

# Overdiagnosis of malaria in patients with severe febrile illness in Tanzania: a prospective study

Hugh Reyburn, Redempta Mbatia, Chris Drakeley, Ilona Carneiro, Emmanuel Mwakasungula, Ombeni Mwerinde, Kapalala Saganda, John Shao, Andrew Kitua, Raimos Olomi, Brian M Greenwood, Christopher J M Whitty

London School of Hygiene and Tropical Medicine, London WC1E 7HT  
Hugh Reyburn  
*clinical senior lecturer*  
Chris Drakeley  
*parasitologist*  
Ilona Carneiro  
*statistician*  
Brian M Greenwood  
*professor*  
Christopher J M Whitty  
*clinical senior lecturer*

Kilimanjaro Christian Medical Centre, Moshi, Tanzania

Redempta Mbatia  
*clinical epidemiologist*  
Ombeni Mwerinde  
*data manager*  
John Shao  
*executive director*  
Raimos Olomi  
*professor*

National Institute of Medical Research, Dar es Salaam, Tanzania

Emmanuel Mwakasungula  
*clinician*  
Andrew Kitua  
*director general*

Mawenzi Hospital, Moshi, Kilimanjaro, Tanzania

Kapalala Saganda hospital  
*superintendent*

Correspondence to: H Reyburn  
hugh.reyburn@lshtm.ac.uk

BMJ 2004;329:1212-5

## Abstract

**Objective** To study the diagnosis and outcomes in people admitted to hospital with a diagnosis of severe malaria in areas with differing intensities of malaria transmission.

**Design** Prospective observational study of children and adults over the course a year.

**Setting** 10 hospitals in north east Tanzania.

**Participants** 17 313 patients were admitted to hospital; of these 4474 (2851 children aged under 5 years) fulfilled criteria for severe disease.

**Main outcome measure** Details of the treatment given and outcome. Altitudes of residence (a proxy for transmission intensity) measured with a global positioning system.

**Results** Blood film microscopy showed that 2062 (46.1%) of people treated for malaria had *Plasmodium falciparum* (slide positive). The proportion of slide positive cases fell with increasing age and increasing altitude of residence. Among 1086 patients aged  $\geq 5$  years who lived above 600 metres only 338 (31.1%) were slide positive, while in children  $< 5$  years living in areas of intense transmission ( $< 600$  metres) most (958/1392, 68.8%) were slide positive. Among 2375 people who were slide negative, 1571 (66.1%) were not treated with antibiotics and, of those, 120 (7.6%) died. The case fatality in slide negative patients was higher (292/2412, 12.1%) than for slide positive patients (142/2062, 6.9%) ( $P < 0.001$ ). Respiratory distress and altered consciousness were the strongest predictors of mortality in slide positive and slide negative patients and in adults as well as children.

**Conclusions** In Tanzania, malaria is commonly overdiagnosed in people presenting with severe febrile illness, especially in those living in areas with low to moderate transmission and in adults. This is associated with a failure to treat alternative causes of severe infection. Diagnosis needs to be improved and syndromic treatment considered. Routine hospital data may overestimate mortality from malaria by over twofold.

## Introduction

In the year 2000 about 42% of hospital diagnoses and 32% of hospital deaths in Tanzania were attributed to malaria,<sup>1</sup> a figure typical of countries in Africa where malaria is endemic.<sup>2</sup> Despite this, little is known about the accuracy of hospital diagnosis or the appropriateness of treatment. A recent study from Tanzania found that of 75 adults diagnosed and treated for cerebral malaria in a teaching hospital only two met World Health Organization criteria for the diagnosis.<sup>3</sup> Studies of district hospitals in Africa have identified frequent problems with the organisation and planning of care.<sup>4 5</sup>

Given the high proportion of admissions attributed to malaria, overdiagnosis of malaria and consequent neglect of alternative diagnoses could lead to avoidable morbidity and mortality. In addition, overdiagnosis burdens health services with costs they can ill afford.<sup>6</sup> Unreliable hospital data hamper health service planning.

