

Arbovirus and its potential to lead the next global pandemic from sub-Saharan Africa: What lessons have we learned from COVID-19?

Elizabeth N. Mbim¹, Uwem Okon Edet^{2,*}, Henshaw Uchechi Okoroiwu³, Francisca O. Nwaokorie⁴, Asanga Effiong Edet⁵, Ayo Owolabi⁶, Mboto Clement I⁷

Abstract

Risk and predisposing factors for viral zoonoses abound in the sub-Saharan Africa (SSA) region with significant public health implications. For several decades, there have been several reports on the emergence and re-emergence of arbovirus infections. The lifetime burden of arboviral diseases in developing countries is still poorly understood. Studies indicate significant healthcare disruptions and economic losses attributed to the viruses in resource-poor communities marked by impairment in the performance of daily activities. Arboviruses have reportedly evolved survival strategies to aid their proliferation in favorable niches, further magnifying their public health relevance. However, there is poor knowledge about the viruses in the region. Thus, this review presents a survey of zoonotic arboviruses in SSA, the burden associated with their diseases, management of diseases as well as their prevention and control, mobility and determinants of infections, their vectors, and co-infection with various microorganisms. Lessons learned from the ongoing coronavirus disease 2019 (COVID-19) pandemic coupled with routine surveillance of zoonotic hosts for these viruses will improve our understanding of their evolution, their potential to cause a pandemic, control and prevention measures, and vaccine development.

Keywords Arboviruses, vectors, transmission, sub-Saharan Africa, pandemic, epicentre, COVID-19.

Introduction

Arboviruses are a complex group of RNA viruses capable of being transmitted to humans and other vertebrates via bites from arthropod vectors such as ticks, mosquitoes, lice, sand flies, and biting midges among others.¹ Studies report that more than 100 species of arboviruses are present in most zoonotic diseases recorded in resource-poor settings like sub-Saharan Africa

(SSA) and this region continues to bear the brunt of these diseases.² Most zoonotic arboviruses belong to two major families: *Flaviviridae* and *Togaviridae*, as well as the order *Bunyavirales*, with their infections presenting with various symptoms such as hemorrhagic fever, polyarthralgia, encephalitis, and death in humans and animals. However, the majority of the arboviral infections are asymptomatic.^{3,4} Also,

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¹PhD, Department of Public Health, Faculty of Basic Medical Sciences, Arthur Jarvis University, Brigadier Dan Archibong Drive, Ikot Effanga Akpabuyo, Cross River State, Nigeria; ²PhD, Department of Biological Sciences (Microbiology), Faculty of Natural and Applied Sciences, Arthur Jarvis University, Brigadier Dan Archibong Drive, Ikot Effanga Akpabuyo, Cross River State, Nigeria; ³PhD, Department of Medical Laboratory Science, Faculty of Basic Medical Sciences, Arthur Jarvis University, Brigadier Dan Archibong Drive, Ikot Effanga Akpabuyo, Cross River State, Nigeria; ⁴PhD, Department of Medical Laboratory Science, College of Medicine, University of Lagos, 12003, Lagos State, Nigeria; ⁵PhD, Department of Chemical Sciences (Biochemistry), Faculty of Natural and Applied Sciences, Arthur Jarvis University, Brigadier Dan Archibong Drive, Ikot Effanga Akpabuyo, Cross River State, Nigeria; ⁶MSc,

Department of Public Health, Faculty of Basic Medical Sciences, Arthur Jarvis University, Brigadier Dan Archibong Drive, Ikot Effanga Akpabuyo, Cross River State, Nigeria; ⁷PhD, Department of Microbiology, Faculty of Biological Sciences, University of Calabar, P.M.B 1115, Etta Agbo Rd, Calabar, Cross River State, Nigeria.

