Vol 6, Issue 1, Jan-Feb 2019 ISSN 2349-7041

Original Article

CONCURRENT MALARIA AND TYPHOID FEVER: THE EFFECTS OF DIAGNOSTIC METHODS

ETEFIA, ETEFIA U.*[1] BEN, SOLOMON A.[2]

Medical Laboratory Science, University of Calabar, PMB 1115, Eta Agbo, Calabar[1]. Medical Laboratory Science, University of Calabar, PMB 1115, Eta Agbo, Calabar[2]

***Email:** etefiaetefia15@gmail.com

ABSTRACT

Objective: This paper on the effects of diagnostic methods of concurrent malaria and typhoid was aimed at reviewing scientific data from studies conducted globally on the effects of diagnostic methods of malaria and typhoid fever coinfection.
Method: An electronic search of titles related to malaria, Plasmodium infections, Salmonella infections, typhoid fever using PUBMED and other bibliographic databases was conducted. The abstracts of relevant articles and full articles available online were accessed and references were reviewed to extend the search.
Results: The prevalence of concurrent malaria and typhoid in this review using RDT/Widal test and microscopy/blood or stool culture for malaria/typhoid diagnosis varied significantly. In this review, the prevalence concurrent malaria and typhoid using rapid diagnosis test (RDT) and Widal test was generally higher than that of microscopy and blood or stool culture which are the gold standard for the diagnosis of malaria and typhoid.
Conclusion: In order to address the challenges of concurrent malaria and typhoid misdiagnosis, timely diagnosis of presumptive cases of malaria and typhoid using the gold standard methods, administration of effective treatments, use of insecticide treated mosquito nets, improved personal hygiene, targeted vaccination and health education are recommended.

Keyword: Blood/stool culture; malaria; microscopy; RDT; typhoid; Widal

INTRODUCTION

Malaria is one of the important public health problems in many countries, especially in tropical and sub-tropical areas [1]. It is transmitted by the bites of infected female Anopheles mosquitoes from one person to another [2]. It is a major cause of global morbidity and mortality with an estimate of 3.4 billion people globally at risk of malaria [3]. Among the 1 billion people infected each year; out of which 1-3 million die due to malaria [2].

According to WHO [4], an estimated 219 million cases of malaria occurred worldwide (95% CI: 203–262 million) in 2017 as against 239 million cases (95% CI: 219–285 million) in 2010 with WHO African Region (92%) recording the most cases, followed by the WHO South-East Asia Region (5%) and the WHO Eastern Mediterranean Region (2%).

Fig 1: Map showing the incidence of malaria in the world

Source: WHO [4]

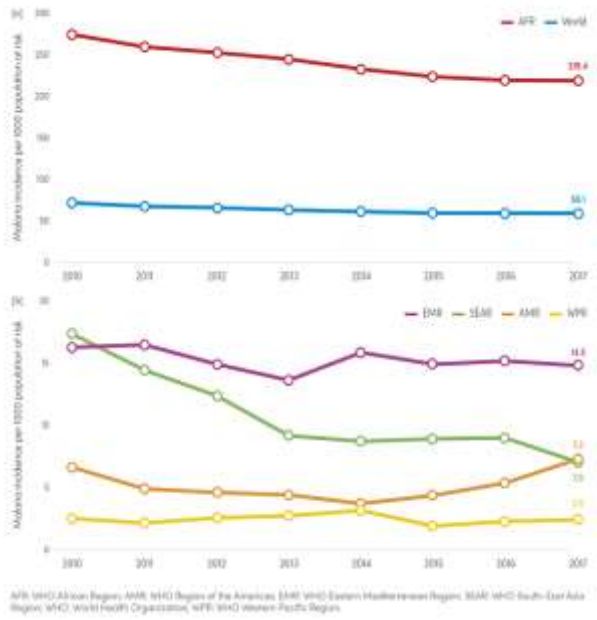

Fig. 2: Trends in malaria case incidence rate (cases per 1000 population at risk), globally and by WHO region, 2010-2017

Source: WHO [4]

Typhoid fever, also known as typhoid is a symptomatic bacterial infection due to *Salmonella typhi* and *Salmonella paratyphi,* and it is common in malaria-affected areas. Several predisposing factors to

this co-infection include dense population and poor hygiene/sanitation practices [5].

