Original article

Pneumonia and malaria in under-five children of southern Ethiopia

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Abstract: An observational and experimental study was conducted to see the proportion of overlap between the clinical and laboratory diagnosis of pneumonia and malaria and the therapeutic effectiveness of cotrimoxazole. Children under five years who presented to the clinic with fever and/or cough or difficulty in breathing were enrolled in the study. Blood smears were done for all enrolled children while chest x-rays were obtained only for those children with parasitaemia or who met the clinical case definition for pneumonia. There were 736 children who met the clinical case definition of malaria, while 731 met the clinical case definition of pneumonia. Of these two groups, 456 (61.9%) of children with clinical malaria and 62.3% of those with clinical pneumonia represent the overlap of children who met both clinical definitions. Specific clinical definition did not differentiate pneumonia and malaria. A single treatment of both diseases by cotrimoxazole is showed to be as effective as a combination of treatment with chloroquine and procaine penicillin. Parasite clearance was better in the cotrimoxazole group than the chloroquine-penicillin group, however the cotrimoxazole group had a higher rate of recurdescences with two out of 41 patients smear positive at day 14. A significant proportion of overlap in the clinical and laboratory diagnosis of pneumonia and malaria is shown and that a three days cotrimoxazole therapy is equally effective in treating both diseases as a combination of chloroquine and procaine penicillin is. [*Ethiop. J. Health Dev.* 1997;11(1):43-50]

Introduction

Pneumonia and malaria are the major causes of mortality and morbidity among children in developing countries including Ethiopia (1-5).

Malaria treatment is recommended for a child living in a malaria endemic area, where microscopy is not available if the child has fever or history of fever with no other obvious cause. In highly malarious areas, malaria treatment is advised for all children with fever whether or not other obvious causes are present (6). Treatment for bacterial pneumonia is recommended for any child with cough or difficulty in breathing who has a high respiratory rate or lower chest wall indrawing(7).

Studies conducted in several countries indicate that there is a significant overlap in the clinical presentation of pneumonia and malaria (8-11). Case management algorithms are based on the premise that a child is likely to have only one disease at a time. Thus a child with fever and cough may meet clinical case definition for both malaria and pneumonia but have only one disease, or none at all and yet receive one or two treatments unnecessarily. Conversely a child may have both disease but be assessed and treated for only one.

Cotrimoxazole, which has a similar effect of pyrimethamine/sulfadoxine (fansidar), is known to be an effective antimalarial in adults and children over 5 years of age. Because of its broad

[1] From the Health Bureau, Southern People's Region, Awassa and [2]Department of Community Health, Faculty of Medicine, P.O. Box 1176, Addis Ababa. spectrum efficacy, low cost, ease of administration and low incidence of adverse effects, cotrimoxazole is the preferred drug in most settings for out patient treatment of bacterial pneumonia. A study of subjects with *falciparum* parasitaemia in Tanzania (12), Mozambique (13) and vivax malaria (14), have reported cotrimoxazole as being effective as chloroquine.

Better definition of the patterns in the clinical presentation of these diseases is needed to permit more effective diagnosis and treatment. Documentation that a single drug is effective against the pathogens of both diseases could both save money and avert deaths.

This paper is a report of a study which was designed to define the overlap in the clinical presentation of pneumonia and malaria and to determine the response to cotrimoxazole treatment of children with these diseases.

Methods

An observational and experimental study (a randomized, double-blind clinical trial) was conducted between September to December 1993 when rates of pneumonia and malaria reach a maximum, according to reviews of health institutions records.

The study was conducted in the two health centres and one hospital located in Awassa Town. Awassa Zuria district has an area of 1875 sq.km with a total population of 307,767. Approximately 23% of the population is urban, and children under five years of age account for 19% of the total. The majority of the population are farmers, and 75% live at altitudes ranging from 500-3500 m. Awassa lake is found in the northwest central part of the district with an area of 129 sq.km and average depth of 10 metres. Most of the area are *Kola* with annual temperature ranging from 4.5 to 34 degree centigrade. There are two rainy seasons in the area, one with heavy rainfall in the month of July to September and the other with light rainfall from January through March. The annual rainfall averaged 1110 mm.

