e-POCT: improving health outcomes of febrile children in Tanzania through innovative point-of-care technologies at the primary care level

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Summary

As in many low-resource countries, febrile illnesses are by far the leading cause for pediatric outpatient consultations in Tanzania. Only a small percentage of children require antibiotic treatment or hospital-based supportive care, such as oxygen therapy. In these settings, the key challenge for clinicians is to identify this minority with serious presentations among the large number of children with self-limiting infections. Health workers tend to prescribe antibiotics in the vast majority of cases, “to be on the safe side”, given the lack of adequate diagnostic tools. Despite this high-volume and indiscriminate antibiotic consumption, mortality from childhood infections remains high.

Outpatient providers rely on disease management algorithms, such as the World Health Organization (WHO) Integrated Management of Childhood Illness (IMCI) chart booklet. The IMCI strategy, with its integrative disease management approach, remains very relevant today. Yet its implementation has faced major challenges, largely related to format and content related shortcomings. For example, IMCI algorithm over-relies on clinical signs and symptoms. These inherently lack diagnostic accuracy in detecting children with serious infections and over-burden the short timeframe allocated for consultations. To address these challenges, an enhanced electronic IMCI-based algorithm, ALMANACH, was developed and evaluated in Tanzania. However, opportunities for improvement remain, especially related to the identification of children with serious infections. Host biomarkers, that can help identify children with bacterial infections, such as C-reactive protein (CRP) and procalcitonin (PCT) have not been considered within the IMCI strategy. In addition, point-of-care tests (POCTs) are available that may help detect children with severe presentations where clinical signs lack diagnostic accuracy, e.g. hemoglobin testing for identifying children with severe anemia. The aim of this project was to improve the clinical outcome of children with acute febrile illnesses through the development and evaluation of a novel electronic disease management tool. Through this tool we sought to improve the detection i) of children with severe disease requiring hospital-referral and ii) of those in need of antibiotic treatment through the integration of key clinical signs with point-of-care host biomarkers into an electronic algorithm. Through this approach we also aimed to increase the rational use of antibiotics and antimalarials. The project had two major components:

(1) Development of a novel, evidence-based electronic algorithm, e-POCT, that integrates clinical signs with point-of-care biomarkers.

(2) Evaluation of this novel algorithm through a controlled, randomized, non-inferiority trial in Tanzania.

The first step of the e-POCT project was to review comprehensively existing evidence on the management of acute febrile illnesses in children, and to identify existing disease management tools. For this purpose we conducted a structured literature review that included both clinical signs and the use of host biomarker POCTs. Though there was a large body of published studies, 'actionable' evidence was scant. This was primarily because the few validation studies with sufficient quality were either performed at inpatient-level, or included clinical signs that would not be assessable by health workers with limited training. Furthermore, validation studies had inherent limitations due to the lack of adequate gold standards (e.g. serious bacterial infection) that could be used as proxies for important clinical outcomes (e.g. cure or death). Outcome-based research and studies at the outpatient level in low-resource settings were scarce. We then assessed the diagnostic accuracy of existing disease management tools identified in detecting serious bacterial infections. We validated retrospectively four prediction rules and five guidelines (including IMCI and ALMANACH) using a dataset from a study that assessed causes of fever in 1,005 febrile Tanzanian children. The diagnostic accuracy of all tools was surprisingly low with positive and negative likelihood ratios ranging from 1.04-1.87 to 0.47-0.92, respectively. Tools that included both clinical and laboratory elements performed better than those using either one only. This retrospective validation exercise further confirmed our overall strategy for the development and validation of e-POCT in that i) the integration of key clinical elements with simple host biomarker POCTs would be the best way forward and ii) outcome-based evaluation, and not gold-standard based validation, would be the most adequate methodology to assess e-POCT against current best practice.

Next, we constructed e-POCT based on the evidence retrieved, complemented with expert experience when requisite. Despite the limitations of available evidence, we could identify several key areas of improvement and innovation. The major innovations of e-POCT were as follows; first, we integrated POCTs to identify children with severe disease (oximeter directly connected to the electronic tablet, hemoglobinometer) and those requiring antibiotic treatment (CRP and PCT rapid tests). Second, we reduced the overall number of clinical elements to include a greater number of clinical signs that can be measured objectively (e.g. heart rate). Third, we made use of the software's ability to incorporate more calculations as background software steps while maintaining simple user interfaces. For the evaluation phase, e-POCT was programmed into an android-based smartphone application (Mangologic©).

Next, given its innovative nature, we sought to evaluate e-POCT's safety when compared to the current best available electronic algorithm (ALMANACH). To this end, we performed a randomized (at patient level), controlled, non-inferiority study among children aged two to 59 months presenting with acute febrile illness to nine outpatient clinics in Dar es Salaam, Tanzania. The primary outcome was the proportion of clinical failure by day seven of follow-up. The secondary outcomes were the proportion of antibiotics prescribed on day 0 and severe adverse events by day 30 (secondary hospitalizations and deaths). We planned a non-inferiority comparison between e-POCT and ALMANACH since we did not necessarily expect benefits in terms of clinical outcome, but rather in terms of antibiotic prescription and the efficiency of the disease consultation process. We enrolled 3192 patients between December 2014 and February 2016. 3169 patients (e-POCT: 1586; control: 1583) completed the intervention and day 7 follow-up. Using e-POCT, the absolute proportion of clinical failure by day 7 was reduced from 4.1% to 2.3% compared to the control arm (risk ratio [RR] 0.57, 95% confidence interval [CI] 0.38-0.85), and the proportion of severe adverse events from 1.5% to 0.6% (RR 0.42, 95% CI 0.20, 0.87). The proportion of antibiotic prescription was substantially lowered from 29.7% to 11.5% (RR 0.39, 95% CI 0.33, 0.45). Using e-POCT, the most common indication for antibiotic prescription was severe diseases (57%, 103/182 prescriptions). With ALMANACH it was non-severe respiratory infections (70%, 330/470 prescriptions). e-POCT identified more patients with severe disease through the use of hemoglobin testing and the improved identification of children with severe malnutrition. The largest reduction in antibiotic prescription occurred in children with respiratory infections. For children with a cough, but without severe symptoms requiring hospital-referral, e-POCT recommends antibiotic treatment using a two-step diagnostic approach of refined age and temperature based respiratory rate cut-offs followed by CRP testing. ALMANACH uses the IMCI-based clinical diagnostic strategy for pneumonia (dichotomous respiratory rate cutoff and lower chest indrawing). In this patient subgroup, the use of antibiotics was reduced from 41% in the ALMANACH arm to 2% in the e-POCT arm. Interestingly, the clinical outcome of children was also improved in the e-POCT arm compared to the control arm. This may have resulted from the enhanced consideration of viral respiratory disease presentations in the e-POCT arm (such as the provision of bronchodilator treatment for viral-induced wheeze). Through the randomized, controlled trial we also showed that the use of host inflammatory marker testing to determine antibiotic prescription in patients with respiratory symptoms (CRP) and fever without source (PCT) was safe in terms of clinical outcome. Though these biomarkers were developed more than 30 years ago, this was the first clinical outcome-based evaluation of these biomarkers in children, which is indeed a crucial step before their routine use in clinical practice.

In conclusion, this project allowed for the development of an innovative electronic disease management algorithm, e-POCT, which has the potential to improve the clinical outcome of children with febrile illnesses in low-resource settings while substantially decreasing the use of antibiotics. Through the integration of key clinical elements with host-biomarker POCTs, e-POCT improved identification of children with severe disease and increased targeting of those in need for antibiotic prescription. This disease management tool will be an important asset to improving the rational use of antimicrobials. This project indeed re-emphasized that very few children with acute febrile illnesses in outpatient settings benefit from antibiotic treatment. Electronic algorithms in general are an important prospect to increase compliance to IMCI—the integration of POCTs would make even better use of such technologies. As implemented in the e-POCT algorithm, POCTs should include both tests for identification of patients with severe disease and for the detection of children with bacterial infections. To make best use of these POCTs they should be integrated into a patient management tool that will not only help to select patient subgroups for which testing is useful, but also help interpret results within an overall patient assessment. This will also promote the continuation of an integrated approach to the treatment of childhood infection, which has been a cornerstone of IMCI. Though areas of further improvement and future research remain, the focus should now shift towards the implementation of novel electronic disease management tools, including e-POCT, in close collaboration with WHO and local governments.

Abbreviations

Advanced Pediatric Life Support (APLS)
Blood pressure (BP)
Body temperature (T)
Capillary refill time (CRT)
Chest X-ray (CXR)
Classification and Regression Tree (CART)
Confidence Interval (CI)
C-reactive protein (CRP)
Electronic IMCI version (e-IMCI)
Fever without source (FWS)
Heart rate (HR)
Hemoglobin (Hb)
Haemophilus influenza type B (HiB)
Human immunodeficiency virus (HIV)
Integrated Management of Childhood Illnesses (IMCI)
Integrated Community Case Management guidelines (iCCM)
Intention to treat (ITT)
Interquartile range (IQR)
Likelihood ratio (LR)
Lower respiratory tract infection (LRTI)
Malaria rapid diagnostic test (mRDT)
Mid-upper arm circumference (MUAC)
Modified intention-to-treat (mITT)
Negative likelihood ration (LR-)
Non-governmental organizations (NGOs)
Outpatient Department (OPD)
Oxygen saturation (SaO2)
Per-protocol (PP)
Pneumococcal conjugate vaccine (PCV)
Point-of-care (POC)
Point-of-care test (POCT)
Positive likelihood ratio (LR+)
Respiratory rate (RR)
Serious bacterial infection (SBI)
Urinary tract infection (UTI)
Upper respiratory tract infections (URTI)
Weight for age (WFA)
Weight for height (WFH)
World Health Organization (WHO)

1. Background

1.1. Acute febrile illnesses at peripheral health care level: decreasing prevalence of bacterial infections, increasing antibiotic use

In Tanzania, as in many low-resource countries, febrile illnesses are by far the leading cause for pediatric outpatient consultations (D'Acremont, Lengeler and Genton, 2010; Feikin *et al.*, 2011). At this level only a small percentage of children require antibiotic treatment or referral for hospital-based supportive care, such as oxygen therapy (Shao *et al.*, 2015). There is increasing evidence that a large proportion of acute febrile illnesses in these settings are caused by viral infections (Chapter 4). A study in Tanzania conducted by Swiss TPH researchers in 2008 as part of a larger project around malaria rapid diagnostic test (mRDT) implementation (IMALDIA) investigated the etiology of febrile illnesses among 1005 children (D'Acremont *et al.*, 2014). In this study, 70.5% of patients had microbiologically confirmed viral infections with a significant overlap between disease etiologies (Figure 1).

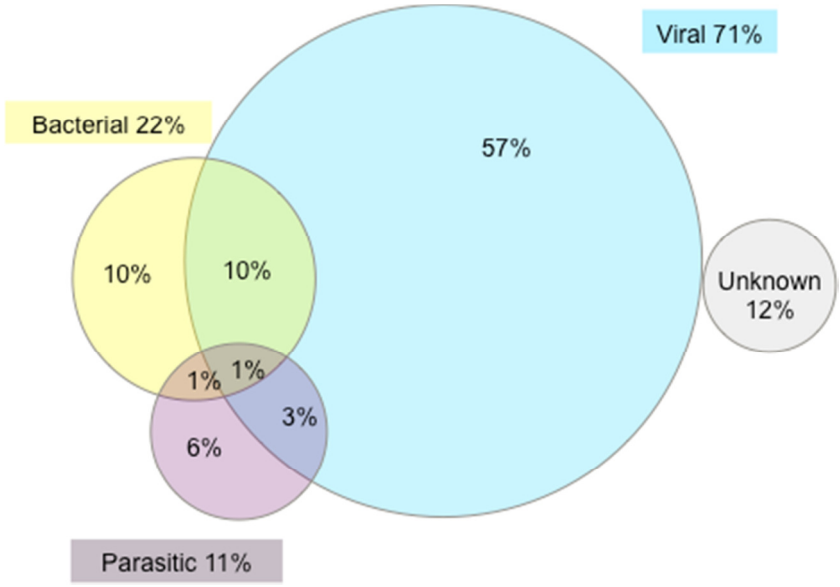

Figure 1 Causes of fever in 1,005 febrile children in Tanzania, % of total diagnoses (D'Acremont *et al.*, 2014)

After the introduction of the pneumococcal conjugative vaccine in Tanzania in 2013, the proportion of bacterial infections has likely decreased further, as it has in other countries (Bressan *et al.*, 2012; Hernandez-Bou *et al.*, 2015). Both viral and bacterial infections caused severe disease: only 20% (16/81) of children with referral criteria had a documented bacterial infection. For example, children with bronchiolitis (a viral infection of the lower respiratory tract) may require hospital-based supportive care such as oxygen therapy and

rehydration.

In these settings, clinicians are challenged to identify and manage the few children with serious infections amongst the large number of children with self-limiting disease. The many causes of fever are difficult to distinguish clinically in children without adequate diagnostic tools and extensive training. The clinical assessment of a child with an acute febrile illness requires integration of a multitude of information such as epidemiological, demographic, clinical, and laboratory data. Several diagnoses have to be considered at once, as children will often present with several concurrent complaints and signs (Horwood *et al.*, 2011). Out of the fear of missing a serious infection, clinicians tend to prescribe antibiotics for the vast majority of children (D'Acremont *et al.*, 2011; Baltzell *et al.*, 2013) "to be on the safe side" (Rambaud-Althaus, Shao, *et al.*, 2015).

Figure 2 Medical record of an 18-month-old study patient. Since birth, the child had consulted for 12 minor illness episodes, of which 11 were treated with antibiotics (orange). He was febrile during 3 visits only.

The increasing availability of antibiotics in low-resource settings has accelerated this widespread over-use, most notably all at the peripheral health care level where most patient consultations occur (Risk *et al.*, 2013). Despite this non-differential approach to antibiotic prescription, mortality from childhood infections remains high (Liu *et al.*, 2014). On the patient-level, over-relying on antibiotic treatment has resulted in the neglect of the correct supportive management of severe infections, such as provision of bronchodilator treatment and rehydration (Østergaard *et al.*, 2012). Antibiotics may also cause life-threatening side effects, such as allergic and immune reactions. From a public health perspective, antibiotic misuse has contributed to the alarming spread of antibiotic resistance in developing countries (Sosa *et al.*, 2010). For example, in studies investigating resistance patterns of *Pneumococcus* in Ghana, Tanzania and Uganda, decreased susceptibility to penicillin was found in 45%, 68%, and 84% of isolates (Joloba *et al.*, 2001; Moyo *et al.*, 2012; Dayie *et al.*,

2013). This compares to 35% in the United States (Jenkins, Brown and Farrell, 2008) and 12% in Switzerland (Kronenberg *et al.*, 2006). Currently, antibiotic resistant strains are mostly affecting older, inexpensive antibiotics. However, the increasing availability and unregulated use of antibiotics in developing countries will most certainly result in resistance to newer agents as well (Sosa *et al.*, 2010). Mitigating the rapid emergence of antibiotic resistance has become a major public health priorities. The World Health Organization (WHO) has initiated a global action plan against antimicrobial resistance (World Health Organization, 2015). The launch of Tanzanian country-level antimicrobial resistance strategy is imminent (Wiedenmayer, personal communication). Having effective disease management tools for the primary health care level will be an important ingredient to any strategy targeting a more rational prescription of antibiotics.

1.2. IMCI and ALMANACH are available disease management algorithms- why is the development of a novel algorithm required?

1.2.1. IMCI

WHO and its partners developed the large *Integrated Management of Childhood Illnesses* (IMCI) program in the 1990s with the goal to tackle the five major causes of childhood death in high mortality, high malaria transmission settings at the time: diarrhea, pneumonia, measles, malaria, and malnutrition. The program combined existing vertical child health programs into one, horizontal strategy (Gove, 1997). Such an integrated approach to the classification and treatment of childhood illnesses has been a cornerstone of IMCI, and remains very relevant today. At the heart of the program is a set of paper-based case management algorithms, the IMCI chart booklet. The IMCI algorithm relies on simple clinical signs for case detection, without laboratory tests other than mRDT (World Health Organization, 2014). Impact studies of the IMCI program as a whole on child mortality and quality of care were performed through a multi-country evaluation program in several high mortality settings—Tanzania was one of the study sites (Victora *et al.*, 2006). In such high mortality settings, effective implementation was associated with reduction in child mortality (pooled estimate from two studies RR 0.85, 0.78-0.93, Gera et al. 2016). Tanzania was a “poster child” for IMCI implementation as one of the only countries that rolled out countrywide expansion.

However, IMCI implementation has faced major challenges through a spectrum of obstacles within the health system, from the macro (policy) to the micro (patient-provider interaction)

level. At the micro level, adherence to the IMCI algorithm is low across geographical settings (Arifeen *et al.*, 2005; Horwood *et al.*, 2009; Baiden *et al.*, 2011). In Tanzania, the IMCI algorithm is hardly applied in practice and clinicians prefer relying on their 'own experience' (Walter *et al.*, 2009; Lange, Mwisongo and Mæstad, 2014; Rambaud-Althaus *et al.*, 2017). This lack of adherence is certainly multifactorial. In a comprehensive qualitative study among health workers in the Dodoma and Morogoro region (Tanzania), Lange et al. found the lack of intrinsic and extrinsic motivation to be crucial contributors for non-adherence, rather than capacity, patient load, or IMCI knowledge (Lange, Mwisongo and Mæstad, 2014); this included the lack of "motisha" (Swahili for financial motivation). However, the general disbelief in the usefulness of following the IMCI guidelines was also an important factor (Lange, Mwisongo and Mæstad, 2014). Here, format and content related shortcomings of the IMCI algorithms play an important role. As for format related barriers, the current IMCI algorithm requires multiple manual disease classifications, treatments, and reporting. It asks health workers to follow flow diagrams, understand and use accessory information on each page, and navigate through 39 pages of the chart booklet (World Health Organization, 2014). Health workers face challenges to manage the complexity of a febrile illness syndrome using IMCI in the 5-6 minutes allocated to a visit. As a result, providers often fall back to narrow diagnoses and the integrative IMCI approach of treating several illnesses at once is not implemented (Walter *et al.*, 2009). This is further accentuated by national reporting requirements where only one diagnosis has to be noted (Rowe *et al.*, 1999). Electronic IMCI versions (e-IMCI) provide a user-friendlier format compared to paper-formats. They may thereby increase algorithm adherence and the consistency of clinical assessments (Mitchell *et al.*, 2013; Rambaud-Althaus *et al.*, 2017). Beyond e-IMCI, electronic algorithms also have the potential to integrate more complex information while maintaining a simple user interface.

In addition to format-related barriers, IMCI implementation also faces content-related challenges. First, the algorithm lacks guidance for about one quarter of febrile children: children without localizing symptoms (fever without source [FWS], also called undifferentiated fever). For such children, IMCI instructs to "give appropriate antibiotic treatment for an identified bacterial cause of fever" but provides little guidance on how to identify a bacterial cause of fever (World Health Organization, 2014). Even if their actual contribution to morbidity and mortality is not well known, negative outcomes of these infections are feared by health care workers and a major motivation for clinicians to over-prescribe antibiotics (Rambaud-Althaus, Shao, *et al.*, 2015). Second, the IMCI algorithm over-relies on clinical signs and symptoms, which inherently lack diagnostic accuracy in detecting children in need for antibiotic treatment or referral for hospital-based supportive care (Thompson *et al.*, 2012, see Chapter 5 for a full

discussion). Third, the clinical signs included into IMCI were either based on small derivation studies, or on expert opinion alone; data from larger, systematic studies was not available at the time of development of IMCI (Gove *et al.*, 1999). These clinical signs need to be reconsidered since the epidemiological context of infections has changed (D'Acremont *et al.*, 2014) and a considerable amount of novel evidence has emerged (Thompson *et al.*, 2012). Fourth, there is concern that IMCI lacks sensitivity for detection of children with severe disease. This is because the limited clinical 'danger signs' to detect children with severe disease are generally specific, but not sensitive (Chapter 5.4).

1.2.2. ALMANACH, an algorithm developed by the research group

Previous work from our group, the PEDIATRICK project, sought to address some of these challenges through creating a revised, IMCI-based algorithm (ALMANACH), including an electronic version (Rambaud-Althaus, Shao, *et al.*, 2015). Its efficacy and usefulness was then evaluated in Tanzania (Shao *et al.*, 2015; Rambaud-Althaus *et al.*, 2017). The major changes in ALMANACH from IMCI were the addition of two clinical signs for severity (jaundice and cyanosis), the introduction of a separate chart for patients without fever, as well as the inclusion of a clinical sign for typhoid (abdominal tenderness) and urine dipstick testing for patients with FWS. The ALMANACH algorithm was compared to routine care in a cluster-randomized trial in Tanzania (Shao *et al.*, 2015). In the control arm, no intervention was done (such as an IMCI refresher training or provision of an IMCI chart booklets). In this study ALMANACH achieved better clinical outcome when compared to routine care (clinical failure was defined as death or secondary admission or lack of clinical cure at day 7 per parental report). At day 0 antibiotics were prescribed to 15% using ALMANACH versus 84% using standard practice. The ALMANACH study included patients with, and without febrile illness. The majority in reduction of antibiotics (67%, 266/395 of reduced antibiotic prescriptions) was achieved through not recommending antibiotics to children without fever or severe disease (Shao, 2015). During a pilot implementation phase, the use of smartphones versus paper was associated with a significant increase in children checked for severe symptoms (Rambaud-Althaus *et al.*, 2017). Both the paper and electronic ALMANACH form resulted in a reduction of antibiotic prescriptions when compared to routine care; the effect was most pronounced in the electronic arm (Rambaud-Althaus *et al.*, 2017). Since this pilot implementation phase, ALMANACH has not been implemented in Tanzania. However, efforts are underway for implementation elsewhere (Table 28), including a revised version in collaboration with Médecins Sans Frontières (MSF e-CARE, Rambaud-Althaus, personal communication). In summary, the PEDIATRICK project generated the following important findings; first, few children at the

outpatient level benefit from antibiotic treatment. Second, antibiotics should be considered only in children with fever (presentation of history) or severe disease. Third, electronic algorithms may lead to more consistent clinical assessment, and hence improve the quality of care.

1.2.3. Persistent challenges

On the other hand, several major persisting challenges were identified, which were the basis for the development of the e-POCT research project. First, the identification of children with severe disease presentations should be improved further. Less children were diagnosed as having severe disease in the ALMANACH arm (0.2%, 2/842) versus the routine arm 1.6% (10/623), p=0.002 (Shao *et al.*, 2015). Though this may have been due to a bias introduced through the cluster design of the study, it raised concern about ALMANACH's performance in detecting children with severe disease. ALMANACH did not appear to improve identification of children with severe disease, which was an aim in developing the algorithm; health workers were unable to detect the additional clinical signs proposed for severe disease (cyanosis, jaundice, Shao, 2015). Second, a large number of patients still received antibiotic treatment for non-severe respiratory infections: 81% (100/124) of antibiotic prescriptions for febrile patients at day 0 were for non-severe respiratory infections (Shao, 2015). In the pilot implementation study, only one third of patients categorized by an expert as 'pneumonia' were identified as having 'pneumonia' by health workers. This proportion did not differ between the routine and ALMANACH arms (Rambaud-Althaus *et al.*, 2017). A large proportion of this diagnostic disagreement was likely due to variability of respiratory rate measurements over time, which is a well-known phenomenon (Simoes *et al.*, 1991). This raised concern again about the usefulness of respiratory rate alone as a criterion for bacterial pneumonia. Overall, the findings from both studies called for an improved targeting of children with non-severe respiratory complaints in need of antibiotic treatment. Third, ALMANACH still relies mainly on clinical signs and symptoms, which lack diagnostic accuracy in detecting children in with bacterial infections or severe presentations (Chapter 5.4). Asking providers to perform such detailed clinical assessment without an evidence base for their usefulness overburdens the short time allocated to consultations. Length was indeed an important factor for non-adherence to the electronic algorithm identified in a qualitative study on tablet use performed during the PEDIATRICK project (Shao *et al.*, 2014). Fourth, the management of children with FWS should be improved. The diseases ALMANACH considers in children with FWS, typhoid and urinary tract infections, only represent a fraction of bacterial infections that would need to be taken into account (D'Acremont *et al.*, 2014). In addition, health workers were unable to detect the proposed clinical sign for typhoid (abdominal tenderness, Shao, 2015).

1.3. Opportunities for improvement of existing algorithms

In addition to updates on disease epidemiology since development of IMCI, evidence on the diagnosis and management of febrile illnesses in children has also evolved. As mentioned earlier, little evidence was available at the time of IMCI development and more recent data suggests that some of the backbones of the IMCI strategy may have limited diagnostic accuracy (Kalter, Burnham, *et al.*, 1997; Kalter, Schillinger, *et al.*, 1997; Weber *et al.*, 1997; Zucker *et al.*, 1997; Pringle *et al.*, 2011; Wingerter *et al.*, 2012; Rambaud-Althaus, Althaus, *et al.*, 2015). In recent years, a large number of clinical predictors for serious bacterial infections (SBI) were studied in children through large primary research efforts in developed countries (Van den Bruel *et al.*, 2010). This calls for a careful revision of the disease management charts that form the basis of syndromic diagnosis and treatments. However, in these recent research efforts, no common set of clinical predictors for identification of SBI could be identified: many of the identified predictors lack external validity. This is not surprising since a uniform pathophysiological disturbance in all serious infections is unlikely, at least at the relatively early stage seen at primary care level. Moreover, given the large number of potential predictors and the relative low prevalence of SBI, data- driven analytical approaches may have resulted in a number of predictors identified by chance but miss true predictors and contribute to the observed lack of external validity (Oostenbrink *et al.*, 2012). In summary, management algorithms of fever in resource-poor settings built on clinical predictors alone will likely remain unsatisfactory given the limited diagnostic value of a small set of clinical predictors that could be assessed reliably by health care workers.

Host biomarkers that can help identify children with bacterial infections, such as C-reactive protein (CRP) and procalcitonin (PCT), have not been considered within the IMCI strategy (Van den Bruel *et al.*, 2011); this is in part because the safety of using CRP or PCT cutoffs to decide on antibiotic prescription in children has never been evaluated. Besides the one trial in Vietnam that evaluated the use of CRP (without provision of additional clinical guidance) to guide antibiotic prescription in mild respiratory infections (Do *et al.*, 2016), all studies of CRP and PCT in children have focused on analytical performance; none have assessed whether using these tests would change patient outcome. These biomarkers are available as point-of-care tests (POCTs) that are implementable at peripheral level (Van den Bruel *et al.*, 2011). They have been routinely used in pediatric care in Europe and may help identify children in need of antibiotic prescriptions.

Other POCTs may help detect children with severe symptoms where clinical signs lack diagnostic accuracy: for example hemoglobin (Hb) testing can detect children with severe anemia. Severe anemia is one of the major presentations of severe malaria in children under five and a major contributor to the morbidity and mortality attributable to malaria; in a study among children with malaria in Malawi, between 32 and 54% of malaria-related deaths were associated with severe anemia (Tayiog *et al.*, 1994). Severe anemia was also a strong predictor of bacterial diseases in the IMALDIA Fever study project (De Santis and D'Acremont, 2017). Simple field-applicable Hb testing tools are widely available in resource-poor settings.

The combination of the: i) content and format related challenges of IMCI, ii) the ALMANACH experience where important challenges remained after the algorithm's development and evaluation, and the iii) availability of new tools and evidence called for the development of an innovative, novel disease management algorithm, rather than additional small modifications of existing disease management tools. The way forward would be to move away from subjective and inaccurate clinical signs and to replace them with more objective diagnostic tools. The diagnostic tools should remain simple and implementable at the point-of-care (POC) level. The novel electronic decision chart would hence include only few critical clinical parameters complemented by key etiologic tests (such as malaria) and several host biomarkers POCTs that could identify children at risk for life-threatening infections and those in need of antibiotic treatment. It would improve identification of children with severe disease presentation and increase targeting of those in need of antibiotic prescription, while being simple and user-friendly.

2. Goals and Objectives

2.1. Goal

The goal of this project was to improve the health outcome of children with acute febrile illness through rapid and accurate identification of those children at increased risk of life-threatening infections and those children that would most likely benefit from antibiotic treatment. We also aimed at a more rational use of antimicrobials, which would contribute to mitigating the development of antimicrobial resistance, and at reducing the misallocation of scarce health resources that are the result of inappropriate drug use.

2.2. Objectives

The project had two, closely related primary objectives.

Primary Objectives

- To develop a novel, evidence-based electronic algorithm, e-POCT, that integrates key clinical signs with POC host biomarkers.
- To compare the clinical outcome of febrile children 2-59 months of age managed either by e-POCT (intervention arm) or ALMANACH (control arm).

Secondary Objectives

- To compare the use of antimicrobials between e-POCT and ALMANACH.
- To evaluate the safety and benefit in terms of reduction of antibiotic prescription of using CRP and PCT testing to decide on antibiotic prescription in children with non-severe respiratory symptoms and children with fever without source.
- To gain further insight into the utility of POCTs to detect children with severe disease.

3. Methodological overview

The project was conducted in two phases, which were implemented sequentially. Phase 1 involved the development of novel, electronic evidence-based algorithm, e-POCT; this novel algorithm was then evaluated in a randomized, non-inferiority study in Dar es Salaam (Phase 2).

3.1. Phase 1: development of a novel decision tree

For the development of the novel algorithm, a structured literature review was carried out with the aim to identify: i) areas that could be modified based on existing evidence, and ii) components amenable for innovation and the generation of new evidence (Chapter 5.3). Where little published evidence was available, information was complemented with input from pediatric specialists from Tanzania, the Unites States, and Switzerland. We also assessed the theoretical performance of existing prediction rules and guidelines identified through the structured literature review in detecting children with SBI through a retrospective validation study on the dataset from the IMALDIA study (Chapter 6.3).

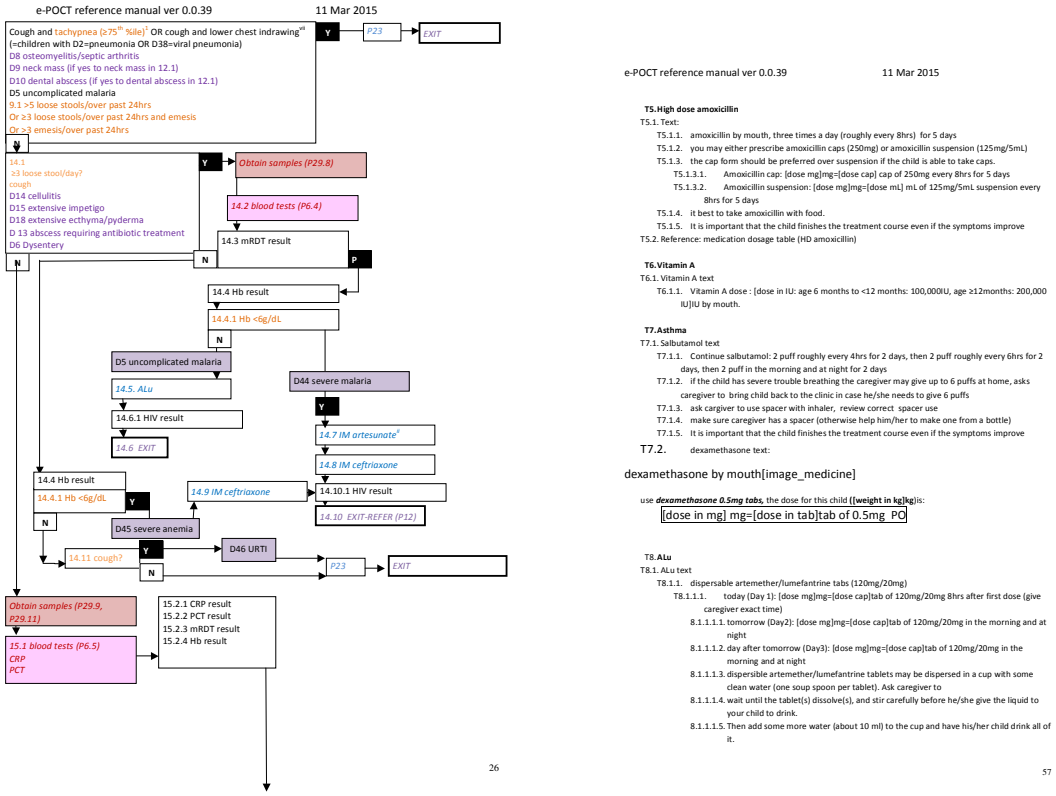

Figure 3: Example pages of the reference manual.

A detailed paper reference manual was developed, which served as the basis for the software programming (Figure 3). Since the novel algorithm included background software calculations that could not be done manually by health-workers, we did not develop a consultation paper chart booklet for clinicians. The 63-page paper reference manual for programming contained the overall logical flow of the algorithm, and also detailed the screen-text for each procedure and treatment (Figure 3). The algorithm was then programmed into an android-based decision support tool for the purpose of this study.

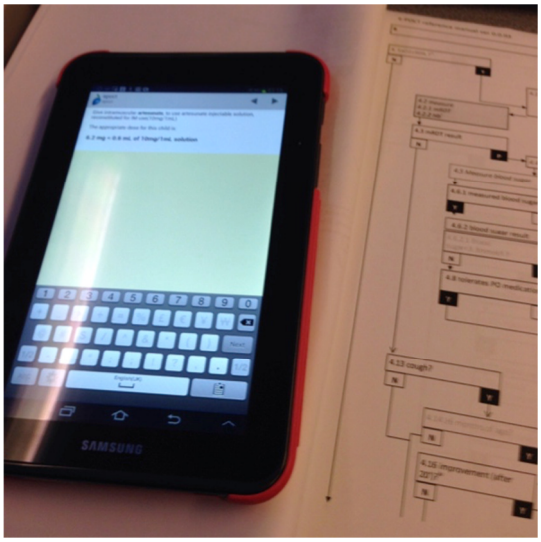

Figure 4 Validation of the e-POCT algorithm

We initially attempted programming of the algorithm into the open-source Open Data Kit (ODK) software, but were limited by the software's simple skip logic. For example, having several disease classifications required permutations of the antibiotic treatment (to prescribe one antibiotic that would work for both disease classifications, instead of a separate antibiotic for each classification). Also, several branches of the algorithms had to be entered at once. We then collaborated with ThingsPrime, a software company that had developed Mangologic©, a software aimed at supporting decisions trees. The algorithm was programmed by ThingsPrime into Mangologic©. We performed detailed internal validation of the software after each modification against a standard set of theoretical patients.

After careful internal validation of the software, the tool was then piloted in 100 patients meeting eligibility criteria to allow final revisions. A local medical doctor and myself supervised all consultations during that phase to assure patient safety. A final version was then created for use in phase 2 (Chapter 5.3). We also attempted to connect several sensors to the algorithm so that the information could be directly fed into the algorithm software without manual input. This was successful for the oximeter probe using the XPod™

USB hub (Nonin Medical Incorporated). However, the electrical power supplied by the tablet USB ports was not sufficient to run the oximeter. An external USB power hub had to be connected in between. The direct USB oximeter feed failed intermittently with software updates, requiring the use of a backup, manual oximeters.

Figure 5 Oximeter connected to tablet (left) and back-up oximeter (right)

As for the lateral flow tests, we tried integrating an automated reader (DekiReader™, Fio Corporation). However, the reader could not be calibrated for the CRP test. In addition, the software was required to be maintained within the reader (instead of the smartphone). Using the Dekireader™ instead of an electronic tablet would not have been suitable.

3.2. Phase 2: evaluation of e-POCT in a randomized, controlled trial

Next, we carried out a randomized, controlled, non-inferiority trial comparing the clinical outcome of febrile children between e-POCT (intervention) and ALMANACH (control arm). The methods of this trial are described in detail in Chapter 7.3. To better assess the impact of CRP-testing on clinical outcomes and antibiotic use among children with non-severe respiratory infections, we performed a subgroup analysis. The methods for this analysis are detailed in Chapter 8.4.

