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Review Article

Emerging and re-emerging arboviral diseases in Southeast Asia

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ABSTRACT

Arthropod-borne viruses (arboviruses) have become significant public health problems, with the emergence and re-emergence of arboviral diseases nearly worldwide. The most populated Southeast Asia region is particularly vulnerable. The arboviral diseases such as dengue (DEN), Japanese encephalitis (JE), West Nile virus (WNV), chikungunya fever (CHIK), hemorrhagic fevers such as Crimean-Congo hemorrhagic (CCHF) fever, Kyasanur forest disease virus (KFDV), etc. are on the rise and have spread unprecedentedly, causing considerable burden of disease. The emergence/re-emergence of these diseases is associated with complex factors, such as viral recombination and mutation, leading to more virulent and adaptive strains, urbanization and human activities creating more permissive environment for vector-host interaction, and increased air travel and commerce. Climate is a major factor in determining the geographic and temporal distribution of arthropods, the characteristics of arthropod life cycles, the consequent dispersal patterns of associated arboviruses, the evolution of arboviruses; and the efficiency with which they are transmitted from arthropods to vertebrate hosts. The present and future arboviral threats must be mitigated by priority actions such as improving surveillance and outbreak response, establishing collaboration and communication intersectorally, and strengthening the prevention and control programmes along with improving biosafety aspects with regards to highly infectious nature of these arboviral diseases. Evidence from research needs to be generated and priority areas for research defined.

Key words Arboviral diseases; arbovirus; emergence; epidemiology; re-emergence

INTRODUCTION

Contagions or rapidly spreading highly infectious diseases, with an estimated high fatality rate of 17 million deaths per year worldwide are major issue of public health concern[1–3]. The most overpopulated and economically backward countries in Southeast Asia are particularly vulnerable. Among the emerging infectious diseases, the arboviral diseases group has particularly warrant attention in global health landscape with its potential for epidemics and its unprecedented spread[4, 5].

The arboviral diseases (arthropod-borne viral) are caused by a wide variety of RNA viruses with a life cycle that requires both a host (birds or mammals) and a vector[6]. The transmission is preceded by a biological replication in an arthropod vector (e.g. mosquitoes, sandflies, ticks, or midges) and these viruses typically circulate among wild animals. More than 130 arboviruses are known to cause human disease, and are responsible for some of the most explosive epidemics of emerging infectious diseases over the past decade. Most arboviruses of public health importance belong to one of three virus genera: *Flavivirus*, *Alphavirus* and *Bunyavirus*. Arboviral diseases include: WNV disease, Yellow fever (YF), DEN, Murray Valley fever (MV), JE, Equine encephalitis, CHIK fever, Rift Valley fever (RFV) and among the tick-borne diseases, tick-borne encephalitis, hemorrhagic fevers except KFDV, CCHF are less common infections.

The evolution and diversification in the tropics of the many arboviruses resulted in more invasive and virulent strains[6, 7]. Although enzootic amplification is one characteristic of the viruses, some like dengue and chikungunya have lost this requirement and exclusively utilize humans as reservoir and amplification hosts, thus able to cause extensive epidemics. A review of the factors that may lead to emergence and re-emergence of arboviral diseases is presented here, with focus on Southeast Asia region.

Current status of arboviral diseases in Southeast Asia

The true magnitude of arboviral diseases and its associated human, economic and social costs are difficult to quantify, thus largely unknown[8]. In one study, the burden of Disability Adjusted Life-Years (DALYs) lost attributable to YFV, JEV, CHIKV, and RFV was estimated to fall between 300,000 and 5,000,000[9]. DEN, consid-

ered as the most important human arbovirus, have increased in incidence by 30-fold in the last decade with an estimated 50–100 million annual cases[10, 11]. From the Southeast Asia region around 1.3 billion people are at-risk of dengue, which is the leading cause of hospitalization and death among children[12]. JE is the leading cause of encephalitis epidemic worldwide, mainly in Korea, China, India, and Indonesia. The virus has large geographical range and it puts more than 3 billion people residing in Asia at-risk, and approximately 30,000–50,000 cases are reported annually[13]. CHIKV, which often mimics the clinical manifestation of dengue disease, started causing epidemics in India and Southeast Asia since 1950s and has become endemic in many countries[14, 15].

The diseases caused by arbovirus are increasingly becoming common causes of severe febrile disease that can progress to long-term physical or cognitive impairment or result in early death. Large number of people is at risk and the limitation in the health system in the endemic areas inevitably results in underestimation of the true burden of arboviral diseases.

Although most arboviral infections are asymptomatic, clinical manifestations range from mild febrile illness to severe encephalitis and are even occasionally fatal. Case definition and adequate surveillance, therefore, are major challenges. Treatment for arboviral diseases is mainly supportive[11, 16].