Malaria-typhoid co-infection was first described in the Medical Literature in the middle of the 19th century and was named typhoid-malarial fever by the United State Army Doctor Joseph J. Woodward (1833-1884) in 1862. Typhoid-malaria fever was found among young soldiers during the American Civil War who were suffering from a febrile illness that seemed to be typhoid rather than a new species of disease [6].

Malaria and typhoid fever are endemic febrile diseases with overlapping signs and symptoms, notably fever, confused state, jaundice, diarrhoea, vomiting, and headache. There have been reports of malaria co-infection with typhoid fever [7,8]. Co-infections can lead to misdiagnosis usually resulting in either under treatment or over treatment. This predisposes transmission of infection from untreated patient to a new host and further irrational use of antibiotics/antimalarial results in increasing surge of drug resistance [2,9].

Although without laboratory support, it is sometimes difficult to clinically differentiate the presentation of typhoid fever from that of malaria, many clinicians usually request that both tests be performed on individuals presenting with fever of typhoid/malarial signs and symptoms [10]. Coinfection with malaria and typhoid is believed to be common, and therefore, the simultaneous treatment of both infections is quite rampant [11].

The objective of this article is to review scientific data from studies conducted in countries endemic for malaria and typhoid fever on the effects of diagnostic methods of malaria and typhoid fever coinfection.

Method

An electronic search of titles related to malaria, *Plasmodium* infections, *Salmonella* infections, typhoid fever using PUBMED and other bibliographic databases was conducted. The abstracts of relevant articles and full articles available online were accessed, and references were reviewed to extend the search.

Results

The prevalence of concurrent malaria and typhoid in this review using the RDT/Widal test and microscopy/blood or stool culture for malaria/typhoid diagnosis varied significantly. In this review, the prevalence concurrent malaria and typhoid using rapid diagnosis test (RDT) and Widal test was generally higher than that of microscopy and blood or stool culture which are the gold standard for the diagnosis of malaria and typhoid. The prevalence of concurrent malaria and typhoid is presented in Table 1.

Table 1: **Prevalence of concurrent malaria and typhoid.**

Source	Year	Location	% Widal only	% of blood/stool culture only for typhoid	% of RDT only	% of malaria microscopy only	% of Widal with RDT	% of blood/stool culture with microscopy	% of Widal test with microscopy	% of blood culture/stool with RDT
Igiri *et al.* [12]	2018	Nigeria	NA	NA	NA	NA	NA	0 (0/216)	22.7 (49/216)	NA
Dabo *et al.* [13]	2017	Nigeria	44.5 (89/200)	0 (0/200)	17.0 (34/200)	21.0 (42/200)	7.0 (14/200)	0 (0/200)	8.5 (17/200)	NA
Matlani *et al.* [14]	2016	India	NA	NA	NA	NA	0.57 (14/1464)	0.41 (6/1464)	NA	NA
Orok *et al.* [15]	2015	Nigeria	46.8 (117/250)	0.8 (2/250)	NA	80.8 (202/250)	0.8 (2/250)	28.0 (70/250)	NA	NA
Birhanie *et al.* [16]	2014	Ethiopia	19.0 (38/200)	0.5 (1/200)	NA	36.5 (73/200)	6.5 (13/200)	0.5 (1/200)	NA	NA
Verma *et al.* [17]	2014	India	NA	NA	NA	4.5 (36/800)	8.5 (68/800)	1.1 (9/800)	4.5 (36/800)	NA
Sharma *et al.* [18]	2010	India	9.97 (300/3010)	1.99 (60/3010)	4.98 (150/3010)	3.48 (105/3010)	3.49 (105/3010)	1.59 (48/3010)	NA	NA
Ekesiobi *et al.* [19]	2008	Nigeria	57.42 (147/202)	14.84 (38/256)	NA	78.9 (202/256)	NA	14.36 (29/256)	57.42 (147/256)	NA
Mbuh *et al.* [11]	2003	Nigeria	36.7 (80/218)	0.46 (1/218)	NA	27.0 (60/218)	NA	0.46 (1/218)	10.09 (22/218)	NA

NA - Not Available

DISCUSSION

Malaria and typhoid are commonly associated with fever often times referred to as pyrexia of unknown origin (PUO) with high prevalence mostly in malaria and typhoid endemic areas [20]. Though several literatures have discussed factors associated with concurrent malaria and typhoid fever in those areas, the exact mechanisms for this coinfection are still not explained [21].

