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Prevalence of typhoid and malaria co-infection among patients attending a public hospital in Yola, Nigeria

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Abstract
Enteric and Malaria fevers with their high morbidity and mortality figures are still major public health problems especially in sub-Saharan Africa. It is common place today to see patients being concurrently treated for the two diseases. This study was undertaken to determine the coinfection status of malaria and typhoid fever in the study area. Two hundred persons were recruited for this study; blood samples obtained from the respondents were screened for malaria parasites by microscopy and RDT while slide and tube widal tests were used to screen for typhoid fever. Results showed that 111 (55.5%) were positive for malaria, 78 (39%) were positive for *Salmonella enterica* serovar Typhi, while 45 (22.5%) of the study subjects were positive for both typhoid and malaria. The occurrence of typhoid- malaria coinfection from this study was 22.5% with 51.1% of the confection occurring among males. Among the males, the highest coinfection was observed among age groups ≤ 10 years (80%) although this difference was not significant at p=0.05. The most common agents of malaria and typhoid fever in this study were *P. falciparum* (88.3%) and *Salmonella* Typhi (64.1%). The malaria and typhoid fever coinfection rate observed in this study is not as high as it is being projected to justify concurrent treatment with antimalarial and antibiotics. It also underscores the need for laboratory testing of suspected cases to increase precision in treatment and prevent the emergence of resistance by pathogens.

Keywords: Coinfection, malaria, typhoid, prevalence

Introduction
Enteric and Malaria fevers are diseases that are still major public health problems due to the high morbidity and mortality figures associated with them especially in sub-Saharan Africa where misdiagnosis and treatment failures pose a significant challenge in the management of these diseases. It is common place today to see patients being concurrently treated for enteric fever and malaria largely because of reliance on symptomatology instead of laboratory confirmed diagnosis. Since ancient times, clinicians have had difficulty in differentiating typhoid fever from malaria because of some overlapping clinical features. This difficulty necessitated the coinage of the term *typhomalaria* by an army doctor, Woodward, in 1862 who worked among young soldiers during the America civil war. He observed that soldiers who were suffering from febrile illness that seemed to be typhoid had intermittent fever patterns suggestive of malaria fever [1, 2].

Malaria has been tagged as one of the world's most deadly and life threatening parasitic diseases especially in tropical and subtropical regions of the world [3, 4]. The causative agents of malaria is a unicellular obligate protozoan parasite of the genus *Plasmodium* and four major species responsible for malaria are *Plasmodium ovale*, *P. vivax*, *P. falciparum*, *P. malariae* [5, 6]. *P. falciparum* has been lined with most severe forms of malaria in sub-Saharan Africa. On the global scale, malaria is one of the main causes of morbidity and mortality affecting people of all age groups and gender especially children in endemic areas such as Nigeria [7]. It poses a major challenge to human capital and economic development among others factors [8]. In the year 2018, the World Health Organisation (WHO) estimates that there were about 228 million cases of malaria and 405,000 malaria related deaths globally with 93.8% of deaths occurring in sub-Saharan Africa [9]. Furthermore, it has been reported that Nigeria accounts for 25% of the global malaria burden at the end of 2018 [9]. The known vector responsible for the transmission of malaria parasite from one person to another is the female *Anopheles* mosquito

which is present in relative abundance in Nigeria. Several factors have been reported to be responsible for malaria abundance in every locality which ranges from environmental factors and seasonal influences that determine vector survival to medical condition and human factors that determine susceptibility to the parasite. It has been reported that over 95% of Nigerian population is at risk to malaria infection especially in the rural area.

Typhoid Fever on the other hand is caused by *Salmonella enterica* subspecies *enterica* serovar Typhi. The milder form (paratyphoid fever) is caused by *Salmonella* Paratyphi. The global burden of typhoid fever in 2010, was estimated to be 27 million new cases and 200,000 deaths [10]. However, the true burden of typhoid fever is not known due to the difficulty of differentiating the disease from other febrile illnesses, the lack of microbiological culture facilities and the generally poor disease-reporting systems in developing countries. This global pathogen is endemic in low and middle income countries because of lack of clean water and poor sanitation and hygiene standards [11]. In industrialized countries on the other hand, the incidence of *Salmonella enterica* serotype Typhi infection is low and associated mainly with chronic carriers, food handlers or acquired during travel to endemic regions [12]. Independently associated risk factors suggesting waterborne transmission include drinking of water from unsafe sources like streams, wells etc. Furthermore, consumption of ice cream, eating from road side cabins and food stalls have been reported as independently associated risks factors suggesting food borne transmission [13].

