Health worker intervention component of Study entitled

A cluster-randomized trial of health worker and community interventions to improve adherence to national guidelines for the use of ACTs in Tanzania:

The TACT trial (Targeting ACT)

TRAINEES

MANUAL

Table of Contents

GLOSSARY

ACT – Artemesinin Combination Therapy

AM – Anti Malarial

CO – Clinical Officer

CQ – Chloroquine

QC – Quality Control

DMO – District Medical Officer

IMCI – Integrated Management for Childhood Illness

HIV – Human Immunodeficiency Virus

ITN – Insectside Treated Nets

JMP – Joint Malaria Programme

KCMC – Kilimanjaro Christian Medical Centre

LSHTM – London School of Hygiene and Tropical Medicine

MoH – Ministry of Health

mRDT – malaria Rapid Diagnostic Test

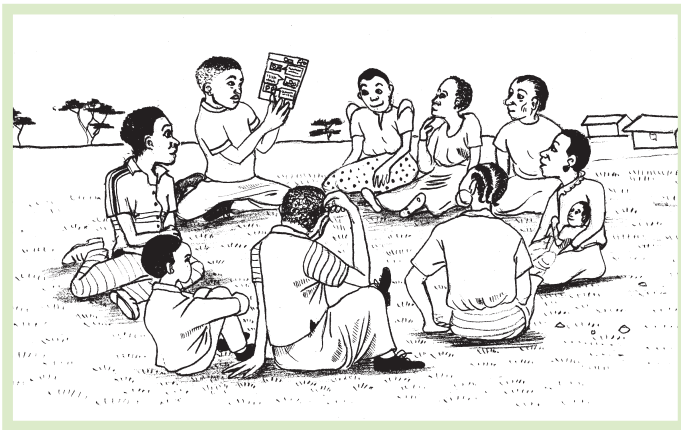NMCP – National Malaria Control Programme

PCM – Paracetamol

RDT – Rapid Diagnostic Test

SP – Salfadoxine Pyrimethamine

TACT – Targeting Artemesinin Combination Therapy

WHO – World Health Organization

Introduction

This manual is a trial-supplement to the "TRAINING GUIDE & FACILITATOR'S MANUAL FOR MALARIA RAPID DIAGNOSTIC TEST" produced by the Tanzania National Malaria Control Programme (NMCP). This manual was produced by the Joint Malaria Programme (JMP), Moshi and aims to assist health workers to implement the new policy for management of febrile illness.

The training recognises the challenges that health workers must overcome when incorporating mRDTs into their practice. Health workers have to change long established practices and cope with community expectations, when diagnosing malaria and treating febrile illnesses. Previously presumptive treatment was the norm, the new guidelines challenge this common practice.

TACT stands for 'targeting ACTs (Artemesinin Combination Therapy)' and aims to find the best ways to use rapid diagnostic tests (RDTs) so that:

• Patients with malaria **DO** get treated

• Patients without malaria **DO NOT** get given ACT but get treated for their likely illness

The TACT trial training uses small group interactive training within the workplace to enable change by developing the capacity of health workers to find feasible ways to adhere to mRDT and so change their practice for the long term.

Welcome to the training – we hope you enjoy the process of change!

Summary of TACT Trial Course

The TACT Trial course aims to assist you to integrate mRDTs into clinical practice.

Module 1	Module 2	Module 3
• Malaria is declining but is commonly over diagnosed.	• You need to effectively assess for other febrile illnesses when mRDT negative.	• Developing an agreed protocol on "How to cope with logistical challenges to using mRDTs" will ensure adherence to the new febrile illness guidelines.
• mRDT can help resolve this problem.	• You need to communicate the results of the mRDT and your management plan and respond to the patient' needs and questions.	• The challenges to implementing and adhering to mRDT recommendations can be complex. You can succeed!
• TACT Trial intends to assist health workers to use mRDTs to ensure ACTs is used appropriately and insures that non-malaria illnesses are treated.	• You need to be confident and build the trust of all patients in the test and in your appropriate management of the fever.	• Adhering to mRDT recommendations requires a strong understanding of the facts, strong communication and clinical skills on the part of you, the health worker/prescriber.
• Tools exist to assist health workers to overcome challenges when using RDTs and adhering to results.		

Adapting to the change

- Handouts
- Worksheets
- Homework

HANDOUTS - MODULE 1

Adapting to the changes in the diagnosis & management of malaria

Module 1 Objectives
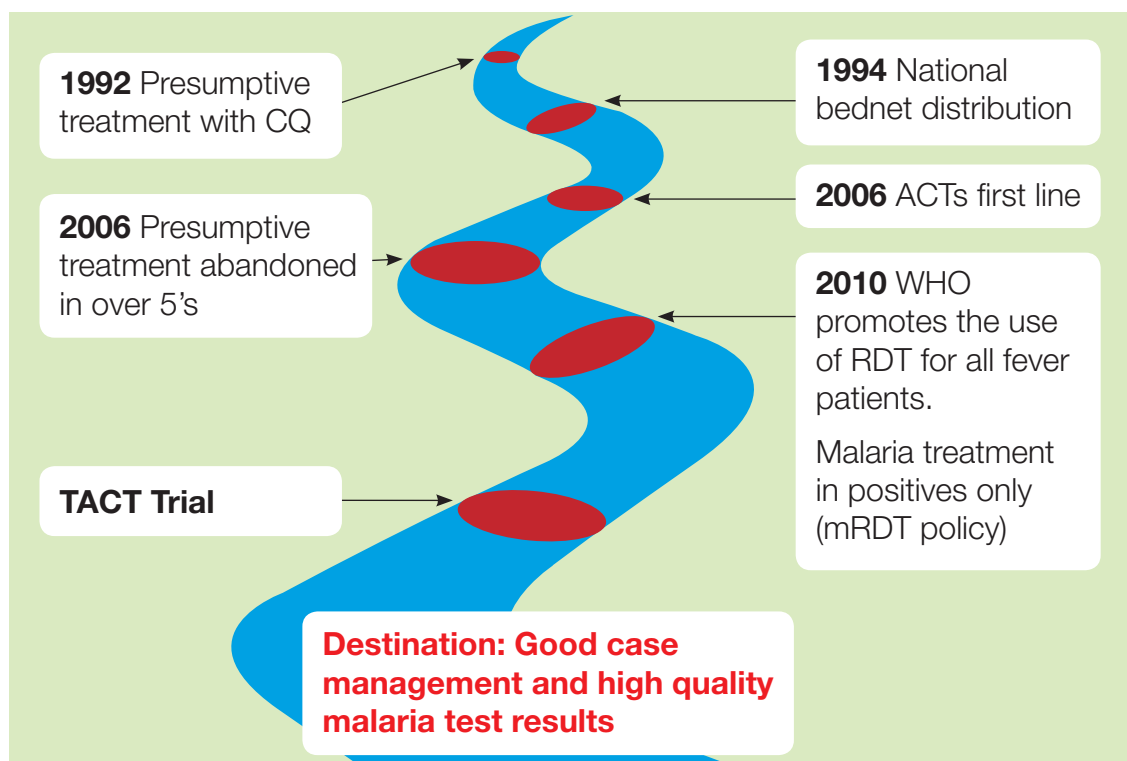
By the end of the module, you should be able to:

1. Understand the aim of the TACT trial.

2. Understand and agree upon the reasons for the changes in diagnosing and managing febrile illnesses, with particular emphasis on malaria.

3. Reflect on the challenges associated with the new approach to malaria diagnosis and management.

Module 1 Overview of Content

- Guidelines have adapted over the years to overcome the hurdles of malaria drug resistance and changing transmission in order to achieve best practice.

- Prescribers have adapted practice to adhere to guidelines on first line drugs but are lagging behind with the new guidelines on mRDTs.

- mRDT has been developed for health workers as a tool to ensure 'Patients with malaria DO get treated and Patients without malaria DO NOT get given ACT but get treated for their likely illness.'

The Malaria Management River Walk: Eliminating malaria – a long journey.

1992 Presumptive treatment with CQ

1994 National bednet distribution

2006 Presumptive treatment abandoned in over 5's

2006 ACTs first line

2010 WHO promotes the use of RDT for all fever patients.

Malaria treatment in positives only (mRDT policy)

TACT Trial

Destination: Good case management and high quality malaria test results

- Despite the low transmission of malaria, we must protect ACT from drug resistance and using mRDTs and adhering to the results when treating fever will ensure that this is possible.

True–false–up for debate quiz!

Understanding malaria over diagnosis and changes in malaria transmission forces us to change the way we manage febrile illnesses.

Look at some of the research findings:

1. **The changing picture of febrile illnesses in our region:**
   What are hospital admissions for malaria: 1999-2007?

Monthly admissions for malaria to Kilifi District Hospital and Mnazi Moja Hospital, Zanzibar
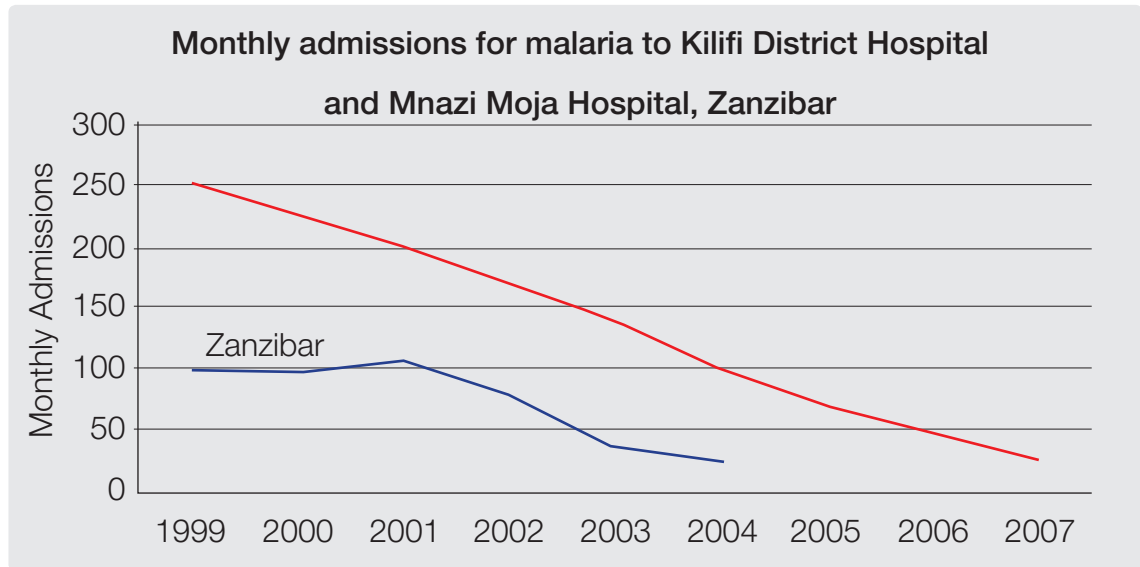
2. **The Revealing Picture of Malaria over diagnosis:**
   How common was malaria over diagnosis in your area in 2009?

= Malaria diagnosis as defined by clinician based on symptoms

= True malaria diagnosis as defined by a reliable malaria test
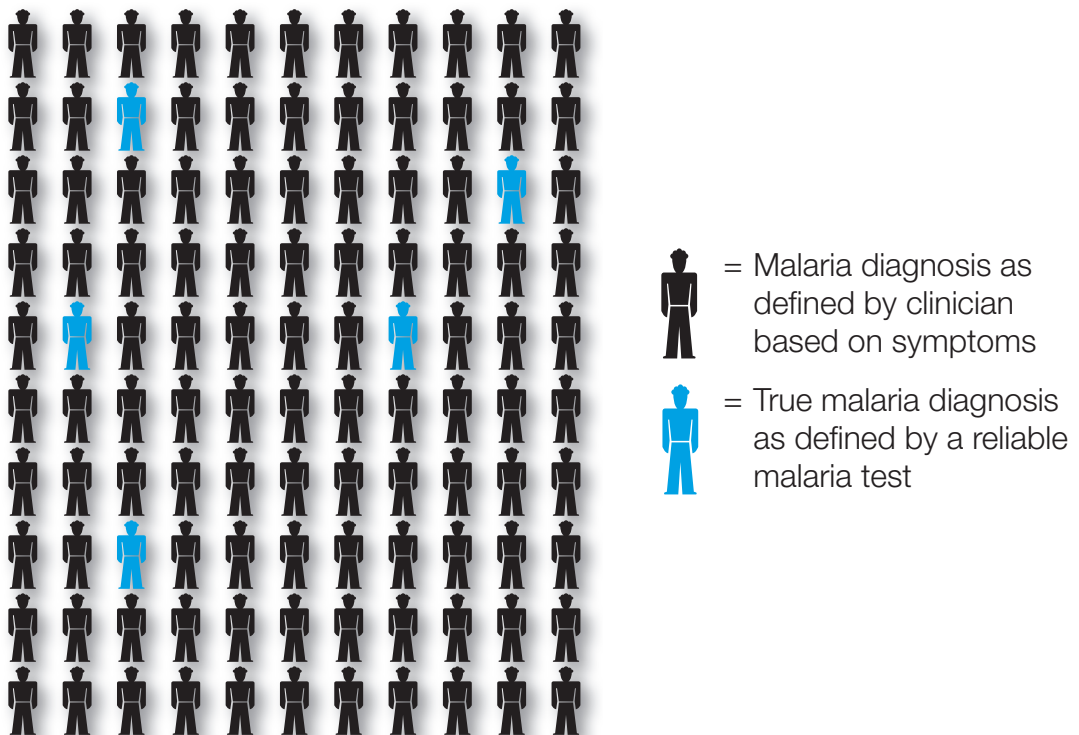
In reality:

- Only 5 out of 100 (5%) 'malaria' patients in Moshi had true malaria in 2009
- Only 10 out of 100 (10%) malaria patients in Muheza had true malaria in 2009
- Similar results in Handeni and Hai District in 2009

3. What are the most common causes of fever when the cause is not malaria?
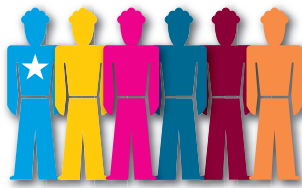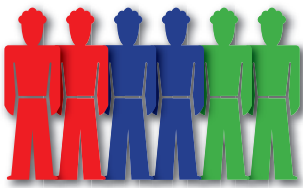
= True malaria diagnosis as defined by a reliable malaria test

A febrile patient with non-severe illness, no 'obvious cause of illness' and a negative RDT probably has a virus infection - this is even more likely if the patient has a runny nose or sore throat.

Three most Obvious Causes of fever – 'Top 3'

Ear infection	History of fever in previous 2 days and any of the following: pus at ear canal, ear ache, child pulls at ears and crying.
Soft tissue infection	Red swelling skin or boil size larger than width of a thumb.
Urinary tract infection	Pain in passing urine, frequency in passing urine, cloudy urine crying when passing urine (in children).

Other causes

Pneumonia	Cough, difficult in breathing and raised RR according to age.
Common cold	Nasal discharge, sore throat.
Upper respiratory tract infection	Cough, sore throat but no difficulty breathing.
Tonsillitis/ Pharyngitis	Severe sore throat, swollen tonsils with pus and sore throat.
Diarrhoea	Passing loose stools more than 3 times in 24hours.

Key messages from the debate include:

- Malaria transmission is declining in this area and in East Africa generally
- Malaria is overdiagnosed
- Overdiagnosis of malaria has negative effects
- Clinical diagnosis of malaria is not reliable
- mRDT is more accurate than routine malaria microscopy
- Antibiotics should not be prescribed for all test negative patients
- Alternative causes of fever are common
- Integrating guidelines into practice: Observing best practice when you integrate guidelines into practice.

Summary of Module 1

- Malaria is declining but is commonly over diagnosed
- mRDT can help resolve this problem
- TACT Trial intends to assist health workers to use mRDTs to ensure ACTs is used appropriately and non-malaria illnesses are treated
- Tools exist to assist health workers overcome challenges when using RDTs and adhering to results

WORKSHEETS - MODULE 1

Module 1 Worksheet 1: Questionnaire for Participants observing the role play skit

Imagine that the clinician(s) in this skit is your colleague – while observing the skit try to answer the following questions;

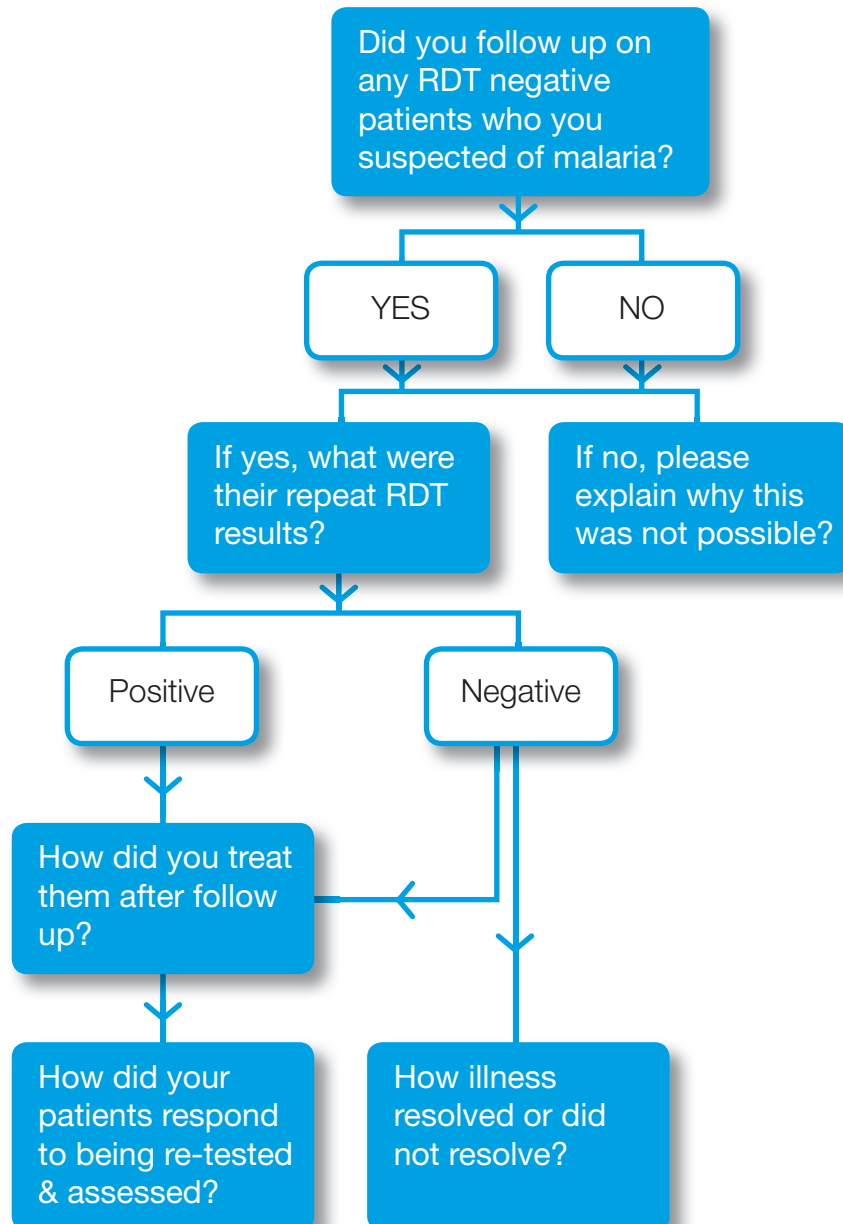| |
|---|
| 1. What are the challenges faced by the clinician in this role play as s/he tries to adhere to malaria practice and febrile illness management? |
| 2. How do you think the clinician in this skit coped with/handled the challenge s/he faced as s/he tried to adhere to practice recommendations? |
| 3. Do you have any other suggestions for the clinician to cope with the demands of the patient and the feedback from her peer? |

HOMEWORK - MODULE 1

Homework: Module 1 Self Assessment managing mRDT Negative Patients

This exercise is a self assessment when managing mRDT negative patients. Follow up 3 patients who were mRDT negative and did not receive anti malarial treatment then complete the questions in the flow chart below.

Consultation / Patient No.1

Did you follow up on any RDT negative patients who you suspected of malaria?

YES → If yes, what were their repeat RDT results?

NO → If no, please explain why this was not possible?

Positive → How did you treat them after follow up? → How did your patients respond to being re-tested & assessed?

Negative → How illness resolved or did not resolve?

Consultation / Patient No.2

Did you follow up on any RDT negative patients who you suspected of malaria?

YES

NO

If yes, what were their repeat RDT results?

If no, please explain why this was not possible?

Positive

Negative

How did you treat them after follow up?

How did your patients respond to being re-tested & assessed?

How illness resolved or did not resolve?

Consultation / Patient No.3

Did you follow up on any RDT negative patients who you suspected of malaria?

YES

NO

If yes, what were their repeat RDT results?

If no, please explain why this was not possible?

Positive

Negative

How did you treat them after follow up?

How did your patients respond to being re-tested & assessed?

How illness resolved or did not resolve?

Practice with Confidence

- Handouts
- Worksheets
- Homework

HANDOUTS - MODULE 2

Practice with Confidence when using mRDTs: Tools to enable change in managing febrile illness

Module 2 Objectives

By the end of the module, you should be able to:

1. Recognise the role of the confidence cycle in adhering to mRDT guidelines.

2. Demonstrate the capacity to communicate effectively including negotiating with patients who disagree with the prescribed clinical management.

Module 2 Overview of Content

• Guidelines have adapted over the years to overcome the hurdles of malaria drug resistance and changing transmission to ensure best practice.

• Prescribers have adapted practice to adhere to guidelines on first line drugs but are lagging behind with the new guidelines on mRDTs

• mRDT has been developed for health workers as a tool to ensure 'Patients with malaria DO get treated and Patients without malaria DO NOT get given ACT but get treated for their likely illness.

The Confidence Cycle

Confident clinician

Trustful client

Trust the test
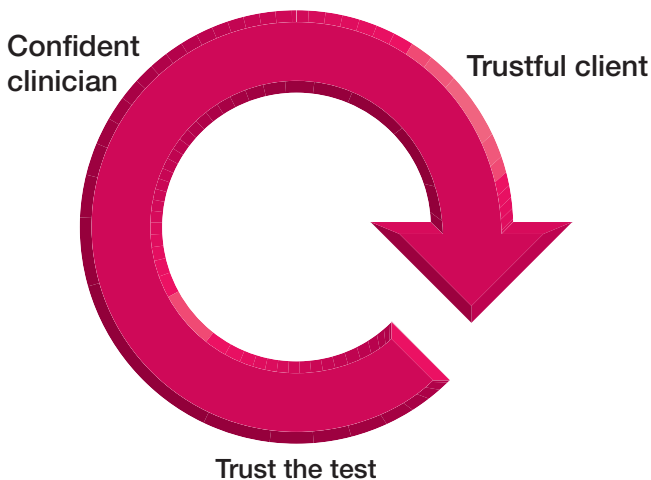
A confident clinician:

1. Knows and understand the facts.

2. Skilfully communicates the importance of mRDT to patients & peers.

3. Builds the trust of patients in the new procedures and helps to change their expectations.

4. Skilfully carries out and interprets the test.

5. Manages the test result and treats appropriately, in line with the test result.

6. Knows now how to proceed if mRDT not available.

7. Accepts feedback from peers and patients.

The Reliability Test - clinical predicators versus mRDT

Potential predictors of clinical malaria in children

Predictor – Indicator of malaria in a child	Odds ratio	Sensitivity	Specificity
Reduced feeding	1.8	72%	49%
Increased sleepiness	1.8	82%	34%
Absence of cough	1.9	65%	60%
Pallor	1.8	43%	79%
Increased RR	1.9	67%	57%
Palpable spleen	4.0	96%	17%
Shivering/chills	1.7	72%	47%

Sensitivity: the percentage of children/patients who have malaria who are identified as having one of the predicted symptoms as well as diagnosed with malaria.

Specificity: the percentage of children/patients who are not sick with malaria and who don't have one of the predictor symptoms.

Odds ratio: this describes the strength of association or relationship between the predictor symptoms and having malaria or not having malaria.

For example

A palpable spleen is the strongest predictor of malaria in children according to this source of data with a very strong association/relationship or odds ratio.

Tools to strengthen your confidence in your practice: The feedback tool

- Health workers require ongoing practice, self reflection and constructive feedback in order to strengthen their skills to confidently and appropriately manage patients presenting with fever and not to treat mRDT negative patients for malaria.

Role Play Checklist/ Feedback Form

Checklist	Very well done Competent	Partly done	Not done
Greet the patient and explain what you are going to do			
Ensure the patient is comfortable (sitting or lying down)			
Assess for fever			
Check for severe illness			
Ask what is the main complaint			
Asks patient if any other complaint or concern			
Examine the patient			
If RDT indicated, explains to patient need for mRDT			
mRDT carried out			
Prescription consistent with RDT result			
Explains negative mRDT to patient & consequences (follow up)			
Overall Communication			
Clear			
Simple			
Accurate			
Listened to patient			
Asked if patient understood treatment			
Demonstrates an overall confidence in test			
Builds patients' confidence in clinician			
Other comments			

Summary of Module 2

As modern confident qualified health worker you must:

- Effectively assess for other febrile illnesses when the mRDT is negative.

- Communicate the results and your management plan and respond to patients' needs and questions.

- Be confident and build the trust of patients in the test and in your appropriate management of their fever.

- Deliver best practice care despite the challenges you face when adhering to mRDTs in your clinical setting.

Homework Module 2

Homework

Describe 3 consultations in the past month when it was difficult or impossible to test patients with non-severe febrile illness suspected of malaria.

For Consultation 1:

1) Define the difficulty or reason why it was difficult or impossible?

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2) Describe why the difficulty occurred?

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3) What did you do to try to overcome the problem?

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4) What was the outcome of the consultation – did you eventually test the patient?

YES   NO

For Consultation 2:

1) Define the difficulty or reason why it was difficult or impossible?

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2) Describe why the difficulty occurred?

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3) What did you do to try to overcome the problem?

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4) What was the outcome of the consultation – did you eventually test the patient?

YES   NO

For Consultation 3:

1) Define the difficulty or reason why it was difficult or impossible?

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2) Describe why the difficulty occurred?

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3) What did you do to try to overcome the problem?

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4) What was the outcome of the consultation – did you eventually test the patient?

YES   NO

Sustaining the change

- **Handouts**
- **Worksheets**
- **Homework**

HANDOUTS - MODULE 3

Sustaining the change in practice

Module 3 Objectives

By the end of the module, you should be able to:

1. Summarise the key outputs of the two previous modules

2. Identify individual stage of change in relation to mRDT adherence.

3. Demonstrate the capacity to problem solve an mRDT logistical challenge.

4. Practice integration of mRDTs using challenging role-plays.

Module 3 Overview of Content

Self assessment – assessing stage of change in practice

- Participants are changing behaviour and moving towards 100% adherence to the mRDT guidelines.

- Developing an agreed protocol on "How to cope with logistical challenges to using mRDTs "will ensure adherence to the new febrile illness guidelines."

Role play

- The challenges to implementing and adhering to mRDT recommendations can be complex.

- Adhering to mRDT recommendations requires a strong understanding, strong communication and clinical skill on that part of the health worker/prescriber.

WORKSHEETS - MODULE 3

Module 3 Worksheet 1: Self assessment on change continuum

Activity A: Self assessment – assessing stage of change in practice

The aim of this exercise is to give you the opportunity to reflect on how YOU think you have changed since the beginning of the course. This information does not have to be shared with anybody.

The line represents the change continuum. When you arrived most of you were at point **A** (all patients with non-severe febrile illness are treated presumptively & not tested). Now you are all further along the line on your way to **Z** (where Z represents that all patients you see with non-severe febrile illness are tested with mRDT & managed in line with results.

Individually mark with an X where you think you have reached today.

Refer to your homework from Module 1 and take time to think whether you are now managing to test patients with fever 25% of the time? 50% of the time? Or 75% of the time? Before you mark the X.

You have 5 minutes.

A

All patients with
non-severe febrile
illness are treated
presumptively
and not tested

Z

All patients with
non-severe febrile
illness are tested with
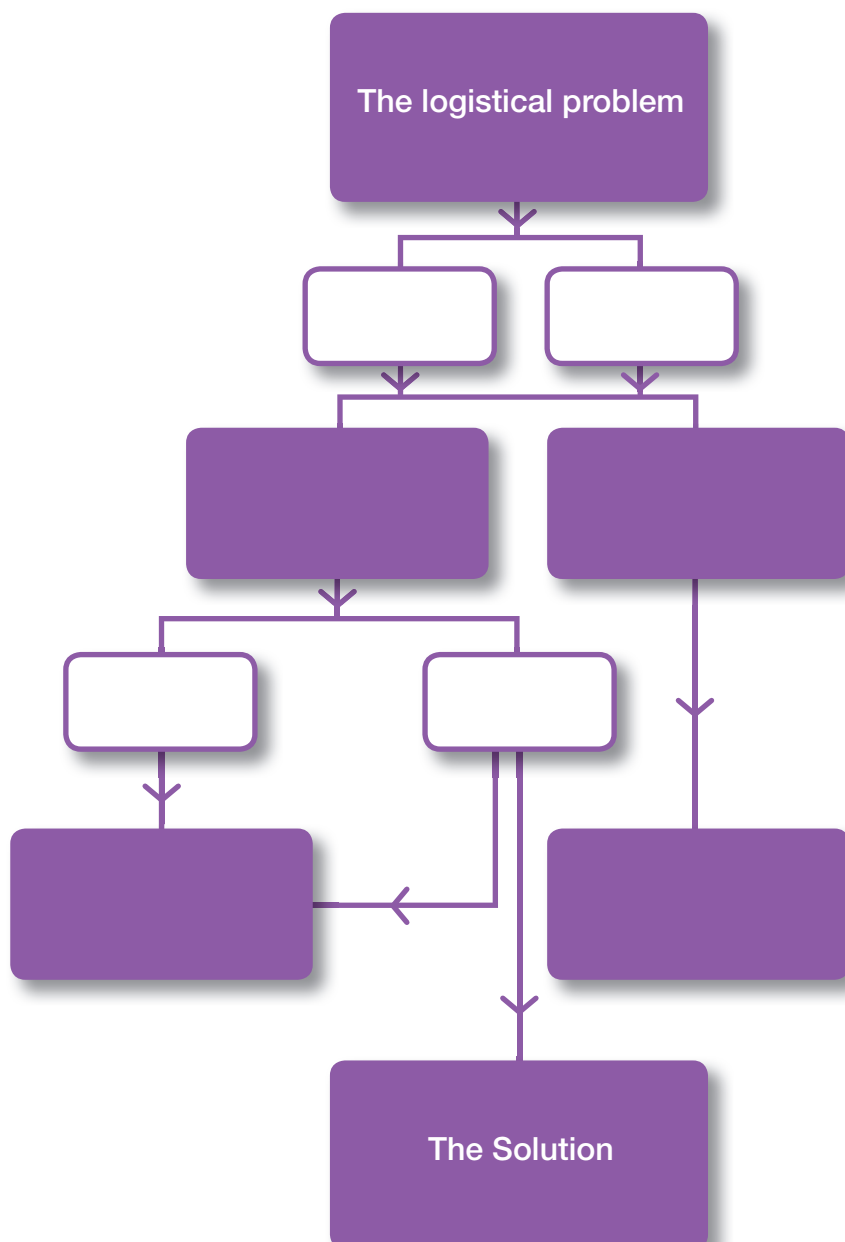mRDT & managed in
line with results

WORKSHEETS - MODULE 3

Module 3 Worksheet 2: Best Practice in the face of challenges adhering to mRDTs

Referring to your homework from Module 2

Choose one of the logistical problems that came up in your homework from Module 2 when you described 3 consultations in the past month when it was difficult or impossible to test patients with non-severe febrile illness suspected of malaria. Use this blank flow chart and discuss the logistical problem you faced. Complete the flow chart with the end goals being:

"Find a way to tackle the logistical challenge in a way that is feasible in your clinic."

