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Arbovirus circulation, epidemiology and spatiotemporal distribution in Uganda

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ABSTRACT

Background: Arboviruses are endemic in Uganda; however, little is known about their epidemiology, seasonality and spatiotemporal distribution. Our study sought to provide information on arbovirus outbreaks from acute clinical presentations.

Methods: Immunoglobulin M (IgM) and confirmatory Plaque Reduction Neutralisation Test (PRNT) results for arbovirus diagnosis of samples collected from patients attending sentinel sites from 2016−19 were analysed retrospectively. Demographic data were analysed with SaTScan and SPSS software to determine the epidemiology and spatiotemporal distribution of arboviruses.

Results: Arbovirus activity peaked consistently during March−May rainy seasons. Overall, arbovirus seroprevalence was 9.5%. Of 137 IgM positives, 52.6% were confirmed by PRNT, of which 73.6% cases were observed in central Uganda with Yellow Fever Virus had the highest prevalence (27.8%). The 5−14 age group were four times more likely to be infected with an arbovirus p=0.003, 4.1 (95% CI 1.3−12.3). Significant arboviral activity was observed among outdoor workers(p=0.05) . Spatiotemporal analysis indicated arboviral activity in 23 of the 85 districts analysed..

Interpretation: Our study shows that arbovirus activity peaks during the March−May rainy season and highlights the need for YFV mass vaccination to reduce the clinical burden of arboviruses transmitted within the region.

Introduction

Arboviruses are arthropod-borne viruses transmitted by mosquitoes, biting midges and ticks; they are grouped within viral families such as Flaviviridae, Rhabdoviridae, Reoviridae, Togaviridae, Nairoviridae, Peribunyaviridae and Phenuiviridae.

The global burden of arboviruses is significant, with up to 700,000 deaths annually attributed to arbovirus-related diseases [1]. Among mosquito-borne arboviruses, Dengue virus (DENV) has a massive impact on public health, with over 390 million cases reported annually, mainly affecting Asia and Latin America [2]. Yellow Fever Virus (YFV), which is mainly a problem in Africa [3] and South America [4], causes over 200,000 global cases and 30,000 deaths annually [5]. In Uganda, serological studies by Henderson *et al.* reported a 16.8% prevalence of West Nile Virus (WNV), YFV, and Zika virus (ZIKV) [6]. The 2010 YFV outbreak in northern Uganda had a case fatality rate of >24%, with a 7.5% seroprevalence amongst the population [7]. Among alphaviruses, the immunoglobulin G (IgG) seroprevalence of Chikungunya virus (CHIKV) and O'nyong'nyong virus (ONNV) is estimated at 31% to 38.6% in Uganda [6]. Although immunoglobulin M (IgM) serology provides evidence of recent transmission, the method is affected by the cross-reactivity of antibodies with envelope proteins of related arboviruses [8] in arbovirus endemic regions. Cross-neutralisation is common in regions where more than one arbovirus circulates or in areas where vaccination is deployed [9]. Therefore, the laboratory testing algorithm for arboviruses at the Uganda Virus Research Institute involves initial serological detection of IgM antibodies to YFV, WNV, DENV , ZIKV and CHIKV, followed by the plaque reduction neutralisation test (PRNT) confirmation and, where possible, RT-PCR for the detection of viral nucleic acids [10].

Despite continuous surveillance, there is little information about the epidemiology, spatiotemporal distribution, and seasonality of mosquito-borne arboviruses in Uganda. The Aedes species (in particular, Aedes africanus Theobald, for Uganda), a known competent virus transmitter of YFV, ZIKV and CHIKV [11], has a significant abundance and distribution within Uganda [12]. However, the co-circulation of these viruses within the country is not known. Therefore, in addition to defining the epidemiology, spatiotemporal distribution and seasonality, this study sought to provide evidence supporting the co-circulation of YFV, ZIKV and CHIKV during outbreaks.