Malaria and typhoid co-infection figures are a lot less available although typhoid and malaria coinfection of 22% among study subjects in Owerri, Imo State Nigeria have been reported [14]. Both typhoid fever and malaria diseases are still common in many developing countries and remain a significant threat to health in sub-Saharan Africa for several reasons. A large percentage of the population in sub Saharan Africa still lack access to clean water a factor that favours the spread of typhoid fever. There is also wide-spread misuse of widal agglutination test for diagnosing typhoid fever [15], a factor that leads to treatment failure due to bacterial drug resistance. For malaria on the other hand, lack of adequate housing and other environmental conditions that favour growth of parasite vectors aggravate the conditions. In Nigeria, malaria is reported as a major public health problem where it is estimated to account for more cases and death than any other country in the world.

Diagnosis of malaria and typhoid fevers in Nigeria and in the study area is based on clinical signs and symptoms as evidenced in patients being treated for both malaria and typhoid fevers even without laboratory confirmation. Such diagnosis could lead to over or under reporting of the actual burden of the two diseases. In cases were laboratory tests are conducted, perverted widal test or culture without enrichment for the typhoid fever bacterium are often employed. Appropriate and precise diagnosis is necessary for suitable treatment of malaria and typhoid fevers as well as for their prevention and control. This work was aimed at determining the occurrence of typhoid fever and Malaria co-infection among patients visiting public hospitals, with a view to ascertaining the necessity of the continued justification of concurrent treatment of patients for typhoid fever and malaria in the study area.

Materials and Methods

Study Area

This study was conducted at Specialist Hospital, Yola, North Eastern Nigeria. Yola lies between latitude 9^0 15' N and longitude 12^0 25' E. Yola has a tropical climate, characterized by dry and rainy seasons. The rainy season sets in May and ends in early October. The mean total rainfall is 1,113.3 mm, with August and September being the wettest months with about 25% of the total annual rainfall in the area occurring during this period. The dry season begins in November and ends in April [16]. Yola peak temperature approximately about 40 ^{0}C in April; while minimum temperatures (which could be as low as 18.3 ^{0}C) are observed between December and early January which marks the harmattan period, occasioned by the north easterly trade winds.

Sample Collection

A total of 200 blood samples were collected from patients attending the parasitology laboratory of Specialist Hospital, Yola. Blood samples of patient suspected to have malaria and typhoid fever were collected by venepuncture 2 ml of blood was collected from each patient using a sterile syringe.

Rapid Diagnostic Test (RDT) for Malaria

The RDT was carried out according to the manufacturer's instructions. Briefly, after collection of blood, 20 µl (2- 3 drops) was spotted on the dipstick followed by the addition of 3 drops of assay diluents to allow for capillary movement of the sample-diluent complex along the dipstick. The ensuing mixture was allowed to stay for 20 minutes for the necessary reactions to take place. A positive result was indicated by the appearance of band at both the control and the test area. Presence of band on the control line alone indicates a negative result while lack of band in the control line indicates as invalid result.

Thick Blood Film for Malaria Parasite Detection

A thick blood film was prepared for each sample and allowed to air dry. The smear was then stained with Field Stain A for 3 seconds and washed in water with slight agitation. The slide was then dipped into Field Stain B, for 3 seconds after which it was washed gently removed under tap water to remove excess stain. The slide was then air dried and observed using oil immersion objective [17].

Widal Test: The two step widal test procedure (Rapid Slide Agglutination Test and Tube Agglutination Test) described below was adopted for the study.

Rapid Slide Agglutination Test: To carry out the test, drops of the patient's serum were pipetted onto a clean tile in pairs and thereafter one drop of the different *Salmonella* antigens (Somatic and flagella antigens) was added to the different pairs of the patients serum and mixed using applicator sticks. Two other wells for a positive and negative control were included for each antigen suspension. The tile was then rocked gently for 3 minutes and observed for agglutination. Any agglutination observed with patient's serum was compared with those of the positive (which shows obvious agglutination) and negative (which shows uniform suspension) controls. The test showing any agglutination was then subjected to further analysis by the tube agglutination method [17].

