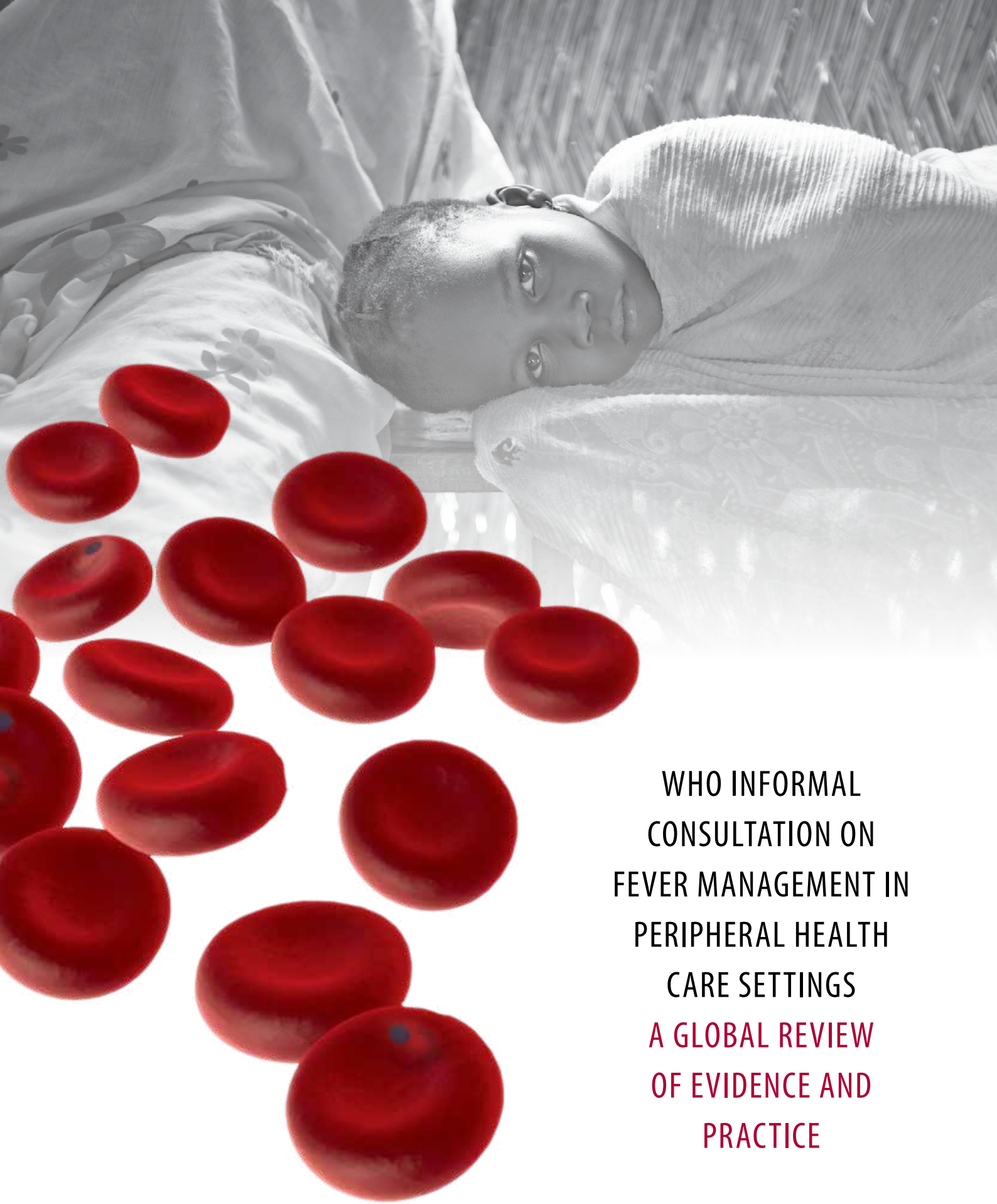


WHO INFORMAL CONSULTATION ON FEVER MANAGEMENT IN PERIPHERAL HEALTH CARE SETTINGS

A GLOBAL REVIEW OF EVIDENCE AND PRACTICE

TDR For research on diseases of poverty
UNICEF • UNDP • World Bank • WHO

World Health Organization

WHO informal consultation on fever management in peripheral health care settings: a global review of evidence and practice

TDR For research on diseases of poverty
UNICEF • UNDP • World Bank • WHO

World Health Organization

WHO Library Cataloguing-in-Publication Data

WHO informal consultation on fever management in peripheral health care settings: a global review of evidence and practice.

1.Malaria – diagnosis. 2.Fever – etiology. 3.Diagnosis, Differential. 4.Anti-bacterial agents. 5.Antimalarials. 6.Inappropriate prescribing. 7.Disease management. 8.Primary health care. 9.Community health centers. I.World Health Organization.

ISBN 978 92 4 150648 9 (NLM classification: WB 152)

© World Health Organization 2013

All rights reserved. Publications of the World Health Organization are available on the WHO web site (www.who.int) or can be purchased from WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland (tel.: +41 22 791 3264; fax: +41 22 791 4857; e-mail: bookorders@who.int).

Requests for permission to reproduce or translate WHO publications – whether for sale or for non-commercial distribution – should be addressed to WHO Press through the WHO web site (www.who.int/about/licensing/copyright_form/en/index.html).

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by the World Health Organization to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the World Health Organization be liable for damages arising from its use.

Cover photograph: © 2008 Pierre Holtz/UNICEF
Red blood cells: © Ingram Publishing

Printed in Malta

Contents

Acknowledgements v
Abbreviations and acronyms vii
Glossary viii
Executive summary 1
1. Background 4
2. Causes and management of febrile illness 6
2.1 Evidence for causes of non-malaria febrile illness 6
2.2 Considerations on studies on the causes of fever 10
2.3 New evidence on effective management of malaria and non-malaria febrile illness 12
2.4 Considerations on studies of effective management of febrile illness 13
3. WHO guidelines and tools for the management of fever 15
3.1 Current WHO guidelines 15
3.2 WHO recommendations for management of fever in adolescents and adults 18
3.3 Implementation of WHO guidelines at country level 21
3.4 New rapid diagnostic tests 22
3.5 Medicines 22
3.6 Considerations on and recommendations for improving existing tools 27
4. Experiences of agencies and nongovernmental organizations with integrated community case management 24
4.1 iCCM Task Force 24
4.2 Results of operational research 24
4.3 Successes in and challenges to scaling-up iCCM in countries 27
5. Public sector experience with community management of fever 29
5.1 Malawi 29
5.2 Senegal 30
5.3 Uganda 30
5.4 Discussion of country experience 33
6. Private for-profit sector experience in community management of fever 35
7. Moving forward: research priorities 40
7.1 Management of fever in children and adults living in various geographical areas 40
7.2 Diseases to be included in adaptations of IMCI, IMAI and other fever management algorithms 42

7.3 Available point-of-care tests for identifying pathogens or host biomarkers for inclusion in fever management algorithms 43
7.4 Febrile patients who would benefit from antibiotic treatment 45
7.5 Use of iCCM programmes to strengthen quality of care and use of IMCI at public and private health facilities 45
8. Key recommendations 47
9. References 48
Annex 1. Management of malaria and non-malaria fever at peripheral level: preliminary review of the evidence 52
A1. Definitions of malaria and non-malaria fever 52
A2. Incidence of fever 52
A3. Treatment-seeking behaviour and malaria testing 53
A4. Adherence of health workers to results of malaria rapid diagnostic tests 57
A5. Fever and associated symptoms 58
A6. Causes of fever 60
A7. Outcomes of patients with non-malaria fever 63
A8. Medicines prescribed to patients with malaria and non-malaria fever 64

Acknowledgements

Preparation of this document was led by the Global Malaria Programme (GMP) with the precious collaboration of the Special Programme for Research and Training in Tropical Diseases (TDR). It was planned in collaboration with several WHO departments, including Maternal, Newborn, Child and Adolescent Health (CAH), HIV/AIDS, Essential Medicines and Health Products (EMP). The contributions of the following WHO colleagues were particularly important (in alphabetical order): Andrea Bosman (GMP), Jane Cunningham (GMP), Elizabeth Mathai (EMP), Josephine Namboze, WHO Regional Office for Africa, Robert Newman, Director GMP, Franco Pagnoni (GMP), Shamim A. Qazi (CAH), John C. Reeder, Director TDR, Johannes Sommerfeld (TDR), Krisantha Weerasuriya (EMP), Cathy Wolfheim (CAH) and Wilson Were (CAH). Valérie D'Acremont, Swiss Tropical and Public Health Institute (WHO consultant) was the main technical resource person during all phases of the meeting, from the preparatory phase, to the summary of published evidence given to all participants before the meeting (Annex 1), to her helpful contributions to the discussions and deliberations at the meeting, the summary of the main areas of consensus and close involvement in preparation of the final report.

The meeting benefited from sound technical presentations and discussion by the invited experts: Phyllis Awor (Makerere University, Uganda), Lawrence Barat (United States Agency for International Development and the President's Malaria Initiative, USA), David R. Bell (Foundation for Innovative New Diagnostics, Switzerland), Zulfiqar Ahmed Bhutta (The Aga Khan University, Pakistan), Anders Bjorkman (Karolinska Hospital, Sweden), Deborah C. Burgess (Bill & Melinda Gates Foundation, USA), John A. Crump (University of Otago, New Zealand), Valerie D'Acremont (Co-rapporteur, Swiss Tropical and Public Health Institute and WHO consultant, Switzerland), Sandra Gove (former WHO staff member, USA), David Hamer (Chairperson, Zambia Centre for Applied Health Research and Development, Zambia), Sim Kheng (National Centre for Parasitology, Entomology and Malaria Control, Cambodia), Ramanan Laxminarayan (Resource for the Future, USA), David Marsh (Co-Chairperson, Save the Children, USA), Saul Morris (Bill & Melinda Gates Foundation, USA), Humphreys Nsona (Ministry of Health, Malawi), Stefan Peterson (Karolinska Institute, Sweden), Jesca Nsungwa-Sabiiti (Ministry of Health, Uganda), David Schellenberg (London School of Hygiene and Tropical Medicine, United Kingdom), Marème Sougou (Ministry of Health, Senegal), Kirsten Vannice (Rapporteur, USA), Cathy Wolfheim (former WHO staff member, Switzerland) and Mark W. Young (UNICEF, USA).

The meeting attracted major interest, and several people attended the meeting as observers, also offering helpful insights during the discussions: Franco Ciro (Management Sciences for Health, USA), John R. Cutler (UNITAID, Switzerland), Iveth Gonzalez (Foundation for Innovative New Diagnostics, Switzerland), Penny Grewal (Medicines for Malaria Venture, Switzerland), Heidi Hopkins (Foundation for Innovative New Diagnostics, Switzerland), Pierre Hugo (Medicines for Malaria Venture, Switzerland), Enric Jane (Bill & Melinda Gates Foundation, USA), Sibylle Koenig (European Union, Belgium), Troy Martin (MalariaCare Project, USA), Jane Miller (Population Services International, Kenya), Sigsbert Mkude (Ministry of Health, United Republic of Tanzania), Eric Mouzin (Roll Back Malaria, Switzerland), Rory Nefdt (UNICEF, Eastern and Southern African Region, Kenya), Nora Petty (Clinton Health Access Initiative, Uganda), Hugh Reyburn

(London School of Hygiene and Tropical Medicine, United Kingdom), Tanya Shewchuck (Population Services International, Kenya), Elizabeth Streat (Malaria Consortium, Uganda), Shunmay Yeung (London School of Hygiene and Tropical Medicine, United Kingdom) and Ambachew M. Yohannes (UNITAID, Switzerland).

In addition to the co-chairpersons, the meeting was facilitated by moderators assigned to specific sections. They not only contributed to preparation of the meeting but also moderated the discussions, which enriched their quality and depth. For additional work, the specific contributions of Lawrence Barat, David Hamer, David Marsh, Saul Morris, David Schellenberg, Cathy Wolfheim and Stefan Peterson are gratefully acknowledged. The two rapporteurs, D'Acremont and Kirsten Vannice, completed the report highly professionally, to reflect the rich body of evidence and experience that were shared at the meeting. Input to the draft report was also provided by Phyllis Awor, Andrea Bosman, David Bell, Anders Bjorkman, John A. Crump, David Hamer, Sandra Gove and David Schellenberg. The final version of the report was reviewed by Valérie D'Acremont, Andrea Bosman, Robert Newman and Kirsten Vannice.

The consultation was made possible through funding from the United States Agency for International Development (USAID), and through the European Union, through a Contribution Agreement to the Special Programme for Research and Training in Tropical Diseases (TDR).

Abbreviations

ACT	artemisinin-based combination therapy
ALMANACH	ALgorithm for the MANAgement of CHildhood illness
ARI	acute respiratory infection
CHW	community health worker
iCCM	integrated community case management
IMAI	integrated management of adolescent and adult illness
IMCI	integrated management of childhood illness
PCR	polymerase chain reaction
RDT	rapid diagnostic test
WHO	World Health Organization

Glossary

Chronic carriage	Long-term presence of a pathogen that is not causing illness
Colonization	Short-term presence of a pathogen that is not causing illness
Disease (infectious)	Presence of symptoms and signs (illness) due to, or considered to be due to, a pathogen, whether documented or not
Infection	Presence of a pathogen that is not necessarily causing illness but may do or has done. The pathogen is thus not necessarily the direct cause of the present illness.
Nonspecific fever	Acute febrile illness with no sign or symptom of localized infection
Polymerase chain reaction	In this report, refers to nucleic acid amplification tests in general

Executive summary

Following the WHO recommendation in 2010 that all patients suspected of having malaria should be tested before treatment, rapid diagnostic tests (RDTs) are being used increasingly. As a result, health workers face the challenge of managing febrile illness when the test result is negative. To improve the compliance of health workers with malaria test results, guidance is needed on managing non-malaria febrile illness, especially in peripheral health care facilities. Improving the management of fever not only reduces unnecessary use of antimalarial drugs, but also ensures appropriate treatment and referral of patients with non-malaria febrile illness, thus reducing morbidity and mortality. In this context, the WHO Global Malaria Programme and the Special Programme for Research and Training in Tropical Diseases convened a meeting in January 2013 to review evidence and current recommendations for the management of fevers at primary health care and community levels, to promote integrated management of fevers and to identify major research gaps in this area.

In order to treat non-malaria febrile illness properly, the pathogens causing the febrile illnesses must be identified. The results of recent studies on the causes of fever show similar findings, even though the distribution of diseases varies by geography and season, the age and immunity of the patient and the level of care. More than half of all young febrile children seen at peripheral health facilities suffer from acute respiratory infections (ARIs), but only a small proportion have radiologically confirmed pneumonia. Furthermore, 10–25% of children have gastroenteritis, while other localized infections, such as meningitis and skin or soft tissue infections, account for < 5% of episodes. The remaining children with fever have no localizing signs of infection, and suffer from urinary tract infections (1–6%) and enteric fever (2–10%), while occult bacteraemia is rare (< 2%). Several studies have confirmed that viral infections are responsible for a high proportion of cases of febrile illness in outpatients. In hospitalized older children and adults, fevers are often associated with HIV-induced immunosuppression and, in addition to ARI, several diseases due to environmental and occupational exposure, such as leptospirosis, rickettsiosis, scrub typhus and brucellosis. Dengue is an important cause of febrile illnesses in Asia and less frequent in Africa, while chikungunya (reported during epidemics in Africa) has been documented for the first time in northern United Republic of Tanzania in febrile patients during inter-epidemic periods. There is thus considerable variation in the prevalence of fever-inducing diseases, and more studies on the causes of fever are needed to guide clinicians and to provide evidence for country adaptations of clinical algorithms for the management of fever, in particular in primary health care facilities. Considerations on the design, case definitions and outcome measures for future studies on the causes and management of fever were discussed in detail.

Emerging evidence on the effective management of malaria and non-malaria febrile illnesses shows that withholding antimalarial drugs from patients with a negative RDT result is safe, even for children living in areas highly endemic for malaria. Use of the "integrated management of childhood illness" (IMCI) algorithm reduces unnecessary antibiotic treatment in the majority of cases, yet still leads to some over-treatment because of the poor specificity of the respiratory rate to diagnose pneumonia in patients with cough or difficult breathing. Recent studies have also shown that severe (but not very severe) pneumonia can be managed safely at community level.

Other studies have shown that clinical algorithms that differentiate between enteric fever that is probably resistant to antibiotics and that which is sensitive lead to high cure rates, limiting the number of second- and third-line treatments prescribed. All these studies confirm that malaria diagnostic testing and treatment should be part of an integrated approach to the management of febrile illnesses in both children and adults.

Several WHO guidelines and tools for the management of fevers are available, covering different age groups and levels of care. All the guidelines are based on an integrated approach, in line with the latest recommendations for malaria diagnosis and treatment; the only exception is the acute care algorithm for integrated management of adolescent and adult illnesses (IMAI), which is being updated. Considerations on the best way to implement the guidelines were discussed, in particular promotion of the core elements of integrated community case management (iCCM) for children presenting with acute fever, cough or diarrhoea. New point-of-care tests to detect pathogens or host biomarkers are needed, but their integration into clinical algorithms should be based on evidence of clinical benefit rather than simply on their availability or their diagnostic performance. Clinicians should be given precise guidance on which patients to test with a new tool, and incentives should be found for health workers to adhere to guidelines and test results.

A review of the literature and recent operational research findings on iCCM suggest that provision of antimalarial drugs at community level can decrease mortality, but there is limited evidence of an effect on the use of antibiotics. In all studies, community health workers (CHWs) adhered well to malaria test results in deciding whether to prescribe antimalarial drugs. Use of the respiratory rate to diagnose pneumonia and to prescribe antibiotics varied, while CHWs in all settings had difficulty in identifying danger signs, especially in newborns. Well-implemented iCCM programmes were shown to change health care-seeking behaviour, and these could be scaled up nationally with support from the iCCM Task Force. Successes of and challenges to implementation in the public sector were discussed on the basis of experience in Malawi, Senegal and Uganda. Some problems were found in the continuum of care, sometimes resulting in back-referral of patients from health facilities to CHWs. iCCM programmes can help to strengthen the quality of care in health facilities, particularly in primary health care centres. Many programmes reported difficulties with regard to supervision, supply chains, monitoring, surveillance and retaining human resources. The best strategies for improving these aspects of programmes should be investigated, including potential use of e-health.

Successful pilot projects of iCCM introduction in the private for-profit sector in Uganda and the United Republic of Tanzania suggest that the private for-profit sector could deliver iCCM. Cambodia, which has a 10-year experience with use of artemisinin-based combination therapy (ACT) and RDTs in the private sector, found problems in supervision and monitoring, resulting in poor quality of care. Because of lack of guidance on the management of non-malaria febrile illness, cocktails of several medicines, including antibiotics, are sold in the private sector to most patients. Programmes to improve the quality of malaria case management in the private sector should thus also include the diagnosis and treatment of common non-malaria causes of fever. The challenges are similar to those in the public sector, and involvement of the community is a key element, as shown in iCCM programmes. Communities are sensitive to branding and official accreditation and appreciate good quality of care; therefore, their capacity should be strengthened through health education.

Several research priorities should be pursued, in particular on the distribution of the causes of fever in children and adults living in various geographical areas, the criteria for inclusion of additional diseases in improved IMCI and IMAI fever algorithms, the point-of-care tests required for each level of care, patients who would benefit from antibiotic treatment (to save lives while reducing the spread of antibiotic resistance), use of iCCM programmes to strengthen the quality of care and use of IMCI in public and private health facilities. When possible, clinical outcomes (e.g. cure

rate at day 7) should be chosen as the main study end-points to ensure that clinical benefits guide the development of new recommendations.

On the basis of the review of the evidence, current recommendations and field and country experiences, seven main recommendations for the management of fever in peripheral health care facilities are proposed as the conclusions of the meeting.

- Diagnostic testing and treatment for malaria should be deployed as part of programmes promoting the integrated management of febrile childhood and adult illnesses.
- Evidence and lessons learnt from implementation should be taken into account in scaling- up iCCM at community level and IMCI and IMAI at health facility level.
- The essential elements of the generic iCCM algorithm should remain unchanged in country adaptations.
- A continuum of care is important in the management of fever. Therefore, iCCM should be accompanied by strengthening of the quality of care in both health centres and hospitals.
- Programmes aiming to improve the quality of malaria case management in the private sector should include the diagnosis and treatment of common non-malaria causes of fever.
- Carefully standardized studies of various diseases and pathogens implicated in the causation of fever, including susceptibility to antimicrobial agents, should be undertaken at different levels of health care and in different epidemiological settings, seasons and age groups.
- Research on new strategies for effective diagnostic testing and treatment of febrile illness should be encouraged, with clinical outcomes as the primary end-points. The results could be used to adapt IMCI and IMAI, by modifying or extending the diseases in the current WHO algorithms on the basis of health care needs.

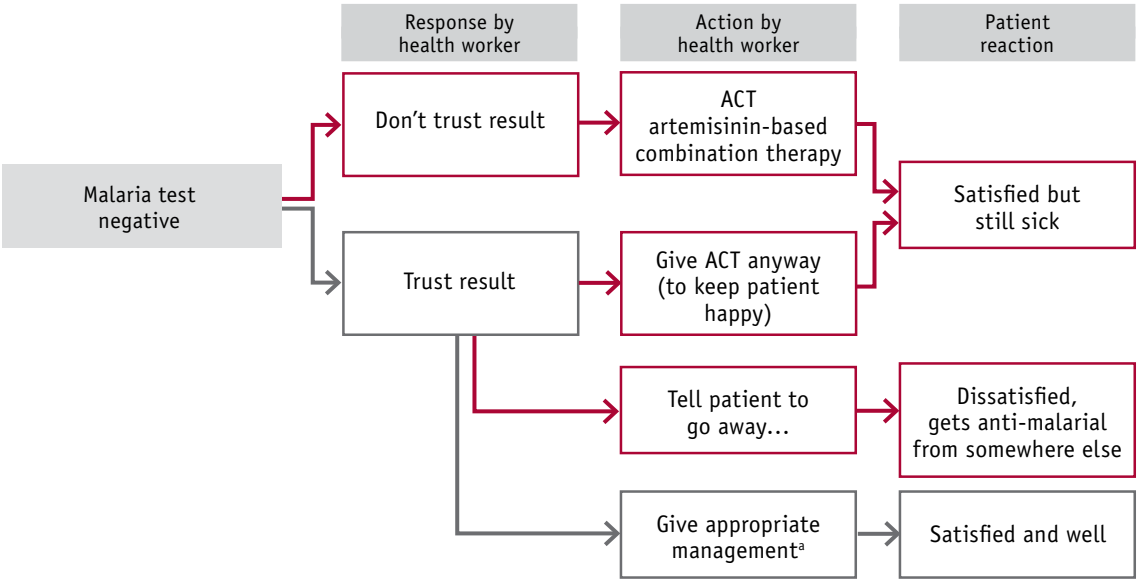
1. Background

Use of ACT to treat malaria has increased significantly in recent years, with an estimated 278 million doses administered in 2011 (WHO, 2012). Use of malaria RDTs has also increased, although to a lesser extent. Microscopy is still used frequently in diagnosing malaria, but widespread use of RDTs has raised the challenge of deciding on the proper treatment of febrile illness when the RDT result is negative (**Figure 1**). Several studies have documented use of antimalarial agents to treat patients with negative RDT results, which undermines the clinical benefits of parasitological confirmation of diagnosis, exacerbates the wastage of antimalarial drugs and increases drug pressure on malaria parasites. There is, however, some evidence that the situation is improving with the development of a new 'diagnostic culture' (see **Chapter 4** and **Figure 4A** in **Annex 1**).

In some settings, use of malaria RDTs has reduced the consumption of antimalarial medicines and increased the use of antibiotics, (Msellem et al., 2009; D'Acremont et al., 2011; Batwala et al., 2011) replacing the problem of misuse of antimalarial agents by misuse of antibiotics. Antibiotics may be an easy default treatment, but they are inappropriate for most patients who will not benefit from them (apart from those with severe disease), and their use accelerates the development of antimicrobial resistance. In order to provide evidence-based guidance on the management of febrile patients, better understanding is required of the burden of acute febrile illnesses in populations and individual patients, the aim being to predict successful treatment, improve health outcomes, reduce the prevalence of severe disease and death and maintain drug effectiveness.

FIGURE 1.

Choices faced by health care workers when the result of a malaria RDT is negative



Red indicates not recommended actions/behaviours.

[a] Treatment for cause other than malaria; explanation of result of malaria test and final diagnosis; counselling on when to return to health facility.

To help health workers to respond appropriately to malaria test results, they need guidance on managing febrile illness associated with malaria and with other illnesses. Clear algorithms for the management of fevers at community level have been prepared for children under the age of 5 years, which are promoted as iCCM (WHO, 2011a), with good support tools. Tools are also available for peripheral health facilities for managing fever in children under 5 (IMCI) (WHO and UNICEF, 2008) and adolescents and adults (IMAI) (WHO, 2011b). Guidance on fever management, updated with new evidence, responds to only part of the challenge. Obstacles remain in access to good clinical management of febrile illness at both community and health facility level and in the private sector, from which a large proportion of the population around the world seeks antimalarial treatment.

The WHO Global Malaria Programme and the Special Programme for Research and Training in Tropical Diseases held a meeting on 22–24 January 2013, with the following objectives:

- to review the evidence and current WHO recommendations for management of fever in primary care and in the community;
- to make practical recommendations and provide operational tools based on successful country experience in the integrated management of fevers in peripheral health facilities and the community;
- to identify research gaps in the management of fevers in children and adults at peripheral level; and
- to collate the information generated by the consultation into a practical document to guide programme managers, researchers and funding agencies.

Improving the management of fever at the peripheral level will promote appropriate treatment and referral and thus reduce the occurrence of severe disease and death. It will also reduce unnecessary prescription of antibiotics and antimalarial agents, thus reducing drug pressure and the development of drug resistance, decrease the risks for adverse effects of the drugs and save money.

2. Causes and management of febrile illness

2.1 Evidence for causes of non-malaria febrile illness

In order to treat non-malaria febrile illness properly (keeping in mind that patients may have malaria concurrently with another disease, especially in highly endemic areas), the pathogens that cause febrile disease must be known. Even if the agent is not identified, knowing the category of pathogen (parasitic, bacterial or viral) is useful for deciding on treatment. The incidence of disease and the prevalence of various pathogens vary by factors such as location, season and urban or rural setting. The age and immunity of patients and their access to different levels of care (reflecting progression to severe disease) also contribute to the distribution of diseases. Although some similarities are seen across settings, more studies are needed in order to increase the geographical specificity of recommendations.

