Arboviruses of Human Health significance in Kenya

Atoni E[1,2#], Waruhiu C[1,2#], Nganga S[1,2], Xia H[1], Yuan Z[1]

1. Key Laboratory of Special Pathogens, Wuhan Institute of Virology, Chinese Academy of Sciences, Wuhan 430071, China
2. University of Chinese Academy of Sciences, Beijing, 100049, China

#Authors contributed equally to this work

Correspondence: Zhiming Yuan, yzm@wh.iov.cn; Tel.: +86-2787198195

Summary

In tropical and developing countries, arboviruses cause emerging and reemerging infectious diseases. The East African region has experienced several outbreaks of Rift valley fever virus, Dengue virus, Chikungunya virus and Yellow fever virus. In Kenya, data from serological studies and mosquito isolation studies have shown a wide distribution of arboviruses throughout the country, implying the potential risk of these viruses to local public health. However, current estimates on circulating arboviruses in the country are largely underestimated due to lack of continuous and reliable countrywide surveillance and reporting systems on arboviruses and disease vectors and the lack of proper clinical screening methods and modern facilities. In this review, we discuss arboviruses of human health importance in Kenya by outlining the arboviruses that have caused outbreaks in the country, alongside those that have only been detected from various serological studies performed. Based on our analysis, at the end we provide workable technical and policy-wise recommendations for management of arboviruses and arboviral vectors in Kenya.

[Afr J Health Sci. 2018; 31(1):121-141]

Introduction

Arthropod-borne viruses (Arboviruses) are a cause of significant human and animal diseases worldwide. In history, Dengue virus, Yellow fever virus, Japanese encephalitis virus have caused notable epidemics, leading to human and animal morbidity and mortality. Recently, the outbreak of Zika virus became a global public security event, due to its ability to cause congenital brain abnormalities, including microcephaly and in some cases, being a trigger of Guillain-Barré syndrome. The control of arboviruses is rapidly becoming a priority in national and global public health systems.

Mosquitoes, ticks, sand flies, and midges are the main vectors responsible transmission of these diseases. For a variety of these viruses, the vector has been alleged to be an important reservoir during non-epidemic cases [1]. The currently known mosquito-borne infections include viruses from the families *Peribunyaviridae* (Rift Valley Fever Virus), *Flaviviridae* (Dengue virus, Yellow Fever Virus, West Nile Virus, Japanese Encephalitis virus, Zika virus), *Togaviridae* (Chikungunya virus, O'nyong-nyong virus, Sindbis virus, Semiliki Forest Virus) [2], [3]. Ticks have been evidenced to transmit viruses from the families *Nairoviridae* (Crimean Congo Hemorrhagic Fever virus), Togaviridae (Eastern Equine Encephalitis virus, Venezuelan Equine Encephalitis virus, Western Equine Encephalitis virus) and *Flaviviridae* (Tick Borne Encephalitis virus), while midges such as culicoides have been reported to transmit livestock viruses such as African Swine Fever virus and Bluetongue virus [4], [5].

Despite the presence of known competent arboviral vectors, together with the emergence and thriving of arboviral diseases [6], the potential risk of the arboviruses to the public health in Kenya is greatly underestimated owing to a lack of reliable monitoring and reporting system, proper clinical screening methods and facilities, continuous countrywide surveillance of viruses and vectors [7]. Several cases of disease are reported and documented during the outbreak episodes and little or no investigations are carried out in the inter-epidemic periods. Furthermore, the public hospitals are quite limited in the diagnostic resources leading to several cases of misdiagnosis based on clinical presentation of diseases. This has inadvertently led to unreliable statistics on the prevalence of arboviral diseases in Kenya. While most disease documentation is limited to the outbreak episodes, serological studies conducted over the past decade have revealed an ongoing circulation of arboviruses at low- levels during the inter-epidemic seasons. This low- level circulation if monitored can provide a guiding avenue for control of diseases which later explode into outbreaks when the factors are suitable. The viruses that have been shown to occur in low-level circulation include Dengue virus, Chikungunya virus, Yellow Fever virus, West Nile Virus, Tick-borne encephalitis virus [8], O'Nyong Nyong virus [9] and Rift valley fever virus [2]. In the past, notable outbreaks caused by these viruses have occurred and some have resulted in severe disease and even deaths.

In this review, we take a journey through the outbreaks and serological surveillance efforts, with regard to Arboviruses in Kenya. The data used in this report was obtained from publicly available disease and outbreak information from various platforms such as published articles, Kenyan government

online resources and WHO online records, for the years 1912- 2017. We present a map of the existing knowledge and gaps in the concerted effort to combat arboviral infections in Kenya. In this, we categorize these arboviral infections into three groups; (1) Arboviruses that have caused an outbreak in Kenya, (2) Arboviruses that have only been detected through serological evidence and (3) Other insect-associated arboviruses that are in low circulation.

Reported Arbovirus outbreaks

In the past, several arbovirus disease outbreaks have occurred in Kenya (Fig. 2). In this section, we discuss the documented arboviruses outbreaks that have had a great public health and socio-economic impact in the country.

Dengue virus (*Flaviviridae*)

Dengue virus (DENV) was first detected in 1943 in Japan and later in 1945 in Hawaii [10]. It is a flavivirus within the family *flaviviridae* and has been classified into four different serotypes; DENV I, DENV II, DENV III and DENV IV). In 2013 a fifth serotype was detected and designated DENV V [11]. *Aedes* species which are drawn to human blood and feed in the daytime are the primary vectors of DENV with *Aedes aegypti* being the most important. DENV has been considered the most important arbovirus owing to its distribution and the characteristically severe disease [12]. The virus causes a febrile illness which can range from a simple febrile illness, to a more severe Dengue Hemorrhagic fever which can progress to a fatal form, Dengue Shock Syndrome (DSS). In 2015 recombinant tetravalent live vaccine, Dengvaxia (CYD-TDV) was licensed and first applied in Mexico. Despite variable efficacy in the four DENV serotypes [13], this vaccine is now commercially available in several Asian and Latin American countries while others are in the clinical phase. Studies have shown that infection with one serotype of dengue provides a lifelong homotypic protection and may provide a short-term cross-protection against other serotypes [14]. However, secondary infections carry the potential of being very severe and advancing to DHF/DSS [13] a mechanism that is not very well understood.

In Kenya, the first recorded case of Dengue outbreak occurred in 1982 when an outbreak of febrile illness occurred in Malindi at the coastal region of Kenya (15). This outbreak was caused by the DENV-2 serotype and spread quickly to nearing towns of Mombasa and Diani. Several years later in 2011, a second outbreak was reported in Kenya in the Northern part of the country, Mandera. In the years preceding this outbreak, Dengue fever continued to occur in other African countries [16]. A serological and virological analysis of arboviruses circulating in Kenya done in 2011 showed presence of the four DENV serotypes in the Coastal population as well as

inland but did not capture the Northeastern region where the outbreak later occurred [8]. The 2011-2014 outbreak occurred in Northeastern Kenya as well as Mombasa in the coastal area of the country and was shown to be caused by DENV1-3 serotypes [17]. This outbreak was larger in geographical range as well as number of infections. Recently, another outbreak occurred in Kenya in May 2017 and it affected 6 sub-counties in the coast region (*The Standard Newspaper*, May 2017*).* This region experiences a significant traffic of tourists as well as business personnel due to the existing trading port. It provides a hotspot for potential exportation of the virus bearing in mind the incubation period of dengue is 1-7 days to onset of fever. Serological studies carried out in this region have shown a continuous low-level circulation of DENV during non-epidemic periods and small sporadic outbreaks that may go unreported.