Tube Agglutination Test: To carry out this test, the test reagents were brought to room temperature and mixed well. Two sets of test tubes (one for somatic and the other for flagella antigens) each containing eight test tubes were set up for each sample positive in the slide agglutination test. To prepare doubling dilution of patient's serum in saline, 1.9 ml of normal saline was pipetted into tube number one while into the remaining test tubes, 1 ml of saline was poured. Thereafter 0.1 ml of patient's serum was added into tube No. 1 and the contents mixed properly. After mixing, 1 ml of the diluted serum was transferred to tube No. 2 and this continued to tube no. 7 (1 ml was also discarded from Tube 7). This provides serial two-fold dilutions of 1:20, 1:40, 1:80, 1:160, 1:320, 1:640 and 1: 1280 in the respective tubes. A micropipette was then used to transfer 50 µl of *Salmonella* Typhi 'O' antigen to one set of tubes (1-8) and *Salmonella* Typhi 'H' antigen to the second set of tubes. The contents of all the tubes were mixed well and incubated for 18 hours at 37 ^{o} C. After the incubation period, the tubes were examined for agglutination under bright light. The dilution where agglutination was last seen was recorded as the titre of the test reaction. The test was read as positive when the O antibody titres were 1/160 for *S.* Typhi.

Results

Of the 200 blood samples collected 104 were from females while the rest (96) were from males. The results of the malaria parasite screening revealed that 111 (55.5%) of the subjects were positive for malaria parasite (Table 1). The highest incidence of malaria (63.4%) was observed among study subjects ≤ 10 years of ages while the least malaria incidence (52.1%.) was among subjects belonging to aged group 21-30 yr. The distribution of malaria with respect to gender revealed that 53.8% of females and 57.3% of males tested positive for malaria. The risk ratio of malaria between females and males showed that males are 1.06 times more likely than the females to have malaria. Chi square analysis revealed that there was a statistically significant difference in the distribution of malaria with respect to age group and gender in the study area at p=0.05.

The results of the two step widal test procedure (Table 2) puts the incidence of typhoid in the study area at 39%. The results also showed that patients aged ≥ 30 years had the highest typhoid occurrence (54%) followed by those in the age group 21-30 years (47%). The least occurrence (17.1%) was among the age group ≤ 10 years. A total of 45 (46.9%) males and 33 (31.7%) females were positive for typhoid fever. The results also showed that the risk of contracting typhoid fever among the males was 1.48 times higher than in females. Statistical analysis showed that there was no significant difference in the distribution of typhoid fever in relation to age and gender in the study area at p=0.05.

Furthermore, findings from this study showed that 45 (22.5%) study subjects have typhoid and malaria coinfection while 56 (28%) tested negative for typhoid and malaria. Further breakdown showed that 66 (33%) subjects had Malaria alone while 33 (16.5%) had only typhoid fever (Figure 1). The distribution of the coinfection by gender revealed that 51.1% of those co-infected with malaria and typhoid fever were males and 48.9% were females. Among the males, the highest coinfection was among age groups ≤ 10 years (80%) and least among age groups 11-20 years. However, among the females, the least coinfection was among age group ≤ 10 years (20%) but highest among subjects belonging to the age group 11 – 20 years (70%) (Table 3). Despite the difference in distribution of coinfection in relation to gender and age group, Chi square analysis showed that such difference was not statistically significant at p=0.05

Also, results obtained showed that *P. falciparum* was the prevalent cause of malaria in the study area as it accounted for 88.3% of the malaria positive samples (the remaining 11.7% was caused by *P. malariae*), while the main typhoid fever pathogen was *Salmonella* Typhi which accounted for 64.1% of typhoid fever cases, while *Salmonella* Paratyphi A accounted for 25.6% (Figure 2).

Discussion

Findings from our study revealed an overall malaria incidence of 55.5% among the participants in this study. This figure is quite high implying that mosquito breeding and transmission is high in the study area. The high incidence could be attributed to environmental factors such as poor drainages, bushy surroundings and careless disposals of items that serve as breeding sites for mosquitoes. Also, the humidity of the area requires that people spend time outside at night thereby increasing the mosquito human contact and consequent transmission. The incidence from this study is higher than the 54.2% reported in Unwana community in Ebonyi state [18] but lower than the 88.8% reported in Wukari, Taraba state [19].

The highest incidence of malaria (63.4%) was observed among the study subjects aged ≤ 10 yr while the least malaria incidence (52.1%) was among those within the 21-30 yr age bracket. The high prevalence among age ≤ 10 yr could be due to environmental factors which favour increased breeding ground for the vector, loss of immunity due to poor living conditions, irregular immunizations and lack of adherence to malaria prevention strategies such as the use of insecticide treated mosquito nets [20, 21].

