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REVIEW

From dengue to Zika: the wide spread of mosquito-borne arboviruses

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Abstract

The worldwide invasion of arthropod-borne viruses (arboviruses) in recent decades is responsible for emerging public health threats. Some factors like climate change, urbanisation and uncontrolled population growth are fuelling their widespread. Arboviruses incorporate a vast collection of genetically diverse viral pathogens including that of dengue, Zika and chikungunya. These viruses are peculiar as they are zoonotic and are a serious harm to the society, with no particular therapy to neutralise their effect. So it is the need of the hour to develop an effective treatment against infections caused by them. This review focuses on some of the common families of mosquito-borne arboviruses and their most known members that are a threat to mankind and discusses their genome organisation, worldwide spread and negative influence on public health.

Keywords Arbovirus · Dengue · Zika · Chikungunya · YFV

Background

Arbovirus is an acronym for ARthropod-BOrne VIRUS. An increase in the emergence and the re-emergence of arboviral infections during the last few decades has indicated that arthropod-borne pathogens continue to be an important threat to public and animal health. Infections like dengue, chikungunya, Zika etc. are occurring at a global level and they are not just limited to any developing or tropical regions in the world [1, 2] (Fig. 1).

Infections caused by the arboviruses are spread by haematophagous insect vectors such as mosquitoes, tick flies and sand flies [2–4]. *Homo sapiens* are the incidental hosts, so they do not take part in transmission of the virus and only acquire infection when a vector feeds on their blood. Supportive care is provided to the suffering person and only precautions can be taken to a certain extent [5]. Rise in global temperature and intrusion and domestication by humans on newer geographical spaces have played a major part in such an overwhelming spread of arboviruses [2].

Arboviruses need multiple hosts to complete their life cycle (i.e. vertebrate hosts and the primary arthropod vectors), thus making their life cycle very complex (Fig. 2). This unusual property is the prime challenge in controlling the spread of arboviruses and therefore makes it so important to study their life cycle, prevention and treatment. Although there are several arboviral families, clinically important mosquito-borne arboviruses belong to four viral families, namely *Flaviviridae*, *Bunyaviridae*, *Togaviridae* and *Reoviridae*, which are discussed in the present review (Table 1). A typical similarity between these families is the presence of RNA genome which redesigns itself with an ever-modifying host and changing environmental conditions; the reason behind the range of emerging viruses nowadays [2].

Family *Flaviviridae*

The family *Flaviviridae* consists of viruses which are spread by mosquitoes, ticks and other vectors. They have positive single-stranded, linear and monopartite RNA genome [6] (Fig. 3a). The whole genome ranges about 9.6 to 12.3 kb in length; these viruses have a diameter ranging from 40 to

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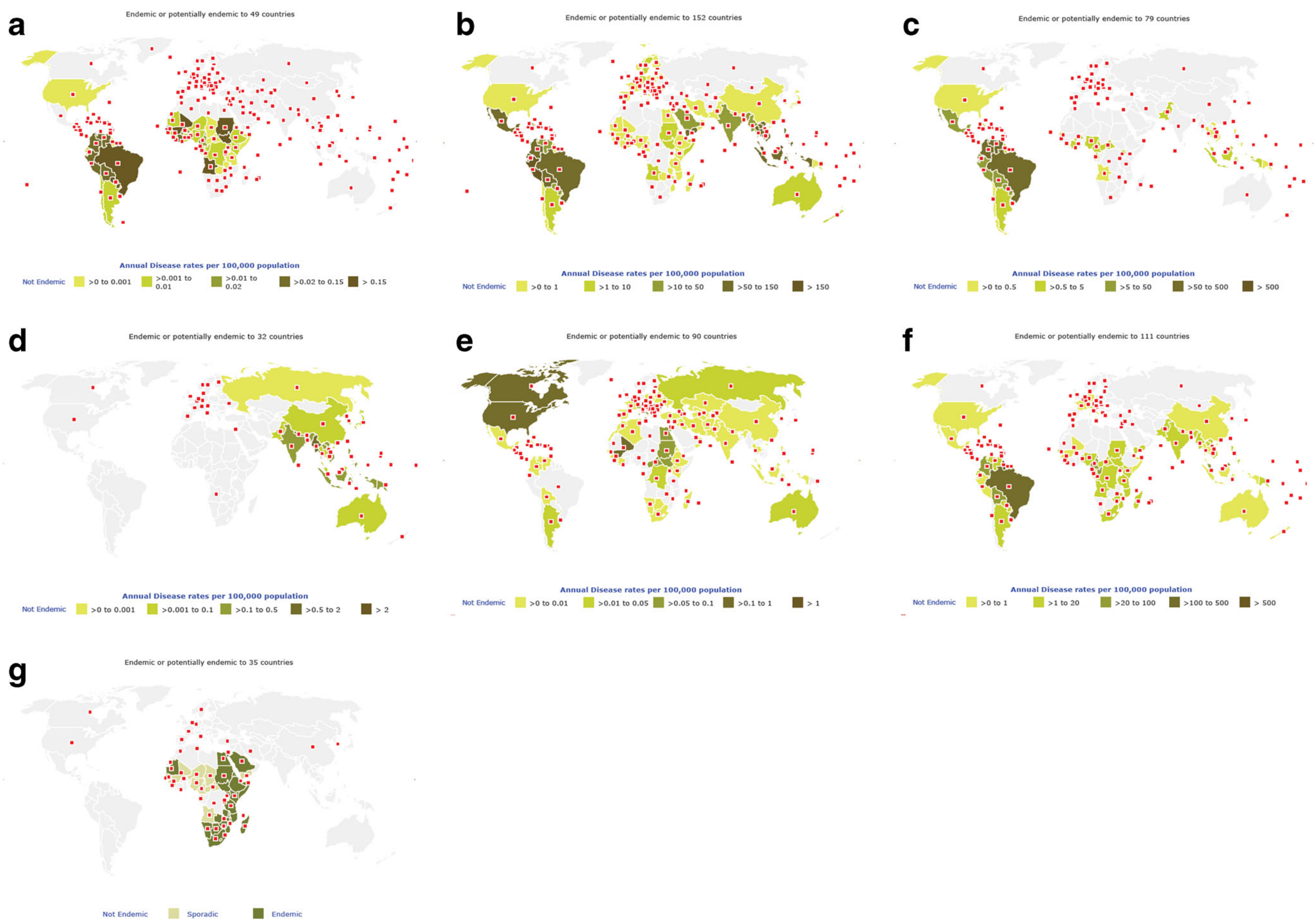