Rift Valley Fever Virus (*Peribunyaviridae)*

RVFV was first identified in the early 1930s in the Rift valley region, Kenya [18]. Previous records have shown a disease with similar characteristics to the RVFV-disease spreading among sheep, lambs and cattle causing high mortalities and abortions [19], [20]. An outbreak in a farm in Naivasha that resulted in the deaths of over 100 sheep led to the identification of RVF as the causative agent of the disease [21] The virus causes both human and livestock disease. Humans contract the virus either from bites from infected mosquitoes or having contact with blood or organs from infected animals. To date, no human-to-human transmission case has been documented. RVFV infection in humans leads to a self-limiting, acute febrile illness. Although a small set of cases do progress to neurological disorders, partial or complete blindness, hemorrhagic fever, or thrombosis. Its incubation period ranges from 2-6 days [22], [23]**.** There is no available safe and effective RVFV vaccine that can protect humans against the great side effects of this virus [24]. However, one vaccine has been applied experimentally in protection of highly exposed personnel like veterinarians and laboratory workers to RVFV [25]. There is however an inactivated vaccine used in animals [26], [27] and it is perceived as a limiting factor for the amplification of the virus and hence reduction of spread and hence transmission to humans**.**

Aedes spp. mosquitoes, such as *Ae. mcintoshi* or *Ae. vexans,* are the main vectors, and it has been determined that the virus can be transmitted into the offspring transovarially [24], [28]. In known endemic regions, heavy rains and floods increase fresh water species of mosquitoes such as *Culex pipens*, which have a key role in RVFV amplification among mosquitoes, animals and humans [29], [30]

RVFV spread and transmission in RVFV-free countries is aided by presence of competent mosquito vectors coupled with global climatic changes, high viraemic titres in viraemic animals, travel and trade; posing a very huge global health threat. The disease is now known to be endemic in sub-Saharan Africa owing to its subsequent spread and resulting epidemics in the region. Major RVFV epidemics have been recorded in several countries including Kenya, Tanzania, Sudan, Somalia, South Africa, Madagascar, Mauritania, Egypt, Senegal, Saudi Arabia and Yemen (22).

In December 1997-1998, RVF outbreak occurred in Garissa District, North Eastern province of Kenya. 170 hemorrhagic deaths were reported. A serological study conducted in the region showed a 14% as the prevalence rate and it further estimated that 27,500 human infections occurred during the period hence making it the largest ever recorded RVFV outbreak to have occurred in sub-Sahara Africa by then [31]

To date, the most significant and extensive RVF outbreak in Kenya occurred in 2006-2007. Thousands of epizootic cases were reported in cattle, sheep, goats, and camels from 29 of 69 administrative districts across six of the eight provinces. 684 human RVF cases including 243 deaths from RVF were reported (WHO); with approximately 85% of these cases experienced in four districts namely; Garissa and Ijara districts in Northeastern Province, Baringo district in Rift Valley Province, and Kilifi district in Coast Province [32], [33]

Chikungunya virus (*Togaviridae*)

Since its detection in 1953 in Tanzania [34], Chikungunya virus (CHIKV) has been reported in several other regions across the world. CHIKV is a single stranded RNA virus belonging to the Togaviridae family, Alphavirus genus. It causes a febrile illness (Chikungunya fever) characterized by sudden onset of high-grade fever and severe chronic incapacitating arthralgia [35]**.** Other possible indications are headache, rash, joints swelling and muscle pain. There are currently no approved vaccines or medications for treatment of the infection and breaking of the transmission cycle relies on mosquito control.

CHIKV is transmitted by *Aedes* mosquitoes (day biting mosquitoes) with several outbreaks being associated with increased mosquito populations after the onset of rainfall [7].This virus is classified into three lineages; West-African genotype, East/Central/South African genotype and Asian genotype based on the nsP4 and E1 gene fragments. These phylogenetically diverse groups have been seen to occur in the distinct spacio-geographic suggested zone with travel-related importations

being reported beyond these zones. For instance in the case of the Caribbean Island of Saint Martin where the first documented autochthonous transmission and outbreak in the Americas resulted from an imported case of the Asian genotype of CHIKV [36].

Before 2004, several small-scale sporadic outbreaks were documented in Democratic republic of Congo [37], Malaysia and Indonesia [38]. Significant urban outbreaks of Chikungunya were first documented in Thailand in the early 1960s as well as India in 1963-1973 (39). In 2004, an outbreak in Mombasa and the Lamu Island of Kenya resulted in a large-scale outbreak which further spread to Comoros Islands, Reunion Island, and other Islands on the Indian Ocean and eventually to India. This outbreak resulted in a 75% infection rate in Lamu Island [40] and an approximated 266,000 people infected in the Indian Ocean Islands of Reunion and Mauritius [38]. The CHKV cycle in Africa has been shown to be maintained by the epizootic and sylvatic cycles [41] and an urban cycle in Asia [42]. In the 2004-2005 outbreak, a mutation in the E1 glycoprotein (A226V) of the East/Central/South-African genotype was evidenced to adapt the CHIKV to the *Aedes alpopictus* consequently increasing transmissibility in the Indian Ocean Islands [42].

In Kenya, a low-level circulation of CHIKV has been documented in several serological studies [2], [8], [40], [43], [44]. A rapid increase of competent vectors is commonly seen in the wet season. In 2016, a sporadic outbreak was reported in Mandera County, an area with no previous CHIKV reports hence expansion to a new geographical area. A substantially high *Aedes* spp. population was reported and a possible association with an outbreak in neighboring Bula Hawa in Somalia [45]. This trend of expansion if not curbed may extend to more areas and due to availability of naïve hosts may present a devastating case of disease. With no available vaccines and antiviral therapy, CHIKV deserves attention and a multifaceted approach to limit transmission while expanding the existing knowledge to develop more specific and targeted tools to combat it.

The 2016 CHIKV outbreak may suffer a challenge in capturing the true magnitude of the outbreak due to resource- limitation as well as low case reporting. In the 2004 outbreak, the Ministry of health reported 1300 confirmed cases while later studies revealed higher infection rates [46]. This underlines the significant need to put in place improved methods and focused efforts to the control of CHIKV in Kenya.

Yellow Fever Virus (*Flaviviridae*)

Yellow fever virus (YFV) is a mosquito-borne flavivirus of major importance in Kenya. *Aedes aegypti* is the primary mosquito vector for YF [47]. It is known to be prevalent in tropical regions of Africa and Americas. There are five known genotypes of YFV namely the Angola, East and Central African, West African, East African and the South American genotype [48]. YF is estimated to have an annual incidence of 200,000 cases with 30,000 deaths worldwide despite availability of an effective vaccine. YF disease-related mortality has been associated with individuals who fail to seek medical attention with 90% of these occurring in Africa [49]. Majority of human cases of the infection are known to be asymptomatic whereas symptomatic cases are characterized by an onset of fever, headache and a mild form undifferentiated febrile illness. Severe YF disease has been shown to cause high mortality rates of 20%–50% [50], [51] and patients present with symptoms such as photophobia, myalgias, arthalgias, epigastric pain, anorexia, vomiting, jaundice and hemorrhagic fever. The YF-17D vaccines (17DD and 17D-204) currently in use globally are based upon a modified attenuated live virus of Asibi strain developed in 1937. Vaccination confers lifelong protection. Presently, there is no scientific or clinical trial data evidence that indicate a specific antiviral or pharmacological therapy being effective in treatment of YF; instead, supportive clinical management is employed [52], [53].

