Original Research *Highlight article*

Analysis of dengue fever disease in West Africa

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Impact Statement

Dengue fever disease (DFD) is increasingly becoming a global health threat, especially in tropical and subtropical regions. However, not much data have been generated to understand the enormity of the problem. This study is a systematic analysis of the existing data on DFD prevalence and incidence, and on dengue fever virus–infected vectors (*Aedes* sp.) in West Africa, and highlights the epidemic risk of the disease in the subregion and the need for more to be done to inform effective control measures.

Abstract

Dengue fever disease (DFD) which is caused by four antigenically distinct dengue viruses (DENV) presents a global health threat, with tropical and subtropical regions at a greater risk. The paucity of epidemiological data on dengue in West African subregion endangers efforts geared toward disease control and prevention. A systematic search of DFD prevalence, incidence, and DENV-infected *Aedes* in West Africa was conducted in PubMed, Scopus, African Index Medicus, and Google Scholar in line with the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines. A total of 58 human prevalence studies involving 35,748 people from 8 countries were identified. Two incidence and six DENV-infected studies were also reviewed. Nigeria and Burkina Faso contributed the majority of the prevalence studies which spanned between 1968 and 2018, with a considerable variation in coverage among the countries reviewed in this study. An average prevalence of 20.97% was observed across both general prevalence and acute DENV infection study categories, ranging between 0.02% and 93%. The majority of these studies were conducted in acute febrile patients with a prevalence range of 0.02–93% while 19% ($n = 11$) of all studies were general population-based studies and reported a prevalence range of 17.2–75.8%. DENV-infected *Aedes aegypti* were reported in four out of the five countries with published reports; with DENV-2 found circulating in Cape Verde, Senegal, and Burkina Faso while DENV-3 and DENV-4 were also reported in Senegal and Cape Verde, respectively. High prevalence of DFD in human populations and the occurrence of DENV-infected *A. aegypti* have been reported in West Africa, even though weaknesses in study design were identified. Epidemiological data from most countries and population in the subregion were scarce or non-existent. This study highlights the epidemic risk of DFD in West Africa, and the need for research and surveillance to be prioritized to fill the data gap required to enact effective control measures.

Keywords: Dengue fever disease, dengue fever virus, dengue epidemiological data, dengue geographical distribution, *Aedes* mosquito vectors, West Africa disease burden

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Introduction

Dengue virus (DENV) is the most important arthropod-borne viral disease of humans with about 3 billion people at risk especially in tropical and subtropical areas.[1] The four antigenically related serotypes of DENV (DENV-1, DENV-2, DENV-3, and DENV-4) cause an estimated 400 million infections each year.[2] Most infections are subclinical but may also exhibit a spectrum of clinical presentations ranging from mild dengue fever disease (DFD) to dengue hemorrhagic fever (DHF) to dengue shock syndrome (DSS) characterized by increased vascular permeability, multiorgan failure, and death.[3]

The two main mosquito vectors of DENV are: *Aedes aegypti* is the primary vector and native to Africa, while *Aedes albopictus*, that has emerged as a vector of the virus especially in temperate regions, was imported into Africa about 30 years ago.[4] The epidemiological data on dengue in West Africa are sparse, with spatial distribution and transmission risks mostly estimated using ecological models.[5,6] West African countries have seen an increase in the number of sporadic and epidemic dengue fever cases in some countries within the subregion such as Mali, Burkina Faso, and Senegal.[7] A dengue fever outbreak in 2016 in Burkina Faso were caused by DENV-2 and 3, with the DENV-3 strain mapped to previous outbreaks in Cape Verde, Senegal, and Côte d'Ivoire.[7] With the implementation of the African Continental Free Trade Area (AfCFTA) agreement and the expected increase in mobility on the African continent, there is an increased risk of DENV serotypes with higher epidemic potential spreading further as seen in Burkina Faso.

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A number of dengue fever cases have been documented among travelers from West Africa in Europe. Between 2006 and 2008, 19 cases originating from West Africa were detected through active surveillance in the European Union. In most cases, there were no reports of dengue outbreaks or epidemics in the originating countries.[8] Despite these evidences of higher than reported burden of DFD and with the majority of recent outbreaks between 2009 and 2017 occurring in the West African subregion,[9] epidemiological data of the disease in most member countries are either scarce, inadequate, or outright lacking. This paucity of epidemiological data has been attributed to limited disease surveillance, a non-existent or poor testing regimen, and low awareness[10] despite the historic presence and recent outbreaks in the region.[11] The clinically approved vaccine for DFD (DengVaxia) is only recommended for dengue seropositive populations,[12] while another live-attenuated dengue vaccine, Qdenga, has emergency approval for use in the European Union and other countries such as Brazil and Indonesia even though significant safety concerns still persist due to risk of antibody-dependent enhancement.[13,14] Qdenga has, however, not been approved for used in some regions such as Africa and the Middle East. Coupled with the increasing global burden of the disease, there is the need for a detailed epidemiological data on the disease, especially in high-risk regions such as West Africa.

This study provides a comprehensive summary of published epidemiological data of DFD prevalence and incidence in the West African subregion. It also assesses entomological studies to identify DENV in the mosquito vectors of the disease in the region, identify gaps in the existing data, and provide a guide for future studies and research priorities.

Materials and methods

Objectives

The goal of this study was to characterize the epidemiology of DFD in West Africa using a systematic analysis of published human prevalence and incidence studies and summarize entomological studies to determine the occurrence of DENV in mosquito vectors (*A. aegypti*).

Study design

A systematic search is carried out using Cochrane Collaboration guidelines,[15] and findings were reported using the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines.[16] The last date searches were conducted are indicated on the search strategies used for each database (Supplemental Table 1). The methodology described by Humphrey *et al.*[17] in their published work "Dengue in the Middle East and North Africa: A Systematic Review" was adapted in this systematic analysis.

Eligibility criteria

Studies that contained data on prevalence and incidence of DFD and/or vector infection in West Africa were considered to be eligible for this analysis with no consideration of the year as an inclusion factor. Case reports, case series, editorials, letters to editors, reviews, commentaries, qualitative studies, basic science research studies, and studies from countries outside West Africa were excluded. Studies with non-empirical research/modeled data, or with infection in other mosquito species, and/or with no extractable primary data were all excluded.

Data sources and search strategy

PubMed, Scopus, the World Health Organization (WHO) African Index Medicus, and Google Scholar were searched without publication date or language restrictions. A search criterion that was based on the combination of relevant terms was designed, adapted for each database, and applied (Supplemental Table 1). A manual search was also carried out by scanning reference lists of eligible studies and relevant reviews were also carried out. This analysis covered the 16 countries included in the West Africa definitions of the WHO, World Bank, and the African Union.

