additional regions for potential future establishment of the species. It is possible that the sandflies have already colonized larger areas than previously reported. Large portions of northwestern and central Europe that are inappropriate for the species today are projected to change during the 21st century towards a climate that can further support the survival of a number of sandfly species. Once they become established, they are very difficult to control.

However, the presence of an arthropod vector is not the only factor determining whether or not a pathogen can become established. Even if the vector is abundant, the values of other factors may result in a situation in which introduction of the pathogen does not lead to a large outbreak. Such factors are often environmentally determined, and include the replication rate of the pathogen, the vector biting rate, the host availability and the infectious life span of either vectors or hosts. We therefore need a tool to predict whether or not sandfly-borne diseases such as canine leishmaniasis or phlebovirus infections can establish after introduction in a certain area and under certain climatic and environmental conditions. At the present time, a higher reported number of imported vectors, an increase in autochthonous transmission of several viral diseases are reported in Europe, especially in southern Europe. These incidents have revealed major obstacles in most European countries such as the lack of updated distribution and/or presence/absence data, cost-effective surveillance, data on species abundance and control strategies. The most important and urgent necessity among the community of entomologists working on phlebotomines is the need to record the extremes of distribution of each species and data on their presence/absence.

Travel-related imported infections in Europe are a major issue of concern for public health authorities. Due to increasing rates of travel, transport and international trade during the past century, European countries are continually at higher risk of the introduction of imported viruses, vectors and hosts that can settle in the newly invaded areas, if biogeographic, climatic and demographic factors prove to be favorable (Odolini et al., 2011; Pysek et al., 2010). Poor socioeconomic conditions that inevitably lead to favourable conditions for the generation of breeding areas for sandflies may help the spread of sandfly-borne phleboviral diseases such as leishmaniasis.

During the past decade, direct and indirect evidence of the presence of sandly-borne phleboviruses such as Toscana virus were increasingly reported from regions where virus circulation was recognized, but also from regions where the virus was unrecognized (Bahri et al., 2011; Bichaud et al., 2013; Brisbarre et al., 2011; Ergunay et al., 2012a,d; Ergunay et al., 2011; Es-Sette et al., 2012; Schultze et al., 2012; Sghaier et al., 2013). A significant number of novel sandfly-borne phleboviruses has also been discovered, and others are expected to be discovered in the future. These agents should therefore be added to the list of viruses requiring regular surveillance and reporting updates. In addition, sandfly-borne phlebovirus cases have been reported from new areas, which point the spread of these viruses (for example, a recent case from Malta) (Schultze et al., 2012). Interestingly, there are no data from southeast Asian countries such as Taiwan, Hong Kong and Malaysia, and no reports from Australia. Whether or not this accurately reflects the absence of sandfly-borne phleboviruses in these regions remains to be investigated, since this could be falsely reassuring due to the lack of specific studies conducted in these regions.

8. Significance for military forces

Because it is likely that European and American military forces will be involved for the indefinite future in the Middle East and other areas where *Phlebotomus* species are present, they provide an excellent source of naturally infected "sentinels" for surveillance of sandfly-borne viral diseases. Here, we will discuss the experience of WW-I and WW-II, and consider recent data in order to address the following question "are sandfly-borne phleboviruses a sufficient threat to military effectiveness to warrant the development of vaccines for soldiers preparing to enter an endemic area?"

In World War II, sandfly fever affected high numbers of British, American, Canadian, Australian, New Zealand, Indian and also Italian and German troops, in the Mediterranean, the Middle East and North Africa (Hertig and Sabin, 1964; Sabin, 1951).The outbreak among New Zealand troops affected so many that the third New Zealand General Hospital was saturated for several days in Stout and Duncan (1954). Recently in Iraq, taking into account 4–40% attack rates during 4 months of active periods of sandflies, an estimated 17–168 soldiers among 420 U.S. troops in Baghdad were at risk of exposure, leading to a potentially important significant impact on the operation (Ellis et al., 2008).

As summarized above, sandlfy fever has always been a problem for immunologically naive soldiers that enter endemic areas when *Phlebotomus* sandflies are active. Although in most cases the disease is relatively benign, the effects of an outbreak in troops may be devastating because of high attack rates, diagnostic uncertainty and acute morbidity. In most cases, military operations are interrupted and postponed. These types of scenario inevitably impact on military strategies in the theatre of operations.

Although sandfly fever is a self-limiting illness, it can be costly to diagnose and to treat when there is a high incidence of clinical disease. Since there is no preventive treatment, sandfly repellents and insecticide spraying are the most effective measures for protecting troops against sandflies. However, insecticide spraying requires knowledge of the habitats of sandflies which is unlikely to be possible if there is no literature about the spread of the flies around the stationed area.

