Arboviruses and Viral Hemorrhagic Fevers (VHF)

Eyal Meltzer, MD, DTM&H[a,b,*]

KEYWORDS

• Arbovirus • Viral hemorrhagic fever • Flavivirus • Filovirus • Arenavirus • Alphavirus • Bunyavirus

KEY POINTS

- Arboviruses are transmitted through the bite of hematophagous arthropods. In addition to humans, many arboviruses infect Avifauna. Through highly mobile reservoirs, rapid and dramatic changes in epidemiology can easily occur.
- Viral hemorrhagic fever (VHF) is typified by a combination of endothelial dysfunction causing a capillary leak syndrome and a bleeding diathesis, caused by thrombocytopenia and diffuse intravascular coagulation.
- In addition to arboviruses, the VHF syndrome may be caused by several rodent and bat viruses (Ebola and Lassa viruses respectively).
- In addition to VHF, arboviruses may cause a variety of organ specific syndromes, including encephalitis, pneumonitis, nephritis and arthritis.
- Several arboviral infections (mainly Flaviviruses) are vaccine preventable. By and large, treatment is supportive, with the exception of Arenaviruses, where ribavirin is the drug of choice.

PREFACE

In 1780, Philadelphia was visited by a massive epidemic of an unusual febrile disease, with fatalities associated with severe hemorrhage.[1] The disease, then described by Dr Benjamin Rush, is now recognized as dengue fever. A century later, a febrile tugboat captain disembarked in Memphis, Tennessee and died within 24 hours. In the following weeks, 1500 Memphians succumbed to yellow fever, the town half depopulated by the ensuing panic.[2] Yet a century later, a Zairian English teacher returned

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[a] Department of Medicine C, Sheba Medical Center, Center for Geographic Medicine, Tel Hashomer 52621, Israel; [b] Department of Internal Medicine, Sackler School of Medicine, Tel Aviv University, Tel Aviv 69978, Israel

* Department of Medicine C, Sheba Medical Center, Center for Geographic Medicine, Tel Hashomer 52621, Israel.

E-mail address: emeltzer@post.tau.ac.il

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home from a field trip with fever and diarrhea; he died of profuse bleeding and shock after 13 days. In the ensuing weeks, most of his family and hospital attendants also died of a similar disease: the first recognized Ebola outbreak.[3]

These outbreaks, although centuries apart, illustrate the dramatic nature of viral hemorrhagic fever (VHF) outbreaks. These agents naturally remain at the focus of medical attention.

Many of the agents causing VHF are arthropod borne, or arboviruses. In addition to the VHF syndrome, arboviruses cause other clinical syndromes, including encephalitis and arthritis. Also, several viruses that are not arthropod borne can cause VHF.

The aim of this review is to describe the epidemiology and clinical features of salient agents of VHF, arboviral and nonarboviral, and of other arboviruses.

ARBOVIRUSES: TAXONOMY AND EPIDEMIOLOGY

Arboviruses are mostly small RNA viruses that belong to 4 families: *Flaviviridae, Bunyaviridae, Reoviridae,* and *Togaviridae* (**Fig. 1**). They are grouped together because of their similar mode of transmission: through the bite of hematophagous arthropods (mosquitoes, ticks, midges, and sandflies). Arboviruses plague all continents and climate zones. By and large, these agents are maintained in a variety of animal reservoirs, especially avian and mammalian, with man being an accidental host. A notable exception is dengue virus, which is anthroponotic. The implications are that with the sole exception of dengue, arboviral diseases are noneradicable. Also, that via highly mobile reservoir hosts (birds and even human travelers), rapid and dramatic changes in arboviral epidemiology can easily occur. This idea was amply illustrated by the 1999 introduction of West Nile virus (WNV) to the Western Hemisphere.[4]

It should also be kept in mind that human arboviral pathogens are only a fraction of all arboviruses and that the potential for emerging infection is real.

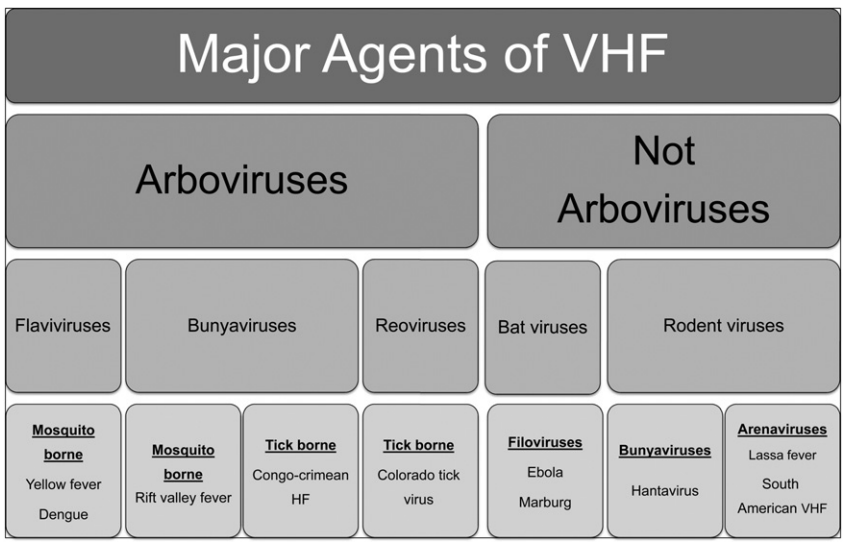

Fig. 1. Agents of viral hemorrhagic fever. Togaviruses, a large family of Arboviruses, are not included because they do not cause the VHF syndrome.

