Tropical Medicine and International Health doi:10.1111/tmi.12635

VOLUME 21 NO 1 PP 149–156 JANUARY 2016

Causes of non-malarial febrile illness in outpatients in Tanzania

Helena Hildenwall[1,2], Ben Amos[2], George Mtove[2,3], Florida Muro[4], Kerstin Cederlund[5,6] and Hugh Reyburn[7]

1 *Global Health – Health Systems and Policy, Karolinska Institutet, Stockholm, Sweden*
2 *Joint Malaria Programme, St Augustine's Hospital, Muheza, Tanzania*
3 *National Institute for Medical Research, Amani Centre, Muheza, Tanga, Tanzania*
4 *Kilimanjaro Christian Medical Centre, Moshi, Tanzania*
5 *Department of Radiology, Karolinska University Hospital, Huddinge, Sweden*
6 *Department of Clinical Science, Karolinska Institutet, Stockholm, Sweden*
7 *London School of Hygiene and Tropical Medicine, London, United Kingdom*

Abstract

OBJECTIVE In sub-Saharan Africa, the use of malaria rapid diagnostic tests (mRDT) has raised awareness of alternative fever causes in children but few studies have included adults. To address this gap, we conducted a study of mRDT-negative fever aetiologies among children and adults in Tanzania.

METHODS A total of 1028 patients aged 3 months to 50 years with a febrile illness and negative mRDT were enrolled from a Tanzanian hospital outpatient department. All had a physical examination and cultures from blood, nasopharynx/throat and urine. Patients were followed on Days 7 and 14 and children meeting WHO criteria for pneumonia were followed on Day 2 with chest radiology.

RESULTS Respiratory symptoms were the most frequent presenting complaint, reported by 20.3% of adults and 64.0% (339/530) of children. Of 38 X-rayed children meeting WHO pneumonia criteria, 47.4% had a normal X-ray. Overall, only 1.3% of 1028 blood cultures were positive. *Salmonella typhi* was the most prevalent pathogen isolated (7/13, 53.8%) and *S. typhi* patients reported fever for a median of 7 days (range 2–14). Children with bacteraemia did not present with WHO symptoms requiring antibiotic treatment. Young children and adults had similar prevalences of positive urine cultures (24/428 and 29/498, respectively).

CONCLUSION Few outpatient fevers are caused by blood stream bacterial infection, and most adult bacteraemia would be identified by current clinical guidelines although paediatric bacteraemia may be more difficult to diagnose. While pneumonia may be overdiagnosed, urinary tract infection was relatively common. Our results emphasise the difficulty in identifying African children in need of antibiotics among the majority who do not.

keywords aetiology, fever, Integrated Management of Childhood Illness, Integrated Management of Adolescent and Adult Illness, non-malaria, Tanzania

Introduction

In 2010, WHO replaced the strategy of antimalarial treatment for children with any non-specific febrile illness ('presumptive treatment') with a policy of restricting antimalarial treatment to patients with a positive parasitological test for malaria [1]. This policy has been adopted throughout Africa, but its implementation challenges the diagnostic capacity of clinicians who for many years have assumed that any unexplained fever is likely due to malaria. The widespread introduction of antigen-based RDTs for malaria (mRDTs) is now showing clinicians that many, and often the large majority, of patients previously treated for malaria in fact have a non-malarial illness [2, 3]. Lack of diagnostic capacity in much of Africa means that there is little evidence of causes of non-malarial illnesses, without which it will be difficult to correct the irrational and wasteful tendency of clinical staff to treat mRDT-negative patients for malaria [4, 5].

Although there are now several studies of causes of febrile illness in African children [6–10], there are few that have compared causes of illness in older children and adults [11, 12]. One reason for this is that the strategy of presumptive treatment for malaria was limited to

young children and never formally extended above that age. However, the practice of presumptive treatment has been commonly applied to all age groups, and these patients often constitute a majority of presumptive treatments for malaria.

In order to fill this gap in evidence, we conducted this study to determine the syndromic diagnosis and likely causative pathogen among febrile patients under the age of 50 years attending an outpatient department (OPD) in a malaria endemic area of Tanzania.