IMCI, and its electronic version ALMANACH, is currently the standard of care for treatment of febrile illnesses in children in resource-poor settings. ALMANACH, instead of the paper-

based IMCI, was chosen to control for the 'electronic support tool effect'. In addition, ALMANACH contains several improvements compared to IMCI (see Chapter 1.2.2).

Our choice of a non-inferiority trial design was based on the expectation that the advantage of e-POCT in terms of antibiotic prescription would be sufficient to tip the risk-benefit ratio in its favor of e-POCT. We expected that e-POCT would achieve similar clinical outcome while further reducing antibiotic prescription.

3.2.1. Ethics

The study protocol and related documents were approved by the Institutional Review Board of the Ifakara Health Institute and the National Institute for Medical Research Review Board in Tanzania, by the Ethikkommission beider Basel in Switzerland, and the Boston Children's Hospital Ethical Review Board. An independent Data Monitoring Committee oversaw the study. The trial was registered in ClinicalTrials.gov, identifier NCT02225769. Major issues discussed with the local Institutional Review Boards were the storage and transfer of samples, including tests to be done in Tanzania, and blood draw volumes.

4. Study setting: Dar es Salaam, Tanzania

Patient recruitment took place in the outpatient department (OPD) of primary health facilities (health centers, dispensaries, and district hospitals) in Dar es Salaam (Figure 6). We chose the Dar es Salaam region because of its relative low endemicity for malaria (allowing better investigation of febrile episodes caused by other diseases than malaria (Figure 7). Several previous studies had already been carried out in the area by our group, which provided additional infrastructural advantages. This was especially important because the innovative character of e-POCT required close monitoring of adverse events, which may have not been possible in more remote areas with the resources at hand for this project. Study sites were selected to represent the general pediatric outpatient population of the region.

Figure 6 Study sites. 1: Sinza Health Center, 2: Tandale Dispensary, 3: Mwananyamala Hospital, 4: Magomeni Health Center, 5: Mburahati Dispensary, 6: Amana Hospital, 7: Temeke Hospital, 8: Kizuiani Dispensary, 9: Rangi Tatu Health Center.

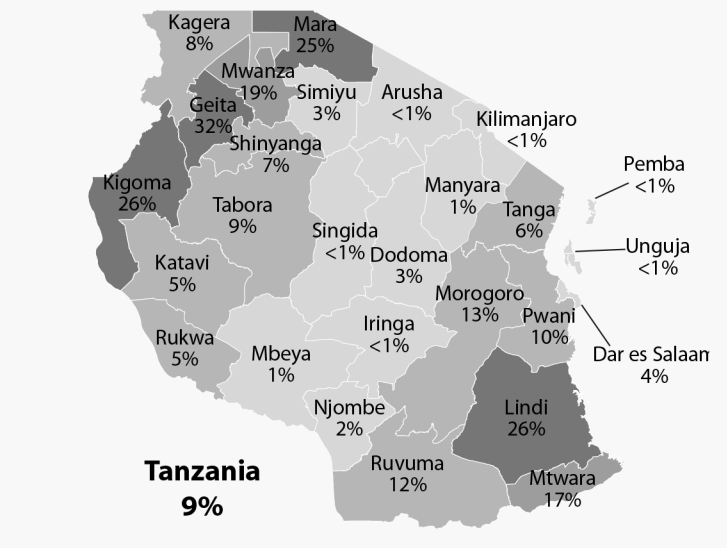

Figure 7 Tanzania malaria prevalence in children by region. % of children who tested positive by mRDT in a 2011/12 survey (Tanzania Commission for AIDS, 2013)

4.1. Child health in Tanzania

Tanzania's under-five mortality was estimated at 48.7/1,000 live births in 2015 by the Child Mortality project (UN Inter-Agency Group for Child Mortality Estimation, 2017), and at 66.5/1,000 live births in a 2012 Tanzanian census (Tanzania National Bureau of Statistics and Tanzania Ministry of Finance, 2015). The country experienced one of the most important declines in child mortality over the past 20 years in Sub-Saharan Africa (Figure 8). A significant proportion of this decline is certainly attributable to improved childhood vaccinations: *Haemophilus influenza type B* (Hib) was introduced in 2009, the pneumococcal conjugate vaccine (PCV) and rotavirus vaccine in 2013. Official coverage reports are above 95% for all three vaccines (World Health Organization, 2017a).

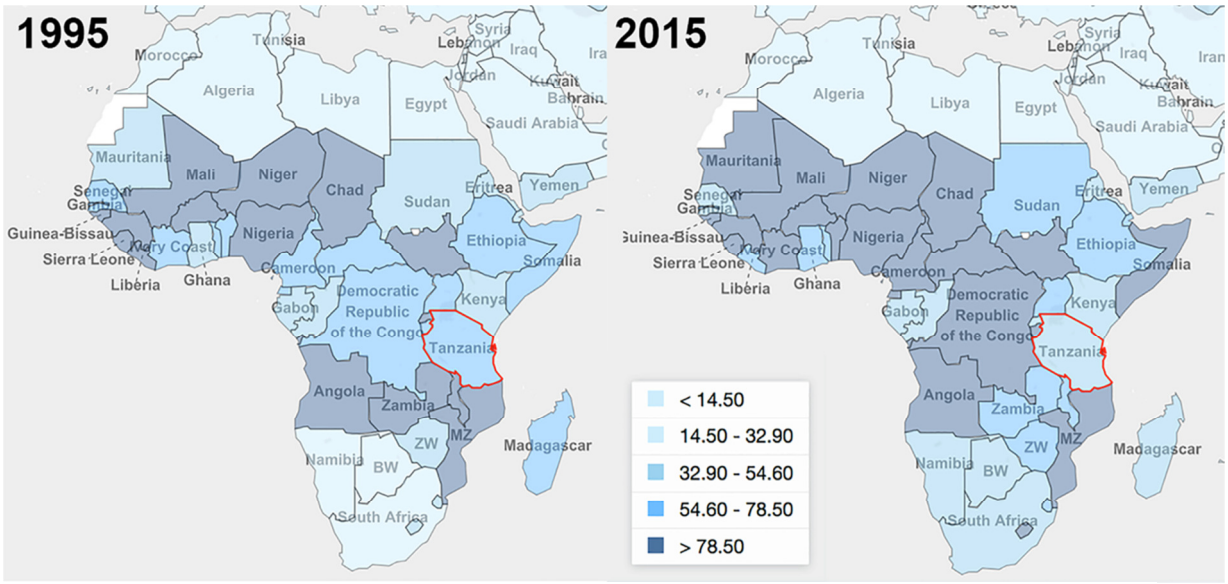

Figure 3 Estimated deaths per 1,000 by age and sex, Tanzania 2012 Census (Tanzania National Bureau of Statistics and Tanzania Ministry of Finance, 2015)

The largest proportion of children under-five die at less than of one year old, largely due to complications in the neonatal period: an estimated 41% of children under-five die within the first months of life. After the neonatal period around 70% of deaths between 1-59 months are estimated to be due to infections (UN Inter-Agency Group for Child Mortality Estimation, 2017). Under-five mortality varies by Region (Figure 9). Dar-es-Salaam's under-five mortality rate is with 72.3/1,000 live births above the national average. Interestingly, in the Tanzanian 2012 census the estimates of under-five mortality rates were higher in urban areas (71 deaths/1,000 live births) in 2012 than those observed in rural areas (66 deaths/1,000 live births). This pattern was reversed from a previous 2002 census (Tanzania National Bureau of Statistics and Tanzania Ministry of Finance, 2015).

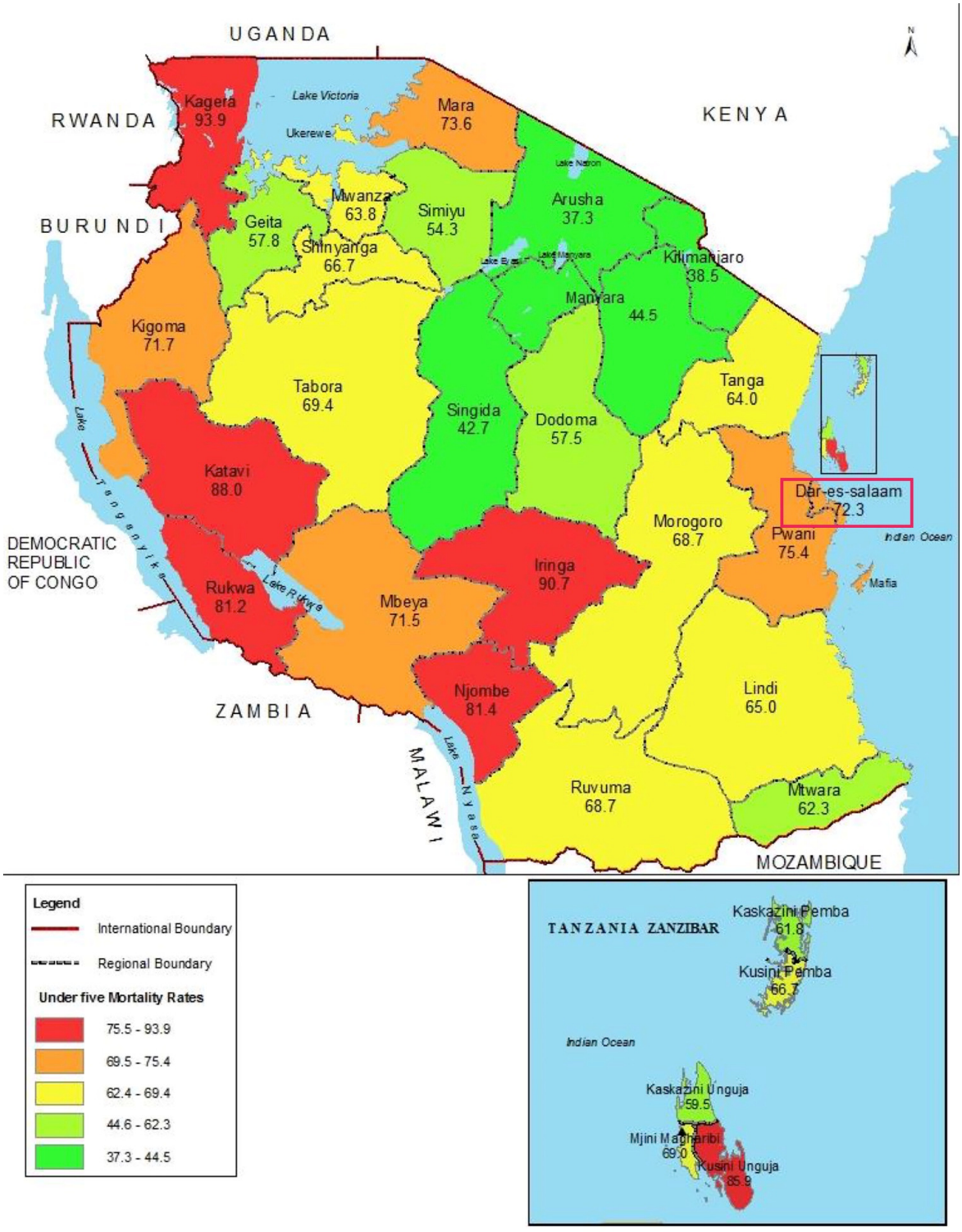

Figure 9 Under-five mortality rate (Tanzania National Bureau of Statistics and Tanzania Ministry of Finance, 2015)

4.2. Causes of fever and antibiotic prescription

Since the IMALDIA project (Chapter 1.1, D'Acremont *et al.*, 2014), several studies to determine the causes of fever in children have been conducted at the outpatient level in Tanzania (Table 1). They varied primarily in the amount and types of investigation performed and none were as comprehensive as the IMALDIA project.

Table 1 Studies on etiologies of acute febrile illness at the outpatient level in Tanzania since the IMALDIA project

Author, year	Location	Time period	Age range (months)	N	Investigations	Documented infections
Msaki *et al.*, 2012	Mwanza City, primary health care facility	February-June 2011	2-60	231	Blood culture, urine culture, blood microscopy	BSI=7.4% UTI=20.3%
Thriemer *et al.*, 2012	Pemba Island, District Hospital OPDs	March 2009-December 2010	2-59	3,105	Blood culture Blood microscopy	Mal= 1% BSI= 4%
Mahende *et al.*, 2014	Korogwe District Hospital OPD	January-October 2013	2-59	863	Blood culture, urine culture, blood microscopy	Mal= 8.3% BSI= 3.2% UTI= 7.6%
Chipwaza *et al.*, 2014 Chipwaza *et al.*, 2015	Kilosa district hospital, OPD	March - October 2013	24–59	364	Blood microscopy, Leptospirosis/ brucellosis serologies, Widal, Urine microscopy ELISA (Dengue, Chikungunya, Rota/Adenovirus), PCR (Dengue)	Mal= 23% Lepto=11.6% Bruc= 7.0% UTI= 18.6% Dengue= 20.9% Chik= 4.7% Influenza=1.4% Rota/Adeno=1.9%
Hildenwall *et al.*, 2016	Muheza District Hospital, OPD	July 2011-November 2012 at	3-59	281	Blood culture Urine culture CXR	Mal not assessed* BSI= 1.4% UTI= 5.6% CXR consolidation= 2.5%**
Elfving *et al.*, 2016	Zanzibar, North A district. Primary health care facilities	April-July 2011 that	2-59	677	mRDT Blood microscopy Malaria PCR Rickettsia/arbovirus blood PCR Streptococcus A throat RDT Pneumococcus urine RDT NPS viral PCR Stool PCR (viral and bacterial) CXR	Mal= 0.2% RSV = 24.5% Influenza= 22.3% Rhinovirus= 10.3% Enterovirus= 8.7% CXR consolidation= 6.2% Shigella stool infection= 4.3% UTI= 1.6%***

*mRDT negative patients included only, **CXR not available in 22 patients with IMCI pneumonia, ***see original publication for additional causes. Outpatient department (OPD), malaria (Mal), blood stream infection (BSI), urinary tract infection (UTI), Leptospirosis (Lepto), Brucellosis (Bruc), Chikungunya (Chic), polymerase chain reaction (PCR), adenovirus (Adeno), rapid diagnostic test (RDT). nasopharyngeal swab (NPS), Respiratory Syncytial Virus (RSV)

Overall, the reported prevalence of bacterial blood stream infections was low, ranging from 1% to 7.5%. Gram-negative bacteria (including *Salmonella*) were the most frequently isolated pathogens (Msaki *et al.*, 2012; Thriemer *et al.*, 2012; Mahende *et al.*, 2014;

Hildenwall *et al.*, 2016). The prevalence of positive urine culture ranged from 1.6% to 20.3%. This large range was likely due to the differences of urine collection techniques and criteria used to define a positive culture. Chipwaza et al. found a high prevalence of zoonotic bacterial infections (Leptospirosis and Brucellosis) in a study conducted in an area in proximity to livestock. Generally, the large variation in the types of viral and zoonotic bloodstream infections reflects their large seasonal and geographic variability, even within a single country in Africa.

Despite increasing evidence that very few children at the outpatient level benefit from antibiotic treatment (Shao *et al.*, 2015), antibiotic overuse at the outpatient level remains high. During the duration of the clinical trial in Dar es Salaam, we also monitored routine care in a cohort of 547 febrile children (same inclusion/exclusion criteria as for main trial, Chapter 7.3). Children were treated by three routine clinicians at Magomeni health center and Tandale dispensary. No intervention was done besides mRDT testing and weight measurements for all children before the consultation. Routine clinicians were asked to document their diagnoses and treatments prescribed. 95% (518/547) of children were prescribed an antibiotic treatment at D0. Table 2 lists the types of antibiotics prescribed at D0.

Table 2 Antibiotics prescribed to 547 children treated per routine care in Dar es Salaam during the study period.

Antibiotic Name	% of 518 patients with antibiotic prescription at day 0 (n)
Amoxicillin	54.4% (282)
Cephalexin	25.9% (134)
Penicillin G*	13.7% (75)
Cotrimoxazole**	10.1% (55)
Ampicillin/flucloxacillin	5.8% (30)
Erythromycin***	3.1% (16)
Azithromycin	1.2% (6)
Amoxicillin/clavulanic acid	1.2% (6)
Ciprofloxacin	1.2% (6)
Metronidazole	0.8% (4)
Gentamicin*	0.4% (2)
Chloramphenicol	0.2% (1)
Ceftriaxone	0.2% (1)

Antibiotics that are part of the 2014 IMCI recommendations are bolded. *For severe infections only, **prophylactic treatment for HIV positive children only, ***treatment for cholera only

Amoxicillin was the antibiotic most frequently prescribed. Second was cephalexin, an antibiotic that is not part of the IMCI recommendations (as were most antibiotics prescribed). Table 3 lists the diagnoses given by the clinicians as reasons for antibiotic prescription. Only 4% of prescriptions (11/282) had a diagnosis for which amoxicillin is an adequate antibiotic choice.

Table 3 Clinician diagnoses for children who were prescribed amoxicillin at day 0

Diagnosis	% of 282 patients prescribed amoxicillin at day 0 (n)
Upper respiratory tract infection	69.5% (196)
Urinary tract infection	11.0% (31)
Gastroenteritis	8.9% (25)
Pneumonia	3.6% (10)
Fever without source	2.5% (7)
Skin infection, other than abscess	1.8% (5)
Oral thrush	1.4% (4)
Ear infection	0.4% (1)
Abscess	0.4% (1)
Bronchiolitis	0.4% (1)
Viral illness	0.4% (1
Gingivitis	0.4% (1)

Diagnoses for which amoxicillin is an adequate antibiotic choice are bolded.

About one quarter of children were prescribed weight-based daily dosing within the range of international guidelines. Only 8% (23/272) were prescribed the exact dose recommended by the 2008 IMCI chart booklet, which was implemented in Tanzania at the time of the study. Alarmingly, most children were under-dosed, which may not only lead to treatment failure, but also accelerate the development of antibiotic resistance.

Table 4 Appropriateness of amoxicillin weight-based dosing at day 0

Reference	Dosing		
	Within range	Too big	Too small
IMCI 2014	29% (78/272)	0% (0/272)	71% (194/272)
IMCI 2008	22% (69/272)	0% (0/272)	78% (213/272)
Red Book*	25% (68/272)	1% (3/272)	74% (201/272)

Dosing prescribed was available for 272 children. *based on American Academy of Pediatrics, 2015. The following dose ranges were considered within range: for respiratory infections 80-100mg/kg/day, all other infections 25-80mg/kg/day.

In summary, antibiotic overuse in the study area remained high during our study. In addition, quality of prescriptions in terms of indications and dosing was low.

5. Improving case management and rational antibiotic use for acute febrile illnesses among children in resource-poor settings: development of e-POCT, an electronic algorithm that integrates host biomarker point-of care tests.

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5.1. Abstract

Objective

To review available evidence of key areas of management of children with acute febrile illnesses at outpatient level, including the use of point-of-care host biomarkers, as a basis for the construction of a novel electronic algorithm that can guide clinicians through the consultation process in resource-poor, outpatient settings. This aim of this novel electronic tool is to improve clinical outcome and rational antibiotic use among children with acute febrile illness.

Methods

We performed a structured literature review focusing on the i) identification of children with severe infections requiring referral, ii) detection of children with serious bacterial infections, including the use of C-reactive protein (CRP) and procalcitonin (PCT) to predict the need for antibiotic treatment and iii) detection of children with dehydration. Using the evidence retrieved, a novel electronic algorithm (e-POCT) was designed.

Findings

The following main changes were made from the 2014 Integrated Management of Childhood Illness version: i) pulse oximetry to identify children with hypoxemia and severe tachycardia; ii) hemoglobin to detect children with severe anemia; iii) construction of a 'severe respiratory distress' classification; iv) refinement of criteria for severe malnutrition; v) two-step approach including respiratory rate and CRP for diagnosing bacterial pneumonia; vi) CRP and PCT to decide on antibiotic prescription for children with fever without localizing symptoms. We constructed a novel electronic algorithm, e-POCT, that was programmed into an android-based mobile tool. The electronic version allowed integrating a greater amount of data, more elaborate calculations and direct connection to the oximeter, without increasing the complexity of the consultation process for the health worker.

Conclusions

We developed a novel, innovative algorithm, e-POCT, that has the potential to improve management of the febrile child in low-resource settings. This new tool should be validated in real conditions of outpatient care in resource-poor settings

5.2. Introduction

Mitigating the rapid emergence of antibiotic resistance has become one of the public health priorities (Sosa *et al.*, 2010). The increasing availability of antibiotics in low-resource settings has been accompanied by a widespread over-utilization, above all at the peripheral health care level where most patient consultations occur and presumptive treatment is the rule (Risk *et al.*, 2013). Among children, acute febrile illnesses make up the bulk of outpatient visits (Shao *et al.*, 2015). There is increasing evidence that at this level the majority of such infectious episodes are attributable to viral infections (D'Acremont *et al.*, 2014) and very few require antibiotic treatment (Shao *et al.*, 2015). Health workers with limited skills are challenged in identifying this minority of children with bacterial infections by the lack of adequate diagnostic tools. As a result, they tend to prescribe antibiotics for the majority of children, just "to be on the safe side" (D'Acremont *et al.*, 2011; Baltzell *et al.*, 2013). Despite this non-differential approach to antibiotic prescription, mortality from childhood infections remains high (Liu *et al.*, 2014). Over-relying on antibiotic treatment has resulted in the neglect of the correct management of severe infections, which can be of viral, parasitic, and bacterial origin (D'Acremont *et al.*, 2014).

The Integrated Management of Childhood Illness (IMCI) chart booklet, a series of disease management algorithms, was developed by the World Health Organization (WHO) in the 1990s with regular improvements (Gove, 1997; World Health Organization, 2014). Besides the rapid diagnostic test for malaria (mRDT), it recommends presumptive treatment based on clinical signs and symptoms (World Health Organization, 2014). Key to IMCI is the concomitant consideration of multiple disease classifications (e.g. malaria and pneumonia). The IMCI strategy remains very relevant today but its implementation has faced major challenges (Arifeen *et al.*, 2005; Horwood *et al.*, 2009; Baiden *et al.*, 2011) related largely to four format-and content related shortcomings. First, the short timeframe attributed to outpatient consultation is overloaded by the number and logical flow of questions and information in the paper chart booklet (Lange, Mwisongo and Mæstad, 2014). Second, IMCI lacks guidance for about a quarter of febrile children, namely the children without localizing main IMCI symptoms, fever without source (FWS). Here, IMCI suggests to "give appropriate antibiotic treatment for an identified bacterial cause of fever" but provides no clear directions on how to identify such an etiology (World Health Organization, 2014). Third, the IMCI algorithm over-relies on clinical signs and symptoms which inherently lack diagnostic accuracy in detecting children in need for antibiotic treatment or referral for hospital-based supportive care (Thompson *et al.*, 2012). Fourth, the diagnostic value of clinical signs that were included into IMCI (based on expert opinion and small derivation studies) needs to be

reconsidered. This is because the epidemiological context of infections has changed (D'Acremont *et al.*, 2014) and a considerable amount of novel evidence has emerged (Thompson *et al.*, 2012).

Some challenges have already started to be addressed. Electronic, "smartphone", IMCI versions (e-IMCI) have a user-friendlier format and may thereby increase algorithm adherence and the consistency of clinical assessments (Mitchell *et al.*, 2013; Shao *et al.*, 2015). One improved e-IMCI-based algorithm, ALMANACH, has already been evaluated in clinical studies in Tanzania (Shao *et al.*, 2015; Rambaud-Althaus *et al.*, 2017) but opportunities for improvement remain. Host biomarkers, that can help identify children with bacterial infections, such as C-reactive protein (CRP) and procalcitonin (PCT) have not been considered within the IMCI strategy (Van den Bruel *et al.*, 2011). Furthermore, point-of-care tests (POCTs) are available that may help detect children with severe symptoms where clinical signs lack diagnostic accuracy: e.g. hemoglobin (Hb) testing for detecting children with severe anemia.

Based on the challenges and opportunities identified in the management of children with febrile illnesses, and building on the experience acquired through the construction and evaluation of the ALMANACH algorithm (Rambaud-Althaus, Shao, *et al.*, 2015; Shao *et al.*, 2015; Rambaud-Althaus *et al.*, 2017), we sought to develop a novel **e**lectronic disease management algorithm that would make use of **POCT**s (**e-POCT**). The overall goal of this algorithm was to i) improve identification of children with severe disease, ii) increase targeting of children in need for antibiotic prescription and iii) enhance the efficiency of outpatient consultations. For the latter we aimed at simplifying clinical elements to few relevant signs and symptoms, as well as using the algorithm's electronic features to integrate data and perform background calculations, while maintaining simple user interfaces. The objective of this paper is to provide a summary of the evidence and rationale used for the construction of e-POCT.

5.3. Methods

Structured Literature Review

We undertook structured literature searches to review publications on the key elements that required update from ALMANACH and IMCI. We focused on the following areas in an ambulatory care setting:

1) Identification of children with severe infections using clinical signs and/or available POC laboratory tests.

2) Management of children with respiratory infections, including identification of children with severe respiratory infections and those in need for antibiotic treatment.
3) The use of clinical signs and available POCTs to decide on antibiotic prescriptions for children with fever without focal symptoms (FWS).
4) Symptoms and signs for dehydration.
5) Diagnosis of severe malnutrition

We constructed three separate searches for questions 1-3, 4, and 5 (Table 5) and merged the resulting records.

Table 5 Search terms

Search	PubMED	Embase
Severe infections/ serious bacterial infections	("Community-Acquired Infections"[Mesh] OR "Sepsis"[Mesh:NoExp] OR "Bacterial Infections"[Mesh] OR "Respiratory Tract Infections"[Mesh] OR "Shock, Septic"[Mesh] OR "Status Asthmaticus"[Mesh] OR "Meningitis"[Mesh:NoExp] OR "Meningitis, Bacterial"[Mesh] OR "Arthritis, Infectious"[Mesh] OR "Bone Diseases, Infectious"[Mesh] OR "Cellulitis"[Mesh] OR "Skin Diseases, Bacterial"[Mesh:NoExp] OR "Skin Diseases, Infectious"[Mesh:NoExp] OR "Ecthyma"[Mesh] OR "Erysipelas"[Mesh] OR "Staphylococcal Skin Infections"[Mesh] OR "Soft Tissue Infections"[Mesh] OR "Diarrhea, Infantile"[Mesh] OR "Dysentery"[Mesh] OR "Urinary Tract Infections"[Mesh] OR "Pyelonephritis"[Mesh:NoExp] OR "Typhoid Fever"[Mesh] OR "Fever of Unknown Origin"[Mesh] OR bacterial infection*[tiab] OR serious infection*[tiab] OR severe infection*[tiab] OR invasive infection*[tiab] OR (death[tiab] AND infection[tiab]) OR severe malaria[tiab] OR severe bronchiolitis[tiab] OR sepsis[tiab] OR meningitis[tiab] OR dehydration[tiab] OR pneumonia[tiab] OR pyelonephritis[tiab] OR urinary tract infection*[tiab] OR typhoid[tiab] OR leptospirosis[tiab] OR rickettsia*[tiab] OR osteomyelitis[tiab] OR cellulitis[tiab] OR bacteremia[tiab] OR bacteraemia[tiab] OR otitis media[tiab]) AND ("Signs and Symptoms"[Mesh:NoExp] OR "Seizures"[Mesh] OR "Abdominal Pain"[Mesh] OR "Vomiting"[Mesh] OR "Pallor"[Mesh] OR "Jaundice"[Mesh] OR "Tachypnea"[Mesh:NoExp] OR "Respiratory Sounds"[Mesh:NoExp] OR "Dyspnea"[Mesh:NoExp] OR "Vital Signs"[Mesh] OR "Tachycardia"[Mesh:NoExp] OR "Diagnostic Tests, Routine"[Mesh] OR "Physical Examination"[Mesh:NoExp] OR "Diagnosis"[Mesh:NoExp] OR "Clinical Decision-Making"[Mesh] OR "Medical History Taking"[Mesh:NoExp] OR "Symptom Assessment"[Mesh] OR "Odds Ratio"[Mesh] OR "Sensitivity and Specificity"[Mesh:NoExp] OR "Predictive Value of Tests"[Mesh] OR "ROC Curve"[Mesh] OR "Severity of Illness Index"[Mesh] OR "Decision Trees"[Mesh] OR "C-Reactive Protein"[Mesh] OR "Anemia"[Mesh:NoExp] OR clinical sign*[tiab] OR clinical syndrome* [tiab] OR "syndromic diagnosis"[tiab] OR clinical variable*[tiab] OR clinical predictor*[tiab] OR vital sign*[tiab] OR clinical feature*[tiab] OR "signs and symptoms"[tiab] OR red flag*[tiab] OR danger sign*[tiab] OR "abnormal mental status"[tiab] OR "altered mental status"[tiab] OR convulsion*[tiab] OR "stiff neck"[tiab] OR meningeal sign*[tiab] OR prostration[tiab] OR "chest wall retraction"[tiab] OR "chest indrawing"[tiab] OR stridor[tiab] OR tachypnea[tiab] OR "fast breathing"[tiab] OR	('bacterial infection'/de OR Infection/de OR 'Enterobacteriaceae infection'/exp OR 'Gram negative infection'/exp OR 'Gram positive infection'/exp OR 'pyonephrosis'/exp OR 'rickettsiosis'/exp OR 'Staphylococcus infection'/exp OR 'Streptococcus infection'/exp OR 'community acquired infection'/exp OR 'sepsis'/de OR 'bacteremia'/de OR 'septic shock'/de OR 'septicemia'/de OR 'respiratory tract infection'/exp OR 'pneumonia'/de 'bronchopneumonia'/exp OR 'asthmatic state'/exp OR 'meningitis'/de OR 'bacterial meningitis'/exp OR 'Haemophilus meningitis'/exp OR 'pneumococcal meningitis'/exp OR 'bone infection'/de OR 'bacterial arthritis'/exp OR 'soft tissue infection'/exp OR 'cellulitis'/exp OR 'bacterial skin disease'/de 'erysipelas'/de OR 'impetigo'/exp OR 'skin abscess'/exp OR 'staphylococcal skin infection'/exp OR 'dysentery'/exp OR 'urinary tract infection'/exp OR 'acute pyelonephritis'/exp OR 'urinary tract infection'/exp OR 'typhoid fever'/exp OR ((bacterial NEXT/1 infection*) OR (serious NEXT/1 infection*) OR (severe NEXT/1 infection*) OR (invasive NEXT/1 infection*) OR (severe NEXT/1 malaria) OR (severe NEXT/1 bronchiolitis) OR sepsis OR meningitis OR pneumonia OR pyelonephritis OR (urinary NEXT/1 tract NEXT/1 infection*) OR typhoid OR leptospirosis OR rickettsia* OR osteomyelitis OR cellulitis OR bacteremia OR bacteraemia OR (otitis NEXT/1 media)):ab,ti) OR ('pallor'/exp OR 'seizure'/de OR 'convulsion'/de OR 'abdominal pain'/de OR 'vomiting'/de OR 'jaundice'/de OR 'abnormal respiratory sound'/exp OR 'dyspnea'/de OR 'tachypnea'/de OR 'vital sign'/exp OR 'heart rate'/de OR 'breathing rate'/de OR 'oxygen saturation'/exp OR 'tachycardia'/de OR 'diagnostic accuracy'/de OR 'diagnostic test accuracy study'/de OR 'classification algorithm'/exp OR 'practice guideline'/de OR 'predictive value'/exp OR 'diagnostic value'/de OR 'diagnostic accuracy'/de OR 'C reactive protein'/exp OR 'procalcitonin'/exp OR 'anemia'/de OR ((clinical NEXT/1 sign*) OR (clinical NEXT/1 syndrome*) OR (clinical NEXT/1 variable*) OR (clinical NEXT/1 predictor*) OR (vital NEXT/1 sign*) OR (clinical NEXT/1 feature*) OR "signs and symptoms" OR (red NEXT/1 flag*) OR (danger NEXT/1 sign*) OR "abnormal mental status" OR "altered mental status" OR convulsion* OR "stiff neck" OR (meningeal NEXT/1 sign*) OR prostration OR "chest wall retraction" OR "chest indrawing" OR stridor OR tachypn*a OR "fast breathing" OR "respiratory rate" OR tachycardia OR "fast heart rate" OR "capillary refill time" OR vomiting OR pallor OR fever OR algorithm* OR

	tachypnoea[tiab] OR "respiratory rate"[tiab] OR tachycardia[tiab] OR "fast heart rate"[tiab] OR "capillary refill time"[tiab] OR vomiting[tiab] OR pallor[tiab] OR fever[tiab] OR algorithm*[tiab] OR decision tree*[tiab] OR prediction rule*[tiab] OR imci[tiab] OR "integrated management of childhood illness"[tiab] OR "severe anemia"[tiab] OR "severe anaemia"[tiab] OR procalcitonin[tiab] OR "C-reactive protein"[tiab] OR "Urine dipstick"[tiab] OR Urine leucocyte*[tiab] OR Urine nitrite*[tiab] OR "diagnostic accuracy"[tiab]) AND ("infant"[Mesh] OR "Child, Preschool"[Mesh] OR infant*[tiab] OR child*[tiab] pediatric*[tiab] OR paediatric*[tiab] OR under-five*[tiab] OR 59 month*[tiab] OR under-5[tiab] OR babies[tiab] OR baby[tiab])	(decision NEXT/1 tree*) OR (prediction NEXT/1 rule*) OR imci OR "integrated management of childhood illness" OR "severe an*emia" OR procalcitonin OR "C-reactive protein" OR "Urine dipstick" OR (Urine NEXT/1 leucocyte*) OR (Urine NEXT/1 nitrite*) OR "diagnostic accuracy"):ab,ti)
Dehydration	(dehydration[tiab] OR "Dehydration"[Mesh]) AND ("Signs and Symptoms"[Mesh:NoExp] OR "Vital Signs"[Mesh] OR "Tachycardia"[Mesh:NoExp] OR "Diagnostic Tests, Routine"[Mesh] OR "Physical Examination"[Mesh:NoExp] OR "Diagnosis"[Mesh:NoExp] OR "Odds Ratio"[Mesh] OR "Sensitivity and Specificity"[Mesh:NoExp] OR "Predictive Value of Tests"[Mesh] OR "ROC Curve"[Mesh] OR "Severity of Illness Index"[Mesh] OR "Decision Trees"[Mesh] OR clinical sign*[tiab] OR clinical predictor* [tiab] OR vital sign* [tiab] OR clinical feature* [tiab] OR "signs and symptoms"[tiab] OR algorithm* [tiab] OR decision tree* [tiab] OR prediction rule* [tiab] OR imci [tiab] OR "integrated management of childhood illness"[tiab] OR "diagnostic accuracy"[tiab]) AND (infant*[tiab] OR child* [tiab] pediatric*[tiab] OR paediatric*[tiab] OR under-five* [tiab] OR 59 month* [tiab] OR under-5 [tiab] OR babies[tiab] OR baby[tiab] OR "infant"[Mesh] OR "Child, Preschool"[Mesh])	(dehydration:ti,ab OR 'dehydration'/exp) AND ((clinical sign* OR clinical syndrome* OR clinical predictor* OR vital sign* OR clinical feature* OR "signs and symptoms" OR algorithm* OR decision tree* OR prediction rule* OR imci OR "integrated management of childhood illness" OR "diagnostic accuracy"):ti,ab OR 'vital sign'/exp OR 'heart rate'/de OR 'tachycardia'/de OR 'diagnostic accuracy'/de OR 'diagnostic test accuracy study'/de OR 'classification algorithm'/exp OR 'practice guideline'/de OR 'predictive value'/exp OR 'diagnostic value'/de OR 'symptom assessment'/de OR 'diagnostic accuracy'/de) AND ((infant* OR child* pediatric* OR paediatric* OR under-five* OR 59 month* OR under-5 OR babies OR baby):ti,ab OR 'preschool child'/exp OR 'infant'/exp)
Malnutrition	(malnutrition[tiab] OR "Malnutrition"[Mesh]) AND ("Anthropometry"[Mesh:NoExp] OR "Body Weights and Measures" [Mesh] OR weight*[tiab] OR *height[tiab] OR *length[tiab] OR MUAC[tiab] OR "mid upper arm circumference"[tiab]) AND (infant*[tiab] OR child* [tiab] pediatric*[tiab] OR paediatric*[tiab] OR under-five* [tiab] OR 59 month* [tiab] OR under-5 [tiab] OR babies[tiab] OR baby[tiab] OR "infant"[Mesh] OR "Child, Preschool"[Mesh])	(malnutrition:ti,ab OR 'malnutrition'/exp) AND ('anthropometric parameters'/exp OR (weight* OR length OR height OR muac OR "mid upper arm circumference"):ti,ab) AND ((infant* OR child* pediatric* OR paediatric* OR under-five* OR 59 month* OR under-5 OR babies OR baby):ti,ab OR 'preschool child'/exp OR 'infant'/exp)

Papers reviewed were in English, and published between inception to June 2014 (which was when the construction of e-POCT was completed). We also checked publications since June 2014 for relevant updates to the retrieved evidence. Databases searched were PubMed and Embase. The literature search was supplemented by hand-checking references of filtered papers, and by snowball search of key papers in Google Scholar. Studies involving only infants below 3 months of age or only adults were excluded. Systematic reviews addressing the questions of interest were also considered.

