



Evidence of Overlapping Infections of Dengue, Malaria and Typhoid in Febrile Patients Attending a Tertiary Health Facility in Uyo, South-South Nigeria

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Authors' contributions

This work was carried out in collaboration between all authors. Author AEM designed the study, wrote the protocol and interpreted the data. Author IAA managed the literature searches and carried out data analysis. Author OSI anchored the research work and wrote part of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Background: Malaria, typhoid, and dengue have become significant diseases worldwide, especially in Africa due to their increasing endemicity. Similarities in signs and symptoms in infected individuals make it difficult for healthcare providers to clinically diagnose these diseases in patients presenting with feverish conditions in the clinics.

Aim: This study aimed to determine the prevalence of malaria, typhoid/paratyphoid and dengue in patients with febrile conditions attending University of Uyo Teaching Hospital, Uyo-Nigeria.

Study Design: This was a cross sectional study of patients with febrile conditions.

Place and Duration of Study: The study was conducted at the University of Uyo Teaching Hospital, Uyo-Nigeria from May - August, 2014.

Methodology: A total of 145 febrile patients were investigated for malaria, typhoid/paratyphoid and dengue using thick Giemsa staining technique, microtitre plate (single antibody titre) quantitative assay (Antibody titre ≥ 160), and dengue NS1 Ag/IgM/IgG serology, respectively.

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Results: Of the 145 patients, 51(35.2%), 10(7.0%) and 7(4.8%) had malaria, typhoid/paratyphoid and dengue, respectively. A total of 20(37.0%) males and 31(34.1%) females had malaria, while 3(2.1%) males and 7(4.8%) females had typhoid. Dengue viral markers were detected in 1(1.9%) male and 3(3.2%) females. The age range of patients in this study was <1-70 years, with mean (\pm SD) age of 34.1 \pm 12.7 years. The highest infected age groups were 61-70 yr, 3(60.0%) for malaria; 41-50 yrs, 3(23.1%) each for typhoid/paratyphoid and dengue, respectively. A significant association existed between age of patients and malaria and not with typhoid and dengue diseases. A total of 2(21.4%) patients had malaria/typhoid/paratyphoid co-infection, while 1(10.7%) had malaria/dengue co-infection. Dengue patients with active disease tested positive with NS1 antigen, 4(2.8%) and specific-IgM antibodies, 2(1.4%).

Conclusion: This study concludes that dengue virus as well as malaria parasite and *S. Typhi*/*S. paratyphi* are among the aetiologic microbial agents of fever in this locality. Hence, differential diagnosis of patients with feverish conditions should not only be limited to malaria and typhoid as is always the case in our hospitals. These findings have raised serious public health concern as outbreaks of dengue may occur unnoticed if suspicion index is not raised among health care practitioners.

Keywords: Dengue; malaria; typhoid; febrile patients; Uyo-Nigeria.

1. INTRODUCTION

Fever, also known as pyrexia or controlled hyperthermia is a complex physiologic response to disease mediated by pyrogenic cytokines, and characterized by a rise in core temperature, generation of acute phase reactants and activation of immune systems [1]. Fever, either continuous or recurrent, is a common finding in patients infected with viral, bacterial, and parasitic or in super-imposed opportunistic infections [2]. The endemic diseases in Nigeria that present with symptoms of fever include malaria (parasitic), typhoid (bacterial) and dengue fever (viral).

Malaria fever is a mosquito-borne parasitic infectious disease of humans caused by the bite of female Anopheles mosquito infected with a parasite of the genus *Plasmodium*. Among the five species of *plasmodium* that can infect humans, are *P. vivax*, *P. ovale*, *P. falciparum*, *P. malariae* and *P. knowlesi*. Severe disease in human is largely caused by *Plasmodium falciparum*. This dreadful disease is a major health problem in most of the countries in the tropics [3]. It affects more than 240 million people, accounting for over 40% of the world's population in more than 100 countries in the tropics, from South America to the Indian Peninsula [4]. In Nigeria, over 95% malaria infection is due to *Plasmodium falciparum* with *P. ovale* and *P. malariae* playing a minor role, while *P. vivax* is not found among indigenous Nigerians. Malaria is responsible for 30% of childhood mortality, 11% of maternal mortality, and more than 50% of outpatient visits in

hospitals. A total of 70-110 million clinical cases per year is recorded [5]. Nigeria accounts for 25% of all cases of malaria in Africa and at least 250,000 Nigerian children below 5 years die yearly from malaria [6].