Studies conducted so far have shown that most (50–75%) febrile episodes in children under 5 years of age presenting at outpatient clinics are associated with ARI (D'Acremont et al., 2013; Björkman et al., unpublished study; Bhutta et al., unpublished study). Only about one fourth of these cases, however, present with clinical pneumonia as defined in the IMCI algorithm, and only a small proportion have radiologically confirmed pneumonia (approximately 5% in all studies). A smaller proportion of fevers (10–25%) are associated with gastroenteritis, while other localized infections, such as meningitis and skin or soft tissue infections, account for < 5%. The remaining episodes present as nonspecific fever, including that due to urinary tract infections, which account for only 1–6% of cases and are limited to very young children, and occult bacteraemia (positive blood culture with no clear, localized source of infection), which is rare (< 2%). Certain diseases are site-specific, with variable proportions due to malaria (0.4–12% in the available studies) and typhoid (2–10%), depending on the local transmission level (D'Acremont et al., 2013; Björkman et al., unpublished study; Bhutta et al., unpublished study). Regarding the type of pathogen, all studies confirm that viral agents cause a high proportion of cases of ARI, although documentation of an infection does not necessarily mean that it is the direct or only cause of an acute episode.

In hospitalized older children and adults, non-malaria febrile illness is often associated with immunosuppression due to HIV infection. In a study of a population with a 3% HIV seroprevalence, 40% of adult hospital admissions for severe febrile illness were in HIV-infected individuals (Crump et al., 2013). Specific infections, such as lepto-spirosis, rickettsiosis, scrub typhus and brucellosis, tend to be more prevalent among adolescents and adults, possibly due to environmental and occupational exposure to pathogens and vectors, such as in forests and from livestock. Specific infections, such as leptospirosis, rickettsiosis, scrub typhus and brucellosis, tend to be more prevalent among adolescents and adults, possibly due to environmental and occupational exposure. Dengue is frequent in studies conducted in Asia (Mayxay et al., 2013) but relatively infrequent in Africa, while chikungunya was reported in the northern part of the United Republic of Tanzania (Crump et al., 2013) but was not searched for in studies on the causes of fever conducted in Asia.

In these studies, most pathogens were identified by either polymerase chain reaction (PCR) or serology. The main limitation of highly sensitive PCR for detecting pathogens in the respiratory tract is its lack of specificity for some organisms. When the results of PCR on samples from febrile patients are compared with those for a control group with either other documented diseases or

who have no symptoms, clear differences in the prevalence of pathogens are not always found, with large variation according to the pathogen (Feikin et al., 2012, 2013). PCR is more specific on blood samples, and is generally highly sensitive for viruses and less sensitive for bacteria; with stool samples, little difference is seen in the prevalence of pathogens detected by PCR between symptomatic and asymptomatic patients.

The specificity of serology is problematic, as antibodies, including immunoglobulin M, persist for some time after an acute episode. This limitation affects estimates of the prevalence of dengue and chikungunya. Furthermore, both serological assays and bacterial PCR methods performed on blood often lack sensitivity. Serological results based on a fourfold rise in titre are generally more reliable but require access to convalescent sera, which might be difficult to obtain, especially at outpatient visits. Laboratory data should therefore always be interpreted in the context of the clinical presentation of patients, and studies on the causes of non-malaria fever should be carefully designed to avoid overestimation of the prevalence and the public health importance of certain pathogens. Use of a control group of asymptomatic individuals can help ensure proper interpretation of laboratory results.

Individual studies

D'Acremont et al. (2013) studied the causes of fever episodes in 1005 children under 10 years of age (of whom 94% were under 5) living in urban and rural United Republic of Tanzania and attending two outpatient clinics. After a full clinical assessment, children with a temperature ≥ 38 °C were examined by chest radiography, and samples were taken for testing with RDTs, for blood, urine and stool culture, for biochemistry, for PCR and for serology to test for a number of pathogens in order to identify the cause of the fever. All investigations were performed according to algorithms, and a diagnosis was computer-generated for each patient. On the basis of the clinical presentations and 25 743 laboratory and radiological investigations, 1232 diagnoses were established, 22.6% of children having more than one diagnosis. ARI was diagnosed in 62% of the children, of whom 5% had radiological pneumonia, 13% a systemic bacterial, viral or parasitological infection (other than malaria or typhoid), 12% a viral infection in the nasopharynx, e.g influenza (without respiratory symptoms or signs), 11% malaria, 10% gastroenteritis, 6% urinary tract infection, 4% typhoid fever, 2% a skin or mucosal infection and 0.2% meningitis. No diagnosis could be made for 3% of the children. A viral disease was found in 71% of the 1005 children (the five most frequent being influenza, rhinovirus, adenovirus, human herpesvirus 6 and coronavirus), 22% a bacterial disease (urinary tract infection, typhoid fever, skin or mucosal purulent infection, bacterial gastroenteritis or occult bacteraemia) and 11% a parasitic disease (malaria, toxoplasmosis or amoebic gastroenteritis). Samples were tested by PCR for vector-borne diseases such as dengue, chikungunya and West Nile and Rift Valley fever, but none tested positive. Nasopharyngeal samples were positive by PCR for at least one virus in 80% of the children with ARI and for *Streptococcus pneumoniae* in 87%. Influenza and parainfluenza viruses were more prevalent in children with ARI than in those with other conditions, but the viral loads (assessed by semi-quantitative PCR) were similar in the two groups. In contrast, the load of pneumococcus (assessed by quantitative PCR) was significantly higher in children with ARI than in those with other diagnoses and in children with severe pneumonia than in children with upper respiratory tract infection. There was, however, significant overlap, and no predictive threshold could be set to differentiate these syndromes. None of the host biomarkers tested to differentiate between bacterial and viral disease performed well enough to be used alone, but some were promising when used in combination. Among other predictors of various causes of fever, age was the strongest; e.g. 83% of urinary tract infections were seen in children under 2 years of age, while 73% of typhoid episodes were seen in children over 2 years of age.

In this study, therefore, more than half the cases of fever in children were due to ARI, one fourth of which were due to influenza, and 81% of the children were infected with one or more viruses. Malaria (diagnosed in 9% of cases), urinary tract infections (5% of cases) and typhoid (3% of

cases) were less prevalent than generally expected by clinicians in Africa. Ubiquitous viral and bacterial diseases were more prevalent than those caused by tropical vector-borne pathogens. Children rarely had more than one significant disease at a time.

Shamim A. Qazi presented a review of studies on causes and severity of pneumonia seen in peripheral health facilities. Viruses were the commonest cause of pneumonia, although bacteria were more often the cause of severe pneumonia. In 20–60% of cases, the cause remained unknown. The bacteria responsible for most cases of pneumonia were *S. pneumoniae*, *Haemophilus influenzae* and *Staphylococcus aureus*. In HIV-positive children, the main causes of severe pneumonia were *Pneumocystis jiroveci* and *S. aureus*, with cytomegalovirus in fatal cases. The rate of tuberculosis was also relatively high in HIV-positive children. Chest radiographs are considered the gold standard for the diagnosis of pneumonia; however, identification of the cause of radiologically confirmed pneumonia remains difficult, as bacteraemia is found in only 5–20% of cases, and isolation of a viral pathogen in the nasopharynx is not a definitive diagnosis as viral infections can occur concomitantly with or precede bacterial infections.

The results of unpublished studies conducted by Bhutta and colleagues in Pakistan on the diagnosis of fever in children at the community level were also presented. Analysis of blood culture isolates in the late 1990s revealed a high proportion of *Salmonella enterica* serovar *Typhi* and *Paratyphi* (about 50% of all blood cultures). A study in 2000–2001 addressed the causes of fever in patients of all ages who presented at a small clinic. A full blood count, blood cultures, RDT for typhoid fever, RDT and blood film for malaria, urinalysis and chest radiography (the last only in patients with suspected pneumonia) were performed. Dengue immunoglobulin M was tested in a subset of patients with nonspecific fever and suspected viral infection. The three commonest causes of 1248 febrile episodes were ARI (47%), diarrhoea or dysentery (23%) and enteric fever (17%). Bacteraemia (other than *Salmonella Typhi* or *Paratyphi*) was found in 2% of cases, urinary tract infection in 0.5% and malaria in 0.4%. Of 112 probable viral infections, about one half were dengue. In a study in 2003–2005, blood from 6850 patients with prolonged fever was tested, showing an adjusted incidence rate of enteric fever of 795 episodes per 100 000 person-years in children aged 2–15 years. About half (54%) of the *Salmonella* isolates had reduced susceptibility to ciprofloxacin, and 66% were resistant to chloramphenicol, ampicillin and co-trimoxazole; multi-drug resistance was associated with a more severe clinical presentation of typhoid. In rural Pakistan, the estimated incidence of typhoid in children under 5 years was 405 episodes per 100 000 person-years. In children under 1 year, the incidence per 100 person-years was 39 for severe pneumonia, 7 for malaria and 1 for nonspecific fever. The study showed that the incidence of febrile illness among Pakistani children under 5 years of age is high, with large differences in incidence and cause between urban and rural settings.

David R. Bell reported the results of studies on non-malaria febrile illnesses in South-East Asia. In two sites in the Lao People's Democratic Republic (Mayxay et al., 2013), febrile patients aged 5 years and older with no identified site of infection (abscess or severe diarrhoea) were tested for malaria, bloodstream infection, melioidosis, leptospirosis, dengue, Japanese encephalitis, influenza and rickettsial infection. The tests used included blood films and cultures, malaria RDTs, PCR and serological tests. Nearly 2000 cases were identified at the study sites in 2008–2010. Clinically, a substantial proportion of patients had respiratory symptoms, diarrhoea or neck stiffness. The pathogen was identified in 41% of patients; scrub typhus (26% of cases), dengue (25%) and Japanese encephalitis (21%) were the commonest diseases, the frequency varying by site. Some known clinical predictors of these diseases were well correlated with the laboratory diagnoses. In view of the pathogens identified, 12% of the patients would theoretically have responded to treatment with doxycycline and 13% to azithromycin.

In Cambodia, 1193 febrile patients and 282 controls were tested for malaria, leptospirosis, rickettsial diseases, scrub typhus, dengue, influenza and bacteraemia (Newton et al., *unpublished*

study). No pathogen was found in about one fourth of the cases. *Plasmodium vivax* and *P. falciparum* were the most frequent pathogens identified with PCR, followed by Leptospira, influenza virus, dengue virus and the bacterium that causes scrub typhus. Both dengue and influenza were highly seasonal. Malaria RDTs were positive in 32% of patients. The clinical manifestations of the non-malaria fevers were upper respiratory tract infection in 76% of cases, lower respiratory tract infection in 0.6% and 'enteric fever' (based on signs and symptoms) in 17%. The prevalence of pathogens detected by PCR between patients presenting with these syndromes and healthy controls differed but to a lesser degree than expected, indicating that these organisms may be present in the absence of disease. Some of the organisms identified were unrelated to the clinical syndrome observed; thus, most of the signs and symptoms were nonspecific. The concentration of C-reactive protein was generally higher in patients with bacterial disease or malaria than in those with viral disease. Because of significant overlap, however, this marker was not a useful predictor of bacterial infection. The paper concluded that the more specific the diagnostic strategy (clinical algorithms < screening at population level < markers of severity or responsiveness to treatment < pathogen-specific point-of-care tests), the more expensive tests will be. Therefore, the introduction of expensive tests should be guided by cost–benefit analyses, the prevalence of diseases of public health importance and the available treatment regimens. Moreover, pathogen-specific tests to guide antibiotic use should be complemented by tests to guide the choice of treatment on the basis of drug sensitivity (e.g. class of antibiotics).

Preliminary results from an unpublished study by Björkman and colleagues on the causes of fever in children aged 2–59 months attending a district hospital and a health centre in Zanzibar, United Republic of Tanzania, were presented. Of the children enrolled, 677 were febrile and 200 were controls who had been healthy for the preceding month. According to the IMCI classification, an ARI was diagnosed in 65% of the patients, of whom 57% had pneumonia, 9% tonsillitis, 4% ear infection and 31% other types of ARI. A viral cause was found for 54% of children with ARI and a bacterial cause for 12%; the cause was not identified for 18%. The virus most frequently identified was respiratory syncytial virus (16%), followed by influenza A and B (9%) and rhinovirus (9%). Watery diarrhoea was observed in 26%, dysentery in 2%, stomatitis in 2% and skin infection in 5%; malaria was found in only 0.2% of cases. In the gastrointestinal infections, the most frequent pathogen found by conventional methods was *Shigella* (3%), followed by *Cryptosporidium*. PCR testing of samples from 165 febrile children with diarrhoea and from 165 asymptomatic controls showed significant differences in the presence of some pathogens (e.g. norovirus in 20% of cases and 2% of controls) but not others (e.g. *Shigella* in 35% of cases and 33% of controls). The viral and bacterial loads determined by semi-quantitative PCR were generally significantly higher in cases than in controls, but the overlap was substantial. When the results were compared with the final diagnosis, the sensitivity of IMCI criteria for identifying children who required antibiotics was 88%, while the specificity was only 30%. Of 16 children with a documented diagnosis of bacterial infection but who did not receive antibiotics, none developed severe disease. Two children died despite having received antibiotics on day 0; in both, a respiratory virus was identified in a respiratory sample. The conclusion of the study was that the IMCI algorithm should be improved to ensure identification of children who require antibiotics but is reasonably accurate for identification of severe disease and referral.

Crump et al. (2013) studied the causes of febrile illness among hospitalized paediatric and adult patients in two hospitals in northern United Republic of Tanzania in 2007 and 2008. A standardized clinical history was taken, a physical examination and chest radiography were conducted, samples were taken, and discharge or death forms were completed; all surviving participants were asked to return 4–6 weeks after admission for collection of convalescent serum, in order to demonstrate increased antibody titres and to define standard serological cases. The laboratory tests performed were a complete blood count, malaria microscopy, HIV antibody testing, HIV-1 RNA PCR, CD4 count or percentage for HIV-infected patients, aerobic and mycobacterial

blood cultures, serum cryptococcal antigen test, detection of *Histoplasma*, *Legionella pneumophila* serogroup 1 and *S. pneumoniae* antigens in urine, microagglutination tests for *Brucella* and *Leptospira*, serology by immunofluorescence for *Coxiella burnetii* (Q fever) and typhus group and spotted fever group *Rickettsia*, and PCR for chikungunya and dengue (immunoglobulin M for the latter included but not part of the case definition). The participants were 467 children aged 2 months to 12 years and 403 adolescents and adults (median age, 38 years). Of these, 12% of children and 39% of adolescents and adults were infected with HIV (median CD4 count, 98 cells/mm^3). The commonest pathogens identified in children by the best laboratory tests available were chikungunya (10.2% of cases), *Leptospira* (7.7%) and *Rickettsia* of the spotted fever group (7.4%). Among infants and children admitted with fever only 4.3% of patients had a positive blood culture (3.4% for a bacterium and 0.9% for a fungus), and only 1.3% tested positive for malaria. Among adolescents and adults, 25.5% had a positive blood culture (17.1% for bacterial pathogens, 5.2% for a fungus and 3.5% for a mycobacterium). Other common pathogens identified were *Leptospira* (in 10.1% of cases), *Rickettsia* of the spotted fever group (8.7%) and *Coxiella* (7.9%). Malaria was the clinical diagnosis of 60.7% of febrile patients but *Plasmodium* was found in 1.3% of the children and 2% of the adults. Of note, *Salmonella typhimurium* was not found more frequently in HIV-infected than in uninfected patients (odds ratio, 0.11; 95% confidence interval, 0.03–0.49), but there were few cases. Cryptococcal disease and bacteraemic disseminated tuberculosis were found only in HIV-infected patients. The main conclusions of the study were that, in adults, HIV has a strong influence on the cause of fever in patients hospitalized with severe febrile illness; this highlights the importance of HIV counselling and testing of all patients presenting with fever in countries with generalized HIV epidemics. Large proportions of patients had bacterial and fungal bloodstream infections, bacterial zoonoses and arboviral infections. Among admitted adults in particular, blood culture is necessary to establish the local epidemiology of febrile illness. Administration of tetracycline should be considered for patients who do not respond to initial presumptive therapy against bacterial sepsis. Inexpensive, reliable RDTs for causes other than malaria are urgently needed. Multi-centre studies should be conducted to identify the main treatable conditions and to generate data for calculating the burden of disease. Research on typhoid is under way in Africa (the Typhoid Surveillance in sub-Saharan Africa Programme), and research on the impact and social ecology of bacterial zoonoses is being conducted in northern United Republic of Tanzania.

The results of these studies are summarized in **Box 1**.

2.2 Considerations on studies on the causes of fever

As the designs of the studies conducted so far are heterogeneous, it is difficult to compare their findings. In order to increase the comparability of future studies, the following conditions should be met: 1) the inclusion criteria should be clearly defined, reproducible and, if possible, the same in all studies; 2) the case definitions for each disease or syndrome associated with fever should be standardized; 3) the use of a healthy control group facilitates the interpretation of results when the clinical significance of diagnostic test results is uncertain; and 4) validated, widely accepted laboratory methods are used to form the basis of rigorous, standardized case definitions for each infection.

Although large-scale projects are under way on the causes of diarrhoea and ARI, studies of the causes of nonspecific fevers are also essential. A common definition of 'nonspecific fever' (e.g. fevers with no sign of localized infection and not associated with malaria, ARI or gastroenteritis) should be developed. Nevertheless, where multiple co-infections still occur frequently, e.g. in children in underserved areas, it might be important to study the entire spectrum of fever. The studies should target not only children under 5 years of age and adults but also children aged 5–15 years and infants aged < 2 months, as there are few data on these age groups. Studies that cover all ages would be useful.

BOX 1. EMERGING EVIDENCE ON CAUSES OF FEVER

Common findings of recent studies[a] on the causes of fever are:

Children < 5 years of age in outpatient settings:

- In four studies conducted in Dar es Salaam, Ifakara, Zanzibar and Karachi, 12%, 9%, 1% and 0.4% of fevers were due to malaria, 49%, 76%, 84% and 47% to ARIs and 9%, 12%, 14% and 23% to gastroenteritis (diarrhoea), respectively. The remaining children had nonspecific fevers with no clinical sign of localized infection, except for 1% children with skin infection and < 0.5% with meningitis.
- Only ≤ 25% of cases of ARI corresponded to clinical pneumonia (WHO definition) and about 5% to radiologically confirmed pneumonia. Most ARIs of all types were due to viruses (mainly influenza and respiratory syncytial viruses).
- The causes of nonspecific fever included a variable prevalence of typhoid (2–10%), a low prevalence of urinary tract infection (1–6%) and a very low prevalence of occult bacteraemia (2%).

Children ≥ 5 years and adults:

- Severe febrile illness in admitted patients is often associated with HIV-related infections in countries with generalized HIV epidemics: 39% of febrile patients admitted in northern United Republic of Tanzania were HIV-positive, while the prevalence in the community is only 3–4%.
- Malaria was found in 2% of inpatients in northern United Republic of Tanzania, 32% of outpatients in Cambodia and 4% of outpatients in the Lao People's Democratic Republic.
- In adult outpatients in Cambodia, 80% of malaria-negative patients had upper respiratory tract infection and 0.6% lower respiratory tract infection.
- In studies in northern United Republic of Tanzania (inpatients), Cambodia and the Lao People's Democratic Republic (outpatients) of non-malaria causes of fever (patients with ARI or other clinically documented local infections included), *Leptospira* was found in 10%, 13% and 12% of patients, dengue in 0%, 7% and 25%, typhus group rickettsioses in 1%, < 1% and 25%, spotted fever rickettsioses in 9%, 0% and 0%, and scrub typhus in 0%, 4% and 26%, respectively. In the United Republic of Tanzania, 8% of patients had Q fever, 5% brucellosis and 6% chikungunya (these three infections were not sought in the studies in Asia).

[a] D'Acremont V et al. (2013). Beyond malaria: etiologies of fever in outpatient Tanzanian children. *New England Journal of Medicine*. in press; Crump JA et al. (2013). Etiology of severe non-malaria febrile illness in northern Tanzania: a prospective cohort study. *PLoS Neglected Tropical Diseases*, 7:e2324; Mayxay M et al. (2013). Causes of non-malarial fever in Laos: a prospective study. *Lancet Global Health*, 1: e46–e54; Björkman et al., unpublished study; Bhutta et al., unpublished study; Newton et al., unpublished study.

The design of future studies on the causes of fever requires careful consideration. A simple design (e.g. focusing on causative agents that influence clinical management) could be used. Both prevalence studies in consecutive febrile patients attending health facilities and incidence studies with active and passive case detection are desirable. Several research networks could provide further information on the burden of disease, such as the Global Enterics Multicenter Study,[1] Pneumonia Etiology Research for Child Health[2] and the Typhoid Surveillance in sub-Saharan Africa Pro-

[1] http://medschool.umaryland.edu/GEMS, accessed 6 September 2013.
[2] http://www.jhsph.edu/research/centers-and-institutes/ivac/projects/perch, accessed 6 September 2013.

gramme.[1] Surveillance systems and notifiable disease reporting systems could be useful. Focus should be placed on diseases that can progress to severe illness, permanent disability or death. Studies should be undertaken at different levels of the health care system (community, peripheral health facilities and hospitals), as disease profiles and the frequency of severe disease vary widely with the level of the system. Studies are also needed on progression from mild to severe disease; however, such studies are methodologically complex, as severe cases are rare and the study conditions would influence care and the risk for progression. Therefore, new study designs are needed with feasible sample sizes. The results of such studies will indicate the best tools and strategies for prompt identification and early treatment of febrile diseases and for the detection of severe disease requiring hospital care.

Laboratory findings must be linked to clinical data to avoid over-interpretation of positive results, particularly from highly sensitive molecular tests. For example, in the presence of positive serology for dengue, the probability that the acute febrile episode is due to dengue is much lower in a patient with ARI or diarrhoea than in a patient with nonspecific fever. One way to avoid over-interpretation of positive results would be to decide not to test patients for whom there is a low probability of having that disease, such as patients who have another obvious cause of fever (e.g. signs of localized infection). When possible, it is helpful to compare laboratory results for febrile patients with those for matched asymptomatic control groups, especially when molecular diagnostic tools are used. Better tools are needed for diagnosis of bacterial infections in the field, after their specificity has been validated in studies with asymptomatic controls. The potential roles of C-reactive protein, procalcitonin and other host biomarkers should be further explored.

Data on the causes of fever are needed to inform clinicians and to adapt WHO guidelines for the management of acute illness at country level, for children and adults and at peripheral and hospital levels, rather than for providing individually adjusted care. This information should also guide priorities for upgrading diagnostic test capacity at different levels of the health system, including rapid tests at community level. Better capacity is also needed for surveillance of specific pathogens and their susceptibility to antimicrobial agents, in order to choose first- and second-line treatments and to guide pre-referral treatment of patients with danger signs.

2.3 New evidence on effective management of malaria and non-malaria febrile illness

Since the WHO recommendation for prompt parasitological confirmation by microscopy or RDT in all patients suspected of having malaria before treatment is started (WHO, 2010a), several studies have confirmed that this strategy is safe, including for children under 5 years of age living in areas highly endemic for malaria. A systematic review by the Foundation for Innovative New Diagnostics is under way. This recommendation is feasible, and health workers have been found to perform RDTs correctly and to adhere to the test results. For the integrated management of childhood illness, a new algorithm to better target antimicrobial prescriptions for the management of childhood illness (ALMANACH) was prepared by Rambaud-Althaus et al. (2011) on the basis of a literature review and the findings of the study on the causes of fever in children in the United Republic of Tanzania. This algorithm differs from IMCI in several ways, including the addition of four danger signs (for a total of eight), different algorithms for febrile and non-febrile patients from the start, use of urine dipsticks for children aged < 2 years and use of abdominal tenderness to diagnose possible bacterial intestinal infection, including typhoid in children ≥ 2 years. Because of its complexity, ALMANACH was introduced in an android application for smart phones and tablets. During its introduction and use in research conditions, antibiotics were prescribed to 15% of 838 patients to which it was applied and to 84% of a control group of 623 patients (Shao et al., 2011). Although use of antibiotics was low in the intervention arm, 97%

[1] http://tsap.ivi.int, accessed 6 September 2013.

of patients were cured by day 7 (one secondary hospitalization, no death), with 92% cured in the control arm (one death). When ALMANACH was used in routine clinical settings, antibiotics were prescribed in 24% of cases of the intervention group and in 70% of the control group. The respiratory rate, for which no validated automatic device is yet available, was not, however, always measured accurately, so that antibiotics may not always have been targeted to the right children.

Challenges to the management of ARI at peripheral facilities include clinical overlap with malaria, lack of availability of chest radiographs, oximeters and oxygen, lack of trained staff and dysfunctional health systems. Under current guidelines, about 80% of children with respiratory symptoms do not need antibiotics and can receive home care for cough and cold. A study in Pakistan (Hazir et al., 2011) on the safety of withholding antibiotics from children with non-severe pneumonia showed no difference in the number of clinical failures on days 3 and 5 in children receiving amoxicillin and those given placebo, indicating that the respiratory rate is not specific for diagnosing pneumonia. Additional studies in Africa and Asia are needed in order to change the current WHO recommendations for the management of pneumonia in children in developing countries. As a result of studies on the management of severe pneumonia, the 2012 version of the IMCI guidelines (WHO and UNICEF, 2012) recommends that pneumonia with chest indrawing but no other danger signs should be managed at the peripheral level, reducing the number of children referred to higher-level care. Several studies in Pakistan and other Asian countries (Bari et al., 2011; Soofi et al., 2012; Addo-Yobo et al., 2011) have shown that CHWs can recognize chest indrawing and treat children in the community. Treatment failure was reduced by half after CHWs were trained in the management of severe pneumonia, with major household savings (US$ 1.46 vs US$ 7.60 for treatment costs) (Bari et al., 2011).

The findings of studies on causes of fever in Pakistan (Bhutta et al., unpublished study) were used to prepare an algorithm for the management of typhoid on the basis of a clinical score that predicts the risk for antimicrobial resistance. This score was based on signs and symptoms predictive of disease progression and on history of previous treatment with first-line antibiotic. Use of this algorithm resulted in a 97% cure rate with first-line therapy (chloramphenicol) in the group classified clinically as 'sensitive typhoid' and an 85% cure rate with second-line therapy (cefixime) in the group classified as 'multi-drug-resistant typhoid'. Given the importance of early triage, diagnosis and appropriate therapy for typhoid, validated algorithms are urgently needed for various settings.

The conclusions from these studies are summarized in **Box 2**.

2.4 Considerations on studies of effective management of febrile illness

In addition to studies on the causes of fever based on 'gold standard' laboratory diagnoses, studies in which clinical outcomes (cure versus treatment failure) are used as the primary end-points are required to assess the real benefit of new fever management strategies. A common definition of 'treatment failure' is therefore required for each syndrome, such as the definition available for malaria. Intervention studies can be used to study the impact of modifications of existing algorithms on the proportion of treatment failures. One example is the study in Pakistan (Hazir et al., 2011) on the safety of withholding antibiotics from children with non-severe pneumonia, in which clinical failure at day 3 was defined as lower chest indrawing or any general danger sign, and that at day 5 as the presence of fast breathing, lower chest indrawing or any general danger sign.

Research to improve the existing diagnostic and treatment algorithm for the management of fevers should provide answers to the following questions:

- What impact will pneumococcal conjugate and Hib vaccination programmes have on the causes of ARI and thus current algorithms for the management of pneumonia?

