Original article

Clinical overlap between malaria and pneumonia: can malaria rapid diagnostic test play a role?

Kingsley N. Ukwaja, Olufemi B. Aina, Ademola A. Talabi

Comprehensive Health Centre, Oke-Ilewo, Abeokuta, Ogun state, Nigeria

Abstract
Introduction: Malaria and pneumonia account for 40% of mortality among children under five years of age in sub-Saharan Africa. Due to lack of diagnostic facilities, their management is based on the integrated management of childhood illnesses (IMCI) strategy. Symptoms of malaria and pneumonia overlap in African children, necessitating dual IMCI classifications at health centres and treatment with both antibiotics and antimalarials. This study determined the prevalence of malaria-pneumonia symptom overlap and confirmed the diagnosis of malaria in these cases using a rapid diagnostic test.
Methodology: Consecutive consultations of 1,216 children (two months to five years old) were documented over a three-month period in a comprehensive health centre. Malaria rapid diagnostic tests were conducted only for children who had symptom overlap.
Results: Of the 1,216 children enrolled, 1,090 (90%) reported cough or fever. Among the children fulfilling the malaria case definition, 284 (30%) also met the pneumonia case definition. Twenty-three percent (284) of all children enrolled met the criteria for both malaria and pneumonia. However, only 130 (46%) of them had a positive result for malaria using a malaria rapid diagnostic test. During a malaria-pneumonia overlap, female children (chi-square 5.9, P = 0.01) and children ≥ one year (chi-square 4.8, P = 0.003) were more likely to seek care within two days of fever.
Conclusion: Dual treatment with antimalarials and antibiotics in children with malaria-pneumonia overlap may result in unnecessary over-prescription of antimalarial medications. Use of rapid diagnostic tests in their management can potentially avoid over-prescribing of malaria medications.

Key words: malaria-pneumonia; overlap; rapid diagnostic tests; Nigeria

Introduction

Globally, pneumonia and malaria respectively account for 19% and 8% of annual childhood deaths, and in sub-Saharan Africa both diseases contribute to almost 40% of the mortality in the age group younger than five years [1]. In Nigeria, over six million new cases of pneumonia are estimated annually and childhood fevers presumed to be malaria account for 30% of all childhood deaths [2,3]. In developing countries, due to weak health systems and lack of laboratory diagnostic tools, the management of childhood illnesses is presumptive and symptom-based, using the World Health Organization (WHO)/UNICEF Integrated Management of Childhood Illnesses (IMCI) algorithm [4]. In these guidelines, "malaria" is defined as presence or history of fever, a symptom which also occur in children with pneumonia. Also, "pneumonia" includes history of cough or difficulty in breathing in the presence of increased respiratory rate according

to age, symptoms that may also indicate malaria. Children who are brought to health centres with malaria-pneumonia symptom overlap are given dual IMCI classifications and are treated with both antimalarials and antibiotics [4,5]. The extent of this overlap has been documented in various settings in Eastern Africa [5,6], but not in routine IMCI practice at the health centre level in Nigeria.

Recently, most countries in sub-Saharan Africa have now adopted artemisinin based combination therapy (ACT) as the first-line antimalarial agent for uncomplicated malaria [7]. Due to its costs and in order to avoid over-prescription of ACT, new guidelines from the WHO recommend that a laboratory test should be performed before treatment [8]. The widespread introduction of rapid diagnostic tests (RDTs) for malaria allows diagnosis to be made even in health settings lacking any laboratory facility. RDTs generally cost less and two meta-analyses have shown that their performance is comparable to that of

expert microscopy [9,10]. The availability of RDTs has led to definitive diagnosis being considered as a strategy to target the use of ACTs, especially in the treatment of childhood fevers – the group with the highest mortality risk [11]. However, the paradox is that the WHO's RDT-based policy is usually restricted to adults and older children, while for under-fives presumptive malaria treatment is still recommended [8].

In 2003, a WHO Consultative Meeting on the management of acute respiratory infections (ARI) recommended that studies to improve the specificity of clinical overlap for malaria and pneumonia diagnosis should be undertaken, and rapid diagnostic tests for malaria should be studied to differentiate malaria from pneumonia [12]. Surprisingly, no study has examined the prevalence of laboratory-confirmed malaria among children with malaria-pneumonia overlap despite its implications for symptom overlap management strategies. Our objectives were to determine the frequency with which children meeting the malaria case definition also met the pneumonia case definition at the health centre level, the prevalence of malaria-pneumonia symptom overlap, and the proportion of children with these overlapping symptoms who truly require antimalarial treatment.

Methodology

The study was performed in the Comprehensive Health Centre Oke-Ilewo, (Abeokuta-South local government area) Ogun state, south-western Nigeria, from August to October 2009. The health centre serves an area of coastal Nigeria with perennial malaria transmission and its out-patients' clinic is attended by approximately 15,000 children a year. During the study period, a total of 1,216 consecutive consultations with children aged two months to five years were documented. After obtaining informed consent, mothers of all eligible children were interviewed and the children examined by a study clinician. Capillary blood was obtained from enrolled children who had malaria-pneumonia overlap and the rapid diagnostic test (Paracheck Pf, Orchid Biomedical Systems, Goa, India) performed for malaria parasitaemia. All results were recorded on IMCI recording forms [4]. The data was double-entered in Epi Info 3.4.1 by two trained technicians. Categorical variables were summarized using percentiles. Group comparisons were made using Chi-square, and a P value of ≤ 0.05 was considered to be statistically significant. Age (≤ 1 year versus > one

year), gender, and presence of symptom overlap were used as primary stratifying variables.

