

**The overlap in the clinical  
presentation and treatment  
of malaria and pneumonia  
in children:  
report of a meeting  
(Geneva, 8 April 1991)**



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## 1. INTRODUCTION

Pneumonia and malaria are common conditions in young children. Pneumonia is the first or second leading cause of mortality in young children in most developing countries. In countries with significant falciparum malaria transmission, malaria is also amongst the leading causes of mortality. It is important that the overlap in their clinical presentations and treatment be understood. Understanding the interaction between the two diseases is important for case management guidelines, for training health workers, for communicating with caretakers of children, and for formulating household survey (and verbal autopsy) questions and interpreting their results.

Epidemiological studies conducted in several settings in Africa indicate that almost all children meeting a pneumonia case definition (cough and fast breathing or chest indrawing) have fever or a history of fever and that a significant proportion of children with fever will meet a pneumonia case definition. Consequently, effective malaria therapy is often required in febrile children with suspected pneumonia.

## 2. OBJECTIVES OF THE MEETING

- 2.1 To review the scientific evidence on the following key questions concerning the overlap in clinical presentation and treatment of malaria and pneumonia:
- What is the extent of the overlap in clinical presentation between pneumonia and malaria in young children? Are health workers able to distinguish the two diseases by clinical criteria, in the absence of laboratory or X-ray facilities?
  - Do children who are receiving cotrimoxazole\* for the treatment of pneumonia require additional antimalarial drug therapy if they also meet the clinical case definition for malaria (fever or history of fever) in areas where P. falciparum malaria is endemic?
  - Will the adoption of cotrimoxazole as the first-line treatment for pneumonia favour the selection of sulfadoxine/pyrimethamine resistant P. falciparum parasites?
- 2.2 To determine whether there is sufficient scientific evidence to suggest changes in the current WHO clinical guidelines and policy recommendations.
- 2.3 To suggest priorities for future research, if there is not sufficient scientific evidence at present to guide policy.

\* Cotrimoxazole is the international name for sulfamethoxazole/trimethoprim.

### 3. TECHNICAL BACKGROUND

#### 3.1 Summary of the current clinical guidelines of the ARI Programme

Pneumonia and malaria are two of the most common causes of childhood mortality in many developing countries. Yet when the ARI Programme reviewed its technical guidelines in 1988, little was known about their possible interactions. The Programme became concerned at that time about both the overlap in clinical presentation and in treatment (1,2).

The Programme presents four antibiotic treatment options for the outpatient management of pneumonia: cotrimoxazole, amoxycillin, ampicillin and procaine penicillin. All are recommended for 5 days. However, most national programmes choose cotrimoxazole because it is the cheapest - on average, US \$0.16 for a 5-day course compared to US \$0.47 for amoxycillin. A central question to be addressed is: Is it necessary to recommend using both cotrimoxazole and an antimalarial (commonly chloroquine) in a child with signs suggesting pneumonia and a fever (or history of fever)? Two white pills (three if paracetamol is given in tablet form) with different dosage schedules will be confusing to many mothers and may reduce compliance. The cost is also greater.

Almost all ARI deaths in young children are due to acute lower respiratory infections and almost all of these are due to pneumonia. The Programme has developed a simple protocol to detect cases of pneumonia, based on looking for fast breathing and chest indrawing in children who present with cough or difficult breathing (3,4,5,6). Fast breathing alone, without an acute illness with cough or difficult breathing, would not be classified as possible pneumonia.

The classification process is based on examining all children who meet the entry criteria (cough or difficult breathing) then classifying the illness based on the presence or absence of:

- danger signs (not able to drink, abnormally sleepy or difficult to wake, convulsions, severe malnutrition, or stridor in a calm child);
- chest indrawing (defined as indrawing of the lower chest wall);
- fast breathing.

The respiratory rate threshold for fast breathing taught to health workers at facilities are age-specific - 60 in young infants (under 2 months of age), 50 in 2-11 month old infants, 40 in 1-4 year old children.

The primary objective is to identify and treat cases of pneumonia from among the many children who present with a cough or cold. Because clinical experience and intervention studies in developing countries have indicated that early treatment with antibiotics can reduce mortality from pneumonia, the Programme recommends giving antibiotic treatment to all children with clinical

signs which may indicate pneumonia. The Programme recognizes that many of these children in fact do not have bacterial pneumonia but accepts a substantial amount of over-treatment in order not to miss early treatment of a bacterial infection.

The treatment protocol refers simply to pneumonia although some children classified as having pneumonia may in fact have bronchiolitis or, in malarious areas, a malarial infection.

The instructions to "TREAT FEVER" are indicated in the treatment summaries on the case management chart (5) for the child who has pneumonia, severe pneumonia (who is being referred) or a simple cough or cold. The fever "box" at the bottom of the chart indicates that an antimalarial should be given if there is any fever or history of fever (or instructs the health worker to follow the national malaria programme's recommendations).

Specific antimalarial therapy and referral is recommended for children with danger signs when cerebral malaria is considered to be a possibility; this includes the child who is not able to drink, who is abnormally sleepy or difficult to wake, or a child who is having convulsions.

Thus, in its present form, the treatment guidelines are safe. Although some children with malaria may be misclassified as having pneumonia, they will receive both an antibiotic and an antimalarial. As the danger signs of very severe disease include signs suggesting severe or cerebral malaria, the ARI guidelines advise adding a specific antimalarial, according to the recommendations of the national malaria programme.

The respiratory rate threshold for fast breathing was lowered from 50 to 40 in 1989 for children 1-4 years old, to improve the sensitivity of the protocol in detecting pneumonia in this age group. This was in response to further scientific evidence and criticism of the guidelines from experts both in developing and in developed countries who emphasized that the Programme's primary responsibility is to ensure that the guidelines will identify most cases of pneumonia. An important consequence, however, is that they became less specific and conditions like malaria (which may also be associated with a raised respiratory rate) may more often be classified as pneumonia.