Fig. 1 Global distribution maps of **a** yellow fever (endemic to 49 countries), **b** dengue (endemic to 152 countries), **c** Zika (endemic to 79 countries), **d** Japanese encephalitis (endemic to 32 countries), **e** West Nile fever (endemic to 90 countries), **f** chikungunya (endemic to 111 countries), **g** Rift Valley fever (endemic to 35 countries). Retrieved from www.gideononline.com on 17th July 2018

60 nm [7]. The ancestral origin of *Flaviviridae* is Africa and is now circulating in the Americas, Asia, Australia and Europe. Major diseases caused by the *Flaviviridae* family include dengue fever, Zika fever, Japanese encephalitis, Kyasanur Forest disease, Murray Valley encephalitis, St. Louis encephalitis, tick-borne encephalitis, West Nile encephalitis, Yellow fever and hepatitis C virus infection [8, 9]. Among all these diseases, five are caused by arboviruses (using arthropod as a vector), i.e. yellow fever, dengue, Zika, Japanese encephalitis and West Nile fever. These viruses hold a significant amount of importance because of the increasing rate of infections and lack of awareness to control them (Fig. 4).

Yellow fever virus

One of the earliest known human pathogenic viruses is yellow fever virus (YFV), a prototypic associate of *Flaviviridae* family and was originated in West Africa. This virus is the cause of illness usually in tropical and sub-tropical regions of South America and Africa due to slave trade between these continents [10]. YFV causes yellow fever, as the name, and its course may range from mild to potentially fatal haemorrhagic fever. Spread of YFV occurs normally through tree-hole breeding mosquitoes like *Aedes aegypti*, *Haemagogus* and *Sabethes* species to primates during monsoon. Sylvatic, intermediate and urban cycles are three modes of secondary transmission of this virus [11]. The sylvatic transmission cycle occurs in tropical rainforests while intermediate in rural regions, but the markable concern arises from urban transmission cycle because of high population density [10] (Fig. 1a). Onset of symptoms occurs after 3–6 days of incubation period. The viral genome is packaged inside the small, icosahedral virion and is single stranded having positive polarity. Capsid, membrane, envelope (structural proteins) forms the virion and other seven non-structural proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b and NS5) perform various functions like pathogenesis, enzymatic activities, viral replication etc. [12] (Table 1). Among these, envelope glycoprotein is responsible for major biological activities (receptor binding, membrane fusion etc.) and immunogenicity. Diagnostics is dependent of IgG and IgM detection in serum [10].