The prevalence of concurrent malaria and typhoid in this review using a rapid diagnostic test (RDT)/Widal test and microscopy/blood or stool culture for malaria and typhoid diagnosis respectively varied significantly. The prevalence of concurrent malaria and typhoid using RDT and Widal test were generally higher than those of microscopy and blood or stool culture. These were because both microscopy for the diagnosis of malaria and blood or stool culture for the diagnosis of typhoid are highly sensitive and specific, hence, the gold standards for the diagnosis of both malaria and typhoid respectively [22,23].

However, microscopy requires the availability of a well-trained malaria microscopist, which often times is difficult to achieve, especially in primary health facilities and in remote areas where health facilities are limited. Also, the lengthy time is taken for the diagnosis to be carried out, and subsequent result to be produced implies that decisions on treatments may be taken without the results [22,23]. Other diagnostic methods are available, but they are neither suitable for wide field application nor for use in routine disease managements and this include: microscopy using fluorochromes, polymerase chain reaction (PCR) based tests and antibody detection by serology [22].

Although RDTs are faster than microscopy in the diagnosis of malaria, they have are limitations which include: lack of sensitivity at low levels of parasitaemia; inability to quantify parasite density; inability to differentiate between *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae* and *Plasmodium knowlese* as well as between the sexual and asexual stages of the parasite; and persistently positive tests (for some antigens) in spite of parasite clearance following chemotherapy [23–25].

Blood or stool culture for the diagnosis of typhoid is not routinely requested for by most physicians because it is expensive; the final results can be obtained at the earliest, three days after specimen collection; sensitivity varies from 48-78%; and the yield is affected by prior antibiotic intake and stage of illness. Alternative methods such as bone marrow cultures may be required even though the latter method is invasive [26,27].

Koeleman [28] noted that antibodies of typhoid-causing *Salmonella* are known to cross-react with other antigens including those from non-typhoidal *Salmonella* and malaria antigens and the use of Widal test as a diagnostic tool in patients with malaria may lead to misleading results. Cross-reactions can due to latency and post-infectious diseases prevalence in the tropics, namely tuberculosis, pneumonia, amoebiasis, rickettsial diseases, rheumatoid arthritis, and chronic active hepatitis [28]. There appears to be more typhoid fever cases in areas of drug resistant malaria and a cross reaction between malaria parasites and *Salmonella* antigens may cause false positive Widal agglutination test [11,29]. Olopoenia & King [30] also pointed out that false positive Widal agglutination could be due to the patient previously suffering from typhoid fever; previous immunization with *Salmonella* antigen; and variability and poorly standardized commercial antigen preparation. Widal reaction for patients with a clinical suspicion of typhoid and malaria depends on individual host immune responses which become stimulated in febrile conditions associated with malaria fever. This memory response could cause positive Widal reactions in previously sensitized patients and accounts for up to reported prevalence of 35% of false positive Widal tests [11,31].

As a result of the diagnostic challenges associated with malaria and typhoid fever, it is very common to see patients especially in the endemic areas undergoing both typhoid and malarial treatments even when their diagnosis has not been confirmed. Erroneous interpretations of RDTs and Widal test results may lead to misdiagnosis and mismanagement of the patient resulting in morbidity; mortality; unnecessary expenditure and antibiotic side-effects; delayed diagnosis and treatment of malaria and other acute febrile illness; multi-drug resistant strains of the causative agents; and cross-reactions of malarial-typhoid antigens in malaria and typhoid endemic regions [11,31].