Study selection

For each search, titles and abstracts were imported into Mendeley, and duplicates were removed. Two investigators independently screened records for eligibility based on titles and abstracts, and full texts of articles that were deemed to be potentially eligible were retrieved, assessed, and were consensually retained studies to be included. Conflicts were resolved by consensus or by an arbitration of a third investigator. "Report" in this analysis was defined as any document (paper, abstract, or public health record) containing an outcome measure of interest, while the outcome measure(s) within that report were referred to as "study."

Data extraction and synthesis

Prepiloted data extraction forms were used to extract data and entered into Microsoft Excel. Data from reports in languages other than English ($n = 5$) were extracted from the abstracts and/or full texts with the aid of Google Translate online software,[18] and translated texts were validated by a native French language speaker. Studies were curated by country and year, using different tables for DFD prevalence, DFD incidence, and vector infection studies.

Prevalence studies were classified as either general prevalence or acute DENV infection. General prevalence studies were defined as seroprevalence studies reporting anti-DENV immunoglobulin G (IgG) prevalence among individuals who were not suspected to have acute DENV infection, including community members, blood donors, military personnel, students, hospitalized patients, and outpatients receiving care for non-febrile illnesses. Acute DENV infection studies were stratified into (1) undifferentiated acute febrile illness (AFI), which referred to studies for which acute dengue infection is differentiated not by clinical grounds alone, but inclusive of IgG prevalence obtained during the acute phase of illness of these studies was presumed to reflect secondary infection and (2) suspected dengue (SD) infection, which referred to studies with defined or undefined clinical criteria for probable dengue infection as an inclusion criterion in the study.

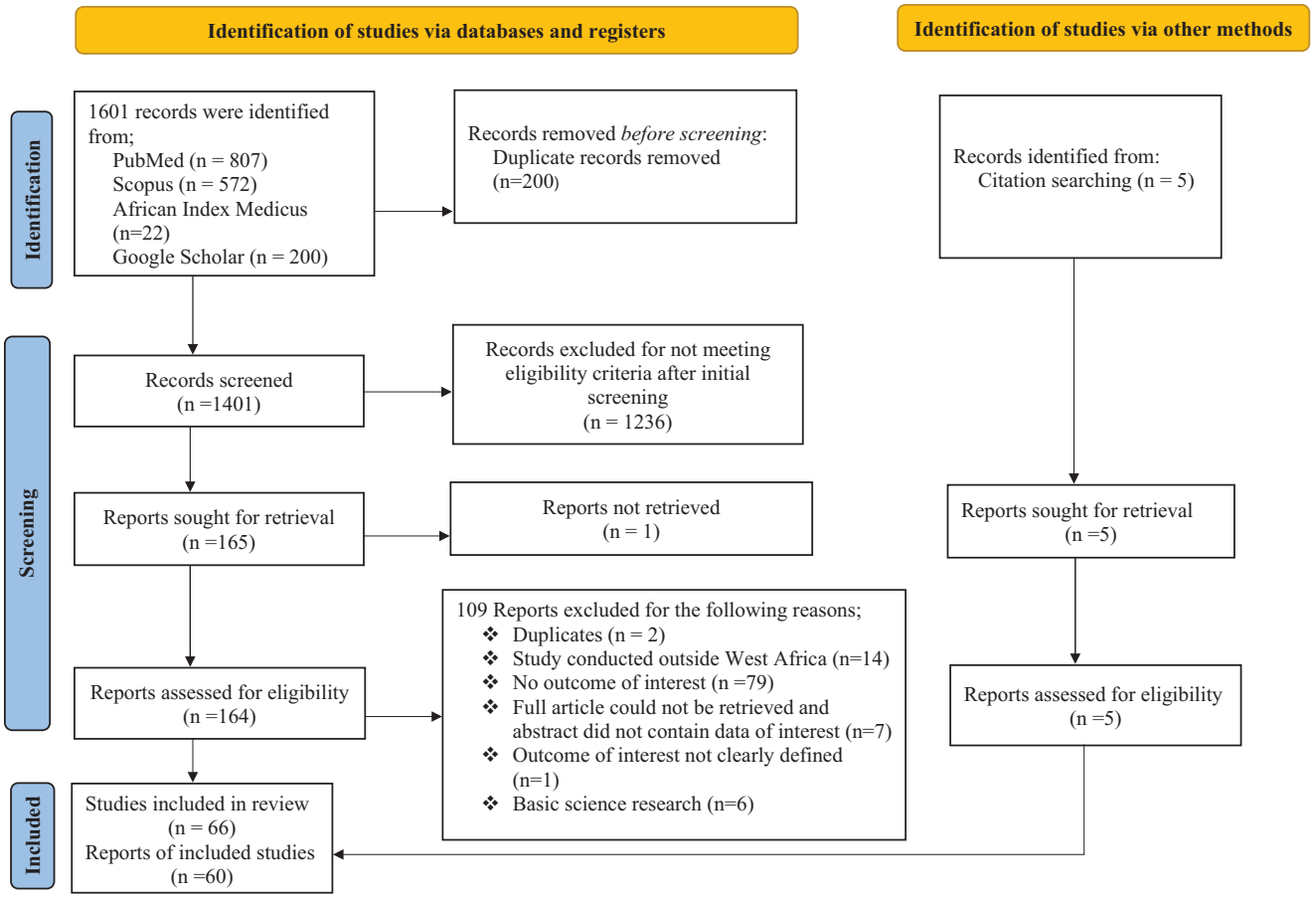

Figure 1. PRISMA flow diagram illustrating the study selection process.

Country-level distribution of all included prevalence and incidence studies was mapped, and a separate map was generated for the studies that reported geographic distribution of DENV in mosquito vectors.

Risk of bias assessment

For the quality of prevalence studies included in this systematic analysis, a risk of bias (ROB) assessment was conducted for each study based on the Cochrane approach and by evaluating the precision of reported measures. The methodology for this assessment is similar to that previously reported by Humphrey *et al*. Briefly, for each DENV prevalence measure, ROB was classified as low, high, or unclear ROB in three domains: sampling methodology, DENV infection ascertainment, and response rate. Response rate is defined as the number of tested individuals divided by the number of persons invited to participate in the study.

ROB was considered low if (1) sampling was probability-based (i.e. using some form of random selection), (2) DENV prevalence measures included viral neutralization testing (VNT) for general prevalence studies or biological assays (i.e. cell culture, polymerase chain reaction [PCR], and non-structural glycoprotein-1 [NS1] enzyme-linked immunosorbent assay [ELISA]) for acute infection studies, and (3) response rate was ⩾80%.