Materials and method

Study area

The study was conducted from July 2011 until November 2012 at St Augustine's Hospital (formally Teule Hospital), the District Designated Hospital of Muheza District, Tanzania. The hospital serves a predominantly rural population exposed to perennial transmission of malaria with seasonal peaks coinciding with the short and long rainy seasons. The prevalence of *Plasmodium falciparum* infection in the area has declined dramatically in recent years [13]. To facilitate patient follow-up, the study area was defined as residence in one of the 85 villages which contributed >10 paediatric admissions to St Augustine's Hospital in 2006.

Procedures

Children between 3 months and 5 years of age were consecutively recruited from the Reproductive and Child Health clinic (RCH); older children and adults up to 50 years of age were recruited from the adult OPD. All patients were screened for absence of life-threatening illness, presence of fever today or yesterday and residency in the study area. A negative HRP-2-based RDT for *P. falciparum* (ParacheckTM; Orchid Biomedical, Mumbai, India) was required to enter into the study.

A second screening excluded patients with a chronic condition except HIV infection – which was only recorded if reported by the patient –, soft tissue infection, patients who had already been enrolled in the same study within the previous month and patients who reportedly had been treated with malaria drugs in the previous two weeks.

If eligible for enrolment, patients or their legal guardian were read the study information, and after patient/caretaker's informed consent had been obtained, a study clinical officer collected information on the patient's symptom progression and any treatment taken before arrival at the hospital. Patients were then examined and treated using WHO's Integrated Management of Childhood Illness (IMCI) or Integrated Management of Adolescent and Adult Illness (IMAI) algorithms [14, 15].

Children under 5 years of age with symptoms suggestive of pneumonia (cough or difficult breathing with a raised respiratory rate or chest indrawings or grunting) had a frontal chest X-ray performed on either the same day of enrolment or at the follow-up visit on Day 2. Chest X-rays were interpreted by ordinary hospital staff according to internal standards to inform any necessary change in treatment. In addition, all X-rays were digitised using high-resolution photography and photographs were sent for interpretation by an experienced chest radiologist (KC) using the WHO document for standardisation of interpretation of paediatric chest radiographs [16].

All patients were followed over a period of two weeks with scheduled follow-up visits at the clinic after one and two weeks. Patients with symptoms suggestive of pneumonia had an additional follow-up visit on Day two, according to the IMCI/IMAI guidelines. Follow-up visits included data collection on symptom progression and patient examination.

Laboratory procedures

All enrolled patients underwent a sterile venepuncture using a butterfly and syringe and drawing a maximum of 10 ml of blood from children and 20 ml from adults. At least 3–6 ml of blood was used for aerobic blood culture in children, and 10 ml was used for adult cultures. Blood was aseptically inoculated into a BactALERTTM (bioMerieux, France) fan bottle and incubated in the BacT/ALERT 3D automated microbial detection system. All bottles were weighed before and after blood inoculation to determine the amount of blood collected. Cultures that flagged positive were Gram-stained and subcultured at 36.5 °C after which isolates were identified to the species level by standard biochemical methods. Cultures positive for non-*Cryptococci* yeasts, coagulase-negative *Staphylococci*, *Micrococci, Corynebacterium and Bacillus spp* were considered contaminants and classified as 'negative culture' unless a pathogenic organism was also isolated. Positive cultures were reported back to the clinicians as soon as identified to allow for immediate follow-up of affected patients.

Venous blood was also used for measurement of haemoglobin (HemocueTM, Ängelholm, Sweden) and point of care tests for a related study (not yet published).

All enrolled patients had a pooled nasopharyngeal/throat swab taken [17]. Samples were transnasally taken using a flexible sterile swab by trained staff where after

throat samples were collected using a stiff flocked swab. Swabs were put in 1 ml of saline and plated on agar plates upon arrival at the laboratory.

All patients provided a urine sample at enrolment. Careful instructions for cleaning before sample collection were given to all patients and caretakers in order to avoid skin pathogen contamination of urine samples. A urine screening multistix dipstick was performed immediately upon receiving the urine, and if leucocyte or nitrate positive, urine was sent for bacterial culture. A urine culture was considered positive if a colony count of greater than or equal to 10^5 colony forming units (cfu)/ml was found on testing clean voided specimens.