BOX 2. EMERGING EVIDENCE ON EFFECTIVE MANAGEMENT OF MALARIA AND NON-MALARIA FEBRILE ILLNESS

- Several studies have shown that withholding antimalarial agents from patients with negative RDT results is safe, even for children living in areas highly endemic for malaria.
- Use of the IMCI algorithm leads to overtreatment with antibiotics, mainly because the respiratory rate lacks specificity for diagnosing pneumonia.
- A study in Pakistan[a] showed that the clinical outcome of children with non-severe pneumonia[b] was no different when they received amoxicillin or placebo.
- Management at community level of severe (but not very severe) pneumonia[a] has been shown to be safe, and the IMCI guidelines have been updated to reflect this.
- The use in Pakistan of a clinical algorithm to differentiate probable antibiotic resistant from sensitive typhoid fever led to a high cure rate, with few second- and third-line treatment prescribed.[c]

---

[a] Hazir T et al. (2011). 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. *Clinical Infectious Diseases*, 52:293–300.

[b] WHO definitions: Pneumonia: no lower chest indrawing but fast breathing; severe pneumonia: lower chest indrawing; very severe pneumonia: inability to drink, convulsions, abnormal fatigue or difficult waking or persistent vomiting

[c] Bhutta et al, *unpublished study*.

- How should nonspecific fevers in children and adults be managed optimally, including the classes of antibiotics for specific patients (e.g. doxycycline for patients with suspected leptospirosis, rickettsiosis or typhus)?
- What are the clinical and laboratory predictors of progression to severe illness and of infections resistant to antimicrobial agents?
- Can reliable point-of-care tests be developed that differentiate between viral and bacterial causes of fever?
- In which clinical situations are laboratory tests of 'disease severity' required?
- What are the benefits of using new respiratory rate counters and pulse oximetry in diagnosis?
- Which additional curable illnesses of public health importance should be included in existing algorithms for the management of febrile patients, such as in country adaptations of the IMCI and the IMAI?
- What is the potential of new tools such as electronic guides and recording devices to improve compliance with decisions charts and data collection?
- Which modelling approaches are most appropriate for defining cost–effectiveness and cost–benefit criteria for developing new diagnostic tools?

Factors other than algorithms and the availability of diagnostic tests influence clinicians' decisions, such as distance to a health facility, economic status, ease of referral and patient demand. Algorithms should be adapted to each level of care and be integrated into the continuum of care, from the community level, to the first level of care, to the hospital.

3. WHO guidelines and tools for the management of fever

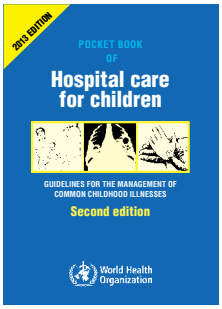
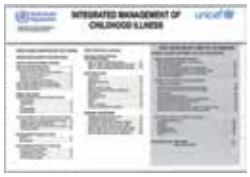
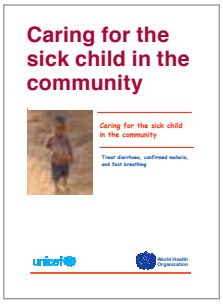
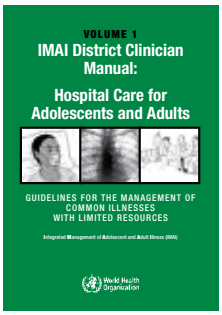
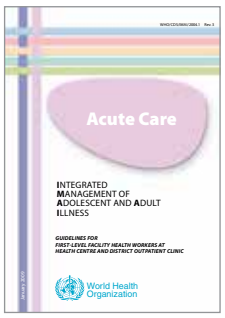
3.1 Current WHO guidelines

WHO has issued a number of guidance documents for the management of acute fever (WHO, UNICEF, 2008; WHO, 2009, 2011a,b, 2013; see **Figure 2**). Many build on each other; e.g. iCCM is a simplified version of IMCI. There are, however, gaps, such as decision charts for adolescents and adults at community level. Many tools are available for supporting HIV testing of adults at home and in the community, but there is no simple integrated management algorithm. In several countries in which iCCM is used, interest has been expressed in extending community-based RDT testing and management of malaria to adults. Guidelines on home-based management of malaria (which do not include diagnostic testing) have been superseded by the iCCM and should no longer be used.

The second edition of the *WHO guidelines for the treatment of malaria* (WHO, 2010a) calls for confirmation of a malaria diagnosis by microscopy or an RDT in all patients suspected of having malaria, including children under 5 years of age living in highly endemic areas. All the existing guidelines on fever for peripheral and community levels have been updated (IMCI, iCCM) or are being updated (IMAI) to include universal confirmation of malaria by diagnostic tests before

FIGURE 2.

WHO publications for differential diagnosis of fever by health workers, including algorithms and guidance, targeting different levels of the health system and different age groups

	Hospital	Primary care	Community
Children < 5 years			
Adolescents and adults			

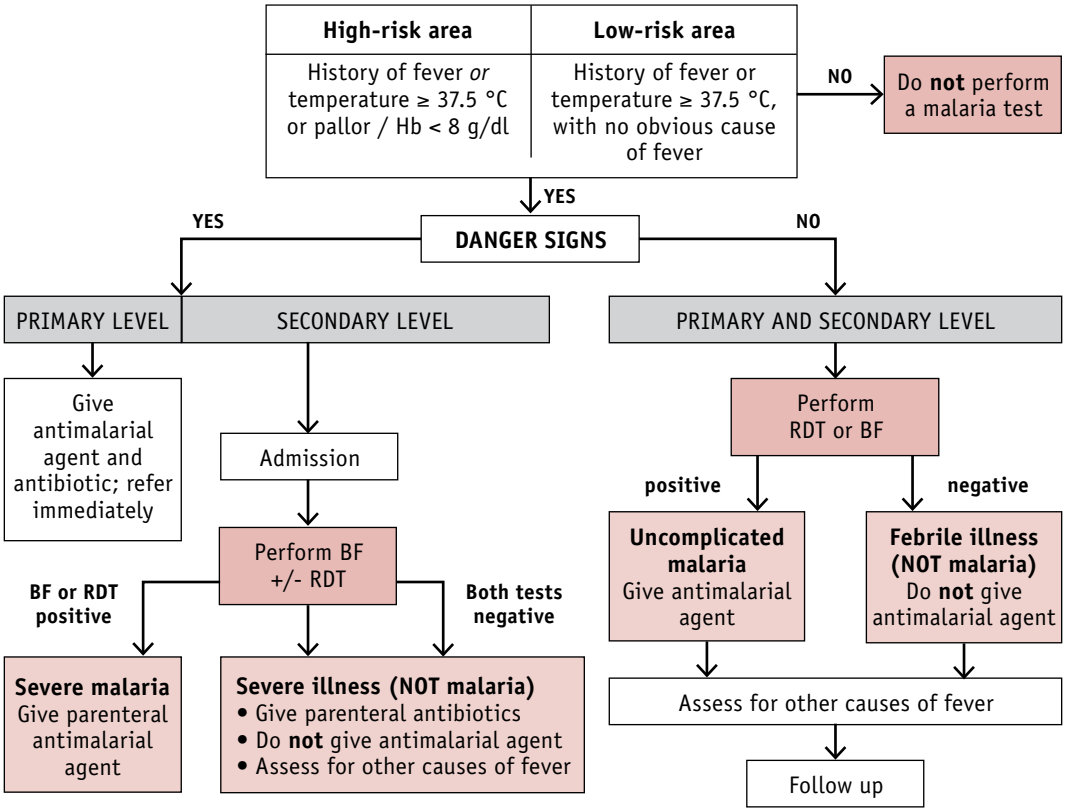
treatment. In these guidelines, malaria diagnostic tests are performed for patients presenting at a first visit with a history of fever or a temperature ≥ 37.5 °C, haemoglobin < 8 g/dl or palmar pallor (children) in areas at high risk for malaria; and a history of fever or a temperature ≥ 37.5 °C, with no obvious cause of fever in areas at low risk for malaria (see **Figure 3**). The IMCI generic threshold for designation of an area as at high or low risk is a 5% malaria positivity rate among febrile children presenting to health facilities. This threshold was originally set to guide decisions on treatment with antimalarial agents on the basis of fever alone; it is now generally considered to be too high to guide appropriate use of malaria diagnostic tests in the absence of other obvious causes of fever. In some countries, a testing threshold of ≤ 1% for the malaria positivity rate among febrile children presenting to health facilities is used instead.

Once a malaria test has been performed, treatment should be given according to the result and an antimalarial medicine prescribed only when the result is positive. Patients with danger signs seen at health facilities with no inpatient service or at community level should be referred immediately, after pre-referral treatment with an antimalarial agent and an antibiotic, without losing time by performing a malaria test (see **Figure 3**).

IMCI was conceived in the early 1990s, with the goal of reducing child mortality by improving the management skills of health workers, health systems and health practices (WHO, UNICEF, 2008). As the leading causes of death among children <5 years of age are still pneumonia, diarrhoea, malaria, and newborn conditions, IMCI is appropriate today and should be widely implemented. IMCI is based on clinical signs and use of malaria RDTs to identify and treat the leading causes of death. In relation to fever, the IMCI algorithm includes (directly or indirectly) the differential diagnosis of diseases of importance:

FIGURE 3.

Current WHO algorithm for malaria diagnosis and treatment (first visit)



BF, blood film; RDT, rapid diagnostic test

- Severe febrile illnesses such as severe malaria, meningitis, sepsis due to bacteraemia and severe dengue are identified by an evaluation of danger signs.
- Fever due to localized infections such as pneumonia, measles, dysentery and acute otitis media is identified from their main signs and symptoms and managed accordingly.
- Some causes of fever that give nonspecific signs and symptoms, such as malaria and viral infections, are detected with specific diagnostic tests (malaria) or the absence of an alternative diagnosis (viral infection).
- Other common causes of persisting fever (> 7 days) are managed by referral for further assessment, to differentiate fevers of viral origin lasting only a few days from conditions that require specific diagnostic and therapeutic interventions, such as tuberculosis, urinary tract infections, relapsing fever, typhoid and osteomyelitis. For the latter infections, the IMCI algorithm assumes that fever will usually last > 7 days and that the infections do not generally require immediate treatment. This assumption is questionable for diseases such as leptospirosis, relapsing fever and enteric fever.

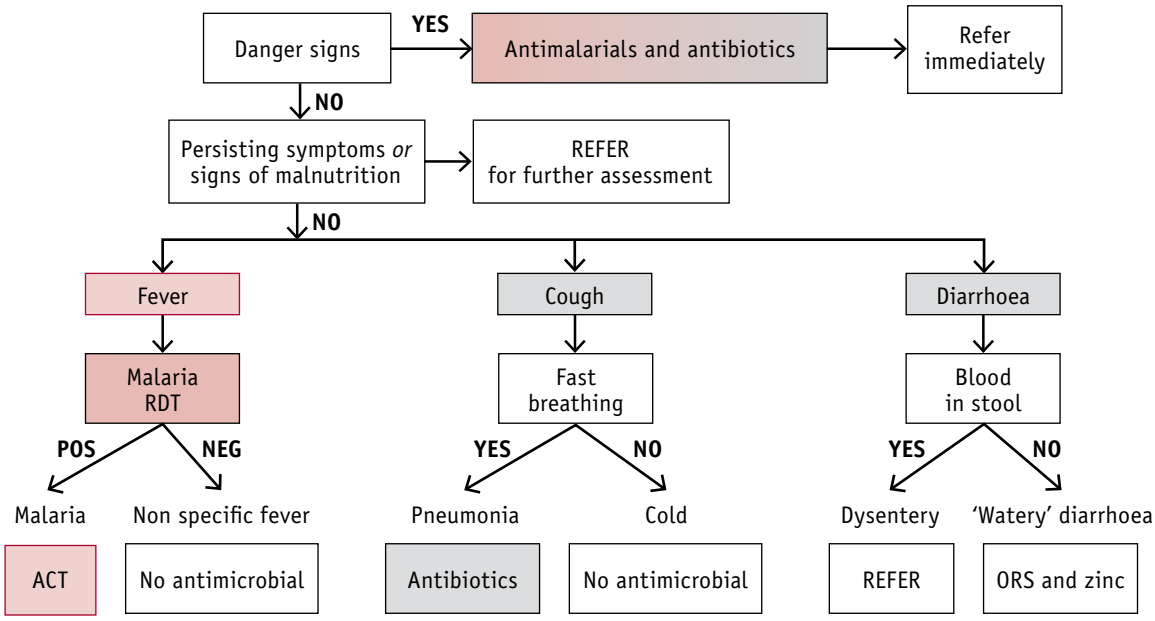
Other diseases that cause fever were considered either to be insufficiently prevalent to be included in the algorithm or to have no specific diagnostic signs or symptoms that would allow their identification.

The advantage of IMCI is that it promotes rational use of antimicrobials. Instead of giving an antimicrobial medicine to all children at their first visit 'to be on the safe side', IMCI recommends prescription of antimicrobial drugs only to children with a clinically (or, for malaria, laboratory) documented disease and follow-up visits in case of persisting symptoms (e.g. 3 days for pneumonia or malaria; 5 days for diarrhoea or nonspecific fever).

The key components of iCCM are identification of signs of illness, referral of children with danger signs and treatment of malaria, pneumonia and diarrhoea at home with appropriate medication (see **Figure 4**). The danger signs are of two types: 'general danger signs' in severe illness that call for

FIGURE 4.

IMCI and iCCM algorithms, with core elements that should be maintained in the decision charts in country adaptations



PID, pelvic inflammatory disease

From WHO (2009), pp. 8–9.

immediate referral to a higher level of care (e.g. convulsions); and 'other problems', corresponding to persistent but non-urgent medical problems requiring assessment and management at a higher level of care (e.g. cough for ≥ 21 days). iCCM targets sick children aged 2 months to 5 years and has three components: caring for sick children in the community, caring for newborns at home and ensuring children's healthy growth and development.

3.2 WHO recommendations for management of fever in adolescents and adults

Although adults and children differ in important ways in terms of disease burden and care, less priority has been given to adolescents and adults, partly because of the high mortality rate at younger ages. IMAI, which provides guidance on acute care for adults at first-level health facilities, takes into account the specificities of the illnesses of adolescents and adults:

- Morbidity and mortality due to malaria is generally lower.
- HIV and TB infections are more prevalent.
- Sexually transmitted infections and reproductive tract infections are prevalent.
- Women may be pregnant.
- Substance abuse may be an important co-morbid condition.
- Occupational exposure to pathogens can occur (fields, forests, agriculture).
- Adults require higher doses of medicine, so that rational use of medicines will result in greater cost savings.

HIV infection affects the section of the IMAI algorithm for fever, as many opportunistic infections present with fever and must be diagnosed and managed acutely, followed by HIV care and antiretroviral therapy. Many opportunistic infections can be managed at peripheral level. HIV infection is also highly prevalent in severely ill adults: in two studies in Uganda (Jacob et al., 2009, 2012), 85% of adults were HIV positive, with a median CD4 count of 65 lymphocytes/mm^3; only 24% were on antiretroviral treatment in 2009, and 20–27% were not aware of their HIV status. Over-diagnosis of malaria in febrile adults can have negative consequences, as HIV-infected patients will not receive life-saving treatment of opportunistic infections; HIV infection presenting as an acute febrile illness is not diagnosed, missing opportunities for prevention of transmission (Sanders et al., 2011) and early initiation of antiretroviral treatment; bacterial sepsis may be wrongly treated as malaria (Nadjm et al., 2012); diagnosis of trypanosomiasis may be delayed; and diagnosis, reporting and infection control measures for serious epidemic diseases such as Ebola or Marburg may be delayed.

A review of WHO guidelines and publications on fever in adolescents and adults in countries with limited resources suggested that the IMAI acute care guidelines for the management of patients with fever should be updated. In line with the WHO guidelines (WHO, 2010a), the IMAI guidelines should recommend that all febrile adolescents and adults at high risk for malaria be tested for malaria and treated with antimalarial agents only if the test is positive. For febrile adolescents and adults at low risk, malaria testing is recommended only in the absence of other apparent causes of fever (dysentery, gastroenteritis, pneumonia, soft tissue or muscle infection, flu-like illness, bronchitis, severe or surgical abdominal conditions, pelvic inflammatory disease, sinusitis, tonsillitis, sore throat, kidney infection or dental abscess). The guidelines should also be updated to simplify the classification of malaria risk, defining 'high risk' as living in or visiting an area with moderate-to-intense transmission or an on-going epidemic or being pregnant or HIV positive and living in an area with low transmission. 'Low risk' is defined as living in an area with low transmission, not being pregnant or HIV positive and not having travelled recently to an area

with high malaria transmission. In addition to malaria tests, a patient's HIV status is the most important test for managing fever in adults appropriately (see **Figure 5**).

As in the IMCI, most causes of fever in the IMAI acute care guidelines are not on the fever page of the algorithm; instead, management of conditions associated with fever is described in sections such as those on cough or difficult breathing, diarrhoea, skin, genitourinary conditions, mouth and throat problems and neurological problems. As fever is an inconsistent sign, at least in HIV-positive patients, it is often not included among those used for classification on these pages of the algorithm.

The IMAI acute care algorithm and the updated IMCI guidelines refer to 'apparent' and 'obvious' causes of fever. Relying on a health worker's clinical estimate of the cause of fever without guidance could, however, be dangerous. Malaria testing is generally not necessary in the presence of one of the following conditions presenting with fever in areas of low endemicity:

- ARIs such as pneumonia, influenza, bronchitis, sinusitis, tonsillitis and pharyngitis (unlike children, adults with a common cold usually do not have fever);
- meningitis;

FIGURE 5.

Updated fever pages in the IMAI acute care guideline module

Does the patient have fever – by history of recent fever (within 48 hours) or feels hot or temperature 37.5 °C or above?

IF YES, ASK:	LOOK AND FEEL
• How long have you had a fever? • Any other problem • What medications have you taken? • Determine if antimalarial and for how long.	• Look at the patient's neurological condition. • Is the patient: Lethargic? Confused? Agitated? • Count the breaths in one minute. Use table on p.16 to determine if fast breathing. If fast breathing, is it deep? • Check if able to drink. • Feel for stiff neck. • Check if able to walk unaided. • Skin rash? • Headache? For how long? • Look for apparent cause of fever – assess all symptoms in this *Acute Care* algorithm.
Decide malaria risk: ☐ High ☐ Low ☐ No • Where do you usually live? • Recent travel to a malaria area? • If woman of childbearing age – are you pregnant? • Is an epidemic of malaria occurring? • HIV positive? **If HIV status unknown, do HIV test**	**Apparent causes of fever:** ☐ Dysentery ☐ Gastroenteritis ☐ Pneumonia ☐ Soft tissue or muscle infection ☐ Influenza/Bronchitis ☐ Severe or surgical abdominal problem ☐ PID ☐ Sinusitis ☐ Tonsillitis ☐ Sore throat ☐ Kidney infection ☐ Dental abscess

HIGH MALARIA RISK	• Living in or visited area with intense or moderate malaria transmission • Epidemic of malaria is occurring • Pregnant • HIV positive	DO MALARIA TEST IN ALL FEBRILE PATIENTS
LOW MALARIA RISK	• Living in area with low malaria transmission • No travel to higher malaria transmission area	DO MALARIA TEST IF NO APPARENT CAUSE OF FEVER
NO MALARIA RISK	• Living in area with no malaria transmission • No travel to area with malaria transmission	NO MALARIA TEST

See *Chronic HIV Care*.

- gastroenteritis, including dysentery but not cholera;
- soft tissue infection (including dental abscess, severe gum or mouth infection) or muscle infection;
- severe or surgical abdominal condition;
- pelvic inflammatory disease;
- kidney infection;
- secondary syphilis;
- opportunistic diseases due to HIV (WHO, 2010b) and acute retroviral syndrome; and
- fever related to antiretroviral treatment or to other drugs.

As in children, ARI is a major reason for outpatient visits by adults. Some ARI episodes are accompanied by fever; the absence of fever generally excludes pneumonia. Clinicians should not use fever alone as the basis for giving antibiotics to patients with ARI. The presence of fever with ARI should prompt an assessment of additional signs that suggest pneumonia or another infection, such as sinusitis or streptococcal tonsillitis. After pneumonia, acute exacerbation of chronic bronchitis (for which antibiotic treatment has been shown to be beneficial) and pertussis (for which antibiotics can reduce transmission) and high risk for complications due to their HIV status have been excluded, patients should not be treated with an antibiotic. Antibiotic treatment of adult pharyngitis benefits only those patients with group A β-haemolytic *Streptococcus*, which is the causal agent in approximately 10% of cases. Patients with influenza may benefit from an antiviral agent in epidemic circumstances or when they have certain characteristics.

The section on assessment and classification of febrile patients in the IMAI acute care algorithm should therefore be updated as shown in **Figure 5**. The section on classification and management of febrile patients should also be updated, to ensure that treatment is guided by test results (**Table 1**).

TABLE 1.

Classification and management of fever in the updated IMAI acute care algorithm

Sign	Classification	Treatment
One or more of the following signs: • confusion, agitation or lethargy, • inability to drink, • inability to walk unaided, • stiff neck or • severe respiratory distress	Very severe febrile illness	• Give artemether (or quinine, if artemether is not available) intramuscularly. • Give first dose of antibiotics intramuscularly. • Give glucose. • Refer urgently to hospital. • If fever is accompanied by bleeding (gums, skin, into eyes or urine) or if jaundice develops within 2 weeks of fever, report case to district clinician.
Malaria test positive	Malaria	Give appropriate oral antimalarial agent. • Look for other apparent cause and treat accordingly. • Consider HIV-related illness (p. 54). • If fever for 7 days or more, consider tuberculosis (send sputum sample, refer). • Follow up in 3 days if still febrile (p. 63).
Malaria test negative and/or other apparent cause of fever (low malaria risk)	Non-malaria fever	• Treat according to apparent cause. • Consider HIV-related illness if unexplained fever for > 30 days (p. 54). • Consider fever related to antiretroviral drugs (see *Chronic HIV care*). • If no apparent cause and fever for 7 days or more, send sputum samples for tuberculosis testing and refer to hospital for assessment (p. 63). • Follow up in 3 days if still febrile.

The review of current IMAI algorithms (WHO, 2009) did not suggest that additional causes of fever should be added to the generic version of the acute care algorithm. Nevertheless, common additional causes of fever in certain countries should be added in their adaptations of the guidelines, including dengue, rickettsial disease, borreliosis, leptospirosis, brucellosis and typhoid; in some settings, locally prevalent neglected tropical diseases that present with fever, such as human African trypanosomiasis and visceral leishmaniasis, should be added.

A good empirical approach to fever management is illustrated by a study of pregnant women on the border between Myanmar and Thailand (McGready et al., 2010), where malaria, rickettsial infections, dengue and leptospirosis account for nearly half of all febrile diseases. Pyelonephritis accounted for 19.7% of fever cases. After malaria, pyelonephritis and ARI had been excluded by clinical examination and microscopy, one third of the febrile infections were due to rickettsia or leptospirosis, both of which responded to azithromycin.

Three types of adaptation could improve the management of febrile patients at country level:

- addition of locally important infectious causes of fever to the clinical algorithm,
- addition of diagnostic tests that could improve care of severe febrile illness at first-level facilities and
- addition of treatments that are effective against locally prevalent diseases and provision of life-saving treatment for severe febrile illness.

Incorporation of simple empirical algorithms into country adaptations should be based on local etiological studies, and on studies on the best use of new diagnostic tests. Microbiology laboratories should be improved at national or regional level, both for etiological diagnosis and to obtain data on antimicrobial susceptibility in order to decide on first- and second-line treatment to guide management of individual patients and to update national treatment guidelines.

3.3 Implementation of WHO guidelines at country level

iCCM, IMCI and IMAI should be widely promoted and implemented. Adherence to the WHO guidelines, particularly at health facility level, is, however, uneven, and strategies for improving adherence are needed, especially with regard to measurement of the respiratory rate. While adherence to the guidelines by health workers is generally good at community level, adherence on a larger scale meets difficulties associated with care-seeking behaviour, resources, training and supervision. To complement the need for continuous in-service training due to staff rotation and attrition, the pre-service curriculum should be revised to include training in use of the WHO algorithms.

Some countries have adapted the IMCI and iCCM algorithms to their context. While this is appropriate, certain core elements should not be changed. For example, all children should be assessed for danger signs, and their caretaker asked about fever, cough and diarrhoea (in parallel rather than sequentially) and treated accordingly (see **Figure 4**). Unfortunately, the first-level IMAI tools have not been updated recently. The present guidance concentrates on HIV care and antiretroviral therapy, and, although the acute care module was adapted in countries in which IMAI was used to scale up HIV services, it is not implemented as widely as IMCI. The *IMAI district clinician manual* (WHO, 2011b) provides guidance on the differential diagnosis of fever and the management of severe febrile illness at hospitals and should be widely implemented. In view of the diversity of disease burden, the algorithms may have to be adapted even within countries, in order to cover geographical, seasonal and urban–rural differences. Like IMCI, IMAI should be adapted by countries or even subnationally, but the epidemiological basis for such adaptations is often lacking. In some settings, adaptations to include typhoid and dengue are required, although the cost–benefit of adding more diseases to the existing algorithms must be carefully evaluated. Simplicity is critical, particularly in view of the poor adherence to the algorithms in health facil-

ities. The current guidelines address the main causes of death. Any adaptation should therefore be based on a high burden of disease, a high case fatality rate, the availability of treatment and the potential for preventing transmission. Clear criteria should be defined to target use of each diagnostic test to specific patients.

3.4 New rapid diagnostic tests

The advent of malaria RDTs was a turning-point in malaria diagnosis and treatment. Additional point-of-care tests are needed to detect causes of febrile illnesses associated with other diseases. Some such tests are already available, with sufficiently good diagnostic performance for use in the clinical management of patients with symptoms suggestive of dengue (Blacksell, 2012; Chappuis et al., 2013), rotavirus (Khamrin et al., 2011), *Entamoeba histolytica* (Leo et al., 2006) and *Leptospira*, (Bajani et al., 2003). Others require improvement, such as tests for typhoid (Chappuis et al., 2013), scrub typhus (Blacksell et al., 2010) and tuberculosis (Lawn et al., 2013). Although the diagnosis of other diseases would benefit from point-of-care tests, the more specific a test, the more expensive will be its use to detect one pathogen. An RDT is available to detect *S. pneumoniae* in urine, but it is poorly specific in children because of their high rate of chronic carriage (Anjay et al., 2008). Another approach would be to develop generic tests to identify patients at risk for severe illness (e.g. with host biomarkers) or those with a particular class of infection (e.g. bacterial or viral). The host response markers that have been studied extensively include C-reactive protein and procalcitonin, especially in developed countries, and validation studies are under way in developing countries. Several groups have identified promising biomarkers for differentiating malaria from bacterial and viral infections: scientists at the Broad Institute (Cambridge, Massachusetts, USA) have identified three or four biomarkers by proteomic analysis of samples from Kenya and Mozambique; researchers at Oxford University (United Kingdom) found two leading biomarkers to differentiate bacterial from viral infections; and workers at the University of Toronto (Canada) in collaboration with the Swiss Tropical and Public Health Institute have identified a combination of biomarkers in children that correlate with radiologically confirmed pneumonia. Urine biomarkers are being evaluated as part of multiplex assays. Studies are being planned to cross-validate the biomarkers and to assess the cost implications of producing a second test rather than adding multiple reagent lines to an existing test.

