Managing the sick child in the era of declining malaria transmission: development of ALMANACH, an evidence-based electronic algorithm for appropriate use of antimicrobials

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Conclusion: This smartphone-run algorithm based on new evidence and two point-of-care tests should improve the quality of care of <5 year children and lead to more rational use of antimicrobials.
research on pneumonia diagnosis and management in order to refine Integrated Management of Childhood Illness

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Prof Simoes has been leading early research for the design and validation of the 'Integrated Management of Childhood Illness' clinical algorithms. He is still leading research to bring new evidence to improve these algorithms.

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<td>Financial Disclosure</td>
<td>The study was part of a larger project which aimed at improving the quality of health care and rational use of drugs for children in Tanzania (PeDiAtrick project), funded by the Swiss National Science Foundation (<a href="http://www.snf.ch">www.snf.ch</a>; Grant Number IZ70Z0 – 124023). The funders played no role in study design, collection, analysis, interpretation of data, writing the report, or in the decision to submit the paper for publication. Pan Africa Clinical Trial registration number PACTR201011000262218</td>
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Dear Editor,

Thank you for considering our manuscript entitled: Managing the sick child in the era of declining malaria transmission: development of ALMANACH, an evidence-based electronic algorithm for appropriate use of antimicrobials for publication as an original research article in Plos One. ALMANACH is a new electronic clinical algorithm derived from the Integrated Management of Childhood Illness algorithm that includes in particular guidance on the management of non-malaria febrile illnesses. Its aim is to improve health workers’ performance at diagnosing bacterial versus viral diseases, in order to ensure optimal clinical outcome and rational use of antibiotics. The algorithm has been developed as an android application for smartphones and tablets to improve adherence of clinicians to the recommendations. This article presents the evidence behind, the method, the content and the technology used for ALMANACH algorithm development.

Our findings and new algorithm address important concerns of stakeholders worldwide, from health workers to policy makers, namely the absence of guidance regarding non-malaria fevers, the low specificity of the criteria used in IMCI to decide on antibiotic prescription and the low compliance of health workers to existing paper guidelines which leads to overprescription of antimicrobials. It takes into account the new evidence gathered from recent studies on etiology of fevers and systematic reviews on clinical predictors, as well as the availability of point-of-care diagnostic tools. Appropriate clinical management of childhood illness is a topic of great importance in low income countries, where trained health workers are scarce, and antibiotic resistance is rapidly spreading.

Our paper is submitted as a companion paper to that of Dr A. Shao et al entitled “New algorithm for managing childhood illness using mobile technology (ALMANACH): a controlled non-inferiority study on clinical outcome and antibiotic use in Tanzania”, which showed that when used in controlled conditions, ALMANACH has led to improved clinical outcome and considerable reduction of antimicrobial prescription.

During a pilot implementation, ALMANACH, used in programmatic conditions, has also shown to lead to higher health workers performance and reduced antibiotic prescription. The paper describing this pilot implementation, in preparation, could also be submitted to Plos One soon.

This paper has not been considered for publication in any other journal.

We hope that you will acknowledge the importance and novelty of this tool that should improve the quality health delivered to children.

Yours sincerely,

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Research Physician, PhD candidate,
Swiss TPH and Basel University
Managing the sick child in the era of declining malaria transmission: development of
ALMANACH, an evidence-based electronic algorithm for appropriate use of antimicrobials

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Word count:


Number of Tables and Figures:

Tables: 2, Figures: 4
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The major changes in ALMANACH compared to IMCI (2008 version) are the following: i) assessment of 10 danger signs, ii) classification of non-severe children into febrile and non-febrile illness, the latter receiving no antibiotics, iii) classification of pneumonia based on a respiratory rate threshold of 50 assessed twice for febrile children 12-59 months; iv) malaria rapid diagnostic test performed for all febrile children. In the absence of identified source of fever at the end of the assessment, v) urine dipstick performed for febrile children <2 years to consider urinary tract infection, vi) classification of ‘possible typhoid’ for febrile children >2 years with abdominal tenderness; and lastly vii) classification of ‘likely viral infection’ in case of negative results.
Conclusion:

This smartphone-run algorithm based on new evidence and two point-of-care tests should improve the quality of care of <5 year children and lead to more rational use of antimicrobials.
Introduction

The rapid spread of resistant pathogens worldwide calls for urgent action to improve the rational use of antimicrobials. In low and middle income countries, where infectious diseases childhood mortality is high[1], substandard drugs, auto-medication and health workers (HWs)’ over-prescription of antimicrobials are driving the rapid spread of antimicrobial resistance. [2,3]

Recent experience in malaria case management has shown that using appropriate diagnostic tools (malaria rapid diagnostic tests – mRDT) has the potential to improve rational use of antimalarial[4–6] without negative impact on health outcome. [4,7–10] Unfortunately it has often been accompanied with an increased antibiotics prescription[4,5,11], reflecting the challenge faced by HWs in front of a negative malaria test result, where diagnostic tools and skills to rule out bacterial diseases are scarce.

