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Concurrent malaria and typhoid fever in the tropics: the diagnostic challenges and public health implications

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Abstract

Background & objectives: Malaria and typhoid fever still remain diseases of major public health importance in the tropics. Individuals in areas endemic for both the diseases are at substantial risk of contracting both these diseases, either concurrently or an acute infection superimposed on a chronic one. The objective of this report was to systematically review scientific data from studies conducted in the tropics on concurrent malaria and typhoid fever within the last two decades (1987–2007), to highlight the diagnostic challenges and the public health implications.

Methods: Using the MedLine Entrez-PubMed search, relevant publications were identified for the review via the key words *Malaria* and *Typhoid fever*, which yielded 287 entries as of January 2008.

Results: Most of the studies reviewed expressed concern that poor diagnosis continues to hinder effective control of concurrent malaria and typhoid fever in the tropics due to: non-specific clinical presentation of the diseases; high prevalence of asymptomatic infections; lack of resources and insufficient access to trained health care providers and facilities; and widespread practice of self-treatment for clinically suspected malaria or typhoid fever.

Interpretation & conclusion: There were considerably higher rates of concurrent malaria and typhoid fever by Widal test compared to the bacteriological culture technique. Although culture technique remains the gold standard in typhoid fever diagnosis, Widal test is still of significant diagnostic value provided judicious interpretation of the test is made against a background of pertinent information. Malaria could be controlled through interventions to minimize human-vector contact, while improved personal hygiene, targeted vaccination campaigns and intensive community health education could help to control typhoid fever in the tropics.

Key words Coinfection – concurrent – diagnosis – malaria – public health – tropics – typhoid fever

Introduction

Malaria and typhoid fever are among the most endemic diseases in the tropics. Both diseases have been associated with poverty and underdevelopment with significant morbidity and mortality. An association between malaria and typhoid fever was first described in the medical literature in the middle of the 19th century, and was named typhomalarial fever by the United States Army[1]. However, by the end of 19th century, laboratory tests had eliminated this theory as they found that it was either one thing or the other, or in rare instances, co-infection with both *Salmonella typhi* and the *Plasmodium* species[1]. In the last two decades, this relationship between the two diseases has been substantiated by studies from Africa and India[2–6].

Malaria remains the most complex and overwhelming health problem, facing humanity in vast majority of tropical and sub-tropical regions of the world, with 300 to 500 million cases and 2 to 3 million deaths per year[7]. About 90% of all malaria deaths in the world today occur in the sub-Saharan Africa and this is because majority of infections are caused by *Plasmodium falciparum,* the most dangerous of the four human malaria parasites (*P. falciparum, P. ovale, P. vivax, P. malariae*), accounting for an estimated 1.4 to 2.6 million deaths per year in this region[8,9]. In addition, the most effective malaria vector, *Anopheles gambiae* is the most wide spread in the region and the most difficult to control[9]. In areas where malaria is highly endemic, a protective semi-immunity against *P. falciparum* is acquired during the first 10–15 years of life, and the majority of malaria-related morbidity and mortality happen in young children[10].

On the other hand, typhoid fever is widely recognized as a major public health problem in most developing tropical countries. It is a systemic infectious disease characterized by an acute illness, the first typical manifestations of which are fever, headache, abdominal pain, relative bradycardia, splenomegaly, and leukopenia[11,12]. The etiological agent of typhoid fever is *Salmonella enterica* sub-sp *enterica* serotype Typhi. Typhoid fever is an important cause of morbidity in many regions of the world, with an estimated 12 to 33 million cases occurring annually[13]. Cases are more likely to be seen in areas like India, South and Central America, and Africa with rapid population growth, increased urbanization, and limited safe water, infrastructure, and health systems. It is estimated that there are more than 13 million cases occurring annually in Asia alone of which a large proportion occur during childhood[14], and in the wake of emerging multidrug-resistant strains of bacteria causing typhoid fever, the disorder is known to be associated with significant morbidity and mortality[15,16]. Human beings are the only reservoir and host for typhoid fever and is transmitted by faecally contaminated water and food in endemic areas especially by carriers handling food[11]. The disease has important socioeconomic impact because, most of the time, several months are necessary for a patient to recover and be able to work again.

