Arboviruses: A Family on the Move

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Abstract

Arboviruses are a diverse group of vector-borne viruses, many of whose members are the cause of significant human morbidity and mortality. Over the last 30 years, the emergence and/or resurgence of arboviruses have posed a considerable global health threat. The ongoing geographical expansion of the dengue viruses (DENV), along with the explosive outbreaks of West Nile virus (WNV), Chikungunya virus (CHIKV) and more recently, Zika virus (ZIKV) have all served as reminders that new epidemics may emerge at any time from this diversity. A clearer understanding of what mechanisms drive these dramatic changes in vector-host transmission cycles that result in the human population becoming significantly more exposed, will help to prepare us for the next emerging epidemic/pandemic. This Chapter seeks to provide a brief overview of the arboviruses, their mode of transmission and some of the known factors that drive their expansion.

Keywords

Arthropod-borne viruses · Zoonotic infections · Virosphere · Arbovirus transmission · Climate change impacts

1.1 Introduction

Arboviruses (a term derived from the descriptor, **ar**thropod-**bo**rne **viruses**) are an amazingly diverse group of viruses that are transmitted from infected to susceptible hosts by a range of arthropod vectors that include mosquitoes, ticks, sand flies or biting midges [20, 21]. Following ingestion of a blood meal from an infected host, viruses multiply in the insect mid-gut and then invade underlying tissues to cause a spreading infection (collectively referred to as the extrinsic incubation period) that ultimately results in a high-titred viral load, particularly in the salivary glands. They are then passed on to humans or other vertebrates during insect biting. Most diseases caused by arboviruses are zoonoses, primarily infections of vertebrates that can occasionally cause incidental infection and disease in humans. Notable exceptions to this are the dengue viruses (DENV), as humans are the primary vertebrate host. Indeed, passage through humans is essential in maintaining the virus transmission cycle. The nature of this two-way dependency prompted Duane Gubler to once remark that "humans could

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R. Hilgenfeld, S. G. Vasudevan (eds.), *Dengue and Zika: Control and Antiviral Treatment Strategies*, Advances in Experimental Medicine and Biology 1062,
https://doi.org/10.1007/978-981-10-8727-1_1

be considered the vector for dengue virus infection in mosquitoes". While monkeys have been implicated as an alternative vertebrate host to humans for dengue in rural settings, it is unlikely that this sylvatic cycle contributes much to the current global impact of this apex arbovirus.

By definition, arboviruses are arthropod-borne, however some are grouped within the arboviruses despite no apparent association with an arthropod vector, primarily because of their close genetic relationship. The naming of individual arboviruses has had a somewhat eclectic history with no formal taxonomic approach having been established. Some refer to dialect names after the illness they induce (chikungunya, o'nyong-nyong, dengue), others recognise the name of the location where they were first discovered (West Nile, Bwamba, Ross River, Zika) and some reflect a characteristic clinical presentation (Western equine encephalitis, yellow fever) [21].

Over the course of the last two decades, a dramatic expansion in the territorial range of a number of arboviruses has seen a significant increase in global epidemic activity. These include West Nile virus and its emergence in New York in 1999 and subsequent march across the North American continent over the next 4 years and subsequent spread, both north and south over the following decade. Chikungunya virus with its sudden expansion on La Reunion in 2005 and spread across the Indian subcontinent, South East Asia and globally. The ongoing expansion of the dengue viruses across the tropical zone and beyond, and of course, the recent explosive epidemic of Zika virus in South America, on the other side of the world from its first isolation in an African forest some 70 years previously. One thing is certain; we will see more of these outbreaks in the years to come [1, 9]. As a brief introduction to the research efforts detailed in the following Chapters, this review provides an overview of the group of viruses we collectively refer to as arboviruses, and addresses some of the issues that are helping to drive their expansion.

1.2 Who Are They?

More than 500 arboviruses have been recognised worldwide [21], a number that is undergoing rapid and exponential revision as researchers interrogate the virosphere using deep sequencing [19]. Estimates have suggested that the arboviruses we have recognised to date may represent less than 1% of the total. Only some of the currently known arboviruses, some 150, are known to cause human disease [21]. Some infect humans only occasionally or cause only mild illness, whereas others are of significant medical importance, causing large epidemics.