Typhoid fever, also known as typhoid is a common worldwide illness, transmitted by the ingestion of food or water contaminated with the faeces of an infected person, which contain the bacterium *Salmonella typhi* and *Salmonella paratyphi* [7]. Nigeria, like many other countries of the world, is endemic for typhoid fever. The disease is related to poor hygiene and sanitary conditions rather than the climate. It is found in large parts of Asia, Africa, Central and South America, where it occasionally causes epidemics. WHO estimates that there are approximately 17 million cases of typhoid a year, which results in 600,000 deaths annually [8]. It is often encountered in tropical countries including Nigeria where they constitute serious sources of morbidities and mortalities. Nigeria is endemic with typhoid as in other developing countries of the world with over 33 million cases and 500,000 deaths due to typhoid fever per year [9].

Dengue fever, also known as break bone fever, is an infectious tropical disease caused by the dengue virus. It is classified among the Neglected Tropical Diseases (NTDs) [8]. There are four strains of the virus, referred to as DENV-1, DENV-2, DENV-3, and DENV-4 [10]. All four serotypes can cause the full spectrum of disease. Dengue is transmitted by *Aedes* mosquitoes, particularly *A. aegypti* [11]. Dengue hemorrhagic fever occurs when a person

contracts a different strain of Dengue virus after a previous infection with a different strain [12].

The global prevalence of dengue has grown dramatically in recent decades. The disease is now endemic in more than 100 countries in Africa, the Americas, the eastern Mediterranean, Southeast Asia, and the Western Pacific, and threatening more than 2.5 billion people [13]. World Health Organization estimates that there may be 50 million to 100 million cases of dengue virus infections worldwide every year, which result in 250,000 to 500,000 cases of dengue hemorrhagic fever and 24,000 deaths each year [14]. A recent study by Baba et al. [15] reported 0.6% prevalence of dengue virus in a multicenter study in Nigeria. Recently, a man lost four children to non-Lassa fever haemorrhagic fever in Kebbi state, Nigeria [16]. This incidence further confirms the possible impending epidemic of dengue fever in Akwa Ibom state.

These three fever causing diseases (malaria, typhoid, and dengue) have become significant diseases worldwide, especially in Africa due to their similarities in symptoms and their endemicity [15]. These symptoms include fever, severe joint and muscle pains, headache, sore throat, fever, running of eyes, malaise, nausea, and an irritating rash. Owing to these similarities in symptomatic presentations, there is a possibility that persons infected with any of these microbial agents could be misdiagnosed when using clinical considerations alone without recourse to laboratory investigations. This is possible in health facilities where laboratories may not be well equipped to carry out proper investigations in order to diagnose the aetiological agents responsible for the fever. This study aimed to evaluate the microbial agents responsible for febrile conditions in patients attending University of Uyo Teaching Hospital, Uyo-Nigeria. The outcome of the study will provide base-line data that would stimulate wide scale surveillance studies of these infections in the state, region and beyond.

2. MATERIALS AND METHODS

2.1 Study Location

This study was carried out in the University of Uyo Teaching Hospital (UUTH), Uyo-Nigeria, a tertiary health facility that serves patients with various illnesses not limited to referrals. Uyo is the capital of Akwa Ibom State and the state is located in the coastal South-southern region of

Nigeria, lying between latitudes 4°32' and 5°33' North and longitudes 7°25' and 8°25' East. Akwa Ibom State belongs to the Deltaic zone in the six ecological zones of Nigeria [16] and is bordered on the east by Cross River State, on the west by Rivers and Abia States, and on the south by the Atlantic Ocean [17].