Although typhoid and malaria are caused by very different organisms—one a gram negative bacilli, the other a protozoan, and transmitted via different mechanisms, both diseases share rather similar symptomatology. However, the precise incidence of the concurrent malaria and typhoid fever in most geographical areas is largely uncertain. Because both typhoid and malaria share social circumstances which are imperative to their transmission, individuals in areas endemic for both diseases are at substantial risk of contracting both these diseases, either concurrently or an acute infection superimposed on a chronic one[17]. While high prevalence of malaria is an established fact, it is only within the last decade that an unusually high number of illnesses have been diagnosed as malaria co-existing with typhoid fever[2–6]. Malaria and typhoid fever often present with mimicking symptoms especially in the early stages of typhoid fever[2,3]. The situation often presents a diagnostic problem and in some cases could lead to diagnostic confusion. As a result of this, the importance of definitive laboratory-based diagnosis cannot be overstated. Before an individual is said to have concurrent malaria and typhoid fever, the presence of *Plasmodium* species and *Salmonella enterica* sub-sp *enterica* serotype Typhi must be demonstrated in the patient's laboratory specimens.

Conventional light microscopy is the established method for the laboratory confirmation of malaria and is the most commonly used method for malaria diagnosis in the tropics. The careful examination by an expert microscopist of a well-prepared and well stained blood film remains currently the "gold standard" for detecting and identifying malaria parasites[18]. In most settings, the procedure consists of: collecting a finger-prick blood sample; preparing a

thick blood smear (in some settings a thin smear is also prepared); staining the smear (most frequently with Giemsa); and examining the smear through a microscope (preferably with a 100x oil immersion objective) for the presence of malaria parasites[19]. Microscopy offers many advantages. It is sensitive, informative, relatively inexpensive, is a general diagnostic technique that can be shared with other disease control programmes, and can provide a permanent record (the smears) of the diagnostic findings and be subject to quality control[18].

The definitive diagnosis of typhoid fever requires the isolation of *Salmonella enterica* serotype Typhi from the patient. Cultures of blood, stool, urine, rose spots, blood mononuclear cell-platelet fraction, bone marrow, and gastric and intestinal secretions can all be useful for diagnosis[11]. However, this requires laboratory equipment and technical training that are beyond the means of most primary health care facilities in the developing world. Consequently, Widal test is the only specific diagnostic investigation available in most tropical regions. The Widal test which is readily available and inexpensive was introduced as a serologic technique to aid in diagnosis of typhoid fever and has been used for more than a century. The test was based on demonstrating the presence of agglutinin (antibody) in the serum of an infected patient, against the H (flagellar) and O (somatic) antigens of *Salmonella typhi*. The role of the Widal test had been to increase the index of suspicion for the presence of typhoid fever by demonstrating a positive agglutination during the acute and convalescent period of infection with evidence of a four-fold rise of antibody titre[20]. The Widal test reaction involves the use of bacterial suspensions of *S. typhi* and *S. paratyphi* 'A' and 'B', treated to retain only the 'O' and 'H' antigens. These antigens are employed to detect corresponding antibodies in the serum of a patient suspected of having typhoid fever. The IgM somatic O antibody appears first and represents the initial serologic response in acute typhoid fever, while the IgG flagella H antibody usually develops more slowly but persists for longer[11,20]. Two types of agglutination techniques are available: the slide test and the tube test.

In most parts of the tropics, the specific diagnosis of concurrent malaria and typhoid fever is based on blood smear microscopy and Widal test and in rare cases with the inclusion of bacterial culture. However, it is of concern that poor diagnosis continues to hinder effective malaria and typhoid control in the tropics. This is due to a combination of factors, including non-specific clinical presentation of the diseases, high prevalence of asymptomatic infections in many areas, lack of resources and insufficient access to trained health care providers and health facilities, and widespread practice of self-treatment for clinically suspected malaria or typhoid fever.

Despite the importance of concurrent malaria and typhoid fever in the tropics, the challenges associated with the diagnosis and the public health implications have not been comprehensively reviewed. The objective of this report was to systematically review scientific data from studies conducted in the tropics that provided information on malaria and typhoid fever coinfection. The implications of findings from these studies and their association with the risk, management, and treatment of the concurrent infection, public health policy, and operational research needs in the endemic areas of the tropics are discussed.

