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Arboviruses in the East African Community partner states: a review of medically important mosquito-borne Arboviruses

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ABSTRACT

Mosquito-borne diseases, including arbovirus-related diseases, make up a large proportion of infectious disease cases worldwide, causing a serious global public health burden with over 700,000 deaths annually. Mosquito-borne arbovirus outbreaks can range from global to regional. In the East African Community (EAC) region, these viruses have caused a series of emerging and reemerging infectious disease outbreaks. Member states in the EAC share a lot in common including regional trade and transport, some of the factors highlighted to be the cause of mosquito-borne arbovirus disease outbreaks worldwide. In this review, characteristics of 24 mosquito-borne arboviruses indigenous to the EAC are reviewed, including lesser or poorly understood viruses, like Batai virus (BATV) and Ndumu virus (NDUV), which may escape their origins under perfect conditions to establish a foothold in new geographical locations. Factors that may influence the future spread of these viruses within the EAC are addressed. With the continued development observed in the EAC, strategies should be developed by the Community in improving mosquito and mosquito-borne arbovirus surveillance to prevent future outbreaks.

Introduction
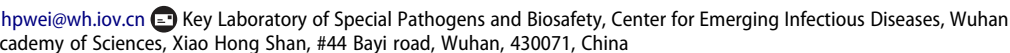
Globally, mosquitoes are regarded as a nuisance as they are perceived to cause more harm than good to humans. These very small vectors belong to the family *Culicidae*, which has approximately 3,500 mosquito species distributed in 41 genera [1]. Mosquitoes are vectors for a lot of disease pathogens which have been the cause of more than 700,000 deaths yearly across the globe [2]. Some of these deaths are caused by viruses of which mosquitoes harbor a great number. Viruses vectored by mosquitoes can be separated into two groups: mosquito-specific viruses and mosquito-borne viruses. This review will focus on the latter which in this context will be referred to as mosquito-borne arboviruses. Arboviruses are viruses that are transmitted by arthropod vectors like mosquitos, ticks, sandflies, midges, and insect bugs [3]. With the global distribution of arboviruses worldwide, some vectors and viruses are establishing a foothold in new geographical locations where they become endemic post initial spread [4]. The geographical distribution of mosquito-borne arboviruses can range from global to regional. Viruses like dengue (DENV), Chikungunya virus (CHIKV), and West Nile virus (WNV) can be located nearly everywhere in the world. While in South and Central Asia, mosquito-borne Japanese encephalitis

virus is widespread, majorly because of factors promoting amplification of the virus in favorable hosts [4]. Mosquito-borne arboviruses replicate in the host mosquito immune system before being transmitted into an appropriate vertebrate cell. This transmission has led to a series of global emerging and reemerging infectious disease outbreaks [2]. Mosquito-borne arboviruses pathogenic to humans can be classified into one of the following families: *Togaviridae, Bunyaviridae, and Flaviviridae* [4]. Each of these families is made up of diverse genera that contain many different viruses. These viruses can cause a wide range of human diseases like dengue fever, chikungunya virus disease, yellow fever (YF), Rift Valley fever (RVF), and Zika virus (ZIKV). This review will focus on mosquito-borne arboviruses that can cause disease in humans within the East African Community (EAC).

The East African Community is an intergovernmental organization made up of six countries; namely Kenya, Uganda, Tanzania, Rwanda, Burundi, and South Sudan [5–7]. Mosquito-borne arbovirus research completed by both governmental and non-governmental research institutes in these countries has been published online. However, no paper has tried to review the common viruses within these countries that share a common language and passport which allows them freedom of transport and trade; some of the factors that have been

highlighted to be the cause of serious emerging and reemerging infectious diseases [8–10]. This review will provide a synoptic overview of medically important mosquito-borne arboviruses present within the EAC countries, and also highlight a few factors that could contribute to the future spread of these viruses within the EAC.

The East African community partner states

The East African Community (EAC) was first established by Kenya, Uganda, and Tanzania in 1967 and dissolved by the three states a decade later (1977). In the year 2000, the three founder states reconstituted the EAC; Burundi and Rwanda joined later in 2007 [6,7,11], which made South Sudan the sixth and final member joining the EAC in 2016 [12–14]. The six EAC member states are governed by a governing institutional structure, five specialized institutions, and several other commissions as highlighted by Ogolla *et.al* [7]. The Great Lakes Region that includes Kenya, Uganda, Tanzania, Rwanda, and Burundi cover a total surface area of 1,817.7 thousand square kilometers; however, the EAC member states vary in size [6,7] as shown in Figure 1. Tanzania is the largest of the member states and also home to the headquarters of the East African Community. In this review, some of the viruses are stated to have been isolated in Sudan and not South Sudan. This is majorly because South Sudan used to be part of Sudan until 9 July 2011, when South Sudan (currently the Republic of South Sudan) gained independence and became Africa's 54th country [15,16].

An overview of medically important mosquito-borne arboviruses in the EAC

Mosquito-borne arboviruses of human significance in the EAC can be grossly summarized into three families, the Bunyaviridae (whose primary genus is *Orthobunyavirus* with a few other important families like the *Phlebovirus*), Togaviridae (composed of the genus *Alphavirus*), and the Flaviviridae (genus *Flavivirus*). An overview of known mosquito-borne arboviruses in these families is summarized below. Table 1 provides a summary of individual viruses including lesser or poorly understood viruses, their characteristics, and location in the EAC. The arrangement of this overview will be alphabetical similar to that of Table 1.

Bunyaviridae

The family name Bunyaviridae originated from Bunyamwera in Western Uganda, which is one of the countries in the EAC [27]. Viruses in the family Bunyaviridae are the largest RNA viruses with three distinct single-stranded, linear, negative or ambisense RNA [28]. This family is composed of more than 300 named member viruses distributed into five genera: *Phlebovirus, Nairovirus, Orthobunyavirus, Hantavirus* and *Tospovirus*. Majority of Bunyaviridae viruses are arboviruses and they have been documented to be the cause of new or emerging viral diseases. Apart from hantaviruses which are spread by specific rodents, arthropod-borne viruses are transmitted by a variety of vectors including midges, biting flies, ticks, or specific mosquitoes [27,29]. Mosquito-borne arboviruses in this
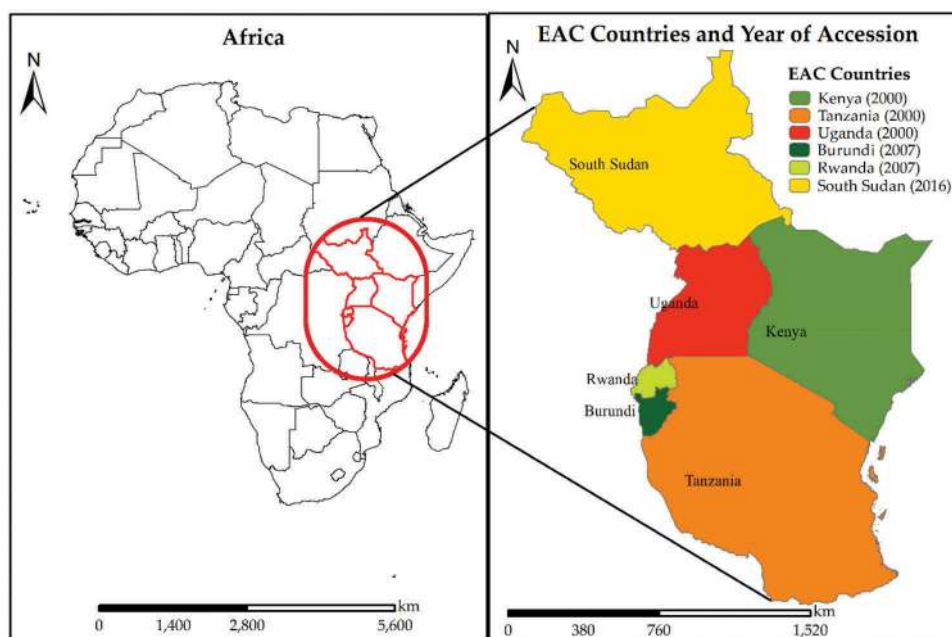

Figure 1. Location of the EAC in Africa and the countries that make up the Community. The legend shows the country names and their year of accession into the EAC in bracket.