Tests of different complexity are used by health workers at hospitals, health clinics and in the community. Devices are needed to measure certain clinical parameters, such as temperature, respiratory rate and oxygen saturation, potentially with new automated techniques or as applications for mobile devices. Manual respiratory rate counters are a step forward but are insufficient, as health workers find it difficult to devote enough time to measure the rate accurately. All new diagnostic tests should meet the WHO criteria of being 'affordable, sensitive, specific, user-friendly, equipment-free and delivered to those who need it' (ASSURED). Point-of-care tests must be designed that are easy to use and acceptable in order to ensure their use at community level.

3.5 Medicines

High-level resistance to first-line antibiotics has been found in many parts of the world, including Africa. The trend to increased antibiotic prescription after RDTs reported in several studies (Msellem et al., 2009; D'Acremont et al., 2011; Batwala et al., 2011) raises concern that resistance will spread further. In view of the high level of resistance to co-trimoxazole (stated in the most recent IMCI), replacing co-trimoxazole with amoxicillin for ARIs is a priority, although not yet widely implemented. Rational use of antibiotics, which will result in an overall reduction in the prescription of antibiotics, can be achieved if health workers adhere to the guidelines. Although the guidelines should be updated to reflect changes in antibiotic resistance, there is often a considerable lag, especially with regard to the IMCI and iCCM guidelines. National guidelines should also better reflect the 'class of antibiotics' and not only recommend prescribing or not prescribing

antibiotics in general. For example, penicillins are generally appropriate for respiratory infections, quinolones for intestinal and urinary infections and doxycycline for some causes of non-specific fever.

Use of artesunate administered rectally is recommended for suspected cases of severe malaria identified at community level. As long as injectable formulations are not recommended for use in the community and no antibiotic is available in a rectal formulation no pre-referral antibiotic treatment can be given at community level for severe febrile illness.

3.6 Considerations on and recommendations for improving existing tools

The increasing prevalence of malaria in children aged 5–15 years warrants greater attention in guidance documents. (O'Meara et al, 2008; Ceesay et al, 2008)

Inclusion of diagnostic testing and treatment for malaria within the IMCI, IMAI and iCCM algorithms is the best approach to malaria case management. Use of ACTs and RDTs in malaria case management can promote implementation of these algorithms.

The updated version of the *Guidelines for the treatment of malaria* will address the criteria for defining areas at high and low risk for malaria to determine whether diagnostic testing is necessary, guidance on testing anaemic children in areas at high risk for malaria, testing for malaria at peripheral level before referral or pre-referral treatment, diagnosis of a new infection or recrudescence on the basis of the interval between two malaria episodes, and management of anaemia with iron and its interaction with malaria. The present WHO guidelines recommend that patients with severe malaria should be referred urgently without testing, although testing in order to avoid unnecessary antimalarial treatment is recommended in some counties with low endemicity.

The research and development priorities with regard to diagnostic tests for fever management are:

- within the next 12 months: evaluation of the performance, planning and introduction of additional diagnostics (for leptospirosis, meningitis) and development of low- cost forehead thermometers;
- within 1–3 years: automated respiratory rate timers and pulse oximeters, RDTs to differentiate bacterial from viral infections, better dipsticks for urinary tract infections; and
- within 3–5 years: a better point-of-care test for tuberculosis, new diagnostic tests based on biomarkers of severe illnesses, prognostic tests for treatment failure or disease progression, and multiplex diagnostic tests for fever.

The present guidelines recommend referral to a higher level of care of many children who could potentially be managed at community level; however, there is increasing evidence that many health workers are unable to identify danger signs. New tools for identifying the patients who are truly at risk for severe illness are needed at both community and primary health care level. A continuum of care for both children and adults, from the community to peripheral health facilities and to hospital, is required, which should be carefully planned. For example, management of a child referred by a community health worker to a health facility must avoid simply repeating what was already done at community level, and skills and tools not available at community level should be made available at health facility level.

New incentives should be found to help health workers adhere to the guidelines. Full assessment of a febrile patient by the IMCI guidelines takes about 10 min, while writing a prescription takes only 30 seconds. Systematic prescription of an antimicrobial agent is easier than telling a patient to come back in case of clinical deterioration. Community awareness and mobilization are important elements for improving health workers' accountability and patients understanding of non-malaria febrile illnesses. Patients and caregivers must know what diagnostic tools and treatment to expect from health workers. Patient counselling should include the information that febrile diseases do not always resolve immediately and advice on when to return for clinical follow-up.

4. Experience of agencies and nongovernmental organizations with integrated community case management

4.1 iCCM Task Force

The iCCM Task Force brings together various multilateral organizations, bilateral agencies, academic institutions, nongovernmental organizations, consortia and foundations. It provides a structure for devising common tools for training in and support of case management, supply chain management, monitoring and evaluation, operational research and policy and advocacy and exchanging experience on country support. A manual is being prepared to guide countries in implementing iCCM and other health packages for newborns. The Task Force is also exploring the potential role of the private sector.

Future activities of the Task Force include more sharing of country information and coordination or support, setting up working groups for emergencies, paediatric AIDS and cost–effectiveness analyses, with the introduction of indicators for countries, a review of evidence and setting research priorities. The Task Force is considering including the health of newborns and children. In many countries, community services cover the entire population, and guidance is needed for older populations.

4.2 Results of operational research

In November 2012, a special supplement on integrated community case management was published in *The American Journal of Tropical Medicine and Hygiene* (Marsh et al., 2012). The 18 papers covered a range of topics, including the impact of iCCM, care-seeking behaviour, health systems, the private sector, iCCM programme issues, quality of care and household costs. The main results of each paper are available as a PowerPoint presentation on the Internet[1] and are briefly summarized below.

In a stepped-wedge, cluster randomized controlled trial in Ghana on the effectiveness of community management of fever with and without antibiotics (malaria RDTs were not used), Chinbuah et al. (2012) found a significant reduction in mortality of 33% after presumptive treatment with artesunate–amodiaquine with amoxicillin and 44% without amoxicillin, as compared with standard care. The difference with and without amoxicillin was not significant.

Another study is about to finish in Uganda, which may clarify the benefit of using antibiotics.

In a cluster randomized trial in Burkina Faso, Ghana and Uganda, in which malaria RDTs and respiratory rate timers were used, Mukanga et al. (2012) found that use of iCCM led to good compliance with RDT results, only 5% of patients who tested negative for malaria being prescribed antimalarial agents. There was, however, overuse of antibiotics, of different degree in the different countries. Fever clearance at day 7 was high (99%) in both the iCCM arm and that given presumptive treatment with antimalarial agents in the three countries, with antibiotics at the discretion of the clinician in Ghana.

[1] http://www.coregroup.org/component/content/article/48-webinars/349-overview, accessed 6 September 2013.

Rutebemberwa et al. (2012) studied the involvement of CHWs in urban and rural areas of Uganda. Rural children were more likely to see a CHW than urban children, who visited health facilities more often. Children in the poorest households consulted a CHW or a private provider less frequently than those in the middle quintiles. Drug shops and private clinics were commonly used for care, and it was concluded that they should be included in iCCM programmes.

Kalyango et al. (2012) studied the use of community medicine distributors and medicine vendors (malaria RDTs were not used) in Uganda in a cluster randomized trial of iCCM for malaria and pneumonia and community management of malaria only. Care-seeking and malaria drug use were both slightly more frequent when both pneumonia and malaria could be managed rather than malaria only.

Seidenberg et al. (2012) examined whether the availability of iCCM influenced care-seeking behaviour for children under 5 years of age in rural Zambia. When iCCM was available, CHWs were used more often than formal health facilities for children with fever. For children with fast or difficulty breathing, there was increased use of CHWs only when they were trained to identify pneumonia and supplied with amoxicillin. iCCM can thus decrease the work load at primary care centres.

In a study of the introduction of newborn care within iCCM, Kayemba et al. (2012) found that CHWs could recall some of the danger signs they were supposed to identify (81% remembered 'infected umbilical cord' and 69% 'skin rash') but missed the most important signs of severe newborn illness (only 43% remembered 'failure to breastfeed'). If CHWs and community members are to help sick newborns more, their ability to identify danger signs and comply with referral must be strengthened. The quality of care at health facilities should also be improved.

Nsona et al. (2012) described their experience in scaling up iCCM in Malawi. Afterwards, an average of 20.7 cases of malaria were treated and 1.0 case was referred each month among 1000 children aged 0–4 years. CHWs made a correct assessment in 77% of cases, classified the disease in 68% and gave the correct treatment in 62%; however, only 37% of the children were assessed for the four physical danger signs, and only 55% were referred when danger signs were identified.

In a comparison of methods for assessing the quality of care in iCCM (no malaria RDTs used) in Malawi, Cardemil et al. (2012) evaluated the performance of 131 CHWs against the gold standard of direct observation with reassessment by an expert. Performance was judged by direct observation without re-examination, registers and case scenarios. No difference was found for correct treatment of uncomplicated fever and of diarrhoea; however, the number of CHWs who prescribed the correct treatment for fast breathing and for severe illness was overestimated with all three methods.

McGorman et al. (2012) designed a 'harmonized framework' based on eight components from the WHO health systems 'building blocks' to facilitate the design, implementation and evaluation of iCCM. They proposed one or two global indicators that could be measured in all iCCM programmes and 39 programme and country-specific indicators that could be measured in relation to the context.

As measures based on distance tend to overestimate real access to care by two- to threefold, Guenther et al. (2012) measured access to health care as the product of several factors, including geographical access and the availability of staff and medicines (effective access). iCCM increased both geographical and effective access, but the latter was still suboptimal on average, with only 75% availability of CHWs and 60% availability of medicines.

George et al. (2012) surveyed iCCM programmes in 28 UNICEF country offices and found that governments that paid CHW monthly salaries or provided financial incentives of any type were generally more likely to implement iCCM in one half or more districts in a country. Some services, such as testing with malaria RDTs, were provided more often by health facilities (in 25 coun-

tries) than by CHWs (in 13 countries), while no difference was found in the provision of other services, such as that of oral rehydration salts or ACTs.

Callaghan-Koru et al. (2012) reported on managers' perceptions of iCCM and on the motivating and demotivating factors reported by CHWs. Managers perceived several benefits of iCCM, at both health facility and community levels, such as reduced caseloads at facilities, cost savings, and reduced use of traditional healers. They nevertheless considered that the scope and mandate of iCCM should be limited. CHWs reported that they were motivated by skills development, social status, recognition by the community and allowances received for meetings and training, while they were demotivated by the heavy workload, irregular working hours, inadequate drug supplies, equipment and supervision, insufficient assistance in solving problems, spending personal funds to run the clinic and anxiety about community perceptions.

Potential use of private drug shops to administer iCCM was studied in Uganda. Awor et al. (2012) found that, in the absence of an iCCM programme, care for most febrile children was first sought from the private sector (53%) rather than the public sector (17%), and that only 10% received appropriate treatment for malaria at drug shops and none received appropriate treatment for symptoms of pneumonia or diarrhoea. The quality of care at drug shops must therefore be improved, for example through iCCM.

The adoption and acceptance of iCCM by the community was assessed qualitatively in Uganda by Nanyonjo et al. (2012). While some advantages of iCCM over other programmes of care were recognized, including quality, cost and the compatibility of iCCM with sociocultural beliefs and expectations, the community was concerned about drug supplies, financial support, safe referral and undesirable CHW behaviour and demotivation.

Strachan et al. (2012) interviewed 15 international agencies with experience in iCCM about interventions to improve the motivation and retention of CHWs. Several interventions in CHW recruitment, training, supervision and incentives were recommended. Other areas evaluated included community involvement and ownership, information and data management, 'm-health' and various cross-cutting issues.

In a study of the availability of essential medicines for CHWs in Ethiopia, Malawi and Rwanda, Chandani et al. (2012) found that more than half of CHWs were out of stock of at least one of the main products at the time of the assessment. Factors that would ensure that medicines reached CHWs were their availability at supply points, understanding of the supply chain and management capacity among CHWs and supervisors and the availability of transport.

Sadruddin et al. (2012) in Pakistan compared the household costs of community management of severe pneumonia (oral amoxicillin for 5 days) with provision of a first oral dose of antibiotics and referral to a higher-level facility. The average cost per episode treated was US$ 1.46 in the group managed in the community and US$ 7.51 in the group that was referred. The financial burden on households would therefore decrease if greater reliance were placed on CHWs, and health system costs would be reduced by fewer admissions.

Lainez et al. (2012) analysed data obtained by monitoring iCCM programmes supported by the International Rescue Committee between 2004 and 2011 in six countries (Ethiopia, Ivory Coast, Rwanda, Sierra Leone, South Sudan and Uganda). iCCM resulted in two- to threefold better access to treatment than health facilities alone, with two to three consultations per child per year. In Sierra Leone, it was found that the more children in the catchment area of a CHW, the less health facilities were used, and an increased frequency of supervisory visits decreased the rate of overtreatment of pneumonia. Despite widespread availability of medicine for diarrhoea, however, the number of episodes treated remained at less than one episode per child per year in all six countries, whereas treatment of 3.2 episodes per child per year was expected.

In summary, the results of these studies suggest that provision of antimalarial agents at community level can decrease mortality; the private sector is an important potential source for iCCM; well-implemented iCCM programmes result in shifts in health care-seeking behaviour; and the challenges to national scaling-up are in supervision, supplies and human resources. Further operational research is needed to develop and update the iCCM strategy, including definition of the diagnostic and treatment package (which diseases to include and which tests to use), the optimal strategy for remuneration and motivation of cadres (volunteers versus paid), integration of iCCM within the larger health system and provision of iCCM through the private sector. A formal review of iCCM research priorities is being conducted with the methods of the Child Health and Nutrition Research Initiative.

4.3 Successes in and challenges to scaling up iCCM in countries

A few countries have attempted to scale up iCCM, but in different ways. For example, some used paid rather than volunteer workers; iCCM was implemented strictly rather than including a wide range of activities; and different data collection methods were used. A 'catalytic initiative' within the 'integrated health system strengthening' programme (UNICEF, 2012), began in 2008 to facilitate the scaling-up of iCCM in six countries with high burdens of pneumonia, diarrhoea and malaria: Ethiopia, Ghana, Malawi, Mali, Mozambique and Niger. The activities supported include policy reform to allow CHWs to give treatment (in particular antibiotics for pneumonia), plans for implementing iCCM within the context of child health, training and deployment of CHWs and system support for CHWs, such as supervision, monitoring and the supply chain. The level of use of iCCM varied by country, but more than 5.5 million courses of treatment were given in the six countries, including three million for malaria and 1.3 million antibiotic prescriptions.

CHWs are known as 'health extension workers' in Ethiopia, 'community-based agents' in Ghana, 'health surveillance assistants' in Malawi, 'relais communautaires' in Mali, 'agente polivalente elementar' in Mozambique and 'agents santé communautaires' in Niger. The length of training varies between 2 weeks and > 1 year, the number of health activities between six and nine and the number of activities for nutrition or newborn health between three and 11. In Ethiopia, Malawi and Niger, CHWs are paid a salary, while other types of financial incentive are used in the other countries. Ghana and Mali also use a system of mark-ups on drugs and non-financial incentives. In some places in Mali, users pay a small fee.

One of the challenges identified during scaling-up of iCCM was retention of CHWs. Possible solutions include new systems to pay them, such as standardized incentive schemes for volunteers and building structures to house both a village clinic and accommodation for CHWs, supported by the community. Optimal strategies for supervision are needed; peer supervision by senior CHWs was found to be more successful than supervision from a health facility. The problem of drug shortages, which can give rise to changes in care-seeking behaviour, was addressed by creating temporary parallel drug distribution systems, incentive systems for re-supply points, vouchers for bicycle maintenance and contracting to a third party. Poor referral practices were a consistently reported problem, but the reasons are not fully understood. Often, CHWs anticipate that families will not take their children to the referral level of care and take a treatment decision at community level. Data collection, monitoring and evaluation will require innovative techniques, such mobile phone technologies. UNICEF (2012) published a working paper describing the lessons learnt from this experience and recommendations.

A survey of the quality of care within iCCM was conducted in Oromia, Ethiopia, in 2012 (Miller, 2013), in which 104 health posts in intervention areas and 46 in control areas were compared. The proportions of health posts that had been supervised in the past 3 months were 87% vs 43%, the availability of ACTs was 88% vs 50%, the availability of antibiotics was 99% vs 2% and the availability of malaria RDTs was 89% vs 63% in intervention vs control areas. Classification of all iCCM

illnesses, as compared to a "gold standard" re-examination of the child, was correct in only 50% of the health posts in the intervention areas, although slightly better than at higher-level facilities in Ethiopia (40%). In a study in Malawi (UNICEF, 2012), classification of all iCCM illnesses at community level was correct in 70% of cases.

A systematic literature review of the evidence on the efficacy of various interventions to promote the malaria component of iCCM is being conducted; 42 studies published between 2000 and 2011 have already been included. Preliminary analyses show that a median of 99% of malaria RDT-positive and 8% of RDT-negative patients received ACTs. When management of malaria was part of iCCM, the quality of care remained high. However, the quality of management of pneumonia was poor: a median of 67% of children with pneumonia as determined by iCCM received an antibiotic. The preliminary results indicate that six strategies could improve targeting of treatment: appropriate demand generation in the community; practical, interactive training; clear guidelines with simple algorithms; pre-packaging of medicines in appropriate course-of-therapy doses; regular supportive supervision; and a functional referral system from the community to health facility level. National leadership and coordination, information-sharing and effective strategies for building skills are also important in scaling up iCCM. The main factors in the long-term sustainability of iCCM programmes should be evaluated, such as the optimal length of basic training and optimal levels of financial and other incentives for adequate motivation and retention. Increasing efficiency by increasing demand for, and use of services and new technologies should also be addressed.

5. Public sector experience with community management of fever

iCCM has been organized and implemented in different ways in different countries. In many, the content of the algorithm has been adapted to the local situation, as have the ways in which training, supervision, data collection, reporting, remuneration and other incentives are conducted. Supply issues have been addressed differently, although a common problem was that countries did not have clear methods for quantifying the demand for different medicines in areas with different prevalences of malaria, pneumonia and diarrhoea and faced stock-outs or surpluses. Another recurrent problem was that quality of care given by CHWs was often better than that provided in health facilities. As patients with severe disease who cannot be managed at the peripheral level must be referred, the continuum of care must be maintained and more specialized services offered at higher levels, so that referred cases are treated appropriately. This may require a change in the type of service provided at facility level, starting with spending adequate time with patients in order to manage them properly. Definition of a minimum package of care and the competence required for workers at health facilities would be valuable. A simple tool is needed to define the major causes of malaria, diarrhoea and pneumonia, and detection of danger signs to decide on referral of patients should be improved. The role of oral amoxicillin in pre-referral treatment of very severe pneumonia at community level should be further evaluated, as should the usefulness of electronic or automated readers to improve measurement of the respiratory rate by CHWs.

5.1 Malawi

iCCM was introduced in Malawi by the Ministry of Health in June 2008 to bring treatment for common childhood conditions closer to home, to promote equity, to empower districts to implement iCCM in accordance with local needs and to increase community treatment of child health problems. Health surveillance assistants, paid by the Ministry of Health, have multiple tasks, including environmental health, immunization, monitoring growth, antenatal care, HIV testing and counselling and distribution of insecticide-treated bednets. They are present in about 4000 hard-to-reach areas (> 8 km or > 1 h walk from a health facility). Five to 15 health surveillance assistants report to one health facility and are trained with materials based on WHO generic 'job aids'. By October 2008, all 28 districts had been included and 84% assistants had been trained in 6-day sessions. Standardized treatment registers and reports based on the national IMCI technical working group framework were introduced. Support was provided by several agencies, including UNICEF, WHO, Save the Children, Population Services International, Support for Service Delivery Integration, and Concern.

Health surveillance assistants are the primary caregivers within iCCM in Malawi. When referral is needed, the village health committee generally provides support for transport of the child to a health facility. The tasks of the assistants within IMCI are:

- to assess, classify and treat the child; currently, malaria is treated presumptively, as RDTs are not available;
- to advise the child's caregiver on continuing treatment at home, on breastfeeding and rehydration, on when to go to the clinic and on a follow-up visit after 3 days;

- to record the details of diagnosis and treatment on a 'patient card' that allows transfer of patient information between the community and health facilities; and
- to register the number of cases, the medicines dispensed and stocks of supplies, with a report sent regularly by mobile phone.

All health centres have senior health surveillance assistants, who supervise quarterly those in the villages. Supervisory support also includes meetings between the senior health surveillance assistants and the district team. Registers are the basis for supervision, and the senior health surveillance assistants use them to collect, compile and send data to district level, where they are integrated into the health management information system. This system appears to be working well according to reports from districts.

iCCM implementation in Malawi has allowed identification of what has worked (**Table 2**) and the bottlenecks to be overcome (UNICEF, 2012). Workers in health facilities complained that the iCCM algorithm has become too complex after the numerous updates. Furthermore, human resource constraints oblige the team to operate on scheduled days and to immunize children only once a week. The team is generally composed of one medical assistant, one nurse and one assistant environmental health officer, who have to cover a large population area. More support is needed in facilities to ensure that IMCI is applied appropriately and that the staff has enough time to supervise the health surveillance assistants. Overall, iCCM has been well integrated into the health system, but there are still weak linkages with other levels of care. System support is needed at all levels of care and is more relevant than providing only iCCM support.

The policy for the iCCM programme in Malawi is under review and the national health authorities are considering the following elements: 1) reducing the radius to 5 km rather than 8 km in order to introduce iCCM into villages remote from health facilities; 2) introducing malaria RDTs at community level (as well as an uninterrupted supply at health facilities to avoid back-referrals); 3) using rectal artesunate as pre-referral medication; and 4) strengthening care for infants aged 0–2 months, with follow-up home visits by health surveillance assistants.

5.2 Senegal

In Senegal, accessing health care is problematic, as 60% of villages are more than 5 km from a health facility. As a consequence, 80% of people who die do so at home without contact with a health worker. There are three levels of CHW 16 key health behaviours; ensure diagnosis and treatment of malaria, ARIs, diarrhoea and malnutrition; and refer severe cases to a higher level of care. The second type are providers of home care, who implement iCCM without the malnutrition component, and the third are 'relais' who are in charge only of sensitization and referral (no treatment).

The 'prise en charge des cas de paludisme à domicile' was conceived to bring treatment close to households, so that the house becomes the 'first hospital'. CHWs only manage malaria cases, with RDTs and ACTs. By 2012, the strategy had been introduced in 10 regions corresponding to 39 districts and 1076 villages. In five districts, 4638 CHWs have been trained to manage ARIs as well, using specifically prepared flow charts. The decision chart for fever specifies that malaria RDTs be performed only after elimination of other causes of fever (such as cough, tonsillitis, rash and ear discharge) and that RDT-negative patients must be referred. Patients with pneumonia are treated with co-trimoxazole, but, as the national policy has changed to the use of amoxicillin, CHWs will be retrained accordingly. The strategy has been well accepted in communities: 75% of households use home care providers first, 96% of home care providers are called within the first 24 h, and 95% of households reported that they were satisfied. No deaths have been notified by the CHWs, and the overall mortality rate from malaria decreased from 18% in 2006 to 4% in 2009. In five pilot districts, 16 588 cases of ARI received treatment, the recovery rate was 98%, and 229 cases with danger signs were referred.

TABLE 2.

Successful activities in the Malawi iCCM programme

Programme component	Successful activities
National orientation and capacity-building	Clear leadership of the Ministry of Health and understanding by partners of their roles and responsibilities
	Minimal adaptation of the generic WHO and UNICEF guidelines
	Orientation of district health management teams, mapping of hard-to-reach areas and joint planning
	Involvement of the national IMCI technical working group
	Proper coordination of support and collaboration of partners for activities in assigned districts
Community ownership and participation	Community dialogue before introduction of services
	Formation of village health committees in each functioning village health clinic
	Involvement of community leaders in managing the village health clinic
Skills-building	Devolution of health surveillance assistant training to district level
	Leadership by district IMCI coordinators and involvement of district health management team members
	Appropriate case loads in district hospitals for inpatient and outpatient clinical practice during training
Supervision	Assignment of specified responsibilities to various cadres of staff (senior health surveillance assistant, environmental officer, community nurse)
	Training supervisors in iCCM and supervisory skills
	Preparation of integrated checklists incorporating elements of the 'sick child recording form'
	Creation of a mentorship programme for periodic reinforcement of the skills of trained health surveillance assistants
Medicines and supplies	Provision of medicines to health surveillance assistants during their monthly visits to their designated health centre
	Guidance on quantification of medicines for district health management teams
	Use of standard operating procedures for logistics management information systems to strengthen use and management of medicines and other supplies
Referral	Designation of health centres to which health surveillance assistants should refer patients
	Use of referral notes and feedback on referrals
	Involvement of village health committees in finding solutions to facilitate referral, such as bicycles or other transport and escorts at night
Monitoring	Monitoring and evaluation desk in the IMCI unit
	An iCCM register based on the 'sick child recording form'
	Assessment of the quality of care provided by health surveillance assistants
Motivation	Recognition of health surveillance assistants as formal members of the health work force
	Identification and provision by village health committees of adequate housing for health surveillance assistants in hard-to-reach areas
	District-based village clinic review meetings to strengthen implementation
Innovations	Provision of mobile phones to health surveillance assistants to facilitate contact and SMS-based reporting
	Commodity-stock reporting

The strengths of this pilot project to implement iCCM were the proficiency of RDT performance and treatment with ACTs; adherence to the recommendation of referring severe cases, infants < 2 months of age, pregnant women and RDT-negative cases; and the acceptance and involvement of community leaders and communities in all activities. The weaknesses were insufficient monitoring of CHWs (who are sometimes involved in several programmes), lack of blood safety tools (such as sharp boxes and gloves), wrong care provision by some CHWs and shortage of medicines in some districts, particularly co-trimoxazole. The next steps for the national health authorities of Senegal are to expand iCCM to remote rural villages, to ensure its sustainability and to improve referral and transport of severe cases to higher levels of care.

5.3 Uganda

In Uganda, groups of CHWs are known as 'village health teams' and are chosen by the community on the basis of their ability to read and write and to ensure a gender balance. There are four or five village health teams per village, two of which care for sick children within iCCM. They identify danger signs in newborns on days 1, 3 and 7 after delivery and refer them if necessary, and they detect malaria with RDTs, pneumonia with respiratory timers, diarrhoea and acute malnutrition in young children. Village health teams receive 5 days of training in basic health promotion and iCCM from district trainers (of whom there are six per district) and are certified. They use laminated pictorial job aids, paper registers and their own mobile phones to report weekly on cases and drug stocks ('mTrack'). They are supervised at quarterly meetings at the district level. They receive no financial compensation but are offered incentives such as bicycles and T-shirts.