Material & Methods

This systematic review was designed to address the following key questions: (a) What are the challenges associated with the diagnosis of concurrent malaria and typhoid fever in the tropics?; (b) What are the limitations of the present conventional diagnostic techniques and tools employed in the diagnosis of malaria and typhoid fever in the tropics?; (c) What are the public health implications of misdiagnosis (under-diagnosis or over-diagnosis) of concurrent malaria and typhoid fever in the tropics?; and (d) What

Table 1. Summary of studies reporting concurrent malaria and typhoid fever in the tropics

Authors (Ref)	Year of publication	Type of study	Study location	Number/Patient category	Prevalence of coinfection/ Typhoid fever laboratory test
Mabey *et al* (30)	1987	Case control	Gambia	NA	11%; Bacterial culture
Onuigbo (27)	1990	Case study	Enugu Nigeria	15 with fever	70%; Widal test (>1:80 for O antigens)
Samal & Sahu (24)	1991	Case study	Burla India	52 with malaria	15.4%; Widal test (>1:80 for O antigens)
Jhaveri *et al* (22)	1995	Case control	Surat India	90 with malaria	14.58%; Widal test (>1:80 for O antigens)
Olopoenia *et al* (23)	1996	Case control	Lagos Nigeria	45 with malaria	12%; Widal test (≥1:80 for O antigens)
Ammah *et al* (2)	1999	Case control	Beau Cameroon	200 with fever	17%; Bacterial culture
					47.9%; Widal test (≥1:80 for O antigens)
Tanyigna *et al* (26)	2001	Case control	Jos Nigeria	23 with malaria	4.4%; Widal test (>1:80 for O antigens)
Ohanu *et al* (3)	2003	Case control	Enugu Nigeria	270 with fever	26.6%; Bacterial culture
Mbuh *et al* (21)	2003	Case control	Zaria Nigeria	218 with malaria	0.5%; Bacterial culture
					10.1%; Widal test (≥1:160 for O antigens)
Smith *et al* (31)	2004	Case control	Lagos Nigeria	50 with fever	18%; Bacterial culture
Ibadin & Ogbimi (25)	2004	Case control	Benin City Nigeria	189 with malaria	27.5%; Widal test (≥1:80 for O antigens)
Khan *et al* (29)	2005	Case control	Karachi Pakistan	1891 with malaria	1.11%; Bacterial culture
Akinyemi *et al* (28)	2007	Case control	Lagos Nigeria	107 with malaria	14.95%; Bacterial culture

NA: Information not accessible.

are the appropriate public health measures required to address concurrent malaria and typhoid fever in the tropics? A Medline Entrez-PubMed search was performed and studies conducted in the tropics on concurrent malaria and typhoid in the last two decades (1987–2007) and reported in English were identified. Combinations of key words such as *Malaria* and *Typhoid fever* were used for the search which yielded 287 entries as of January 2008. Selected publications obtained from Google search using the key words *Malaria*, *Typhoid fever, Coinfection* and *Tropics* relevant to the topic were also identified and used as additional literature for the review. Bibliographies of all publications obtained were checked for additional relevant references and were obtained and included in the review. Particular attention was paid to articles providing information on the diagnosis of concurrent malaria and typhoid fever. The various reports were systematically reviewed with respect to the method of sample collection/analysis, location, population, the period, setting, and the type of study to enhance comparison between studies.

Results

In all thirteen studies, which provided sufficient information on concurrent malaria and typhoid fever to enable meaningful and reasonable comparisons, were identified and reviewed. These 13 studies fulfilled the following inclusion criteria: (i) Study conducted between 1987 and 2007; (ii) Study conducted in tropical countries endemic for malaria and typhoid fever; (iii) Study design is case-control investigation; (iv) Both malaria and typhoid fever screening conducted on the study population; and (v) Laboratory diagnosis of malaria using blood smear microscopy and typhoid fever using either Widal test or bacterial culture or both. The summary of findings is presented in Table 1. All the 13 studies reviewed were case-control investigations and made use of thick and thin blood smear microscopy for laboratory diagnosis of malaria. Two studies used both Widal and bacteriological culture techniques[2,21], five studies used only

the bacteriological culture techniques, while the remaining six studies used only the Widal technique (Table 1). Eight of the studies were conducted in Nigeria, two from India, one each from Cameroon, Gambia and Pakistan.

