

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

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Briefing paper for the MPAC

by V. D'Acromont and A. Bosman, Global Malaria Programme, WHO

1. Background

With the increasing deployment of universal parasitological confirmation (RDTs) of suspected malaria prior to treatment, and the decreasing trend of malaria transmission in many endemic areas, an increasing proportion of febrile patients are being diagnosed as not having malaria.

Despite this, following many years' practice of treating fever as assumed malaria, health workers may ignore negative test results and still treat the patient with an antimalarial. This problem is made more difficult to resolve given the absence of guidance and medicines for the management of non-malaria febrile illnesses. This undermines the clinical benefits of parasitological confirmation of diagnosis, and aggravates the wastage of antimalarial drugs and drug pressure on parasites. In places where clinicians have been convinced not to prescribe antimalarials in RDT negative patients, limited guidance has resulted in over-prescription of antibiotics, another poor practice which will promote the emergence of antibiotic resistance, replacing one problem by another.

Over the recent years, clear algorithms for the management of fevers at community level have been developed for children under five, and are being promoted as "integrated community case management" (iCCM), with good implementation support tools. Other tools are available for peripheral health facilities for children under five years of age (Integrated Management of Childhood Illness - IMCI) and adolescents and adults (Integrated Management of Adolescent and Adult Illness - IMAI). To review the available evidence and current practices in the management of fevers in peripheral health care settings, the WHO Global Malaria Programme and the Special Programme for Research and Training in Tropical Diseases convened a WHO Informal Consultation in January 2013.

2. Purpose of the WHO Informal Consultation

The purpose of the meeting was to a) review existing evidence and guidance on the management of malaria and non-malaria fevers at primary care and community levels; b) provide practical recommendations and operational tools based on research findings and successful country experiences for the implementation of integrated management of fevers at peripheral health facility and community level; and c) to identify and discuss major research gaps.

The aims of improving management of fevers at peripheral level are:

- a) to increase appropriate treatment and referral in order to
 - reduce severe diseases and deaths
 - reduce morbidity (length of febrile episode...)
- b) to reduce unnecessary prescription of antibiotics and antimalarials in order to
 - reduce "drug pressure" and development of drug resistance
 - decrease the risk of drug adverse events
 - save money

The main conclusion and recommendations of the WHO Informal Consultation are reported in the sections below.

3. Review on etiologies and management of febrile illness

Emerging evidence on etiologies of fevers

Common and divergent research findings emerging from recent studies on etiologies of fevers:

Children <5 years:

- 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% of fevers to Acute Respiratory Infections (ARI), and 9%, 12%, 14% and 23% to gastroenteritis (diarrhea) respectively. The remaining children had unspecific fevers without any clinical sign localised infection, except for 1% children with skin infection and very few with meningitis.
- Most (>90%) ARI were upper respiratory tract infections due to viruses (mainly influenza)
- Causes of unspecific fevers:
 - typhoid low in Tanzania (2-5%), high in Pakistan (17%)
 - urinary tract infection always low (1-6%)
 - occult bacteremia very low (2%)

Children ≥5 years and adults:

- Fevers are mainly associated with HIV: 40% of admitted febrile patients in Northern Tanzania were HIV positive while the prevalence in the community is only 3-4%
- 7%, 32% and 4% had malaria in Northern Tanzania, Cambodia and Laos respectively
- In adult outpatients in Cambodia, 80% of malaria-negative patients had upper respiratory infection (URI) and 0.6% lower respiratory tract infections.
- In studies conducted in Northern Tanzania, Cambodia and Laos, among non-malaria causes of fevers (patients with a diagnosis of ARI or other clinically documented local infections were however not excluded), *Leptospira* was found in 10%, 13% and 12% of the patients, dengue in 0%, 7% and 25% and *Rickettsia*/typhus in 10%, 4% and 26%, respectively. In Tanzania, 8% of these patients had Q fever, 5% brucellosis and 6% Chikungunya (these 3 diseases were not searched for in the Asian studies).

Recommendations for future studies on etiologies of fever

Studies conducted so far are quite heterogeneous in terms of study design, and this makes findings difficult to compare. To increase the comparability among studies in future studies:

Inclusion criteria of patients:

- Focus should be mainly on unspecific fevers (without any sign of localized infection and not associated with malaria, ARI or gastroenteritis), except where multiple diagnoses are frequent, i.e. in children in underserved areas;
- Inclusion criteria should be clearly defined, reproducible and, if possible, aligned with previous studies. A common definition for unspecific fever should be used (see above);
- Studies should also be targeting children 5-15 years and infants <2 months.

