

The Relative Prevalence of Typhoid and Malaria in Febrile Patients in Freetown, Sierra Leone

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Abstract

Malaria and typhoid fever are debilitating diseases responsible for the deaths of thousands of lives annually. Over the last decade both diseases have received increasing attention with particular focus on malaria. However, recent reports indicate an increasing co-infection rate between malaria and typhoid fever. Familiar signs and symptoms of both diseases have led to the belief in some communities that it's a new disease. In this study, we investigated the relationship between malaria and typhi O and H antigens among patients reporting with fever. Patients reporting with fever from April 2013-March 2014 were recruited for the study. Our results showed that there was no association between having malaria and typhoid fever infection. However, having fever was associated with having both diseases. Also, fever among patients was more likely to be caused by *Salmonella typhi* O and H antigens than plasmodium parasites. Infections of both diseases were higher in wet season than in dry season. The study recommends that malaria and typhoid fever intervention programs are increased in endemic areas. Also attention should be paid to typhoid fever infection rates in the country.

Keywords

Fever, Malaria, Typhoid Fever, Widal Test, Co-Infection

1. Introduction

Malaria and typhoid fever are endemic diseases with life threatening consequences especially in Sub-Saharan

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Africa. Malaria infection is caused by the plasmodium parasite through the bites of an infected vector, usually an anopheles mosquito. Four species of the plasmodium parasite cause malaria in humans (*P. falciparum*, *P. vivax*, *P. malaria* and *P. Ovale*). However *P. falciparum* is the most common causative agent and contributes to the highest fatality. Typhoid fever is caused by a gram negative bacterium called *Salmonella typhi*. Infection usually occurs through ingestion of contaminated food or water. Serology tests usually measure for agglutinations of antibodies against flagella (H) and somatic (O) antigens of the bacterium. Both diseases have similar clinical manifestations such as fever, nausea, appetite loss, headache and constipation. Complications are common for both diseases and usually lead to death.

Malaria and typhoid fever are usually associated with areas or regions with high poverty and under development [1]. In 2012, the World Health Organization (WHO) estimated that there was an approximately 207 million cases of malaria with an estimated 627,000 deaths [2]. Annual typhoid fever infection is estimated at 21 million cases with a case fatality rate of 1% - 4%. These statistics become worse when related to countries where these diseases are endemic. 90% of all malaria deaths occur in Sub-Saharan Africa [2]. According to a study by Crump *et al.*, (2004) typhoid fever incidence rate for Asia, Africa and Latin America was 274/10, 50/10 and 53/10 respectively, compared to rates of 15/10, 3/10 and 1/10 for Oceania, Europe and North America respectively [3]. Despite these high rates, in recent years, there has been a decrease in malaria's morbidity and mortality (www.cdc.gov/features/worldmaliaday).

Geographic distribution of both diseases shows that a co-infection of both diseases is imperative. Also overlap in the social dynamics of communities with high incidence of both diseases gives further credence to the co-infection of both diseases [4]. Due to common clinical manifestations of both diseases, there is a common belief in most endemic communities that malaria and typhoid fever are concurrent diseases and therefore should be treated as such [1]. Diagnostics procedures for malaria and typhoid fever infections are crude and inaccurate in most of these communities, as a result data on co-infection are usually flawed and misleading [5].

In an endemic area such as Sierra Leone, there is an increase in the belief that co-infection is a new disease and should be treated as such. Also, most medical practitioners treat patients presenting with signs and symptoms of any one of the two diseases with treatments for both diseases. Considering the mutational property of the plasmodium parasite and Salmonella bacteria, drug misuse will lead to resistivity of both pathogens, as has been proven in recent years [2]. Understanding the relationship between typhoid fever and malaria with regard to patients presenting with a similar symptom such as fever, will help to improve knowledge and perspectives towards both diseases and also explain possible relationships (if any), that might exist between malaria and typhoid fever. In this study we investigated the relationship between malaria and typhoid fever infections among patients presenting with fever in a 12-month period at a referral hospital. We also investigated monthly trends of both diseases.