Table 1. Summary of some characteristics of mosquito-borne arboviruses within the EAC.

Family/Genus	Virus	Known mosquito host species	Location in the EAC [a]	Disease symptoms in humans	Known/Likely amplifying host	Reference
Bunyaviridae						
Orthobunyavirus	Batai (BATV)	Aedes simpsoni, Culex gelidus, Anopheles barbirostris, An. maculipennis, Aedes punctor	Uganda, Sudan	Flu-like illness	N/A	[50,58,59,242]
	Bunyamwera (BUNV)	Ae. circumluteolus, Ae. mcintoshi, An. funestus	Kenya, Uganda	Fever, headache, joint pain, rash	Geese and other water birds	[4,32,58,88]
	Bwamba (BWAV)	Ae. furcifer, An. coustani, An. funestus, An. gambiae, Mansonia uniformis	Kenya, Rwanda, Tanzania, Uganda	Fever, headache, backache, fatal hemorrhagic complications	N/A	[36–40,46,78,88]
	Germiston (GERV)	Cx. rubinotus	Uganda	Fever, headache, lower back pain	N/A	[4,188]
	Ilesha (ILEV)	An. Gambiae	Uganda	Fever, headache, myalgia, fatal meningo-encephalitis	N/A	[4,17,18]
	Ngari (NRIV)	Ae. mcintoshi, Ae. simpsoni, An. funestus	Kenya, Sudan, Tanzania	Fatal hemorrhagic fever	N/A	[32,49,58]
	Nyando (NDV)	An. funestus	Kenya, Uganda	Moderate to severe febrile illness	N/A	[19,20]
	Pongola (PGAV)	Ae. circumluteolus, Ae. mcintoshi	Uganda, Kenya	Fever, headache, joint pains	N/A	[21,133]
	Witwatersrand (WITV)	Cx. robinotus	Uganda	N/A	Birds suspected	[4,188]
Phlebovirus	Rift Valley fever (RVFV)	Ae. aegypti, Ae. caballus, Ae. cumminsii, Ae. circumluteolus, Ae. dentatus, Ae. juppi, Ae. mcintoshi, Ae. ochraceus, Ae. pembaensis, An. squamosus, Cx. bitaeniorhyncus, Cx. quinquefasciatus, Cx. poicilipes, Cx. theileri, Cx. univittatus, Cx. zombaensis, Eretmapodites quinquevittatus, Mansonia africana, Mansonia uniformis	Kenya, Rwanda, Tanzania, Uganda, South Sudan.	Mild febrile illness with malaise, headache, myalgia, nausea, severe symptoms can be fatal	Cattle, Sheep, goats	[4,22–24,69,70,75]
Flaviviridae						
Flavivirus	Banzi (BANN)	Cx. rubinotus	Kenya, Tanzania	Febrile illness	Rodents likely	[85,88,90,218]
	Dengue (DENV)	Ae. aegypti, Ae. albopictus	Kenya, Rwanda, Sudan, Tanzania, Uganda	Arthlagia, fever, severe headache, retro-orbital pain, myalgia, and maculopapular rash. For DHF, bleeding, high fever, persistent vomiting, and intense abdominal pains	Originally non-human primates, but currently humans	[98,100,108,111,113,114,201]
	Ntaya (NTAV)	Culex spp.	Kenya, Uganda	Headache, fever, rigors, myalgia	N/A	[121–123]
	Uganda S (UGSV)	Ae. longipalpis	Uganda	N/A	N/A	[92,93]
	Usutu (USUV)	Ae. albopictus, Ae. caspius, An. maculipennis, Coquellittidia aurites, Cx. neavei, Cx. perexiguus, Cx. perfuscus, Cx. quinquefasciatus, Mansonia africana, Cx. pipiens, Cx. univittatus,	Kenya, Uganda	Fever, rash, jaundice, neuroinvassion	Birds, horses, and possibly bats	[4,130,132]
	West Nile (WNV)	Cx. modestus, Cx. neavei, Cx. perexiguus, Cx. pipiens, Cx. quinquefasciatus, Cx. univittatus, Cx. theileri	Kenya, Rwanda, South Sudan, Tanzania, Uganda	Febrile illness associated with fever, headache, rash, muscle pains, myalgia, joint pains and arthralgia; severe infections may result in paralysis, seizures, or cerebellar ataxia that can cause neurological impairment	Birds	[142–150]

(Continued)

Table 1. (Continued).

Family/Genus	Virus	Known mosquito host species	Location in the EAC [a]	Disease symptoms in humans	Known/Likely amplifying host	Reference
	Yellow fever (YFV)	Ae. Aegypti, Ae. africanus, Ae. albopictus, Ae. furcifer/taylori, Ae. leucocelaenus, Ae. luteocephalus, Ae. metallicus, Ae. opok, Ae. simpsoni Complex, Ae. vittatus, Haemagogus capricorni, Haemagogus equines, Haemagogus janthinomys, Haemagogus leucocelanus, Haemagogus mesodentatus, Haemagogus spegazzinii, Sabethes chloropterus	Burundi, Kenya, Rwanda, South Sudan, Uganda	Mild symptoms are nonspecific and include fever, headache and constitutional problems. Severe cases include, fever, headache, lower back pain, chills, malaise, nausea, generalized myalgia, and dizziness, often manifesting Faget's sign (increasing temperature with decreasing pulse rate)	Monkeys, chimpanzees, mangabey, baboons, bush babies, capuchin, marmosets, spiders, howler, and possibly hedgehogs	[4,8,153,156–158, 160,163,165,167]
	Zika (ZIKV)	Ae. aegypti, Ae. africanus, Ae. albopictus, Ae. furcifer, Ae. jamoti, Ae. opok, Ae. flavicollis, Ae. grahami, Ae. taeniorostris, Ae. tarsalis, Ae. vittatus, Ae. dalziella, Ae. fowleri, Ae. luteocephalus, Ae. metallicus, Ae. minimus, Ae. neoafricanus, An. gambiae, Eretmapodites inornatus, Eretmapodites quinquevittatus, Mansonia uniformis	Burundi, Kenya, Rwanda, Sudan, Tanzania, Uganda	Common symptoms include, arthralgia, myalgia, fever, rash, fatigue, edema, conjunctivitis, and headache	Different species on non-human primates	[4,25,26,149,174,177–179]
Togaviridae						
Alphavirus	Babanki (BBKV)	Ae. africanus, Ae. mcintoshi, Ae. ochraceus, Ae. simpsoni, Culex spp.	Kenya, Uganda	Febrile illness accompanied by rash and arthritis	N/A	[55,133,188,189]
	Chikungunya (CHIKV)	Ae. aegypti, Ae. africanus, Ae. albopictus, Ae. cordellieri, Ae. furcifer, Ae. fulgens, Ae. luteocephalus, Ae. neoafricanus, Ae. taylori, Ae. vittatus	Burundi, Kenya, South Sudan, Tanzania, Uganda	Common symptoms: fever, headache, rash, arthralgia, and myalgia. Less common symptoms: vomiting, diarrhea, hemorrhage, and inflammation of the ear and ocular disease. Severe manifestations may be fatal and include, myocarditis, neurological disease and multiorgan failure.	Non-human primates, humans	[115,149,192,195–197, 200–202]
	Ndumu (NDUV)	Ae. circumluteolus, Ae. mcintoshi, Ae. ochraceus, Ae. sudanensis Ae. tricholabis, Cx. rubinotus, Mansonia uniformis	Kenya, Uganda	N/A	N/A	[133,214,219]
	O'nyong-nyong (ONNV)	An. funestus, An. gambiae, Mansonia uniformis	Kenya, Sudan, Tanzania, Uganda, Uganda	Acute fever, joint pains, skin rash, lymphadenopathy, immobilization for up to 4 days, arthralgia		[220–222,226]
	Semliki Forest (SFV)	Ae. abnormalis-group, Ae. argenteopunctatus		Mild febrile illness, encephalitis	N/A	[229,230,232,233]
	Sindbis (SINV)	Cx. univittatus, Cx. neavei, Cx. pipiens, Cx. torrentium, Culiseta morsitans, Coquillettidia fuscopennata, Mansonia fuscopennata	Kenya, Uganda	Febrile illness, fever, arthritis, maculo-papular rash	Birds	[4,236,237,244]

[a]Viruses with Sudan as a country were islolated before South Sudan gained independence in 9 July 2011

family that are of medical significance can be found in the genus *Orthobunyavirus* and *Phlebovirus*.