To support HWs’ decision making in the management of a sick child in low resource settings, WHO and UNICEF have developed the Integrated Management of Childhood Illness (IMCI) clinical algorithm in the mid 90’s[12]. The IMCI guidelines rely on the classification of patients based on clinical signs that can be recognized by trained HWs even if their educational background is limited[12]; no laboratory test was included in the IMCI version of 2008: presumptive malaria treatment was recommended for all febrile children (in high malaria risks area). Other causes of fever were not considered (except if the child presented also a complaint leading to another branch of the algorithm). With the advent of new evidence on etiologies and management of childhood illness and reliable point-of-care tests (POCTs), there is a need to rethink the IMCI guidelines and to propose a new algorithm for the management of acute medical illness for children aged 2 to 59 months living in low resource settings. This new algorithm should integrate reliable POCTs and, when the latter are not available, clinical predictors for
acute illnesses, so that evidence-based guidance is provided to clinicians to decide on withholding antimalarials and antibiotics when not beneficial to the child.

An algorithm developed for HWs in remote primary health care facilities (PHCF) should rely on simple clinical signs and easy-to-perform POCTs. Its structure should remain simple, although addressing a larger set of diseases may require a more complex one. The use of hand-held electronic technology to deliver the algorithm may facilitate the use of a complex clinical algorithm by HWs of varying backgrounds. Smartphones and tablets have the potential to facilitate the scale-up of the evidence based recommendations in low resource settings.

**Methods**

**Structured literature reviews**

In order to identify the relevant diseases to be addressed in the algorithm, data on the causes of global childhood mortality and morbidity from the Child Health Epidemiology Reference Group (CHERG)[13] publications, and from the Global Burden of Disease website[14] were reviewed to assess the burden of diseases in African children. A structured literature review (SLR) was also conducted to understand the clinical presentation (accurate clinical predictors) and diseases’ distribution in children under 5 years of age (U5) attending PHCFs in developing countries, as well as appropriate POCTs for the diagnosis of the targeted diseases.

Medline (PubMed), Embase (Ovid), and the Cochrane Database of Systematic Reviews (CDSR) were explored from inception to December 31st 2010, looking for articles assessing i) the prevalence of diseases and clinical features in U5 attending outpatient facilities in developing countries, and ii) the accuracy of diagnostic procedures for each of the targeted diseases. The detailed search strategy is described in Table 1. Papers involving U5 managed for acute medical conditions in ambulatory settings were selected. Studies involving only infants below 3 months
of age or only adults were excluded. For prevalence of syndromes and diseases at PHCF, studies
describing the clinical presentation and/or diagnoses presented by U5 attending outpatients
facilities in developing countries were selected. For diagnostic procedures of targeted diseases,
studies assessing accuracy of either clinical predictors or POCT were chosen. Systematic reviews
addressing the questions of interest were also considered. An additional hand searching of
reference lists of selected papers completed these searches. In order to better explore the accuracy
of the clinical diagnosis for pneumonia, a systematic review of the literature and meta-analyses of
studies assessing the diagnostic accuracy of clinical predictors was conducted, reported elsewhere
(Rambaud Althaus et al, submitted).

**Findings of the study on causes of fever in outpatient Tanzanian children**

In a recently published study on etiologies of fever conducted in outpatient clinics in Tanzania
(Tanzanian fever study), clinical assessments and laboratory tests were performed in 1005 febrile
children aged 2 months to 10 years (95% were U5) to establish the most probable causes of
fever[15]. The distribution of diagnoses, overall and stratified by age, in severe and non-severe
children was taken into account to select the targeted disease included in the final algorithm. The
clinical predictors for the targeted diseases identified in the Tanzanian fever study were also used
to build the new algorithm (De Santis et al, in preparation).