2. Methodology

2.1. Study Site

Study data was collected from the Kingharman Road Government Hospital. The hospital is a fully functioning government hospital with more than five hundred visits per day. It is located in the central part of Freetown, the capital city of Sierra Leone. Sierra Leone is in the western part of Africa with a size of about 71,740 km square (27,699 square miles). In the last census report, Sierra Leone had a population of 6 million (2011 United Nations estimate) and the population of Freetown was approximately 772,873. The ratio of male to female in was 0.97 male(s)/female of the population are under the age of 30. The country has a tropical climate with a wet season from May to October and a dry season from November to April. It has an average temperature of about 27°C and an annual rainfall average of 3150 mm.

The hospital is one of the main referral hospitals in Sierra Leone and is one of the main surveillance units for diseases in the country, especially malaria and typhoid. On a daily basis, the hospital has about 150 to 200 patients tested for malaria and typhoid combined.

2.2. Study Participants and Sample Collection

The study was conducted from April 2013 to March 2014. Patients with fever reporting for malaria and typhoid testing were recruited in the study. A total of 11,069 patients with fever were recruited during the study period.

Patients were tested for malaria and typhoid (O and H) infections. Study participants included males (47.38%), and females (52.62%). All patients were above the age of five. Under-fives were not included in the study because of inconsistencies in recruiting them for the study and also issues involving safety and consent solicitation.

Trained and licensed laboratory technicians obtained blood samples from all enrolled participants. Blood samples of about 3 mls were collected from the vein of each patient and tested for malaria parasites, *Salmonella typhi* O and H antibodies. Samples were stored in test tubes and stored at 15°C - 30°C prior to laboratory analysis.

2.3. Laboratory Analysis

Conventional light microscopy method was used for confirmation of malaria. This is one the most popular and established method for malaria laboratory confirmation in the tropics and most developing societies. This method involves making a thick and thin dry blood film. The dry blood film was then stained with Giemsa and examined under the microscope, using the oil immersion objective lens. The patient was confirmed of having malaria parasites if stained parasites are seen by the technician. The parasites were counted by a simpler method called the plus system which uses a code of between one and four plus signs, as follows:

+ = 1 - 10 parasites per 100 thick film fields

++ = 11 - 100 parasites per 100 thick film fields

+++ = 1 - 10 parasites per single thick film field

Serological diagnosis was carried out using widal agglutination test to determine the antibody titres of the sera against salmonella H (flagella) and O (somatic) antigens. Widal test is the main method for typhoid fever diagnosis in many African countries like Sierra Leone. The serological testing was done in accordance with manufacturers guidelines. The significant in this hospital were figures $\geq 1:80$ for both typhi O and H.

2.4. Statistical Analysis

Data were analyzed using SPSS 20.0. Chi square test was used for significance inspection and Pearson's correlation coefficient was for the inspection of associations.

2.5. Ethical Considerations

Before data collection, permission was solicited from the hospital ethics committee and confirmed by the ethics committee of the Ministry of Health and Sanitation. Laboratory procedures and personnel were scrutinized and approved by the safety department of the hospital. Informed consent was solicited from patients or their guardians (for patients under 18 years).

3. Results

3.1. General Characteristics and Age Distribution

The study investigated the association between malaria, *S. typhi* O and *S. typhi* H infections among patients with fever symptoms that reported for testing at the Kingharman road government hospital from April 2013 to March 2014. During the study period, a total of 11,069 fever patients reported for testing, of these, 5245 (47.38%) were males and 5824 (52.62%) were females. Only 147 (1.3%) fever patients did not test positive for any of the three diseases or infection. A total of 8849 (79.94%) fever patients tested positive for the plasmodium parasite. Among these, positive male cases were 4180 (37.76%) and female positive cases were 4669, $\chi^2 = 0.431$, $p < 0.05$. 5992, 2809 and 48 patients that tested positive for the plasmodium parasite, had parasites loads of +, ++ and +++ respectively. Patients with reactive widal agglutinations titres for *S. typhi* O and *S. typhi* H were 9247 (83.54%) and 9603 (86.75%) respectively. Male *S. typhi* O and *S. typhi* H cases were 4336 and 4911 respectively. Female *S. typhi* O cases were 4911 and *S. typhi* H female cases were 5098. 4974 cases had *S. typhi* O titres $\geq 1:80$ and 4581 cases had *S. typhi* H titres $\geq 1:80$ (**Table 1**).