A nurse asked each mother or other care taker why the child had been brought to the clinic, and up to three reasons were recorded for each child. Every child brought to the clinic because of fever and/or cough or difficulty in breathing whose mother gave verbal informed consent for participation, was enrolled in the study. Children with severe cases of pneumonia and malaria or those who had any history of taking antimalarial medication in the past two weeks were considered ineligible for the clinical trial.

At enrolment, care-takers were interviewed to obtain data including the name, address, age, sex, history of fever, cough, difficulty in breathing, rapid breathing and any medication taken, physical examination and laboratory tests.

The axillary temperature was taken using an ordinary mercury thermometer for at least one minute and respiratory rate was counted for one full minute when the child was calm or undisturbed. Weight and height were measured using a standard scale in the health institutions. Using the clinical history and physical findings, the children were categorized into groups based on whether they met the clinical definition of malaria and/or pneumonia.

After the clinical diagnosis was recorded, the children under-went laboratory investigation. Haemoglobin in gm/100dl was determined for all children using Sahel's method. Thick and thin blood films of all enrolled children were made and stained with Giemsa, then examined under oil immersion. Asexual forms of *plasmodium* were typed and their density assessed by counting against 200 white blood cells. Densities were expressed as parasites/mm^3 assuming 8000 WBC/mm^3 of blood. Blood films were reported as negative only after examination of 100 high power fields. Chest radiography was performed only for children with parasitaemia or for those meeting the clinical definition of pneumonia. Children who didn't have malaria parasitaemia and who didn't have radiography were assumed to have negative chest radiographs. Laboratory technicians and radiologists were not aware of the clinical diagnosis and were not allowed to see any child before completing diagnostic tests.

Based on results of the laboratory and chest x-ray investigation, patients were given final diagnosis. Mothers or other caretakers of children with both laboratory diagnosed malaria and radiographically diagnosed pneumonia were invited to be participants in the clinical trial. Participating children were randomly allocated into the two treatment groups using table of random numbers.

Group one received cotrimoxazole at standard dosage (trimethoprim 6mg/sulphamethoxazole 30mg/kg body weight in two divided doses daily, administered orally as syrup, crushed powder or tablets) for three days.

Group two received the standard regimen of chloroquine base (10mg chloroquine phosphate base/kg of body weight followed by 5mg/kg 6-8 hours later and 5mg/kg on each of the second and third days orally as syrup, crushed powder or tablets) and procaine penicillin at a dose of 50,000 units/kg body weight intramuscular daily for five days.

All patients were invited for a return visit on the 7th and 14th days after initiation of treatment. To improve compliance, the cost of medication, investigation and transportation were covered by the research fund and it was explained that the child would be seen at each visit with the minimum of waiting time.

During each follow up visit, parents were asked about the compliance with the medication regimen and whether their child had been ill or had experienced fever, cough, difficulty in breathing, vomiting, diarrhoea or poor appetite. The child was examined for the presence of chest indrawing and other danger signs. The temperature and respiratory rates were recorded and blood film performed.

Malaria therapy was considered to have been successful if no parasites were detected on day seven and 14. All patients with parasitaemia on day seven were treated with a single dose of Fansidar (25mg pyrimethamine and 500 mg sulfadoxine).

A child was considered ill if he or she had fever and/or one more symptom of vomiting, diarrhoea, cough or loss of appetite or three of these symptoms without fever. The overall condition was recorded as worsened, same or improved.

Clinical malaria was diagnosed in the presence of a fever or history of fever. Fever was defined as an axillary temperature of 37.5 or more. Clinical pneumonia was diagnosed in the presence of chest indrawing, cough or difficulty in breathing with a rapid breathing rate of 60 per minute or more for children less than two months of age; 50 or more breathe for children 2-11 month of age; and 40 or more for children 12 months of age or older. Severe pneumonia was diagnosed if chest indrawing was present.

