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Emergence and re-emergence of mosquito-borne arboviruses

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Arthropod-borne viruses (arboviruses) are ecologically distinct from many other pathogens because of the involvement of arthropod vectors and animal reservoirs. Several mosquito-borne arboviruses have emerged in various geographic regions during the past few decades. Since the beginning of the 21st century, the emergence of two mosquito-borne arboviruses, chikungunya and Zika, has taken place globally. Millions of infections have not only changed the epidemiology of previously obscure viruses, but also put the world's public health capability to the test. Newly recognized pathogenic mechanisms and modes of transmission demand the development of new strategies for disease control and treatment. The advancement of vaccine candidates in various phases of clinical trials and the evaluation of vector control strategies in the field provide the promise of new solutions for endemic or emerging diseases. In this review, the emergence of six medically important mosquito-borne arboviruses and new tools for disease control will be discussed.

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The evidence demonstrating that mosquitoes can transmit viruses was discovered over a hundred years ago. Yellow fever virus (YFV) was the first arbovirus proven to be pathogenic to humans and vectored by *Aedes aegypti* [1]. Emergence and re-emergence of mosquito-borne arboviruses are of great public health importance, resulting in numerous outbreaks worldwide. Members of at least four virus families, *Flaviviridae*, *Peribunyaviridae*, *Phenuiviridae*, and *Togaviridae*, are known to cause human and animal diseases under diverse ecological conditions involved in different transmission cycles. For example, arboviruses vectored by *A. aegypti* often utilize humans as amplification hosts to sustain the transmission of arboviruses in urban cycles. With the exception of YFV, arboviruses transmitted by *Aedes* species mosquitoes such as chikungunya virus (CHIKV), dengue virus (DENV), and Zika virus (ZIKV) rarely cause mortality but often lead to large numbers of cases with debilitating diseases. Symptoms, associated with for example CHIKV infection, can be chronic and last for years [2]. Epizootic transmission of mosquito-borne arboviruses from animal reservoirs can also cause human diseases. As incidental hosts for zoonotic arboviruses, including Japanese encephalitis virus (JEV), Venezuelan equine encephalitis virus (VEEV) and West Nile virus (WNV), humans often succumb to neurotropic diseases. Although it is nearly impossible to discuss all outbreaks caused by arboviruses, this article summarizes some major events associated with emergence and re-emergence of mosquito-borne arboviruses in the 20th and 21st centuries and recent developments in control strategies.

Yellow fever virus

As the prototypic member in the *Flaviviridae* family, YFV has a long recorded history of causing viral hemorrhagic fever in humans. In addition to diseases historically endemic in Africa, YFV is the first arbovirus in human public health history capable of developing intercontinental dispersal after its arrival to the New World through the trans-Atlantic slave trade [3]. Research on its mode of transmission and development of the live-attenuated vaccines in the first half of the 20th century has profoundly impacted the epidemiology of YFV and other mosquito-borne arboviruses.

Identification of *A. aegypti* as a principle vector species for urban transmission of YFV provides the basis for vector control strategies. Suppressing *A. aegypti* populations became an efficient strategy in controlling yellow fever (YF) and directly reduced the mortality during construction of the Panama Canal. The subsequent effort in eradicating *A. aegypti* in the Americas further reduced the disease burden of YF in the Americas with the last known urban transmission of YFV in Bolivia in 1997 [4]. Although a majority of the endemic regions have experienced aggressive re-infestation of *A. aegypti*, the recent

increase in the incidence of YF in Latin America remains limited to diseases caused by epizootic outbreaks [5]. To date, vector control remains an integral part of public health response to disease outbreaks.

Development of the live-attenuated 17D vaccine is the most successful example of disease control for mosquito-borne viruses. Vaccination programs initiated at the end of World War II led to a significant decrease in the incidence of human diseases in endemic regions [6]. The high coverage of vaccination has successfully reduced urban transmission of YFV in Latin America, where epizootic outbreaks continue to be reported [7]. In West Africa, disease incidence has also significantly decreased due to the substantial increase of vaccine coverage [8]. To effectively control the movement of infected individuals that could introduce the virus and cause outbreaks by being fed upon by susceptible mosquitoes, some counties now require proof of vaccination in addition to traditional travel documents for entry.