Accuracy of hospital diagnosis of malaria is likely to depend on the epidemiological probability of the disease (defined by intensity of malaria transmission and age of patients) and this is important as most of the population of sub-Saharan Africa live in areas of moderate or low malaria transmission.<sup>7</sup> We thus prospectively examined the diagnosis and outcome in all patients admitted and treated for severe or potentially complicated malaria during one year in 10 hospitals serving people living under varying levels of malaria transmission. A clinician's decision to admit a patient for treatment of malaria defined those eligible for inclusion in the study.

## Methods

The study was conducted in north east Tanzania, which has a populated altitude ranging from sea level to about 1800 metres. In this area, altitude has been shown to be a valid proxy for the intensity of malaria transmission<sup>8</sup> with measured entomological inoculation rates of 300 infectious bites per year on the coast, 30 at an altitude of 930 metres, and  $< 1$  above 1500 metres.

We selected 10 hospitals that provided a well organised service and had trained staff willing to participate. This represents most government hospitals in the area. The study ran at nine hospital sites from February 2002 to February 2003. Because of the large number of admissions to the district hospital at the lowest altitude, patients aged  $< 13$  years were recruited on alternate days (a 50% sample of paediatric admissions).

All patients admitted for the treatment of malaria were eligible for the study. After the patients (or parents) gave informed consent, researchers collected details of age, sex, and village of residence for every case. Patients were assessed for potentially severe disease based on WHO criteria for severe malaria<sup>9</sup> with the addition of moderate anaemia (haemoglobin  $< 80$  g/l). If any of these were present, the researcher also recorded axillary temperature, respiratory pattern and rate, and Blantyre coma score.<sup>10</sup> Blood glucose was measured if the Blantyre coma score was  $< 5$ . As staining methods varied between hospitals, a separate blood film was taken ("research slide") in addition to the



This is the abridged version of an article that was posted on bmj.com on 12 November 2004: <http://bmj.com/cgi/doi/10.1136/bmj.38251.658229.55>

hospital slide, though only the hospital slide result was available to contribute to the patient's care.

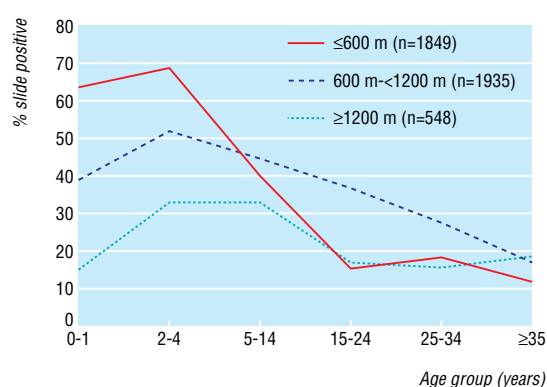
Research laboratory staff stained research blood slides with Giemsa stain and counted the number of *Plasmodium falciparum* asexual parasites per 200 leucocytes; a slide was considered negative if no parasites were found after 100 high power fields were scanned. All slides were read twice independently by microscopists blind to other data. Discordant slides were read a third time. The majority result was accepted for positive/negative discrepancies. Analyses relate to the research slide result unless specified otherwise. Villages from which people with malaria had been admitted were visited by a field assistant, and a global positioning point was taken from the central point in the village.

### Analysis

We double entered data in Microsoft Access and used Stata 8 (StataCorp, College Station, TX) for the statistical analysis. Univariate analyses examined the distribution of slide positivity and case fatality overall and within categories. We used random effects logistic regression to assess the adjusted effect of covariates on slide positivity and mortality and to adjust for correlation within hospitals. When logistic regression was used the data were weighted to adjust for the sampling of children on alternate days in one district hospital and stratified by two six month periods.