9. Countermeasures against sandfly-borne phleboviruses

There are currently no available approved vaccines or specific antiviral therapies for these diseases.

9.1. Vaccines

The development of a broad-spectrum vaccine may be justified for army troops stationed in endemic areas, for people who travel

to endemic regions, and of course for populations living in areas where endemicity is documented or is considered an at-risk area. Because of the generally favorable outcome of infections with Sicilian and Naples virus, it is likely that an effective vaccine would fulfill a useful purpose mainly for military personnel, to reduce the risk of short-term decimation of army forces. For instance, 12 of 23 febrile soldiers among British troops in Afghanistan were diagnosed as being infected by sandfly fever virus, and they were treated with doxycycline since there is no specific treatment for sandfly fever (Bailey et al., 2011).

A study on prevention from infection by Toscana virus reported that a combination of recombinant Toscana virus structural proteins N-Gc, used as a vaccine, protected 100% of mice infected with a lethal, neurovirulent strain of Toscana virus (Gori Savellini et al., 2008). Because of the extensive genetic and antigenic diversity observed between Naples and Sicilian virus, a vaccine developed against one of these viruses has little chance of being effective against the other virus. Moreover, whether or not a vaccine developed against Toscana virus would have a induce cross-protection against Naples virus is uncertain and should be experimentally investigated. The concept of a broad-spectrum vaccine would therefore probably have to rely upon the development of at least a triple-virus vaccine.

9.2. Insecticides

Other than prevention and antiviral therapy, repellents and insecticides are the principal options to reduce the spread of sandfly-borne diseases. Spraying campaigns are usually focused on inhabited areas and thus efficient against anthoponotic sandflies, such as *P. papatasi* (Tesh and Papaevangelou, 1977). The efficacy is much lower against non-anthoponotic sandflies, such as those belonging to the *Laroussius* subgroup. However, without precise mapping of sandfly habitats and breeding areas, insecticide spraying is likely to be poorly effective. Because so little is known about natural breeding sites of sandflies (Killick-Kendrick, 1987), the preimaginal stages are rarely targeted by control measures. In campaigns against the adult sandflies, assessments of efficacy and cost/benefit are difficult to make because there are few properly controlled studies, and the results of different interventions are seldom compared. Insecticide spraying significantly decreases the incidence of *Phlebotomus*-transmitted diseases only if spraying is continuous; sporadic campaigns are considered to be ineffective.

On the other hand, the efficacy of spraying campaigns was demonstrated when DDT was used to eradicate malaria in Europe and India during 1950s and 1960s. Indoor residual spraying with organochlorines (DDT, dieldrin, lindane, BHC, and methoxychlor), organophosphates (malathion, fenitrothion, pirimiphos methyl, chlorophos), carbamates (propoxur, bendiocarb) and synythetic pyrethroids (permethrin, deltamethrin, lambdacyhalothrin, alphacypermethrin, cyfluthrin, and cypermethrin) may be a simple method to decrease the adult population. For instance, indoor residual spraying was reported to be effective in India (Mukhopadhyay et al., 1996) and in the Peruvian Andes (Davies et al., 2000). However this method is ineffective in the long-term and outdoors. Insecticide spraying of resting places failed in Panama (Chaniotis et al., 1982), but it worked better in Brazil (Ready et al., 1985) and Kenya (Robert and Perich, 1995).

Resistance to DDT was detected in India for *P. papatasi*, *P. argentipes*, and *S. shortii*, whereas DDT tolerance has been reported for some species in other countries (Alexander and Maroli, 2003). Establishment of baseline insecticide susceptibility data is required to decide the formulations and frequency of spraying. Insecticide spraying of resting places away from houses, such as trunks of trees, termite hills, and rodent burrows has also been attempted to control sandflies, which are sylvatic and seldom enter habitations, with mostly disappointing results (11–30% reduction) (Killick-Kendrick, 1999).

Following claims of the successful control of mosquito vectors of malaria with bed nets impregnated with pyrethoids, attempts have been made to control sandflies in the same way. Insecticide-impregnated bed nets trials have been in progress against exophilic and endophilic sandfly species in foci of visceral and cutaneous leishmaniasis in many countries of both Old and New World such as Colombia, Sudan, Afghanistan, Syria, Israel and Turkey for a long time (Alten et al., 2003; Elnaiem et al., 1999; Faiman et al., 2009; Jalouk et al., 2007). It was concluded that insecticide impregnated bed nets may provide a practical means of controlling sandflies entering houses, although the result suggest that further trials are needed. The peak of biting activity of most vector species is shortly after sundown before children are in bed suggesting that impregnated bed nets may have little effect. However, if impregnated bed nets cause a fall in the life expectancy of sandflies, risk of an infection may be reduced. An assessment of the efficacy of this intervention cannot be made until the trials are completed (Killick-Kendrick, 1999). However, long-lasting insecticide-impregnated bed nets, which are produced by companies in recent years, had a limited effect on the exposure to sandfly bites (Gidwani et al., 2011).