The prevalence of malaria and typhoid coinfection using only the Widal technique ranged from 4.4% to 70%[22–27], on the other hand, the prevalence of concurrent malaria and typhoid fever using only the bacteriological culture technique ranged from 1.11% to 26.6%[3,28–31]. The two studies that used both Widal and bacteriological culture techniques reported considerably higher rates of coinfection with Widal test as compared with the bacteriological culture technique, in Nigeria (10.1% *vs* 0.5%)[21] and in Cameroon (47.9% *vs* 17%)[2] (Table 1).

Because the knowledge about baseline titres of O and H antibodies in a population is necessary for accurate interpretation of results of the Widal test, the eight studies that employed the Widal technique reported the local cut-off titer values denoting a positive Widal test. Although there was no consensus on the diagnostic titer for a single Widal test, all the studies reported a "positive" Widal test based on a fourfold rise in O agglutinins in repeated tests or a titer of 1:80 or greater in a single test (Table 1).

Discussion

Malaria and typhoid fever still remain diseases of major public health importance in the tropics. Both malaria and typhoid fever are major aetiological considerations in both acute and prolonged fever of unknown origin (PUO) in the tropics. Because of the high prevalence of typhoid fever and malaria in the tropics, co-infections are common. However, the actual and precise underlying mechanisms to explain the association between malaria and *Salmonella* species infection is still uncertain, although there are few postulations which may explain why malaria may predispose to salmonella bacteremia and sepsis[17]. It has been shown that antibody response to O antigen of *S. typhi* was markedly reduced in acute episode of malaria compared with that in controls where humoral immunity is transiently impaired[32]. It has been demonstrated in a murine model of infection with *Salmonella murium* that haemolysis which occur in malaria may predispose to gram-negative organism as what has been seen in haemolytic disease caused by sickle-cell disease and bartonellosis[33].

Although the signs and symptoms of malaria and typhoid fever do overlap, it was observed in Pakistan that subjects with dual infection had significantly higher rates of nausea, vomiting, abdominal pain, and diarrhoea, all common presenting features of enteric fever[29]. Furthermore, it was noted that unlike the intermittent fever pattern generally seen with malaria, patients with dual infection tended to exhibit a continuous fever more typical of enteric fever[29]. This latter pattern, as well as the delayed resolution of fever (>24 hours) after starting antimalarial treatment have clinical implication as it should raise the clinical suspicion of dual infection in areas endemic for the two diseases. However, it is imperative that definitive diagnosis be made to confirm the presence of coinfection by the demonstration of the presence of *Plasmodium* sp and *Salmonella enterica* sub-sp *enterica* serotype Typhi in the patient's laboratory specimens. This can most often be problematic particularly in local settings of the tropics.

Concerning malaria diagnosis, it is pertinent to state that two malaria diagnostic approaches currently used most often, do not allow a satisfactory diagnosis of malaria. Clinical diagnosis, the most widely used approach, is unreliable because the symptoms of malaria are very non-specific. Microscopic diagnosis, the established method for laboratory confirmation of malaria, presents technical and personnel requirements that often cannot be met, particularly in facilities at the periphery of the health care system. In addition, delays in the provision of the microscopy results to the clinician mean that decisions on treat-

ment may be taken without the benefit of the results[18,19]. The rapid diagnostic tests (RDTs) for malaria which use immunochromatographic methods to detect *Plasmodium*-specific antigens in a finger prick blood sample, can be performed in approximately 15 min by individuals with minimal training, using test kits (available from several manufacturers) that require no electricity and no special equipment[19]. Compared to microscopy, the main disadvantages of currently available RDTs are: lack of sensitivity at low levels of parasitaemia; inability to quantify parasite density; inability to differentiate between *P. vivax*, *P. ovale* and *P. malariae*, as well as between the sexual and asexual stages of the parasite; persistently positive tests (for some antigens) in spite of parasite clearance following chemotherapy; and relatively high cost per test[18,19,34]. Other diagnostic methods are available, but they are neither suitable for wide field application nor for use in routine disease management and this include; microscopy using fluorochromes, polymerase chain reaction (PCR) based tests and antibody detection by serology[18].