### Results

A total of 17 313 cases were recruited into the study over one year. Of these, 12 643 patients had a diagnosis of malaria but did not have any study criteria for severe disease, of whom 120 (1.0%) died. In total 4670 patients had at least one of the study criteria for severe disease and were treated for severe malaria, in 95% of cases with quinine. Of these patients, 196 (4.2%) had a missing or unreadable blood slide. Among the 4474 remaining patients, 2062 (46.1%) had a positive blood slide as determined by the presence of *P falciparum* asexual parasites on the research slide (slide positive). Most adults at every altitude band and most children under 5 years living above 600 metres had a negative slide (table 1). The proportion of patients with positive



Percentage of patients with at least one study criterion of severe disease who had a positive research blood slide for any *P falciparum* asexual parasites by age and altitude of residence

**Table 1** Patients admitted to hospital with diagnosis of malaria with at least one study criterion of severe disease by research blood slide result, age, and altitude (metres) of residence

Altitude	Total*	No (%) slide positive	No (%) slide negative
<b>Age &lt;5 years</b>			
<600 m	1392	958 (68.8)	434 (31.2)
600-<1200 m	1185	584 (49.3)	601 (50.7)
≥1200 m	212	46 (21.7)	166 (78.3)
<b>Age ≥5 years</b>			
<600 m	457	88 (19.3)	369 (80.7)
600-<1200 m	750	264 (35.2)	486 (64.8)
≥1200 m	336	74 (22.0)	262 (78.0)

\*Altitude of residence missing in 141 cases, age missing in 1 case

**Table 2** Prevalence of selected clinical features by research blood slide result and age

Age (years)	No (%) slide positive	No (%) slide negative
<b>Respiratory distress*:</b>		
<5	162 (10.1)	241 (19.5)
5-14	27 (13.9)	25 (10.3)
≥15	26 (10.3)	108 (11.7)
<b>Severe anaemia†:</b>		
<5	654 (40.7)	337 (27.8)
5-14	47 (24.4)	69 (28.8)
≥15	43 (17.8)	211 (23.5)
<b>Altered consciousness‡:</b>		
<5	77 (5.4)	78 (7.2)
5-14	42 (264.5)	34 (16.9)
≥15	60 (25.1)	202 (23.8)

\*Presence of chest indrawing (intercostals or subcostal recession) or abnormally deep breathing. Data missing or incomplete in nine cases.

†Haemoglobin <50 g/l from fingerprick sample. Data missing or incomplete in 80 cases.

‡Inability to localise painful stimulus (or, in those under 1 year, no motor response to pain) in absence of hypoglycaemia (blood glucose <2.2 mmol/l) and without convulsion in preceding 60 minutes or administration of anticonvulsant in previous six hours. Data missing or incomplete in one case.

slides decreased systematically with increasing age and with increasing altitude of residence (figure).

When we used logistic regression, controlled for clustering within hospitals, the odds of a positive slide decreased by 10% (odds ratio 0.90, 95% confidence interval 0.86 to 0.94,  $P < 0.001$ ) with each 100 metre increase in altitude. Age had a significant effect in the model ( $P < 0.001$ ). Compared with children under the age of 2 years the odds of a positive slide was higher among 2-4 year olds (1.35, 0.96 to 1.89) and then declined with age to 0.74 (0.39 to 1.40) at 5-15 years and 0.24 (0.10 to 0.59) at over 15 years. There was no significant difference in distribution of the three main categories of severe disease (severe anaemia, respiratory distress, and altered consciousness) between slide positive and slide negative patients stratified by age group, except that in children under the age of 5 years severe anaemia was more common among slide positive patients ( $P < 0.001$ ) and respiratory distress was more common among slide negative patients ( $P = 0.027$ ) (table 2). (See [bmj.com](http://bmj.com) for full details.)

The unadjusted odds of dying among slide negative patients were higher than among slide positive patients (1.85, 1.37 to 2.49,  $P < 0.001$ ), an effect observed across all age groups (table 3). Respiratory distress, severe anaemia, altered consciousness, age, and altitude of residence were all significantly associated with death (see [bmj.com](http://bmj.com)). After we controlled for these, patients who were slide negative still had increased odds of dying but the difference was of borderline significance (1.55, 0.94 to 2.53,  $P = 0.08$ ).

Mortality increased with age and decreased with increasing altitude.

When we used the definitive double read research slide as the reference, only 2949/4451 hospital slides were correct (66% agreement,  $\kappa=0.33$ ,  $P<0.0001$ ) with 988 false positives (39% of positives) and 514 false negatives (27% of negatives). This equates to a sensitivity, specificity, and positive predictive value of hospital slides in this group of 75%, 59%, and 61%, respectively.