Practical Solutions to Logistical Problems

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            ┌──────────────────────┐
            │ The logistical problem│
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          ┌────────────┴────────────┐
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      │       │                 │       │
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   │                     │    │            │
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   └──────────┬──────────┘    └────────────┘
         ┌────┴─────┐
         │The Solution│
         └──────────┘
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ANSWERS TO COMMON QUESTIONS

Q. How common is malaria?

A. There has been a marked decline in malaria over the last 10 years throughout East Africa. The reasons for the decline are not certain but seem to be due to the introduction of SP in 2001 and the continuous increase in the use of ITNs by young children.

A study in Kenya showed that, the estimated proportional decline in malaria cases in Kilifi, Kwale and Malindi was 63%, 53% and 28% respectively (Okiro at el, 2007). Another study in Zanzibar showed malaria admissions in children less than 14 years decreased by 77%. (Bhattarai at el, 2007).

Q. Is it true that malaria is overdiagnosed in Tanzania?

A. Yes, Studies have shown that of all patients who were prescribed antimalarial medication, only few of them actually has the disease. In areas where malaria is low, up to 95% malaria diagnosis is not accurate (Reyburn et al, 2006). In an area where it used to be hyperendemic for malaria, 99.6% of individuals who were treated with ACTs were in fact free of malaria parasites. (Mwanziva et al, 2008). Malaria is commonly overdiagnosed in patients presenting with severe illnesses which results in failure of treating alternative causes of severe infections. (Reyburn et al, 2004).

Q. Is it possible to distinguish malaria from other common causes of fever?

A. Not really, Malaria is a non specific disease because its features are overlapping with those of other diseases (Chandramohan et al, 2002). It is difficult to clinically diagnose malaria without parasitological confirmation.

Q. Is the mRDT accurate?

A. No test is perfect. Sometimes someone without malaria has a positive mRDT (false positive) and sometimes someone with malaria has a negative mRDT (false negative). mRDT was found to be more accurate than routine microscopy. (Reyburn et al, 2007, Zurovac et al, 2006).

Q. Who should I be testing by using mRDTs?

A. Guidelines say all non-severe patients with non-severe illness should be tested. That means we should NOT give an antimalarial drug unless there is a positive mRDT.

Q. What if I got a lot of mRDT negatives, should I trust the test?

A. The mRDT is a good test; we have seen it is 95% accurate. The probability of an mRDT result being true is determined by two things: how good the test is and how common the disease is, in the region. If you are in an area where only 10% of patients truly have malaria a NEGATIVE result is HIGHLY LIKELY TO BE TRUE!

ANSWERS TO COMMON QUESTIONS

Q. What about the sustainability of the RDTs?

A. mRDTs are now proven by the Tanzania Food and Drug Administration and recommended for use in diagnosing non-severe malaria in primary care facilities by NMCP in Tanzania. Since early 2010, NMCP with the Global Fund support has started to roll out these mRDTs and they are still doing so.

Q. What if I use my experience and clinical judgment to treat malaria?

A. We have already seen that malaria is a non specific disease. By using clinical judgment and your own experience, there is a possibility of missing other causes of fever which may require a different treatment for example Pneumonia.

Q. If the test is negative, how should I be sure is not malaria?

A. The mRDT is 95% accurate. False negative results ('missed malaria diagnoses) are rare but this category of patient needs to be looked at more closely. These patients can be examined for other causes of fever and if not obvious they can be given paracetomol and asked to come back if not better and the mRDT can be repeated.

Q. If not malaria what else could be?

A. There are a number of common diseases that cause fever, for example URTI, common colds, Pneumonia, viral infections etc. Also Urinary Tract Infections, skin infections and Ear infections also cause fever but these three conditions have been outlined in guidelines as "Obvious alternatives causes of fever".

Q. What if ALu is out of stock, should I use other antimalaria drugs like SP?

A. No. ALu should always be 1st line treatment for non-severe malaria (Tz guideline). To avoid being in such a situation make sure your HF does not run out of stock particularly on ALu. SP is meant for Intermittent Preventive Treatment in pregnant women.

Research papers

Use of clinical algorithms for diagnosing malaria[1]

Daniel Chandramohan, Shabbar Jaffar and Brian Greenwood

Department of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, London, UK

Summary   Several attempts have been made to identify symptoms and signs based algorithms for diagnosing malaria. In this paper, we review the results of published studies and assess the risks and benefits of this approach in different epidemiological settings. Although in areas with a low prevalence the risk of failure to treat malaria resulting from the use of algorithms was low, the reduction in the wastage of drugs was trivial. The odds of wastage of drugs increased by 1.49 (95% confidence limit 1.45–1.51) for each 10% decrease in the prevalence of malaria. In highly endemic areas the algorithms had a high risk of failure to treat malaria. The odds of failure to treat increased by 1.57 (95% confidence limit 1.50–1.65) for each 10% increase in the prevalence. Furthermore, the best clinical algorithms for diagnosing malaria were site-specific. We conclude that the accuracy of clinical algorithms for diagnosing malaria is not sufficient to determine whether antimalarial drugs should be given to children presenting with febrile illness. In highly endemic areas where laboratory support is not available, the policy of offering antimalarial drugs to all children presenting with a febrile illness recommended by the integrated child management initiative is appropriate.

keywords algorithm, malaria, diagnosis

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Introduction

An accurate diagnosis of malaria is essential to ensure that individuals who suffer from malaria receive appropriate treatment and that antimalarial drugs are not wasted on treatment of patients with other conditions. But as symptoms and signs of uncomplicated malaria overlap with several other febrile illnesses, even experienced physicians have difficulties in diagnosing malaria: paediatricians in The Gambia (Olaleye *et al.* 1998) and Tanzania (Rooth & Bjorkman 1992) diagnosed malaria in children using their clinical skills alone with sensitivities of 86% and 99% and specificities of 61% and 52%, respectively. In many malaria-endemic areas, most patients with an acute febrile illness receive antimalarial drugs from primary health care workers (based in a clinic or community) or pharmacy assistants with little clinical training or from shop keepers and drug vendors who have had no formal training in the diagnosis

of malaria. As these treatment providers offer antimalarial drugs to almost every one with a history of fever, the sensitivity of their diagnosis of malaria will be close to 100%, but the specificity of their diagnosis is likely to be very low. For example, diagnosis of malaria by rural medical aides in Tanzania (Rooth & Bjorkman 1992) had a specificity of only 13%. In Niger diagnosis of malaria by urban primary health workers had a specificity of 21% during dry season and 0% during wet season (Oliver *et al.* 1991).

Prescribing presumptive treatment for malaria with a low threshold of suspicion was reasonable at a time when all malaria parasites were sensitive to chloroquine, as chloroquine is safe and cheap. However, a higher degree of accuracy in diagnosis is needed in areas of chloroquine resistance because of the need for treatment with more expensive and potentially more dangerous drugs. One approach that has been tried to improve the accuracy of the diagnosis of malaria by primary health care providers has been to train them in using simplified algorithms based on symptoms and signs. The key assumption in this syndromic approach is that clinical malaria infection has a recognizable constellation of symptoms and signs. Several attempts have

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D. Chandramohan *et al.* **Clinical algorithms for diagnosing malaria**

been made to test this assumption and to identify syndromes with best predictive values for diagnosing clinical malaria.

Methodology of studies evaluating syndromic approach to diagnosis of malaria

The methodology of studies that have evaluated the syndromic approach to the diagnosis of malaria in children, and the demographic and epidemiological characteristics of the study populations are summarized in Table 1. Studies that did not separate data of children from adults were excluded from this review. Of studies that included both children and adults, the data of children only were included in the analysis.

All studies were conducted among children presented to a health facility with fever or a history of fever (Table 1). One study included patients identified during home visits as well as those who presented to a clinic (Gomes *et al.* 1994). The study period included both high and low transmission seasons in most studies conducted in areas of seasonal transmission. The level of transmission of malaria varied between sites ranging from hypo to holoendemic and the proportion of febrile illness attributable to malaria in the study populations ranged from 6 to 73% (Table 3). Some studies included only patients with *Plasmodium falciparum* infection while others included cases of either *P. falciparum* or *P. vivax* infection.

In most studies, patients were classified as malaria cases if the blood slide was positive for malaria parasite and non-malaria controls if the blood slide was negative. In two studies, parasitaemia above a threshold level was required for a diagnosis of malaria. The strength of association between individual symptoms/signs (predictors) and a diagnosis of malaria was assessed by estimating relative risk (or odds ratios) of presence or absence of predictors in cases compared with non-malaria controls. All studies have identified diagnostic algorithm for malaria by adding predictors with a strong positive or negative association with malaria cases. Recent studies in The Gambia and India have developed a scoring system by a simple count of predictors from a list of signs and symptoms chosen on the basis of statistical significance and clinical judgement. In all studies the sensitivity, specificity and/or predictive values of diagnostic algorithms were estimated by comparing the diagnoses reached by the diagnostic algorithms based on predictors with the 'gold standard' diagnosis reached on the basis of blood slide results.

Predictors of clinical malaria

The statistical strength of association between certain signs and symptoms (frequently evaluated predictors of malaria)

and clinical malaria, and their sensitivity and specificity for diagnosing malaria are shown in Table 2. The relationship between several potential predictors and clinical malaria varied between study populations. For instance children with malaria were two times more likely to have a history of reduced feeding in The Gambia but in India and in Ethiopia malaria cases were less likely to give a history of reduced feeding (OR 0.65 and 0.83, respectively). Similarly, two studies in The Gambia reported a strong association between feeling hot on palpation and malaria (RR 11.6 and 15.3) but this was not observed in India (OR 1.4). On the other hand absence of cough, presence of pallor of palm or nail bed, and palpable spleen were associated with clinical malaria in several study populations. However, none of the predictors individually had an acceptable level of sensitivity and specificity. In The Gambia hot body and normal chest on examination had the highest sensitivity (99 and 96%, respectively), but they had very poor specificity (20 and 17%, respectively). In India, intermittent fever and normal chest examination had high sensitivity (96 and 95%) but poor specificity (9 and 4%). In Thailand, clinical anaemia, palpable spleen and palpable liver had high specificity (> 90%) but very low sensitivity (5–19%). Furthermore, the sensitivity and specificity of potential predictors of malaria varied between sites. For example, increased respiratory rate had a moderate sensitivity and specificity in The Gambia (70 and 62%, respectively), but it had a poor sensitivity (10%) and high specificity (91%) in Thailand.

Syndromes with best predictive values

The sensitivity, specificity, and positive and negative predictive values of syndromes with the best predictive values for diagnosing malaria in children are shown in Table 3. The syndromes with best predictive values differed between sites. For example, intermittent fever for 2–3 days had reasonable sensitivity and specificity in Tanzania but this was not observed in any other study. Similarly, rectal temperature ≥37.7 °C and/or nail bed pallor and/or splenomegaly had a reasonably high sensitivity (85%) in Malawi, but not in other study areas. The predictive values of the syndrome, history of fever + (chills or sweating) varied significantly between the studies from The Philippines and peri-urban Gambia. Furthermore, positive and negative predictive values which are influenced by prevalence varied significantly between high and low transmission seasons in Ethiopia.

Assigning a numerical score to predictors of malaria that are strongly associated with malaria and determination of a cumulative score for each individual gave a promising result in The Gambia. Using a scoring system based on nine

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Table I Study setting and methodology of studies exploring predictors of clinical malaria in children

Reference	Setting	Transmission seasons*	Age group	Enrolment criteria and sample size	Gold standard diagnosis of malaria	Sample size Malaria	Sample size Non-malaria
Rooth and Bjorkman (1992)	Tanzania; Rural area; Hyperendemic	High and low combined	< 9 years	All children attending the study clinic with a history of fever	Parasitaemia and temperature ≥ 37.5 °C	395**	273**
Gomes et al. (1994)	Philippines; Rural area; Hyperendemic	High and low combined†	< 10 years	All children having fever or a history of fever identified at home during active surveillance or presenting to the study clinic	Parasitaemia and (fever or history of fever)	97†† 28‡‡	47†† 38‡‡
Genton et al. (1994)	Papua New Guinea; Rural area; Holoendemic	High and low combined	< 10 years	All children diagnosed clinically as malaria by a nurse at the study health centre	Parasitaemia and (fever or history of fever)§	1077	406
Redd et al. (1996)	Malawi; Rural area; Hyperendemic	High only	< 5 years	A random sample of children (every fourth child in hospital 1 and two of every three children in attending for any illness hospital 2)	Parasitaemia and (fever or history of fever)§	672	452
Weber et al. (1997)	The Gambia; Peri-urban area; Hypoendemic	High and low combined	< 5 years	A random sample of children attending the study hospital with any illness (first seven children seen on each day of enrolment)	Parasitaemia and (fever or history of fever)¶	28	379
Luxemburger et al. (1998)	Thailand; Rural area; Mesoendemic	High	2–15 years	All children attending study clinic with fever or a history of fever within the previous 3 days	Parasitaemia and (fever or history of fever)	299§§	299§§
Muhe et al. (1999)	Ethiopia; Rural area; Mesoendemic	High and low separately	2 months – 5 years	A random sample (every second child) presenting with fever or a history of fever at the study health centre	Parasitaemia and (fever or history of fever)§	511¶¶ 48***	1175¶¶ 756***
Olaleye et al. (1998)	The Gambia; Peri-urban area; Hypoendemic	High only	6 months – 9 years	All children presenting with a history of fever within the previous 3 days or temperature ≥ 37.5 °C at the study health centre	Parasitaemia ≥ 5000/µl and axillary temperature ≥ 38 °C	189	248
Bojang et al. (2000)	The Gambia; Peri-urban area; Hypoendemic	High only‡	5 months – 9 years	All children presenting with a history of fever within in the previous 48 h at the study health centre	Parasitaemia ≥ 5000/µl and axillary temperature ≥ 37.5 °C	138	249
Chandramohan et al. (2001)	India; Urban area; Hypoendemic;	High and low combined	<14 years	All children presenting with fever or a history of fever at the study hospital and who had no history of drug intake for the present illness	Parasitaemia and (fever or history of fever)	139	1806

* Transmission seasons included in the assessment of predictors of malaria.
† Predictive values in high and low transmission periods were also studied separately but this analysis included both children and adults.
‡ Children enrolled in the low transmission season were not included in the analysis as only very few satisfied the criteria of malaria (6/136).
§ A cut off point of ≥ 10000 parasites per µl was also used in a secondary analysis.
¶ A cut off point of parasites ≥ 5000/µl was also used in a secondary analysis.
** The 249 children presented with 688 febrile episodes; †† children enrolled at home; ‡‡ children enrolled at the study clinic; §§ matched for age and sex; ¶¶ children enrolled in high transmission season; *** children enrolled in low transmission season.

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Table 2 Relative risk, sensitivity and specificity of potential predictors of clinical malaria in children

Predictors	The Gambia[1] RR	Sen	Spe	The Gambia[2] RR	Sen	Spe	India[3] OR	Sen	Spe	Thailand[4] OR	Sen	Spe	Papua New Guinea[5] OR	Sen	Spe	Ethiopia[6] OR	Sen	Spe
Symptoms																		
Reduced feeding	1.8*	72	49	2.0*	90	23	0.65	27	76	NR	NR	NR	NR	NR	NR	0.83	NR	NR
Increased sleepiness	1.8*	82	34	1.7*	67	51		1	99	NR	NR	NR	NR	NR	NR	NR	NR	NR
Shivering/chills	1.7*	72	47	1.7*	68	51	0.87	49	57	NR	NR	NR	NR	NR	NR	2.7	44	86
Absence of cough	1.9*	65	60	1.3	37	73		54	64	NR	NR	NR	2.4*	57	65	2.4*	48	69
Intermittent fever	NR	NR	NR	NR	NR	NR	1.3	96	9	1.6*	60	53		NR	NR	1.7*	NR	NR
Vomiting	NR	NR	NR	1.8	69	51	2.1*	24	81	2.7*	29	87	1.0	73	83	NR	NR	NR
Headache	NR	NR	NR	NR	NR	NR	1.0	37	68	3.6*	83	42	NR	NR	NR	NR	NR	NR
							1.3											
							1.2											
Signs																		
Feels hot on palpation	11.6*	99	20	15.3*	98	39	1.4	37	70	NR	NR	NR	NR	NR	NR	NR	NR	NR
Temperature ≥ 38 °C	NR	NR	NR	NR	NR	NR	1.7*	41	71	2.5*	51	71	1.8*	79	67	NR	NR	NR
Abnormally sleepy	1.4*	16	91	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Pallor of conjunctiva	1.7*	33	84	1.1	33	71	1.0	32	68	4.2*	5	99	NR	NR	NR	NR	NR	NR
Pallor of palm/nailbed	1.8*	43	79	1.2	28	77	1.1	31	70	1.1	10	91	NR	NR	NR	2.8*	54	82
Increased respiratory rate	1.9*	67	57	2.5*	70	62	NR	NR	NR	3.9*	11	97	NR	NR	NR	1.2	NR	NR
Palpable liver	1.8*	19	93	1.3*	32	78	3.5*	4	99	28.9*	17	97	NR	NR	NR	2.7*	NR	NR
Palpable spleen	1.7*	14	94	1.6*	36	79	1.9*	13	93	NR	NR	NR	3.3*	86	81	3.7*	50	90
Normal chest exam	4.0*	96	17	NR	NR	NR	0.6	95	4	NR	NR	NR	NR	NR	NR	NR	NR	NR
							1											

* *P* < 0.05. RR, Relative risk, OR, odds ratio, Sen, sensitivity expressed in percentage, Spe, specificity expressed in percentage, NR, not reported.
[1] Olaleye *et al.* (1998); [2] Bojang *et al.* (2000); [3] Chandramohan *et al.* (2001); [4] Luxumburger *et al.* (1998); [5] Genton *et al.* (1994); [6] Muhe *et al.* (1999).

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Table 3 Validity of clinical diagnostic criteria for diagnosing non-severe malaria in children

Setting	SPR	Parasite species (%)	Criteria with the best predictive values	Sen	Spe	PPV	NPV
Rural Tanzania[1]	59	Pf 97, Pm 3	Intermittent fever 2–3 days	73	98	99	71
Rural Philippines[2]	67*	Pf 67, Pv 22	History of fever + (chills and/or sweating)	55*	79*	84*	46*
Rural Papua New Guinea[3]	37†, 73	Pf 55, Pv 22, Mixed 11	Enlarged spleen + no cough	50†, NR	89†, NR	77†, 90	70†, NR
Rural Malawi[4]	32‡, 60	Pm 6, Mostly Pf	Temperature ≥ 38 °C‡; Rectal temperature ≥ 37.7 °C or nailbed pallor or splenomegaly	NR, 85	NR, 41	46‡, 68	NR, 64
Peri-urban Gambia[5]	7	Mostly Pf	Chills, sweating or shaking	93, 94§	19, 19§	8, 5§	97, 99§
Rural Thailand[6]	24	Pf 43, Pv 50, Mixed 7	History of fever + head ache + no cough	51	72	64	59
Rural Ethiopia[7]	30%¶, 6%**	Pf 58, Pv 42, Mixed 1	History of fever + (history of previous malaria attack or absence of cough or pallor)	83¶, 75**	51¶, 60**	42¶, 11**	87¶, 97**
Peri-urban Gambia[8]	39††	Mostly Pf	Weighted Malaria Score ≥ 8§§; Weighted Malaria Score ≥ 9§§	88††, 61††	64††, 82††	65††, 72††	87††, 73††
Peri-urban Gambia[9]	35%‡‡	Mostly Pf	Weighted Malaria Score ≥ 7§§; Weighted Malaria Score ≥ 8§§	89‡‡, 70‡‡	63‡‡, 78‡‡	56‡‡, 63‡‡	90‡‡, 82‡‡
Urban India[10]	7%	Pf 16, Pv 83, Mixed 1	Unweighted Malaria Score ≥ 3¶¶; Unweighted Malaria Score ≥ 4¶¶	80, 60	37, 61	10, 11	95, 94

SPR, slides positive rate ≥ 1 malaria parasite of any species unless a cut-off point of parasite density is specified; Sen, Sensitivity (%); Spe, specificity (%); PPV, positive predictive value (%); NPV, negative predictive value (%); Pf, *Plasmodium falciparum*; Pv, *Plasmodium vivax*; Pm, *Plasmodium malarie*.

* Among children enrolled at home; † among children enrolled at the study clinic; ‡ SPR and the predictive values refer to diagnosing malaria with parasite density ≥ 10000/µl. § Predictive values refer to diagnosing malaria with parasite density ≥ 5000/µl; ¶ SPR and predictive values refer to low transmission season; ** SPR and predictive values refer to high transmission season; †† SPR and predictive values refer to malaria with temperature ≥ 38 °C plus parasite density ≥ 5000/µl; ‡‡ SPR and predictive values refer to malaria with temperature ≥ 37.5 °C and parasitaemia ≥ 5000/µl.

§§ *Weighted Malaria Score* was calculated from the following nine predictors: Sleepy, reduced feeding, absence of cough, shivering, feels hot, cough not heard, pallor of palm, absence of rash, increased respiratory rate. Each predictor was given a score of 1 if present and 0 if absent except feeling hot which was given 3 if present and 0 if absent.

¶¶ *Unweighted Malaria Score* was calculated from the following 10 predictors: chills, feeling cold, vomiting, absence of cough, absence of runny nose, absence of diarrhoea, feels hot, palpable spleen, palpable liver, axillary temperature ≥ 37 °C. Each predictor was given a score of 1 if present and 0 if absent.

[1] Rooth and Bjorkman (1992); [2] Gomes *et al.* (1994); [3] Genton *et al.* (1994); [4] Redd *et al.* (1996); [5] Weber *et al.* (1997); [6] Luxemburger *et al.* (1998); [7] Muhe *et al.* (1999); [8] Olaleye *et al.* (1998); [9] Bojang *et al.* (2000); [10] Chandramohan *et al.* (2001).

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predictors (Table 3), a cut-off score of eight had a sensitivity of 88% and a specificity of 64% for the diagnosis of clinical malaria; values comparable with those achieved by an experienced paediatrician's diagnosis using clinical criteria alone (sensitivity 86% and specificity 61%). When this scoring system was field tested in another population in The Gambia, the cut-off score was reduced to seven to reproduce same levels of predictive values. The list of predictors used for calculating a malaria score and the cut-off score for diagnosing clinical malaria in urban India differed from The Gambia because of the difference in the association between predictors and clinical malaria.

Relationship between prevalence and misclassification error of syndromic approach

For each of the syndromes with the best predictive values for diagnosing malaria, we calculated the wastage of antimalarial drugs, i.e. the proportion of febrile children who are falsely classified as malaria by the syndrome and treated with antimalarial drugs unnecessarily [(1-positive predictive value) × (proportion of children classified as malaria by the syndrome)] and the risk of failure to treat clinical malaria, i.e. the proportion of febrile children who are falsely classified as non-malaria by the syndrome [(1-negative predictive value) × (proportion of children classified as non-malaria by the syndrome)]. To assess the relationship between either wastage of drug or failure to treat and the prevalence of malaria, we fitted logistic regression models of proportions of drug wastage or failure to treat against the percentage prevalence of malaria.

The relationship between prevalence of malaria and wastage of drugs or failure to treat resulting from the use of clinical syndromes is shown in Fig. 1. At low prevalence of malaria the risk of failure to treat malaria was low, but the wastage of antimalarial drug was high. The odds ratio of wastage of drugs increased by 1.49 (95% confidence limit 1.45–1.51; $P < 0.0001$) for each 10% decrease in the prevalence of malaria. The risk of failure to treat malaria increased with increasing levels of prevalence. The odds ratio of failure to treat increased by 1.57 (95% confidence limit 1.50–1.65; $P < 0.0001$) for each 10% increase in the prevalence of malaria.

Discussion

In studies that were conducted in highly endemic areas misclassification of non-malaria controls as cases cannot be ruled out as a high proportion of the population have parasitaemia. For example, malaria parasite was found in over 90% blood films obtained from children aged 1–4 years in a rural area in Tanzania (Smith *et al.* 1993). Even in areas of low malaria endemicity asymptomatic infections may occur. Thus, detection of malaria parasite in a patient does not necessarily mean that the current illness is due to malaria, it could be coincidental. In addition, misclassification of cases as controls could result from false
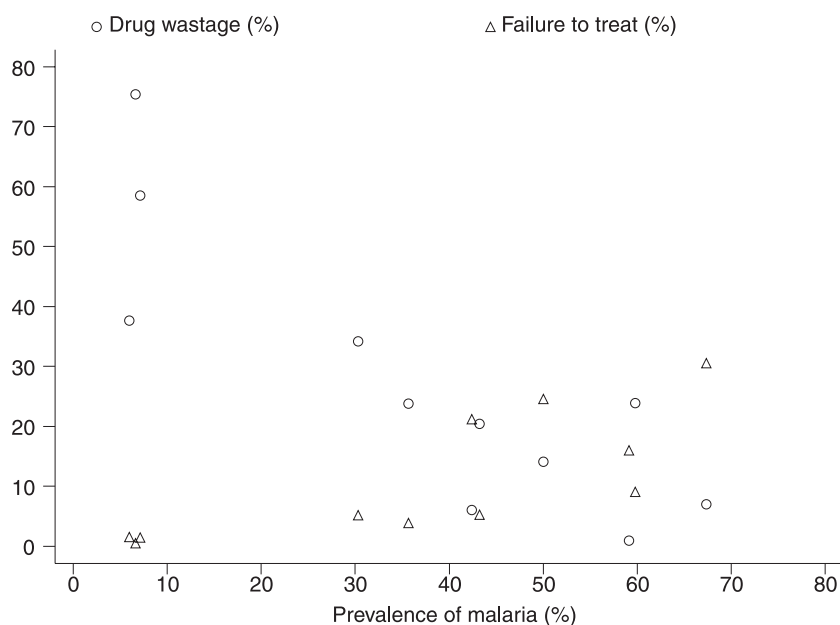
Figure 1 The relationship between drug wastage, failure to treat, and prevalence of malaria.

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negative blood film results, especially in areas of low endemicity where clinical malaria may result from low density parasitaemia. Although the extent of misclassification of cases and controls cannot be assessed in the reported studies, the bias introduced by this on the accuracy of the syndromic approach is unlikely to be of major significance.

The criteria with the best predictive values for the diagnosis of malaria varied between population. This may have been due to differences in cultural perceptions, the endemicity of malaria, species of malaria, definition of gold-standard diagnosis, or clinical experience of investigators between study sites. It was not possible to assess the variations in the validity of each reported syndrome between sites as these were not recorded uniformly. For example, positive predictive value (PPV) of intermittent fever 2–3 days for malaria was 75% in Tanzania, but this was not reported from the studies in Malawi, Papua New Guinea, or Thailand. A re-analysis of the existing data sets and a comparison of the usefulness of the reported syndromes for diagnosing malaria across different epidemiological and geographical settings would be useful.

Wastage of drugs and failure to treat malaria cases by the use of syndromes with the best predictive values in each study setting varied depending on the prevalence of malaria. These data suggest that the syndromic approach will result in only a modest reduction in the use of antimalarial drugs whilst resulting in a substantial level of false diagnosis of malaria who may thus be placed at risk of serious illness. The risk of failure to treat malaria will be least in areas of low endemicity, often encountered in urban and periurban areas. However, the reduction in the wastage of antimalarial drugs in these settings will be minimal.

The integrated management of childhood illnesses (IMCI) guidelines recommend to offer antimalarial drugs to all children with a history of fever or feels hot or temperature > 37.5 °C in high malaria risk areas. This is appropriate given that the risk of missing clinical malaria is high if any other symptoms or sign are added to the IMCI diagnostic algorithm. In low malaria risk areas the IMCI guidelines recommend to offer antimalarial drugs if a child has (fever or feels hot or temperature > 37.5 °C) plus (no runny nose or no measles or no other causes of fever). In a low endemic urban area in India and during low transmission season in rural Ethiopia, a history of no runny nose had a sensitivity of 73% and 71%, respectively, for diagnosing malaria (Muhe *et al.* 1999; Chandramohan *et al.* 2001). This raises the question whether the current IMCI guidelines for management of febrile children in low risk areas are appropriate. Further studies to evaluate the IMCI criteria for offering antimalarial treatment in low risk areas are needed urgently.

Conclusions

The accuracy of the syndromic approach to diagnose malaria is not sufficient for deciding on offering antimalarial drugs to patients presenting with a febrile illness. This approach may be useful for screening patients in order to reduce the number of patients requiring microscopy or dipstick test. This approach may also be useful to screen febrile children for offering second line drug therapy for malaria. However, algorithms for diagnosing malaria are site specific and thus the reported algorithms have to be field tested before recommending their use for these purposes. In highly endemic areas where laboratory support is not available, the policy of offering antimalarial drugs to all febrile illnesses is appropriate. The consequences of delays in offering appropriate treatment for malaria probably outweigh the benefits of reducing the wasteful use of antimalarial drugs.

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Impact of Artemisinin-Based Combination Therapy and Insecticide-Treated Nets on Malaria Burden in Zanzibar

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ABSTRACT

Background

The Roll Back Malaria strategy recommends a combination of interventions for malaria control. Zanzibar implemented artemisinin-based combination therapy (ACT) for uncomplicated malaria in late 2003 and long-lasting insecticidal nets (LLINs) from early 2006. ACT is provided free of charge to all malaria patients, while LLINs are distributed free to children under age 5 y ("under five") and pregnant women. We investigated temporal trends in *Plasmodium falciparum* prevalence and malaria-related health parameters following the implementation of these two malaria control interventions in Zanzibar.

Methods and Findings

Cross-sectional clinical and parasitological surveys in children under the age of 14 y were conducted in North A District in May 2003, 2005, and 2006. Survey data were analyzed in a logistic regression model and adjusted for complex sampling design and potential confounders. Records from all 13 public health facilities in North A District were analyzed for malaria-related outpatient visits and admissions. Mortality and demographic data were obtained from District Commissioner's Office. *P. falciparum* prevalence decreased in children under five between 2003 and 2006; using 2003 as the reference year, odds ratios (ORs) and 95% confidence intervals (CIs) were, for 2005, 0.55 (0.28–1.08), and for 2006, 0.03 (0.00–0.27); p for trend < 0.001. Between 2002 and 2005 crude under-five, infant (under age 1 y), and child (aged 1–4 y) mortality decreased by 52%, 33%, and 71%, respectively. Similarly, malaria-related admissions, blood transfusions, and malaria-attributed mortality decreased significantly by 77%, 67% and 75%, respectively, between 2002 and 2005 in children under five. Climatic conditions favorable for malaria transmission persisted throughout the observational period.

