

# Phleboviruses (Family: Phenuiviridae) Worldwide, with Emphasis on the Middle East: A Systematic Review Study

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## Abstract

**Background:** The prevalence of arboviruses is increasing worldwide. Their vectors are widely distributed in different continents of the world. Despite the importance of the phleboviruses, unfortunately data about the spread of the viruses in human and animal communities is very limited.

**Methods:** This study is a systematic review of phlebovirus and its vectors worldwide, with emphasis on Middle East countries including Iran. Accordingly, all English language articles which were conducted up to the end of 2020 were found by searching the databases, including Web of Science, PubMed, Google Scholar, Science Direct, and Scopus. Furthermore, the authors used the Strobe checklist to evaluate the quality of the articles.

**Results:** *Phlebotomus perniciosus* was the main vector of the Tosca virus in the Mediterranean regions such as Italy, France, and Greece. In African counties, *Aedes* species were more important vectors of phleboviruses, especially Rift Valley fever. As these diseases can easily spread to even uninfected areas of Asia, permanent monitoring is needed to control phleboviruses.

**Conclusion:** Practical methods have been used to control the vectors and hosts of phleboviruses. Some important methods are listed as follows: impregnated bed nets/curtains, residual spraying, repellents, establishment of the robust surveillance of animal and their products, and limited movement of livestock during outbreak time. These methods can minimize the risk of transmission of phleboviral diseases, especially RVF infection.

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**Keywords:** Phlebovirus, Systematic review, Insect vector, worldwide, Iran

## Introduction

Arboviruses diseases are the most significant challenge for medical researchers in arthropod-borne diseases. For instance, humans have been infected by various viruses such as Powassan virus, Colorado tick fever virus, deer tick virus, Heartland virus, and Bourbon virus infect in North America.<sup>1</sup> Sand flies known as *Phlebotomus* and *Lutzomyia* are able to transmit Leishmania to humans and other animals like dogs and cats.<sup>2</sup> Additionally, sand fly-borne phleboviruses, including Toscana Virus (TOSV), Sand fly Fever Naples virus (SFNV), Sand fly

Fever Sicilian Virus (SFSV), and Cyprus virus (CYPV) are among the most important health problems in Europe and North African counties. Indeed, TOSV is spread along the Mediterranean basin causing meningitis and encephalitis in humans.<sup>3</sup> Rift Valley Fever (RVF) caused massive mortality in livestock in Africa in the past, so it has veterinary importance as well.<sup>4</sup> Notably, climatic change affects the distribution of this virus in endemic areas. For example, the RVF prevalence coincides with heavy rainfall in Kenya where outbreaks have occurred several times.<sup>5</sup> This virus can spread from endemic areas to clean regions and cause an epidemic in a new

destination.<sup>6</sup> Other viruses such as Heartland virus and SFTS are transmitted through host feedings by ticks in the USA and in some Asian countries, respectively.<sup>7</sup> Viral diseases are spreading quickly to new regions because of commercial transportation, globalization, ecosystem changes, urbanization, and destruction of animal habitats. These processes cause humans to get closer to vectors.<sup>4</sup> This systematic review emphasizes the distribution of *Phlebovirus* in the world and related vectors. We investigate all diseases related to this virus across the globe.

## Methods

### Protocol and Search Strategy

The authors conducted a systematic review to investigate the Phlebovirus and its vectors and applied PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standard checklists.<sup>8</sup> Accordingly, they searched the titles, abstracts, and keywords of all English language articles published about phleboviruses and their vectors in Middle East countries up to the end of 2020 in the Web of Science, Science Direct, PubMed, Scopus, and Google scholar databases.

To search the databases mentioned above, the authors used medical subject headings (MeSH) and the keywords, including Arbovirus, *Phlebovirus*, *Phenuiviridae*, TOSV, RVFV, Sand fly fever virus, Salehabad virus, tick virus, Mediterranean countries,

viral disease, arthropod-borne diseases, and virus taxonomy in isolation or combination. Boolean operators were used to search by a combination of words.<sup>9</sup>

### Inclusion and Exclusion Criteria

The authors included all globally-published and good quality English-language articles which investigated the vectors and diseases associated with Phlebovirus. Low quality articles, case reports, review studies, case series, and meta-analysis studies were excluded.