Studies with missing information for any of the domains were classified as having unclear ROB for that specific domain. Sampling strategy for acute infection studies were not evaluated because convenience sampling was employed. Studies with sample size ⩾100 individuals were considered to have high precision.[17]

Results

The PRISMA guidelines were used in the selection of studies that were included in this analysis as illustrated in Figure 1. A total of 1601 reports were identified from databases searches (PubMed: 807, Scopus: 572, African Index Medicus: 22, and Google Scholar: 200), with 55 reports included in this study after the selection process (Figure 1). Briefly, 86 duplicates were removed using the duplication tool in the Mendeley Software, a further 1401 records did not meet the inclusion criteria while 1 report could not be retrieved. Out of the remaining 164 records which were screen for eligibility, 109 reports were deemed ineligible (studies with no outcome of interest [$n = 79$], studies conducted outside West Africa [$n = 14$], studies where full articles could not be retrieved and abstracts did not contain outcomes of interest [$n = 7$], studies involving basic science research [$n = 6$], duplicates reports [$n = 2$], and studies with outcomes of interest not clearly defined [$n = 1$]) while 55 eligible reports were found. A manual search of relevant bibliographies and systematic reviews yielded five additional reports. Sixty reports containing 66 studies met the inclusion criteria and were included in this analysis.

Characteristics of included studies

There were 58 out of the 60 eligible reports that contained data on DFD prevalence studies in West Africa and these have been summarized in Table 1. Studies were identified in 8 out of the 16 countries in the study area, with Nigeria contributing almost half of the included studies ($n = 27$). Other countries with DENV human prevalence data included Burkina Faso ($n = 12$), Ghana ($n = 6$), Senegal ($n = 5$), Cote d'Ivoire ($n = 3$), Sierra Leone ($n = 3$), Guinea ($n = 1$), and Mali ($n = 1$). Over 70% ($n = 41$) of prevalence studies were conducted in patients presenting with AFI while 19% ($n = 11$) were conducted in the general population in apparently healthy individuals. Majority of studies ($n = 46$) utilized serologic assays, with ELISA being the most common diagnostic tool. Table 2 provides a summary of the outcomes of interest from the DFD prevalence studies, and the spatial distribution of the studies included in this review. A single report[19] had two incidence studies from Cote d'Ivoire and Senegal as summarized in Table 4, and six studies on DENV-infected mosquitoes are shown in Table 5.

ROB assessment

Assessment of the quality of the DFD prevalence studies that were included in this analysis has been summarized in Table 3. Details of the assessment are provided in Supplemental Table S2. Majority of the studies had a high precision score, with 81.03% ($n = 47$) utilizing sample sizes greater than 100 persons. All the studies had unclear ROB for response rate, with none of the studies providing data on that parameter. Most of the studies used assays with low ROB; the assays employ biologic tests either as an initial screening test or as a confirmatory test. The study designs for the general population studies are prone to high ROB, with only 36.36% ($n = 4$) utilizing a form of random sampling.

DFD incidence in West Africa

A report on French overseas soldiers presenting with suspected cases of dengue produced two incidence studies – one each from Cote d'Ivoire and Senegal (Table 4).

DENV occurrence in mosquito vectors in West Africa

Six studies in four countries attempted to identify DENV in *A. aegypti* (Table 5) – two studies each were carried out in Burkina Faso and Senegal and with one study each carried out in Ghana and Cape Verde. Geographic distribution of DENV occurrence in mosquito vectors in West Africa has been mapped and presented in Figure 2, with *A. aegypti* being the identified species in all the reported studies. With the exception of Ghana,[20] four other studies performed in Cape Verde, Senegal, and Burkina Faso reported a positive presence of DENV in mosquito vectors.[21] DENV-2 positive *A. aegypti* were detected in Cape Verde, Senegal, and Burkina Faso. DENV-3 and DENV-4 were also detected in Senegal and Cape Verde, respectively, all in *A. aegypti* (Table 5).

Discussion

Very few countries in the West African subregion had published data on DFD prevalence, with Nigeria and Burkina Faso providing more than 65% of the data. The paucity of data DFD incidence was further illustrated, with only two studies being reported – one study each from Senegal and Cote d'Ivoire.[19] The occurrence of DENV-infected mosquito vectors is an important risk factor that has been used to estimate DFD outbreak potential. However, majority of the countries in the West African subregion did not have any data on the circulation of DENV-infected vectors, with four countries accounting for all the available data.

DFD prevalence and incidence in West Africa

Anti-DENV antibodies and/or DENV antigens were detected in all the studies identified in eight countries of the 16-member subregion. Wide variation in DFD prevalence measures were observed in the included studies (Table 1), ranging from 0.02% reported in Senegal to 93% observed in Mali. The observed prevalence among the study categories were within the range reported in reviews that looked at dengue in the Middle East and North Africa[17] and the African continent.[22]

Out of the 11 general population studies, 4 were carried out prior to 1990, 3 studies conducted between 1990 and 2010 while 3 were conducted in the last decade. The licensed dengue vaccine for use in the Africa region, DengVaxia, can only be deployed in Dengue seropositive populations as the vaccine efficacy and safety is much more improved in these populations.[12] However, the paucity of this critical population-wide seroprevalence epidemiological data on DFD in West Africa will hinder vaccine-based control measures in the subregion. Unavailability of any published data on DFD epidemiology in 8 out of the 16 West African states (Cape Verde, Gambia, Guinea-Bissau, Liberia, Mauritania, Niger, and Togo) only compounds the barriers to vaccine deployment control measures. The geographic distribution of positive cases of DFD (Figure 3) suggests that the absence of data from these countries is likely due to lack of testing or surveillance and not the absence of DFD.

Larval reported the only DFD incidence in West Africa which looked at cases of suspected dengue among French overseas soldiers over a period of 1 year (2010–2011). Three biomarkers of DENV (IgM antibodies, NS1 antigen, and Viral RNA) were tested for in these studies. An incidence rate of 1/1000 persons per year was recorded in Cote d'Ivoire while no positive case of DFD was recorded in Senegal among the study population.[19] The low incidence rate observed in Cote d'Ivoire correlates with an IgM prevalence of 0.4% in AFI patients reported by L'Azou *et al.*,[23] within the same study period. These observations contrast with a similar study that recorded IgM prevalence of 25%, albeit a high ROB in terms of sample size.[24] Even though DFD is known to be present in Senegal, with prevalence ranging from 0.02% to 28.2%,[25,26] no comparable prevalence study was identified within the study period. Low exposure rates may be a key factor accounting for the low incidence reported, considering the setting and the study population.[19]

Table 1. Dengue human prevalence studies in West Africa ($N = 58$).