Study design:

- 'Prevalence' studies in a sample of consecutive febrile patients attending health facilities as well as incidence studies with active and passive case detection are desirable;
- Studies should be undertaken at different levels of health care (from community to hospital) and in different epidemiological settings, seasons and age groups;
- A simplified design (e.g. investigating selected rather than all possible microbiological etiologies) should be used to avoid repeating extensive (and expensive) etiological studies;
- Common case definitions between studies should be used;
- Always link clinical data to laboratory results to avoid over-interpretation of positive results. Indeed the post-test probability of positive *Rickettsia* serology is much lower in a patient with ARI or diarrhea than in a patient with unspecific fever. Another way is to exclude patients with other causes of fever (e.g. signs of localized infection) for this type of lab test.
- When possible, compare laboratory results of febrile patients with those found of matched control groups among asymptomatic people, especially when using molecular tools, also to avoid over-interpretation of positive results.

4. Available WHO guidelines and tools for the management of fevers

Available tools

Several algorithms developed by WHO are now available targeting different levels of the health system and different age groups:

	Hospital	Health facility	Community
Children	Pocket book ¹	IMCI ²	iCCM ³
Adults	District manual ⁴	IMAI ⁵	N/A

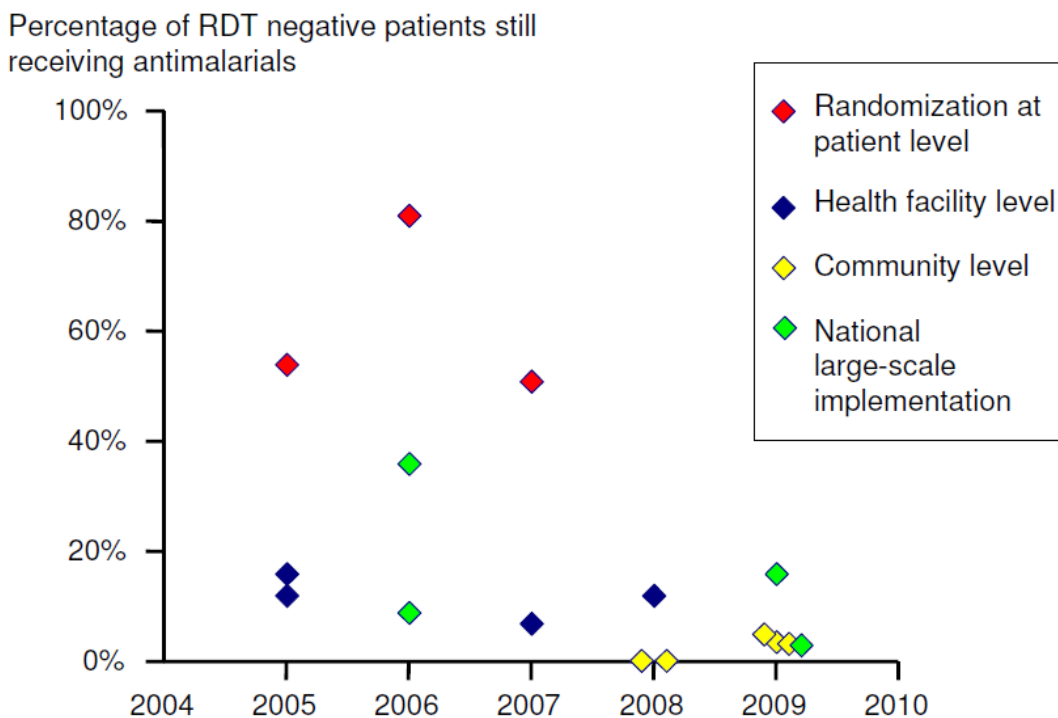
No guidelines are available for the management of adults at community level. Guidelines for 'adults' are also targeting children above 10 years. No algorithm exists for children 5 to 10 years old.

iCCM, IMCI & IMAI should be promoted more actively. An informal review of available studies suggests that adherence to iCCM by community health workers is generally good while adherence to IMCI by clinicians at health facilities is often problematic (see Figure 1).