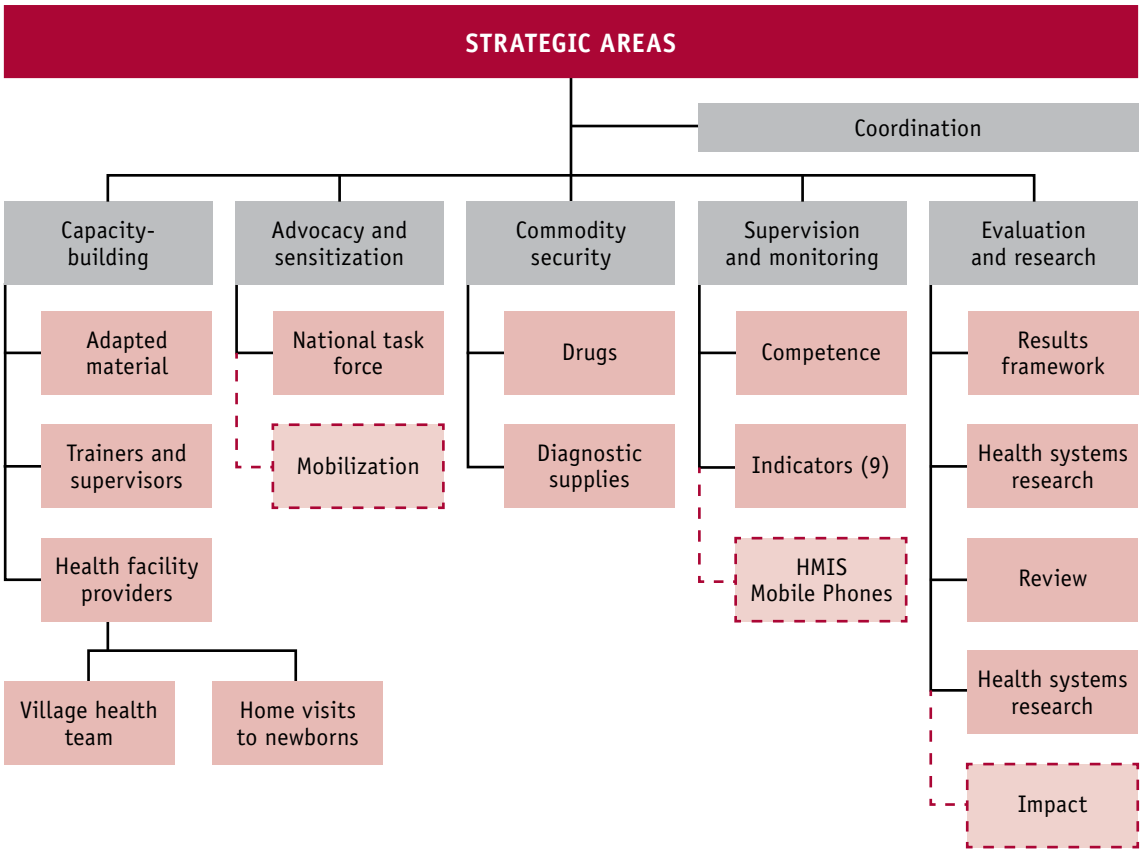
In the algorithm used by village health teams, all cases, including severe febrile illness, are tested for malaria with RDTs to minimize the risk for stock-outs of medicines at health facilities and to maximize compliance with referral. Pneumonia is treated on the basis of fast breathing only; cough or difficult breathing is not a necessary symptom. Children with severe RDT-negative febrile illness still receive pre-referral rectal artesunate but no antibiotics.

The programme (**Figure 6**) is led by the Ministry of Health, supported by WHO and UNICEF, and has been implemented in 54 districts. Four years elapsed between the start of preparation of the programme up to the planning of its implementation at national scale (112 districts). The two main indicators out of nine are that 80% of children < 5 years with non-severe illness receive appropriate treatment within 24 h of the onset of illness and that 80% of severe cases, including newborns with danger signs, are promptly referred to formal providers.

Scaling-up to national level is based on a comprehensive proposal funded by the Global Fund to Fight AIDS, Tuberculosis and Malaria (round 10) and includes preparation of a national medical store to supply medicines in response to information provided by the SMS-based reporting system 'mTrac', analysis of the results of a review of early implementation of the programme, pilot implementation of iCCM in the private informal sector and formation of stronger links between health facilities and village health teams in a quality improvement model. To address the last aim, pages to be filled in by village health teams have been added to the 'mother–child health passport'.

The mTrac reporting system has had good results; more than 80% of village health teams reporting no stock-outs of target medicines. The distribution of diseases was found to vary geographically, malaria representing 27–67% of cases, pneumonia 20–46% and diarrhoea 13–39% of cases with a documented diagnosis. Compliance of village health teams was lowest for treatment with zinc, followed by antimalarial agents; however, as zinc tablet are co-blistered and strips have to be cut, their use may be poorly recorded. Some types of artemether–lumefantrine blister packs ran out more rapidly than others, so that village health teams had to divide the dose, by cutting the treatment packs. As rectal artesunate was used less often than foreseen (in 0.9–3.4% of cases), the doses tended to expire. Oral rehydration salts were used rarely, and better diarrhoea treatment is

FIGURE 6.
Components of the iCCM programme in Uganda



necessary. Malaria RDTs were also not always used, and patients with non-severe malaria were sometimes referred to the nearest health facility without a test.

The main problems were with drug supply through the national distribution system, links with health facilities, integration of iCCM (including health information) into the district structure, health facility staffing, the skills of village health teams, particularly with regard to newborns, and coordination of partners and programme inputs. Some lessons learnt are that motivation of village health teams (in Uganda, they are not paid) and the availability of drugs are essential for proper implementation; public sector support is required to ensure sustainability; working with partners who invest in health facilities from the start allows better integration of iCCM into the health system; resources must be mobilized; and appropriate resources should be invested in advocacy.

5.4 Discussion of country experience

Some common challenges, such as in the supply chain and supervision and the fact that community workers are more compliant to guidelines than health workers at health facilities, were seen in all three national programmes, even though they were organized differently. Various models of CHW services have been used, depending on the health system and the cadres of CHWs available. In some countries, CHWs travel door-to-door, while in others they are based at health posts or small village clinics. The definition of CHWs should be kept flexible to allow their integration into different systems. The common purpose of these systems is to provide services as close to the household as possible.

Various algorithms have also been used in different countries. Although some adaptation to local conditions is necessary, a number of evidence-based elements of the algorithm are universally applicable and should not be changed (see **Figure 3** page 16). One is to assess malaria RDT negative children for cough and diarrhea rather than to refer them all; another is that all febrile children with danger signs should receive pre-referral antibiotics, especially when the result of a malaria test is negative. Ideally, an injectable antibiotic should be given to such children, but in most countries the use of injectable formulations at community level is considered inappropriate. Another element is to refer severely febrile children without wasting time performing a malaria RDT. This latter recommendation might however change in the future with decreasing malaria transmission. In Zanzibar, for example, severe cases are tested for malaria before referral because the prevalence is now extremely low, and documentation of each case is essential in order to receive certification of elimination. Amoxicillin should be used for first-line treatment of pneumonia, because information on pneumococcal sensitivity to co-trimoxazole is rarely available at country level. Furthermore, treating pneumonia at community level with amoxicillin has been shown to be safe, and there is limited evidence of any benefit of the use of co-trimoxazole, which is best reserved for prophylaxis in HIV-infected patients. Many national programmes are keeping co-trimoxazole for the treatment of pneumonia until a cheap formulation of amoxicillin for children and an adapted formulation (small quantity) for newborns become available.

Not all referrals from the community are for life-threatening conditions, some being for persisting conditions. Health facilities often do not have protocols to manage them and do not offer better care than that provided at community level. In certain situations patients could benefit from direct referral to hospitals, especially in countries such as Malawi, where the distance between health centres and hospitals is shorter than that between CHWs and health centres. In Senegal, referral to a hospital through a health centre is mandatory. Whatever referral system is chosen, the problem of low compliance to protocols by health facility workers remains, with the paradoxical result that facility-based providers often give poorer service than CHWs. The quality of care in health facilities, including hospitals, must therefore be improved, and the minimum package of care that should be available at each level should be defined. Implementation of iCCM provides an opportunity to improve the quality of care by creating and strengthening synergy between the community and other levels of care.

Quantification of tests and medicines was a challenge in all countries implementing iCCM. Supplies for CHWs should be integrated into the drug supply system of health facilities, not only to ensure sustainability but also because the shift of patients treated in the community rather than at a facility affects the number and type of tests and medicines needed in each location.

Supervision is also an issue, because there were few personnel at health facilities to supervise CHWs. Peer-to-peer supervisory visits in the community have been found to be successful, although supervision by health facility staff helps to strengthen the continuity of care between the two levels.

The reporting of community-level data on malaria, pneumonia, diarrhoea and cases referred to a health centre is often not included in the data reported at district or national level. The national health information system should report as separate data, the cases treated for the three conditions and cases referred at the community level.

Operational research should be conducted during implementation of iCCM, including studies of the clinical outcome of febrile children with no obvious cause of fever and negative RDT results, children with severe pneumonia and newborns with bacterial sepsis; for the last group, initial results should be available at the beginning of 2014. Such research is necessary to monitor the impact of iCCM on health and to test practical changes to the current iCCM algorithms.

6. Private for-profit sector experience in community management of fever

The private-for-profit sector is a diverse group of entities that make a profit by delivering care. They range from private establishments staffed with clinicians to accredited drug dispensers and informal street drug vendors. They play an important role of the health care system in many countries: 30–70% of febrile children in Africa are treated in the private sector, especially informal drug sellers (WHO, 2011c). As the private sector is so diverse, all segments must be considered in strategies for interventions, monitoring and research. Involvement of the sector can be enhanced by positive incentives, such as transmission of knowledge and training, accreditation or certification schemes, profit, social recognition and social marketing.

The services offered vary by location, but, wherever medicines are sold over the counter, overtreatment with antimalarial agents and antibiotics is a common problem; the worldwide threat represented by increasing drug resistance means that such practices in the private sector cannot be maintained or encouraged. In the absence of regulations and enforcement mechanisms to ensure that certain medicines are delivered only by prescription, more effective systems must be used to protect these medicines from misuse. One solution is to promote diagnostic testing, with a confirmatory diagnosis at the site at which the antimicrobial agent is sold. If there is no compensation mechanism, however, this strategy may represent a direct financial conflict of interest for the provider; solutions must be found to promote selling the correct treatment even at the risk of losing revenue. Use of malaria RDTs can decrease overtreatment and thus decrease the risk for development of resistance, direct the patient and provider to an alternative diagnosis and appropriate treatment for non-malaria disease and rationalize health system expenditure. Malaria RDTs are promising for malaria diagnosis in the private sector. The main reason for overtreatment with antibiotics in both the public and the private sector is the risk of pneumonia, for which there is presently only a clinical test (measurement of respiratory rate) and no diagnostic device. While clinical determination of the respiratory rate is cheap, it is better performed when tools such as timers are used. Diarrhoea is often erroneously treated with antibiotics, especially in the private sector, when effective treatment such as oral rehydration salts and zinc should be given instead.

Currently, few malaria RDTs are used in private clinics or sold in pharmacies, and they are often expensive and of variable quality. In a survey of RDT stocks, prices, and quality in private outlets in the Central African Republic, Nigeria, Peru, the Philippines, Senegal and the United Republic of Tanzania, RDTs were available in 35 of 324 (11%) private facilities, the prices ranged from US$ 1.00 to $16.81, and only 64% passed quality control (Albertini et al., 2012). These results suggest that quality assurance and quality control are essential in the private sector, as in the public sector. Consideration should be given to monitoring, as enforcement of regulations is difficult in the for-profit sector.

Use of malaria RDTs in the private sector could be increased in a number of ways. Their use could be promoted in all settings, but a better approach would be to apply certain criteria, such as starting in areas with low rather than high malaria prevalence, where management of non-malaria febrile illnesses is available, and in the formal rather than the informal private sector. Financing and delivery mechanisms should also be carefully considered. Rather than financing ACTs only,

programme aiming to improve the quality of malaria case management in the private sector should include financing and delivering of RDTs, ACTs, as well as diagnostics and medicines for the integrated management of non-malaria fevers. Financial incentives should be introduced to promote use by both retailers and consumers of RDTs rather than clinical diagnosis; retailers should not decide the choice of treatment after a RDT result; consumers should demand the correct medicine after a RDT result; and bodies that finance initiatives targeting the private sector should support use of both RDTs and ACTs rather than ACTs only. Several solutions have been proposed by Ramanan Laxminarayan to tie the financing of RDTs and ACTs: subsidize RDTs to make them more profitable for retailers, who would then prescribe ACTs according to the RDT result; give consumers only the appropriate treatment, thus saving costs; and ensure that the costs of subsidies for RDTs are covered by the savings on ACTs. One study showed that subsidizing RDTs can increase the use of RDTs, without decreasing the use of microscopy (Cohen et al., 2012). For example, ACTs could be sold at a retail price of US$ 1.00 if bought without a RDT but could be free of charge if an RDT has been purchased at a price of US$ 0.40. If the profit margin on ACTs was US$ 0.30 and that on an RDT at least US$ 0.30, the retailer would be better off with a two-step sale. Such models could be applied in malaria programmes covered by vertical funding but not in programmes for pneumonia and other non-malaria causes of fever, as there is no integrated programme targeting the private sector. Programmes to improve the quality of care in the private sector should be linked to the 'universal health care' agenda[1] for primary health care.

In Uganda, two thirds of febrile children are treated in the private sector, especially drug shops, where the quality of care is poor and medicines are used irrationally. Implementation of the 'affordable medicines facility for malaria' in this country resulted in overuse of ACTs for non-malaria causes of fever. A pilot project (Awor et al., *unpublished study*) was therefore initiated to introduce integrated case management of malaria, pneumonia and diarrhoea in drug shops. During 8 months, 44 drug shops were given subsidized pre-packaged drugs, free malaria RDTs, respiratory rate timers and training in social marketing. They were supervised once a week for 4 weeks, then twice a month and then once a month. Intervention shops were compared with 40 control shops in similar districts, where presumptive treatment with ACTs was customary and amoxicillin prescribed without respiratory rate measurement. Caregivers were interviewed on leaving the shops, and before-and-after household surveys were conducted. The characteristics of the patients were similar at baseline and at follow-up, as well as for intervention and control. After the intervention, RDT use increased by almost 90% in the intervention group, and, 74% of children in the intervention group who had cough and fast breathing received amoxicillin as compared with only 33% in the control group. The respiratory rate was counted in 55% of children with cough in the intervention group. While co-trimoxazole and overall antibiotic use decreased compared to the pre-intervention period, 60% of children in the intervention group and 74% in the control group still received an antibiotic. The respiratory rate was measured by 78 of the 80 vendors surveyed. Of children with diarrhoea, 77% were treated with oral rehydration salts and zinc in the intervention group and only 5% in the control group. The household survey showed that more people chose drug shops for care and fewer used private clinics after the intervention, while use of public health facilities remained the same. The conclusion was that integrated management of malaria, pneumonia and diarrhoea in the private sector is possible and improves the quality of care for diarrhoea; the results for malaria and pneumonia are still being analysed. Diagnostic testing became more popular, and parents were willing to take their children to drug shops, at the expense of attendance at private clinics but not at public facilities.

Cambodia, which has embarked on a malaria elimination programme, has 10 years of experience with use of ACTs and RDTs in the private sector. A package of social marketing interventions that mirrored activities in the public sector was tested (Sim et al., *unpublished study*), includ-

[1] **http://www.who.int/universal_health_coverage/en**, accessed 6 September 2013.

ing providing accessible high-quality medicines and tests and having responsible providers and informed patients. A major component was communication to change behaviour in both private sector providers and communities. This included training and medical information for providers and mass communication campaigns via radio and mobile video units for communities. The same RDT and ACT products are used in the public and private sectors but with different brand names. Pricing is configured to be affordable for patients (adult dose of ACT, US$ 0.62; RDT, US$ 0.25) while also giving providers large profit margins to encourage testing (adult dose of ACT, US$ 0.21; RDT, US$ 0.20). Training of providers is important and includes how to act on an RDT result, which drugs to prescribe, which patients to refer, national treatment guidelines, the ban on monotherapy and updated information (e.g. on discontinuation of chloroquine). This information is covered in a 1-day training course. 'Medical detailing teams' consisting of doctors and pharmacists visit the drug vendors to reinforce the training, answer questions and provide support. In 2012, 1854 private providers were trained, 5870 supervisory visits made to 1404 outlets and 106 355 RDTs performed, of which 80% were negative. In a survey of the response to 'mystery clients', 42% of the providers advised a blood test, and 54% of these offered to do the test. Formally trained providers were more likely to offer the test than untrained providers, and most providers were reluctant to sell antimalarial agents without a prior blood test. Some, however, still believed that RDTs cannot 'see the parasite'. Problems were encountered in performance of the test: only 38% of providers used the correct volume of blood because of difficulty in using a pipette, only 40% waited the full time (20 min) before reading the result, and only 16% disposed of the lancet in a sharps box. The commonest presumptive diagnosis in RDT-negative patients was typhoid (67%), and they were given the drug 'cocktails' that unfortunately remain popular. During ACT stock-outs, the price increased and ACTs were replaced by chloroquine rather than artemisinin monotherapy, the stocks of which decreased, from 6% to 1%. Thus, in order to maintain the quality of services in the private sector, an integrated package of interventions should be provided that includes provider training and supervision, consistent supplies, patient information and monitoring.

In Cambodia, a public–private mix programme has been launched by the Ministry of Health to address the growing problem of drug resistance. The objectives include ensuring that counterfeit drugs and monotherapy are no longer available, all patients receive a parasitological diagnosis and appropriate treatment according to the national policy, and routine surveillance data are collected from the private sector. The activities included mapping, assessment, orientation, preparation of resource material, training of public and private providers, establishment of a referral system for the private sector (with a referral slip), supervision and establishment of a surveillance system. The programme has experienced some success. Private sector providers better understand disease management and referral of clients, and public sector providers are seeing more patients with less severe disease because of earlier referral. Patients have better access to appropriate diagnostic and treatment services. Regular supervision, a committed public sector team and reporting mechanisms were found to be important in order to document where patients seek treatment and what they do after they are referred. The programme is being scaled-up nationally to include companies and industries.

The ACT consortium has undertaken operational research on malaria in the private sector in the United Republic of Tanzania (Briggs et al., 2012). In the rural provinces of Mwanza and Mtwara, data were collected on clients attending randomly selected private sector outlets in order to obtain baseline information on the parasite prevalence in this population and to determine whether patients with documented malaria received antimalarial treatment. Of the 13.5% clients with malaria, only 69% bought an ACT, while 80% of the people who bought ACTs did not have malaria. Five studies linked to the ACT consortium are determining whether RDTs can improve targeting of ACTs in the private sector.

In Uganda, a pragmatic cluster-randomized trial of RDTs is being conducted in registered drug shops in Mukono district (Mbonye et al., 2012). Preliminary data showed that 58% of clients tested with an RDT were positive. Of these, 99% were treated with ACT, while only 2% of RDT-negative clients received ACTs. At the time of the meeting, the treatment status of one of three of RDT-negative clients was unknown. Even in the worst-case scenario – that all those who received unknown treatment were non-compliant to test result – the overall adherence rate was at least 81%. A qualitative assessment indicated that RDT testing at drug shops was well accepted by both patients and providers. Only 1% refused to pay for an RDT. Drug vendors referred 25% of RDT-negative clients, although referral slips were almost never used. When clients of private drug shops were asked how much they were willing to pay for RDTs and ACTs, 70% said they would pay ≥ US$ 0.35 and 25% would pay ≥ US$ 1 for an RDT, while 70% would pay ≥ US$ 1 and 25% would pay ≥ US$ 3 for an ACT. The studies required to understand how RDTs should be deployed in the private sector overlaps to a certain extent with that identified for the public sector, such as the best strategies for managing malaria-negative clients and the transmission intensities that are priorities. Other issues are specific to the private sector, such as the optimal costs and profit margins for RDTs and medicines; how best to persuade clients and providers to act appropriately; how to integrate private sector services into the broader health system; the effects on the public sector of introduction of RDTs in the private sector; and integration of surveillance systems and tracking of cases. Despite these questions, it appears to be possible to use RDTs in at least some segments of the private sector, with appropriate support.

General discussion

The challenges to improving the management of febrile patients in the private sector are similar to those faced in the public sector. Interventions in the private sector must be surveyed and monitored routinely, just as in the public sector, ideally as part of other health management systems. Quality of care and quality of products are especially hard to ensure in the private sector. Empowerment of consumers, by giving them information and managing their expectations, might maintain consistency and quality in this sector, as in the public sector. Branding and social franchising could help consumers to identify good-quality products and services, representing 'soft regulation' to encourage the private sector conform to quality standards. Formal regulatory and policy measures could also be considered, such as to prohibit medicines that should no longer be used, including monotherapy with sulfadoxine–pyrimethamine or an artemisinin.

A notable observation in Uganda was that drug vendors welcomed inspectors rather than fearing them, because of the positive association with formal authorization. Authorization to officially diagnose malaria and pneumonia and to dispense antimicrobials stimulated them to fill in registers and to interact more openly with the public sector. It also gave them credibility in the community. The registers will be useful for monitoring and supervision.

One lesson learnt from the 'affordable medicines facility for malaria' (AMFm) is that the private sector can effectively distribute commodities even in remote areas. In the management of fever, quality must be ensured and services provided rather than only commodities. The public sector might therefore oversee the private sector to guarantee quality of care. How the quality of care in the private sector should be measured is not clear but could be studied by methods used in iCCM programmes, if they can be used for all types of private providers.

Different countries are at different stages with regard to malaria prevalence, use of the public and private sectors and access to RDTs and ACTs. In Uganda, the prevalence of malaria is still high and there are inadequate resources to ensure universal access to diagnosis and treatment. It is therefore unclear whether Uganda should encourage private sector involvement. Realistic, feasible guidance should be given to countries on providing access to RDTs. Although pilot studies have been conducted in the private sector, the only country to have deployed RDTs and ACTs

for several years on a large scale is Cambodia. Moreover, it is not known whether proper use of RDTs can be achieved in the private sector without subsidies or whether other strategies should be investigated, such as using wholesalers and profit margins in national distribution systems to contain prices in the private sector. Subsidies are often the only way to promote demand for high-quality products.

Country experiences have brought to light a number of issues. A recurrent problem is the management of febrile patients with negative RDT results: selling a cocktail of drugs, as in Cambodia, and selling antibiotics or referring patients systematically, as in Uganda, are not appropriate solutions. Referral was poor in most settings because referral is considered a failure by drug vendors. It was found that the intense supervision during pilot implementation cannot be sustained on a larger scale. During wide-scale implementation in Cambodia, supervision did not significantly improve the quality of care provided by drug shops. The question of whether investment in the private sector should be a long-term or an interim solution is legitimate, as the private sector may never provide high-quality care in resource-constrained settings. When health care providers are fully trained, supervised and monitored and the government subsidizes high-quality commodities, little difference is seen with private entities, public health facilities or with CHWs. The accredited drug dispensing outlets in the United Republic of Tanzania have nevertheless become official bases for interventions led by the public sector, and formal private clinics are fully integrated into the health care system, with performance equivalent to that in the public sector. In India, free treatment of tuberculosis is available through the private sector. Interestingly, most care in some developed countries is given by private providers who are managed and regulated by the public sector. In many developed countries the private sector is strongly regulated and the informal private sector is virtually inexistent. Only regulated pharmacies administer treatment, while private practitioners and clinics provide care to patients in order to avoid potential conflicts of interest. In southern Switzerland, for example, the right of private practitioners to sell medicines directly to patients was revoked , and several laboratory procedures can no longer be performed by the clinicians as part of their private clinical practice .

The quality of care also varies widely in the public sector. For example, in India, unqualified, untrained providers work in Government health facilities in the rural south of the country, while fully qualified medical doctors work in Government health facilities in Northern cities (Das et al., 2012). One study (Das et al., *unpublished study*) showed that clinicians working in parallel in both sectors provided better quality of care in their private practice. Expansion of the private sector with strong vertical supervision by the public sector will require strengthening of the latter. Community involvement might improve the accountability of the informal private sector, as shown in iCCM programmes. Communities are sensitive to branding and official accreditation. Parents can often appraise the quality of care, and their capacity should be strengthened by health education.

7. Moving forward: research priorities

7.1 Management of fever in children and adults living in various geographical areas

Much research is required on the causes and management of fever (**Box 3**). Further studies are needed to measure the burden of diseases, to study clinical outcomes of patients with different conditions, to form the basis for the development of new diagnostics, vaccines and other preventive modalities; and to form the basis for new management strategies and health interventions, including changing care-seeking behaviour.

In view of the diversity of diseases and their context-specific determinants, multi-centre, multi-country studies should be conducted in low- and middle-income countries in Africa and Asia. The number of study sites necessary to obtain representative data on the distribution of febrile illnesses is difficult to fix because the epidemiological determinants of diseases associated with fever vary by site, country, region and continent. For each illness, the right diagnostic test (e.g. the best test to detect acute disease rather than chronic carriage) and the right sample (e.g. blood, urine, nasopharyngeal swab) must be selected carefully to form the basis for a robust case definition. Studies of single pathogens or diseases are unhelpful as they do not address the prevalence of the disease among all febrile illnesses or in relation to other diseases. Studies that include severe cases are most likely to produce results that can avert deaths. Once the causes of fever are known, however, giving clinicians long lists of all the possible diseases that cause fever should be avoided and focus placed on prevalent illnesses, those that cause substantial morbidity or mortality and those that require special clinical management.

BOX 3. RESEARCH QUESTIONS RELATED TO CAUSES AND MANAGEMENT OF FEVERS

- Distribution of causes of fever of various levels of severity (mild, moderate, severe)
- Distribution of the causes of fever in different age groups (including adults, children aged 5–10 years, newborns)
- Distribution of the causes of fever in different geographical areas
- Clinical predictors to differentiate diarrhoea, ARIs and nonspecific fever syndromes
- Point-of-care tests to identify patients with severe febrile illness
- Point-of-care tests to identify patients with ARIs who require antimicrobial treatment
- Point-of-care tests to identify patients with nonspecific fever who require antibiotic treatment
- Specific microbiological point-of-care tests for patients living in specific geographical areas (e.g. for scrub typhus in adults in Asia)

Information on resistance to first-line antimicrobial agents is essential for updating treatment guidelines and policies. The information should be based on susceptibility in the laboratory and, when appropriate, on the results of new studies of the clinical outcomes (cure or treatment failure) of patients, keeping in mind that currently available diagnostic tools to detect bacterial sepsis lack sensitivity.

Interest is growing in morbidity and mortality due to viruses, particularly those of respiratory origin. The intention of the 'battle against respiratory viruses' (BRaVe) initiative,[1] launched by WHO and UNICEF, is to identify gaps in knowledge and tools for effective interventions against respiratory viruses and to draw up a research agenda that reflects priorities in public health in this area. A multi-country case–control study, called 'pneumonia etiology research for child health' (PERCH),[2] is under way, led by the Johns Hopkins School of Public Health, in which hospitalized children with severe lower respiratory tract illness are being enrolled to determine the causes (both viral and bacterial) of severe pneumonia and the risk factors associated with the syndrome.

Current iCCM, IMCI and IMAI algorithms could be used as references, but research should be conducted to identify the gaps in the present algorithms. The studies should not be limited to conditions or diagnostic tests that can be managed by CHWs or clinicians at peripheral health care facilities but also include prevalent diseases that require management at the hospital level.