Data management and analysis

Data were doubled entered in MS Access and analysed using Stata12. Proportions with confidence intervals were calculated for prevalence of symptoms and pathogens. Wilcoxon rank-sum test was used to compare continuous variables between groups while chi-square test was used to compare proportions. Logistic analysis was used to calculate prevalence odds ratios with 95% confidence intervals between groups.

Ethics

Written informed consent was obtained from enrolled patients or, for children, the legal guardian on their behalf. If illiterate, the study information was read to the patient after which they were asked to sign by putting their thumbprint at the place for signing with a witness confirming the thumbprint with his/her signature. The Ethical Review Boards of the National Institute for Medical Research in Tanzania approved the above consent procedures and the study (NIMR/HQ/R.8aN 01. IX/1 087).

Results

Overall 2427 patients between 3 months and 50 years of age were screened and 1028 were enrolled in the study; 428 were children <5 years of age, 102 were aged 5–12 years, and 498 were between 13 and 50 years of age. At enrolment screening, 59 of 1024 (5.8%) of under-fives, 52 of 190 (27.4%) of children aged 5–12 and 96 of 1268 (7.5%) of patients 13 years and older were excluded due to a positive mRDT. A total of 964 of 1028 (93.8%) patients were followed with return visits at the clinic to Day 14, 36 of 1028 (3.5%) were followed up by phone and 28 of 1028 (2.7%) patients were lost to follow up after the day of enrolment.

Clinical features on enrolment

Table 1 shows basic details at enrolment. Measured fever (>37.5°C per axilla) was more common among children <5 years of age than in older children and adults. Patients 13 years of age or older reported a longer duration of fever than younger patients ($P < 0.01$). HIV infection was reported by 19/498 (3.8%) of adults and 1/102 (1.0%) of children between 5 and 12 years of age. No child <5 years of age was reported to be infected with HIV.

The most common presenting symptom at enrolment for all age groups was cough, reported in 279 of 428 (65.2%) of all under-fives and almost the same proportion among older children; 58/102 (56.9%). Table 2 provides an overview of symptom presentation at enrolment in all age groups. Non-severe pneumonia as defined in the IMCI/IMAI guidelines was more common among under-fives than adults (OR 3.4, 95% CI 1.8–6.4) while 15 of 102 (14.7%) of children aged 5–12 years fulfilled criteria of 'severe pneumonia' whereas 15 of 428 (3.5%) of young children and 19 of 498 (3.8%) of adults ($P < 0.01$) did.

Results of bacterial cultures

Results of bacterial cultures from urine, nasopharyngeal/throat swabs and blood are presented in Table 3.

Blood cultures

A bacterial pathogen was isolated from only 13 of 1028 (1.3%) of blood cultures, and a further 30 of 1028 (2.9%) grew an organism judged to be a contaminant. The most commonly identified pathogen was *Salmonella typhi* (7/13, 53.8%) followed by *Escherichia coli* (3/13, 23.1%) and *Streptococcus pneumonia* (2/15, 13.3%). One young child's blood grew group A betahemolytic

Table 1 Basic characteristic of enrolled patients per age group

	3–59 months (n = 428)	5–12 years (n = 102)	13–<50 years (n = 498)
Females, n (%)	195 (45.6)	52 (51.0)	370 (74.3)
Temp >37.5, n (%)	196 (45.8)	19 (18.6)	51 (10.2)
Days with fever, Mean (median)	3.3 (3)	3.5 (3)	5.8 (4)
Haemoglobin, Mean (median)	10.9 (11.0)	12.7 (13.0)	13.4 (13.7)
Reportedly HIV positive, n (%)	Nil	1 (1.0)	19 (3.8)
Admitted*, n (%)	27 (6.3%)	1 (1.0)	6 (1.2)

*Admitted during the study period (d0–d13).