Algorithm construction

ALMANACH, an electronic algorithm derived from IMCI, was used as a starting point for construction of the new algorithm. We used the evidence retrieved from the literature search

to propose modifications when relevant. Diagnostic criteria to be included should not only have adequate accuracy at primary care level but also be assessable by health workers in resource-poor settings. A new decision tree, e-POCT was constructed including a detailed reference paper version that was used to program the algorithm onto an android-based electronic support tool using the Mangologic™ software (http://www.mangologic.com/). Each branch of the electronic algorithm was validated against a standardized set of theoretical patient scenarios. A final version was piloted during a pilot phase in primary care facilities in Dar es Salaam, Tanzania, that included 100 pediatric consultations, which were directly supervised by a medical doctor or pediatrician. The final algorithm was evaluated later in a clinical trial which is described elsewhere (Chapter 7).

5.4. Results

Figure 10 displays the retrieved and included publications.

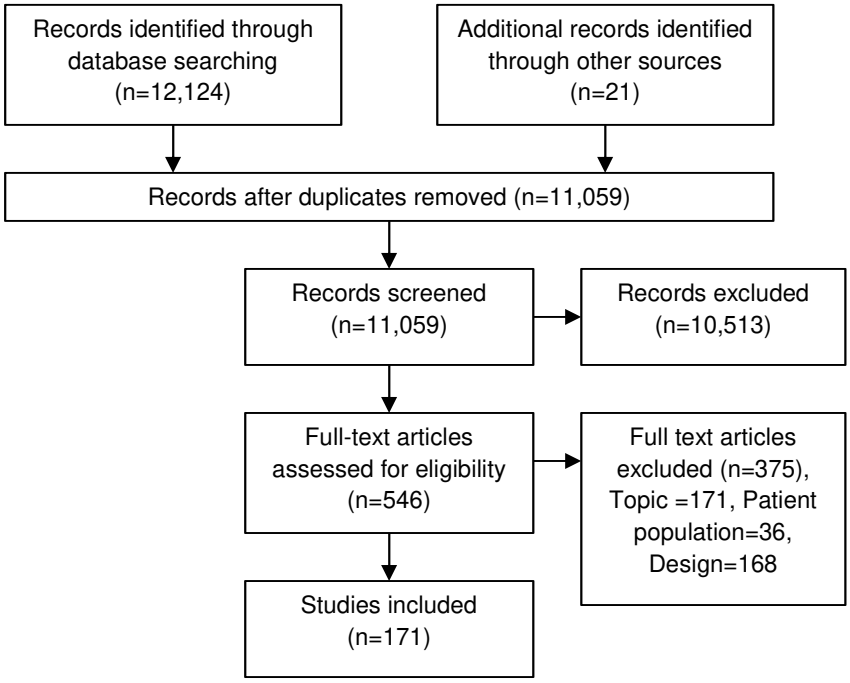

Figure 4 Flowchart of literature search results and included publications

5.4.1. Identification of children with severe infections: how can current referral criteria be improved?

What is the evidence for currently employed IMCI danger signs?

The 2014 IMCI algorithm recommends immediate hospital transfer in the presence of any one of the general or disease specific danger signs (Table 6).

Table 6 Summary of the main differences between e-POCT, ALMANACH, and the 2014 IMCI version.

		e-POCT			ALMANACH (Rambaud-Althaus, Shao, *et al.*, 2015)			IMCI (World Health Organization, 2014)		
	Classification	**Clinical signs/symptoms**	**Vital sign**	**POCT**	**Clinical signs/symptoms**	**Vital sign**	**POCT**	**Clinical signs/symptoms**	**Vital sign**	**POCT**
Severe disease	**CNS infection**	- Severe lethargy - Stiff neck - ≥2 convulsions			- Severe lethargy, - Stiff neck - ≥1 convulsions			- Severe lethargy, - Stiff neck ≥1 convulsions		
	Severe pneumonia	- Severe respiratory distress[1]	- Severe tachypnea[2]	SaO2 <90%	- Chest indrawing - Cyanosis - Stridor			- Stridor - Chest indrawing and HIV positive		HIV positive
	Severe anemia			Hb <6g/dl	- Severe palmar pallor			- Severe palmar pallor		
	Severe dehydration	- Not tolerating oral liquids		Severe tachycardia[3]	- Vomits everything or two of: Lethargic/ unconscious; Sunken eyes; Not able to drink/drinks poorly; Skin pinch very slow			- Vomits everything or two of: Lethargic/ unconscious; Sunken eyes; Not able to drink/drinks poorly; Skin pinch very slow		
	Severe malnutrition		- Very low WFA and/or MUAC[4]		- Severe wasting - Edema of both feet			- Edema of both feet or - Very low WFH/MUAC combined with complications[6]		
	Other severe disease	None			- Jaundice - Tender swelling behind ear - Infected skin lesion or lump larger than 4 cm or with red streaks or with tender nodes or multiple abscesses			- Tender swelling behind ear		
	Severe malaria	Any severe classification and		Positive mRDT	Not considered			Not considered		
CNon-severe disease	**Clinical pneumonia**	- Not considered			- Cough and	Very fast breathing[7]		- Cough and	-Fast breathing[7] - Chest indrawing	
	Bacterial LRTI	- Cough and	- Tachypnea[6] and -	CRP≥80 mg/L	- Not considered			Not considered		
	Viral LRTI/ bronchiolitis	- Cough and	- Tachypnea[6] and	CRP<80mg/L	- Not considered			Not considered		

	Upper respiratory infection	- Cough and	- No tachypnea[6]			- Cough and	No very fast breathing[7]			Cough and	No fast breathing[8]	
	Gastrointestinal infection with dehydration	- Significant diarrhea and /or vomiting[9]				- Two of: Restless irritable; Sunken eyes; Drinks eagerly, thirsty; Skin pinch slow				- Two of: Restless irritable; Sunken eyes; Drinks eagerly, thirsty; Skin pinch slow		
	Skin infection	Skin infection without additional severe diagnosis[10]				- Infected skin lesion smaller than 4 cm and without red streaks and without tender nodes or single abscesses				Not considered in main algorithm		
	Fever without source, likely bacterial infection			CRP≥80mg/L and/or PCT≥4 µg/L		- Purulent ear discharge		Positive urine dipstick (<2 years only) or positive typhoid test (≥2 years only)		Not considered		
	Fever without source, likely viral infection			CRP<80mg/L and PCT<4 µg/L				Negative urine dipstick (<2 years only) and negative typhoid test (≥2 years only)		Not considered		
	Uncomplicated malaria			Positive mRDT				Positive mRDT				Positive mRDT

Abbreviations: Central nervous system (CNS), oxygen saturation (SaO2), human immunodeficiency virus (HIV), weight-for-age (WFA), mid-upper arm circumference (MUAC), point-of-care test (POCT), respiratory rate (RR), heart rate (HR), rapid test for malaria (mRDT), C-reactive protein (CRP), procalcitonin (PCT), lower respiratory tract infections (LRTI).

1: Severe respiratory distress: Speaks only single words or grunts or speaks short phrases only or short cries and lower chest wall indrawing

2: Severe tachypnea: RR ≥97th %ile for age and temperature (Nijman *et al.*, 2012).

3: Severe tachycardia: Heart rate ≥90th %ile for age and temperature (Thompson, Harnden, *et al.*, 2009).

4: Weight for age <-3 z-score and/ or MUAC <11.5cm and age >6 months

5: Weight for length/height <-3 z-score and/ or MUAC <11.5cm and age >6 months; complications defined as: feeding problem or medical problem

6: Tachypnea: Respiratory rate (RR) ≥75th %ile for age and temperature

7: Very fast breathing: RR≥50/min, regardless of age

8: Fast breathing: RR≥40/min and age <12 months or RR≥50/min and age≥ 12 months.

9: >5 loose stools/over past 24hrs or ≥3 loose stools/over past 24hrs and emesis or >3 emesis/over past 24hrs

10: algorithm provides diagnoses and specific treatment recommendations for 13 common skin diseases (abscess, cellulitis, impetigo/pyoderma, tinea corporis, pityriasis versicolor, candidiasis, tinea capitis, scabies, chicken pox, herpes, larva migrans, eczema, urticarial)

These danger signs were chosen based on expert opinion and refined during the initial IMCI development studies (Gove, 1997; Perkins *et al.*, 1997; Weber *et al.*, 1997). They were then evaluated in two studies conducted in hospital outpatient departments in Kenya and Bangladesh between 1993 and 1995 (Paxton *et al.*, 1996; Kalter, Schillinger, *et al.*, 1997). These studies determined the accuracy of the IMCI danger signs to predict hospitalization when compared to clinical judgment of a medical doctor or clinical officer. The Kenyan (2799 children, 779 admissions) study found a sensitivity and specificity of 46% and 80%, respectively.—a similar range compared to what was observed in the initial development studies (Perkins *et al.*, 1997; Weber *et al.*, 1997). Stiff neck, stridor, corneal ulceration, and tender swelling behind the ear were detected in none of the children. The Bangladeshi study (668 children, 226 admissions) reported a sensitivity of 86% and a specificity of 64% (Kalter, Schillinger, *et al.*, 1997). The heterogeneity of reported accuracy is probably related to differences in the studied population and in the outcome assessment. Since the overall performance of IMCI severity criteria was low, we sought to identify additional studies that evaluated and complemented single criteria. In order to identify criteria with higher performance that would be implementable in primary care facilities in low resources settings, we looked at pediatric triage tools, severity scores predicting mortality, and diagnostic tools to identify serious infections.

Should additional signs from pediatric triage tools be considered?

Several triage tools exist that are design to help prioritize treatment of sick children at hospital level. Two scales have been tailored to low resource environments: the WHO Emergency Triage and Treatment Tool (ETAT, World Health Organization, 2016a), and the Pediatric South African Triage Scale (PSATS, Twomey *et al.*, 2013). However, only ETAT has been evaluated in a low-income country (Malawi, Robertson and Molyneux, 2001). The ETAT guidelines rely on clinical discriminators using an ABCD concept (Airway, Breathing, Circulation/Coma/Convulsion, Dehydration, World Health Organization, 2013).

Should we include criteria from available pediatric severity scores?

In well-resourced countries, a number of pediatric severity scores have been developed such as the Pediatric Risk of Mortality (PRISM) score (Pollack, Patel and Ruttimann, 1996; Gerardin *et al.*, 2006), the Pediatric Index of Mortality (PIM, Shann *et al.*, 1997), the Pediatric Early Warning System (PEWS, Duncan, Hutchison and Parshuram, 2006), Bedside PEWS

(Parshuram, Hutchison and Middaugh, 2009), and Pediatric Advanced Warning Score (PAWS, Egdell, Finlay and Pedley, 2008). Besides PAWS, these scores are neither designed for use in outpatient nor resource-poor settings and rely on complex clinical assessments and laboratory data. Rather, the scores were designed to predict inpatient death. The PAWS score uses a full set of vital signs (respiratory rate [RR], heart rate [HR], oxygen saturation [SaO2], blood pressure [BP], body temperature [T]) and work of breathing, inspirated O2, CRT, and the Alert, Voice, Pain, Unresponsive (AVPU) scale. When validated among 49 pediatric patients admitted from the emergency department of a tertiary care hospital to the intensive care unit versus 46 controls admitted to the regular pediatric floor, it's accuracy was moderate: the sensitivity and specificity were 83% and 65% for of a score ≥2 and 70% and 90% for a score ≥3 (Egdell, Finlay and Pedley, 2008). For comparison, a child with fever and chest indrawing and no other criteria would have a PAWS score of at least 4.

Similarly, general and disease-specific risk scores have been developed in resource-limited settings that aim at predicting death among hospitalized patients (Shann, Barker and Poore, 1989; Marsh K, Forster D, Waruiru C, Mwangi I, Winstanley M, Marsh V, Newton C, Winstanley P, Warn P, Peshu N, 1995; Berkley, 2003; Helbok *et al.*, 2006). The Signs of Inflammation in Children that Kill (SICK), a score to predict in-hospital mortality, was derived from 1,099 (44 deaths) children in a tertiary care setting and validated among 125 children in the same setting (23 deaths), as well as 3,895 (58 deaths) children in another Indian hospital and 1,473 children (5 deaths) in a UK hospital (Kumar *et al.*, 2003; Bhal *et al.*, 2006; Gupta *et al.*, 2010). Second, the Lambaréné Organ Dysfunction Score (LODS), a tool to predict death among children hospitalized with malaria, was developed based on data from 23,809 hospitalized children in Africa (1,004 deaths, Helbok *et al.*, 2009). A study among 8,091 (436 deaths) hospitalized children in Kenya identified predictors for immediate, early, and late death (PEDIA, Berkley, 2003; Kotloff *et al.*, 2013). We did not identify additional signs that could be assessed by health workers at primary care level from these scores. One sign of PEDIA, jaundice, was also included in ALMANACH as an additional danger sign. This was because jaundice was a good predictor for documented bacterial disease (positive likelihood ratio [LR+] 2.9), in particular typhoid (LR+ 6.2), and against documented viral disease (LR+ 0.11) in a study on fever etiologies in 1005 children in Tanzania (D'Acremont *et al.*, 2014; De Santis and D'Acremont, 2017) and, because it was hypothesized that primary health care workers could detect clinical jaundice (Rambaud-Althaus, Shao, *et al.*, 2015). Jaundice was, however, detected in none of the children in the ALMANACH arm during the initial evaluation studies (Shao, personal communication).

What evidence exists from studies on clinical signs to identify children with serious infections?

The body of evidence has been growing for the use of clinical signs to identify children with serious infections (essentially infections that require hospital-based treatment) in outpatient high-resource settings. A systematic review of 30 studies assessed the performance of clinical signs in predicting serious infections (Van den Bruel *et al.*, 2010; Thompson *et al.*, 2012). Likelihood ratios (LRs) were constructed to represent the ability of single predictors to rule in (LR+ >5) and rule-out (negative likelihood ratio [LR-]<0.2) serious infections. The following predictors of signs that would be measurable by low-level health workers had rule-in value in settings with low-prevalence of serious infections: cyanosis (LR+ 52.2), poor peripheral perfusion (LR + 38.8), shortness of breath (LR+ 9.3), rapid breathing (LR+ 9.78), meningeal irritation (LR +25.7), seizures (LR+ 20.7), and unconsciousness (LR+ 19.8). These findings are in line with findings from studies on predictors of mortality in low-resource settings (Marsh K, Forster D, Waruiru C, Mwangi I, Winstanley M, Marsh V, Newton C, Winstanley P, Warn P, Peshu N, 1995; Berkley, 2003; Berkley, Maitland, *et al.*, 2005; Bhal *et al.*, 2006; Helbok *et al.*, 2009; von Seidlein *et al.*, 2012). Most of these estimates were based on a prospective derivation study conducted among 3981 children (31 admissions for serious infection) in Belgium (Van den Bruel *et al.*, 2007). From this study a multivariable triage instrument to predict serious infections requiring hospitalization was constructed using classification and regression tree (CART) analyses. The tool consisted of the clinician's feeling "that something is wrong", dyspnea, temperature, age, and presence of diarrhea. It had a sensitivity of 96.8% at a specificity of 88.5%. The triage tool was assessed in another study including 8962 acute illness episodes (283 serious infections, Van den Bruel *et al.*, 2007). Sensitivity was 100% at a specificity of 83.6% in the general practitioner setting with 17% of children testing positive. Thompson et al. assessed the diagnostic performance of vital signs in distinguishing 313 children with serious infections from 339 patients mild infections and 48 children with no infections in one outpatient department in England (Thompson, Coad, *et al.*, 2009). The LR+ and LR- were as follows: temperature ≥39°C 2.1 and 0.8, tachypnea 1.3 and 0.8, tachycardia 1.5 and 0.7, prolonged CRT 17.7 and 0.9, SaO2≤94% 2.7 and 0.9. Advanced Pediatric Life Support (APLS) cut-offs were used for definition of tachypnea and tachycardia. Having a derangement in any of the vital categories had a LR+ of 1.3 at a LR- of 0.5.

Criteria from triage-, severity- and serious infection-scores integrated into e-POCT

All current general IMCI danger signs were kept in the e-POCT algorithm. This was because all have high LR+. i.e. value as “red flags” (Thompson, Coad, *et al.*, 2009). However, they lack sensitivity and we hence added additional criteria. From ETAT, we included oximetry, and severe respiratory distress into the e-POCT algorithm (see severe pneumonia section below). The circulatory signs were not included since the reliability of CRT and ‘weak pulse’, when measured by low-level health workers at primary care level, have not been assessed sufficiently (Fleming *et al.*, 2015). Cyanosis, which was added into ALMANACH, was not included into the e-POCT algorithm since we integrated oximetry. From the single criteria of the PAWS score and the diagnostic accuracy studies for detection of serious infections, severe tachycardia was added to the e-POCT algorithm to represent “poor peripheral perfusion”. Tachycardia is indeed a well-recognized criterion for septic shock in children (Biban *et al.*, 2012). Given that an oximeter was included into e-POCT (see below), the HR could be fed into the algorithm without requiring additional measurements by the health worker. Like for RR cutoffs (see below), we chose age-and temperature-based percentiles for HR as opposed to APLS-based cutoffs. The electronic algorithm format allowed integration of these more complex calculations. As shown above, APLS thresholds for HR had clinically irrelevant diagnostic accuracy (Thompson, Coad, *et al.*, 2009). HR and RR vary with age but also with temperature (Simoes *et al.*, 1991; Campbell, Byass and O’Dempsey, 1992; O’Dempsey *et al.*, 1993; Thompson, Harnden, *et al.*, 2009; Fleming *et al.*, 2011; Nijman *et al.*, 2012). Recently compiled age centile charts were in large disagreement with previously publishes reference ranges, including APLS (Fleming *et al.*, 2011). In the study by Thompson et al., the diagnostic performance for severe tachycardia improved drastically if age-and temperature-based percentiles were used: a HR exceeding the 90th centile was highly specific (88%), though not sensitive (24%), for serious infection compared to minor infection (Thompson, Coad, *et al.*, 2009). Again, CRT and cyanosis were not included from the severity- and serious infection-scores for the reasons stated above. Dyspnea and tachypnea were addressed in the pneumonia-section of the algorithm (see below). We did not consider the Belgian triage tool since the physician’s statement that “something is wrong” was paramount for the tree (Van den Bruel *et al.*, 2007). The physician’s general impression is likely strongly correlated to the degree of training. Consequently, we hypothesized that it would not be useful to integrate the Belgian triage tool into the assessment of general danger signs for low-level health workers.

Should hemoglobin screening be included?

Systematic hemoglobin screening was integrated for all children into e-POCT based on the following rationale: First, severe anemia is an important cause of mortality. In a systematic review, Brabin et al. estimated the relative risk of in-hospital mortality for children with severe anemia at around twice that of less anemic children (Brabin, Premji and Verhoeff, 2001). Subsequent studies have confirmed that anemia is an important predictor for inpatient death (Djelantik *et al.*, 2003; Helbok *et al.*, 2009). Second, severe anemia is associated with bacteremia in febrile children (Calis *et al.*, 2008; De Santis and D'Acremont, 2017). Third, anemia cannot be detected based on clinical signs and at-risk groups cannot be clearly defined. In a meta-analysis, Chalco et al. found a low sensitivity for conjunctival and palmar pallor in detecting severe anemia (Chalco *et al.*, 2005). The pooled sensitivity and specificity of conjunctival pallor and palmar pallor were 43.6 (95% CI 41.7–45.6) and 81.4 (95% CI 78.6–83.9), respectively, and 39.2 (95% CI 37.4–41.1) and 86.7 (95% CI 84.6–88.5, Chalco *et al.*, 2005). Two studies identified since the meta-analysis confirmed these findings (Butt *et al.*, 2010; Aggarwal *et al.*, 2014). On the other hand, receiving transfusion early improves survival in children with severe anemia (Lackritz *et al.*, 1992). Children with severe anemia should be referred to higher-level facilities for monitoring of signs that indicate the immediate need for blood transfusion, Lackritz *et al.*, 1992; English *et al.*, 2002). POC hemoglobinometer are already in us for other indications in peripheral, resource-limited settings.

5.4.2. How can the management of children with respiratory illness be improved?

Based on the results from a recent modeling effort, our priority was to integrate a diagnostic test for bacterial pneumonia and a test for severe pneumonia. In this model, the benefits of these test would also largely depend on the infrastructure required and the resulting level of access to the test, i.e. the test should be performable at peripheral care level and results should be obtainable within one hour. The targeted sensitivity and specificity of the tests from the model was 95% and 85%, respectively, for the bacterial pneumonia test and 85% and 90% for the severe pneumonia test (Lim *et al.*, 2006).

Severe pneumonia

IMCI Severe Pneumonia classification is given in the presence of any danger signs or stridor in a calm child (World Health Organization, 2014). Before 2014, children with a cough and lower chest indrawing were also classified as severe pneumonia (World Health

Organization, 2008). This sign was removed subsequently, as a result of a series of clinical studies (Addo-Yobo *et al.*, 2004, 2011; Hazir *et al.*, 2008; Bari *et al.*, 2011; Soofi *et al.*, 2012; Das and Singh, 2013; Agweyu *et al.*, 2015; Patel *et al.*, 2015)**,** referred to henceforth as "severe pneumonia trials". In these studies, intravenous antibiotic treatment and/or hospital-based treatment were not found to be beneficial in children with severe pneumonia based on chest indrawing alone. However, they have several limitations raising the question whether chest indrawing should truly be disregarded as a sign for severe pneumonia. First, like in the early IMCI pneumonia studies, prevalence of chest indrawing was considerably higher in children in the South Asian studies compared to African studies (Paxton *et al.*, 1996; Kalter, Schillinger, *et al.*, 1997). Whether this reflects differences in diagnosis or epidemiology is not clear. Second, case-fatality rate for children included was low (<1%) though the case-fatality rate for severe pneumonia globally has been estimated at 7.2% and others have reported 18% (Pépin *et al.*; Nair *et al.*, 2013). Third, the presence of hypoxemia was not reported. Fourth, it is unclear whether hospital-based supportive interventions, such as provision of oxygen or rehydration, were provided adequately in the control arms. For respiratory infections especially, the need for antibiotic treatment does not necessarily overlap with the need for hospital-based supportive care. Children with bronchiolitis, for example, do not require antibiotic treatment at all but may require respiratory support or rehydration therapy. It is hence essential to identify children in need for hospital-based supportive care, regardless of the microbiological etiology. This was reflected in results from a hospital-based cohort study in Kenya that included 2803 children with respiratory infections. The prevalence of invasive bacterial infection with severe pneumonia syndrome was similar to that with mild pneumonia syndrome, but case fatality was greater among children with severe pneumonia syndrome (Berkley, Maitland, *et al.*, 2005). Among 310 children with pneumonia (cough and chest indrawing), two viruses causing bronchiolitis (*Respiratory Syncytial Virus* and human *Metapneumovirus*) were associated with treatment failure for pneumonia (Kelly *et al.*, 2015).

Since the introduction of IMCI, several severity scores for bronchiolitis (Voets, van Berlaer and Hachimi-Idrissi, 2006; Duarte-Dorado *et al.*, 2013) and asthma (Hurwitz *et al.*, 1984; Conway and Littlewood, 1985; Chalut, Ducharme and Davis, 2000; Arnold *et al.*, 2011) have been developed in high-resource settings with varying degrees of quality and validation (Bekhof, Reimink and Brand, 2014). The Respiratory Index of Severity in Children (RISC) score and its modified versions were developed to predict in-hospital death in South Africa (Reed *et al.*, 2012), Kenya (Emukule *et al.*, 2014) and Malawi (Hooli *et al.*, 2016). From the highest quality asthma and bronchiolitis scores, as well as studies in low-income settings that aimed at identifying children with hypoxemia and those at risk for adverse outcome from respiratory infections (Pépin *et al.*; Shann, Barker and Poore, 1989; Demers *et al.*, 2000;

Kelly *et al.*, 2000; Djelantik *et al.*, 2003; Berkley, Maitland, *et al.*, 2005; Mamtani *et al.*, 2009; Reed *et al.*, 2012; Corrard *et al.*, 2013; Jain, Sarathi and Jawalekar, 2013; Wandeler *et al.*, 2015), we identified the following clinical criteria that could be used by low-level health workers: respiratory rate (RR), accessory breathing muscle use (lower chest indrawing), vocalization (short phrases/weak cry, unable to speak/cry), grunting, HR, inability to drink, malnutrition, severe anemia, and level of consciousness (Bekhof, Reimink and Brand, 2014). Inability to drink, level of consciousness, malnutrition, severe anemia, and HR were integrated into the general danger signs (see above). We then constructed the "severe respiratory distress" classification as presence of a cough and two of the following signs: severe tachypnea (very fast breathing), chest indrawing, decreased vocalization (speaks in short sentences or unable to speak/cry), or grunting. We used a combination of two signs to increase the specificity of detecting children that may require hospital-based supportive care, as suggested in previous studies (Pépin *et al.*). For example, children with chest indrawing alone could be safely managed with home-based treatment as in "severe pneumonia trials"(see above). Fast breathing alone was not found to be related to asthma severity (Roofe *et al.*, 2014). However, fast breathing in addition to chest indrawing has been identified as a predictor for treatment failure among children with WHO severe pneumonia in the "severe pneumonia trials" and other observational studies (Addo-Yobo *et al.*, 2011; Fox *et al.*, 2013; Jain, Sarathi and Jawalekar, 2013; McCollum *et al.*, 2015). Similarly lower chest indrawing in combination with grunting was suggested as a criterion for hospitalization for children with WHO severe pneumonia (Pépin *et al.*). RR is known to vary with age and also with temperature in pediatric patients. Consequently, like for HR, we used age and temperature-corrected respiratory centile cutoffs to define tachypnea and severe tachypnea (Nijman *et al.*, 2012), Table 6. The 97th %ile provided the best cutoff for severe tachypnea in terms of sensitivity and specificity when applying it to the "fever study dataset" (D'Acremont *et al.*, 2014). We also included hypoxemia as a criterion for severe pneumonia. Hypoxemia was proposed in the 2014 IMCI chart booklet but has not been implemented (World Health Organization, 2014). Though it is still unclear at what level of care oximeters are most useful (health center versus hospital-based triage), we did include oximetry into e-POCT to be able to assess its utility at peripheral health care level.

In the era of *Haemophilus influenza type B* (Hib) vaccine, bacterial epiglottitis causing stridor has become very rare. For croup, a viral upper respiratory infection, stridor alone is not sufficient for severe classifications (Taussig *et al.*, 1975; Westley, Cotton and Brooks, 1978). Most children with stridor and severe disease also have other signs of respiratory distress, such as lower chest indrawing (Pépin *et al.*). Finally, stridor is difficult to recognize for low-level health workers (Simoes and McGrath, no date; Perkins *et al.*, 1997) and rare (Pépin *et*

al.; Shao, 2015). Stridor was therefore omitted in the ePOCT algorithm as a sign for severe pneumonia.

Non-severe pneumonia

For the “bacterial pneumonia” test, i.e. a test that would identify children in need for antibiotic treatment among children with non-severe respiratory symptoms, we developed a two-step approach of a clinical ‘rule-out-step’ with high sensitivity (fast breathing and/ or chest indrawing) and a subsequent biomarker ‘rule-in-step’ with high specificity. This two-step approach was chosen due to the low prevalence of bacterial pneumonia at peripheral health care level, and the high frequency of respiratory complaints. Using a sensitive, clinical criterion as a first step would select children with a relevant probability of having bacterial pneumonia and therefore i) increase the positive predictive value of the biomarker and ii) avoid unnecessary testing of children at very low risk of having bacterial pneumonia.

Rambaud-Alhaus et al. recently reviewed clinical predictors for radiographic pneumonia and found that they all had very low accuracy, including age-related fast breathing (pooled positive and negative likelihood ratio 1,55 and 0,63, Rambaud-Althaus, Althaus, *et al.*, 2015). However, age-related fast breathing was the most sensitive predictor among all studied. Some of the lack in diagnostic accuracy of RR may be related to its variation over time (in the order of 10 counts within one hour, Simoes *et al.*, 1991; Muro *et al.*, 2015) and between observers (English *et al.*, 1995). RR decreases with age until adolescence with the steepest decline apparent in infants during the first 2 years of life (Fleming *et al.*, 2011). It also increases with body temperature (Campbell, Byass and O’Dempsey, 1992; O’Dempsey *et al.*, 1993; Nijman *et al.*, 2012). Using arbitrary simple binary cutoffs probably oversimplifies the complex relationship between RR and pneumonia (Spruijt *et al.*, 2013). We thus used the 75th percentile of RR for age and temperature derived by Nijman et el. as a cutoff for tachypnea (fast breathing, Nijman *et al.*, 2012). We added lower chest indrawing as another criterion to further increase sensitivity. This identified 94% (29/31) of children with radiographic pneumonia in the ‘Fever Study’ dataset (D’Acremont *et al.*, 2014).

We found evidence that CRP would be helpful in identifying children with bacterial pneumonia. First, there is evidence from pneumococcal vaccine trials that a CRP cutoff of 140 mg/L was shown to identify pneumococcal pneumonia in children with changes seen on chest radiograph (Madhi and Klugman, 2007). Moreover, in a study among hospitalized children in Mozambique CRP values were significantly higher in 89 children with bacterial pneumonia (positive blood culture) compared to 87 children with viral pneumonia (Díez-

Padrisa *et al.*, 2010). In a systematic review that included 8 studies the diagnostic accuracy of CRP for pneumonia was moderate overall, with sensitivities ranging from 35%-100% at specificities from 40-100% [100]. CRP concentrations exceeding 35–60 mg/L occurred significantly more often in children with bacterial pneumonia. However, the outcome definitions for pneumonia were very heterogeneous, including clinical, radiological, and microbiological feature. This reflects an overall major limitation of studies assessing the accuracy of biomarkers for pneumonia: an acceptable gold standard remains yet to be developed (Lynch *et al.*, 2010). Lynch et al. reviewed systematically the diagnosis of pneumonia and found that authors used 11 different gold standards for 25 of the studies included (Lynch *et al.*, 2010). Radiographically defined pneumonia is often used as a proxy for bacterial pneumonia since it is known that they are correlated: Hib and pneumococcal conjugate vaccines (PCV) reduced radiographic pneumonia by circa 20% in vaccine trials (Mulholland *et al.*, 1997; Levine *et al.*, 1999; Cutts *et al.*, 2005). However, reliable data is missing on the true proportion of bacterial pneumonia among cases with chest X-ray (CXR) consolidation (Lynch *et al.*, 2010). Furthermore, studies included into the systematic review contained different populations, including populations with a high prevalence of malnutrition (Babu *et al.*, 1989), Malnourished children have distinct inflammatory responses to infection (Page *et al.*, 2013). The review by Flood et al. was further limited by different CRP cutoffs used (ranging from 35-60mg/L, Flood, Badik and Aronoff, 2008).

Since these reviews, Koster et al. published data on the accuracy of CRP in predicting CXR consolidation in 286 children in a Dutch emergency department. Cutoffs of 20, 50, 75, and 100 mg/L yielded sensitivities of 81%, 55%, 51%, and 32%, respectively, at specificities of 53%, 78%, 87%, and 93% (Koster *et al.*, 2013). In the Tanzanian 'Fever Study', using CART analysis, a combination of CRP and Chitinase 3-like-1 discriminated between end-point pneumonia (n=30) and non-end-point pneumonia (n=125) among children with a cough and fast breathing with 93% sensitivity and 81% specificity (Erdman *et al.*, 2015). A CRP cutoff point of >44 mg/L had a LR+ of 3.8 and a LR- of 0.25 and had the strongest association with end-point pneumonia among all biomarkers studied. Galetto-Lacour et al. found that CRP (≥100 mg/L) had a LR+ of 2.33 and a LR- of 0.13 in differentiating 37 patients with presumed pneumococcal pneumonia from 38 patients with non-pneumococcal pneumonia (Galetto-Lacour *et al.*, 2013). In a hospital-based study in 119 children in Italy, CRP values above 49 mg/L were correlated with CXR consolidation and pleural effusion (Agnello *et al.*, 2016). In another hospital-based study that aimed at establishing a prediction model to differentiate bacterial pneumonia (CXR consolidation and positive microbiological testing for typical and/or atypical bacteria) from viral pneumonia (CXR consolidation and positive viral PCR), CRP>80mg/L was the most significant predictor for bacterial pneumonia (Elemraid *et*

al., 2014). An analysis among 124 children with clinical signs of pneumonia and radiographic changes found that a CRP >80mg/L and >40mg/L had a LR+ of 6.4 and 5.1, and a LR- of 0.38 and 0.32 in detecting 50 children with endpoint pneumonia (Alcoba *et al.*, 2017). For identifying 24 children with complicated pneumonia (pleural effusion and/or bacteremia), the LR+ and LR- for a CRP >80mg/L and >40mg/L were 2.67 and 1.69, and 0.11 and 0.17, respectively. In a multicenter study in the United States including children with pneumonia, bacteremic patients had higher median CRP values (200mg/L, interquartile range 90-320), compared to those with negative blood culture (median 67mg/L, interquartile range 24-190, Myers *et al.*, 2013). A study in a tertiary care center in India found that a CRP cutoff of 60mg/L 93% sensitive and 64% specific in differentiating 28 patients with WHO very severe pneumonia from 22 with WHO severe pneumonia-all had CXR endpoint consolidation (Yadav *et al.*, 2015).

Several studies have addressed the accuracy of PCT differentiating bacterial and viral pneumonia in children(Heiskanen-Kosma and Korppi, 2000; Toikka *et al.*, 2000; Korppi and Remes, 2001; Moulin *et al.*, 2001; Korppi, Remes and Heiskanen-Kosma, 2003; Prat *et al.*, 2003; Leroy *et al.*, 2007; Nascimento-Carvalho *et al.*, 2010; Cohen *et al.*, 2012; Galetto-Lacour *et al.*, 2013). Results are conflicting: some report an advantage over CRP (Moulin *et al.*, 2001; Prat *et al.*, 2003) and others don't (Toikka *et al.*, 2000; Galetto-Lacour *et al.*, 2013). CRP outperformed PCT in predicting end-point pneumonia in the 'Tanzanian fever study' (Erdman *et al.*, 2015). No added value was found in a study that combined the two biomarkers over using them alone (Toikka *et al.*, 2000). Given that i) there is no clear benefit in terms of diagnostic accuracy of using PCT over CRP, ii) the availability of a semi-quantitative lateral-flow rapid test and iii) the lower blood volume required to perform CRP versus PCT testing, we decided to use CRP alone as a second step for the diagnosis of bacterial pneumonia, using a relatively high cutoff in the 60-100mg/L range to ensure high specificity. Given the semi-quantitative cutoffs provided by the manufacturer of the test used for the evaluation of e-POCT in a clinical trial (Bionexia™, Biomerieux), we chose 80mg/L as a cut-off.