Study year(s)	Study place/ region	Setting; pop (age range)	Clinical present	Sampling (timing)	Assay type‡	Make of assay	Sample size (DENV positive)	Prevalence (%)	Additional tests and comments	Author (reference)
Burkina Faso ($n = 12$)										
2017	Ouagadougou	Clinical; pregnant women (16–49 years)	AFI	Cohort (Retro)	ICT	Bioline	424 (121)	28.54		Tougma[20]
2015–2017	Ouagadougou	Comm (1–55 years)	AH	RS SLS (Pros)	ELISA	PanBio	2897 (1651)	67.9	66.3% of participants were IgG+ at enrollment	Lim[21]
2014–2017	Ouagadougou	Clinical (1–55 years)	AFI Non-malaria	NS	ELISA IgM/IgG NS1	PanBio	2929 (740)	25.3	PCR confirmatory test (42%+). Included an outbreak period (Oct–Dec, 2015) 87% of patients were from non-outbreak periods	Lim[22]
2016	Bobo-Dialasso	Clinical; children and adults (N/S)	AFI	CS (Pros)	ELISA	Bioline	85 (19)**	22.35	IgM+ prevalence was 7.06% 4 patients were IgM/G+	Ouangre[23]
2016	Ouagadougou	Comm; blood donors (18–60 years)	AH	CS (Pros)	ELISA	PanBio	1056 (801)	75.8	870 units of blood were processed into 1056 blood components	Sawadogo[24]
2013–2014	Ouagadougou	Clinical (N/S)	SD	NS Retro	ICT	Bioline	343 (98)	28.6	NI	Diallo[25]
2011–2013	Multiple	Clinical; children and adults (1–19 years)	AFI typhoid patients	(Pros)	PCR	TaqMan Array Card	53 (6)	11	NI	Marks[26]
2013–2014	Ouagadougou	Clinical (all ages)	AFI Malaria	CS (Pros)	ICT NS1, IgM/G	Bioline Dengue Duo	379 (33)	8.7	(15/60) were PCR+ DENV-2, 3, and 4 observed	Ridde[27]
2013	Ouagadougou	Clinical (4–63 years)	SD		ICT	Bioline	43 (7)	16.3	48.8% (21/43) were PCR+	Tarnagda[28]
2003-2004	Nouna	Comm: pregnant women (16–45 years), blood donors (14–48 years)	AH	RS	ELISA	PanBio	289 (76)	26.3§	Dot blot assay (Genelabs) – 26.3+	Collenberg[29]
	Ouagadougou	Comm; pregnant women (16–43 years), blood donors (16–46 years)	AH	RS	ELISA	PanBio	394 (124)	36.5§	Dot blot assay – 36.5	
1982	Ouagadougou	Clinical (N/S)	SD	NS	IFI		30 (9)**	30	Isolation of DENV-2 on Vero cells	Gonzalez[30]
Cote d'Ivoire ($n = 3$)										
2011-2012	Abidjan	Clinical (all ages)	AFI	Pros	ELISA IgM	In-house CDC	812 (3)**	0.4	PCR, Virus isolation (DENV-3) 28.9 of patients were malaria+	L'Azou[31]
2010	Abidjan	Clinical (⩾18 years)	SD	(Retro)	PCR ELISA(IgM)	In-house	28 (7)	25**	PCR+ for DENV-3 in 4 cases IgM+ in 3 cases	Aoussi[32]
2008	Abidjan	Clinical	AFI	(Pros)	ELISA	In-house CDC	432 (33)	7.6	PCR detection of DENV-3 ($n = 12$) 9+ for both YF and DENV IgM	Akoua-Koffi[33]
Ghana ($n = 6$)										
2016-2017	Accra, Kintampo	Clinical; children (1–15 years)	AFI	(Pros)	PCR	TagMan	166 (2)	1.21**	IgM+/IgG+ after 2 months follow-up	Amoako[34]
2016–2017	Accra	Clinical (NS)	SD	CS (Pros)	ELISA IgM/G	Abcam CDC Bio-Rad	260 (180)**	69.23	15% IgM+ 66.2% IgG+ CHIKV – 27.69% Zero positive PCR	Manu[35]

(Continued)

Table 1. (Continued)

Study year(s)	Study place/ region	Setting; pop (age range)	Clinical present	Sampling (timing)	Assay type‡	Make of assay	Sample size (DENV positive)	Prevalence (%)	Additional tests and comments	Author (reference)
2014–2016	Whole country	Clinical (NS)	AFI (suspected Ebola virus disease)	(Retro)	ELISA	Abcam	150 (85)	56.67**	32 samples were IgM+. IgM+ were tested for NS1 Ag (4+) 4 samples were PCR+ DENV-2 (1), DENV-3 (3)	Bonney[36]
2014	Whole country	Clinical (NS)	AFI Suspected yellow fever patients	CS (Pros)	ELISA	PanBio	417 (182)**	43.6	NI	Pappoe-Ashong[37]
2013–2015	Agogo, Techiman, Kumasi	Comm; blood donation centers (16–60 years)	AH	CS (Pros)	ELISA IgM PCR	AccuDiag™	188 (42)	22.3	All samples were IgG and PCR negative	Narkwa[38]
2011–2014	Kintampo, Accra, Navrongo	Clinical; children (2–14 years)	AFI Malaria	(Retro)	ELISA	Capture DxSelect	218 (47)	21.6	PCR negative 3.2% (7/218) were IgM+	Stoler[39]
Guinea ($n=1$)										
20062007	N'Zerekore, Faranah	Clinical (NS)	AFI		ELISA IgM	PanBio	47 (1)	2	PRNT90 confirmation	Bausch[40]
Mali ($n=1$)										
2006	Bamako	Clinical (1–80 years)	AFI	(Retro)	IFA, ELISA	In-house	95 (87)	93	0% IgM+ 46% of samples ($n=6$) showed no neutralizing activity	Phoutrides[41]
Nigeria ($n=27$)										
2019	Anyiba, Kogi State	Clinical (NS)	AFI	RS CS (Pros)	ELISA	Biopanda	200 (42)	20.5	NI	Omatola[42]
2018	Alimusho, Orile-Agege	Clinical (1–60 years)	AFI	– CS (Pros)	PCR		130 (11)	8.5	Alimusho area had a prevalence of 12.2%. Orile-Agege area – 3.6% DENV-1 and 3 detected; DENV-1 (genotype 1), DENV-3 (genotype 1)	Ayolabi[43]
2018	Kura	Clinical (all ages)	AFI	SRS	ELISA	CTK Biotech	137 (13)	9.4	8 samples were positive for both malaria and dengue	Nas[44]
2018	Maiduguri, Bono State	Clinical (all ages)	AFI	NS	ELISA	In-house	197 (176)	89	NI	Oderinde[45]
2017	Abuja	Clinical (NS)	AFI (HIV+)	– CS (Pros)	ELISA	Euroimmune	178 (79)	44.4	44.2% were co-infected with *Plasmodium falciparum*	Mustapha[46]
2017	Cross River State	Clinical (1–99 years)	AFI	RS CS (Pros)	LFIA IgM/G	CTK	420 (25)**	6	Positive samples confirmed by ELISA	Otu[47]
2016	Ille-Ife, Osun State	Clinical (NS)	AFI	NS	ELISA IgM	DIA. PRO	179 (46)**	25.7	26.5% in male 25% in female 9% had no detectable malaria parasite	Adesina[48]
2016	Ilorin	Clinical (all ages)	AFI	– CS (Pros)	ELISA IgM	Wkea	176 (76)	46	2.8% had co-current dengue and malaria (48/95) of IgM– samples were IgG+ 6.3 (11/95) were PCR+	Kolawole[49]