Table 2 Clinical features presentation at enrolment by age group

	3–59 months *n* (%, 95% CI)	5–12 years *n* (%, 95% CI)	13–<50 years *n* (%, 95% CI)
Cough/difficult breathing	281 (65.7, 61.1–70.2)	58 (56.9, 47.2–66.5)	101 (20.3, 16.7–23.8)
Coryza/runny nose	91 (21.3, 17.3–25.1)	10 (9.8, 4.0–15.6)	30 (6.0, 3.9–8.1)
Rapid breathing for age*	68 (15.9, 12.4–19.4)	7 (6.9, 1.9–11.7)	297 (59.6, 55.3–64.0)
Diarrhoea or vomiting	117 (27.3, 23.1–31.6)	16 (15.7, 8.6–22.8)	39 (7.8, 5.5–10.2)
Fever without other symptoms	36 (8.4, 5.8–11.0)	14 (13.7.0–20.4)	132 (26.5, 22.6–30.4)
IMCI/IMAI non-severe pneumonia	57 (10.5, 8.8–14.6)	1 (0.9, −0.9–2.9)	24 (4.8, 2.9–6.7)
IMCI/IMAI severe pneumonia	15 (3.5, 1.8–5.3)	15 (14.7, 7.8–21.6)	19 (3.8, 2.1–5.5)

*Increased respiratory as defined by IMCI/IMAI algorithms per age group, 1–12 months > 50 breaths/minute, 1–5 years > 40 breaths/minute, 5–12 years > 30 breaths/minute, above 13 years > 20 breaths/minute.

Table 3 Results from bacterial cultures from blood, urine and respiratory tract per age group

	3–59 months, *n* (%)	5–12 years, *n* (%)	13–<50 years, *n* (%)
Blood			
Bacteria	6 (1.4)	3 (2.9)	4 (0.8)
Urine			
Bacteria	24 (5.6)	Nil	29 (5.8)
Respiratory			
Bacteria	139 (32.5)	11 (10.8)	41 (8.2)

Streptococcus. *Salmonella* was the only pathogen isolated from children between 5 and 12 years of age ($n = 3$). Patients with *S. typhi* reported fever for a median 7 days (range 2–14). Adults with *E. coli* in blood also reported on urinary tract symptoms and positive growth of *E. coli* in urine cultures ($n = 2$). *S. pneumonia* was only seen in children aged <3 years ($n = 2$), and these children both reported cough but none of them presented with symptoms of severe focal or systemic disease which would lead to treatment with antibiotics following the IMCI algorithm. One young child with *E. coli* in blood presented with symptoms of severe pneumonia while the child with group A betahemolytic *Streptococcus* in blood had no signs of antibiotic-requiring illness. None of the patients with reported HIV infection had a positive blood culture.

Urine cultures

A total of 318 of 1028 (30.9%) patients presented with leucocytes in urine and had their urine sent for bacterial culture. Table 3 shows proportions of positive urine cultures by age group. The most common pathogen found was *E. coli*, present in 19 of 24 (79.2%) of urine cultures in young children and 22 of 29 (75.9%) of adult cultures. *Klebsiella* was the second most common pathogen. The assessing physician correctly diagnosed more adults than children with urinary tract infections (UTI), based on reported symptoms and results of urine dipstick (14/24, 58.3% and 23/29, 79.3%, respectively). There was a higher risk of a positive urine cultures among patients with a measured fever at enrolment compared to patients with a normal temperature (OR 2.1, 95% CI 1.1–4.2).

Nasopharyngeal/throat cultures

Isolation of a potential pathogen from nasopharyngeal/throat swabs was significantly more common among young children compared to older children and adults (OR 5.1, 95%CI 3.6–7.2) (Table 3). The main pathogens were *S. pneumonia e* 124/191(64.9%) and *Haemophilus influenza* 73/191(30.4%). Positive respiratory culture was unrelated to an IMCI/IMAI diagnosis of non-severe or severe pneumonia (OR 1.5, 95% CI 1.0–2.4).

Pneumonia X-rays

Of 45 children meeting IMCI criteria of non-severe pneumonia, 51.1% had a readable chest X-ray, of which 60.9% were normal and 13.0% showed consolidation while 26.1% showed pathology other than consolidation, mainly interstitial infiltrates suggestive of viral infection. All children fulfilling criteria for IMCI severe pneumonia ($n = 15$) had a readable X-ray with four normal (26.7%) and four with consolidation (26.7%). Seven of 15 (46.7%) of children classified with IMCI severe pneumonia had an X-ray showing diffuse pathology, suggestive a viral aetiology as the most likely cause of illness. Table 4 shows relations between proportions of children with cough or difficult breathing, IMCI pneumonia and X-ray findings.