### 3.2

#### **Summary of the current clinical guidelines of the Malaria Action Programme**

In endemic areas, most cases of malaria are diagnosed on clinical grounds, without laboratory confirmation of parasitaemia. The diagnosis is based on the presence of fever or a history of fever. In endemic areas, in children, it is usually not possible to refine further the diagnostic criteria of malaria by history-taking or clinical examination. A history of convulsions or the presence of anaemia or splenomegaly strengthen the suspicion of malaria but these signs are present in only a minority of children with malaria.

The presence of asexual *P. falciparum* parasites in the blood can help confirm the clinical diagnosis. However, in relatively few cases, a child suffering from malaria may present with a negative slide; this is more frequent after the start of treatment. Much more common is the problem of a positive slide in a child that is not suffering from malaria. The child is infected but not clinically ill from malaria. In endemic areas, up to 90% of children under five may have a positive slide at any time and, by and large, this also holds true for patients suffering from diseases other than malaria. A high parasite density increases the probability of clinical malaria, but the relationship between parasite density and clinical disease varies with the intensity of transmission as well as with age group and it is never possible to define an exact cut-off point. Children with fever who have malaria parasites detected in blood by microscopy should be treated for malaria. However, many children with such evidence of malaria infection will not be suffering from the disease, malaria.

Since fever is a symptom of many acute childhood illnesses, many children treated for malaria do not have malaria. Current guidelines stress treating all children who may have malaria because clinical findings are insufficiently specific to identify which children with fever or history of fever do not have malaria. In the absence of microscopy, children living in malarious areas with fever are presumed to have malaria unless signs of another illness that could cause fever are present. In highly endemic areas, children with fever should be treated for malaria even when signs of another fever-causing illness are present. If this policy were fully implemented each child living in a malaria endemic area would receive up to 6 courses of malaria therapy each year.

For uncomplicated *falciparum* malaria, the treatment of choice is chloroquine. In areas where there is resistance to chloroquine, the clinical response to chloroquine may still be acceptable on a population basis to justify its continued use. Only when an important proportion of clinical attacks in a given age group do not respond satisfactorily to chloroquine, is it recommended to replace this drug with an alternative first-line treatment, usually sulfadoxine/pyrimethamine. Chloroquine treatment failures should be confirmed by microscopy, if possible, and treated with sulfadoxine/pyrimethamine. Cases that do not respond to sulfadoxine/pyrimethamine are usually treated with oral quinine. In areas where resistance to sulfadoxine/pyrimethamine is widespread, such as in South-East Asia, this combination is usually replaced with mefloquine.

Severe *falciparum* malaria is usually treated with parenteral quinine, except in the very few areas of the world where parasites are fully sensitive to chloroquine, making the latter the drug of choice. Quinine resistance is emerging in some areas of South-East Asia and it is likely that artemisinin derivatives will become the treatment of choice there.

For malaria caused by *P. vivax*, *ovale* and *malariae*, the treatment of choice is always chloroquine in a dosage of 25 mg/kg over 3 days.

3.3

### **Current global status of *P. falciparum* resistance to chloroquine and sulfadoxine/pyrimethamine**

Chloroquine resistance has spread throughout Africa south of the Sahara. The frequency of clinical chloroquine therapy failures has recently been evaluated in studies of children < 5 years of age in western Kenya and urban and rural sites in Malawi. Approximately 50% of these children, the age group at greatest risk of developing severe *P. falciparum* infections, clinically failed therapy within a mean of 9 days after initiation of chloroquine therapy and approximately 9% failed with minimal or no decrease in parasite density and persistence of malaria illness 48-72 hours after initiation of therapy. Results such as these suggest that in certain areas of Africa, chloroquine may not be an acceptably efficacious therapy for *P. falciparum* malaria in young children.

Parallel studies of sulfadoxine/pyrimethamine for the treatment of *P. falciparum* infections in the groups defined above showed a greater efficacy than that seen with chloroquine therapy. Despite sporadic reports of sulfadoxine/pyrimethamine resistance in Africa, the drug remains generally very effective and will become increasingly the preferred primary therapy of malaria in very young children. Resistance of *P. falciparum* to sulfadoxine/pyrimethamine does, however, limit the operational usefulness of this drug in Thailand, Cambodia, Myanmar, some areas of South America (the Amazon basin) and Papua New Guinea.

The epidemiology of drug resistance in *P. falciparum* is characterized by geographic extension and intensification of the degree of parasitological and clinical resistance over time. This is related to drug pressure and perhaps to the use of subcurative dosages. Limiting widespread drug use, by treating microscopically proven *Plasmodium* infections as opposed to presumptively treating fever or malaria-like illness and ensuring completion of therapy, may delay the advent or intensification of drug resistance. In many areas, however, there are major obstacles to the implementation of these measures.

3.4

### **Previous knowledge concerning cotrimoxazole as an antimalarial**

Cotrimoxazole is known to be an effective antimalarial in adults and children over 5 years of age. Studies conducted in the 1970s showed that treatment of *P. falciparum* and *P. vivax* infections with 2 to 7 days of cotrimoxazole was as effective as treatment with chloroquine or sulfadoxine/pyrimethamine with cure rates over 98% (7,8,9,10,11,12) although *P. falciparum* recrudescences were noted in some studies. The results are summarized in Tables 1 and 2. These studies were conducted in malaria endemic areas and were limited to school-age children and adults who likely had partial immunity to malaria. Because the efficacy of cotrimoxazole for the treatment of *falciparum* malaria might be reduced in children under 5 years, due to lesser immunity, studies in this age group were encouraged (1). The results of these studies are presented in section 5.

Although cotrimoxazole has long been known as an effective antimalarial, it has not been used as such for several reasons. It is more expensive than chloroquine and must be administered more frequently and for a longer time (twice daily for 5 days for cotrimoxazole, compared to once daily for 3 days (or at 0, 6, 24 and 48 hours) for chloroquine. The incidence of rare but serious side-effects with cotrimoxazole is higher than with chloroquine; the incidence of mild side-effects, such as itching and gastric intolerance, is higher with chloroquine. In addition, some experts have suggested that chloroquine should be preferred to antifolate-sulfa combinations because it is more rapidly acting and that in areas with significant chloroquine resistance, sulfadoxine/pyrimethamine use should be combined with quinine (13). Other experts point out that antifolate-sulfa drugs are not "slow-acting" *in vivo*; parasite clearance times are comparable to 4-aminoquinolones and quinine (14). However, antifolate-sulfa drugs do have a narrow stage specificity of action (confined to deoxyribonucleic acid synthesis in the late-stage trophozoite). This might limit their efficacy in the treatment of severe malaria (15).