Table 1: **General characteristics of the study population, Awassa (southern Ethiopia) 1993.**

Characteristics	Number (%)
1. Sex	
male	601 (54.5)
Female	492 (45.5)
2. Age (months)	
0-12	439 (40.2)
25 - 36	212 (19.4)
37 - 48	158 (14.4)
49 - 60	152 (14.4)
3. History of medication	
Antimalarial	243 (22.2)
Antibiotic	13 (1.2)
Procaine penicillin	98 (9.0)
Chloramphenicol	41 (3.8)
Bacterium	1 (0.1)
Ampicillin	4 (0.4)
Other	51 (4.7)
Others	1 (0.1)
4. Smear positive	253 (23.1)

Type of *plasmodium*	
Falciparum	88 (34.8)
Vivax	165 (65.2)
Parasite density	
1 - 4999	87 (34.4)
5000 - 9999	99 (39.1)
10000 - 14999	29 (11.5)
15000 - 19999	12 (4.74)
$\geq$ 20000	26 (10.5)
5. Nutritional status	
Stunted	282 (25.8)
Under weight	230 (21.0)
Wasted	228 (20.9)

Laboratory diagnosis of malaria was made in presence of asexual parasites in the blood smear. Cases of severe malaria included those children with parasite density exceeding 250,000/ mm^3 and with a haemoglobin level of 7.5gm/100ml or less. Radiographic pneumonia was defined as the presence of parenchemal density compatible with pneumonia as interpreted by the radiologist. Radiographs showing lobar consolidation or involvement of more than one lobe were classified as severe.

The Epi Info (version 5) and the Statistical Analysis System (SAS, version 6.04) programs were used to analyse the data collected. Data on the parasite density were transformed to natural logarithm scale before they were used in statistical analysis.

Parents/care takers of the potential children for the study were informed about the aims, methods, anticipated benefits and potential hazards of the study and verbal consent was obtained. Severe cases of either pneumonia or malaria were admitted and treated appropriately and considered ineligible for the clinical trial. The study was approved by both a review committee of the Department of Community Health and the Research and Publications Committee of the Faculty of Medicine.

Results

A total of 1093 children were enrolled in the study. A summary of the general characteristics of the study population at the time of entry into the study is summarized in Table 1. The average age of children enrolled was 25 months.

Of the total children enrolled, fever, cough or difficulty in breathing or both were reported in 305 (27.9%), 218 (19.9%) and 570 (52.2%) of the children by mothers or other care takers, respectively. The parasite densities ranged from 130 to 320000, but only three cases had a parasite density of more than 100,000. Among those who had history of taking procaine penicillin and ampicillin, 22% and 7.8%, respectively, and also 14.8% of those taking other medication were found positive for plasmodium. Of 13 who had history of taking antimalarial two (15.4%) had positive smears, of which one was *falciparum* and the other *vivax* malaria.

Of the total of 843 children who had radiographic investigation, 403 (47.8%) had positive findings. Among these, 33 (8.2%) were severe pneumonia, 360 (89.3%) none severe, and 10 (2.5%) had other diagnosis. Among those who had history of taking antibiotic, 38.8% were found to have radiographic pneumonia, while 15.4% of those who had taken antimalarial had radiographic pneumonia. Six children who had history of taking injections of procaine penicillin were found to have both radiographic pneumonia and parasitaemia.

There was significant overlap in clinical as well as laboratory diagnosis of pneumonia and malaria. The clinical definition of both pneumonia and malaria was met by 456 (41.7%) children (Table 2).

Table 2: **Number of children under five with fever and/or cough or difficulty in breathing meeting clinical and laboratory definition for malaria and pneumonia, Awassa (southern Ethiopia) 1993.**

Clinical	Number (%)	Laboratory	Number (%)
1.Malaria alone	280 (25.6)	a. Malaria	81 (28.9)
		b. Both	14 (5.0)
		c. Neither	185 (66.1)
		Total	280 (100)
2.Pneumonia alone	275 (25.2)	a. Malaria	11 (4.0)
		b. Pneumonia	107 (38.9)
		c. Both	15 (5.5)
		d. Neither	142 (51.6)
		Total	275 (100)
3.Both	456 (41.7)	a. Malaria	50 (10.9)
		b. Pneumonia	176 (38.6)
		c. Both	81 (17.8)
		d. Neither	149 (32.7)
		Total	456 (100)
4.Neither	82 (7.5)	Neither	82
Total	**1093(100)**		

Children who satisfied the clinical definition for both pneumonia and malaria were more likely to have radiographic pneumonia (OR=4.76, 95%CI: 3.62-6.26), parasitaemia (OR=1.75, 95%CI: 1.312.35) and both at the same time (OR=4.53, 95%CI: 2.85-7.23) than children who do not meet the definition.