### Quality Assessment

The quality of the articles was evaluated using the Strengthening the Reporting of Observational Studies in Epidemiology (Strobe) checklist. This checklist has 22 sections, each of which receiving a different score based on its importance. The minimum and maximum scores were 15 and 33, respectively, and the acceptable score was 20.

### Screening and Data Extraction

At first, all results were imported in “Endnote X9” software, and we removed duplicate studies, based on authors and title. Then, the authors collected all articles the title, abstract, or keywords of which consisted of Phlebovirus. Next, they prepared a list of abstracts. After being blinded to the profile of the articles, such as the year of a published study, two

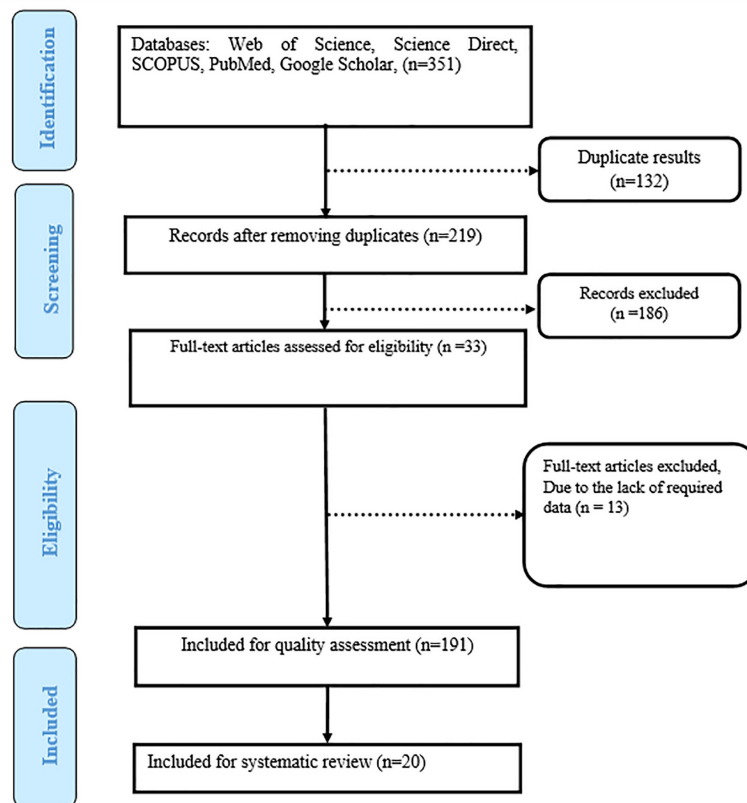


Figure 1: The PRISMA flow diagram

researchers (Z.N, K. A) and an expert (epidemiologist, S.D) reviewed each qualified full text independently. If an article was rejected, the reason was also mentioned, and when reviewers disagreed and had different recommendations, a third reviewer was invited to review that article.

## Results

Totally, 132 out of 351 articles were excluded from duplicate articles. It was followed by the exclusion of 186 irrelevant articles and 13 articles without the required information about vectors and Phlebovirus-related diseases. Figure 1 and Table 1 show the final 20 articles with the required criteria which were included in the systematic review process.

## Discussion

### *Taxonomy and Structure of genus Phlebovirus, Phenuiviridae family, Bunyvirales order*

Phlebovirus (family: Phenuiviridae, order: Bunyvirales) genomes are single-stranded RNA with negative polarity, organized into three segments, spherical, and 80–120nm in diameter, including 37 viruses grouped into nine species with 16 tentative species like Adria, Aguacate).<sup>10-12</sup> According to the new category, *Phlebovirus* is composed of 10 species from the old and new world such as fever

with thrombocytopenia syndrome (SFTS) virus, Rift Valley Fever Virus (RVFV), Uukuniemi phlebovirus, Bujaru phlebovirus, Candiru phlebovirus, Chilibre phlebovirus, Frijoles phlebovirus, Punta Toro phlebovirus, Salehabad phlebovirus, and SFNV.<sup>13-15</sup>