Of 2375 patients who were slide negative by research results, 1571(66.1%) were not treated with antibiotics in addition to the antimalarial drug. A substantial proportion of these died, many of them were also slide negative according to the hospital slide (table 4).

## Discussion

### Patients treated for severe malaria often have no malaria parasites

Considerable advances have been made in the management of people with febrile illness in Africa and in ensuring that those who are severely ill get to hospital.<sup>11-13</sup> What happens when they reach hospital has received less attention, despite considerable scope for improvement.<sup>4</sup> Malaria is the commonest reason given for admission to hospital and for death in many African countries. Even small improvements in the management of severe febrile illness classified as malaria therefore have the potential to lead to important health gains.

While overdiagnosis of malaria is widely suspected, it has not previously been shown systematically at different levels of malaria transmission and at different ages. With the exception of children aged under 5 living in areas of high malaria transmission, most children and adults treated for malaria had no evidence of parasites on carefully examined research slides, and the chances of an episode treated as malaria actually being malaria decreased systematically with decreasing intensity of transmission.

Attempts to improve management of people diagnosed with severe malaria, however well implemented, will have little impact if most of those treated do not, in fact, have the disease. The proportion of admitted patients treated for malaria who were slide positive was similar to the local prevalence of malaria parasitaemia,<sup>14</sup> suggesting that malaria was often used as a default diagnosis for severe febrile illness.

### Patients without parasites are often not treated with antibiotics

Mortality was higher in slide negative patients than slide positive patients in all age groups, a result also found in another recent study.<sup>15</sup> Our study was not designed to determine the aetiology of febrile illness not caused by malaria, but it does suggest the need for the wider use of antibiotics in slide negative cases. Two thirds of patients treated for severe malaria but with a negative hospital slide result were not treated with antibiotics. It may be that doctors do not trust slide results. The poor correlation of hospital slides with double or triple read research slides suggests this may be justified. If clinicians are unsure of the diagnosis in a patient with severe febrile illness it is reasonable to treat for malaria, but if they do it seems difficult to justify not treating with antibiotics as well. Almost half (43%) of patients who died and had a negative hospital slide result (available to clinicians at diagnosis) did not receive an antibiotic in hospital.

It is possible, but unlikely, that our study hospitals were atypical of east African hospitals generally. The area of Tanzania where the study was conducted is stable, and study hospitals included most district hospitals in the region. Clinicians knew hospital practice was being observed and any alteration to their practice as a result of the study was likely, if anything, to have stimulated more careful diagnosis. The clear cut nature of the measures (age, altitude of residence, pattern of disease, outcome, and double read blood slides) and the consistency of the findings both internally and with other studies from east Africa also suggest the findings are robust.<sup>16 17</sup>

**Table 3** Case fatality by research blood slide result and age among cases with at least one study criterion of severe disease

Age* (years)	Total	Slide positive		Slide negative	
		No of cases	No (% of deaths)	No of cases	No (% of deaths)
<2	1855	1016	67 (6.6)	839	82 (9.8)
2-4	996	598	27 (4.5)	398	28 (7.0)
5-14	441	196	21 (10.7)	245	29 (11.8)
≥15	1181	252	27 (10.7)	929	153 (16.5)

\*Age missing in one (non-fatal) case.

**Table 4** Number (%) of all cases and fatal cases treated with any antibiotic during hospital admission, according to hospital blood slide result and research blood slide result

Hospital slide result†:	All cases*		Fatal cases	
	No of patients	Not treated with antibiotic	No of patients	Not treated with antibiotic
Negative	1897	1236 (65.2)	248	99 (39.9)
Positive	2499	1999 (80.0)	174	101 (58.0)
Research slide result‡:				
Negative	2375	1571 (66.1)	290	120 (41.4)
Positive	2043	1680 (82.2)	142	86 (60.6)

\*Antibiotic treatment refers to record of antibiotic treatment during hospital admission; all cases were treated with antimalarial.