*Corresponding author: Uwem Okon Edet, uwemedet27@gmail.com

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more families have demonstrated pathogenicity in humans, including the *Reoviridae*, *Rhabdoviridae*, and *Orthomyxoviridae* families.³

Worthy of note is the fact that most arbovirus-infected humans are often categorized as either incidental or dead-end hosts because they do not produce a high level of viremia capable of eliciting a host-vector-host transmission cycle. However, a few infections with dengue and chikungunya viruses are known to cause significant viremia capable of being transmitted to uninfected invertebrate hosts, which initiate the human-vector-human transmission cycle.¹ It is now known that almost all mosquito-borne viruses isolated from Africa and recognized as zoonotic have gained intercontinental spread, making them a significant public health challenge. Furthermore, some of these viruses maintain sylvatic cycles with the capacity to infect humans and serve as “time bombs” awaiting future impact.⁵

The ecology of arboviruses is somewhat complex, including several reservoirs, bridging vectors, and amplifying hosts with the capacity to influence their transmission and potential spill-over into vertebrate hosts. Prior to their international emergence, these viruses were responsible for undetected diseases in Africa, spreading between vectors and vertebrate hosts and extending to sensitive species during climatic events causing severe diseases.⁴ Geographical dispersions of arboviral diseases are associated with anthropogenic activities and ecological factors. In other words, the abundance of vectors such as *Aedes*, *Culex*, *Anopheles* mosquitoes, rodents, *Ixodes* ticks and sand flies; forest dispersions, warm eco-climates, moorlands, and steep ecosystems considerably influence their transmission.⁶ Furthermore, animal reservoirs such as migratory birds, rodents, and nomadic livestock are present in large numbers, especially in areas where arboviral diseases have emerged.^{3,4} Thus, the availability and epidemiology of vectors, animal reservoirs, and favorable climates are considered significant determinants of arboviral disease outbreaks locally, regionally, and internationally.⁴

With coronavirus disease 2019 (COVID-19) SSA's index case reported in Egypt in 2020, available data two years into the pandemic indicates a total of 11,386, 025 cases, 251,845 deaths, and 10,755,951 recoveries as of April 2022, making it the region with the least number of cases and deaths from COVID-19. However, these low figures are in line with the significantly low number of tests which stood at 104,427,090 tests for the same period, less than 20 percent of the total population in the region. The same region is also endemic to human immunodeficiency virus (HIV) and malaria, two infections for which effective cures are still being sought and can even lead to co-infection probably due to geographic overlap among other factors.⁷ Viral pandemic always seems to be a step ahead of science, thus preventing such epidemics or pandemics appears to be more effective than controlling their occurrence. The concerns and potential of a co-infection with COVID-19 is already reported in Pakistan⁸ and an increased incidence of arboviruses was documented by the World Health Organization (WHO) and placed at over 1.6 million cases in the first few weeks of 2020 alone in the WHO regions of America. This increase in the incidence of cases was attributable to dengue (97%), chikungunya (>2%), and zika (<1%) viruses.⁹ While the WHO report was not for SSA, the region is well-known for arboviral diseases that have emerged and re-emerged for several decades.⁹ There is increasing concern over the potential of co-infection between arboviruses and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which could further worsen control and vaccination efforts, stretch their already fragile and poorly-funded healthcare systems in SSA, and increase co-morbidities. This is an overview of zoonotic arboviruses in SSA, the disease burden, management, prevention and control, mobility, determinants, and vectors of infections, and the potential to co-infect with SARS-CoV-2 and other pandemic viruses.

Diversity of arboviruses in sub-Saharan Africa

First reported by the Rockefeller foundation between the 1930s and 1970, there are well over

100 species of arboviruses belonging to the *Flaviviridae*, *Togaviridae*, and *Reoviridae* families as well as members of *Bunyavirales* order.^{2,4} Commonly implicated families include those in the *Flaviviridae* and *Togaviridae* families and the order *Bunyavirales*. The following section highlights the most important arboviruses and their basic biological properties.