In sum, children with a cough and tachypnea (RR above or equal to the 75th percentile age and temperature) and/or chest indrawing underwent CRP-testing. Children with CRP values equal or above 80mg/L were classified as bacterial pneumonia and antibiotic treatment was recommended, except for children with malaria since malaria alone raises CRP values (Díez-Padrisa *et al.*, 2010). The relatively high cutoff of 80mg/L was chosen to guarantee high rule-in value at the primary care level and to avoid unnecessary antibiotic treatment.

5.4.3. How can we improve diagnosis of serious bacterial infections among children with fever without source?

When the probable cause of a febrile illness cannot be determined by history or physical examination, the illness is labeled as fever without source (FWS, alternatively fever without localizing signs, fever without a focus or undifferentiated fever). Though the majority of children with FWS have self-limiting viral diseases, a small proportion will have bacterial infections; the most common are urinary tract infection (UTI), occult bacteremia, and occult pneumonia. Before the introduction of Hib and PCV, 3-4% of children aged 3-24 months with FWS had occult bacteremia in outpatients studies in the United States, the majority due to Hib and *Pneumococcus* (MCGowan *et al.*, 1973; Baron *et al.*, 1980). In studies conducted in Europe and United States, the overall bacteremia rate for children 3-36 months dropped to <0.5% in settings with high PCV coverage (Bressan *et al.*, 2012; Hernandez-Bou *et al.*, 2015). UTIs occur in approximately 7% of children with FWS (Shaikh *et al.*, 2008; Roberts, 2011). To address UTI, urinary dipstick testing was introduced into ALMANACH (Rambaud-Althaus, Shao, *et al.*, 2015). A meta-analysis reported a pooled LR+ of 6.1 (4.3, 8.6) and LR- of 0.20 (0.16, 0.26) for a positive urine dipstick in diagnosing a positive urine culture (Whiting *et al.*, 2005). The test accuracy in children younger than 2 years is lower compared to older children (Mori *et al.*, 2010). Obtaining clean urinary samples is however challenging in small children, i.e. those at highest risk for urinary tract infection (Roberts, 2011). In the tropics, malaria is an important cause of FWS, which can be readily diagnosed by mRDT (D'Acremont *et al.*, 2014). For bacterial infections, typhoid fever, rickettsial diseases, scrub typhus, and Leptospirosis cause FWS, with seasonal and geographic variation. ALMANACH included abdominal tenderness as a predictor for typhoid disease (Rambaud-Althaus, Shao, *et al.*, 2015). However, assessment of abdominal tenderness requires advanced pediatric clinical skills. It was detected in none of the 842 patients assessed in the ALMANACH study (Shao, 2015). In studies using methodologies without gold standard diagnosis, available pathogen-specific POCTs for typhoid have low accuracy with sensitivities of approximately 60% and specificities of approximately 80% (Islam *et al.*, 2016).

In order to improve identification of children in need for antibiotic treatment among those with FWS, we first evaluated clinical signs. Van den Bruel et al. systematically reviewed clinical signs for identifying children with serious bacterial infections (Van den Bruel *et al.*, 2010). No additional clinical signs could be identified from this review. More recently, De Santis *et al.* evaluated clinical predictors of bacterial disease in the Tanzanian fever study. In addition to the signs that were already included in the severe disease classification (see above), low weight (weight for age [WFA] <2 standard deviations (World Health Organization, 2006), adjusted LR+ 4.6], cervical, axillary or inguinal lymphadenopathy (adjusted LR+ 3.5) and

fever duration of >3 days (adjusted LR+ 1.6) were identified (De Santis and D'Acremont, 2017). Abdominal tenderness was a predictor of typhoid (adjusted LR+ 7.0). However, we did not keep "abdominal tenderness" due to its unproven reliability (see above).

Next, we assessed whether CRP or PCT (which are available as POCT), or a combination of both biomarkers would be helpful in detecting children in need for antibiotic prescription among children with FWS. Van den Bruel et al. summarized the diagnostic value of laboratory tests in identifying serious infections in children (including children with FWS) in a systematic review (Van den Bruel *et al.*, 2011). The best performing biomarkers were PCT (LR+ 1.75 to 3.11; LR- 0.08 to 0.35) and CRP (LR+ 2.40 to 3.79; LR- 0.25 to 0.61). An earlier review focusing on CRP only found similar results (Sanders *et al.*, 2008). For UTI specifically, we identified 6 and 13 studies that addressed the diagnostic accuracy of PCT and CRP respectively for the diagnosis of pyelonephritis (confirmed by DMSA scan) in children. All studies were summarized in a recent systematic Cochrane review (Shaikh *et al.*, 2015): PCT, at a cutoff of 0.5 ng/mL, and CRP, at a cutoff of 20mg/L had a sensitivity of 86% and 94% and a specificity of 74% and 39% respectively. Test accuracies for higher cutoffs were not reported. We found two relevant studies that assessed the diagnostic accuracy of CRP in detecting invasive *Salmonella* infection. In the first study, a CRP cutoff of 35mg/L was found to be 55% sensitive at a specificity of 88% (Meloni *et al.*, 1999). The accuracy was lower when clinical and/or microbiological confirmation were used in other studies (Choo *et al.*, 2001; Cooper *et al.*, 2014). We could not identify relevant studies on the diagnostic accuracy of CRP or PCT for leptospirosis, rickettsial disease nor scrub typhus.

The overall evidence of retrieved studies was not sufficient to inform on cutoffs of CRP and PCT to be used in patients with FWS in resource-poor settings. In general, there was little benefit in combining two tests in the study by van den Bruel et al (Van den Bruel *et al.*, 2011). However, we postulated a theoretical benefit since PCT and CRP are positive at different time-points of the disease. Currently, IMCI does not recommend antibiotic prescription for children without severe symptoms but with FWS. In order to avoid over-prescription of antibiotics in such children with a low pre-test probability of having a serious bacterial infection, we chose cutoff values with strong rule-in value, i.e. PCT 4ng/mL and CRP 80mg/L.

5.4.4. How should severe malnutrition be measured? Should it be included as a danger sign?

Severe malnutrition is recognized as an important risk factor for severe outcome from infections (Reed *et al.*, 2012; Jain, Sarathi and Jawalekar, 2013; Gowraiah *et al.*, 2014). In a study among 10,580 pediatric admissions in Kenya severe malnutrition accounted for 21% (141/659) of invasive bacterial infections and 38% (200/533) of deaths. Eighty-one percent (959/1183) of these admissions did not meet criteria for antibiotic treatment based on other symptoms, making anthropometry or kwashiorkor the sole basis for antibiotic treatments (Berkley, Maitland, *et al.*, 2005). This justifies systematic antibiotic treatment for children with fever and severe malnutrition, and possibly hospital referral.

IMCI defines severe malnutrition as severe wasting (weight for height [standing] or weight for length [lying flat] less than -3 z-scores), or mid-upper arm circumference (MUAC) less than 115 mm, or visible clinical signs of severe malnutrition (World Health Organization, 2014). The use of several signs is out of the recognition that all signs are very specific for acute severe malnutrition and that they are not necessarily overlapping. For example, in a study among 8190 hospitalized children in Kenya (359 deaths), sensitivity and specificity for subsequent inpatient death were, respectively, 46% and 91% for MUAC less than or equal to 11.5 cm, 42% and 92% for wasting, and 47% and 93% for visible severe wasting (Berkley, Mwangi, *et al.*, 2005). The three indices identified different subgroups of children and were independently associated with mortality.

Myatt et al. reviewed the performance of different methods for detection of severe malnutrition at community level (Myatt, Khara and Collins, 2006). The review concluded that weight for height/length (WFH)-based case-detection perform worse, in terms of precision, accuracy, sensitivity, and specificity than any alternative anthropometry-based method. WFH was neither found to be simple, cheap, or acceptable. MUAC in turn was found to be the best performing method, followed by WFA. One concern with using WFA is that, in populations with a high prevalence of chronic stunting, low WFA will lack specificity, as it will misclassify children with chronic stunting as having severe acute malnutrition. Interestingly, chronic stunting has increasingly been recognized as an independent risk factor for infectious complications and mortality (Smedman *et al.*, 1987; Pelletier *et al.*, 1995; Kossmann *et al.*, 2000; Black *et al.*, 2008; Olofin *et al.*, 2013; Prendergast and Humphrey, 2014). Accordingly, WFA was found to be a better predictor for mortality than WFH in several studies. However, MUAC, as a measure for acute malnutrition remained the best predictor in most studies (Chen, Chowdhury and Huffman, 1980; Briend and Zimicki, 1986; Alam, Wojtyniak and Rahaman, 1989; Vella *et al.*, 1994). An important practical restraint of

length measurements at peripheral level is that they likely not feasible given the short time available for consultation and the challenges involved when children are irritable and sick (Myatt, Khara and Collins, 2006). For example, in a survey of IMCI implementation in Bangladesh, weight measurement was done in 20% of 842 eligible children but length measurement in only 0.6% (Saha *et al.*, 2015). Precision of measurement by trained community health workers was found to be lowest for WFL and highest for WFA (Velzeboer *et al.*, 1983). Based on the evidence summarized above, we included MUAC measurement into e-POCT for all children above 6 months and, because there is currently not enough data to recommend it as sole measurement (Roberfroid *et al.*, 2013), we replaced WFH with WFA using a cutoff of <-3 z-score (Center for Disease Control and World Food Programme, 2005). Clinical signs for severe malnutrition (wasting, edema) were not included since there is conflicting and little data regarding the accuracy of detection of such signs by low-level health workers (Hamer *et al.*, 2004; Mogeni *et al.*, 2011). However, the inclusion of edema in areas with significant risk of severe protein energy malnutrition may be considered in the future, as only MUAC, and not WFA, is able to detect children with Kwashiorkor given the fluid retention associated with this condition (Myatt, Khara and Collins, 2006).

5.4.5. How can the diagnosis of severe dehydration be improved?

The WHO dehydration scale currently used in IMCI has never been formally derived nor validated. In the initial IMCI evaluation studies, all signs of the WHO dehydration scale showed low sensitivity when compared to physician diagnosis (overall sensitivity 51%, ranging from 27% for general condition and 64% for thirst, Perkins *et al.*, 1997). The clinical signs also had low reliability when assessed by IMCI-trained low-level health workers compared to medical doctors (Simoes *et al.*, 1997). Two small hospital-based validation studies have been carried out in Rwanda since then. In the first study including 50 patients (29 with severe dehydration), the WHO scale had an area under the curve (AUC) for moderate and severe dehydration of 0.58 for both (Pringle *et al.*, 2011). In the second study including 127 children (17 with severe dehydration), the AUC was 0.72. The optimal cutoff of ≥2 points had a sensitivity of 68% at a specificity of 67% (Levine *et al.*, 2013). Several dehydration scales have been developed in high-resource-settings which include clinical and laboratory features (Mackenzie, Barnes and Shann, 1989; Duggan *et al.*, 1996; Gorelick, Shaw and Murphy, 1997; Vega and Avner, 1997; Friedman *et al.*, 2004; Steiner, DeWalt and Byerley, 2004; Falszewska, Dziechciarz and Szajewska, 2014). Only one, the Clinical Dehydration Scale (CDS) was developed using formal measurement methodology, including the evaluation against several outcome measures (Friedman *et al.*, 2004). The assessment of several outcomes is of importance since most studies only have used post-illness weight gain to estimate weight loss (Mackenzie, Barnes and Shann, 1989; Duggan *et al.*, 1996;

Gorelick, Shaw and Murphy, 1997; Vega and Avner, 1997; Friedman *et al.*, 2004; Steiner, DeWalt and Byerley, 2004), which is not a sufficiently validated gold-standard (Gorelick, Shaw and Murphy, 1997). CDS contains 4 clinical items: general appearance, eyes, mucous membranes, and tears. In emergency department populations in high-resource settings the CDS was found to be useful in predicting weight gain (Gravel *et al.*, 2010; Kinlin and Freedman, 2012), the need for intravenous rehydration (Goldman, Friedman and Parkin, 2008; Gravel *et al.*, 2010; Kinlin and Freedman, 2012), need for hospitalization (Gravel *et al.*, 2010; Kinlin and Freedman, 2012), and hospital length of stay (Goldman, Friedman and Parkin, 2008; Bailey *et al.*, 2010; Kinlin and Freedman, 2012). However, it only had a moderate inter-observer reliability (k= 0.52, Kinlin and Freedman, 2012). For resource-poor settings, the accuracy of the CDS has been assessed in 2 hospital-based studies in Rwanda (Pringle *et al.*, 2011; Levine *et al.*, 2013). In the first study its sensitivity was 68% and its specificity 45% for predicting 5% body weight gain (moderate dehydration) in 48 children (Pringle *et al.*, 2011). The second study used a composite outcome of 10% body weight or death present in 8% of patients (11/140 patients). In this study the scale had an area under the curve of 0.80 (Levine *et al.*, 2013). No studies have assessed the feasibility and usefulness of using the CDS in outpatient resource-poor settings.

Given that the evidence for the WHO scale was poor and that for the CDS limited in terms of reliability and use in low-resource outpatient settings, we decided to use a practical “at-risk approach” using variables of the modified Vesikari severity scale (Ruuska and Vesikari, 1990) for gastroenteritis. This scale was validated in a multicenter study and is used to classify severity of diarrhea in clinical trials and epidemiological studies (Freedman, Eltorky and Gorelick, 2010; Schnadower *et al.*, 2013). Based on the Vesikari scale we considered that children with ≥5 loose stools/over past 24hrs OR ≥3 loose stools/over past 24hrs and emesis OR ≥3 emesis/over past 24hrs were at risk for dehydration and offered oral fluids. If these children would be unable to drink or would experience persistent vomiting, they would be referred for further hospital-based hydration treatment.

5.4.6. Algorithm design

We designed a novel algorithm (e-POCT) that integrated the modifications and additional elements developed based on the structured literature searches described above. We developed a paper flowchart that summarizes e-POCT’s logic (Figure 11).

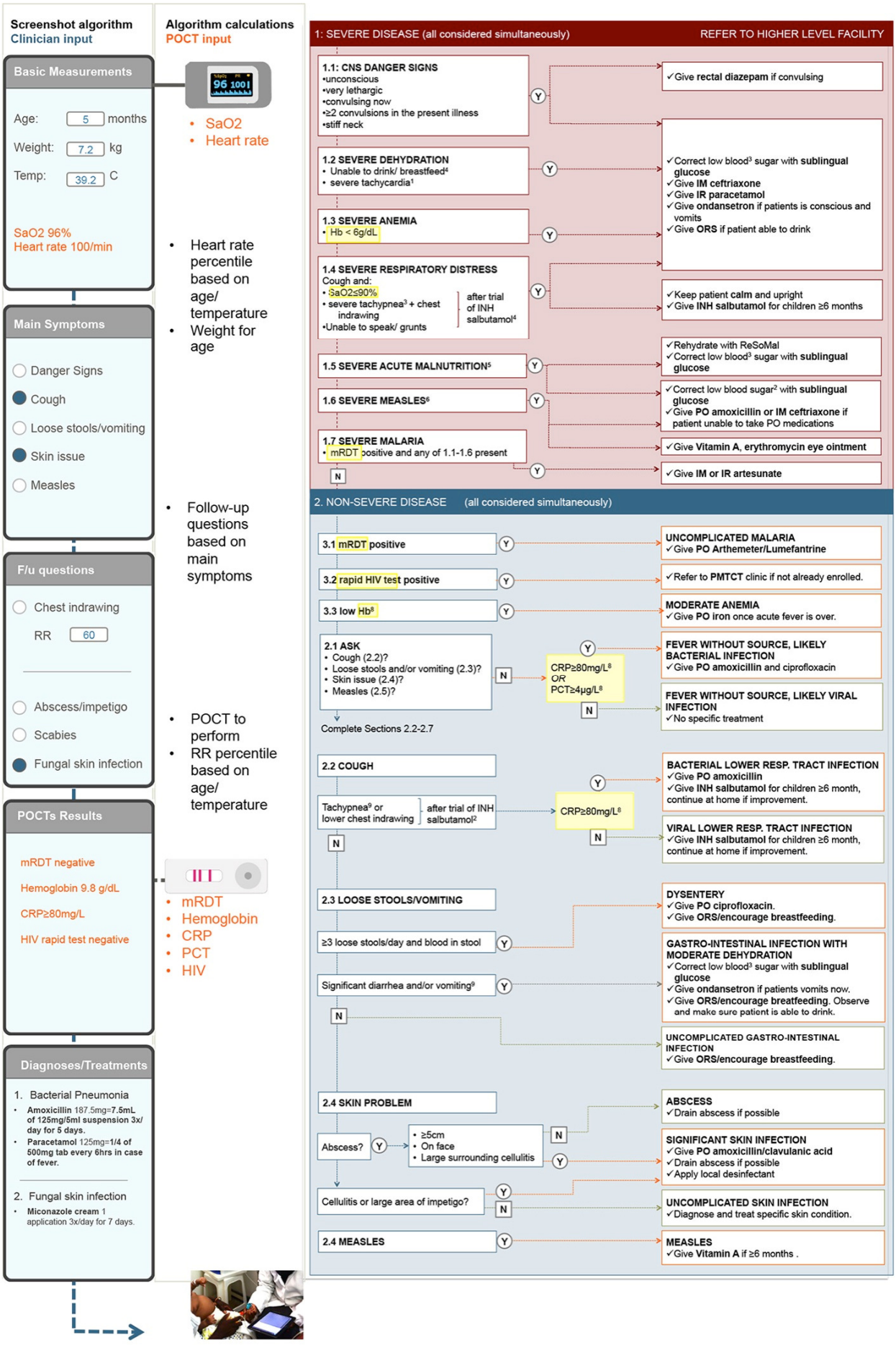
Screenshot algorithm
Clinician input
Algorithm calculations
POCT input
Basic Measurements
Age: 5 months
Weight: 7.2 kg
Temp: 39.2 C
SaO2 96%
Heart rate 100/min
• SaO2
• Heart rate
• Heart rate percentile based on age/ temperature
• Weight for age
Main Symptoms
Danger Signs
Cough
Loose stools/vomiting
Skin issue
Measles
F/u questions
Chest indrawing
RR 60
Abscess/impetigo
Scabies
Fungal skin infection
• Follow-up questions based on main symptoms
POCTs Results
mRDT negative
Hemoglobin 9.8 g/dL
CRP≥80mg/L
HIV rapid test negative
• mRDT
• Hemoglobin
• CRP
• PCT
• HIV
• POCT to perform
• RR percentile based on age/ temperature
Diagnoses/Treatments
1. Bacterial Pneumonia
• Amoxicillin 187.5mg=7.5mL of 125mg/5ml suspension 3x/ day for 5 days.
• Paracetamol 125mg=1/4 of 500mg tab every 6hrs in case of fever.
2. Fungal skin infection
• Miconazole cream 1 application 3x/day for 7 days.
1: SEVERE DISEASE (all considered simultaneously)
REFER TO HIGHER LEVEL FACILITY
1.1: CNS DANGER SIGNS
•unconscious
•very lethargic
•convulsing now
•≥2 convulsions in the present illness
•stiff neck
✓Give rectal diazepam if convulsing
1.2 SEVERE DEHYDRATION
• Unable to drink/ breastfeed[4]
• severe tachycardia[1]
1.3 SEVERE ANEMIA
• Hb < 6g/dL
1.4 SEVERE RESPIRATORY DISTRESS
Cough and:
• SaO2≤90%
• severe tachypnea[3] + chest indrawing
•Unable to speak/ grunts
after trial of INH salbutamol[4]
✓Correct low blood[3] sugar with sublingual glucose
✓Give IM ceftriaxone
✓Give IR paracetamol
✓Give ondansetron if patients is conscious and vomits
✓Give ORS if patient able to drink
✓Keep patient calm and upright
✓Give INH salbutamol for children ≥6 months
1.5 SEVERE ACUTE MALNUTRITION[5]
✓Rehydrate with ReSoMal
✓Correct low blood[3] sugar with sublingual glucose
1.6 SEVERE MEASLES[6]
✓Correct low blood sugar[2] with sublingual glucose
✓Give PO amoxicillin or IM ceftriaxone if patient unable to take PO medications
1.7 SEVERE MALARIA
• mRDT positive and any of 1.1-1.6 present
✓Give Vitamin A, erythromycin eye ointment
✓Give IM or IR artesunate
2. NON-SEVERE DISEASE (all considered simultaneously)
3.1 mRDT positive
UNCOMPLICATED MALARIA
✓Give PO Arthemeter/Lumefantrine
3.2 rapid HIV test positive
✓Refer to PMTCT clinic if not already enrolled.
3.3 low Hb[8]
MODERATE ANEMIA
✓Give PO iron once acute fever is over.
2.1 ASK
• Cough (2.2)?
• Loose stools and/or vomiting (2.3)?
• Skin issue (2.4)?
• Measles (2.5)?
Complete Sections 2.2-2.7
CRP≥80mg/L[8] OR PCT≥4µg/L[8]
FEVER WITHOUT SOURCE, LIKELY BACTERIAL INFECTION
✓Give PO amoxicillin and ciprofloxacin
FEVER WITHOUT SOURCE, LIKELY VIRAL INFECTION
✓No specific treatment
2.2 COUGH
Tachypnea[9] or lower chest indrawing
after trial of INH salbutamol[2]
CRP≥80mg/L[8]
BACTERIAL LOWER RESP. TRACT INFECTION
✓Give PO amoxicillin
✓Give INH salbutamol for children ≥6 month, continue at home if improvement.
VIRAL LOWER RESP. TRACT INFECTION
✓Give INH salbutamol for children ≥6 month, continue at home if improvement.
2.3 LOOSE STOOLS/VOMITING
≥3 loose stools/day and blood in stool
DYSENTERY
✓Give PO ciprofloxacin.
✓Give ORS/encourage breastfeeding.
Significant diarrhea and/or vomiting[9]
GASTRO-INTESTINAL INFECTION WITH MODERATE DEHYDRATION
✓Correct low blood[3] sugar with sublingual glucose
✓Give ondansetron if patients vomits now.
✓Give ORS/encourage breatfeeding. Observe and make sure patient is able to drink.
UNCOMPLICATED GASTRO-INTESTINAL INFECTION
✓Give ORS/encourage breastfeeding.
2.4 SKIN PROBLEM
Abscess?
• ≥5cm
• On face
• Large surrounding cellulitis
ABSCESS
✓Drain abscess if possible
SIGNIFICANT SKIN INFECTION
✓Give PO amoxicillin/clavulanic acid
✓Drain abscess if possible
✓Apply local desinfectant
Cellulitis or large area of impetigo?
UNCOMPLICATED SKIN INFECTION
✓Diagnose and treat specific skin condition.
2.4 MEASLES
MEASLES
✓Give Vitamin A if ≥6 months .

Figure 11a (left, previous page)

Example of input- and output screens, sensor input, and background algorithm calculations

Point-of-care test (POCT), oxygen saturation (SaO2), rapid test for malaria (mRDT), C-reactive protein (CRP), procalcitonin (PCT), human immunodeficiency virus (HIV), respiratory rate (RR)

Figure 11a (right, previous page) Content of e-POCT algorithm

1: Heart rate ≥90th %ile for age and temperature (Thompson, Harnden, *et al.*, 2009); 2: <3.3mmol/l; 3: Respiratory rate ≥97th %ile for age, temperature(Nijman *et al.*, 2012); 4: Children ≥6 months only; 5: Weight for age <3z-score per WHO 2006 growth charts AND/OR mid-upper arm circumference <11.5cm and age>6months; 6: Clouding of cornea OR severe mouth ulcers OR cough and tachypnea (respiratory rate ≥75th %ile for age and temperature, Nijman *et al.*, 2012); 7: Hb (g/dL): 2-6 months<9, 7-24months<10, 25-59months<11; 8: measured for patients with negative mRDT only; 9: Respiratory rate ≥75th %ile for age, temperature (Nijman *et al.*, 2012); 10:>5 loose stools/over past 24hrs or ≥3 loose stools/over past 24hrs and emesis or >3 emesis/over past 24hrs; Abbreviations: central nervous system (CNS), intramuscular (IM), per os (PO), intrarectal (IR), inhaled (INH), oral rehydration solution (ORS), prevention of mother-to-child transmission (PMTCT), respiratory (resp), Hemoglobin (Hb)

For each patient, the algorithm asks for 5 main symptoms, follow-up with additional questions if needed based on the initial input screen, recommends laboratory testing, and gives a classification and treatment recommendation (Fig2). All medication dosages are weight-based. Like in ALMANACH, all danger signs are evaluated at the start of the algorithm, including the disease-specific danger signs. This allows rapid assessment and referral of severe patients. Since children with severe disease and positive malaria tests are at high risk of bacterial infections (Berkley, Maitland, *et al.*, 2005), both antibiotic and anti-malaria treatment are recommended. Whenever possible oral antibiotics were recommended for increased patient safety (Li *et al.*, 2015). We also added a section on common skin diseases, including picture examples of common tropical skin infections. Skin diseases have indeed been under-addressed within IMCI since its start (Perkins *et al.*, 1997).

The electronic support tool allowed for the automated steps (Figure 11A). First, since we managed to connect the oximeter probe directly to the android support tool, the measurements of SaO2 and HR could be fed directly into the algorithm without further manual input. Second, the software calculated automatically weight-based medication dosages and reference values (HR and RR percentiles based on age and temperature, WHO growth chart percentiles). When necessary, the software allowed entering several sub-branches simultaneously. If an antibiotic was needed for two different infections, the algorithm was able to integrate the information and to recommend one antibiotic that would work for both infections, instead of one for each disease. Third, the software recommended laboratory tests based on the signs and symptoms entered on a single screen (instead of a separate screen for each suspected disease classification). Forth, the electronic algorithm integrated all clinical signs and symptoms, as well as results of

all laboratory tests performed. It then provided disease classifications and treatments based on this integrated data. Overall, the use of software allowed integration of more complex data while maintaining simple input and output screens. This allowed inclusion of additional clinical and laboratory parameters that could not be handled during a routine, “manual” consultation.

5.5. Discussion

We here provide a detailed rationale for the construction of e-POCT, a novel electronic algorithm that integrates POCTs for management of febrile illnesses in under-fives in low resource settings. The algorithm is built on an IMCI backbone and maintains IMCI’s integrative approach to the management of childhood infections. In the construction of e-POCT, we sought to address IMCI’s major challenges through a structured review of key IMCI elements, and the integration of POCTs. To our knowledge, this was the most comprehensive effort to “revisit” the IMCI case management chart considering a broad range of literature that has been published since development of IMCI, including host biomarkers. This effort was further strengthened by the experience acquired through the development and evaluation of the ALMANACH algorithm (Rambaud-Althaus, Shao, *et al.*, 2015; Shao *et al.*, 2015; Rambaud-Althaus *et al.*, 2017).

The evidence retrieved allowed us to perform major useful modifications: for the identification of patients with severe illness, pulse oximetry was integrated to identify patients with hypoxemia and severe tachycardia. Cutoffs for HR and RR were updated based on recent epidemiological studies and are corrected automatically for age and temperature by the algorithm. Systematic Hb screening was added to identify children with severe anemia. e-POCT uses MUAC and WFA to improve detection of children with severe malnutrition. For the management of children with respiratory infections, we constructed a ‘severe respiratory distress’ category and added a two-step diagnostic approach for bacterial pneumonia using RR and a CRP POCTs. Bacterial infections in children with FWS were addressed through CRP and PCT POCTs. The low-evidence and complex WHO dehydration scale was replaced with a simple ‘at-risk’ approach based on 24hr parental recall. We aimed at increasing the user-friendliness through the use of an electronic format, the reduction of clinical elements, and a simple user-interface.

Overall, the design of the algorithm was limited by the scarcity of evidence of some of the key areas that required revision. This was especially true for evidence from low-

resource settings. Prospective studies on the accuracy of danger signs (especially the sensitivity) are lacking. All studies that assess IMCI danger signs were hospital-based (Paxton *et al.*, 1996; Kalter, Schillinger, *et al.*, 1997). Hence, they can only give estimates on the specificity of danger signs. Some additional clinical signs, such as CRT or jaundice have been shown to be valid in predicting severe illness. However, their reliability when measured by low-level health workers has not been demonstrated. Since development of e-POCT, some of the pediatric severity scores have been further validated (Conroy *et al.*, 2015). Two additional score have been developed (George *et al.*, 2015; Mpimbaza *et al.*, 2015). However, the reliability and usefulness of the scores at peripheral health care level remains to be determined. Unfortunately, there is no clinical discriminator for anemia, requiring systematic Hb screening of all children. Given the high mortality from anemia, such an approach may be justified. However, this will likely lead to higher referral of patients and has to be met with improved hospital-based blood transfusion capacity. Furthermore, the majority of severe anemia used to occur in children with malaria (Biemba *et al.*, 2000; Koram *et al.*, 2000; Owusu-Agyei *et al.*, 2002). With declining malaria transmission this proportion has decreased (Pedro *et al.*, 2010) and the usefulness of systematic Hb screening has to be assessed in low malaria transmission areas. Alternative approaches to Hb screening, such as the Hemoglobin scale may be a future option, though its accuracy had to be improved (Marn and Critchley, 2016). Identification of children with severe respiratory infections is limited by low-level evidence of discriminatory signs. Lower chest indrawing has been omitted as a sign for severe pneumonia since it has been demonstrated that children with severe pneumonia do not benefit from intravenous antibiotic treatment. This is, however, not surprising since a great proportion of children with severe pneumonia suffer from viral infections (Ali *et al.*, 2013). Further studies should evaluate predictive signs for the need of hospital-based supportive care, regardless of the microbiological etiology. For the diagnosis of bacterial pneumonia, the role of RR as a marker for pneumonia is unclear. It was constructed as a very sensitive diagnostic criterion, but more recent evidence suggests that the current WHO cutoffs are neither sensitive nor specific (Rambaud-Althaus, Althaus, *et al.*, 2015). The validity of using RR as an initial rule-in criterion for the diagnosis of bacterial pneumonia has to be evaluated further. One reason may be that binary cutoffs over-simplify correlation of RR with pneumonia. This is why we used updated RR cutoffs, corrected for age and temperature. A prospect may be the utilization of ‘digital stethoscopes’ that can detect children with bronchiolitis who do not require CRP testing (Simoes *et al.*, 1991). Overall, the evidence for the use of CRP to diagnose bacterial pneumonia in children was moderate. Outcome studies are lacking. A recent study in Vietnam demonstrated that CRP could reduce antibiotic prescription for

respiratory infections in children (Do *et al.*, 2016). However, the trial was not powered to assess clinical outcome. Newer studies have assessed the accuracy of PCT in diagnosing childhood pneumonia (Bivona *et al.*, 2015; Agnello *et al.*, 2016). PCT is indeed a useful marker for bacterial pneumonia in adults (Shaddock, 2016). Using PCT for detecting bacterial pneumonia in children could be considered. As for FWS, little evidence could be retrieved on the most useful cutoff for diagnosing bacterial infections in a low prevalence setting. We used higher cutoffs for both biomarkers to avoid over-treating children at low risk for bacterial infections with antibiotics. The accuracy of biomarkers depends on the time point of measurement within the course of an illness (Melbye *et al.*, 2004). Previous efforts to improve management of children with FWS have included urine dipstick testing to detect children with UTI (World Health Organization, 2005; Rambaud-Althaus, Shao, *et al.*, 2015). The high CRP and PCT cutoffs may miss children with UTI raising the concern for the development of renal scarring. However, recently, specialists have proposed that less aggressive testing strategies UTI, such as testing of children with several days of fever only, may be just as adequate (Salleeh *et al.*, 2010; Newman, Shreves and Runde, 2013). Overall, obtaining clean urine samples in children in resource-limited setting is challenging. This could be considered when more detailed evidence is available. Overall, all studies on predictors reviewed were limited by the fact that they were mostly conducted in emergency department settings. This may limit the applicability of the findings for the settings targeted by e-POCT with a lower prevalence of bacterial infections. Finally, the involvement of parental judgment, which has shown to be useful in studies in high-resource-settings has not been explored for the IMCI setting (Van den Bruel *et al.*, 2007).

e-POCT has the potential to improve management of the febrile child in low-resource settings through integration of recent evidence of fever management, novel, POCTs, and electronic technology. This new tool should be validated in real conditions of primary care in resource-poor settings.

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6. Validation of prediction rules for serious bacterial infections in Tanzanian febrile children

Detecting bacterial infections in tropical settings

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What's Known on This Subject

Clinical algorithms designed developing countries (e.g. IMCI) have not been validated for their performance in detecting serious bacterial infections (SBI) using stringent criteria. Prediction rules and guidelines for SBI from well-resourced countries showed moderate performance in a European validation study.

What This Study Adds

In the Tanzanian outpatient setting, all prediction rules and guidelines examined had insufficient accuracy for ruling SBI in or out. IMCI had a low sensitivity. Rules using a combination of clinical and laboratory criteria (instead of either one) performed better.

Contributors' Statement

Dr Keitel conceptualized and designed the study, carried out the analysis, and drafted the initial manuscript, and approved the final manuscript as submitted. Prof. D'Acremont created the validation dataset, reviewed and revised the manuscript, and approved the final manuscript as submitted. Mrs Kilowoko and Mrs Kyungu collected the clinical data, and approved the final manuscript as submitted. Prof. Genton revised and commented on the manuscript.

6.1. Abstract

Background and Objectives

Health-workers in developing countries rely on clinical algorithms, such as the Integrated Management of Childhood Illnesses (IMCI), for the management of patients, including diagnosis of serious bacterial infections (SBI). The diagnostic accuracy of IMCI in detecting children with SBI is unknown. Prediction rules and guidelines for SBI from well-resourced countries have not been evaluated in resource-limited countries at outpatient level. The aim of this study was to estimate the diagnostic accuracy of existing prediction rules and clinical guidelines in identifying children with SBI in a cohort of febrile children attending outpatient health facilities in Tanzania.

Methods

Structured literature review to identify available prediction rules and guidelines aimed at detecting SBI and retrospective, external validation on a dataset containing 1,005 febrile Tanzanian children with acute infections. The reference standard, SBI, was established based on rigorous clinical and microbiological criteria.

Results

Four prediction rules and five guidelines, including IMCI, could be validated. All examined rules and guidelines had insufficient diagnostic accuracy for ruling-in or ruling-out SBI with positive and negative likelihood ratios ranging from 1.04-1.87 to 0.47-0.92, respectively. IMCI had a sensitivity of 36.7% (95% CI 29.4-44.6%) at a specificity of 70.3% (67.1-73.4%).

Conclusions

Revised clinical algorithms including simple point-of-care tests with improved accuracy for detecting SBI targeting in tropical resource-poor settings are needed. They should undergo careful external validation against clinical outcome before implementation, given the inherent limitations of gold standards for SBI.

6.2. Introduction

Acute febrile illnesses are the most common presentation of young children attending outpatient settings worldwide (Burton *et al.*, 2011). Serious bacterial infections (SBI) are infections that may results in life-threatening complications without antibiotic treatment, such as bacteremia, meningitis, pneumonia, osteomyelitis, and febrile urinary tract infections (UTI). Children with these infections often present with non-specific clinical signs and several concomitant symptoms (Horwood *et al.*, 2011). Like in well-resourced settings, SBI in resource-poor settings have become increasingly rare with improving vaccination coverage and hygiene (D'Acremont *et al.*, 2014). This combined makes the assessment of children with acute infections challenging—especially in developing countries where health care workers lack diagnostic tools and resources. Sub-standard management of children with infections has resulted in persistent high mortality from common childhood infections(Liu *et al.*, 2014) and high-volume over-prescription of antibiotics (Risk *et al.*, 2013).