Most of the cases tested were with the age groups of 5 - 34, consisting of 60.94% for malaria positive cases, 34.55% for typhi O and 31.98% for typhi H cases $\geq 1:80$ (**Table 2**). Not surprisingly, this age group (5 - 34 years) accounted for most of the positive malaria and typhi O and H cases. However, compared to typhi O and H cases,

Table 1. Gender and disease distribution among all fever patients from April 2013-March 2014.

		Gender		Total
		Male	Female	
Malaria	None	1065	1155	2220
	+	2829	3163	5992
	++	1329	1480	2809
	+++	22	26	48
	Total	5245	5824	11,069
		$\chi^2 = 0.431$	$p > 0.05$	
Typhi O	Non-reactive	909	913	1822
	<1:80	2115	2158	4273
	$\geq 1:80$	2221	2753	4974
	Total	5245	5824	11,069
			$\chi^2 = 27.13$	$p < 0.01$
Typhi H	Non-reactive	740	726	1466
	<1:80	2433	2589	5022
	$\geq 1:80$	2072	2509	4581
	Total	5245	5824	11,069
			$\chi^2 = 16.425$	$p < 0.01$

Table 2. Age distribution of fever patients testing for malaria, *S. typhi* O and *S. typhi* H.

		Malaria				Typhi O			Typhi H		
		Parasite load				Titre			Titre		
		Not seen	+	++	+++	Non-reactive	<1:80	$\geq 1:80$	Non-reactive	<1:80	$\geq 1:80$
Age group	5 - 9	336	899	404	8	260	661	726	215	736	696
	10 - 14	245	680	344	4	204	452	617	163	573	537
	15 - 19	296	792	362	3	246	550	657	199	637	617
	20 - 24	304	845	375	7	255	563	713	204	662	665
	25 - 29	251	665	328	7	185	520	546	152	590	509
	30 - 34	270	699	314	9	222	505	565	189	587	516
	35 - 39	96	254	132	1	77	166	240	67	229	187
	40 - 44	112	329	151	3	97	235	263	84	291	220
	45 - 49	66	184	83	3	66	142	128	40	160	136
	50 - 54	94	240	125	1	90	183	187	64	205	191
	55 - 59	29	94	40	0	33	65	65	14	80	69
	60 - 64	70	169	78	1	43	120	155	41	143	134
	65 - 70	18	27	19	0	15	25	24	13	26	25
	>70	33	115	54	1	29	86	88	21	103	79

+ = 1 - 10 parasites per 100 thick film fields; ++ = 11 - 100 parasites per 100 thick film fields; +++ = 1 - 10 parasites per single thick film field; ++++ = more than 10 parasites per single thick film field.

parasites load in patients having the plasmodium parasite were lower (in terms of causing malaria symptoms) than typhi O and H cases with titres $\geq 1:80$ (also in terms of causing diseases).