Hospital-based studies of severe cases are important in assessing management strategies that can reduce mortality rates. The hospital admission process must be understood in order to interpret the data and to identify possible selection bias, which could explain why some infections are not reported. Outpatients should also be studied in a case–control design to understand possible risk factors (clinical, biological, social, economic and environmental) for progression to severe disease in order to improve the triage of patients for admission; strategies to prevent severe disease and death; and predictors of severe disease. These predictors, once validated, could then be included in IMCI or IMAI.

Standard protocols, case report forms, case definitions, sample collection, diagnostic testing and case definitions are essential. When possible, case definitions should reflect the IMCI and IMAI classifications and those in the differential diagnosis tables of hospital manuals. A history of fever or elevated temperature should be the signal, as the vast majority of acute infectious diseases present with fever. Diagnosis of a disease that causes fever should be based on both clinical and laboratory results. In the absence of clinical data, colonisation, chronic carriage and concomitant infections (that are not the direct cause of the acute febrile episode) can be wrongly interpreted as the cause of fever. Similarly, clinical data alone are insufficient, as they are neither sensitive nor specific enough for most diseases that cause fever. To differentiate possible pathogen colonization or concomitant infection, the case–control study design would be appropriate with asymptomatic individuals selected as controls.

In order to estimate incidence and prevalence rates of disease, it is moreover necessary to define the profile of the patients and the reference population; however, it is not always easy to obtain estimates of the number of patients admitted with fever, the number of febrile patients attending health facilities, the number of febrile episodes in a community or the proportions of sick people in the community who seek treatment in health facilities and in the private sector. One solution might be to conduct studies in areas where such data are monitored in a demographic surveillance system or where recent household surveys have been conducted. In the absence of such data, it is difficult to estimate incidence or prevalence rates of diseases causing fever.

Much international research is focused on pneumonia and diarrhoea in children. Etiological studies should therefore address nonspecific (non-localizing) fever after exclusion of patients with

[1] http://www.who.int/influenza/patient_care/clinical/brave/en, accessed 6 September 2013.
[2] http://www.jhsph.edu/research/centers-and-institutes/ivac/projects/perch, accessed 6 September 2013.

pneumonia or diarrhoea. The diagnostic criteria for pneumonia should be improved, as cough or difficult breathing plus fast breathing, the criteria used in iCCM and IMCI, are sensitive but not specific. In addition the criteria for clinical diagnosis and management of adult pneumonia need better understanding. Some studies indicate that fever could be added to the pneumonia algorithm to increase its specificity for young children. In newborns, fast breathing is not a good predictor of either pneumonia or bacterial sepsis. A study of the etiology of neonatal infection in South Asia (ANISA)[1] is under way in four communities in Bangladesh, India and Pakistan, in which village health workers are following up mothers throughout pregnancy and after delivery in order to monitor newborns closely after birth.

Studies on the causes of fever raise a number of ethical issues. Often, patients are treated with antimicrobial agents in the absence of evidence-based criteria. Ethical review committees might consider a study unethical if certain groups are deliberately excluded from receiving antimicrobial treatment, even in the absence of clear evidence in favour of the treatment. Ethical questions also arise when samples are taken from patients for future testing before it is known which laboratory tests will be performed. Double informed consent is generally required – one for the study itself and the other for sample and data repository – and this is often not obtained. In the same way that good-quality care must be ensured for febrile patients included in etiological studies, there should be standard national guidelines for the level of care at which patients are recruited. The results of diagnostic testing performed on site should be given immediately to health care workers to guide patient management. As in other clinical studies, all data should be made anonymous, although a logbook with personal information may be kept in order to find the patient if medical follow-up is needed on the basis of the results of laboratory examinations.

7.2 Diseases to be included in adaptations of IMCI, IMAI and other fever management algorithms

Adaptations of the IMCI and IMAI algorithms and new algorithms for the management of fever should be focused on diseases that cause high mortality, are treatable and have clear implications for patient management or for reduction of transmission. For example, emerging infectious diseases are epidemic-prone, so that, even if they are difficult to treat, they must be identified by clinicians in order to control infection and apply other interventions.

The first criterion should be that the disease contributes to mortality attributable to an acute febrile illness, with a combination of high incidence and a high case fatality rate; such data are not currently available for many non-malaria febrile illnesses. The potential benefit of including diseases that are frequent but not dangerous (e.g. tonsillitis in children under 5 years), are uncommon or occur in epidemics (e.g. borreliosis) in algorithms should be carefully weighed.

The next criterion is that the disease is treatable. For example, typhoid in children should be diagnosed and treated promptly (even if it is mild in the majority of cases), to avoid complications. Pyelonephritis is an important cause of severe sepsis in young admitted children, while the short and long-term risk of not treating a low urinary tract infection in a child with mild fever is not well understood. Acute otitis media in children is usually of viral origin and delayed antibiotic prescription in children with no danger signs is a widely used strategy in developed countries that could be considered also in developing countries. Rickettsiosis, scrub typhus, leptospirosis, brucellosis, histoplasmosis and borreliosis, that can lead to serious complications and death, should be considered for integration into algorithms in the settings in which they are prevalent (at least for adult inpatients in whom these diseases contribute to a significant proportion of fever episodes). In HIV-infected patients with low CD4 counts, cryptococcosis and tuberculosis are serious and treatable by particular antimicrobial agents; for example, the detection and referral

[1] http://www.chrfbd.org/ongoing-studies/anisa, accessed 6 September 2013.

of cryptococcal meningitis are already included in the IMAI acute care algorithm. Tuberculosis, brucellosis, trypanosomiasis and leishmaniasis should be suspected in patients, in particular when fever is lasting for more than one week.

Acute HIV seroconversion must be considered in adult febrile patients, because the virus is by far the most transmissible during this stage. In industrialized countries, influenza is actively sought in patients with severe ARI who could benefit from antiviral treatment (which is not the case for mild episodes, at least in the absence of co-morbidity) and in children admitted in winter, so that they can be grouped in wards by pathogen to avoid nosocomial infections. The benefit for tropical countries of using the existing influenza point-of-care test is unclear, because it lacks sensitivity in adults and there is no test specific enough to detect concomitant bacterial infection in children. The same problem applies to the rapid test for respiratory syncytial virus.

Some infections with no specific therapeutic implications are considered important by clinicians even if they are not dangerous; their management may result in overuse of antibiotics. Clinicians should be given guidance on the best management of upper respiratory tract infections, which are usually of viral origin and self-limiting. Clinicians often consider urinary tract infections to be a common cause of non-malaria fevers in children, while in fact they represent < 5% of cases; in the absence of guidance, clinicians tend to prescribe antibiotics.

Some diseases cannot be included in the algorithms because of lack of information on the relevance of doing so, and the appropriate level of care at which they should be managed. Literature reviews should be conducted to integrate new evidence, although compilation of results may be difficult if different study designs are used. An alternative approach would be to use new tests able to identify types of pathogens (viruses, bacteria or parasites) rather than individual pathogens to guide treatment (see below).

7.3 Available point-of-care tests for identifying pathogens or host biomarkers for inclusion in fever management algorithms

Point-of-care tests, able to guide clinical decisions (as it is the case for malaria RDTs), should be included in algorithms for the management of fever. Tests for diseases under surveillance might also be useful, even if detection of the causative agent has no implications for management (e.g. dengue). New diagnostic tests should be included in algorithms on the basis of performance characteristics and the decisions in the algorithm that will be guided by the results, and not simply on their availability.

A point-of-care test to identify patients at risk for progression to severe illness ('marker of prognosis'), irrespective of the cause, would be useful at peripheral level. Even a point-of-care test to detect severe disease ('marker of severity') would be useful, especially for children, in whom danger signs are often difficult to detect. Pulse oximeters and similar devices to measure oxygen saturation and respiratory rate could be used in combination with other tests; if all the results are negative, health workers can be reassured that the patient does not require critical care and can be sent home. If the results are positive, the patient might have be admitted or followed up closely as an outpatient. Studies of clinical and laboratory predictors of severe or significant disease would guide management choices.

Some categories of patients who are only moderately ill but are presently referred according to iCCM, IMCI and IMAI because of danger signs would be better managed at the peripheral level. For example, children under 5 years with cough and chest indrawing (classified as severe but not very severe pneumonia) can be managed safely at the peripheral level and don't need referral (WHO and UNICEF, 2012). Moderately ill children presenting clinically with ARI or malaria could be assessed and treated in the community or at a peripheral health facility rather than referred to a hospital. Point-of-care tests for severity or prognosis would be useful in this context.

Tests to identify bacterial infections in general are also needed. C-reactive protein and procalcitonin can now be measured semi-quantitatively by a POCT, but it is not clear how the tests perform for specific bacterial infections, different age groups and in different geographical areas. Host biomarkers of inflammation are candidates but have not been studied extensively in developing countries. Such tests would be particularly useful at community level, despite some limitations, such as the fact that they provide no information on the class of antibiotic needed or the antimicrobial resistance of pathogens. Point-of-care tests for respiratory viruses (influenza, respiratory syncytial virus) are generally not useful because they do not exclude concomitant bacterial infections in children and are not sensitive enough in adults.

Randomized controlled trials should be conducted to assess the clinical benefit of adding a new point-of-care test, by comparing the health outcomes of patients managed with iCCM, IMCI or IMAI with those of patients managed with an algorithm that includes the test. Trials should be conducted in settings where referral is possible and a higher level of care provides an acceptable quality of care. All tests should be evaluated to determine at which level of care they could be used. A CHW would find it difficult to handle a large number of different tests, and the cost and capacity required to introduce new tests should be evaluated. Not all patients would have to be tested with all available tests, and clinicians would need guidance to be able to identify which patients require which tests. For example, if a test for pneumonia were available, it would be more cost–effective to use it for patients with cough or difficult breathing and increased respiratory rate rather than for all patients with cough. Several studies have shown, however, that many health workers cannot accurately measure the respiratory rate. Ethical issues, such as ensuring the availability of life-saving measures on site when tests are introduced at peripheral level (e.g. oxygen where pulse oximeters are used), should also be considered. Cost–effectiveness studies are essential for determining the feasibility of using diagnostics, with different thresholds for applying tests.

Table 3 lists existing (in blue) and projected (red) point-of-care tests for children under 5 years of age by level of care, particularly primary care. It is based on the assumption that iCCM is practised in the community and IMCI in health facilities. For adults, in addition to those listed in the table, point-of-care tests to detect leptospirosis, rickettsiosis and scrub typhus would be valuable in highly endemic areas, for use in high-level health facilities.

7.4 Febrile patients who would benefit from antibiotic treatment

All febrile patients with diseases including pneumonia, bacterial sepsis or meningitis, group A β-haemolytic streptococcal pharyngitis, tuberculosis and certain sexually transmitted infections would benefit from antibiotic treatment. Patients with a few other diseases causing fever would also benefit from antibiotics according to the local epidemiology. Based on a study of causes of fever (Mayxay et al., 2013) the Lao People's Democratic Republic has proposed that patients > 5 years with a negative malaria test receive doxycycline, as approximately 20% of these cases have leptospirosis. Adaptations of IMCI and IMAI to include new diseases should be guided by local studies showing not only a beneficial impact on individual health outcomes but also potential public health considerations (e.g. potential impact on drug resistance).

This question of antibiotic use also depends on the level of care; in general, illnesses seen at the peripheral and community level are less severe than those seen in higher-level facilities. The cost–effectiveness of giving antibiotics to patients with non-severe illness at community level should be evaluated. In the absence of tests to define which patients would benefit from antibiotics, some overtreatment is necessary, while minimizing the risk for the development of antimicrobial resistance. For example, an evaluation of the feasibility and impact of introducing automated respiratory rate counters is needed to determine whether their use can reduce unnecessary antibiotic use at community level for patients with respiratory complaints.

TABLE 3.

Point-of-care tests to be included in algorithms for the management of febrile children aged 2 months to 5 years at primary care level (available tests in blue, projected tests in red)

Level of care (commodities available)	POCTs detecting a pathogen or disease	POCTs of severity or prognosis
Communities in which iCCM is used (pre-referral antimalarial medicines and antibiotics, rectal or parenteral if possible)	Malaria Typhoid (if highly endemic) Biomarker of bacterial pneumonia[a]	Haemoglobinometer (to guide referral) Respiratory rate device[b] Pulse oximeter (to guide referral) Biomarker of severity (to guide referral and/or provision of antibiotics)
Health facilities at peripheral level in which IMCI is used (oxygen, injections, basic intravenous fluids)	Malaria HIV (if high prevalence) Urine dipstick (children < 2 years) Typhoid (any level of endemicity) Biomarker of bacterial pneumonia[a]	Haemoglobinometer (to guide referral) Respiratory rate device[b] Pulse oximetry (to guide use of oxygen and referral) Biomarker of severity (to guide referral and/or provision of antibiotics)
High-level health facilities in which IMCI and parts of the IMCI district hospital manual are used (oxygen, injections, all types if intravenous fluids, blood bank)	Malaria Dengue HIV (any level of prevalence) Urine dipstick (children < 2 years) Typhoid (any level of endemicity) Biomarker of bacterial pneumonia[a]	Haemoglobinometer (to guide admission for transfusion) Respiratory rate device[b] Pulse oximetry (to guide use of oxygen and admission) Glucometer (to guide admission for glucose administration) Lactate (to guide admission) Biomarker of severity (to guide admission and antibiotic administration)

[a] C-reactive protein, procalcitonin or new host biomarkers
[b] To guide provision of antibiotics as long as a test for bacterial pneumonia is not available, and to select patients to be tested for bacterial pneumonia once a test is available.

Another approach to evaluating whether antibiotics would be beneficial to a patient is to postpone their prescription to the time of follow-up and assessment 48 or 72 h after the first visit if the patient is not cured. This approach is effective for managing acute otitis media in children and sinusitis in adults in Europe. Algorithms for following-up febrile children should be evaluated in well-conducted clinical studies and be incorporated into health worker training, which currently includes little guidance on follow-up of patients. The feasibility of follow-up visits and the distance between the home and a health facility should be taken into account in making decisions on antibiotic prescription. Use of this strategy for antimalarial treatment in the United Republic of Tanzania was, however, deleterious, as health workers used this consideration as a reason to give antimalarial agents to most patients with a negative test.

7.5 Use of iCCM programmes to strengthen quality of care and use of IMCI at public and private health facilities

The operations research group of the iCCM task force raised a number of questions for research on all aspects of iCCM. They address improving the quality of care at health facilities to which patients should be referred by CHWs and the continuum of care between community and health facility levels.

- What approaches convince clinicians, iCCM workers and private providers to adhere to recommended fever management algorithms?
- Why do CHWs adhere to guidelines better than facility-based providers?

- What are the effects of iCCM on case load and case mix at first-level health facilities?
- Does increased community awareness about non-malaria fevers increase providers' adherence to good practice?
- What approaches can be used to educate consumers about what to expect from health workers at community and health facility levels?
- What are the criteria for selecting appropriate private sector providers to maximize coverage of sick children with curative services?
- How can access to health care be increased through the private sector without undermining the public sector?
- What approaches would increase the acceptability of iCCM workers to health workers in formal health facilities?
- How can vertical programmes (for malaria, tuberculosis, HIV) be included in iCCM for integrated management of fever?
- How can countries and partners integrate curative care with preventive services (for newborns, health promotion, preventive chemotherapy) in the community, in the private sector and at health facilities?
- What models of interaction between public and private sectors – including 'empowered demand' – would ensure the complementarity of services?

8. Key recommendations

- Diagnostic testing and treatment for malaria should be deployed as part of programmes promoting the integrated management of febrile childhood and adult illnesses.
- Evidence and lessons learnt from implementation should be taken into account in scaling- up iCCM at community level and IMCI and IMAI at health facility level.
- The essential elements of the generic iCCM algorithm should remain unchanged in country adaptations.
- A continuum of care is important in the management of fever. Therefore, iCCM should be accompanied by strengthening of the quality of care in both health centres and hospitals.
- Programmes aiming to improve the quality of malaria case management in the private sector should include the diagnosis and treatment of common non-malaria causes of fever.
- Carefully standardized studies of various diseases and pathogens implicated in the causation of fever, including susceptibility to antimicrobial agents, should be undertaken at different levels of health care and in different epidemiological settings, seasons and age groups.
- Research on new strategies for effective diagnostic testing and treatment of febrile illness should be encouraged, with clinical outcomes as the primary end-points. The results could be used to adapt IMCI and IMAI, by modifying or extending the diseases in the current WHO algorithms on the basis of health care needs.

9. References

Addo-Yobo E et al. (2011). Outpatient treatment of children with severe pneumonia with oral amoxicillin in four countries: the MASS study. Tropical Medicine and International Health.16:995–1006.

Albertini A et al. (2012). Preliminary enquiry into the availability, price and quality of malaria rapid diagnostic tests in the private health sector of six malaria-endemic countries. Tropical Medicine and International Health, 17:147–152.

Anjay MA et al. (2008). Diagnostic utility of rapid immunochromatographic urine antigen testing in suspected pneumococcal infections. Archives of Disease in Childhood, 93:628–31.

Awor P et al. (2012). Private sector drug shops in integrated community case management of malaria, pneumonia, and diarrhea in children in Uganda. American Journal of Tropical Medicine and Hygiene, 87:92–96.

Bajani MD et al. (2003). Evaluation of four commercially available rapid serologic tests for diagnosis of leptospirosis. Journal of Clinical Microbiology, 41:803–9.

Bari A et al. (2011). Community case management of severe pneumonia with oral amoxicillin in children aged 2–59 months in Haripur district, Pakistan: a cluster randomised trial. Lancet, 378:1796–803

Batwala V et al. (2011). Antibiotic use among patients with febrile illness in a low malaria endemicity setting in Uganda. Malaria Journal, 10:377.

Blacksell SD et al. (2010). Accuracy of rapid IgM-based immunochromatographic and immunoblot assays for diagnosis of acute scrub typhus and murine typhus infections in Laos. American Journal of Tropical Medicine and Hygiene, 83:365–9.

Blacksell SD. (2012). Commercial dengue rapid diagnostic tests for point-of-care application: recent evaluations and future needs? Journal of Biomedicine and Biotechnology, 2012:151967.

Briggs M et al. (2012) Prevalence of malaria parasitemia and medication utilization patterns among clients seeking care for malaria or fever in drug shops in Tanzania, March–May 2012. (Abstract). In: 61th Annual Meeting of the American Society of Tropical Medicine and Hygiene, Atlanta, Georgia, 11–15 November 2012. Deerfield, Illinois, American Society of Tropical Medicine and Hygiene, 2012 (**http://www.abstractsonline.com/Plan/SSResults.aspx**, accessed 6 September 2013).

Callaghan-Koru JA et al. (2012). Health workers' and managers' perceptions of the integrated community case management program for childhood illness in Malawi: the importance of expanding access to child health services. American Journal of Tropical Medicine and Hygiene, 87:61–68.

Cardemil CV et al. (2012). Comparison of Methods for Assessing Quality of Care for Community Case Management of Sick Children: An Application with Community Health Workers in Malawi. American Journal of Tropical Medicine and Hygiene, 87:127-136.

Ceesay SJ et al. (2008), Changes in malaria indices between 1999 and 2007 in The Gambia: a retrospective analysis. Lancet, 372: 1545–54.

Chandani Y et al. (2012). Factors affecting availability of essential medicines among community health workers in Ethiopia, Malawi, and Rwanda: solving the last mile puzzle. American Journal of Tropical Medicine and Hygiene, 87:120–126.

Chappuis F et al. (2013). Rapid diagnostic tests for non-malarial febrile illness in the tropics. Clinical Microbiology and Infection, 19:422–31.

Chinbuah MA et al. (2012). Impact of community management of fever (using antimalarials with or without antibiotics) on childhood mortality: a cluster-randomized controlled trial in Ghana. American Journal of Tropical Medicine and Hygiene, 87:11–20

Cohen J, Dupas P, Schaner S (2012). Price subsidies, diagnostic tests and targeting of malaria treatment: evidence from a randomized controlled trial. Cambridge, Massachusetts, National Bureau of Economic Research (**http://www.nber.org/papers/w17943**, accessed 6 September 2013).

Crump JA et al. (2013). Etiology of severe non-malaria febrile illness in northern Tanzania: a prospective cohort study. PLoS Neglected Tropical Diseases, 7:e2324.

D'Acremont V et al. (2011). Reduction of anti-malarial consumption after rapid diagnostic tests implementation in Dar es Salaam: a before-after and cluster randomized controlled study. Malaria Journal, 10:107.

D'Acremont V et al. (2013). Beyond malaria: etiologies of fever in outpatient Tanzanian children. New England Journal of Medicine. in press.

Das J et al. (2012). In urban and rural India, a standardized patient study showed low levels of provider training and huge quality gaps. Health Affairs, 31:2774-2784.

Feikin DR et al. (2012). Etiology and Incidence of viral and bacterial acute respiratory illness among older children and adults in rural western Kenya, 2007-2010. PLoS One, 7:e43656.

Feikin DR et al. (2013). Viral and bacterial causes of severe acute respiratory illness among children aged less than 5 years in a high malaria prevalence area of western Kenya, 2007-2010. Pediatric Infectious Diseases Journal, 32:e14-9

George A et al. (2012). Community health workers providing government community case management for child survival in sub-Saharan Africa: Who are they and what are they expected to do? American Journal of Tropical Medicine and Hygiene, 87:85–91.

Guenther T et al. (2012). Beyond distance: an approach to measure effective access to case management for sick children in Africa. American Journal of Tropical Medicine and Hygiene, 87:77–84.

Hazir T et al. (2011). 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. Clinical Infectious Diseases, 52:293–300.

Jacob ST et al. (2009). Severe sepsis in two Ugandan hospitals: a prospective observational study of management and outcomes in a predominantly HIV-1 infected population. PLoS One, 4:e7782.

Jacob ST et al. (2012). The impact of early monitored management on survival in hospitalized adult Ugandan patients with severe sepsis: a prospective intervention study. Critical Care Medicine. 40:2050–2058.

Khamrin P et al. (2011). Comparison of the rapid methods for screening of group a rotavirus in stool samples. Journal of Tropical Pediatrics, 57:375–7.

Kalyango JN et al. (2012). Increased use of community medicine distributors and rational use of drugs in children less than five years of age in Uganda caused by integrated community case management of fever. American Journal of Tropical Medicine and Hygiene, 87:36–45.

Kayemba CN et al. (2012). Introduction of newborn care within integrated community case management in Uganda. American Journal of Tropical Medicine and Hygiene, 87:46–53.

Laínez YB et al. (2012). Insights from community case management data in six sub-Saharan African countries. American Journal of Tropical Medicine and Hygiene, 87:144–150.

Lawn SD et al. (2013). Advances in tuberculosis diagnostics: the Xpert MTB/RIF assay and future prospects for a point-of-care test. The Lancet Infectious Diseases, 13:349–61

Leo M et al. (2006). Evaluation of Entamoeba histolytica antigen and antibody point-of-care tests for the rapid diagnosis of amebiasis. Journal of Clinical Microbiology, 44:4569–71.

Marsh D et al. (2012). Introduction to a special supplement: evidence for the implementation, effects, and impact of the integrated community case management strategy to treat childhood infection. American Journal of Tropical Medicine and Hygiene, 87:2–5.

Mayxay M et al. (2013). Causes of non-malarial fever in Laos: a prospective study. Lancet Global Health, 1: e46–e54.

Mbonye A et al. (2012). Introducing rapid diagnostic testing for malaria into the private sector: evidence from an intervention in registered drug shops in Uganda. (Abstract). In: 61th Annual Meeting of the American Society of Tropical Medicine and Hygiene, Atlanta, Georgia, 11–14 November 2012. Deerfield, Illinois, American Society of Tropical Medicine and Hygiene, 2012 (**http://www.abstractsonline.com/Plan/SSResults.aspx**, accessed 6 September 2013).

McGready R et al. (2010) Arthropod borne disease: the leading cause of fever in pregnancy on the Thai–Burmese border. PLoS Neglected Tropical Diseases, 4(11):e888. doi:10.1371/journal.pntd.0000888

McGorman L et al. (2012). A health systems approach to integrated community case management of childhood illness: methods and tools. American Journal of Tropical Medicine and Hygiene, 87:69–76.

Miller N. (2013) Assessment of ICCM implementation strength and quality of care in Oromia, Ethiopia. Baltimore: Johns Hopkins Bloomberg School of Public Health, Institute for International Programs and UNICEF (unpublished document).

Msellem MI et al. (2009). Influence of rapid malaria diagnostic tests on treatment and health outcome in fever patients, Zanzibar: a crossover validation study. PLoS Medicine, 6:e1000070.

Mukanga D et al. (2012). Integrated community case management of fever in children under five using rapid diagnostic tests and respiratory rate counting: a multi-country cluster randomized trial. American Journal of Tropical Medicine and Hygiene, 87:21–29.

Nadjm B et al. (2012). Severe febrile illness in adult hospital admissions in Tanzania: a prospective study in an area of high malaria transmission. Transactions of the Royal Society of Tropical Medicine and Hygiene, 106:688–695.

Nanyonjo A et al. (2012). Community acceptability and adoption of integrated community case management in Uganda. American Journal of Tropical Medicine and Hygiene, 87:97–104.

Nsona H et al. (2012). Scaling up integrated community case management of childhood illness: update from Malawi. American Journal of Tropical Medicine and Hygiene, 87:54–60.

O'Meara WP et al. (2008). Effect of a fall in malaria transmission on morbidity and mortality in Kilifi, Kenya. Lancet, 372: 1555–62.

Rambaud-Althaus C et al. (2011). Management of childhood illnesses: development of a new algorithm (ALMANACH) to promote evidence-based medicine and rational use of drugs. In: Abstracts of the 7th European Congress on Tropical Medicine and International Health, 3–6 October 2011, Barcelona, Spain. European Journal of Tropical Medicine and International Hygiene, 16(Suppl.1):308.

Rutebemberwa E et al. (2012). Use of community health workers for management of malaria and pneumonia in urban and rural areas in eastern Uganda. American Journal of Tropical Medicine and Hygiene, 87:30–35.

Sadruddin S et al. (2012). Household costs for treatment of severe pneumonia in Pakistan. American Journal of Tropical Medicine and Hygiene, 87:137–143.

Sanders E et al. (2011). Most adults seek urgent healthcare when acquiring HIV-1 and are frequently treated for malaria in coastal Kenya. AIDS, 25:1219.

Seidenberg PD et al. (2012). Impact of integrated community case management on health-seeking behavior in rural Zambia. American Journal of Tropical Medicine and Hygiene, 87:105–110.

Shao A et al. (2011). Safety of a new algorithm for the management of childhood illness (ALMANACH) to improve quality of care and rational use of drugs. In: Abstracts of the 7th European Congress on Tropical Medicine and International Health, 3–6 October 2011, Barcelona, Spain. European Journal of Tropical Medicine and International Hygiene, 16(Suppl.1):60.

Soofi S et al. (2012).Effectiveness of community case management of severe pneumonia with oral amoxicillin in children aged 2–59 months in Matiari district, rural Pakistan: a cluster-randomised controlled trial. Lancet, 379:729–37.

Strachan DL et al. (2012). Interventions to improve motivation and retention of community health workers delivering integrated community case management (iCCM): stakeholder perceptions and priorities. American Journal of Tropical Medicine and Hygiene, 87:111–119.