**Algorithm construction**

With the IMCI algorithm for children 2-59 months of age as departure point, the evidence
retrieved from the SLRs and from the Tanzanian fever study was used to propose modifications
and new recommendations when relevant, and to design a new decision tree. Diseases were
included in the algorithm if they were treatable, and responsible for i) high child mortality and
morbidity, ii) high attendance rate at outpatient facilities, and, iii) high antimicrobial prescription rate. Clinical features that could easily be assessed by HWs of varying background and POCT easy to deploy in low resource ambulatory settings were integrated in the classification procedures, when its use improved the classification accuracy. Once the new algorithm was finalized, both a paper booklet and an electronic software running on android smartphones and tablets were developed.

**Results**

Flow diagrams of studies selection for the SLRs are available in Figure 1. All modifications made to the IMCI content based on new findings are presented in Table 2. The major changes concerned: malaria and pneumonia diagnosis; otitis media treatment; the addition of urinary tract infection (UTI) and possible typhoid fever; and a new classification entitled “likely viral infection”. The most important modifications are discussed below.

**Selection of syndromes or diseases to be addressed by the algorithm**

Estimations of burden of diseases by CHERG[1] and IHME[14,16] reported that low respiratory tract infections/pneumonia, malaria, and diarrhea were the leading causes of child mortality in 2010, globally and in Sub Saharan Africa (SSA). These 3 infectious diseases were estimated to be responsible for more than 40% of U5 deaths in SSA. They were also the leading causes of morbidity, responsible for 41% of the total 2010 DALYs in SSA[14]. Other frequent causes of child mortality were HIV/AIDS (3.5 to 4% of U5 deaths in SSA[1,14]), meningitis (3 to 4%[1,14]), measles (1%[1,14]), and tuberculosis (0.8%[14]). In infants aged 1 to 11 months, pertussis (2.8% of deaths in 1-11 months infant in SSA) and syphilis (2.3%) were also frequent causes of death[14]. In children aged 1 to 4 years, typhoid fever was estimated to be responsible...
for 0.6% of both DALYs and deaths, and bacterial skin diseases for 0.7% of DALYs, and 0.2% of deaths[14].

The SLR identified 22 articles assessing either symptoms or diagnoses distributions, or both, in children attending outpatient facilities in developing countries. In all selected papers assessing symptoms, fever (by history or measured, hereafter referred as fever), cough and diarrhea were the most frequent symptoms reported, respectively by 65 to 93%[17–22], 44 to 82%[17–19,21,22], and 22% to 45%[17–19,21] of children. Diseases of potential bacterial origin reported in the studies retrieved by the SLR were: pneumonia (reported in 5 to 30% of children[15,17–19,22–29]), typhoid fever (3 to 13%[15,22,24]), dysentery (3 to 12% [17,26,27]), otitis media (2 to 12%[7,17–19,26–29]), UTI (1 to 7%[15,22,26,28,30,31]); and meningitis (0 to 3%[17,23,26]).

Tonsillitis was reported in 1% of 1005 children in the Tanzanian fever study; all had a negative streptococcal diagnostic test[15]. Another study reported tonsillitis or pharyngitis in 10% of the children, but no streptococcal test was performed[28].

Among the bacterial infections frequently reported, only typhoid fever, UTI and tonsillitis were not yet addressed in IMCI. The fear of these 3 infections is often a reason to prescribe antibiotics in low resource setting. With regards to tonsillitis, early recognition and treatment of streptococcal tonsillitis is of high importance to prevent rheumatic fever and its complications, but prevalence of group A β-hemolytic streptococcus is much lower in U5 than in older children[32], and close to zero in children under 2 years of age[33]. Moreover, acute rheumatic fever and rheumatic heart disease are rare in U5[34,35]. Therefore addressing streptococcal tonsillitis in the management of U5 was considered not to be necessary. UTI and typhoid fever were thus selected to be addressed in the new algorithm, together with the other diseases already addressed in IMCI.

**Identification of severe illnesses**
In the IMCI algorithm, urgent referral to hospital is recommended in the presence of any of 5 general danger signs (difficulty in drinking, repeated vomiting, had convulsion, lethargy or unconsciousness, convulsing) or in presence of any of the 8 syndrome-related danger signs (fever: stiff neck; cough: stridor or chest indrawing; measles: clouding of cornea or extensive mouth ulcers; malnutrition: severe wasting or oedema of both feet; anemia: severe palmar pallor).