Conclusions

Following deployment of ACT in Zanzibar 2003, malaria-associated morbidity and mortality decreased dramatically within two years. Additional distribution of LLINs in early 2006 resulted in a 10-fold reduction of malaria parasite prevalence. The results indicate that the Millennium Development Goals of reducing mortality in children under five and alleviating the burden of malaria are achievable in tropical Africa with high coverage of combined malaria control interventions.

The Editors' Summary of this article follows the references.

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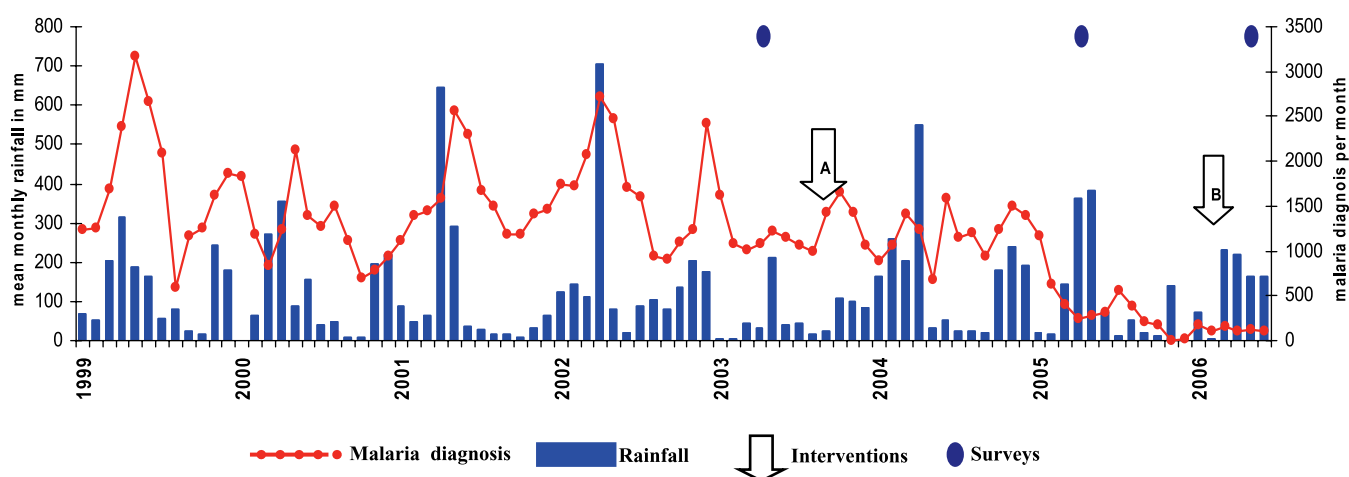
Figure 1. Malaria Interventions, Cross-Sectional Surveys, Monthly Rainfall, and Reported Clinical Malaria Diagnoses in Children under 5 Years of Age in North A District, Zanzibar

(A) Start of the implementation of artemisinin-based combination therapy for treatment of uncomplicated malaria in September 2003.
(B) Introduction of LLINs in February 2006. Promotion of ITNs started in January 2004; the use of conventional ITNs, however, remained low, until the introduction of LLINs. Outpatient data for 2006 are up to June.
doi:10.1371/journal.pmed.0040309.g001

Introduction

The increased malaria-related morbidity and mortality, especially in children under the age of 5 y ("under five"), due to emerging resistance of *Plasmodium falciparum* to conventional antimalarial drugs calls for immediate actions to "Roll Back Malaria" in sub-Saharan Africa. This need has been clearly recognized in the Millennium Development Goals "to halt and begin to reverse malaria incidence" [1] as well as in the Abuja Declaration objective to halve malaria mortality in Africa by 2010 through implementation of combined control strategies [2].

In the year 2000, the overall treatment failure of chloroquine was found to be 60% in a 14-d efficacy trial; consequently the Zanzibar Ministry of Health and Social Welfare decided in November 2001 to change both first- and second-line treatment guidelines for uncomplicated malaria from chloroquine and sulfadoxine-pyrimethamine to artemisinin-based combination therapies (ACT) [3]. The ACT policy was implemented in September 2003, when Zanzibar became one of the first regions in sub-Saharan Africa to recommend routine use of ACT. This action was followed by strengthened vector control, culminating in a nation-wide distribution campaign of long-lasting insecticidal nets (LLINs) from early 2006.

Both ACT and vector control measures have independently proven to be efficacious malaria control strategies. Ecological studies have credited ACT with enhancing treatment efficacy, reducing malaria transmission, and possibly forestalling drug resistance in low-endemicity areas [4,5]. Moreover, specific African trials have indicated that the use of insecticide-treated nets (ITNs) or indoor residual spraying can reduce mortality of children under five in Africa [6–9]. This is, however, to our knowledge the first study to examine the public health impact of wide-scale deployment of ACTs alone and combined with ITNs through the general health structure/channels on malaria indices and general health parameters in an endemic area in sub-Saharan Africa.

Methods

Study Site

The study was conducted in North A District, Zanzibar, situated just off the coast of mainland Tanzania. The district is rural and has a population of about 85,000. Subsistence farming and fishing are the main occupations. *Plasmodium falciparum* is the predominant malaria species and *Anopheles gambiae* complex is considered the main vector. Malaria transmission is stable with seasonal peaks related to rainfall in March–May and October–December. Malaria transmission in the district prior to the interventions has been reported to be high, but specific entomological data are not available to allow a precise characterization of malaria transmission intensity. However, during the screening process of a major antimalarial drug trial conducted in 2002–2003, a *P. falciparum* prevalence exceeding 30% was observed in febrile children under five [10], suggesting that North A District had been a high transmission area prior to ACT implementation in September 2003.

North A District has one Primary Health Care Centre, which includes a hospital with inpatient and laboratory services, e.g., blood transfusion and malaria microscopy services. Basic medical treatment services without laboratory support are provided in 12 Primary Health Care Units located in different shehias (the smallest political administrative unit in Zanzibar). Drugs, including conventional and artemisinin monotherapies, are also available in private shops throughout the district.

Malaria Control Interventions

Figure 1 illustrates time of implementation of the two malaria control interventions.

First intervention—ACT. A loose combination of artesunate and amodiaquine (AS+AQ; from various suppliers with preapproval from WHO) and a fixed combination of artemether–lumefantrine (Coartem; Novartis, Basel, Switzerland), were implemented as first- and second-line treatment, respectively, for uncomplicated malaria in all public health

facilities from September 2003. In a pre-implementation assessment of the new treatment policy, partly conducted in North A District 2002–2003, both AS+AQ and artemether–lumefantrine were highly efficacious with PCR-adjusted cure rates by day 28 above 90% [10]. Quinine remained the drug of choice for severe malaria and sulfadoxine-pyrimethamine for intermittent preventive treatment during pregnancy. From September 2003, chloroquine was withdrawn from all health facilities and replaced by free provision of ACT to all malaria patients. Total treatment courses of AS+AQ dispensed in North A 2004 and 2005 were 34,724 and 12,819, respectively. The supply of ACT has been uninterrupted, with no reports of AS+AQ being out of stock from any public health facility in the district during 2003–2006 (unpublished data). ACTs were purchased with support from African Development Bank and Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM).

Second intervention—vector control. A policy to distribute conventional ITNs to the most vulnerable groups—children under five and pregnant women—free of charge through antenatal clinics or local shehia leaders was officially launched in 2004. However, ITN coverage and use remained low in North A District 2004 and 2005 due to limited number of ITNs distributed, 4,026 and 1,550, respectively. A mass campaign was therefore initiated early 2006, with distribution of 23,000 LLINs to the two most vulnerable groups in North A. This campaign was supported by GFATM and the US Agency for International Development.

Cross-Sectional Surveys

Three cross-sectional surveys with the primary objective to determine *P. falciparum* prevalences were conducted in North A District between 2003 and 2006. A two-stage cluster sample technique was used. First shehias and then the households were randomly selected from the sampling frame obtained from the Office of Chief Government Statistician, Zanzibar. The sampling frame was updated before each survey.

The first exploratory survey, conducted in May 2003, included 625 households and provided baseline data prior to ACT and widespread ITN implementation. Sample size calculations for the follow-up surveys conducted in May 2005 and 2006 were based on the proportion of children under five with malaria parasitemia in 2003, about 9%, and an assumed relative error of 20%. The calculated number of households to be included was 490 after adjusting for a design effect of 2.

Trained interviewers visited all selected households. Interviews and blood sample collection were initiated upon written consent from head of each household and proxy consent from the mother or guardian of each child. Information was recorded using a structured questionnaire on recent febrile illness, mosquito net use, and care-seeking behavior from each individual present in the household at the time of the survey. We did not replace households in which residents were not present at time of survey, could not be located, or refused to participate.

Thick blood films were collected from all consenting participants, stained with 5% Giemsa for 30 min, and examined by experienced microscopists for presence and density of *P. falciparum* parasites. If fewer than ten parasites were detected per 200 white blood cells, examinations were extended to 500 white blood cells. Blood slides were considered negative if no asexual parasites were found in 200 high-power fields. High-density parasitemia was defined as presence of $\geq$ 5,000 parasites/µl [11]. Quality control was conducted for all positive slides and 10% of the negative slides [12].

Health Facility Records

Malaria-related indicators, i.e., outpatient attendances, hospital admissions and blood transfusions, from all 13 public health facilities in North A District were obtained from the Health Management and Information System (HMIS) records of the Zanzibar Ministry of Health and Social Welfare. The existing HMIS records were about 90% complete for the period 2000–2004. Data were validated and missing information retrieved by retrospective review of source documents from all 13 health facilities. This confirmed the HMIS records and resolved missing or inconsistent data, which increased the completeness to nearly 100%. A database of malaria-related indicators was created on the basis of this retrospective review. Data from 2005 were abstracted on quarterly basis.

Vital Statistics

Records of vital events, i.e., births and deaths, for the period 1998–2005 were obtained from the District Commissioner's Office (DCO) in North A. Annual crude mortalities of children under five were estimated from these data. Demographic estimates were obtained from Tanzania National Population and Housing Census 2002.

Rainfall

Complete records of monthly rainfall during 1999–2005 were obtained from official registers of the Tanzania Metrological Agency of the Ministry of Communications and Transport. On Unguja island, rainfall is centrally measured in one weather station, situated 26 km (radially) from North A District. The mean annual rainfalls recorded in 2003, 2004, 2005, and 2006 were 702, 1,934, 1,231, and 1,214 mm, respectively. The corresponding mean seasonal rainfall (March–May) between 2003 and 2006 was 285, 786, 890, and 613 mm, respectively. During the post-ACT intervention period (2004–2006) the mean annual and seasonal rainfall was 8%–12% lower than the pre-ACT intervention period (2000–2002). However, the only year with a marked reduction in the mean annual and seasonal rainfalls was the year 2003 with two- to three-fold lower rainfall, as compared to both the preceding and subsequent 3 y.

Data Processing and Analysis

Data were entered and validated using Microsoft Access and Excel. Statistical analyses for cross-sectional surveys, health facility records, vital statistics, and rainfall data were performed using Stata version 8. Analysis for the surveys was corrected for multi-stage sampling errors using the Rao-Scott second order correction [13]. A logistic regression model with robust standard errors (robust cluster) was used to adjust for the effect of age, sex, sleeping under a mosquito-net, and asset index on asexual *P. falciparum* prevalence and gametocyte carriage across the study years. Households were the primary sampling units in the surveys and were defined as clusters. Wald test was used to assess the fit of the model and interactions between covariates incorporated in the model. Odds ratios were adjusted for the complex sampling design and covariates listed above. Pearson correlation coefficients were calculated to assess the linear relationships between

Table 1. Number of Households Surveyed and Characteristics of Survey Participants

Survey Characteristics	2003	2005	2006
Households, *n*	621	471	483
0–5 y, *n* (%)	520 (43%)	326 (44%)	320 (47%)
6–14 y, *n* (%)	688 (57%)	416 (56%)	363 (53%)
Males, *n* (%)	579 (45%)	377 (51%)	340 (49%)
Children under five sleeping under any mosquito net, *n* (%)	182 (35%)	193 (59%)	296 (93%)
Children under five sleeping under an ITN, *n* (%)	20 (4%)	28 (9%)	288 (90%)

ITNs were defined as any mosquito net treated with an insecticide within 6 mo preceding the respective surveys. In 2006, ITN refers to LLINs.
doi:10.1371/journal.pmed.0040309.t001

monthly rainfall and outpatient malaria diagnosis, and malaria-attributed deaths.

Ethical Approval

Protocols for the household surveys were reviewed and approved by the Medical Research Coordinating Committee of the Tanzanian Commission on Science and Technology, the Zanzibar Health Research Council and the institutional review board of US Centers for Disease Control and Prevention.

Results

Cross-Sectional Surveys

The timings of the cross-sectional surveys in relation to start of each malaria control intervention and seasonal rainfalls are presented in Figure 1. The number of households enrolled and participant characteristics in the respective surveys are shown in Table 1. Over 95% of all participants agreed to both answer questionnaires and provide blood samples in the respective surveys.

The parasite prevalences and odds ratios (ORs) of asexual *P. falciparum* parasitemia and gametocyte carriage at the time of cross-sectional surveys are shown in Table 2. Between 2003 and 2005 the parasite prevalence was reduced by about 50%

in children under five. A further 10-fold decrease in *P. falciparum* prevalence was observed between 2005 and 2006, following mass distribution of LLINs specifically targeting this age group. Concomitant reductions of parasite prevalence were observed in children over the age of 5 y, although only by about 3-fold, between 2005 and 2006 (OR 0.41, 95% confidence interval [CI] 0.13–1.21), $p = 0.08$).

High-density parasitemia ($\geq$5,000/μl) was found in 14 (2.7%) and 2 (0.6%) children under five in 2003 and 2005, respectively. No child carried high-density parasitemia in 2006.

Reported fever within 14 d prior to the survey was similar in 2003 and 2006 among children under five (2003, 13% [95% CI 11–17]; 2006, 12% [95% CI 9–16]), whereas care-seeking at public health facilities by recently febrile children under five increased significantly (2003 was reference year; 2005, OR 3.91 [95% CI 0.85–17.9]; 2006, OR 5.5 [95% CI 2.3–13.3]; *p*-value for trend < 0.001).

The proportions of children under five sleeping under effective ITNs were below 10% in both 2003 and 2005 (Table 1), whereas in 2006, 90% were reported sleeping under an LLIN on the night before survey.

Health Facility Surveillance

All reported clinical outpatient malaria diagnoses in North A District between January 1999 and June 2006 among children under five are shown by month in Figure 1 and by year in Table 3. Between 2002 and 2005 the total number of out-patient malaria diagnoses decreased by 77%. The annual incidences of malaria diagnoses standardized per 1,000 children under five in North A District were 843, 786, and 233 in 2003, 2004, and 2005, respectively. The total number of children under five attending public health facilities for any cause during 1999 and 2005 remained relatively constant, ranging from 31,069 to 39,374 annually. Up to 2003 malaria accounted for about 50% of all outpatient diagnoses in this age group, whereas in 2005 this proportion had decreased to 13%.

Malaria-related hospital admissions, non-malaria admissions, and blood transfusions in children under five between 2000 and 2005 are also shown in Table 3. From 2002 to 2005, malaria-related admissions, blood transfusions, and malaria-attributed mortality decreased by 77%, 67%, and 75%, respectively.

Table 2. Parasite Prevalence and ORs of *P. falciparum* Asexual Parasitemia and Gametocytemia in Children 0–14 Years of Age in North A District, Zanzibar, in May 2003, 2005, and 2006

P. falciparum Parasitemia	Age Group	Year	*n* (%)	Crude OR (95% CI)	Adjusted OR[a,b] (95% CI)
Asexual	0–5 y	2003	45 (9.0)	1.00	1.00
		2005	17 (5.3)	0.56 (0.31–1.00)	0.55 (0.28–1.08)
		2006	1 (0.3)	0.03 (0.00–0.23)	0.03 (0.00–0.27)
	6–14 y	2003	85 (12.9)	1.00	1.00
		2005	17 (4.2)	0.30 (0.17–0.51)	0.30 (0.15–0.57)
		2006	6 (1.7)	0.11 (0.05–0.27)	0.11 (0.04–0.28)
Gametocytes	0–14 y	2003	17 (1.5)	1.00	1.00
		2005	3 (0.4)	0.28 (0.08–0.96)	0.26 (0.07–0.93)
		2006	3 (0.4)	0.30 (0.08–1.03)	0.26 (0.06–1.14)

[a]The ORs were generated in a logistic regression model and adjusted for potential clustering within households, age, sex, sleeping under mosquito net, and asset index. To construct an asset index, information on household goods, ownership of farm and livestock, materials used to construct the house, and access to electricity and piped water were recorded for each household. Using principal component analysis, an asset index was generated for each household.
[b]*p*-Values for trend in the decrease in adjusted OR of asexual parasitemia (in children aged 0–5 and 6–14 y) and gametocytemia (in children 0–14 y) were <0.001 and 0.002, respectively. All *p*-values for trend were calculated by Wald test.
doi:10.1371/journal.pmed.0040309.t002

Table 3. Outpatient Malaria Diagnoses, Hospital Admissions, Blood Transfusions, and Malaria-Attributed Deaths in North A District, Zanzibar, between 2000 and 2005

Year	Outpatient Malaria Diagnoses	Malaria Admissions	Non-Malaria Admissions	Blood Transfusions	Malaria-Attributed Mortality
2000	14,882 (0.72)	1,189 (0.94)	865 (1.43)	169 (0.89)	36 (0.90)
2001	18,797 (0.91)	1,162 (0.92)	586 (0.97)	213 (1.13)	26 (0.65)
2002	20,634 (1)	1,261 (1)	607 (1)	189 (1)	40 (1)
2003	14,761 (0.72)	930 (0.74)	654 (1.08)	102 (0.54)	39 (0.98)
2004	14,280 (0.69)	445 (0.35)	475 (0.78)	77 (0.41)	18 (0.45)
2005	4,817 (0.23)	296 (0.23)	955 (1.57)	62 (0.33)	10 (0.25)

Ratio (in parenthesis) of each year compared with 2002.
doi:10.1371/journal.pmed.0040309.t003

Crude Mortality Data

A total of 23,200 live births and 1,032 deaths in children under five (49% females) were registered between January 1998 and December 2005. The annual mortality figures for children under five, children (1–4 y), and infants (0–1 y) are shown in Table 4. Between 2002 and 2005, crude under five, infant, and child mortality decreased by 52%, 33%, and 71%, respectively.

Relationships between Rainfall and Malaria Diagnosis and Deaths

In the pre-ACT intervention period (2000–2002), significant positive correlations were found between monthly rainfall and both outpatient malaria diagnoses (Pearson correlation coefficient $[r_p] = 0.59$, $p < 0.001$) and malaria-attributed deaths ($r_p = 0.75$, $p < 0.001$), when data were adjusted to allow for a 1-mo lag between rainfall and malaria diagnoses and deaths. However, in the post-ACT intervention period (2003–2005), no significant correlations were found between monthly rainfall and outpatient malaria diagnosis ($r_p = -0.05$; $p = 0.75$) or malaria-attributed deaths ($r_p = 0.23$; $p = 0.20$).

Discussion

Malaria burden in Zanzibar, as in most parts of sub-Saharan Africa, has remained high and in many areas even increased during the last 10–20 y, a major reason being rapid spread of resistance to commonly used monotherapies against malaria. This problem has necessitated urgent implementation of new and effective control strategies to "Roll Back Malaria." Two main cornerstones in this effort are the introduction of ACTs for treatment of uncomplicated malaria and the promotion of ITN use. The targets for the implementation of these new strategies have been defined by the UN Millennium Development Goals [1] and the Abuja Declaration [2], to be achieved by the years 2015 and 2010, respectively.

Deployment of ACTs

The ACTs were dispensed free of charge to all patients in the study area through public health facilities from September 2003 onwards. The ACT implementation and deployment was very rapid, effective, and with high coverage. Monitoring of drug supplies confirmed that ACTs were available throughout the study period in all 13 public health care settings in North A District. This outcome also indicates that estimates were adequate of the needed and thus deployed numbers of ACT treatments in the district. This result was accomplished despite an apparent two-fold increase in care seeking among children under the age of 5 y at public health facilities as observed in the cross-sectional surveys. We believe that the observed shift in treatment-seeking behavior at public facilities may be related to availability of free, effective ACTs. A previous study in Zanzibar showed that people's attitudes towards health seeking at public health facilities (biomedical practices) are negatively influenced by the distribution of ineffective antimalarial drugs [14].

High ACT coverage was rapidly achieved in malaria patients despite availability of other drugs in the private sector. This achievement was probably influenced both by comprehensive information to the public and health care staff and by the strong commitment of the Zanzibar government to rapidly ensure free coverage of the ACTs. Also, in North A District, as well as in Zanzibar generally, the entire population has relatively easy access to public health facilities, which are located within 5 km from any community and are served by good transport links. However, the absence of co-formulation or even of co-blistering of the two compounds in the first-line treatment, artesunate and amodiaquine, may have resulted in some degree of monotherapy with either compound.

Mortality Impact

Our study provides the first, to our knowledge, observation of a reduction in mortality of children under five following introduction of ACTs solely in a stable malaria-endemic setting.

The highly significant reduction of 52% in crude under-five mortality according to vital statistics between 2002 and 2005 also highlights the importance of malaria as a major cause of death among children in malaria-endemic areas. The 71% reduction among children aged 1–4 y indicates that the relative contribution of malaria to crude mortality is particularly important in this age group. Major reductions in crude under-five mortality has also been observed in previous randomized intervention studies with ITNs [6,7] and community-based malaria treatment [15,16], but the reduction rates (between 25% and 40%) have been less pronounced than those in our study in Zanzibar.

We believe our findings are valid and represent a true picture of the effects of ACT deployment in North A District, Zanzibar. No other major political, socioeconomic, or health-care change with the potential to halve mortality in children under five occurred in Zanzibar after 2002. This includes Expanded Programme on Immunization coverage, which

Table 4. Mortality of Children under 5 Years of Age in North A District, Zanzibar between 1998 and 2005

Year	Under Five	Infants (0–1 y)	Children (1–4 y)
1998	161 (1.21)	87 (1.30)	74 (1.12)
1999	165 (1.24)	97 (1.45)	68 (1.03)
2000	157 (1.18)	91 (1.36)	66 (1.00)
2001	131 (0.98)	86 (1.28)	45 (0.68)
2002	133 (1)	67 (1)	66 (1)
2003	125 (0.94)	63 (0.94)	62 (0.94)
2004	97 (0.73)	57 (0.85)	40 (0.61)
2005	64 (0.48)	45 (0.67)	19 (0.29)

Ratio (in parenthesis) of each year compared with 2002.
doi:10.1371/journal.pmed.0040309.t004

remained constantly above 80% in the district during 1999–2005. Furthermore, there was no significant change in rainfall that may have contributed to the observed reduction in malaria transmission. Indeed, the only year with reduced rainfall with potential influence on vector capacity occurred before the introduction of ACTs—in 2003. Increased use of ITNs may also represent a potential confounding factor in our study. However, the ITN use was below 10% during 2004 and 2005 as reported and observed during the cross-sectional surveys. A significant improvement in ITN coverage was only achieved in 2006 after the introduction of LLINs (see further below) and only affected the 2006 cross-sectional results.

We chose 2002 as reference year in our analyses of health facility surveillance and under-five mortality, because 2002 represents the last complete year before ACT introduction in September 2003. Routinely collected mortality statistics may underestimate the true values. However, such data have been shown to provide valid mortality trends [17,18].

Morbidity Impact

A significant reduction was found with regard to hospitalization of malaria patients and incidence of blood transfusions, which may be considered proxy indicators of severe malaria. The reduction of severe malaria showing a similar pattern thus supports the under-five mortality trends. This health impact probably represents effects of improved case management of uncomplicated malaria with ACT, thus preventing the development of severe manifestations of the disease. The decrease in malaria morbidity (and mortality) at health facilities between 2003 and 2005 confirms the therapeutic efficacy of ACT [10], but the reduction in outpatient malaria diagnoses may also reflect some transmission blocking effect of artemisinin derivatives through its gametocytocidal activity. Reduction in transmission potential has been suggested after the introduction of artemisinin derivatives (before vector control) for routine treatment in a low and seasonal malaria transmission setting in Thailand [4].

Data obtained from routine health facility records have inherent potential pitfalls and need to be interpreted cautiously. However, the fact that they all show the same downward trend after improved coverage of malaria prevention and treatment interventions, and with no change in the climatic conditions that are favorable for malaria transmission, supports the plausible conclusion that enhanced malaria control interventions contributed to the observed public health benefits.

Deployment of ITNs

The deployment of LLINs in early 2006 provided a high coverage, i.e., over 90% reported use in children under five in the cross-sectional survey in May 2006. Importantly, this high mosquito-net use was observed after strong government commitment and after free LLIN distribution to children under five and pregnant women.

The most significant decrease in prevalence of asymptomatic parasitemia was achieved in 2006, when LLINs were widely used by the children under five, whereas the major impact on the under-five mortality was achieved earlier with ACT use only.

Strengthened vector control and the use of ACT also resulted in marked and sustained malaria control in South Africa [5]. The similar public health benefits observed in North A supports the concomitant use of vector control and ACT for malaria control. However, it should be emphasized that our study captures short-term trends in malaria control in North A, which may be too short to generalize long-term trends in the burden of malaria. Sustained coverage and use of LLINs by vulnerable groups is yet to be demonstrated, especially under declining malaria endemicity and if the free LLIN distribution scheme were to be changed.

Conclusions

The declining under-five mortality, malaria morbidity, and malaria prevalence observed in our study is the first comprehensive evidence supporting the major public health benefits of ACT and ITNs in a stable endemic malaria transmission setting in sub-Saharan Africa.

The findings suggest that ACTs with high coverage of ITN use may potentially even eliminate malaria as a public health problem in highly endemic areas of sub-Saharan Africa. High community uptake of the two interventions is probably required but indeed achievable if, as in our study, they are easily available free of charge.

The UN Millennium Development Goals to alleviate malaria as a major public health problem and substantially reduce the under-five mortality in sub-Saharan Africa are thus achievable even in settings with historically intense malaria transmission. The sustainability of these efforts as well as surveillance to prevent resurgence of malaria represent key research and programmatic follow-up issues of malaria control in Africa.

the study and takes full responsibility for the integrity of the data and accuracy of the data and its analysis. Study concept and design: Bhattarai, Kachur, Gerstenmaier, Abdulla, and Björkman. Acquisition of data: Bhattarai, Ali, Kachur, Abbas, Al-mafazy, Ramsan, Rotllant, Molteni, and Abdulla. Analysis and interpretation of data: Bhattarai, Kachur, Mårtensson, Montgomery, and Björkman. Drafting of the manuscript: Bhattarai, Kachur, Mårtensson, and Björkman. Statistical analysis: Bhattarai, Kachur, Mårtensson, Montgomery, Kaneko, and Björkman. Obtained funding: Ali, Kachur, Ramsan, and Molteni. Administrative, technical, and material support: Bhattarai, Ali, Kachur, Abbas, Khatib, Al-mafazy, Ramsan, Rotllant, Gerstenmaier, Molteni, and Björkman. Study supervision: Bhattarai, Ali, Kachur, Molteni, Abdulla, and Björkman. Critical revision of the manuscript for important intellectual content: All authors.

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Editors' Summary

Background. Malaria kills about one million people every year, many of them young children living in sub-Saharan Africa. The parasite responsible for these deaths—*Plasmodium falciparum*—is transmitted to people when they are bitten (usually at night) by an infected mosquito. In the human body, the parasites reproduce in the liver before invading red blood cells. Here, they multiply again before bursting out and infecting more red blood cells as well as causing a high fever and sometimes damaging vital organs. The transmission cycle is completed when a mosquito bites an infected person and ingests parasites with its blood meal. To reduce the global burden of malaria, this cycle needs to be broken. This can be done in several ways. First, mosquitoes can be controlled with insecticides. Second, individuals can avoid mosquito bites by sleeping under insecticide-treated nets. Finally, antimalaria drugs can reduce the illness and death caused by the malaria parasite and can lessen the likelihood that a mosquito will pick up the parasite when it bites a person. The World Health Organization (WHO) currently recommends artemisinin-based combination therapies (ACTs) for malaria control. These contain a natural antimalarial compound from sweet wormwood and a synthetic drug. The use of insecticide-treated nets is also now being strongly promoted.

Why Was This Study Done? The Roll Back Malaria Partnership—a coordinated global approach to fighting malaria—recommends that the strategies described above be combined to control malaria. But, although the public-health impact of insecticidal nets (ITNs) has been investigated, the large-scale effect of ACT use and the combined ACT/ITN effect in a malaria-endemic area has not been studied. This information is needed to allow governments and international agencies to use their resources as effectively as possible to control malaria. In this study, the researchers have asked how the introduction of ACT, first alone and later combined with distribution of long-lasting insecticidal nets (LLINs), affected the malaria burden in Zanzibar, a malaria-endemic country. People with malaria have had free access to ACT in Zanzibar since late 2003; children under the age of 5 y and pregnant women have been given free LLINs since early 2006.

What Did the Researchers Do and Find? The researchers counted the parasites in the blood of a group of children under the age of 14 years in the North A District of Zanzibar in May 2003, 2005, and 2006 (the seasonal peaks for malaria in Zanzibar occur in March–May and October–December). They also looked in local health records for malaria-related outpatient visits and admissions between 2000 and 2005 and analyzed the overall death records for the region over the same period. Between 2003 (before the introduction of ACT) and 2005, the proportion of children under five with *P. falciparum* in their blood halved (a 2-fold decrease). It decreased another 10-fold between 2005 and 2006 after the distribution of LLINs to this age group. Deaths from all causes in children under five halved between 2002 and 2005, and malaria-related admissions and death attributed to malaria in 2005 in these children were one-fourth of those recorded in 2002. The climate in Zanzibar remained favorable for malaria transmission throughout this period.

What Do These Findings Mean? These findings show that malaria-associated illness (outpatient malaria diagnosis) decreased by 77% and overall deaths in children decreased to about half in Zanzibar within two years of the introduction of ACT. Free distribution of LLINs from early 2006 to children under five produced a further significant reduction in parasite prevalence in this age group and a smaller but also important reduction in parasite prevalence in older children. Because these results only show short-term trends in the malaria burden associated with the introduction of these control strategies, they need confirmation in longer studies. They also need confirmation in other countries because the malaria burden in Zanzibar could have fallen for reasons unrelated to ACT or LLINs, such as other changes in medical practice. Nevertheless, these results strongly suggest that ACTs together with the widespread use of LLINs could help achieve the goal of eliminating malaria as a public-health problem in sub-Saharan Africa, provided the poor countries in this region can sustain these control strategies over the long term.