Most arboviruses causing human disease belong to three families; Togaviridae (genus *Alphavirus*), Flaviviridae (genus *Flavivirus*) and Bunyaviridae (*Bunyavirus*, *Orthobunyavirus*, *Nairovirus* and *Phlebovirus* genera), with members of three further families, Rhabdoviridae, Orthomyxoviridae and Reoviridae also contributing (Fig. 1.1). The alphaviruses and flaviviruses are enveloped, linear single-stranded, positive-sense RNA viruses. They are spherical in shape, with an underlying capsid and measure from 40 to 70 nm. The bunyaviruses are enveloped, segmented, circular negative-strand RNA viruses. They are generally spherical and measure 80–120 nm in diameter.

The most important group, at least from a human disease perspective, are the flaviviruses with a number of viruses in this group being of global health concern; dengue virus (DENV), West Nile virus (WNV), Zika virus (ZIKV) and yellow fever virus (YFV) [11]. Others, including Japanese encephalitis virus (JEV), tick-borne encephalitis virus (TBEV), Venezuelan equine encephalitis virus (VEEV) and St. Louis encephalitis virus (SLEV) are usually restricted to specific regions. However, the spread of arboviruses across several regions have lead to major international health concerns. WNV with its jump from the Middle-East into the Americas, chikungunya virus (CHIKV) moving into islands in the southwest Indian Ocean, and from there to Southeast