The state's population is about 4 million and many of the indigenes are in the diaspora. Based on its tropical location and proximity to the sea, the climate of Akwa Ibom State is generally humid with abundant rainfall, good sunshine, with average temperature of 27°C. The state experiences two main seasons: the Wet or rainy season occurring between April to October; and the dry season between November to March [17].

2.2 Study Population

The study population included male and female aged 2 years and above (mean age of +/- yr), suspected of having malaria or typhoid fever by physicians at the outpatient clinic of the hospital. A total of 145 patients having fever (temperature $\geq 38^\circ\text{C}$) between 1 to 14 days from onset, were recruited into the study. Fifty apparently healthy blood donors' samples were used as controls.

2.3 Ethical Consideration

Informed consent was obtained from all patients recruited into the study. Where children are concerned, parental consent was sought. The protocol of this study was reviewed and approved by the institutional review board of the University of Uyo Teaching Hospital, Uyo.

2.4 Study Design

This was a descriptive cross-sectional study involving patients with febrile conditions attending the outpatient clinic of the hospital. Patient socio-demographical data and other clinical information were accordingly documented. The study was conducted between May and October, 2013.

2.5 Sample Collection

Five millilitres (5 ml) of venous blood samples was aseptically collected from the antecubital fossa vein using tourniquet and vacutainer blood collection devices. Thick peripheral blood smears were made on a grease-free microscope slide

from EDTA bottles for malaria investigation. For typhoid and dengue investigations, blood samples were collected into plain bottles and allowed to clot for 10-15 minutes before centrifuging at 2,500 rpm for 10 mins. Serum was separated using a sterile Pasteur pipette into 2 ml cryovials and stored at -20°C until ready for use.

2.6 Laboratory Investigations

Laboratory assays were carried out to detect the presence or absence of malaria parasite, dengue non-structural (NS1) antigen and antibody (IgM and IgG) assays, as well as significant titres (≥ 160) for *Salmonella typhi* and *S. paratyphi* (A, B, C) somatic 'O' antibodies.

2.7 Giemsa Staining For Malaria Parasite

The procedure was done as described by Cheesbrough [18]. Briefly, dried thick blood films of each patient were placed in a Coplin jar containing 10% Giemsa stain for 10 mins. The back of the slides were wiped and allowed to air dry. A drop of immersion oil was placed on the stained film and observed under a light microscope with x100 objective for malaria parasites.

2.8 Dengue Antigen and Antibody Serology

The assay was carried out using standard procedures as previously described by Shu and Huang [19]. A commercial test kit approved by WHO, SD Dengue NS1 Ag + Ab (IgM/IgG Combo Test kit) (Standard Diagnostics, South Korea) was used for the study. The procedure was as described by the manufacturers. Briefly, using a disposable dropper, 3 drops of serum was added onto the sample well on the cassette marked "S" for NS1Ag test. For IgM/IgG antibody assay, 10 μ l of serum was added to the sample well marked "S" and 4 drops of assay diluent added. The test results were interpreted within 15-20 mins. The presence of only one colour line within the result window indicated a negative result while the presence of two and three colour lines indicated a presence of dengue NS1 Ag and IgG or IgM antibody respectively.

2.9 Quantitative Widal Agglutination Test

The assay was conducted using the microtitre plate technique as previously described by Mohammed et al. [20]. The commercial Widal

antigen kit (Cromatest, UK) was used in the assay. Briefly, the procedure included serial dilution of patient serum using physiological saline (0.9%) in microtitre plate wells and addition of equal volume of diluted Widal antigens (1:30 dilution for *Salmonella paratyphi* groups A, B and C somatic 'O' and flagella 'H' antigens and 1:40 dilution for *Salmonella typhi* group D 'O' and 'H' antigens) into each corresponding wells in the microtitre plate. The plate was mixed with a gentle tap before incubating in a moist chamber at room temperature for 18-24 hrs or overnight. Patient serum antibody titre was considered as the reciprocal of lowest serum dilution showing full or partial (50%) agglutination. Positive and negative sera were included as controls. Single serum antibody titre of ≥ 160 for somatic 'O' antigen was regarded as significant as documented by Onuigbo [21].