Although vector control and vaccination have been proven effective for controlling YF, re-emergence of YFV continues to be reported in both Sub-Saharan Africa and Latin America as summarized in Figure 1 [5]. Between 2015 and 2018, outbreaks of YF not only led to the resurgence of human diseases in endemic areas but also caused the significant concern over the intercontinental dispersal of YFV. In 2015, the first re-emergence of the Angola genotype since 1971 led to the report of travel-associated YF cases in Asia [9]. Similarly, since 2017, epizootic outbreaks of YFV in South America [10] led to the inter-continental dispersal to multiple European countries [11].

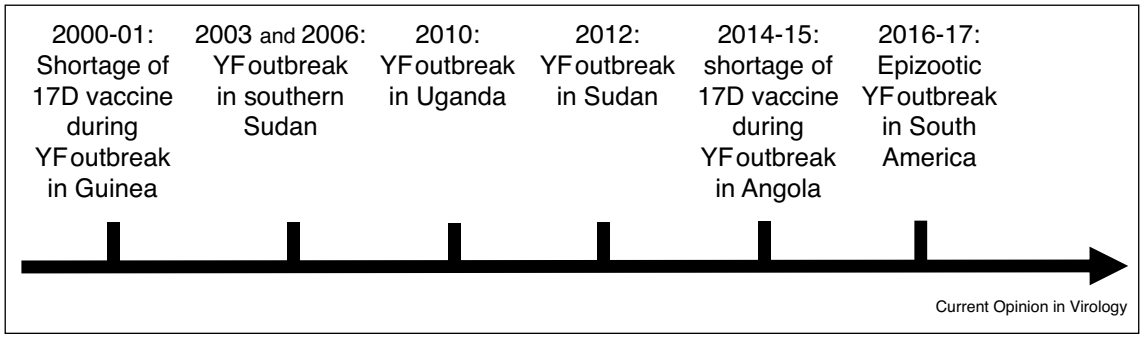
As a result of the excellent safety and immunogenicity profile of 17D vaccine, vaccination remains the most efficacious method for controlling YF diseases, with the ultimate goal of eliminating YF epidemics by 2026. However, major shortages in the global stockpiles of YF vaccines have previously coincided with several major outbreaks and negatively impact disease control [12]. Fractional dosages of YF vaccine were implemented as an alternative strategy to maintain the coverage of vaccination in response to disease outbreaks [13]. The use of available modern technologies to resolve the recurring shortage of vaccines will be a critical factor for disease control of YF.

Dengue virus

As a pathogen endemic in the majority of tropical and subtropical regions worldwide, DENV is primarily transmitted by the vector species *A. aegypti*. With a greater than 30-fold increase in the global incidence of DENV infection in the past five decades, DENV continues to negatively affect human health in multiple regions infested with *A. aegypti*. For instance, a significant increase in the disease burden has been documented among urban areas in the West Pacific region [14]. In Southeast Asia, the increase of case numbers has been attributed to rapid population growth and urbanization; whereas, the re-emergence of DENV in the Americas has been linked to re-infestation of *A. aegypti* [15,16]. In addition to outbreaks in large metropolitan areas that are historically endemic for DENV, the virus has also successfully spread to other ecological settings, presumably through the expanded distribution of *A. aegypti* [17]. For example, multiple epidemics have also been documented in the temperate zone of Nepal with the continuous introduction of multiple serotypes since 2004 [18,19].

Another worrisome reality is the increase in the incidence and magnitude of autochthonous transmission of DENV involving *A. albopictus*. Historically, the species is regarded as a secondary vector for DENV and rarely supports large scale outbreaks. However, transmission of DENV-1 by *A. albopictus* led to one of the largest outbreaks in human public health history. With over 37 000 laboratory confirmed cases in Guangzhou, China in 2014, the species demonstrated its capability of initiating and maintaining large outbreaks in an urban

Figure 1



Major yellow fever outbreaks and shortage of 17D vaccines in the 21st century.

environment [20]. As a competent species that can survive in a variety of climatic conditions, the dispersal of *A. albopictus* has also facilitated the global re-emergence of DENV. In 2014, the first autochthonous outbreak of DENV in Japan since 1945 occurred in Tokyo and was vectored by *A. albopictus* [21,22]. In Europe, the species further presents a risk to the Mediterranean region, where *A. aegypti* has been successfully eradicated [23]. Individuals infected with DENV have been identified in multiple countries around the Mediterranean basin including Croatia, Italy, and France since 2010 [24] and recently in the Netherlands and Spain. Albeit the limited number of cases, the outbreak in Nîmes France in 2015 demonstrated that the establishment of *A. albopictus* can potentially lead to the re-emergence of DENV in the region [25]. Although one can certainly argue that transmission of DENV by *A. albopictus* is mainly associated with mild and transient epidemics, there is little doubt that the species is becoming increasingly important for the dispersal of DENV [26].