Occurrence of emerging and re-emerging diseases in the last decade

In the past decade there have been sporadic outbreaks of a number of emerging and remerging zoonotic viral diseases in the Southeast Asia. In 2001–02 an outbreak of Nipah virus (NiV) disease in Malaysia among the pigs and pig farmers has claimed many lives. The *Pteropus* bats (fruit bats) are mainly thought as the reservoir for this virus. The NiV has been responsible for similar outbreaks in the neighbouring countries of Bangladesh and India (Siliguri, West Bengal in 2010–11).

Another highly infectious arboviral disease, the CCHF virus has claimed many lives in the Gujarat state of India in 2010–12 period. The CCHF virus is mainly transmitted via infected tick bites or contact with an infected person or through nosocomial transmission in the hospital setting.

Similarly, in enzootic state, KFD virus circulates through small mammals such as rodents, shrews, ground birds and an array of tick species, however, the species *Haemaphysalis spinigera* is considered as the main vector and maintained an enzootic in small mammal and monkeys in the forest. A recent outbreak of KFDV was reported during 2011–12, affected 80 villages across the Shimoga district of Karnataka.

Factors responsible for arboviral diseases emergence

Emergence and re-emergence of arboviral infections undoubtedly are increasing phenomena in the last decade. The changing epidemiology and the responsible factors for the dramatic resurgence of arboviral diseases are complex and represent the evolutionary conflicts between rapidly evolving and adapting viruses and their evolving hosts[6, 17].

The progress of arboviral disease to epidemic level requires competent vector intersecting with vertebrate host population within an environment that is permissive for such interaction. A large proportion of the arboviral diseases of humans are zoonotic. Further the catalysis by focal and/global environmental, societal and demographic changes will lead to causing spillover infection to humans.

The inherent ability of the RNA viruses to recombine and reassort can lead to genetic mutations and change in host range. The population of reservoir hosts or intermediate insect vectors also undergoes changes that are mainly linked to human movement and urbanization[5, 7, 18].

Dengue is one example of arboviral disease for which the urbanization factor is strongly associated with its emergence. As the vectors (*Aedes aegypti*) prefer artificial water containers as its larval habitat thus human habitations became its choice. The four different serotype of DENV can co-circulate and causing hyperendemicity in many areas[19], consequently give them greater epidemic potential and more likely to be transmitted from human to human[20, 21].

WNV has spread to north America in the western hemisphere and caused major concern[4, 22, 23]. The globalization, land use and development of rapid transportation systems are thought to be the underlying factors for the WNV invasion[24]. It is initially known to be endemic across tropical parts of Africa and Asia. With mosquitoes (*Culex* species) as the principal vectors along with a bird-mosquito natural cycle, in India the role of ardeid birds in the maintenance of WNV has been described[25]. The spread of WNV has also been reported from endemic area JEV, where a substantial proportion of the acute encephalitis syndrome cases can actually be attributed to emerging WNV[26]. Wider epidemiological spread of WNV can be attributed to quick adaption of the virus to infect local mosquito vectors[27]. Although normally humans are dead-end hosts for WNV, the risk of infection is greatly increased by the zoonotic viral amplification and its persistence in the environment.

JEV is closely related to WNV and is maintained in an enzootic cycle involving aquatic birds and primarily *Culex* species mosquitoes. However, other animals such as pigs have been shown to play a role as amplification hosts and contribute to the increasing risk of the disease to human and equine alike[4, 28]. The widespread expansion of JEV cannot be separated from the growth in human populations, land use for irrigated rice agricultural activity and in pig farming[13, 29]. The existence of JEV in India, Pakistan and Nepal where swine farming is limited may indicate an expanding role for migratory birds in JEV amplification[6, 30].

Another factor that contributes to remarkable arbovirus invasions is air transport, which is inevitable in the world with dramatic increase in commerce and traffic volume. This in conjunction with adaptation for replication at higher temperature in mosquito vectors is crucial in enhancing urban transmission where previously the virus was unknown.

The seasonality and inter-annual variation in incidence of diseases are more pronounced for arboviral diseases, as the vector reservoirs are so susceptible to seasonal changes. Climatic conditions and disease transmission dynamics are interlinked, and as more knowledge on meteorological parameters is built, the impact of climate change can and should be mitigated. During the past 50 years or so, patterns of emerging arboviral diseases have changed significantly[8, 18]. Climate is a major factor in determining the geographic and temporal distribution of arthropods, the characteristics of arthropod life cycles, the consequent dispersal patterns of associated arboviruses, the evolution of arboviruses and the efficiency with which they are transmitted from arthropods to vertebrate hosts[18, 31].