FLAVIVIRUSES

Of the 70 flavivirus species only a few are major human pathogens, including yellow fever, dengue, WNV, St Louis encephalitis (SLEV), Japanese encephalitis (JEV), Murray Valley encephalitis, and tick-borne encephalitis (TBE). As illustrated in **Fig. 2**, most of the world's population is at risk of flaviviral infections. A brief epidemiology of the major flaviviruses follows.

Dengue Virus

Dengue is by far the most prevalent human arboviral infection, with some 50 million infections yearly, and probably 500,000 fatalities.[5] Although a sylvatic cycle among Asian simians may exist,[6] dengue is largely an anthroponosis and may, therefore, be a target for eradication. Although well described since the eighteenth century,[1] the second half of the twentieth century had seen a spectacular growth in the burden of dengue. *Aedes aegypti,* the main vector of dengue virus, is extremely well adapted for survival in urban settings. The rapid urbanization of much of the tropics and subtropics has created ideal conditions for the vector, which, coupled with the dense human population and the long duration of viremia, underlies the burden of dengue. In fact, in many tropical locales in Southeast Asia, most of the adult population will have antibodies against all circulating dengue serovars.

Human activity (eg, car tire shipments) can lead to infected aedes mosquitoes being transported thousands of miles, resulting in the introduction of dengue to new areas. Thus, a massive outbreak of the dengue 2 virus (DEN-2) in Cuba in 1981 was in fact an introduction of the Southeast Asian virulent strain of DEN-2.[7]

Dengue is often perceived as a tropical disease. However, aedes mosquitoes range throughout the eastern seaboard of the United States. Autochthonous cases of dengue have been documented in Texas,[8] raising the threat of major urban outbreaks in the future. In Eurasia, *Aedes albopictus*, another dengue vector, is currently increasing its range throughout the Levant and Europe. Autochthonous cases of dengue have recently been documented in Croatia[9] and France.[10] In the twenty-first century, dengue is set to become everybody's problem rather than a third world disease.

Yellow Fever

Yellow fever is also a mosquito-borne flavivirus, transmitted by *A aegypti* from primate reservoirs. It occurs in sub-Saharan Africa, from Mauritania and Ethiopia in the north to

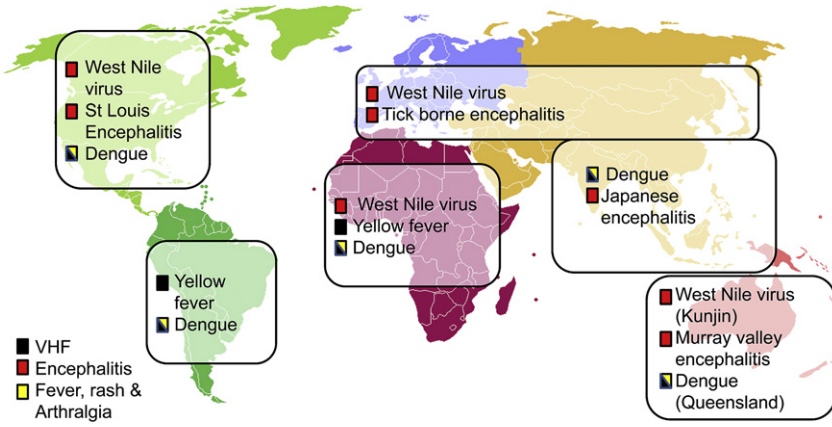

Fig. 2. Geographic distribution of major Flaviviruses.

Angola and Kenya in the south, and in most of tropical South America. However, its epidemiology is different in the two continents. In South America, sylvatic transmission is the rule and most cases occur in people traveling to the Jungle. In Africa, in addition to sylvatic transmission, urban transmission occurs, leading to occasional large-scale urban outbreaks. Most world cases are currently reported from Africa. In fact, in several West African countries, yellow fever is actually a reemerging disease, where the discontinuation of mass vaccination approximately 30 years ago has created a large, susceptible population.[11]

Japanese Encephalitis

The JEV serologic group of flaviviruses includes 8 virus species, including JEV, WNV, SLEV, Murray Valley encephalitis virus, and other minor species (see **Fig. 2**). Most of these viruses have avian hosts and are transmitted by culicine mosquitoes. For JEV, pigs may serve an important role as additional amplifying hosts. The range of JEV extends throughout East and Southeast Asia, from the Russian Far East in the north to the Torres Strait region in Northern Australia. Its range has been increasing in the latter half of the twentieth century. Within this vast range, several epidemiologic patterns exist: from marked seasonal outbreaks in temperate and monsoon dependent regions to holoendemic regions with year-round transmission. The actual burden of human disease differs greatly between regions, probably reflecting varying degrees of anthropophilia of local *Culex* species.[12]

SLEV and Murray Valley encephalitis virus are closely related to JEV and cause a similar neuroinvasive disease in the Americas and Australia respectively. SLEV was the leading diagnosed cause of viral encephalitis in the United States until it was eclipsed by WNV.[13]

West Nile Virus

WNV was initially described and recognized in Africa and the Levant. It is transmitted by mosquitoes from avian reservoirs and in many areas (eg, the Balkans and Israel) occurs seasonally, in time with the annual migration of birds from Eurasia to Africa. For reasons that are unclear, occasional years are epidemic. Thus, in 2000 and 2010, the incidence in Israel was markedly high.[14] In 1999, WNV was first detected in the Western Hemisphere. By 2005, it had spread throughout Latin America down to Argentina. However, although several large epidemics have occurred in the United States, minimal human disease has been described in Latin America despite active circulation in birds and horses.[4] Reasons for this absence are unclear but data suggests a role for antibodies against other flaviviruses (yellow fever and dengue), which are almost universal in many tropical locales.[4] Genomic studies suggest that WNV had spread to most regions (eg, Australia and India) through single introductory events, similar to the New York event in 1999.[15] Currently, clade 1 WNV dominates throughout most of Eurasia and the Americas. The possibility of new introductions of other African clades should be kept in mind.