3.2. Distribution of Malaria, Typhi O and Typhi H

Table 3 shows the distribution of malaria parasite load, *S. typhi* O and H widal agglutination titres among fever patients. Among the 11,069 fever patients tested for the plasmodium parasite, *S. typhi* O and *S. typhi* H, only 147 (1.3%) tested negative or non-reactive for either the pathogen or bacteria. 66% (7353) of cases had all three infections. 1894 negative cases of malaria were reactive for both *S. typhi* O and *S. typhi* H titres, of these, 422 cases had titres $< 1:80$ for *S. typhi* O and *S. typhi* H. Also, 324 cases had titres $\geq 1:80$ (**Table 3**). 403 non-reactive cases for *S. typhi* H and *S. typhi* O had + malaria parasite load and 301 cases with malaria parasite load of ++ were reactive for both *S. typhi* O and *S. typhi* H. Only 48 patients had +++ malaria parasite load, among them, 3 were non-reactive for *S. typhi* O and *S. typhi* H, 20 had titres $< 1:80$ for *S. typhi* O and H and 11 had titres $\geq 1:80$ for *S. typhi* O and H. Also from **Table 3**, among fever patients with *S. typhi* O and typhi H, only 7% (854) were non-reactive for either *S. typhi* O or *S. typhi* H. 2451 patients had titres of $< 1:80$ for *S. typhi* O and H and also 2655 had titres $\geq 1:80$ for *S. typhi* O and *S. typhi* H (**Table 3**).

3.3. Association between Malaria, Typhi O and Typhi H

Results from **Table 4** show a significantly strong positive association between presence of the parasite or bacteria and fever.

Table 3. Malaria, typhi O and typhi H distribution among all fever patients from April 2013-March 2014.

Malaria	Typhi O	Typhi H			Total
		Non-reactive	$< 1:80$	$\geq 1:80$	
Not seen	Non-reactive	147	98	81	326
	$< 1:80$	63	422	324	809
	$\geq 1:80$	64	467	554	1085
	Total	274	987	959	2220
+	Non-reactive	403	272	261	936
	$< 1:80$	169	1304	865	2338
	$\geq 1:80$	134	1095	1489	2718
	Total	706	2671	2615	5992
++	Non-reactive	301	157	97	555
	$< 1:80$	103	705	295	1103
	$\geq 1:80$	77	473	601	1151
	Total	481	1335	993	2809
+++	Non-reactive	3	1	1	5
	$< 1:80$	1	20	2	23
	$\geq 1:80$	1	8	11	20
	Total	5	29	14	48
Total	Non-reactive	854	528	440	1822
	$< 1:80$	336	2451	1486	4273
	$\geq 1:80$	276	2043	2655	4974
	Total	1466	5022	4581	11069

Table 4. Pearson's correlation coefficient for gender, age group, malaria cases and typhi O and H cases.

		Gender	Age group	Positive malaria cases per parasite load	All positive malaria cases	Typhi O cases per bacteria load	Typhi H cases per bacteria load	All positive typhi O cases	All positive typhi H cases
Gender	r	-	0.021*	0.004	0.006	0.045**	0.038**	0.022*	0.023*
Age group	r	0.021*	-	0.004	0.001	-0.017	-0.012	-0.01	0.001
Positive malaria cases per parasite load	r	0.004	0.004	-	0.778**	-0.059**	-0.067**	-0.044**	-0.048**
All positive malaria cases	r	0.006	0.001	0.778**	-	-0.039**	-0.020*	-0.024*	-0.012
Typhi O cases per bacteria load	r	0.045**	-0.017	-0.059**	-0.039**	-	0.345**	0.780**	0.363**
Typhi H cases per bacteria load	r	0.038**	-0.012	-0.067**	-0.020*	0.345**	-	0.330**	0.730**
All positive typhi O cases	r	0.022*	-0.01	-0.044**	-0.024*	0.780**	0.330**	-	0.437**
All positive typhi H cases	r	0.023*	0.001	-0.048**	-0.012	0.363**	0.730**	0.437**	-

*Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed).

Correlation analysis between fever patients and patients with ≥ 10 plasmodium parasites per single thick film field was $r = 0.778$, $p < 0.01$. Also, association between fever patients and *S. typhi* O and H cases was $r = 0.780$, $p < 0.01$ and $r = 0.730$, $p < 0.01$ respectively. However, correlation was weak and negative between malaria and *S. typhi* O, $r = -0.059$, $p < 0.01$. Association was also weak between malaria and *S. typhi* H, $r = -0.067$, $p < 0.01$. There was positive association between *S. typhi* O and *S. typhi* H cases with titres $\geq 1:80$, $r = 0.345$, $p < 0.01$.

