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Dengue data and surveillance in Tanzania: a systematic literature review

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Abstract

OBJECTIVE Although there is evidence that dengue virus is circulating in Tanzania, the country lacks a dengue surveillance system. Consequently, the true estimate of dengue seroprevalence, as well as the incidence in the population, the frequency and magnitude of outbreaks is unknown. This study therefore sought to systematically review available dengue data from Tanzania.

METHODS The systematic review was conducted and reported using the PRISMA tool. Five databases (PubMed, Embase, Web of Science, WHOLIS and Google Scholar) were searched for articles using various keywords on the illness, data and geographical location. Identified articles were assessed for inclusion based on predefined eligibility criteria. Data were extracted from included articles, analysed and reported.

RESULTS Based on the 10 seroprevalence studies in defined populations with estimates of acute confirmed infections that were included in the review, the estimated seroprevalence of past dengue infection in Tanzania ranged from 50.6% in a health facility-based study to 11% in a population-based study. Acute confirmed infections of dengue were estimated to be as high as 38.2% of suspected cases. Only one study reported on an outbreak.

CONCLUSIONS It is evident that dengue needs to become part of regular disease surveillance in Tanzania. Control measures need to be instituted with a focus on building human resource capacity and integrating dengue control measures in ongoing health programmes, for both preventive and curative interventions. Systematic reviews are valuable in assessing health issues when surveillance data are not available.

keywords dengue, surveillance, Tanzania

Introduction

Dengue is a vector-borne disease of major public health concern due to its high morbidity and – to a lesser degree – mortality, especially in low- and middle-income countries. It is estimated that there are nearly 400 million dengue infections globally each year [1]. With the global extension of dengue [2] and the vectors being present in most areas of the tropics and subtropics including East Africa [3], control efforts seem to be failing. Clinically, approximately one quarter of those infected exhibit clinical signs and symptoms of dengue, including fever, myalgias and rash, while one in ten will progress to more severe forms of the disease [4]. Severe dengue (SD) is defined by the presence of plasma leakage and shock, severe bleeding and organ failure. Case fatality rates can be as high as 10–15%, although in countries with good clinical management of dengue, they are consistently below 1% [5].

Yet, the global distribution and burden of dengue remain highly uncertain [4]. Nowhere is this epidemiological uncertainty more pronounced than in Africa, where

the requisite infrastructure for diagnosis, surveillance and case reporting is lacking [5]. Despite the scarce data from the region, modelling frameworks suggest that Africa's dengue burden may be similar to that of other high-transmission areas, such as the Americas, with estimates as high as 16 million annual infections [6]. The distribution of DENV in Africa is also far from certain. All four DENV serotypes have been documented to circulate in Africa, although DENV-2 has been reported most frequently [7].

The indirect evidence for the existence of endemic dengue transmission in Tanzania, however, is strong. There are high levels of precipitation and temperature suitability for dengue transmission, the *Aedes aegypti* mosquito, the primary vector of DENV, is endemic in much of Tanzania, and there have been case reports of dengue infections in European and Asian travellers returning from Tanzania [7, 8]. Other factors favouring the spread of endemic dengue transmission to Tanzania include an increasingly globalised economy and rapid urbanisation [9, 10].

There is also increasing direct evidence of endemic transmission in Tanzania. In 2014, the Tanzanian Ministry of Health (MoH) reported a dengue outbreak in Dar es Salaam to WHO [10, 11]. This outbreak spread to seven regions of mainland Tanzania and to regions on the island of Zanzibar. A total of 1018 cases were confirmed, of 2129 suspected cases. The response focused on surveillance, case management and vector control.

To date, no systematic review of the scientific literature has been undertaken to examine the evidence for endemic dengue transmission in Tanzania. This study aimed to systematically review all available data on dengue transmission in Tanzania specifically: seroprevalence studies and outbreak reports, to provide recommendations for inclusion of dengue in regular disease surveillance and control programmes.