Tick-Borne Encephalitis

Tick-borne flaviviruses that are human pathogens are all transmitted by hard (ixodid) ticks. Their natural reservoirs are mostly rodents, ungulates, and lagomorphs (rabbits, hares, and so forth). Their nomenclature used to be complicated by a bewildering variety of local names. Thus, the diseases known in the past as Russian spring summer encephalitis, Central European encephalitis, Far Eastern Encephalitis, and others are all in fact varieties of TBE.

Most tick-borne flaviviruses tend to be restricted to small endemic foci with human disease occurring in small numbers. Thus, Kyasanur Forest virus, its varieties of Alkhurma and Nanjianyin viruses, and the Omsk virus (all of whom cause a VHF syndrome) are restricted to southern India, Saudi Arabia, Western China, and Siberia respectively. TBE, however, is widely distributed in a great arc across Eurasia, from the Russian Far East to central Europe and Scandinavia.[16] Within this range, there are foci of hyperendemic disease, whereby most of the population tests seropositive. It is likely that the actual range of TBE is in fact larger (serosurveys suggest its existence in Italy and Anatolia for example);[17,18] however, cross-reacting antibodies to animal tick-borne flaviviruses hampers the interpretation of serosurveys if neutralizing antibody tests are not used. TBE can occasionally be acquired by the ingestion of milk from infected animals or by handling animal carcasses.

BUNYAVIRUSES

Bunyaviruses are a large family of RNA viruses that affect animals and plants. Of the 5 Bunyavirus genera, 4 include human pathogens: *Orthobunyavirus, Nairovirus, Phlebovirus*, and *Hantavirus* (**Fig. 3**). All but the Hantaviruses are Arboviruses and their epidemiology are discussed here.

Orthobunyavirus: Oropouche, Tahyna, La Crosse, and Related California Encephalitis Viruses

These phleboviruses are mosquito borne, with small mammals serving as reservoirs.

La Crosse virus is the most prevalent of the California virus group of Bunyaviruses (which also include California encephalitis virus and Jamestown Canyon virus. Its main hosts are squirrels and chipmunks. Most cases occur in the Mississippi and Ohio River basins during the summer months and are often associated with recreational activities in wooded areas.

Tahyna virus is another member of the California virus group. It is reported as a cause of a mild, nonspecific febrile disease from Central Europe to Russia and China and also in Africa.[19,20] It can occasionally be a cause of meningoencephalitis.

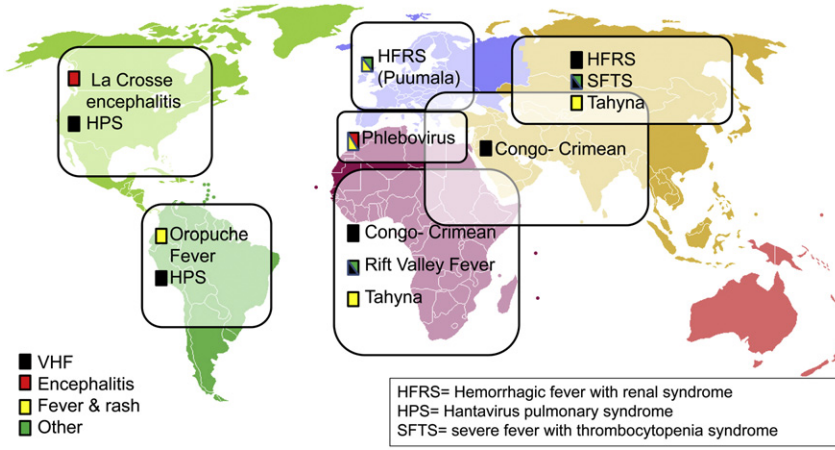

Fig. 3. Geographic distribution of major Bunyaviruses.

Oropouche is another Orthobunyavirus that is prevalent throughout much of South America and some Caribbean islands. It is unique in having a midge vector (*Culicoides paraensis*), which enables urban transmission. Large outbreaks have been described, especially in the Brazilian Amazon basin, where Oropouche is second only to dengue as a cause of arboviral fever.[21] In a recent study evaluating acute febrile patients in South America, Orthobunyaviruses were the third diagnosed group after dengue and the Alphaviruses. In this study, Oropouche was second to group C Orthobunyaviruses, a varied group of viruses that are clinically indistinguishable from the Oropouche virus.[22]

Nairoviruses: Congo-Crimean Hemorrhagic Fever

Congo-Crimean hemorrhagic fever (CCHF) is endemic in all of Africa, the Balkans, the Middle East, and Central and Southern Asia. *Hyalomma*, its principal tick vector, is found south of the 50°N, which serves as the northern geographic limit of the disease. Within this vast area, some countries report cases/outbreaks yearly, in others human cases have not been recorded despite evidence of viral circulation, and in some countries CCHF has not been recorded at all (eg, Israel, Jordan, and Lebanon). The largest number of cases is reported from Turkey, Iran, southern Russia, and Uzbekistan.[23]

Phleboviruses: Toscana and Related Viruses, Severe Fever With Thrombocytopenia Syndrome, and Rift Valley Fever

Phleboviruses differ markedly in their epidemiology, vectors, and clinical features.