Therefore, with gradually increasing surface temperatures, urbanization, irrigation practices and commerce, it seems that the arboviruses will continue to emerge in new regions. For example, the CCHF reported from India[32, 33], unexpected but successful establishment of CHIK fever in northern Italy[34–36], the sudden appearance of WNV in North America[22, 24, 37], the increasing frequency of RVF epidemics in the Arabian Peninsula[38, 39], and relatively recent emergence of bluetongue virus in northern Europe[40, 41.]

As arthropods are dependent on specific climate for their epidemicity and the effect of climate on alteration of the natural cycles are well-documented, there is little doubt that climate change indeed play a role in the transmission dynamics of arboviral diseases. Table 1 summarizes the emerging arboviral diseases in SEA region, and Table 2 shows the categorization of re-emerging/newly emerging arboviral diseases, important viruses that may emerge and less important viruses, but may emerge in the Region.

Priority actions for the perpetual challenges

Disease surveillance is corner stone of response to emerging disease threats. Risk assessment and outbreak preparedness are imperative. Surveillance indicates where a disease has appeared and gives vital clues about how the emerging infectious agent may spread in nature. After surveillance has brought attention to the problem, however, actual prevention and control measures ultimately require additional information provided by the scientific research.

Countries in Southeast Asian region have not been able to give emerging disease surveillance, the priority status it deserves. Much of the surveillance in the region is centered in a few well-established laboratories where there is adequate expertise, sufficient funding and warranted commitment. Mathematical modeling can be used to forecast the risk of arboviral diseases more precisely and to determine the impact of emerging epidemics. Vector control efforts cannot be undermined in this realm and understanding their biology and adaptability are mandatory.

Considerable progress has been made in recent years to develop vaccines for the arboviruses, such as JE[42] and DEN[11]. Novel candidates of vaccines are now being trialed for WNV[2]. Advances in clinical case management have decreased case fatality rates for DEN, yet there remain many challenges in diagnosing and treating other less common arboviral infection[43].

However, it can be stated that surveillance and other activities that traditionally fall within the domain of public health are not sufficient to adequately address the problem of emerging diseases. Basic, translational and operational research efforts to develop more effective and advanced tools to combat the resurgence of the arboviruses are of critical importance. Understanding the changing pattern and epidemiology of different diseases is imperative[44].

Strengthening the health system as a whole can definitely be beneficial as well, because resurgence of disease often worsened due to the breakdown in public health measures and inadequate capacity of the system to respond. Policy to improve surveillance, prevention and control programmes for arboviral and other zoonotic disease frequently being established late after the outbreak or epidemics had occurred.

Research priorities

With the constant evolution ongoing for the viruses,

Table 1. Summary of emerging arboviruses in Southeast Asia

Arbovirus	Animal group(s) affected	Transmission	Clinical signs	Severity	Treatment	Prevention and control	Zoonotic	Reference Nos.
Kyasanur forest disease virus (KFDV)	Mammals: Primarily gray langurs (*Semnopithecus* sp.) and the red-faced bonnet monkey (*Macaca radiate*), shrew (*Suncus murinus*), rats, birds, squirrels, porcupine and bats	Vector: Ticks, specifically nymphal stages of *Haemaphysalis spinigera* (primarily). Other *Haemaphysalis* sp. and *Ixodid* sp. Direct contact with an infected animal (rodent, monkey)	Biphasic: Fever, tussis, dehydration, encephalitis, epistaxis, diarrhoea, shock and death	Mild to fatal	No specific treatment. Supportive care especially for treatment of dehydration and hemorrhage	Vector control including insect repellents and protective clothing; Proper vaccination and assessment	Yes. Mortality in humans in enzootic areas	45–48
Japanese encephalitis virus (JEV)	Primarily pigs and the ardeid birds. Mortality in equines may occur	Vector: Specifically *Culex tritaeniorhynchus*. Other Culicine sp. By the bite of infected mosquito	Fever, incoordination, convulsions and death	Mild to fatal. Recovered persons may develop Permanent sequele like-Parkinson's disease abnormalities	No specific treatment. Symptomatic treatment as antipyretics, anticonvulsants, isotonic fluid therapy. IV mannitol to reduce the intracranial pressure	Vector control including insect repellents and bednets	Yes. Mortality in humans in enzootic areas	5, 13, 28, 29
Dengue virus (DENV)	Primarily man and certain areas lower primates	Vector: Specifically *Ae. aegypti*. Other *Ae. albopictus*. By the bite of infected mosquito	Fever, headache, bodyache, petechial hemorrhages and low blood pressure	Mild to fatal	Symptomatic treatment, fluid therapy	Vector control [source reduction] including insect repellents	Yes. Antibodies have been demonstrated in monkeys. No death in domestic or feral animals have been recorded	10, 11

(contd...)