Methods

Study population, sentinel sites and period

Demographic and laboratory data were selected from a cohort of patients enrolled at hospital-based sentinel sites to monitor arboviruses across Uganda [13]. In regions with no sentinel sites, samples were ob-

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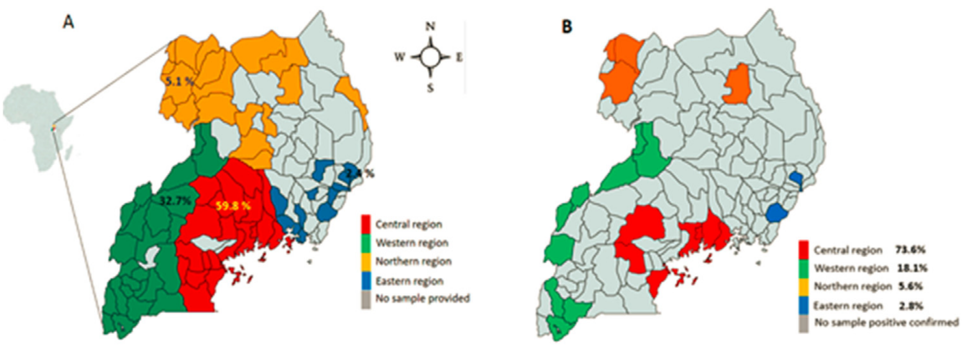

Figure 1. Sample collection and arboviruses distribution by region: A. Extract of the map of Uganda showing sample collection by region, further divided into districts. The orange represents the north, green for the west, red for the central, blue for the east, and grey shows areas with no sample collection. The number of samples collected from each region is represented as a percentage of the total collection. B. Regions with arboviruses confirmed by PRNT. The map divisions represent districts and are coloured to represent geographical regions. The uncoloured districts represent areas where no arbovirus has been confirmed. The maps are not drawn to scale.

tained through physician laboratory requests for YFV or any other haemorrhagic fever testing. The data were collected from 2016 to 2019 from patients ≥2 months with a recorded temperature of ≥37.5°C or a history of fever for no more than 7 days at the time of presentation.

Laboratory detection of arboviruses

Laboratory analyses were carried out and interpreted as described by Kayiwa *et al.* [14]. Briefly, IgM antibodies for YFV and ZIKV were detected using the CDC IgM antibody capture- enzyme-linked immunosorbent assay (CDC-MAC-ELISA) [15]. Diagnosis of WNV, DENV and CHIKV was made using the InBios West Nile Virus Detect IgM Capture ELISA, DENV Detect IgM Capture ELISA, and the CHIKjj Detect IgM Capture, respectively (InBios international, inc., Seattle, WA, USA). Furthermore, IgM-positive samples were confirmed by carrying out the PRNT test and interpreted using the algorithm described by Lindsey *et al.*, 2018 [8].

Univariate analysis was carried out using SPSS v.26. Spatial and spatiotemporal data analyses were conducted using the SaTScan software package (version 10) [16]. A retrospective analysis of positive cases defined by purely spatial and space-time models was made relative to the district population projections predicted by the Uganda Bureau of Statistics for 2016–19 [17]. A Poisson distribution was assumed to determine the number of expected positive cases within the population of a given district. Risk factors for arboviral infection were assessed by categorising patients into 3 groups: outdoor workers (farmers, fishmongers, security personnel, butchery operators, builders, soldiers and business persons); indoor workers (patients with office-related jobs, homemakers, students, teachers, children, bar and hotel workers and tailors); and healthcare workers (nurses, veterinary officers, clinical and medical officers, and laboratory technicians). Participants provided written consent where necessary.

Results

Description of the study population characteristics

Demographic and laboratory data were available for 1900 anonymised samples collected from Uganda's northern, central, western and eastern regions (Figure 1a). Of the 1900 samples, complete data were available for 1441 results, of which 137 (9.5%) had a positive IgM result for an arbovirus. Of the 137 positives, 72 (52.6%) were confirmed positive by PRNT. Among the PRNT confirmed cases, 53 (73.6%) were from the Central, 13 (18.1%) from the Western, and 6 (8.3%) from the eastern and northern regions (Figure 1b). Flaviviruses accounted for 55.6% of the total PRNT confirmed cases, whilst the rest (44.4%) were confirmed as alphavirus infections. YFV had the highest prevalence of the total positives with 20 cases (27.8%), while the PRNT test confirmed no DENV.

