

## Serological evidence of chikungunya and malaria co-infection among febrile patients seeking health care in Karagwe district, Tanzania

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### Abstract

**Background:** Chikungunya is an emerging mosquito-borne viral illness of major public health concern and is becoming a common infection in many geographical areas of Tanzania. This study was carried out to determine the incidence of malaria and chikungunya infections among febrile patients seeking medical care in Karagwe district, Tanzania.

**Methods:** Febrile patients were enrolled into the study at Nyakahanga district designated hospital and Kayanga health centre in May and June 2015. Questionnaires were administered to collect clinical and socio-demographic characteristics of patients. All participants were tested for malaria using malarial rapid diagnostic test and those tested positive by mRDT were confirmed by microscopy. Both outpatients tested malaria positive and negative were further screened for immunoglobulin M (IgM) and G (IgG) antibodies for chikungunya using enzyme-linked immunosorbent assay.

**Results:** A total of 400 febrile patients were enrolled in the study. Out of 400 febrile outpatients tested for malaria, 116 (28.75%) tested positive with mRDT. Microscopy confirmed presence malaria parasites in 112 (96.55%) of the malaria RDT-positive. The overall seroprevalence of chikungunya infection was 24.25% (97/400). Out of those chikungunya seropositive subjects, 89 (91.75%) had no malaria. Co-infection rate of chikungunya and malaria was found to be 7.14% (8/112).

**Conclusions:** Our findings confirmed the existence of chikungunya and malaria co-infection among febrile patients seeking health care in Karagwe district. Chikungunya should be considered in the differential diagnosis of malaria for appropriate case management and in order to monitor the public health burden and to inform possible preventative and control measures.

**Keywords:** Chikungunya, malaria, co-infection, seroprevalence, Tanzania

### Introduction

Chikungunya is a mosquito-borne virus infection transmitted to humans through the bite of infected mosquitoes of the genus *Aedes*. *Aedes aegypti* and *Aedes albopictus* are the primary vectors of Chikungunya virus (CHIKV), but also the virus is maintained in sylvatic cycles involving primates and forest dwelling *Aedes* species (Deller & Russell, 1968; Mohan *et al.*, 2010; Thiberville *et al.*, 2013). The CHIKV (genus Alphavirus, family Togaviridae) was first recognized and isolated in 1952 from Makonde Plateau in southern Tanzania (Robinson, 1955). The word “chikungunya” originates from Makonde language referring to the bending stance in afflicted patients due to severe musculoskeletal pain (Lumsden, 1955; Hertz *et al.*, 2012; Thiberville *et al.*, 2013).

Chikungunya is currently of a global public health concern due to its continued spread and escalating epidemic trends throughout the tropical and subtropical regions of the world (Deller & Russell, 1968; Mohan *et al.*, 2010). This is attributed to the expansion of the vectors’ geographical range, global travel, unplanned urbanization and climate change (Thiberville *et al.*, 2013). Since the 1960s, CHIKV has repeatedly been isolated in Africa, Asia and Latin America. In Africa, chikungunya outbreaks have been reported in 25 countries (CDC, 2016). In Tanzania, chikungunya has been reported in southern, south-western, northern and central regions of the country (Robinson, 1955;

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Hertz *et al.*, 2012; Crump *et al.*, 2013; Weller *et al.*, 2014; Chipwaza *et al.*, 2014; Kajeguka *et al.*, 2016; Faustine *et al.*, 2017).

Malaria is the primary cause of fever in all age groups and contributes to considerable mortalities in Sub Saharan Africa including Tanzania (Mboera *et al.*, 2007). In Tanzania, malaria is primarily transmitted by female *Anopheles gambiae*, *An. arabiensis* and *An. funestus*. Four malaria causative agents (plasmodia species), namely *Plasmodium falciparum*, *P. vivax*, *P. malariae*, and *P. ovale* are prevalent in the country (Mboera *et al.*, 2013). Chikungunya may occur concurrently with malaria and non-malaria febrile illnesses (Sow *et al.*, 2016). Co-infection of chikungunya and malaria is possible in geographical locations where the vectors co-exist (Sow *et al.*, 2016). As the species of mosquitoes responsible for transmission of these infections are present in Tanzania (Ndotsi *et al.*, 2016; Bisimwa *et al.*, 2018), co-infection is expected to occur.