UNICEF (2012). Review of systematic challenges to the scale-up of integrated community case management: emerging lessons and recommendations from the Catalytic Initiative (CI/IHSS). New York, United Nations Children's Fund
(**http://www.unicef.org/infobycountry/files/Analysis_of_Systematic_Barriers_cover_1163.pdf**, accessed 6 September 2013).

WHO (2009). Integrated management of adolescent and adult illness: interim guidelines for first-level facility health workers at health centre and district outpatient clinic: acute care. Geneva, World Health Organization
(**http://www.who.int/entity/hiv/pub/imai/acute_care.pdf**, accessed 6 September 2013).

WHO (2010a). WHO guidelines for the treatment of malaria. 2nd ed. Geneva, World Health Organization
(**http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf**, accessed 6 September 2013).

WHO (2010b). Antiretroviral therapy for HIV infection in adults and adolescents. Recommendations for a public health approach. Geneva, World Health Organization
(**http://whqlibdoc.who.int/publications/2010/9789241599764_eng.pdf**, accessed 6 September 2013).

WHO (2011a). Integrated management of childhood illness: caring for newborns and children in the community. Geneva, World Health Organization
(**http://whqlibdoc.who.int/publications/2011/9789241548045_Manual_eng.pdf**, accessed 6 September 2013).

WHO (2011b). IMAI district clinician manual: hospital care for adolescents and adults. Guidelines for the management of illnesses with limited resources. Geneva, World Health Organization
(**http://www.who.int/hiv/pub/imai/imai2011/en**, accessed 6 September 2013).

WHO (2011c). World malaria report. Geneva, World Health Organization
(**http://apps.who.int/iris/bitstream/10665/44792/2/9789241564403_eng_full.pdf**, accessed 6 September 2013).

WHO (2012). World malaria report. Geneva, World Health Organization
(**http://www.who.int/iris/bitstream/10665/78945/1/9789241564533_eng.pdf**, accessed 6 September 2013).

WHO (2013). Pocket book of hospital care for children. Geneva, World Health Organization
(**http://www.who.int/iris/bitstream/10665/81170/1/9789241548373_eng.pdf**, accessed 6 September 2013).

WHO and UNICEF (2008). Integrated management of childhood illness chart booklet. Geneva, World Health Organization
(**http://whqlibdoc.who.int/publications/2008/9789241597289_eng.pdf**, accessed 6 September 2013).

WHO and UNICEF (2012). Integrated management of childhood illness chart booklet. Geneva, World Health Organization, in press.

Annex 1.

MANAGEMENT OF MALARIA AND NON-MALARIA FEVER AT PERIPHERAL LEVEL: PRELIMINARY REVIEW OF THE EVIDENCE

Valérie D'Acremont, WHO Global Malaria Programme and Swiss Tropical and Public Health Institute

A1. Definitions of malaria and non-malaria fever

For the purpose of this review, 'fever' is defined as an acute febrile episode in a child or adult identified from a report of recent fever (≤ 7 days) or elevated axillary temperature (≥ 37.5 °C). If fever is accompanied by danger signs or other signs of severe illness, the patient may require referral for assessment and hospital admission. When the result of a malaria test (rapid diagnostic test [RDT] or microscopy) is positive for a patient with fever, as defined above, the episode is considered to be malaria. When the result is negative, the fever is considered not to be due to malaria and is sometimes referred to as 'non-malaria febrile illness'.

These definitions are suitable for the clinical management of patients and hence decisions on treatment. All patients with a positive malaria test result should be treated with an antimalarial medicine, while those with a negative result do not require such treatment. A positive test result does not necessarily correspond to the unique cause of the illness, as fever in some patients with a low *Plasmodium* parasite density might be due to a disease other than malaria. From the clinical point of view, all patients should be fully assessed, as they may have more than one disease (e.g. malaria and pneumonia) and would require more than one treatment.

A2. Incidence of fever

There are no reliable data on the incidence of febrile episodes in countries endemic for malaria. The incidence rates of malaria have been reported but not those of fever in general. In the few available studies, the incidence in children < 5 years was 2–7 per person per year. In a review of three studies in Zimbabwe, two in northern Sudan and one each in Mali, The Gambia and Sao Tome and Principe, the mean incidence in children < 5 years was 5.98 episodes per person per year (Gething et al., 2010). In a study in the United Republic of Tanzania, the incidence of fever reported in children under 5 in the community decreased between 2005 to 2008 from 4.9 to 3.2 per person per year (Alba et al., 2011). In Papua New Guinea, the incidence in children under 3 years was four episodes per person per year (Senn, 2011). All the studies were based on either weekly active case detection or community cross-sectional surveys of fever in the previous 2 weeks. Interestingly, in a study in Kenya of episodes that had occurred during the past week in a rural area, the incidence was 9.8 episodes per person per year in children under 5 and 3.8 in people over 5 years. For people in the same age groups but living in urban areas, the incidence was 2.4 and 0.6 episodes per person per year, respectively. When episodes that had occurred during the previous week were counted, however, the incidence was two to four times lower in rural areas and 1.5 and 2 times lower in the urban setting because of recall bias (Felkin et al., 2010).

The rates measured thus varied widely among studies because of differences in the definition of fever, the type and frequency of surveillance, the sampled population, the epidemiological setting and season.

References

Alba S et al. (2011). Assessing the impact of malaria interventions on morbidity through a community-based surveillance system. International Journal of Epidemiology, 40:405–416.

Feikin DR et al. (2010). Evaluation of the optimal recall period for disease symptoms in home-based morbidity surveillance in rural and urban Kenya. International Journal of Epidemiology, 39:450–458.

Gething PW et al. (2010). Estimating the number of paediatric fevers associated with malaria infection presenting to Africa's public health sector in 2007. PLoS Medicine, 7:e1000301.

Senn N (2011). Exploring the context and potential benefits of implementing an intermittent preventive treatment for malaria in infants (IPTi) in Papua New Guinea. PhD thesis, University of Basel (http://edoc.unibas.ch/28467, accessed 6 September 2013).

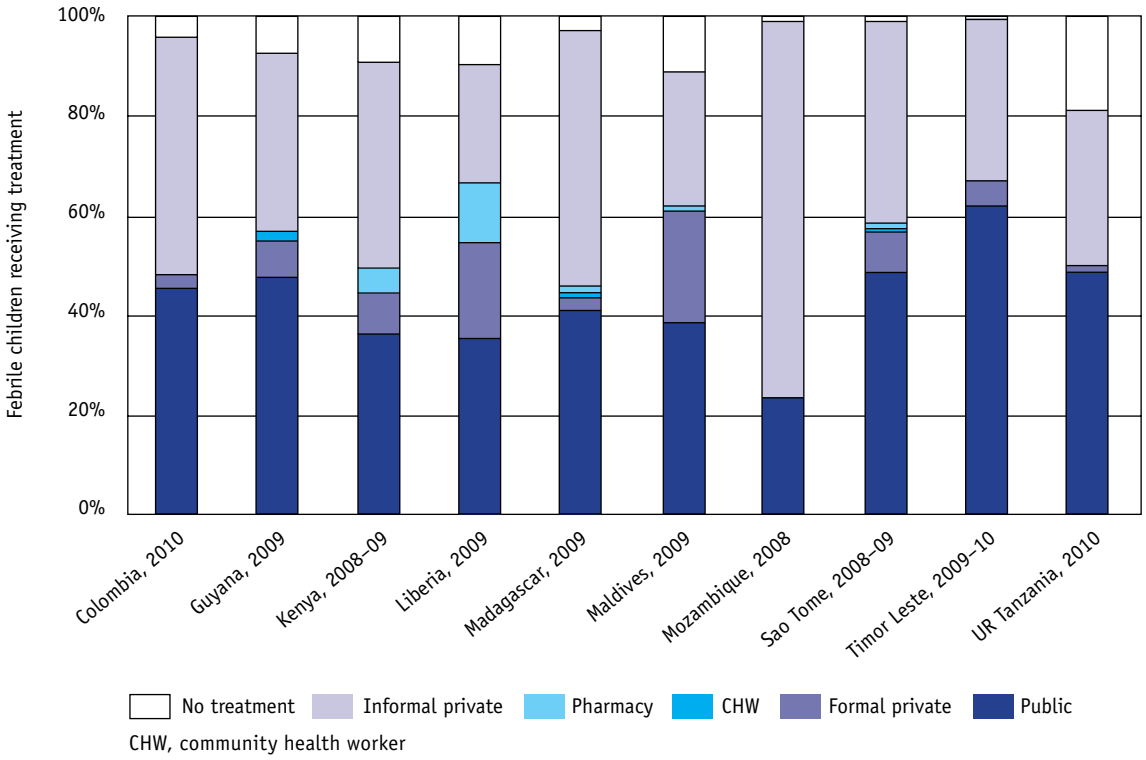
A3. Treatment-seeking behaviour and malaria testing

Patients presenting with fever might decide to see a community health worker, go to a public primary health care facility or a private health facility, go directly to a pharmacy or drug shop or stay at home with or without automedication. The proportions of patients who take each decision depends on the structure of the health system, including whether it serves children or adults, whether it is a public or private system, the distance to the nearest facility, the availability of transport and local habits.

According to the 2011 *World malaria report* (WHO, 2011), about 25% of febrile children globally receive treatment in the public sector, 3% at community level, 10% in the formal private sector, 5% in pharmacies and 30% in the informal private sector; 30% do not receive treatment. Large variations are seen by region and country (**Figure A1**).

FIGURE A1.

Proportion of febrile children receiving treatment from different sources, 2008–2010



Source: WHO (2011), Figure 6.6, p. 41.

In a review, Crowell (2013) found that about half of all cases of fever received some treatment in the official health sector in most studies, and the proportion was higher for cases of greater perceived severity (Deming et al., 1989; Mwenesi, Harpham, Snow, 1995; Ruebush et al., 1995; McCombie, 1996; Théra et al., 2000; Salako et al., 2001). The studies included in the review were, however, 11–22 years old, and practices may have changed.

Household surveys to determine treatment-seeking behaviour for febrile children in six African countries in 2008–2010 demonstrated a continuing dominance of the private sector for treatment of fever in children (Littrell et al., 2011). Most caregivers sought treatment outside the home, and private outlets were commonly the sole external source of treatment (except in Zambia).

Influence of urban versus rural setting

In the six studies reviewed by Crowell (2013), recourse to public health facilities was generally higher in urban areas. In coastal Kenya, however, 52% of lifelong rural resident mothers and 47% of urban resident mothers used only shop-bought drugs for recent episodes of childhood febrile illness. Urban mothers were more likely to contact a private clinic (24% vs 15%) and less than half as likely to consult a Government service (10% vs 22%) (Molyneux et al., 1999). Another study in coastal Kenya showed that 80% of adults and children with acute illness in a rural area received some treatment (of which 55% was self-treatment), while 91% of those in an urban area received some treatment (of which 50% was self-treatment) (Chuma, Gilson, Molyneux, 2007). Delays in seeking treatment in the formal sector appear to be substantial, even where access to care was relatively good (Rutebemberwa et al., 2009).

Influence of age

Few studies of adults are available. In coastal Kenya, small children were more likely to be taken to a health centre than adults (Molyneux et al., 1999); however, there was no significant difference by age in treatment-seeking for recent fever (Guyatt, Snow, 2004).

Influence of availability of tests and medicines

In Zanzibar, twice as many children received care at public health facilities after the introduction of free ACT (Molyneux et al., 1999). In Dar es Salaam in 2008, 80% of patients coming to public health facilities expected a malaria test, while only 30% expected an antimalarial medicine (J. Kahama et al., in preparation).

Proportion of febrile patients tested for malaria

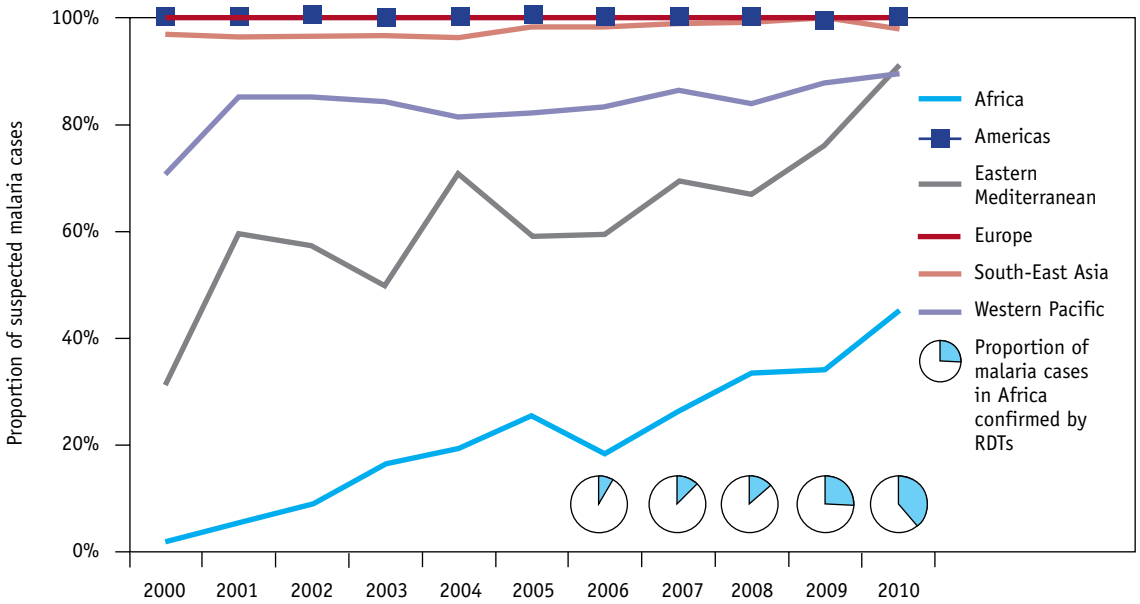
The rate of testing in the WHO Eastern Mediterranean Region was 80% in 2010, while that in the African Region rose from 20% in 2005 to 45% in 2010 (WHO, 2011). Much of the increase in the African Region was due to use of RDTs, which predicted 39% of confirmed cases diagnosed in 2010 (**Figure A2**). Surveys conducted by ACT Watch showed that the proportion of children under 5 with fever who received a blood test for malaria was lower in the private sector (**Figure A3**) (Littrell et al., 2011).

Conclusions

- About one third of febrile children attended public facilities. Few data were available on adults, but the percentage appeared to be the same as that for children or lower.
- Few children received a diagnosis and treatment for malaria from community health workers.
- One half of children were treated in the private sector (of whom about three quarters in the informal sector), while one quarter did not seek any treatment.

FIGURE A2.

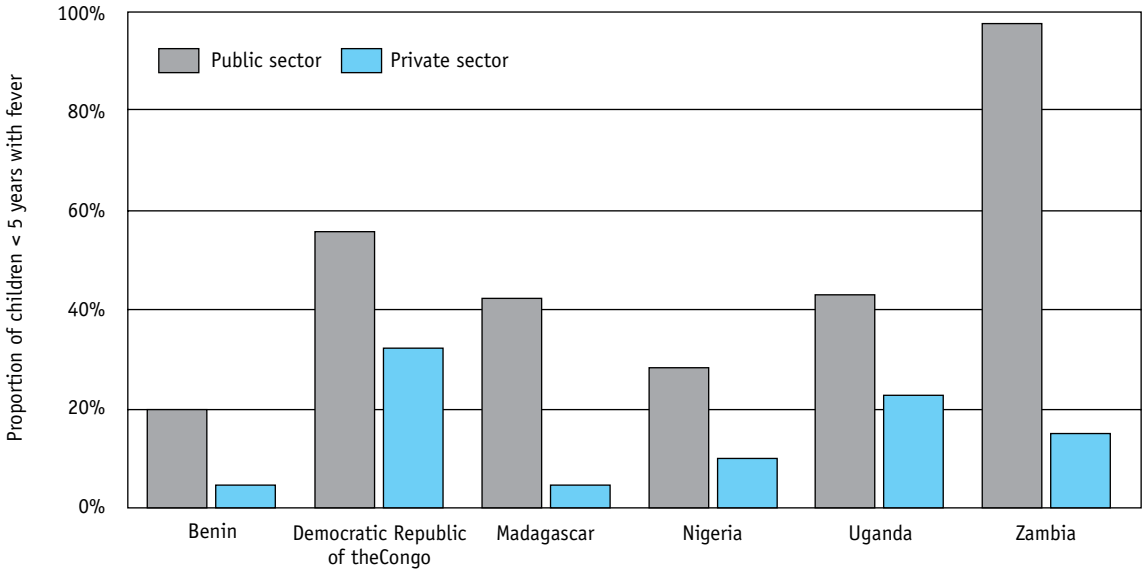
Proportion of suspected malaria cases attending public health facilities tested by RDT or microscopy



Source: WHO (2011).

FIGURE A3.

Proportion of children under 5 years with fever who received a blood test for malaria, by sector



Source: Littrell et al. (2011)

- Little difference was found between urban and rural settings, suggesting that the distance to the next facility was not the main determinant of treatment-seeking. The availability of drugs and testing was possibly important.
- Almost half the febrile patients who reached a public health facility were tested for malaria, while the proportion was probably much lower for those attending the private sector.

References

Crowell V (2013). Predicting the cost-effectiveness of strategies for case management of "plasmodium falciparum" malaria in Sub-Saharan Africa. 2013. PhD thesis, University of Basel (**http://edoc.unibas.ch/diss/DissB_10321**, accessed 6 September 2013)

Chuma J, Gilson L, Molyneux C (2007). Treatment-seeking behaviour, cost burdens and coping strategies among rural and urban households in coastal Kenya: an equity analysis. Tropical Medicine and International Health, 12:673–686.

Deming MS et al. (1989). Home treatment of febrile children with antimalarial drugs in Togo. Bulletin of the World Health Organization, 67:695–700.

Guyatt HL, Snow RW (2004). The management of fevers in Kenyan children and adults in an area of seasonal malaria transmission. Transactions of the Royal Society of Tropical Medicine and Hygiene, 98:111–115.

Littrell M et al. (2011). Monitoring fever treatment behaviour and equitable access to effective medicines in the context of initiatives to improve ACT access: baseline results and implications for programming in six African countries. Malaria Journal, 10:327.

McCombie SC (1996). Treatment seeking for malaria: a review of recent research. Social Science and Medicine, 43:933–945.

Molyneux CS et al. (1999). Maternal responses to childhood fevers: a comparison of rural and urban residents in coastal Kenya. Tropical Medicine and International Health, 4:836–845.

Mwenesi H, Harpham T, Snow RW (1995). Child malaria treatment practices among mothers in Kenya. Social Science and Medicine, 40:1271–1277.

Ruebush TK et al. (1995). Self-treatment of malaria in a rural area of western Kenya. Bulletin of the World Health Organization, 73:229–236.

Rutebemberwa E et al. (2009). Determinants of delay in care-seeking for febrile children in eastern Uganda. Tropical Medicine and International Health, 14:472–479.

Salako LA et al. (2001). Treatment of childhood fevers and other illnesses in three rural Nigerian communities. Journal of Tropical Pediatrics, 47:230–238.

Théra MA et al. (2000). Child malaria treatment practices among mothers in the district of Yanfolila, Sikasso region, Mali. Tropical Medicine and International Health, 5:876–881.

WHO (2011). World Malaria Report 2011, Geneva, World Health Organization (**http://apps.who.int/iris/bitstream/10665/44792/2/9789241564403_eng_full.pdf**, accessed 6 September 2013).

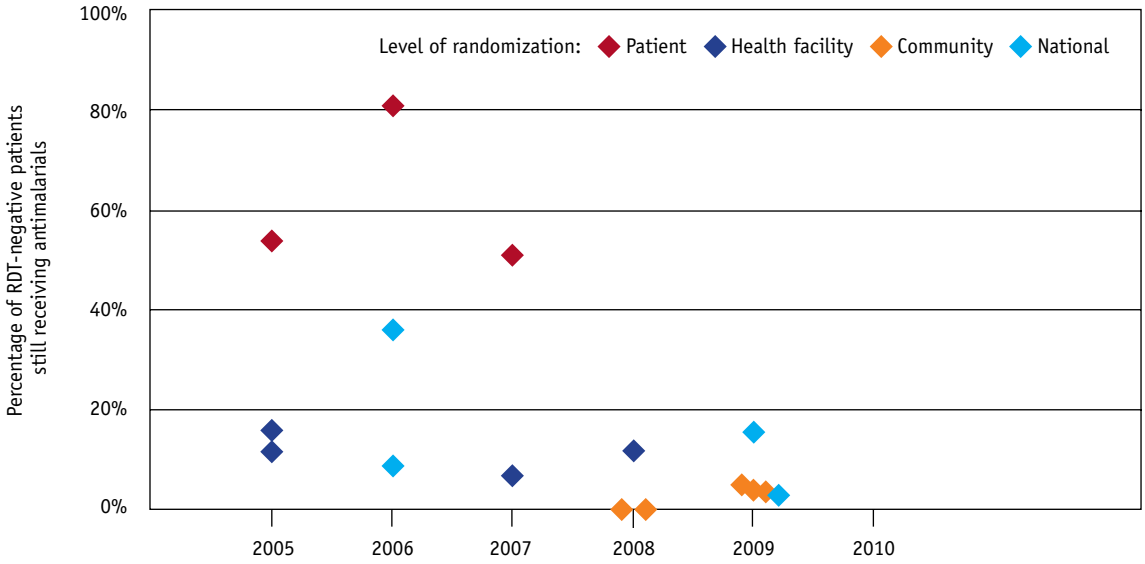
A4. Adherence of health workers to the results of malaria rapid diagnostic tests

Adherence of health workers to malaria RDT results varied widely according to the design of the study (especially the degree of randomization), whether RDTs were used in a pilot study or nationally and the level of the health system (health facility or community) (**Figure A4**) (Hamer et al., 2007; Reyburn et al., 2007; Williams et al., 2008; Bisoffi et al., 2009; Msellem et al., 2009; Skarbinski et al., 2009; Ansah et al., 2010; Mawili-Mboumba et al., 2010; Yeboah-Antwi et al., 2010; Chanda et al., 2011; D'Acremont et al., 2011; Thiam et al., 2011; Mukanga et al., 2012).

Adherence tended to improve with time. It was low when clinicians enrolled in pilot studies had to change their attitude for each patient (randomization at patient level) but higher when all clinicians and other health staff of the facility had been trained in use of RDTs and used them all the time. The lower the level of the health system and the shorter the medical training of health workers, the better the adherence. The level of adherence on a national scale was similar to that in pilot studies in all but one health facility.

FIGURE A4.

Level of adherence of health workers to the results of malaria RDTs by type of study



References

Ansah EK et al. (2010). Rapid testing for malaria in settings where microscopy is available and peripheral clinics where only presumptive treatment is available: a randomised controlled trial in Ghana. BMJ, 340:c930.

Bisoffi Z et al. Rapid malaria diagnostic tests vs. clinical management of malaria in rural Burkina Faso: safety and effect on clinical decisions. A randomized trial. Tropical Medicine and International Health,14:491–498.

Chanda P et al. (2011). Community case management of malaria using ACT and RDT in two districts in Zambia: achieving high adherence to test results using community health workers. Malaria Journal, 10:158.

D'Acremont V et al. (2011). Reduction of anti-malarial consumption after rapid diagnostic tests implementation in Dar es Salaam: a before-after and cluster randomized controlled study. Malaria Journal, 10:107.

Hamer DH et al. (2007). Improved diagnostic testing and malaria treatment practices in Zambia. JAMA, 297:2227–2231.

Mawili-Mboumba DP et al. (2010). Evaluation of rapid diagnostic tests for malaria case management in Gabon. Diagnostic Microbiology and Infectious Diseases, 66:162–168.

Msellem MI et al. (2009). Influence of rapid malaria diagnostic tests on treatment and health outcome in fever patients, Zanzibar: a crossover validation study. PLoS Medicine, 6:e1000070.

Mukanga D et al. (2012). Integrated community case management of fever in children under five using rapid diagnostic tests and respiratory rate counting: a multi-country cluster randomized trial. American Journal of Tropical Medicine and Hygiene, 87(5 Suppl):21–29.

Reyburn H et al. (2007). Rapid diagnostic tests compared with malaria microscopy for guiding outpatient treatment of febrile illness in Tanzania: randomised trial. BMJ, 334:403.

Skarbinski J et al. (2009). Effect of malaria rapid diagnostic tests on the management of uncomplicated malaria with artemether-lumefantrine in Kenya: a cluster randomized trial. American Journal of Tropical Medicine and Hygiene, 80:919–926.

Thiam S et al. (2011). Major reduction in anti-malarial drug consumption in Senegal after nation-wide introduction of malaria rapid diagnostic tests. PLoS One, 6:e18419.

Williams HA et al. (2008). Dispensary level pilot implementation of rapid diagnostic tests: an evaluation of RDT acceptance and usage by providers and patients – Tanzania, 2005. Malaria Journal, 7:239.

Yeboah-Antwi K et al. (2010). Community case management of fever due to malaria and pneumonia in children under five in Zambia: a cluster randomized controlled trial. PLoS Medicine, 7:e1000340.

A5. Fever and associated symptoms

Primary care

Studies of adherence to IMCI by clinicians provide information on the most frequent complaints and clinical diagnoses in children under 5 years attending primary care facilities. In the evaluation of IMCI conducted in Brazil, Uganda and the United Republic of Tanzania (Gouws et al., 2004), 80% of children in last two countries but only 30% in Brazil presented with fever, 60% with cough and 25% with diarrhoea (**Figure A5**). Pneumonia was diagnosed on the basis of fast breathing in 50% of children with cough in the last two countries but only 7% in Brazil.

In a study of IMCI (not iCCM) by community health workers in Kenya (Rowe et al., 2007), 88% of children had a history of fever, 44% of cough and 22% of diarrhoea; 36% had more than one diagnostic classification. One or more danger signs were found in 10%, and 17% were classified diagnostically as having severe illness necessitating referral to the next health facility.