CONCLUSION

The prevalence of malaria and typhoid coinfection is high especially in areas where these diseases are endemic. This high prevalence in many cases represents false results due to misdiagnosis in the techniques used in investigating these diseases. In order to address these challenges of concurrent malaria and typhoid misdiagnosis, the following public health measures which could help prevent and control malaria and typhoid infections are recommended: timely diagnosis of presumptive cases of malaria to determine confirmed cases of malaria using the recommended method for malaria microscopy and administration of effective treatments based on WHO recommended antimalarial drugs; use of insecticide-treated mosquito nets as well as indoor spraying of insecticide to reduce human-vector contact; improved personal hygiene; targeted vaccination campaigns; and intensive community health education.

REFERENCES

1. Caraballo, H. (2014). Emergency department management of mosquitoborne illness: Malaria, Dengue, and West Nile Virus. Emergency Medicine Practice, 16: 123.
2. World Health Organization (2013). World Malaria Report 2013 retrieved from https://www.who.int /malaria/ publications/ world_malaria_report_2013/en/ on the 12th December, 2019.
3. Crump, J.A., Ram, P.K., Gupta, S.K., Miller, M.A. and Mintz, E.D. (2010). Global trends in typhoid and paratyphoid Fever. Clin Infect Dis, 50: 241–46. Doi: 10.1086/649541
4. World Health Organization (2018). World Malaria Report 2018 retrieved from https://apps.who.int/iris/bitstream/handle/10665/275867/ 9789241565653-eng.pdf on the 12th December, 2019.
5. Wain, J., Hendriksen, R.S., Mikoleti, M.L., Keddy, K.H. and Ochiai, R.L. (2015). Typhoid fever. Lancet, 385 (9973): 1136–45. Doi: 10.1016/S0140-6736(13)62708-7
6. Bynum, B. (2002). Typhomalaria. Lancet, 360 (9342): 1339.
7. Ammah, A., Nkuo-Akenji, I., Ndip, R. and Deas, J.E. (1999). An Update on concurrent malaria and typhoid fever in Cameroon. Trans R Soc Trop Med Hyg, 93 (2): 127–29.
8. Gopinath, R., Keystone, J.S. and Kain, K.C. (1995). Concurrent falciparum malaria and Salmonella bacteraemia in travelers; report of two cases. Clinical Infectious Diseases, 20 (3): 706–8. PMID: 18330069
9. Leslie, T., Mikhail, A., Mayan, I., Anwarfield, M., Bakhtashfield, S., Nader, M., Chandler, C., Whitty, C.J.M. and Rowland, M. (2012). Overdiagnosis and mistreatment of malaria among febrile patients at primary healthcare level in Afghanistan: observational study. BMJ, 345: e4389. Doi: https://doi.org/10.1136
10. Rooth, I. and Bjorkman, A. (1992). Fever episodes in a holoendemic malaria area of Tanzania: Parasitological and clinical findings and diagnostics aspects related to malaria. Trans R Soc Trop Med Hyg, 86 (5): 479–82.
11. Mbuh, F.A., Gialadima, M. and Ogbadu, L. (2003). Rate of co-infection with malaria parasites and Salmonella typhi in Zaria, Kaduna State. Annals of African Medicine, 2 (2): 64–7.
12. Igiri, B.E., Ejezie, G.C., Inyang-Etoh, P.C. and Jimoh, O. (2018). Incidence of malaria and salmonellosis co-infection in Ahmadu Bello University Teaching Hospital, Zaria, North-West Nigeria, ClinSci Res Rep, 1 (2): 1–5. Doi: 10.15761/CSRR.1000109
13. Dabo, N.T., Sarkinfada, F. andTijjani, N.Z. (2017). Diagnosis of malaria and typhoid fevers using basic tools: a comparative analysis of a retrospective data with a prospective evaluation in an endemic setting. Bayero Journal of Pure and Applied Sciences, 10 (1): 448–54. Doi: http://dx.doi.org/10.4314/bajopas.v10i1.87S
14. Matlani, M., Sharma, B. and Gaind, R. (2016). Malaria and Typhoid Coinfection: Need to Interpret Serological Results Cautiously. Journal of Clinical and Diagnostic Research, 10(2): DL01. Doi: 10.7860/JCDR/2016/17144.7257
15. Orok, D.A., Usang, A.I., Ikpan, O.O., Duke, E.E., Eyo, E.E., Edadi, U.E., Ati, B.U. and Udida, J.A. (2016). Prevalence of Malaria and Typhoid Fever Co-infection among Febrile Patients Attending College of Health Technology Medical Centre in Calabar, Cross River State, Nigeria. Int. J. Curr Microbiol App Sci, 5 (4): 825–35. Doi: http://dx.doi.org/10.20546/ijcmas.2016.504.095
16. Birhanie, M., Tessema, B., Ferede, G. and Enawgaw, B. (2014). Malaria, typhoid fever, and their coinfection among febrile patients at a rural health center in Northwest Ethiopia. Advances in Medicine, 8 (531074): 1–8. Doi: http://dx.doi.org/10.1155/2014/531074
17. Verma, D., Kishore, S. and Siddique, M.E. (2014). Comparative evaluation of various tests for diagnosis of concurrent malaria and typhoid fever in a tertiary care hospital of Northern India. JCDR, 8 (5): DC41–DC4. Doi: 10.7860/JCDR/2014/7745.440
18. Sharma, B., Matlani, M., Gaind, R. and Pandey, K. (2016). Malaria and typhoid co-infection in India: a diagnostic Difficulty. Journal of Dental and Medical Sciences, 15 (9): 101–04. Doi: 10.9790/0853150911101104
19. Ekesiobi, A.O., Igbodika, M.C. and Njoku, O.O. (2008). Co-infection of malaria and typhoid fever in a tropical community. Animal Research International, 5 (3): 888–91. Doi: http://dx.doi.org/10.4314/ari.v5i3.48754
20. Uneke, C.J. (2008). Concurrent malaria and typhoid fever in the tropics: the diagnostic challenges and public health implications. J Vector Borne Dis, 45 (2): 133–42.
21. Keong, B.C.M. and Sulaiman, W. (2006). Typhoid and malaria coinfection–an interesting finding in the investigation of a tropical fever. Malaysian J Med Sci, 13 (2): 64–5.