(Continued)

Table 1. (Continued)

Study year(s)	Study place/ region	Setting; pop (age range)	Clinical present	Sampling (timing)	Assay type‡	Make of assay	Sample size (DENV positive)	Prevalence (%)	Additional tests and comments	Author (reference)
2016	Abuja	Clinical (NS)	AFI	CS	ELISA NS1	Euroimmune	171 (74)	43.3	8.89 (15/171) were NS1+	Nasir[50]
2015	Maiduguri	Clinical (NS)	AFI	NS	ELISA IgM	Commercial	91 (34)	37.4	9.9% (9/91) were NS1+	Hamisu[51]
2014	Osogbo, Osun State	Clinical (0–70 years)	AFI	– CS Pros	ELISA	MONOLISA	100 (77)	77	33% co-occurrence of Dengue and *P. falciparum*	Adeleke[52]
2014	Simawa, Sagamu; Ogun State	Clinical; (3–70 years)	AFI	– – (Pros)	ICT	Standard diagnostics	60 (1)	1.7	NI	Ayorinde[53]
2014	Kafanchan	Clinical (all ages)	AFI	CS	ELISA IgM	Diag. Auto/ Cortez Diag.	122 (89)	72.9	NI	Bello[54]
	Zara	Clinical (all ages)	AFI	CS	ELISA IgM	Diag. Auto/ Cortez Diag.	122 (59)	48.36	NI	
	Birnin-Gwari	Clinical (all ages)	AFI	CS	ELISA IgM	Diag. Auto/ Cortez Diag.	122 (42)	34.42	NI	
2014	Ibadan	Clinical (all ages)	AFI	CS (Pros)	ELISA IgM	Diagnostic Auto	274 (64)	23.3	PCR test for flavivirus (WNV, YFV, and ZIKV) – all negative	Onoja[55]
2014	Jos, Maiduguri	Clinical (NS)	AFI (malaria+ or suspected)	– CS Pros	ELISA	PanBio	529 (111)**	21**	418 (79%) were negative for all test	Onyedibe[56]
2014*	Ogbomoso	Comm (all ages)	AH	NS	ELISA IgM	WKEA	93 (16)	17.2	NI	Oladipo[57]
2013*	Ilorin, Kwara State	Clinical; children (>5 years)	AFI	NS	ELISA IgM	IVD Research	130 (40)	30.8	NI	Adedayo[58]
2013	Ibadan	Clinical (4–82 years)	AFI	Random CS	ELISA	Diagnostic Auto	188 (138)	73	1.6 (3/188) IgM+ NS1+ (10/19)	Oyero[59]
2011	Maiduguri, Borno State	Clinical (suspected malaria and/or typhoid) (all ages)	AFI	CS	VNT Cell culture-based	In-house	256 (26)	10.1	NI	Idris[60]
2008	Maiduguri, Borno State	Clinical; suspected malaria/typhoid (NS)	AFI		VNT (PRNT)	In-house	285 (193)	67.71	NI	Baba[61]
1980	Kainji Lake area	Comm; general pop. (NS)	AH	– (Pros)	HI	In-house	267 (124)	46	Suspected cross-reaction with other flavivirus (ZIKV, YFV)	Adekolu-John[62]
1972	Shaki, Oyo State	Comm (NS)	AH		Serology	ns	304 (164)**	54	NI	Fagbami[63]
1977*	Multiple locations in Nigeria	Comm; children and adults	AH	NS (Retro)	VNT HI	In-house	1816 (811)	45	38% (486/1275) of persons tested were HI+ for DENV-1 NT in Swiss suckling mice. 48% of monkeys tested had dengue NAbs 25% of galagus also had Dengue NAbs	Fagbami[64]

(Continued)

Table 1. (Continued)

Study year(s)	Study place/ region	Setting; pop (age range)	Clinical present	Sampling (timing)	Assay type‡	Make of assay	Sample size (DENV positive)	Prevalence (%)	Additional tests and comments	Author (reference)
1975	Igbo-ora	Comm (NS)	AH	NS	HI	NS	78 (52)**	67	DENV-1–67% DENV-2–45% DENV-1 isolated	Fagbami[65]
1968–1969	Igbo Ora	Comm (⩾6 months)	AH	NR CS	HI	In-house	216 (136)	63**	NI	Guyer[66]
Senegal ($n=5$)										
2015–2016	Dakar	Clinical (<10 years)	AFI	(Pros)	RPA	NS	104 (3)	2.88**	IgM– Isolation of 2 DENV Detection of DENV-1	Dieng[67]
2015	Guediawaye, Pikine, Dakar	Clinical; children (<10 years)	AFI Malaria	(Pros)	PCR ELISA	In-house	106 (3)	2.83**	All 3 PCR+ samples were negative by ELISA	Gildas Boris[68]
2009–2013	Kedougou	Clinical (1–90 years)	AFI	NS	ELISA IgM PCR	NS	13845 ($n=3$)	0.02**	NI	Sow[69]
2009	Dakar Thies	Clinical (NS)	SD	NS	PCR ELISA IgM	NS	696 (196)	28.2	5/196 confirmed cases developed DHF 1 fatality 49 DENV-3 isolates from confirmed case patients	Faye[70]
1992–2004	Dakar	Clinical (NS)	AFI	NS	ELISA PCR	InBios	224 (11)	9.3	NI	Herrara[71]
Sierra Leone ($n=3$)										
2016*	Kenema	Clinical (NS)	AFI	NS (Pros)	VNT (PRNT50)	In-house	149 (117)	78.52	PRNT80	de Araújo Lobo[72]
2012-2013	Bo	Clinical (⩾16 years)	AFI	NS	ICT	Bioline	1795 (81)	4.5	NI	Bockarie[73]
2006-2008	Eastern S. Leone†	Clinical; suspected Lassa fever patients (NS)	AFI	NS (Pros)	ELISA IgM	In-house	253 (11)	4.3	IgM+ were tested for IgG by ELISA and/or PRNT	Schoepp[74]

DENV: dengue virus; AFI: acute febrile illness; SD: suspected dengue; AH: apparently healthy; Pros: prospective study; Retro: retrospective study; CS: cross-sectional study; NS: not stated; Ag: antigen; ELISA: enzyme-linked immunosorbent assay; ICT: immunochromatography test; PCR: polymerase chain reaction; HI: hemagglutination inhibition; RPA: recombinase polymerase assay; NS1: non-structural glycoprotein-1; IFA: immunofluorescence antibody test; VNT; viral neutralization test; PRNT; plaque reduction neutralization test; Pop.: population; SRS: simple random sampling; RS: random sampling; NR: non-random sampling; NI: none identified or not related to outcome of interest; IgG: immunoglobulin G; IgM: immunoglobulin M.