Viruses in the genus orthobunyavirus (bunyaviridae)

The majority of mosquito-borne viruses in this Bunyaviridae family that are of medical importance occur in the genus *Orthobunyavirus* and are mostly transmitted by *Culex* mosquitoes. Other mosquito species like *Aedes* and *Anopheles* constitute an important group of vectors in the genus [4]. Viruses in this genus include:

Bunyamwera virus (BUNV)

Bunyamwera virus was first isolated in 1943 from the *Aedes* mosquito species found in an uninhabited area of Semliki Forest in Western Uganda known as Bunyamwera. During this time there were more than 20 known arboviruses including the Yellow fever virus which were unrelated to the virus, hence it was named Bunyamwera [30,31]. The virus has spread across many regions over the past decades and remains an important virus due to its ability to cause human diseases. Symptoms of human infections with BUNV include mild fever with rash [31]. A study in Kenya showed the presence of the virus still in circulation in the Northern part of the country [32]. In 1955 a different strain of the virus was isolated from *Aedes circumluteolus* mosquitoes in the northern coastal area of KwaZulu-Natal Province in South Africa [33]. Subsequent isolation of this virus in the same locality of South Africa from a patient who was an adult mosquito catcher presenting severe headache, fever and stiffness followed [34], including another study in the same KwaZulu-Natal Province resulting in 54% seropositivity in adult humans [35].

Bwamba virus (BWAV)

Bwamba virus was first isolated in the 1930s by Smithburn et.al. from 9 febrile road construction workers working in the Bwamba Forest located in Uganda [36–38]. The Ugandan patients presented a rapid onset of the virus including symptoms like fever, headache and backache. It was also reported that no fatalities were recorded at the time, with the symptoms persisting for 5–7 days and later clearing without sequelae [39]. Human fatalities have however been recently reported to occur on Rwandan refugees, with the affected victims showing hemorrhagic complications (bleeding from the oral mucosa into the gastrointestinal tract) that suggest the virus to be a cause of severe disease manifestations [38,40]. Another study has also reported that BWAV is fatal to mice when injected intra-cerebrally and not intra-peritoneally [36]. BWAV virus has also been isolated from various regions within the EAC and beyond. African countries that have been reported to have the virus include: Kenya, Tanzania [39], Nigeria [37,41], Cameroon, South Africa [42], Mozambique [43], and Central African Republic [44]. BWAV is spread by

mosquito vectors, primarily by *Anopheles funestus* and *Anopheles gambiae* [45]. Other mosquito vectors that spread BWAV include; *Mansonia uniformis, Anopheles funestus, Anopheles gambiae, Aedes furcifer, Anopheles coustani*, and *Aedes (Neomelanoconion)* spp [38,46,47].

Ngari virus (NRIV) and Batai virus (BATV)

The first cases of both isolation of the *NRIV* virus in humans (1993), and the vector *Aedes simpsoni* (1979) were in Senegal [48,49]. In the following years (1997 and 1998), large-scale outbreaks of the virus have occurred in the East African countries including Kenya, Tanzania and Somalia, with the outbreaks being incorrectly described by other publications to be closely related to *Batai virus* (BATV) [32,50]. Studies on NRIV genome have classified the virus to be a reassortment between Bunyamwera virus and Batai virus. NRIV virus genome is composed of 3 segments; two of which are believed to originate from BUNV (S and L segments), and one from BATV (M segment) [50,51]. NRIV has been said to be more virulent than BUNV and BATV even though studies have said it is a reassortment originated from the two viruses [49].

BATV has been said to be one of the most widespread orthobunyaviruses with initial isolations and serological evidence across the globe in various countries like Russia [52], India [53], Slovakia [54], South-East Asia [55], and also in the East African countries [50]. In Africa, serological evidence of viruses closely related to BATV was documented in Uganda in 1967 [56], and 1988 in Sudan [57]. From this, scientists wanted to answer the question as to if the M segment of the Sudanese isolate KV-141 and the Ugandan isolate UgMP-6830 closely matched that of the Kenyan NRIV than those of BATV available in other distant geographic locations. Sequence analysis results revealed that KV-141 and UgMP-6830 M segments were closely related to the Kenyan NRIV. Partial S and L segment sequence of KV-141 (Sudan) were also shown to be identical to that of NRIV (Kenya). From these studies, it was concluded that the Batai-related virus isolated from Ugandan mosquitoes [56] are real isolates of BATV, unlike the isolates from the 1988 Sudan febrile disease outbreak which were actually NRIV [50]. BATV causes a mid-flu like illness in humans while NRIV has been associated with fatal hemorrhagic fever in humans [58]. Mosquito vectors where BATV has been isolated from include *Aedes simpsoni, Culex gelidus, Anopheles barbirostris, A. maculipennis* and *Aedes punctor* [58].

From the 1988 Sudan outbreak, a total of 77,500 patient cases were recorded with 18% of the cases being diagnosed as malaria, a small portion of 7% were reported to be due to NRIV after testing 195 sera serologically [4,59]. Following the outbreak in Kenya and Somalia, which is estimated to have affected about 89,000 people in the year 1997–1998, a total of about

250 deaths were recorded. This outbreak was considered to be a Rift Valley fever (RVF) outbreak; however, some patients recorded hemorrhagic fever and further investigation on these cases reported that 27% of the cases had evidence of acute NRIV [50,51].

Viruses within the EAC in this genus with less information online are summarized in Table 1.

Viruses in the genus phlebovirus (Bunyaviridae).

The genus Phlebovirus consists of 38 distinct viruses that show varying degrees of cross-reactivity using standard serological tests [60]. Arboviruses in this genus can taxonomically be divided into; dipteran- and tick-borne arboviruses. *Phlebotomus* sandflies account for the majority of dipteran-borne phleboviruses, with the Rift Valley fever virus (RVFV) representing an outlier due to its associations with mosquito species [60–62].