In Kenya, the first reported case of YF was in the year 1942 in Kitale, subsequently the second case occurred in 1943 in Ngong Road, Langata Forest Reserve, the west of Nairobi [54], [55]. In the mid-1992 to March 1993, a large outbreak caused by the East African genotype occurred in the south Kerio Valley region, Rift Valley Province resulting in high mortality rates. Until the outbreak event, this genotype had seemingly disappeared for a period of almost 40 years and had yet to be confirmed in a clinically apparent outbreak. The main mosquito vectors identified during this epidemic were *Ae. africanus and Ae. keniensis* confirming the outbreak was a result of a sylvatic cycle [56]. Interestingly, despite the rapid urbanization in Kenya, the East African genotype has yet to emerge in the urban cycle vectored by *Ae. (Stegomyia) aegypti* [57]. The 1992/93 outbreak led to the launch of a widespread vaccination program in the endemic region, which reduced the transmission levels and hence results in diminished severity of the outbreak.

Kenya is not considered a holoendemic country although more than half of the country is considered an endemic zone for YF transmission (Fig. 1). There exists an outward increased risk of YF in Kenya as she borders countries like Sudan, Uganda and

Ethiopia where YF is endemic or major epidemics have occurred. For instance, as recently as 2003, a major epidemic occurred in Equatoria Province, in a bordering area of Sudan [58]; and in 1966 an epidemic occurred in the Gamo Gofa Province of Ethiopia near the Kenyan border [59]. All this describes why Kenya highly remains in the red-zone radar for YF infections.

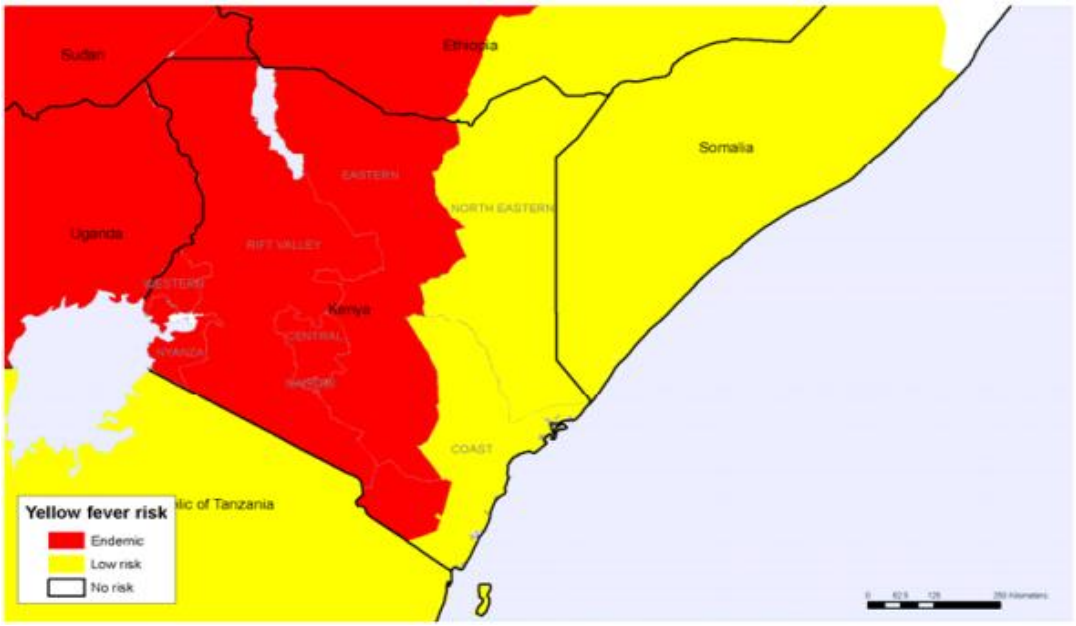


***Figure 1**: YF risk map of Kenya.* *Source: WHO*

The most recent notable cases of YF in Kenya were reported in March of 2016 in two imported cases. The Kenyan nationals, both working in Angola presented symptomatic cases, and prior to their travel they were not vaccinated for YF [60].

Serological case evidence and single case reports

Several arbovirus serological surveillance programs conducted within the country on humans and animal hosts indicate that there is an unnoticed widespread distribution of arboviruses infections. This section discusses the arboviruses that have been identified in the conducted serological studies.

West Nile Virus (*Flaviviridae*)

West Nile virus (WNV) is a mosquito-borne virus that is classified in the family *Flaviviridae*, genus *Flavivirus* and closely associated to other viruses like Japanese encephalitis, Saint Louis encephalitis, Usutu, Kunjin, Kokobera, Stratford, Alfuy and Murray Valley encephalitis all belonging to the Japanese encephalitis serocomplex [61]. It was first

detected in East Africa, first isolated in Uganda's West Nile Province in 1937.

The geographical distribution of WNV is wide and presently known to be in Africa, Europe, Russia, the Middle East, India, Australia, North and South America and the Caribbean[62]–[65], with recent outbreaks also reported in Israel, France, Tuscany region in Italy, Greece, South Africa, Hungary, southeast Romania and Texas in USA [66]–[70].

Avian species are important vertebrate amplifying hosts and their migratory pattern has greatly influenced the re-emergence and global spread of WNV [71], [72]. Mosquitoes are infected when they suck blood-meal from infected birds. Thereafter, they spread the virus on the next susceptible host they bite. The primary vectors of WNV are *Culex pipiens pipiens* and *Culex pipiens quinquefasciatus* [73].

A sero-survey conducted thereafter in the years 1939 to 1940 showed a widespread human sero-positivity in Uganda, Kenya, Democratic Republic of Congo and Sudan [74]. In 1950, WNV was isolated for the second time in Egypt during a sero-survey that demonstrated presence of WNV neutralizing antibodies in 70% of participants [75] indicating a widespread transmission in the local population. West Nile virus is endemic in Kenya and has been isolated from mosquitoes [76], [77] and ticks *(Rhipicephalus pulchellus)* [78] in North Eastern Kenya.

There has been no reported case of WNV outbreak in Kenya. However, studies have demonstrated its presence in field mosquitoes collected from North Eastern Province [79], [80] and Turkwell Gorge Hydroelectric station in West Pokot, Rift Valley Province where vertical transmission was observed in *Culex univittatus* mosquitoes [81]. Other implicated potential vectors are *C. quinquefasciatus* and *Culex vansomereni*. In addition, circulation of WNV among wild birds has been confirmed in Tana River, Kenya [82]. A sero-epidemiological survey involving local communities in Tana River and Ijara Kenya indicated that people from irrigated areas were 1.27 times more likely to get exposed to WNV than those from pastoral areas. A similar survey conducted in the local health centers among patients that sought treatment for febrile illnesses also showed presence of WNV antibodies [83].

Although the WNV has been known for a long period of time and it still remains a pathogen of public health concern in Africa and the world at large, there is still no established vaccination or curative regimen for it.

On'yong-nyong Virus (*Togaviridae*)

O'nyong-nyong (ONN) virus is an alphavirus within the *Togaviridae* family with three documented

genotypes; SG650, Igbo Ora and 37997. It was first isolated during a febrile illness outbreak of that occurred in 1959/60 affecting the Lake Victoria basin in Uganda and Kenya and extending to Tanzania (82). This was an extensive outbreak with over 2,000,000 individuals infected. The infection is characterized by fever, severe joint pain, rash as well as generalized lymphadenopathy. The symptoms are quite similar to those caused by Chikungunya and Dengue viruses. There are no vaccines or antiviral drugs for ONNV and control is dependent on vector management. *Anopheles gambiae* complex and *Anopheles funestus* are the major vectors for the transmission of ONNV. These mosquitoes are prevalent in the tropics of Africa and dwell in close association with humans increasing chances of transmission.

In 1996/97, after 35 years of seeming disappearance, the disease emerged in the Southern areas Uganda [85]. The infecting strain was shown to be of the SG650 strain closely related to the Igbo Ora strain of ONNV and CHIKV [86]. In 1978, ONNV was also isolated from a sample of pooled Anopheles mosquitoes during a non-epidemic period [87]. These studies showed a presence of ONNV in East Africa in the periods leading up to the epidemic of 1996/97 in Uganda. Several serological studies investigating the status of arboviral diseases in the inter-epidemic periods in Kenya have shown an ongoing low-level transmission and therefore probably smaller undocumented infections especially in the coastal regions [9], [43], [88].