Additional Information. Please access these Web sites via the online version of this summary at http://dx.doi.org/10.1371/journal.pmed.0040309.

- The MedlinePlus encyclopedia contains a page on malaria (in English and Spanish)
- Information is available from the World Health Organization on malaria (in English, Spanish, French, Russian, Arabic and Chinese)
- The US Centers for Disease Control and Prevention provide information on malaria and on insecticide-treated nets (in English and Spanish)
- Information is available from the Roll Back Malaria Partnership on its approach to global control of malaria, on malaria in Zanzibar, part of the United Republic of Tanzania, on artemisinin-based combination therapy, and on the use of insecticide-treated nets

Malaria Journal

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Research

Overuse of artemisinin-combination therapy in Mto wa Mbu (*river of mosquitoes*), an area misinterpreted as high endemic for malaria

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Abstract

Background: Adequate malaria diagnosis and treatment remain major difficulties in rural sub-Saharan Africa. These issues deserve renewed attention in the light of first-line treatment with expensive artemisinin-combination therapy (ACT) and changing patterns of transmission intensity. This study describes diagnostic and treatment practices in Mto wa Mbu, an area that used to be hyperendemic for malaria, but where no recent assessments of transmission intensity have been conducted.

Methods: Retrospective and prospective data were collected from the two major village health clinics. The diagnosis in prospectively collected data was confirmed by microscopy. The level of transmission intensity was determined by entomological assessment and by estimating sero-conversion rates using anti-malarial antibody responses.

Results: Malaria transmission intensity by serological assessment was equivalent to < 1 infectious bites per person per year. Despite low transmission intensity, > 40% of outpatients attending the clinics in 2006–2007 were diagnosed with malaria. Prospective data demonstrated a very high overdiagnosis of malaria. Microscopy was unreliable with < 1% of slides regarded as malaria parasite-positive by clinic microscopists being confirmed by trained research microscopists. In addition, many 'slide negatives' received anti-malarial treatment. As a result, 99.6% (248/249) of the individuals who were treated with ACT were in fact free of malaria parasites.

Conclusion: Transmission intensity has dropped considerably in the area of Mto wa Mbu. Despite this, most fevers are still regarded and treated as malaria, thereby ignoring true causes of febrile illness and over-prescribing ACT. The discrepancy between the perceived and actual level of transmission intensity may be present in many areas in sub-Saharan Africa and calls for greater efforts in defining levels of transmission on a local scale to help rational drug-prescribing behaviour.

Background

Adequate diagnosis and prompt treatment of malaria remain major difficulties in rural settings in sub-Saharan Africa. In these areas, more than 70% of individuals with symptoms suggestive of malaria treat fevers with anti-malarial drugs without visiting the formal health sector for diagnosis [1,2]. If people do visit a health facility, an accurate diagnosis is not guaranteed. Microscopic examination of a blood smear is the gold standard method for the diagnosis of malaria, but is often unavailable at sub-district facilities [3]. In the absence of microscopy, malaria diagnosis is based on clinical symptoms that are known to lack specificity [4], or treatment is administered presumptively. Even if microscopy is available, there is substantial overdiagnosis of malaria [5]. There is an urgent need to review these diagnostic and treatment practices with the wide-scale implementation of the relatively expensive artemisinin-combination therapy (ACT) and in the light of changing patterns of malaria transmission.

Presumptive treatment of malaria remains a useful tool for malaria control in areas where malaria is common, the risk of progression to severe malaria is significant, and diagnostic facilities are lacking. In these areas, presumptive treatment is an effective strategy to increase the coverage of anti-malarials and may act to reduce transmission of malaria [6]. However, the strategy may not be justifiable for low endemic areas where the majority of febrile episodes are not due to malaria [7] and over-diagnosis and over-treatment of malaria are very common [4,8,9]. Knowledge of malaria transmission intensity can guide clinicians in defining algorithms for dealing with febrile patients. However, reliable estimates of malaria transmission intensity are frequently unavailable and transmission intensity can change over time as a result of interventions [10,11] or natural fluctuations [12]. Across the African continent, there are reports of recent reductions in malaria transmission intensity (reviewed in [6]).

Investigating how rural health systems function in the current climate of changing transmission and efforts to control and eliminate malaria seems pertinent. Here, diagnostic and treatment practices in rural health centres in Mto wa Mbu are described, an area that was historically hyperendemic for malaria [13], but where no recent assessments of transmission intensity have been conducted.

Methods

Study site

This study was conducted in Mto wa Mbu (latitude 3° 21'S; longitude 35° 51' E), which is translated from Kiswahili as 'River of Mosquitoes'. The town is located in the northern highlands of Tanzania at an altitude of 960 m – 1478 m above sea level and rain fall is largely restricted to the short (Oct-Nov) and long rainy season (March-July). According to a national census that was conducted in 2002, the town has 16,068 inhabitants. Retrospective and prospective data were collected from the two major village health clinics: the clinic of the Evangelical Lutheran Church (KKKT) and the Roman Catholic Health Facility (RCHF).

Retrospective data

Both clinics routinely used microscopy for diagnosing malaria and reported malaria to be their primary diagnosis in outpatients. Retrospective data consisted of information from outpatient registers of the years 2006 and 2007. For each individual that presented at the clinic the visit date, age and sex was recorded, as well as if they were diagnosed with malaria (either by clinical assessment or after detection of parasites by the clinic microscopist) and whether anti-malarial treatment was given. Climatic data were obtained from the nearby Lake Manyara National Park.

Prospective data

Data was prospectively gathered from all individuals attending the clinics as patients in the months May-August 2007, at the end of the long rains when a high number of malaria cases was expected [12,14]. All patients were informed about the purpose of the study and asked to give written consent before inclusion in the study. Once enrolled, a brief questionnaire was administered to collect information on: age, sex, bed net use, use of antibiotics or anti-malarials in the previous two weeks and symptoms. A single finger prick blood sample was taken for serum collection on Whatman 3 MM filter paper [Whatman, Maidstone, UK]. If individuals were referred for malaria diagnosis, a finger prick blood sample was taken for malaria parasite detection by Rapid Diagnostic Test (RDT) and two blood slides. ParaHIT® RDTs [Span Diagnostics Ltd, Surat, India]. RDTs were used according to the manufacturer's instructions and were based on the detection of Histidine Rich Protein 2. The first of the two blood slides was stained at the clinic according to the clinic's routine practice and scored by the microscopist working at the clinic. This slide result and the RDT result were made available to the clinician for diagnosis. The second slide was later stained in a research lab and read by two experienced research-microscopists. Parasite density per 200 white blood cells was determined on the thick smear and the slide was considered negative if no parasite was observed in 100 microscopic fields. Results of the two research microscopists were compared for validation and all discordant were read by a third microscopist.

Individuals who were diagnosed with malaria by the clinician received artemether-lumefantrine in line with the Tanzanian national policy. This study received ethical

clearance from the ethical board of the Kilimanjaro Christian Medical Centre (KCMC Ethical Clearance certificate 2007 #167).

Entomology

Mosquitoes were collected in 10 houses that were selected to be representative of the different housing structures in the village. Mosquitoes were caught with a standard Centre for Disease Control light traps (CDC, Atlanta, GA, USA) every fortnight for three months (May – September 2007). Traps were hung at the end of an occupied bed with an untreated bed net that was newly provided by the investigators. Traps were set for 12 hours, from 7 pm to 7 am [15,16]. In the morning, traps were collected and mosquito species determined and counted. Male *Anopheles* mosquitoes, Culicines and non-vector Anophelines were discarded. Female *Anopheles* mosquitoes were stored on silica gel for circumsporozoite protein (CSP) ELISA as described by Wirtz *et al* [17]. The head and thorax were removed for every mosquito, prepared for ELISA [17] and stored in an uncoated 96-well microtitre plate until the assays were performed. Samples were prepared individually and assayed with positive mosquitoes repeated. Insectary reared unfed female Anophelines were used as negative controls together with a commercially provided CSP positive control [CDC, Atlanta, USA]. Samples were read by eye and on an ELISA plate reader at 495 nm. The EIR and confidence intervals were calculated as described by Drakeley *et al.* [18]. A conversion factor was used to adjust for the difference between light trap catches and man biting catches, giving the formula: infectious bites per person per month = 1.605 * (number of positive mosquitoes/number of traps) * 30 [18].

MSP-1 ELISA

Serum was eluted from filter papers as described by Corran *et al* [19]. Immunoglobulin G antibodies against blood stage antigens were detected by indirect ELISA, as previously described [20] using recombinant MSP-1$_{19}$ (Wellcome genotype), which were produced as described previously [21]. Briefly, flat bottom 96-well plates [Immulon 4HBX, Thermo] were coated overnight with 50 µL of 0.5 mg/mL dilution of the specific antigen. After washing with PBS-0.05% Tween [(PBS-T), 200 µL of blocking buffer (1% skimmed milk in PBS-T) was added for 3 hours at room temperature. After washing, plasma samples were added in duplicate at a single dilution of 1/1000 and incubated at 4°C overnight. 100 µL of rabbit anti-human IgG HRP Conjugate [Dako, Ely, UK] was added and incubated for 1 hour at room temperature. Plates were developed with o-phenyline-diamine [Sigma]-H_2O_2 and the reaction was stopped with 50 µL H_2SO_4. Plates were read at 490 nm. To generate an OD cut-off value above which samples were deemed antibody positive, the distribution of OD values was fitted as the sum of two Gaussian distributions (assuming a narrow distribution of seronegatives and a broader distribution of seropositives) using maximum likelihood methods [19].

Data analysis

Statistical analyses of data were performed using SPSS version 14.0 and Stata 9.2 (Stata Corp, College Station TX, USA). Categorical variables were compared between groups by the Pearson Chi-square test or Fisher's Exact test, odds ratios (OR) with 95% confidence intervals (95% CI) were calculated. MSP-1$_{19}$ ELISA data were used to generate an age-seroprevalence plot. OD values were expressed as percentage of the positive control (normalised OD) The annual seroconversion rate, λ, and the annual rate of reversion to seronegativity, ρ, were estimated by fitting a simple model of the acquisition and loss of antibodies to the age-specific prevalence of the antibodies using maximum likelihood methods assuming a binomial distribution [20]. The equivalent annual entomological inoculation rate (EIR) was then estimated using a calibration curve derived from previously determined values [22].

Results

The perceived burden of malaria

In the period January 2006 – November 2007, the two clinics registered a total of 22,553 outpatient visits. In this period, 62.9% (1696/2696) of the outpatient visits of children below five years of age were diagnosed with and treated for malaria at the KKKT clinic, compared to 39.2% (3284/8382) in individuals ≥ 5 years. In the RCHF, these figures were 42.9% (1914/4466) and 42.1% (2948/7009), respectively. There was no evident seasonal pattern in the total number of malaria cases while clear peaks in rainfall were recorded in the months of March-June and October-December (Figure 1). Total rainfall was 650 mm per annum.

The measured burden of malaria

Malaria case management and microscopically confirmed parasitaemia

The clinical management of malaria cases was observed in the period June – August 2007 at both clinics. In the KKKT clinic, 240 individuals attended the clinic with symptoms that the clinician interpreted as suggestive of malaria (Figure 2); in the RC clinic this number was 88 (Figure 3). Reported complaints, age and socio-demographic factors were similar between the two clinics. The most commonly reported complaint was fever (80.9%, 263/325) followed by respiratory complaints (41.8%, 136/325). The median age of suspected malaria cases was 26.5 years (IQR 10.0 – 38.0) and 51.5% (168/326) reported the use of antimalarials in the two weeks preceding their visit. Bed net use was reported by 85.1% (417/490) of the individuals without information on (recent) impregnation.
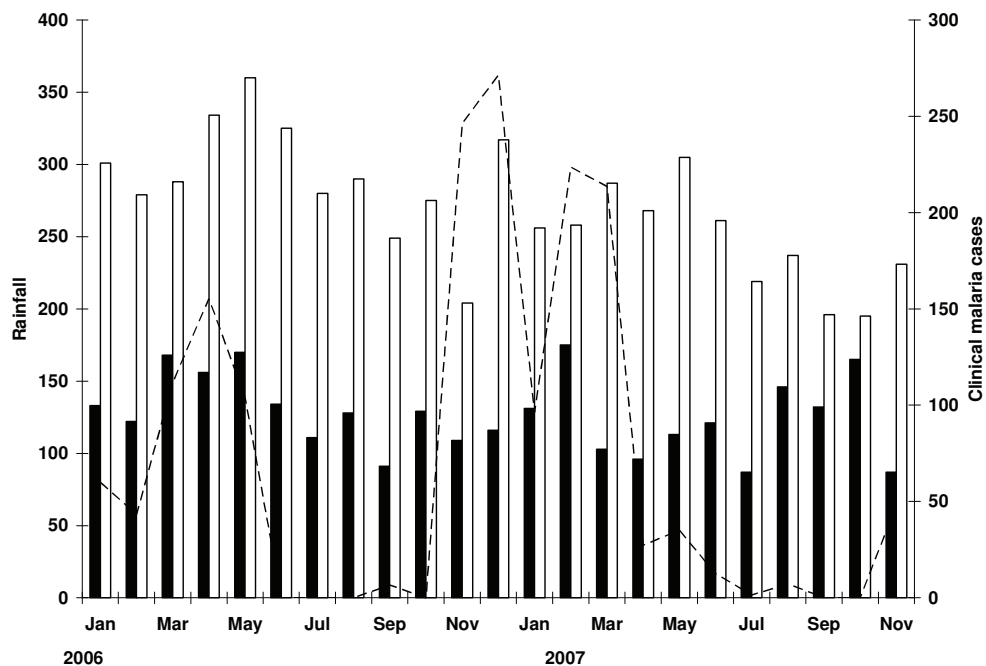
Figure 1
Rainfall distribution and number of outpatient visits diagnosed with malaria. Bars indicate the number of clinically diagnosed malaria patients younger than five years of age (closed bars) or ≥ 5 years of age (open bars) in the KKKT and RCHF clinics combined in the period January 2006 – November 2007. The dashed line indicates the total monthly rainfall in mm/month measured at the nearby Lake Manyara National Park.

Slide and RDT results and the prescribed anti-malarial treatment were summarized in Figures 2 and 3. A slide was requested for almost all individuals with suspected malaria (99.3% (326/328); the remaining two received anti-malarials without laboratory testing. All individuals who had parasites on their blood slide according to the clinic microscopist received anti-malarial treatment, both at the KKKT clinic and the RC clinic. Of those who were considered parasite free by the clinic microscopist, 58.7% (88/150) and 59.5% (22/37), nevertheless received anti-malarials at the KKKT and RC clinic, respectively. At the KKKT clinic 37.2% (89/239) of all requested slides were scored positive by the microscopist but only one of these 'positive slides' was confirmed by the research microscopists. The proportion of 'positive slides' was even higher in the RC clinic where 57.5% (50/87) of all requested slides was considered positive by the clinic microscopist and none of these were positive when stained and read by the research microscopists. One parasite positive slide was missed by the microscopist in the KKKT clinic (parasite density: 27,760 parasites/µL) and was also RDT negative; this person received antibiotics, but no anti-malarials. There was no statistically significant association between slide positivity by the clinic microscopists and the research microscopists (p = 0.84). Ten

individuals were positive by RDT, one of them was also slide positive and two others reported the previous use of anti-malarials.

When data of the two clinics were combined, the following factors were associated to prescription of anti-malarial drugs: the chance of receiving anti-malarials was increased when the slide was scored positive by the clinic microscopist (OR 1.70; 95% CI 1.51–1.92) and decreased in case of reported cough (OR 0.50 95% CI 0.30 – 0.84). Reported fever and reported previous use of anti-malarials or antibiotics were not associated with the chance of receiving anti-malarials at the clinic.

The entomological inoculation rate by mosquito sampling
A total of 70 CDC light traps were set in the period May-September 2007. Of the mosquitoes caught, 15.6% (331/2774) were of the *Anopheles* genus and 261 were female. All female mosquitoes were processed and included in the CSP ELISA, one was CS positive. This resulted in an estimated entomological inoculation rate (EIR) of 0.69 (95% CI 0.02 – 3.83) infectious bites per person per month for the period surveyed.
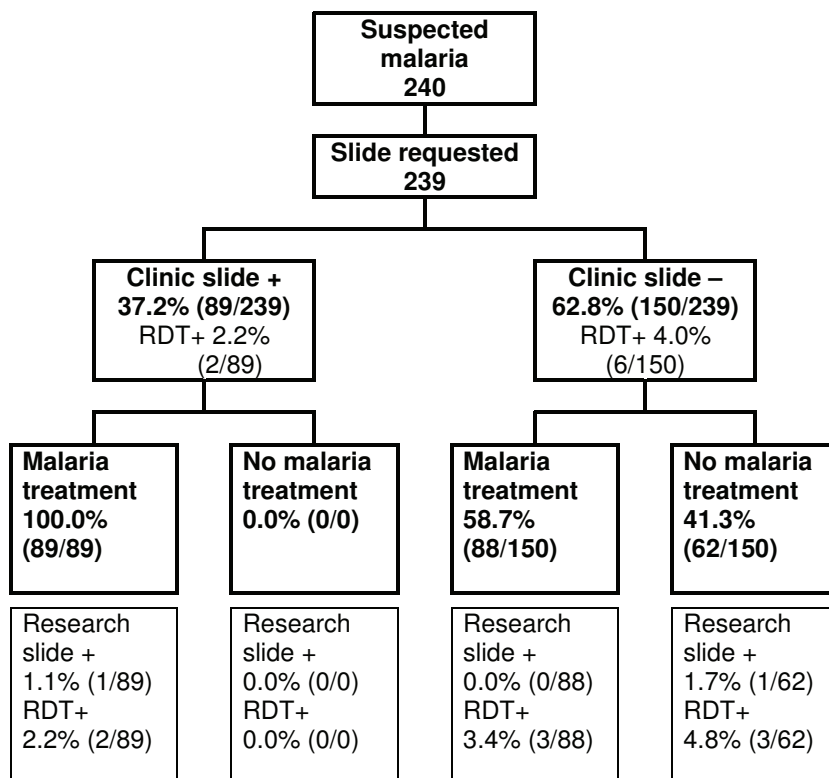
Figure 2
Management of individuals with suspected malaria at the KKKT clinic. Clinic slide = slide stained and read by clinic microscopist; research slide = slide stained and read by trained research microscopist; RDT = rapid diagnostic test

The entomological inoculation rate equivalent generated from seroprevalence data
A total of 464 serum samples were tested in the $MSP1_{19}$ ELISA. The overall seroprevalence of $MSP1_{19}$ antibodies was 29.5% (137/464) and there was a clear increase in seroprevalence with age (Figure 4). Based on the fitted curve, the λ was estimated at 0.026 (95% CI 0.016 – 0.042), which corresponds to an estimated EIR of 0.70 (0.26 – 1.87) infectious bites per person per year.

Discussion
In the study area of Mto wa Mbu that is characterised by low transmission intensity, an unrealistically high perceived burden of malaria was observed. Forty percent of outpatients were treated for malaria while this diagnosis was not supported by blood slide or rapid test and was improbable in the light of the actual level of transmission intensity.

The level of malaria transmission intensity, as determined by rapid entomological assessment and MSP-1_{19} age-seroprevalence data [20], was low in the area of Mto wa Mbu. The EIR estimate by entomological assessment was 0.7 infectious bites per person per month. This estimate was obtained in the period after the long rains and probably represents the peak exposure to infected mosquitoes. It is, therefore, not surprising that it exceeds the EIR estimate based on the $MSP1_{19}$ age-seroprevalence curve (0.7 infectious bites per person per year) although the confidence intervals for both methods overlap. In general, EIR by entomological assessments is susceptible to seasonal fluctuations [12], fluctuations that are smoothened out by the immunologic assessment [20,22] that may, therefore, give a more robust estimate. Either method will lead to the conclusion that transmission intensity in Mto wa Mbu is low. This is in contrast with cross-sectional surveys from 1981 [13], when parasitological surveys indicated that the area was having a level of transmission intensity 'certainly equal to and probably higher than that found in Muheza-Ubembe' [13], an area that is still known to be hyperendemic for malaria [23]. Malaria transmission intensity clearly decreased in last 25 years but the period in which the reduction took place is unclear. (Recent) reductions in transmission intensity can be detected in age seroprevalence curves when the force of infection (λ) is allowed to change over time [22]. However, a variable λ did not improve the fit of our curve (data not shown), and we found no indications for a recent reduction in EIR. Similar
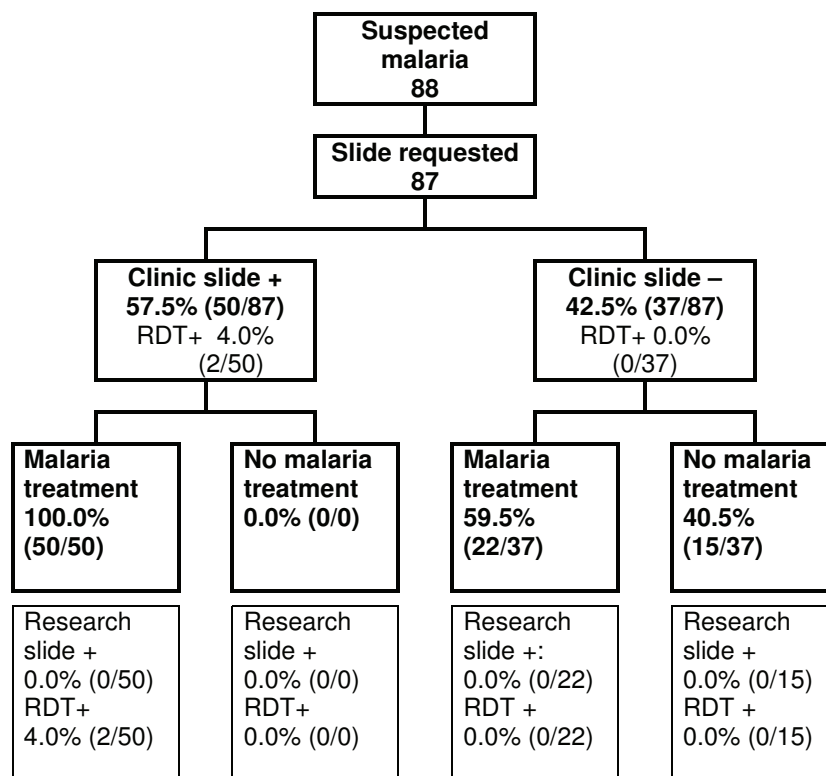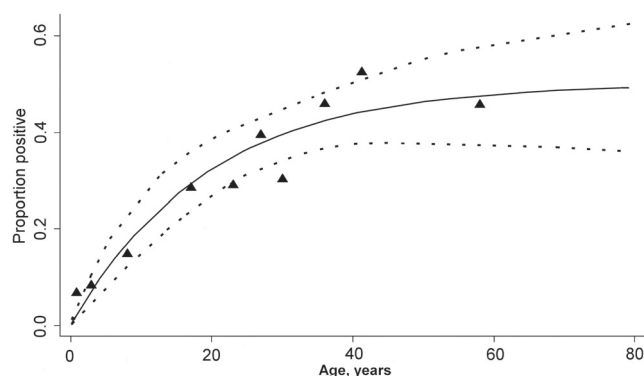
Figure 3
Management of individuals with suspected malaria the RCHF clinic. Clinic slide = slide stained and read by clinic microscopist; research slide = slide stained and read by trained research microscopist; RDT = rapid diagnostic test

to its timing, the reasons for the reduction in EIR are unclear. The use of chloroquinized salt can not explain this since it was used in the 1960s and 70s and parasite rates of 50–60% in children < 10 years of age were still reported in 1981 [13]. Bed net coverage was high in the study area, but the coverage with ITNs has only increased in recent years [24] and also provides no plausible explanation. Similar to other areas in Africa [6], the drop in transmission intensity is not easily explainable. The high use of anti-malarials for any fever treatment, as demonstrated in this study, could have acted as mass prophylaxis and reduced transmission over time [6], but this cannot be proven.

Despite the low transmission intensity in the area of Mto wa Mbu, more than forty percent of all outpatients who attended two major clinics over a period of almost two years were diagnosed with malaria. There was no seasonal pattern in malaria diagnoses, as is commonly observed [12,14]. Prospective data from more than 400 suspected malaria cases demonstrate that there was a massive over-diagnosis of malaria in the two clinics. Despite the availability of microscopes, experienced microscopists and clinicians, who frequently requested slides, the targeting

of anti-malarials appeared to be unimproved [5,25]. One major explanation for this was that slide readings were unreliable in the clinics included in this study: less than 1% of slides that were regarded as malaria parasite-positive by clinic microscopists were confirmed by trained research microscopists. In addition, clinicians appeared to use blood slide results more as a tool to confirm their clinical suspicion rather than to rule out malaria [25]. All individuals with 'positive slides' received anti-malarial treatment although a 'negative slide' did by no means rule out treatment [9]. This could be a result of the deeply entrenched belief in slide negative malaria. It is true that clinical malaria can result from low density parasitaemia in low endemic areas and malaria can therefore not always be ruled out in slide-negative cases [4]. However, these are exceptional cases and restricting anti-malarials to true microscopy-positives is a safe approach, even in areas of low endemicity [8]. The prescription of anti-malarials in Mto wa Mbu was clearly out of proportion. An astounding 99.6% (248/249) of the individuals who were treated with artemether-lumefantrine (AL) was free of malaria parasites.

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Figure 4
Age specific seroprevalence plot of anti-MSP-1$_{19}$ antibodies. The vertical axis shows the proportion of seropositive individuals in each age group, the horizontal axis shows the midpoint age of each age group. Filled triangles represent the raw data; the lines represent the fitted equation with parameters $\lambda = 0.026$ and $\rho = 0.026$ and the 95% confidence interval.

Although a recently published hypothesis suggests that overdiagnosis and overtreatment of malaria can have a beneficial prophylactic effect in malaria control [6], the current findings are worrying for several reasons. Firstly, our area is of low endemicity and a beneficial prophylactic effect is unlikely [6]. Secondly, diagnosis of malaria and according treatment may simply be a 'convenient' clinical strategy avoiding the more complicated search for other causes of the presenting illness [25]. Treatment of all febrile episodes as malaria is likely to result in underdiagnosis of other fever-causing disorders such as childhood pneumonia [2]. Thirdly, over-treatment occurred with the expensive AL. AL and other ACTs are typically 10-times more expensive then previously used drugs as sulphadoxine-pyrimethamine [26,27] making reliable diagnosis crucial for cost-effective use [28]. The artemisinin component in ACT also do not have the prophylactic effect that was suggested to be beneficial in 'opportunistic presumptive treatment' [6]. Artemisinin is eliminated from the circulation in a matter of hours [29] leaving the partner drug, in this case lumefantrine, unprotected. That leads us to the fourth reason for unease. There is concern for a reduced susceptibility of *P. falciparum* parasites for ACT [29] and the spread of parasites with reduced susceptibility to ACT may be enhanced by irrational drug use [30]. Reports on allelic selection after artemether-lumefantrine [31] provide additional warnings against over-use of ACT.

For a way forward, it is important to understand why there is so much overdiagnosis and overtreatment in the study area. A recent study elsewhere in Tanzania has demonstrated that patient pressure, traditionally mentioned as a major contributor [32], may not be important in overtreatment [33]. Patients often prefer to be slide-tested and treated in line with results [33]. In the clinics in Mto wa Mbu, slide reading was clearly inadequate. Microscopists will need additional training and in addition, more objective diagnostic tools such as RDTs can play a role in the improvement of diagnosis. Clinicians in this study felt uncomfortable to rule out malaria based on a negative RDT (and one patient in our study was in fact a false RDT negative). Time will be needed to make them consider RDTs as useful diagnostic tools [34]. Perhaps delivering a message to health workers and the public explaining that malaria control has been successful in some areas and malaria has truly been reduced may improve the situation. If both health staff and public understand that this fever may not be due to malaria quality of care may improve and "routine overdiagnosis" may be a story of the past.

Conclusion
The observed discrepancy between the perceived and actual level of transmission intensity may be present in many areas in sub-Saharan Africa and calls for greater efforts in defining levels of transmission on a local scale. National policies may have to give way to more sensible local policies that use proven multiple interventions in areas of high-moderate transmission and focus on accurate diagnosis and treatment in low transmission settings.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
CM, AN, BM and SM were responsible for data collection and were involved in data analysis and manuscript preparation; SS and HM were involved in statistical data analysis and manuscript preparation; FM and RS in study design; CD, RG and TB were responsible for study design, data interpretation and manuscript preparation.

Acknowledgements

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Malaria Journal

Research

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The decline in paediatric malaria admissions on the coast of Kenya

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Abstract

Background: There is only limited information on the health impact of expanded coverage of malaria control and preventative strategies in Africa.

Methods: Paediatric admission data were assembled over 8.25 years from three District Hospitals; Kilifi, Msambweni and Malindi, situated along the Kenyan Coast. Trends in monthly malaria admissions between January 1999 and March 2007 were analysed using several time-series models that adjusted for monthly non-malaria admission rates and the seasonality and trends in rainfall.

Results: Since January 1999 paediatric malaria admissions have significantly declined at all hospitals. This trend was observed against a background of rising or constant non-malaria admissions and unaffected by long-term rainfall throughout the surveillance period. By March 2007 the estimated proportional decline in malaria cases was 63% in Kilifi, 53% in Kwale and 28% in Malindi. Time-series models strongly suggest that the observed decline in malaria admissions was a result of malaria-specific control efforts in the hospital catchment areas.

Conclusion: This study provides evidence of a changing disease burden on the Kenyan coast and that the most parsimonious explanation is an expansion in the coverage of interventions such as the use of insecticide-treated nets and the availability of anti-malarial medicines. While specific attribution to intervention coverage cannot be computed what is clear is that this area of Kenya is experiencing a malaria epidemiological transition.

Background

Since the inception of the Roll Back Malaria (RBM) movement in 1996 [1], billions of health dollars have been committed by the international donor community to reduce the burden of malaria in Africa [2], estimated to be over a million deaths directly due to *Plasmodium falciparum* annually [3]. However there are remarkably few documentations of changes in disease burden associated with increases in access and use of interventions funded by new international donor agency money.

In Kenya the expansion of coverage of both ITN and effective ACT therapy (artemether-lumefanthrine) has occurred very recently. Between 2004 and 2005 ITN coverage among children aged less than five years rose from 7% to 24% and by the end of 2006 had risen to 67% coverage [4]. Despite delays in implementing the revised drug policy supporting the use of AL [5], over 85% of rural clinics had AL in stock between August and December 2006 [6]. Paediatric admission time-series from three Kenyan hospitals were assembled to explore the impact of parallel changes in intervention coverage and malaria disease burden.