Rift Valley fever virus (RVFV)

The first description of Rift Valley fever (RVF) was done in 1931 by Daubney [63] and his colleagues following an outbreak that caused sudden deaths and abortions in sheep located along the shores of Lake Naivasha in the Great Rift Valley of Kenya [63]. Daubney also later stated that there might have been a possibility of much earlier outbreaks of RVFV occurring in the region that may have been undocumented due to various reasons [64]. Other papers have also highlighted that RVFV might have been existent from as early as 1911, with some speculations as to whether the virus would have been the fifth plague documented biblically in the book of Exodus which described an epizootic disease affecting livestock [65–67]. The geographical distribution of the virus has grown since then to include many countries in Africa and beyond [68]. RVF disease is an enzootic and epizoonotic disease that mainly affects animals through mosquito-borne transmission cycles. Human beings may be affected indirectly during associations with infected animals especially during outbreaks [66]. In the EAC, RVFV was first reported in Kenya in the 1930s [63]. Since then, the virus has sparked a lot of concern in regards to human and animal health with outbreaks occurring in different EAC countries. In the years 1997–1998, a large outbreak occurred in the northeastern part of Kenya following the El Niño rains and heavy flooding that resulted in many deaths of both humans and livestock [69]. During this period, human infections were majorly linked to contact with livestock and animal body fluids [70]. No outbreak was recorded again in the EAC until the 2006–2007 outbreak. In the 2006–2007 outbreak that occurred in Kenya, Somalia, Tanzania, and Sudan, also a large number of humans and animals were affected [71,72]. In other EAC countries like Uganda, large-scale outbreaks of RVF have not been reported since 1968, whereby 7 cases were recorded in Entebbe Uganda [73]. From then, it was only in March 2016 that 2 acute human RVF cases were reported in Kabale

district located in southwestern parts of Uganda [74]. A Serological study done in livestock in Uganda near the Rwandan border provided evidence of a possible spillover of the virus between the two countries due to livestock exchange in this transportation corridor [70]. A serosurvey of circulating RVFV done in livestock located in Rwandan borders showed 16.8% seropositivity, with high seropositivity being observed in districts close to the Tanzanian border than in the 2 districts near the Ugandan border [75]. In East Africa, the important mosquito vectors that are responsible for the transmission of RVF include *Aedes ochraceus, Aedes mcintoshi, Aedes dalzieli, Culex pipiens*, and *Aedes vexans* [76]. Detection of infected vector species *A. ochraeus* in Garissa, Kenya, represented a new RVFV-vector in the EAC [77]. The vector *A. ochraeus* is known to be distributed in West Africa [78], with documentations in Somalia and Sudan which are neighboring countries of Kenya [79,80]. The different mosquito species have been suggested to be the cause of complex epidemiological RVFV patterns in East Africa [81].

Flaviviridae

Africa has been suggested to be the ancestral origin of all mosquito and tick-borne flaviviruses based on phylogenetic classification trees [82,83]. Members of the Flavivirus genus are globally distributed and composed of many species that have been taxonomically identified (currently there are more than 50, with more than 40 human pathogens) [10]. Viruses in the genus Flavivirus can be divided into four ecological groups that include two mosquito-borne groups, a tick-borne group, and a group of no-known vectors or non-vectored flaviviruses [83,84]. Pathogenic mosquito or tick-borne flaviviruses can cause an array of clinical diseases with disease symptoms including rash, mild/severe febrile illness, and in some cases encephalitis or hemorrhagic disease [10]. Mosquito-borne arboviruses of medical significance in this family include:

Banzi virus (BANV) and Uganda S virus (UGSV)

Banzi virus was first isolated from a 9-year-old boy with febrile illness in Tongaland, South Africa in 1956 [85]. Subsequent isolation of the virus in Tanzania, Kenya and many southern African countries followed [85–88]. Serological studies have shown that BANV is closely related to the Uganda S and Yellow fever virus with the virus being classified as belonging to the Uganda S serocomplex [89]. The primary vector believed to spread the virus is *Culex rubinotus* [87,90], with rodents being said to be the virus' natural host [91].

Just like in the case of BANV little is known about the epidemics of Uganda S virus. The first case of isolation of the virus was in Uganda from a pool of wild-caught *Aedes* mosquitoes [92]. 5.8% of the total 121 human sera screened by neutralization tests

demonstrated antibodies to Uganda S virus with only a single serum out of 6 testing positive for UGSV in wild monkeys. UGSV virus is highly neurotropic for mice only and no clinical signs and symptoms are produced by other laboratory animals [92]. Boorman *et.al.* highlighted a study done previously that showed the presence of UGSV in Ilobi, a village 30 miles to the north of Lagos, Nigeria [93]. The study suggested that human infections with the virus were not uncommon. Boorman *et.al* [93]. also demonstrated that under experimental conditions UGSV can last in the vector *Ae. aegypti* for a period of up to 79 days and the vector could transmit the virus by biting after only a short incubation time [93].

Dengue virus (DENV)

Literature citing the history of Dengue suggests that the virus may have existed for centuries [94]. The virus is believed to have existed as early as the Chin Dynasty (AD 265 to 420) where reports of some illness similar to dengue fever were recorded in a Chinese 'encyclopedia of disease symptoms and remedies' [95]. The records were later edited through the following dynasties; Tang Dynasty (AD 610), and the Northern Sung Dynasty (AD 992) [96]. In the following centuries and decades, the virus was believed to have spread across the globe especially during migration, trade and urbanization activities [95]. However blurred the history of Dengue is, the first epidemics were said to have occurred across three continents: Asia, Africa and North America between the period 1779–1780 [97]. In Africa, Dengue was reported in the late 19th and early 20th centuries [98] in various countries including Zanzibar (1823, 1870), Egypt (1887, 1927), and Senegal (1927–1928) [97–99]. DENV is composed of four serotypes (DENV 1–4) that have antigenic cross-reactivity. Infection from one of the serotypes does not guarantee cross-protection from other serotypes [100], this means that people living in a DENV endemic region can get infected with all four serotypes in a lifetime [97]. DENV can be transmitted among humans through mosquito vectors *Ae. aegypti* and *Ae. albopictus*, with the former being mostly found in urban settings while the latter being located in peri-urban and rural locations [101–104]. Worldwide 50–100 million cases of dengue fever and 250–500,000 cases of DHF are reported annually [94]. Dengue can cause more illness and death than other human arbovirus diseases [105]. Patients suffering from DF may show symptoms which include arthralgia, fever, severe headache, retro-orbital pain, myalgia, and maculopapular rash. For DHF, bleeding, high fever, persistent vomiting, and intense abdominal pains, which may deteriorate to failure of the circulatory system and altered mental status are common symptoms [4].

In the EAC, the first four outbreaks occurred in Tanzania in the period between 1823 and 1926 [106], with the 1826 and 1870 outbreaks being considered more of a Chikungunya virus outbreak [107,108]. The 1870 dengue pandemic started in Tanzania and spread toward various countries including Egypt, India, Saudi Arabia, Yemen, Indonesia and China [109]. Between 1952–1953 another dengue outbreak was reported at the Makonde Plateau of Tanzania [110,111]. In Kenya, the first dengue outbreak was reported in Malindi and Kilifi in the years 1860 to 1868 [106], with the first laboratory-confirmed dengue outbreak being reported in 1982 around the same coastal towns of Malindi and Kilifi [112]. In 1985–1986, outbreaks were reported in the Eastern part of Port Sudan city involving 17 cases [113]. In 2004–2005 DENV-3 reemerged again in the same port with 312 DHF cases being reported and a total of 12 lives lost. The virus later spread to the Northern parts of Kenya that border Sudan [114]. In 2010, reemergence of Dengue occurred in two countries with reports of 100 cases in Tanzania [115] and 3,765 cases in Sudan (Port Sudan city) [116]. In 2011, another outbreak occurred also in South Kordofan (Sudan) which involved 299 cases resulting in 71 deaths [100]. Interestingly also in May and October 2011, an outbreak was confirmed in Somalia (Mogadishu) among African Union Mission Soldiers (AMISON) working there [100,117]. Somalia borders Mandera town (located in the Northern parts of Kenya) where dengue positive virus samples were reported by the Kenyan Ministry of Health (MoH) [112]. More cases of Dengue were reported in 2013 in Tanzania [118]. In the same year, cases were reported in Mandera/Wajir (Kenya), with the outbreak later spreading to the coastal region of Kenya (Mombasa town) [119,120]. Dengue presence has been reported in 34 countries across Africa including all countries in the East African Community with no data available for Burundi [4,98].