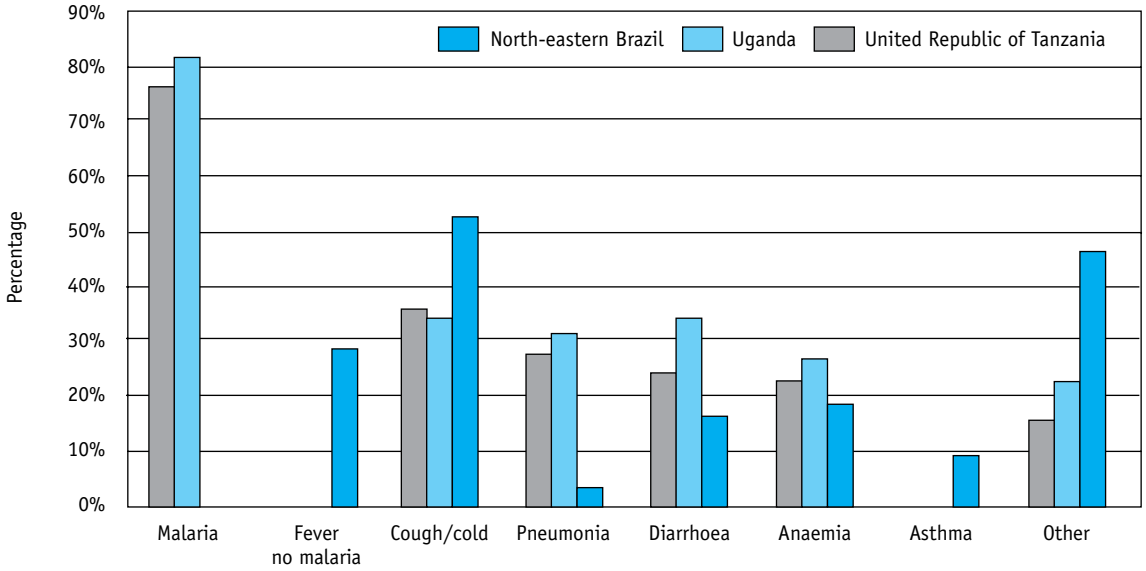
In a study in the United Republic of Tanzania of 1005 children aged < 10 years with a temperature ≥ 38 °C, 46% had cough, 46% a runny nose, 2% difficult breathing, 0.5% throat pain, 10% diarrhoea, 1% ear pain and 1% skin problems (D'Acremont et al., 2013). Fast breathing was found in 40% of children with cough and 12% of children without cough.

In another study in the United Republic of Tanzania, in which a clinician used a modified version of IMCI on a mobile phone, 73% of 842 children had fever, 53% had cough (of whom 22% had fast breathing), 18% had diarrhoea (of whom 1% had blood in stools), 10% had skin problems, 1% had an acute ear discharge and 0.8% had measles (Shao et al., 2011).

Few data are available on children > 5 years and on adults. In Kenya, 79% of 359 consecutive patients > 5 years attending 17 facilities had a history of fever (Zurovac et al., 2006). In a study in the United Republic of Tanzania of 2528 patients of all ages attending 12 outpatient facilities for an acute medical condition, 84% of those aged < 5 years and 74% of those aged ≥ 5 years had fever, 46% of those aged < 5 years and 24% of those aged ≥ 5 years had cough, 17% of those aged < 5 years and 6% of those aged ≥ 5 years had diarrhoea, 2% of any age had difficult breathing, 1% had ear problems and 5% had skin problems; 79% of all patients with cough and 77% of those with diarrhoea also had fever (D'Acremont et al., 2007).

FIGURE A5.

Illnesses among children under 5 years of age presenting for care at first-level health facilities in north-eastern Brazil (n = 653), Uganda (n = 516) and the United Republic of Tanzania (n = 419)



Source: Gouws et al. (2004).

Community level

In Zambia where community health workers performed a malaria RDT and counted the respiratory rate, a history of fever was found in 95% of 1017 children, cough in 68%, difficult breathing in 17% and fast breathing in 38% (diarrhoea was not assessed); 28% were classified as having both malaria and pneumonia (Yeboah-Antwi et al., 2010).

In a similar study in Uganda, 78% of children had malaria, 35% pneumonia and 29% both (Mukanga et al., 2012a). In three studies of iCCM in Burkina Faso, Ghana and Uganda, 83%, 60% and 58% of the children had a temperature ≥ 37.5 °C; 48%, 21% and 57% had cough; and 26% and 36% had diarrhoea (not assessed in Uganda) (Mukanga et al., 2012b). The final classification was malaria in 74%, 84% and 88%; pneumonia (based on fast breathing with or without cough) in 44%, 24% and 54%; and both diseases in 33%, 22% and 47% of cases.

Conclusions

In most studies, about 80% of adult or child patients attending primary care facilities in Africa for an acute medical condition had fever, 40% had cough and 20% had diarrhoea. Many patients had multiple complaints. The findings of the studies were remarkably consistent.

Most patients attending a facility for an acute medical condition had a history of fever or elevated temperature, at least in Africa: in one study, only 7% had cough without fever and 3% diarrhoea without fever. The target group of patients for the management of fevers is thus similar to that of IMCI and IMAI.

At community level, for which data were available only for children under 5 years, more than 90% had fever, 20–60% had cough and about 30% had diarrhoea.

The proportion of patients with cough who also had fast breathing (and were thus classified as having pneumonia) was about 50%, except in Brazil, but the respiratory rate was probably not measured exactly as recommended in the last version of IMCI, which states that it should be

assessed in a calm child after three rounds of bronchodilatation in cases of wheezing. In the study in the United Republic of Tanzania with a modified IMCI algorithm on a mobile phone, in which the respiratory rate was measured strictly according to the IMCI recommendation by a trained clinician, only 22% of children with cough also had fast breathing.

The clinical findings and final classifications in studies on integrated management of fevers are summarized in **Table A1**.

References

D'Acremont V et al. (2011). Reduction of anti-malarial consumption after rapid diagnostic tests implementation in Dar es Salaam: a before-after and cluster randomized controlled study. =, 10:107.

D'Acremont V et al. (2013). Beyond malaria: etiologies of fever in outpatient Tanzanian children. New England Journal of Medicine (in press).

Gouws E et al. (2004). Improving antimicrobial use among health workers in first-level facilities: results from the multi-country evaluation of the Integrated Management of Childhood Illness strategy. Bulletin of the World Health Organization, 82:509–515.

Mukanga D et al. (2012a). Can lay community health workers be trained to use diagnostics to distinguish and treat malaria and pneumonia in children? Lessons from rural Uganda. Tropical Medicine and International Health, 16:1234–1242.

Mukanga D et al. (2012b). Integrated community case management of fever in children under five using rapid diagnostic tests and respiratory rate counting: a multi-country cluster randomized trial. American Journal of Tropical Medicine and Hygiene, 87(Suppl. 5):21–29.

Rowe SY et al. Longitudinal analysis of community health workers' adherence to treatment guidelines, Siaya, Kenya, 1997-2002. Trop Med Int Health 2007;12:651–63

Shao A, Rambaud-Althaus C, Perri S, et al. (2011). Safety of a new ALgorithm for the MANAgement of CHildhood illness (ALMANACH) to improve quality of care and rational use of drugs. In: Abstracts of the 7th European Congress on Tropical Medicine and International Health, 3–6 October 2011, Barcelona, Spain. European Journal of Tropical Medicine and International Hygiene, 16(Suppl.1):60.

Yeboah-Antwi K et al. (2010). Community case management of fever due to malaria and pneumonia in children under five in Zambia: a cluster randomized controlled trial. PLoS Medicine, 7:e1000340

Zurovac D et al. (2006). Microscopy and outpatient malaria case management among older children and adults in Kenya. Tropical Medicine and International Health, 11:432–440

A6. Causes of fever

Studies not designed to determine the causes of fever

Three studies provide an indication of the clinical spectrum of diseases in febrile patients, although they were not designed to determine the causes of fever, with no systematic screening for specific bacterial, parasitic or viral disease.

The first study (Niama-Meya et al., 2007), conducted in an area of Uganda meso-endemic for malaria (parasite prevalence among children, 17%), included children < 10 years with a history of fever in the previous 24 h or tympanic temperature ≥ 38.0 °C, who were attending the study clinic of a tertiary hospital. A blood slide was negative for malaria in 68% of the 1602 febrile episodes. Standardized guidelines consisting of a short description of typical symptoms, signs and investigative findings for each disease were provided to assist the research clinicians in diagnosis. An ARI was diagnosed in 93% of malaria-negative children, an upper respiratory tract infection in 47%, a common cold (the difference between this diagnosis and the previous one is not clear) in 29%, pharyngitis in 12%, pneumonia in 4% and otitis media in 1%; 10% had diarrhoea, 2% urinary tract infection and 8% skin infection, although patients may have had more than one diagnosis per episode. For 15% no cause was found.

TABLE A1.

Clinical findings and final classifications in studies on integrated management of fevers

Level of health care	Health facilities (outpatients)							Community health workers (children < 5 years)			
Reference	**Gouws**	**Gouws**	**Gouws**	**D'Acremont**	**D'Acremont**	**D'Acremont**	**Shao**	**Rowe**	**Mukanga**	**Mukanga**	**Mukanga**
Year(s) of study	**2000**	**2000**	**2002**	**2007–08**	**2007–08**	**2008**	**2011**	**97–02**	**2009**	**2009**	**2009**
Country	United Republic of Tanzania	Uganda	Brazil	United Republic of Tanzania	United Republic of Tanzania	United Republic of Tanzania	United Republic of Tanzania	Kenya	Uganda	Burkina Faso	Ghana
Algorithm used	Original IMCI	Original IMCI	Original IMCI	Usual care	Usual care	Modified IMCI	Modified IMCI	Original IMCI	iCCM	iCCM	iCCM
Age group (years)	< 5	< 5	< 5	< 5	> 5	< 10	< 5	< 5	< 5	< 5	< 5
Total no. of patients	419	516	653	1270	1254	1005	842	7151	182	525	584
% with one or more danger sign						5		10			
% who required referral						8		17			
% with fever	76	81	29	84	74	100	73	88			
% positive RDT results among febrile patients						10	3		78	74	84
% with cough	35	33	52	46	24	46	53	44		48	21
% with difficult breathing				2	1	2					
% with fast breathing among those with cough						40	22			44	24
% with chest indrawing among those with cough						2					
% with pneumonia	28	31	3			18	12		35		
% with diarrhoea	24	34	17	17	6	10	18	22		26	36
% with blood in stools among those with diarrhoea						5	1				
% with ear pain				2	1	1	1				
% with measles					0.1	0	0.8				
% with skin problems				7	3	8	10				
% with more than one diagnostic classification								36	29	33	22

The second study (Yacoub et al., 2005), conducted in Pemba, Zanzibar, included children aged < 5 years with a history of fever or axillary temperature ≥ 37.5 °C, who were attending the outpatient department of a district hospital. Malaria alone was diagnosed in 61% of 207 children (> 2000 parasites/ml), malaria and ARI in 7%, ARI alone in 16%, gastroenteritis in 3% and 'other' in 14%, which included a mixture of viral illnesses, skin infections and fevers of unknown origin.

The third study (Animut et al., 2009), conducted in Ethiopia, included febrile (history of fever in the past 3 days or temperature ≥ 37.5 °C) children aged 3–17 years attending three health centres and one hospital. The method of making final diagnosis was left to the discretion of the physicians at the health facilities. Of the 653 patients, 62% had malaria, 7% pneumonia, 6% typhoid, 5% typhus, 3% brucellosis and 2% relapsing fever; 28% were free of these diseases. The prevalence of other common diagnoses, such as upper respiratory tract infection and diarrhoea, was not reported.

Studies of specific diseases

A few studies of specific diseases have been conducted, such as investigations of urinary tract infections (Rabasa, Gofama, 2009) and acute otitis media (Alabai et al., 2009) in Nigeria, diseases caused by arboviruses on the Kenyan coast (Morrill et al., 1991) and a study of Q fever and *Rickettsia* spp. in northern United Republic of Tanzania (Prabhu et al., 2011). Other studies (Okwara et al., 2004; Ayoola, Adeyemo, Osinusi, 2005; Berkley et al., 2005; Brent et al., 2006; Bronzan et al., 2007; Punjabi et al., 2012) were limited to hospitalized patients, especially those with bacteraemia. The prevalence of each of the diseases among all febrile patients studied could not, however, be calculated because of inclusion bias introduced by the design of the studies.

Studies designed to assess the causes of fever

The results of a study of the causes of fever in the United Republic of Tanzania (D'Acremont et al., 2013), a study in children < 5 years in Zanzibar with a negative malaria RDT (Björkman et al., unpublished study), a study in Pakistan on the diagnosis of fever in children at the community level (Bhutta et al., unpublished study) and studies of non-malaria febrile illness in adults in Tanzania (Crump et al. 2013), Cambodia (Newton et al., unpublished study) and the Democratic Lao People's Republic (Mayxay et al., 2013) were presented during the meeting. The summary of these studies are presented in Section 2.1 of the report.

References

Alabi BS et al. (2009). Prevalence of acute otitis media among children with pyrexia in a Nigerian hospital. Auris, Nasus, Larynx, 36:532–535.

Animut A et al. (2009). Febrile illnesses of different etiology among outpatients in four health centers in Northwestern Ethiopia. Japanese Journal of Infectious Diseases, 62:107–110.

Ayoola OO, Adeyemo AA, Osinusi K (2005). Concurrent bacteraemia and malaria in febrile Nigerian infants. Tropical Doctor, 35:34–36.

Berkley JA et al. (2005). Bacteremia among children admitted to a rural hospital in Kenya. New England Journal of Medicine, 352:39–47.

Brent AJ et al. (2006). Incidence of clinically significant bacteraemia in children who present to hospital in Kenya: community-based observational study. Lancet, 367:482–488.

Bronzan RN et al. (2007). Bacteremia in Malawian children with severe malaria: prevalence, etiology, HIV coinfection, and outcome. Journal of Infectious Diseases, 195:895–904.

Crump JA et al. (2013). Etiology of severe non-malaria febrile illness in northern Tanzania: a prospective cohort study. PLoS Neglected Tropical Diseases, 7:e2324.

D'Acremont V et al. (2013). Beyond malaria: etiologies of fever in outpatient Tanzanian children. New England Journal of Medicine (in press).

Mayxay M et al. (2013). Causes of non-malarial fever in Laos: a prospective study. Lancet Global Health, 1: e46–e54.

Morrill JC et al. (1991). Serological evidence of arboviral infections among humans of coastal Kenya. Journal of Tropical Medicine and Hygiene, 94:166–168.

Njama-Meya D et al. (2007). Treatment of malaria restricted to laboratory-confirmed cases: a prospective cohort study in Ugandan children. Malaria Journal, 6:7.

Okwara FN et al. (2004). Bacteraemia, urinary tract infection and malaria in hospitalised febrile children in Nairobi: is there an association? East African Medical Journal, 81:47–51.

Prabhu M et al. (2011). Q fever, spotted fever group, and typhus group rickettsioses among hospitalized febrile patients in northern Tanzania. Clinical Infectious Diseases, 53:e8–e15.

Punjabi NH et al. (2012). Etiology of acute, non-malaria, febrile illnesses in Jayapura, northeastern Papua, Indonesia. American Journal of Tropical Medicine and Hygiene, 86:46–51.

Rabasa AI, Gofama MM (2009). Urinary tract infection in febrile children in Maiduguri north eastern Nigeria. Nigerian Journal of Clinical Practice, 12:124–127.

Yacoub S et al. (2005). Clinical predictors of malaria and other febrile illnesses in children under five on Pemba Island, Tanzania. Tropical Doctor, 35:78–81.

A7. Outcomes of patients with non-malaria fever

Health facilities

In the study in Uganda of the outcomes of 1602 febrile children with a negative malaria test result (Njama-Meya et al., 2007), none died but 22 (1.4%) were hospitalized for non-malarial illness (six pneumonia, two fractures, two pyomyositis, two fever of unknown origin, one abscess, one sinusitis, one febrile convulsions, one cellulitis, one severe weakness of unknown cause, one asthma, one lead poisoning, one chicken-pox, one diarrhoea and one tonsillitis).

In a study in the United Republic of Tanzania of the safety of withholding antimalarial agents from 603 RDT-negative children (D'Acremont et al., 2010), 97% were cured on day 7, as compared with 98% of 396 children with malaria. Of the children with a negative RDT result, 8% were brought spontaneously to the dispensary before day 7, while 3% of children with a positive result were brought. As disease management was left to the discretion of the clinician in charge (except for malaria), however, 95% of RDT-negative children and 19% of RDT-positive children received an antibiotic. Five children (0.5%) were subsequently admitted to hospital for severe sepsis with exanthema, severe pneumonia (two children), gastroenteritis with severe dehydration and severe anaemia without fever; two died.

In another study in the United Republic of Tanzania with a modified version of IMCI on a mobile phone (Shao et al., 2011), full adherence to the algorithms was included in the study design. A malaria test was positive in 3.4% of cases, and 15% received an antibiotic. With regard to outcomes, 97% of the 842 children were cured by day 7, one (0.1%) was admitted, and none died. In another study with the same modified IMCI (Rambaud-Althaus et al., 2012), 4 of 338 (1.2%) children should have been referred to hospital for severe disease, according to an expert evaluation.

Community

In Zambia, 1017 children were treated with antimalarial agents only if an RDT was positive (28% of cases) and with antibiotics only in cases of fast breathing (36% of cases). Adherence by community health workers to disease classification and to treatment was high. By day 7, 91% of the children were cured, while most of the others still had fever or fast or difficult breathing. Four (0.4%)

children were hospitalized for non-malaria diseases, and two died (Yeboah-Antwi et al., 2010). In the studies on iCCM in Burkina Faso, Ghana and Uganda, only 0.4%, 1.1% and 0.8% of the children were still febrile by day 7. No hospitalization or death was recorded (Mukanga et al., 2012).

Conclusions

- Children < 5 years who were tested for malaria, given an antimalarial drug only when the result was positive and given an antibiotic only if they had fast breathing (and in some studies given oral rehydration salts of they had diarrhoea) were cured by day 7 in more than 95% of cases at health facility level and 91–99% at community level.
- The rate of hospitalization at health facility level was 0.1–1.4%, and that at community level was 0–0.4%.
- Death occurred in 0–0.2% of children, mostly due to non-malaria causes (generally severe pneumonia or severe sepsis).

References

D'Acremont V et al. (2010). Withholding antimalarials in febrile children who have a negative result for a rapid diagnostic test. Clinical Infectious Diseases, 51:506–511.

Mukanga D et al. (2012) Integrated community case management of fever in children under five using rapid diagnostic tests and respiratory rate counting: a multi-country cluster randomized trial. American Journal of Tropical Medicine and Hygiene, 87(Suppl. 5):21–29.

Njama-Meya D et al. (2007). Treatment of malaria restricted to laboratory-confirmed cases: a prospective cohort study in Ugandan children. Malaria Journal, 6:7.

Rambaud-Althaus C, Shao A, Swai N, et al. Smartphones to improve health workers performance and rational use of drugs for the management of childhood illnesses in a low resource setting (Abstract). In: 61th Annual Meeting of the American Society of Tropical Medicine and Hygiene, Atlanta, Georgia, 11–15 November 2012. Deerfield, Illinois, American Society of Tropical Medicine and Hygiene, 2012 (**http://www.abstractsonline.com/Plan/SSResults.aspx**, accessed 6 September 2013).

Shao A et al. (2011). Safety of a new algorithm for the management of childhood illness (ALMANACH) to improve quality of care and rational use of drugs. In: Abstracts of the 7th European Congress on Tropical Medicine and International Health, 3–6 October 2011, Barcelona, Spain. European Journal of Tropical Medicine and International Hygiene, 16(Suppl.1):60.

Yeboah-Antwi K et al. (2010). Community case management of fever due to malaria and pneumonia in children under five in Zambia: a cluster randomized controlled trial. PLoS Medicine, 7:e1000340.

A8. Medicines prescribed to patients with malaria and non-malaria fever

The frequency with which antimalarial agents, antibiotics and other essential medicines are prescribed to febrile patients depends on the level of adherence of clinicians to the guidelines.

Health facility level

In a study conducted in Yemen (Hogerzeil et al., 1989) in 19 health posts with an 'essential drug programme' and in seven control health posts, health workers prescribed antibiotics to 46% and 67% of patients of any age, respectively, while analysis of morbidity data for Yemen showed that probably about 23% of these patients actually required antibiotics.

In the study in Uganda of the outcomes of 1602 febrile children with a negative malaria test result, 45% of all febrile episodes were treated with an antibiotic (Njama-Meya et al., 2007). Adherence of clinicians to national guidelines (no antibiotic for common colds or diarrhoea without blood) was low, and 45% of upper respiratory tract infections or common colds and 28% of non-specific fevers were still treated with antibiotics.

In a study in Morocco of IMCI without malaria testing, 40% of children were classified as having a condition that requires antibiotics according to the gold standard (Naimoli et al., 2006). In the evaluation of IMCI in Brazil, Uganda and the United Republic of Tanzania (Gouws et al., 2004), about 30% of all children attending in the last two countries were classified as requiring treatment with a course of antibiotics according to the gold standard, in 90% of the cases because of pneumonia.

In Dar es Salaam, when malaria RDTs were not yet available, 82%, 55% and 40% of febrile children < 5 years and 81%, 41% and 28% of older children and adults were prescribed an antimalarial agent, an antibiotic or both drugs, respectively (D'Acremont et al., 2011). After the introduction of malaria RDTs and training in the management of malaria (but no training on management of non-malaria fever) in the same health facilities, the rates changed to 18%, 79% and 8% of febrile children < 5 years and 32%, 64% and 10% of older children and adults.

In the study in the United Republic of Tanzania in which the research clinician adhered strictly to a modified IMCI (adding antibiotics for children with a positive urine dipstick and with abdominal tenderness but restricting antibiotics to children with a respiratory rate ≥ 50/min, after three rounds of bronchodilatation in cases of wheezing, instead of ≥ 40/min), 15% of children in the intervention arm and 84% in the control arm received antibiotics (Shao et al., 2011). The low rate in the intervention arm was due partly to double-counting of the respiratory rate and the use of bronchodilators. In cases of non-severe pneumonia and wheeze, the respiratory rate is known to decrease below age-specific cut-offs in 46–62% children (Hazir et al., 2004; Awasthi et al., 2008).

Community level

In the studies on iCCM in areas of Burkina Faso, Ghana and Uganda highly endemic for malaria, 75%, 85% and 89% received an antimalarial agent, 56%, 51% and 54% an antibiotic and 42%, 40% and 47% both drugs (Mukanga et al., 2012). Adherence to the guidelines was good for antimalarial agents but poor for antibiotics, with about 40% overuse and 20% underuse of antibiotics. The number of medicines prescribed was much lower in the iCCM intervention groups than in controls in Ghana, where 95% of patients received an antimalarial agent, 64% an antibiotic and 61% both drugs.

Appropriateness of antibiotic prescription according to IMCI in the light of recent studies

In the study in the United Republic of Tanzania (D'Acremont et al, 2013) on the causes of fever (temperature ≥ 38 °C), 27% of the children should have received an antibiotic according to the final clinically and microbiologically documented diagnosis. If the IMCI criteria had been applied to the same children, 25% would have received an antibiotic; however, 13% would not have required one, and 15% of bacterial diseases would have been missed. Over-prescription of antibiotics within IMCI was due mainly to the non-specific definition of pneumonia. A study in Pakistan showed that children with non-severe pneumonia according to IMCI criteria do not benefit from antibiotic treatment (Hazir et al., 2011). Under-prescription of antibiotics within IMCI was mainly for bacterial diseases that are not included in IMCI, such as typhoid fever, urinary tract infection and bacteraemia, which cannot be identified with existing point-of-care tests.

These considerations are based on the assumption that all documented bacterial diseases should be treated with antibiotics, which is not the case. Some bacterial diseases (e.g. typhoid fever and occult bacteraemia) can lead to mild febrile episodes that tend to resolve by themselves. Studies of clinical outcome rather than 'gold standard diagnosis' (as undertaken in Pakistan for non-severe pneumonia) are needed to understand which patients would really benefit from antibiotic treatment.

Conclusions

- The rate of prescription of antimicrobial agents by health workers varied according to their adherence to guidelines.
- When adherence was 100% and children were managed according to the original version of IMCI (without malaria tests), 80–90% were treated with antimalarial agents and 25–40% with antibiotics. The variation in the latter rate is probably due mainly to the way in which the respiratory rate was measured.
- When the new version of IMCI (which includes a malaria test and bronchodilators), the rate of antimalarial prescription should be close to the malaria test positivity rate, and the antibiotic prescription rate should be similar to or lower than that in the original IMCI. In a study with a modified IMCI, the proportion of children treated with an antibiotic was 15%.
- At community level, when iCCM guidelines (including a malaria test and respiratory rate count) were used, 25% of children should have received an antimalarial agent and 55% an antibiotic. The actual rate was higher because of suboptimal adherence of health workers to the guidelines.
- No data are available on adults, except a study in Yemen in 1989 that showed that 23% of febrile patients in all age groups would require an antibiotic.

References

Awasthi S et al. (2008). Does 3-day course of oral amoxycillin benefit children of non-severe pneumonia with wheeze: a multicentric randomised controlled trial. PLoS One, 3:e1991

D'Acremont V et al. (2011). Reduction of anti-malarial consumption after rapid diagnostic tests implementation in Dar es Salaam: a before-after and cluster randomized controlled study. Malaria Journal, 10:107.

D'Acremont V et al. (2013). Beyond malaria: etiologies of fever in outpatient Tanzanian children. New England Journal of Medicine (in press).

Gouws E et al. (2004). Improving antimicrobial use among health workers in first-level facilities: results from the multi-country evaluation of the Integrated Management of Childhood Illness strategy. Bulletin of the World Health Organization, 82:509–515.

Hazir T et al. (2004). Assessment and management of children aged 1–59 months presenting with wheeze, fast breathing, and/or lower chest indrawing; results of a multicentre descriptive study in Pakistan. Archives of the Diseases of Childhood, 89:1049–1054

Hazir T et al. (2011). 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. Clinical Infectious Diseases, 52:293–300.

Hogerzeil HV et al. (1989). Impact of an essential drugs programme on availability and rational use of drugs. Lancet, i(8630):141–142.

Naimoli JF et al. (2006). Effect of the Integrated Management of Childhood Illness strategy on health care quality in Morocco. International Journal for Quality in Health Care, 18:134–144

Njama-Meya D et al. (2007). Treatment of malaria restricted to laboratory-confirmed cases: a prospective cohort study in Ugandan children. Malaria Journal, 6:7

Shao A et al. (2011). Safety of a new algorithm for the management of childhood illness (ALMANACH) to improve quality of care and rational use of drugs. In: Abstracts of the 7th European Congress on Tropical Medicine and International Health, 3–6 October 2011, Barcelona, Spain. European Journal of Tropical Medicine and International Hygiene, 16(Suppl.1):60.

Improving access to quality diagnostic testing and effective malaria treatment for all people at risk of malaria is critical to reducing malaria transmission and ensuring that antimalarial medicines are used rationally and correctly. On World Malaria Day 2012, WHO launched a new initiative called T3: Test. Treat. Track, urging malaria-endemic countries, donors and the global malaria community to scale up diagnostic testing, treatment and surveillance for malaria. The T3 initiative bundles together the following key WHO recommendations: every suspected malaria case should be tested, every confirmed case should be treated with a quality-assured antimalarial medicine, and the disease should be tracked through timely and accurate surveillance systems.

The recent expansion of malaria diagnostic testing in endemic countries has shown that the majority of febrile patients who visit health clinics do not actually have malaria, especially in countries where control interventions have driven down malaria transmission. There is therefore an urgent need for health workers to be adequately trained and equipped so that they can provide accurate diagnosis and proper treatment to patients who have tested negative for malaria. In January 2013, the WHO Global Malaria Programme and the Special Programme for Research and Training in Tropical Diseases convened a technical consultation to review evidence and operational experiences regarding the correct management of febrile illnesses in primary health care facilities and at the community level, and to consider existing WHO guidance on the issue, as well as research priorities.

For more information, please contact:

Global Malaria Programme
20 avenue Appia
1211 Geneva 27
Switzerland

infogmp@who.int
http://www.who.int/malaria

ISBN 978 92 4 150648 9