Family Togaviridae

The *Togaviridae* is a family of small, enveloped viruses with single-stranded, positive-sense RNA genomes of 10-12 kb. This family comprises two genera: *Alphavirus* and *Rubivirus*.¹⁰ Within the family, the genus *Alphavirus* includes many diverse species, while the genus *Rubivirus* contains a single species: the rubella virus.¹⁰ The majority of the zoonotic arthropod-borne viruses belonging to the genus *Alphavirus* have about 30 documented species that exist in well-defined geographical areas, especially where malaria-carrying mosquitoes abound.⁴ Most alphaviruses which are mosquito-borne are pathogenic to their vertebrate hosts. As a family of enveloped, single-stranded positive RNA viruses, arboviruses are less clustered than flaviviruses, with *Culex*, *Aedes*, and *Anopheles* mosquito species being the most significant vectors.⁵ Many are significant human and veterinary pathogens, such as the chikungunya virus and eastern equine encephalitis virus. Rubella virus is transmitted through the respiratory tract among humans. Currently, seven viruses from this family are known. The likely amplifying hosts and modes of dissemination are unknown for Ndumu, Middleburg, Semliki virus, and Babanki viruses. Furthermore, the sub-genomic promoters and dual polyproteins in this group of arboviruses are associated with influencing rapid mutations and frequent changes in vectors and hosts, thus enhancing rapid genetic recombination and spread of the virus¹¹ (Figure 1). Figure 1 shows the various viruses, their vectors, antigenic complexes, likely amplifying hosts, vertebrate hosts, human infections and associated mortalities, and likely modes of dissemination of *Togaviridae*.

Family Flaviviridae

Figure 2 illustrates the biology of *Flaviviridae*. This family of zoonotic arboviruses is grouped into distinct clusters ranging from non-vector, unknown vector, tick-borne, and mosquito-borne viruses.^{4, 5} It is a large family with at least 13 described viruses. This group of viruses is pathogenic to humans and animals. Evidence shows Uganda S, Ntaya, Kedougou, Banzi, Nairobi sheep, and Bouboui viruses have unknown mortalities. Flaviviruses are enveloped single-stranded positive-sense RNA viruses with a genome size of 11 kb.³ Members of this family possess a genome that encodes three significant structural proteins: capsid, pre-membrane, and envelope proteins and seven non-structural proteins. These viruses are known to be pathogenic to animals and humans.¹² Figure 2 shows the various viruses, their vectors, antigenic complexes, likely amplifying hosts, vertebrate hosts, human infections and associated mortalities, and likely modes of dissemination.

Order Bunyavirales

Bunyavirales is a large order comprising a cluster of twelve families with more than 300 clinically significant viruses.^{4,5} Viruses which induce hemorrhagic fevers belong to the families: *Hantaviridae*, *Phenuiviridae*, *Arenaviridae*, *Nairoviridae* and *Peribunyaviridae* with the latter four identified as arthropod-borne and majorly transmitted by vectors including mosquitoes, ticks, and sand flies while the fourth family (*Hantaviridae*) is non-arthropod-borne.^{4,5,13} Studies suggest that viruses in the *Bunyavirales* order originate from arthropods due to their deep node association.¹⁰ Their mortality and modes of dissemination are still unknown or elusive. Except for hantavirus, a genus of viruses transmitted by rodents, members of the order *Bunyavirales* are transmitted by arthropods, particularly mosquitoes, ticks, phlebotomines and biting midges. Although most of these viruses infect vertebrate hosts, including laboratory animals (hamsters and rats), more commonly used for virus isolation, only a few are responsible for zoonotic infection. The most common of these is the Rift Valley fever (RVF) virus