Ntaya virus (NTAV)

Ntaya virus was originally isolated in 1951 from mice inoculated intracerebrally with a mixed pool of mosquitoes captured at Ntaya swamp located in Western Uganda [121]. Twenty different mosquito species were identified in the pool of 1,318 mosquitoes collected, and of the 20 species, 1,284 belonged to the *Culex* genus [4,121]. At this time, all 43 sera tested from persons living near the Ntaya swamp tested negative for neutralization of the virus [121]. This meant that the natural host for the virus remained unknown. Antibodies against the virus have been found in human sera in various African countries, specifically Kenya, Uganda, Cameroon, Central African Republic and Nigeria

[122]. NTAV symptoms have been associated with headache, fever, rigors and myalgia [122]. A study of the full genome sequence of NTAV revealed molecular characteristics of the virus that can help in the development of molecular diagnostic tests [123]. According to a study in Romania, NTAV can also be found in migratory birds and domestic animals (1.6% to 13.9% in cattle, sheep, goats, pigs) [124–126].

Usutu virus (USUV)

Usutu virus was first isolated in Natal (South Africa) from a female adult *Culex neavie* mosquito in January 1959 [127]. The virus has been shown to infect birds across Europe and Africa mostly leading to the death of some bird species with observed symptoms like: neural necrosis, hepatosplenomegaly, and necrotic changes of the liver, spleen, and heart [128]. African birds have been said to show some level of resistance to the virus compared to the European species, with less mortality rates compared to those located in Europe [129]. Phylogenetic analysis shows the possible distribution of the virus by migratory birds via various routes connecting to Europe; an east Atlantic pathway linking Africa to Western Europe (Spain), a Black Sea/Mediterranean route to central Europe, and East Africa/West Asian route [4]. Human infections of the virus have been documented both in Africa and Europe [130,131]. The two patients of Europe were both immunocompromised showing the virus' ability to infect immunocompromised humans [132]. Two human cases were also reported in Africa with very little clinical information. The first case was reported in 1981 from a patient in the Central African Republic who had fever and rash, the second case was reported in Burkina Faso from a 10-year-old patient with symptoms of fever and jaundice in 2004 [130]. The geographical distribution of USUV shows the virus to be located in most African countries including countries in East Africa like Kenya, Uganda and Tunisia [130]. In the EAC, USUV has been isolated in Kenya in a study done between 2007–2012 from *Culex pipens* [133], and in Uganda from *Coquillettidia azurites* in 1962 [134] and *Culex sp* in 1968 [73]. More seroprevalence studies should be done across the EAC and Africa to acquire more data on infections and epidemics of USUV.

West Nile virus (WNV)

In 1937 WNV was isolated from one sample taken from a febrile 37-year-old female patient from Omogo, West Nile district in the Northern Province of Uganda [135]. Multiple lineages of WNV have been identified based on sequencing, with the two major lineages 1 and 2 being identified in Africa following the first isolation of WNV in Uganda [136,137]. Since this first isolation in Uganda, the virus has spread globally and some highlight that the virus' introduction, re-introduction, and spread across Europe [138,139] and the Americas [140,141] was majorly aided by migratory birds. WNV is a mosquito-borne arbovirus that can affect both humans and animals, with ticks also being implicated to be a vector of WNV even though their importance has not been established [137]. Human WNV infections develop symptoms of febrile illness associated with fever, headache, rash, muscle pains, myalgia, joint pains and arthralgia; severe infections may result in paralysis, seizures, or cerebellar ataxia that can cause neurological impairment [142–144]. In the EAC the only case of WNV isolation was reported in Uganda, the other countries only document serological evidence of the virus from various mosquito species and humans. The virus was serologically identified from a male *Cx. univittatus* mosquito for the first time in Kenya during a fieldwork investigation, which also suggested the vertical transmission nature of WNV to humans [145]. In Rwanda, the first evidence of WNV was reported by *Seruyange et.al* [146] in 2017 when they screened 874 serum samples from human blood donors in Rwanda using commercially available kits. In the study, 10.4% of the sera tested positive for virus-specific immunoglobulin G antibodies [146]. The virus has also been serologically detected in human sera in Tanzania [147]. Serological detection has been reported in South Sudan [148–150], with also no available data of the virus in Burundi [137].

Yellow fever virus (YFV)

The virus yellow fever derived its name from the human clinical characteristics of jaundice (typical yellowing of the skin) associated with liver dysfunction [151]. Historically, the virus is believed to have originated in Africa and later spread to other regions of the world including Europe and the Americas via slave trade [8,152]. A review on the virus evolution done by Mutebi *et.al* [153] highlighted that the nucleotide sequence and phylogenetic analysis of YFV may place the virus' origin in East and Central Africa, extending to West Africa, and finally transported from West Africa to South America [153]. The disease yellow fever (YF) caused by YFV is primarily transmitted to humans by mosquitoes [154]. The transmission cycle of YFV shows that the virus can infect both humans and non-human primates in tropical regions of Africa and the Americas. This cycle occurs between forest mosquitoes and wild primates, with secondary human transmission occurring in three cycles involving sylvatic, intermediate, and urban cycles [155,156]. The sylvatic transmission cycle in Africa is aided primarily by the vectors *Ae. metallicus, Aedes africanus, Ae. furcifer/taylori, Ae. opok, Ae. luteocephalus*, and *Ae. vittatus* [153,157,158].

The African sylvatic hosts involve a variety of primates including monkeys, baboons, mangabey, hedgehogs, chimpanzees, bush babies, and possibly hedgehogs [4]. The urban cycle has been highlighted to be the deadliest of the three cycles occurring in Africa due to human to human transmission via the mosquito *Ae. aegypti* [153] which is located in most African countries. YF is still a major public health problem globally, with 90% of the total cases of infection occurring in Sub-Saharan Africa [153,159], where it is approximated that 51,000 to 380,000 cases occur yearly with about 19,000 to 180,000 deaths [160,161]. Symptoms of the disease have been reviewed extensively in many papers [151,156,160,162,163]. These symptoms range from mild to severe with mild symptoms often being nonspecific, manifested as fever, headache and constitutional problems. In such scenarios, patients recover after a few days with no further sequelae. In severe cases, however, patients show symptoms of fever, headache, lower back pain, chills, malaise, nausea, generalized myalgia, and dizziness, often manifesting Faget's sign (increasing temperature with decreasing pulse rate) [156]. In East Africa and the EAC, the disease is endemically maintained in a monkey- *Ae. (Stegomyia) africanus* jungle transmission cycle and can periodically be seen emerging in intermediate sylvatic or urban cycles that involve human to human transmissions [162]. Evidence of YF in East Africa was discovered in the mid-1930s where no known outbreaks or human diseases of YF were known, and since this time many outbreaks have been reported in East Africa [164]. The transmission of YFV by *Ae. (Stegomyia) africanus* cycle was first described in an outbreak in Uganda in the year 1948 and since then the virus has been seen to circulate in forests all over Africa [163]. In the EAC, outbreaks of YF have been reported in Kenya [165], Uganda [163], and South Sudan [166,167] with little evidence of the virus being reported in Rwanda and Burundi [4]. Even though the greatest taxonomic diversity of YF vectors are located in East and Central Africa, it is difficult to establish which mosquito species are YF-competent vectors in nature [168].

Zika virus (ZIKV)

Zika virus was first isolated in the year 1947 from a febrile rhesus macaque monkey, and later from *Aedes africanus* mosquitoes both located in Zika Forest of Uganda [169]. In 1954, the first 3 reported human cases occurred in Nigeria [170] with the virus spreading to other countries in Africa, Asia, and Oceania [171]. Phylogenetic analysis of Zika virus show distinct African and Asian lineages: East African lineage (MR766 prototype cluster), West African (Nigerian cluster), and Asian lineages [172]. All the lineages of ZIKV are believed to have emerged from the East African lineage in the late 1800s or early 1900s [173]. ZIKV is primarily transmitted by the *Aedes* mosquito species. The virus can be spread by 17 different *Aedes* mosquito species including the malaria vector *Anopheles gambiae*, two *Eretmapodites* species, and *Mansonia uniformis* mosquitoes [174]. Approximately 80% of ZIKV infections are asymptomatic [175,176]. If symptoms occur they can be mild, self-limiting, and nonspecific common to other arbovirus infections [171]. The common symptoms include arthralgia, myalgia, fever, rash, fatigue, edema, conjunctivitis, and headache [177,178]. Severe cases are often rare and need hospitalization with fewer fatalities [4].