Two studies have assessed the accuracy of these IMCI referral criteria to predict hospital referral as decided by routine clinicians in Kenya (sensitivity 46%, specificity 79%) [36], or by a study pediatrician in Bangladesh (sensitivity 86%, specificity 64%) [37]. In the Kenyan study, accuracy of these criteria to predict death in admitted U5 patients was also assessed (sensitivity 89%, specificity 44%) [36]. A systematic review for children in developed countries [38] has also identified reduced consciousness, convulsions, cyanosis, rapid breathing, and slow capillary refill as the strongest predictors of severe illness. Meningeal irritation was also a strong predictor of serious bacterial infection in 3 reported studies [positive likelihood ratio (LR+) ranging from 2.57 to 275] [38]. One of the aims of the present algorithm being to allow early identification and referral of severe conditions and serious bacterial infections, all the IMCI referral criteria were kept although underlying evidence was scarce and criteria’s specificity seemed low. In addition, 2 signs that are broadly recognized to be predictors of severity were added to the IMCI general danger signs: cyanosis [38] and jaundice [39]. In order to improve and fasten the identification of severe patients, all general danger signs, were grouped together with stiff neck, severe wasting, and severe pallor at the beginning of the assessment chart, instead of having some of them included in the branches for each syndrome.

**Malaria diagnosis**

Decline in the proportion of fevers due to malaria [40] together with the availability of easy-to-use, reliable POCTs—i.e. mRDTs—have driven the WHO recommendations to shift in 2010 from
presumptive to test-based malaria case management[41]. The safety of a mRDT-based malaria case management in U5 has been demonstrated[7–10,42–44]. Several African countries have now changed their malaria diagnosis policy and adopted the use of mRDTs in their national programs. Following the new WHO malaria treatment guidelines, the use of mRDTs was integrated in present algorithm. mRDTs were also recently added officially to the WHO/UNICEF generic IMCI algorithm[45].

**Pneumonia diagnosis**

In a recent meta-analysis of clinical predictors for radiological pneumonia (Rambaud Althaus et al, submitted), the clinical features with the higher pooled LR+ were respiratory rate >50 breaths/min (1.90; 95%CI 1.45-2.48), grunting (1.78; 1.10-2.88), lower chest indrawing (1.76; 0.86-3.58), and nasal flaring (1.75; 1.20-2.56). The features with the best (lowest) pooled LR- were: history of fever (0.53; 0.41-0.69), and respiratory rate <40 breaths/min (0.43; 0.23-0.83).

Cough had also a good but heterogeneous LR- (0.30; 0.09-0.96). The IMCI criterion for non-severe pneumonia classification, i.e. age-related fast breathing (>50/min from 2 to 11 months, and >40/min from 12 to 59 months) showed low diagnostic performance in the meta-analysis, with a pooled LR+ of 1.55 (0.44-5.42) and a pooled LR- of 0.63 (0.16-2.55). In the Tanzanian fever study, the best predictors to include radiological pneumonia among all febrile children were difficult breathing (LR+ 7.9, 2.8-22.1), chest indrawing (7.1; 2.9-17.6), nasal flaring (7.0; 2.5-19.4), respiratory rate >50/min (6.1; 3.5-10.4) and abnormal chest auscultation (5.5; 3.7-8.1). No feature was good at excluding the diagnosis. In the present algorithm, in the absence of a reliable point-of-care diagnostic test, we decided to combine the best available clinical predictors (history of fever, cough, difficult breathing and fast breathing), except nasal flaring and grunting because of the difficulty for low level health workers to detect these signs, and abnormal chest auscultation because most clinicians do not have a stethoscope or are not familiar with its use.
Chest indrawing was kept but to decide on referral to hospital rather than to diagnose pneumonia, because of the relatively high proportion of these children that harbor hypoxemia[46] Regarding fast breathing, because using an age-related threshold did not improve the diagnostic test accuracy in the meta-analysis (Rambaud Althaus et al, submitted), a single threshold of >50/min for all age groups was chosen; 50/min rather than 40/min was chosen to ensure a reasonable specificity, knowing that most of pneumonias in young children are due to viruses[47]. The recommendation in the present algorithm is thus to prescribe antibiotics for pneumonia to children with [history of fever or elevated temperature] AND [cough or difficult breathing] AND respiratory rate >50/min,

**Otitis Media**

In the SLR 7 articles and a systematic review that addressed the question of the accuracy of symptoms and signs for the diagnosis of otitis media were retrieved[48]. In these studies, some otoscopic signs were strongly associated with otitis media diagnosis[48], but in low resource settings otoscopy is not available in ambulatory care. Other symptoms, such as earache, ear rubbing, and fever, although reported as associated with otitis media in 4 old studies (LR+ 3.03 to 7.3[49–51]), were not associated with this diagnosis when reported by parents of children aged 6 to 36 months attending primary care offices in a more recent study(52). Otitis media is often a self-limiting condition in young children. The 2010 Coker[48] and Sanders’ Cochrane[52] reviews, looking at available evidence of the benefit of antibiotic treatment for otitis media, report that there is little benefit (compared to placebo) and no evidence that antibiotics reduce complications or recurrence[48,52]. An individual patient data meta-analysis from 6 randomised trial reported that antibiotics were more beneficial in children aged less than 2 years with bilateral otitis media, and in those with both otitis media and otorrhoea. In children with otorrhoea, 60% of controls and 25% of those on antibiotics still had pain, fever or both at 3-7 days, with a rate
difference of -36% (95%CI -53% to -19%) and a number needed to treat of 3, whereas in children without otorrhoea the rate difference and NNT were respectively -14% (-23% to -5%) and 8[53].