The results obtained in this study indicate that the incidence of typhoid from the study area is 39%. This incidence is higher than the 17.5% and 20% reported for Numan and Mayo Belwa respectively [22]. It is however lower than the 42% reported in Owerri [14]. Furthermore, the results showed that subjects age ≥ 30 years had the highest incidence of 54% followed by the study subjects aged 21-30 years (47%). The least incidence (17.1%) was among age group ≤ 10 yr. This is in contrast to the popular view that children less than 10 and those 11-20 years of age have higher prevalence rates. The high occurrence among those aged ≥ 30 years can be attributed to the fact that most people within the age group are working class and usually patronize food vendors and canteens whose hygiene might have been compromised thereby contaminating the food with the pathogen.

A total of 45 (46.9%) of males and 33 (31.7%) of females were positive for typhoid fever. The risk ratio for typhoid fever among the study subjects revealed that it is 1.48 times more among males than females. This is at variance with the slightly higher prevalence rate of 64.2% among females compared to males (63.6%) in Wukari [19]. This higher frequency of typhoid fever in males may be due to the fact that they regularly eat outside the home, often from unhygienic sources, because of the nature of their work or because they drink water from unsafe sources.

The result obtained showed that the incidence of malaria and typhoid fever coinfection from this study is 22.5% (Table 3). The value obtained from this study is higher than the 4.5% for

Abuja, Nigeria [23] but lower than the 36.3% and 56% that have been reported in Ebonyi [18] and Wukari [19] respectively. The distribution of the coinfection by gender revealed that 51.1% those co-infected were males while 48.9% were females. This was at variance with the figures reported in Wukari, Taraba State where co-infection rate was higher in females (58.9%) than in males (52.3%) [19]. This is somewhat not strange because males spend more times outside and eat out exposing themselves to greater risk of infection.

Among the males, the highest coinfection was among age groups ≤ 10 years (80%) and least among age groups 11-20 years. However, among the females, the least coinfection was among age group ≤ 10 years (20%) but highest among age group 11 – 20 years (70%).

The results obtained also show that *P. falciparum* was the prevalent cause of malaria in the study population accounting for 88.3% of malaria cases while the remaining 11.7% was caused by *P. malariae.* This finding is not surprising as it has been reported that *P falciparum* has the highest frequency of occurrence followed by *P. malaraie* [23]. The challenge however is that the most common malaria parasite found in the area is associated with the most severe and lethal form of the disease. This implies that without prompt and correct treatment of malaria in the study area, the case fatality rates may be very high. This therefore calls for more rapid, laboratory confirmed diagnosis and correct treatment to reduce parasitaemia quickly. *P. falciparum* is associated with the hotter parts of the world, chiefly sub-Saharan Africa and Nigeria [24, 25].

The results obtained also showed that 66 (33%) of the subjects enrolled in this study had only malaria while 56 (28%) of the subjects had neither malaria nor typhoid fever on the basis of laboratory findings. Furthermore, among those being managed for Typhoid fever and malaria concurrently, only 45 (30.8%) had coinfection out of the 146 that had either malaria or typhoid or 22.5% of the total study subjects. This implies that other pathogens may be responsible for febrile illness seen in these patients. This is a cause for concern as it implies that several people are given antibiotics or antimalarial that they don't actually need basically because of reliance on symptomatology as the main stay for diagnosis [26]. The implication of this misdiagnosis and hence mistreatment is also that the finances of patients in the short run is wasted in buying drugs that will not benefit them and the possible emergence of resistance in the long run because of misuse or overuse of drugs. The results show that there is therefore a need for improvement in the diagnosis of the cause of febrile illness in our populations in order to ensure that treatment is effective and also to prevent the emergence of resistance by pathogens to available drugs

Table 1: Incidence of malaria in relation to age and gender

	Infection Status			
Group	**Not infected**	**Infected**	**Total**	**P=Value**
≤ 10	34 (82.9)	7 (17.1)	41	
11-20	40 (65.6)	21 (34.4)	61	0.0017
21-30	25 (52.1)	23 (47.9)	48	
> 30	23 (46.0)	27 (54.0)	50	
Total	122 (61.0)	78 (39.0)	200	
Female	71 (68.3)	33 (31.7)	104	
Male	51 (53.1)	45 (46.9)	96	0.0283
Total	122 (61.0)	78 (39.0)	200	

Key: The values in parenthesis are percentage (%)

Table 2: Distribution of Typhoid fever in relation to age and gender

	Infection Status			
Age Group	**Not infected**	**Infected**	**Total**	**P Value**
≤ 10	15 (36.6)	26 (63.4)	41	
11-20	29 (47.5)	32 (52.5)	61	0.682
21-30	23 (47.9)	25 (52.1)	48	
> 30	22 (44.0)	28 (56.0)	50	
Total	89 (44.5)	111(55.5)	200	
Female	48 (46.2)	56 (53.8)	104	
Male	41 (42.7)	55 (57.3)	96	0.624
Total	89 (44.5)	111 (55.5)	200	