A total of 107 out of 283 (37.8%) with radiological signs consistent with pneumonia and a negative blood film, and 15 out of 110 (13.0%) with radiological signs consistent with pneumonia and a positive blood film, satisfied the clinical case definition for pneumonia.

However 61 out of 142 (43.0%) of those satisfying the clinical case definition of malaria with a positive blood film and no radiological evidence of pneumonia, also satisfied the clinical case definition of pneumonia.

The likelihood of radiographic pneumonia was higher in smear positives than smear negatives (OR=1.53, 95%CI: 1.15-2.04). There was no difference observed in relation to age, sex, haemoglobin, nutritional status, type of parasite or parasite density.

The comparability of the children in the two treatment groups is demonstrated in Table 3. There was no significant difference in their general characteristics except for weight-for-height z-scores. Only three children were lost in the follow up.

Table 3: **General characteristics of the treatment groups, Awassa (southern Ethiopia) 1993.**

	GROUP-1	GROUP-2	P-VALUE
Number of children	42	52	
1. Age mean ± sd	28 ± 17.6	31 ± 17.7	p=0.60
2. Sex Male	20	29	
Female	22	43	p=0.43
3. Temperature Febrile	35	44	
Afebrile	7	8	p=0.87

4. Haemoglobin			
mean ± sd	8.68 ± 1.27	8.7 ± 0.88	p=0.91
5. Nutritional status			
mean ± sd HAZ	-0.31 ± 1.92	-0.59 ± 2.06	P=0.50
WAZ	-1.42 ± 1.40	-1.03 ± 1.29	P=0.17
WHZ	-1.41 ± 1.13	-0.65 ± 1.69	P=0.01
6. Density			
log.mean ± sd	3.823 ± 0.369	3.914 ± 0. 481	p=0.30
7. Type *Falciparum*	16	23	
Vivax	26	29	p=0.55

Treatment in group-1 = Cotrimoxazole; group-2 = Chloroquine + Procaine WHZ= Weight-for-height z-scores; WAZ= Weight-for-age z-scores; WHZ= Height-for-age z-scores.

During the first scheduled follow up visit on the 7th day of treatment, those taking cotrimoxazole alone had a higher risk of fever and fast breathing but had less risk of having cough, vomiting, diarrhoea or smear positivity than those taking procaine penicillin and chloroquine. The proportion of children who clinically improved was higher in group-1 than group-2, although the difference was not statically significant (Table 4).

At the time of the second follow up visit on day 14, those treated with cotrimoxazole had a higher risk of fever, vomiting, diarrhoea and positive blood smears than the chloroquine and penicillin treatment group, although the difference was not statiscally significant. The two cotrimoxazole treated children who were smear positive had *vivax* malaria (Table 5).

Discussion

Malaria transmission in the study area is perennial with peak incidence at the end of heavy rains from June to August. In the study year, lower average rainfall than previous years was associated with a low prevalence of positive smears of 23.1%. *P.vivax* was found to be the predominant species, accounting for 65% of cases detected. Radiographic pneumonia, on the other hand, was recorded in a larger proportion (25.8%) of children enrolled in the study than might have been expected based on data from previous years.

Health institutions in the district treat cases of pneumonia and malaria empirically based on history and physical examination. Study findings suggest that at least 13% of those treated with antibiotics suffer from untreated malaria and 15% of those treated for malaria have undetected and untreated pneumonia.