Admission

Admissions were more common among children <5 years of age ($n = 27$, 6.3%) compared to older children ($n = 1$) and adults ($n = 6$, OR 5.7, 95%CI

Table 4 Proportions of upper respiratory tract infections (URTI), non-severe, and severe pneumonia as defined by the Integrated Management of Childhood Illness (IMCI) and X-ray findings in children 3–59 months of age

	URTI	IMCI non-severe pneumonia	IMCI severe pneumonia
Total number (% of children <5 years)	221 (65.7)	45 (10.5)	15 (3.5)
X-ray unavailable, *n* (% of diagnosis)	–	22 (48.9)	–
Normal X-ray, *n* (% of X-rayed)	–	14 (60.9)	4 (26.7)
Consolidation on X-ray, *n* (% of X-rayed)	–	3 (13.0)	4 (26.7)
Other pathology* on X-ray, *n* (% of X-rayed)		6 (26.1)	7 (46.7)

*Other pathology on X-ray defined as any non-consolidation abnormality such as interstitial infiltrates.

2.5–13.2). The main reason for admissions among young children, according to the admitting clinician, was pneumonia (18/27, 66.7%). Among adult admissions, diarrhoea and UTI were the most common diagnoses and one of the adult patients with reported HIV infection was admitted due to anaemia. Among patients with a positive blood culture, only one was admitted – an infant with symptoms of severe pneumonia and growth of *E. coli* in blood who was admitted immediately after enrolment (d0).

Discussion

Consistent with other studies from similar settings, our results provide evidence of low levels of invasive bacterial illness among children and adult outpatients in a hospital in north-east Tanzania [9, 18, 19]. While bacteraemia among paediatric inpatients is associated with substantial mortality, only one of the patients with growth of *E. coli* in blood was considered sick enough to require admission and none of the patients with bacteraemia had developed severe illness upon being contacted by the study team to adjust treatment.

The association between malaria and non-typhoidal *Salmonella* (NTS) infection is now well established although details of how the prevalence of NTS infection varies with malaria endemicity are still unclear [20, 21]. The results of this study suggest that NTS becomes rare when the prevalence of malaria in older children drops below 30%. More studies are needed to elucidate the details of this association. This study also suggests an inverse relationship between malaria and *S. typhi* that has been found in other studies [22] and for which, if true, there is currently no explanation and is an area of further research. Typhoid fever is associated with a substantially lower case fatality than blood stream NTS infection [23] but may be difficult to diagnose. Patients with *S. typhi* bacteraemia in our study had non-specific symptoms, as is often the case with typhoid fever. However, all but one reported fever for at least five days prior enrolment, directing the clinician at enteric fever [24].

Respiratory symptoms were the most common presenting complaint of fever in all age groups with the highest proportion of patients with symptoms of severe pneumonia among children between 5 and 12 years of age. The current IMAI algorithm (applied to patients over the age of 5 years) uses the presence of cough or difficult breathing in combination with a pulse rate of 120 beats per minute or more as one definition of severe pneumonia. As children have a higher pulse rate than adults during normal conditions, the pulse rate cut-off may contribute to the high proportion of children between 5 and 12 years of age who fulfilled criteria of severe pneumonia and revisions to improve specificity may be needed in this age group.

The presence of bacterial growth from nasopharyngeal/throat samples was more common in young children than in adults, but no significant difference in nasopharyngeal growth was seen between those who fulfilled criteria of IMCI/IMAI pneumonia and those with no or non-severe respiratory problems. Asymptomatic carriage of bacteria, and viruses, is common and cannot confirm pneumonia diagnosis. Although nasopharyngeal bacteria may point at the causative organism in patients with pneumonia symptoms, the analysis of nasopharyngeal samples does not seem to add much in aetiology studies unless the analysis of viral pathogens is added.