Otitis media being often a self-limiting condition in young children, in the absence of accurate non-otoscopic clinical predictors the new algorithm propose to limit antibiotic prescription to children presenting with ear discharge.

**Urinary tract infection**

Two articles and 12 reviews assessing the accuracy of clinical predictors for the diagnosis of UTI in children were retrieved from the SLR. No additional article since the most recent review published in 2007 was found[54]. The following predictors were identified: temperature >40°C (2 studies, LR+ 3.3; 1.3-8.3[55] and LR+ 3.2; 0.7-15.6[56]), jaundice (LR+ 2.1; 0.3-17.4)[57], and suprapubic tenderness (LR+ 4.4; 1.6-12.4)[58]. The absence of another source of fever on examination increased the probability of UTI (3 studies, summary LR+ 2.8; 1.9-4.3)[54]. Among children ≥2 years, abdominal pain (LR+: 6.3; 2.5-16.0) [57], dysuria (LR+ 2.4; 1.8-3.1)[59] and new-onset of urinary incontinence (LR+ 4.6; 2.8-7.6)[59] also increased the probability of UTI. In the Tanzanian fever study, the following predictors to include UTI were found: pollakiuria (LR+ 3.5; 1.4-8.8), temperature >40°C (3.1; 1.4-7.1), fever for more than 3 days (2.1; 1.2-3.6) and age<2 years (1.4, 1.22-1.57); the best predictors to exclude UTI were: age<3 years (LR- 0.22; 0.07-0.66), no headache (0.27; 0.04-1.89) and no diarrhea (0.33; 0.08-1.32) (De Santis et al, in preparation). Based on these predictors, several national and international guidelines recommend to consider this condition in febrile children below 2 years of age, with no obvious cause of fever[30,60]. No symptom or sign, nor combination of them is predictive enough in this age group to appropriately identify children with UTI. The gold standard (urine culture) is generally not available in low resources ambulatory setting. Urinalysis with urine dipsticks detecting leucocyte esterase and nitrite has been evaluated in many settings: 4 systematic reviews with
meta-analyses estimated sensitivities for leucocyte esterase and/or nitrites to be 81%[61], 88%[62,63], and 93%[30] and specificities 72%[30], 79%[63], 93%[62] and 97%[61]. A dipstick urinalysis negative for both nitrites and leukocyte esterase had a LR- of 0.2 (95% CI, 0.16-0.26)[54]. With either leucocyte esterase or nitrite positive the LR+ was 6.1 (95% CI, 4.3-8.6), increasing to 28 (95% CI, 17-46) when both leucocyte esterase and nitrite were positive[61]. In 2005, the WHO department of Child and Adolescent Health and Development recommended the use of urinalysis by urine dipstick for the diagnosis of UTI in children wherever dipstick were feasible[60]. With the implementation of the WHO focused antenatal care guidelines, urine dipstick for proteinuria detection have been implemented and are thus available in PHCFs in many African countries. Based on the good diagnostic performance of urine dipstick, and it’s feasibility in low resource setting, the new algorithm proposes to perform urine dipstick for the diagnostic of UTI in the patients at higher risk of UTI, i.e. children below 2 years of age having fever with no cause identified during the assessment (but regardless of the malaria test result). For children from 2 to 5 years of age, only those complaining of dysuria are proposed a dipstick urinalysis. Antibiotic treatment for UTI is recommended when either leucocyte esterase or nitrite, or both are positive.