Methods

Paediatric admission data

Three district hospitals were selected purposively along a 170 km stretch of the Kenyan coast at Malindi, Kilifi and Msambweni (located in Kwale district). They are located in three different districts of Coast Province, and all serve populations who share similar climatic, ecological and economic characteristics (Figure 1).
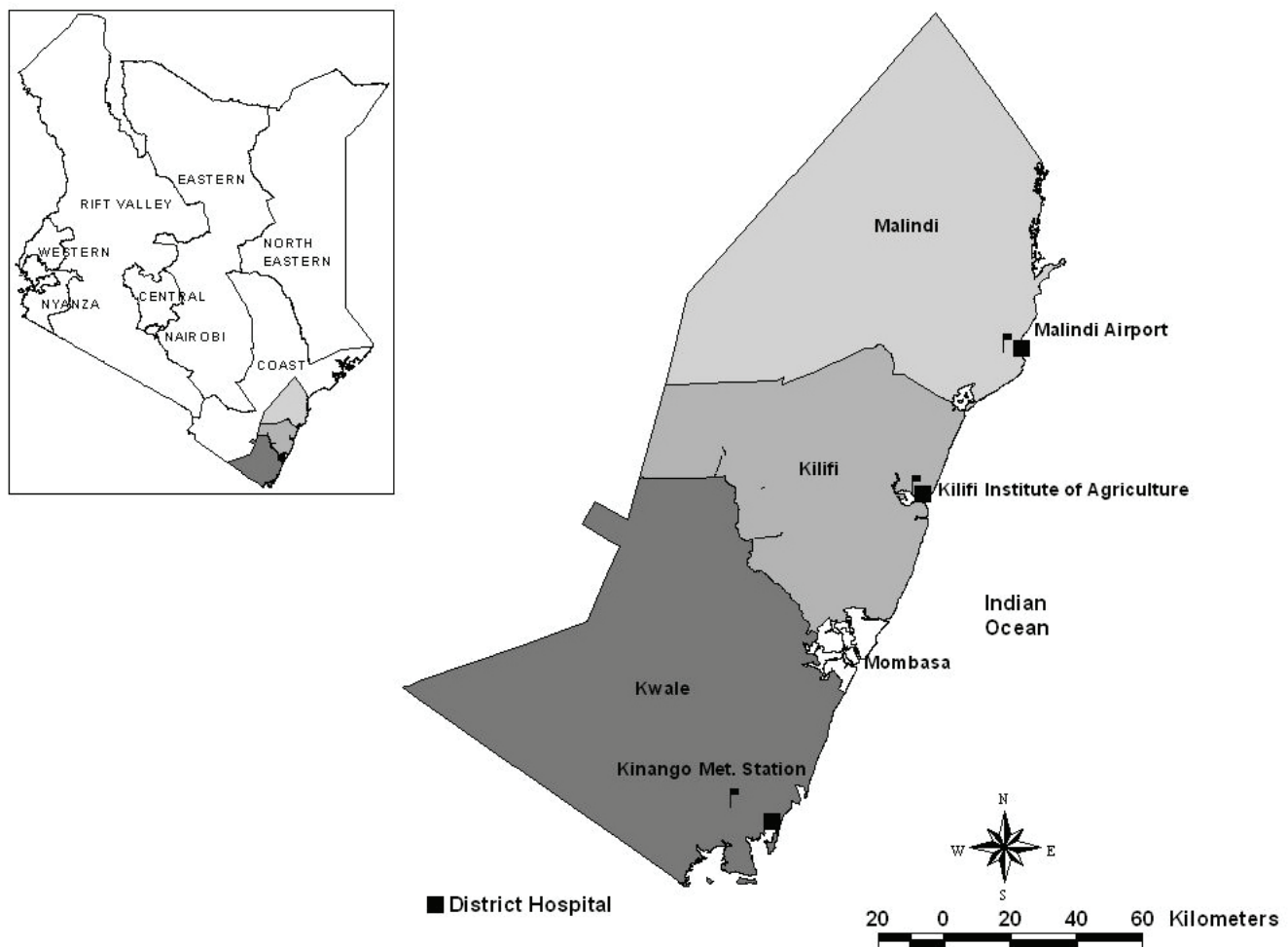
Figure 1
Map showing the three study districts and the location of the metrological station in relation to the hospital facility. Inset is a map of Kenya showing location of three districts.

Paediatric ward in-patient registers at Malindi and Msambweni were identified for all months from January 1999 to March 2007. These were arranged serially to check whether these represented a continuous, uninterrupted series. Each admission entry in the registers was recorded on a separate tally sheet indicating the month of admission, whether a primary working diagnosis of malaria had been defined for the child, whether the admission diagnosis was not malaria and whether the child had survived admission. Separately, hospital death certificates were reviewed for the same period to identify any paediatric deaths that may have not been recorded in the admission ward books. All paediatric admissions were assumed to be aged between birth and 15 years. Individual register entries were not reconciled with patient notes and thus we have assumed that the admission diagnosis remained the clinical management diagnosis and it is used here as the diagnosis of analysis. The reliability of slide confirmed malaria diagnosis at admission was not validated from hospital or laboratory records as these procedures are variously performed in most Kenyan district hospitals [7] and results are rarely used to refine a diagnosis [8-10].

At Kilifi district hospital a sophisticated paediatric ward surveillance system has been *in situ* since 1989 to form the basis of a series of clinical studies on the pathogenesis of malaria, pneumonia, malnutrition and neonatal illness [11-14]. Clinical and laboratory coverage is provided 24 hours each day throughout the year. Demographic details and clinical histories are recorded on every admission and a finger prick blood sample taken for malaria parasitology and basic haematology. Following a clinical examination at admission further clinical and laboratory investigations are undertaken as indicated. Clinical and laboratory findings, clinical progress and response to therapy were reviewed at discharge to derive a primary diagnosis and recorded on a standard admission proforma later entered onto a centralized database. Data for the present study were reassembled for the period January 1999 through to March 2007 and summarized by month as a discharge diagnosis of malaria or non-malaria for all admissions aged between birth and 15 years of age.

Ancillary data
Seasonal patterns of malaria hospitalization are related to monthly rainfall precipitations along the Kenyan coast [15] and relate principally to the population dynamics of the dominant vector species [16]. Monthly rainfall data in decimal mm were obtained from meteorological offices located 3 km (Malindi), 2 km (Kilifi) and 25 km (Msambweni) from the respective district hospitals and were complete across the same time-period as the paediatric ward surveillance (Figure 1). The Kenyan coast is an area where sporogony in the vector population and hence malaria transmission, is not limited by ambient tempera-

ture and therefore temperature data were not included in the analysis.

Natural population growth over the 8.25 observation years is likely to have affected the size of population accessing these three hospitals. Precise rates of admission adjusted for monthly denominator size were not possible for the hospitals as the catchment for these services cannot be rigorously defined over time [17]. Non-malaria admissions data were also collected, however, to help calibrate for population and other issues affecting hospital usage.

Data analysis
Analysis was undertaken using STATA version 9.2 (Statacorp 2003, College Station, USA). Hospital admission data obtained over the 99 months of surveillance between January 1999 and March 2007. Malaria admission case totals were assembled chronologically by admission month and non-malaria admissions similarly assessed for comparison purposes. They were examined with time series analysis that used malaria admission cases as the main outcome.

Smoothing techniques (moving averages) were used to filter short-term annual fluctuations and thus highlight longer-term trends present in the each of the data series. Malaria, non-malaria and rainfall, time series data from Kilifi, Kwale and Malindi were subject to 13-point moving average to aid visual interpretation of trends. Deviations in monthly rainfall were also examined by comparing monthly values of these parameters obtained during the study period with synoptic mean values computed from the 8.25 years of surveillance. The disparity between long term values and current values was referred to as an anomaly and had either positive or negative values.

A regression model expressing malaria cases as a linear combination of non-malaria cases and rainfall was used to test for trend. The non-malaria cases and rainfall allow trend statistics to be presented that are "aware" of other potential longitudinal influences on malaria admissions. A continuous variable indicating the time in months from the start of the observation period was included in the regression model. The coefficient of time in the model estimates the trend in the series (i.e. the month-to-month change in the number of admission cases). A P-value of < 0.05 was considered significant. There were strong seasonal fluctuations observed for malaria admissions, with a higher proportion of admissions recorded in the rainy season than in the dry season. To control for the confounding effect of seasonality on the trend, seasonal effects were included in the regression model by the use of indicator terms (dummy variables). The 11 dummy variables are constructed as time series with the value one for observations falling in a given month and zero when not.

The final month was used as the baseline for comparison. There are thus 11 potential intercepts generated depending on the choice of baseline month for comparison; we elected to plot and discuss the intercept and trend that had the maximum correlation with the 13-point moving average. These analyses were conducted separately for each district.

A key assumption when using ordinary least squares regression is that the model residuals are independent [18] and this is often violated by longitudinal data [19]. In the presence of autocorrelation standard errors of parameter estimates are underestimated resulting in an overestimation of significance. The Durbin-Watson statistic was hence used to test for serial autocorrelation [20]. Serial correlation was found in all malaria admission data series (results not shown) indicating that correction was necessary. An analysis of autocorrelation and the sample partial autocorrelation function of deseasonalised data [19,21] showed that a correction of this serial correlation with a lag of two months was optimal. Newey-West standard errors [21,22] with a lag of two months were therefore used to correct for autocorrelation and potential heteroscedasticity.

Results
Descriptions of the data
Longitudinal data was obtained from all the hospitals for the period starting January 1999 to March 2007. During the 8.25 years of surveillance there were a total of 76,101 paediatric admissions: 41,715 admissions in Kilifi, 13,492 in Kwale and 20,894 admissions in Malindi. A total of 34% of the total admissions had a diagnosis of malaria; 32% (13,919) in Kilifi, 40% (5,361) in Kwale, and 36% (7,498) in Malindi.

The annual number of malaria admissions declined with time (Table 1) in all three locations. In 1999 the proportion of admissions due to malaria was 46% in Kilifi, 51% in Kwale and 45% in Malindi. In 2006, seven years after the start of surveillance, this proportion had declined to 13% in Kilifi, 26% in Kwale and 24% in Malindi. The proportional decline was greatest in Kilifi (-72%) and lowest in Malindi (-38%). Conversely, within the same period, the proportion of admissions diagnosed as non-malaria increased (Table 1). The largest proportional increase in non-malaria cases was observed in Malindi at 64% while the lowest increase was recorded in Kwale 15%. The proportional increase in non-malaria admissions in Kilifi was 52%.

Seasonally adjusted linear regression analysis of admissions
Malaria admissions in all three study sites were observed to show significant downward trends (Table 1). When adjusting for the increases in non-malaria admissions the decreasing trend in malaria admissions became more pronounced in Kilifi and Malindi (Table 2; $P < 0.001$). By March 2007 the estimated proportional decline in malaria cases was 63% in Kilifi, 53% in Kwale and 28% in Malindi. Values of the intercepts and coefficients of trends are detailed in Table 1 and shown in Figure 2 – left panel. Including rainfall as an additional covariate had little effect on the intercept and slope of the trends observed so that the trends were indistinguishable on Figure 2 (results not shown).

Table 1: Trends in paediatric admissions during the period January1999 to March 2007 at three sites on the Kenyan coast.

	1999	*2006*	*Change (%)*	*Intercept (95% confidence interval)*	*Trend (95% confidence interval)*
Malaria Admissions					
Total across sites	4611	1796	-61		
Kilifi	2395	660	-72	259.57 (155.64, 363.49)	-1.67† (-2.29, -1.05)
Kwale	1053	418	-60	80.12 (58.88, 101.35)	-0.43† (-0.65, -0.21)
Malindi	1163	718	-38	119.15 (84.00, 154.31)	-0.33† (-0.59, -0.08)
Non-Malaria Admissions					
Total across sites	5215	7724	48		
Kilifi	2791	4243	52	236.72 (194.95, 278.50)	1.37† (0.92,1.81)
Kwale	1022	1175	15	73.47 (50.16, 96.78)	-0.01‡ (-0.31, 0.29)
Malindi	1402	2306	64	79.45 (57.55, 101.35)	0.91† (0.60, 1.23)
Rainfall					
Kilifi	1197.7	2099.7	75	81.98 (38.27, 125.58)	0.10‡ (-0.65, 0.85)
Kwale	1591.1	1910.2	20	48.96 (4.55, 93.37)	-0.04‡ (-0.89, 0.80)
Malindi	1020.7	1505.2	47	84.32 (52.82, 115.83)	0.02‡ (-0.40, 0.44)

†$p < 0.001$. ‡Not significant ($p > 0.05$).

Table 2: Trend of monthly malaria admissions during period the period January 1999 to March 2007 at three sites on the Kenyan coast.

Parameters	coefficient	NW SE*	t-stat	P-value	95% confidence interval	
Kilifi						
Intercept	145.887	71.50	2.04	0.044	3.69	288.08
Trend	-2.320	0.40	-5.80	0.000	-3.12	-1.52
Non-mal cases	0.478	0.19	2.47	0.016	0.09	0.86
Rainfall	0.094	0.05	1.92	0.058	0.00	0.19
Kwale						
Intercept	52.933	12.62	4.20	0.000	27.84	78.02
Trend	-0.425	0.10	-4.19	0.000	-0.63	-0.22
Non-mal cases	0.377	0.08	4.64	0.000	0.22	0.54
Rainfall	-0.018	0.02	-0.78	0.435	-0.06	0.03
Malindi						
Intercept	95.395	19.54	4.88	0.000	56.53	134.26
Trend	-0.574	0.15	-3.78	0.000	-0.88	-0.27
Non-mal cases	0.262	0.14	1.84	0.069	-0.02	0.55
Rainfall	0.007	0.07	0.11	0.910	-0.12	0.14

*NWSE: Newey-West standard errors.

Significant (P < 0.001) upward trends in non-malaria admission cases were shown in both the Kilifi and Malindi hospitals over the study period (Table 1). There was no statistically significant difference in Kwale. By March 2007, non-malaria admission cases in Kilifi and Malindi were estimated to have increased by 56% and over 100% respectively (Figure 2 – right panel) while remaining relatively consistent in Kwale. Again including rainfall as an additional covariate had little effect on the intercept and slope of the trends observed (results not shown).

Seasonally adjusted linear regression analysis of rainfall and anomalies
The trend in rainfall patterns remained relatively stable during the 8.25 years of surveillance. There was no evidence of consistent changes in rainfall patterns over the period with no significant synoptic trends identified in any of the three study sites (Table 1, Figure 3 – left panel). The anomaly analyses show that during the period 2004–2005, monthly rainfall in all the three study sites was lower on average than the computed long term means (Figure 3 – right panel). Thus there were no notably drier years except during this period. This was followed by considerable increase in rainfall in 2006 in all the study sites.

Discussion
Between January 1999 and March 2007 (8.25 years) admissions due to malaria have systematically declined at three sites along the Kenyan coast. These declines were examined in relation to possible changes in overall hospital utilization by a naturally growing paediatric population size and within and between year variations in

rainfall. The fact that the significant decline in malaria admissions occurred against a significant rise in non-malaria admissions in Kilifi and Malindi and remained unchanged at Kwale during the surveillance period (Figure 1, right panel) suggests that the declining admissions due to malaria were specific to malaria. It could be argued that an increase in non-malaria cases might be attributed to a changing diagnostic pattern over the surveillance period with fewer misclassifications or more doctors accepting as true malaria test results. This cannot be ruled out at Malindi or Kwale but at Kilifi standardized diagnostic practices have applied to all paediatric admissions throughout the entire surveillance period and thus changes in the pattern of diagnosis seem an unlikely explanation for the trends observed.

The monthly incidence of malaria is coupled to seasonal rainfall patterns on the Kenyan coast. The addition of rainfall as a covariate to the model had no effect on the slope or intercept of seasonally corrected trend lines because rainfall patterns were shown to have remained relatively constant during the observation period with no significant increasing or decreasing trends observed in any of the study sites. Attributing the long-term reduction in malaria cases to a constant change in rainfall is implausible as there was no evidence of a substantial decline in rainfall except for the anomaly recorded in 2004/5, where rainfall was lower on average than that expected (Figure 3, right panel). This was however followed by a considerable substantial increase in amount of rainfall recorded in 2006. Despite this there was no associated increase in malaria admissions observed in 2006 or early 2007.
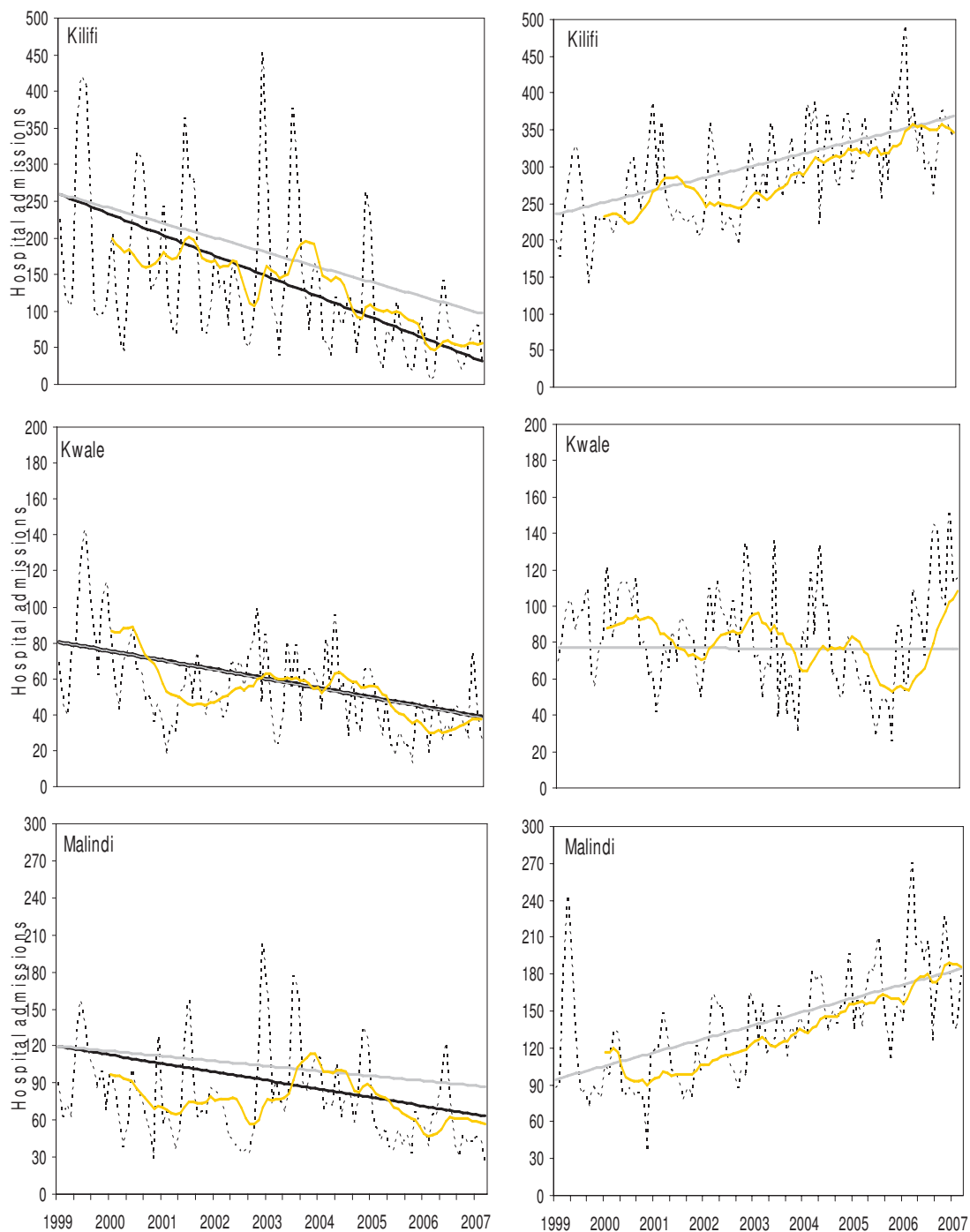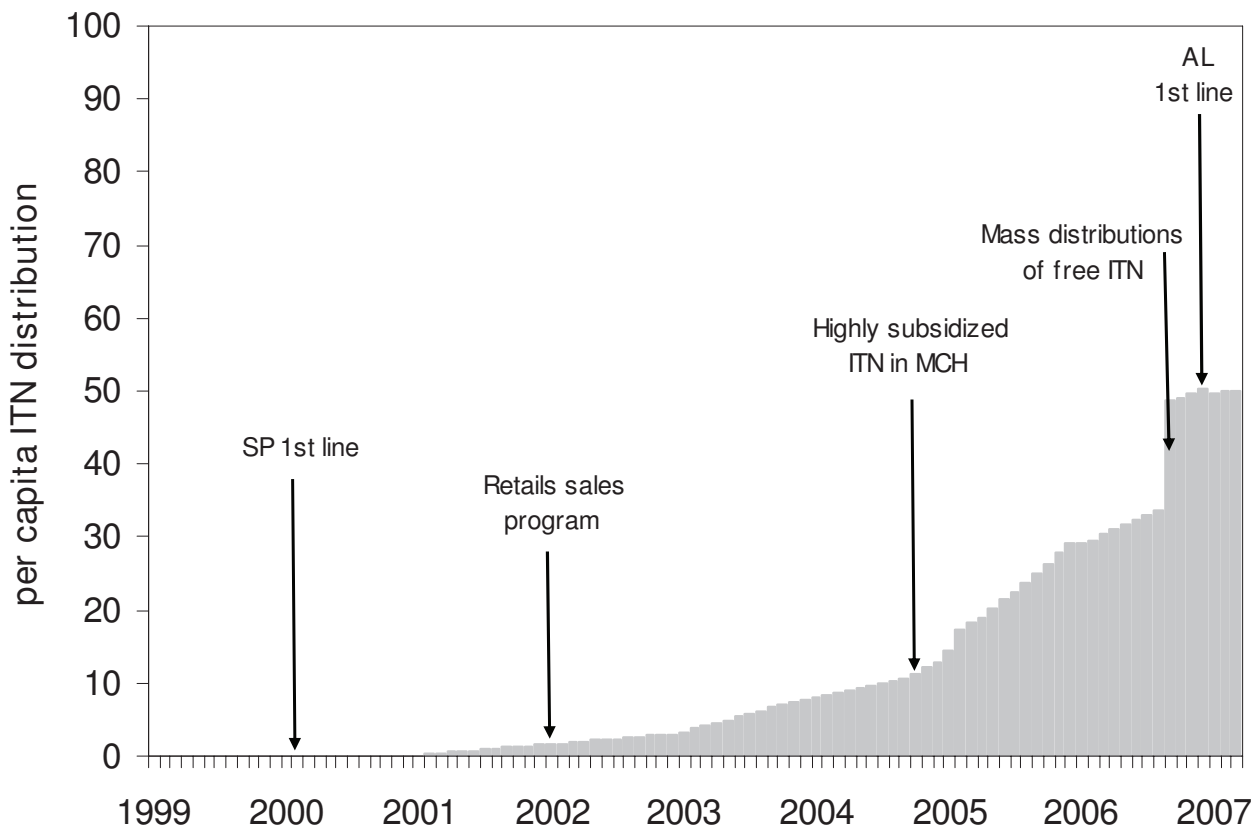
Figure 2
Admissions by month for the period January 1999 to March 2007 at three sites on the Kenyan coast. The top row is Kilifi, the middle row Kwale and the bottom Malindi. The graphs show malaria admissions (left column) and non-malaria admissions (right column) as dashed lines. The yellow solid line is a 13-point moving average applied to filter seasonal variation and high-light the long-term movements in the data. The two solid tone lines illustrate the change in admissions adjusted for seasonality (light grey) and seasonality, rainfall and non-malaria admissions (black). The intercept was chosen (from the potential 11) based on the maximal correlation with the 13-point m.a.
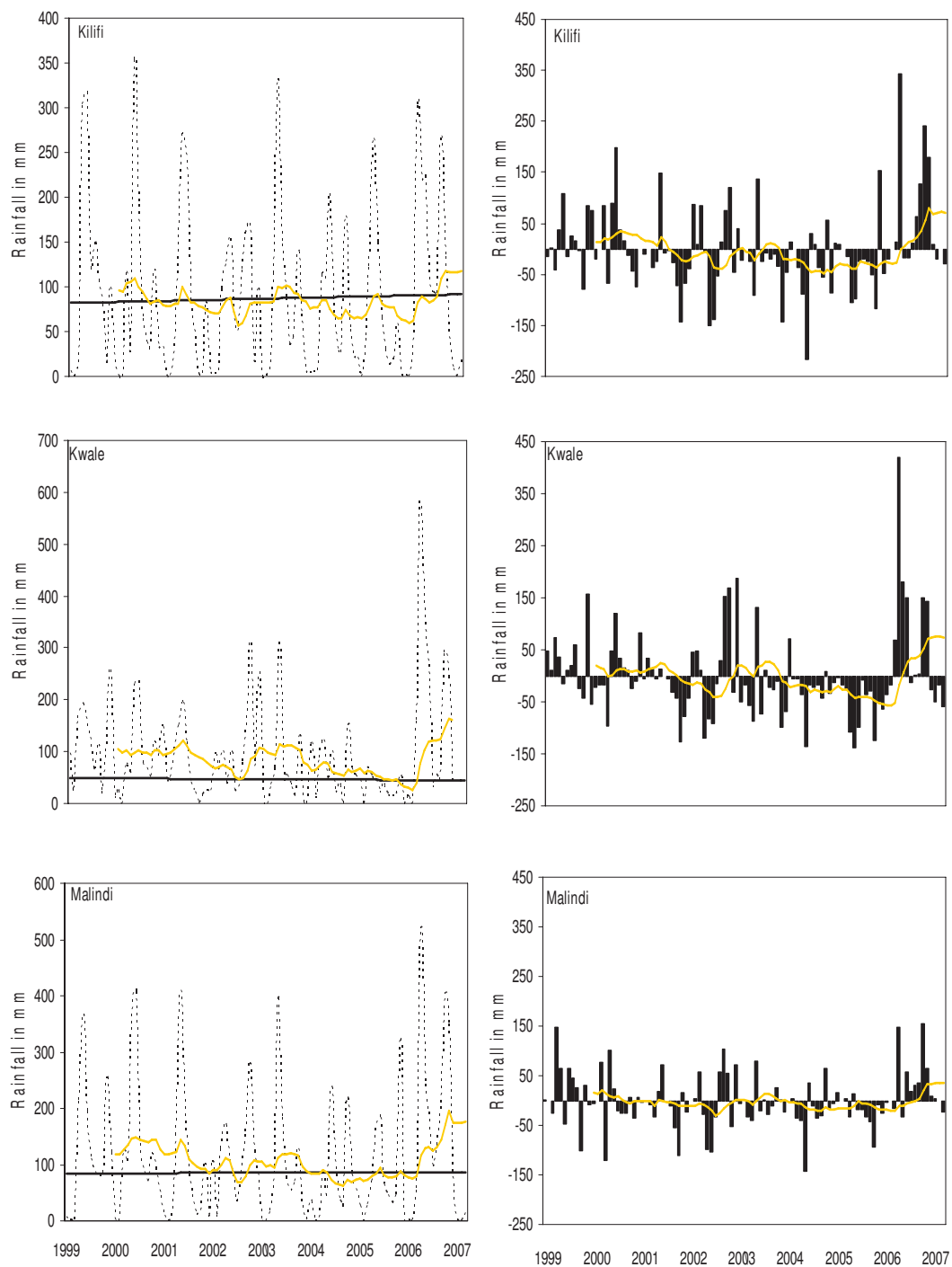
Figure 3
Rainfall per month for the period January 1999 to March 2007 at three sites on the Kenyan coast. The top row is Kilifi, the middle row Kwale and the bottom Malindi. The graphs in the left column show the monthly rainfall in mm as dashed lines. The yellow solid line is a 13-point moving average applied to filter seasonal variation and highlight the long-term movements in the data. Trends corrected for seasonality are shown in black. The rainfall expressed as anomalies relative to 1999–2007 monthly mean for each site are shown in the middle column. The 13-point moving average is again also shown. The intercept was chosen (from the potential 11) based on the maximal correlation with the 13-point m.a.

The use of three different hospital admission series increases the external validity of a single observation from one hospital. We consider the data from Kilifi as the diagnostic gold standard based on the use of microscopy and a discharge diagnosis supported by review of clinical notes. Using this as our point of reference, external validity of this result is provided by data from Msambweni (Kwale) and Malindi. It is reassuring then that a consistent declining pattern in malaria admission is maintained across all study sites lending weight to the strength of the findings. By 2006, annual malaria admissions had decreased by an average of 57% compared to 1999 across all sites.

There are several possible factors that might explain these observations and are considered as plausibility arguments, as proposed by Habicht [23] and Victora [24], rather than measurable correlates. The most notable programmatic change over the 8.25 years of surveillance has been the increasing use of ITNs [4]. We have assembled a population adjusted estimate of the per capita ITN distri-

bution patterns between 1999 and 2007 across the three districts combined (Figure 4). At the start of the observation period ITN distribution in all the three study sites was negligible. During the period 2001–2004, there was a steady increase in the cumulative per capita ITN distribution (Figure 4). One year after initiation of a retail sector programme (beginning of 2003), cumulative ITN distribution was estimated to be 3% per capita across the three districts. By December 2004, three months after the inception of an MCH clinic sales programme, cumulative ITN distribution was over 13 nets per 100 people. The largest increase occurred in September 2006 during the mass distribution campaign from an estimated 0.34 nets per capita in August 2006 to 0.49 nets per capita by September 2006. Extending the surveillance from 2006 into March 2007 corresponds to a period of highest ITN "coverage", implementation of a new effective first line treatment policy and increasing rainfall. Even so the anomaly in malaria admissions recorded was greatest during this period with an average of -79 in Kilifi, -34 in Malindi and -14 in Kwale. It should, however, be recognized that the decrease

Figure 4
Cumulative monthly ITN distribution volumes expressed per capita across the three districts of Malindi, Kilifi and Kwale.

in malaria cases started before the major expansion of prevention coverage in 2006, reasons for this remain unclear.

Data on the serial use of prompt, effective antimalarial treatment in each of the three districts was not possible to assemble. However a semi-qualitative, temporal description of drug efficacy is possible in accordance with national first line recommendations for treatment between 1999 and 2007. Between January 1999 and early 2000 chloroquine was still the only available antimalarial in government clinics despite wide-spread resistance documented on the coast [25]. Between mid-2000 and April 2006 sulphadoxine-pyrimethamine (SP) was the nationally recommended first line drug available in most government clinics and drug efficacy declined rapidly over this period in Kilifi and Kwale until most studies showed at least 25% failure rates when undertaken after 2002 [26,27]. The policy was changed in April 2004 to artemether-lumefathrine (AL) but was not effectively implemented until December 2006 [5]. The efficacy of AL was defined in Kilifi as in excess of 94% in 2002–2003 [28]. Patient access to antimalarials within 48 hours of onset of symptoms has been documented in Kwale district in 2001 (15%) and 2006 (17%) ([29]; unpublished data), both representing very low estimates of prompt access and we assume not dissimilar to anticipated access figures for Kilifi and Malindi districts during the same period. However, the widespread availability of even sub-efficacious SP over-the-counter from 2000 onwards in Kwale [30,31] and Kilifi [32] may have had a suppressive effect on clinical disease risks operating similar to strategies prompting intermittent presumptive treatment in young children [33].