2.10 Data Analysis

Statistical analysis was performed on Statistical Package for Social Sciences Software (SPSS) (Version 17). Univariate analysis using logistic regression and Pearson Chi square test (Fisher exact test where appropriate) were to investigate the association or relationship of the three diseases, malaria, typhoid/paratyphoid and dengue in the study population. In this study, P -value ≤ 0.05 was considered statistically significant.

3. RESULTS

The frequency of malaria, typhoid, dengue and dengue/malaria, multiple infections in patients with feverish conditions in UUTH, Uyo is presented in Table 1. Of the 145 febrile patients, 7(4.8%) tested positive for dengue, malaria 51(35.2%) and typhoid/paratyphoid 10(6.9%). Only 1(0.7%) patient was co-infected with dengue and malaria, while 2(1.4%) patients were co-infected with malaria and typhoid/paratyphoid. The prevalence of malaria was significantly higher than Typhoid/Paratyphoid and Dengue ($P < 0.05$) among feverish patients. However, there was no significant difference in the frequency of patients with multiple infections compared to those with single infection ($P > 0.05$).

Age and sex distribution of patients infected with dengue, malaria and typhoid/paratyphoid are presented in Table 2. Patients within the age group 21-30 years were mostly infected with malaria, 20(54.1%) whereas those in the age

bracket 41-50 years were mostly infected with either dengue or typhoid/paratyphoid, 3(23.1%) each. The age group 41-50 years was significantly associated with dengue compared with other age groups, OR=12.30 (1.15-131.10), P<0.05. Malaria affected patients in all the age groups but increased in frequency among children aged <1-10 yr, 1(4.3%) and peaked among young adults aged 20-30 yr, 20(54.1%). Thereafter, infection decreased as age increased. There was a significant difference in the age groups of those with malaria (P<0.05). Similarly, infection with dengue increased with age from 1(2.4%) in children 11-20 yr., and peaked among those in the older age bracket, 41-50 yr, 3(23.1%). The age variation and frequency of dengue infection was not statistically significant (P>0.05). Males, 20(37.0%) and 5(9.3%) were mostly infected with malaria and typhoid/paratyphoid, respectively than their female counterparts, 31(34.1%) and 5(5.5%). This is unlike the case of dengue, where there was female preponderance (3.7% versus 5.5%). There was no gender bias in the

infection rates with dengue, malaria and typhoid/paratyphoid among the patients (P>0.05). Only two (4.8%) patients in the age bracket 11-20 yr had multiple infections of malaria and typhoid/paratyphoid, and were each male, 1(1.9%) and female, 1(1.9%). The only male patient infected with both malaria and dengue virus was in the age group 41-50 yr, 1(7.7%) (Table 3).

The distribution of dengue virus specific-markers (NS1 Ag, IgM, and IgG) is presented in Table 4. The frequency of detection of NS1 Ag was 4(2.8%), Dengue-specific IgM, 2(1.4%) and Dengue-specific IgG, 1(0.69%). Majority of patients detected with dengue NS1 Ag were females, 3(3.2%), and one each had dengue-specific IgM and IgG antibodies. Male patients that tested positive for NS1 Ag and Dengue IgM were 1(1.9%) each and none had Dengue IgG. A combination of dengue NS1 Ag and IgM specific marker gave a higher detection rate of 5(3.5%) among the 7 patients diagnosed with dengue virus infection.