†Data on antibiotic treatment of hospital slide result missing in 78 cases (including 12 fatal cases).

‡Data on antibiotic treatment missing in 56 cases (including two fatal cases).

### What is already known on this topic

Falciparum malaria is a major cause of morbidity and mortality in Africa

Around half of all hospital admissions in much of Africa are attributed to malaria

Diagnostic facilities in most hospitals in Africa are limited, and diagnosis of many diseases, including malaria, is often inaccurate

Certain presentations, especially raised respiratory rate and reduced level of consciousness, are predictive of poor outcome in children with malaria

### What this study adds

Except for children in areas of high transmission, children diagnosed and treated for severe malaria often have no parasites on their blood film

Most adults at every transmission level who are treated for severe malaria do not have laboratory evidence of disease

Many of those with severe febrile illness with no malaria parasites are not treated with antibiotics

The syndromes associated with poor outcome in severe childhood malaria are also predictive of poor outcome in febrile children without malaria, and in adults with and without malaria

True slide negative cases of severe malaria are rare. A positive slide, however, is a common incidental finding in areas where many people are semi-immune to malaria and have asymptomatic parasite carriage. The predictive value of positive slides for clinical malaria may be improved by considering parasite density.<sup>18</sup> If our definition of malaria had included a parasite density of >1000 asexual *P falciparum* parasites per microlitre, the number of cases defined as not malaria would have increased by about 15%. We therefore think our estimate of overdiagnosis of malaria is conservative.

As in previous studies, respiratory distress and altered consciousness were the strongest predictors of mortality.<sup>16 17</sup> Our findings emphasise that these associations with mortality apply to both severe malaria and other severe febrile illness and to adults as well as children.

### Conclusion

Overdiagnosis of malaria is widespread and is evidence of the need to improve basic standards of hospital care in Africa, where massive need has to be met with limited resources. Current evidence suggests that many of the existing guidelines are not followed,<sup>4</sup> laboratory workload compromises quality,<sup>19</sup> and triaging hospital admissions to prioritise care is rare.<sup>5</sup> One option to improve the situation is to improve diagnostic accuracy, although this is not easy. An alternative is to move to a more syndromic approach to hospital care in Africa, concentrating efforts on treating the probable causes of severe febrile illness.<sup>20 21</sup> Our results

suggest that the age of the patients and the local transmission intensity of malaria are often not taken into account in making a diagnosis and that patients with severe illness and a negative blood slide have high case fatality and often do not receive appropriate treatment. If the unacceptable levels of mortality due to treatable infections in Africa are to be reduced these problems need to be addressed.

We thank the patients and their families who participated in this study. We also thank the clinical and laboratory staff who assisted in data collection: Mark Swai, Werner Shimana, Cleopa Mbwambo, Justina Mushi, Francis Assenga, Joseph Minja, Alan Minja, William Silayo, Richard Mcharo, Raymond Urassa, Richard Collins, Hilda Mbakilwa, Sia Nelson, Nsia Muro, Elizabeth Msoka, Theresia Mtui, Sarah Mushi, Michael Irira, Esther Lyatu, Alutu Masokoto, Frank Magogo, Nico Funga, Lincoln Male, William Chambo, and Zacharia Zafaelli.

Contributors: See bmj.com

Funding: Medical Research Council, UK (grant No 9901439). CJMW is supported by the Gates Malaria Partnership.

Competing interests: None declared.

Ethical approval: The ethical committees of the National Institute of Medical Research, Tanzania, and the London School of Hygiene and Tropical Medicine approved the study.