A study in Malawi (9) evaluated children under five years of age with cough or fever brought to the outpatient department of Kamuzu Central Hospital in Lilogwa. Of 1599 enrolled children, 566 (35%) had parasitaemia and 116 had radiographic evidence of pneumonia; 43 had both radiographic pneumonia and parasitaemia. Of the 471 children who met the clinical definition for pneumonia, 449 (95%) also met the malaria clinical definition. Among children with radiographic evidence of pneumonia, the clinical definition for malaria was not predictive of parasitaemia (sensitivity 93% and specificity 5%). Whether malaria parasitaemia was present or absent, the pneumonia clinical definition distinguished children with and without radiographic evidence of pneumonia (sensitivity and specificity > 60%). Children who satisfied the pneumonia clinical definition were more likely to have radiographic evidence of pneumonia (OR = 10.4, 95% CI: 5.2-20.7), parasitaemia (OR = 1.6, 95% CI: 1.2-2.2) or both at same time (OR =4.2, 95% CI: 2.1-8.4) than were children who did not meet the clinical definition.

Table 4: **Response to treatment in the first week of follow up, Awassa (southern Ethiopia) 1993.**

	GROUP-1	GROUP-2	Relative Risk (95% CI)
Number of children	42	49	
1.Fever	8 (19.0)	5 (10.2)	1.87 (0.66-5.27)
2.Cough	2 (4.8)	5 (10.2)	0.47 (0.10-2.28)
3.Vomiting	1 (2.4)	5 (14.3)	0.23 (0.03-1.92)
4.Diarrhoea	4 (9.5)	7 (14.3)	0.67 (0.21-2.12)
5.Temperature Febrile	6(14.3)	4 (8.2)	1.75 (0.53-5.79)
6.Fast breathing	1(2.4)	0	= =
7.Smear Positive	(2.4)	3 (6.1)	0.39 (0.04-3.60)
8 .Condition			
Same	1 (2.4)	3 (6.1)	
Improved	4	1	46 0.39 (0.04-3.60)

Treatment in group -1 = Cotrimoxazole
group-2 = Chloroquine + Procaine

In the Gambia (10) a community based study of respiratory diseases in the eastern region monitored all under-five children in seven rural villages for respiratory complaints and febrile illness. Children were enrolled in the study if they had rapid respiratory rate and based on the mothers subjective impression that the child was ill. Those children with cough or fever but no fast breathing and children with chest indrawing but no fast breathing were not enrolled.

The study showed that 775 children (99.0%) satisfied the clinical case definition of malaria and 665 (84.9%) children satisfied the clinical case definition for pneumonia. Of those who met the clinical case definition for pneumonia 659 (99.0%) also satisfied the clinical case definition of malaria. Of 134 children with radiographic sign of pneumonia and negative blood films, 129 (97.0%) satisfied the clinical case definition for pneumonia. Of 107 children with radiographic signs of pneumonia and a positive blood film, 91 (85.0%) satisfied the clinical case definition for pneumonia. However, of 410 children with clinical and laboratory diagnosis of malaria but with negative radiographs, 326 (79.5%) also satisfied the clinical case definition of pneumonia. Parasitaemia was present in 520 (66.4%) of the 783 children with raised respiratory rate, and in 418 (62.9%) of the 665 who satisfied the clinical case definition of pneumonia. Only 107 (44.4%) out of 241 children with radiographic pneumonia had parasitaemia whereas 413 (76.2%) of 542 children with no radiological evidence of pneumonia had parasitaemia. Malaria parasitaemia of 5000/ mm^3 and over was associated more often with abnormal chest x-ray findings in this group of children than would be expected by chance.

Like the Malawi and Gambia studies, our study showed a significant proportion of overlap in pneumonia and malaria case definitions. The overlap in clinical definitions of pneumonia and malaria of over 60% is lower than that found in the Malawi and Gambia studies. This difference could be due to the lower rate of parasitaemia and predominance of *vivax* malaria in this study when compared to the other studies. The overlap in laboratory diagnosis of both parasitaemia and radiographic pneumonia was similar to that found in the Mozambique study.