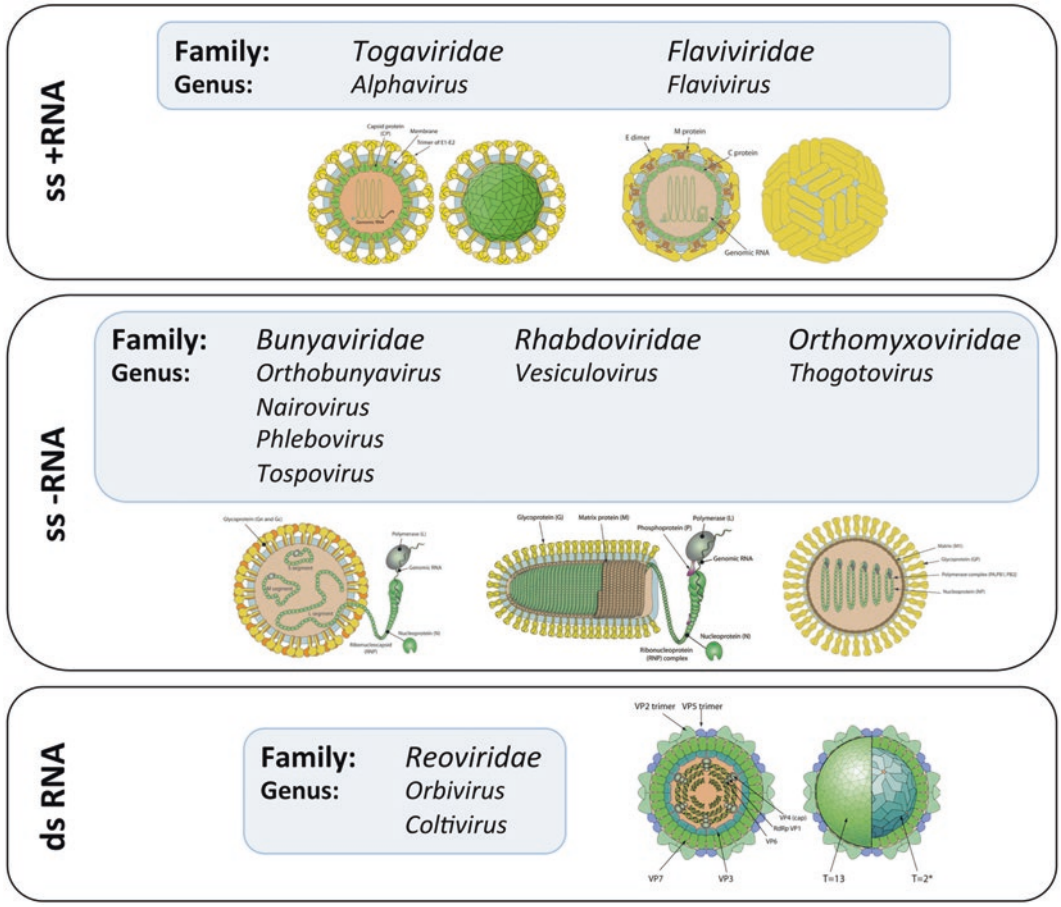

Fig. 1.1 Arboviruses and virion schematics. Viruses are grouped according to genome composition: single-stranded positive-sense RNA, ss + RNA; single-stranded negative-sense RNA, ss-RNA; double-stranded RNA, dsRNA. Arboviruses that are associated with human disease are mostly found within the Togaviridae, Flaviviridae and Bunyaviridae families. Virus schematics provided by ViralZone, Swiss Institute of Bioinformatics

Asia and the Americas, and Zika virus which spilled out of Africa to Southeast Asia, the islands of Polynesia and then to Brazil in an explosive epidemic in 2015–2016 (Fig. 1.2).

1.3 How Are They Maintained and Spread?

Three key elements are required for effective maintenance of arbovirus transmission: the vector (mosquito, tick, sandfly, biting midge), the vertebrate host(s) and appropriate environmental conditions. Some transmission cycles are relatively simple (involving one vector and one host, e.g., DENV and ZIKV) while some are highly complex (involving multiple vectors and hosts, e.g., JEV, WNV and Rift Valley Fever virus, RVFV). The epidemiology of human arboviral disease usually involves one of two transmission cycle scenarios (Fig. 1.3). In the first, the virus is stably and naturally maintained via transmission between vectors and wild animals in a sylvatic (jungle) cycle with spillover occurring when an infected arthropod bites either a domestic animal or human that has strayed into that ecological niche. This mode of infection results in small clusters of cases initiated at the same site. The second is the urban cycle where a person or domestic animal, infected via the sylvatic mode