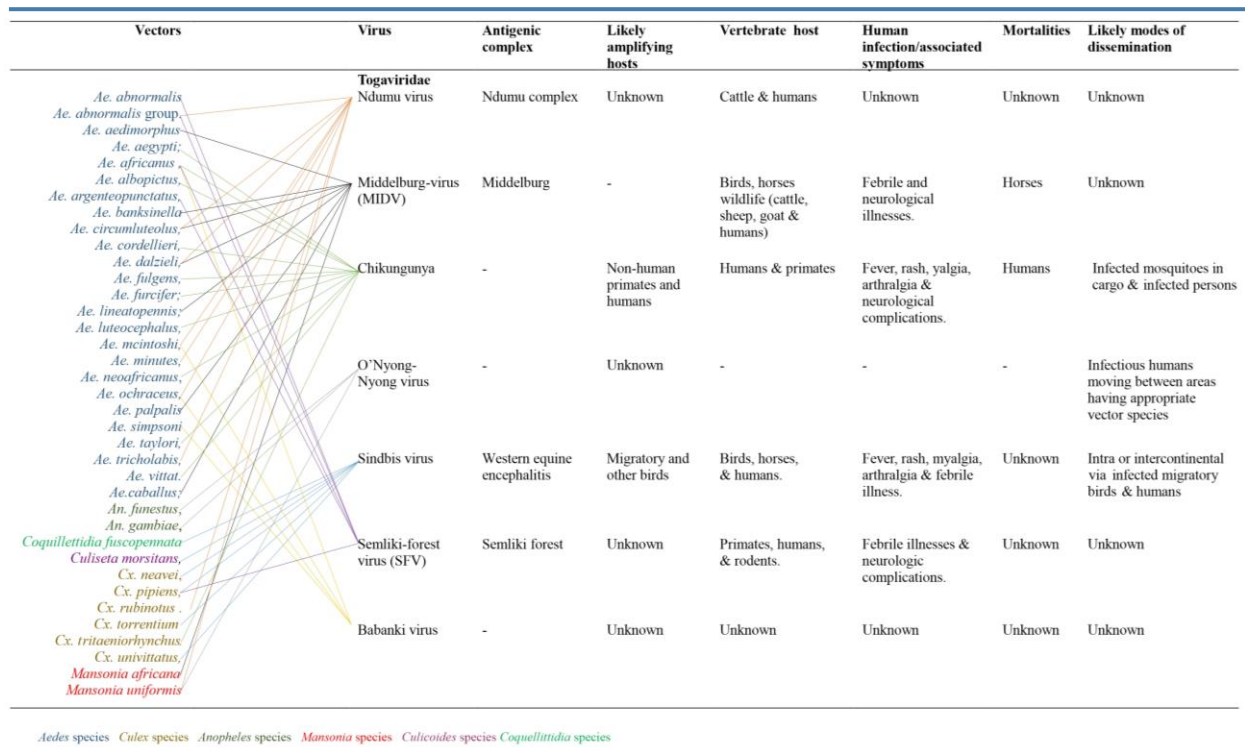


Figure 1. Viral hosts, mobility and transmission of *Togaviruses*

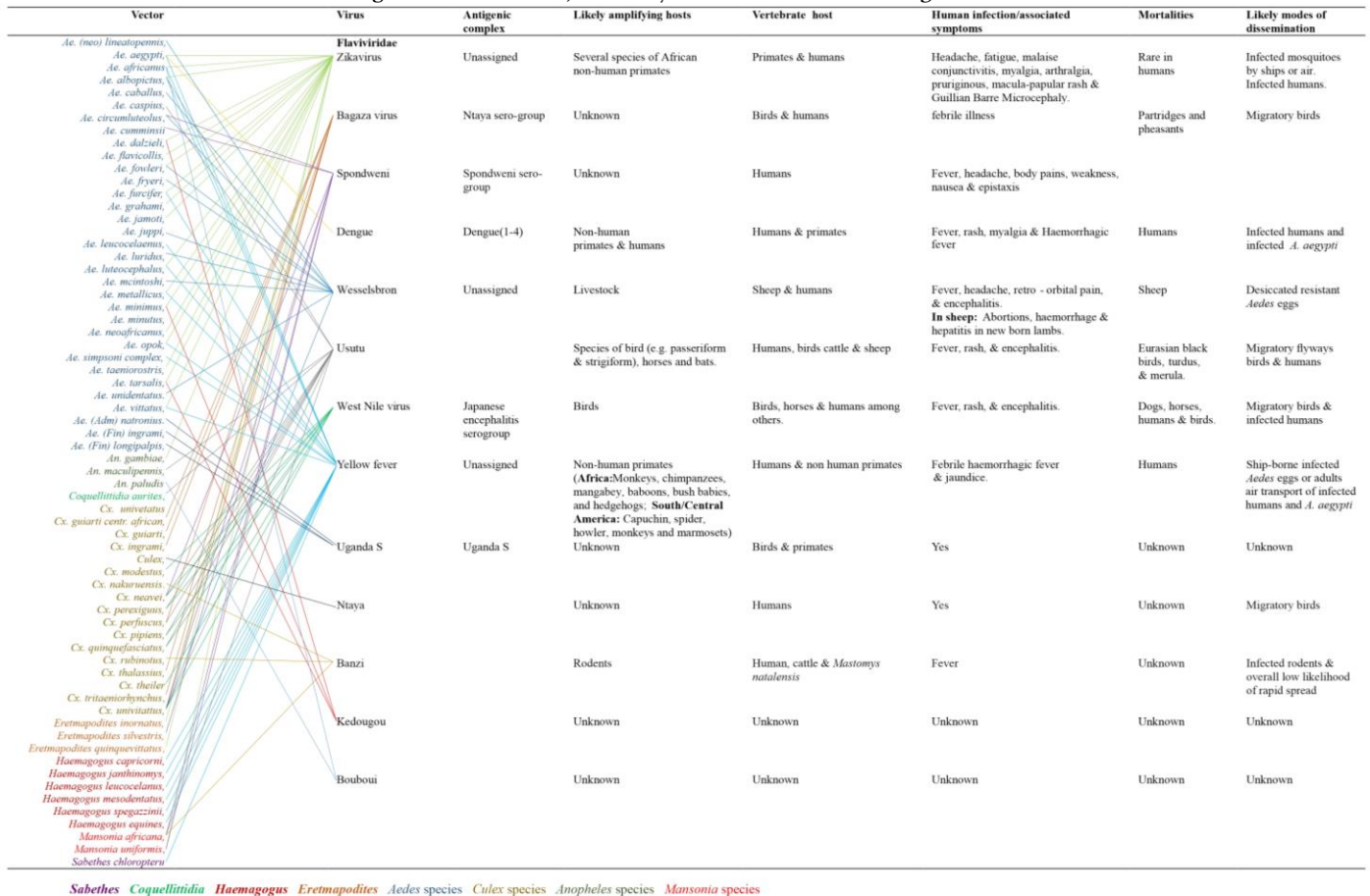


Figure 2. Viral hosts, mobility and transmission of *Flaviviruses*

transmitted by mosquitoes to animals in SSA.¹⁴ Most of the other viruses have a common tropism for fetal tissues and cause embryonic and fetal death, stillbirths and multiple congenital malformations. These viruses belong to different families, genera and serogroups and are extensive. Among bunyaviruses, Akabane from the Simbu serogroup situate in Australia, Asia, and the Middle East, and Cache Valley from the Bunyamwera virus serogroup is present in North America.¹⁴ Among members of the family *Nairoviridae*, Nairobi sheep virus circulates in East Africa and India. In addition to these viruses, Crimean-Congo hemorrhagic fever virus infects domestic animals from which humans become infected.¹⁵⁻¹⁷ This virus is widespread throughout Africa, the Middle East, southern Europe, and Asia, from livestock to birds such as ostriches where they cause asymptomatic infection.^{16, 18} Figure 3 shows the various viruses, their vectors, antigenic complexes, likely amplifying hosts, vertebrate hosts, human infections and associated mortalities, and likely modes of dissemination.

Arthropod vectors associated with arboviruses mobility and distribution