Radiological abnormalities are likely to increase the specificity of pneumonia diagnosis, and our results suggest that almost half of young children with IMCI pneumonias had normal X-ray findings. The IMCI algorithm is expected to ensure 80% of children with pneumonia receive an antibiotic while accepting that 20–30% of those prescribed an antibiotic will not need it [25]. However, a placebo-controlled trial from Pakistan failed to find a significant difference in study outcomes between children with IMCI non-severe pneumonia who received antibiotics compared to placebo [26]. This questions the proportion of children with IMCI pneumonia that are responsive to antibiotic treatment and suggests many may suffer a viral illness. Children with chest indrawings (thus fulfilling definitions for severe pneumonia according to

the IMCI algorithm) had a higher prevalence of consolidation on X-ray than those with non-severe pneumonia but were otherwise not severely ill. This finding supports the revised definitions of chest indrawing as part of the IMCI non-severe pneumonia algorithm [27].

Streptococcus pneumonia bacteraemia was only identified in young children. The absence of severity signs in these children combined with findings of *S. pneumonia* in nasopharynx corresponds well to the criteria of occult pneumococcal bacteraemia [28]. These children were thus at risk of developing a focal or more severe invasive infection. Still, as much as 97% of occult pneumococcal bacteraemia manage to clear the infection without any treatment [29] and the benefits of treating this group is thus unclear. The prevalence of occult pneumococcal bacteraemia in our study population is similar to that reported from paediatric emergency settings in the United States [29, 30], where the prevalence declined after the introduction of pneumococcal vaccines [31].

While overtreatment in sick patients is generally a reasonable approach, the decline in bacterial pneumonia associated with the use of vaccines against *H. influenza* and *S. pneumococci* suggests an increasing number of patients with acute respiratory illness may suffer from a viral illness [9].

More than 5% of young children and adults had a significant bacterial growth in their urine. UTI in children can have long-term consequences that include renal scarring [32] with the potential development of hypertension and end-stage renal disease. Moreover, even in the absence of urinary tract anomalies, the recurrence rate for UTI in young children is substantial [33], which puts these children at increased risk from invasive illness and possible sepsis. While diagnosis is less complicated in adults, who usually report on symptoms related to the infection, evidence of high rates of antimicrobial resistance [34] is of concern for appropriate treatment [35], and we report on two adult female who had developed *E. coli* bacteraemia as a result of urinary tract infection. UTIs have received limited attention in the sub-Saharan African health systems, but this study along with evidence of similar or higher proportions of UTIs among febrile patients in nearby settings [9, 34] highlights the need for improved management of these infections.

Study limitations

Our laboratory methods were restricted to those available at the study hospital, and patients may have been infected with pathogens that were beyond the diagnostic ability of our laboratory. In particular, viral diagnostics could not be performed although viral infections probably caused the majority of fevers. As pathogen identification by use of multiplex polymerase chain reaction has been made possible, a number of studies have pointed at the importance of pathogens that were previously rarely considered as major causes of infectious diseases [7, 36, 37]. Still, our study offers insight on the prevalence of clinically important diagnoses that can be confirmed in a reasonably well-equipped laboratory in a sub-Saharan African hospital. Many of the study patients were enrolled on the basis of reported but not objective fever and this probably reduced the proportions of positive bacterial cultures. The identification of the causative pathogen in pneumonia is a clinical challenge and also a limitation of this study. Due to the frequent power interruptions not all children with pneumonia were X-rayed. Also, we cannot report on the sensitivity or specificity of the IMCI pneumonia algorithm as those who did not fulfil criteria for pneumonia were not X-rayed.

Conclusion

Our study presents a low prevalence of bacteraemia in Tanzanian outpatients and adds to the growing knowledge of aetiologies of non-malarial fevers in sub-Saharan Africa. Our results suggest that symptoms from the respiratory tract are the most frequently reported but many young children with WHO pneumonia have normal X-rays. While adult patients with bacteraemia presented with symptoms indicating bacterial illness, many children with bacteria in blood had no symptom that would lead to antibiotic treatment using the IMCI algorithm. Also, young children with UTI remain difficult to diagnose. Presumptive treatment of non-malarial fevers with antibiotics is likely to continue as long as there are no tools to assist the differentiation between bacterial and self-limiting viral infections.

Acknowledgements

We thank the patients and their guardians who kindly participated in this study. We are grateful to the staff at Joint Malaria Programme and St Augustine's (Teule) Hospital for their cooperation during the study. The following were involved in the clinical and laboratory data collection: Regina Malungu, HedwigaMrema, Selemani Mtunguja, Marwa Mwikwabe, Aikande Shoo, Selina Wycliffe, Juma Kimera, Agnes Mswaga, Benadina Ruta. HH was funded from the Swedish Research Council for Health, Working Life and Welfare/the European Commission under a COFAS Marie Curie Post-Doctoral Fellowship.