The use of hospital data provides a useful indicator of the long-term and short-term impact of scaling-up malaria interventions. It is not possible to definitely attribute carefully controlled and adjusted changes in malaria admission rates to expanded coverage of preventative and curative interventions; however these seem to be the most parsimonious explanations for the observations reported here along the Kenyan coast.

Authors' contributions

EA Okiro assembled all the hospital data, developed the analytical models and wrote the manuscript; SI Hay provided technical support for the time-series models and contributed to the drafting of the manuscript; PW Gikandi supervised the collection of all the hospital data since 1999; SK Sharif was the Provincial Medical Officer for Coast province between 1999 and 2005 responsible for the delivery of services and collection of health information and contributed to the final draft of the manuscript; AM Noor was responsible for the assembly of the ITN data in each district and contributed the final manuscript; N Peshu and K Marsh were overall responsible for the data provided by Kilifi district hospital and contributed to earlier drafts of the manuscript. RW Snow was responsible for the conception and continued funding of the project and its overall scientific management, analysis, interpretation and preparation of the final manuscript. All authors read and approved the final manuscript.

Appendix

Table 1

Footnote: The intercept refers to the seasonally adjusted level of malaria and non-malaria cases and rainfall at the start of the observation period. Models for malaria and non-malaria included a covariate for rainfall. The regressions were performed with Newey-West standard errors with a lag of two months for models with malaria and non-malaria case outcomes and a lag of one month for models with rainfall.

Table 2

Footnote: The intercept refers to the seasonally adjusted level of malaria cases at the start of the observation period. Models included a covariate for non-malaria cases and rainfall. The regression was performed with Newey-West standard errors with a lag of two months for models with malaria and non-malaria case outcomes.

Figure 4

Footnote: Information on net deliveries was assembled from a variety of sources for each district. We assumed that ITN coverage was less than 5% between January 1999 and December 2002. This position is supported by reviews of net use undertaken in Kenya during this period [34]. In Kilifi district a large scale trial of ITN was completed in 1993 [35] and by 1997 there were few net replacements or net re-treatments [36]. From 2002 Population Services International (PSI) had launched a retail sector, social marketing campaign for ITN distribution [37]. Annual sales figures for the coast were obtained from PSI for the period January 2002 through to December 2004. Toward the end of 2004 PSI delivered heavily subsidized ITN through clinics and monthly sales by geopositioned clinics in each of the three districts were available for the period November 2004 to March 2007. In September 2006 the Ministry of Health launched a large-scale free distribution campaign of free ITN to children under the age of five years [4]. Net distribution volumes were recorded per geo-located distribution point within each district. Finally, small-scale community distribution projects over the surveillance by the district heath management team, NGO's and philanthropic organizations were recorded through interviews with DHMT members

and district stakeholders and recorded as volumes of distribution and month of delivery. Cumulative monthly ITN distribution volumes per district were computed per capita using population size estimates derived from national census data and annual growth rates. This was implemented with projected population growth rate curves from national inter-censal district-specific annual rates of net population increase derived in 1989 and 1999 [38].

Acknowledgements

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Malaria Journal

Research

The contribution of microscopy to targeting antimalarial treatment in a low transmission area of Tanzania

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Abstract

Background: There is a need for improved targeting of antimalarial treatment if artemisinin combination therapy is to be successfully introduced in Africa. This study aimed to explore why malaria slides are requested and how their results guide treatment decisions in an area of low transmission of *P. falciparum*.

Methods: Outpatients attending a district hospital in a highland area of Tanzania were studied over a 3-week period. Clinical and social data were collected from patients who had been prescribed an antimalarial or sent for a malaria slide. Hospital slides were re-read later by research methods.

Results: Of 1,273 consultations 132(10%) were treated presumptively for malaria and 214(17%) were sent for a malaria slide; only 13(6%) of these were reported positive for *P. falciparum* but 96(48%) of the 201 slide-negative cases were treated for malaria anyway. In a logistic regression model, adults (OR 3.86, P < 0.01), a history of fever (OR1.72, P = 0.03) and a longer travel time to the clinic (OR 1.77 per hour travelled, P < 0.01) independently predicted the request for a malaria slide. Only a history of a cough predicted (negatively) the prescription of an antimalarial with a negative slide result (OR 0.44, P < 0.01). The sensitivity and specificity of hospital slide results were 50% and 96% respectively.

Conclusion: Progress in targeting of antimalarials in low malaria transmission settings is likely to depend on consistent use of malaria microscopy and on the willingness of health workers to be guided by negative slide results. Further studies are needed to identify how this can be achieved.

Background

In Tanzania, as in a number of African countries, existing antimalarial treatment (sulphadoxine-pyrimethamine, SP) is being replaced by artemesinin combination treatment (ACT) as first line treatment for non-severe malaria.

However, at 5–10 times the cost of SP, its introduction creates an urgent need to review the diagnostic and treatment practices that have evolved over many years of cheap and safe antimalarials [1-3].

Where there is no access to microscopy presumptive diagnosis of malaria (fever with no obvious alternative cause) is widely practiced and results in a large degree of unnecessary use of antimalarials, especially at low transmission and in older children and adults in endemic areas [4]. Where available, microscopy offers a way forward but there is evidence that it has little impact as health workers frequently prescribe antimalarials in spite of a negative result [5]. Anecdotal reports also suggest that many patients are treated presumptively for malaria even when microscopy is available and it is not clear if slides are requested to confirm or exclude malaria or if patient demand or ability to pay for the slide also influence the decision to request a slide. There are few studies that have addressed these questions especially in low transmission settings in spite of the fact that approximately a third of the population of Africa lives in such areas [6]. This study was thus conducted in the outpatient clinic of a district hospital in a low transmission area of Tanzania to understand more about why a malaria slide is requested and how the results guide treatment.

Methods
The study area
Njombe town (population 42,332) is situated in the southern highlands of Tanzania at an altitude of between 1,800 and 1,920 metres and with a rainy season between November and May. Economic activity in the area consists of subsistence agriculture with some commercial farming of pyrethrum and coffee.

The 'Malaria Assessment of Risk in Africa' initiative (using projected rainfall and temperature) classifies the level of *P. falciparum* transmission in the Njombe area as 'unstable or absent' [7]. A survey of 100 consecutive children under the age of 15 years who were waiting for a medical consultation in Njombe Hospital in July 2004 found that only 4% were positive for *P. falciparum* [8].

Njombe District hospital serves the population of the town and surrounding villages, most of which are served by a dispensary without malaria microscopy. According to routinely collected data in 2003 there were 53,546 outpatient consultations, 19,812(37%) of which resulted in a diagnosis of malaria; 10,165 blood slides were examined in the hospital laboratory by 4 trained staff supported by 2 unqualified assistants. The mean number of slides/working day/slide reader was 10.6(SD 2.0). Malaria slides were charged at approximately $0.2 (U.S.) each for patients over the age of 5 years.

Clinical and social data collection
All patients exiting from a medical out-patient consultation during a 3-week period and who had been prescribed an antimalarial or who had a request for a malaria slide were identified. Following consenting procedures, data were collected on age, sex, village of residence, distance and travel time to the clinic and the presence within the previous 2 days of cough, fever, vomiting or diarrhoea, 'body pain', or any other symptom. Possible indicators of socio-economic status were identified from local interviews and from opinions of researchers in Tanzania. Data on 8 items (household possession of a car, motorbike, bicycle, radio, mobile phone, television, fridge and any bed net) were analysed for correlation; household possession of a bicycle or bed net were dropped due to poor correlation and the remaining factors were found to highly correlate (alpha = 0.77) and added to produce a socio-economic score.

Patients were identified on exit from the review consultation and any changes to their medication were noted. Any patient who appeared too ill to participate was referred back to the clinic medical staff and not included in the study.

Data were collected by locally recruited research assistants who were not part of the normal hospital staff.

Laboratory data collection
Blood slide results were tracked at the end of each day and the results were recorded from the laboratory results register, although it was not possible to determine if there had been an error in transcribing results to the register. Blood slides in the hospital laboratory were stained with Giemsa and 50 high power thick film fields were examined before declaring a slide to be negative, with no system of reporting parasite densities. All clinic blood slides were marked with the patient study number and retained for later research-quality reading where the number of *P. falciparum* asexual parasites per 200 leucocytes was counted on Giemsa-stained thick blood films. A slide was considered negative only after scanning 100 high power fields. All slides were read twice independently with a third reading if there was discordance, the majority result was accepted as final.

Ethical approval and data management
Verbal consent of outpatient staff and written consent from patients was obtained in all cases. Ethical approval for the study was obtained from the review committees of Kilimanjaro Christian Medical Centre, Tanzania and the London School of Tropical Medicine and Hygiene.

Data were double-entered in Access (Microsoft Corporation, Redmond, WA) and statistical analysis was performed using STATA 8 (Stata Corporation, College Station, TX).

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Table 2: Logistic regression model* of factors affecting the decision to request a malaria slide.

	Antimalarial with no slide request (n = 132)	Slide request (n = 214)	Initial adjusted OR	P	Final adjusted OR	P
Age 15 years or over, n (%)	47(36%)	139(65%)	4.03	<0.01	3.86	<0.01
Male (%)	58(44%)	78(37%)	1.01	0.16		
Distance from village/km†: median (IQR)‡	5(5–25) kms	10(5–25) kms	1.02	0.78		
Hours to travel to clinic: median (IQR)	1(1–2) hrs	2(1–2) hrs	1.95	<0.01	1.77	<0.01
Socio-economic score§: mean	0.97	1.05	1.16	0.26		
Number of days ill: median (IQR)	3(2–4) days	4(3–7) days	0.97	0.15		
Antimalarial used in previous 48 hrs: n (%)	3(2.3%)	8(3.8%)	0.90	0.89		
Fever in previous 48 hrs: n (%)	85(64%)	149(70%)	2.23	0.03	1.72	0.03
'Body pain' in previous 48 hrs: n (%)	92(70%)	168(79%)	1.06	0.84		
Cough in previous 48 hrs: n (%)	71(54%)	97(46%)	0.93	0.79		
Diarrhoea or vomiting in prev. 48 hrs: n (%)	55(43%)	82(38%)	0.87	0.60		
Other symptom in previous 48 hrs: n (%)	33(25%)	46(22%)	0.66	0.18		

*Logistic regression model with dependant variable = slide requested (1) or not requested (0), independent variables in model: aged 15 years or over, socio-economic score, distance to village, hours of travel to clinic, number of days ill, use of an antimalarial in 48 hrs before attendance, a report in the previous 48 hours of: fever, body pain, cough, diarrhoea or vomiting, or 'other' symptom (not specified). Variables were eliminated in a backwards fashion if p >= 0.1. All binary variables used the negative response as the baseline odds (i.e. OR = 1).
†Estimated distance between hospital outpatient clinic and village of residence.
‡IQR = Interquartile range
§Socio-economic score was derived from principal components analysis of reported possession in the household of the following: car, motorbike, radio, mobile phone, television, or refrigerator.

Results
Cases in the study, slide results and treatment given
During the 3-week period of the study there were there were 1,273 outpatient attendances, 240(19%) of which resulted in treatment for malaria. (Figure) Of the 346 patients who were recruited into the study approximately half (160, 46%) were under the age of 15 years. Females predominated in the 186 patients over the age of 15 years (129, 69%).

A blood slide was requested for 214 patients and all of these had a hospital laboratory slide result recorded. Thirteen (6%) of these were reported by the hospital laboratory as positive for *P. falciparum* asexual parasites and an additional 35(16%) were reported as positive for *P. falciparum* gametocytes. No other *Plasmodium* species was reported. Twelve (92%) of the cases reported as positive for asexual parasites were treated with an antimalarial. Thirty-three (94%) of the 35 patients with gametocytaemia reported by the hospital laboratory were also treated with an antimalarial and all were reported as negative for asexual parasites. Since gametocytes do not cause human illness these cases have been classified as 'slide negative'.

The sensitivity and specificity of hospital slide results for asexual parasitaemia (using the research slide result as the reference) were 50% (95% CI 43–57) and 96% (95% CI 93–98) respectively, and positive and negative predictive values were 31% (95% CI 26–37) and 98% (95% CI 96–100) respectively. Five slides were judged to be unreada-

ble (all had been reported as negative by the hospital laboratory). *P. falciparum* asexual parasite densities of the 8 positive research slide results were 2 at <2000/µl, 2 at 2000–4,999/µl, and 4 at >5,000/µl. The research slide results identified only 3 positive slides for gametocytes, 2 of which were reported as negative by the hospital laboratory.

Factors associated with blood slide requests and treatment decisions
In a logistic regression model the request for a malaria slide (as compared to presumptive treatment with no slide request) was independently predicted by being aged 15 years or over (OR 3.86, P < 0.01), reporting a history of fever in the previous 48 hours (OR 1.72, P = 0.03) and reporting a longer travel time to the clinic (a 77% increase in odds per hour travelled, P < 0.01). The request for a malaria slide request was not significantly associated with the socio-economic score (P = 0.26).(Table 2).

Of the 201 patients whose slide was reported as negative, 44(22%) were treated with an antimalarial only, 52(26%) with an antimalarial and an antibiotic, 68 (34%) with an antibiotic only, and 37(18%) with neither an antimalarial nor an antibiotic. Thus overall, 96(48%) of patients whose slide was reported as negative were treated with an antimalarial and of these 29(30%) did not report a fever within the previous 48 hours. Similarly, 47(36%) of those treated presumptively for malaria also denied having a fever within the previous 48 hours.
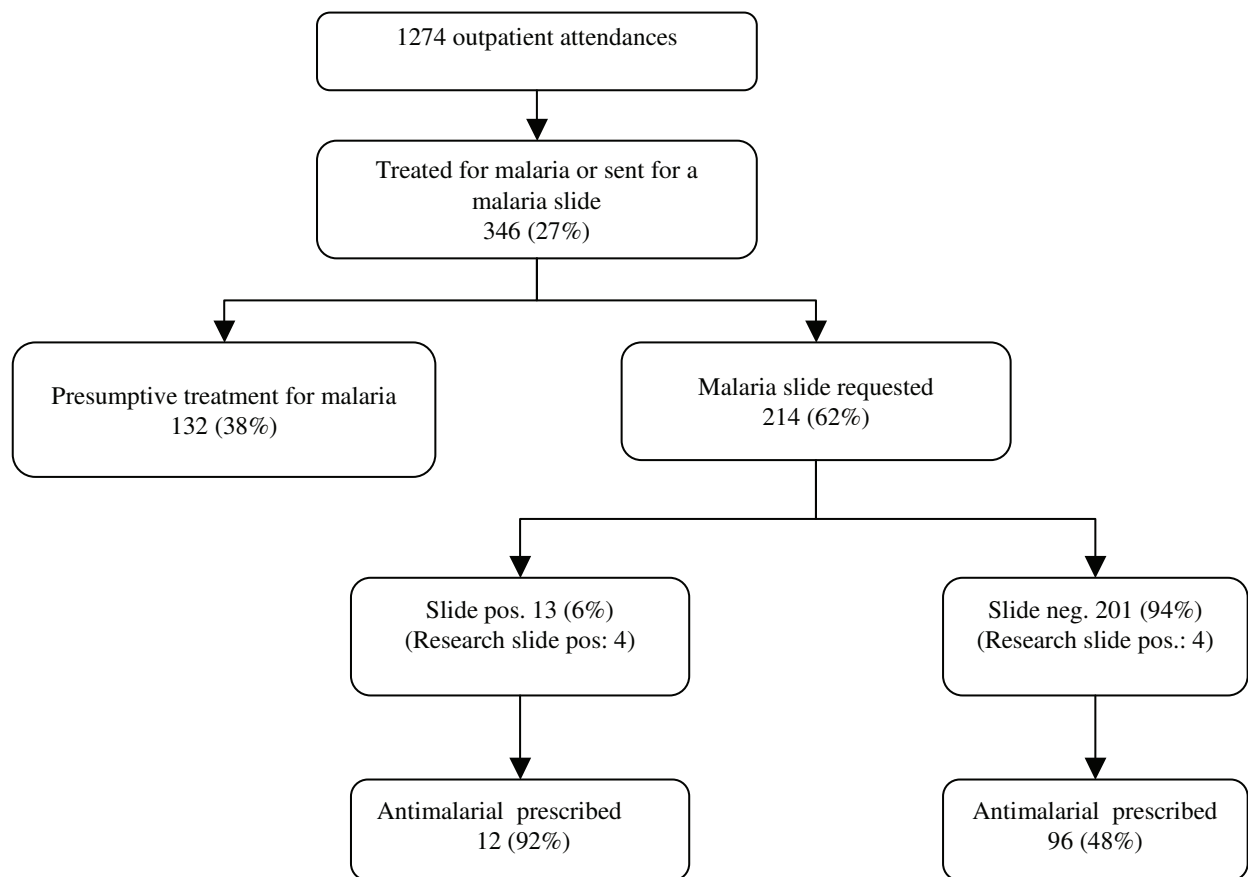
Figure 1
Cases in the study by malaria slide result and treatment given.

A logistic regression model using the same factors listed in Table 2 was used to test for an association with prescribing (compared to not prescribing) antimalarial treatment where the hospital slide result was reported as negative; the only factor found to be independently predictive was a negative association with a history of cough within the previous 48 hrs (OR 0.44, P < 0.01). Using the same variables to test the odds of being prescribed an antimalarial irrespective of whether a malaria slide was requested, only being under the age of 15 years was independently predictive (OR 2.25, p < 0.01).

Discussion
In this study almost 20% of all outpatients were diagnosed and treated for malaria and routine data reported this proportion as almost 40% in the previous year, suggesting a possible moderating influence of the study itself. Blood slides were not collected from presumptively treated cases for fear of influencing clinical practice, but even if twice as many of these were positive compared to

those who were sent for a malaria slide, well over 90% of treated cases did not have malaria, a finding consistent with other studies [4,9]. Hay et al. have estimated that over a third of the population of malaria-endemic countries in Africa lives under low or epidemic-prone transmission levels of malaria[6] and, although there are insufficient data to make a detailed extrapolation, it seems likely that a substantial proportion of avoidable antimalarial treatments in Africa is dispensed in these settings.

Health workers demonstrated unrealistic confidence in their ability to make a clinical diagnosis of malaria. Thus, as would be reasonable in a high transmission area, children tended to be treated presumptively. The failure to request a blood slide did not seem to be justified by excessive workload (although it is likely to be a factor in many settings) and data were not collected on the influence of waiting times on the request for a slide. However, if a blood slide is requested it is logical to expect the result to guide treatment decisions but almost half of those with a

Table 1: Total outpatient attendances during the 21-day period of the study according to primary diagnosis.

Diagnosis	*Age <5 yr	Age 5+ yr	Total
Acute respiratory infection	184(40%)	174(21%)	358(28%)
Malaria	96(21%)	144(18%)	240(19%)
Diarrhoea	58(13%)	59(7%)	117(9%)
Skin infection	23(5%)	21(3%)	44(3%)
Intestinal helminths	17(4%)	9(1%)	26(2%)
Ear infection	7(2%)	7(1%)	14(1%)
Urinary tract infection	3(1%)	11(1%)	14(1%)
Anaemia	2(0.4%)	10(1%)	12(1%)
Other	70(15%)	378(46%)	448(35%)
Total	460	813	1,273

*Age groups determined by routine reporting of outpatient attendances according to Ministry of Health guidelines.

negative result were treated with an antimalarial anyway. If the clinical suspicion of malaria is strong then this might override the slide result (although logically one could ask why request a slide at all?) but 30% of slide-negative cases treated for malaria did not report a recent history of a fever. When requested, it was not clear if slide results were being used to confirm or exclude malaria; while children were almost 4 times less likely than adults to be slide-tested, those sent for a slide were more likely to have reported a recent history of fever than those treated presumptively.

Our results suggest that malaria slides in clinics may fulfil a social or ritual function. In this study, a slide request was more likely if patients had travelled further (suggesting patient motivation to attend a facility where microscopy was available) although there was no association with socio-economic status suggesting that the cost of the slide does not play a major role. Clearly, for health workers, malaria is a convenient and acceptable label for non-specific illness but little is known about the understanding of malaria that leads to such practice and whether the phenomenon is driven more by patients or health workers.

Presumptive diagnosis of malaria is an effective strategy to increase coverage of antimalarials in high transmission areas where malaria is common, the risk of progression to severe malaria is significant, and diagnostic facilities are lacking. In low transmission areas the justification for presumptive diagnosis is much less clear. Current Malaria Guidelines in Tanzania[10] do not vary by transmission intensity (although the most recent version does distinguish between those over and under the age of 5 years) but the introduction of ACTs creates a strong economic case that in low transmission areas treatment for malaria should, wherever possible, be restricted to parasitologically proven cases [1]. Such an approach will have additional benefits in that patients are more likely to be treated for the actual cause of their illness and generation of more reliable routine data can support improved health planning as well as give early warning of epidemics. How to achieve a situation where health workers respect negative slide results is unclear; in a teaching hospital it has been possible in patients over the age of 5 years[11] but, as far as we are aware, there are no similar reports in less supervised settings where the majority of patients are seen. While clear national guidelines, improved laboratory standards and RDTs all have a role, it is optimistic to expect these to have a major impact without addressing prescribing behaviour and patient expectations about which there is currently little in-depth knowledge.

The accuracy of slide reading in this study was low although the negative predictive value (being dependent on prevalence) was still in excess of 95%, providing a high likelihood that a decision to withhold an antimalarial on the basis of a negative slide would be correct. In spite of this there is clearly an urgent need to improve laboratory standards; Bates et al.[12] have shown that this can be achieved with a relatively simple system of quality control and further improvements are likely if laboratory staff more frequently see that their results actually influence clinical decisions.

Conclusion
Reducing the overuse of antimalarials is an important and complex challenge. The criteria that are used to request a malaria slide are inconsistent and, where requested, negative results are often disregarded. If RDTs are introduced on a wide scale in Africa similar questions regarding consistent use, quality control and use of the results will need to be addressed.

Authors' contributions
HR and CD conceived of the study and its design and drafted the manuscript. JR coordinated the data collection and OM analysed the data; both JR and OM made critical comments to the manuscript.

Acknowledgements

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Rapid diagnostic tests compared with malaria microscopy for guiding outpatient treatment of febrile illness in Tanzania: randomised trial

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RESEARCH

Rapid diagnostic tests compared with malaria microscopy for guiding outpatient treatment of febrile illness in Tanzania: randomised trial

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ABSTRACT

Objective To compare rapid diagnostic tests (RDTs) for malaria with routine microscopy in guiding treatment decisions for febrile patients.

Design Randomised trial.

Setting Outpatient departments in northeast Tanzania at varying levels of malaria transmission.

Participants 2416 patients for whom a malaria test was requested.

Intervention Staff received training on rapid diagnostic tests; patients sent for malaria tests were randomised to rapid diagnostic test or routine microscopy

Main outcome measure Proportion of patients with a negative test prescribed an antimalarial drug.

Results Of 7589 outpatient consultations, 2425 (32%) had a malaria test requested. Of 1204 patients randomised to microscopy, 1030 (86%) tested negative for malaria; 523 (51%) of these were treated with an antimalarial drug. Of 1193 patients randomised to rapid diagnostic test, 1005 (84%) tested negative; 540 (54%) of these were treated for malaria (odds ratio 1.13, 95% confidence interval 0.95 to 1.34; P=0.18). Children aged under 5 with negative rapid diagnostic tests were more likely to be prescribed an antimalarial drug than were those with negative slides (P=0.003). Patients with a negative test by any method were more likely to be prescribed an antibiotic (odds ratio 6.42, 4.72 to 8.75; P<0.001). More than 90% of prescriptions for antimalarial drugs in low-moderate transmission settings were for patients for whom a test requested by a clinician was negative for malaria.

Conclusions Although many cases of malaria are missed outside the formal sector, within it malaria is massively over-diagnosed. This threatens the sustainability of deployment of artemisinin combination treatment, and treatable bacterial diseases are likely to be missed. Use of rapid diagnostic tests, with basic training for clinical staff, did not in itself lead to any reduction in over-treatment for malaria. Interventions to improve clinicians' management of febrile illness are essential but will not be easy.

Trial registration Clinical trials NCT00146796.

INTRODUCTION

Malaria is the most common single diagnosis made in most countries in Africa,[1] but the accuracy of clinical diagnosis is limited by the low specificity of symptoms and signs of malaria.[2-4] Presumptive antimalarial treatment for any fever with no obvious alternative cause is widely practised, and studies suggest that this leads to significant overuse of antimalarial drugs throughout Africa.[5-9] This over-diagnosis of malaria in the formal healthcare sector coexists with under-diagnosis of malaria in the community, with the result that antimalarials are given to people who do not need them and not given to children who do.

With the growth of resistance to older antimalarial drugs, newer but more expensive drugs need to be used, and artemisinin combination treatment is now being introduced in most African countries.[10 11] The cost of these drugs – up to 10 times that of current antimalarial drugs – is their major constraint, and deployment to people who need them is likely to depend on subsidy.[12] This may become unsustainable if most antimalarial drugs continue to be given to patients who do not have malaria. If patients with bacterial disease, an important cause of avoidable death in children in Africa,[13 14] are treated as malaria cases they may not receive appropriate treatment.[8] Improving the diagnosis of acute febrile illness so that antimalarial drugs are targeted to patients who need them and alternative diagnoses sought in others is therefore a public health priority in Africa.

Rapid diagnostic tests have considerable potential as a tool to improve the diagnosis of malaria.[15 16] Several commercially available tests are sensitive, specific, and stable under operational conditions.[17] Although microscopy remains the gold standard for diagnosis of malaria, its accuracy under operational conditions in Africa is often low, and clinicians are aware of this.[4] Results of rapid diagnostic tests are rapidly available, less liable to the theoretical risk of being falsely negative due to parasite sequestration, and visible to both prescriber and patient, and they may result in

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greater respect for test results. Initial data indicate that the cost effectiveness of rapid diagnostic tests is reasonable in an era of more expensive drugs such as artemisinin combination treatment, and their use could result in significant savings, especially in areas of low transmission.[18] The national malaria control programmes of several countries, including Tanzania, are therefore considering deploying rapid diagnostic tests in the formal healthcare system as part of the roll out of artemisinin combination treatment. Although studies of the technical performance of rapid diagnostic tests (sensitivity, specificity, and stability) are well advanced, no studies have examined whether their use actually leads to a change in prescribing practice compared with current diagnostic methods, which is fundamental to whether their deployment will be effective and cost effective. We set out to compare rapid diagnostic tests with routine microscopy in guiding treatment decisions for febrile patients in outpatient settings in northeast Tanzania.

METHODS

We did the study in three typical government designated public hospitals in northeast Tanzania, one each in areas in which transmission of *Plasmodium falciparum* is very low, low-moderate and high (<1, 1-10, and >100 infected bites/person/year). We phased the study to include the peak malaria transmission season at each site. In low transmission areas malaria is seasonal, peaking in January-March; in high transmission areas it is perennial, peaking in June-August.[19] In common with most hospitals in southern Africa, outpatient care in the study hospitals is largely provided by clinical officers with three years' clinical training.

We invited clinical staff to participate; all agreed and attended training designed to meet or exceed what could be provided by a national malaria control programme. Training included discussion of rapid diagnostic tests and specifically Paracheck (Orchid Pharmaceuticals), a *P falciparum* specific (histidine rich protein-2) test recommended by the national malaria control programme in Tanzania that meets World Health Organization standards for malaria diagnosis and costs approximately $0.7 (£0.4; €0.5) per test in Tanzania.[20 21] The trainers discussed studies showing 94-100% sensitivity and 89-100% specificity for Paracheck and outlined the advantages of visible test results less prone to false negatives caused by parasite sequestration. They reviewed Tanzanian national guidelines for diagnosis and treatment of malaria to emphasise that negative malaria tests should lead to alternative diagnoses being considered.[21]

Malaria tests were free for the duration of the study, irrespective of whether patients consented to the study. Before the trial, we did a baseline observational study to determine the pattern of routine diagnosis of malaria. We inspected the prescriptions of all patients leaving an outpatient consultation and asked them whether a malaria test had been requested. For those sent for testing, we recorded the result and subsequent prescription. A reference slide was taken at the same time as the routine slide.

The entry criterion for the main trial was a clinician's decision to request a malaria test in a patient of any age. The only patients excluded were those for whom the clinician specified microscopy or who were admitted as inpatients for severe disease. Patients with a clinician's request for a malaria test were invited to take part. If they or their guardians gave informed consent, a standardised history was taken, followed by randomisation to rapid diagnostic test or blood slide by computer generated random numbers in blocks of 10; allocations inserted into opaque envelopes were opened in front of the patient on recruitment. All slips had to be accounted for.

Laboratory staff in the clinic did the rapid diagnostic tests, recorded their result, and gave the test strip to the patient for the clinician to interpret independently and record in the review consultation. We used results recorded by clinicians in the primary analysis of prescribing. Patients randomised to microscopy were tested according to routine hospital practice, and clinicians were given results of the test. We obtained a reference slide for later double reading in both arms. Two experienced microscopists blind to allocation stained reference slides with Giemsa and counted parasites against 200 white blood cells; they examined 100 fields before declaring slides negative. We took a third reading of discordant results as final.

Clinic staff with the test result (rapid diagnostic test or hospital slide) reviewed patients in the study and made clinical decisions that they felt were appropriate. As patients left, study staff inspected their prescriptions and recorded them as an objective record of clinicians' decisions.

Sample size calculation

We designed the study to detect a reduction from an estimated 45% over-prescription to 25% over-prescription in the rapid diagnostic test arm. We needed 128 cases with negative test results in each arm to detect this with 95% confidence and 90% power. Estimating that at high, moderate, and low transmission 40%, 70%, and 90% of cases respectively would be slide negative and allowing for a 25% rate of refusal, we needed a total of 800, 457, and 356 cases at the three transmission bands. To avoid the possible bias between sites of a tendency for practice to change over time as health workers became more familiar and better informed about the rapid diagnostic test, we decided to recruit 800 cases at each site.

Statistical analysis

We entered data in Microsoft Access and analysed them with Stata version 9. We finalised the analytical plan before analysis. The primary outcome of the study was the proportion of patients in each arm for whom clinicians requested a malaria test, received a negative result, and prescribed an antimalarial drug anyway. We calculated unadjusted odds ratios and then adjusted them in a logistic regression model with the pre-defined potential confounding factors of age,

Table 1 | Baseline characteristics of patients randomised to blood slide or rapid diagnostic test. Values are numbers (percentages) unless stated otherwise

Characteristic	Slide (n=1204)	Rapid test (n=1193)
Median (IQR) age (years)	11.4 (2-30)	7.3 (2-29)
Female	679 (56)	668 (56)
Fever in previous 48 hours	979 (81)	952 (80)
Cough in previous 48 hours	493 (41)	499 (42)
Previous antimalarial drug use in current illness	66 (5.5)	66 (5.5)
Less than eight years' education*	888 (74)	876 (73)
Less than one hour's travel to clinic	698 (58)	685 (57)
Median (IQR) reported days ill	3 (2-4)	3 (2-4)

IQR=interquartile range.
*Patient or patient's mother if patient aged under 15.