Toscana, Sicily, Naples, and some other Phleboviruses are transmitted by Phlebotomine sandflies. Their natural reservoir host has not been definitely determined. They are prevalent in the Mediterranean region, where they cause sandfly fever (also known as papataci fever), a nonspecific febrile disease often with rash and myalgias. However, they also cause meningitis and encephalitis. In fact, in some countries, such as Italy, Toscana virus has been found to be a major cause of aseptic meningitis during the summer months.[24]

Severe fever with thrombocytopenia syndrome (SFTS) is a newly described phleboviral disease that has caused several outbreaks in China. Although details are sparse, it is probably transmitted by tick bites, causing a mild nonspecific fever but occasionally severe illness with multiorgan failure, bleeding, and 12% fatalities.[25] Recently, additional data from China raises the possibility of person-to-person transmission of SFTS via contact with infected blood.[26] The extent of this infection is still not clear. However, its probable vector, *Haemaphysalis longicornis*, is prevalent throughout much of East Asia and Oceania: from China, Korea, and Japan to Australia, the Pacific Islands, and New Zealand.

Rift Valley fever virus (RVFV) has long been recognized as a major cause of severe VHF in Africa. RVFV is transmitted by aedes mosquitoes. It is endemic throughout arid and savannah areas of sub-Saharan Africa and mostly affects ungulate hosts.[27] As such, it can cause large-scale epizootics among livestock. During epizootics, many human cases are probably not transmitted through mosquitoes but rather through the handling of infected animals and ingestion of contaminated meat and milk. In 2000, a large outbreak of RVFV occurred in the Arabian Peninsula, with more than 800 cases in Saudi Arabia and many more in Yemen.[28] More recently, an RVFV outbreak in South Africa has led to nearly 200 cases, mostly among farmers and veterinarians, resulting in the death of 10% of the affected population.[29]

REOVIRUSES

Reoviruses comprise a numerous family of animal and plant viruses, including such human pathogens as rotavirus. Arthropod-borne reoviruses belong to 2 genera: Coltiviruses, which are tick-borne, and Seadornaviruses, which are mosquito-borne (**Fig. 4**).

Coltiviruses: *Colorado tick fever virus* is found in the Rocky Mountain region of the United States and in Canada. The virus's distribution follows that of its vector, *Dermacentor andersoni*.[30] Additional Coltiviruses circulate in this area, including the Salmon River virus and perhaps others. All cause a similar illness: a nonspecific fever that is sometimes accompanied with rash and occasionally with meningoencephalitis. *Eyach virus* is a Coltivirus circulating in Central and Western Europe, which causes a similar disease.[31]

Seadornaviruses: These mosquito-borne viruses have only been associated with human disease in the last 2 decades. *Banna virus* is associated with febrile disease and with meningoencephalitis in China. It can infect a variety of vertebrate hosts. The virus may in fact circulate throughout much of Southeast Asia where cases are commonly mistaken for those of the cocirculating JEV.[32] Additional Seadornaviruses are currently known and are at the frontier of emerging infection research. To date, similar viruses have not been documented outside of Asia.

TOGAVIRUSES: ALPHAVIRUSES

All human Alphaviruses are mosquito borne. As illustrated in **Fig. 5**, they exist on all continents. In addition to encephalitis and fever with rash, Alphaviruses can cause a unique form of viral arthritis that can lead to prolonged morbidity, which will be described later.

Chikungunya Virus

Chikungunya virus (CHIK) emerged in Africa where it is maintained by primate reservoirs and transmitted by aedes mosquitoes. Urbanization, by combining a large concentration of susceptible hosts and allowing explosive proliferation of aedes mosquitoes, has enabled large epidemics of the disease. CHIK was documented in Southeast Asia early in the twentieth century; in fact, when dengue hemorrhagic fever

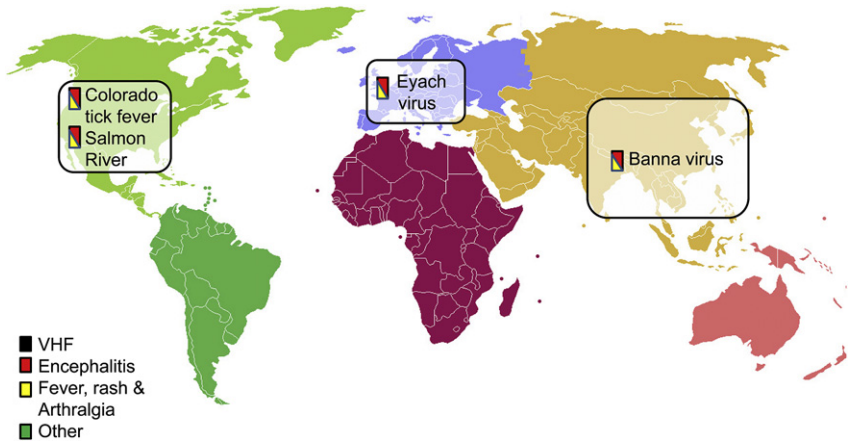

Fig. 4. Geographic distribution of major reoviruses.