The World Health Organization (WHO) developed the Integrated Management of Childhood Illnesses (IMCI) strategy in the 1990s. The cornerstone of the IMCI strategy is a set of algorithms that recommends presumptive treatment based on clinical signs and symptoms (besides the rapid diagnostic test for malaria that was introduced in the 2014 version, World Health Organization, 2014). The Integrated Community Case Management guidelines (iCCM) is a simplified version of IMCI, geared towards community health workers (UNICEF and World Health Organization, 2011). More recently, an improved version of IMCI was developed and validated, ALMANACH, that includes urinary dipstick testing (Rambaud-Althaus, Shao, *et al.*, 2015). Due to the lack of available evidence when IMCI was initially developed, the algorithm was based mainly on expert opinion in addition to small derivation studies. Though IMCI and iCCM have been implemented globally, their performance in detecting children with SBI has not been validated to date using stringent microbiological, instead of expert clinical diagnosis (and chest radiograph [CXR] in some studies, USAID, 1998). In a 1995 outpatient department study in Bangladesh, Factor et al. included blood culture in the outcome definition for SBI, the remaining SBI definition were, however, based on pediatrician's clinical diagnosis and CXR only (Factor *et al.*, 2001). In economically developed countries a series of clinical and laboratory prediction rules and clinical guidelines, with different degrees of validation, have been designed for the management of febrile children in the ambulatory setting (American College of Emergency Physicians Clinical Policies Committee, 2003; Thayyil *et al.*, 2005; Van den Bruel *et al.*, 2007; Bleeker *et al.*, 2007; Lacour, Zamora and Gervaix, 2008; Bilkis *et al.*, 2010; Craig *et al.*, 2010; Brent *et*

al., 2011; Neuman *et al.*, 2011; Thompson *et al.*, 2012; National Institute of Health and Care Excellence, 2013; Nijman *et al.*, 2013). There is a growing body of evidence that the causes of acute febrile illnesses in children in low- and high resource settings are in fact quite similar (D'Acremont *et al.*, 2014). Such clinical prediction rules and guidelines may thus be an attractive prospect for improving case management in low-resource settings. However, external validation to support their use in resource-poor settings is lacking.

The aim of this study was to estimate the diagnostic accuracy of existing prediction rules and clinical guidelines, including IMCI and iCCM, in identifying children with SBI in a resource-poor setting, using retrospective external validation on dataset collected prospectively in Tanzania(D'Acremont *et al.*, 2014).

6.3. Patients and Methods

We used the Standard for Reporting of Diagnostic Accuracy (STARD) guidelines for study reporting(Bossuyt *et al.*, 2003). The protocol of the validation dataset was approved by the regional ethics committee in Basel, Switzerland, and by the national ethics committee in Tanzania (D'Acremont *et al.*, 2014).

Participants

The study population comprised 1005 children from a study on causes of fever in rural and urban Tanzania, the 'Tanzanian Fever Study'(D'Acremont *et al.*, 2014).Details of the study are reported elsewhere(D'Acremont *et al.*, 2014). Briefly, children aged two months to 10 years with fever (axillary temperature of ≥38°C) were enrolled consecutively. Children with severe malnutrition and/or those requiring immediate live-saving procedures were excluded. Recruitment in Tanzania took place at the outpatient clinic of Amana District Hospital in Dar es Salaam (urban setting) from April to August 2008, and at the outpatient clinic of the St-Francis Designated-District Hospital in Ifakara, Kilombero District (rural setting) from June to December 2008.

Outcome definition

The outcome, SBI, i.e. a bacterial infection requiring antibiotic treatment, was defined as presence of one of the following: bacteremia (positive blood culture for a known pathogen), *Salmonella typhi* infection (positive blood-or stool culture, or positive specific IgM rapid diagnostic test), radiographic pneumonia, urinary tract infection (positive urine dipstick and urine culture), meningitis, bacterial gastroenteritis (positive stool culture), significant skin/soft

tissue infections and other systemic bacterial infections (Rickettsiosis, Coxiellosis, and Leptospirosis). Definitions were based on the methodology used in the 'Tanzania Fever Study': for each patient, the final diagnosis (or diagnoses) was established with a computer-generated algorithm based on pre-defined clinical and microbiological criteria(D'Acremont *et al.*, 2014). These criteria were derived from international guidelines as well as systematic reviews.

Clinical and laboratory assessment

Investigators used standardized case report forms to record clinical findings. The form included 23 symptoms and their respective duration, potential travel history and/or sick contacts, known chronic conditions, and 49 clinical signs. At the initial visit a systematic set of investigations was performed according to predefined algorithm (D'Acremont *et al.*, 2014). If a clinical or laboratory diagnosis could not be made at the initial visit, a follow-up visit was scheduled for day 7 when an identical, full clinical and laboratory assessment was performed again for those with persistent fever or those who experienced new symptoms. In all cases, blood samples and pooled nasal and throat swabs were taken for microbiologic testing (cultures and rapid tests) on site and further serologic and molecular work-up in Switzerland and the USA. CXR were performed on site in the subgroup of cases fulfilling the WHO clinical definition of pneumonia (World Health Organization, 2013). Images were reviewed by a pediatric radiologist in Switzerland who was blinded to the presumed diagnosis and who classified the radiographic findings according to WHO's Pneumococcal Trialist Ad Hoc Committee recommendations (Cherian *et al.*, 2005). The diagnosis of radiological pneumonia was made in cases where CXR showed 'primary endpoint consolidation'. If the IMCI clinical criteria for a suspected human immunodeficiency virus (HIV) infection were present, voluntary HIV testing was recommended to the child's guardian.

Selection of prediction rules and guidelines

All available prediction rules (laboratory and clinical) for identifying any SBI in children in the outpatient settings were identified through a structured literature review in Medline and Embase as part of the development of a novel disease management algorithm (Chapter 5.3). The search was modified based on previously published systematic review and a European validation study (Thompson *et al.*, 2012; Verbakel *et al.*, 2013). Prediction rules and guidelines that target the neonatal period, i.e. < 3 months, were excluded. We also did not include prediction rules that primarily aim at predicting death (such as the PEDIA [Berkley, 2003], LODS [Helbok *et al.*, 2009], and SICK [Bhal *et al.*, 2006] scores), or the need for referral to the pediatric intensive care unit at in-patient level. Scores aimed at

identifying dehydration for patients with gastroenteritis, or at detecting children with meningitis (there were only 2 patients with meningitis in the dataset) were also not included. When variables of the dataset were not entirely matching the variables of the original rule or guideline, we identified proxies where possible. For instance, the variable 'ill-appearance' of the Rotterdam Fever Model was not recorded in the dataset. We therefore used 'lethargic' or 'drowsy' as proxies. When more than 20 percent of the required variables were not recorded in the dataset, the rule/guideline was not included in the validation. This was based on the assumption that missing more than 20% of predictor variables was not clinically sensible. Missing data on variables used in the validation were not imputed because the necessary missing-at-random assumption was likely to be incorrect given that all data was collected based on a predefined algorithm. For example, urine testing was obtained in children per pre-defined criteria and not randomly. We report the number of observations available for analysis of each prediction rule after application of the above assumptions. Where rules generated sum scores, previously published cut-offs were applied.

Statistical analysis

The accuracy of the included prediction rules and guidelines was estimated retrospectively in the prospectively collected 'Tanzania Fever Study' dataset by calculating sensitivity, specificity, and likelihood ratio (LR). To assess the influence of the age range, we performed several sensitivity analyses by comparing the 95% confidence intervals (CIs) of the diagnostic accuracy results in the target age group of the rules/ guidelines with that in the entire age range of validation dataset, Since some predictors (fast breathing in IMCI, iCCM, and ALMANACH, and a positive CXR in the American Academy of Emergency Physicians [AAEP] guideline) was part of the diagnostic criterion for pneumonia in the validation dataset, we also did sensitivity analyses by comparing the full dataset with a dataset excluding pneumonia cases for these 4 guidelines. The same was done for UTI for prediction scales and guidelines that use urinary dipstick (Bleeker Score, Lab Score, ALMANACH and AAEP). Malaria is known to raise C-reactive protein (CRP) values(Naik and Voller, 1984). We hence performed a sensitivity analysis comparing malaria negative patients with the full dataset for prediction rules that contain C-reactive protein. All analyses were performed with Stata version 13.1. We used a web-based tool to generate Venn diagrams (http://jura.wi.mit.edu/bioc/tools/venn.php).

6.4. Results

Prediction rules and guidelines

Through the structured literature review (Chapter 5.4), we identified 34 prediction rules/guidelines for the use in febrile children. Sixteen were designed to predict SBI at the outpatient level (Figure 12).

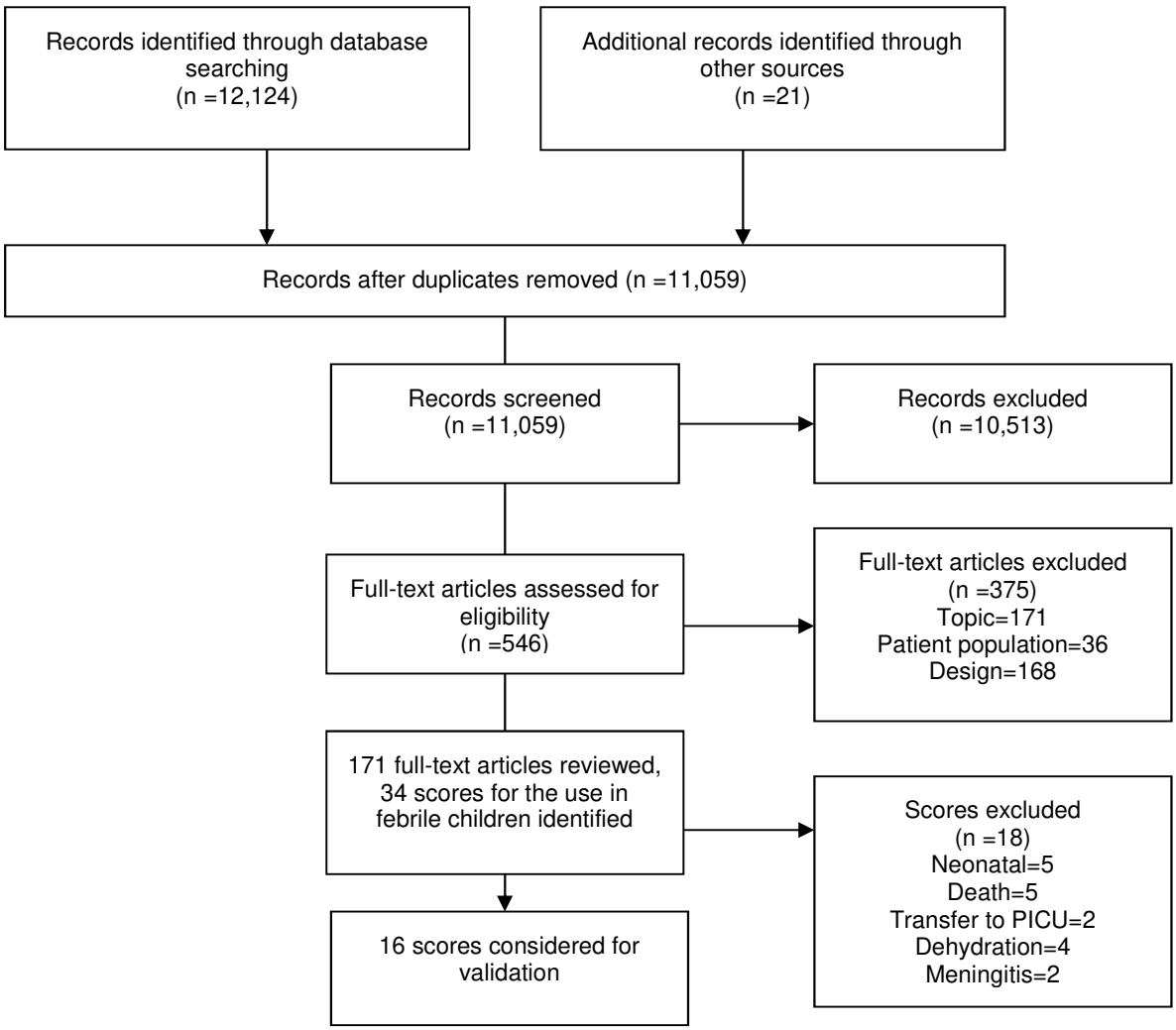

Figure 12 Flowchart of scores identified and considered for validation. Adapted from **Figure 10**, Pediatric Intensive Care Unit (PICU)

The NICE guideline is intended to predict 'serious disease' among children with acute febrile illness, and not to indicate antibiotic treatment. However, given that it was the only guideline designed for the use by healthcare professionals in primary care with various levels of training, we decided to include it in the validation exercise. The prediction rules and

guidelines identified are summarized in Table 7. In addition to the prediction rules and guidelines from the systematic review and European validation study (Thompson *et al.*, 2012; Verbakel *et al.*, 2013), we found one additional prediction rule for diagnosis of SBI (Craig *et al.*, 2010), and two prediction rules for pneumonia(Bilkis *et al.*, 2010; Neuman *et al.*, 2011). We also identified one additional clinical guideline (AAEP, American College of Emergency Physicians Clinical Policies Committee, 2003) in addition to IMCI, iCCM, and ALMANACH (UNICEF and World Health Organization, 2011; World Health Organization, 2014; Rambaud-Althaus, Shao, *et al.*, 2015). Appendix 1 displays which rules and guidelines could be used for retrospective validation. For the prediction rules, validation was possible for the Bleeker Score, Thavyil Score, Lab Score and the Rotterdam Fever Model. More than 20% of predictors were missing for other prediction rules, including 3 pneumonia rules. All clinical guidelines identified could be used for validation. The proxy variables used for certain predictors are also shown in Appendix 1.

Validation dataset

The median age of children included in the validation dataset was 18 months (interquartile range 10-34), 33% of children were younger than 12 months. The full details on the demographic and clinical characteristics of the study population are provided in the original study report (D'Acremont *et al.*, 2014). A SBI was identified in 16% (162/1005) of patients in the validation dataset. Table 8 shows the prevalence and overlap of the different SBI categories.

Table 7A Clinical and laboratory prediction rules for management of acute febrile illnesses in children*

Name of Prediction Rule	Age Group	Predictors																Derivation study
All serious infections																		
Yale Observation Scale	<24m	Quality of Cry		Reaction to parents' stimulation		State Variation		Color		Hydration		Response to social overtures						Mccarthy *et al.*, 1982
		Strong OR not crying(1) Whimpering (3) Weak (5)		Cries briefly (1) Cries on/off (3) Continual cry (5)		Stays awake (1) Awakes with stimulation (3) Falls to sleep (5)		Pink (1) Pale extremities (3) Pale OR cyanotic (5)		Skin normal (1) Dry mouth (3) Skin doughy (5)		Smiles OR Alert (1) Brief smile OR alerts briefly (3) No smile OR face anxious (5)						
		Sum of all six feature values (cut-offs used in literature: 8, 9 or 10)																
Five Stage Decision Tree	0-16 y	Clinician instinct that something is wrong		Dyspnea		Temperature > 39.95°C		Diarrhea				Age 15-25m						Van den Bruel *et al.*, 2007
		No Yes or unknown	0 1	No or unknown 0 Yes 1		No Yes	0 1	No or unknown Yes	0 1			No or unknown Yes	0 1					
		If yes to any of these five features																
Bleeker	<36m	Duration fever Days (points)		H/o vomiting		Ill appearance		Chest wall retractions+ tachypnea		Poor peripheral circulation		WBC		CRP (mg/l)		Urine WBC		Bleeker *et al.*, 2007
		0.5 (0), 1(2), 1.5 (4),2-2.5(5), 3-3.5(6), 4-4.5(7), 5-6(8), 6.5-8.5(9), ≥ 9(10)		Y=5		Y=4		Y=12		Y=7		<10(0), 10-19(2), 20-29(4), 30-39(6), ≥ 40(8)		Divide value by 10 and round to lower integer, max.=16 points		≥ 70 WBC/µl =9		
		Total points, described cutoffs: clinical: 10, lab: 8																
Thayyil	1-36m	PCT (ng/ml)				CRP (mg/l)						WBC						Thayyil *et al.*, 2005
		>2				>50						>15						
		Cutoff: All positive																
Lab Score	7d-36m	PCT (ng/ml)				CRP (mg/l)						Urine Dipstick						Lacour, Zamora and Gervaix, 2008
		<0.5 (0), ≥0.5 (2), ≥2 (4)				<40 (0), 40-99 (2), ≥100 (4)						Positive leucocyte or nitrite						
		Cutoff: 3																
AUS fever model	0-5 y	General appearance, cough, temperature, breathing difficulty, abnormal chest sounds, chronic disease, capillary refill time, urinary symptoms, respiratory rate, chest crackles, pneumococcal vaccine, heart rate, felt hot, meningococcal vaccine, infectious contacts, crying, fluid intake, respiratory symptoms, diarrhea, bulging fontanelle, male, focal bacterial infection, abnormal ear, nose, and throat signs, age rash, stridor, wheeze																Craig *et al.*, 2010
		Model risk estimate																

Name of Prediction Rule	Age Group	Predictors								Derivation study
SBI risk score	1m-15y	Developmental delay	Infection risk factor	State variation	T (°C)	CRT	Hydration	Tachypnea*	Hypoxia	(Brent *et al*., 2011)
		No (0) Yes (4)	No (0), Yes (2)	Eyes open (0) Eyes close briefly (1) Falls asleep (2)	<37.5 (0), 37.5 – 38.3 (1) ≥38.4 (2)	<2 (0) ≥2 (2)	Well hydrated (0) Dry mucous membranes (2) Reduced skin turgor (4)	No (0) Yes (1)	No (0) Mild (1) Severe (2)	
Rotterdam Fever model	1m-16y	Age<1, Sex, Duration of Fever, Height of Fever, Tachypnea, Tachycardia, SaO2<94%, CRT >3sec, Chest Wall retraction, Ill-appearance, CRP								(Nijman *et al*., 2013)
		Model risk estimate								
Pneumonia										
Pneumonia Rule n°1	0-16 y	Parental concern illness is different				Shortness of breath				(Van den Bruel *et al*., 2007)
Values		If yes to any of these two features								
Pneumonia Rule n°2	0-21y	SaO2	Triage T	Wheeze	Decreased breath sounds		Focal rales	Chest pain	History of fever	(Neuman *et al*., 2011)
Values		Classification of Regression Tree/ clinical model								
Pneumonia Rule n°3	1-16y	Grunting	Cough		Rales		Decreased breath sound	Vomiting		(Bilkis *et al*., 2010)
		Model risk estimate								

Table 7B: Guidelines for management of acute febrile illnesses in children*

Name of guideline	Age Group	Clinical and laboratory features				Publication
IMCI	2m-5y	CNS	Hydration/ nutrition	Respiratory	Other	
Danger signs		- Lethargic or unconscious -h/o convulsions or currently seizing -stiff neck	- Vomits everything -Unable to drink/ breastfeed -Severe malnutrition AND medical complications OR feeding issue -Severe dehydration (Two of the following) --Lethargic or unconcious --Sunken eyes --Not able to drink or drinking poorly --Reduced skin turgor	- Stridor in a calm child -SaO2 <90% on RA (if available) -Chest indrawing and HIV positive	-Tender swelling behind ear -Severe palmar pallor -Severe complicated measles	(World Health Organization, 2014)
Indications for antibiotic treatment			-Uncomplicated severe malnutrition	-Cough and tachypnea and/or chest indrawing after trial of bronchodilator (2-12m: RR >50/min; ≥12m: RR> 40/min)	-Ear pain or ear discharge <14 days -Blood in stool	
	If yes to any of the danger signs: referral and IM antibiotics If yes to any of the antibiotic signs: oral antibiotic treatment					
iCCM	2m-5y	CNS	Hydration/ nutrition	Respiratory	Other	

Danger signs	- Lethargic or unconscious -h/o convulsions or currently seizing	-Vomits everything -Unable to drink/ breastfeed -Severe malnutrition (low MUAC or bilateral edema)	-Chest indrawing	-HIV positive -Blood in stool	(World Health Organization, 2014)
Indications for antibiotic treatment			-Cough and tachypnea (2-12m: RR>50/min; ≥12m: >40/min)		
	If yes to any of the antibiotic signs; oral antibiotic treatment If yes to any of the danger signs: referral and oral antibiotics				

Name of guideline	**Age Group**	**Clinical and laboratory features**					**Publication**
ALMANACH	2m-5y	CNS	Hydration/ nutrition	Respiratory	Other		
Danger signs		- Lethargic or unconscious -h/o convulsions or currently seizing -stiff neck	-Vomits everything -Unable to drink/ breastfeed -Severe wasting -Severe dehydration (Two of the following) --Lethargic or unconscious --Sunken eyes --Not able to drink or drinking poorly --Reduced skin turgor	-Chest indrawing -Stridor in a calm child -Cyanosis	-Tender swelling behind ear -Severe pallor -Jaundice -Severe soft tissue infection		(Rambaud-Althaus, Shao, *et al*., 2015)
Indications for antibiotic treatment				Cough and RR > 50/min	Acute ear discharge Blood in stool Urine dipstick (Positive leucocyte or nitrite) Abdominal tenderness		
		If yes to any of the antibiotic signs; oral antibiotic treatment If yes to any of the danger signs: referral and IM antibiotics					
NICE traffic light system	<5y	Colour	Activity	Respiratory	Circulation and Hydration	Other	(National Institute of Health and Care Excellence, 2013)

Red- high risk		- Pale/mottled/ Ashen/blue	-No response to social cues -Appears ill to healthcare professional -Does not wake or if roused does not stay awake -Weak high-pitched or continuous cry	- Grunting - RR>60/min - Moderate/severe chest indrawing	- Reduced skin turgor	- Age 0-3m & T≥38°C - Non-blanching rash - Bulging fontanelle - Neck stiffness - Status epilepticus - Focal neurological signs - Focal seizures	
Amber- intermediate risk		- Pallor	- Not responding normally to social cues - Wakes only with prolonged stimulation - Decreased activity - No smile	- Nasal flaring - Tachypnea (6-12m: RR>50/min; >12m: > 40/min) - SaO2≤ 95% - Crackles	-Tachycardia(<12m: >160bpm; 12-24m: >150bpm; 2-5y: >140bpm)- Dry mucous membranes - Poor feeding in infants - CRT≥ 3 seconds - Reduced urine output	- fever ≥5 days - swelling of a limb or joint - non-weight bearing limb/not using extremity - age 3-6m, T≥39°C	
Values		If yes to any of these 5 categories, each scoring 2 to 13 features					
American Academy of Emergency Physicians Guidelines	3-36 m	Ill appearing	Positive chest radiography (to be obtained if:T≥39°Cand WBC >20K/mm3 or “clinical evidence of lower respiratory infection”		Positive urine leucocyte + nitrite (to be obtained in male <1 year and female <2 year)	T≥39°C And WBC>15K/mm3	(American College of Emergency Physicians Clinical Policies Committee, 2003)
Values		If yes to any of these features					

***Modified and appended from Verbakel** et al., 2013, ** Advanced pediatric life support cutoff, beats per minute (bpm), capillary refill time (CRT), C-reactive protein (CRP), history of (h/o), months (m), oxygen saturation (SaO2), procalcitonin (PCT), respiratory rate (RR), body temperature (T), yes (Y), years (y), white blood cell count (WBC)

Table 8 Cross table of serious bacterial infection (SBI) categories

	SBI categories, % (n), N=1005								
	Meningitis	Pneumonia	Bacteremia	UTI	Typhoid	Cellulitis/ Abscess	Bacterial gastroenteritis	Leptospirosis	Intracellular bacteria
Meningitis	**2 (0.2)**	**0**	0	0	0	0	0	0	0
Pneumonia		**3.1 (31)**	0	0	0.4 (4)	0	0	0	0
Bacteremia*			**1.7 (18)**	0.4 (4)	0.4 (4)	0	1 (0.1)	0	0
UTI				**5.9 (59)**	0.1 (1)	0	0	0	0
Typhoid					**3.7 (37)**	0	0.2 (2)	0	0
Cellulitis/ Abscess						**0.5 (5)**	0	0	0
Bacterial gastroenteritis							**1.4 (14)**	0	0
Leptospirosis								**0.4 (4)**	0
Intracellular bacteria									**1.1 (11)**

Validation results

The diagnostic accuracy for all included prediction rules and guidelines was low to moderate (Table 9). The Bleeker rule, Rotterdam Fever Model (2.5% risk cutoff), and NICE guidelines had the highest sensitivity, ranging from 77.3% to 83.7%. However, the specificity of the Bleeker score was only 40.8% (95% CI 36.9%-44.9%), and those of the Rotterdam Fever Model (2.5% risk cutoff), and NICE guidelines even lower: 35.6% (95% CI 32.4%-39.0%) and 25.2% (95% CI 22.6%-28.6%), respectively. IMCI (like iCCM) had a very low sensitivity of 37.0% (95% CI 29.4%-44.6%) and a moderate specificity of 70.3% (95% CI 67.1%-73.4%). Compared to IMCI, ALMANACH had a higher sensitivity of 63.3% (55.4%-70.6%). However, ALMANACH's specificity was lower compared to IMCI (63.2%, 95% CI 59.8%-66.4%). None of the scores had LRs that would be considered helpful for ruling in or ruling-out SBI in low-prevalence settings (LR+ greater 5 or LR- lower than 0.2, Oostenbrink *et al.*, 2012).

Table 9 results of external validation of prediction rules and guidelines to rule-in and rule-out serious bacterial infection

Prediction rule/guideline	n/N*	%test positive	% sensitivity (95% CI)	% specificity (95% CI)	Likelihood ratio (95% CI)	
					positive	negative
Bleeker	126/731	62.9%	81.0 (73.0-87.4)	40.8 (36.9-44.9)	1.37 (1.23-1.52)	0.47 (0.32-0.68)
Thayyil	162/1001	5.2%	31.7 (24.7-39.4)	74.4 (71.3-77.4)	1.24 (0.96-1.60)	0.92 (0.82-1.03)
Lab Score	126/731	68.3%	70.6 (61.9-78.4)	32.2 (28.5-36.1)	1.04 (0.92-1.18)	0.91 (0.68-1.22)
Rotterdam fever model						
2.5% risk	161/985	66.50%	77.3 (70.1-83.5)	35.6 (32.4-39.0)	1.21 (1.10-1.32)	0.64 (0.47-0.86)
5% risk	161/985	55.53%	69.9 (62.3-76.9)	47.3 (43.9-50.8)	1.33 (1.18-1.50)	0.64 (0.50-0.81)
15% risk	161/985	36.24%	49.7 (41.8-57.6)	66.4 (63.1-69.6)	1.48 (1.23-1.78)	0.76 (0.65-0.89)
IMCI	164/1005	30.8%	36.7 (29.4-44.6)	70.3 (67.1-73.4)	1.22 (0.97-1.55)	0.90 (0.79-1.02)
iCCM	164/1005	30.5%	36.7 (29.4-44.6)	70.7 (67.5-73.7)	1.25 (1.00-1.57)	0.89 (0.79-1.01)
ALMANACH	164/1005	44.3%	63.3 (55.4-70.6)	63.2 (59.8-66.4)	1.72 (1.48-1.99)	0.58 (0.47-0.71)
NICE	164/1005	76.0%	83.7 (77.2-89.0)	25.5 (22.6-28.6)	1.12 (1.04-1.22)	0.64 (0.44-0.92)
AAEP	164/1005	41.7%	68.1 (60.4-75.1)	63.5 (60.2-66.8)	1.87 (1.63-2.14)	0.50 (0.40-0.63)

*Number of children with SBI out of all children included into validation.

Figure 13 illustrates the overlap between SBI classification (reference) and antibiotic treatment classifications by the algorithm or rule. The Bleeker score and NICE guideline achieved the highest proportion of correct classifications (14% of the total population) but at the expense of many unnecessary antibiotic prescriptions: 49% and 69% of patients, respectively. IMCI, iCCM and the Thavyil score resulted in the lowest proportion of correct classifications (6% of patients).

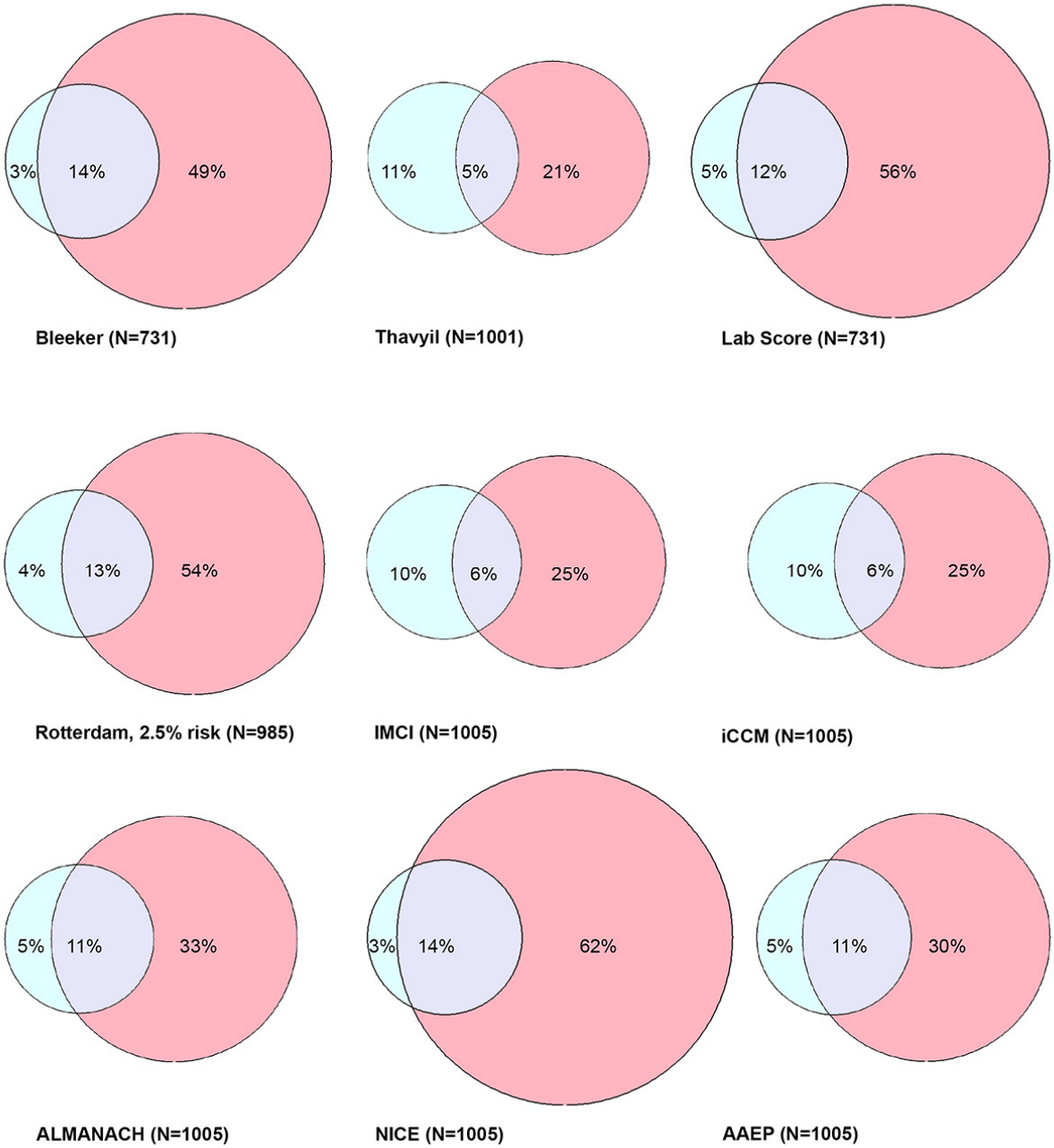

Figure 13 Overlap of serious bacterial infection classification (blue) and antibiotic treatment classification per rule or guideline (pink).

Figure 14 shows the missed cases of SBI according to different classifications. Not surprisingly, IMCI , iCCM, and AAEP missed very few pneumonia cases since the classifications used by these guidelines were part of the outcome definition (see sensitivity analysis). Similarly, missed UTI cases were fewer in scores that use urine laboratory testing. All rules and guidelines, besides the Rotterdam model at low cutoff and the NICE guideline, missed a large amount of patients with bacteremia (50%-75% of bacteremia cases).

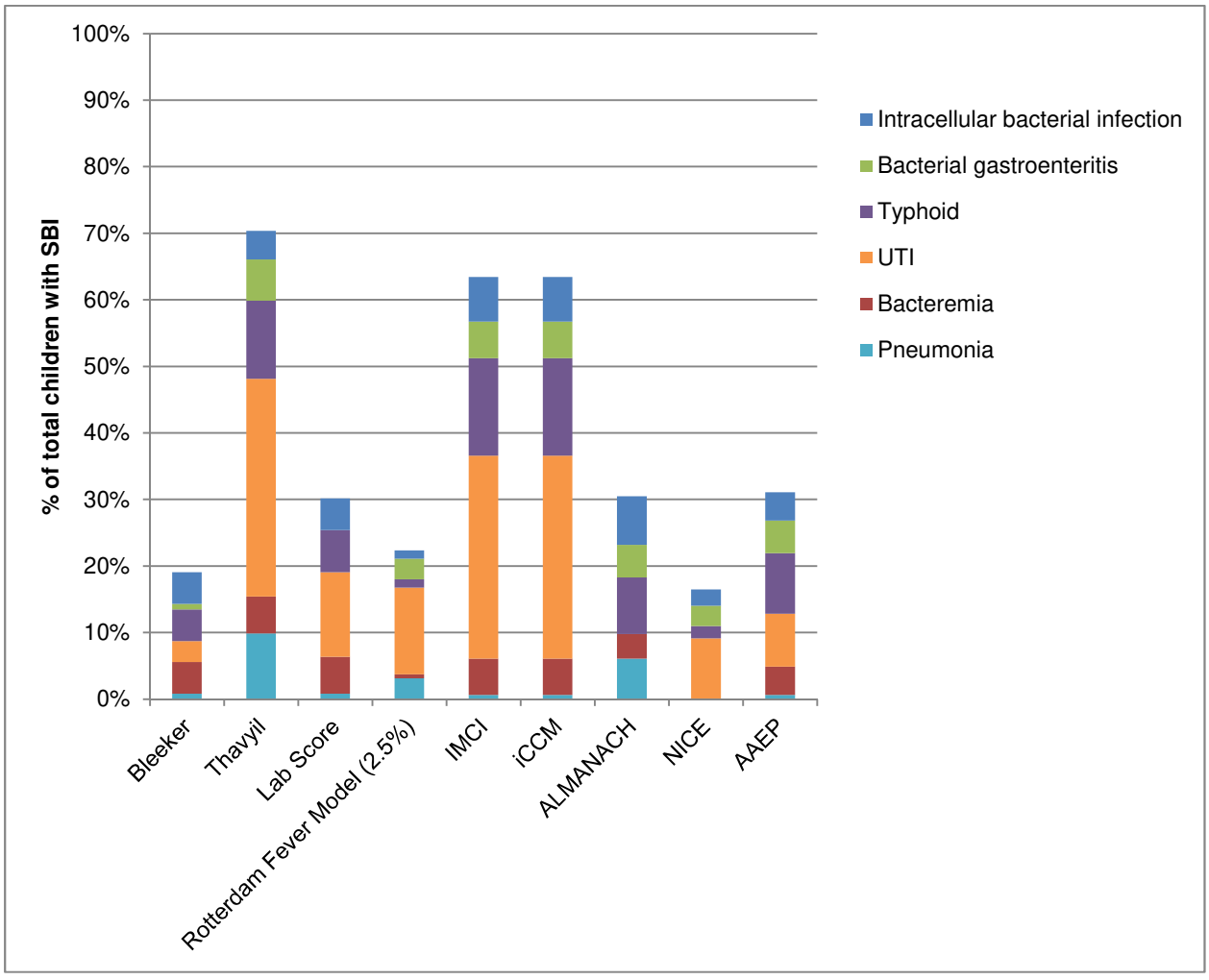

Figure 14 Missed cases of serious bacterial infections (SBI)

Sensitivity analysis

Applying the rule only to the age group for which it was originally designed, resulted in a significantly higher specificity for the Bleeker rule, Thavyil score, Lab Score and AAEP guideline (Appendix 2). The sensitivity of the Thavyil score was reduced. We found similar results for relevant scores when including patients without pneumonia or without malaria only, when compared to the full validation dataset (Appendix 2). The specificity of

ALMANACH was increased when applying to patients without UTI only otherwise we noted no significant differences in diagnostic accuracy.