Deployment of ACTs and RDTs for malaria case management should promote the implementation of IMCI/iCCM enforcement. The current WHO recommendations for malaria diagnosis and treatment are well integrated in most WHO guidelines for integrated management of illnesses, except for IMAI for primary health facilities. Home Based Management of Malaria, based on presumptive treatment of malaria in children under five, should not be implemented anymore and WHO documents (published in 2002-2005) should be put in archives.

Figure 1: Level of adherence of health workers to malaria RDT result by type of study

Source: reviewed by D'Acromont



¹ *Pocket book of hospital care for children: Guidelines for the management of common illnesses with limited resources.* Geneva, World Health Organization, 2005.

² *Integrated Management of Childhood Illness for high HIV settings: chart booklet.* Geneva, World Health Organization/UNICEF, 2008.

³ *Integrated Management of Childhood Illness: Caring for Newborns and Children in the Community. Manual for the Community Health Worker.* Geneva, World Health Organization, Unicef 2011.

⁴ *IMAI District Clinician Manual: Hospital Care for Adolescents and Adult. Guidelines for the Management of Common Illnesses with Limited Resources.* Volumes 1 and 2. Geneva, World Health Organization, 2011.

⁵ *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, 2009. In press.

Need for development and update

- Guidelines for management of adults at community level are needed.
- Guidelines for children 5 to 10 years should be developed.
- Continuous update based on evidence is needed, in particular (for malaria):
 - Criteria for high and low malaria risk area;
 - Malaria testing of anemic children in high malaria risk areas;
 - Malaria testing before referral/pre-referral treatment;
 - Time interval for considering a new malaria infection (presently >14 days).
- New strategies are needed to improve adherence to IMCI by clinicians working at HF level.

Criteria for integrating new diagnostic tests

- Priority should be for treatable illnesses with high disease burden (mortality, but also morbidity), detectable through reliable tests.
- In general the more specific the tests, the more expensive:
clinical → epidemiological → severity test → pathogen-specific test
- Electronic tools should be evaluated to measure essential clinical parameters (respiratory rate, O₂ saturation, etc.).
- Some pathogen-specific point-of-care tests (POCTs) are already available: some have excellent diagnostic performance (e.g. dengue), others not (e.g. typhoid fever, with RDTs having 75% sensitivity and 65% specificity in most studies).
- New POCTs are in development:
 - that specifically detect one pathogen
 - that 'generically' identify: - patients at risk for progression to severe disease
- patients in need for antibiotics
- There is a need to define, for each diagnostic test, clear criteria to target the use of diagnostics to specific patients.

Issues with integrated management of febrile illness that need attention

- How specific should algorithms be in relation to place and time? Should they be different in different parts of the country? Should they be different according to season?
- Algorithm should be adapted by level of health care system, and must remain simple for use at the community level
- Because health workers often leave the working place after receiving in-service training, efforts should be put in revising the pre-service training curriculum. The latter should be more evidence-based and include training on WHO algorithms.
- An algorithm to diagnose and manage typhoid fever in high endemic areas is urgently needed
- The cost/benefits of a new diagnostic test should be carefully evaluated before including it in the existing algorithm (e.g. dengue)
- The existing IMCI booklet is already demanding for health workers: maybe sections on care for acute illness could be separated from the topics, such as nutrition, vaccinations?
- How can health workers cope with the very complex differential diagnosis (that includes 20 diseases) proposed in the fever box of the IMAI district manual?

Issues with treatment that need attention

- High level of bacterial resistance to first line treatments has been observed
 - How to quickly adapt guidelines to changes in antibiotic resistance?
 - How to replace co-trimoxazole by amoxicillin (dispersible for children) for ARI?

- Consideration in terms of ‘class of antibiotics’ is important (not only yes/no): e.g penicillins are generally appropriate for respiratory infections, quinolones for intestinal and urinary infections, doxycycline for some causes of unspecific fevers...
- Rectal artesunate is recommended for suspected cases of severe malaria identified at the community level. However, no efficacious pre-referral antibiotic for severe febrile illness can be given as long as injectables remain not recommended for use at this level and no rectal antibiotic is available.
- WHO does not recommend differentiating the list of essential medicines between the health facility and the community level – this is considered the responsibility of countries.