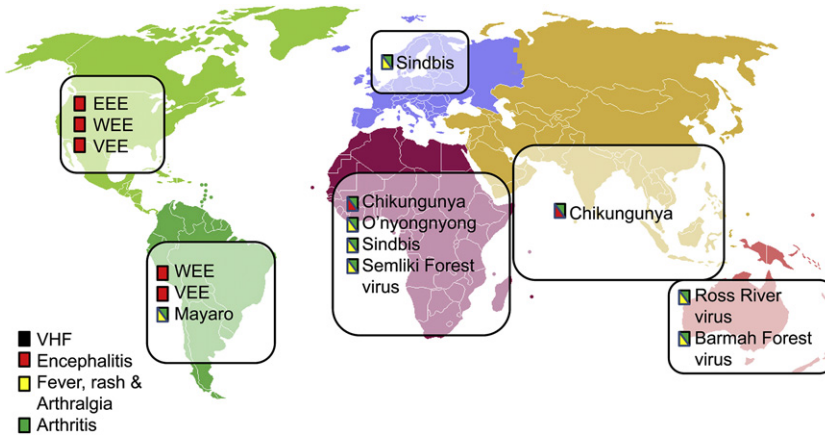

Fig. 5. Geographic distribution of major Alphaviruses. EEE, Eastern equine encephalitis; WEE, Western equine encephalitis; VEE, Venezuelan equine encephalitis.

(DHF) emerged in Thailand in the 1960s, CHIK was initially considered as a possible causative agent.[33] More recently, in 2005, a massive outbreak of CHIK developed in the Mascarenes, involving most of the population in Reunion and Mauritius. From this focus, CHIK involved many Indian Ocean countries, affecting especially India, where 1,400,000 of cases occurred.[34] The reasons for the dramatic Indian Ocean outbreak remain unclear. However, genetic studies have demonstrated viral point mutations causing enhanced viral transmission by aedes albopictus mosquitoes.[35]

Aedes albopictus (commonly referred to as the Asian tiger mosquito) is an emerging vector with increasing presence in many regions. It has become established in the Middle East and in some Southern European countries. In 2006, more than 200 cases of CHIK were diagnosed in the Emilia-Romagna region in Northern Italy. The outbreak was probably initiated by a viremic traveler returning from India in an area where *A albopictus* was well established.[36] In 2010, an autochthonous case of CHIK was diagnosed in Southeast France, again resulting from an Indian strain introduced by travelers.[37] The likelihood of similar importations in the future is high.

Other Arthritogenic Alphaviruses

Semliki forest and *O'nyongnyong* circulate in tropical Africa and cause a disease similar to CHIK.[38] For unclear reasons, CHIK predominates, whereas the others tend to cause smaller and rarer outbreaks. *Mayaro virus* is endemic to tropical regions of South America. Outbreaks have been described in Manaus, Brazil, Venezuela, and elsewhere.[39] The main Alphaviruses occurring in Australia are *Ross River virus* (RRV) and *Barmah Forest virus* (BFV). In 2008, more than 7000 cases have been reported in Australia, composing 78% of all arboviral infections.[40] RRV and BFV are mostly reported from Queensland and New South Wales.

Sindbis virus is a mosquito-borne Alphavirus. It shares avian reservoirs and Culicine vectors with WNV. In agreement with bird migration in Eurasia, Sindbis is documented from Scandinavia to South Africa. However, for reasons that are unclear, human disease is largely limited to the extremes of this range. In the northern reaches of Scandinavia and Western Russia, a disease typified by fever, rash, and arthropathy is variously known as Pogosta, Karelian fever, and Ockelbo disease.[41] Disease activity seems to peak in a 7-year cycle.

Encephalitic Alphaviruses: Eastern, Western, and Venezuelan Equine Encephalitis Viruses

These viruses are restricted to the Americas. Eastern equine encephalitis (EEE) virus is a summertime disease in the Gulf and east coastal areas of the United States, whereas Western equine encephalitis (WEE) virus is mostly diagnosed in states west of the Mississippi River. EEE is maintained in avian hosts, with horses and humans serving as dead end hosts because viremia is usually low. WEE causes higher-level viremia, and horses may, therefore, have a larger role in the virus ecology. Venezuelan equine encephalitis (VEE) virus is maintained in an enzootic cycle among rodents in South America. Intermittently, some strains cause large epizootics among horses, with concomitant epidemics in humans. The largest in recent times has been an epidemic in Venezuela and Colombia, which, in 1995, caused an estimated 100,000 human cases, 3000 of which experienced neurologic complications, with 300 associated deaths.[42] As these numbers suggest, most cases of VEE do not evolve into severe neuroinvasive disease. It is probable that in endemic countries a significant portion of disease currently diagnosed as dengue fever may in fact be attributed to VEE.[43]

NONARBOVIRAL AGENTS OF VHF: FILOVIRUSES, ARENAVIRUSES, AND HANTAVIRUSES

The VHF syndrome is not unique to Arboviruses. In fact, some of the most virulent agents of VHF are not Arboviruses. Arenaviruses and Hantaviruses have rodent reservoirs in common, and infection is usually caused via exposure to rodent excreta (**Fig. 6**). Filoviruses are probably bat viruses. Much regarding their epidemiology is conjectured, but human exposure may result from exposure to bush meat. Infected wild animals, such as apes or ungulates, may have acquired the virus via ingestion of fruit dropped by bats and contaminated by their saliva.[44] Some of these agents are unique among all the VHF agents in their ability for human-to-human infection. This fact underlay the inadvertent creation of hospital-based epidemics of VHF.