### *Sand fly/mosquito-borne Phlebovirus RVFV*

Cattle, sheep, goats, camels, and humans are the main hosts of RVFV.<sup>16</sup> The virus was discovered after massive mortality and abortions among sheep, particularly young ones, during an outbreak in the Rift valley (RV) of Kenya in 1930.<sup>16</sup> In an epidemic that occurred in Kenya from 2006 to 2007, about 90 humans and many livestock were dead. It was followed by financial problems and loss of market.<sup>5</sup> Two epidemics occurred in Mayotte (an island situated in the southwestern Indian Ocean and northwest Madagascar) in 2007 and 2018. Indeed, patients mostly had close contact with livestock, blood, and fluids.<sup>17, 18</sup> In addition to Africa, Saudi Arabia and Yemen also contracted the disease in 2000.<sup>19</sup> In humans, the incubation period lasts 18 h to 7 days. Clinical demonstration of RVF is unspecific, beginning with flu-like symptoms, diphasic fever, and myalgia. However, hemorrhagic fever and encephalitis are the most critical signs in 1% to 2% of cases.<sup>20</sup> Viruses are transmitted to humans by infected bites of female mosquitoes or infected animal tissue and

**Table 1:** Phlebovirus articles that were eligible for this systematic review

Reference	Place of study	Year of study	Vector family/species		Isolated Phlebovirus species
43	Italy	2013	Sand fly	<i>P. perniciosus</i> , <i>P. perfiliewi</i>	TOSV
80	Morocco	2015		<i>P. longicuspis</i> , <i>P. sergenti</i> ,	TOSV
64	Cyprus	2014		<i>P. perfiliewi</i> , s.l., <i>P. tobbi</i>	TOSV
81	Turkey	2010		<i>P. perfiliewi</i>	TOSV
39	France	2009		<i>P. perniciosus</i>	Massilia
82	Iran	2018		<i>P. papatasi</i> , <i>Sergentomyia sintoni</i>	SFNV, Salehabad
11	Tunisia	2010		<i>P. longicuspis</i>	Punique
75	Portugal	2015		<i>P. perniciosus</i>	Alcube (Arbia-like virus)
70	Albania	2019		<i>P. neglectus</i>	Drin
18	Mayotte (Africa)	2020		Mosquito	<i>Aedes aegypti</i> , <i>Ae. circumluteolus</i> , <i>Anopheles coustani</i> , <i>Culex pipiens</i> , <i>Cx. quinquefasciatus</i> , <i>Cx. antennatus</i> , <i>Eretmapodites quinquevittatus</i> , <i>Mansonia uniformis</i>
34	Kenya	2019	<i>Ae. dentatus</i> , <i>Ae. mcintoshi</i> , <i>Ae. tarsalis</i> , <i>Ae. ochraceus</i> , <i>Cx. zombaensis</i> , <i>Cx. theileri</i> , <i>Cx. pipiens</i> , <i>Cx. poicilipes</i> , <i>Cx. univittatus</i> , <i>Cx. vansomereni</i> , <i>Ma. uniformis</i> , <i>An. squamosus</i> , <i>An. funestus</i> , <i>An. coustani</i>		RVF
6	Sudan	2014	<i>Cx. pipiens</i> , <i>Cx. Poicilipes</i> , <i>An.arabiensis</i> , <i>An. coustani</i> , <i>Ae.aegypti</i>		RVF
83	Mauritania	2014		<i>Ae. vexans</i> , <i>Cx. poicilipes</i> , <i>Cx. antennatus</i> , <i>Ma. uniformis</i>	RVF
84	Saudi Arabia	2002		<i>Ae. vexans arabiensis</i> , <i>Cx. triteniorynchus</i>	RVF
85	Tunisia	1994	Tick	<i>Argas reflexus hermanni</i>	Tunis
86	USA	2020		<i>Amblyomma americanum</i>	Heartland
50	Vietnam	2019		<i>A. testudinarium</i>	SFTS
48	China	2014		<i>Haemaphysalis longicornis</i>	SFTS
60	Greece	2018		<i>Haemaphysalis parva</i>	Lesvos
87	Colombia	2020		<i>Dermacentor nitens</i> , <i>Rhipicephalus microplus</i>	Lihan Tick virus

fluids.<sup>21</sup> Climate change and flooding can facilitate the spread of RVF disease.<sup>22</sup>