5. Agencies and NGOs experience with iCCM

Emerging evidence on iCCM implementation

- Mortality has decreased with the deployment of antimalarials in the context of Home based Management of Malaria. Studies of impact on mortality of the introduction of antibiotics in the context of iCCM are ongoing.
- Compliance to algorithms was high for laboratory based tests, such as malaria RDT, but lower for clinically based tests, such as respiratory rate measurement
- CHWs were not good at picking up danger signs⁶, especially in newborns. Although frequency of danger signs is expected to be lower at community than at health facility level (due to milder presentation of disease in general), the poor performance observed was concerning.
- Patients were often not referred by CHWs to the nearest health facilities although this practice is recommended. The reasons are not very clear: one hypothesis is that they anticipate difficult compliance with referral by patients and prefer to try to manage these children on site.
- Implementation of iCCM and utilization rates of CHWs are increasing. However, the numbers of episodes for each type of disease managed by CHWs were still largely below the expected numbers based on incidence data for the same diseases, especially for diarrhea.
- Several methods for assessment of quality of care have been compared. Direct observation of the CHW versus evaluation of registries versus interviews of health workers on specific “case studies” were as good when compared to direct observation with reassessment by an expert, except for assessing ability to pick up danger signs and to diagnose pneumonia.
- Distance-based measures overestimated access to case management for childhood illness 2 to 3-fold. It is indeed critical to consider not only geographical access to the place but also access to the service, i.e physical availability of staff and of medicines.
- Salaries and other financial incentives showed to be helpful in improving retention of CHWs.
- Regarding costs, it was significantly cheaper to manage severe pneumonia at community level rather than referring patients to the next health facility.

Lessons learned from iCCM implementation

Experiences and lessons learned should be taken into account when planning scale-up of Integrated Community Case Management

⁶ In iCCM, the ‘General danger signs’ (signs of severe illness requiring immediate referral) have been mixed together with the ‘Other danger signs to refer’ (signs of persistent illness or severe malnutrition that cannot be managed at community level and need thus to be referred but not immediately), which has brought confusion around the definition of ‘Danger signs’. Studies on iCCM have up to now not distinguished between these two categories of danger signs.

Definitions: **‘General danger signs’**: Not able to drink or feed anything, Unusually sleepy or unconscious, Convulsions, Chest indrawing (will be removed in the next update), Vomits everything. **‘Other danger signs to refer’**: Fever for the last 7 days or more, Cough for 21 days or more, Diarrhoea for 14 days or more, Blood in stool, Red on MUAC (mid-upper arm circumference) strap, Swelling of both feet.

- Supervision of CHWs is well performed by a senior peer CHW, rather than by clinicians based at HF, who have often not received specific training on iCCM or IMCI, and do not have experience in using clinical algorithms.
- Country-specific solutions should guide, from the start, strategies for the retention of CHWs.
- To tackle problems of repeated drug shortages, most iCCM programmes have introduced a parallel drug distribution system: during the iCCM scale-up phase the efficiencies and sustainability of such systems need to be assessed.
- To improve treatment seeking behaviour, appropriate communication activities are needed so that communities know the type of care they can expect.
- M&E for iCCM tend to be weak. It is therefore necessary to use innovative technologies, including using telephone communications.
- Extension of CHW tasks: Newborn and healthy child care should probably be integrated to iCCM. Care for children 5-15 years and for adults has not been included in WHO guidelines for integrated management at community level, but there is increasing demand for these by many countries who are addressing care of all age-groups at community level.