The IMCI case definition for malaria was a child with fever or whose mother reported a recent history of fever. The pneumonia case definition was a history of cough or difficult breathing along with clinician counting of respiratory rates above the IMCI cut-offs. A rate of 40/minute for children 12 months to 5 years and above 50/minute for children 2 months to 12 months was considered fast breathing. All children with malaria-pneumonia symptom overlap received dual IMCI classifications. Also, the health centre follows the current WHO recommendation of presumptive antimalarial treatment for all under-fives with fever [8,13]; therefore, all children with malaria-pneumonia overlap having a negative RDT result received both antimalarials and antibiotics.

Approval for this study was given by the Department of Primary Health Care and Disease Control research committee, Abeokuta-South local government area, Ogun state, Nigeria, and all participants gave voluntary informed consent for inclusion in the study.

Results

Of the 1,216 children enrolled, 700 (58%) were males; 694 (57%) were infants (≤ 1 year); and 1,090 (90%) reported cough or fever. A total of 954 children (78%) satisfied the clinical case definition for malaria and 366 (30%) children satisfied the clinical case definition for pneumonia. The proportions of various clinical presentations of the study children are as shown in Figure 1. Among the children fulfilling the malaria case definition, 284/954 (30%) also met the pneumonia case definition. Furthermore, 284 (23%) of all children enrolled satisfied the criteria for both malaria and pneumonia and thus received dual treatment with antibiotics and antimalarials. Of these, only 130 (46%) had a positive result for malaria using a malaria rapid diagnostic test.

The proportion of positive malaria tests among those with overlap pneumonia-malaria symptoms did not significantly differ across gender (male versus female; 45% versus 47%, chi-square 0.038, P = 0.8) or age categories (≤ 1 year versus > 1 year; 44% vs 55%, chi-square 3.49, P = 0.061). Similarly, no significant differences existed between the occurrence of symptom overlap and the child's age, gender, or parental seeking of care within two days of fever (Table 1). However, during malaria-pneumonia symptom overlap, female children were more likely

Figure 1. Proportion of symptoms and signs among 1216 consecutive Nigerian children 2 months to 5 years seeking care at an IMCI practicing health centre
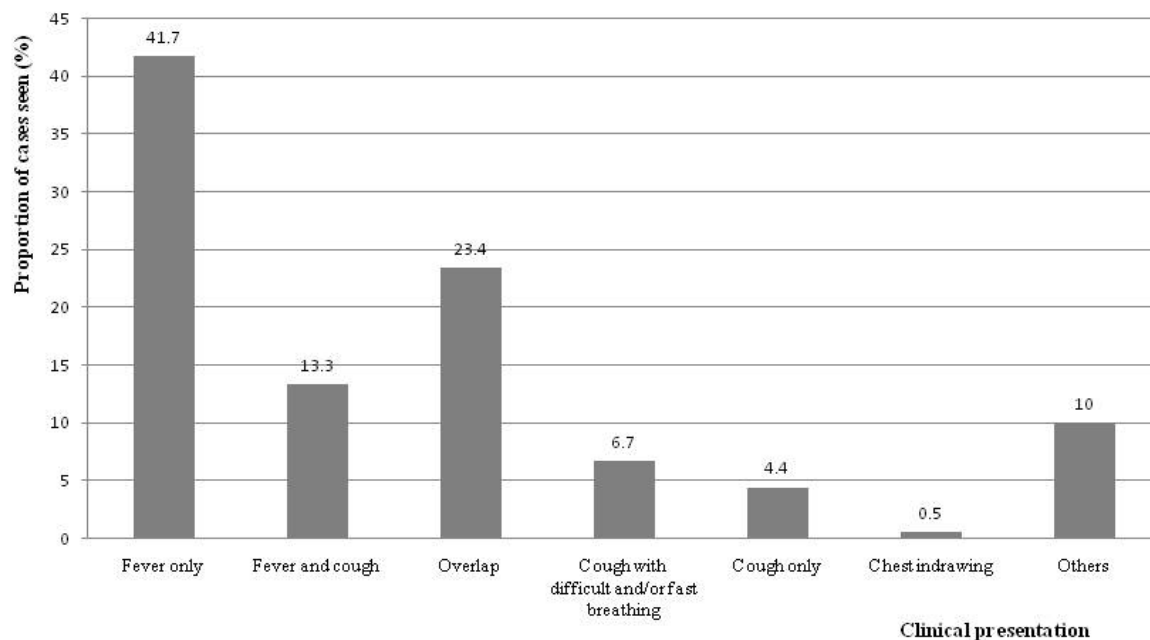
to receive care within two days of fever compared to males (64% versus 50%, chi-square 5.9, P = 0.01). Similarly, during an overlap, children > 1 year of age were more likely to receive care within two days of fever compared to children ≤ 1 year (68% versus 51%, chi-square 8.9, P = 0.003). Female gender and the child's age (> 1 year) were independent predictors of early parental care seeking among children with symptom overlap with an odds ratio of 2.2 (95% CI 1.3 - 3.3) and 2.1 (95% CI 1.3 - 3.6) respectively. Age (> 1 year), gender, and care seeking within two days of fever were not predictors of symptom overlap.