Tanzania is experiencing a change in aetiologies of febrile illnesses as it is for many other African countries. While the numbers of malarial febrile illnesses are decreasing in sub-Saharan Africa (O'Meara *et al.*, 2008; Mboera *et al.*, 2013), the numbers of non-malarial febrile cases are increasing (Mtove *et al.*, 2006; Ligon, 2006; Hercik *et al.*, 2017). Arboviruses are considered the likely cause of some non-malarial febrile illnesses and are gaining more prominence as observed through increased mosquito-borne viral disease epidemics (Crump *et al.*, 2013). Patients with non-malarial febrile illnesses such as chikungunya may present with clinical signs similar to those of other febrile illnesses, thus laboratory confirmation is essential but often lacking (D'Acromont *et al.*, 2014). Recent studies in Tanzania have revealed that patients with acute dengue and chikungunya infections are often misdiagnosed and treated with antimalarials or antibiotics, mainly due to lack of differential diagnosis (Chipwaza *et al.*, 2014). Screening of aetiologies of fever cases which occur concurrently with malaria is not commonly practiced in most health facilities in Tanzania. This study aimed to determine the seroprevalence of chikungunya and malaria co-infections among febrile patients seeking medical care in Karagwe district of north-western Tanzania.

## Materials and Methods

### Study Site

This study was carried out in Karagwe district, located in Kagera region in north-western Tanzania. The district is characterized by mountain ranges with swampy valley bottoms and wetlands. The altitude ranges between 1,500 and 1,800 meters above sea level. The annual average temperature is 26°C. Rainfall distribution is bi-modal with peaks between September-December and March-May. Most parts of Karagwe district receive average rainfall between 800 mm and 1000 mm annually. The major economic activity of the majority of the population in the district is agriculture with banana, coffee and maize being the main crops. Similarly, inhabitants are involved in rural subsistence fishing and livestock keeping. Karagwe district has experienced malaria epidemics for many years with unstable transmission of varying seasonality (Mboera & Kitua, 2001; Mashauri *et al.*, 2013). Significant malaria epidemic was recorded in 1997/1998, which was associated with unusually heavy El Nino-Southern Oscillation (ENSO) rains (Carlstedt, 1997; Lindsay *et al.*, 2000).

### Study design

This facility based study involved Nyakahanga District Designated Hospital and Kayanga Health Centre and was carried out in May and June 2015. It involved outpatients presenting with high fever (axillary or rectal temperature  $\geq 38^{\circ}\text{C}$ ) at the facilities. Participants who had recent or in evidence of previous fever 2-5 days and other clinical manifestations such as headache, skin rashes, joint ache, muscle and body pains were also considered. Thus, febrile patients who gave their consent were enrolled into the study. Exclusion criteria included participants with chronic diseases, which required instant medical intervention.

### Data collection

Whole blood samples were obtained from the febrile patients by venipuncture and transferred into plain vacutainer tubes. Few drops of whole blood (2-3drops) were used for malaria parasite detection (mRDT), approximately 18µl of which was used to prepare blood smear (BS) for malaria parasite identification. The remainder of the whole blood sample from each patient was centrifuged and the sera were used for chikungunya serological tests. The blood smears were stained with 20% Giemsa stain for plasmodium parasite identification. A structured questionnaire was administered to collect socio-demographic and clinical data. Upon recruitment of eligible patients, the clinician documented sex, age, clinical manifestations of the patient and date of onset of disease.

### Serological assays

Malarial rapid diagnostic test (mRDT-Paracheck Pf<sup>®</sup>, Orchid Biomedical system) was used to test presence of malaria antigens at the health facility. Serum sample from each patient was tested for anti- CHIKV IgM and IgG antibodies using ELISA (EUROIMMUN AG, Lübeck, Germany) at the College of Veterinary Medicine and Biomedical Sciences of the Sokoine University of Agriculture. The results of mRDT and ELISA serologic analyses were interpreted according to the manufacturers' protocol.

### Data analysis

The statistical analysis was performed using Microsoft Office-Excel 2007 (Microsoft, USA) and Epi Info version 7.0.8.0 (CDC, Atlanta, USA). Data on proportions were compared using Chi Square. All tests were performed at  $P \leq 0.05$  and were considered statistically significant.

### Ethical considerations

The study was approved by the Medical Research Coordinating Committee of the National Institute for Medical Research, Tanzania (Approval number NIMR/HQ/R.8a/Vol.1X/1946). Questionnaire and laboratory results were stored separately under unique study identity number without any biodata. All minors were included in the study only if their parent/guardian provided consent.

## Results

### The demographic and clinical profiles of enrolled outpatients

A total of 400 febrile patients composed of 152 (38.00%) males and 248 (62.00%) females were enrolled. Most of febrile subjects were between 20 and 29 years (25.25%), followed by those aged 10-19 years (23.25%), and only 14.00% were at least 50 years old (Table 1). The most common symptoms and signs exhibited among febrile patients were headache (69.00%), joint aches (68.25%), Vomiting (61.50%), leg weaknesses (59.50%) and laboured breathing (58.00%). The least observed symptoms were abdominal pains (41.75%), neck stiffness (33.75%), and skin rashes (33.00%), (Table 2).