References

1. WHO. *Guidelines for the Treatment of Malaria*. Geneva: World Health Organization, 2010.
2. Feachem RG, Phillips AA, Hwang J *et al.* Shrinking the malaria map: progress and prospects. *Lancet* 2010: **376**: 1566–1578.
3. Reyburn H, Mbatia R, Drakeley C *et al.* Overdiagnosis of malaria in patients with severe febrile illness in Tanzania: a prospective study. *BMJ* 2004: **329**: 1212.
4. Mubi M, Kakoko D, Ngasala B *et al.* Malaria diagnosis and treatment practices following introduction of rapid diagnostic tests in Kibaha District, Coast Region, Tanzania. *Malar J* 2013: **12**: 293.
5. Nicastri E, Bevilacqua N, Sane Schepisi M *et al.* Accuracy of malaria diagnosis by microscopy, rapid diagnostic test, and PCR methods and evidence of antimalarial overprescription in non-severe febrile patients in two Tanzanian hospitals. *Am J Trop Med Hyg* 2009: **80**: 712–717.
6. Berkley JA, Lowe BS, Mwangi I *et al.* Bacteremia among children admitted to a rural hospital in Kenya. *N Engl J Med* 2005: **352**: 39–47.
7. Crump JA, Morrissey AB, Nicholson WL *et al.* Etiology of severe non-malaria febrile illness in Northern Tanzania: a prospective cohort study. *PLoS Negl Trop Dis* 2013: **7**: e2324.
8. Crump JA, Ramadhani HO, Morrissey AB *et al.* Invasive bacterial and fungal infections among hospitalized HIV-infected and HIV-uninfected children and infants in northern Tanzania. *Trop Med Int Health* 2011: **16**: 830–837.
9. D'Acremont V, Kilowoko M, Kyungu E *et al.* Beyond malaria–causes of fever in outpatient Tanzanian children. *N Engl J Med* 2014: **370**: 809–817.
10. Mahende C, Ngasala B, Lusingu J *et al.* Aetiology of acute febrile episodes in children attending Korogwe District Hospital in north-eastern Tanzania. *PLoS One* 2014: **9**: e104197.
11. Crump JA, Ramadhani HO, Morrissey AB *et al.* Invasive bacterial and fungal infections among hospitalized HIV-infected and HIV-uninfected adults and adolescents in northern Tanzania. *Clin Infect Dis* 2011: **52**: 341–348.
12. Nadjm B, Mtove G, Amos B *et al.* Severe febrile illness in adult hospital admissions in Tanzania: a prospective study in an area of high malaria transmission. *Trans R Soc Trop Med Hyg* 2012: **106**: 688–695.
13. Ishengoma DS, Mmbando BP, Segeja MD, Alifrangis M, Lemnge MM, Bygbjerg IC. Declining burden of malaria over two decades in a rural community of Muheza district, north-eastern Tanzania. *Malar J* 2013: **12**: 338.
14. WHO/UNICEF. *Integrated Management of Childhood Illness Chart Booklet*. Geneva: WHO/UNICEF, 2008.
15. WHO. Integrated management of adolescent and adult illness. Geneva: 2009 Contract No.: WHO/CDS/IMA I/2004.1.
16. WHO. Standardization of interpretation of chest radiographs for the diagnosis of pneumonia in children. Geneva: 2001 Contract No.: WHO/V&B/01.35.
17. Lambert SB, Whiley DM, O'Neill NT *et al.* Comparing nose-throat swabs and nasopharyngeal aspirates collected from children with symptoms for respiratory virus identification using real-time polymerase chain reaction. *Pediatrics* 2008: **122**: e615–e620.
18. Mtove G, Hendriksen IC, Amos B *et al.* Treatment guided by rapid diagnostic tests for malaria in Tanzanian children: safety and alternative bacterial diagnoses. *Malar J* 2011: **10**: 290.
19. Brent AJ, Ahmed I, Ndiritu M *et al.* Incidence of clinically significant bacteraemia in children who present to hospital in Kenya: community-based observational study. *Lancet* 2006: **367**: 482–488.
20. Takem EN, Roca A, Cunnington A. The association between malaria and non-typhoid Salmonella bacteraemia in children in sub-Saharan Africa: a literature review. *Malar J* 2014: **13**: 400.
21. Scott JA, Berkley JA, Mwangi I *et al.* Relation between *falciparum* malaria and bacteraemia in Kenyan children: a population-based, case-control study and a longitudinal study. *Lancet* 2011: **378**: 1316–1323.
22. Biggs HM, Lester R, Nadjm B *et al.* Invasive Salmonella infections in areas of high and low malaria transmission intensity in Tanzania. *Clin Infect Dis* 2014: **58**: 638–647.
23. Ao TT, Feasey NA, Gordon MA, Keddy KH, Angulo FJ, Crump JA. Global burden of invasive nontyphoidal Salmonella disease, 2010. *Emerg Infect Dis* 2015: **21**: 941–949.
24. WHO. *Pocket Book of Hospital Care of Children, Guidelines for the Management of Common Childhood Illnesses* Geneva: WHO, 2013.
25. Gove S. Integrated management of childhood illness: conclusions. WHO Division of Child Health and Development. *Bull World Health Organ* 1997: **75** (Suppl 1): 119–128.
26. Hazir T, Nisar YB, Abbasi S *et al.* Comparison of oral amoxicillin with placebo for the treatment of world health organization-defined nonsevere pneumonia in children aged 2-59 months: a multicenter, double-blind, randomized, placebo-controlled trial in Pakistan. *Clin Infect Dis* 2011: **52**: 293–300.
27. WHO. *Integrated Management of Childhood Illlness Chart Booklet*. Geneva: WHO, 2014.
28. Joffe MD & Alpern ER. Occult pneumococcal bacteremia: a review. *Pediatr Emerg Care* 2010: **26**: 448–454; quiz 55-7.
29. Alpern ER, Alessandrini EA, Bell LM, Shaw KN, McGowan KL. Occult bacteremia from a Pediatric Emergency Department: current prevalence, time to detection, and outcome. *Pediatrics* 2000: **106**: 505–511.
30. Lee GM, Harper MB. Risk of bacteremia for febrile young children in the post-Haemophilus influenzae type B era. *Arch Pediatr Adolesc Med* 1998: **152**: 624–628.
31. Wilkinson M, Bulloch B, Smith M. Prevalence of occult bacteremia in children aged 3 to 36 months presenting to the emergency department with fever in the postpneumococcal conjugate vaccine era. *Acad Emerg Med* 2009: **16**: 220–225.