Methods

The systematic review was conducted and reported using Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [12]. A systematic literature search was conducted independently by two researchers using five databases: Embase, Google Scholar, PubMed, Web of Science and WHOLIS. The last search was completed on 31 August 2016. The search terms were derived from three major categories, with one term of each category to be combined for all possible combinations on all databases:

- Illness (Dengue, DF (Dengue fever), Dengue Haemorrhagic (Hemorrhagic) Fever, DHF);
- Data (Surveillance, survey, incidence and prevalence for one arm of the study and outbreak for the second arm of the study); and
- Geographical location (Tanzania).

Contacts with principal investigators of relevant studies identified and institutions in Tanzania, specifically the MoH and WHO offices, were made for additional studies and signposting sources of grey literature. DengueNet [13] and ProMED-mail were identified as sources for grey literature.

No restriction was placed on study design and year of publication during the systematic literature search in databases. Relevant studies identified were exported to EndNote X7 (Philadelphia, PA, USA). Duplicates were removed, and data were abstracted from eligible studies into Microsoft Excel (Redmond, WA, USA). We also manually searched reference lists of identified studies to identify further relevant studies.

Eligibility was assessed using the following inclusion criteria: (i) peer-reviewed articles on dengue infections and outbreaks in Tanzania published in scientific journals; (ii) grey literature reporting on dengue infections and outbreaks in Tanzania; and (iii) studies on serological or laboratory investigations of dengue infections with seroprevalence as primary outcome. Studies or reports on the following were excluded: (i) dengue infections in travellers returning from Tanzania; (ii) entomological surveillance data on dengue; (iii) characterisations of dengue virus serotypes; (iv) non-human subjects; and (v) studies conducted in East Africa excluding Tanzania.

Articles identified in the systematic literature search were first screened for eligibility by title, and later by abstract. Full texts of studies that fulfilled the eligibility criteria at the title and abstract screening stage were further screened for eligibility. Studies identified through manual searches of reference lists were subjected to the same screening procedure. The quality of included studies was appraised using a tool designed by the Effective Public Health Practice Project (EPHPP) for quantitative studies [14] and the Critical Appraisal Skills Programme (CASP) Tool [15].

One example of such a search – in this case the second arm of the study concerning outbreak reports – is the combination of Dengue (illness), outbreak (data) and Tanzania (geographical location) on PubMed. This search generated only 12 articles, with one relevant hit for outbreak reports (reported later in the results section). Variations of the term *dengue* did not generate any further hits.

Data on the following items were extracted and tabulated from the included individual studies: references, title, study design, objective, study population, exposure

of interest (dengue infections and outbreaks) and outcomes (presumptive acute, past and confirmed acute DENV infections for seroprevalence and epidemiological factors associated with dengue infections).

From the included studies, we conducted a descriptive analysis of the extracted data, with outcomes focusing on seroprevalence and outbreaks. Seroprevalence data were extracted using the percentage of presumptive acute and past infections, as suggested by the presence of anti-DENV IgG (past) or IgM (acute). With the difficulties of interpretation of diagnostic tests in the context of dengue [5], these are classified as past infections (PIs), presumptive acute infection (PAI) and confirmed acute infections (CAI). CAI are presented using the percentage of CAI of suspected dengue cases, determined by viral RNA (RT-PCR) [5]. Analysis of outcomes was based on categorisation of study characteristics such as study design and demographics of study population and geographical location.

Results

For the first arm of the systematic review, seroprevalence studies, nine articles [16–24] meeting the eligibility criteria were included. A report of dengue cases from Tanzania was identified at ProMED-mail website [25]. A total of 72 articles were initially identified as potentially relevant based on title, of 147 152 search results from five databases. After the removal of 60 duplicates, a manual search of references and contacting study authors yielded another six relevant studies. Further screening via abstract and full-text reading resulted in exclusion of nine articles.

For the second arm of the study, outbreak reports, 16 articles were potentially relevant based on title of 31 131 search results from five databases. A total of 10 duplicates were removed, and upon abstract and title screening, only one study [26] met the eligibility criteria.