Seasonality of arboviruses

The East African region has two main rainy seasons, March–May and October–December [18]. Arbovirus activity occurred through-

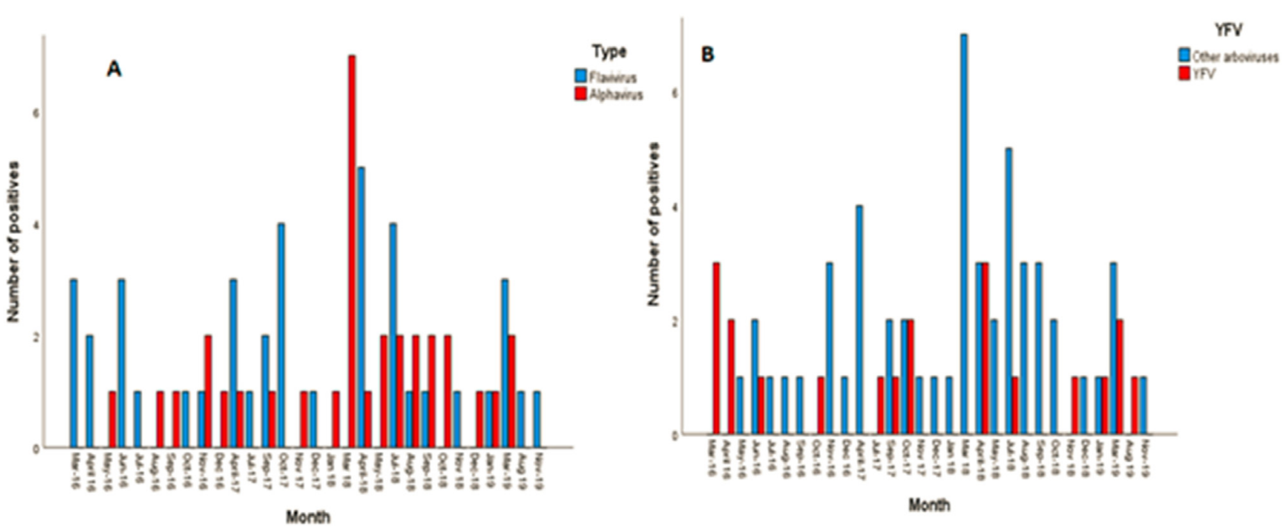

Figure 2. Seasonality of arboviruses in Uganda: A. Number of arbovirus positives by month in Uganda from March 2016 to November 2019. The alphaviruses (red) and flaviviruses (blue) incidences peaked between March and May every year. The March-May 2016 and 2019 peaks coincide with the YFV outbreak in Masaka and Koboko districts. B. PRNT confirmed YFV (red) and other arboviruses (blue) observed in Uganda from 2016 to 2019. Four distinct YFV outbreaks were observed, with the first occurring in the central region March-May 2016 in the central and western regions. The second was in September-October 2017 (Masaka district) and the third in April 2018 (Wakiso district), while the fourth spread across the central, north, and west regions from March to September 2019.

Table 1
Epidemiological characteristics of arboviruses. Abbreviation: HCW- Healthcare workers.

	Total positive	Total negative	Univariate	CHI Square test: pValue, OR (95% CI)
	{n= 72 (%)}	{n= 1369, (%)}		
Prevalence (n= 1441)	**4.9**			
GENDER				
Female	39 (54.2)	670 (48.9)		
Male	33 (45.8)	699 (51.1)		
AGE GROUP				
0-4 yrs	Nil	83 (6.1)		
5-14 yrs	**3 (4.2)**	**231 (16.9)**	**F(1,1439)= 8.2, p=0.004**	**4.1 (1.3- 12.3)**
15-34 yrs	37 (51.4)	584 (42.7)		0.08 (0.6- 1.0)
35-54 yrs	24 (33.3)	322 (23.5)		0.7 (0.5- 1.0)
55-64 yrs	3 (4.2)	81 (5.9)		**1.4 (0.5- 4.4)**
65+ yrs	5 (6.9)	68 (4.9)		
REGION				
Central region	**53 (73.6)**	**809 (59.1)**	**F(1, 1439)= 6.0, p=0.014**	0.8 (0.6-0.93)
Western region	**13 (18.1)**	**459 (33.5)**	**F(1, 1439)= 7.5, p=0.006**	**p0.006, 1.9 (1.1- 3.1)**
Northern region	4 (5.5)	69 (5)		0.9 (0.3-2.4)
Eastern region	2 (2.8)	32 (2.4)		0.8 (0.2-3.1)
OCCUPATION				
Outdoors	44 (61.1)	674 (49.2)	**F(1,1439)= 3.9, p=0.05**	**p0.05, 1.6(1.0 - 2.6)**
Indoors	13 (18.1)	526 (38.4)	F(1,1439)= 3.4, p=0.07	p0.08, 0.6 (0.3- 1.1)
HCW	3 (4.2)	28 (2)		**1.6 (0.2- 11.4)**
Other	12 (16.7)	141 (10.3)		0.6 (0.4- 1.1)