#### **4. OVERLAP IN THE CLINICAL PRESENTATION BETWEEN MALARIA AND PNEUMONIA**

Examination of the clinical and laboratory manifestations of malaria and acute respiratory infections provides an opportunity to explore the interaction of what are generally considered to be two distinct disease processes.

##### **4.1 Results from Malawi**

The study evaluated children under 5 years of age with cough or fever brought to an outpatient department of an urban African hospital, to determine the frequency with which children meeting the malaria case definition also met the pneumonia case definition, and the frequency with which children with malaria parasitaemia also had radiographic pneumonia.

The study was conducted at the children's outpatient department of Kamuzu Central Hospital in Lilongwe, Malawi, during the rainy season, the peak season for hospitalization due to pneumonia and malaria.

The clinical case definition for malaria was a child with fever or whose mother reported a history of fever in the previous 48 hours. The clinical case definition for pneumonia was a child whose mother reported a history of cough or difficulty breathing and who had a rapid respiratory rate or lower chest wall indrawing.

Of 1599 children enrolled, 557 (35%) had parasitaemia, 116 (7%) had radiographic evidence of pneumonia and 43 (3%) had both radiographic pneumonia and parasitaemia. Among children meeting the clinical case definition for pneumonia, 96% also met the malaria clinical case definition. Children meeting the WHO clinical case definition for pneumonia were significantly more likely to have parasitaemia, radiographic pneumonia, or both

parasitaemia and radiographic pneumonia simultaneously, than children who did not.

Children were equally likely to have *P. falciparum* parasitaemia, whether or not radiographic pneumonia was present.

The results are summarized in Table 4.

#### 4.2

##### Results from Gambia

The study was incorporated into a surveillance system for the detection of pneumococcal disease in the southern half of the Upper River Division, Gambia.

Children who attended clinics at health centres and mobile clinics were referred by a trained MRC field assistant to the MRC field station at Basse if their respiratory rate was raised (greater than or equal to 50 breaths/minute for children under 12 months; greater than or equal to 40 breaths/minute for children 12-60 months of age), and if the mother felt that the child was ill. Children with cough or fever but no fast breathing, and children with indrawing but no fast breathing were not enrolled (unlike the study in Malawi).

For the purposes of the present analysis, the following clinical case definitions have been used: pneumonia is cough or difficulty breathing and a raised respiratory rate ( $\geq 60$ /minute for age  $< 2$  months,  $\geq 50$ /minute for age 2-11 months,  $\geq 40$ /minute for age 1-4 years); malaria is a fever or history of fever.

Investigation of children referred included examination of a thick blood film, measurement of the packed cell volume (PCV) and a chest radiograph. Blood films were classified as positive or negative after examination of 100 high power fields. Chest radiographs were reviewed by a paediatric radiologist (Dr. A. Lamont) and classified as normal or abnormal. Abnormal chest radiographs were sub-classified as showing signs consistent with pneumonia, other types of ALRI, or those suggesting heart disease.

During the time of peak malaria transmission (August-November 1990) 894 children aged less than 5 years were referred to the MRC field station at Basse with a respiratory rate greater than or equal to those recommended by WHO for the diagnosis of pneumonia. Satisfactory thick blood films and chest radiographs were obtained on 783 (87.6%) children whose features are described below.

A total of 775 children (99.0%) satisfied the clinical case definition for malaria, and 665 (84.9%) children satisfied the clinical case definition for pneumonia, 659 (99.0%) of whom also satisfied the clinical case definition for malaria. A total of 129 out of 134 children (97.0%) with radiological signs consistent with pneumonia and with a negative blood film, and 91 out of 107 children (85.0%) with radiological signs consistent with pneumonia and a positive blood film, satisfied the clinical case definition for pneumonia. However, 326 out of 410 (79.5%) of those satisfying the clinical case definition for malaria, with a

positive blood film and no radiological evidence of pneumonia, also satisfied the clinical case definition for pneumonia.

When applied to the study cohort of children with raised respiratory rate, the clinical case definition for pneumonia had a sensitivity of 91.7% and a specificity of 18.1% for detecting patients with radiological pneumonia, with a positive predictive value of 33.2%, and a negative predictive value of 16.9%. The specificity and positive predictive value of the protocol are higher in the dry season.

Parasitaemia was present in 520 of the 783 (66.4%) children with raised respiratory rate, and in 418 of the 665 (62.9%) who satisfied the clinical case definition for pneumonia. Based on previous studies of the Gambia, approximately 40% of children aged 1-4 years in the general population would be expected to have parasitaemia during peak malaria transmission. As anticipated, children with parasitaemia were significantly more anaemic than those with negative blood films. The mean PCV for children with radiological evidence of pneumonia and no parasitaemia was 29.8%, that of children with radiological evidence of pneumonia and parasitaemia 25.3%, and that of those with parasitemia and no radiological evidence of pneumonia 24.2%.

Only 107 out of 241 (44.4%) children with radiological pneumonia had parasitaemia (O.R. = 0.25,  $X^2 = 74.2$ ,  $P < 0.001$ ), whereas 413 out of 542 (76.2%) children with no radiological evidence of pneumonia had parasitaemia. The presence of interstitial or perihilar changes in children with radiological pneumonia was associated significantly with parasitaemia (O.R. = 3.38,  $X^2 = 16.9$ ,  $P < 0.001$ ). The presence of alveolar or mixed alveolar, interstitial or perihilar changes in children with radiological pneumonia was associated negatively with parasitaemia (O.R. = 0.30,  $X^2 = 16.9$ ,  $P < 0.001$ ).