Details of reasons for exclusion at each screening stage are provided in Figures 1 and 2, and characteristics of included studies are presented in Table 1.

Studies reporting on seroprevalence

Four studies [18–20, 22] reported on both PAI and PI and two on PI only [16, 21]. The percentage of PAI and PI ranged from 0–20.9% and 6.6–50.6%, respectively. The highest seroprevalence of PAI was 20.9% in a study with only children as study participants [18], and absence of PAI was recorded in a study with both children and adults as participants [22]. A low PI seroprevalence of 6.6% was reported in children [18], with a higher seroprevalence of 50.6% in adults [21]. A population-based study conducted retrospectively provided a PI seroprevalence estimate of 11% [16].

Studies reporting on confirmed acute infections

A total of five studies [18–20, 22, 23] reported on this outcome; one study conducted in the southern part of mainland Tanzania reported 38.2% CAI [18]. The four remaining studies conducted in the northern and southern part of the mainland in the island of Zanzibar revealed no cases of CAI. The studies were mostly derived from health centre-based patient cohorts, with different sizes.

Study reporting on dengue outbreaks

One study [26] reported on dengue outbreaks in 62 localities of Tanzania, with a higher percentage of acute cases on the plateau than in the lowlands – 94% and 12%, respectively. The number of acute cases in two of three plateau regions was significantly lower in adult males than children ($x^2 = 11.71$, and 6.66, $P < 0.01$). In the lowlands, acute cases were identified only in adult males and females.

Dengue and age distribution

All studies reporting on the association between dengue infections and age confirmed an increase in the risk of past infections with increasing age [18–21]. One study reported a significant increase in the odds of dengue infection with every 5-year increase in age [21].

Dengue and its relation to seasonality and place of residence

One study found a strong association between CAI of dengue and the dry season with an odds ratio of 5.03 (95% CI: 1.68–15.01, $P = 0.004$) [18], while another reported no association with seasonality 1.3 (95% CI: 0.73–2.2, $P = 0.381$) [19]. This study further reported that past dengue infections were common in the rural community (OR = 1.8, $P = 0.027$) [19], while another study observed frequent infections in the urban population (adjusted OR = 4.09, 95% CI: 2.72–6.17, $P < 0.001$) [21].

Dengue and other febrile diseases, including co-infections

Misdiagnosis of dengue by medical personnel and co-infections with other febrile illnesses were reported by two studies [18, 19]. As many as 52% and 28% of people with CAI actually had urinary tract infection (UTI) and malaria, respectively, as their main diagnosis [18]. In another study, 45% of people with PAI had malaria as provisional