Unlike the diagnosis of malaria, typhoid fever presents a greater diagnostic challenge. Typhoid fever diagnosis is still based on clinical presentation and on diagnostic tests that are associated with numerous limitations. Blood culture, which is the gold standard for diagnosis of typhoid fever, is not routinely requested by most physicians because it is expensive and final results can be obtained at the earliest, three days after specimen collection[12]. Although this test is highly specific, sensitivity varies from 48–78%[35] and the yield is affected by prior antibiotic intake and stage of illness and alternative methods such as bone marrow cultures may be required even though this latter method is invasive[36]. The Widal test is inexpensive and readily available in most health care settings in the tropics, but serious doubts have been raised regarding its validity. It is now regarded as inaccurate, non-specific, poorly standardized, confusing and of limited diagnostic value[37–40]. Cross-reactions can occur as a consequence of latent and post-infectious diseases prevalent in the tropics namely tuberculosis, pneumonia, amoebiasis, rickettsial diseases, rheumatoid arthritis and chronic active hepatitis[38]. In addition, the test has to be interpreted against a baseline titer in the same geographical area since titers of diagnostic significance differ in endemic and non-endemic areas[39].

As a result of the diagnostic challenge associated with malaria and typhoid fever, it is very common to see patients in many parts of the tropics, undergoing both typhoid and malarial treatment even if their diagnosis has not been confirmed[21]. There appears to be more typhoid fever cases in areas of drug resistant malaria and a cross-reaction between malarial parasites and salmonella antigens may cause false positive Widal agglutination test[21,22]. It seems that the outcome of the 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 35% of false positive Widal test which have been reported[21,41]. This can be accounted for by the demonstrated high prevalence of Salmonella antibodies in local healthy population and the fact that 50% of the patients had detectable levels of antibodies to the somatic antigen[21,23,27].

It is interesting to note that an association between non-typhoidal salmonellosis and/or typhoidal salmonellosis and malaria was reported in the studies reviewed. The predominance of typhoidal salmonellosis over non-typhoidal salmonellosis as cause of salmonella bacteraemia was demonstrated in a study of dual malaria-salmonella infection in Karachi, Pakistan, in which 21 of 22 positive blood cultures for salmonellae grew *S. typhi* (16/21) or *S. paratyphi* A or B (5/21) (one patient with *S. enteritidis* was excluded from analysis)[29]. In Lagos, Nigeria,16 *Salmonella* spp made up of seven each of *S. typhi* and *S. enteritidis*, and two of *S. paratyphi* were isolated with

Plasmodium spp from patients with complications[28]. Two other studies in Nigeria that employed bacterial culture identified only typhoidal salmonellosis as responsible for the typhoid fever in coinfected cases[3,31]. In contrast, the non-typhoidal salmonellosis predominated in the reports from Cameroon and Gambia. In the study of 200 febrile patients in Cameroon, Ammah *et al*[2] reported a 32.5% incidence of microbiologically-proven concurrent infection with malaria and *S. typhimurium* (diagnosed via blood and/or stool positive for salmonellae) compared with *S. typhi* (17%) and *S. paratyphi* (2%) ($p < 0.05$). In Gambia, malarial infection was present in 11% of patients with *S. typhi* septicaemia and 42% of patients with non-typhoidal salmonellae[30]. The implication of the high rate of the non-typhoidal Salmonella infection is increase in the rate of false positive Widal test results, due to the presence of cross-reacting antigens[42,43].