**Typhoid fever**

Regarding the diagnosis of enteric fever, 6 articles assessing clinical predictors of enteric fever were retrieved [64–69]. Only 2 were conducted in outpatients: one included patients above 15 years of age[67] and the other patients above 4 years of age[66]. None of the studies thus included our target population of U5 outpatients. In the Tanzanian fever study[15], the following predictors to include typhoid where identified: liver pain (LR+ 9.8; 2.7-35.5), abdominal tenderness (7.0; 3.3-15.2), jaundice (6.2; 3.1-12.4) and age >2 years (2.0; 1.6-2.4). To exclude typhoid, only ‘rainy season’ was predictive (LR- 0.50; 0.27-0.92) (De Santis et al, in
preparation). Jaundice being already included as danger sign and liver pain being difficult to assess in a child, the new algorithm recommends to look for abdominal tenderness in children ≥2 years of age having fever with no cause identified during the child’s assessment (regardless of the malaria test result). When present, antibiotic treatment for typhoid fever is indicated.

**Likely viral infection**

Likely viral infection is a classification proposed in the present algorithm that does not exist in IMCI. Unnecessary antibiotics are often prescribed in febrile children by HWs when they do not manage to reach a diagnosis after their assessment, because they fear to have potentially missed a life-threatening bacterial infection. Because in the present algorithm most of the frequent bacterial infections have been assessed for, the probability that the child is still suffering from one is low if all findings are negative. Therefore, in the absence of danger signs, cough or fast breathing, diarrhea, ear discharge, symptoms of measles, infected skin lesion, abdominal tenderness, a positive dipstick urinalysis and a positive malaria RDT, the child is classified as having a “Likely viral infection”. HWs are then proposed to withhold antibiotics and antimalarials, prescribe symptomatic treatment for fever if any, and advise the caretaker on when to come back if symptoms persist or worsen.

**Design of the algorithm**

Based on the modifications and adjunctions to IMCI that were retained, a new algorithm for the management of childhood illnesses (ALMANACH) was designed. The IMCI assessment in 3 steps was kept - “Assess, Classify, and Treat” - , as well as the color-coded triage system: red for conditions that require urgent referral, orange for conditions requiring specific treatment, and green for condition needing simple counseling and symptomatic home management[12]. The main difference with IMCI is however that ALMANACH is divided into 3 charts. The first chart provides recommendations for assessment of general danger signs and management of severe
patients, the second chart provides recommendations for patients with fever, and the last one for patients without fever (see Figure 2 for an overview of ALMANACH’s structure). This 3-charts structure allows fastening the assessment and management of severe children, for whom all recommendations are available in the very first part of the algorithm. This structure also allows a more comprehensive assessment of febrile children, with pneumonia, malaria, UTI and typhoid fever being considered only in febrile children.

ALMANACH was first designed as a paper booklet, for which efforts were made to keep the ALMANACH structure simple and graphically easy to follow by HWs (Figure 3). It was then developed as an android application for smartphones, coding the different steps of the algorithm into a Java-Rosa X form run by OpenDataKit and OpenMRS software[70,71]. The electronic ALMANACH (e-ALMANACH) guides HWs through the child’s assessment up to the classification and treatment recommendations (Figure 4). Treatment dosages are computed according to the body weight or age when weight is not available. Moreover e-ALMANACH collects in real time information on child demographic characteristics, disease classification and treatment prescribed. This information is stored by the mobile device, can be sent to a server and feed health information systems.
Discussion

The aim of ALMANACH is to provide evidence-based guidance to health workers on antimicrobial prescription, in order to treat only children aged 2 to 59 months who will potentially benefit from them. Apart from malaria, IMCI was not directly addressing causes of fever, leaving HWs with their fear of life-threatening conditions once malaria was ruled out by mRDT. On the other hand, viral infections that represent the vast majority of the causes of fever in U5 children[15] are never explicitly mentioned or proposed as diagnosis in IMCI, giving a wrong impression to health workers that bacterial infections are frequent and that children should often be prescribed antibiotics. Using the best available and feasible diagnostic procedures for the main causes of acute illness in children attending PHCFs, the present new algorithm should address most of the concerns of HWs regarding bacterial infections and remind them that children often suffer from self-limited viral conditions that do not warrant any specific treatment beside antipyretics. By providing tools to rule out malaria, UTI, and typhoid fever and by proposing a new ‘Likely viral infection’ classification, the use of ALMANACH has thus the potential to improve the health outcome of febrile children and at the same time decrease unnecessary antimalarial and antibiotic prescriptions.