#### TOSV

TOSV associated with *Phlebovirus* (serotype Naples serocomplex) has been found in the Mediterranean basin including France, Croatia, Spain, Portugal, Cyprus, Italy, Bulgaria, Turkey, and some countries in the north of Africa.<sup>23-25</sup> The impact of TOSV on CNS was recorded for the first time in Italy in 1971. Then, it was considered a causative agent of meningitis in the late 1990s.<sup>26</sup> Although its reservoirs are not well investigated, it is found in dogs, goats, cattle, and sheep.<sup>27, 28</sup> Remarkably, this virus is observed with *Leishmania infantum* and West Nile virus simultaneously.<sup>29, 30</sup> TOSV has separated from sand flies, and it has been transmitted through transovarial transmission or sexual offspring. It does not cause serious health problems but involves the central nervous system (CNS); subsequently, acute meningitis, encephalitis, and neurological symptoms have been recorded.<sup>27</sup>

#### SFSV

SFSV and SFNV were seen in serum samples of troops during World War II in Italy.<sup>31</sup> SFSV, SFNV, and TOSV cause a fibril illness called three-day fever.<sup>32</sup> SFSV, like TOSV, is prevalent along the Mediterranean region.<sup>33</sup> Human cases of this species have been recorded from some African countries such as Kenya, Uganda, Somalia, Djibouti, and Ethiopia.<sup>34</sup> It was also presented in Iranian troops by indirect immunofluorescence assay (IFA).<sup>35</sup> Some known reservoirs for this virus are rodent species (*Apodemus* spp., *Mus musculus*, *Rattus rattus*, *Insectivora* (Soricidae and Talpidae), and Weasel (*Mustela nivalis*).<sup>36</sup>

#### SFNV Complex

This group antigenically consists of SFNV, TOSV, Tehran virus (TEHV), Massilia virus (MASV), Karimabad virus (KARV), Granada virus (GRV), and Punique virus (PUNV).<sup>37-39</sup> SFNV complex was isolated from infected sand flies in Portugal.<sup>40</sup> Also, the Punique virus is isolated from sand flies captured in Tunisia.<sup>11</sup>

#### Sicilian-like Viruses

Sand fly fever Cyprus virus and Sand fly fever Turkey virus were isolated from human blood and sand flies, respectively.<sup>41, 42</sup>

#### Salehabad Virus

Salehabad virus was isolated from sand flies in Iran in 1959.<sup>43</sup> Moreover, it was detected in *Phlebotomus* species in Italy and Turkey.<sup>44</sup> The clinical signs and

symptoms of this virus are not clear either in humans or animals.<sup>45</sup>

#### Punta Toro Virus (PTV)

PTV was detected in human blood and caused fever in the Panama Canal Zone in 1966. Clinical symptoms are uncertain yet, but it is a febrile syndrome misdiagnosed with dengue fever.<sup>46</sup>

#### Tick-borne Phlebovirus

##### Severe Fever with Thrombocytopenia Syndrome Virus (SFTSV)

This tick-borne virus was introduced in China in 2010 for the first time. Afterward, it appeared in Korea, Japan, Pakistan, Vietnam, and the United States of America.<sup>47-50</sup> This emerging virus infects humans with around 10% mortality.<sup>51, 52</sup> It is genetically associated with the Heartland virus.<sup>53</sup> Results have shown that zoonotic SFTSV can be transmitted from a person to another if they have a history of direct blood contact.<sup>54</sup> SFTSV was isolated from various animals including goats and sheep, cattle, dogs, chickens, pigs, etc. Anyway, it sounds this is a tick-borne disease.<sup>55</sup>