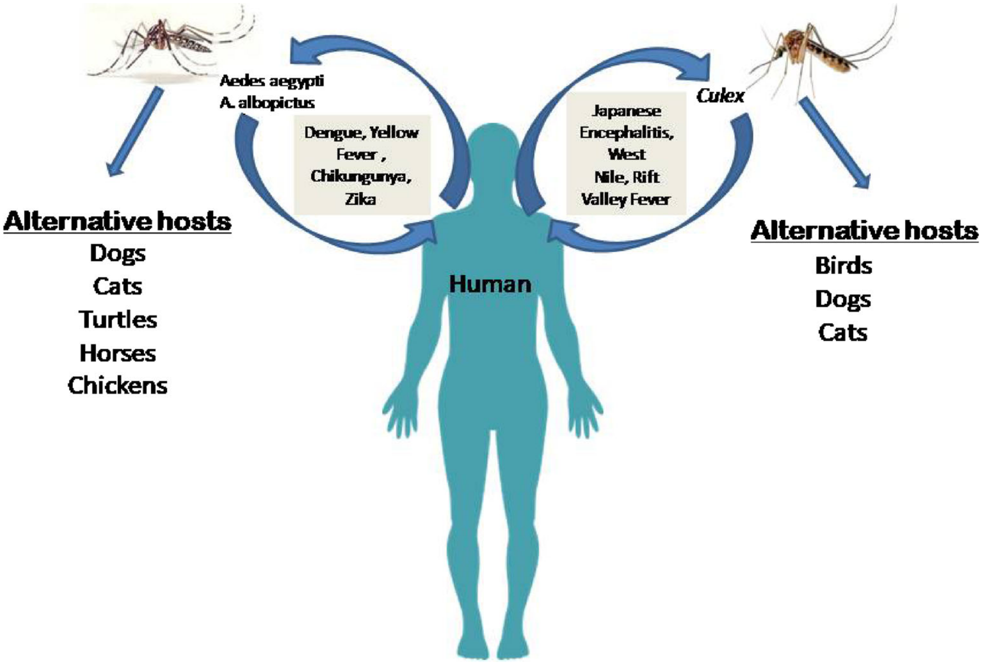

Fig. 2 Zoonotic cycle of mosquito-borne arboviruses involving human and other vertebrates as the hosts

There is no treatment for YF as no specific antiviral drug is available. But the live attenuated Yellow Fever 17D (YF17D) vaccine is widely adopted for immunisation against yellow fever virus [10]. In recent years, there have been increased incidences of this viral infection despite the successful vaccine, as the unvaccinated travellers visiting the endemic zone may get infected and can cause spread to other areas [10]. As in the case of 2016 outbreak in Brazil, an approximate of 1987 yellow fever cases were reported in a span of 4 months, while it spread beyond the borders of Brazil to new realms of Latin America. Similarly, Africa and other countries apart from Brazil have also reported many yellow fever cases. Thus, the risk of small outbreaks turning into a significant epidemic cannot be avoided, when migration of infected individuals to new geographic zones and stresses of various ecological factors can play a major part in the spread of the disease [13].

Dengue virus

Another arthropod-borne virus which infects the humans most importantly is the dengue virus, and the vectors responsible for its spread are *A. aegypti* and *A. albopictus*. As these vectors are anthrophilic in nature, they prosper near human settlements [14]. Major parts of the world that are affected by it are Southeast Asia, the Pacific and the Americas, whereas Africa and the East Mediterranean are getting increasingly affected [15] (Fig. 1b). The worldwide incidence of dengue cases has increased by many folds in recent times, with an increase of 32,749,000 in 2005 to 79,609,000 in 2015 [16]. According to the recent statistics, 390 million people are affected by dengue virus every year [17].

Dengue virus (DENV) comes from the family *Flaviviridae* under the genus *Flavivirus*. Structural features of this virus are distinctive as it is spherical in shape with diameter of about 40–50 nm and also has a lipopolysaccharide envelope. It is a single-stranded RNA virus having a length of approximately 11 kb. DENV has a single open reading frame which encodes 10 genes in total, where three are structural (capsid (C), membrane (M) and envelope (E) glycoproteins) and seven are non-structural, i.e. NS1, NS2A, NS2B, NS3 (protease helicase), NS4A, NS4B and NS5 (methyltransferase-polymerase) [18, 19]. These structural viral proteins carry out various functions like genome packaging, viral attachment and maturation of viral particles (Table 1). NS1 is an important non-structural protein as it is crucial for immune recognition and also for dengue diagnoses. The most conserved and the largest protein of dengue virus is NS5 which plays an important role for pathogenesis [20].

DENV has four serotypes namely DENV-1, DENV-2, DENV-3, and DENV-4 [19, 21]. The different serotypes, however, show 60–80% similarity with one another. For humans, the variation is seen in the surface proteins of the serotypes. After the recovery of infection by one serotype happens, it ensures lifelong immunity for that particular one but not for other serotypes, one of the reasons for no proper therapeutic available [15]**.** Dengue infection can be of two types, mild dengue fever (DF) and severe haemorrhagic fever (DHF). Factors like presence of secondary infections, age, viral load as well as infecting serotype and genotype are influential in the development of severe form of dengue [22]. The infection with secondary DENV-2 is more likely to result in severe disease compared with other serotypes [23, 24]. DENV infections are also diagnosed using IgG and IgM kits. Owing to its high risk worldwide, dengue vaccine development has been in progress since the virus was first isolated in 1944 in Hawaii. Although the first ever live attenuated tetravalent vaccine to be licenced named Dengvaxia by Sanofi Pasteur is available since 2015, the efficacy of this vaccine for all the serotypes is still a challenge [25].

Zika virus

After dengue, the next dreadful virus is Zika (Fig. 4). The recent worldwide emergence of Zika virus (ZIKAV) has forced researchers in health communities to show unprecedented concern towards it. This virus also belongs to the family *Flaviviridae* and the genus *Flavivirus*, having a single-stranded positive sense RNA genome. Zika virus was first separated from monkey (Rhesus) in April 1947 from the forest of Zika, Uganda, thus drawing its name from the place of isolation [26–28]. In the year 2007, the first major outbreak of Zika occurred in the Yap Island of Micronesia [29]. Later outbreaks occurred in years 2013 and 2014 in French Polynesia and Pacific islands, respectively [30]. Similarly, Central and South America also came under the Zika clouds in 2015 after the infections were reported in Brazil while the United States encountered their first outbreak in 2016 in the state of Florida [29, 30].