- 1 Ministry of Health. *Health statistics abstract 2002. Burden of disease and health utilization statistics. Vol 1.* Dar Es Salaam, Tanzania: Ministry of Health, 2002.
- 2 World Health Organization. *The Africa malaria report.* Geneva: WHO, 2003:1093. (WHO/CDS/MAL/2003.)
- 3 Makani J, Matuja W, Liyombo E, Snow RW, Marsh K, Warrell DA. Admission diagnosis of cerebral malaria in adults in an endemic area of Tanzania: implications and clinical description. *QJM* 2003;96:355-62.
- 4 English M, Esamai F, Wasunna A, Were F, Ogutu B, Warnae A, et al. Assessment of inpatient paediatric care in first referral level hospitals in 13 districts in Kenya. *Lancet* 2004;363:1948-53.
- 5 Nolan T, Angos P, Cunha AJ, Muhe L, Qazi S, Simoes EA, et al. Quality of hospital care for seriously ill children in less-developed countries. *Lancet* 2001;357:106-10.
- 6 Jonkman A, Chibwe RA, Khoromana CO, Liabunya UL, Chapanda ME, Kandiero GE, et al. Cost-saving through microscopy-based versus presumptive diagnosis of malaria in adult outpatients in Malawi. *Bull World Health Organ* 1995;73:223-7.
- 7 Snow RW, Craig M, Deichmann U, Marsh K. Estimating mortality, morbidity and disability due to malaria among Africa's non-pregnant population. *Bull World Health Organ* 1999;77:624-40.
- 8 Bodker R, Akida J, Shayo D, Kisinza W, Msangeni HA, Pedersen EM, et al. Relationship between altitude and intensity of malaria transmission in the Usambara Mountains, Tanzania. *J Med Entomol* 2003;40:706-17.
- 9 WHO. Severe falciparum malaria. *Trans R Soc Trop Med Hyg* 2000;94:1-2.
- 10 Molyneux ME, Taylor TE, Wirima JJ, Borgstein A. Clinical features and prognostic indicators in paediatric cerebral malaria: a study of 131 comatose Malawian children. *QJ Med* 1989;71:441-59.
- 11 WHO. Integrated management of childhood illness. [www.who.int/child-adolescent-health/publications/IMCI/WHO\\_FCH\\_CAH\\_00.40.htm](http://www.who.int/child-adolescent-health/publications/IMCI/WHO_FCH_CAH_00.40.htm) (accessed 7 Oct 2004).
- 12 Bryce J, el Arifeen S, Pariyo G, Lanata C, Gwatkin D, Habicht JP. Reducing child mortality: can public health deliver? *Lancet* 2003;362:159-64.
- 13 World Health Organization. *Africa malaria report 2003.* Geneva: WHO, 2003. (WHO/CDS/MAL/2003.1093 ed.)
- 14 Bodker R. *Variations in malaria risk in the Usambara Mountains, Tanzania.* Charlottenlund, Denmark: Danish Bilharzia Laboratory, 2000:56-84.
- 15 Planché T, Agbenyega T, Bedu-Addo G, Ansong D, Owusu-Ofori A, Micah F, et al. A prospective comparison of malaria with other severe diseases in African children: prognosis and optimization of management. *Clin Infect Dis* 2003;37:890-7.
- 16 Marsh K, Forster D, Waruiru C, Mwangi I, Winstanley M, Marsh V, et al. Indicators of life-threatening malaria in African children. *N Engl J Med* 1995;332:1399-404.
- 17 Schellenberg D, Menendez C, Kahigwa E, Font F, Galindo C, Acosta C, et al. African children with malaria in an area of intense Plasmodium falciparum transmission: features on admission to the hospital and risk factors for death. *Am J Trop Med Hyg* 1999;61:431-8.
- 18 Smith T, Schellenberg JA, Hayes R. Attributable fraction estimates and case definitions for malaria in endemic areas. *Stat Med* 1994;13:2345-58.
- 19 Mundy C, Ngwira M, Kadeweze G, Bates I, Squire SB, Gilks CF. Evaluation of microscope condition in Malawi. *Trans R Soc Trop Med Hyg* 2000;94:583-4.
- 20 WHO. *Management of the child with severe infection or severe malnutrition.* Geneva: WHO, 2000.
- 21 English M, Berkley J, Mwangi I, Mohammed S, Ahmed M, Osire F, et al. Hypothetical performance of syndrome-based management of acute paediatric admissions of children aged more than 60 days in a Kenyan district hospital. *Bull World Health Organ* 2003;81:166-73.

(Accepted 8 September 2004)

doi 10.1136/bmj.38251.658229.55