ONNV was previously believed to be restricted to the African continent but in 2013 it was imported to Europe, Germany by a tourist from East Africa and it was documented that she acquired the infection in the Kenyan Lake region [89]. This importation did not cause further transmissions perhaps due to the absence of the competent *Anopheline* vectors in Europe. It has been suggested that the Aedes mosquito may be a competent vector for ONNV [90], however this requires further investigation. Aedes mosquito species are more widely distributed and adapted in other continents apart from Africa, and their potential ability to transmit this virus is a serious concern for the global public health.

Crimean Congo Hemorrhagic Fever Virus (*Nairoviridae*)

Crimean-Congo hemorrhagic fever virus (CCHFV) is a severe tick-borne hemorrhagic fever virus that belongs to the family *Nairoviridae.* It is the causative agent for Crimean-Congo hemorrhagic fever. CCHFV was foremost described as a clinical entity in 1944–45 in soviet military soldiers in Cremia just before World War II [91]. Thereafter, Crimean haemorrhagic fever virus was proven to be antigenically indistinguishable from Congo virus,

which had been isolated from a febrile patient in Belgian Congo [Democratic Republic of the Congo] in 1956 (90) hence its current name.

CCHF disease has a wide global distribution ranging from eastern Europe and the Crimea, to the Middle East and western China, Pakistan, and Africa. This correlates the distribution of *Hyalomma* ticks; the principle viral transmission vectors to humans [93]–[96].

CCHF is a fatal disease with its clinical manifestation varying from a subclinical disease to a multiple organ failure and shock case. Naturally, its symptoms include high fever, headache, malaise, arthralgias, nausea, myalgias, abdominal pain, and in rare cases diarrhea [97], [98].

Prior to the year 2000, CCHFV had been detected only once in 1970s in *Rhipicephalus pulchellus* ticks which were obtained from a dying sheep in a veterinary laboratory in Kabete town, near Nairobi [99]. Then the first documented case of human infection with CCHFV infection in Kenya was made on October 21, 2000 from 25-year-old male farmer who was admitted to a mission hospital in western Kenya with an acute hemorrhagic illness: this was later confirmed to be CCHF [100].

Ongoing arbovirus surveillance systems through screening of *Hyalomma* spp ticks from livestock have shown evidence of CCHFV circulation in North Eastern Kenya hence indicating a possible human exposure [101].

In 2010-2011 period, a seroprevalence study done in North-Eastern province showed a rate of 23% in Sangailu and 14% in Ijara region and the most exposed persons were of age 40–49 years and farmers had a 29% probability of exposure compared to other occupations. Also, this study identified age, location and contact to donkeys as significant risk factors associated with CCHV exposure [102].

Previous evidence for C-CHFV in Kenya is limited and based on serology (human and bovine) and two isolations of C-CHFV from non-human sources.

Other Arboviruses reported in Kenya

Metagenomic and other studies of arthropod vectors as well as the human population in Kenya have shown quite a notable prevalence of arboviral agents in circulation. In mosquitoes and ticks viruses such as Ndumu virus, Sindbis virus, Bunyamwera virus, Pongola virus, Usutu virus, Ngari virus, Babanki virus, Chaoyang-like virus, Quang Binh-like virus, Wesselsbron virus, Middelburg virus, Bhanja virus, Dugbe virus, Hazara virus, Middelburg virus, Semiliki Forest virus, Thogoto Virus, Dhori virus, Kadam virus, Barur virus as well as Foot-and-Mouth disease virus [3], [88], [103] have been reported. Some of these viruses have been associated with human disease, such as Babanki virus (Central

African Republic), Bunyamwera virus (several African countries), Sindbis virus (Uganda, South Africa and Australia), Pongola virus (Uganda), Usutu virus (Africa and Italy), Ngari virus (Africa including Kenya), Semiliki Forest Virus (Africa and Asia), Bhanja virus (USA and Europe), Dugbe virus (Africa), Thogoto virus(Africa including Kenya), Kadam virus (Uganda),Dhori (India), Wesselsbron (Afica) and Middelsburg (Africa). Some of the above viruses have been isolated from patients presenting with febrile illness or encephalitis while antibodies against others have been detected by neutralization assays in patient sera (102). In Kenya, fevers of unknown origin (FUO) are severally treated as malaria owing to limitations in diagnostic techniques. There is need to develop and provide kits and systems for arbovirus diagnostics for the healthcare system. These viruses are most likely circulating in the population undetected and have a large potential to lead to outbreaks in the future. This is a recipe for mismanagement and hence disaster in the case where outbreaks meet unpreparedness.

Overall arboviruses risk assessment in Kenya

Many arbovirus diseases are uncontrolled and the involved causative viruses are not only a unique issue to Kenya, but also form a larger part of the global issue on emerging and reemerging pathogens that can cause serious human diseases. Arboviruses have a vast choice of arthropod vectors that are capable of being infected and in turn transmitting the disease. Mosquitoes, ticks, midges, sandflies and bugs are the major arthropods that are involved in transmission cycle of the arboviruses [105] although the most predominant ones are mosquitoes and ticks. More than 300 species of mosquitoes can transmit arboviruses. *Aedes spp* and *Culex spp* mosquitoes are able to transmit more than 100 types of arboviruses [104]. In Kenya, rich abundance of competent arbovirus vectors has been determined in various studies hence leading to high arbovirus transmission risks [80], [106]–[108]. Typical tropical climate features such as rainfall, wind, temperature and humidity have been described to influence the growth and thriving of arbovirus vectors [109]. Kenya lies squarely in the tropical region and some of these factors may be playing a major role in the evident thriving of these vectors and at large the transmission cycle of arboviruses. Limited capacity/ preparedness of Kenyan public health systems in detection and diagnosing of a variety of infections are also a major key issue in the fight against arboviruses. Clinical hospitals rely mostly on symptomatic case analysis which may lead to disease misdiagnosis. Therefore, the potential risk of the arboviruses, arboviral diseases and their transmitting vectors should be carefully evaluated and immediate

approaches to mitigate the risks should be developed and implemented.