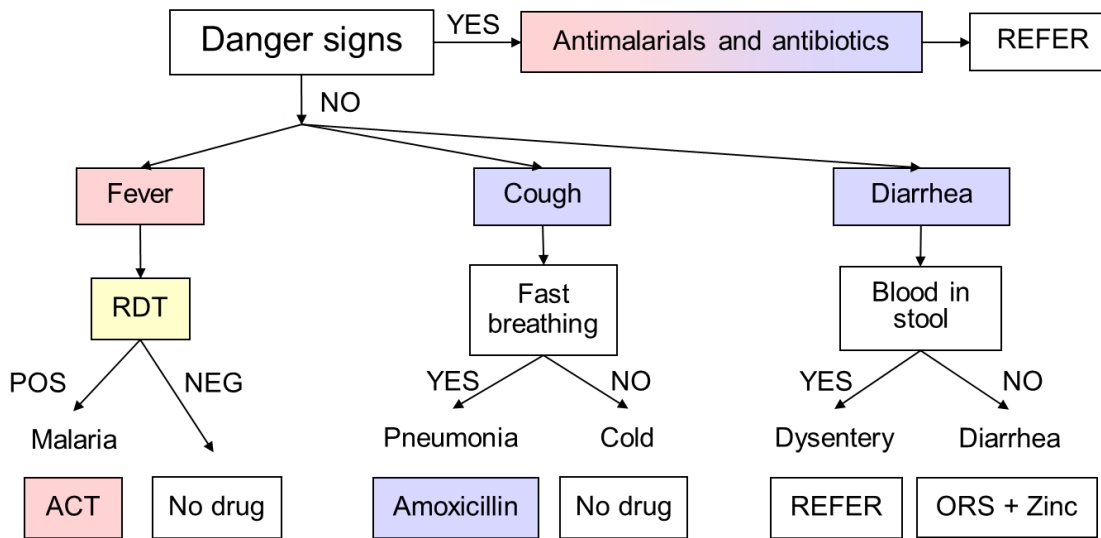
6. Country experiences with community case management of fevers in the public sector

The iCCM algorithm has been adapted to various degrees in different countries. Some adaptation is obviously needed but the core of the generic iCCM algorithm (see Figure 1) should not be modified when used in countries implementation programs. Indeed the core elements of the algorithm are evidence based and should not be changed from place to place.

The core elements of the WHO algorithm that should not be modified are the following:

- Management of fever should always include not only diagnostic testing and treatment for confirmed malaria, but also assessment and management of ARI and diarrhea
- Malaria-negative children presenting without general danger signs should not be systematically referred: these children need assessment for other conditions.
- Children with severe febrile illness should always be given pre-referral antibiotics prior to referral (especially if the malaria test has still been performed and is negative)
- Fever should not be treated presumptively with antimalarials. A diagnostic test should always be performed (except in patients with danger signs in need for immediate referral)
- Children who have a negative diagnostic test and who do not have evidence of severe illness should not be systematically treated with antibiotics. They need assessment for other conditions and antibiotics only if indicated.
- There is no need to assess fast breathing in the absence of cough or difficult breathing. This would lead to overtreatment with antibiotics

Figure 2: Core of the iCCM algorithm that should not be modified in country adaptations



The major problems that arose during iCCM implementation were due to the low quality of care at health facilities to which CHWs are supposed to refer patients. The consequences of the limited efforts in HF strengthening in parallel to iCCM implementation were the following:

- Supervision: clinicians of HFs were not able to provide supportive supervision to CHWs
- Supply chain: RDTs and medicines were often available at community but not HF level
- Quality of care: services at community level outperformed quality of care at HFs
- Access to care: 'opening hours' of CHWs were broader than that of HFs
- M&E: reliable data from community was available but not used at primary care level

All these problems led sometimes to back referral of patients from health facilities to CHWs.

7. Country experiences with community case management of fevers in the private sector

Use of malaria RDT, ACT and correct management of non-malaria febrile illnesses should be promoted not only in the public but also in the private sector, for the following reasons:

- The private sector is an important source of care in many (but not all) settings.
- Pneumonia kills an even greater number of children than malaria.
- In high endemic areas, a patient can often have both malaria and other diseases, because the clinical presentations do overlap or because they suffer from more than one disease at the same time (e.g. malaria and pneumonia).
- In low endemic areas, most patients have a negative RDT result. If management of other cause of fevers is not provided, this means that almost all patients will not receive appropriate care and will need to be referred to the nearest health facility.
- However, case management is a service, not a commodity, which means that it is more difficult to implement than the deployment of new medicines.

Therefore, when subsidized malaria RDTs are made available for the private sector, diagnosis and treatment for common non-malaria causes of fever should also be provided.

What needs to be done to provide diagnosis & treatment for non-malaria fevers in private sector

- Clear analysis and segmentation of the private sector should be done (e.g. drug peddlers, retail shops, non-registered and registered drug shops, private clinics (by level), not-for-profits...).

- The approaches need to be adapted to the target segment of the private sector (e.g. also providing appropriate incentives)
- The appropriate mechanisms for supervision and efficient surveillance methods should be piloted on a small scale and progressively extended based on the lessons learnt.
- The effective mechanisms for quality assurance of diagnostics, medicines and quality of care, which are operational for the public sector, should be progressively extended to the private sector.
- The need for consumers to be well informed and empowered through appropriate interventions (e.g. 'branding' of the accredited shops).
- The microeconomics of private sector outlets, and factors affecting consumer demand, need to be better understood.