Table 2 | Patients with negative test result treated with any antimalarial drug by malaria test method and age group, stratified by transmission intensity of *Plasmodium falciparum*
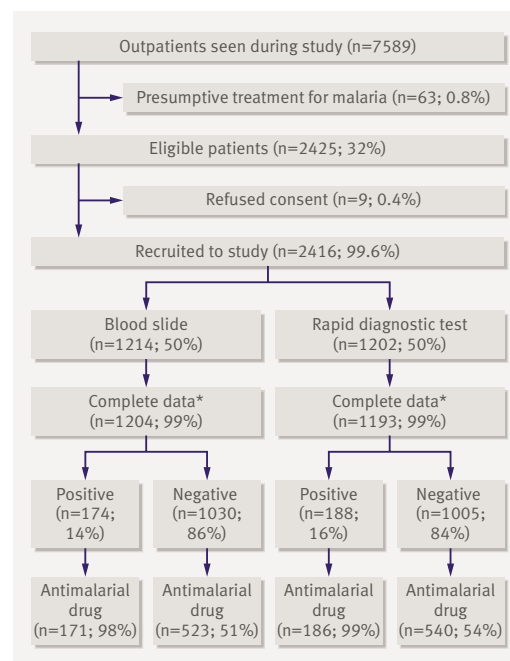
Age group (years)	Slide negative		Rapid diagnostic test negative		P value*
	No	No (%) given antimalarial	No	No (%) given antimalarial	
Low transmission					
‹5	185	116 (63)	172	129 (75)	0.013
5-15	38	17 (45)	35	18 (51)	0.568
›15	193	94 (49)	194	86 (44)	0.388
Total	416	227 (55)	401	233 (58)	0.308
Low-moderate transmission					
‹5	141	88 (62)	171	110 (64)	0.727
5-15	55	39 (71)	59	44 (75)	0.660
›15	171	103 (60)	156	88 (56)	0.484
Total	367	230 (63)	386	242 (63)	0.995
High transmission					
‹5	88	20 (23)	78	32 (41)	0.012
5-15	29	14 (48)	25	9 (36)	0.364
›15	130	32 (25)	115	24 (21)	0.486
Total	247	66 (27)	218	65 (30)	0.459
All sites					
‹5	414	224 (54)	421	271 (64)	0.003
5-15	122	70 (57)	119	71 (60)	0.719
›15	494	229 (46)	465	198 (43)	0.240
Total	1030	523 (51)	1005	540 (54)	0.182

*Statistical significance of associations in each stratum assessed with fully interacted logistic regression model that included interactions between treatment and indicator variables for each stratum as covariates.
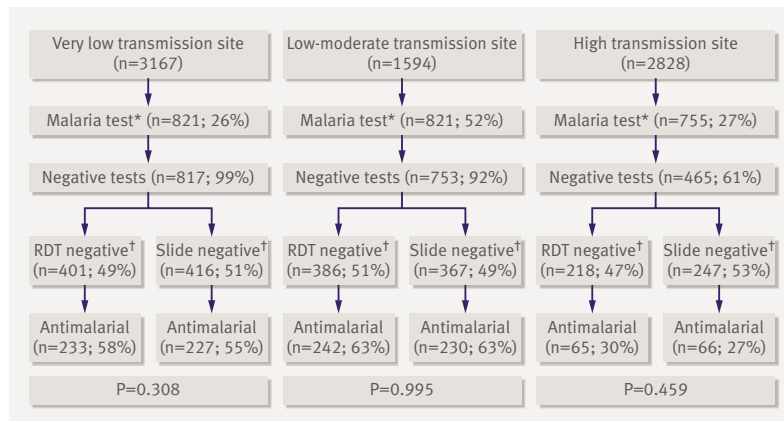

Fig 1 | Total clinic attendances and patients recruited to study by malaria test result and antimalarial treatment prescribed. Data missing from nine patients randomised to rapid diagnostic test (eight missing test result, one missing age) and 10 patients randomised to slide testing (nine missing slide result, one missing age)

request for a malaria slide. For 1813 (90.2%) patients the slide was reported as negative, and 962 (53.1%) of these were treated for malaria.

The intervention ran from January to August 2005. Of 7589 consultations, 63 patients (0.8%) were treated presumptively for malaria and 2425 (32.0%) were sent for a malaria test, of whom 2416 (99.6%) consented to participate and were randomised to rapid diagnostic test or blood slide (fig 1). Data were incomplete in 19 (0.8%) patients, and results are shown for the remaining 2397 cases. Characteristics of patients in each arm were similar (table 1).

In all, 523/1030 (50.8%) patients with a negative hospital slide and 540/1005 (53.7%) patients with a negative rapid diagnostic test were prescribed an antimalarial drug (odds ratio 1.13, 95% confidence interval 0.95 to 1.34; P=0.18). Rapid diagnostic tests showed no advantage in any of the transmission settings (fig 2); the odds ratio was 1.16 (0.88 to 1.52) at the low transmission site, 1.00 (0.76 to 1.35) at low-moderate transmission, and 1.17 (0.78 to 1.75) at high transmission. We found a trend towards an age effect, in that children aged under 5 were more likely to be treated with an antimalarial drug if they tested negative by rapid diagnostic test than if they tested negative by routine slide (table 2). The proportion of test negative patients treated with an antimalarial drug did not vary with the duration of the trial, whether tested by blood slide (odds ratio 0.99 (0.95 to 1.05) per week of trial duration) or by rapid diagnostic test (1.02 (0.97 to 1.07) per week).

hospital site, a history of fever, a history of cough (used as an indicator of a possible non-malarial cause of illness), and clustering in study sites. We did further analyses by study site and age group. Secondary outcomes were the proportion of febrile patients given an antibiotic by test outcome and the proportions of patients for whom antimalarial drugs were correctly prescribed, defined as antimalarial drugs given to patients with malaria parasites seen and not given to those with no parasites seen on the research slide. We also used the double read research slide as a gold standard to calculate the sensitivity and specificity of the rapid diagnostic test and hospital slide for each site.

RESULTS

In the one month baseline study, 4081 consultations took place; 70 (1.7%) of these resulted in presumptive treatment for malaria, and 2011 (49.3%) resulted in a

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Fig 2 | Clinic attendances, malaria test results, and antimalarial treatment prescribed at each of the study sites. *Data are shown for cases with complete data; 3, 3, and 13 cases had incomplete data in the low, low-moderate, and high transmission sites. †Positive test results at low, low-moderate, and high transmission hospitals were: rapid diagnostic test 3, 15, and 168; blood slide 1, 53, and 168. All but five patients with positive tests results were treated with an antimalarial drug; reason for omission of treatment in these five not known

Table 3 | Crude and adjusted odds of prescribing antimalarial drug in presence of negative test result for malaria

	Crude		Adjusted*	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Diagnostic test				
Blood slide	1		1	
Rapid test	1.13 (0.95 to 1.34)	0.182	1.11 (0.97 to 1.26)	0.128
Age group (years)				
‹5	1		1	
5-15	0.97 (0.72 to 1.30)	0.829	1.01 (0.44 to 2.33)	0.978
›15	0.55 (0.46 to 0.67)	‹0.001	0.60 (0.38 to 0.94)	0.025
Transmission intensity				
Low	1		1	
Low-moderate	1.30 (1.07 to 1.60)	0.010	1.26 (1.20 to 1.31)	‹0.001
High	0.30 (0.24 to 0.39)	‹0.001	0.28 (0.28 to 0.29)	‹0.001
Fever in previous 48 hours				
No	1		1	
Yes	1.37 (1.11 to 1.69)	0.004	1.56 (1.48 to 1.64)	‹0.001
Cough in previous 48 hours				
No	1		1	
Yes	1.07 (0.90 to 1.28)	0.430	0.86 (0.72 to 1.05)	0.133

*Logistic regression model in which dependent variable was prescription of antimalarial drug with a negative malaria test result (1) compared with no antimalarial drug (0); independent variables as specified in table. Standard errors for adjusted odds account for clustering within study sites.

We used a logistic model to explore associations between presenting features and prescription of an antimalarial drug for a patient with a negative test result. Adults and patients with a history of fever in the previous 48 hours were more likely to be prescribed an antimalarial drug despite a negative test; we found no significant association with the type of test used (table 3). In 203/1063 (19.1%) of cases in which treatment for malaria was given with a negative test result, the patient did not report a history of fever.

Antibiotics were prescribed to 51/362 (14.1%) patients who tested positive for malaria and to 1044/2035 (51.3%) with a negative test (odds ratio 6.42, 4.72 to 8.75; P<0.001); the difference was especially marked in children aged under 5 (16.8, 11.3 to 25.1; P<0.001) (table 4). Prescription of an antibiotic was not influenced by test method: 525/1030 (51.0%) slide negative patients and 519/1005 (51.6%) rapid diagnostic test negative patients were prescribed an antibiotic (P=0.76), and 308/414 (74.4%) slide negative and 310/421 (73.6%) rapid diagnostic test negative children aged under 5 were prescribed an antibiotic (P=0.80).

When we used double read research slide results as a gold standard, 269/1420 (18.9%) patients prescribed an antimalarial drug had *P falciparum* parasitaemia, and in the low and low-moderate transmission sites this proportion fell to 20/1004 (2.0%). Among children aged under 5, 3/99 (3.0%) tested by rapid diagnostic test had >2000 asexual *P falciparum* parasites/µl on the research slide and did not receive an antimalarial drug, compared with 4/72 (5.6%) in the hospital slide group (P=0.41). If we define a correct prescription of an antimalarial drug as one that is prescribed when parasites are present on research slides and not prescribed when they are not, 616/1193 (51.6%) of patients randomised to the rapid diagnostic test and 606/1204 (50.3%) randomised to a slide test had a correct

prescription of an antimalarial drug (odds ratio 1.05, 0.90 to 1.12; P=0.524).

We compared hospital slide and rapid diagnostic test results with the double read research slide (table 5). Rapid diagnostic tests generally performed well (both sensitive and specific) under field conditions. However, in seven cases the rapid diagnostic test result was negative according to both the prescribing health worker and the laboratory assistant but the research slide was positive; in five of these the parasite density was >5000 *P falciparum* parasites/l. In two cases, non-falciparum species were detected. Hospital laboratory slide results were less sensitive than rapid diagnostic tests (71.3% *v* 95.4%), and 39 reference slide positive cases were reported as slide negative by the hospital laboratory; in 13 of these the parasite density was >5000/l. The agreement between the health worker and the laboratory assistant in interpreting the rapid diagnostic test result was high (κ=0.913); 4/996 (0.4%) of rapid diagnostic tests were reported as negative by the health worker and positive by the laboratory assistant, and 22/1014 (2.2%) were reported as positive by the health worker and negative by the laboratory assistant.

DISCUSSION

Malaria is the single most common diagnosis in most hospitals in Africa and consumes a considerable proportion of available resources. During an era of cheap

and virtually limitless antimalarial drugs, the policy for treating malaria has assumed that it is safer to treat several cases of non-malarial febrile illness with an antimalarial drug than to miss one true case. Our study shows that this policy is associated with high levels of overuse of antimalarial drugs, especially in low-moderate transmission settings where a significant proportion of people in malaria endemic countries of Africa live.[22] Clinicians frequently requested tests, but they paid limited attention to negative results, irrespective of intensity of transmission. At the low transmission site, less than 1% of patients treated with an antimalarial drug had malaria parasites in their blood.

Impact of over-diagnosis on cost effectiveness

The potential impact of this level of over-prescription is considerable. Substantial numbers of cases of potentially fatal febrile illness treatable with affordable antibiotics are almost certainly being missed.[23] Over-diagnosis of malaria on this scale also threatens the sustainability of deployment of artemisinin combination treatment. These highly effective drugs are essential in east Africa, where alternative treatments are failing, but they are considerably more expensive than current monotherapy and depend on subsidy from the Global Fund and others if they are to reach the poorest groups who are most vulnerable to malaria.[24] Sustaining the subsidy for artemisinin combination treatment, which is essential for malaria in Africa, will be possible only if this regimen is seen to be cost effective. These drugs are cost effective if used for malaria in areas where other drugs have failed, but this depends on the drug being used for children with true malaria, as cost effectiveness rapidly falls away at high levels of

misdiagnosis.[25] Recognising the increasing importance of accurate diagnosis in an era of more costly artemisinin combination treatment, governments, encouraged by expert opinion, have been placing substantial orders for rapid diagnostic tests to guide treatment of febrile illness. Although rapid diagnostic tests are significantly more costly than microscopy in a hospital setting, they are potentially cost effective, but only if clinicians using the test act on the result.[26]

Finding realistic ways to improve the quality of health care in hospitals in Africa is a priority.[27] Although the literature on improving prescribing in developed countries is extensive, a recent WHO review identified only 36 trials of strategies to improve prescribing behaviour in developing countries, of which six included antimalarial prescribing as a major outcome.[28] Improving diagnosis of febrile illness is essential but will not be easy. It depends first on improvements in diagnostic facilities so that clinicians can rely on diagnostic tests, but then on changes in longstanding diagnostic behaviour by clinicians. Both of these are difficult with limited resources, but experience from Europe in changing antibiotic prescribing behaviour suggests that encouraging changes in clinicians' behaviour will be the harder of the two.

The challenges for diagnostic laboratories in Africa, which include defective microscopes, intermittent power, poor consumables, and limited time to examine slides, are well known.[29] Improving hospital laboratories to the point where their results are as accurate as a rapid diagnostic test is neither simple nor easy to sustain.[30] Rapid diagnostic tests are the only new tool on offer for improving diagnosis of malaria both within the formal sector and where diagnosis is currently

Table 4 |Prescription of any antibiotic for patients with positive or negative malaria tests by age group

Age group (years)	Positive test		Negative test			
			Antimalarial drug		No antimalarial drug	
	No	No (%) given antibiotic	No	No (%) given antibiotic	No	No (%) given antibiotic
‹5	228	33 (14)	495	365 (74)	340	253 (74)
5-15	50	7 (14)	141	49 (35)	100	55 (55)
›15	84	11 (13)	427	143 (33)	532	179 (34)
Total	362	51 (14)	1063	557 (52)	972	487 (50)

Table 5 |Sensitivity, specificity, and predictive values of rapid diagnostic test or routine blood slide as judged against research slide results

	Research slide*		Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Negative predictive value (%)	Positive predictive value (%)
	Positive	Negative				
Rapid diagnostic test†						
Positive	146	42	95.4 (94.2 to 96.6)	95.9 (94.8 to 97.0)	99.3	77.7
Negative	7‡	985				
Hospital slide						
Positive	97	77	71.3 (68.8 to 73.9)	92.8 (91.3 to 94.3)	96.2	55.8
Negative	39§	991				

*Slide results are positive or negative for any *Plasmodium falciparum* asexual parasites; in addition, two slides were positive for *P malariae* asexual parasites.
†Positive by either laboratory technician or prescribing health worker.
‡Parasite densities/l were ‹1000, 0; 1000-4999, 2; 5000-100 000, 2; ›100 000, 3.
§Parasite densities/l were ‹1000, 15; 1000-4999, 11; 5000-100 000, 8; ›100 000, 5.

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syndromic, and they have considerable potential to improve diagnosis. In this study, rapid diagnostic tests were more accurate than routine slide testing, and both patients and clinicians reported liking them. Introducing them into routine care, free of charge and after delivering targeted training had, however, no impact on the overuse of antimalarial drugs. Incurring the cost of a test and then prescribing antimalarial drugs for patients with a negative result represents the worst possible outcome economically. Deployment of rapid diagnostic tests or any other diagnostic test to promote the sustainability of artemisinin combination treatment in Africa is likely to fail unless ways can be found to bring about a major change in current prescribing behaviour.

Although rapid diagnostic test and slide results were equally disappointing in guiding antimalarial treatment, the fact that they both seemed to influence the decision to prescribe antibiotics is potentially encouraging given the increasing realisation of the importance of bacterial disease as a cause of infant and childhood mortality.[23] Clinicians with a positive test for malaria were, however, highly unlikely to prescribe anything except an antimalarial drug; this is not always appropriate, as dual infection occurs in all ages.

Potential limitations of rapid diagnostic tests and this study

Current rapid diagnostic tests have limitations. This study showed false negative results in patients with high parasite counts, but we cannot determine whether this was because the test was done incorrectly or because of technical limitations of the test. Possible technical problems include deletion of HRP-2 genes in certain parasites,[31] "flooding" of the antigen capture sites, and defects in the device membrane (Anthony Moody, personal communication, 2006). This supports the legitimate concern that in areas of very high malaria transmission, withholding antimalarial drugs from children under 5 with febrile illness is potentially hazardous even in the face of negative test results, although where clinicians intend to treat for malaria anyway it makes little sense to request a test. In other epidemiological settings and age groups, the negative predictive value of tests will be excellent and the risks of withholding antimalarial drugs from patients with negative tests will be minimal.

Three reasons exist why this trial might not reflect reality in the rest of Africa and may wrongly lead to an impression that deploying rapid diagnostic tests without major additional interventions will have a limited impact. Firstly, prescribers might have altered their normal practice as a result of the study (Hawthorne effect); however, if anything, this is more likely to have encouraged them to follow national policy and take test results into account. Secondly, the levels of over-diagnosis were atypical, but all the available evidence indicates that the findings of over-diagnosis are wholly typical of hospitals throughout the continent[5-9]; these are well run, government designated hospitals in a stable area, with staff who have received training typical for healthcare providers in Africa. Thirdly, the training provided in the trial was not adequate, but as it was considerably more intensive and tailored to individual settings than would be possible in a national roll out, this seems unlikely to have led to bias against rapid diagnostic tests. The fact that rapid diagnostic tests were a newly introduced technology might have affected their use either positively or negatively, but we found that the tendency to respect negative rapid diagnostic tests did not vary with the duration of the trial.

Deploying more expensive antimalarial drugs may lead to behavioural change, so theoretically the results of this trial will not reflect what will happen if clinicians are prescribing artemisinin combination treatment. The cost of centrally subsidised artemisinin combination treatment to both clinicians and patients will, however, be the same as existing drugs, so it seems unlikely the cost will in itself lead to marked behavioural change. The study reflects behaviour in a hospital setting, and a substantial proportion of febrile illness (often the great majority) is treated outside hospital or not treated at all; a paradox of malaria treatment throughout Africa is that simultaneously with a high proportion of patients given antimalarial drugs not having malaria, a significant proportion (and often the majority) of those who have malaria are not given an antimalarial drug.[32]

Can behaviour be changed?

Rapid diagnostic tests could, if they guided results, have a major impact on the management of malaria in Africa.[33] This trial shows that providing quick and reliable diagnostic tools with basic training may, in itself, have little impact on overuse of antimalarial drugs. The combination of artemisinin combination treatment and rapid diagnostic tests creates an important opportunity to both reduce the burden of mortality from malaria in Africa and improve the treatment of bacterial disease. Understanding the reasons for, and then changing, the habit of over-prescribing antimalarial drugs will need to be a priority if the potential benefits of artemisinin combination treatment are to be realised; simple technical fixes are unlikely. Our findings indicate an urgent need to identify and implement more effective ways to improve the use of antimalarial and antibiotic treatment in Africa.

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WHAT IS ALREADY KNOWN ON THIS TOPIC

Cases of malaria in the community are often missed, but at the same time over-diagnosis of malaria is widespread in Africa

Rapid diagnostic tests are sensitive and specific for falciparum malaria, and could be cost effective if their use guided practice

WHAT THIS STUDY ADDS

In areas of low or moderate malaria transmission, malaria is massively over-diagnosed in hospital outpatients and microscopy results are often ignored

Deploying rapid diagnostic tests for malaria, with standard training, made no difference to the over-diagnosis of malaria in febrile patients

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

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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

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 ≥ 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,[1] a figure typical for countries in Africa where malaria is endemic.[2] Despite this striking statistic, 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,[3] and two studies of district hospitals in Africa identified several problems with the organisation and planning of care.[4] [5]

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.[6] Unreliable hospital data hamper health service planning and make progress towards targets such as those set by the Roll Back Malaria initiative impossible to assess. The spread of drug resistance means that there is a need to move to considerably more expensive drugs, but if a large proportion of the people treated for malaria do not have the disease this will substantially increase the costs of change.

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 is important as most of the population of sub-Saharan Africa live in areas of low or moderate malaria transmission.[7] We 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 for areas with various transmission intensities. 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, an area characterised by the Eastern Arc mountains with 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[8] with measured entomological inoculation rates of 300 infectious bites per year on the coastal plain, 30 at an altitude of 930 metres, and < 1 above 1500 metres.

We selected hospitals that provided a well organised service and had trained staff willing to participate. This represents most government hospitals in the area. Six were highland district hospitals at altitudes ranging from 940-1450 metres, one regional and one referral hospital served a semiurban area of 200 000 people at an altitude of 900-970 metres, and two were district hospitals on the coastal plain at 320 metres and 198 metres.

The study ran at nine hospital sites from 16 February 2002 to 15 February 2003, with an additional hospital for six months (from 15 August 2002). Because of the large number of admissions to the district hospital at the lowest altitude, patients aged < 13 years were recruited on alternate days (that is, a 50% sample of paediatric admissions). At the three busiest hospitals

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research staff were based in the paediatric ward and visited other wards two to three times daily. In the seven remaining district hospitals, one dedicated clinician and a team of clinical and laboratory staff from within each hospital collected data in the course of their normal work, supported by twice weekly visits from a project clinician.

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[9] with the addition of moderate anaemia. Criteria included haemoglobin <80 g/l (HaemoCue AB Angelhom), inability to drink or suck (observed), inability to sit unsupported in patients aged >1 year, inability to localise pain in patients aged >1 year, confusion in patients aged >5 year, lower chest indrawing or deep breathing, and jaundice. If any of these were present, the researcher also recorded axillary temperature, respiratory pattern and rate, and Blantyre coma score.[10] Blood glucose was measured (Accu-Check Active, Roche Diagnostics) 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 hospital slide, though only the hospital slide result was available to contribute to the patient's care. Outcome and treatment received were recorded at discharge or death.

Research laboratory staff stained 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, and the geometric mean density of positive readings used for parasite density. Analyses relate to the research slide result unless specified otherwise.

Villages from which people with malaria had been admitted were visited by a trained field assistant and a global positioning point for altitude, latitude, and longitude 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. Initial tabulations and 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. Data are presented on actual cases recruited except where logistic regression has been used and 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 to allow for the hospital that was included in the study only for the latter six months.

Results

A total of 17 313 cases were recruited into the study over one year (fig 1). 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 admitted to hospital and treated for 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
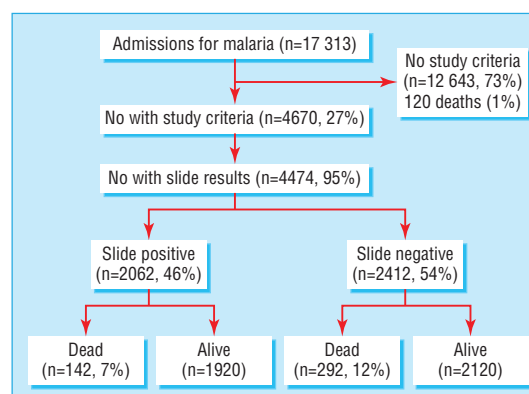
Fig 1 Patients admitted to 10 hospitals with diagnosis of malaria over one year by outcome, presence of any *P falciparum* asexual parasites on the research blood slide, and case fatality

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 slides decreased systematically with increasing age and with increasing altitude of residence (fig 2).

When we used logistic regression, controlled for clustering within hospitals and adjusted for differential sampling at one hospital, 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

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
Age <5 years			
<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)
Age ≥5 years			
<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 one case.
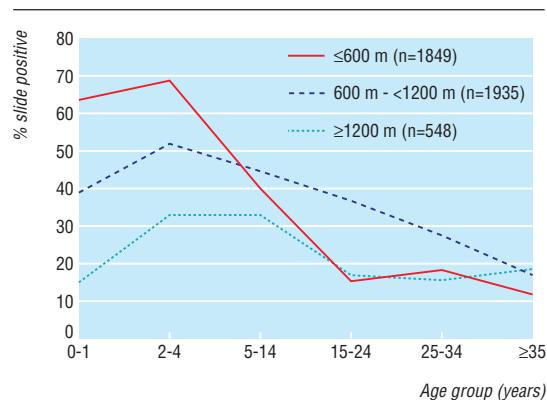
Fig 2 Percentage of patients with at least one study criterion of severe disease who had a positive research blood slide for any *P falciparum* asexual parasites by age and altitude of residence

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

Age (years)	No (%) slide positive	No (%) slide negative
Respiratory distress*:		
<5	162 (10.1)	241 (19.5)
5-14	27 (13.9)	25 (10.3)
≥15	26 (10.3)	108 (11.7)
Severe anaemia†:		
<5	654 (40.7)	337 (27.8)
5-14	47 (24.4)	69 (28.8)
≥15	43 (17.8)	211 (23.5)
Altered consciousness‡:		
<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.

1.40) at 5-15 years and 0.24 (0.10 to 0.59) at over 15 years. Adjustment for the reported use of antimalarial drugs in the 48 hours before admission and rainy season did not alter the effect of age and altitude and neither factor had a significant association with slide result. 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).

The unadjusted odds of dying among slide negative patients was higher than among those who were slide positive (1.85, 1.37 to 2.49, P < 0.001), an effect observed across all age groups (table 3). Table 4 shows the odds ratios from a logistic regression model for mortality after adjustment for clustering within hospitals. Respiratory distress, severe anaemia, altered consciousness, age, and altitude of residence were all significantly associated with case fatality. After we controlled for these variables, those 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). After adjustment for the effect of the slide result, respiratory distress and altered consciousness were associated with the largest increase in the odds of a fatal outcome. Mortality increased with age and decreased with increasing altitude.

In 683/4474 (15%) patients there were discrepancies in the reading of the research slides between the first and second research microscopists. These slides were read again by a third microscopist. When we used the definitive agreed result as the reference, only 2949/4451 hospital slides were correct (66% agreement, κ = 0.33, P < 0.0001), with 988 false positive (39% of positives) and 514 false negative (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. The research slide was not immediately available to clinicians as it was read later but the hospital slide result was available to clinical staff at the time of diagnosis. Patients with negative hospital slides were more likely to have received antibiotics (661/1897, 34.8%) compared with those with positives slides (500/2499, 20.0%) ($\chi^2 = 122.1$, 2 df, P < 0.001). Among patients with negative hospital slides, those who died were more likely to have received antibiotics than those who survived ($\chi^2 = 13.5$, 2 df, P < 0.001) (table 5).

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.[11–13] What happens when they reach hospital has received less attention, despite considerable scope for improvement.[4] 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.

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. While overdiagnosis of malaria is widely suspected, it has not previously been shown systematically at different levels of malaria transmission and at different ages.

Our findings have importance for individual case management and for public health. 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,[14] 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,[15] although the reduced effect in the adjusted model raises the possibility of residual confounding. Our study was not designed to determine the cause of febrile illness not caused by malaria, and we cannot determine whether the mortality in slide negative patients was preventable by antibiotic treatment, but it does identify the wider use of antibiotics as one possible

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.

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Table 4 Logistic regression model* of predictors of mortality among cases with at least one study criterion of severe disease

	Actual cases (deaths, %)	Projected cases† (deaths, %)	Odds ratio (95% CI)	P value‡
Age group (years):				
0-1	1855 (149, 8.0)	2465 (223, 9.1)	1.0	0.057
2-4	996 (55, 5.5)	1164 (74, 6.4)	0.87 (0.56 to 1.32)	
5-15	441 (50, 11.3)	483 (52, 10.8)	1.15 (0.63 to 2.11)	
≥15	1181 (180, 15.2)	1181 (180, 15.2)	1.70 (1.19 to 2.42)	
Respiratory distress§:				
No	3876 (251, 6.5)	4542 (297, 6.5)	1.0	<0.001
Yes	589 (179, 30.4)	741 (228, 30.8)	6.61 (5.25 to 8.33)	
Severe anaemia§:				
No	3033 (285, 9.4)	3445 (330, 9.6)	1.0	0.02
Yes	1361 (138, 10.1)	1766 (188, 10.7)	1.42 (1.06 to 1.90)	
Altered consciousness§:				
No	3476 (229, 6.6)	4209 (299, 7.1)	1.0	<0.001
Yes	493 (112, 22.7)	517 (125, 24.2)	3.83 (2.43 to 6.03)	
Slide positive¶:				
No	2412 (292, 12.1)	2661 (336, 12.6)	1.0	0.08
Yes	2062 (142, 6.9)	2633 (193, 7.3)	1.55 (0.94 to 2.53)	
Altitude of residence (100 m)**:				
<600	1849 (193, 10.4)	2616 (285, 10.9)	0.91 (0.84 to 0.97)	0.01
600-<1200	1936 (149, 7.7)	1974 (152, 7.7)		
≥1200	548 (65, 11.9)	549 (65, 11.8)		

*Based on predicted numbers of cases when adjusted for sampling methods as described in methods. Factors tested in model but found to contribute no significant effect (P>0.1) were rainy season, reported treatment for malaria before admission, literacy of patient or mother if patient <15 years of age.
†Predicted cases (%) after adjustment for sampling of 50% of children under the age of 13 years admitted to one low altitude hospital; the projected numbers correspond to number of cases if sampling at this site was 100%.
‡Wald test for linear trend.
§Case definitions as in table 2; incomplete data in 9 cases of respiratory distress, 80 cases of anaemia, and 505 cases of altered consciousness. Missing age in one case, and missing altitude of residence in 141 cases.
¶Research blood films double read for presence of any *P falciparum* asexual parasites as described in methods.
**Model estimates for every 100 m increase in altitude of village of residence. Descriptive data shown for grouped altitude bands.

intervention. Two thirds (66%) of admitted patients treated for severe malaria but with a negative hospital slide result were not treated with antibiotics, suggesting that clinicians ignored 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. What is more surprising is that when clinicians had doubts about the diagnosis they chose not to treat patients with antibiotics. The case fatality of those treated with antibiotics in hospital (in addition to antimalarial drugs) was higher than in those treated with antimalarial drugs alone, probably because clinicians identify the most critically ill patients for dual therapy. However, almost half (43%) of patients who died and had a negative hospital slide result (available to clinicians at diagnosis) did not receive an antibiotic while 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 well ordered, and study hospitals included most district hospitals in the region. Clinicians knew hospital practice was being observed (possible Hawthorn effect) 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.[16] [17]

True slide negative cases of severe malaria are rare (although it can be confirmed only by postmortem examination). A positive slide is, however, 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.[18] If our definition of malaria had included a parasite density of >1000 asexual *P falciparum* parasites per μl, 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.

Table 5 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

	All cases*		Fatal cases	
	No of patients	Not treated with antibiotic	No of patients	Not treated with antibiotic
Hospital slide result†:				
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).

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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

As in previous studies, respiratory distress and altered consciousness were the strongest predictors of mortality.[16] [17] 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 an important part 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,[4] laboratory workload compromises quality,[19] and triaging hospital admissions to prioritise care is rarely practised.[5] One option is to try 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.[20] [21] For severe febrile disease the most effective approach is likely to depend on the setting and on the true incidence of malaria. We have shown that this is a major priority in all age groups and at all transmission intensities. Efforts to improve the management of clinically diagnosed severe malaria are as important in areas of low transmission and in adults as in the young children in high transmission areas who constitute the majority of the over one million deaths from malaria every year.