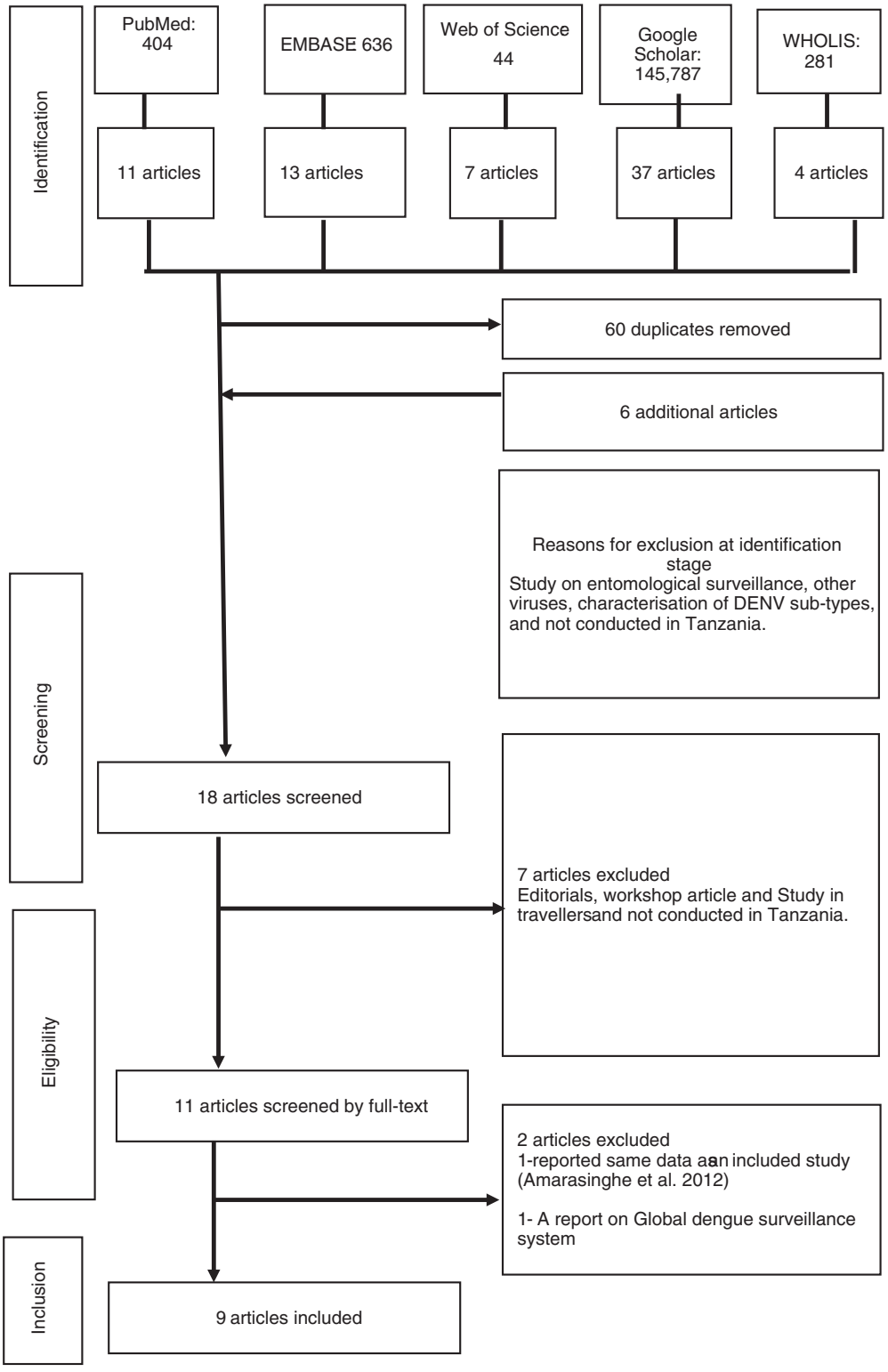

Figure 1 PRISMA flow chart for the first arm of the study (dengue data from Tanzania).