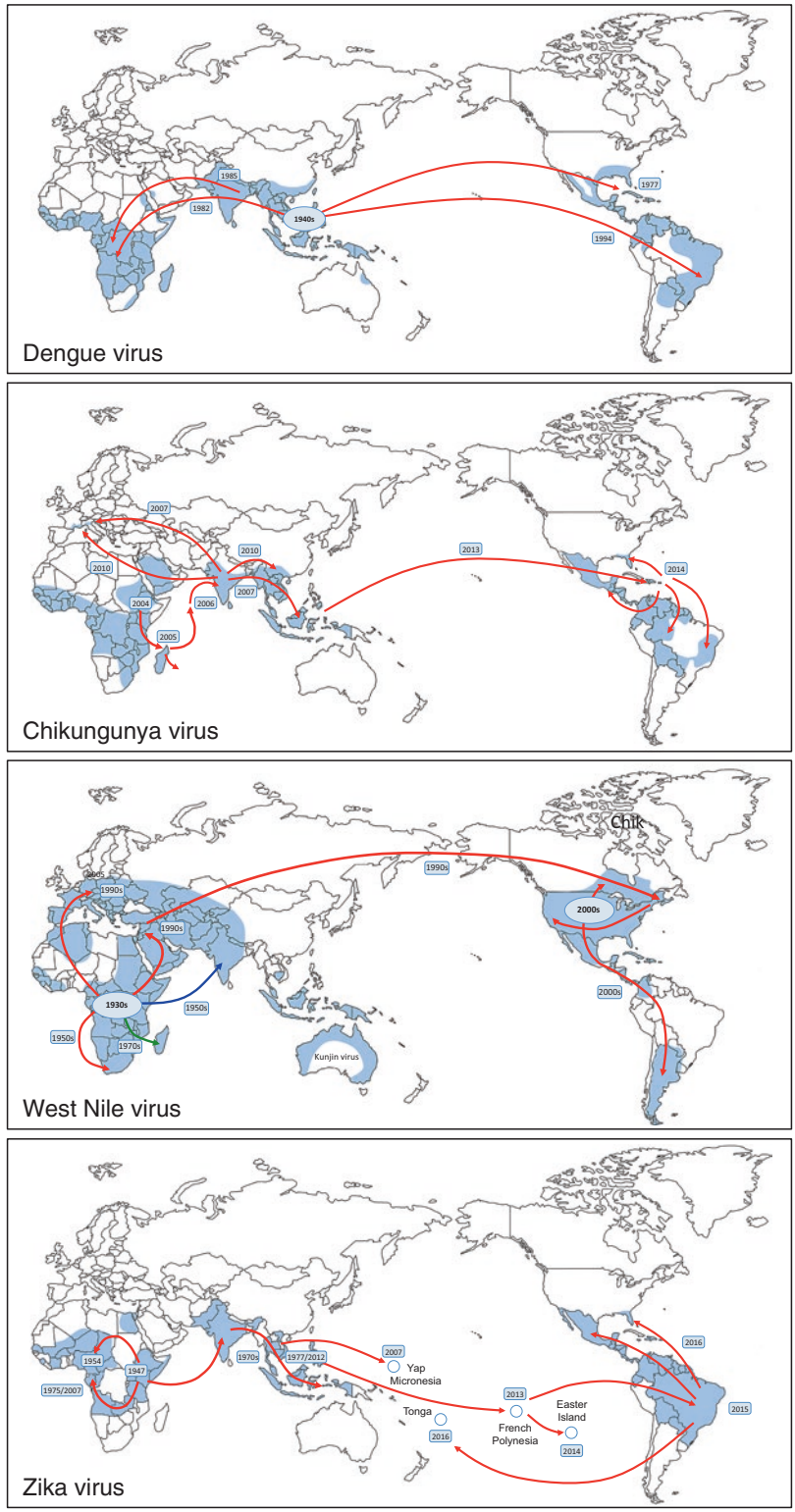

Fig. 1.2 Arbovirus epidemiology. Four examples of arboviruses that have emerged as globally distributed threats to human health. Geographical regions shaded in blue indicate historical, ongoing and recent viral activity with dates highlighting key epidemic translocation events. Dengue virus (DENV); the four serotypes of dengue virus

or moving from another area with urban activity, acts as an amplifier host in the transfer of the virus to other persons or domestic animals in the community. These cases occur as epidemics or epizootics in nature (Fig. 1.3) The vector involved in the urban cycle may be the same or different to that in the sylvatic cycle and indeed, there may be multiple vector species playing a role in transmission in either cycle.

The primary arboviral hosts are mammals and birds with the potential for virus dispersal depending on the type of vertebrate host involved [21]. Migratory birds can facilitate virus movement over large distances, such as occurred with the spread of WNV through the Americas, whereas transmission through most terrestrial hosts result in virus activity that is restricted to a particular region.

Animal hosts that are essential for arbovirus transmission and for the maintenance of virus populations are referred to as reservoir hosts, with the immune status of these hosts impacting on transmission rates. Their long co-evolution with their viral passengers is characterised by high titre viraemia that enables vector mediated virus transmission to occur, often in the absence of overt disease. A wide variety of reservoir host species have been implicated in arbovirus diseases. These include birds, mammals (including primates), rodents, marsupials and bats. Individual arboviruses may have more than one host species involved in transmission cycles. For example, birds (herons in particular) are considered to be the major maintenance hosts for the flavivirus JEV. In Asia however, pigs have also been shown to amplify the virus to high titres. Feeding mosquitoes can therefore be readily infected, with transmission of the virus to humans who live in close proximity. The life cycle of Ross River virus (RRV) in Australia involves complex relationships between multiple vectors and zoonotic (marsupials, horses, possums, bats) reservoirs across multiple environments including urban, inland (freshwater wetlands) and coastal (estuarine wetlands) regions [3].