out the study period, with higher peaks consistently observed in the March–May than in the October–December rainy season (Figure 2). The observed flavivirus peak in March–May 2016 (Figure 2a) is consistent with the YFV outbreak in the central and western regions (Figure 2b) [19] that continued until June 2016. In addition, three previously unregistered YFV outbreaks occurred, with the first occurring in the central region in September–October 2017 (Masaka district) and the second in April 2018 (Wakiso district), while the third spread across the central, north and west regions in March–September 2019. Alphaviruses generally circulate throughout the year without a specific pattern (Figure 2a). Only 1 CHIKV and 7 ONNV positives were confirmed by PRNT, whilst 24 cases were unspecific alphaviruses.

Risk factors for arbovirus infections

On univariate analysis, the risk of arbovirus infection was not associated with the patient's sex (Table 1). No arbovirus IgM antibodies were observed among the 1–4 year age group. However, the risk of an arbovirus infection, especially flaviviruses, was significant in the 5–14 year age group F (1–1439) = 8.2, *p= 0.004*. In addition, patients in the 5–14 year age group were 4 times more likely to be infected with an arbovirus (OR=4.1 (95% CI 1.3–12.3), *p=* 0.003). Patients in the 55–64 year age group were 1.4 times more likely to test positive for an arbovirus infection. Despite IgM antibody and PRNT confirmation of arboviruses within the 15–34, 35–54 and >65 year age groups, these patients had a lower risk of arbovirus infection.

Patients in the central and western regions had a significantly high likelihood of arboviral infection F(1, 1439)= 6.0, *p=0.014* and F(1, 1439)= 7.5, *p=0.006*, respectively, than patients from the northern and eastern regions. Furthermore, patients from the central region were 1.9 times (95% CI 1.1–3.1), *p=0.006* more likely to have an arboviral infection than other regions.

Of the 72 PRNT confirmed positives, 44 (61.1%) were patients identified as outdoor workers (*p=0.05),* and 13 (18.1%) were indoor (*p=0.08*). Outdoor workers were 1.6 times (95% CI 1.0–2.6) more likely to have an arboviral disease than any other occupation category. Univariate analysis by linear regression confirmed that type of occupation (Outdoor workers, p=0.05) was significantly associated with the risk of infection (Table 1).

Spatial and spatiotemporal analysis of arboviruses

Spatial and spatiotemporal analyses were used to understand arbovirus transmission patterns by analysing districts with more than expected arbovirus incidences. Arboviral incidences were analysed by applying a cluster restriction of 3 cases for areas with high rates and a maximum spatial cluster size set at a radius of 50 km. Upon spatial analysis, 23 of the 86 districts analysed had arboviral activity with 5 distinct clusters in six districts (Figure 3i). Of the 5 clusters, cluster A, in the Buikwe district (geographical Coordinates 0.301 N, 33.012 E) comprised 15 cases observed within an average population of 194,530. Two clusters, B and C, overlapped Masaka (0.341 S, 31.736 E) and Sembalule districts (0.066 S, 31.483 E), with an average radius of 41.47 km and consisted of 16 cases in an average population of 142,091. Three spatial clusters (D–F) were observed in the south-western region of Uganda, comprising the districts of Ntungamo (0.881 S, 30.25 E), Rubanda (1.183 S, 29.85 E) and Rukungiri (0.783 S, 29.33 E), respectively. These clusters covered an average radius of 45.4 km comprising 4 cases in an average population of 23,481.