6.5. Discussion

In the outpatient setting in Tanzania, none of the prediction rules and guidelines examined had sufficient diagnostic accuracy to detect children with SBI. IMCI and iCCM, which were designed to be sensitive for detecting SBI in these settings, actually had very low sensitivities when applied to our validation dataset. The Bleeker score, NICE guidelines, and Rotterdam Model at low cutoff showed the highest, though moderate, sensitivity, indicating a value in ruling-out children for SBI in low-prevalence, peripheral health care settings. However, at the same time, they classified many children as having a SBI, i.e. requiring antibiotic treatment. The use of such rules or guidelines would hence require further confirmatory testing to avoid antibiotic over-prescription. Rules that use a combination of clinical and laboratory testing, the Bleeker score, Rotterdam Model, ALMANACH, and AAEP guideline had better performance compared to rules and guidelines using only clinical and or laboratory elements.

This study has several limitations. Only a single dataset from one country was available for validation, which limits the generalizability of our findings. There are multiple sources of heterogeneity. The most obvious one is the difference in setting for all prediction rules and two out of the four guidelines. Difference in bacterial pathogens, such as typhoid and rickettsial diseases, substantially limits the applicability of “Northern” guidelines to tropical settings. In addition, the presence of co-factors affecting the overall inflammatory state, such as malaria and sickle cell disease, may lead to different clinical presentation and laboratory values. Variation in recorded values is another major limitation for this analysis. Other sources of heterogeneity include differences in inclusion criteria and immunization coverage. Though this study used robust, predefined reference criteria with extensive microbiological testing, the gold standards for SBI certainly remain imperfect. For pneumonia end-point consolidation on CXR has been used though it is known that only an (unknown) percentage of consolidations are of bacterial origin (Lynch *et al.*, 2010). The diagnostic accuracy of all available tests for typhoid is poor (Crump *et al.*, 2015) and hence the typhoid classification in this cohort, even if based on a combination of rapid test and blood and stool cultures, was certainly suboptimal. Bag urine collection was used in the validation cohort, which certainly resulted in a number of false positive UTI diagnoses (Roberts, 2011). Despite the comprehensive collection of clinical and laboratory predictors in the validation dataset, we were able to validate only four of the nine prediction rules plus all guidelines. We had to use

proxies for several predictors. For the Bleeker score, for example, “ill-appearance” was likely underestimated in our validation dataset since the variables “lethargy, and very sick child” refer to a sicker child. On the other hand, using the urine leucocyte dipstick test instead of the urine WBC likely overestimated the presence of UTI.

To our knowledge, this was the first comprehensive attempt to examine the accuracy of IMCI and other prediction rules and guidelines in diagnosing SBI in a tropical, low-resource outpatient setting against a robust gold standard. Besides one 1995 study in Bangladesh that performed blood cultures and CXR (Factor *et al.*, 2001), guidelines developed for low-resource-settings (IMCI, iCCM, ALMANACH) have never been validated against carefully established gold standards (contrary to expert opinion). During its development, IMCI was validated against pediatrician’s diagnosis among 440 children in the Gambia(Weber *et al.*, 1997). Pneumonia was the only SBI included; the reported sensitivity and specificity were 81% and 89%. Similarly to our study, the higher diagnostic accuracy for this subgroup of patients may have resulted from the fact that similar criteria (respiratory rate) were used both as predictors and to establish the reference standard. Investigations for other SBI, such as bacteremia and UTI were not performed in the Gambian validation study. Overall guidance for SBI other than pneumonia and dysentery are lacking in the current IMCI guidelines, which specifies only “to give antibiotic treatment if a bacterial source of infection is identified”. But identifying such bacterial infections without guidance is challenging for low-level health workers. Alarmingly, the sensitivity of IMCI was very low—IMCI was originally designed to be very sensitive at the expense of being specific for detection of infections requiring antibiotic treatment. The diagnostic accuracy of ALMANACH sought to address these challenges through adding urinary dipstick testing and a clinical predictor for typhoid (Rambaud-Althaus, Shao, *et al.*, 2015). Indeed, sensitivity was improved but at the cost of a lower specificity in our dataset. Generally, very few studies have validated outpatient prediction rules and clinical guidelines for SBI systematically. One recent study validated systematically four clinical prediction rules and two national guidelines retrospectively across datasets from primary care and emergency departments in Europe (Verbakel *et al.*, 2013). The diagnostic accuracy of the prediction rules and guidelines also validated in our study were generally higher. This may be due to the fact that the original derivation population was more similar to the validation datasets of the European validation study. Other studies in the African setting have evaluated scores for SBI and death at the inpatient level. Nadjm et al. evaluated prospectively the accuracy of WHO hospital-level clinical criteria for presumptive antibiotic treatment in detecting SBI (positive blood and/or cerebrospinal fluid culture) among 3,639 admitted children in Tanzania (Nadjm *et al.*, 2010). The sensitivity was higher when compared to IMCI in our study (67.4%, 95% CI 65.9%-69.0%), at a lower specificity of 51.5% (95% CI 49.9% -53.1%). Reported sensitivities of a similar study by Berkley at al.

were even higher (Berkley, Maitland, *et al.*, 2005). However, the comparison of results from these studies with the present analysis is extremely limited by the difference in prevalence of SBI in the inpatient versus outpatient setting, and the restricted number of investigations for SBI performed (blood and cerebrospinal fluid culture only). Conroy et al. validated three scores to predict in-hospital (and not outpatient) mortality among Ugandan children with fever (Conroy *et al.*, 2015). Through mortality is a relevant and robust outcome, its use at the outpatient level, where death is a rare event, is difficult.

Our findings have several implications for clinical practice and research in low-resource settings. First, the efforts should be made to increase the sensitivity of current screening tools for SBI. With the increasing availability of vaccines, the overall prevalence of SBI will likely decrease further. Simple but sensitive clinical criteria will be needed to quickly rule-out children with SBI. Such an approach would have to be complemented with second-stage laboratory testing, such as point-of-care biomarkers, in order to avoid unnecessary antibiotic treatment. Second, in resource-poor settings with high-volume of patients and limited clinical skills and diagnostics, clinicians will continue to rely on case management algorithms. No algorithm will have perfect diagnostic accuracy making safety netting (follow-up) an important component of clinical care. Third, disease management algorithms should undergo careful external validation before implementation. Ideally, such validation studies should be performed against clinical outcome, and not against a microbiological gold standard only. Validation studies are limited by the imperfect gold standards for SBI. In addition, viral infections, such as bronchiolitis, may cause severe disease. The guidance on supportive measures for viral infections by a clinical algorithm designed for the low-resource outpatient setting may be become equally important with declining prevalence of SBI. ALMANACH, for example, achieved better clinical outcome in a validation study against routine care in Tanzania (Shao *et al.*, 2015).

6.6. Conclusions

None of the examined prediction rules and guidelines had sufficient diagnostic accuracy to detect children with SBI in a tropical, low-resource setting. IMCI and iCCM, which were designed to be sensitive for detecting SBI in these settings, actually had very low sensitivities when applied to our validation dataset. Some prediction rules and guidelines had higher sensitivity and hence showed promise to rule-out SBI in our dataset. However, they also classified a larger number of patients as having a SBI, calling for additional second-stage testing, such as point-of care inflammatory markers, and tests for severity such as oximetry and hemoglobin. New clinical algorithms should undergo careful external validation studies against clinical outcome before implementation in routine care.

7. A novel electronic algorithm using host biomarker point-of-care-tests for the management of febrile illnesses in Tanzanian children (e-POCT): a randomized, controlled, non-inferiority trial

Point-of-care technologies to improve management of febrile illnesses in children

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7.1. Abstract

Background

The management of childhood infections remains inadequate in resource-limited countries, resulting in high mortality and irrational use of antimicrobials. Current disease management tools, such as the Integrated Management of Childhood Illness (IMCI) algorithm, rely solely on clinical signs and have not made use of available point-of-care tests that can help to identify children with severe infections and children in need for antibiotic treatment. e-POCT is a novel electronic algorithm based on current evidence of pediatric febrile illness management. It guides through the entire consultation and recommends treatment based on a few clinical signs and point-of-care test results (C-reactive protein, procalcitonin, hemoglobin, oximeter, glucometer, malaria rapid diagnostic test). The objective was to determine whether the clinical outcome of febrile children managed by the e-POCT tool was non-inferior to a validated electronic algorithm derived from IMCI (ALMANACH) while reducing the proportion of antibiotic prescription.

Methods and Findings

We performed a randomized (at patient level), controlled non-inferiority study among children aged 2-59 months presenting with acute febrile illness to 9 outpatient clinics in Dar es Salaam, Tanzania. The primary outcome was the proportion of clinical failure by day 7 of follow-up. The secondary outcomes were the proportion of antibiotics prescribed on day 0 and severe adverse events by day 30 (secondary hospitalizations and deaths). We enrolled 3192 patients between December 2014 and February 2016. 3169 patients (e-POCT: 1586; control: 1583) completed the intervention and day 7 follow-up. Using e-POCT, the absolute proportion of clinical failure by day 7 was reduced from 4.1% to 2.3% compared to the control arm (risk ratio [RR] 0.57, 95% confidence interval [CI] 0.38-0.85), and the proportion of severe adverse events from 1.5% to 0.6% (RR 0.42, 95% CI 0.20, 0.87). The proportion of antibiotic prescription was substantially lowered from 29.7% to 11.5% (RR 0.39, 95% CI 0.33, 0.45). Using e-POCT, the most common indication for antibiotic prescription were severe diseases (57%, 103/182 prescriptions); with the control algorithm non-severe respiratory infections (70%, 330/470 prescriptions).

Conclusions

e-POCT, an innovative electronic algorithm using host biomarker point-of-care tests, including C-reactive protein and procalcitonin, has the potential to improve the clinical outcome of children with febrile illnesses while reducing antibiotic use through improved identification of children with severe infections, and better targeting of children in need for antibiotic prescription. Future implementation studies should evaluate whether this effect can be sustained in routine settings.

7.2. Introduction

Febrile illnesses comprise the vast majority of pediatric outpatient consultations in resource-poor settings (Burton *et al.*, 2011). Only a small percentage of these children require antibiotic treatment or referral for hospital-based supportive care, such as oxygen therapy (Shao *et al.*, 2015). However, correct identification of this minority of children is pivotal; sub-standard management of children with infections has led to two major public health challenges. First, persistent high mortality from common childhood infections (Liu *et al.*, 2014); second, the tremendous over-prescription of antibiotics at peripheral health care level (Risk *et al.*, 2013), which contributes to spreading antimicrobial resistance (Okeke *et al.*, 2005).

Though common, the management of childhood infections requires integration of a multitude of information such as epidemiological, demographic, clinical, and laboratory data. It also necessitates the consideration of multiple diagnoses at once, as children will often present with several concurrent complaints and symptoms (Horwood *et al.*, 2011). Such an integrated approach for the classification and treatment of childhood infections is reflected in the current World Health Organization (WHO) strategy, Integrated Management of Childhood Illnesses (IMCI, World Health Organization, 2014). Though a positive impact on child mortality could be shown (Gera *et al.*, 2016), its implementation has faced major challenges through a spectrum of obstacles within the health system, from the macro (policy) to the micro (patient-provider interaction) level. At the micro level the cornerstone of the IMCI strategy remains a set of paper-based algorithms that recommends presumptive treatment based on clinical signs and symptoms (besides the rapid diagnostic test for malaria [mRDT] that was introduced in the 2014 version, World Health Organization, 2014). Adherence to the IMCI guidelines is low across geographical settings (Arifeen *et al.*, 2005; Horwood *et al.*, 2009; Baiden *et al.*, 2011). Electronic IMCI versions (e-IMCI) provide a user-friendlier format and may thereby increase algorithm adherence and the consistency of clinical assessments (Mitchell *et al.*, 2013; Shao *et al.*, 2015). Beyond e-IMCI, electronic algorithms also have the potential to integrate more complex information while maintaining a simple user interface.

In addition to format-related barriers, IMCI implementation also faces content-related challenges. First, the algorithm lacks guidance for a significant proportion of febrile children, such as children without localizing symptoms (fever without source [FWS]). For such children, IMCI instructs to “give appropriate antibiotic treatment for an identified bacterial cause of fever” but provides no guidance on how to identify a bacterial cause of fever (World Health Organization, 2014). Before introduction of mRDT-based treatment, IMCI classified all children with fever presumptively as having malaria. Now that mRDTs are used, and lacking adequate diagnostics for bacterial infections, clinicians have practically exchanged antimalarial against non-selective antibiotic treatment for patients with negative mRDTs (D’Acremont *et al.*, 2011). This has led to a tremendous overuse of antibiotics at the peripheral level (Risk *et al.*, 2013). To address this challenge of diagnosing bacterial infections in children with FWS, a revised, IMCI-based algorithm was developed (ALMANACH). It includes urine dipstick testing and a clinical predictor or rapid test for typhoid (Rambaud-Althaus, Shao, *et al.*, 2015). However, these two diseases only represent a fraction of bacterial infections that would need to be considered (D’Acremont *et al.*, 2014). Second, the IMCI algorithm relies on clinical symptoms alone which inherently lack diagnostic accuracy in detecting children in need for antibiotic treatment or referral for hospital-based supportive care (Thompson *et al.*, 2012, Chapter 5). Host biomarkers, that can help identify children with bacterial infections, such as C-reactive protein (CRP) and procalcitonin (PCT), have not been considered within the IMCI strategy (Van den Bruel *et al.*, 2011). The safety of using CRP or PCT cutoffs to decide on antibiotic prescription in children has never been evaluated. Besides the one trial in Vietnam that evaluated CRP for the use of CRP without provision of clinical guidance to guide antibiotic prescription in mild respiratory infections (Do *et al.*, 2016), all studies of CRP and PCT in children have focused on analytical performance; none have assessed whether using these tests would change patient outcome. Furthermore, some point-of-care tests (POCTs) may help detect children with severe symptoms where clinical signs lack diagnostics accuracy: for example hemoglobin (Hb) testing can detect children with severe anemia in need of blood transfusions. Lastly, the diagnostic value of clinical signs that were included into IMCI (based on expert opinion and small derivation studies) has changed. The epidemiology context of infections has indeed shifted away from bacterial and parasitic infections towards viral infections (D’Acremont *et al.*, 2014). Additionally, since development of IMCI 30 years ago, a considerable amount of novel evidence on such clinical signs has emerged, which has not been integrated into IMCI thus far (Thompson *et al.*, 2012).

Based on the challenges and opportunities identified we constructed a novel electronic patient management algorithm, e-POCT, onto the IMCI backbone. e-POCT is derived from the latest evidence of pediatric fever management based on studies both from low-and high-income

settings (Chapter 5). It is built into an android application, which guides the clinician through the entire consultation and recommends management based on a few clinical elements, as well as POCTs. The POCTs used aim at triaging children with severe disease who require referral to a higher level of care (oxygen saturation [SaO2], heart rate, Hb), detecting malaria infection (mRDT) and distinguishing between bacterial and viral diseases (CRP, PCT). Given the innovative approach of the algorithm, we first sought to assess its safety when applied to children presenting with febrile illnesses in a low-resource-setting. Hence, the objectives of this study were to determine whether e-POCT was non-inferior in terms of clinical outcome to a validated electronic algorithm derived from IMCI (ALMANACH) when managing febrile illness in under-fives and to compare the proportion of antibiotic prescription and severe adverse events (deaths and secondary hospitalizations) between the two arms.

7.3. Methods

Study design

This was a randomized (at patient level), open, controlled trial to investigate whether a novel, electronic algorithm using point-of-care testing (e-POCT) was not inferior in terms of clinical outcome to a validated electronic algorithm derived from IMCI (ALMANACH) when treating febrile infections in children under-five. The protocol for this trial and supporting CONSORT checklist are available as supporting information (S1 Appendix, S2 Appendix).

Ethics

The study protocol and related documents were approved by the Institutional Review Board of the Ifakara Health Institute and the National Institute for Medical Research Review Board in Tanzania, by the Ethikkommission beider Basel in Switzerland, and the Boston Children's Hospital Ethical Review Board. An independent Data Monitoring Committee oversaw the study. The trial was registered in ClinicalTrials.gov, identifier NCT02225769.

Participants

This study was conducted in the city of Dar es Salaam, Tanzania. Malaria endemicity in this region is relatively low with about 10% of fever positive for malaria; transmission is perennial with a peak in the post-rainy season [15]. Consecutive patients presenting for acute care during normal business hours at the outpatient departments of 3 district hospitals and 6 health centers in Dar es Salaam were screened for eligibility. Recruitment sites were chosen to represent the pediatric outpatient population in Dar es Salaam. Inclusion criteria were: age 2 to 59 months,

history of fever for 7 days or less and axillary temperature ≥37.5 °C at presentation. Exclusion criteria were: weight less than 2.5kg, main complaint being an injury or acute poisoning, or previous medical care for the present illness. Children satisfying the inclusion and exclusion criteria were enrolled if the parent or guardian had received full information on the study and signed written informed consent.

Randomization

Patients were enrolled by the study clinicians and then randomized to one of the two management arms. They were individually randomized in blocks of four according to a computer-generated randomization list provided by an independent, off site researcher. Sealed, opaque forms were used for allocation concealment and opened only after the patient's enrollment.

Interventions and Study Procedures

The intervention consisted in having study clinicians using the e-POCT algorithm during the consultation to manage the patient. Children enrolled in the intervention arm were assigned to study clinicians using ePOCT during 2 weeks while children enrolled in the control arm were managed by other study clinicians using ALMANACH. In order to minimize a cluster effect at clinician level, clinicians then switched arms and thus algorithms every 2 weeks. Based on their assignment enrolled children were directed either to the e-POCT or ALMANACH clinician.

The development and content of e-POCT are described elsewhere (Chapter 5). Compared to the IMCI-based algorithm (ALMANACH) used by study clinicians in the control arm, e-POCT uses fewer clinical symptoms and signs. It rather relies on signs that can be measured objectively, hypoxemia and severe tachycardia, (oximeter), severe anemia (POC hemoglobinometer), hypoglycemia (POC glucometer), as well as host biomarkers of inflammation predictive of bacterial infection (elevated CRP using a rapid semi-quantitative lateral-flow test and elevated PCT using a POC immunoassay system). The main differences between the intervention and control algorithm, as well as IMCI, are summarized in Table 6.

We chose ALMANACH, instead of the paper IMCI, as a control group, since ALMANACH is also built into an android support tool: we were interested in comparing the impact related to the content of the algorithms rather than the format and technological features. In addition, since our goal was to reduce antibiotic prescription while ensuring optimal clinical patient outcome, and since a reduction in both antibiotic prescription and clinical failures using

ALMANACH versus routine care has already been demonstrated, we regarded ALMANACH as the current gold standard in terms of antibiotic prescription and used it for the control arm [2].

POCTs were performed on site as recommended by the algorithms. mRDT testing was done for all patients using either the SD BIOLINE Malaria Ag P.f/Pan™ (Standard Diagnostics Inc.) or CareStart Malaria HRP2™ (Access Bio, Inc.) assays. According to Tanzanian national guidelines, voluntary screening for human immunodeficiency virus (HIV) antibodies using the Determine™ HIV-1/2 (Alere Inc.) was offered to all patients when HIV test kits were available at the health facilities. In the e-POCT arm, Hb measurement (HemoCue 201+™ photometer) and oximetry (NONIN XPod™ with pediatric probe) was done in all patients. Children with clinical signs of lower respiratory tract infection (LRTI, Table 6) underwent CRP testing to decide on antibiotic prescription for pneumonia. For children with FWS, the e-POCT algorithm uses combined CRP and PCT testing (Table 6). For CRP testing we used a POC semi-quantitative assay (bioNexia CRPplus™, Biomérieux). PCT values were determined on site using the B.R.A.H.M.S PCT™ assay on the miniVIDAS™ platform (Biomérieux, Thermo Scientific). Using ALMANACH, children less than 2 years with FWS underwent urine dipstick testing, as well as older children with dysuria (Table 6). Children 2 years or older with FWS were tested for typhoid using the Typhidot assay™ (Reszon Diagnostics International Sdn. Bhd. Malaysia).

Figure 15 Lab Manager performing POCTs at Rangi Tatu Health Center

Follow-up

All caregivers were asked to return with the child for scheduled visits on days 3 and 7, or at any time if the parent was concerned about the child's condition. Patients cured at day 3 were

followed-up by phone only on day 7. Field workers traced patients missing the day 7 follow-up. For admitted patients, the scheduled visits were done in the hospital. Patients not cured before day 7 were treated again per the assigned algorithm, i.e the ePOCT algorithm if they were part of the intervention arm or ALMANACH if in the control arm. Patients not cured at day 7 were treated per the clinician's judgment and another follow-up visit was performed at day 14 to assure that the child was cured. All patients were called by phone at day 30. When the algorithm recommended referral, a field worker escorted the patient to the nearest referral hospital. Patients were then admitted (or discharged home) and managed at the discretion of the responsible medical doctor in the referral hospital.

Outcomes

The primary outcome measure was the risk of clinical failure (Table 10) by day 7.

Table 10 Defintion of clinical failure by day 7 (primary outcome measure)

At any time between initial assessment and day 7:	**At day 3:**	**At day 7:**
• Severe disease: - Coma - More than 2 convulsions within 24hr - Inability to drink or breastfeed - Hypoxemia - Severe tachypnea - Severe tachycardia	• Clinical pneumonia: - History of cough and tachypnea - History of cough and lower chest indrawing • Significant dehydration	• Fever or temperature ≥38°C • Clinical pneumonia: - History of cough and tachypnea - History of cough and lower chest indrawing • Diarrhea • Significant dehydration • Serious skin infection • A new significant symptom or sign related to the acute episode but not present at day 0.

Clinicians were unaware of these criteria that were not used for patient management. To guarantee equal assessments of the primary outcome in both arms, the following additional measures were taken: Patients were considered "not cured" and treated again using the respective algorithms either i) if the caregiver considered that the child was still ill or ii) still had fever when assessed by trained field workers who did not know the content of the algorithms nor the criteria for clinical failure. The secondary outcome measures were the risk in antibiotic prescription at day 0 and by day 7, the risk of primary referrals at day 0, as well as of severe adverse events (secondary hospitalizations and death) by day 30.

Sample Size and Statistical Analyses

The sample size was computed for the primary analysis based on a 97.5% (one-sided) confidence interval (CI). To prove non-inferiority the lower limit of this CI was to be within 3%. This non-inferiority margin was considered as a clinically meaningful difference in clinical failure by day 7. The proportion of clinical failures by day 7 was estimated to be 10% in both arms

based on prior studies using ALMANACH in the same area (Shao *et al.*, 2015). Assuming 80% statistical power, 3,140 patients were needed to show that the difference in clinical failure by day 7 between e-POCT and ALMANACH arm was within 3%.

Interim analyses of the clinical failure rates were performed after inclusion of the first 200 and 1,000 patients. A stopping rule was predefined as the absolute difference in clinical failure by day 7 of more than 5%. Both intention-to-treat (ITT) and per-protocol (PP) study populations were defined. The ITT population comprised all randomized patients (and per definition, patients who were lost for follow-up were treated as clinical failures). The PP population included all randomized patients who received the intervention and completed the day 7 assessment (Figure 16).

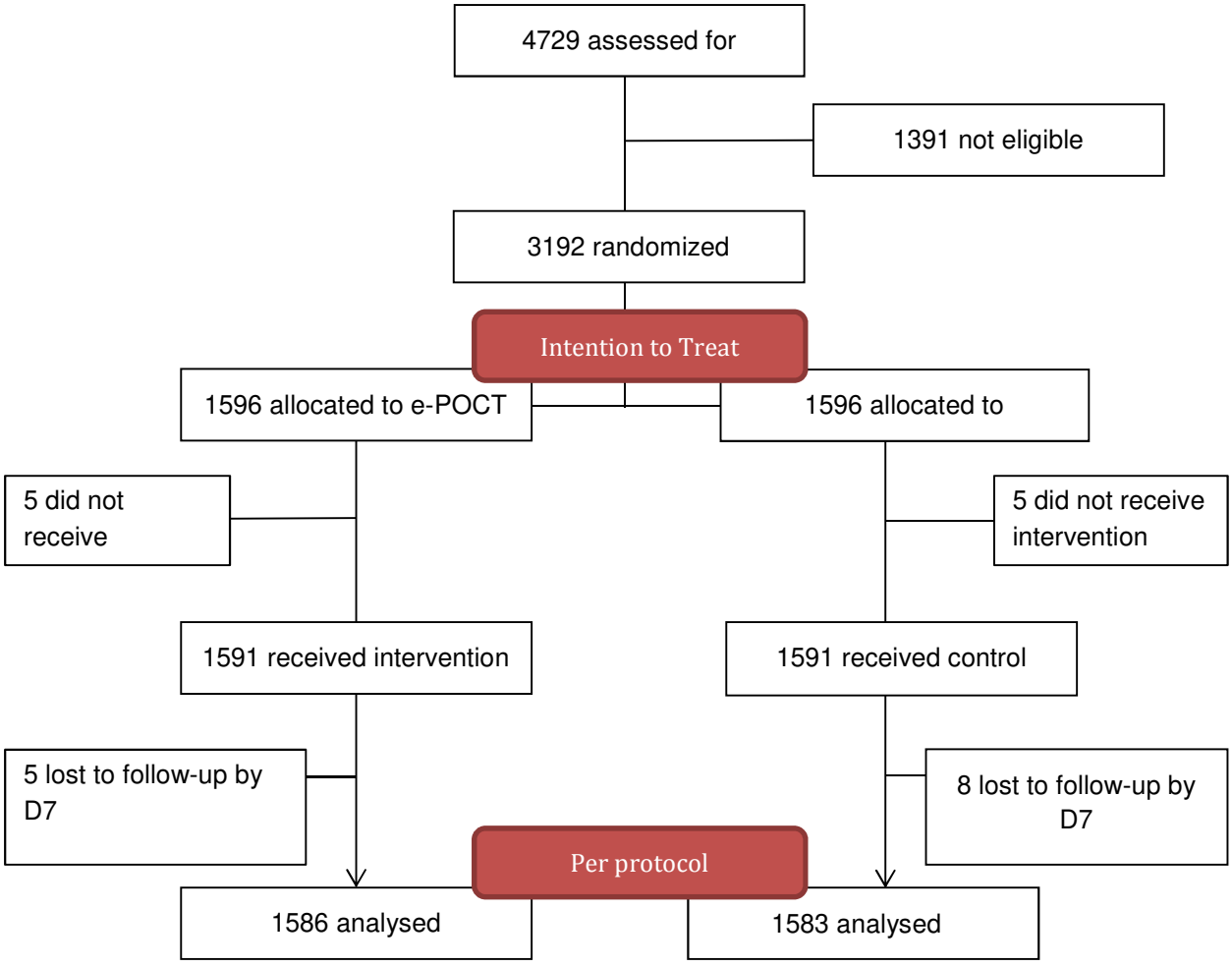


Figure 16 Patient flowchart

Since this was a non-inferiority trial, and bias towards the null would tend to favor non-inferiority, we used a PP analysis as our primary analysis. Accordingly, all results are displayed according to PP analyses if not stated otherwise. Risk difference (RD) and relative risks (RR)

with 95% CI were calculated to estimate the intervention effects on the main study outcomes. Stratified analyses with Mantel–Haenszel estimates for RR were performed to explore statistical heterogeneity of effect between health centers and clinicians (Joseph Newton *et al.*, 2009). For the primary outcome, mixed effects logistic regression was used to adjust for possible confounding covariates. Changes in odds ratio (OR) were used as approximated changes in RR since the primary outcome was rare. Kaplan-Meier survival analysis was used to compare the duration of fever between the two study arms.

7.4. Results

Recruitment and follow-up

Overall, between December 2014 to February 2016, 4729 patients were screened, and 3192 randomized (ITT population, Fig 1). Eight hundred fifty eight (27%) patients were recruited in the rainy season, 736 (23%) in the post-rainy season and the remaining 1598 (50%) in the dry season. The PP population consisted of 3169 patients (1598 in the intervention, and 1583 in the control arm): four patients in the intervention and 5 in the control group, respectively, withdrew consent after randomization. There was only one algorithm deviation in the e-POCT and none in the ALMANACH group. Five and 8 patients were lost to follow-up for the day 7 outcome assessment in the e-POCT and control arm, respectively. The day 30-phone follow-up could not be completed in 20/1586 patients (1.3%) in the e-POCT arm and 25/1583 patients (1.6%) in the control arm. In both arms follow-up intervals for the day 3 and day 7 outcome assessments were 3 (IQR 3-3, range 2-5) and 7 (IQR 7-7, range 6-12) days, respectively. Baseline characteristics did not differ between the two groups (Table 11).

Table 11 Baseline Characteristics

Characteristic	N	ePOCT n (%)	ALMANACH n (%)
Demographic			
Male Sex	3192	891 (56)	875 (55)
Age group	3192		
2 – 11 months		686 (43)	721 (45)
12 – 23 months		553 (35)	501 (32)
≥24 months		357 (22)	374 (23)
Primary caregiver other than mother	3113	64 (4)	66 (4)
Mother's highest grade of education	3106		
None		137 (9)	152 (10)
Primary		1060 (68)	1015 (65)
Post-primary		354 (23)	388 (25)
Number of children in household**	3100	2 (1-3)	2 (1-3)
Medical History			
Main reasons for consultation	3192		
Fever only		214 (13)	216 (14)
Cough		917 (57)	890 (56)
Rhinorrhea/nasal congestion		669 (42)	696 (44)
Diarrhea		313 (20)	328 (21)
Vomiting		312 (20)	286 (18)
Duration of fever	3180		
1 day or less		1004 (63)	982 (62)
2-4 days		569 (36)	591 (37)
5 days or more		16 (1)	18 (1)
Duration of cough	1827		
2 days or less		629 (68)	606 (67)
3-6 days		282 (31)	292 (32)
7 days or more		12 (1)	6 (1)
Clinical signs			
WFA z-score[$]	3189	-0.8 (1.3)	-0.7 (1.3)
WFA z-score <-3z or MUAC<11.5cm and age >6 months[$]	3189	64 (4)	50 (3)
Respiratory rate**	3180	41 (36-49)	41 (36-51)
Heart rate*	3142	145 (17)	143 (16)
Tachypnea per IMCI [$$]	3180	419 (26)	416 (26)
Severe symptom per IMCI [$$$]	3192	22 (1)	23 (1)

Numbers are displayed as % (n) if not marked otherwise: *mean (SD); **median (IQR); [$] WHO 2006 growth curve [22];
[$$] <12 months and RR≥50/min, ≥12 months and RR≥40/min; [$$$] positive meningeal signs, convulsion or history of convulsion, lethargy, severe anemia, HIV positive with chest indrawing, severe malnutrition[$] with complications

Clinical Failure and Severe Advert Events

Table 12 shows the primary and secondary study outcomes.

Table 12 Primary and secondary study outcomes

	e-POCT % (n/N)	ALMANACH % (n/N)	Risk Difference (95% CI)	Risk Ratio (95% CI)
Primary Outcome				
Clinical Failure by day 7 (PP)	2.3 (37/1586)	4.1 (65/1583)	-1.7 (-3.0, -0.5)	0.57 (0.38-0.85)
Clinical Failure by day 7 (ITT)	2.9 (47/1596)	4.9 (78/1596)	-1.9 (-3.3, -0.6)	0.60 (0.42-0.86)
Secondary Outcomes (PP)				
Primary referrals	6.6 (104/1586)	2.9 (46/1583)	3.6 (2.2, 5.1)	2.26 (1.61, 3.17)
Antibiotic prescription at day 0	11.5 (182/1586)	29.7 (470/1583)	-18.2 (-21.0, -15.5)	0.39 (0.33, 0.45)
Severe adverse events by day 30	0.6 (10/1586)	1.5 (24/1583)	-0.9 (-1.6, -0.2)	0.42 (0.20, 0.87)
Secondary admissions	0.4 (7/1586)	1.2 (19/1583)	-0.8 (-1.4, -0.1)	0.37 (0.15, 0.87)
Deaths	0.2 (3/1586)	0.4 (6/1583)	-0.2 (-0.6, 0.2)	0.50 (0.12, 2.0)

In the PP population, 2.3 % (37/1586) of patients experienced clinical failure by day 7 using e-POCT group versus 4.1% (65/1583) of patients treated with the control algorithm (RD -1.7, 95% CI -3.0, -0.5, RR 0.57 95% CI 0.38-0.85). There was a 43% reduction in relative risk for clinical failure in the e-POCT arm compared to the control arm. The non-inferiority plot of clinical failure in the ITT and PP populations is displayed in Figure 17.

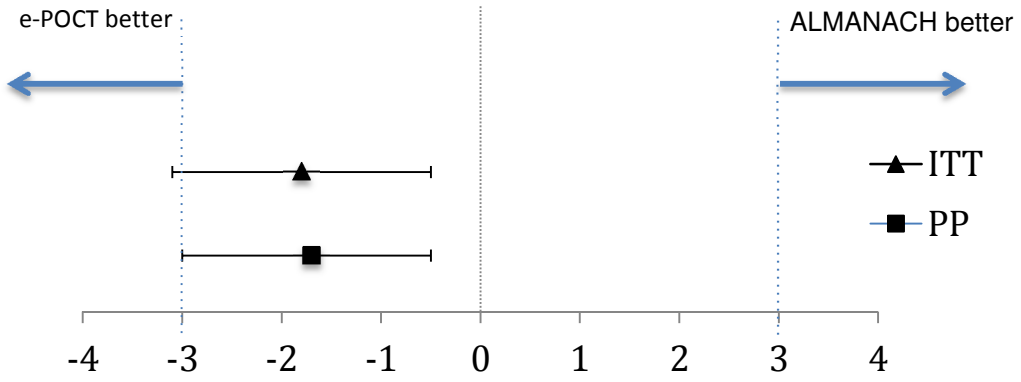


Figure 17 Non-inferiority plot comparing clinical outcome by day 7 in the intervention and control arm.

As depicted in Table 13, the main reduction in clinical failure between the two algorithms occurred by day 3 (RR 0.39, 95% CI 0.22, 0.67)—there was no significant difference in clinical failure from days 4-7 (RR 0.93, 95% CI 0.51, 1.72).