It is important to note that the entry criteria for this study differ from those used in Malawi; only children with fast breathing were included in the Gambian study. This results in most children in the Gambian study meeting both the malaria and pneumonia clinical definitions whereas, in Malawi, most children presenting to clinic met the malaria clinical definition alone.

The results are summarized in Table 5. In Table 6, the 116 children with malaria are subdivided into those with and without other apparent cause of fever; the parasite density is also presented. Table 7 presents the paediatrician's main final diagnosis for 894 children enrolled with fast breathing.

#### 4.3

#### Results from Mozambique

From April to October 1990, 200 children between 2 months and 4 years of age were admitted to the Department of Paediatrics of the Central Hospital in Maputo, Mozambique, with a diagnosis of pneumonia. They were classified as follows:

- (1) 120 cases of severe pneumonia, with cough, fever, a respiratory rate of 50 per minute or more, plus chest indrawing or nasal flaring.
- (2) 100 cases of very severe pneumonia, as above plus one or more of the following: cyanosis, inability to feed, malnutrition, hepatomegaly, pulse rate of 160 per minute or more.

All the children had a chest X-ray and a blood film for malaria, in addition to other laboratory tests.

Nineteen of 220 children (8.6%) with pneumonia also had P. falciparum parasitemia; 12 (63%) of those with parasitemia were classified as very severe pneumonia. In these 19 children the duration of cough and fever before admission was longer, 5.5 days, than in the remaining cases, 2.0 days. Eleven of 19 (58%) had haemoglobin levels less than 7 grams/100 ml. Out of 19, 15 (79%) had segmental pneumonia on X-ray, while the remaining 4 had only perihilar infiltrates. All 19 pneumonia/malaria cases were treated with antibiotics as appropriate plus sulfadoxine/pyrimethamine; 3 children also received intravenous quinine. All recovered, but the average period for fever clearance was 3.2 days compared to 2.0 days in the remaining 201 children (16).

#### 4.4 **Why the overlap in clinical presentation between malaria and pneumonia?**

##### 4.4.1 Overlap in clinical presentation due to common signs of illness

The data indicate that there is a significant overlap in the clinical presentation of malaria and pneumonia. Current malaria treatment guidelines would classify some children with cough and fast breathing who have pneumonia as malaria and treat them with an antimalarial only. A child with malaria who is classified as a case of pneumonia on account of fast breathing and/or indrawing may have severe malaria, a condition with a high mortality unless treated promptly and effectively. The current ARI case management guidelines would classify and treat some children with malaria as pneumonia, while also providing them with an antimalarial. (See section 3.1).

The clinical case definitions for empirical treatment of suspected pneumonia and malaria were developed as tools to guide health workers in their use of antibacterial and antimalarial therapy. The objective remains to identify as many cases of potentially fatal illness as possible using clinical findings that can be taught and readily recognized. In the case of both clinical entities, this has resulted in the recommendation of protocols based on a limited number of signs which have high sensitivity but only moderate specificity. The case definition of malaria, fever or a history of fever, may be sufficient to justify empirical treatment with an antimalarial when P. falciparum is endemic, but is obviously not specific enough to exclude other diseases. Fever is common in children with ARI.

It is not yet clear why malaria results in a raised respiratory rate in some children. This may be mediated by high fever alone. Anaemia, high level parasitaemia and lung pathology due to malaria may also contribute. It is also

possible that in some cases of malaria with fast breathing there is an associated pneumonia; some experts have speculated that this might be caused by immunosuppression due to malaria. Counting the respiratory rate is an important part of the assessment of a child whose main complaint is fever but who also has a cough. Is fast breathing in a child with malaria a sign of severe disease? The topic requires further research.

#### 4.4.2 Is there an interaction between malaria and pneumonia?

Do the two conditions occur together more frequently than expected by chance? In a recent study in Gambia in which approximately 500 children under the age of five years were surveyed for clinical features of malaria or pneumonia over a one-year period, children with a high level of malaria parasitaemia and an abnormal chest X-ray were encountered more frequently than would have been expected by chance (17).

If malaria and pneumonia are associated more frequently than would be expected by chance it is of interest to consider why this might be the case. There are three main possibilities:

(i) It is possible that pneumonia can activate a latent malaria infection. In malaria endemic areas a high proportion of children have a modest malaria parasitaemia but remain well. It is conceivable that the host factors that have been successful in keeping this infection under control are depressed by a concurrent pneumonia. On theoretical grounds this seems unlikely as malaria parasites are, in general, sensitive to the action of cytokines such as TNF and acute phase reactants, such as C reactive protein, whose production is likely to be enhanced by a bacterial infection.

(ii) Malaria suppresses the resistance of the host to bacterial or viral pathogens which then cause a pneumonia. There are strong theoretical grounds for considering that this may occur. It has been shown clearly that acute malaria infections suppress the immune system. Whilst suppression is most marked against malaria antigens, acute malaria also induces non-specific immunosuppression. Thus, children with acute malaria respond poorly to bacterial vaccines and T cell control over Epstein-Barr-Virus infected B cells is abrogated during the acute phase of the infection. It is likely that malaria also damages the ability of the host to cope with bacterial infections in other ways. Thus, children who have recently experienced an attack of malaria have an increased susceptibility to non-typhoidal salmonella infections, in common with patients with sickle cell disease or bartonellosis. The mechanism of this enhanced susceptibility is not known but is likely to be related in some way to haemolysis. There are, therefore, strong grounds for believing that during an acute attack of malaria, susceptibility to both bacterial and viral causes of pneumonia might be enhanced.

(iii) Malaria causes lung pathology thus producing the symptoms and signs of an acute bacterial or viral pneumonia. There is good evidence that, in non-immune adults, malaria can cause the shocked lung syndrome. It is much less certain

whether lung damage occurs in less severe forms of malaria and, especially, whether it occurs in partially immune children. Sequestration of malaria parasites within pulmonary vessels and consequent tissue damage provides one possible mechanism by which lung changes could be brought about in these children.

## 5. COTRIMOXAZOLE AS AN ANTIMALARIAL IN CHILDREN LESS THAN 5 YEARS OLD WITH SIGNS SUGGESTING PNEUMONIA

Table 3 summarizes the results from Malawi and Gambia.