Assay abbreviation: CDC (Centers for Disease Control and Prevention, USA); Euroimmune (Lubeck, Germany); SD Bioline (Standard Diagnostics, Korea); Genlab (Genlab Diagnostics, Singapore); PanBio (Brisbane, Australia); Diag. Auto. (Diagnostic Automation, CA, USA); CTK Biotech (CTK Biotech Inc. USA); Bio-Rad (Marnes-la-Coquette, France); Abcam (Cambridge, MA, USA); AccuDiag™ (Diagnostic Automation/Cortez Diagnostic, Inc. Calabasas, CA, USA); Capture DxSelect (Focus Diagnostics, Inc., Cypress, CA, USA); Biopanda Diagnostics (Belfast, UK); and Wkea (Wkea Med Supplies Corp., China).

*Indicates year of publication when year(s) of data collection not available in report.

†Indicates the region with the majority of study participants in multicountry study that were not properly defined.

‡All serologic assays were IgG unless otherwise stated.

§Indicates studies where prevalences were extrapolated by author(s).

**Indicates inferred data from available information in the study.

Table 2. Summary of DFD prevalence studies.

Study parameter	General population (*n* = 11)	Undifferentiated febrile illness (*n* = 41)	Suspected dengue (*n* = 6)	Total (*n* = 58)
Sample size (cases)	7598 (3997)	26750 (3004)	1400 (497)	35748 (7498)
Pooled prevalence (range)	52.61 (17.2–75.8%)	11.23 (0.02–93%)	35.5 (16.3–69.2%)	20.97 (0.02–93%)
Period of study				
Pre-1990s	3 (27.27%)	0	1 (16.67%)	4 (6.90%)
1990–2010	3 (27.27%)	6 (14.63%)	2 (33.33%)	11 (18.97%)
2011–2020	5 (45.45%)	35 (85.37%)	3 (50.00%)	43 (74.14%)
Study setting				
Community	11 (100%)	0	0	11 (18.97%)
Clinical environment	0	41 (100%)	6 (100%)	47 (81.03%)
Assay type				
ELISA IgG	4 (36.64%)	15 (36.59%)	1 (16.67%)	20 (34.48%)
ELISA IgM	2 (18.18%)	13 (31.71%)	0	15 (25.86%)
IFA	0	1 (2.44%)	1 (16.67%)	2 (3.45%)
ICT	0	4 (9.76%)	2 (33.33%)	6 (10.34%)
HI	3 (27.27%)	0	0	3 (5.17%)
Cell culture (VNT)	1 (9.09%)	3 (7.32%)	0	4 (6.90%)
PCR	0	4 (9.76%)	2 (33.33%)	6 (10.34%)
RPA	0	1 (2.44%)	0	1 (1.72%)
Not specified	1 (9.09%)	0	0	1 (1.72%)
Assay make				
Commercial	6 (54.55%)	30 (73.17%)	3 (50.00%)	39 (67.24%)
In-house	4 (36.36%)	8 (19.51%)	1 (16.67%)	13 (22.41%)
Not specified	1 (9.09%)	3 (7.32%)	2 (33.33%)	6 (10.43%)

n: number of studies; HI: hemagglutination inhibition; IFA: immunofluorescence antibody test; VNT: viral neutralization test; ELISA: enzyme-linked immunosorbent assay; PCR: polymerase chain reaction; RPA: recombinase polymerase assay.

Table 3. Summary of risk of bias assessment.

Risk of bias parameters	General population (*n* = 11)	Undifferentiated febrile illness (*n* = 41)	Suspected dengue (*n* = 6)	Total (*n* = 58)
Assay				
Low ROB	4 (36.64%)	28 (68.29%)	6 (100%)	38 (65.52%)
High ROB	6 (54.55%)	13 (31.71%)	0	19 (32.76%)
Unclear ROB	1 (9.09%)	0	0	1 (1.72%)
Sampling methodology				
Low ROB	4 (36.36%)	N/A	N/A	–
High ROB	7 (63.64%)	N/A	N/A	–
Unclear ROB	0	N/A	N/A	–
Response rate				
Low ROB	0	0	0	0
High ROB	0	0	0	0
Unclear ROB	11 (100%)	41 (100%)	6 (100%)	58 (100%)
Precision				
Low	2 (18.18%)	6 (14.63%)	3 (50%)	11 (18.97%)
High	9 (81.82%)	35 (85.37%)	3 (50%)	47 (81.03%)

n: number of studies; ROB: risk of bias; N/A: not applicable.

Assays and cross-reactivity

Serological assays were the most commonly tool used tests in the analyzed studies, with enzyme-linked immunosorbent assays (ELISAs) being the most deployed test for DFD in West Africa; similar to other reviews that has been conducted in other parts of Africa.[17,22] IgG and IgM ELISAs accounted for 34.48% and 25.86%, respectively, of tests used in the initial screening of study participants. Cell culture–based viral neutralization assays which are considered the gold standard in DFD diagnostics and nucleic acid tests (PCR and recombinase polymerase assay [RPA]) were used as the initial screening test in approximately 7% and 12%, respectively, of all human prevalence studies reviewed (Table 2).

At least 67% of all assays used were obtained from commercial sources while 22% were developed in-house (Table 2). The use of commercial assays is likely to increase reproducibility of these studies compared to in-house assays that are subject to variations in sensitivity and specificity between laboratories. However, the use of different commercial kits

Table 4. Summary of dengue human incidence studies in West Africa ($n=2$).

Period of study	Duration of follow-up	Country of study	Setting; population	Clinical presentation	Type of assay	Make of assay	Sample size (cases)	Incidence (persons per year)	Author (reference)
2010–2011	1 year	Cote d'Ivoire	Community; military (French overseas soldiers)	SD	ELISA (IgM) RT-PCR, NS1	In-house	972 (1)	1/1000	De Laval19
		Senegal	Same	SD	Same	In-house	1217 (0)	0	

SD: suspected dengue, ELISA: enzyme-linked immunosorbent assay, RT-PCR: reverse transcriptase polymerase chain reaction; NS1: non-structural protein 1.