DENV and Zika share too many similarities as far as their genome organisation and vectors are concerned (Fig. 3a and Table 1). The length of genome is 10,794 kb and its open reading frame (ORF) encodes for 10 proteins similar to dengue virus genome [28, 31]. The competent vectors of its transmission cycle are also same as that of dengue virus, i.e. *A. aegypti* and *A. albopictus* [26, 32]. The enzootic lifecycle of ZIKAV is sustained in non-human primates and mosquitoes [31]. But there have been isolated cases, where certain species of cow, buffalo, camel, sheep and bats have shown the presence of antibodies [33].

Some reports also suggest that the virus is communicable in humans sexually or by blood transfusion, breast feeding or materno-foetal transmission [31]. Symptomatic cases of viral infections are quite low, about 18% of the total, in which no harsh effects are seen except some mild signs such as headache, retro-orbital pain, oedema, nausea, rashes, conjunctivitis, elevated body temperature and arthralgia [15, 18, 28]. Most of the

Table 1 Functions of various proteins found in mosquito-borne arboviruses having human as the host

Family	*Flaviviridae*	*Togaviridae*	*Bunyaviridae*	*Reoviridae*
Members	YFV, DENV, ZIKA, JEV, WNV	CHIKV	RVFV	ROTAVIRUS
Proteins	Capsid: genome packaging	Capsid: viral particle formation; RNA packaging	Ribonucleic proteins (RNP) package nucleoprotein N and RNA-dependent RNA polymerase L	VP4 and VP7: neutralise antigen VP6: inner capsid
	Envelope: viral-host cell membrane fusion; viral entry	E2 (S) and (E1) proteins: fusion virion–host cell membrane	M segment (G_n) and (G_c): virion–host cell membrane fusion; viral entry	VP4: viral entry
	Membrane: formation, maturation of viral particle; interaction with host proteins	E3 (S) cleaved from E2 (S): cause viral spike maturation		VP3: capping enzyme VP2: core protein
	NS1: immune recognition; cofactor for DNA complex	NSP2: virulence factor; inhibits host antiviral response; viral replication complex; helicase	*NSs: promotes post-transcriptional downregulation of dsRNA-PKR, immune response	NSP4: enterotoxin NSP2: NTPase
	NS2a: RNA synthesis, replication; viral assembly	NSP1: RNA synthesis initiation; guanine-7-methyltransferase; viral RNA capping	NSm: anti-apoptotic function and pathogenesis	VP1–VP3: replication complex
	NS2b: cofactor for viral serine protease complex with NS3	6K (structural protein): viral budding		NSP5: phosphophoretin
	NS3: RNA helicases, RNA triphosphatases, nucleotide triphosphatases; proteases	NSP2, NSP3, NSP4: helicase; protease; phosphatase; RNA-binding activity; RNAi suppressor activity		NSP3: translational enhancer
	NS4a: helps in translocation of NS4B through ER; host membrane rearrangement			VP7: glycosylated
	NS4b: inhibits signal transduction cascade of interferon; affects NS3 helicase activity			NSP1: interferon antagonist
	NS5: RNA-dependent polymerase activity; interferes with interferon signalling pathway; pathogenesis		*L segment codes L protein: RNA-dependent RNA polymerase	VP1: RNA-dependent RNA polymerase