Table 13 Details of clinical failure by day 7

	e-POCT			ALMANACH		
Criteria for clinical failure	**Clinical Failure**	**Secondary Admission**	**Death**	**Clinical Failure**	**Secondary Admission**	**Death**
Day 0-3:						
Coma/convulsion	1	-	-	5	1	5
Hypoxemia/severe tachypnea	1	1	-	7	2	1
Other severe symptom	5	4	1	9	6	-
Cough and tachypnea/ chest indrawing	10	2	1	23	3	-
Total at day 0-3 % (n/N)	**1.1 (17/1586)**	**0.4 (7/1586)**	**0.1 (2/1586)**	**2.8 (44/1583)**	**0.8 (12/1583)**	**0.4 (6/1583)**
Day 4-7:						
Hypoxemia/severe tachypnea	1	-	1	-	-	-
Severe anemia	-	-	-	1	1	-
Persistent fever	13	-	-	16	5	-
Cough and tachypnea/ chest indrawing	3	-	-	2	-	-
Diarrhea/vomiting	2	-	-	1	-	-
Significant skin infection	1	-	-	1	1	-
Total at day 4-7 % (n/N)	**1.3 (20/1569)**	**0 (0/1579)**	**0.1 (1/1584)**	**1.4 (21/1539)**	**0.4 (7/1571)**	**0 (0/1577)**

The crude OR (0.56, 95% CI 0.37-0.84) for clinical failure by day 7 was similar to the adjusted OR (0.55, 95% CI 0.36-0.84) when adjusting for significant covariates and random effects (age, axillary temperature, weight for age z-score (World Health Organization, 2006), respiratory rate, clinician, and health center). We did not note statistical heterogeneity between health centers or clinicians for both primary and secondary outcome measures. There was a 68% reduction in relative risk of severe adverse events (secondary hospitalizations and deaths) in the e-POCT arm (0.6%, 10/1586) compared to the control arm (1.5%, 24/1583), (RR 0.42, 95% CI 0.20, 0.87). 0.5% (8/1586) of patients in the e-POCT arm versus 1.4% (22/1583) of children in the ALMANACH arm developed severe symptoms during follow-up (RR 0.36, 95% CI 0.16, 0.81), Table 13. Within both algorithms, having a severe classification at D0 was associated with a higher, and having a likely viral infection classification with a lower risk of clinical failure,

respectively (Table 14). Within the ALMANACH algorithm, patients with a clinical pneumonia classification also had a higher risk of clinical failure (Table 14).

Table 14 Association between clinical failure and disease classification.

	e-POCT		ALMANACH	
Algorithm classification	**Clinical failure by day 7 % (n/N)**	**RR (95% CI)**	**Clinical failure by day 7 % (n/N)**	**RR (95% CI)**
Severe disease	5.8 (6/103)	2.79 (1.19, 6.53)	23.6 (13/55)	6.9 (4.03, 11.98)
Clinical pneumonia	-		6.4 (21/330)	1.81 (1.09. 3.00)
Bacterial, respiratory infection	0 (0/10)	NA	-	
Viral, respiratory infection	3.0 (13/429)	1.46 (0.75, 2.84)	-	
Upper respiratory infection	3.1 (12/391)	1.47 (0.05, 2.89)	3.7 (20/542)	0.85 (0.51, 1.43)
Gastrointestinal disease with dehydration	2.4 (4/169)	1.02 (0.36, 2.83)	4.7 (14/296)	1.19 (0.67, 2.13)
Skin infection	2.7 (2/75)	1.13 (0.28, 4.61)	1.4 (1/69)	0.34 (0.05, 2.44)
FWS, likely bacterial infection	1.9 (1/52)	0.82 (0.11, 5.86)	4.3 (3/70)	1.05 (0.34, 3.25)
FWS, likely viral infection	0.6 (2/349)	0.20 (0.05, 0.84)	1.1 (4/357)	0.23 (0.08, 0.62)
Uncomplicated malaria	0 (0/166)	NA	2.8 (5/180)	0.65 (0.27, 1.61)
Antibiotic treatment recommended (non-severe disease)	1.3 (1/79)	0.59 (0.08, 4.29)	5.8 (24/415)	2.30 (1.35, 3.92)

Days to resolution of fever was not different between the two arms (Figure 18).

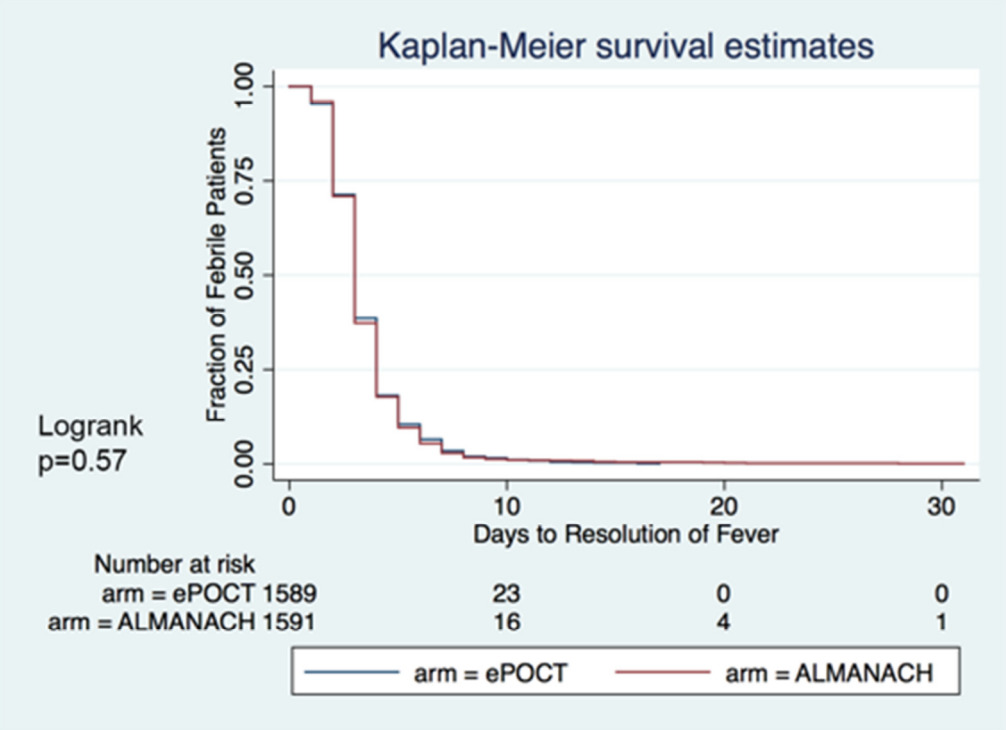


Figure 18 Days to resolution of fever

Identification of patients with severe disease at inclusion

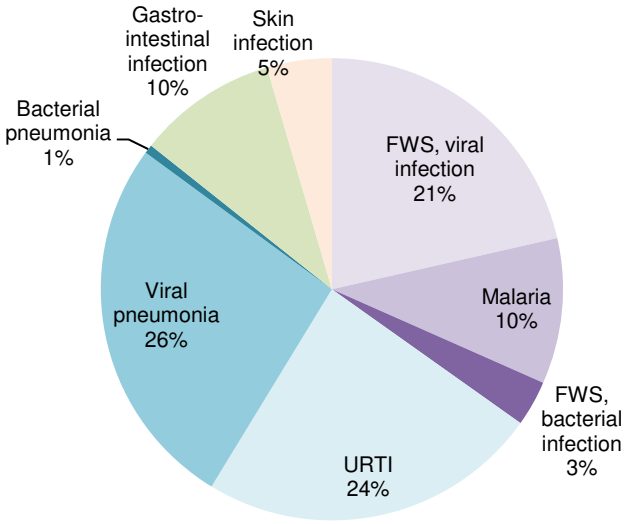
The results of the POCTs are summarized in Table 15 and the algorithm classifications in Fig 4.

Table 15 Results of point-of-care tests (POCTs)

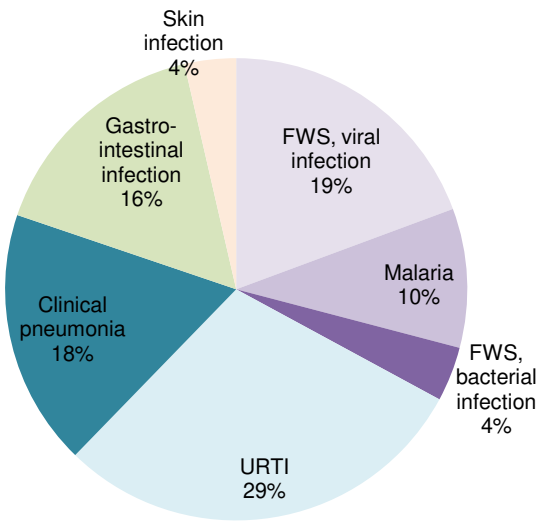
Characteristic	N	e-POCT % (n/N)	ALMANACH % (n/N)
POCTs for identification of patients with severe disease			
SaO2 <90%	1591	0.3 (4/1591)	-
Severe tachycardia	1591	0.4 (6/1591)	
Hemoglobin (g/dL)*	1591	9.7 (1.5)	-
Hemoglobin <6 g/dL	1591	1.3 (20/1591)	-
POCTs for Identification of patients in need for antibiotic treatment			
CRP (mg/L)	823		
0-9		63.4 (522/823)	-
10-39		28.4 (234/823)	-
40-79		5.8 (48/823)	-
≥80		2.3 (19/823)	-
PCT (µg/L)	407		
<0.5		70.3 (286/407)	-
0.5-0.9		8.6 (35/407)	-
1.0-1.9		5.2 (21/407)	-
2.0-3.9		3.9 (16/407)	-
≥4.0		12.0 (49/407)	-
CRP ≥80 mg/L and PCT ≥4.0 µg/L	406	0.7 (3/406)	
Positive Typhidot®, D0	152	-	0.7 (1/153)
Positive urine dipstick**	370		13.5 (50/370)
Other POCTs			
Malaria RDT positive	3182	12.0 (191/1591)	11.6 (186/1591)
HIV-1/2 antibody positive	2917	1.4 (21/1466)	1.1 (16/1451)

Numbers are displayed as % (n) if not marked otherwise: *mean (SD

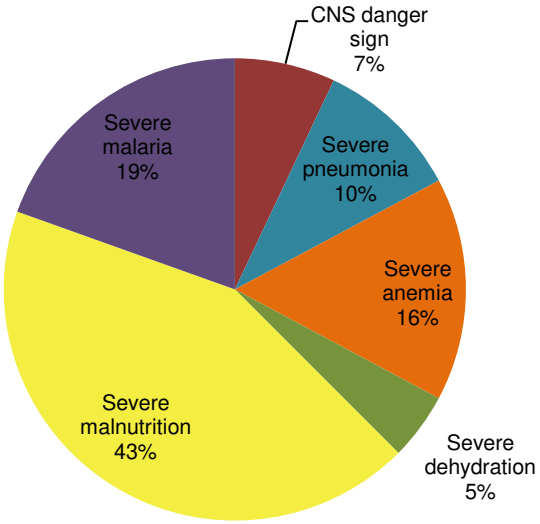
Figure 19 (next page): Algorithm classifications and reasons for antibiotic prescription at day 0. A: Non-severe classifications, e-POCT; B: Non-severe classifications, ALMANACH; C: Severe classifications, e-POCT; D: Severe classifications, ALMANACH; E: Percent of patients with antibiotic prescription at day 0 with reasons. Please note that one patient may have several disease classification



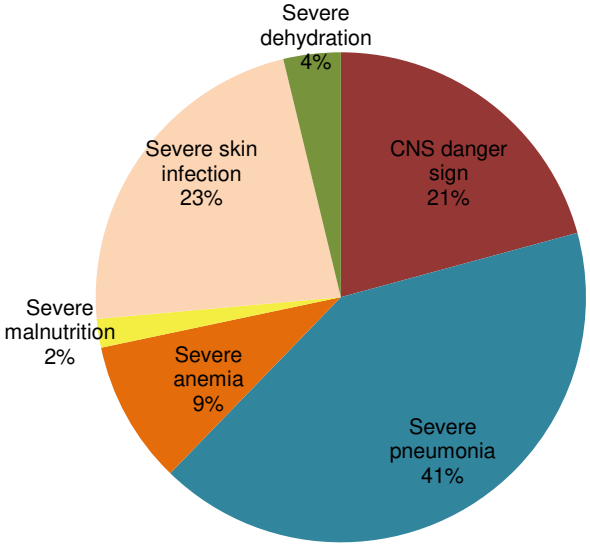
A **e-POCT 1483 patients, 1628 diagnoses**



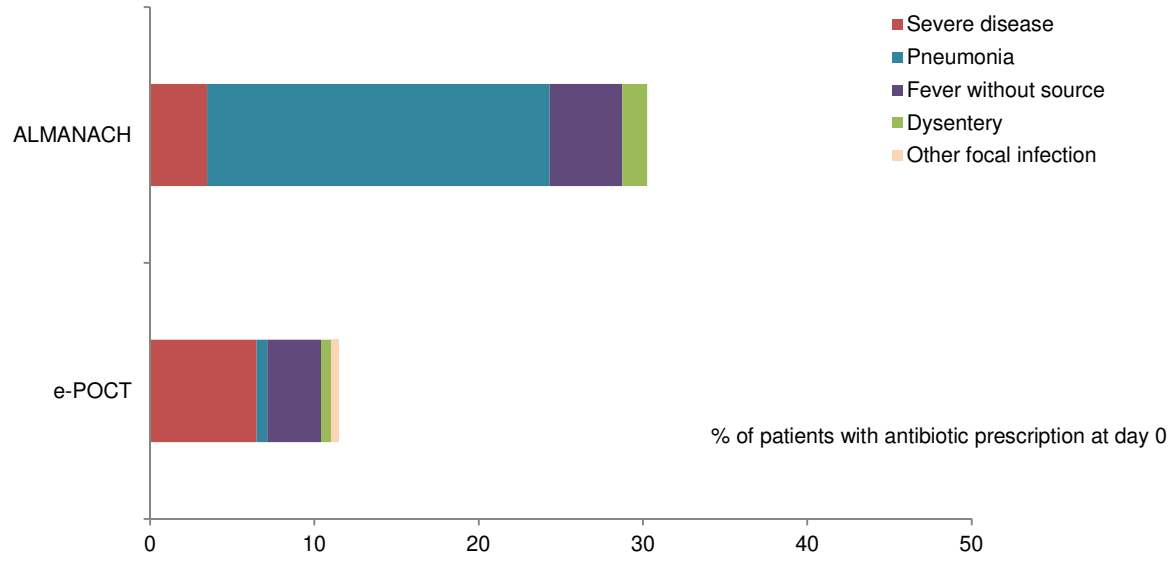
B **ALMANACH 1528 patients, 1829 diagnoses**



C **e-POCT 103 patients, 128 diagnoses**



D **ALMANACH 55 patients, 55 diagnoses**



E

Compared to the control algorithm e-POCT categorized around twice as many patients as having severe disease (and recommended referral) at day 0: 6% (103/1586) versus 3% (55/1583, Figure 19). A large proportion of this difference was attributable to the severe malnutrition and severe anemia classifications: e-POCT identified 3.5% (55/1586) of patients with severe malnutrition, ALMANACH 0.1% (1/1583), p<0.001. With e-POCT 1.3% (20/1586) were classified as severe anemia using Hb testing versus 0.3% (5/1583) based on clinical symptoms in the ALMANACH arm (p<0.003).

Antibiotic prescription

In the intervention arm, 11.5% (182/1586) participants were prescribed an antibiotic treatment at day 0 versus 29.7% (470/1583) in the control arm (RR 0.39, 95% CI 0.33, 0.45, Table 12). An additional 4% (53/1404) and 4% (49/1113) of patients who had not been prescribed an antibiotic at day 0, received antibiotics between day 1 and day 6 in the e-POCT and control arms, respectively. Out of these antibiotic prescriptions after the initial consultation, 47% (25/53) e-POCT and 65% (32/49) of ALMANACH patients received antibiotics through consultation with non-study physicians. The majority (57%, 103/182) of antibiotic prescriptions in the e-POCT arm resulted from severe classification (Figure 19). In the control arm, (non-severe) clinical pneumonia was the leading cause for antibiotic treatment (70%, 330/470) while a severe classification was the reason for 12% (55/470) of these prescriptions (Figure 19). In contrast to that, non-severe respiratory infections were the reason for only 6% (10/182) of antibiotic prescriptions in the e-POCT arm (Figure 19). Importantly, among patients with non-severe classification, antibiotic prescription was associated with clinical failure in the ALMANACH arm, but not in the e-POCT arm (Table 14).

Use of POCTs in the e-POCT arm

0.3% (4/1591) of children were detected as having hypoxemia, 0.4% (6/1591) severe tachycardia and 1.3% (20/1591) severe anemia (Table 15). Among children with non-severe signs and symptoms, 2.3% (19/1591) met the CRP cutoff criterion (≥80mg/L) for antibiotic treatment: out of the 19 children with high CRP (≥80mg/L), 53% (10) presented with respiratory symptoms and 47% (9/19) had fever without localizing signs. Another 2.9% (46/1591) of patients with fever without localizing symptoms and low CRP values had PCT values of ≥4.0 µg/L, hence met the criterion for antibiotic treatment. In sum, a total of 13% (52/401) of children with fever without localizing symptoms were classified as having a likely bacterial infection using PCT and CRP testing in e-POCT, compared to 17% (70/424) in the ALMANACH arm using clinical signs, urine dipstick testing, and a rapid typhoid diagnostic test (Figure 19). There was no statistically significant difference in the risk of clinical failure in patients without

localizing symptoms between the two arms: 0.7% (3/401) for e-POCT versus 1.4% (6/415) for ALMANACH (RR 0.52, 95% CI 0.13, 2.05).

7.5. Discussion

In this multicenter non-inferiority, randomized controlled trial including 3192 children with febrile illnesses in Dar es Salam Tanzania, we showed that e-POCT, a novel patient management algorithm using host biomarker POCTs, was non-inferior to a reference electronic IMCI-based algorithm (ALMANACH) in terms of clinical outcome. e-POCT actually achieved a reduction of 43% in the proportion of clinical failure by day 7 and of 58% in the proportion of severe adverse events compared to ALMANACH while substantially lowering the proportion of antibiotic prescription from 30% to 11%. e-POCT categorized more patients as having severe disease on day 0. Using e-POCT, the pattern of antibiotic prescription was shifted away from non-severe respiratory infections towards patients with severe disease when compared to the IMCI-based control algorithm.

Though the study was designed as a non-inferiority trial, the very low attrition rate makes a type-I error unlikely when interpreting the results towards superiority. One could argue that a superiority trial would have been more adequate from the start. However we rather opted for a non-inferiority design, since it was already been demonstrated that ALMANACH was superior in terms of clinical outcome when compared to routine care (Shao *et al.*, 2015). We hence did not expect an additional benefit in terms of clinical outcome. Rather, given the innovative features of e-POCT, we wanted to assess its safety and evaluate whether e-POCT would provide additional benefits in terms of detection of children with severe illness and reduction of antibiotic prescription compared to ALMANACH. We used an individual randomization scheme, instead of cluster randomization, since the available clusters in the study region were limited. We were concerned about bias from a strong inter-cluster correlation. Given that study clinicians swapped algorithms every two weeks, and given that the electronic format guaranteed full algorithm adherence, the overall concern about a bias towards the null, was low. The criteria used to define clinical failure was based on previous pneumonia management trials (Hazir *et al.*, 2011; Fox *et al.*, 2013). The validity of some of the criteria used for non-severe disease classifications should certainly be re-evaluated for future trials. For example one could argue that having persistent “clinical pneumonia” on day 3 actually does not represent clinical failure but may rather be the natural course of illness of a viral respiratory tract infection (Thompson *et al.*, 2013). Similarly, patients with persistent fever after several days have in fact a high likelihood of having a viral infection, such as Epstein-Barr virus or

Cytomegalovirus infection (Begovac, Soldo and Presecki, 1988). We included febrile children only, instead of all children presenting with acute medical complaints, since children without fever have a very low risk of having an infection that requires antibiotics (Shao *et al.*, 2015). Consequently, the results should be generalizable even more to non-febrile children.

In terms of using host biomarkers of inflammation for the management of febrile illness, this was the first trial that assessed the safety of using CRP and/or PCT testing to decide on antibiotic prescription in children in a resource-limited country. CRP and PCT testing in our study even improved clinical outcome. One recent open, randomized trial evaluated the impact of using a CRP POC testing in Vietnam among patients with respiratory symptoms, including 287 children less than 6 years of age (Do *et al.*, 2016). This trial was underpowered to detect differences in clinical outcome as sample size calculations were done based on reduction of antibiotic prescription. Several randomized trials have assessed CRP and PCT for deciding on antibiotic prescription in respiratory infections in adults (Burkhardt *et al.*, 2010; Schuetz, Briel and Mueller, 2013; Aabenhus *et al.*, 2014). A series of studies assessed the accuracy of CRP and PCT in diagnosing bacterial infections in children in outpatient setting in well-resourced settings (Van den Bruel *et al.*, 2011; Lubell *et al.*, 2015). These studies found moderate diagnostic accuracy of both CRP and PCT. However, one has to bear in mind that diagnostic gold standards are often imperfect. For example, for pneumonia, the most recognized current gold-standard is “WHO endpoint pneumonia”, i.e. consolidation on chest radiograph (Erdman *et al.*, 2015). However, only a (undefined) proportion of WHO endpoint pneumonia is bacterial in origin. Besides the one trial in Vietnam that included both children and adults, all studies of CRP and PCT in children have focused on analytical performance; none have assessed whether using these tests would change patient outcome.

In terms of impact on antibiotic prescription when using host biomarkers POCTs, a much smaller effect in terms of reduction in antibiotic prescription can be expected when these POCTs are provided without guidance (i.e. performed on all patients). For example, in the Vietnam trial, the reduction of antibiotic prescription observed was from 74% to 68% by day 14 (Do *et al.*, 2016). Such small reductions in prescription rates could be achieved on clinical grounds alone: in our study 43% (392/920) of patients in the intervention arm with cough did not meet clinical criteria for CRP testing and were categorized as having an upper respiratory infection. This was also demonstrated in a cluster-randomized trial assessing the use of ALMANACH (Shao *et al.*, 2015). To make best use of CRP and PCT testing we decided to include them in a patient management tool. It guided clinicians on which patient to select for testing and how to use the result in the clinical context. We also employed higher cut-offs (80mg/L for CRP and 4ug/L for PCT) to rule-in patients that likely require antibiotic treatment (instead of ruling out patients with a very low probability of having a bacterial infection using

lower CRP cutoffs, such 10mg/L in the Vietnam trial, Do *et al.*, 2016). This was based on the analyses of host biomarkers results in the Tanzanian etiology of fever study (Erdman *et al.*, 2015) and on the fact that patients in outpatient settings have a very low pre-test probability of having a bacterial infection (D'Acremont *et al.*, 2014). We indeed selected few patients that required antibiotic treatment with this strategy: 1.2% (10/833) of patients with non-severe respiratory classifications, and 13% (53/402) of patients with fever without localizing symptoms.

e-POCT also uses POCTs for detecting children with severe disease: an oximeter to detect hypoxemia and severe tachycardia, and a POC hemoglobinometer to identify children with severe anemia. e-POCT indeed classified around twice as many children as having severe disease than the control algorithm. However, this was only partially due to the POCTs employed: only very few children with hypoxemia and/or severe tachycardia were identified. The use of oximeters as part of IMCI has been advocated. However, their utility at peripheral health care level should be assessed further (Enoch, English and Shepperd, 2015). e-POCT diagnosed 4 times as many patients with severe anemia than the IMCI-based control algorithm (and only 1/5 patients in the control algorithm with severe anemia diagnosis actually had a low Hb value). This confirms findings from previous studies that severe anemia cannot be detected using clinical signs (Chalco *et al.*, 2005). However, severe anemia, in turn, is an important risk factor of death from severe infections and associated with severe infections (Brabin, Premji and Verhoeff, 2001; Calis *et al.*, 2008). Given that children cannot be preselected for Hb testing based on clinical elements, all children would have to undergo Hb testing to detect the few children with severe anemia. This strategy will only become feasible once low-cost Hb tests can be deployed to the peripheral health care level, if possible that can be directly connected to tablets. e-POCT also detected and referred more than twenty times as many children with a severe malnutrition classification using combined weight-for-age (WFA) and mid-upper arm circumference (MUAC) testing (compared to clinical signs in the control arm). Severe malnutrition is recognized as an important risk factor for severe outcome from infections (Reed *et al.*, 2012; Jain, Sarathi and Jawalekar, 2013; Gowraiah *et al.*, 2014). Overall, the adequacy of the referral criteria could not be assessed in this study, which is certainly a limitation. This is because the hospital-based care is often low in quality and non-standardized. As a result neither admission decisions nor admission diagnoses could hence be used as a diagnostic gold standard (English *et al.*, 2004).

Overall, our data provides evidence that e-POCT not only reduced the proportion of antibiotic prescription but also increased the targeting of children in need for antibiotic treatment. Antibiotic treatment was indeed shifted away from non-severe respiratory infections towards severe disease classifications. Furthermore, in addition to the overall improved clinical outcome using e-POCT, antibiotic prescription was associated with clinical failure in the control arm, but

not in the e-POCT arm. This may be because children who received unnecessary antibiotic prescription in the control arm suffered from antibiotic side effects, or the neglect of other important supportive treatments for viral infection (such as bronchodilator treatment or rehydration).

Our study has several limitations that need to be addressed in further study. First, this was a multi-center but single region study, which limits the generalizability of our findings. Given the innovative character of e-POCT we opted for a study setting where good oversight and pediatric back up could be guaranteed. Key algorithm components should be re-assessed in different geographical settings and populations with higher HIV- and malnutrition rates. Second, there are concerns of using CRP testing to detect bacterial infections in patients with malaria (malaria infection in itself will lead to high levels of CRP and PCT, Naik and Voller, 1984; Lubell *et al.*, 2015). However, antibiotic prescription is generally not indicated in patients with uncomplicated malaria. Bacterial co-infections are nevertheless common in patients with severe malaria (Church and Maitland, 2014). Using enhanced severity criteria, such as Hb testing, may actually improve detection of patients with severe malaria and may thus help to identify children in need for concomitant anti-malarial and antibiotic treatment. Third, equipment-based treatment, rather than treatment based on clinical grounds alone, are faced with challenges in terms of supply chain, and possibly cost. However, antibiotic over-prescription is also associated with costs on an individual and societal level (Lim *et al.*, 2006). Finally, the true utility of e-POCT can only be evaluated through open implementation studies since adherence to the algorithm will be an important factor to make use of its advantages in terms of clinical outcome and antibiotic prescription.

7.6. Conclusion

e-POCT, an innovative electronic algorithm using host biomarker point-of-care tests has the potential to improve the clinical outcome of children with febrile illnesses in low-resource settings while reducing antibiotic use through improved identification of children with severe infections and increased targeting of children in need for antibiotic prescriptions. Using CRP and PCT cutoffs, integrated into an overall disease management algorithm, for the management of children with respiratory infections and FWS was safe in terms of clinical outcome. Notwithstanding the need for replication of these findings in other geographical settings and further implementation studies, our results provide first evidence that such an innovative patient management approach is beneficial. Electronic algorithms in general are an important prospect to increase compliance to IMCI—the integration of POCTs would make

even better use of such technologies. A key advantage of using host biomarkers tests, as compared with a series of disease etiology tests, is that such an approach is likely more robust to seasonal and geographic variations in disease etiology. POCTs should include both tests for identification of patients with severe disease (for example with severe anemia) and for detection of children with bacterial infections (such as CRP and PCT). To make best use of these POCTs, they should be integrated into a patient management tool that will help not only to select patient subgroups for which testing is useful, but also to help interpret results within an overall patient assessment. This will also allow the continuation of an integrated approach to the treatment of childhood infections as it has been implemented through IMCI.

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8. Efficacy and safety of using point-of-care C-reactive protein testing to reduce inappropriate antibiotic prescription for respiratory infections in febrile children: an individually randomized, controlled non-inferiority trial in the Tanzanian outpatient setting.

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8.1. Summary

Background

The safety and efficacy of C-reactive protein (CRP)-based antibiotic prescription in febrile children at risk for pneumonia has not been assessed.

Methods

This was a multi-center, open-label randomized controlled trial in nine primary health care centers in Dar es Salaam, Tanzania. Children aged 2-59 months with fever and cough and without severe disease requiring hospital referral were enrolled as part of a larger non-inferiority trial evaluating a novel electronic algorithm (e-POCT). Patients were randomized 1:1 to either a CRP-based strategy or the World Health Organization strategy for classification of bacterial pneumonia. In the intervention arm antibiotic was given in case of tachypnea and a CRP of greater than 80mg/L. The primary outcome was clinical failure by day 7. Secondary outcomes were antibiotic use, and severe adverse events (secondary hospitalization or death). All analyses were per-protocol. ClinicalTrials.gov, identifier NCT02225769

Findings

From December 2014 to February 2016, 3192 children were randomized into the main study; 1727 non-severe respiratory disease (intervention: 868, control: 859). 0·4% (7/1727) were lost to follow-up by day 7. The proportion of clinical failure by day 7 was 2·9% (25/865) in the intervention versus 4·9% (42/855) in the control algorithm (RR 0·59, 95% CI 0·36, 0·96, RD……). 2·3% (20/865) of children in the intervention versus 40·6% (347/855) in the control arm received antibiotics at day 0 (RR 0·06, 95% CI 0·04, 0·09). There were fewer severe adverse events using the C-reactive protein based strategy; 0·5 % (4/865) versus 1·5% (13/855, RR 0·30, 95% CI: 0·10, 0·93).

Interpretation

CRP testing, integrated into a clinical decision algorithm, has the potential to improve outcome in febrile children with respiratory infections while substantially reducing antibiotic prescription. Future implementation studies should assess this strategy in routine care.

8.2. Research in context

Evidence before this study

Respiratory infections are the most important drivers for antibiotic over-prescription in children, especially in low-resource setting. In a 2014 Cochrane review, Aabenhus et al. systematically reviewed randomized controlled trials (RCTs) on the use of C-reactive protein (CRP) to decide on antibiotic prescription. Studies in children were lacking. We searched MEDLINE, Embase with a combination of “respiratory tract infection”, “antibiotic”, “C-reactive protein”, and “child/pediatric”. We found one additional RCT in Vietnam that included 287 children less than six years of age. C-reactive protein testing resulted in a moderate reduction in antibiotic prescription in children at low risk for pneumonia (without tachypnea).

Added value of this study

This is the first RCT, both in low-and high-resource settings, designed to assess the clinical outcome of children with respiratory tract infections when treated based on an antibiotic prescription strategy using point-of-care CRP. It is also the first trial that included children with significant risk of having bacterial pneumonia (children with tachypnea). Point-of-care CRP testing included into a clinical algorithm improved clinical outcome in children presenting with febrile respiratory infections in low-resource setting, while substantially reducing the amount of antibiotic prescription, when compared to the World Health Organization-based strategy.

Implication of all the available evidence

This C-reactive protein based strategy has the potential to improve clinical outcome in children with febrile respiratory infections and to increase rational use of antibiotics. Evaluating of such strategies in routine care, and outcome-based studies in high-resource settings should be the objective of future research.

8.3. Introduction

Respiratory tract infections, including upper respiratory tract infections (URTI), pneumonia, and viral lower respiratory tract infections (LRTI) are the most important drivers for antibiotic over-use in children, contributing to the increasing rate of antibiotic resistance. Over-prescription is in particular an issue in low-resource settings where antibiotics are now increasingly available. Here, health workers lack adequate diagnostic support and prescribe antibiotics indiscriminately to the vast majority of children—to be 'on the safe side' (Risk *et al.*, 2013). Despite this non-differential approach to antibiotic prescription, childhood mortality from respiratory infections remains high(Liu *et al.*, 2014). Over-relying on antibiotic treatment has resulted in the neglect of the correct management of viral respiratory infections, such as reactive airway disease (Nantanda *et al.*, 2013).

The majority of respiratory infections are of viral etiology (D'Acremont *et al.*, 2014), with introduction *Haemophilus influenzae type B* (HiB) and pneumococcal conjugate vaccines (PCV) the proportion of bacterial pneumonia has decreased further (Lucero *et al.*, 2009). Accordingly, in the outpatient setting, very few children require antibiotic treatment(Hazir *et al.*, 2011; Shao *et al.*, 2015). The diagnosis of bacterial pneumonia relies principally on clinical criteria (e.g., cough, dyspnea, fever) and chest radiography to document lung infiltrates (McIntosh, 2002). In low-resource settings, since radiography is not readily available, the diagnosis of bacterial pneumonia is based clinical features only (fast breathing, chest indrawing and auditory wheezing), as recommended by the World Health Organization (WHO, World Health Organization, 2014). However, data on the usefulness of these tools has been contradictory: other than wheezing, clinical features, including respiratory rate (RR), were largely uniform across the spectrum of microbiological etiology in a series of studies (McIntosh, 2002; Rambaud-Althaus, Althaus, *et al.*, 2015). Similarly, though it has been shown through vaccines trials that radiographic lung infiltrates are correlated with bacterial pneumonia (Klugman, Madhi and Albrich, 2008), several studies have shown that radiographic infiltrate cannot be used to distinguish between bacterial and viral etiology (McIntosh, 2002).

C-reactive protein (CRP), available at point-of-care (POC), has been proposed as a non-microbiological test to diagnose childhood bacterial pneumonia. The reported diagnostic accuracy varied widely across studies with sensitivities of 35%-100% at specificities of 40-100%, depending on the cut-off and gold standard used (Flood, Badik and Aronoff, 2008; Erdman *et al.*, 2015). These diagnostic accuracy studies were generally limited by the lack

of an acceptable gold standard for bacterial pneumonia (Lynch *et al.*, 2010). Clinical outcome studies are lacking. In adults, as reviewed in a 2014 systematic review, CRP has been shown to reduce antibiotic prescription for respiratory infections in primary care, without differences in clinical recovery (Aabenhus *et al.*, 2014). Its use has started to be explored in children (Do *et al.*, 2016) but neither controlled studies sufficiently powered to detect differences in clinical outcome, nor studies in children with clinical signs suggestive of pneumonia have been performed.

We developed a two-step approach for diagnosis of bacterial pneumonia at outpatient level using cough, fever, and refined RR-cutoffs as an initial 'rule-out' step, followed by POC CRP testing as a 'rule-in' step. This was part of a larger effort to improve management of febrile illnesses in children in low-resource settings through the development and evaluation of a novel electronic algorithm (e-POCT), that uses POC testing (Chapter 3). Within the algorithm, CRP testing was not used to decide on antibiotic treatment in children with severe disease or severe malnutrition requiring hospital referral. This was because, first, children with severe disease likely benefit from antibiotic treatment and are rare in primary care (Shao *et al.*, 2015). Second, children with severe malnutrition have distinct inflammatory responses that have not been adequately characterized (Page *et al.*, 2013). We hence concluded that the risk of missing bacterial infections outweighed the possible benefit in terms of reduction of inappropriate antibiotic prescription.

The aim of this analysis were to determine whether using POC CRP-testing, integrated into a clinical algorithm, to decide on antibiotic prescription in under-fives presenting with febrile respiratory symptoms, can reduce unnecessary antibiotic prescription, while being non-inferior in terms of clinical outcome, compared to the WHO-recommend diagnostic and treatment approach.

8.4. Methods

Study design

This was a subgroup analysis of an individually randomized, open, controlled trial to investigate whether a novel, electronic algorithm using POCTs (e-POCT) was not inferior in terms of health outcomes to a validated electronic algorithm derived from IMCI (ALMANACH) when treating febrile infections in under-fives. The study was conducted at nine public outpatients clinics in Dar es Salaam, Tanzania, from December 2014 to March

2016. Recruitment sites were chosen to represent the pediatric outpatient population in Dar es Salaam. The overall methods and results of this trial are reported elsewhere (Chapter 7).

The study protocol and related documents were approved by the Institutional Review Board of the Ifakara Health Institute and by the National Institute for Medical Research Review Board in Tanzania, by the Ethikkommission beider Basel in Switzerland, and by the Boston Children's Hospital Ethical Review Board.

Participants

Consecutive patients presenting for care during normal business hours were screened for eligibility. Inclusion criteria were: age two to 59 months, history of fever for more seven days or less, and axillary temperature ≥37·5°centigrade at presentation. Exclusion criteria were: weight less than 2·5kg, main complaint injury or acute poisoning, and previous medical care for the present illness. Children satisfying the inclusion/exclusion criteria were enrolled if the guardian signed a detailed written informed consent. For this subgroup analysis, we included all children with febrile non-severe respiratory symptoms. This comprises all children presenting with cough but without severe symptoms (convulsion or positive meningeal signs, hypoxemia, cyanosis, severe respiratory distress, unable to tolerate oral liquids, severe dehydration, severe anemia, severe acute malnutrition, Figure 20).