### 5.1 Results from Malawi

A recent study in Lilongwe, Malawi (18) demonstrated that amongst ill children presenting with *P. falciparum* parasitaemia (of which 37% also had cough and fast breathing), cotrimoxazole was highly effective in rapidly clearing parasitaemia and malaria illness. In addition, all patients remained clinically well for 14 days following initiation of therapy. All but one of 44 children remained aparasitaemic on day 14; this child had 300 asexual/ul on day 14 but no parasites on days 15, 16, 19 and 21 without additional treatment.

### 5.2 Results from Gambia

A recent study in Gambia (19) used cotrimoxazole to treat 65 asymptomatic children (aged 7-23 months) who were found in the course of a malaria survey to have a malaria parasitemia of 2500/ul or greater; 3.3% of blood films remained positive 6 days after the start of treatment and 7.7% were positive after 21 days. Cotrimoxazole was also used to treat 10 sick children with ARI and malaria; all responded clinically but 1 of 10 had a positive film on day 4 but was negative thereafter.

### 5.3 Conclusions regarding cotrimoxazole as an antimalarial in children under 5 years of age with signs suggesting pneumonia

The meeting concluded that cotrimoxazole for 5 days is an effective antimalarial in young children and that, where laboratory facilities are not available, there is sufficient evidence to suggest that the recommendation to treat with both an antibiotic and an antimalarial (in children in malarious areas with fast breathing and fever) should be changed. Cotrimoxazole can be recommended as a single treatment for these children.

A policy involving the use of cotrimoxazole as dual therapy for clinically-diagnosed pneumonia and malaria is relevant only to those areas where:

- Malaria is moderately to highly endemic;
  - The predominant malaria parasite being transmitted is *P. falciparum* (as occurs in Africa south of the Sahara, Papua New Guinea, Haiti and the Amazon basin). *P. vivax* may be resistant to the drug combinations such as cotrimoxazole and sulfadoxine/pyrimethamine, whereas it generally retains susceptibility to chloroquine;
- and
- *P. falciparum* remains sensitive to sulfadoxine/pyrimethamine.

Because of the likelihood of poor compliance with a five-day, twice daily regimen, cotrimoxazole would not be an appropriate candidate for use as an antimalarial drug outside the context of co-presentation with pneumonia. The availability and efficacy of sulfadoxine/pyrimethamine, as well as its advantage as a single dose therapy, further diminishes any role cotrimoxazole might have as a therapy for uncomplicated malaria.

## 6. COTRIMOXAZOLE AND SULFADOXINE/PYRIMETHAMINE INTERACTIONS

### 6.1 Possibility of antimalarial and antibacterial cross-resistance

The introduction of ARI programmes in developing countries will affect drug use in different ways. Antibiotic use for ARI may decrease, as demonstrated in Fiji (2) due to decreased inappropriate treatment. In many countries, however, use will increase due to better availability. Concern has been expressed that the increased use of cotrimoxazole would render sulfadoxine/pyrimethamine ineffective against P. falciparum parasites.

It is not known whether cotrimoxazole use in ARI programmes will promote resistance to sulfadoxine/pyrimethamine. There is no data yet which demonstrates the induction of cross-resistance. In Thailand, quinine-cotrimoxazole efficacy against P. falciparum declined in parallel with quinine-sulfadoxine/pyrimethamine efficacy. Sulfadoxine/pyrimethamine was, indeed, being supplied widely for malaria treatment both by the Government malaria programme and from private sources (doctors, dispensers, pharmacies, general markets). It is likely that cotrimoxazole was also used widely for a variety of indications during the same period, since it was easily available over the counter in all parts of the country. It is impossible to assess the relative importance of the use of the two medications in selection for resistance, although it is known that at that time, 15-20 million tablets of sulfadoxine/pyrimethamine were being imported into the country for antimalarial use and the malaria control programme was using only a small fraction of this amount.

Some experts feel cross-resistance is inevitable, based on drug action. Others points to the specificity of the molecular alteration resulting in pyrimethamine resistance (20) as evidence against the induction of resistance. Trimethoprim is a chemical analog of pyrimethamine and proguanil. It is assumed to have a similar mode of action, directly inhibiting dihydrofolate reductase in the parasite's (and to a lesser the human's) biochemical pathway of folate production. Recent biochemical work has shown that there may be different mutations by which parasites become resistant to proguanil and to pyrimethamine (20). Whether a separate mutation for trimethoprim occurs has not been studied. Some mutations lead to cross-resistance whereas others do not. In vitro work suggests that there is some degree of cross-resistance between proguanil and pyrimethamine but that it is not absolute.

Pyrimethamine prophylaxis can induce resistance rapidly, although this has not happened in Gambia where pyrimethamine has been given for prophylaxis in combination with dapsone.

The meeting concluded that the theoretical risk that increased use of cotrimoxazole in ARI programmes will contribute to sulfadoxine/pyrimethamine resistance does not present a sufficient threat to alter the selection of cotrimoxazole within an ARI strategy. It will, however, be important to assure that high levels of compliance are stressed in the development of ARI programmes. Attempts to define shorter courses of cotrimoxazole for pneumonia (e.g., to 3 days) should also consider their efficacy against P. falciparum. Data from South-East Asia suggest that 3 days of cotrimoxazole may not completely cure P. falciparum infections and would, therefore, intensify selection pressure for less sensitive parasites.

There is no evidence from the use of other drug combinations that the concurrent use of cotrimoxazole and chloroquine would reduce the possibility of the induction of resistance to sulfadoxine/pyrimethamine as compared to cotrimoxazole use alone.

Overall, the benefits of using cotrimoxazole for the treatment of pneumonia in areas where malaria is common are likely to outweigh its dangers, as this policy is likely to save the lives of a substantial number of children with malaria masquerading as pneumonia. However, if widespread use of cotrimoxazole is adopted, it is important that the effects of this policy on the development of resistance to this and related drugs should be monitored carefully both in bacteria, such as the pneumococcus, and in malaria parasites.