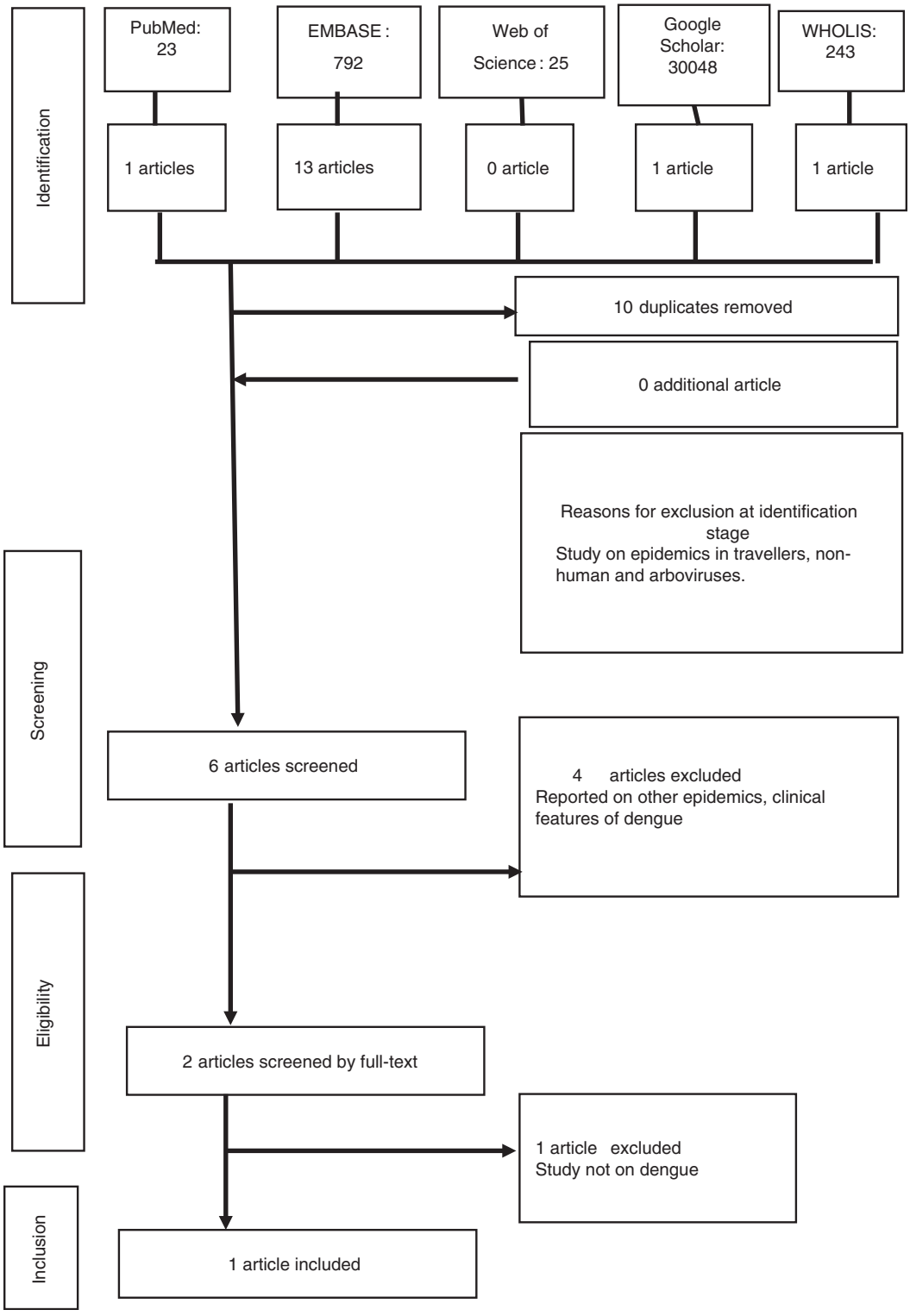

Figure 2 PRISMA flow chart of the second arm of the study (dengue outbreak data from Tanzania).