Host species may move virus from an area of active transmission to another location. Movement by viraemic waterbirds has been suggested as a mechanism of spread for a number of arboviruses including Murray Valley encephalitis virus (MVEV), JEV, WNV and Eastern equine encephalitis virus (EEEV). Arboviruses can also be introduced into new areas by the movement of humans, particularly as air travel now enables movement between two destinations anywhere in the world, all within the time window of a typical viraemic period. Infected arthropod vectors may also disseminate disease if they are carried on air, marine, rail or road transport. This has been pro-

Fig. 1.2 (continued) continue to spread across the globe, with serotype subsets cycling in sequence with developing local herd immunity and virus evolution. The sudden and dramatic expansion of dengue in the early 1940s with the influx of naive adult hosts during the Pacific campaign of WWII seeded much of the subsequent global epidemic activity. After successful vector eradication programs in the first half of the twentieth century, dengue was re-introduced into the Americas, first into Cuba in 1977 with subsequent spread throughout tropical South America as its vector, *A. aegypti* reclaimed its earlier territory. Chikungunya virus (CHIKV); CHIKV exploded out of Africa following a large epidemic on the island of La Reunion in 2005. A single mutation in the virion surface protein facilitated a spillover into a new mosquito host, *A. albopictus* and further, global spread, reaching the Americas in 2014. West Nile virus (WNV); WNV was known to circulate within Africa from the 1930s when it was first isolated, spreading to the Middle East and Europe in the 1990s. What is thought to be a single transportation event resulted in WNV landing in New York from Israel in 1999. The subsequent march of WNV west across the North American continent was driven primarily by migration of its bird hosts, resulting in its wide distribution across the Americas over the subsequent decade. Zika virus (ZIKV); ZIKV was first isolated in 1947 but it wasn't until 1954 that the first human cases were reported in Nigeria. While its spread across Africa and into India and South East Asia were noted, it wasn't until a large epidemic on the island of Yap in 2007 highlighted the potential importance of ZIKV to human health. The subsequent epidemic in French Polynesia in 2013/2014 was thought to be the seed for its emergence in Brazil in 2015. The cause of the explosive nature and severity of the resulting epidemic over 2015–2016 is still the subject of considerable conjecture – the presence of a naïve population primed with a high level of potentially enhancing dengue-specific antibody, viral genome mutation or a combination of both along with additional factors remain possibilities