Japanese encephalitis virus

Similar to YFV, vaccination programs have significantly reduced the number of human infections with JEV. Although morbidity and mortality in humans has declined, transmission of JEV remains active in enzootic cycles involving avian and swine species as amplifying hosts. Epidemiology of JEV has become increasingly complicated as co-circulation of multiple genotypes has been reported in multiple endemic countries. In East Asia, strains belonging to the clade b of genotype I (GI-b) have replaced genotype III (GIII) and become the dominantly circulating genotype since the 1990s. After several decades of silent transmission, genotype V (GV) has been repeatedly detected in this region. The mechanisms driving the emergence of GI-b and GV remain poorly understood as GI-b and GV can be vectored equally efficiently by medically important *Culex* species mosquitoes as GIII [27,28]. There is also no demonstrable difference in virulence between GI-b and GIII [29–32].

While there is no direct evidence indicating that currently licensed vaccines fail to confer protection against heterologous genotypes, the switch of endemic genotypes from GIII to GI and the emergence of GV has been reported to be associated with the increase of human cases in countries with high vaccination coverage. This potential cause and effect demands the re-evaluation of current vaccination regimen [33,34]. Since maintenance of JEV in nature is achieved through enzootic transmission, controlling the emergence of JEV will inevitably require the One Health approach by not only preventing the epizoosis through vaccination, but also must involve monitoring the emergence from enzootic transmission cycles [31,32,35–37].

West Nile virus

Originally known to cause relatively mild diseases in Africa, the introduction of WNV into the New World in 1999 led to the reports of numerous life-threatening human infections. It has not only established endemic transmission but also continues to evolve into different genotypes in North America, leading to the emergence of the NA/WN02 genotype [38]. In Europe, the endemic strains of WNV, which belong to a separate cluster under the lineage 1a, also caused a significant increase in the incidence of human disease during this period [39,40]. While it remains unclear how genetically distinct variants of WNV aggressively spread through different regions, its exceptional capability of adapting to different ecological conditions by infecting multiple species of mosquitoes plays a critical role in the establishment of transmission cycles. As WNV begins to emerge in South America, it is certain that dispersal of WNV in the New World will continue for the foreseeable future.

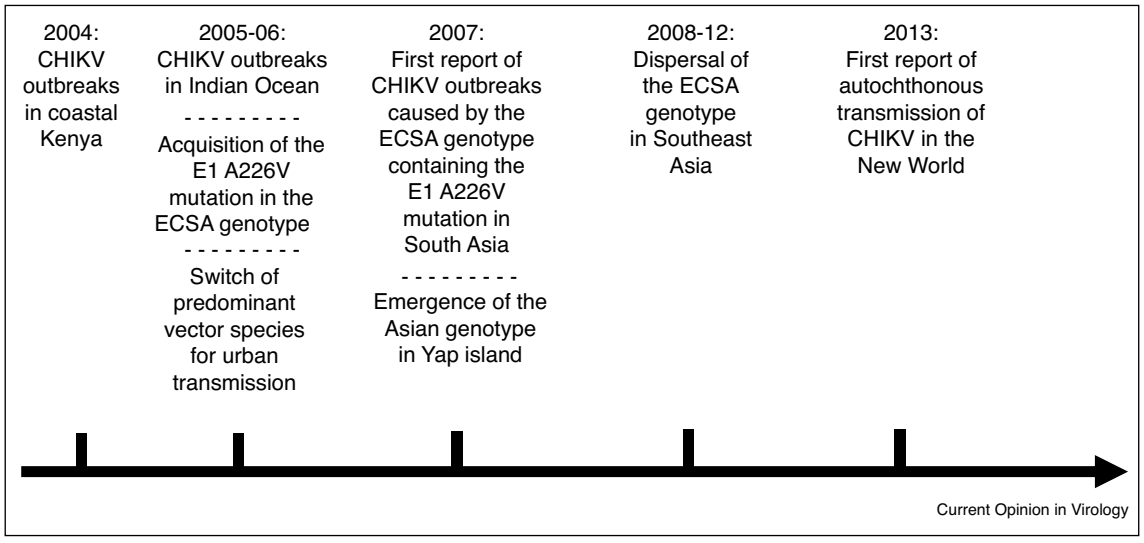
Chikungunya virus

As summarized in Figure 2, emergence of CHIKV in the 21st century involved the dispersal of two endemic genotypes, the East-Central-South Africa (ECSA) genotype and the Asian genotype. The two events significantly expanded the geographic distribution of CHIKV, which can now be found on five major continents.