Table I Studies included in the systematic review

Reference and study design	Title	Objectives	Study population	Diagnostics used	Exposure of interest	Outcome and summary measures
Vairo F. *et al.*, (2012) [20] (Cross-sectional study)	Seroprevalence of dengue infection: A cross-sectional survey in mainland Tanzania and on Pemba Island, Zanzibar.	Estimate the prevalence of dengue.	Banked sera of febrile outpatients of two hospitals in southern Tanzania and Zanzibar. (n = 202).	Immunofluorescence Assay (IFA) PCR	Dengue	Seroprevalence, Incidence Confirmed (CA) – 0% Presumptive acute (PAI) – 0% Past infections (PIs) Pemba – 7.7% Mainland – 1.8% Prevalence ratio >15 years *vs.* <15 years 8.3, P = 0.03
Vairo F. *et al.*, (2014) [21] (Cross-sectional study)	IgG against dengue virus in healthy blood donors, Zanzibar, Tanzania.	Estimate the prevalence of dengue.	Adult blood donors in Zanzibar (n = 500)	ELISA IFA	Dengue	Seroprevalence PI – 50.6% OR Every 5 years increase 1.32 (1.19 –1.47: P < 0.001) 26–35 years *vs.* 36 and above 3.13 (1.97–4.98 P < 0.001) Place of Residence Common in urban area OR- 4.09, (2.72–6.17; P < 0.001)
Chipwaza B. *et al.*, (2014) [18] (Cross-sectional study)	Dengue and Chikungunya fever among viral diseases in outpatient febrile children in Kilosa district hospital, Tanzania.	Investigate viral causes of febrile illness and concurrent infections in children.	2–13 years children who presented with fever at an OPD of district hospital Southern Highlands. (n = 364)	PCR ELISA	Dengue and co-infections	Seroprevalence, Incidence CA- 38.2% PAI-20.9% PI – 6.6% Odds Ratio>5 years *vs.* < 5 years PI – 2.69 (1.10–6.56; P = 0.03) PAI- 2.28 (1.35–3.86: P = 0.002) CA- 6.51 (1.78–23.87: P = 0.005) Seasonality Common in dry season 5.03 (1.68 –15.01; P = 0.004) Misdiagnosis of CAI Malaria – 27.6% Sore Throat – 3.4% Pneumonia – 13.8% UTI – 51.7% Other – 17.2% Co-infections Malaria – 8.5% Chikungunya – 1%

Table I (*Continued*)

Reference and study design	Title	Objectives	Study population	Diagnostics used	Exposure of interest	Outcome and summary measures
Dobler G. *et al.*, (2010) [16] (Cross-sectional study)	Seroprevalence Of Antibodies Against Arboviruses In Mbeya Region, Southwestern Tanzania.	Estimate the prevalence of antibodies against arboviruses in human.	Banked sera of participants of an on-going study in Mbeya, south-west Tanzania. (n = 1233)	IFA	Dengue	Seroprevalence PI – 11%
Lumsden W., (1952) [26] (Cross-sectional study)	An epidemic of virus disease in Southern Province, Tanganyika territory in 1952–53.	Investigate an outbreak in Tanganyika.	Acute cases with the disease. (sample size not provided)	Not stated	Dengue Epidemic	Percentage of acute cases Plateau 1 Children – 83% Adult Males (M) – 94% Adult Females (F) – 91% Plateau 2 Children – 76%, M- 33%, F - 68% Plateau 3 Children – 88%, M - 62%, F - 86% Lowlands Children – 0%, M - 12%, F- 17% Cases lower in males than children in two plateau regions ((x^2 = 11.71, and 6.66, $P < 0.01$)
D'Acremont V. *et al.*, (2014) [23] (Cross-sectional study)	Beyond Malaria-Causes of Fever in Outpatient Tanzanian Children	Investigate the aetiology of fever in children.	2 months- 10 years' febrile outpatient children in two district hospitals of southern and coastal Tanzania. (n = 1005).	PCR	Dengue	Incidence CA – 0%
Crump J. *et al.*, (2013) [22] (Cohort study)	Aetiology of severe non-malaria febrile illness in Northern Tanzania: A prospective cohort study.	Determine the aetiology of febrile illness among hospitalised patients.	Febrile children from 2 months to 13 years and adolescents/adults from 13 years hospitalised in two district hospitals of northern Tanzania. (n = 870).	ELISA PCR	Dengue	Incidence CA – 0%

Table I (*Continued*)