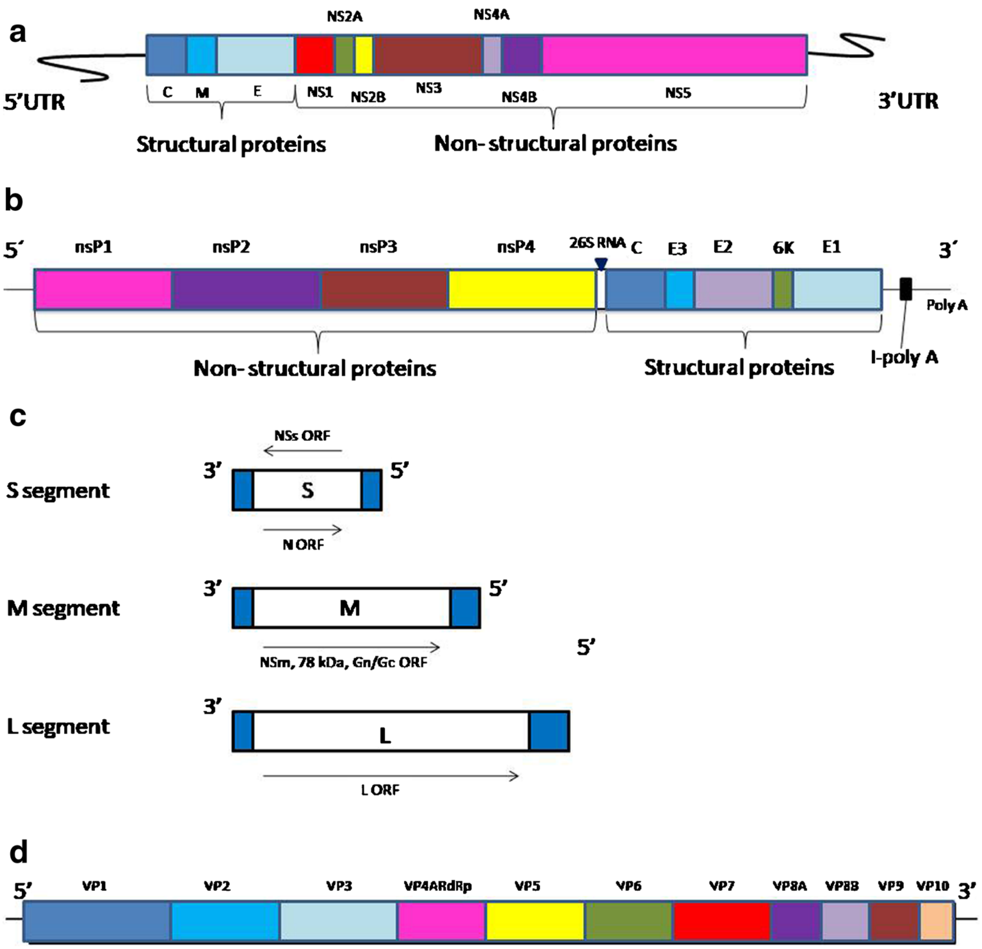

Fig. 3 Schematic representation of genomes of arboviral families (not to scale). **a** DENV (*Flaviviridae* family): boxes represent the structural (C, M, E) and non-structural (NS1, NS2A, NS2B, NS3, NS4A, NS4B NS5) proteins. **b** Chikungunya (*Togaviridae* family): non-structural (nsP1, nsP2, nsP3 and nsP4) and structural (C, E3, E2, 6K and E1) proteins. **c** RVFV (*Bunyaviridae* family): S segment, M segment and L segments; black shaded regions of each segment indicate terminal sequences that are complementary to each other. **d** Linear dsRNA genome of Rice stagged stunt virus (RSSV) (*Reoviridae* family)

symptoms are the same as in case of dengue, but major outcomes of ZIKAV infections are Guillain–Barre syndrome (GBS) and microcephaly in neonates; the former is an autoimmune disease which causes flaccid paralysis and the latter is a neurodevelopmental disorder [26–28, 31–34]. Like all other flaviviruses, even ZIKAV does not have a specific vaccine and is treated symptomatically [28, 31], but recently Inovio Pharmaceuticals and GeneOne Life Sciences developed a

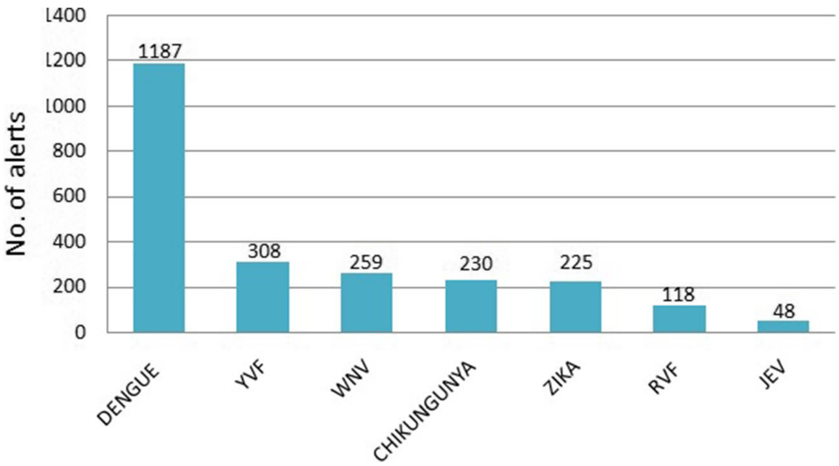

Fig. 4 Graph showing mosquito-borne arboviruses dealt in this review and number of alerts in the last 6 months (January–July 2018). Retrieved from http://www.healthmap.org/en/ on 17th July 2018

DNA vaccine, GLS-5700, by using multiple strains of infected virus, and the trials are expected to end by 2018 [35].

Japanese encephalitis virus

The next most significant epidemic encephalitis *Flavivirus* globally is Japanese encephalitis virus (JEV). In 1817, JEV was first identified in Japan and the very first isolation of JEV was done in 1935 [36, 37]. It is estimated that the JEV causes at least 50,000 cases of clinical diseases and approximately 10,000–15,000 deaths each year [38, 39]. JEV exists in a zoonotic cycle between pigs and mosquitoes and/or birds, and humans are dead-end hosts [40]. The disease is mostly transmitted by mosquito, *Culex tritaeniorhyncus*, between the vertebrate (pigs, humans and sometimes horses) hosts [8]. The difference between JEV and other arboviruses is that it requires an amplifying host to complete the transmission process. It is so because pigs and humans share a close relation in terms of their housing habits [40]. The symptoms like headache, fever and vomiting progress to mental status changes, neurologic deficits and movement disorders after an incubation period of 5–15 days [41]. This human and livestock pathogen has a size of 10 kb and codes for 10 functional proteins: three structural and seven non-structural. The former is necessary for virion formation while the latter has the responsibility to carry on the viral life cycle [41, 42]. There is no ideal (specific, safe, low cost, effective and long lasting) vaccine for JEV, but various inactivated (JE-VAX), live attenuated (SA14-14-2) and recombinant (ChimeriVax-JE) vaccines are available in many parts of the world [43].