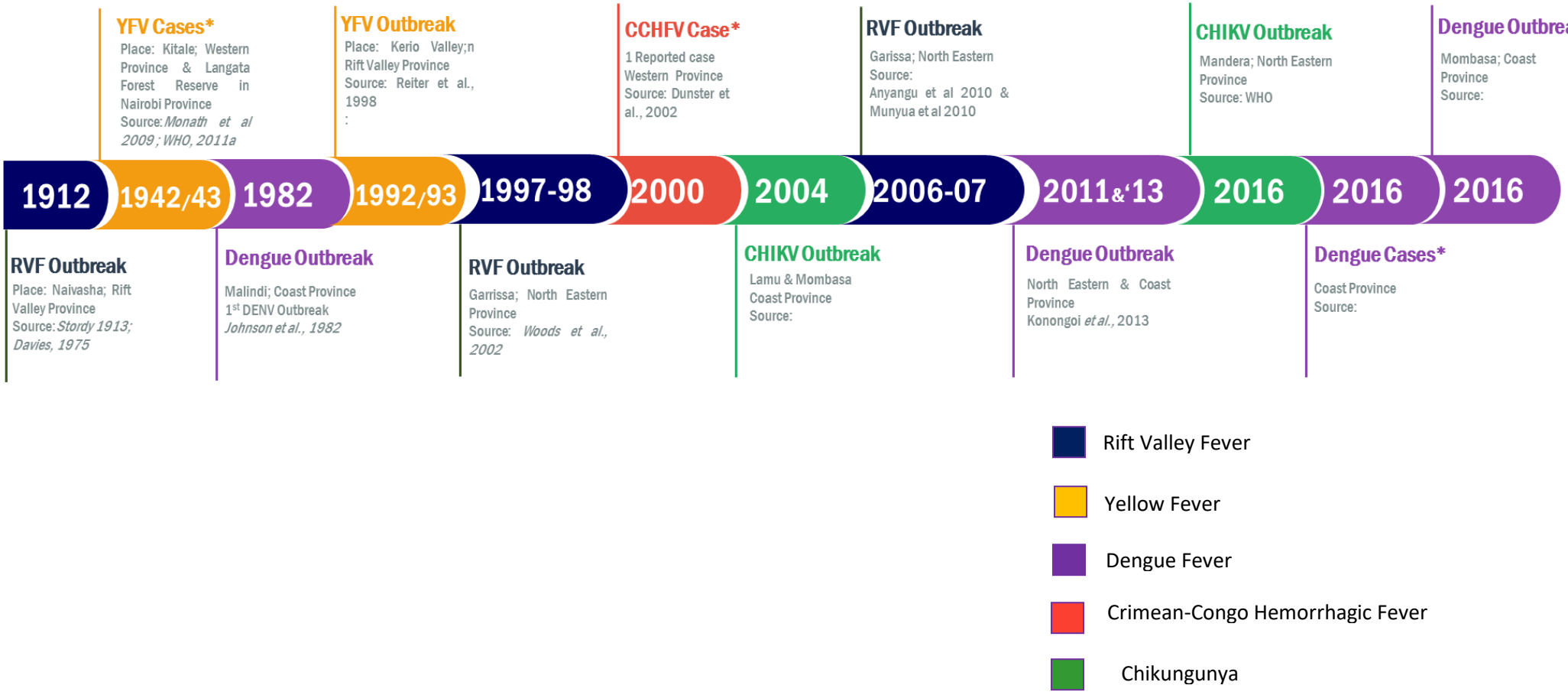
Conclusion

Serological studies have shown that Arboviruses continue to circulate in the inter-epidemic periods in Kenya. Several cases of infections go undetected due to cases of misdiagnosis or under-reporting and eventually go undocumented hence the arbovirus burden in Kenya is very likely higher than the current estimates as a number of site-limited studies have confirmed. To effectively reduce and henceforth combat the arboviral risk in Kenya, there is urgent and solemn need to; **[1]** Implement rigorous control strategies of arboviral vectors guided by accurate diagnostics in the both epidemic and inter-epidemic periods, especially in regions where outbreaks have occurred in the past. The various, already proven vector-control strategies, can include the application of biolarvicides that utilize application of certain strains of *Bacillus sphaericus* and *Bacillus thuringiensis* that produce very effective mosquitocidal toxins even at low doses against mosquito larvae and are deemed safe to other non-target organisms [110]–[112] together with the most recent novel strategies involving the development of transgenic mosquitoes that harbor dominant toxic genes, the introduction of arbovirus-blocking microorganisms into mosquitoes, and the development of acquisition-and-transmission-blocking therapeutics [113]; **[2]** Invest in efficient modern day diagnostic test methods and tools that have a high specificity and sensitivity to arboviruses. This is a critical part of determining and differentiating arboviral infections as their clinical presentations are often non-specific. The currently applied tools have the limitation of cross-reactivity especially for flaviviruses, impacting reliability of the results obtained; **[3]** Countrywide surveillance studies should be undertaken to obtain a clear outlook of the true burden of arboviral disease. Characterization of the circulating viruses will provide key knowledge on the viruses' genome, evolution and adaptations may provide insight for vaccine or drug development. Also, vector control strategies should be a priority put in place especially in outbreak hotspots as outlined by already gathered surveillance data.

Acknowledgment: This work is supported by the Ministry of Science and Technology of China (Science and Technology Basic Work Program 2013FY113500) and Sino-Africa Joint Research Center, Chinese Academy of Sciences (SAJC201605).

INFORGRAPHICS - ARBOVIRUS CASES

Figure 2: A timeline showing Arbovirus outbreaks and reported cases since 1912 to 2016. Each color represents one virus type.



References

[1] J. Lutomiah *et al.*, "Dengue Outbreak in Mombasa City , Kenya , 2013 – 2014 : Entomologic Investigations," pp. 2013–2014, 2016.

[2] C. Ochieng *et al.*, "Seroprevalence of Infections with Dengue , Rift Valley Fever and Chikungunya Viruses in," *PLoS One*, vol. 10, no. 7, pp. 1–13, 2015.

[3] J. Villanger, M. Mbaya, D. Ouso, P. Kipanga, J. Lutomiah, and D. Masiga, "Arbovirus and insect-specific virus discovery in Kenya by novel six genera multiplex high resolution melting analysis," *Mol. Ecol. Resour.*, no. September, 2016.

[4] C. Foxi, G. Delrio, G. Falchi, M. G. Marche, G. Satta, and L. Ruiu, "Role of different Culicoides vectors (Diptera : Ceratopogonidae) in bluetongue virus transmission and overwintering in Sardinia," *Parasit. Vectors*, pp. 1–13, 2016.

[5] C. Masembe *et al.*, "Viral metagenomics demonstrates that domestic pigs are a potential reservoir for Ndumu virus," *Virol. J.*, vol. 9, 2012.

[6] J. M. Mwangangi *et al.*, "Mosquito species abundance and diversity in Malindi, Kenya and their potential implication in pathogen transmission," *Parasitol. Res.*, vol. 110, no. 1, pp. 61–71, 2012.

[7] C. N. Ngoi *et al.*, "Dengue and Chikungunya Virus Infections among Young Febrile Adults Evaluated for Acute HIV-1 Infection in Coastal Kenya," *PLoS One*, vol. 11, no. 12, 2016.

[8] L. J. Sutherland *et al.*, "Short Report : Serologic Evidence of Arboviral Infections among Humans in Kenya," *Am. J. Trop. Med. Hyg*, vol. 85, no. 1, pp. 158–161, 2011.

[9] A. D. Labeaud *et al.*, "High Rates of O ' Nyong Nyong and Chikungunya Virus Transmission in Coastal Kenya," *PLoS Negl. Trop. Dis.*, vol. 9, no. 2, pp. 1–14, 2015.

[10] G. C. E. Smith, "Isolation of three strains of type 1 dengue virus from a local outbreak of the disease in Malaya," *J. Hyg. (Lond).*, vol. 54, no. 4, pp. 569–580, 1956.

[11] D. Normile, "Surprising New Dengue Virus Throws a Spanner in Disease Control Efforts," *Science (80-.).*, vol. 342, no. 6157, pp. 415–415, 2013.

[12] S. Bhatt, P. Gething, O. Brady, J. Messina, A. Farlow, and C. Moyes, "The global distribution and burden of dengue," *NIH-PA Author Manuscr. Nat.*, vol. 496, no. 7446, pp. 504–507, 2012.

[13] World Health Organization, "Weekly Epidemiological Report: Dengue vaccine WHO position paper," *World Heal. Organiszation*, vol. 30, no. 30, pp. 349–364, 2016.

[14] N. G. Reich *et al.*, "Interactions between serotypes of dengue highlight epidemiological impact of cross-immunity," *J. R. Soc. Interface*, vol. 10, no. 86, pp. 20130414–20130414, 2013.

[15] B. K. Johnson, S. Musoke, D. Ocheng, A. Gochogo, and P. H. Rees, "Dengue-2 virus in Kenya," *Lancet*, pp. 208–209, 1982.

[16] R. C. Sang, "Dengue in Africa," *J. Med. Entomol.*, vol. 2, no. December, pp. 3–6, 2005.