Filoviruses: Ebola and Marburg Viruses

The filoviruses derive their name from their elongated, hairlike appearance on electron microscopy. Human pathogenic filoviruses are restricted to Africa (a nonvirulent

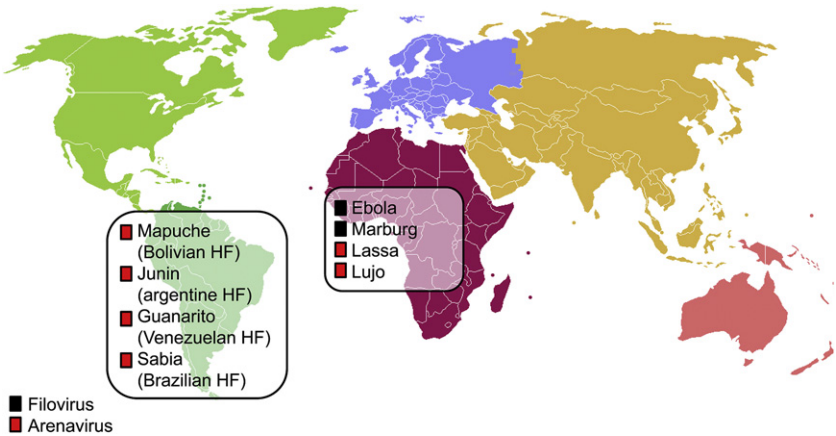

Fig. 6. Geographic distribution of Arenavirus and Filovirus agents of VHF.

filovirus, Ebola Reston, has been detected in the Philippines). Their natural hosts are fruit bats that occur from Gabon to Sudan in the north to Angola in the south.

Ebola epidemics or cases have been recorded in the Democratic Republic of Congo, Sudan, Cote d'Ivoire, and Uganda, with different serotypes in each case. As was seen in the first Ebola outbreak in Yambuku, Zaire,[3] close contact with infected persons was the main risk factor for infection. Hospitals, through the reuse of syringes, and absence of minimal infection-control measures, have served as the most important form of disease dissemination. However, with standard infection-control measures, the likelihood of secondary cases is probably low. This can be inferred from a case of Ebola that was treated in a South African hospital. Despite the fact that the diagnosis was only made after the patient was discharged from hospital, of more than 300 hospital personnel with significant exposure, there was only one secondary case and that was in all likelihood attributed to a needle-stick exposure.[45] Another important epidemiologic feature of Ebola virus VHF is that the testis is often involved in the infection (sometimes with clinical orchitis) and that viral shedding in semen may continue for weeks. Prevention of sexual transmission through barrier control or abstinence until negative viral culture is, therefore, important.

Marburg virus owes its name to the first recorded outbreak, which involved imported West African green monkeys and laboratory personnel in Marburg, Germany. More recently, large epidemics have been documented in Angola. Gold mining has been associated with Marburg outbreaks,[46] with exposure to bat excreta as the probable link. However, here, as with Ebola, hospitals served as outbreak amplifiers, mainly through the absence of barrier nursing and the reuse of injection equipment in vaccine administration.[47]

Arenaviruses: Lassa Fever and South American HF Viruses

Arenaviridae is a large family of viruses, most of whom are not pathogenic to humans. All share rodents as natural reservoir hosts. Humans mostly become infected through ingestion or inhalation of rodent ejecta, directly or through contaminated food. As illustrated in **Fig. 6**, VHF caused by Arenaviruses is restricted to Africa and South America. Other Arenaviruses cause neuroinvasive disease, including the globally distributed *Lymphocytic choriomeningitis virus* and the more recently recognized *Whitewater Arroyo* virus in the United States, but are not be discussed here.

Lassa fever is restricted to West Africa. Its reservoir is the multimammate rat (*Mastomys natalensis*), which is a highly prevalent peridomestic rodent. It is not surprising, therefore, that the annual number of Lassa cases in West Africa may be as high as 300,000.[48] Similar to the Filoviruses, Lassa can be transmitted from person to person, through close contact, and probably sexual contact. Secondary cases among hospital personnel are not rare.

The South American VHFs: Argentinean, Bolivian, and Venezuelan HF are caused by *Junin, Machupo, and Guanarito* viruses respectively. Brazilian HF is caused by another lethal Arenavirus, *Sabia virus*, but is only recognized from one known natural case and 2 laboratory accidents.[49]

All South American VHFs are probably acquired by exposure to rodents, mostly in agricultural and rural settings, either through direct contact, aerosolization of rodent body fluids in harvest machinery, or via food contamination. Occasional secondary cases, with household or hospital exposure, have been described[50]; however, the incidence of person-to-person transmission is probably much lower than for Lassa fever.

Hantaviruses

Hantaviruses are extant in both the Old World and the New (see **Fig. 3**). All are hosted by rodents, and person-to-person transmission is not important for these Bunyaviruses. In Eurasia, Hemorrhagic fever with Renal Syndrome (HFRS) is recognized from Eastern Russia, Korea (where the virus was first recognized), and China to the Balkans (where it is known as Dobrava disease or Balkan nephropathy). The agents of HFRS, *Hantaan virus* and *Dobrava virus,* predominate in Eastern Asia and in Europe respectively and are hosted by field mice; most cases are described in rural areas, with dramatic differences in incidence even within countries. Thus, in China, northeastern provinces account for most cases, with peak incidence in the spring and fall.[51]

Puumala fever is a milder form of HFRS, it is also known as nephropathia epidemica or vole fever. Its reservoir hosts are indeed voles, which inhabit both rural and suburban habitats. Puumala is mostly recognized in Northern Europe, including Scandinavia and Western Russia. The true incidence of Puumala is probably grossly underestimated. Even so, thousands of cases are reported yearly in Europe.[52] An unusual feature of Puumala is a cyclic surge in cases. Vole populations tend to peak every several years, probably in association with abundant mast seasons in European beech forests, which may correlate with increases in human disease.[53]