Table 1. Frequency of dengue, malaria and typhoid/paratyphoid infections in patients with febrile illness (N=145)

Infection	No. positive (%)	Chi square (X ²)	P value
Single infection			
Dengue	7(4.8)	-	-
Malaria	51(35.2)	-	-
Typhoid/Paratyphoid	10(6.9)	-	-
Multiple infection			
Dengue/Malaria	1(0.7)	0.61	0.44
Dengue/Typhoid/Paratyphoid	0	-	-
Malaria/Typhoid/Paratyphoid	2(1.4)	0.49	0.49

Table 2. Age and sex distribution of dengue, malaria and typhoid/paratyphoid in patients with febrile illness

Variable	No. tested	Dengue (%)	Malaria (%)	Typhoid/Paratyphoid (%)
Age (yr)				
<1-10	7	0	1(14.3)	0
11-20	42	1(2.4)	5(11.9)	0
21-30	37	1(2.7)	20(54.1)	4(10.8)
31-40	32	2(6.3)	14(43.8)	3(9.4)
41-50	13	3(23.1)	5(38.5)	3(23.1)
51-60	9	0	4(44.4)	0
61-70	5	0	2(40.0)	0
Sex				
Male	54	2(3.7)	20(37.0)	5(9.3)
Female	91	5(5.5)	31(34.1)	5(5.5)

Table 3. Age and Sex distribution of multiple infections in patients with febrile illness

Variable	No. tested	Dengue/Malaria (%)	Malaria/ Typhoid/Paratyphoid (%)
Age (yr)			
<1-10	7	2(4.8)	0
11-20	42	0	0
21-30	37	0	0
31-40	32	0	0
41-50	13	0	1(7.7)
51-60	9	0	0
61-70	5	0	0
Sex			
Male	54	1(1.9)	1(1.9)
Female	91	1(1.1)	0

Table 4. Distribution of dengue virus-specific markers in relation to sex of patients

Sex (No. tested)	Dengue NS1 Ag No. Positive (%)	Dengue IgM No. positive (%)	Dengue IgG No. positive (%)
Male (n=54)	1(1.9)(14.3)	1(1.9)(14.3)	0
Female (n=91)	3(3.2)(42.9)	1(1.1)(14.3)	1(1.1)(14.3)
Total (n=145)	4(2.8)(51.1)	2(1.4)(28.6)	1(0.69)(14.3)

4. DISCUSSION

Among the febrile patients in this study who were clinically suspected of having either typhoid or malaria, about one-third, 51(35.2%) had malaria and 10(6.9%) were diagnosed with typhoid/paratyphoid, while 7(4.8%) were diagnosed with dengue. Malaria was observed as the major cause of febrile illness among the patients and is consistent with the findings of a study in Owerri, Southeastern Nigeria where a prevalence of 39% was reported [22]. Due to the high endemicity of malaria in Nigeria, and varied clinical features of the disease, it has been suggested to be considered as a differential diagnosis for most clinical problems particularly those associated with fever [23]. In this study, typhoid and dengue that are endemic in Nigeria also featured significantly among the febrile patients. The result of this study therefore revealed that 6.9% and 4.8% of the feverish patients having typhoid/paratyphoid and dengue respectively would have escaped diagnosis in settings where these infections are not primarily considered in differential diagnosis, even as few patients, 2(1.4%), had both malaria and typhoid coinfection. Although, the role of qualitative Widal test in diagnosis of typhoid may be controversial owing to its low sensitivity and specificity, the quantitative method employed in this study is considered diagnostic [20].