The level of evidence provided by the literature was generally low. The heterogeneity of the findings may be due to uneven quality in study designs, or to the insufficient performance of clinical predictors for the diagnosis of bacterial infections. Within the current project, only the POCTs currently available in low resource settings were considered, constraining the new algorithm to rely mostly on the best available simple clinical predictors. To further improve the quality of the management of pediatric illnesses and the rational use of medicines, accurate and affordable POCTs for bacterial, or even viral infections are highly needed.
While broadening the spectrum of diseases to be addressed, the algorithm became more complex than IMCI. This might be an issue for the targeted audience, i.e. HWs of different background working in low resource ambulatory settings. In order to facilitate understanding and usability of the decision chart, the 3 steps IMCI structure (Assess, Classify and Treat) and the color coded triage, already known by IMCI trained HWs, were kept. Electronic algorithms, by guiding HWs step by step through the algorithm, allow to using a more complex structure with lower risk of misuse. The electronic version of ALMANACH running on smartphones and tablets was designed to address these needs.

The paper and electronic ALMANACH have the potential to improve the management of the sick child. This has been demonstrated in a recently completed feasibility study, which showed the ALMANACH algorithm to improve health outcome of children managed with this tool and to drastically reduce antibiotic prescription (Shao et al, submitted). Further improvement could be brought by integrating other POCT detecting key pathogens once they become available, or even better, by integrating host biomarkers able to predict children in need of antibiotics or at risk of dying.

Acknowledgement

We would like to thank Wilson Were, MD and Mario Gehri, MD for useful discussions and comments on the content and design of the clinical algorithm, and Fabrice Althaus for his participation to the literature reviews and input on methodology.
References


**Figures legends:**

- **Figure 1.** Flow diagrams of study selection process in the structured literature reviews
- **Figure 2.** Overview of ALMANACH's structure
- **Figure 3.** Samples of ALMANACH in paper format
- **Figure 4.** Samples of ALMANACH in electronic format

**Tables**

**Table 1. Structured literature reviews: search strategy**

<table>
<thead>
<tr>
<th></th>
<th>Pubmed</th>
<th>Ebase</th>
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<tr>
<td>1</td>
<td>&quot;primary health care&quot; OR &quot;outpatients&quot; OR &quot;family practice&quot; OR &quot;emergency service&quot; OR &quot;ambulatory care&quot;</td>
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</tr>
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<td>2</td>
<td>&quot;fever/etiology&quot;[MeSH Terms] OR &quot;fever/diagnosis&quot;[MeSH Terms] OR &quot;fever/epidemiology&quot;[MeSH Terms]</td>
<td></td>
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<tr>
<td>3</td>
<td>&quot;developing countries&quot;</td>
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<td>prevalence OR epidemiology OR incidence</td>
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</tr>
<tr>
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<td>&quot;predictive value of tests&quot;[MeSH Terms] OR &quot;sensitivity and specificity&quot;[MeSH Terms] OR &quot;reproducibility of results&quot;[MeSH Terms] OR diagnostic test OR diagnostic tests OR &quot;physical examination&quot;[MeSH Terms] OR &quot;medical history taking&quot;[MeSH Terms]</td>
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</tr>
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<td>6</td>
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<tr>
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<td>11</td>
<td>Filters: Infant: 1-23 months; Preschool Child: 2-5 years</td>
<td>'child'/exp</td>
</tr>
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**Prevalence**

- 1 AND (2 OR (3 AND 4)) AND 11

**Diagnostics**

- 6 AND 5 AND 11
- 7 AND 5 AND 11
- 8 AND 5 AND 11
- 9 AND 5 AND 11
- 10 AND 5 AND 11
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Table 2. Major changes in ALMANACH as compared to IMCI algorithm based on evidence

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Fever is defined by either history of fever or axillary temperature above 37.5°C or child feels hot.
Figure 1. Flow diagram of study selection
Click here to download high resolution image
Management of children aged 2 months up to 5 years

Does the child have any of 10 General danger signs?

Yes

Management of very severe diseases section
(Two dedicated pages for urgent management and referral instructions)

No

Does the child have Fever?

Yes

≥ 1 symptom(s) present

Follow dedicated chart(s)

Age?

<2 years

Positive urine dipstick?

Yes

Abdominal tenderness?

Yes

Possible typhoid fever

≥ 2 years

No

No diagnosis reached And mRDT negative

For all patients with fever: mRDT

Positive

Malaria

Negative

Likely viral infection

Assessment of febrile childhood illness

Ask for 5 main symptoms:
- Cough or difficulty breathing
- Diarrhea
- Ear problem
- Measles
- Skin problem

≥ 1 symptom(s) present

<2 years

No

Positive urine dipstick?