**Table 1: Age and sex distribution of the enrolled participants**

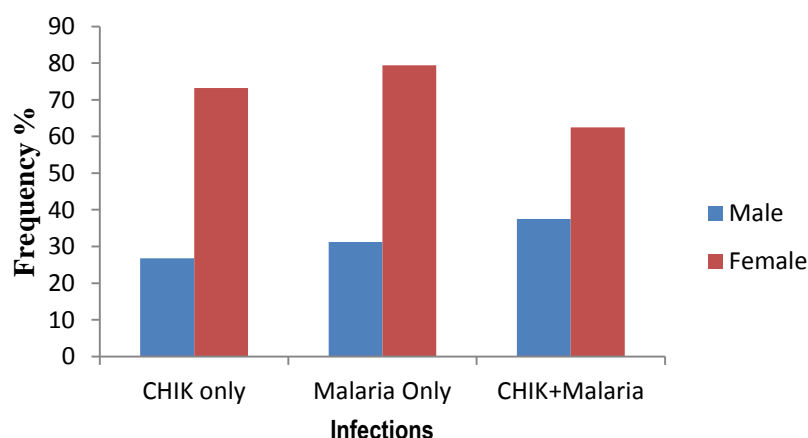
Age (Year)	Enrolled subjects (%) n=400	Male (%) n=152	Female (%) n=248	CHIK n=97	Mal n=112	CHIK+MAL n=8
1-9	48 (12.00)	15(9.87)	33 (13.31)	6	9	0
10-19	93 (23.25)	39(25.66)	54 (21.77)	8	14	0
20-29	101 (25.25)	52(34.21)	49 (19.76)	52	37	6
30-39	63 (15.75)	18(11.84)	45 (18.15)	18	21	2
40-49	39 (9.75)	15(9.87)	24 (9.68)	5	12	0
≥50	56 (14.00)	13(8.55)	43 (17.34)	8	11	0

**Table 2: Clinical and demographic characteristics of febrile patients stratified by chikungunya and malaria infections**

Characteristics	No. of subjects (n=400)	CHIKV (n=9)	IgM (n=88)	IgG (n=88)	Malaria (n=112)
<b>Sex</b>					
Male	152 (38.00%)	1 (11.11%)	25 (28.41%)	35 (31.25%)	35 (31.25%)
Female	248 (62.00%)	8 (88.89%)	63 (71.59%)	77 (68.75%)	77 (68.75%)
<b>Clinical characteristics</b>					
Headache	276 (69.00%)	5 (55.56%)	55 (62.50%)	82 (73.21%)	82 (73.21%)
Nausea	221 (55.25%)	2 (22.22%)	14 (15.91%)	56 (50.00%)	56 (50.00%)
Vomiting	246 (61.50%)	1 (11.11%)	4 (4.55%)	63 (56.25%)	63 (56.25%)
Joint ache	273 (68.25%)	8 (88.89%)	74 (84.10%)	44 (39.29%)	44 (39.29%)
Stiff neck	135 (33.75%)	0 (0.00%)	5 (5.68%)	3 (2.68%)	3 (2.68%)
Seizures	141 (35.25%)	0 (0.00%)	0 (0.00%)	8 (7.14%)	8 (7.14%)
Leg weaknesses	238 (59.50%)	4 (44.44%)	49 (55.68%)	66 (58.93%)	66 (58.93%)
Skin rash	132 (33.00%)	6 (66.67%)	68 (77.27%)	2 (1.79%)	2 (1.79%)
Abdominal pains	167 (41.75%)	0 (0.00%)	0 (0.00%)	33 (29.46%)	33 (29.46%)
Pallor	217 (54.25%)	0 (0.00%)	1 (1.14%)	26 (23.21%)	26 (23.21%)
Jaundice	226 (56.50%)	0 (0.00%)	0 (0.00%)	2 (1.79%)	2 (1.79%)
Laboured breathing	232 (58.00%)	0 (0.00%)	1 (1.14%)	14 (12.50%)	14 (12.50%)

### Malaria and Chikungunya infections

Out of 400 clinical specimens analysed, 116 tested positive for malaria by mRDT, 96.55% (112) were confirmed by microscopy. Chikungunya specific antibodies were detected in 97 patients, out of which 83 (20.75%) tested IgG positive whilst 14 (3.50%) tested IgM positive only (Table 2). Out of 97 CHIKV seropositive subjects, 89 (91.75%) subjects had no malaria. Chikungunya and malaria co-infection was found to be 7.14% (8/112). The highest seropositivity was in the 20 to 29 years old group accounting for 53.61% (n=52) seropositive CHIKV febrile patients (Table 1). The proportion of participants who were IgG seropositive was higher than the proportion of participants who were IgM seropositive for all age groups (Table 2). High frequency of malaria and chikungunya infections was recorded among females. Within the group infected with chikungunya alone, females had infection rate of 73.20% whilst males had 26.80% (Figure 1).