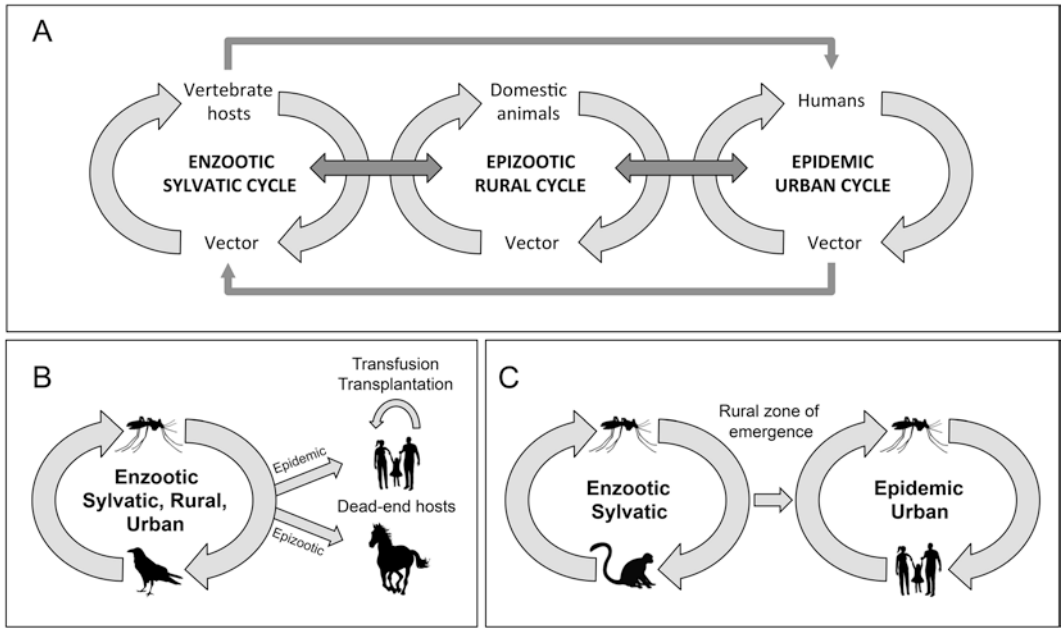

Fig. 1.3 Arbovirus transmission cycles. A. Enzootic (low level endemic virus transmission within native animals), epizootic (higher level epidemic transmission, usually within domestic animals) and epidemic cycles within humans are inextricably linked for many arboviruses, with spillover events driving the dynamics of each cycle. B. For some arboviruses (e.g., WNV) the epidemic and epizootic spillover from the enzootic cycle are unimportant for arbovirus survival, as these are dead-end hosts that do not act as reservoirs for further rounds of transmission. Exceptions are driven by specific human activity; e.g., transfusion and transplantation. C. For some arboviruses (e.g., DENV and ZIKV), the epidemic cycle in humans can be self-sustaining given the high levels of viraemia resulting in efficient transmission between vector and humans without the need for an enzootic amplification host. Nevertheless, occasional spillover events from the enzootic sylvatic cycle have been recorded

posed as the most likely mechanism for introduction of WNV into the USA in 1999.

Some hosts that become infected may not be sufficiently viraemic or may not be infected with sufficient regularity to contribute to the stable maintenance of virus populations and are referred to as incidental hosts. Incidental hosts may or may not show symptoms. For many arbovirus infections, humans are usually an incidental host, often being a dead end in the transmission chain.

Arthropod-borne viruses are distinguished from other animal viruses because of their ability to infect both vertebrate and invertebrate hosts. The virus replicates within the cells of the arthropod vector before being transferred to a susceptible host [16]. Occasionally, arthropods may also transmit viruses by mechanical transmission with the vector simply transferring the virus from an infected to a susceptible host without replication in the vector itself. Direct transfer from an infected to an uninfected vector during co-feeding on a naïve host has also been reported.

Invertebrate hosts include mosquitoes, sandflies, ticks and culicoides (biting midges) although most arboviruses have been recovered from mosquitoes. While transmission of arboviruses most often follows the bite of the infected arthropod, transmission has also been reported in other ways. European TBEV can be acquired by drinking the milk of infected goats, VEEV (in cotton rats) apparently via urine or faeces infecting the nasopharynx, WEEV possibly through aerosol from a patient and WNV and DENV has been transmitted by blood transfusion. DENV, JEV, WNV and CHIKV have all been transmitted from mother to foetus following infection during pregnancy, but this is considered rare. In contrast, an unusually high rate of maternal to foetal transmission has been observed in the recent ZIKV outbreak in Brazil. The finding of Zika virus in a

range of bodily fluids including semen, tears and sweat, as well as the apparently high rate of CNS invasion following foetal infection remains to be fully explained [18].

1.4 What Diseases Do They Cause?

The vast majority of arboviral infections lead to either an asymptomatic or non-specific mild illness. Only a handful of those who are infected develop clinical symptoms for which the individual arbovirus is known. For the flaviviruses, the case to infection ratio varies considerably, from very low (e.g. around 1:300 for encephalitis due to JEV) to quite high (1:4 for fever as a result of DENV infection). It may be higher during epidemic (rather than endemic) disease activity, and will be modified by a range of other factors, including host susceptibility and virus strain. The major burden of disease is at the extremes of life, the very young and the elderly. For alphavirus infections, particularly those causing arthritis, the ratio of symptomatic to asymptomatic infection is typically higher than that of the flaviviruses, from 1:40 to 1:3. If clinical manifestations arise after infection they do so after an intrinsic incubation period lasting from a few days to a week or more. During that time the virus replicates at the site of inoculation, then further amplifies within the reticuloendothelial system before it becomes viraemic and spreads to target organs.