Association between gender and all three diseases was weak, but significant ($p < 0.05$) for *S. typhi* O and *S. typhi* H.

3.4. Malaria, Typhi O and Typhi H Monthly Trend

Monthly trend for malaria, *S. typhi* O and *S. typhi* H followed almost similar trend (Figure 1).

Trend analysis for malaria, during the 12 month period was, $\chi^2 = 16.926$, $p < 0.01$. *S. typhi* O and *S. typhi* H chi square trend analysis were $\chi^2 = 16.425$, $p < 0.01$ and $\chi^2 = 0.10604$, $p > 0.05$ respectively. For all three infections, the lowest cases were recorded in March. Malaria, *S. typhi* O and *S. typhi* H cases in March were 483, 453 and 458 respectively. The highest cases for all three diseases were recorded in June and July. Malaria cases in June and July were 1054 and 1163 respectively, *S. typhi* O cases were 1173 and 1126 respectively for June and July and *S. typhi* H cases for June and July were 1184 and 1204 respectively. Cases increase sharply for all three diseases from May to June, with an increase of almost 30%. Also, there was a decline in the number of cases testing positive for malaria or reactive for *S. typhi* O and H in the months from July to August and August to September.

4. Discussion

This study investigated the association and monthly trend of Malaria, *S. typhi* O and *S. typhi* H among fever patients at the Kingharman Government Hospital Freetown in a 12-month period. Gender had no significant relationship with malaria, but was significant for *S. typhi* O and typhi H. Females were significantly more infected than males for both *S. typhi* O and *S. typhi* H. This result is in line with results from the study conducted by Levine et al. [6]. Considering the mode of transmission of typhoid, in endemic areas it is common for women to be more affected than men. Also, infection rate among age groups was consistent with national figures, indicating a high fever incidence as well as high malaria and typhi O and H infection rates. These results despite discouraging have been the trend in malaria and typhi O and H infections for decades now. Almost every fever patient was positive or reactive for at least one of the diseases in this study. The high rate of infection can be attributed to poor sanitation hygiene, other socio-economic factors and also the optimum temperatures that favors the reproductive cycle of these bacteria or parasites [7]-[9]. Also, over 60% of all patients were infected with all three