In the EAC no outbreak of the virus has been reported. Only serological investigations have been reported in the EAC countries including cases of isolation of the virus in human sera. A review on the epidemiology of Zika virus 1947–2007 reported by Posen *et. al* [179] highlights the percentage of sera in many countries including countries in the EAC. In this review, the percentage sera in Kenya was 14.9% (3719 sera tested), Tanzania 12.7% (1063 sera tested), Uganda 6.3% (4236 sera tested), Burundi 1.4% (623 sera tested), and Sudan 0% (109 sera tested) [179]. Human infections were also reviewed and in the EAC, an incident was reported in Burundi between 1980–1982 [180], 4 article reports in Kenya between 1961–1962 and 1966–1969, 3 article reports in Tanzania between 1945–1948, 1961–1962 and 1967–1969, a single report in Sudan in 1976, and eight article reports in Uganda between 1945–1948, 1961–1962, 1967–1969, 1970, and 1984 that can be seen in the review by Posen *et. al* [179]. The only evidence seen online about ZIKV in Rwanda was highlighted in a conference proceeding on December 14–15, 2017 by *Seruyange et.al* whereby 874 viral-specific immunoglobulin G from blood donors were screened using commercial ELISA kits [146]. From this study, the seroprevalence of ZIKV was said to be low at 1.4% despite the virus being isolated in its neighboring countries. A review written by *Anna et.al* also highlights the virus' presence in the EAC member states [171].

Togaviridae

The term Togavirus was first suggested by Lwoff and Tournier to be used in the classification of enveloped RNA viruses having nucleocapsids with cubical symmetry [181]. At this time the term was not formally accepted [182]. Following the use of the term as a jargon name describing group A and group B arboviruses [183], the group proposed the family name Togaviridae in 1978 which became formally accepted and approved [184–186]. Initially, the Togaviridae group contained two genera: *Alphavirus* (from group A arboviruses) and *Flavivirus* (from the group B arboviruses), and later on two more genera

were approved: *Rubivirus* and *Pestivirus* [185] yielding a total of 4 genera. From that period until now the classification of the virus has changed. Currently, only two genera of the virus are maintained and accepted: *Alphavirus* and *Rubivirus*. The genus *Rubivirus* has a single species which is the *Rubella virus* that is of less importance in this review since it is not transmitted by mosquito vectors. The *Alphavirus* genus, however, has more than 30 species most of which are mosquito-borne arboviruses transmitted between mosquito vectors and vertebrate hosts including humans, rodents, birds, reptiles, pigs, amphibians, equids, and non-human primates [187]. A summary of the important alphaviruses spread by mosquito vectors include:

Babanki virus (BBKV)

This virus species is poorly understood and little information is available about it online. However, online sources indicate that Babanki virus was first isolated in Northwest Cameroon in 1969. The virus is closely related to the Sindbis virus which will be discussed later [133]. BBKV is said to be a strain of Sindbis virus and has been recovered from humans suffering from febrile illness accompanied by rash and arthritis in various African countries including Cameroon, Madagascar, and the Central African Republic [55,133]. The virus is usually associated with migratory birds that nest next to lakes during breeding times [133]. In Kenya, the virus was isolated from *Culex* species mosquitoes located around lake Naivasha and Victoria [133]. In Uganda however, the first isolation of the virus was in a study from late 2008 and early 2009 (Sempaya, Kikusa, and Nkokonjeru) [188]. BBKV was isolated from six mosquito pools in the study: five pools of *Cx. perfuscus* and a single pool of *Culex* species. The virus sequence in this study showed a similarity to BBKV of 98–99.8% [188]. In Uganda also, the virus was isolated in two wild bats from a study of 323 bats caught from various locations in the country [189].

Chikungunya virus (CHIKV)

According to the local Tanzanian dialect (Makonde), Chikungunya is a term that means a disease that bends up the joints [190]. The first outbreak of CHIKV was reported in the Newala and Masisi districts located in the Southern Province of the former Tanganyika territory currently known as Tanzania, from July 1952 to March 1953. The incidence rate at this time was said to be 23% and the disease was considered as a febrile disease that caused an onset of crippling joint pain with occasional rash symptoms [191–193]. Clinical manifestations of CHIKV have been documented in many papers [190,194–196] and they include fever, rash, myalgia, and headache. More symptoms including severe cases and diagnostics have been documented by *Sam et.al* [197]. The virus has been considered not to be life-threatening in the past until an outbreak accompanied by mother-to-child transmission, neurologic and hemorrhagic manifestations and mortality occurred in La Reunion in 2006 [198,199]. CHIKV belongs to the Semliki Forest complex and is closely related to O'nyong-nyong virus, another virus in the same genus *Alphavirus* identified in the preceding year, 1959, in Ugandan patients presenting symptoms similar to those of CHIKV [191,192]. CHIKV genotypes have been identified and they include the East/Central/South African (ECSA), West African and Asian genotypes [192,193]. Transmission of CHIKV is maintained in enzootic cycles among non-human primates and is transmitted by Aedes mosquito species. Human infections always occur after a bite from infected mosquitoes [200]. Transmission of CHIKV in Africa is maintained in a sylvatic transmission cycle that involves a variety of mosquito species including: *Ae. aegypti, A. africanus* in East Africa; *Ae. furcifer, Ae. taylori, Ae. dalzieli, Ae. luteocephalus*, and *Ae. vittatus* in West Africa; and *Ae. taylori* and *Ae. cordellieri* in South Africa and non-human primates [192,201,202]. Outbreaks of CHIKV have occurred across the globe [1] since the first outbreak in Tanzania. The first major outbreaks, however, occurred in Thailand and India in the 1960s and 70s [203]. From this period no other major outbreaks were recorded globally up until 2004, when a large outbreak occurred in Lamu located along the Kenyan coast and about 13,500 cases were reported [204]. In 2005, the outbreak subsequently spread to the La Reunion and Comoros Islands along the Indian Ocean with over 500,000 cases being reported, which included fatalities [205,206].

Reported cases and outbreaks of CHIKV have been recorded in all countries across the East African Community. In all the countries the ECSA lineage is common. The first case is in Tanzania where the first outbreak was also reported worldwide in 1952. Another combined outbreak of DENV and CHIKV was also reported in Tanzania in 2011–2014 [115,207,208]. In Burundi, the first outbreak was recorded between 1980–1982 [195]. In the same period, the first outbreak was also reported in Kenya in 1982, followed by the large epidemic of 2004 in Lamu and Mombasa with an attack rate of 75% [204]. More than 150 Kenyans have succumbed to the disease [194]. Another combined outbreak of CHIKV and DENV was also recorded in Kenya in 2013 similar to Tanzania [208]. Outbreaks have also been reported in Mandera county of Kenya in 2016 that borders Somalia, where reported outbreaks of CHIKV were ongoing at the same time. The most recent outbreak was reported after 2016 in the coastal city of Mombasa in 2018 [209]. In Uganda, several outbreaks of the virus have been reported between 1985–1971 [210,211]. In Sudan, the first case was reported in 1989 where 12% of the population tested were positive for

CHIKV. Subsequent outbreaks in Sudan have been recorded in 2005, 2012, and 2013 [212]. Another report on Mongolian peacekeepers deployed to South Sudan highlighted that the virus is common in South Sudan and its borders [149]. Rwanda however, has had no reported outbreaks despite outbreaks being reported all over its neighboring countries. However serological evidence was reported in a study in 2018. In this study 874 Rwandan sera were screened using commercially available ELISA kits, the seroprevalence was reported to be high at 47% [146].