32. Roberts KB. Urinary tract infections and renal damage: focusing on what matters. *JAMA Pediatr* 2014: **168**: 884–885.
33. Schlager TA. Urinary tract infections in children younger than 5 years of age: epidemiology, diagnosis, treatment, outcomes and prevention. *Paediatr Drugs* 2001: **3**: 219–227.
34. Msaki BP, Mshana SE, Hokororo A, Mazigo HD, Morona D. Prevalence and predictors of urinary tract infection and severe malaria among febrile children attending Makongoro health centre in Mwanza city, North-Western Tanzania. *Arch Public Health* 2012: **70**: 4.
35. Blomberg B, Manji KP, Urassa WK *et al.* Antimicrobial resistance predicts death in Tanzanian children with bloodstream infections: a prospective cohort study. *BMC Infect Dis* 2007: **7**: 43.
36. Manock SR, Jacobsen KH, de Bravo NB *et al.* Etiology of acute undifferentiated febrile illness in the Amazon basin of Ecuador. *Am J Trop Med Hyg* 2009: **81**: 146–151.
37. Suttinont C, Losuwanaluk K, Niwatayakul K *et al.* Causes of acute, undifferentiated, febrile illness in rural Thailand: results of a prospective observational study. *Ann Trop Med Parasitol* 2006: **100**: 363–370.

Corresponding Author Helena Hildenwall, Global Health – Health Systems and Policy, Department of Public Health Sciences, Karolinska Institutet, SE-171 77 Stockholm, Sweden. E-mail: Helena.Hildenwall@ki.se