Reference and study design	Title	Objectives	Study population	Diagnostics used	Exposure of interest	Outcome and summary measures
Hertz J. *et al.*, (2012) [19] (Cohort study)	Chikungunya and Dengue Fever among hospitalised febrile patients in Northern Tanzania	Determine the extent of dengue and chikungunya infections in hospitalised febrile patients.	Febrile children from 2 months to 13 years and adolescents/adults from 13 years hospitalised in two district hospitals of northern Tanzania. (n = 870).	ELISA PCR	Dengue and co-infections	Seroprevalence, Incidence CA – 0% PAI – 9.5% PI – 10.7% OR >13 years *vs.* <13 years PI – 3.36 (1.97–5.73; $P < 0.001$) Seasonality 1.3 (95% CI: 0.73–2.2, $P = 0.381$) Place of residence Common in rural area (−1.8, P-value - 0.027) Misdiagnosis of PAI Malaria – 45.1% Pneumonia – 29.6% Meningitis – 7.0% Other – 18.3% Co-infections Malaria – 7.3% Chikungunya – 13.4% Bacterial zoonoses – 12.7% Bloodstream infections – 16.9%
Amarasinghe A. *et al.*, (2011) [17] (Systematic literature review)	Dengue virus infection in Africa	Estimate the extent of DENV infections and dengue in Africa.	People with dengue infections in Africa.	N/A	Dengue	Evidence suggests ongoing dengue transmission in Africa including Tanzania. Reports of dengue epidemic in Zanzibar 1823, 1870, however not laboratory confirmed.
WHO, (2000) [24] (Report)	WHO Report on Global Surveillance of Epidemic-prone Infectious Diseases	Report on epidemic-prone diseases	Global population	N/A	Dengue	Reported areas in Africa with dengue transmission (shown in a map)

diagnosis [19]. Furthermore, 8.5% of people with dengue infections had co-infections with malaria and 1% had co-infections with chikungunya [18]. In another study, concurrent infection with chikungunya was 13.4%; with malaria, 7.3%; and with HIV, 8.8% [19].

Discussion

This discussion follows categories derived thematically from included studies and their respective results during the analysis: (i) Dengue and seroprevalence studies, (ii) Dengue and CAI, (iii) Dengue outbreak, (iv) Dengue and age distribution (v), Dengue, seasonality and place of residence and (vi) Dengue and other febrile illnesses. Dengue data from Tanzania are based on studies conducted in some parts of Tanzania, as there is no specific dengue surveillance system in place. However, this is a result of the study, and no attempt was made to generalise the findings, or to extrapolate to the population. Data from this systematic review are presented in following the principle high quality *vs.* moderate and low quality, as determined by the quality analysis.

Dengue and seroprevalence studies

As expected, the seroprevalence of antidengue IgG, representative of past infection, was higher than IgM and was more common in adults than children [18, 21]. Peyerl-Hoffman's [27] study confirms this observation which is probably due to the increasing risk of exposure over time. The highest estimate of PAI was observed in children [18]. This finding is similar to results of studies conducted in Vietnam [28], and dengue is one of the common acute childhood illnesses in endemic countries [29]. A large population-based study reported an estimate of 11% for seroprevalence; this might be the best estimate for the true prevalence of dengue in the Tanzanian population encountered in this systematic review [16].

Dengue and CAI

All CAI were in children between the ages of 2 and 13 years [18]. A similar pattern of increased PAI was seen in a study conducted among Vietnamese children, whereas in another study conducted in South Laos, past infections were rather common [27, 28].

Dengue outbreak

As only one study – of moderate quality – reported on this outcome [26], evidence from our systematic review with regard to dengue outbreaks in Tanzania is very weak. Recently, there have been reports of a dengue outbreak in Dar es Salaam [10]. However, a search for literature revealed no publication on this outbreak. This further highlights that even in an epidemic situation, reporting and scientific documentation of dengue outbreaks are non-existent in Tanzania, and confirming the assertion by Amarasinghe and Were that most outbreaks in Africa are under-reported [9, 17].

Dengue and age distribution

All studies reported an increase in past dengue infections among adults with one study showing an increase in infection with every 5 years [21]. Guo [30] states that this association suggests endemicity of dengue in a population, as the disease pattern shows an increase in past infections in adults coupled with the wide spread of competent vectors (*Aedes aegypti*) [3].

Dengue and seasonality

There was a discrepancy in data on whether seasonality is associated with the frequency of dengue infections, with inconclusive results. Whereas one study found no association with seasonality [19], another reported that dengue infections were more likely to occur during the dry season [18]. A search for a possible explanation of this phenomenon revealed that transmission occurs year-round in endemic countries, although cases are frequent in the rainy season as demonstrated in a study conducted in China and Thailand [31, 32]. Occurrence in the dry season may be linked to storage of water due to erratic supply.