As an alternative to bed nets some trials have been made with insecticide impregnated curtains (Maroli and Majori, 1991), insecticide impregnated dog collars (Killick-Kendrick et al., 1997) and insecticide-treated sugar bates are also novel approach for control (Mascari and Foil, 2010; Müller and Schlein, 2011).

Other than insecticides, there are some novel sustainable approaches such as pheromone dispenser baits (Bray et al., 2010, 2009) and cultivation of noxious plants against sandflies (Schlein and Jacobson, 2002).

9.3. Treatment

Based on cell culture studies, Selenazole was reported to be an effective inhibitor of Sicilian virus (Kirsi et al., 1983). Ribavirin was used to treat volunteers experimentally infected with Sicilian virus using an oral dose of 400 mg every 8 h beginning 1 day before infection for 8 days (Huggins, 1989). None of the volunteers treated with Ribavirin became sick. A combination of human recombinant interferon-α and Ribavirin was proposed based on *in vitro* efficacy against Sicilian virus (Crance et al., 1997). Interferon-induced MxA protein was reported to inhibit Sicilian virus *in vitro* by affecting the early step of viral replication (Frese et al., 1996). In another study, the pyrazine derivatives T-705 and T-1106, showed *in vitro* activity against Naples virus with a lower toxicity than Ribavirin (Gowen et al., 2010, 2007).

10. Potential for further evolution and emergence

Several properties of the sandfly-borne phleboviruses make them good candidates for further emergence as human pathogens. Because the geographic distribution of these agents is dictated by the distribution of their vectors, climate change can modulate at-risk areas and human populations. The high rate of mutation of these viruses due to the lack of proofreading activity of the viral RNA polymerase generates quasispecies populations, a situation favoring the selection of variants with modified phenotypes, potentially including increased virulence and/or transmission efficiency. The propensity for genetic reassortment or recombination under conditions of mixed infections may result in recombinant viruses with significantly altered pathogenicity characteristics, as has been observed with other genera in the *Bunyaviridae* family (Bowen et al., 2001; Gerrard et al., 2004). By definition all arbovi-

ruses have the capacity to infect and replicate in both vertebrates and invertebrates. Thus, arboviruses have evolved the capability of infecting widely different hosts that present very distinct biochemical challenges. This "plasticity" in their life cycles increases their capacity to cross species barriers (Elliott et al., 2000), an essential requirement for virus emergence.

11. Directions for future research

Sandfly-borne phlebovirus infections have been reported since the early 20th century and obviously new cases will continue to be observed within local populations where phleboviruses are already known to circulate. In addition, the increasing movement of humans, animals and commercial goods will inevitably lead to the introduction of phleboviruses, most likely from the introduction of selected species of sandflies, in countries where, currently, there are no reported cases. All regions where *Phlebotomus* sandflies are present should be considered at potential risk. Because sandflies are also the vector of leishmaniasis, interactions between sandfly-borne phleboviruses and *Leishmania* parasites do occur regularly. Intriguingly, whether or not such interactions have biological significance remains to be investigated. However, understanding and defining the complex nature of such interrelationships will necessitate a range of transdisciplinary approaches involving ecology, virology, parasitology, epidemiology and immunology at both medical and veterinary levels.

Toscana virus is the sandfly-borne phlebovirus with the greatest known virulence for humans. The many questions that arise from this discussion include: Is there a vertebrate host for Toscana virus? What proportion of the world's population is at risk of infection with Toscana virus and other sandfly-borne phleboviruses? Do recently discovered related phleboviruses present a risk to global public health? Can the cost of detailed genomic studies of these viruses be justified? Current sequence data are fragmentary, thus jeopardizing the development of efficient diagnostic tools and limiting the volume of data that could be compiled for large-scale epidemiological investigations. Studies are needed to decipher the different modes of transmission of sandfly-borne viruses within individual sandflies and in populations. The discovery of drugs active against these viruses could prove worthwhile, because these viruses circulate widely and often in remote areas difficult to cover by conventional public health systems. In conclusion, the evidence of the emergence of many other RNA viruses during recent decades should raise our awareness of the possibility that phleboviruses could be a major problem waiting to arise.

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