#### Heartland Virus (HRTV)

Heartland virus was initially observed in 2009 in two Missouri farmers in the USA with symptoms like headache, myalgia, leukopenia, and thrombocytopenia.<sup>56</sup> White-tailed deer and Raccoon are considered hosts for this virus.<sup>57</sup>

#### Uukuniemi Group Viruses (UUKV)

Uukuniemi group viruses (UUKV) are categorized into five distinct species, including Uukuniemi, Murre, Grand Arbaud, Precarious Point, and Manawa viruses.<sup>58</sup> This virus was separated from *Ixodes ricinus* captured from Uukuniemi, southeast Finland in 1959.<sup>59</sup> Also, this virus was reported in the Czech Republic.<sup>60</sup>

#### Bhanja Viruses

The virus was isolated from a tick collected from a goat in Bhanjanagar, India, in 1954. Then, it has been frequently recorded from southern Asia, Europe, Africa.<sup>61</sup> Based on serology studies, BHAV was seen in domestic cattle, sheep, humans, hedgehogs, and the African ground squirrel, causing encephalitic disease in man.<sup>62</sup> Also, meningoencephalitis and leucopenia were observed in lambs and cattle, respectively.<sup>63</sup>

#### Phleboviruses in the Middle East

The Middle East countries generally include the countries on or near the Arabian Peninsula, including Bahrain, Cyprus, Lebanon, Syria, Iraq, Iran, Palestine, Jordan, Saudi Arabia, Kuwait, Qatar, United Arab Emirates, Oman, Turkey, and Yemen (Figure 2).



Figure 2: Map of the Middle East (By authors)

Phleboviruses of TOSV, SFNV, SFSV, and CYPV spread in the Middle East, the Mediterranean regions of Europe, Asia, and Africa, and are of the highest medical significance.

Cyprus, located in the eastern Mediterranean Sea, is the third largest island in the Mediterranean region. This country shares borders with Turkey, Palestine, Lebanon, Syria, Greece, and Egypt. Nicosia is the capital of Cyprus (Figure 3A).

During 2002, after an outbreak of febrile syndrome occurred among the Greek Army forces, molecular and serological tests revealed a Sicilian-like phlebovirus

as the causative agent of the disease. Phylogenetic analysis on partial L RNA segment sequences revealed that the SFSV strain isolated from Cyprus differed (by 6.7%) from S at the nucleotide level.<sup>41</sup>

SFNV, SFSV, and TSOV were separated from 396 serum samples of Cypriot patients and soldiers hospitalized in medical clinics or hospitals from 1985 to 1986.<sup>64, 65</sup> Wild sand flies specimens collected from 17 locations in Lefkosa, Girne, Magosa and Guzelyurt provinces of northern Cyprus revealed that *Phlebotomus perfiliewi s.l.* and *P. tobbi* were infected with TOSV genotype A. Moreover, co-infection of

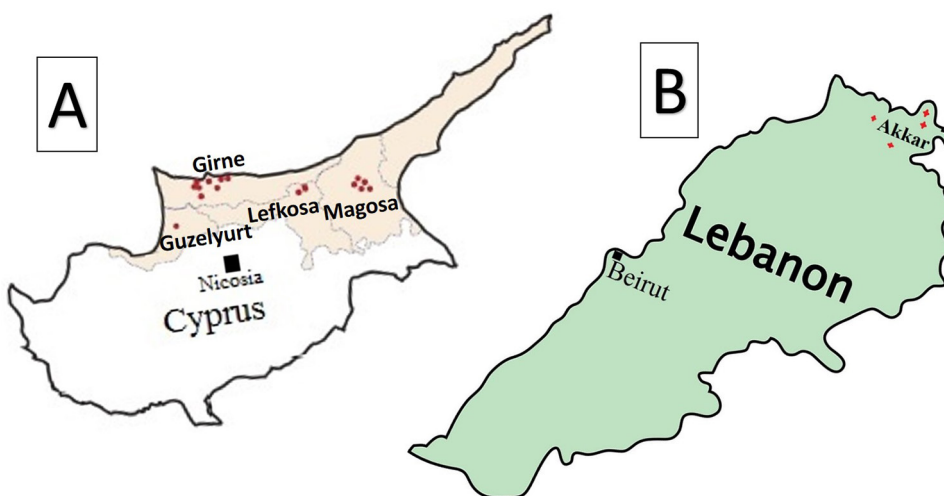


Figure 3: Map of infected sand flies with phleboviruses in Cyprus (A) and Lebanon (B) (By authors).