Arboviruses are known to have evolved a long-term survival strategy. One such strategy is their ability to utilize a wide range of arthropod vectors globally, with common ones being ticks and mosquitoes.² The diversity and widespread distribution of arthropod species greatly influence the rapid global spread of arboviruses.^{3,12,19} According to research, an estimated 300 species of mosquitoes harbor arboviruses.^{2,3,12} Studies report that ticks are the most prevalent arboviral vectors, with about 116 species currently known to transmit arboviruses.² There is evidence linking arbovirus-associated diseases with specific vectors, as is the case during epidemics.² However, in cases where the availability of specific hosts is limited, the vectors may utilize available hosts to continue their transmission cycle. These vectors are shown in Figures 1 to 3 for the various families of the arboviruses.

Although a few of the arboviruses in temperate regions spread among wildlife species, the majority of arboviruses gravely implicated in

animal and human diseases in the tropics and sub-tropics have circulated basically where arthropod vectors are in abundance.^{2, 20} This implies that the nature, type, species, and the number of specific arthropods in a region determines the type and nature (sporadic, endemic, or epidemic) of the prevalence of arboviruses.

The distribution of arboviruses in sub-Saharan Africa

Figure 4 illustrates the distribution of arboviruses showing a wide distribution in SSA. A closer look at the distribution of the viruses indicates that the West African and South African regions have the highest spread or distribution of the virus.