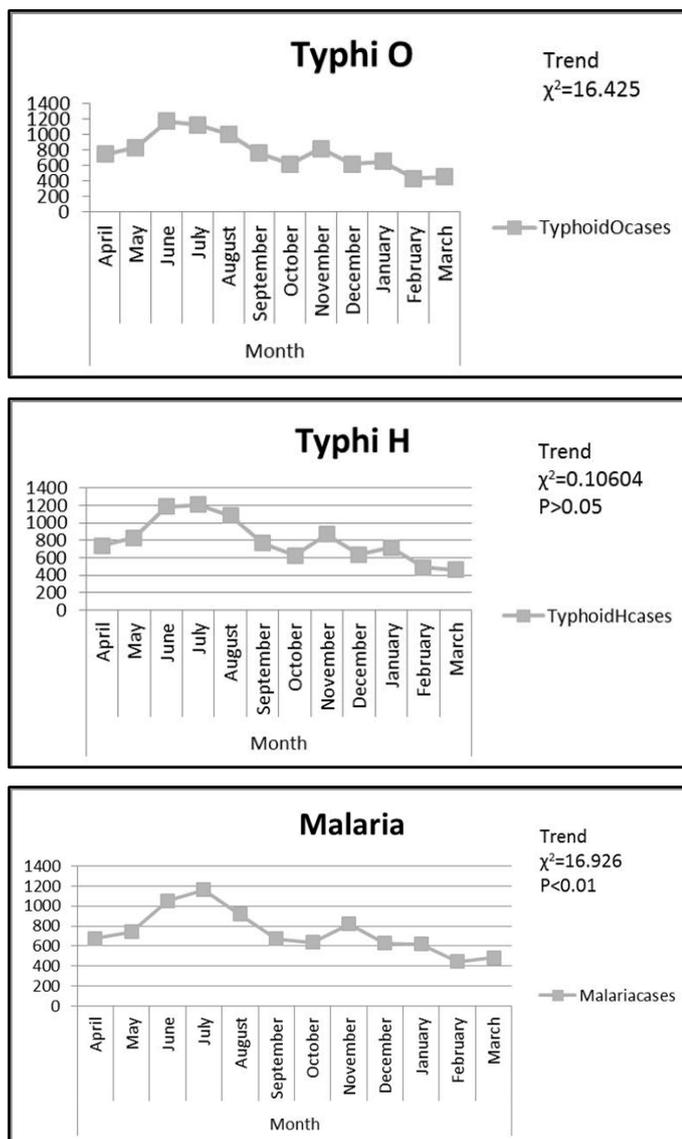


Figure 1. Monthly malaria, typhi O and H trend among fever patients from April 2013-March 2014.

diseases. Malaria cases with parasite loads of less than 10 parasites per 100 thick film fields were higher than cases with parasite loads of more than 10 parasites per 100 thick film fields. Major interventions aimed at reducing malaria morbidity and fatalities are some of the reasons for low plasmodium parasite loads [10]. Accessibility and availability of effective antimalarial drugs are other factors that might be responsible for lower malaria parasite load [11]. *S. typhi* O and H cases were higher than malaria cases. Compared to previous years when malaria infections were greater than typhoid infections, there has been a reverse in this trend in recent years [12] [13]. These results were not surprising, taking into consideration the resistance of the *Salmonella typhi* bacterium to antibiotics and also the complex nature of typhoid [14]-[17]. Despite high *S. typhi* O and H infections especially in endemic areas, interventions aimed at reducing typhoid infections have been lower compared to malaria interventions. These results show that vigorous health interventions can be highly effective in reducing disease morbidity and mortality. Considering the public health relevance of typhoid fever, higher infection rates should be treated as a public health emergency and trend reversed as to lower and acceptable values to avoid an outbreak or possible epidemics. In line with previous studies, this study did not find any association between malaria and typhoid fever infections [12] [18] [19].

There was a strong association between having fever and having malaria parasites with loads greater than 10 parasites per 100 thick film fields. Similar results were recorded by Anmah *et al.*, (1999) [20]. Also, there was strong positive association between *S. typhi* O and H infections with titres $\geq 1:80$ and fever patients. These associations' further helps to consolidate already known data that malaria and *S. typhi* H and O infections are the main causes of fever symptoms in areas endemic to the two diseases [19] [21].

Malaria and typhoid fever infections are higher in the raining/wet season than drier seasons. This is mainly due to the mode of transmission and reproductive cycles of the plasmodium parasite and Salmonella bacteria. This study recorded higher malaria and typhoid infections especially in the peak periods of the raining season and lower rates in the peak period of the dry season. Infections for both diseases were high from the months of June-August, coinciding with months of heavy rainfall. Trend analysis from this study showed a reduction in the number of malaria and typhoid cases as rainfall reduces. However, there was an increase in the number of malaria and typhoid cases from October to November. Lower temperatures and reduced water levels that favor disease transmission is a possible reason for the increase in rate from October-November.

5. Conclusion

Almost every patient presenting with fever symptoms had malaria, *S. typhi* O or *S. typhi* H infections, but *S. typhi* O and H infections were higher than malaria infections. There was no association between patients having malaria and typhoid fever. However, there was a strong association between having fever and that of having malaria or *S. typhi* O and *S. typhi* H infections. Also fever among patients was more likely to be caused by *Salmonella typhi* O and H antigens than plasmodium parasites. Malaria, *S. typhi* O and H infections are higher in the raining/wet periods of the year than in drier periods. The study recommends that intervention programs aimed at reducing malaria and typhoid infections are increased in endemic areas, especially in the wet seasons. Also particular attention should be paid to typhoid fever infection rates in the country.

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