Ndumu virus (NDUV)

Ndumu virus was first isolated in the northern KwaZulu-Natal area of the eastern seaboard of South Africa from *Mansonia uniformis* in 1959 [213]. Since then, the virus has spread to other parts of Africa. NDUV infections have not been studied much but the virus is said to affect humans with no morbidities [214]. The virus has shown morbidity in mice experimentally infected with the virus [213]. The virus has also been shown to cause no morbidity in non-human primates. A study done in a nonimmune verevet monkey inoculated intracerebrally showed viremia with no signs of illness [55,213]. Serological evidence provided evidence of the widespread nature of the virus in South Africa where the virus was isolated from mosquito species *Mansonia uniformis* and *Aedes circumluteolus* [213]. NDUV has been isolated from livestock in domestic settings including the first isolation of the virus in pigs located in Uganda [214] with the suggestion of possible isolation of the virus in goats [215]. The virus was also isolated from other vertebrates in Kenya including *Rhipicephalus pulchellus* collected from cattle, and warthogs [216]. In Kenya, the virus has been isolated from more than 10 mosquito species including: *Ae. sudanensis, Ae. mcintoshi, Ae. ochraceus*, and *Cx. rubinotus* [133,215,217]. NDUV is highly isolated in the *Cx. rubinotus* mosquito species [133], this may mean that the mosquito that occurs in abundance in riverine lakes [218] may play an important role in the maintenance and transmission of the virus [219].

O'nyong-nyong virus (ONNV)

Similar to the way Tanzanians described CHIKV as a 'disease that bends up the joints' [190], the Acholi people of northwestern Uganda called the disease 'O'nyong-nyong' a term in their local dialect to mean 'very painful weakening of joints' [220]. ONNV was first isolated during a major epidemic that began in Gulu, located in north-west Uganda in 1959 and spread regionally to adjacent countries including Congo, Sudan, Kenya, Tanzania and along the shores of Lake Victoria to southeastern Africa by 1962 [220,221]. Another epidemic of ONNV occurred during 1996–1997 in south-central Uganda with high infection rates of up to 48% [221]. During the outbreak, people infected showed symptoms

that included: acute fever, joint pains, skin rash, lymphadenopathy, immobilization for up to 4 days, arthralgia that lasted for 6 days, and viremia [221,222]. ONNV is a member of Semliki Forest antigenic complex and together with CHIKV they form a monophyletic group within this complex [192]. ONNV has got a variety of strains including the 1996 Uganda strain [223], and 2001 ONNV Kenya strain that has got a nearly identical sequence to that of Uganda Gulu strain from 1959 [224,225]. ONNV is transmitted by mosquitoes and is unique among other alphaviruses in that it can be transmitted primarily by night-feeding anopheline mosquitoes; *Anopheles funestus* and *Anopheles gambiae* which can also transmit malaria parasites [220,226]. The lack of ONNV in one particular area in Uganda lacking the two anopheline mosquitoes gives strong proof of the capabilities of the two anthropophilic mosquitoes in transmitting ONNV [192]. The virus has also been isolated from *Mansonia uniformis* [227]. In East Africa, ONNV is said to have caused large epidemics infecting millions of persons and disappearing for a long period of time before reemerging. It is speculated that during this time, the virus is probably being maintained through an enzootic cycle, whose hosts remain unknown [225]. Among the EAC countries, isolations and outbreaks have been reported in Kenya, Uganda, Tanzania, and Sudan [220,226,228].

Semliki Forest virus (SFV)

Semliki Forest virus was first isolated in Uganda from the *Aedes abnormalis* group of mosquitoes captured in 1942 [229]. Subsequent isolation of the virus followed in many African countries including from *Ae. argenteopunctatus* species from central Mozambique in 1959 [230]. Since this time the virus has been used as a model for studying the molecular biology of RNA viruses because it grows well with high titers in cells [231]. Laboratory injected rabbits with SFV developed fever and paralysis [229], while mice developed hindleg paralysis and convulsions which were followed by death [229,230]. Rhesus infected monkeys, on the other hand, did not develop any symptoms [229], but vervet monkeys showed fever with no other symptoms manifesting [230]. The only outbreak of SFV recorded online occurred in Bangui (found in the Central African Republic) during October-December 1987, where patients including French soldiers working there showed mild febrile illness symptoms [232]. The virus was classified to be a Biosafety Level 3 virus in USA after a person died with suspicion of SFV infection in the laboratory with human encephalitis symptoms [233]. In other European countries, the virus is classified as a Biosafety Level 2 virus [231]. Two strains of the virus exist: the original virulent isolate of SFV designated L10 [231] and the avirulent strain designated A7 isolated from mosquitoes in Mozambique [230]. Uganda is the only country within the EAC that the virus has been isolated, other African countries where

the virus has been isolated include Mozambique, South Africa, Cameroon, Central African Republic, Senegal, Congo, and Nigeria [4,234].

Sindbis virus (SINV)

Sindbis virus was first isolated in 1952 from a group of 63 *Culex* mosquitoes captured in Sindbis Health district, located north of Cairo, Egypt [235]. The first human signs and symptoms of SINV were however not reported until 1961 when humans in Uganda presented symptoms of the viral disease [236]. Human infections cause symptoms that include: febrile illness, fever, arthritis, and maculopapular rash [237]. Sindbis virus is said to be the most widely distributed arbovirus [238]. The spread of SINV internationally has been attributed to migratory birds [239]. Seasonal migration of these birds has indeed shown the correlation of migration, with geographical distribution of SINV genotypes [240]. SINV is grouped into six genotypes (SINV I-IV) that are antigenically distinct based on their difference in the *E2 glycoprotein* gene. The distribution of the virus genotypes includes SINV-I circulating mainly in Africa, Europe, and the Middle East; SINV-II in Australia and Malaysia; SINV-III in India and Philippines; SINV-IV in Azerbaijan and China; SINV-V in new Zealand; and finally SINV-VI in south-west Australia [241]. Transmission of the virus to birds occurs through ornithophilic mosquitoes (*Culex* and *Culiseta* spp.), while in humans the virus is spread from opportunistically feeding bridge vectors [242]. More about the virus strain and transmission has been reviewed by Adouchief *et.al* [241]. In South Africa, outbreaks of the virus have occurred concurrently with the outbreak of West Nile virus in the years 1974 [90], 1983 and 1984, where hundreds of Sindbis human cases were reported [4]. In the EAC, the virus has only been isolated in Uganda and Kenya. In Uganda, the virus was isolated from humans and the mosquito *Mansonia (Coquillettidia) fuscopennata* [236,243]. In Kenya however, the virus has only been isolated from a wide range of *Culex* and *Aedes* mosquito species captured from different regions around Kenya [133,217]. A study done by Sigei *et.al* on the evolutionary traits of Sindbis virus strains isolated from mosquitoes captured in Kenya between 2007 and 2013 confirmed that there is circulation of SINV-I genotype in Kenya that has been associated with human diseases in South Africa and northeastern Europe [244].

Viruses within the EAC in this family with less information online are summarized in Table 1.