The spatial-temporal (space-time) scan for clusters applies a cylinder whose circular base covers the geographical area analysed, whilst the height measures the time frame of infection activity in the given area [20]. Overall, 6 clusters were detected, of which only 2 were associated with high rates of arbovirus incidence (Figure 3ii). Clusters A to D were associated with low rates and occurred in Buikwe (A), Mukono (B, coordinates, 0.481 N, 32.771 E), Kampala (C, coordinates 0.363 N, 32.61 E), and Wakiso (D, 0.167 N, 32.5 E) districts. In contrast, clusters E and F were associated with high rates and were observed in Masaka and Sembabule districts, respectively. The cluster in Masaka (cluster E) was significant (*p=0.024*), with 3 cases giving an annual incidence of 21.2 cases per 100,000 from March to May 2016. The second cluster occurred from September to November 2017 and overlapped between the Masaka and Sembabule districts, with 5 cases and an annual arboviral incidence of 7.5 cases per 100,000 (*p=0.059*).

Spatial and spatiotemporal distribution of YFV in Uganda

The arboviral activity was further investigated to analyse the role of each viral species relative to districts and time. In Uganda, the disease threshold for a YFV alert is when there is 1 suspected or confirmed case

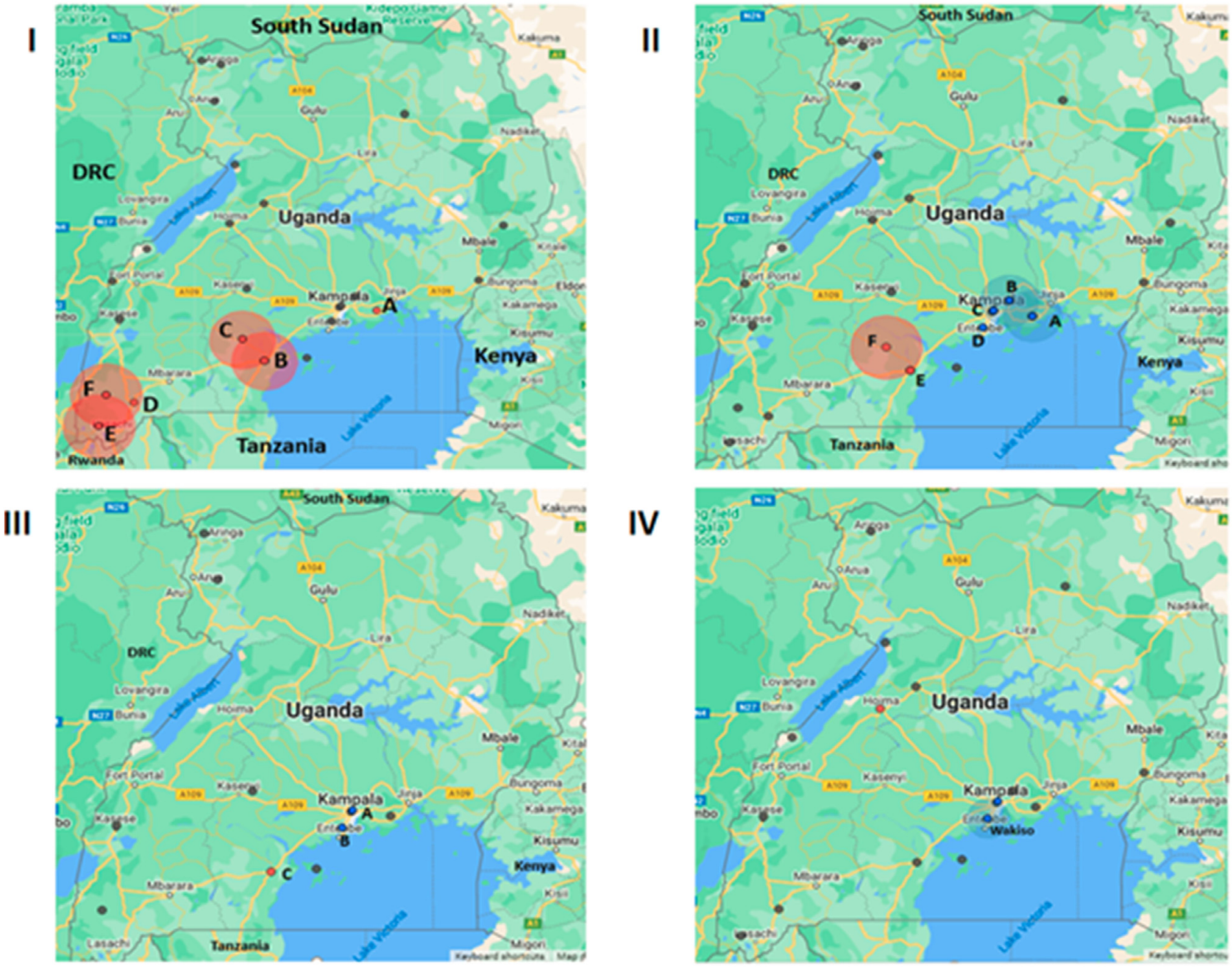

Figure 3. Spatio-temporal distribution of arboviruses in Uganda in clock-wise direction. I. Spatial analysis of arboviruses showing their distribution in Uganda. Arboviral incidences were observed in 23 districts (black and red dots). Red circles represent clusters in districts from which more than two arboviruses were detected, indicated as loci A- F. Districts A-F are: A. Buikwe, B. Masaka, C. Sembabule, D. Ntungamo, E. Rubanda, and F. Rukungiri. Abbreviation: DRC- Democratic Republic of Congo. II. Space-time scan of arbovirus activity in Uganda. The blue, black and red spots show areas where arbovirus activity was observed. Two clusters E (Masaka) and F (Sembabule) had high arboviral rates and occurred from March-May 2016 in Masaka district. Cluster F overlapped with E but occurred from September to February 2017. The blue dots represent districts with low arboviral rates. A- Buikwe, B- Mukono, C- Kampala