22. World Health Organization (2000). Malaria diagnosis new perspectives: report of a joint WHO/USAID informal consultation.
23. Payne, D. (1998). Use and limitations of light microscopy for diagnosing malaria at the primary health care level. Bulletin World Health Organization, 66 (5): 621–26.
24. Moody, A. (2002). Rapid diagnostic tests for malaria parasites. Clin Microbiol Rev, 15(1): 66–78. Doi: 10.1128/CMR.15.1.66-78.2002
25. World Health Organization (1997). World malaria situation in 1994. WHO Weekly Epidemiol Rec, 72 (38): 285–92.
26. Pang, T. and Puthucheary, S.D. (1983). Significance and value of the Widal test in the diagnosis of typhoid fever in an endemic area. J Clin Palhol, 36 (4): 471–75.
27. Gilman, R.H., Terminel, M., Levine, M.M. and Hornick, R.B. (1975). Relative efficacy of blood, urine, rectal swab, bone-marrow and rose spot cultures for recovery of Salmonella typhi in typhoid fever. Lancet, 305 (7918): 1211–213. Doi: https://doi.org/10.1016/S0140-6736(75)92194-7
28. Koeleman, J.G. (1992). Retrospective study to determine the diagnostic value of Widal test in nonendemic country. Eur J Clin. Microbiol Infect Dis, 11(2): 167–70.
29. Jhaveri, K.N., Nandwani, S.K., Mehta, P.K., Surati, R.R. and Parmar, B.D. (1995). False positive modified Widal test in acute malaria. J Assoc Physicians India, 43 (11): 754–55.
30. Olopoenia, L.A. and King, A.L. (2000). Widal agglutination test-100 years later: still plagued by controversy. Postgrad. Med J, 76 (892): 80–4. Doi: 10.1136/pmj.76.892.80
31. Petit, P.L. and Wamola, I.A. (1994). Typhoid fever: a review of its impact and diagnostic problems. East African Med J, 71(3): 183–88.