In vitro testing for cotrimoxazole and sulfadoxine/pyrimethamine (21) and simplified in vivo resistance study protocols (22) are available.

## 6.2

### Potential toxicity due to the co-administration of the two drugs

In areas where sulfadoxine/pyrimethamine becomes the first-line therapy for malaria (29) and cotrimoxazole is the first-line therapy for the outpatient treatment of pneumonia, some children will receive both drugs, even if cotrimoxazole alone is recommended for children presenting with cough, fever and fast breathing. For example, children who were treated with sulfadoxine/pyrimethamine for suspected malaria and return with signs suggesting pneumonia (cough and fast breathing) and receive cotrimoxazole. Co-administration should be cautious, given the absence of clinical experience and published data on the possible toxicity of cotrimoxazole and sulfadoxine/pyrimethamine given together. Co-administration should be minimized by recommending the use of cotrimoxazole alone for children who need to be treated for the possibility of both malaria and pneumonia.

### 6.2.1 **Potential toxicity due to the co-administration of two sulfa compounds**

It has not been shown that the use of sulphonamide combinations increases the risk of sulphonamide toxicity. Sulphonamide combinations are marketed in many countries for the treatment of adult urinary tract infections. The total sulphonamide dosage resulting from co-administration of sulfadoxine/pyrimethamine and cotrimoxazole, in their recommended dosage, would not be excessively high. Higher sulphonamide (and anti-folate) dosages are used in the treatment of pneumocystis pneumonia.

The risk of hypersensitivity reactions (mucocutaneous reactions, drug fever and organ damage) is increased by more frequent use and longer duration of therapy; the rate of these reactions will increase when sulfadoxine/pyrimethamine is used as first-line therapy for malaria since many children and adults will probably receive several courses of treatment each year. These reactions appear to be dose-independent although a few reports suggest a higher rate of reactions following an increased dose of sulfadoxine (23,24). No data exist on sulfadoxine plus sulfamethoxazole in combination. However, the rate of serious reactions is much higher following sulfadoxine, a long-acting sulfa, than following sulfamethoxazole. Given the relative safety of sulfamethoxazole regarding hypersensitivity reactions, single therapy with cotrimoxazole is preferable to co-administration with sulfadoxine/pyrimethamine. An increased rate of hypersensitivity reactions from co-administration is not anticipated but, given the lack of specific information, surveillance for adverse effects from co-administration should be pursued as a research topic.

### 6.2.2 **Potential toxicity due to the co-administration of two anti-folates**

Both pyrimethamine and trimethoprim can cause folate deficiency anaemia, neutropenia, and thrombocytopenia but these problems are rare when the correct dosage is administered for an acute illness. Co-administration of the two drugs would not result in an excessively high dosage of antifolate. However, it is possible that co-administration would result in a higher incidence of folate deficiency, particularly in children with nutritional deficiencies. Pyrimethamine is a much more potent inhibitor of mammalian dihydrofolate reductase than trimethoprim (25). The combination of cotrimoxazole with methotrexate, an even more potent inhibitor, has not caused folate deficiency problems.

There have been several case reports of megaloblastic anaemia when a course of cotrimoxazole was administered in women taking a higher than recommended dosage of pyrimethamine alone for malaria prophylaxis (on a chronic basis) (26,27).

It was concluded that the problems of toxicity do not outweigh the advantages of sulfadoxine/pyrimethamine for treatment of uncomplicated malaria without signs suggesting pneumonia. Since co-administration would probably not offer any therapeutic advantage, but could theoretically result in increased toxicity, health workers should be clearly instructed against concomitant co-

administration. Cotrimoxazole alone should be used for children presenting with signs of both malaria and pneumonia.

## 7. RECOMMENDATIONS FOR ARI AND MALARIA CONTROL PROGRAMMES

It is important that health workers be provided with guidelines that ensure adequate treatment of both pneumonia and malaria. In clinical settings without the availability of microscopic detection of parasitaemia, the following strategies should be considered.

In geographic areas or epidemiological settings where *P. falciparum* is endemic and retains sensitivity to sulfadoxine/pyrimethamine (based on clinical experience or laboratory results), cotrimoxazole given on a 5-day twice daily basis constitutes adequate therapy for *P. falciparum* in patients being treated for pneumonia. ARI programme managers should consult with local malaria programme officers and clinicians to determine the current status of sulfadoxine/pyrimethamine efficacy. Compliance with 5 days of therapy is important since adequate efficacy has only been demonstrated for this duration of treatment.

In areas where *P. vivax* is transmitted, either singly or in combination with *P. falciparum*, cotrimoxazole cannot be relied on to provide fully effective malaria therapy (28).

Coverage for malaria infection in pneumonia patients is complex in South America, South-East Asia, Oceania and the Indian subcontinent due to the extensive distribution of sulfadoxine/pyrimethamine resistant *P. falciparum* and the co-endemicity of *P. falciparum* and *P. vivax*. In areas such as these where sulfadoxine/pyrimethamine sensitivity persists, cotrimoxazole combined with chloroquine might give the broadest pneumonia/malaria coverage. In areas of sulfadoxine/pyrimethamine resistance, pairing of the pneumonia drug therapy with an alternative antimalarial drug such as mefloquine or quinine, neither of which has antibacterial action, should be considered.

Part of the management protocol for febrile children should be to check for cough or difficult breathing; if this is present, the patient should be assessed for possible pneumonia (by counting the respiratory rate and observing the child for chest indrawing). In a malarious area, if there is no cough or difficult breathing, or if there is no fast breathing in a child with cough or difficult breathing, this child should be treated for malaria alone.

Treatment of children with fever and signs of pneumonia in areas with <u>P. falciparum</u> malaria				
Fever	Cough	Fast Breathing	Danger Signs	Treatment
■				Specific antimalarial alone
■	■			Cotrimoxazole alone (no additional antimalarial)
■	■	■		Refer to hospital after first dose cotrimoxazole; add specific antimalarial if signs of severe malaria*
■	■		■	Refer to hospital after first dose cotrimoxazole; add specific antimalarial if signs of severe malaria*

\* Usually parenteral quinine if available

If sulfadoxine/pyrimethamine or mefloquine are the primary therapy for malaria, this approach is particularly relevant (see section 6.2).