Key: The values in parenthesis are percentage (%)

Table 3: Prevalence of Co-infection with Respect to Age and Sex

Sex	**Male**	**Female**	**Total**	**P=Value**
≤ 10	4 (80.0)	1(20.0)	5	
11-20	3 (30.0)	7 (70.0)	10	0.136
21-30	11 (64.7)	6 (35.3)	17	
> 30	5 (38.7)	8 (61.5)	13	
Total	23 (51.1)	22 (48.9)	45 (22.5)	

Key: The values in parenthesis are percentage (%)

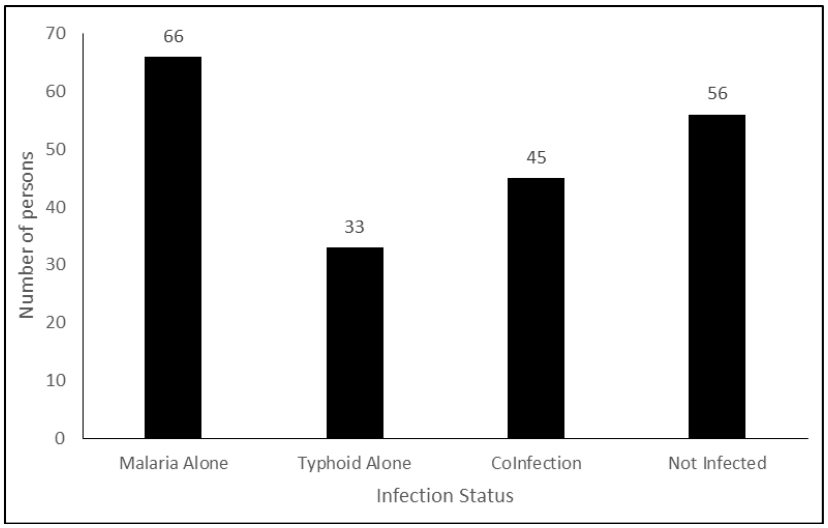

Fig 1: Distribution of Typhoid and malaria infection in study area

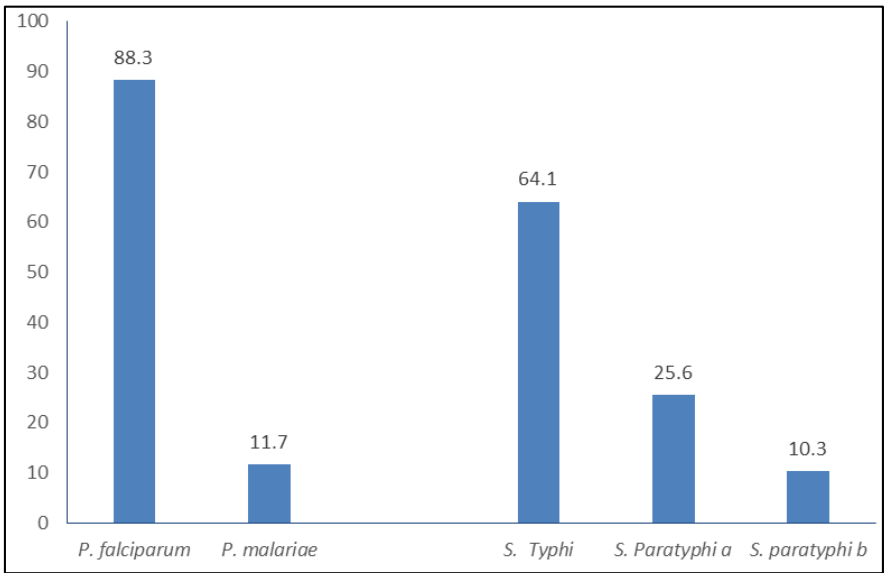

Fig 2: Occurrence (%) of Typhoid and malaria Pathogens among the study subjects

Conclusion

The occurrence of malaria and typhoid coinfection from this study was 22.5% of the study subjects or 30.8% of those subjects that test positive for typhoid or malaria fevers with more of the coinfection observed among males than females. *Plasmodium falciparum*: the causative agent of severe malaria was the most common etiologic agent in the study area with an occurrence of 88.3%. Furthermore, among those with symptomatology similar to malaria and typhoid fevers, 56 (28%) tested negative for typhoid and malaria fevers. This underscores the need for rapid laboratory screening for the presence of malaria parasite so that evidence based therapy will be administered instead of treating all fevers for malaria and typhoid concurrently.

Conflict of interest: We declare that no personal or financial conflict of interest exists.

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