and D – Wakiso. III. Spatial Analysis of YFV activity. The blue, black and red spots show areas where YFV activity was observed. Cluster C (in Masaka) represent significant YFV activity, whilst clusters A (Kampala) and B (Wakiso) showed low activity. All but the eastern region showed YFV activity. IV. Spatial distribution of alphaviruses May 2016 - March 2019. The black, grey and red spots show the 16 locations where alphaviruses were detected. The red spot shows the Hoima district cluster with a high rate of alphavirus activity, whilst the blue spots represent areas of low virus rates in Kampala and Wakiso.

in the country [32]. For this reason, whilst setting up the data analysis parameters for YFV activity, we considered a cluster to contain at least 2 PRNT-confirmed cases. Between March 2016 and August 2019, 20 confirmed YFV cases were detected in 10 districts (Figure 3iii). Within the 10 districts, YFV was more significant in Masaka district (C), with 6 cases giving an incidence of 4.1 per 100,000 ($p^{<}0.001$). YFV activity was detected in all but the eastern region. Space-time analysis of YFV activity in Uganda showed a significant cluster in Masaka from March to May 2016, with 3 cases and an incidence of 22 cases per 100,000 ($p^{<}0.001$).

Spatial and spatiotemporal distribution of alphaviruses in Uganda

Uganda has no defined threshold to track alphavirus outbreaks. Therefore, we analysed the spatial and space-time distribution of alphaviruses in Uganda using ≥4 cases as the definition of a high-rate cluster. Spatial analysis revealed 16 districts with 32 cases between May 2016 and March 2019. Low rates of alphavirus activity were detected within the Wakiso, Kampala and Hoima (1.43 N, 31.35 E) districts (Figure 3iv). On space-time analysis, the cluster observed in the Wakiso district occurred between August and December 2017, while the Hoima district cluster occurred from January to May 2018.

Discussion

Our study describes the epidemiological pattern of arboviruses, highlighting the role of YFV in morbidity among patients in Uganda. In addition, this study describes the seasonality of arboviruses, defines the patient demographics during the acute phase of illness, and determines the country's high-risk areas.