On balance, the use of cotrimoxazole as combined therapy for a child with a clinical presentation which may indicate either disease is safer than asking the health worker to attempt to distinguish the two diseases. Mistakes can be fatal, either by treating a child with falciparum malaria with amoxicillin alone, or treating a child with pneumococcal pneumonia with chloroquine alone.

Case management recommendations and training should be planned so that both infections are adequately treated empirically when children present with cough, fever and fast breathing (in areas where falciparum malaria is transmitted).

The transmission of sulfadoxine/pyrimethamine sensitive P. falciparum malaria is an additional strong reason for national ARI control programmes to choose cotrimoxazole as the first-line therapy for pneumonia.

## 8. RECOMMENDATIONS FOR RESEARCH

- i. Further exploration of the overlap in clinical presentation between pneumonia and malaria. Since malaria epidemiology varies widely, studies are needed in several locations.
- ii. Field trials of the clinical recommendations listed in section 7.

- iii. Further investigations into management strategies which do not isolate diseases but rather accept the overlap in clinical presentations. Prospective cohort studies of paediatric febrile illness may be helpful in further defining the overlap and in guiding clinical management.
- iv. Determine whether interstitial radiological findings can be primarily due to falciparum malaria in a child who is not severely ill.
- v. Determine whether 3 days of cotrimoxazole are adequate for the treatment of falciparum malaria and for the treatment of pneumonia.
- vi. In vitro investigations of the potential efficacy of sulfadoxine/pyrimethamine as an antibacterial agent.
- vii. Further trials of cotrimoxazole for the treatment of different strains of P. falciparum in patients with little or no immunity and under conditions where it is possible to follow patients for 28 days, to distinguish reinfection from recrudescence, and to evaluate the degree of resistance to sulfadoxine/pyrimethamine.
- viii. Relationship between cotrimoxazole use and the induction of resistance to sulfadoxine/pyrimethamine resistance.
  - (a) In vitro test for cotrimoxazole sensitivity of strains of P. falciparum with known resistance to sulfadoxine/pyrimethamine.
  - (b) Monitor for resistance after the introduction of cotrimoxazole in national ARI control programme activities in areas with little prior use and no sulfadoxine/pyrimethamine resistance to P. falciparum.
  - (c) Test strains of P. falciparum which recrudescence after treatment with cotrimoxazole for in vitro sensitivity to cotrimoxazole and sulfadoxine/pyrimethamine and by determining clinical efficacy and parasitological cure achieved by sulfadoxine/pyrimethamine.
- ix. Determine the impact of (a) mass chemoprophylaxis with dapsone/pyrimethamine or periodic sulfadoxine/pyrimethamine on ARI mortality and (b) the effect of of ARI control programme implementation using cotrimoxazole on malaria morbidity and mortality.
- x. Determine the effect of fever on respiratory rate and examine whether this relationship is affected by cause of the fever.
- xi. Determine the implications of the overlap in clinical presentation of malaria and pneumonia for verbal autopsies and household morbidity surveys.
- xii. Where possible, add pneumonia surveillance to ongoing community malaria studies.

- xiii. In an area introducing both sulfadoxine/pyrimethamine as first-line therapy for P. falciparum malaria and cotrimoxazole as first-line therapy for clinical pneumonia, institute monitoring for adverse reactions to (inadvertent) co-administration or closely-spaced administration as a research activity (24).

**Table 1** Treatment of *P. falciparum* with cotrimoxazole in adults and school-age children

Country	Age (years)	Number of tablets <sup>a</sup> / day <sup>b</sup> or mg/kg	Days of treatment	Number of patients	Number parasitaemic on day 6 (%)	Mean days to clearance of asexual parasites
Mozambique	2-62	4	3-4	100	100 (100)	2.1
Pakistan	Adults	5	22	22	(100)	2.2
Nigeria	5-12	0.1/kg	1	42	42 (100)	1.3
		0.5/kg	1	44	43 (98)	2.0
United Rep. Tanzania	5-60	4	1-7	547	535 (98)	2.5
Thailand	12-47	4	2.5-10	14	14 (100)	4.1
		4	5-10	10	10 (100)	2.7
Brazil	?	4	4	20	? 2-5	

**Table 2** Recrudescences during 28-day follow-up after treatment of *P. falciparum* infections

Drug	Daily dose <sup>b</sup>	Days of treatment	Number of patients	Number of recrudescences (%)
Mozambique Cotrimoxazole <sup>a</sup>	4	3	34	11 (32)
	4	4	28	3 (11)
Chloroquine, 25mg/kg Sulfadoxine/ pyrimethamine <sup>c</sup>		3	60	4 (7)
	2-3	1	62	0
United Rep. Tanzania Cotrimoxazole <sup>a</sup>	4	1	135	41 (30)
	4	3	139	25 (18)
	4	5	133	25 (19)
	4	7	139	22 (16)
Chloroquine	600 mg	1	138	22 (16)
	1500 mg	3	135	8 (6)
	2100 mg	5	138	6 (4)

<sup>a</sup> One tablet contains 80 mg trimethoprim and 400 mg of sulfamethoxazole.

<sup>b</sup> Adult dosage.

<sup>c</sup> One tablet contains 25 mg of pyrimethamine and 500 mg of sulfadoxine.

**Table 3**  
**Treatment of *P. falciparum* with 5 days of twice-daily cotrimoxazole in children under 5 years of age**

Country/ patient characteristics	No. of patients	Percent aparasitaemic on Day 3*	Response on Day 6 (Gambia) or Day 7 (Malawi)	Follow-up: Day 14	Follow-up: Day 21	Mean days to clearance of sexual parasites
<u>Malawi</u>	46		100 % aparasitaemic; 100 % clinical response	98 %* aparasitaemic; 100 % clinical response		2.7 days
<u>Gambia</u>						
Asymptomatic children with <i>P. falciparum</i> on smear	65		96.7 % aparasitaemic (57/59); 100 % asymptomatic		92.7 % aparasitaemic (48/52) 100 % asymptomatic	
ARI (7 pneumonia 3 otitis media)	10	90 %	100 % aparasitaemic; 100 % clinical response	100 % aparasitaemic; 100 % clinical response		

\* The single child with parasitaemia was subsequently aparasitaemic on days 15, 16, 19 and 21 without additional treatment.