(contd. Table 1*)*

Arbovirus	Animal group(s) affected	Transmission	Clinical signs	Severity	Treatment	Prevention and control	Zoonotic	Reference Nos.
West Nile virus (WNV)	Primarily pigs and the ardeid birds. Equines may succumb to death	Vector: Specifically *Culex tritaeniorhynchus*. Other Culicine sp. By the bite of infected mosquito	Fever, convulsions and death	Mild to fatal. Recovered persons may develop loss of memory	Symptomatic treatment, fluid therapy	Vector control including insect repellents and bednets	Yes. Mortality in equines and crows may be considered as the indicator	23–27
Chikungunya virus (CHIKV)	Primarily man	Vector: Specifically *Ae. aegypti*. Other *Ae. albopictus*. By the bite of infected mosquito	Fever, myalgia, arthralgia and headache	Mild to fatal	Symptomatic treatment, fluid therapy	Vector control (source reduction) including insect repellents	Yes. No domestic or feral animal mortality reported.	34–36
Chandipura virus (CDV)	Primarily human	Vector: Specifically sandfly *P. argentipes*. By the bite of infected sandfly	Fever, convulsions, headache and death	Mild to fatal	Symptomatic treatment especially for fever, reducing the intracranial pressure and isotonic fluid therapy	Vector control including insect repellents and bednets. Maintaining cleanliness and hygiene at animal sheds and houses	Yes. No mortality reported in domestic or feral animals	49–51
Crimean-Congo hemorrhagic virus (CCHV)	Primarily sheep, goat, cattle and buffalo	Vector: Ticks, specifically nymphal stages of *Hyalloma* and *Ixodid* sp. Direct contact with an infected domestic animals and their tissues/blood	Fever, bodyache, abdominal pain, epistaxis, hemoptysis and melena	Fatal	Symptomatic treament for hemorrhagic abnormalities	Vector control including insect repellents and protective clothing. Proper PPEs while handling animals and human patients.	Yes. Mortality in humans in enzootic areas	32, 33

Table 2. Re-emerging and newly emerging arboviruses

Arbovirus	Natural cycle	Vector	Reference Nos.
Dengue 1, 2, 3, 4, and Chikungunya	Mosquito, human, monkey	*Aedes*	10, 11, 23–27
Japanese encephalitis	Mosquito, bird, pig, horse	*Cx. triaeniorhynchus*	5, 13, 28, 29
Kyasanur Forest disease	Rodent + Lower primates	Tick; *Haemaphysalis* sp.	45–48
West Nile	Bird + Horse	*Cx. vishnui* gr.	23–27
Chandipura encephalitis	Sandflies, human	Sandflies; *S. argentipes*	49–51
Crimean-Congo hemorrhagic fever	Domestic animals, Hyalomma ticks	Tick *(Hyalomma)*	32–33
	Important and may emerge		
Rift Valley fever virus	Mosquito, human, large animals	Culicine sp.	1–5
Yellow fever	Mosquito, human, monkey	*Aedes*	9
	Less important but may emerge		
Bagaza virus flavivirus	Pigs?	Culicine sp.	51
Zika like DEN	Mosquito, human	*Aedes*	52, 53
Banna Reo virus encephalitis – China like JE	Pigs?	Culicine sp.	54
Usutu virus mosquito-borne flavivirus	Pigs?	Culicine sp.	55, 56
Ingwavuma	Pigs?	Culicine sp.	57–59

vectors and host, there is scarcity in the evidence generated from research in the arboviral diseases. Among others, the research priorities in this field should encompass: understanding environmental factors which facilitate emergence, maintenance and transmission of these diseases; studying the evolution of pathogenic infectious agents resulting in changes in infectivity, virulence, transmissibility and adaptations, host factors influencing emergence of new infection and their transmission; development of tools for diagnosis, management, control and prophylaxis; training and infrastructure for responding to emerging diseases; and information sharing on emerging infections and development of research-based evidence to influence policy modifications with respect to the public health improvement.

CONCLUSION

The history of emergence of arboviruses involves several mechanisms, notably geographical expansion linked to human transportation and development, enhanced transmission in peridomestic area and spillover of zoonotic cycle. Global warming increases vector distribution and transmission dynamics. The inherent ability of some arboviruses with *Aedes* vector to adapt also poses greater risk for explosive epidemics and wider epidemiological spread. The factors associated with the emergence and re-emergence of arboviral diseases are complex and mutually influenced with each other. Collaboration among academia and public health communities is critical in efforts to contain the menace of arboviral diseases emergence/resurgence.

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