An additional *Hantavirus*,– *Seoul virus*, is hosted by the gray rat (*Rattus norvegicus*) and in fact is distributed globally, along with its host. Surprisingly, few cases are recorded worldwide but some have occurred in facilities and personnel involved with animal medical research.[54]

In the Americas, a phylogenetically divergent group of Hantaviruses causes a different disease: Hantavirus pulmonary syndrome (HPS). In addition to *Sin Nombre virus,* the type species isolated during the first recognized outbreak of HPS in 1993, many other species exist from Canada to Argentina, each with its attendant rodent host.[55] There are large differences in the virulence of Hantavirus strains in the Americas. Thus, although HPS has been described only occasionally from Latin American countries, the true incidence of Hantavirus infections is much higher. For example, the seroprevalence of Hantavirus infection in rural communities in Panama ranged from 16.5% to 60.4%; however, all acute cases presented with a nonspecific fever and none with HPS.[56]

CLINICAL FEATURES: MAIN SYNDROMES

It is unfortunately beyond the scope of this article to describe in detail the clinical features of each of the agents previously discussed. However, despite the large number of agents, most cases will fall within a few clinical syndromes. A few illustrative examples are given here. It should be kept in mind that apart from a few agents like Ebola, most cases of most arboviral diseases will not be typical but rather nonspecific febrile illnesses or even clinically unapparent infections.

Fever With Rash and Arthralgia: Classical Dengue Fever

After an incubation period of 4 to 7 days, fever develops abruptly and is often accompanied by severe frontal headache and retro-orbital pain. Severe musculoskeletal and lumbar pain combined with hyperesthesia of the skin may interrupt locomotion. Anorexia, vomiting, and loose stools may occur. After 3 to 4 days, with defervescence, an indistinct macular/scarlatiniform rash develops, sparing the palms and soles; areas of spared skin within the rash are typical and are evocatively described as white islands in a red sea. A second bout of fever and symptoms may ensue (saddleback pattern). Localized clusters of petechiae and minor bleeding (eg, epistaxis) can occur.

As described by Rush,[1] recovery may be followed by a prolonged period of listlessness, easy fatigability, and even depression; the disease was also aptly named break-heart fever.

The VHF Syndrome

The symptoms of VHF result from a combination of endothelial dysfunction that causes a capillary leak syndrome, and a bleeding diathesis caused by thrombocytopenia and diffuse intravascular coagulation. The resultant shock leads to death, although specific organ dysfunction (eg, brain, liver, heart, lungs, and gut) may contribute to the picture.

Typical VHF: Dengue Hemorrhagic Fever/Dengue Shock Syndrome

DHF/Dengue Shock Syndrome (DSS) is mostly described in infants but may occur in all age groups. In a small minority of patients with dengue, defervescence is accompanied with signs of shock manifested by central cyanosis, restlessness, diaphoresis, and cool, clammy skin and extremities. Abdominal pain is a common complaint. A rapid and weak pulse, a narrowing of the pulse pressure to less than 20 mm Hg, and in the most extreme cases, an unobtainable blood pressure are accompanied by diffuse petechiae, ecchymoses, and bleeding from mucosal and venipuncture sites. Noncardiogenic pulmonary edema and myocardial dysfunction may complicate the course. However, capillary leakage usually resolves spontaneously in 48 hours with a rapid resolution of the VHF syndrome.

Most Severe VHF: Ebola Virus

After an incubation period that ranges from 2 to 19 days, fever begins abruptly, accompanied by myalgia and headache. The fever is joined by some combination of nausea and vomiting and especially diarrhea, abdominal, and chest pain. Other common features include photophobia, conjunctival injection, sore throat, and lymphadenopathy. Central nervous system involvement is often manifested by somnolence, delirium, or coma. As the disease progresses, bleeding manifestations, such as petechiae, hemorrhages, ecchymoses around needle puncture sites, and mucous membrane hemorrhages, occur in most patients. Around day 5, most patients develop a maculopapular rash, prominent on the trunk, followed in a few days with either recovery or death from shock and multiorgan dysfunction. Convalescence is protracted and may be accompanied by arthralgia, orchitis, recurrent hepatitis, uveitis, and rarer phenomena.

VHF with prominent liver involvement (*yellow fever*): The course of yellow fever follows a saddleback, 3-stage pattern. These stages were described since very early times as the early period of infection, indistinguishable from early dengue as described previously, a period of remission whereby after several days the fever resolves for a few hours to several days, and then a period of intoxication whereby a capillary leak leads eventually to multiorgan failure and death. During this period, severe hepatitis causes clinical jaundice (the source of the disease's name) and is accompanied by encephalopathy and by mucosal and other bleeding, especially from the gut (the ominous black vomit). Although jaundice may be profound, should patients survive this period, recovery is usually complete without chronic liver damage.

VHF with prominent kidney involvement (*hantavirus HFRS*): After an incubation period of typically 2 weeks, fever, headache, myalgias, conjunctival injection, and blurred vision develop, followed by a blanching erythematous rash. After 4 to 7 days, a severe capillary leak syndrome ensues, with shock, oliguria, and bleeding phenomena. This phase, if not fatal, is resolved by a period of polyuria, heralding renal

recovery, and protracted asthenia. Milder forms, such as Puumala, although lacking the VHF phase, will still evolve through an oliguric and polyuric phase, usually with hematuria and proteinuria. Although cases of severe HFRS usually resolve completely, the milder forms may lead to chronic renal injury and contribute to hypertension and chronic renal failure in endemic locales.