Symptomatic arbovirus infection often presents as a systemic febrile illness. In the early stages, this illness may be non-specific or even suggestive of other viral illnesses, including gastrointestinal and respiratory infections. In a developing world setting featuring an increased burden of disease, this can be particularly problematic, often delaying appropriate clinical management. On-going development of low cost, point-of-care diagnostics to provide early and effective diagnosis, remains an important goal of current research efforts. Headache is common and may be severe and accompanied by meningitis. Muscle and joint aches and pains are common, especially with alphavirus infections where many also develop joint swelling and stiffness. Rash may be present and is usually generalised and maculopapular, although occasionally vesicular. Petechial rashes are less common and may be an early indicator of haemorrhagic fever. In the vast majority of cases, febrile illness is followed by recovery. In the remainder, illness may progress to one of the more severe forms of disease, sometimes following a few days of remission. These can be broadly grouped into those arboviruses causing haemorrhagic fever, encephalitis or polyarthralgic illness (for further discussion see [21]).

1.5 What Is Driving Arbovirus Expansion?

As noted above, humans are often no more than incidental hosts for arbovirus infection. However, their behaviour, along with environmental factors can play a significant role in the activity and spread of these viruses [20] with many human activities known to encourage transmission [4, 7, 17, 21]. The construction of dams and extensive areas of irrigation promotes the breeding of large numbers of mosquitoes that is otherwise unusual for these geographical locations. For instance, the development of rice fields encourages breeding of *Cx. tritaeniorhynchus* in Sarawak that in turn fosters the spread of JEV, and *Mansonia uniformis* and *Anopheles gambiae* in Kenya spreading CHIKV, o'nyong-nyong virus (ONNV) and Sindbis virus (SINV). The seasonal removal of old vegetation in Sarawak leads to heavily polluted pools that support large populations of culicines. Driving cattle into marginal forest areas in India promotes the growth and transport of ticks, and the incursion of people into forest areas exposes them to infection with YFV and the tick-borne diseases. In many countries, the practice of using large containers for water storage has helped to increase *Aedes aegypti* populations and the consequent transmission of DENV, CHIKV and other viruses vectored by this species.

Environmental conditions, particularly rainfall, temperature and humidity, also have an important role to play in arbovirus transmission

cycles with the result that arbovirus activity is often seasonal. For example, the alphaviruses transmitted by mosquitoes in temperate regions cause disease in summer during periods of increased vector activity [2]. In tropical areas, human infections caused by arboviruses usually occur during the wet season, with increased virus activity again coinciding with periods of high vector numbers. As mosquito larvae and pupae are aquatic, the abundance of arthropod vectors is directly affected by the amount of rainfall and flooding in a particular region. Rainfall is also required to maintain permanent water bodies, or in some cases create temporary water bodies that provide a sanctuary and breeding grounds for water birds that act both as mechanisms for introducing the virus into that area and for amplifying the virus. Humidity can also play a role, with increased humidity facilitating increased survival of mosquitoes. Temperature can also affect the length of the extrinsic incubation period with most studies showing that the extrinsic incubation period for mosquitoes is shorter at 30 °C than at lower temperatures thereby ensuring that mosquitoes become 'infectious' in a shorter time after ingestion of an infected blood meal. High external temperatures on the other hand may have adverse effects on vector survival.

Global climate change will significantly impact on arbovirus transmission cycles over time [7]. The amount and extent of rainfall, frequency and heights of high tides, temperature, humidity and consequent movement of vertebrate hosts and human populations will all contribute. The extent and timing of these environmental changes is unknown, but because of the complex interactions between these viruses, their hosts and vectors as well as the environment, it is likely that even minor changes will affect arbovirus activity in different regions. This may result in an increased number of cases and/or a greater geographical spread of these viruses [5, 12–14]. Climate change impacts on arbovirus transmission are already being played out, such as in the dramatic resurgence of West Nile virus in the US in 2012. This emergence was linked to a record-breaking drought across the US in combination with sporadic, end of season rains and local complacency with regards vector control. Mosquito numbers in metropolitan areas surged, with consequent increased transmission of WNV.

As noted above, the last two decades have seen a dramatic increase in the emergence and/or re-emergence of a number of serologically distinct arboviruses [6, 15, 21]. Ecological factors have played a pivotal role in this expansion with a rich array of demographic, cultural and societal changes impacting arbovirus transmission between vectors and hosts. Understanding some of these mechanisms will provide insight into future predictions of arboviral activity, disease risk assessment and control.