The general prevalence of arboviruses from 2016 to 2019 was defined based on the PRNT results, highlighting potential outbreaks. Several previous studies have analysed arbovirus seroprevalence based on IgG studies [21], and a few more have attempted to analyse recent arboviral infections using IgM results [22]. Our study provides more accurate epidemiological and public health information on the nature of the outbreaks by using PRNT-confirmed results.

It is unclear why the central region had a higher prevalence of arbovirus infection; however, one possibility is that Lake Victoria may play a significant role in arboviral prevalence in the region. Secondly, the trend of increasing temperatures and flooding [23] observed in Uganda, together with probable house infestation with mosquitoes, may promote the survival of arboviral vectors, increase the risk of arbovirus transmission and, in turn, explain the endemicity of arboviruses within the region. Such an effect would not be unprecedented; a study in Brazil identified that environmental factors such as temperature played a vital role in the distribution of arboviruses in high-risk areas [24]. Furthermore, the factors that favoured the dominancy of YFV and its expansion from the central and western regions into the northern region by 2019 are unknown, despite sharing a common vector with ZIKV, DENV and CHIKV.

High arbovirus infection levels among outdoor workers may be associated with the vectors' feeding and resting behaviour patterns [25]. In addition, climate change has affected farmers' agricultural patterns [26], which may impact the length and period of exposure to arboviral vectors whilst on the fields. In our study, the arboviral incidence among healthcare workers cannot be concluded as a work-related occurrence. However, before the 1970s, frequent arbovirus infection of laboratory personnel involved in studies manipulating arboviruses was common, with over 2700 cases and 107 fatalities [27]. There was no arbovirus infection among patients aged 1-4 years in contrast to a Puerto Rico report that recorded CHIKV infections in infants <1 year old [28]. Our study agrees with previous findings of arboviral infections in patients ≥5 years old [29].

Spatial and spatiotemporal analysis mapped the arbovirus distribution and time pattern of YFV. However, we did not analyse the spatiotemporal distribution of WNV, ZIKV and DENV due to insufficient data to support statistical analysis. Furthermore, the arbovirus species' definitive spatial and spatiotemporal distribution could not be fully defined due to the existence of unspecified alpha and flaviviruses. The diagnosis of unspecific alpha and flaviviruses highlights the importance of early detection by applying assays such as molecular detection by PCR. With only a few PRNT-confirmed CHIKV infections, our study could not confirm CHIKV co-circulation with YFV. However, spatiotemporal analysis using presumptive IgM results identified a possible CHIKV outbreak in the Buikwe district co-occurring with the YFV outbreak in the Masaka and Rukungiri districts in February–May 2016. Simultaneous circulation of CHIKV and YFV has been reported elsewhere [30], yet notifiable YFV outbreaks overshadow CHIKV activities.

YFV cases were detected throughout the study period (2016–19), with 80% observed within the central region. The reduction in YFV cases from 2017 to 2019 is attributed to mass vaccination [31], although new YFV activity was detected in northern Uganda. It is important to note that according to our study, no previous mass vaccinations had been conducted in northern Ugandan areas with new YFV activity.

Our study is limited to patients with acute febrile illnesses self-presenting to sentinel health facilities; thus, we could not detect asymptomatic and non-sentinel site-associated cases in the country. Furthermore, the study does not account for population movements which may facilitate the introduction of competent and virus-infested vectors into new regions/niches. In addition, a study characterising arbovirus in indoor and outdoor vectors and the species involved needs to be carried out to explore the high arboviral incidence.

Conclusion

Arbovirus infections, mainly YFV, occur during the rainy seasons in Uganda. There is a need to reduce the transmission of arboviruses among outdoor and indoor workers through mass vaccination. Early mass vaccination of the 5–14 year age group will significantly lower YFV cases in the country. In addition, because the northern and eastern regions have limited sentinel sites, active capture of arboviral outbreaks in the regions is dependent on incidence reporting by referral hospitals. Thus, vital information on the epidemiology of outbreaks may be missed.

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Ethical approval statement

Ethical approval was waived due to the existing approval granted by the Uganda Virus Research Institute research ethics committee and the Uganda National Council of Science and Technology to the Department of Arbovirology.

Conflict of interest

All authors declare no conflict of interest.

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