[17] L. Konongoi *et al.*, "Detection of dengue virus serotypes 1 , 2 and 3 in selected regions of Kenya : 2011 – 2014," *Virol. J.*, vol. 13, no. 182, pp. 1–11, 2016.

[18] M. Pepin, M. Bouloy, B. H. Bird, A. Kemp,

and J. Paweska, “Rift Valley fever virus(Bunyaviridae: Phlebovirus): an update on pathogenesis, molecular epidemiology, vectors, diagnostics and prevention.,” *Vet. Res.*, vol. 41, no. 6, p. 61, 2010.

[19] F. G. Davies, “Observations on the epidemiology of Rift Valley fever in Kenya,” *J. Hyg., Camb*, vol. 75, 1975.

[20] R. J. Stordy, “Mortality among lambs. Annual report, Department of Agriculture, British East Africa, for the year 1912–13,” 1913.

[21] R. Daubney, J. R. Hudson, and P. C. Garnham, “Enzootic hepatitis or Rift Valley fever, an undescribed virus disease of sheep, cattle and man from East Africa,” *J. Pathol. Bacteriol.*, vol. 34, pp. 545–579, 1931.

[22] T. Ikegami and S. Makino, “The pathogenesis of rift valley fever,” *Viruses*, vol. 3, no. 5, pp. 493–519, 2011.

[23] T. A. Madani *et al.*, “Rift Valley Fever Epidemic in Saudi Arabia: Epidemiological, Clinical, and Laboratory Characteristics,” *Clin. Infect. Dis.*, vol. 37, no. 8, pp. 1084–1092, Oct. 2003.

[24] M. Pepin, M. Bouloy, B. H. Bird, A. Kemp, and J. Paweska, “Rift Valley fever virus(Bunyaviridae: Phlebovirus): an update on pathogenesis, molecular epidemiology, vectors, diagnostics and prevention.,” *Vet. Res.*, vol. 41, no. 6, p. 61, 2010.

[25] WHO, “Rift Valley fever,” *WHO*, 2016. [Online]. Available: http://www.who.int/mediacentre/factsheets/fs207/en/. [Accessed: 24-Jun-2017].

[26] S. Ahmed Kamal, “Observations on rift valley fever virus and vaccines in Egypt.,” *Virol. J.*, vol. 8, p. 532, Dec. 2011.

[27] K. C. Smithburn, “Rift Valley Fever; The Neurotropic Adaptation Of The Virus And The Experimental Use Of This Modified Virus As A Vaccine.,” *Br. J. Exp. Pathol.*, 1949.

[28] K. J. Linthicum, F. G. Davies, A. Kairo, and C. L. Bailey, “Rift Valley fever virus (family Bunyaviridae, genus Phlebovirus). Isolations from Diptera collected during an inter-epizootic period in Kenya.,” *J. Hyg. (Lond).*, vol. 95, no. 1, pp. 197–209, Aug. 1985.

[29] A. S. Anyangu *et al.*, “Risk factors for severe Rift Valley fever infection in Kenya, 2007.,” *Am. J. Trop. Med. Hyg.*, vol. 83, no. 2 Suppl, pp. 14–21, Aug. 2010.

[30] K. J. Linthicum, A. Anyamba, C. J. Tucker, P. W. Kelley, M. F. Myers, and C. J. Peters, “Climate and Satellite Indicators to Forecast Rift Valley Fever Epidemics in Kenya,” *Science (80-.).*, vol. 285, no. 5426, 1999.

[31] C. W. Woods *et al.*, “An outbreak of Rift Valley fever in Northeastern Kenya, 1997-98.,” *Emerg. Infect. Dis.*, vol. 8, no. 2, pp. 138–44, Feb. 2002.

[32] P. Munyua *et al.*, “Rift Valley fever outbreak in livestock in Kenya, 2006-2007,” *Am. J. Trop. Med. Hyg.*, vol. 83, no. 2 SUPPL., pp. 58–64, 2010.

[33] A. S. Anyangu *et al.*, “Risk factors for severe Rift Valley fever infection in Kenya, 2007.,” *Am. J. Trop. Med. Hyg.*, vol. 83, no. 2 Suppl, pp. 14–21, Aug. 2010.

[34] M. C. Robinson, “An epidemic of virus disease in Southern Province, Tanganyika territory, in 1952–1953. I. Clinical Features,” *Trans. R. Soc. Trop. Med. Hyg.*, vol. 49, no. 1, pp. 28–32, 1955.

[35] G. Borgherini *et al.*, “Persistent Arthralgia Associated with Chikungunya Virus : A Study of 88 Adult Patients on Reunion Island,” *CID*,

vol. 47, pp. 469–475, 2008.

[36] W. Van Bortel, F. Dorleans, J. Rosine, A. Blateau, D. Rousset, and S. Matheus, "Chikungunya outbreak in the Caribbean region , December 2013 to March 2014 , and the significance for Europe," *Euro Surveill*, vol. 19, no. 13, 2014.

[37] B. Pastorino *et al.*, "Epidemic resurgence of Chikungunya virus in democratic Republic of the Congo: Identification of a new central African strain," *J. Med. Virol.*, vol. 74, no. 2, pp. 277–282, Oct. 2004.

[38] S. Lam *et al.*, "Chikungunya Infection - An Emerging Disease In Malaysia," *Southeasth Asian J. Trop. Med. Public Heal.*, vol. 32, no. 3, pp. 447–451, 2001.

[39] G. Pialoux, B.-A. Gauzere, S. Jaureguiberry, and M. Strobel, "Chikungunya , an epidemic arbovirosis," *Lancet Infect Disieases*, vol. 7, pp. 319–327, 2007.

[40] K. Sergon *et al.*, "Seroprevalence of Chikungunya Virus (CHIKV) Infection on Lamu Island , Kenya , October 2004," *Am. J. Trop. Med. Hyg*, vol. 78, no. 2, pp. 333–337, 2008.

[41] D. L. Vanlandingham *et al.*, "Development and characterization of a double subgenomic chikungunya virus infectious clone to express heterologous genes in Aedes aegypti mosqutioes," *Insect Biochem. Mol. Biol.*, vol. 35, no. 10, pp. 1162–1170, 2005.

[42] I. Schuffenecker *et al.*, "Genome Microevolution of Chikungunya Viruses Causing the Indian Ocean Outbreak," *PLoS Med.*, vol. 3, no. 7, 2006.

[43] C. Tigoi, O. Lwande, B. Orindi, Z. Irura, J. Ongus, and R. Sang, "Seroepidemiology of Selected Arboviruses in Febrile Patients Visiting Selected Health Facilities in the Lake/River Basin Areas of Lake Baringo, Lake Naivasha, and Tana River, Kenya," *Vector-Borne Zoonotic Dis.*, vol. 15, no. 2, pp. 124–132, 2015.

[44] A. D. LaBeaud *et al.*, "High rates of o'nyong nyong and Chikungunya virus transmission in coastal Kenya.," *PLoS Negl. Trop. Dis.*, vol. 9, no. 2, p. e0003436, Feb. 2015.

[45] WHO, "Chikungunya – Kenya," *World Health Organization*, 2016. .

[46] WHO, "Chikungunya – Kenya," *World Health Organization*, 2016. [Online]. Available: http://www.who.int/csr/don/09-august-2016-chikungunya-kenya/en/. [Accessed: 18-Jul-2017].

[47] W. Reed, J. Carroll, And A. Agramonte, "The Etiology Of Yellow Fever.," *J. Am. Med. Assoc.*, vol. XXXVI, no. 7, p. 431, Feb. 1901.

[48] J. Mutebi *et al.*, "Genetic Relationships and Evolution of Genotypes of Yellow Fever Virus and Other Members of the Yellow Fever Virus Group within the," *Society*, vol. 78, no. 18, pp. 9652–9665, 2004.