**Figure 1: Frequency of chikungunya and malaria infections by sex**

### Discussion

Chikungunya is among the febrile illnesses in patients seeking health care in Karagwe district. Chikungunya-malaria co-infection was prevalent in the area. Patients with malaria and CHIKV infections were clinically manifested by related clinical characteristics. In malaria endemic areas

most febrile illnesses have been and are still treated as malaria cases due to lack of diagnostic capacity to properly rule-out malaria as a cause of fever and as well, identify alternative fever causative agents (Chipwaza *et al.*, 2014; Sow *et al.*, 2016; Kajeguka *et al.*, 2017).

The proportion of chikungunya seropositivity was not comparable between febrile patients, indicating variations in the exposure among age groups. The IgG positivity was significantly higher in adults than in children. The increase of IgG seropositivity indicates previous exposure to CHIKV among adults. The seroprevalence of 24.25% observed in this study is four times as higher than that (4.7%) previously reported in central Tanzania (Chipwaza *et al.*, 2014). The observed variations in the prevalence of chikungunya between different studies may be attributed to geographical zones where the studies were done, targeted age groups, seasonal variations, agricultural activities and time factor (Hertz *et al.*, 2012; Crump *et al.*, 2013; Weller *et al.*, 2014; Kajeguka *et al.* 2017). Previous studies have also indicated the occurrence of presumptive and prior exposure to CHIKV infections in the country (Chipwaza *et al.*, 2014; Kajeguka *et al.*, 2016). Our results showed that anti-CHIKV IgM antibodies were found among a very few patients within 7 days after the onset of fever hence suggesting possibility of acute infection (presumptive acute CHIKV infections). Most often, in acute CHIKV infections IgM antibodies appear first and can be detected during the first week of the disease particularly from day 5 while IgG antibodies appear shortly afterwards (Chipwaza *et al.*, 2014). The detection of IgM antibodies in patients who had a history of fever for less than 5 days, possibly indicate a recent previous CHIKV exposure rather than acute infection.

Age and sex are proxy-factors for specific behaviour that cause higher exposure to mosquito bites. Outdoor stays during the daytime and dusk favours bite by *Aedes* mosquitoes. These practices and lifestyle of adults whose ages range 20-39 years may make them be vulnerable to these mosquito-borne arbovirus diseases (Sow *et al.*, 2016; Furuya-Kanamori *et al.*, 2016), unlike in malaria transmission (Mboera *et al.*, 2007; Moshi *et al.*, 2017). Females indicated the highest infection rate of the two infections than their counterpart males. Owing to low immunity in lactation and pregnancy, these physiological differences may contribute to different susceptibility levels (Sow *et al.*, 2016).

The study has drawn a significant association between clinical characteristics and the probability of a positive diagnosis of chikungunya and malaria. These findings are in line with other studies that reported joint pain, headache, nausea, vomiting, myalgia, and skin rash were associated with chikungunya and malaria infections (Mtove *et al.*, 2011; Chipwaza *et al.*, 2014; Furuya-Kanamori *et al.*, 2016). However, these symptoms are common and non-specific, and thus could be mistakenly identified as caused by a variety of other febrile illnesses such as malaria, typhoid, dysentery, and bacterial meningitis and pose a challenge to differential diagnosis. Therefore, it is recommended to establish a better means of diagnosis of fever to circumvent mistreatment of medical important diseases.

The study has some limitations. Since this study was cross-sectional, a cautious interpretation of this finding is necessary, particularly in the absence of comparison between acute and convalescent serum from the same patient. Another limitation was inability to perform molecular technique such as reverse transcriptase-Polymerase chain reaction (PCR) analysis for CHIKV due to lack of positive controls for the test.

In conclusion, chikungunya and malaria infections exist in all age groups of febrile patients seeking health care in Karagwe district. Since there is no routine diagnosis of mosquito-borne viral diseases in Tanzanian health facilities, it is likely that such infections go unnoticed or when causing fever end up being treated as other common infections such as malaria, bacterial or fungal infections.

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## Competing interests

Authors have declared that no competing interest.

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