West Nile virus

West Nile virus (WNV), another member of *Flaviviridae* family, is a neuropathogen. WNF was firstly isolated in West Nile from the blood of a febrile patient in 1937 [44, 45]. Earlier, this virus spread its wings to Africa, Asia, Europe and Australia. In 1999, it was introduced to North America in New York City [45]. The infection in the northern hemisphere is still expanding to new places [46] (Fig. 1e). WNV circulates well in warm climates which are favourable for the vector development [14].

Two strains of this virus exist based on the phylogenetic analysis of the virus genome, i.e. strain 1 which spreads worldwide [47, 48] and strain 2 which is only exclusively present in Africa [49, 50]. WNV is an enveloped protein having positive-sense and single-stranded RNA genome encoding three structural and seven non-structural proteins. While structural proteins are needful for viral entry, fusion and encapsidation, viral replication is the onus of non-structural proteins [51]. The life cycle is an enzootic cycle involving mosquitoes (*Culex pipiens*) and bird species; transmission to mammals (humans and horses) occurs due to mosquito bites. Birds serve as primary amplifying hosts, whereas humans and horses act as intermediate hosts [52]. After the mosquito vector of genus *Culex* bites the host, the primary infection spreads to the reticuloendothelial system. Thereafter, the secondary viraemia occurs in the CNS [53]. When the illness occurs, the incubation period may last for 2–14 days. It may be prolonged for up to 21 days in the hosts which have weak immunity. About 20% of the infected people are marked by fever, fatigue, myalgia, nausea and lymphadenopathy. In a few cases, it also leads to meningitis, encephalitis and poliomyelitis. For equines, various licenced inactivated, recombinant vector and chimeric vaccines are available which do not work for humans [51, 54].

Usually, diagnosis rests on detection of IgM antibody in serum fluid or cerebrospinal fluid. Treatment is only supportive as of now, but there is no approved vaccine or treatment available for humans [55, 56].

Family *Togaviridae*

Alphaviruses, the genera of family *Togaviridae*, are arthropod-borne viruses responsible for diseases in humans. The examples are chikungunya virus, Western Equine Encephalitis virus, Eastern Equine Encephalitis virus and Venezuelan Equine Encephalitis virus. These viruses have principal vectors belonging to genera *Culex* and *Aedes*. They have a single, positive sense RNA genome which consists of 9500–11,500 nucleotides and have a nucleocapsid as well as an envelope [7]. Among these, chikungunya has emerged as a major threat to mankind, hence will be discussed over here.

Chikungunya virus

Chikungunya virus (CHIKV) is a known member of family *Togaviridae* which was first identified in Africa in the year 1952 during an epidemic where humans suffered from fever, serious arthralgia and rashes [14, 57, 58]. In the recent decades, a chain of major outbreaks occurred leading to the apparent global re-emergence, beginning from Kenya in 2004 and then later on moving to Southwest Indian Ocean (2005) and Indian Subcontinent (2006). The latter outbreak in India reported an approximate of 1.4 million cases [59]. Most recently, CHIKV outbreak marked its presence in America in the year 2013 where for the period of 2013–2014, a total number of 22,796 confirmed cases were reported by Pan American Health Organisation [59, 60]. It is one of the re-emerging infections influencing millions of people globally (Fig. 1f).

These viruses are small, spherical and enveloped having a diameter of range 60–70 nm [58]. Like all other alphaviruses, chikungunya also have a lone-stranded positive sense RNA genome (12 kb) and encodes for five structural and four non-structural proteins (Fig. 3b) [1, 58, 61]. The CHIK virus is also passed on by *Aedes* mosquitoes in the cycle, mostly by the species *aegypti* and *albopictus* [14, 62]. The enzootic cycle between non-human primates and forest-residing mosquitoes (*Aedes*) is mostly observed in Africa. The transmission rate varies drastically in enzootic and epidemic cycle. The former depends on the seasons and availability of non-human primate host while the latter is relatively stable [62].

CHIK virus had been noticed worldwide including India, islands of Indian Ocean, Southeast Asia, Italy and USA [26]. This virus is pathogenic to man of all age categories and in both genders. The CHIKV infection leads to sudden onset of symptoms in patients like headache, fever, muscle pain (myalgia), nausea, vomiting and severe arthralgia after an incubation period of 2–4 days [14, 58]. These signs of infection are confusing with that of DENV infection; this was the reason why it remained unnoticed and undiagnosed for a long time as a crucial arbovirus [14, 26]. As in the case of DENV infections, there is no specific drug against CHIKV infections as well. Patients in this case are also cured symptomatically with inflammatory drugs such as ibuprofen, acetaminophen, ribavirin or paracetamol. Widespread distribution of CHIKV globally has led to designing of several vaccines. Many novel vaccine candidates, for example TSI-GSD-218, CHIKV181/25 or CHIKV/IRES, were developed but none of them showed promising results [57, 58].