**Table 4**

**Number of children under 5 with cough or fever meeting clinical and laboratory definitions for malaria and pneumonia - Malawi**

Clinical definition	No	(%)	Laboratory definition	No	(%) <sup>a</sup>
History of fever ("malaria alone")	979	(61)	Parasitaemia	300	(31.6)
			Radiographic pneumonia	14	(1.5)
			Both	13	(1.4)
			Neither	620	(65.5)
Cough or difficult breathing and fast breathing or chest indrawing ("pneumonia alone")	22	(1)	Parasitaemia	2	(11.1)
			Radiographic pneumonia	2	(11.1)
			Both	0	(0)
			Neither	14	(77.8)
Both clinical definitions	449	(28)	Parasitaemia	148	(41.3)
			Radiographic pneumonia	55	(15.4)
			Both	27	(7.5)
			Neither	128	(35.8)
Neither clinical definition	149	(10)	Parasitaemia	15	(10.3)
			Radiographic pneumonia	2	(1.4)
			Both	3	(2.0)
			Neither	126	(86.3)

<sup>a</sup> Excluding patients with missing laboratory data.

Table 5

Number of children under 5 with respiratory rate  $\geq 50$ /minute in infants,  
 $\geq 40$  in children 1-4 years old meeting clinical and laboratory definitions for  
malaria and pneumonia - Gambia<sup>a</sup>

Clinical definition	No	(%)	Laboratory definition	No	(%) <sup>a</sup>
Fever or history of fever ("malaria alone")	116	(14.8)	Parasitaemia	84	(72.4)
			Radiographic pneumonia	4	(3.4)
			Both	16	(13.8)
			Neither	12	(10.7)
Cough and fast breathing or chest indrawing ("pneumonia alone")	6	(0.8)	Parasitaemia	1	16.7)
			Radiographic pneumonia	1	(16.7)
			Both	0	(0)
			Neither	(66.6)	
Both clinical definitions	659	(84.2)	Parasitaemia	326	(49.5)
			Radiographic pneumonia	129	(19.6)
			Both	91	(13.8)
			Neither	113	(17.1)
Neither clinical definition	2	(0.29)	Parasitaemia	2	(100)
			Radiographic pneumonia	0	(0)
			Both	0	(0)
			Neither	0	(0)

<sup>a</sup> Results of 783 patients with complete laboratory data.

**Table 6**

**Summary of results from Gambia**

Clinical malaria split into:

"Malaria alone" = Fever or history of fever without other obvious cause.

"Malaria plus" = Fever or history of fever with other obvious cause.

Parasite density included.

Clinical definition	No	(%)	Laboratory definition	No	(%)
"Malaria alone"	101	(12.9)	Parasitaemia < 2,500/ul	5	(4.9)
			Parasitaemia ≥ 2,500/ul	70	(69.3)
			Radiographic pneumonia	3	(3.0)
			Both, para. < 2,500/ul	2	(2.0)
			Both, para. ≥ 2,500/ul	13	(12.9)
			Neither	8	(7.9)
"Malaria plus" other causes of fever	15	(1.9)	Parasitaemia < 2,500/ul	2	(13.3)
			Parasitaemia ≥ 2,500/ul	7	(46.7)
			Radiographic pneumonia	1	(6.7)
			Both, para. < 2,500/ul	0	(0)
			Both, para. ≥ 2,500/ul	1	(6.7)
			Neither	4	(26.7)
"Pneumonia alone"	6	(0.8)	Parasitaemia < 2,500/ul	1	(16.7)
			Parasitaemia ≥ 2,500/ul	0	(0)
			Radiographic pneumonia	1	(16.7)
			Both	0	(0)
			Neither	4	(66.6)
Both clinical definitions	659	(84.2)	Parasitaemia < 2,500/ul	46	(7.0)
			Parasitaemia ≥ 2,500/ul	280	(42.5)
			Radiographic pneumonia	129	(19.6)
			Both, para. < 2,500/ul	22	(3.3)
			Both, para. ≥ 2,500/ul	69	(10.5)
			Neither	113	(17.1)
Neither clinical definition	2	(0.2)	Parasitaemia < 2,500/ul	1	(50.0)
			Parasitaemia ≥ 2,500/ul	1	(50.0)
			Radiographic pneumonia	0	(0)
			Both	0	(0)
			Neither	0	(0)

Table 7

## Results from Gambia

Paediatrician's main final diagnosis for 894 children enrolled  
with raised respiratory rate

Clinical definition	No	(%)	Final diagnosis	No	(%)
"Malaria alone"	129	(14.4)	Malaria	108	(83.7)
			AURI <sup>a</sup>	5	(3.9)
			Septicaemia	6	(4.7)
			Pneumonia	2	(1.6)
			Other ALRI <sup>b</sup>	1	(0.8)
			Meningitis	1	(0.8)
			Miscellaneous <sup>c</sup>	6	(4.7)
"Pneumonia alone"	7		AURI	4	(57.1)
			Other ALRI	2	(28.6)
			Malaria	1	(14.3)
Both clinical definitions	756	(84.6)	Malaria	406	(53.7)
			Pneumonia	148	(19.6)
			AURI	65	(8.6)
			Other ALRI	55	(7.3)
			Septicaemia	30	(4.0)
			Meningitis	4	(0.5)
			Miscellaneous	48	(6.3)
Neither clinical definition	2	(0.2)	Malaria	2	(100)

<sup>a</sup> AURI (acute upper respiratory infections).<sup>b</sup> Other ALRI (acute lower respiratory infections) = wheezy bronchitis, bronchiolitis.<sup>c</sup> Includes dysentery, gastroenteritis, urinary tract infection, skin sepsis and various other minor complaints.

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