Table 5. Summary of dengue virus occurrence in *Aedes aegypti* studies in West Africa ($n=6$).

Author (reference)	Year(s) of study	Country; region	DENV serotype(s)	Comment
Amoa-Bosompem[75]	2015–2016	Ghana	NI	No DENV was detected or isolated
Guedes[76]	2014–2015	Cape Verde; Praia	2, 4	161 female *A. aegypti* analyzed in 34 pools. 8 pools were positive. MIR = 8/34
Ridde[27]	2013–2014	Burkina Faso; Ouagadougou	NI	No DENV detected in mosquito via PCR
Faye[70]	2009	Senegal; Darkar Thies	3	NC
Traore-Lamizana[77]	1990	Senegal	2	NC
Robert[78]	1983–1986	Burkina Faso; Bobo-Dioulasso	2	NC

n: number of studies; DENV: dengue virus; NI: none identified; NC: no comment.

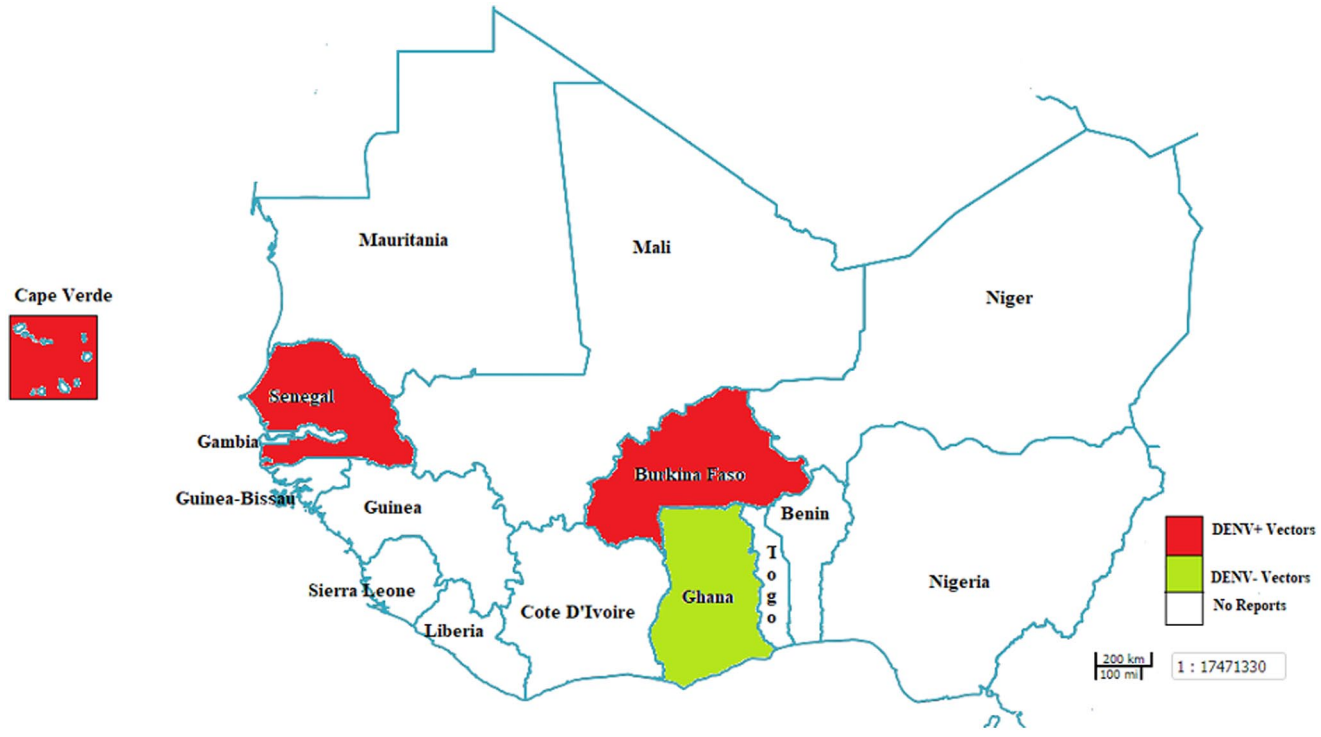

Figure 2. Geographic distribution of DENV occurrence in *Aedes* mosquito in West Africa.

from different suppliers with that have varying degrees of test accuracy and sensitivity, and the differences in study designs and sampling design makes comparison between different studies and countries difficult.

DENV share genomic and antigenic similarity with other flaviviruses such as yellow fever virus (YFV), West Nile virus (WNV), Chikungunya virus (CHIKV), and Zika virus (ZIKV) which either endemic or co-circulate in sub-Saharan Africa,[25,27] and are known to induce cross-reactive antibodies. With most people in West Africa receiving YFV vaccines, the risk of cross-reactive antibodies leading to false-positives is high. Serological assays which are susceptible to cross-reactions were the most widely used test assay in the included studies.[28–30]