Family *Bunyaviridae*

The family *Bunyaviridae* is a large group of viruses of about 300 members. The unifying characteristic of this family is that the viruses have a tripartite, single-stranded positive sense RNA genome. They are generally spherical and sometimes elongated virions of 80–120 nm in diameter. They have a lipid bilayer outer covering envelope which is about 5–7 nm thick [63]. The interior of the virions has a filamentous or coiled bead appearance, which shows the presence of a helical nucleocapsid structure composed of the nucleocapsid protein and the genome segments. Members of *Bunyaviridae* family are mosquito-borne Rift Valley fever, La Crosse, Snowshoe hare and Cache Valley viruses; tick-borne Nairobi sheep disease, Soldado and Bhanja viruses; and biting midges-borne Main Drain, Akabane, Aino, Shuni and Schmallenberg viruses [64, 65]. Among these, only Rift Valley fever virus will be discussed here as its host is human.

Rift Valley fever virus

A member of genus *Phlebovirus* (*Bunyaviridae* family), Rift Valley fever virus (RVFV) is found in Africa and Arabian Peninsula (Fig. 1g) and unlike *Flaviviridae* it has a tripartite negative-sense single-stranded RNA genome (~11.9 kb) comprising three segments, namely S, M and L (Fig. 3c) [66–68]. Nucleocapsid and NSs (non-structural protein) are encoded by segment S while segment M codes for both glycoproteins (Gn and Gc) and non-structural protein (Nm). Protein N forms ribonucleoprotein complexes (RNPs) (Table 1) [67].

RVFV is carried and dispatched by mosquitoes (*Aedes vexans*, *Culex tritaeniorhyncus*) and has a more severe effect on animals than on humans. It was first spotted in 1931, in greater Rift Valley of Kenya where sudden deaths and abortion storms were noticed in livestock, but later it also emerged in the Arabian Peninsula [66]. Over a decade, several outbreaks in various African countries have been reported with RVFV infections, with the most recent (2016) incidence in Republic of Niger where 105 suspected cases were documented [69]. Disease caused by RVFV is marked by a growth period of 2–6 days and then the patient faces sudden elevation in body temperature (38.8–39.5 °C), muscular and joint pain, retinitis, weakness, insomnia, constipation and in more severe cases the person may also suffer from haemorrhagic fever and thrombosis [70].

Several vaccines like MP-12, NDBR-103 and TSI-GSD 200 have been tested and have received conditional licensure [68].

Family *Reoviridae*

Family *Reoviridae* is known for its diverse host range and comprises 15 genera, viz. *Seadornavirus*, *Rotavirus*, *Phytoreovirus*, *Oryzavirus*, *Orthoreovirus*, *Orbivirus*, *Mycoreovirus*, *Idnoreovirus*, *Fijivirus*, *Cypovirus*, *Coltivirus*, *Mimoreovirus*, *Cardovirus*, *Dinovernavirus* and *Aquareovirus* [71]. Viruses of this family are not enveloped, have a diameter of approximately 600–800 Å and possess a double-stranded RNA genome [71, 72]. Viral RNA genome consists of 9–12 unattached segments encased by two proteinaceous concentric shells which are inner core and outer capsid except single layered in cytoplasmic polyhedrosis viruses (CPVs) (Fig. 3d) [72–75].

Some of the most common examples of this family are *Mammalian Orthoreovirus* (MRV), *Rotavirus* (RV), *Bluetongue virus* (BTV), *Rice ragged stunt virus* (RRSV), *African horse sickness virus* (AHSV) and *Kemerovo virus* (KEMV). Out of the 15 genera of *Reoviridae* family, *Seadornavirus*, *Rotavirus*, *Orthoreovirus*, *Orbivirus* and *Coltivirus* are known to infect humans and animals and most of them are transmitted by mosquitoes and tick vectors [71].

Rotavirus is the most common gastrointestinal pathogen in infants and young children. It is transmitted via vomits and faecal–oral route [71]. Similarly, via oral–faecal transmitted *Mammalian Orthoreovirus* or *Reovirus*, the abbreviated name for Respiratory Enteric Orphan

Virus, is known to cause mild upper respiratory tract or enteric infections in young children [71].

In case of genus *Orbivirus*, economically significant pathogenic viruses like Blue Tongue Virus, African Horse Sickness Virus and Epizootic Hemorrhagic Disease Virus are all transmitted by *Culicoides* midges. Some species like Yunnan *Orbivirus*, Orungo virus and Peruvian horse sickness virus are known to be mosquito-borne viruses infecting animals. Mosquito-borne Orungo virus has been isolated from humans, sheep, goats and cattle of Africa. Cases of the infected ones with the virus reported 23% sera with neutralising antibodies, with some incidents of mild fever, myalgia, cough, vomiting and few deaths [76, 77].