Most of these interventions are similar to what is required for the public sector, and it may be useful to think about the challenges holistically across both public and private sectors

8. Moving forward: research priorities

Emerging evidence on effective strategies for diagnosis and treatment of febrile illness

- Withholding antimalarials in patients with a negative RDT is safe even in high endemic areas (several studies; a formal systematic review is ongoing)
- IMCI leads to overtreatment with antibiotics (poor specificity of respiratory rate measurement to diagnose pneumonia)
- One study in Pakistan, has indicated that the clinical outcome of children with pneumonia (IMCI definition) was not different when receiving amoxicillin or placebo (Hazir *et al*)⁷
- Several studies have shown that management of severe (but not very severe) pneumonia (WHO definition)⁸ is safe at community level. Update of IMCI on this point is in progress.
- Several studies have shown that management of children under five according to iCCM is safe at community level

Recommendations for research on effective strategies to improve diagnosis and treatment of febrile illness

- Study design: clinical outcomes (cure versus treatment failure) rather than laboratory diagnosis should be the primary endpoints of the study. A common definition of 'treatment failure' should be defined for each disease, as attempted for ARI.
- Studies on the safety of withholding antibiotics for "non-severe" pneumonia in children should be repeated in Asia and undertaken in Africa.
- Research should aim to define optimal care of non-specific fevers in children and adults.
- Studies are needed on cure rates of specific classes of antibiotics in patients with non-specific fevers (e.g. doxycycline for patients suffering potentially from leptospirosis or rickettsiosis/typhus).
- Risk factors (clinical and laboratory) for disease progression to severe illness need to be assessed.
- Research should clarify the need for 'disease severity' vs 'pathogen-specific' laboratory tests.
- Studies should assess the benefit of using new respiratory rate counters and pulse oximetry.
- Research should build on existing algorithms for management of febrile patients and target additional curable illnesses of public health importance.
- Research should evaluate usefulness of new tools, e.g. electronic guides, to improve compliance and data collection.
- Modeling research is needed to define appropriate cost-effectiveness thresholds for the target product profiles of new diagnostic tools.

⁷ Hazir T, Nisar YB, Abbasi S, et al. Comparison of oral amoxicillin with placebo for the treatment of world health organization-defined nonsevere pneumonia in children aged 2-59 months: a multicenter, double-blind, randomized, placebo-controlled trial in Pakistan. *Clin Infect Dis* 2011;52(3):293–300.

⁸ Definitions: **Pneumonia:** Children with no lower chest indrawing who have fast breathing; **Severe pneumonia:** Children with lower chest indrawing; **Very severe pneumonia:** Children unable to drink, with convulsions, abnormally tired or difficult to wake, or with persistent vomiting.

9. Summary of recommendations to programs and countries

These recommendations are based on the emerging evidence presented during the meeting and summarized in the grey boxes above, as well as on lessons learned from pilot programs and scaling-up efforts discussed during the meeting.

1. Studies on etiologies of fevers should be undertaken at different levels of health care and in different epidemiological settings, seasons and age groups (based on Section 3).
2. Malaria diagnostic testing and treatment should be deployed as part of promoting programmes for the integrated management of fevers, based on WHO algorithms available for different age groups and levels of care (based on Section 4).
3. Evidence from studies and lessons learned from implementation should be taken into account when planning scale-up of integrated Community Case Management (iCCM) (based on Section 5).
4. The core elements of the generic WHO iCCM algorithm should not be modified when the algorithm is going through local adaptation for the use in countries implementation programs (based on Section 6, first part).
5. iCCM programs should be implemented together with strengthening quality of care at health facilities level, based on IMCI and IMAI for primary care and hospital levels (based on Section 6, second part).
6. When subsidized malaria medicines and RDTs are made available for the private sector, diagnosis and treatment for common non-malaria causes of fever should also be provided, based on WHO algorithms for iCCM (based on Section 7).
7. Research looking at new strategies for effective diagnostic and treatment of febrile illness should be encouraged, using clinical outcomes as primary study endpoints rather than laboratory results, in order to modify or expand the current WHO algorithms (based on Section 8).