VHF with prominent pulmonary involvement (*hantavirus HPS)*: HPS presents as a nonspecific fever, similar to early HFRS. However, after usually 4 to 5 days, mild cough and dyspnea rapidly evolve to noncardiogenic pulmonary edema and respiratory failure. This pulmonary capillary leak syndrome is of short duration and should patients survive with supportive care, rapid and complete recovery will occur in a few days.

Arboviral encephalitis: There is little to distinguish arboviral from other causes of encephalitis. However, it is important to recall that apart from a generic encephalitic syndrome of fever, headache, altered consciousness (and possibly seizures), almost any form of acute neurologic syndrome has been described, including meningitis, acute flaccid paralysis mimicking polio, cranial neuropathies, polyradiculopathies, cerebellitis with ataxia, or damage to basal ganglia, with late-onset parkinsonism. A varying proportion of patients remain with long-term sequelae.

Alphavirus arthritis (*Chikungunya)*: Although arboviral encephalitis is similar to other encephalitides, *Alphavirus arthritis* is a unique syndrome. Following an incubation period of up to 12 days, fever ensues, accompanied by headache, photophobia, retro-orbital pain, pharyngitis, and vomiting. An accompanying blanching erythematous or maculopapular rash completes this early denguelike picture. Fever may abate and recrudesce, giving rise to a saddleback pattern. Arthralgia is, however, the leading feature, often polyarticular, involving small joints and sites of previous injuries; joints may swell without significant effusion. These symptoms may last from 1 week to several months and are accompanied by myalgia. Studies following the large Indian Ocean outbreak have demonstrated that a significant proportion of patients will be disabled for 2 years and more.[57] Follow-up of large numbers, with the use of advanced laboratory and imaging methods, has shown persistent arboviral arthritis to be an active inflammatory process, with erosive arthritis.[58] The implications regarding the long-term morbidity burden of Alphavirus outbreaks when millions of cases are infected are clear.

DIAGNOSIS OF VHF

As can be expected from the earlier descriptions, an exhaustive differential diagnosis of VHF-causing agents may include most of the medical conditions affecting humans and is, therefore, beyond the scope of this review. Indeed, milder forms of infections of VHF agents can be mistaken for anything between influenza, gastroenteritis, primary HIV, syphilis, and so forth. However, when considering the manifestations of severe forms of VHF, whether one is practicing in endemic regions or caring for returning travelers, it is important to keep in mind fulminant hepatic failure from viral hepatitis or toxins, severe leptospirosis (Weil disease), malaria, typhoid, rickettsial diseases, and Borrelia with relapsing fever.

The diagnosis of a specific agent can be achieved by either demonstrating seroconversion or by viral isolation. However, viral culture should only be attempted in well-equipped Biosafety level-4 laboratories because most of the VHF agents pose a real risk for laboratory personnel. The viral RNA can be demonstrated by polymerase chain reaction in blood samples during acute illness; however, for some agents, viremia is brief and at a low level, and the negative predictive value of genomic tests is variable and tends to be low. Serum antigen tests exist commercially for a few of

these agents (eg, NS-1 protein for dengue). A definitive serologic diagnosis usually requires plaque reduction studies, which may only be available at a national or even international level. A variety of serologic tests are marketed for many of the major arboviral agents. However, these are hampered by cross-reactivity between many Arboviruses. In the case of travelers, interpretation is further complicated by previous *Flavivirus* (yellow fever, JEV, and TBE) vaccination.

TREATMENT AND PREVENTION OF VHF

In the management of the 1873 Memphis yellow fever epidemic, iced champagne was highly recommended (and gratefully received).[2] It is unfortunate that for most of the VHF agents, therapeutics have not greatly improved. Supportive care, with fluid repletion, correction of coagulopathy, and specific target organ support (from dialysis to ventilatory support) are the mainstay of treatment. For simpler forms of VHF, such as DHF/DSS, supportive care with intravenous volume repletion leads to a fatality rate that should not be more than 1%.[4]

Exceptions to this rule are Arenavirus infections. Ribavirin, a purine nucleoside, was found to be highly effective in patients with Lassa fever in all stages of the disease. If given before the seventh day of illness, ribavirin reduced the mortality rate from 55% to 5%.[59] Although the evidence base for its use in other Arenavirus infections is less rigorous, ribavirin is also recommended for cases of South American HF viruses.[60] Some evidence suggests that ribavirin may be beneficial in early Hantavirus HFRS[61]; however, its use in HPS has not been shown to be beneficial.[62]

With the absence of effective therapies for most agents, the onus has remained on prevention. Improved housing, rodent proofing, and vector control seem to be straightforward measures. However, urbanization and perhaps even climate change have actually increased the scope of some vectors, which is manifested by the resurgence of *A aegypti* and the spread of *A albopictus*.

The twentieth century saw the introduction of some arboviral vaccines: the yellow fever vaccine, one of the most successful in history, Japanese encephalitis vaccine, and the TBE vaccine (in Europe). However, for all other arboviruses, there is no vaccine available.

For no arboviral disease is a vaccine more urgently needed as it is for dengue. A plethora of vaccine candidates has been discussed in the literature over decades; at long last a vaccine candidate, Sanofi Pasteur's live, attenuated tetravalent dengue vaccine (based on a yellow fever 17D vaccine strain), is currently undergoing field trials and may enter phase 3 trials soon.[63] That many of these infections are neglected tropical diseases has all but abolished the economic incentive of pharmaceutical companies for development of arboviral vaccines.

SUMMARY

As they have in the past, VHFs continue to pose a major threat in most world regions today. VHF agents, especially arboviruses, are at the forefront of emerging infection detection. The absence of specific therapy and vaccine prevention for most of these pathogens poses a grave concern for human health in the developing and developed worlds alike.

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