In the line of mosquito-borne human pathogens in this family, Banna virus (BAV) from the genus *Seadornavirus* have been isolated from regions where there have been a precirculation of mosquito-borne viral diseases like dengue fever and Japanese encephalitis. Mosquito genera like *Anopheles*, *Culex* and *Aedes* act as vectors and amplifying hosts while human, pig and cattle become incidental hosts. This genus of *Reoviridae* family is endemic to Southeast Asian countries like China and Indonesia [78]. Another pathogenic genus of *Reoviridae* family is *Coltivirus*, the type species is Colorado Tick Fever Virus (CFTV), which causes Colorado tick fever in humans and rodents. Ticks of the family *Ixodidae* act as the main vector for disease transmission. Clinical manifestations of CFTV in humans occur in the form of encephalitis and haemorrhage [79].

So far, vaccine development researches are aimed towards *Rotavirus* due to its ability to cause severe gastroenteritis globally. Vaccines like RotaTeq and Rotarix are available in the market and are administered to infants [72]. Extensive studies are not conducted on *Reoviridae* family due to its comparatively less clinical significance compared to other arboviral families. As the virulence pattern changes, there would be more scope of development of preventive and control measures [80].

Prevention is better than cure, but where are we?

The aetiological executors of arboviral diseases are predominantly zoonotic pathogens that circulate in cycles involving arthropod spread among a variety of vulnerable reservoir hosts. In humans, the most pertinent disease-transmitting arthropods are mosquitoes [81]. Not all mosquitoes that feed on blood are vectors for arboviruses; there are several factors that determine the competency of a vector. External factors such as environment temperature, precipitation and mosquito health play a key role. After the ingestion of viraemic blood from the vertebrate host, mosquito provides a favourable environment to the virus for its replication in the epithelial cells of midgut. These viruses eventually reach the salivary gland wading through various barriers, which is then transmitted to an uninfected host [82, 83].

The primary mosquito species which serve as a vector for these diseases are *Aedes* and *Culex*. *Aedes* is a small, dark-coloured mosquito with white markings and bands on legs (zebra mosquito), and a competent vector for dengue, Zika, chikungunya, Rift Valley fever virus etc., whereas *Culex* is a brownish grey mosquito and carrier for Japanese encephalitis, West Nile and Rift Valley fever virus among others. *Aedes aegypti* and *A. albopictus* are endemic to tropical and temperate regions, respectively. *Culex* usually acquires its blood meal from avian hosts instead of mammalian ones. These vectors have a lifecycle which is limited by the topography, temperature, climate of the environment and availability of host. Mosquito vectors thrive on warm conditions; therefore, tropical and temperate regions are the most affected ones [81]. Lately, global warming–induced rise in temperature has remarkably favoured mosquito replication. Another major reason for widespread breakthrough is that, over the time through mutations and resulting variations, the viruses have increased their virulence and their vectors have adapted well to compromising conditions. There have been many efforts to make therapeutics and vaccines, but control of vectors have remained primary or the basic methods of approach to deal with these arthropod-borne diseases. Environmental management (removal of vector habitats), biological control (predatory organism use), chemical control (insecticides) or physical separation from host (bed nets) can be ways of eradication [84, 85]. Recent advancements have enabled genetic strategies—IIT (Incompatible Insect Technique), SIT (Sterile Insect Technique), RIDL (Release of Insects carrying a Dominant Lethal), etc. with population suppression strategies—sterile males. As the name suggests, these techniques involve the release of sterile males in the population which then mates with females and reduce the reproductive potential of the latter [86]. Another type of genetics-influenced biological control is using *Wolbachia*, a gram-negative bacterium. Mosquitoes when infected by this bacterium block the transmission of arboviruses. *Wolbachia* can be used in two ways—for reducing reproductive ability or potential and inducing resistance to RNA viruses. This can be a helpful tool for controlling spread of arboviruses, but more research is required in this field [84, 85, 87].

Further research is on to develop chemical or biological interventions. As there is no registered therapeutic against these viral diseases, vector control is the only alternative at present.

Comparative genomics: a common solution?

As there are no major specific treatments or prophylactics to combat these arboviral illnesses, it is crucial to design or develop specific vaccine or drug particularly to respective viruses. A promising approach to this can be the technique of comparative genomics, in which the genomes of several viruses be studied comparatively to determine a common target. Comparative genomics of foot-and-mouth disease virus, Ebola virus, Epstein-Barr virus and many other viruses have been conducted earlier as well to study the mechanism of action with respect to humans [88–90]. Studies are also being conducted to explore the dynamics of mosquito genomes [91]. Relative studies of different serotypes of dengue have been performed individually, for example DENV 1 [92], DENV 2 [93] and DENV 3 [94], but the problem of heterotropic infection persists until all the serotypes are compared. Comparative genomics may not only shed light on the evolution of dengue virus but this can further be used to design a single drug or vaccine for human immunisation, which will be equally effective on all the serotypes.

Conclusion

Arboviruses are creating a boom in this era. These are the most harmful viruses which have struck the society in different parts of the world and are posing significant threats to humans. The viruses which have been discussed in this article primarily infect human beings. Even after decades of research, no treatment is present today to combat these diseases. Many researchers are working on different techniques to fight with these pathogens; some have been tested and some are still in their infancy. Novel targets are urgently needed to tackle these viruses because they are dreadful to mankind. But for the present scenario, precautions and eradications of the vectors seem to be the only possible solution.

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