In contrast to the study in Malawi, our investigation revealed no reduced incidence of parasitaemia in the presence of radiographic pneumonia. In addition, radiographic pneumonia was more often detected in this study, though not in Malawi, among those who met the clinical case definition for pneumonia when the smear was negative than positive. But the findings of this study were similar to those in the Gambia, where radiographic pneumonia was more often detected among those who

met the clinical case definition of pneumonia when they were smear negative than when they were smear positive.

However, the overall likelihood of radiographic pneumonia was higher for smear positive than smear negatives. This relationship was unaffected by differences in age, sex, haemoglobin, or parasite type and density. This result contrasts with findings of previous studies.

Table 5: **Response to treatment in the second week of follow up, Awassa (southern Ethiopia) 1993.**

	GROUP-1	GROUP-2	Relative Risk (95% CI)
Number of children	41	46	
1.Fever	3 (7.3)	2 (4.4)	1.68 (0.30-9.58)
2.Cough	0	1 (2.2)	= =
3.Vomiting	2 (4.9)	0	= =
4.Diarrhoea	4 (9.8)	3 (6.5)	1.50 (0.36-6.29)
5.Temperature Febrile	2 (4.9)	2 (4.4)	1.12 (0.17-7.61)
6.Fast breathing	0	0	= =
7.Smear Positive	2 (4.9)	0	= =
8 .Condition			
Same	2 (4.9)	0	
Improved	39	46	= =

* Treatment in group -1 = Cotrimoxazole
group-2 = Chloroquine + Procaine

A facility-based study in Nigeria (8) evaluated the risk of malaria with bacteraemia in preschool children. Six hundred and forty two febrile preschool children without localizing signs were found to have a prevalence of bacteraemia which was comparable in those with malaria (43/446, 9.6%) to those without malaria (24/196, 12.2%, $p < 0.5$). In Mozambique a study was conducted among 220 children between two, four months and four years of age admitted with the diagnosis of pneumonia (11). Of 220 children with pneumonia, 19 (8.6%) also had *P.falciparum* parasitaemia. Among those with parasitaemia 12 (63%) were classified as having severe pneumonia. The 19 children with pneumonia and parasitaemia had a longer mean duration of cough and fever before admission (5.5 days compared to two days).

The study in Nigeria showed a higher prevalence of both malaria and bacteraemia among anaemic infants while the study in Mozambique documented lower haemoglobin levels among children with pneumonia and malaria. In the study in the Gambia, chest x-ray changes were associated with higher parasite densities while in Nigeria, no correlation was observed between parasite density and overlap of pneumonia and malaria (8-11).

The specificity of the clinical definitions of malaria and pneumonia were not adequate to differentiate between the two diseases. Inclusion of other additional criteria to improve the specificity of the clinical definition might reduce over treatment, but would still not permit pneumonia to be distinguished clinically from malaria. The presence of a palpable spleen in malaria and crepitation in pneumonia increased the predictive value of the case definitions, but these findings were present in only a small proportion of the cases. This study was similar to previous studies in finding a low predictive value of fever in pneumonia, while maternal reports of fast or difficult breathing were better predictors of the presence of pneumonia.

Cotrimoxazole was found to be as effective in the treatment of malaria as chloroquine. All patients in both groups had a statistically significant response. Parasite clearance rates were better in the cotrimoxazole than the chloroquine group, however the cotrimoxazole group had the highest rate of

recurdescenses. This finding is similar to that of the Tanzania and Mozambique studies, which showed a higher rate of recurrence with cotrimoxazole despite an effectiveness in parasite clearance equal to that of chloroquine.

The chloroquine group was less likely to have persistent fever, though more likely to have gastrointestinal complaints. Further studies are needed to assess chloroquine resistance in the area.

In conclusion, the study shows a significant proportion of overlap in the clinical and laboratory diagnosis of pneumonia and malaria shown and that a three-day cotrimoxazole therapy is equally effective in treating both diseases as a combination of chloroquine and procaine is.

Since, the overlap in the clinical presentations is unaffected by the type of *plasmodium* and the risk for malaria and pneumonia are similar throughout the country, the results of this study can be generalized within Ethiopia to assist clinical management of children under 5 years old age.

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