Discussion

This study shows that of all IMCI malaria in children, almost one third of them also met the case definition for pneumonia. This is consistent with the results of a previous study [5]. Based on the IMCI guidelines, these children require treatment with both antimalarials and antibiotics. However, the Nigerian Home Management of Malaria Treatment Guideline, like most in Africa [5,13], recommends antimalarial treatment only for all children with fever and there is no policy for home/community management of ARI [14]. Although the results of this study may not be

Table 1. Socio-demographic characteristics of 1216 children and the occurrence of malaria – pneumonia symptom overlap

Variables	All n (%)	Overlap n (%)	No Overlap n (%)	Chi-square	P- Value
Age					
≤ 12 months	694 (57)	168 (24.2)	526 (75.8)		
> 12 months	522 (43)	116 (22.2)	406 (77.8)	0.64	0.43
Total	1216 (100)	284 (23.4)	932 (76.6)		
Gender					
Male	700 (57.6)	160 (22.9)	540 (77.1)		
Female	516 (42.4)	124(24.0)	392 (76.0)	0.21	0.61
Total	1216 (100)	284 (23.4)	932 (76.6)		
Care-seeking within two days of fever.					
Yes	609 (50.1)	153 (25.1)	456 (74.9)		
No	607 (49.9)	131(21.6)	476 (78.4)	2.42	0.12
Total	1216 (100)	284 (23.4)	932 (76.6)		

directly applicable to the community, treating all childhood fever as malaria will result in malaria being over-treated continuously in the community, resulting in other potentially severe infections such as ARI being overlooked.

There is substantial evidence showing decreasing malaria transmission, morbidity and mortality in African countries where large-scale malaria control interventions have been implemented [15]. With this decreasing trend of malaria, treating all childhood fever with ARI symptoms in the health centre or community with antimalarials may not be as safe as it used to be. Managing febrile illnesses in children using results based on RDT is cost-effective, prevents drug wastage and shortage, and ensures the rational use of antimalarial drugs [15]. Also, it prevents unnecessary adverse drug reactions such as gastro-intestinal disturbances, neutropenia, cardiotoxicity, ototoxicity, hepatotoxicity and neurotoxicity associated with artemisinin-based therapies [15]. Moreover, recent investigations have demonstrated the high sensitivity and specificity of RDTs compared to expert microscopy, and confirmed the safety of not treating RDT malaria-negative children [9,10,16].

It is possible that the mere recommendation of malaria RDTs in high-malaria endemic areas would not necessarily ensure their use because it is generally argued that RDTs are far too expensive to justify their use in areas of high malaria prevalence [17]. However, at a confirmed malaria prevalence of 46% in under fives with malaria-pneumonia symptom overlap in this study, malaria RDTs may be cost effective and should be recommended because recent studies have demonstrated that RDTs are clearly cost saving in populations with between 30% and 52% of clinically diagnosed confirmed malaria cases [11,18,19]. Besides, since the Global Fund to fight AIDS, Tuberculosis and Malaria is currently scaling up the use of free malaria RDTs in primary health care facilities in some African countries such as Nigeria [20], patients may not incur additional financial burden in performing the RDT.

Almost one fourth of children in this study had malaria-pneumonia symptom overlap. This is lower than the 30% reported by a Ugandan study [5]. The observed differences may be due to differences in sample size and in the qualifications of the health workers who collected the data in both studies. Interestingly, just over two fifths of the children had a positive RDT result for malaria. This shows that utilizing the IMCI guidelines in the management of

malaria-pneumonia symptom overlap over-estimates malaria in more than half of the cases and thus risks massive over-prescription of antimalarials. Based on these findings, we argue that antibiotics and antimalarial treatment should only be given to all under-fives with malaria-pneumonia symptom overlap who have a positive parasitological test, while those with a negative test should receive antibiotics only.

The following are some limitations of this study. As with most hospital-based investigations, this study suffers from selection bias due to care seeking practices. It excludes a significant proportion of children with overlapping symptoms in the community. Also, though the data was collected by well-trained clinicians, the possibility of observer bias may not be ruled out.

As the use of RDTs are being pilot tested in the home management strategies in Africa, more studies are needed to improve our understanding of the role of RDTs in the management of malaria-pneumonia symptom overlap at health centres and in the community. We are currently investigating the clinical outcome of treating children with symptom overlap based on RDT results.

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Corresponding author
Dr Ukwaja Kingsley Nnanna
Comprehensive Health Centre
Oke-Ilewo, Abeokuta, Ogun State, Nigeria
Telephone: +234 08036243196;
Email: ukwajakingsley@yahoo.co.uk