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(Accepted 8 September 2004)

doi 10.1136/bmj.38251.658229.55

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Papers

Microscopy and outpatient malaria case management among older children and adults in Kenya

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Summary

OBJECTIVE   To evaluate the accuracy of routine malaria microscopy, and appropriate use and interpretation of malaria slides under operational conditions in Kenya.

METHODS   Cross-sectional survey, using a range of quality of care assessment tools, at government facilities with malaria microscopy in two Kenyan districts of different intensity of malaria transmission. All patients older than 5 years presenting to outpatient departments were enrolled. Two expert microscopists assessed the accuracy of the routine malaria slide results.

RESULTS   We analysed 359 consultations performed by 31 clinicians at 17 facilities. Clinical assessment was suboptimal. Blood slide microscopy was performed for 72.7% of patients, who represented 78.5% of febrile patients and 51.3% of afebrile patients. About 95.5% of patients with a positive malaria microscopy result and 79.3% of patients with a negative result received antimalarial treatment. Sulphadoxine–pyremethamine monotherapy was more commonly prescribed for patients with a negative test result (60.7%) than for patients with a positive result (32.4%). Conversely, amodiaquine or quinine were prescribed for only 14.7% of patients with a negative malaria microscopy result compared to 57.7% of patients with a positive result. The prevalence of confirmed malaria was low in both high (10.0%) and low-(16.3%) transmission settings. Combining data from both settings, the sensitivity of routine microscopy was 68.6%; its specificity, 61.5%; its positive predictive value, 21.6% and its negative predictive value, 92.7%.

CONCLUSIONS   The potential benefits of microscopy are currently not realised because of the poor quality of routine testing and irrational clinical practices. Ambiguous clinical guidelines permitting treatment of older children and adults with a negative blood slide also undermine rational use of antimalarial drugs.

keywords malaria, microscopy, interpretation, accuracy, Kenya

Introduction

In malaria endemic areas of Africa, the rates of severe disease and death due to *Plasmodium falciparum* malaria decline rapidly over the first 5 years of life (Snow & Marsh 1998). The incidence of mild clinical attacks declines more slowly but there is a threefold lower rate of disease among children aged 5–14 years compared to children aged 0–4 years (Snow *et al.* 2003) and incidence is generally very low in adults (Trape & Rogier 1996; WHO 2000; Snow *et al.* 2003). Despite the lower risk of uncomplicated malaria among populations aged more than 5 years, the absence of valid clinical predictors to diagnose malaria in this age group (Genton *et al.* 1994; Chandramohan *et al.* 2001; Mwangi *et al.* 2005) has lead to frequent recom-

mendations promoting presumptive malaria diagnosis for all febrile older children and adults across most malaria endemic areas of Africa (WHO 2000,2003a). Such recommendations and current diagnostic practice result in a massive over-diagnosis of malaria (Font *et al.* 2001; Amexo *et al.* 2004).

Arguably over-diagnosis and over-treatment has been tolerated when conventional first-line drugs such as chloroquine and sulfadoxine–pyrimethamine (SP) were inexpensive and safe. With increased treatment failure rates to most of the first-line therapies in East and Southern Africa (East African Network for Monitoring of Antimalarial Treatment (EANMAT) 2003; Myint *et al.* 2004; Talisuna *et al.* 2004) new drugs that are more expensive, more complex to use and with less certain safety-margins, such

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as artemisinin-based combination therapies (ACT), are gradually being introduced across Africa (WHO 2001a; Bosman & Olumese 2004). In the era of ACT, the presumptive diagnosis and treatment of patients without malaria becomes economically and clinically less accepta- ble. While it seems reasonable to continue presumptive treatment among children 0–4 years living in high-malaria transmission settings, for older children and adults para- site-based diagnosis is likely to be the only potential solution to increase diagnostic specificity (Nosten & Brasseur 2002; Barnish *et al.* 2004).

During the 1990s the Kenyan Ministry of Health (MoH) expanded microscopic diagnostic services into nearly all government hospitals and health centres (Ministry of Health 2001). However, there have been relatively few attempts to examine the influence of microscopy on malaria diagnosis and treatment practices in older children and adults where it might be most useful (Barat & Kramer 1999). In this paper, we present an observational study on the effects of microscopy on outpatient malaria case management among patients above 5 years and the accuracy of routine malaria slides.

Methods

Study sites

Two districts representing different malaria ecologies in Kenya were purposively selected to reflect the two common malaria transmission settings in Kenya. The first district was Kwale, a hyper- to holo-endemic area along the Indian Ocean coast and below 650 m altitude with 48 government health facilities of which 14 had functional microscopy in 2002. The prevalence of *P. falciparum* infection reported from four community-based surveys undertaken in August 2003 in children <5 years of age ranged from 55.1 to 87.0% (V. Marsh, unpublished data). The second district was Greater Kisii, supporting hypo- to meso-endemic transmis- sion and located in the Western highlands at altitude between 1400 and 2200 m with 10 of 48 government facilities with functional microscopy in 2002. The preva- lence of *P. falciparum* infection reported from six com- munity-based surveys undertaken between March and May 2000 in children <5 years of age ranged from 3.1 to 17.7% (D. Zurovac, unpublished data). The study was conducted during malaria seasons between August–September 2002 in Kwale and March–April 2003 in Greater Kisii.

Study design and data collection

We studied outpatient malaria case management practices in patients above 5 years of age using a cross-sectional,

cluster sample survey at randomly selected facilities with functional microscopy. A cluster was defined as all older children and adult outpatient consultations occurring at each facility over two consecutive survey days. Data were collected using quality of care assessment methods (WHO 2002) modified for the present study including: observation of consultations, independent re-examination of each patient, malaria blood slide examination and interviews with health workers. After the patient or caretaker provided informed written consent, one surveyor silently observed all consultations and recorded the performance of various clinical tasks. The observed health worker performed consultations and recorded the patient's clinical notes, laboratory requests and results, diagnosis and treatment on a blank study form. When the patient left the consultation room the study physician, blind to the findings of the first consultation, performed a structured clinical re-examination recording clinical findings on a separate study form and in the patient-held cards. The study physician was responsible for patients' clinical management plans. When a blood smear was requested during the initial health worker consultation a further study malaria thick smear was prepared from the same finger prick, stained with Giemsa 10% and taken by the study team for later, expert examination. Finally, at the end of the second survey day at each facility interviews were conducted with health workers to collect basic information on their demographics, pre-service training and working experience.

Approximately 2 months after the facility surveys two independent expert microscopists examined study slides at KEMRI/Wellcome Trust laboratories in Nairobi, without any knowledge of the results from the routine clinical slide. For each slide 100 high-power magnification fields were examined before the slide was regarded as negative. Where results between the two expert microscopists were dis- cordant, a third microscopist reread the blood slide and the majority decision was accepted as the final result. The KEMRI national ethical review committee provided ethical clearance for this study (reference no. 681).

Data entry, definitions and statistical analysis

Data were double-entered and verified using Access 2000 (Microsoft Inc, Redmond, WA, USA) through customised data-entry screens with range and consistency checks and analysis was performed using STATA, version 8 (Stata- Corp, College Station, TX, USA). The precision of proportions (95% confidence interval) was estimated accounting for the cluster sampling design using the health facility as the primary sampling unit. The analysis was performed for each district separately and for two districts combined. Our primary analysis was on febrile patients

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presenting for an initial consultation without signs of severe disease. A patient was considered to have fever if during the re-examination a history of fever was reported in the last 48 h or axillary temperature was ≥37.5 °C. A patient's initial visit was defined during the re-examination as the first visit to this facility for the presenting illness episode. Treatment as an outpatient by the facility clinician was used as proxy for non-severe disease. Clinical assessment tasks were judged as performed if health worker asked about the presence of symptom, the patient spontaneously reported the symptom or the observer could obviously tell the patient had the information of interest. The sensitivity, specificity and positive and negative predictive values (NPV) of the routine reading of malaria slides were calculated against the gold standard of any parasitaemia defined by concordant findings from two expert microscopists. The positive likelihood ratio was calculated according to the following formula: sensitivity/1-specificity.

Ethical approval

The KEMRI national ethical review committee provided ethical clearance for this study (reference no. 681).

Results

Description of the survey sample

We assessed 478 outpatient consultations for patients aged above 5 years seen by 31 health workers at 17 health facilities with functional microscopy in two districts. No health workers or patients refused to participate in the survey. Of 478 consultations, the exit examination could not be performed for 42 patients (8.8%) and these patients were excluded from the analysis. Of the remaining 436 patients, 27 patients were attending a follow up visit, 23 were referred for hospitalisation and 27 had missing values that prevented definite classification as an outpatient during an initial visit. Our final analysis therefore, includes 359 patients, 203 (56.6%) from Kwale and 156 (43.5%) from Greater Kisii. Nearly half of consultations (47.1%) were performed at sub-district hospitals, 37.3% at health centres and 15.6% at dispensaries. The majority of the patients were above 15 years of age (79.7%) and the majority of consultations were performed by clinical officers (61.0%) rather than nurses (36.5%).

### Characteristics of clinical assessment

For 359 consultations analysed, mean and median consultation time was 4.7 and 4.0 min, respectively. Health workers routinely assessed 61.0% (95% CI: 47.2–75.0) of patients for a history of fever, yet only 16.4% (95% CI: 3.7–29.1) had a temperature routinely measured. Conjunctival pallor was checked for 60.6% (95% CI: 52.3–68.8) of patients. Cough was assessed in 36.8% (95% CI: 30.7–42.9) of patients. The following clinical tasks were performed in 13.9–21.7% of patients: assessment of chest pain, diarrhoea and vomiting; auscultation of chest and palpation of spleen. Less than 6% of patients had the following tasks performed: assessment of difficult breathing, ear problem, running nose and throat pain; measurement of respiratory rate; and inspection of throat and ears. No significant difference in performance of any task was observed between the districts or groups subsequently categorized as referred for routine microscopy or not, or if categorized according to the result of the routine blood slide (positive and negative).

Use and interpretation of malaria slide

Figure 1 shows the district-specific pattern of current routine clinical practice at the 17 health facilities on the use and interpretation of blood slide results with respect to the presence of fever and prescription of antimalarial treatment. The proportion of patients coming for an initial visit and treated as outpatients who reported a history of fever or who had an axillary temperature ≥37.5 °C was 78.8% (95% CI: 73.0–84.7) with no significant difference between the two districts. Overall, 261 patients (72.7%, 95% CI: 60.8–84.6) had a malaria slide performed, more commonly in Greater Kisii (90.4, 95% CI: 85.1–95.6) than in Kwale (59.1, 95% CI: 44.4–73.8). Only 26 (9.1%) patients were referred for microscopy but did not have a blood slide done. Among all patients with fever, a malaria slide was performed for 78.5% of patients (95% CI: 69.5–87.4), however, 51.3% (95% CI: 28.4–74.2) of all patients without fever also had a blood slide performed. Among all patients who had a blood slide performed 42.5% (95% CI: 30.5–54.6) had a positive blood slide reported through routine microscopic practices. A positive routine malaria slide was more commonly reported in Greater Kisii (56.0, 95% CI: 41.2–70.8) than in Kwale district (26.7, 95% CI: 16.7–36.6). Interestingly, among the 39 patients without fever that had a routine blood slide at the health facility, 12 (30.8%) were reported as positive but none were confirmed as positive on the examination of the study slides by the expert microscopists.

Nearly all patients with a routinely reported positive malaria slide received antimalarial treatment (95.5, 95% CI: 91.3–99.7), however, health workers prescribed an antimalarial treatment for 79.3% (95% CI: 65.8–92.9) of patients with a routinely reported negative slide.

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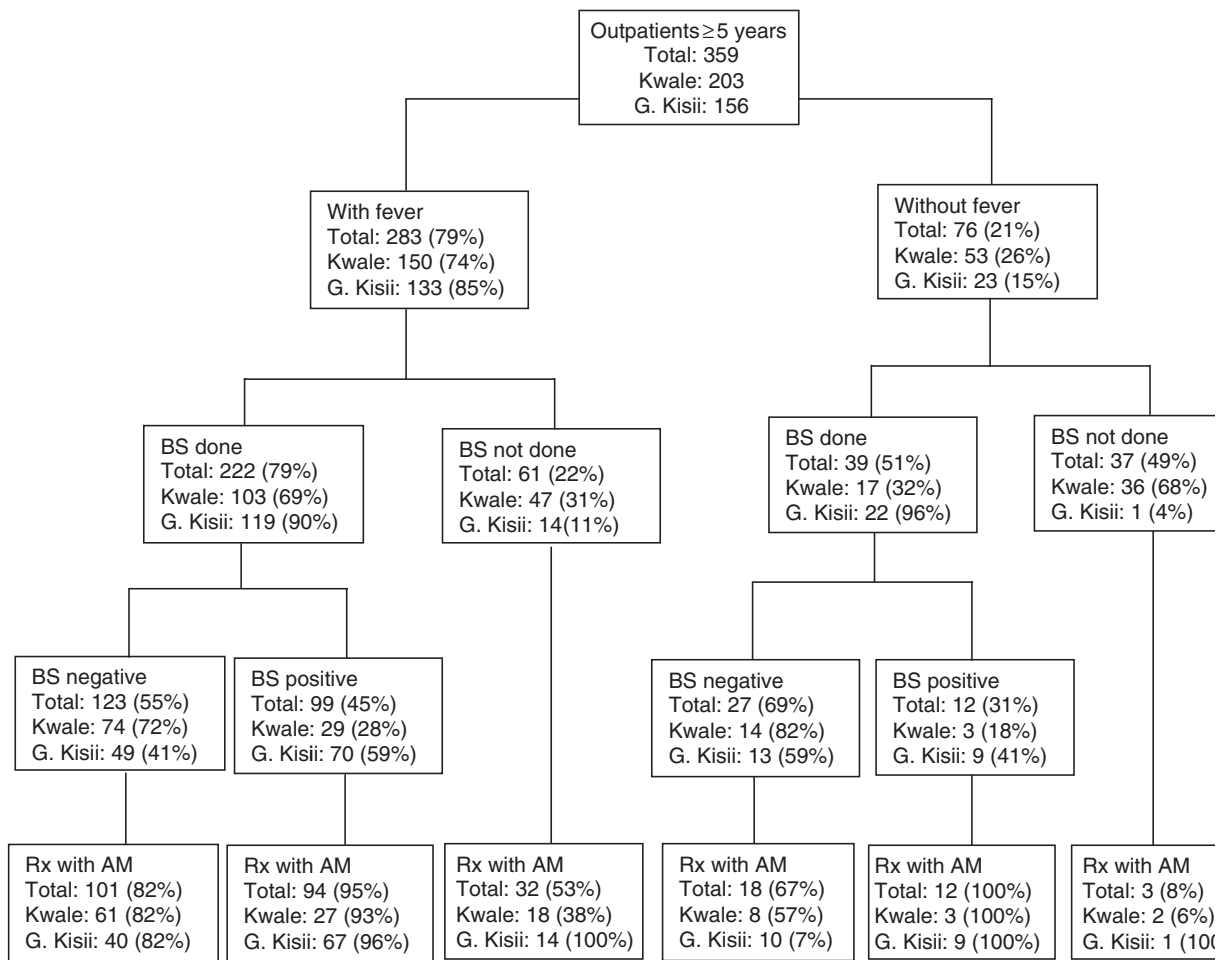
Figure 1 The clinical process for older children and adults presenting to 17 health facilities with a functional microscopy indicating th and interpretation of blood slide (BS) results with respect to the presence of fever and treatment (Rx) with an antimalarial (AM) c results from districts of high (Kwale) and low (Greater Kisii) malaria transmission in Kenya.

Variability of this practice between individual clinicians could not be meaningfully compared because of the small number of observations per clinician, however, all clinicians were observed to ignore some negative results. Significantly fewer patients who did not have a malaria slide performed had an antimalarial drug prescribed (35.7, 95% CI: 19.2–52.2). There was no significant difference observed in the prescription of antimalarial treatments for a routine negative malaria slide between the two districts: 78.4% (95% CI: 54.9–100) of patients in Kwale district and 80.6% (95% CI: 68.7–92.6) in Kisii district had antimalarial drugs prescribed.

A significant difference was observed in treatment practices depending on the blood slide result (Table 1). The SP monotherapy, recommended first line therapy for

uncomplicated malaria in Kenya, was more common prescribed in patients with a negative malaria slide (6 95% CI: 48.5–72.8) than in patients with a positive (32.4, 95% CI: 19.9–45.0). Conversely, second-line were more commonly prescribed for patients with po slide reports than for patients with a reported negativ malaria slide (Table 1). Amodiaquine or quinine, eith monotherapies or in combination with other antimal drugs, were prescribed for only 14.7% (95% CI: 4.4– of patients with a negative slide compared to 57.7% (CI: 44.0–71.4) of patients with positive slide. The sin pattern in the use of first and second line drugs with r to routine reports of positive and negative slides were observed in both districts and no statistically significa difference has been demonstrated between the distric

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Treatment prescribed	BS positive (*n* = 111)		BS negative (*n* = 150)		BS not done (*n* = 98)		Total (*n* = 359)	
	No	(%)	No	(%)	No	(%)	No	(%)
SP*	36	32.4	91	60.7	19	19.4	146	40.7
Amodiaquine†	38	34.2	16	10.7	10	10.2	64	17.8
Quinine†	13	11.7	5	3.3	2	2.0	20	5.6
SP + quinine	6	5.4	0	0	0	0	6	1.7
SP + chloroquine	4	3.6	3	2.0	3	3.1	10	2.8
Amodiaquine + quinine	3	2.7	0	0	0	0	3	0.8
SP + amodiaquine	2	1.8	1	0.7	0	0	3	0.8
Artemisinins	2	1.8	1	0.7	0	0	3	0.8
Chloroquine + amodiaquine	2	1.8	0	0	1	1.0	3	0.8
Proguanil	0	0	2	1.3	0	0	2	0.6
No antimalarial treatments	5	4.5	31	20.7	63	64.3	99	27.6
Antipyretic prescribed	106	95.5	137	91.3	69	70.4	312	86.9
Antibiotic prescribed	57	51.4	88	58.7	62	63.3	207	57.7

Table 1 Prescriptions for older children and adults treated as outpatients following an initial visit according to the routine results of blood slides (BS)

* Sulfadoxine–pyrimethamine (SP) is nationally recommended first-line drug for uncomplicated malaria.
† Amodiaquine and quinine are nationally recommended second-line drugs for uncomplicated malaria.

There was a high use of antipyretics and antibiotics irrespective of whether the slide was reported as positive (95.5 and 51.4%, respectively), negative (91.3 and 58.7%, respectively) or not requested (70.4 and 63.3%, respectively).

Accuracy of routine malaria microscopy

An additional study slide was prepared for 261 patients who had a routine malaria slide performed and was read by two expert microscopists during the post-survey work. The slide positivity rate of expert microscopy was 13.4% (95% CI: 7.8–19.0), without significant difference between the districts of high and low-malaria transmission: 10.0% (95% CI: 6.1–13.9) of blood slides in Kwale district and 16.3% (95% CI: 6.1–26.5) in Greater Kisii district were malaria positive on the expert microscopy.

Using data pooled across both districts the sensitivity and the specificity of the routine blood slide results for identifying a positive blood slide by expert microscopy were 68.6% (95% CI: 55.2–82.0) and 61.5% (95% CI: 48.6–74.5), respectively. The positive predictive value (PPV) was very low, 21.6% (95% CI: 10.4–32.9) while the NPV was high, 92.7% (95% CI: 89.7–95.6). No significant difference in predictive values was observed between districts: the PPVs were 18.8% (95% CI: 9.0–28.5) and 22.8% (95% CI: 4.2–41.4) in Kwale and Greater Kisii districts, respectively, while the NPVs were 93.2% (95% CI: 90.0–96.3) and 91.9% (95% CI: 85.4–98.4), respectively. The positive likelihood ratio was low in both districts

(2.08 in Kwale and 1.50 in Greater Kisii), as well as in the two districts combined (1.82). The results on the accuracy of the routine microscopy across two districts are presented in Table 2.

Discussion

Parasite-based diagnosis of malaria is receiving renewed attention in the face of widespread deployment of new more expensive drugs with possibly lower safety margins (Nosten & Brasseur 2002; Amexo *et al.* 2004; Barnish *et al.* 2004). Our study in 17 health facilities with functional microscopy in Kenya in two areas of different malaria transmission showed that malaria microscopy was commonly used among older children and adults. However, clinical indications for its use were frequently inappropriate: over half of patients without evidence of fever were referred for microscopy, and despite the laboratory reporting that 31% of these patients had evidence of infection this was not confirmed in any case by expert examination of a parallel slide. Furthermore, while nearly all routine reports of positive slides were treated for malaria (96%), the clinical interpretation of negative malaria slide results was characterised by an overwhelming tendency to ignore the result and prescribe an antimalarial (79%). These findings are consistent with observations made in Benin (Holtz & Kachur 2000), Zambia (Barat *et al.* 1999) and Bungoma district in Kenya (Barat & Kramer 1999).

There are a number of possible explanations for this practice. First, prescribers may view blood slide diagnosis

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Table 2 The slide positivity rate and the accuracy of routine malaria microscopy compared to a gold standard microscopy: results fro
health facilities across two districts of different malaria transmissions in Kenya

	Kwale (high transmission)			Greater Kisii (low transmission)			Total		
	No/N	%	95% CI	No/N	%	95% CI	No/N	%	95
Slide positivity rate (routine microscopy)	32/120	27	17, 37	79/141	56	41, 71	111/261	43	31
Slide positivity rate (expert microscopy)	12/120	10	6, 14	23/141	16	6, 27	35/261	13	8
Sensitivity	6/12	50	19, 81	18/23	78	64, 93	24/35	69	55
Specificity	82/108	76	68, 84	57/118	48	28, 68	139/226	62	49
Positive predictive value	6/32	19	9, 29	18/79	23	4, 41	24/111	22	10
Negative predictive value	82/88	93	90, 96	57/62	92	85, 98	139/150	93	90
Positive likelihood ratio	2.08			1.50			1.82		

more as a tool to confirm their clinical suspicion rather than to rule out malaria. In support of this possibility we observed that an antimalarial treatment is more commonly prescribed for patients with a blood slide performed compared to patients without a blood slide. Second, a malaria diagnosis and treatment may be simply a 'convenient' clinical strategy avoiding the more complicated search for other causes of the presenting illness. In our study patients with a negative slide were more likely to be prescribed SP compared to patients with a positive slide who were commonly prescribed second-line treatments and we could not demonstrate that assessment practices were more thorough for patients with reported negative slide compared to patients with positive slide result. Third, clinicians may doubt the quality of microscopy leading to a lack of confidence when a negative malaria slide result is reported. Our observation was that the NPV of routine microscopy was high (93%), which should provide some confidence among prescribers that negative slides are truly negative. Although this in part reflects the fact that in both high and low-transmission settings studied the prevalence of confirmed malaria was low in these age groups.

The low prevalence of 'true malaria' in both transmission settings in those aged 5 or more years (10% in the high-transmission area and 16% in the low-transmission area) also in part explains the low PPV of routine microscopy for detecting true malaria in both settings. Thus approximately four of five routinely reported positive slides were in fact negative. These findings are similar, to those from a recent study in Tanzania where the positivity rate of research slides among patients >5 years of age admitted to hospital with severe malaria did not differ between lowland, high (19%) and highland, low (22%) malaria transmission settings (Reyburn *et al.* 2004). However, while the low prevalence of true malaria helps explain the low PPVs there is clearly a major problem with the quality of routine microscopy. Even at a prevalence of

true malaria of 10% the PPV of routine microscopy rise to 50% with a positive likelihood ratio of 9 if ro microscopy was 90% sensitive and 90% specific comp with gold standard microscopy – not an unreasonabl standard for a laboratory quality assurance scheme. acknowledge that the age is likely to have further effe the prevalence of 'true malaria' and predictive values however, a small number of observations in older chi 5–14 years, precluded any meaningful comparisons w adult patients.

Finally we would like to emphasise the potential ro ambiguous national guidelines. They state that *'in ce cases a slide may be negative even when the patient malaria'* (Ministry of Health 1998). Similar recomme tions can be found in international guidelines (WHO 2003a) and similar instructions continue to be promo for the interpretation of malaria rapid diagnostic test (WHO 2003b). Such ambiguous statements undermin purpose of introducing diagnostics aiming to promot rational drug use. Changing international and nation guidelines, at least for older children and adults in w the risk of disease is rapidly declining, seems a pre-req to improving the value of diagnostic services in mala case management.

Effective change of current diagnostic behaviour m yield significant savings on antimalarial drug costs. Ir hospital in Malawi the introduction of microscopic d nosis for adult patients accompanied by instructions respect negative results produced annual savings of 3 the hospital's overall annual drug budget (Jonkman *e* 1995). In Kenya, artemether-lumefantrine (AL), chara terised by a 30-fold more expensive adult treatment c compared to SP, has been announced as the new first treatment for uncomplicated malaria (Ministry of He 2004). A single change of diagnostic practice, respect negative parasitological results, could produce signifi savings under AL treatment policy in Kenya even if t

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accuracy of microscopy was not improved. However, our study suggested that such change of practice would be done at the cost of reducing sensitivity for identifying true cases by 31% and would result in 1 of 24 outpatients above 5 years of age being sent home without an antimalarial drug when they are in fact parasitaemic. The risks of such a trade-off are essentially unknown, however, they might be expected to be low in older children and adults with uncomplicated malaria who are considerably less vulnerable to developing severe, potentially fatal complications.

The ideal solution, reducing the risk of failure to treat true cases and creating even more significant antimalarial drug cost savings would be improvement in the accuracy of malaria microscopy accompanied by a change of diagnostic practice. An ideal 100% accuracy of malaria microscopy is probably an unrealistic target under field conditions. Sensitivities and specificities of above 90% are more realistic and sufficiently acceptable targets to justify interventions focusing on a change of clinical diagnostic practice. Improvements of accuracy of malaria microscopy present a challenge for currently poorly functional laboratory services in Kenya. However, the recent positive experiences reported from Ghana suggest that significant nationwide improvements in the accuracy of malaria microscopy can be achieved (Bates *et al.* 2004). Improvements in diagnostic services would then need to be translated into improved clinical practice, particularly with regard to respect for negative slide results. Change of any clinical practice is a challenging task and interventions have been variously successful (Ross-Degnan *et al.* 1997; WHO 2001b), however, several recent studies suggest that improving the quality of outpatient care in Africa is possible (Armstrong-Schellenberg *et al.* 2004; Gouws *et al.* 2004). Combining laboratory and clinical improvements would appear to have great scope for reducing antimalarial drug costs in the era of ACTs.

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Microscopie et prise en charge des patients malariques ambulatoires chez les enfants plus âgés et les adultes au Kenya

OBJECTIF   Evaluer la précision de la lecture des lames et de l'interprétation des résultats dans la microscopie de la malaria sous des conditions opérationnelles.

MÉTHODES   Etude transversale basée sur une série d'outils d'évaluation de la qualité de la prise en charge dans des services gouvernementaux réalis une microscopie pour la malaria, dans deux districts du Kenya avec différentes intensités de la transmission de la malaria. Tous les patients de plus ans se présentant dans le département des patients ambulatoires ont été inclus dans l'étude.

RÉSULTATS   359 consultations ont été réalisées par 31 cliniciens dans 17 services. L'évaluation clinique était sub-optimale. Une microscopie de fro sanguin a été effectuée pour 72,7% des patients représentant 78,5% des patients fébriles et 51,3% des patients non fébriles. 95,5% des patients a frottis microscopiquement positif et 79,3% des patients avec un frottis négatif ont reçu un traitement antimalarique. La monothérapie à sulphadox pyremethamine était plus couramment prescrite pour les patients avec un test négatif (60,7%) que pour les patients avec un test positif (32,4%). Cependant, l'amodiaquine ou la quinine était prescrite chez seulement 14,75% des patients avec un test négatif comparé à 57,7% des patients ave test positif. La prévalence de malaria confirmée était faible autant dans la région à haute (10,0%) que dans celle à faible (16,3%) transmission d malaria. D'après les données combinées des deux endroits, la sensibilité de la microscopie en routine était de 68,6%, sa spécificité 61,5%; sa va prédictive positive 21,6% et sa valeur prédictive négative 92,7%.

CONCLUSION   Les bénéfices potentiels de la microscopie ne sont pas actuellement atteints à cause de la faible qualité du test de routine. En plus, directives cliniques ambiguës pour le traitement des enfants moins jeunes et des adultes à frottis sanguins négatifs compromettent l'usage rationnel médicaments antifébriles.

mots clés malaria, microscopie, interprétation, précision, Kenya

D. Zurovac *et al.*   **Malaria microscopy in Kenya**

Manejo microscópico y en consultas externas de casos de malaria en niños y adultos en Kenia

OBJETIVO   Evaluar la exactitud de la lectura por microscopía de láminas para malaria, y la interpretación correcta de los resultados, bajo condiciones operacionales en Kenia.

MÉTODOS   Estudio croseccional, utilizando una serie de herramientas para evaluar la calidad, en centros gubernamentales con microscopía para malaria en dos distritos de Kenia con diferente intensidad de transmisión de malaria. Todos los pacientes de más de 5 años que se presentaron en consultas externas fueron incluidos en el estudio. Dos microscopistas expertos evaluaron la exactitud de los resultados de las lecturas de rutina de las láminas.

RESULTADOS   Analizamos 359 consultas realizadas por 31 clínicos en 17 centros. La evaluación clínica fue deficiente: se realizaron láminas a 72.7% de los pacientes, que representaban un 78.5% de los pacientes con fiebre y 51.3% de los pacientes sin fiebre. Un 95.5% de los pacientes con un resultado positivo en la lectura de la lámina por microscopía y un 79.3% de los pacientes con un resultado negativo, recibieron tratamiento antimalárico. La monoterapia con sufadoxina-pirimetamina más comúnmente prescrita a pacientes con una resultado negativo en la lectura de la lámina (60.7%) que a pacientes con un resultado positivo (32.4%). Por otro lado, la amodiaquina o la quinina fueron prescritas a solo un 14.7% de los pacientes con un resultado negativo por microscopía, comparado con un 57.7% de los pacientes con un resultado positivo. La prevalencia de malaria confirmada fue baja, tanto en áreas de alta (10.0%) como de baja (16.3%) transmisión. Al combinar los datos de ambos lugares, la sensibilidad de la microscopía de rutina fue del 68.6%; la especificidad del 61.5%; su valor predictivo positivo, 21.6% y su valor predictivo negativo, 92.7%.

CONCLUSIONES   Los beneficios potenciales de la microscopía no son actualmente evidentes debido a la mala calidad de las pruebas de rutina. Unas guías clínicas ambiguas que permiten el tratamiento de niños mayores y adultos con una lámina negativa, también debilitan el uso racional de los medicamentos para malaria.

palabras clave malaria, microscopía, interpretación, exactitud, Kenia