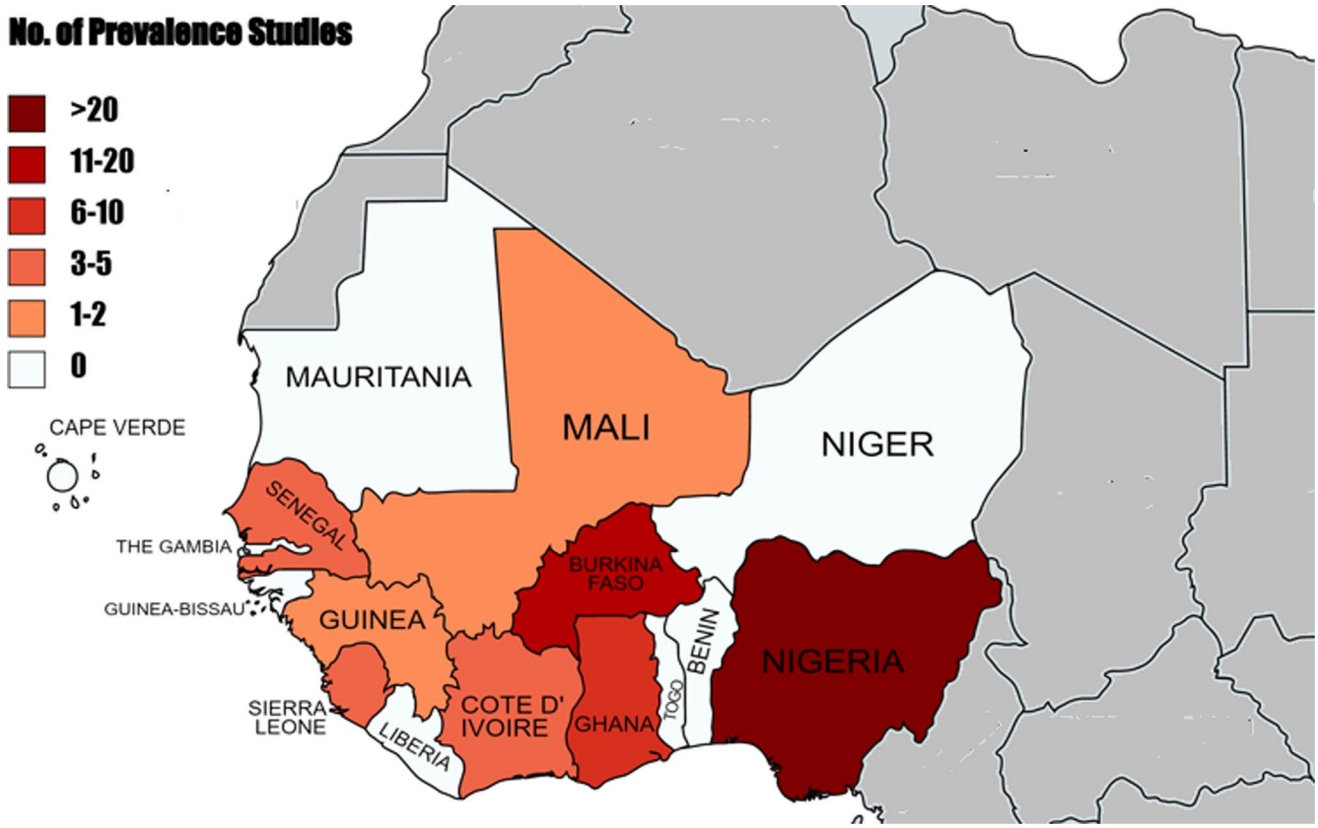

Figure 3. Geographic distribution of dengue fever disease prevalence studies in West Africa.

The possibility of cross-reactions raises questions about the accuracy of prevalence measures reported, especially in the absence of VNTs which is the gold standard in most of the reviewed studies. Only 5.17% ($n=3$) of the studies that were used in the analysis performed VNT as confirmatory tests; one study in apparently healthy individuals (Fagbami *et al.*[31]) and two studies in patients with undifferentiated febrile illness.[32,33] Humphrey *et al.*[17] reported a similar observation in respect to VNT deployment rates in studies conducted in Middle East and North Africa.

This is the first known analysis to the best of our knowledge that looks at the presence of DENV in *A. aegypti* and/or *A. albopictus* in West Africa. *A. aegypti* is endemic in tropical and subtropical Africa, while *A. albopictus* which were imported from temperate regions is quickly gaining a foothold in Africa.[34–36] The presence of DENV-infected *A. aegypti* mosquitoes points to possible autochthonous transmission of dengue in the four West African countries (Table 5). The circulation of DENV-2 and 3 in *A. aegypti* mosquitoes in the region potentiate possible epidemic outbreaks.[37] The lack of detection of DENV in majority of the countries in West Africa *Aedes* mosquitoes does not preclude their circulation and most likely due to the absence or ineffective entomological surveillance programs.

Dengue epidemic risk factors in West Africa

A. aegypti, the primary vector of DENV, is hypothesized to have originated from Africa and native tropical or subtropical regions including West Africa.[36,38] The presence of DENV-infected *A. aegypti* (Table 5) is a major epidemic risk factor since it signifies possible local transmission especially in periurban areas. *A. albopictus* which was imported into Africa from Asia has been rapidly increasing its geographic range and its presence has been detected across Africa.[5] *A. albopictus* has emerged as a competent secondary vector for DENV. Notwithstanding the absence of data on the occurrence of DENV-infected *A. albopictus* in the West African subregion, the high prevalence of DFD in the region makes infection of this vector possible. This also increases the risk of dengue outbreaks especially in rural areas where *A. albopictus* preferentially circulate.[39]

Rapid, and most often, unplanned urbanization taking place across West Africa, and ineffective or non-existing vector control measures do not only predispose the region to dengue outbreaks, but also poses a global health threat.[17,22] Increasing insecticide resistance in mosquito vectors and DENV adaptation to new hosts which increases its range only exacerbate the risk of outbreaks. Recent outbreaks in Burkina Faso and Côte d'Ivoire fit into the trend of increasing incidence of the disease across sub-Saharan Africa.[17]

Challenges and research priorities

The true burden of dengue in West Africa still remains under-reported. This analysis did not identify any epidemiological study in 8 out of 16 countries in the region, with 3 out of the 8 reporting countries having $\leqslant 3$ studies (Table 1). Entomological surveillance to detect DENV in mosquito vectors is lacking; limited studies identified in only four

countries (Figure 2), with three of the studies conducted in the last decade. Data-driven control measures are required to contain the threat of DFD and inform resource allocations. The paucity of epidemiological data in West Africa as evident in this analysis undermines decision-making and the needed policy measures required to control the disease. If DENV diagnostics integrated into the healthcare systems in West Africa, the true burden of DFD will not be known, and the disease will continue to be misdiagnosed.

DFD research should, as a matter of priority, focus on providing representative epidemiological data on prevalence in the general population in West Africa. This is necessary to assess the feasibility of DengVaxia and Qdenga vaccine deployment in the subregion. Entomological surveillance is also required to assess DENV infection and determine the magnitude of insecticide resistance in the *Aedes* vectors. Data from such studies will also make a strong argument for the integration of dengue diagnostics into the healthcare structure.

Globally, DENV serotypes and genotypes with greater epidemic potential are rapidly replacing those with lower epidemic impact;[9,12] thus, molecular characterization of circulating DENV in both humans and vectors is needed. The impact of changing climatic conditions, human host and viral factors on DFD dynamics is also needed for implementation of effective control measures.

Study limitations

This study was limited by the databases of published reports screened, since not every available database was used. This study did not also consider the occurrence of *Aedes* mosquito only, which could have provided dengue risk indicators as well as outbreak reports and cases in travelers originating from West Africa.

Conclusions

This analysis shows a high prevalence of DFD among the populace and the circulation of DENV-infected vectors in West Africa, albeit weaknesses in study design and limitations. It also highlights the scarcity of epidemiological data on DFD prevalence and incidence, and DENV occurrence in mosquito vectors across the West African subregion. These findings and the neglected tropical disease (NTD) status of DFD should spur research aimed at bridging the data gap, incorporating DFD into differential diagnostics in healthcare system, and including DFD vector control measures and disease research in West Africa.

AUTHORS' CONTRIBUTIONS

PG and OQ contributed to conceptualization. PG, MBY, and OQ contributed to methodology. PG, MBY, and OQ contributed to manuscript draft. PG, MBY, and OQ contributed to critical review and editing. All authors read and approved the final version of the manuscript.

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SUPPLEMENTAL MATERIAL

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