Because typhoidal Salmonella antibodies are known to cross-react with other antigens including those from non-typhoidal Salmonella and malaria antigens, the use of Widal test as diagnostic tool in patients with malaria may lead to misleading results as demonstrated by some studies from Nigeria. Although, in Benin City, Nigeria, Widal agglutination reaction at >1.80 were significantly more in malaria patients (27.5%) than in controls (16%) ($p < 0.05$) and also significantly higher in controls with malaria parasitaemia (27.8%) than those without parasitaemia (12.9%) ($p < 0.02$)[25], a correlation analysis in a similar study in Zaria, Nigeria, showed that the presence of malaria parasites had no specific relationship with *S. typhi* O and H antibody levels in malaria patients and carriers of malaria parasites using Widal test[21]. Furthermore, in another study in Enugu, Nigeria, there was no statistical significant difference ($p > 0.05$) between Widal titres of malaria and culture-proven typhoid cases, and the study indicated that using Widal test alone, one cannot differentiate typhoid fever from malaria[3]. In yet another study in Lagos, Nigeria, which investigated Widal agglutinin in malaria-infected individuals, it was found that 85% of patients with a negative *S. typhi* culture but positive malaria smear had Widal titers of 1:40, 12% had titers of 1:80, and 3% had titers of 1:160; in contrast, 45% of patients with both *S. typhi* cultures and malaria smears negative had Widal titers of 1:40, 15% had titers of 1:80, and 10% had titers of 1:160[23]. The study noted that the presence of Widal agglutinin under conditions of positive malaria smear, negative *S. typhi* culture and negative prior typhoid immunization would suggest that malaria parasite may have some undefined antigenic determinants similar to *S. typhi* which can induce antibody production and could explain the febrile condition seen in some of the patients. Furthermore, the presence of Widal agglutinin under conditions of negative malaria smear, negative *S. typhi* culture and negative prior immunisation against typhoid fever suggests that other infectious agents, in addition to Salmonella and malaria parasite, may also share common antigenic determinants with *S. typhi.* Hence, malaria could interfere with diagnosis of typhoid fever using Widal test and thereby lead to over diagnosis of typhoid fever.

The interpretation of Widal test results, when diagnosing concurrent malaria and typhoid fever must therefore be done with a lot of caution. This is because negative or positive Widal agglutination test is neither definitive nor completely informative. Apart from the influence of the results by malaria, Olopoenia and King[20], have identified the following as causes of a positive Widal agglutination test; the patient being tested has typhoid fever, previous immunisation with Salmonella antigen, cross-reaction with non-typhoidal Salmonella, variability and poorly standardized commercial antigen preparation, infection with other enterobacteriaceae and other diseases such as dengue. Also identified are the following as causes of a negative Widal agglutination test; absence of infection by *S. typhi,* the carrier state, an inadequate inoculum of bacterial, antigen in the host to induce antibody production, technical diffi-

culty or errors in the performance of the test, previous antibiotic treatment, and variability in the preparation of commercial antigens. In fact, Ammah *et al*[2] concluded from their study that the number of fever cases diagnosed as malaria co-existing with typhoid fever is actually overestimated. It is important therefore to state that erroneous interpretation of the test result may lead to misdiagnosis and mismanagement of the patient, resulting in major morbidity and mortality. This is because misdiagnosis of typhoid fever leads to unnecessary expenditure and exposure of patients to the side-effects of antibiotics. In addition, misdiagnosis may result in delayed diagnosis and treatment of malaria, and other acute febrile illness[44].

As a public health measure, patients with malaria who have marked gastrointestinal symptoms, continuous pattern of fever and persistence of fever for more than 24 h after appropriate antimalarial therapy, should be investigated or empirically treated for concurrent enteric fever. The absence of the above clinical features in patients with uncomplicated malaria should reassure physicians that there is no concurrent typhoid fever[29]. Although the Widal test is far from being a perfect diagnostic tool, in endemic areas, the Widal test is still of significant diagnostic value provided judicious interpretation of the test is made against a background of pertinent information, especially data which relate to agglutinin levels in normal individuals and in non-typhoidal fevers common in the region[45]. A single Widal test has even being pointed out to be of diagnostic value in the early stage of disease and thus help in reducing morbidity and mortality from typhoid[42,45].

Malaria control is too complex to be addressed by a single approach, and any attempt to do so is fraught with danger. It is important to tailor control and preventive strategy to the prevailing ecological and epidemiological conditions. The strategy of mortality control involves detecting presumptive cases, determining which cases are parasite positive, and administering effective treatment. Focal interventions to minimize human-vector contact can be effected by the use of insecticide-treated mosquito nets as well as indoor spraying of insecticide[7]. On the other hand, improved personal hygiene, targeted vaccination campaigns and intensive community health education have been identified as public health measures that could help to prevent and control typhoid[5]. The financial and human resource constraints of health systems in the tropics most affected by malaria and typhoid fever, and the shared determinants of vulnerability for both diseases, indicate the need for integration of preventive and curative services for malaria and typhoid fever and strengthening the health systems that deliver these services. Delivery of malaria and typhoid fever interventions within existing health services may permit effective utilization of human resources and address serious resource constraints. The challenge is to ensure coherence at each level of the health system, and to maximize the use of available resources for integrated service delivery.

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