In a similar study recently conducted in Jos, Nigeria, typhoid accounted for 2.3%, while dengue prevalence was 2.2% among patients with febrile illness [24]. The documented dengue prevalence was based on presence of the NS1 antigen in the blood of the patients. These findings agree with the report by Baba et al. [15] that suggested that these diseases including dengue are endemic in Nigeria. Fever is commonly expressed in those with malaria and typhoid and is usually observed with any of the arboviral infections including dengue fever that are endemic in Nigeria [25]. Findings in this study indicates that one adult male patient (1.9%) had multiple infections of dengue and malaria. Earlier report of dengue and malaria co-infection has also been made by Thangarathan et al. [26], while Raut et al. [27] reported Chikungunya, dengue and malaria co-infection. The presence of antibodies to dengue virus in Nigeria has been demonstrated in seven ecological zones namely: Rainforest, Sudan savanna, Wooded/Grass savanna, Deltaic savanna, Guinea savanna, Guinea savanna and Sahel savanna [15]. The city of Uyo where this study was conducted is located in the Deltaic savanna area of Nigeria. With dengue prevalence of 4.8% recorded in this study, there is no doubting the fact that dengue endemicity in Nigeria is real and factual. WHO Report stated that incidence of dengue has increased by 30-folds between 1960 and 2010

and attributed this to a combination of urbanization, population growth, increased international travels and global warming [28]. In the USA, 2.9% - 8.0% returnees from countries endemic with dengue have been diagnosed with dengue, second to malaria among the exposed population [29].

In this study, there was female preponderance with dengue (5.5%) against their male counterparts (3.7%) unlike malaria where more males (37.0%) than females (34.1%) were infected. A similar study conducted in Jos, Nigeria also reported female preponderance where 3(2.9%) of the 5 dengue positive patients were females and 1(1.3%) male. These results indicate host gender preference for both dengue and malaria. Aside from the fact that the two diseases are vectored by mosquitoes of different strain, *Aedes* for dengue and *Anopheles* for malaria, the reason for the gender bias with the two diseases is not clear. However, there are varied reports about gender preference. For instance, Farin [30] opined that men are more likely to be attacked by mosquito than are women and advanced reasons such as larger body size, greater relative heat and increased CO₂ exhalation.

Among the dengue infected persons in this study, those in the age group 41-50 years had the highest infection rate, 23.1% and was statistically significant compared to other age groups, OR=12.30 (95%CI 1.15-131.10), P<0.05. Similar occurrence was observed among those with typhoid/paratyphoid infection but in contrast to Jos study where infections were mostly seen in the younger age group [24], just like malaria occurred in this study. However, the Jos study found no age bias attributed to infection with dengue.

Findings in this study have shown that the utilization of standard dengue specific markers such as the dengue NS1 antigen, IgM antibodies for acute cases and IgG antibodies for past infections can be suggestive or diagnostic for dengue, especially in resource-limited settings. As observed in this study, dengue positive patients in the early stages of infection with active disease were detected with NS1 antigen and IgM antibodies at the rate of 4(2.8%) and 2(1.4%), respectively. The 2.2% prevalence reported in Jos study [24] based on the presence of NS1 antigen is comparable to 2.8% NS1 antigen observed in this study. The result of this study therefore indicate that using a combination

of NS1 antigen and IgM antibodies, diagnosis of active dengue virus infection at early stage of the disease could yield more positive results than depending on one diagnostic marker alone. This observation has also been canvassed by Dawurung et al. [24], where a higher yield was gotten using both dengue NS1 antigen and IgM antibodies detection. Moreover, Gubler [14] in his report, had stipulated a 2-weeks apart testing of all initial dengue IgG positive patients to establish a 4-fold rise in antibodies as diagnostic. The sampling in this study however, did not include acute and convalescence testing to establish a 4-fold rise in dengue IgG antibodies. Moreso, the study design was cross sectional and protocol did not include follow up sampling and testing.

5. CONCLUSION

In conclusion, results of this study have revealed that dengue virus is one of the microbial agents causing febrile illnesses in our locality. Hence, dengue should be considered in the differential diagnosis of patients with febrile illnesses in this locality. The practice whereby physicians only investigate patients presenting with febrile illnesses for malaria and typhoid alone, has been limiting the diagnosis of other prevailing microbial agents of fever such as dengue virus. Since Nigeria is among countries endemic for malaria, typhoid and dengue, it is high time the suspicion index for dengue infection be raised among physicians. Dengue can be diagnosed at early stage using simple standardized reagents for its detection even in resource-limited settings.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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