Southeast Asia has experienced an exponential increase in the number of arbovirus related epidemics; YFV and RVFV cases are on the rise in Africa; South America has seen the re-emergence of DENV and YFV and the emergence of ZIKV; and the incursion into North America and Europe of some arboviruses previously restricted to the tropical zone (e.g., CHIKV and DENV) all serve to emphasize that no region of the globe is resistant to these threats. Their spread has been linked to a range of complex factors.

It is recognized that biodiversity plays an important role for arbovirus maintenance with African, Southeast Asian and South American tropical regions, particularly their rainforests, considered reservoirs for many of these arboviruses. However, it is the demographic and societal changes in the human population during the past two to four decades that has had the biggest impact on the revival of arbovirus infections. Unprecedented population growth has been the underlying driver of many of the changes that have affected transmission dynamics. These include rapid urbanization, deforestation, new dams, an expansion in irrigation, and a lack of closed water storage containers. The resulting increase in mosquito populations and their closer contact with human communities has contributed to increased virus, and hence disease transmission. The changing demographics that have resulted from modern transportation have also played a significant role in the distribution and transmission dynamics of arboviruses. While the

geographic distribution of some arboviruses and their mosquito vectors has expanded, resulting in recurrent and larger outbreaks (e.g., DENV), others have invaded new geographic regions having taken advantage of susceptible mosquito vectors and hosts to become established (e.g., WNV, CHIKV and ZIKV). Clearly, factors such as the absence of herd immunity and a lack of vector control have been instrumental in the re-emergence of several arboviral infections (e.g., CHIKV, JEV, and more recently, ZIKV).

The changing epidemiological patterns of arboviruses are complex and unique to each virus, however virus evolution can also be an important driver of the emergence of these new disease threats. One clear example of how virus evolution has re-defined the epidemiology of an arbovirus infection is the re-emergence and spread of CHIKV. Sequence analyses have shown that CHIKV originated from Africa and was later introduced in to Asia with the delineation of three phylogenetic distinct clusters: East-, Central- and South-African (ECSA), Asian, and West-African clusters [10]. Analysis of CHIKV strains isolated from the Indian Ocean outbreaks indicated that it was more closely related to the ECSA cluster than the Asian or West African clusters. However, 90% of the CHIKV strains isolated revealed a nucleotide mutation leading to an alanine to valine change at position 226 in the virus E1 glycoprotein. This single amino acid change was of particular interest as it was exclusively found in CHIKV isolated from *Ae. albopictus*. This mutation was subsequently shown to be associated with adaptation to *Ae. albopictus* with an increased fitness in this vector attributable to the loss of cholesterol dependence for virus growth. This adaptation has allowed CHIKV to replicate and disseminate more efficiently in *Ae. albopictus*.

More recently, another arbovirus that has generated significant interest is ZIKV. First isolated from sentinel primates in the Zika forest of Uganda in 1947, it was also isolated in sub-Saharan Africa and South East Asia [8]. Few human cases were previously noted but in 2007, major human outbreaks were reported on Yap Island, Micronesia. Preliminary phylogenetic data showed two distinct ZIKV lineages circulating in Africa and a third lineage formed by the Micronesia and Malaysia strains [8]. The subsequent spread of ZIKV to the Americas in 2015 and the extensive epidemic it caused is now being attributed, in part, to specific mutations found in these circulating South American viruses.

1.6 Conclusion

In a world of rapid travel and transportation, many other arboviruses have the potential to spread geographically and cause serious outbreaks. What is of concern is that most of these new introductions are not detected until an epidemic or some unusual situation signals the alarm, often too late to effect control. The world is finally coming to grips with the notion of epidemic preparedness and the realization that significant and coordinated effort will be required to effectively deal with the inevitable future threats to global health posed by arboviruses on the move.

Acknowledgements This brief overview has been adapted, in part from [21]. The author wishes to express his thanks for ongoing funding support from the Australian National Health and Medical Research Council and to ViralZone, SIB Swiss Institute of Bioinformatics for granting their permission to use the virus schematics in Fig. 1.1.

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