Survival potentials of arboviruses

Arboviruses have evolved a series of potentials to ensure their successful long-term survival and dispersal. This significantly reflects their environmental preferences.² First, the arboviruses survive by maintaining a sylvatic cycle once an epidemic runs its course, sometimes for years, and remain dormant until favorable conditions ensue. A second strategy involves non-viremic transmission in which infected and non-infected arthropods such as ticks feed on small animals in the wild, further enhancing the long-term survival of the viruses. This is possible because it influences the direct transmission of the viruses between these insects.²¹ Several studies noted the horizontal transfer of viral genome into susceptible hosts (arthropods).^{2,22-25} Other studies highlight the desiccation of resistant eggs by some arthropod vectors as a crucial survival factor.²⁶ Viral mutation via genome segment recombination or reassortment is reported to not only enhance their survival and efficient transmission by previously inefficient vectors but also leads to the emergence of new viruses with unique virulence and pathological implications.²⁷ In addition to the viral mutation, vector mutation and adaptation have reportedly enhanced the survival and improved their involvement in the spread of arboviruses.⁵ The survival potentials collectively and individually exhibited by these viruses ensure their survival

and possible re-emergence, causing severe epidemics in animals and humans.²

Determinants of arbovirus emergence and transmission

The ability to acquire, maintain and transmit a virus (vector competence) by a vector is a complex phenomenon between the pathogen and the vector. Intrinsic and extrinsic factors influence this phenomenon.²⁸ Studies report that in addition to the virus and the vector, there is a need for appropriate virus replicating hosts such as birds and primates to ensure the perpetuation of the virus cycle.⁵ Similarly, vector density, survivability, and host density influence the ability of vectors.²⁹ In addition to rapidly adapting to hosts (arthropods, humans, and non-human vertebrates), arboviruses are known for their transmission efficiency, antigenicity, environmental/ecological conditions adaptation, and alteration of receptor specificity. Climate change significantly influences the occurrence of mutation, and human activities are significant determinants of the emergence of arboviruses.² The reservoir for arboviruses in wild species impedes the control of its emergence. Arthropods transmit arboviruses to humans and vertebrate animals, causing significant mortality. Studies reveal that trans-generational vertical transmission has also been reported among vector species, aiding the transfer of arboviruses from adult vectors to their offsprings.³⁰⁻³³

Most infected arthropod vectors (in varying developmental stages) are dispersed via human travels.³⁴ In addition, more engagements in tourism, humanitarian services, pilgrimages, host density, displaced refugees from arthropod-endemic regions (including Africa, Asia, and the Pacific), import demands, and improved world trade have significantly broadened the global distribution of arboviruses.⁵ Studies further reveal that most arthropods exhibit significant competitive potential upon arrival, aiding them in successfully establishing a stronghold and dispersing.^{5,34} In similar studies,^{35,36} dangers associated with regional movements of livestock are linked to the distribution of most arthropods incriminated in arboviral diseases.

Burden associated with arbovirus-related diseases in sub-Saharan Africa

The burden associated with arboviruses correlates with the occurrence and distribution of arthropod vectors, especially in SSA.⁵ This is because SSA is home to all types and categories of vectors especially the arthropod vectors, due to the abundance of tropical and sub-tropical climates.^{2,4,5} Similarly, as a result of lack of adequate facilities and diagnostic tools to aid the evaluation of arbovirus-related diseases in the region, there is an increased risk of misdiagnosis, further limiting the accurate estimation of disease burden in SSA. More complicating is the lack of knowledge of the existence of arbovirus-related diseases in SSA further militating against their isolation. As revealed in a study,³⁷ arboviral infections contribute to a significant proportion of debilitating fever syndromes. Symptoms ranging from asymptomatic infections to severe undifferentiated fever are associated with these viruses in their acute phase.^{2,4,5}

However, a few have been associated with complications comprising meningitis, hemorrhage, encephalitis, which result in long term physical and cognitive impairment and even death.^{2,4,36,37} Studies show that approximately 100 arboviruses observed to cause diseases in humans and transmitted via varying routes are characterized by their ability to cause encephalitis and/or hemorrhagic fever.³⁷ Currently, more serious and severe cases occur as the viruses spread to new areas. These cases lead to post-infectious, long-term complications such as neurologic, ophthalmologic, and mental impairment, among others.³⁸ The incidence of arbovirus co-infections with diseases including malaria in SSA has further questioned the authenticity of cerebral sequelae due to malaria when almost all the reported arboviruses are capable of inducing neurologic and mental complications in susceptible hosts.