Dengue and place of residence

Findings from one of the studies suggest that past infections were common in rural areas [19] and another reported a higher seroprevalence in urban areas [21]. It is possible that movement of people between communities and presence of breeding sites may account for this observation. Gubler [6] confirms that rapid urbanisation, globalisation and absence of control measures to eliminate vectors and their breeding sites are elements that facilitate the spread of dengue infections. There is no reason to assume that dengue has a different residential distribution, as reported in countries with a functional surveillance system.

Issues arising from dengue data in Tanzania

Although dengue is often misdiagnosed as malaria [33, 34], results from this review suggest that patients with dengue

are also commonly given presumptive diagnoses of UTI and pneumonia [18, 19]. Low level of dengue awareness among health workers and unavailability of appropriate diagnostic tools for determining causes of fever in dengue-endemic settings account for dengue misclassification [5, 35, 36]. Another factor contributing to the misdiagnosis of dengue is asymptomatic malaria parasitaemia, which is common in high-transmission, malaria-endemic areas such as Tanzania.

PAI and PI of dengue were identified by the presence of immunoglobulins IgM and IgG, respectively, and CAI detected by viral ribose nucleic acid (RNA) isolation (RT-PCR). IgM is detectable 5 days to 2–3 months post-infection and IgG from 2 to 3 months and lasts a lifetime [5]. For those studies [18, 19, 22, 23] in which samples were collected before the 5th day of infection, serological tests may produce false-negative results leading to underestimation of infections. Due to the long detectable duration of IgM and a lifelong presence of IgG, a more accurate means of differentiating past and acute infection is by analysis of both acute and convalescent serum as performed in one study [22].

The risk of cross-reaction with antibodies of other flaviviruses such as yellow fever, West Nile and Zika could have resulted in overestimation of dengue seroprevalence by producing false-positive results. Performance of a neutralisation test or other confirmatory tests would have helped in obtaining relatively accurate results [5]. Additionally, the sensitivity and specificity of diagnostic tools employed in the studies are not completely accurate, resulting in either under- or overestimation of dengue seroprevalence [5, 37]. This setback was mitigated to some degree using immunofluorescence assays as a reference to compensate for the low specificity of ELISA [20, 21].

Limitations

Most of the studies that reported on dengue seroprevalence were hospital-based studies, with only one population-based study [16]. Furthermore, the studies did not cover the country geographically. These factors undermine the ability to generalise findings to the entire Tanzanian population. However, this bias was limited through the reporting of results of this review, carefully considering any assumptions about true population data.

Publication bias

To reduce publication bias, a predetermined study protocol was employed, including different search elements (which was also used for the ethics committee) and following all search elements as suggested by the PRISMA checklist.

Conclusion and recommendations

This systematic review, based on data from seroprevalence studies and outbreak reports, suggests ongoing dengue activity in Tanzania, often up to high levels. The need for integrating dengue into the national surveillance system, including concepts for confirmatory laboratory diagnosis, is clear. Also, as no dengue surveillance exists currently, it has to be established whether healthcare personnel is aware of dengue as a reason for febrile illness, and perhaps capacity-building in terms of dengue diagnosis, identification and appropriate case management especially for severe dengue cases should be recommended. This would help to treat cases of severe dengue and related mortality, and avoid cases of misdiagnosis. Future outbreaks of dengue could have more severe cases and capacity needs to be built to mitigate their impact on health services.

It is further recommended to consider integration of dengue as a target disease in ongoing vector control programmes, particularly in the light of other *Aedes*-transmitted diseases – however also considering efficacy, effectiveness and cost-effectiveness of *Aedes* control.

Further studies investigating the epidemiology of dengue and how best to integrate dengue control efforts into ongoing disease control programmes are needed. Systematic reviews prove to be valuable in assessing health issues when no surveillance data are available.

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