*Leishmania infantum* and TOSV was recorded in *P. tobbi*.<sup>66</sup> On the other hand, some studies indicated that phlebotomine sand flies such as *P. longicuspis*, *P. sergenti*, *P. neglectus*, and *Sergentomyia minuta* were infected with TOSV (Figure 3A).<sup>67</sup>

Lebanon, known as the Lebanese Republic, is located in the west of Asia continent and is bordered by Syria to the north and east and Palestine to the south; Cyprus lies to its west across the Mediterranean Sea and its capital is Beirut. Sand fly fever outbreak was reported from Akkar, Dinnieh districts, North Province of Lebanon during 2007, and this was the first report of Pappatsi fever in this country.<sup>68</sup> Some serological studies revealed that European soldiers were at risk of Phlebovirus infections during their missions in Middle East including Lebanon in 2019.<sup>69</sup> In this study, All IgG positive samples were tested for IgM antibodies against TOSV, SFNV, SFSV and CYPV, by the indirect immunofluorescence test. SFNV was found in one sample in a soldier returned from Lebanon (Figure 3B).

Syria, known as the Syrian Arab Republic, is a country in the West of Asia, bordering the Mediterranean Sea to the west, Lebanon to the southwest, Iraq to the east, Turkey to the north, Jordan to the south, and Palestine to the southwest. Its largest and capital city is Damascus. SFNV was the main infection and was reported from Austrian soldiers who returned from their missions in Syria during 2019.<sup>69</sup> In Iran, the Salehabad phlebovirus species comprise Adria, Alcube, Arabia, Adana, Arumowot, Medjerda Valley, Odrenisrou, Salehabad, Olbia, Bregalaka, and Zaba.<sup>70</sup>

## Conclusion

Climate change is a suitable component for the growth of mosquitoes. Also, human decisions such as importing domestic animals from endemic African countries to other regions might affect them with zoonotic diseases.<sup>71</sup> Like other arthropod-borne diseases, phlebovirus, particularly RVF, is more prevalent in tropical areas such as Africa, but it also spreads to Saudi Arabia. For instance, more than 30 species of mosquitoes with various ecological niches and feeding behaviors serve as a vector of RVF.<sup>72</sup> Many strategies have been accomplished, but not all were successful. As we know, some of them have various primary or potential vectors with an uncertain role in the transmission to humans, and it is challenging to control the phlebovirus diseases.<sup>71</sup>

The RVF virus has been circulated in mosquitoes like *Aedes spp.* for a long time in dry seasons by transovarial transmission, which has caused outbreaks of RVF in endemic regions.<sup>73,74</sup> Besides, the researchers are unfamiliar with the pathogenicity of other phleboviruses to humans, such as Massilia, Granada, or Punique viruses. Although they are isolated from

some sand flies, there is still a significant gap in their vectorial capacity.<sup>75</sup> Molecular epidemiology can describe the genetic model of viruses and how they circulate into the population. Also, studies about the host, environment, vector variable, and their interaction through the Spatio-temporal model predict the potential transmission of the virus and recognize the virulence and health threats, especially for sand flies and mosquito-borne diseases.<sup>76</sup>

The practical methods such as impregnated bed nets/curtains, residual spraying, and repellents have been used for a long time in controlling sand flies.<sup>77</sup> Establishing the robust surveillance of animals and their products and limited movement of livestock in outbreak time minimize the risk of viral diseases transmissions, especially RVF infection.<sup>76,78</sup> Moreover, vaccination is an effective solution. Recently, it's been used to control RVF in livestock.<sup>79</sup>

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## Authors' Contribution

ZN, KA contributed to the design of the project. ZN, MA, D, and MK prepared and contributed to the analysis and manuscript preparation. All authors read and approved the final manuscript.

**Conflicts of Interest:** None declared.

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