[49] B. R. Ellis and A. D. T. Barrett, "The enigma of yellow fever in East Africa," *Rev. Med. Virol.*, vol. 18, no. 5, pp. 331–346, Sep. 2008.

[50] J. E. Staples and T. P. Monath, "Yellow Fever: 100 Years of Discovery," *JAMA*, vol. 300, no. 8, p. 960, Aug. 2008.

[51] J. E. S. Mark D. Gershman, "Yellow Fever - Chapter 3 - 2018 Yellow Book | Travelers' Health | CDC," 2017. [Online]. Available: https://wwwnc.cdc.gov/travel/yellowbook/2018/infectious-diseases-related-to-travel/yellow-fever. [Accessed: 25-Jun-2017].

[52] T. P. C. Monath, "Neutralizing Antibody Responses In The Major Immunoglobulin Classes To Yellow Fever 17d Vaccination Of

Humans," *Am. J. Epidemiol.*, vol. 93, no. 2, pp. 122–129, Feb. 1971.

[53] WHO, "Yellow fever," *World Health Organization*, 2016. [Online]. Available: http://www.who.int/mediacentre/factsheets/fs100/en/. [Accessed: 25-Jun-2017].

[54] WHO, "Background for the Consultation on Yellow Fever and International Travel , 2010 (update February 2011)," vol. 2010, no. February, pp. 1–47, 2011.

[55] T. P. Monath, M. Gershman, D. R. Hill, N. Marano, J. E. Staples, and A. Wilder-Smith, "Yellow fever recommendations for tourists to Kenya: A flawed risk assessment," *J. Travel Med.*, vol. 16, no. 2, p. 146, 2009.

[56] P. Reiter *et al.*, "First recorded outbreak of yellow fever in Kenya, 1992-1993. II. Entomologic investigations.," *Am. J. Trop. Med. Hyg.*, vol. 59, no. 4, pp. 650–6, Oct. 1998.

[57] B. R. Ellis and A. D. T. Barrett, "The enigma of yellow fever in East Africa," *Rev. Med. Virol.*, vol. 18, no. 5, pp. 331–346, Sep. 2008.

[58] C. O. Onyango *et al.*, "Yellow fever outbreak, southern Sudan, 2003.," *Emerg. Infect. Dis.*, vol. 10, no. 9, pp. 1668–70, Sep. 2004.

[59] P. Ardoin, F. Rodhain, and C. Hannoun, "Epidemiologic study of arboviruses in the Arba-Minch district of Ethiopia.," *Trop. Geogr. Med.*, vol. 28, no. 4, pp. 309–15, Dec. 1976.

[60] WHO, "Yellow Fever – Kenya (Disease Outbreak News)," *WHO*, 2016. [Online]. Available: http://www.who.int/csr/don/6-april-2016-yellow-fever-kenya/en/. [Accessed: 25-Jun-2017].

[61] M. Poidinger, R. A. Hall, And J. S. Mackenzie, "Molecular Characterization of the Japanese Encephalitis Serocomplex of the Flavivirus Genus," *Virology*, vol. 218, no. 2, pp. 417–421, Apr. 1996.

[62] H. Artsob *et al.*, "West Nile Virus in the New World: Trends in the Spread and Proliferation of West Nile Virus in the Western Hemisphere," *Zoonoses Public Health*, vol. 56, no. 6–7, pp. 357–369, Aug. 2009.

[63] M. Venter *et al.*, "Lineage 2 west nile virus as cause of fatal neurologic disease in horses, South Africa.," *Emerg. Infect. Dis.*, vol. 15, no. 6, pp. 877–84, Jun. 2009.

[64] A. E. Garmendia, H. J. Van Kruiningen, and R. A. French, "The West Nile virus: its recent emergence in North America," 2001.

[65] WHO, "West Nile virus in the WHO European Region," 2011.

[66] G. L. Autorino *et al.*, "West Nile virus epidemic in horses, Tuscany region, Italy.," *Emerg. Infect. Dis.*, vol. 8, no. 12, pp. 1372–8, Dec. 2002.

[67] M. Venter *et al.*, "Transmission of West Nile virus during horse autopsy.," *Emerg. Infect. Dis.*, vol. 16, no. 3, pp. 573–5, Mar. 2010.

[68] D. Pervanidou *et al.*, "West Nile virus outbreak in humans, Greece, 2012: third consecutive year of local transmission," *Eurosurveillance*, vol. 19, no. 13, p. 20758, Apr. 2014.

[69] T. Bakonyi *et al.*, "Explosive spread of a neuroinvasive lineage 2 West Nile virus in Central Europe, 2008/2009," *Vet. Microbiol.*, vol. 165, no. 1, pp. 61–70, 2013.

[70] Y. Lustig *et al.*, "West Nile virus outbreak in Israel in 2015: phylogenetic and geographic characterization in humans and mosquitoes," *Clin. Microbiol. Infect.*, 2017.

[71] R. C. Sang and L. M. Dunster, "The growing

threat of arbovirus transmission and outbreaks in Kenya: A review," *East Afr. Med. J.*, vol. 78, no. 12, pp. 655–661, 2001.

[72] J. H. Rappole and Z. Hubalek, "Migratory birds and West Nile virus," *J. Appl. Microbiol.*, vol. 94, no. s1, pp. 47–58, May 2003.

[73] A. Diaz-Badillo *et al.*, "The distribution of potential West Nile virus vectors, Culex pipiens pipiens and Culex pipiens quinquefasciatus (Diptera: Culicidae), in Mexico City," *Parasit. Vectors*, vol. 4, no. 1, p. 70, 2011.

[74] K. C. Smithburn and H. R. JACOBS, "Neutralization-Tests against Neurotropic Viruses with Sera Collected in Central Africa.," *J. Immunol.*, vol. 43, no. 5, pp. 9–23, 1942.

[75] J. L. Melnick, J. R. Paul, J. T. Riordan, V. H. Barnett, N. Goldblum, and E. Zabin, "Isolation from Human Sera in Egypt of a Virus Apparently Identical to West Nile Virus.," *Exp. Biol. Med.*, vol. 77, no. 4, pp. 661–665, Aug. 1951.

[76] A. D. LaBeaud *et al.*, "Arbovirus Prevalence in Mosquitoes, Kenya," *Emerg. Infect. Dis.*, vol. 17, no. 2, pp. 233–241, Feb. 2011.

[77] M. Crabtree *et al.*, "Arbovirus Surveillance of Mosquitoes Collected at Sites of Active Rift Valley Fever Virus Transmission: Kenya, 2006?2007," *J. Med. Entomol.*, vol. 46, no. 4, pp. 961–964, Jul. 2009.

[78] O. W. Lwande *et al.*, "Isolation of tick and mosquito-borne arboviruses from ticks sampled from livestock and wild animal hosts in Ijara District, Kenya.," *Vector Borne Zoonotic Dis.*, vol. 13, no. 9, pp. 637–42, Sep. 2013.

[79] M. Crabtree *et al.*, "Arbovirus Surveillance of Mosquitoes Collected at Sites of Active Rift Valley Fever Virus Transmission: Kenya, 2006?2007," *J. Med. Entomol.*, vol. 46, no. 4, pp. 961–964, Jul. 2009.

[80] A. D. LaBeaud *et al.*, "Arbovirus Prevalence in Mosquitoes, Kenya," *Emerg. Infect. Dis.*, vol. 17, no. 2, pp. 233–241, Feb. 2011.

[81] B. R. Miller *et al.*, "First field evidence for natural vertical transmission of West Nile virus in Culex univittatus complex mosquitoes from Rift Valley Province, Kenya," *Am. J. Trop. Med. Hyg.*, vol. 62, no. 2, pp. 240–246, 2000.