No

UTI

Assessment of non febrile childhood illness

Ask for 4 main symptoms:
- Cough/diff. breath
- Diarrhea
- Ear problem
- Skin problem

≥ 1 symptom(s) present

Follow dedicated chart(s)
A. Assessment: Cough in febrile children

**ASSessment of FEBRIle CHILDHOOD ILLNESSES**

**COUGH or DIFFICULT BREATHING?**

- Chest indrawing OR Stridor in a calm child?
  - Yes: Severe pneumonia
    - Give Pre-Oral Fluids
    - Perform a malaria test; if positive
    - IM Ampicillin + Gentamicin (see page 2)
    - Refer Urgently
  - No: Give inhaled bronchodilators, and assess response after up to 3 cycles
    - Yes: Resistant wheezing
      - Refer to Hospital
      - Continue inhaled bronchodilators
    - No: wheezing episode
      - See Instructions, p. 11
    - Persistent cough or Recurrent wheezing
      - Refer for Assessment
    - Pneumonia
      - See Instructions, p. 11
    - Upper respiratory tract infection
      - See Instructions, p. 11

**DIARRHOEA?**

**B. Assessment: Fever**

**FOR ALL CHILDREN WITH FEVER OR HISTORY OF FEVER: CONSIDER MALARIA**

**CONSIDER MALARIA:** Perform a malaria RAPID DIAGNOSIS TEST (mRDT)
If mRDTs are not available, perform a blood-slide.

If you answered NO to all the questions, the child has fever with no obvious cause, no danger sign, and the malaria test is negative. The child is likely to have a Viral infection. She does NOT need neither antibiotic nor antimalarial. Prescribe symptomatic treatment for fever (see page 12).
Reassure the caretaker and advise him/her to return immediately if the child is not able to drink or becomes sicker. Advise him/her to come back after 2 days if fever persists.

**C. Management: recommendations for cough related classifications**

**Severe pneumonia or Very severe disease**
- Give IM Ampicillin and Gentamicin (see page 2 for instructions)
- Give inhaled bronchodilators if wheezing (see below)
- Refer Urgently

**Resistant wheezing**
- Continue inhaled bronchodilators, using a spacer, on the way to hospital (see below)
- Refer Urgently

**Persistent cough or recurrent wheezing**
- Refer to hospital for further assessment for Tuberculosis or Asthma

**Pneumonia**
- Give Amoxicillin 25mg/kg, 2 times daily, for 5 days
- Diclectin HIV infection
- Advise caretaker to:
  - Come back immediately if the child is not able to drink or breastfeed, or becomes sicker
  - Come back after 2 days if fever or difficult breathing persist

**Wheezing episode**
- Treat the wheezing in the clinic following the symptomatic treatment instructions below. If the child has a good response to the treatment, and doesn’t need referral, continue the treatment at home:
  - Continue treatment with inhaled salbutamol, 3 to 4 times a day, for 5 days.
  - Use oral salbutamol (2 months up to 12 years: 1mg, then twice daily; 12 months up to 4 years: 2mg, 3 to 4 times daily).
- Advise caretaker to:
  - Come back immediately if the child is not able to drink or breathe, becomes sicker, or develops fever
  - Come back if the wheezing difficult breathing persists after treatment

**Upper respiratory tract infection (URTI)**
- Explain the mother that the URTI is a viral disease that is self-limiting
- Advise caretaker to:
  - Relieve cough and soothe the throat with breast milk for an infant breastfed, or with tea with lemon or tea with honey for an older child
  - Come back immediately if the child is not able to drink or breathe, becomes sicker, develops fever, or develops fast difficult breathing or wheezes
  - Come back after 5 days if the symptoms persist
A Assessment

**ASSESS:** Does the child have any DANGER SIGNS?
- Lethargy/unconsciousness
- Has been convulsing
- Pallor
- Jaundice
- Cyanosis
- Stiff neck
- Convulsing now
- Unable to drink/breastfeed
- Vomits everything
- Severe wasting
- None of the above

**ASK:** Has the child had FEVER, now or in the current illness?
- Yes
- No

B Classification

**CLASSIFIED:**
- Malaria

C Treatment

**TREATMENT:** Select formulations

What Paracetamol do you have?
- Syrup 120mg/5ml
- 500mg Tablet

**TREATMENT:** Instructions

Based on WEIGHT, 1.2 kg

Alu (ARTHEMETER + LUMEFANTRINE)

**GIVE:** 1 tablet(s) NOW.

Observe for one hour; if child vomits: repeat the dose.

Then continue at home: Give 2nd dose after 8 hours. Then 2 times daily, every 12 hours, for 2 days. NOTE: Alu should be given with food

**PARacetamol**

**GIVE:** 10ml syrup every 6 hours until fever or pain is gone.
Companion paper submitted concomitantly
Click here to download Other: ALMANAC Safety paper submitted PONE-S-14-56956.pdf