Factors that may contribute to the future spread of mosquito-borne arboviruses within the East African Community

Transport

Transportation has been cited to be the cause of emerging and reemerging infectious diseases across the globe. This is the case also with mosquito-borne arboviruses. A lot of research has highlighted that transportation has played a key role in the spread of mosquito vectors and their associated arboviruses into new locations leading to epidemics of emerging and reemerging arboviral infections [70,98,245]. Different transport routes exist throughout the EAC. Some of these routes involve corridors that link landlocked countries to the busy seaport of Mombasa where mosquito vectors that contain arboviruses in this review have been isolated. Reported outbreaks of arboviruses have also been recorded including CHIKV and DENV outbreaks [120,201]. The Port of Mombasa located in Kenya serves as a gateway to East and Central Africa, and is one of the largest and busiest Ports along the East African coastline. The only other country with a port in the EAC is Tanzania with the Port of Dar Es Salaam [246]. In regards to roads linking the EAC countries, the Northern corridor is the most important as it links all the 6 countries within the EAC [5]. The Northern Corridor is the largest in the EAC and serves as a transportation corridor linking landlocked countries of the Great Lakes region like the Democratic Republic of Congo, Rwanda, Burundi, and Uganda to the port of Mombasa in Kenya. The corridor is 2,000 km and serves other countries in the EAC including Tanzania and South Sudan [5,247]. Railway lines also exist including the Kenya-Uganda Railway and the ongoing construction of the Standard Gauge Railway (a joint project between countries in the EAC with the Chinese One Belt One Road initiative) that aims to link the seaport of Mombasa to other countries in East and Central Africa [248,249]. Citizens of the various countries within the EAC can now travel freely within countries in the EAC due to the countries agreement to share a common passport. These transportation facts may play a role in the spread of arboviruses within the EAC.

Trade

From this review, some of the arboviruses have been said to be spread across the continent from one region to the other due to trade. A classic example includes the Yellow fever virus that was said to have originated in Africa and later spread to other parts of the world due to slave trade that dated back as far as 1650 [8,157,191]. Large numbers of slaves were imported from Africa who were said to be YFV-infected and along with them the *Ae. aegypti* mosquito was also transported, this caused infections mainly to nonimmune white people in the Caribbean [4]. In a review done by Pfeffer and Dobler, they highlighted the spread of different viruses from one location to another and the important roles of humans and animals in arbovirus spread because of trade [9]. A customs trade union exists within the EAC that ensures freedom of moving goods produced within the community imposing some form of barrier to external trade [14]. Among the commodities that are traded within the EAC include livestock. Livestock found in different countries within the EAC are known to be associated with mosquito-borne

viruses including Rift Valley fever, and Ndumu virus [75,214]. The transportation corridors discussed above serve also as routes for trade within the EAC. Some of the countries within the EAC like Uganda are landlocked and rely on access to seaports of Mombasa (a region with high mosquito-borne arbovirus outbreaks like CHIKV and DENV) [119,201] and Tanzania (Dar-es-Salam) (also endemic to mosquito borne arboviruses) for trade [246].

Climate

In their review of the impact climate change has had on the spread of arboviruses globally, Gould and Higgs highlighted various possible factors that have influenced the emergence of arboviruses in the past 50 years [250]. They state that climate is a major factor in determining: the geographic and temporal distribution of arthropods; characteristics of arthropod life cycles; dispersal patterns of associated arboviruses; the evolution of arboviruses; and the efficiency by which arboviruses are transmitted from arthropods to vertebrate hosts [250]. Meanwhile, other literature have associated arboviral spread with fluctuating climatic conditions [4,9,68,250]. The EAC member states experience climatic conditions that are atypical to equatorial regions [246]. These conditions are surprisingly cool and dry for its latitude despite it having a generally high altitude, and the rain shadow of the westerly monsoon winds from the Ethiopian Highlands and Ruwenzori Mountains. In East Africa, moderate temperatures are experienced, except for the hot and humid coastal belt. Different altitudes experience different temperatures: altitudes of up to 1,500 meters have a temperature range between highs of 25°C (77°F) and lows of 15°C (59°F), while above 2,500 meters frost is common in dry seasons with maximum temperatures of about 21°C (70°F) or less [7]. In the EAC, periodic outbreaks of mosquito-borne arboviruses like DENV, CHIKV, RVFV, Ngari virus have seen outbreaks that were preceded by heavy rainfall and floods that were said to be good breeding sites of mosquitoes [4,77,112,198].

Conclusion

From this review, it is evident that a substantial number of mosquito-borne arboviruses exist within the East African Community partner states as shown in Figure 2. Some of these viruses like RVFV, ZIKV, and
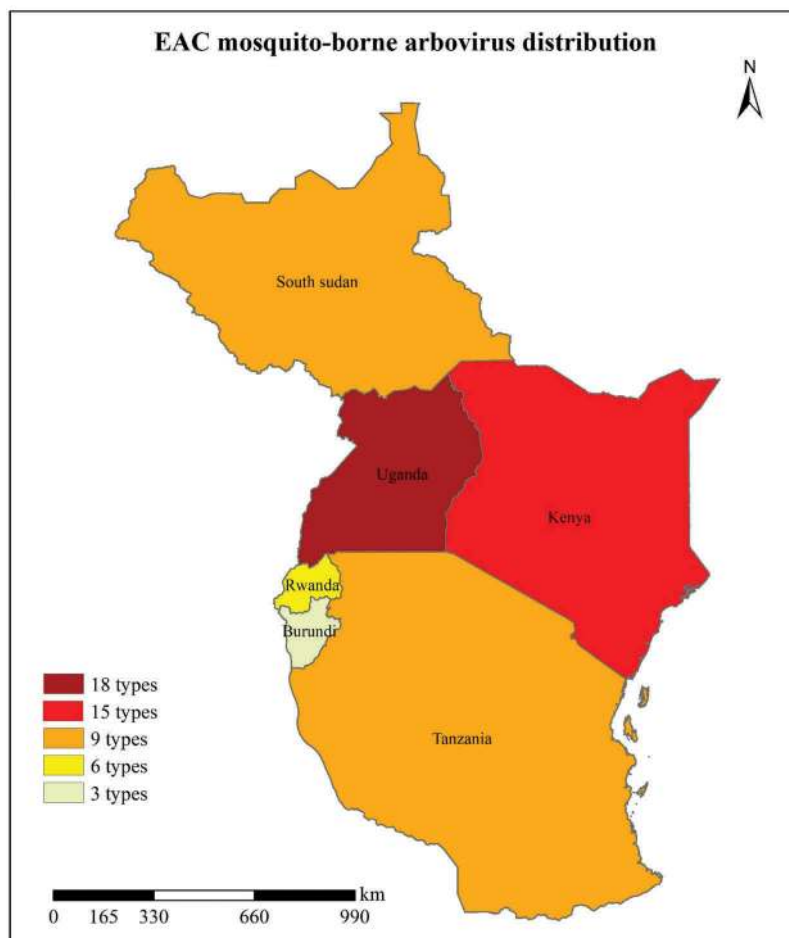

Figure 2. Distribution of mosquito-borne arboviruses across the East African Community. A total of 24 different mosquito-borne arboviruses (Table 1) are located within the EAC with high prevalence in Uganda, Kenya, Tanzania and South Sudan.

WNV have originally been isolated for the first time in the EAC and spread to other countries worldwide where they become endemic and cause devastating public health outbreaks post initial spread. It is also clear that the majority of viruses are located in Uganda and Kenya with less evidence of virus isolations in Rwanda and Burundi respectively. This raises concerns that can only be addressed by further research to establish the true prevalence of mosquitoes and mosquito-borne arboviruses in these countries. The future spread of mosquito-borne arboviruses from country to country within the EAC may be facilitated with the rapid expansion in trade, transport and fluctuating environmental conditions. Already transport routes like the Northern corridor and other routes linking the seaport of Mombasa to other landlocked countries like Uganda and Burundi exist. All these factors may provide a 'perfect environment' for future arbovirus outbreaks within the EAC. Surely, all it takes is the introduction of vectors or viruses by humans into new locations where they become quiescent until under perfect sylvatic conditions they can spread and cause devastating outbreaks. We, therefore, recommend that the EAC governing structure: 1) make it a priority to increase vigilance of the spread of mosquito vectors and also monitor the introduction/spread of new arboviruses within the EAC; 2) come up with routine arbovirus surveillance activities especially with regards to less studied arboviruses like BBKV, SFV, and BATV; 3) and if possible set up a joint research institution for arbovirus research in the EAC. Since an incredible number of novel viruses have been isolated in the EAC, it is also probable that other novel mosquito-borne arboviruses still exist within the Community waiting for the perfect conditions to cause devastating outbreaks.

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