[82] D. Nyamwaya *et al.*, "Detection of West Nile virus in wild birds in Tana River and Garissa Counties, Kenya," *BMC Infect. Dis.*, vol. 16, no. 1, p. 696, Dec. 2016.

[83] B. Bett *et al.*, "Land use change and the risk of selected zoonotic diseases: Observations from a case study in an arid/semi-arid area in Kenya," Nov. 2015.

[84] M. C. Williams and J. P. Woodall, "O ' Nyong-Nyong Fever : An Epidemic Virus Disease In East Africa," *Trans. R. Soc. Trop. Med. Hyg.*, vol. 55, no. 2, pp. 135–141, 1961.

[85] E. B. Rwaguma *et al.*, "Emergence of Epidemic O'nyong nyong Fever in Southwestern Uganda, After an Absence of 35 years," *Emerg. Infect. Dis.*, vol. 3, no. 1, p. 1997, 1997.

[86] R. S. Lanciotti *et al.*, "Emergence of Epidemic O ' nyong-nyong Fever in Uganda after a 35-Year Absence : Genetic Characterization of the Virus," *Virology*, vol. 268, pp. 258–268, 1998.

[87] B. K. Johnson *et al.*, "Recovery of o ' nyong-nyong virus from Anopheles Kenya funestus in Western," vol. 75, no. 2, pp. 239–241, 1981.

[88] C. Ochieng *et al.*, "Mosquito-borne arbovirus

surveillance at selected sites in diverse ecological zones of Kenya ; 2007 – 2012," pp. 1–10, 2013.

[89] D. Tappe *et al.*, "O'nyong-nyong virus infection imported to Europe from Kenya by a traveler," *Emerg. Infect. Dis.*, vol. 20, no. 10, pp. 1766–1767, 2014.

[90] D. L. Vanlandingham *et al.*, "Differential Infectivities Of O ' Nyong-Nyong And Chikungunya Virus Isolates In Anopheles Gambiae And Aedes Aegypti Mosquitoes," vol. 72, no. 5, pp. 616–621, 2005.

[91] H. Hoogstraal, "Review Article: The Epidemiology of Tick-Borne Crimean-Congo Hemorrhagic Fever in Asia, Europe, and Africa," *J. Med. Entomol.*, vol. 15, no. 4, pp. 307–417, May 1979.

[92] J. W. Simpson D, Knight E, Courtois, Williams, M, Weinbren, M, Kibukamusoke, "The East African medical journal : the organ of the Medical Association of East Africa.," *East Afr. Med. J.*, vol. 44, no. 2, pp. 87–92, 1967.

[93] S. B. Appannanavar and B. Mishra, "An update on crimean congo hemorrhagic Fever.," *J. Glob. Infect. Dis.*, vol. 3, no. 3, pp. 285–92, Jul. 2011.

[94] S. Shayan, M. Bokaean, M. R. Shahrivar, S. Chinikar, H. JW, and S. C, "Crimean-Congo Hemorrhagic Fever," *Lab. Med.*, vol. 46, no. 3, pp. 180–189, Aug. 2015.

[95] D. A. Bente, N. L. Forrester, D. M. Watts, A. J. McAuley, C. A. Whitehouse, and M. Bray, "Crimean-Congo hemorrhagic fever: History, epidemiology, pathogenesis, clinical syndrome and genetic diversity," *Antiviral Res.*, vol. 100, no. 1, pp. 159–189, Oct. 2013.

[96] A. Gargili, A. Estrada-Peña, J. R. Spengler, A. Lukashev, P. A. Nuttall, and D. A. Bente, "The role of ticks in the maintenance and transmission of Crimean-Congo hemorrhagic fever virus: A review of published field and laboratory studies," *Antiviral Res.*, vol. 144, pp. 93–119, 2017.

[97] M. Bray, "Comparative Pathogenesis of Crimean-Congo Hemorrhagic Fever and Ebola Hemorrhagic Fever," in *Crimean-Congo Hemorrhagic Fever*, Dordrecht: Springer Netherlands, 2007, pp. 221–231.

[98] H. Bodur, E. Akinci, S. Ascioglu, P. ?ng?r?, and Y. Uyar, "Subclinical Infections with Crimean-Congo Hemorrhagic Fever Virus, Turkey," *Emerg. Infect. Dis.*, vol. 18, no. 4, Apr. 2012.

[99] H. Hoogstraal, "Review Article: The Epidemiology of Tick-Borne Crimean-Congo Hemorrhagic Fever in Asia, Europe, and Africa," *J. Med. Entomol.*, vol. 15, no. 4, pp. 307–417, May 1979.

[100] L. Dunster *et al.*, "First Documentation of Human Crimean-Congo Hemorrhagic Fever, Kenya," *Emerg. Infect. Dis.*, vol. 8, no. 9, pp. 1005–1006, Sep. 2002.

[101] R. Sang *et al.*, "Crimean-Congo hemorrhagic fever virus in Hyalommid ticks, northeastern Kenya.," *Emerg. Infect. Dis.*, vol. 17, no. 8, pp. 1502–5, Aug. 2011.

[102] O. W. Lwande *et al.*, "Seroprevalence of Crimean Congo hemorrhagic fever virus in Ijara District, Kenya.," *Vector Borne Zoonotic Dis.*, vol. 12, no. 9, pp. 727–32, Sep. 2012.

[103] S. Baker *et al.*, "Viral antibody dynamics in a chiropteran host," 2013.

[104] N. Karabatsos, "International catalogue of arboviruses," *American Society of Tropical Medicine and Hygiene*. 1985.

[105] C. H. Calisher, "Medically important

arboviruses of the United States and Canada.," *Clin. Microbiol. Rev.*, vol. 7, no. 1, pp. 89–116, Jan. 1994.

[106] R. Sang *et al.*, "Distribution and abundance of key vectors of Rift Valley fever and other arboviruses in two ecologically distinct counties in Kenya," *PLoS Negl. Trop. Dis.*, vol. 11, no. 2, p. e0005341, Feb. 2017.

[107] S. O. Arum *et al.*, "Distribution and diversity of the vectors of Rift Valley fever along the livestock movement routes in the northeastern and coastal regions of Kenya.," *Parasit. Vectors*, vol. 8, p. 294, May 2015.

[108] J. Lutomiah *et al.*, "Abundance, diversity, and distribution of mosquito vectors in selected ecological regions of Kenya: public health implications.," *J. Vector Ecol.*, vol. 38, no. 1, pp. 134–42, Jun. 2013.

[109] P. S. Mellor and C. J. Leake, "Climatic and geographic influences on arboviral infections and vectors.," *Rev. Sci. Tech.*, vol. 19, no. 1, pp. 41–54, 2000.

[110] P. K. Mittal, "Biolarvicides in vector control: challenges and prospects.," *J. Vector Borne Dis.*, vol. 40, no. 1–2, pp. 20–32.

[111] J. M. Mwangangi *et al.*, "Wide-scale application of Bti/Bs biolarvicide in different aquatic habitat types in urban and peri-urban Malindi, Kenya," *Parasitol. Res.*, vol. 108, no. 6, pp. 1355–1363, Jun. 2011.

[112] O. Skovmand and E. Sanogo, "Experimental formulations of Bacillus sphaericus and B. thuringiensis israelensis against Culex quinquefasciatus and Anopheles gambiae (Diptera: Culicidae) in Burkina Faso.," *J. Med. Entomol.*, vol. 36, no. 1, pp. 62–7, Jan. 1999.

[113] M. J. Conway, T. M. Colpitts, and E. Fikrig, "Role of the Vector in Arbovirus Transmission," *Annu. Rev. Virol.*, vol. 1, no. 1, pp. 71–88, Nov. 2014.