In 2004, the ECSA genotype was first shown to cause human diseases in coastal Kenya, where silent transmission of CHIKV had led to a far greater number of infected individuals [41]. CHIKV quickly spread to the islands along the coast of Africa in the Indian Ocean followed by the adaptation to the transmission cycle vectored by *A. albopictus* on Réunion Island. The switch of vector species was linked to the E1-A226V mutation unique to the ECSA genotype and accelerated the dispersal of CHIKV through other islands, where *A. aegypti* was nearly eradicated from urban areas by the use of dichlorodiphenyltrichloroethane shortly after the Second World War. Transmission of the ECSA genotype by *A. albopictus* continued to cause epidemics for the next decade, leading to millions of infections in Asia, Africa, and Europe.

Although it remains unclear why an urban cycle of CHIKV was not established, the introduction of CHIKV to the Americas was known to occur once from Africa in the 1800s [42]. In December of 2013, the autochthonous transmission of CHIKV was reported in Saint Martin Island followed by dispersal through the Americas. This outbreak can be viewed as a part of the continuous emergence of the Asian genotype since 2011. Numerous infections in the Americas have changed the epidemiology of CHIKV as the dispersal of virus has been found to be bidirectional between the New World and the Old World [43].

Figure 2



Re-emergence of the East-Central-South African and Asian genotypes of chikungunya virus.

Zika virus

Before the outbreak on Yap Island in 2007, the public health significance of ZIKV was not regarded as significant. There had been only 14 human case reports of Zika fever, which normally shows mild febrile illness [44]. The emergence of ZIKV highlights how an obscure and understudied pathogen can emerge and negatively affect human health on a global scale. Because of the recent outbreak, our knowledge of transmission and disease pathogenesis of ZIKV has exponentially increased over the past few years.

The first unanticipated discovery was that multiple routes of transmission can support the spread of human to human ZIKV. Despite the limited number of cases, ZIKV was the first arbovirus found to be sexually transmitted among humans [45]. The observations were later complemented by the epidemiological findings and animal models, as infectious viruses and viral RNA can be detected in the reproductive organs and fluid of infected humans and non-human primates. However, it remains poorly understood if such a route of transmission contributes to urban transmission and viral maintenance in the sylvatic cycle.

Severe previously unseen forms of ZIKV infection were also reported during the outbreaks in French Polynesia [46]. Neurotropic diseases caused by ZIKV are mainly associated with Guillian-Barre syndrome and rarely cause mortality in adults. While this is not the first report suggesting arboviruses are capable of causing developmental abnormality in fetus, neonatal microcephaly caused by ZIKV infection during pregnancy quickly created a public health emergency in the Americas. The range of symptoms associated with ZIKV, and with CHIKV infection, are discussed by Halstead [2].

As human immunological responses to ZIKV and other related flavivirus such as DENV can be highly cross-reactive, the long-term effect of ZIKV introduction to the epidemiology of DENV remains to be seen [47]. It will inevitably become a critical factor for formulation of control strategies such as vaccine development in the future.

Conclusion

Although it is certain that ZIKV will not be the last mosquito-borne arbovirus that emerges with medical importance and high impact, based on experience, we still seem to perform poorly with regards to predicting which virus will emerge next. It is likely that it will be a zoonotic virus and it has been suggested that Mayaro or Oropouche viruses are candidates for emergence [48]. Over the years, the advancement of science has added tools for disease control, creating a sense of optimism. Multiple vaccine candidates for DENV have shown promise to control the disease with additional examples of applying the platforms for the development of vaccine candidates for other related viruses [49]. Field trials and release of *Wolbachia* and genetically modified mosquitoes provides new tools for integrated vector management targeting *A. aegypti*, the urban vector for CHIKV, DENV, YFV, and ZIKV [50,51]. A One-Health approach proactively targeting the emergence of arboviruses by blocking

transmission and diseases in animal reservoirs may provide a much-needed solution to combat the next emerging mosquito-borne arbovirus.

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