As evident in tropical diseases, a study notes that most minor and disabling complications associated with arboviruses affect resource-poor communities.³⁷ These complications impair individuals' daily activities and could be chronic depending on the nature of the virus and the available susceptible host. Studies further reveal

that the lifetime burden of these diseases, especially in developing countries, is poorly understood due to a lack of long-term longitudinal childhood impact studies of arboviral diseases.³⁷ Clinical data reveal significant healthcare challenges and economic losses associated with arboviral diseases.^{5,37-38} It is worth noting that only the disease burdens of dengue and Japanese encephalitis are currently in the WHO global burden of disease estimates. The implication is that any significant long-term related morbidity associated with arboviruses other than those captured by WHO remains a substantial health deficit.³⁷ In addition, as the world becomes more globalized, vectors and viruses have continually evolved, making their diagnosis, treatment, and prevention even more challenging.³³

Management, prevention, and control of arboviral diseases

There is evidence that arboviral-related infections often occur in epidemics and have pandemic potential.^{2,5} Adequate planning and routine surveillance of acute-chronic, case-fatality, incidence as well as conversion rates from clinical cases may help reduce the severity of diseases associated with these viruses and help employ preventive approaches.^{2,5,34} Due to the outbreak potential associated with these viruses, vaccine development for arboviruses, either singly or as a group, remains a necessity in ameliorating incidences and disease burden. Developing therapeutic drugs and vaccines to treat arboviral diseases and simplifying the procedures for establishing the safety and efficacy of antivirals may reduce the risk of arboviral diseases in animals and humans.

Due to a lack of specific treatment for arboviral infections, several studies suggest continuously evolving vector control strategies and public health surveillance for arboviral-related infections as significant steps toward preventing these diseases.^{2,37} Experimental vector eradication and vaccine development can effectively mitigate the arboviral-related infections in SSA.³⁷ Similarly, utilizing unified vector-controlled strategies that will ensure the survival of wildlife species is the right step in the right

direction. Practical procedures to mitigate the risks associated with arthropods may be most effective in reducing the transmission and spread of arboviral-related infections. One way to achieve this is by implementing localized arthropod control measures, especially during epidemics.^{2,5}

The development of training and research programs that will identify the occurrence, pathogenicity, evolution, epidemiology, and disease burden associated with arboviral diseases is also important.² In addition, promoting and strengthening levels of cooperation between governments, academic institutions, and drug/vaccine development companies will significantly contribute to the eradication of arboviruses. Programmes to educate citizens on local preventive measures, monitoring and evaluating at the community level, border, harbor, airports, and hamlets, among others, may reduce the influx of arboviral vectors to new regions.^{2,38}

Co-infection with SARS-CoV-2

There is evidence that HIV and Ebola virus are not just zoonotic but originated from Africa with significant public health implications.^{39,40} Furthermore, SARS-CoV-2 has also joined the group of emerging pathogens.⁴⁰ Although the COVID-19 response has been effective with the arrival of vaccines in less than a year since the pandemic began,^{7,40} other infections are yet to get a vaccine years after they emerged. Due to the geographical overlap of this infection endemicity, there is a greater risk of co-infections, as evident in HIV and malaria.⁷ The COVID-19 pandemic exposed the weakness of existing healthcare infrastructures in SSA. With the potential of COVID-19 co-infecting with arboviruses, already reported in Pakistan, there is a pressing need for health policy makers across SSA to take a cue from the COVID-19 response. Throughout SSA, the health systems are inadequate due to a lack of trained staff, infrastructure deficits, facilities, and funding among others. There is a need to consciously build up capacity to avoid co-infection in the region.

Conclusions

Arthropod vectors and arboviruses are endemic in sub-Saharan Africa (SSA). Although most of these viruses do not infect humans, a few have jumped their sylvatic cycles due to several factors that have influenced their effective dissemination to many regions with significant public health implications. Arboviruses have evolved survival strategies creating new favorable niches in the process. These viruses present with disabling syndromes with significant personal and health burdens and losses, yet the lifetime burden of arboviral diseases in developing countries and regions is still poorly understood. Given the potential to lead the next pandemic, there is a need for more studies aimed at the prediction, prevention, and control of arbovirus-related diseases.

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