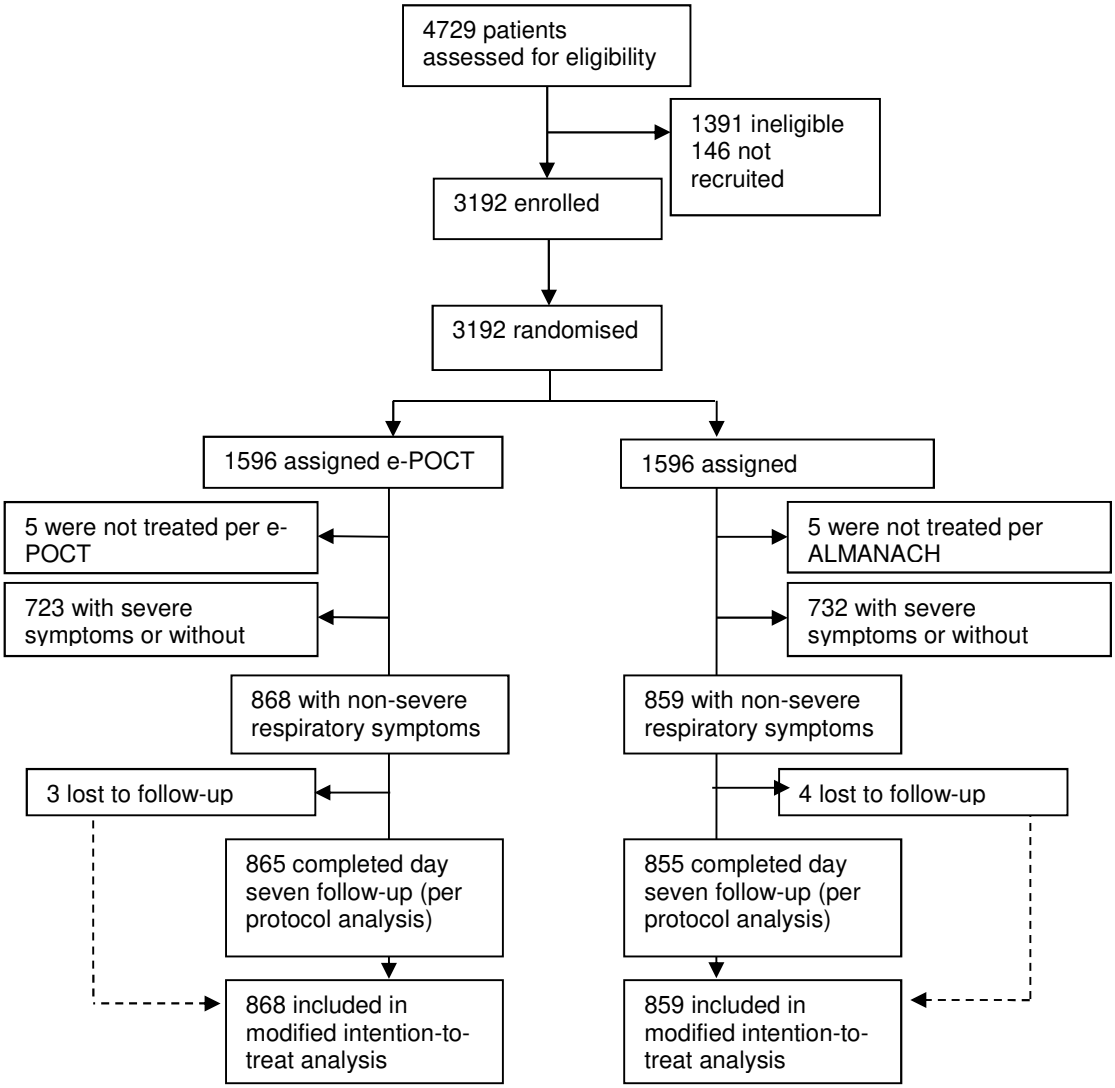

Figure 20 Trial profile

Randomization

Patients were enrolled by the study clinicians and then randomized to one of the management arms. Patients were individually randomized in blocks of four by the study clinicians according to a computer-generated randomization list provided by an independent, off site researcher. Sealed, opaque forms were used for allocation concealment and opened only after the patient's enrollment.

Procedures

The intervention consisted in having study clinicians using the e-POCT algorithm during the consultation to manage the patient. Children enrolled in the intervention arm were assigned to two study clinicians using e-POCT while two other study clinicians using ALMANACH managed children enrolled in the control arm. In order to minimize a possible type I error

through differences in the care between clinicians, clinicians switched arms and thus algorithms every two weeks. The development and content of e-POCT are described elsewhere (Chapter 5). For children with cough (and without severe symptoms) e-POCT makes a diagnosis of LRTI in patients with RR equal or above the 75th %ile for age and temperature according to a European derivation study(Nijman *et al.*, 2012). The algorithm asks for CRP testing for all children with LRTI. Antibiotic prescription was recommended for children with CRP-values of 80mg/L or above (presumed bacterial LRTI). Children with CRP-values less than 80mg/L were not treated with antibiotics (presumed viral LRTI), except if a concomitant bacterial infection from another source was documented. Children with positive mRDT were not given with antibiotics since malaria infection is associated with elevated CRP values (Díez-Padrisa *et al.*, 2010). Inhaled salbutamol treatment was given to all children greater than six months of age with LRTI. If the clinician observed an improvement in respiratory symptoms, salbutamol was prescribed for home treatment. The control group was treated using a WHO IMCI-based electronic algorithm (ALMANACH, Rambaud-Althaus, Shao, *et al.*, 2015). We chose an electronic IMCI algorithm-based as a control since were interested in comparing the content of the algorithms, rather than the format. ALMANACH is the only validated electronic IMCI-based algorithm and hence the current gold standard (Shao *et al.*, 2015). In addition, ALMANACH recommends antibiotic treatment for all children with RR equal or greater than 50/min, instead of the more conservative WHO IMCI cutoff of 50/min for children less than 12 month and 40/min for children aged 12 month to five years. Using a slightly higher cutoff already results in a reduction in antibiotic prescription. Using ALMANACH, inhaled salbutamol treatment was given and prescribed for patients with auditory wheezing. All children from the intervention and control arm were prescribed amoxicillin at 80-100mg/kg/day for five days unless another concomitant infection (e.g. skin infection) required broadening of antibiotic coverage.

Laboratory POCTs were performed on site as recommended by the algorithms. mRDT testing was done for all patients in both arms using either the SD BIOLINE Malaria Ag P.f/Pan™ (Standard Diagnostics Inc.) or CareStart Malaria HRP2™ (Access Bio, Inc.) assays. According to Tanzanian national guidelines, voluntary screening for HIV antibodies using the Determine™ HIV-1/2 (Alere Inc.) was offered to all patients in both arms when HIV test kits were available at the health facilities. For CRP testing in the intervention arm we used a POC semi-quantitative assay (bioNexia CRPplus™, Biomérieux).

All caregivers were asked to return with the child for scheduled visits on days three and seven post randomization (day 0), or if the parent was concerned about the child's condition. Patients cured at day three were followed-up by phone only on day seven. Field workers traced patients missing the day seven visit. Patients not cured at day three were managed

per the assigned algorithm and attended again at day seven; patients not cured at day seven were treated per the clinician's judgment and another follow-up visit was performed at day 14 to assure that the child was cured. All patients were called by phone at day 30 to inquire about interim hospitalizations or deaths.

Outcomes

The primary outcome measure was the proportion of clinical failure (see definition in Table 10) by day seven. Clinicians were unaware of the clinical failure criteria and these criteria were thus not used for clinical management of the patient. In addition, to guarantee equal assessments of the primary outcome in both arms, the following additional measures were taken: Patients were considered "not cured" and treated again using the respective algorithms either i) if the caregiver considered that the child was still ill or ii) still had fever when assessed by trained field workers who did not know the content of the algorithms nor the criteria for clinical failure. The secondary outcome measures were the risk in antibiotic prescription at day 0 and by day seven, the risk of primary referrals at day 0, as well as of severe adverse events (secondary hospitalizations and death) by day 30.

Statistical Analysis

For the larger trial, the sample size for the overall study was computed for the primary analysis based on a 97·5% (one-sided) confidence interval (CI). To prove non-inferiority the lower limit of this CI was to be within 3%. This non-inferiority margin was established based on what was considered a clinically meaningful difference in clinical failure by day seven (see main publication for details on sample size calculation including stopping rules). In this subgroup analysis, for the observed clinical failure rate of 5·0% in the control arm and total sample size of 1727 subjects, the attainable power was 81%.

Both modified intention-to-treat (mITT) and per-protocol (PP) study populations were defined. The mITT population comprised all randomized patients for which the inclusion criteria for this subgroup analysis could be assessed (all patients who received the day 0 intervention). Per definition, patients who were lost for follow-up were treated as clinical failures. The PP population included all randomized patients who received the intervention and completed the day seven assessment (Figure 20). The primary outcome was calculated for both the mITT and PP populations. Because of the very small, and equal, proportion of loss to follow-up in both arms, all results are displayed according to PP analyses if not stated otherwise. Risk difference (RD) and relative risks (RR) with 95% CI were calculated to estimate the intervention effects on the main study outcomes. Stratified analyses with Mantel–Haenszel estimates for RR were performed to explore statistical heterogeneity of the

effect between clinicians(Joseph Newton *et al.*, 2009). For the primary outcome, mixed effects logistic regression was used to adjust for possible confounding covariates. Changes in odds ratio (OR) were used as approximated changes in RR since the primary outcome was rare. Kaplan-Meier survival curves were generated to compare the time to fever clearance between the two groups. An independent Data Monitoring Committee oversaw the study. The trial was registered prior to the enrolment of the first patient in ClinicalTrials.gov, identifier NCT02225769. We used Stata version 13·1 for the analysis.

Role of funding source

Neither the funders of the study nor Biomérieux (who provided the CRP test kits) had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

8.5. Results

Recruitment took place from December 10, 2014 to February 10, 2016. Overall, 4729 febrile patients aged two to 59 months were screened, and 3192 randomized into the main study (Figure 20). Five patients in each arm did not receive the intervention. The mITT population of patients with non-severe respiratory symptoms included 1728 patients: 868 (50%) in the e-POCT and 859 (50%) in the control arm. Three and four patients were lost to follow-up for the day seven outcome assessment in the e-POCT and control arms, respectively. The day 30 phone follow-up could be completed in 99% (852/865) of patients in the e-POCT arm and 99% (844/855) in the control arm. In both arms follow-up intervals for the day three and day seven outcome assessments were three (interquartile range [IQR] three to three, range two to five) and seven (IQR seven to seven, range six to 12) days, respectively.

Baseline characteristics did not differ between the two groups (Table 16).

Table 16 Baseline characteristics.

Characteristic	e-POCT (N=868)	ALMANACH (N=859)
Demographic		
Male Sex	486 (56%)	466 (54%)
Agegroup		
2 – 11 months	387 (45%)	408 (48%)
12 – 23 months	300 (35%)	272 (32%)
≥24 months	181 (21%)	179 (21%)
Received PCV vaccine*	443/461 (96%)	451/470 (96%)

Received HiB vaccine*	447/461 (97%)	456/470 (97%)
Primary caregiver other than mother*	40/850 (5%)	41/841 (5%)
Mother's highest grade of education*		
None	79/847 (9%)	76/841 (9%)
Primary	559/847 (66%)	550/841 (65%)
Post-primary	209/847 (25%)	216/841 (26%)
Number of children in household*	2 (1-3)	2 (1-3)
Medical History		
Reasons for consultation other than cough and		
Rhinorrhea/nasal congestion	487 (56%)	504 (59%)
Diarrhea or vomiting	230 (27%)	222 (26%)
Skin problem	26 (3%)	30 (4%)
Duration of fever		
1 day or less	530 (61%)	502 (58%)
2-4 days	327 (38%)	345 (40%)
5 days or more	11 (1%)	12 (1%)
Duration of cough*		
2 days or less	585/847 (69%)	570/846 (67%)
3-6 days	252/847 (30%)	271/846 (32%)
7 days or more	10/847 (1%)	5/846 (1%)
Clinical characteristics		
Weight for age z-score**	-0.6 (1.2)	-0.6 (1.2)
Respiratory rate	41 (36-50)	43 (36-52)
Heart rate*	145 (17)	143 (16)
Tachypnea per IMCI***	386 (45%)	375 (44%)
Lower chest wall indrawing	7 (1%)	10 (1%)
Laboratory values		
mRDT positive	85 (10%)	85 (10%)
HIV-1/2 antibody positive*	10/807 (1%)	6/794 (1%)

Data are n (%), median (IQR), mean (SD), or n/N (%).*Data not available for all randomized patients; **WHO 2006 growth curve(World Health Organization, 2006); *** <12 months and RR≥50/min, ≥12 months and RR≥40/min.

Participants had the typical features of children presenting to outpatient clinics with infectious complaints in areas with good health care supply: young age, a high frequency of multiple complaints, and presentation shortly after the onset of illness (Table 16). The vaccine record was available at consultation in 54% (931/1727) of patients; PCV and HiB coverage among these patients was >95%. HIV rapid tests were available at 92% (1595/1727) of consultations; 1% of patients tested had a positive result (10/807 and 6/794 in the intervention and control arm, respectively).

In the PP population, 2·9% (25/865) of patients experienced clinical failure by day seven treated using e-POCT versus 4·9% (42/855) of patients treated with the control algorithm (RD -2·0, 95% CI -3·8, -0·2; Table 17).

Table 17 Primary and secondary study outcomes

	e-POCT	ALMANACH		
Primary Outcome	**% (n/N)**	**% (n/N)**	**Risk Difference (95% CI)**	**Risk Ratio (95% CI)**
Clinical failure by day seven (PP)	2·9 (25/865)	4·9 (42/855)	-2·0 (-3·8, -0·2)	0·59 (0·36, 0·96)
Clinical Failure by day seven (mITT)	3·2 (28/868)	5·4 (46/859)	-2·1 (-4·0, -0·2)	0·60 (0·38, 0·95)
Secondary Outcomes (PP)	**% (n/N)**	**% (n/N)**	**Risk Difference (95% CI)**	**Risk Ratio (95% CI)**
Antibiotic prescription at day 0	2·3 (20/865)	40·6 (347/855)	-38·2 (-41·7,-34·8)	0·06 (0·04, 0·09)
Antibiotic prescription by day 7*	6·8 (59/865)	43·9 (375/855)	-37·0 (-40·7, -33·3)	0·16 (0·12, 0·20)
Severe adverse events by day 30	0·5 (4/865)	1·5 (13/855)	-1·0 (-2·0, -0·1)	0·30 (0·10, 0·93)
Secondary admissions	0·5 (4/865)	1·4 (12/855)	-0·9 (-1·9, 0)	0·33 (0·11, 1·02)
Deaths	0 (0/865)	0·2 (2/855)	-	-

* 17 patients in the e-POCT and 20 patients in the ALMANACH received antibiotics by non-study physicians between day 0 and day seven. Per protocol (PP), modified intention to treat (mITT).

There was a reduction in the relative risk of clinical failure of 41% using e-POCT compared to ALMANACH (RR 0·59, 95% CI 0·36, 0·96). The main difference in clinical outcome between the two arms occurred before day three (RR 0·35, 95% CI 0·17, 0·72, Table 18)—there was no significant reduction in the risk of clinical failure from days four to seven (RR 1·04 95% CI 0·50, 2·13.). The Mantel–Haenszel estimate for RR in clinical failure by day seven when stratifying by clinician was not significant (p=0·49). The crude OR (0·59, 95% CI 0·36, 0·95) was similar to the adjusted OR (0·59, 95% CI 0·36, 0·97) when adjusting for relevant covariates and random effects (age, axillary temperature, weight for age z-score(World Health Organization, 2006), respiratory rate, clinician, and health center). In the PP population, 2·3% (20/865) of participants in the intervention versus 40·6% (347/855) in the control arm were prescribed an antibiotic treatment at day 0 (Table 17). Using IMCI RR cutoffs for antibiotic treatment, 44% of patients in the ALMANACH arm would have been prescribed an antibiotic at day 0 (Table 16). Additional 39 and 28 (out of which 17 and 20 through consultation with non-study-physicians) patients received antibiotics between day one and day seven in the e-POCT and control arms, respectively. There was a significantly lower proportion of secondary admissions and deaths in the e-POCT arm compared to the control arm: 0·5 % (4/865) versus 1·5% (13/855, RR 0·30, 95% CI: 0·10, 0·93), respectively (Table 17). We did not note statistical heterogeneity between clinicians for any of the secondary outcome measures. 0·2% (2/865) of patients in the e-POCT versus 1·2% (10/855) of patients in the ALMANACH arm experienced severe symptoms at follow-up (RR 0·20, 95% CI 0·04, 0·90, Table 18).

Table 18 Details of clinical failure and severe adverse events

	e-POCT			ALMANACH			
Criteria for clinical failure	**Clinical Failure**	**Secondary Admission**	**Death**	**Clinical Failure**	**Secondary Admission**	**Death**	**RR for clinical failure (95% CI)**
Hypoxemia/severe tachypnea	1	1	-	4	2	-	
Other severe symptom	1	1	-	5	4	2	
Cough and tachypnea/ chest indrawing	8	2	-	19	1	-	
Total at day 0-3 % (n/N)	**1·2% (10/865)**	**0·3% (3/865)**	**-**	**3·3% (28/855)**	**0·8% (7/855)**	**0·2% (2/855)**	**0·35 (0·17, 0·72)**
Other severe symptom	-	-	-	1	1	-	
Persistent fever	11	-	-	10	3	-	
Cough and tachypnea/ chest indrawing	1	-	-	2	-	-	
Diarrhea/vomiting	2	-	-	-	-	-	
Significant skin infection	1	-	-	1	1	-	
Total at day 4-7 % (n/N)	**1·8% (15/855)**	**0·1% (1/862)**	**-**	**1·7% (14/827)**	**0·6% (5/848)**	**-**	**1·04 (0·50, 2·13)**
Total severe failure criteria day 0-7 % (n/N)	**0·2% (2/865)**			**1·2% (10/855)**			**0·20 (0·04, 0·90)**

Data are n and % (n/N).

Figure 21 displays the Kaplan-Meier curves for time to fever clearance for the intervention and control group- we did not observe a difference in time to fever clearance.

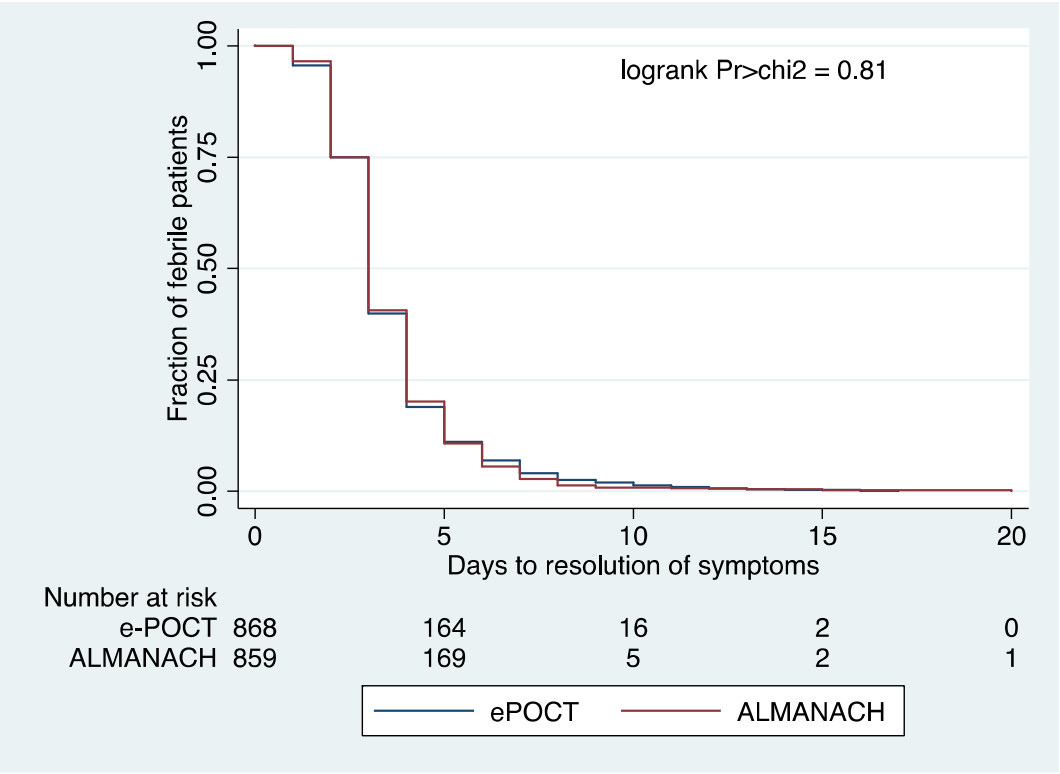

Figure 21 Kaplan-Meier estimates of time to fever clearance

Out of 780 patients with negative mRDT in the e-POCT arm, 50% (393) met criteria for CRP testing, i.e. had a RR ≥75th %ile for age and temperature (Table 19).

Table 19 Clinical failure and antibiotic prescription by algorithm classification at day 0 for patients with negative mRDT.

	e-POCT (n=780)			ALMANACH (n=770)			
Algorithm classification at day 0	**Antibiotic prescription at day 0**	**Antibiotic prescription by day 7**	**Clinical failure by day 7**	**Antibiotic prescription at day 0**	**Antibiotic prescription by day 7**	**Clinical failure by day 7**	**RR for clinical failure (95% CI)**
Upper respiratory tract infection	0·5% (2/387)**	5·4% (21/387)	3·1% (12/387)	4·6% (22/480)**	10·4% (50/480)	3·8% (18/480)	NA*
Viral LRTI	1·6% (6/383)**	6·8% (26/383)	3·4% (13/383)	NA	NA	NA	NA
CRP <10 mg/L	1·2% (3/256)**	7·0% (18/256)	3·9% (10/256)				NA
CRP 10-39mg/L	1·8% (2/111)**	6·3% (7/111)	2·7% (3/111)				NA
CRP 40-79mg/L	6·2% (1/16)**	6·2% (1/16)	0% (0/16)				NA
Bacterial LRTI (CRP≥80mg/L)	100% (10/10)	100% (10/10)	0% (0/10)	NA	NA	NA	NA
Clinical pneumonia	NA	NA	NA	100% (290/290)	100% (290/290)	8·1% (23/284)	NA
Antibiotic treatment at day 0	NA	NA	0% (0/18)	NA	NA	7·7% (24/312)	NA
No antibiotic treatment at day 0	NA	NA	3·3% (25/762)	NA	NA	3·7% (17/458)	0·8 (0·48, 1·62)

Data are % (n/N) unless otherwise specified. *No statistical comparison was made between the two study arms because the criteria for upper respiratory tract classification were different between e-POCT and ALMANACH. **Antibiotic treatment was prescribed for concomitant bacterial infections (skin infections, dysentery, and ear infections).

Two percent (10) of the 409 tested patients had a CRP of ≥80 mg/L and were thus treated with an antibiotic. Only three out of the 10 patients with CRP values of ≥80 mg/L had a RR of more than 50/min. Ten additional patients in the e-POCT met criteria for antibiotic treatment based on other algorithm classifications: five had dysentery, four skin infections, and one suspicion for osteomyelitis (Table 5). All clinical failures occurred in patients with CRP values below 40mg/L (Table 19). One patient with low CRP-values on day 0 was hospitalized on day one for bronchiolitis with severe respiratory distress. Seven additional patients with low CRP values met clinical failure criteria at day three. Five out of these seven patients recovered without antibiotic treatment by day seven (clinical failure criteria were not used for clinical decision making), suggesting that they suffered from a viral respiratory infection. Another five patients with CRP values of less than 40mg/L met clinical failure criteria at day seven. Among patients who received antibiotic treatment in the e-POCT arm, 0% (0/20) patients experienced clinical failure by day seven versus 6·9% (24/348) in the ALMANACH

Within the ALMANACH arm, patients who received antibiotic treatment were approximately twice at risk of clinical failure compared to patients who did not receive antibiotic treatment at day 0 (RR 2·07, 95% CI 1·13, 3·79). There was no statistically significant difference in the risk of clinical failure between the two arms among patients who did not receive antibiotics at day 0 (Table 19).

8.6. Discussion

This is the first randomized, clinical trial designed to evaluate a CRP-based antibiotic prescription strategy in terms of clinical outcome among children with febrile respiratory infections. We found that a two-step approach of refined age-and temperature-based RR percentiles, followed by POC CRP testing to decide on antibiotic treatment improved clinical outcome when compared to the currently recommend WHO approach. Children treated with the CRP-based strategy had a lower risk in: clinical failure by day seven, in the development of severe symptoms by day seven, and in severe adverse events (secondary hospitalizations and deaths) by day 30. Using the CRP-based strategy, antibiotic prescription at day 0 was reduced substantially from 41% to 2% in these controlled settings.

No previous studies have assessed clinical outcome of children with respiratory infections when treated using a CRP-based antibiotic prescription strategy. A safety study in children was an important first step because reported accuracies of CRP to detect bacterial

pneumonia in children have been very heterogeneous(Flood, Badik and Aronoff, 2008). This is largely due to the lack of an adequate gold standard(McIntosh, 2002). Several clinical trial have been performed in adult outpatients, summarized in a 2014 Cochrane review (Aabenhus *et al.*, 2014). CRP-based strategies in adults with respiratory symptoms were non-inferior in terms of clinical recovery to standard care (Aabenhus *et al.*, 2014). Keeping these previous studies in adults in mind, we designed our study as a non-inferior study since we were primarily interested in investigating the safety of our CRP-based approach. We hypothesized that the CRP-based strategy would be beneficial in terms of reduction of antibiotic prescription. Several mechanisms could have resulted in a better clinical outcome of patients in the intervention arm: first, the overreliance antibiotic treatment could have resulted in a neglect of supportive measures for viral respiratory infections, such as salbutamol treatment for asthma (Nantanda *et al.*, 2013). Second, the adverse effects from inappropriate antibiotic prescription could have had a negative effect. Both are supported by the fact that antibiotic prescription was associated with clinical failure in the control arm. However, we cannot be sure whether the improved outcome in the intervention arm was truly due the “respiratory package” or rather the entire electronic algorithm. Both treatment strategies were integrated into overall disease management algorithms. As an unblinded study the trial was certainly at risk of ascertainment bias. However, this was likely minimal since clinicians were unaware of the criteria used to assess the primary outcome.

In this efficacy trial, the CRP-based strategy was associated with an approximately twentyfold reduction in antibiotic prescription when compared to the control arm. A recent study in Vietnam, that investigated the effect of indiscriminate POC CRP testing on antibiotic prescription rates for respiratory infections, found a moderate reduction in antibiotic prescription (Do *et al.*, 2016). The study included 287 children less than six years of age. The study was limited by the fact that the applied CRP cut-off (10mg/L in children) was low, allowing a “rule-in” of many low-risk children for antibiotic treatment. Furthermore, the study only selected children with a very low pre-test probability of pneumonia. i.e. patients without fast breathing (RR≥40/min). The majority of these children have a very low benefit from CRP testing. Biomarker tests should ideally be used to rule-in a high risk of severe infection in situations when there is uncertainty whether antibiotic prescription is likely to be beneficial. It should not be used as an initial screening test. To make best use of CRP testing, we hence used a two-step diagnostic approach in which we first selected patients at higher risk of having bacterial pneumonia (fever, cough, and tachypnea/ lower chest indrawing). Within this population, we employed a higher CRP cut-off (80mg/L) to rule-in bacterial pneumonia, making use of the specificity of the test. Indiscriminate pre-consultation CRP-testing did indeed not reduce antibiotic prescription rates when compared to physician-guided testing

for febrile and respiratory infections in pediatric outpatient patients in a recent study in Norway (Rebnord *et al.*, 2016). Similar to a physician-guided approach, the integration of CRP testing in an overall disease management algorithm, e-POCT, allowed guidance for selection of patients who would benefit most from CRP testing, and assisting low-level health workers in interpreting test results. In addition, the integration of the "CRP package" into an overall disease management algorithm maintains an integrated approach to the management of children with infectious complaints: the majority of patients in our study had complaints in addition to cough that required medical attention.

Very few children in our trial met CRP criteria for antibiotic treatment. This raises the question whether CRP testing (or antibiotic treatment) is actually useful at all. Indeed, a controlled-randomized trial in Pakistan found placebo to non-inferior to amoxicillin in treatment of WHO non-severe pneumonia among 873 under-fives (Hazir *et al.*, 2011). However, epidemiological data suggests that a proportion of children with respiratory infections continue to suffer from bacterial pneumonia and require antibiotic treatment—even after the introduction of HiB and PCV vaccines (McIntosh, 2002). The Pakistani trial may have been limited in terms of power to detect differences in unfavorable outcomes. Furthermore, severe adverse events were not systematically assessed. The generalizability of the findings is unclear given the high percentage of patients with viral wheeze. Further studies are currently ongoing that will assess the usefulness of antibiotics in patients with WHO pneumonia further (Jehan *et al.*, 2016). Around half of clinical failures in the e-POCT arm occurred in the URTI category, i.e. in patients with a RR<75th %ile for age and temperature (Nijman *et al.*, 2012). A similar number of patients experienced clinical failure in the control group using a simple RR cutoff of 50/min. The WHO age-based RR cutoffs were developed initially to be sensitive in detecting pneumonia (Rambaud-Althaus, Althaus, *et al.*, 2015). This was because the focus was on detecting as many children with bacterial pneumonia. The benefit of increasing the number of children treated for bacterial pneumonia outweighed the risk of over-treating children with viral respiratory tract infections. However, more recent data, both from high-resource and low-resource settings, suggests that RR has a low accuracy, i.e. is neither sensitive nor specific, in diagnosing pneumonia (Rambaud-Althaus, Althaus, *et al.*, 2015). Future approaches may consider using different rule-out criteria for bacterial pneumonia, for example the absence of wheezing. Children with auscultatory wheezing have a low chance of bacterial pneumonia and would not require CRP testing (McIntosh, 2002). Low-level health workers have difficulty in accurately detecting auscultatory wheezing (Simoes *et al.*, 1991). However, new applications based on digital stethoscopes are currently under development (Abeyratne *et al.*, 2013) that could be integrated into future electronic algorithms. Such future technologies could also help detect

children with reactive airway disease who benefit most from salbutamol treatment. We chose ALMANACH as a control arm since it was the best validated IMCI-based algorithm available. However, RR-based detection of bacterial pneumonia, as recommended by WHO, is certainly inferior to a complex clinical assessment as practiced in high-resource settings. Generalizability of our findings to high-resource settings is thus limited- we would not expect the same benefit in terms of clinical outcome in such settings- however, a benefit in terms of antibiotic prescription is more likely. The generalizability of this study is further limited by the fact that it was a single country, urban study with low HIV prevalence. Ultimately, the impact of this CRP-based strategy will depend on clinician compliance. Previous evidence in adults suggests that POC CRP works best with educational components (Little *et al.*, 2013); electronic algorithms provide exciting opportunities in terms of continuous provider education.

This trial provides first evidence that POC CRP-based strategies, integrated into an overall disease management algorithm, have the potential to improve clinical outcome in children with febrile respiratory infections in low-resource settings, while substantially improving the rational use of antibiotics. This was also the first trial that included children at significant risk of bacterial pneumonia. Given the morbidity and mortality of respiratory infections in developing countries, and the high-volume antibiotic overuse, our findings have significant implications on child health and antimicrobial stewardship efforts. Based on studies in adults, it is probable that a CRP-based approach would not necessarily improve health outcomes in children with access to high-quality pediatric care. However, CRP-based strategies have the potential to improve antibiotic use in high-resource settings. Future research efforts should focus on outcome-based studies in high-resource settings, and implementation studies.

Contributions

KK, BG, and VD jointly designed the study and applied for funding. Data were collected by JM, JS, HT, ZS, with supervision from FK and KK. WS and FK assisted in getting ethics approval and coordinated work with the study sites. TM was responsible for laboratory work. KK and VD led the statistical analysis and had full access to the database. The first and subsequent version of the manuscript were written by KK, edited by BG and VD, and revised critically by all authors. All authors participated in data collection, data analysis, and data interpretation, and have approved the final study report.

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9. Complementary findings from the e-POCT project

9.1. Use of point-of-care tests

The following three sections describe the use of different POCTs more in detail. The use of CRP for the diagnosis of bacterial pneumonia is covered in Chapter 8.

9.1.1. Oximetry

Background

Hypoxemia (SaO2 < 90%) may occur as a complication of an acute febrile illness, primarily respiratory infections. Children with hypoxemia should receive hospital-based oxygen therapy. Oxygen therapy has become increasingly available; but the implementation of oximeters, especially at primary care level, has lagged behind (Mccollum *et al.*, 2016). The most recent 2014 WHO guidelines for the Integrated Management of Childhood illness (IMCI) at primary care level mention that any child with hypoxemia should be referred if oximetry is available (World Health Organization, 2014). However, the utility of routine use of pulse oximetry as a triage tool at peripheral health care level remains to be determined. First, the prevalence of hypoxemia at peripheral health care level has only started to be documented. A recent primary care-based study on the implementation of oximetry in Malawi reported that 5% (652/13,266) of SaO2 measurements were <90% in children with WHO criteria for pneumonia (Mccollum *et al.*, 2016). A previous systematic review estimated the prevalence of hypoxemia among children with WHO non-severe pneumonia at 2.0% and among children with severe or very severe pneumonia at 13% (Subhi *et al.*, 2009). However, this study included almost only hospital-based studies. Second, measuring SaO2 in small children (who are at highest risk of hypoxemia) can be challenging and may take up a considerable amount of consultation time (Mccollum *et al.*, 2016). Though hypoxemia cannot be detected reliably on clinical exam alone, several clinical predictors for severe pneumonia are also associated for hypoxemia (Ayieko and English, 2006; Chisti *et al.*, 2013; Wandeler *et al.*, 2015). However, these clinical signs may be difficult to detect for health workers with limited pediatric experience. The true “added value” of using oximetry in addition to current referral criteria remains to be determined.

The objective of this analysis was to determine the usefulness of oximetry in detecting febrile children with severe respiratory distress requiring referral to a higher level of care among the patients enrolled in the e-POCT arm.

Methods

Clinical study personal was trained in oximeter use. Oxygen measurement was performed in all children in the e-POCT arm at enrollment. The oximeter probe, connected directly to the tablet, displayed pulse waveforms, which allows for the assessment of the signal quality.We considered a measurement interpretable when a consistent, high-amplitude plethysmographic waveform and a stable oxygen saturation was seen. Moreover, oxygen measurement was observed in 50 patients (4 clinicians) in the last 3 months of the study and the duration of the procedure was assessed.

Figure 22 pulse oximetry measurement in a study patient

Results

Pulse oximetry measurements could be performed in all 1,591 patients who were treated using the e-POCT algorithm at day 0. 58% (923/1,591) patients had a cough at day 0. The distribution of SaO2 above 92% was not different between patients with and without a cough (Figure 23 and Table 20). There were more patients with SaO2 below 92% in patients with a cough compared to patients without a cough (p=0.024).

Table 20 Distribution of SaO2 in patients with and without a cough

	All patients (N=1,591)	**No cough (N=668)**	**Cough (N=923)**
SaO2 level (%)			
<90	0.3% (4)	0% (0)	0.4% (4)
90-91	0.3% (3)	0% (0)	0.3% (3)
92-93	1.9% (30)	2.3 % (15)	1.6% (15)
94-95	7.5% (119)	6.4% (43)	8.2% (76)
96-97	26.5% (422)	26.1% (174)	26.9% (248)
≥98	63.7% (1,013)	65.3% (436)	62.5% (577)

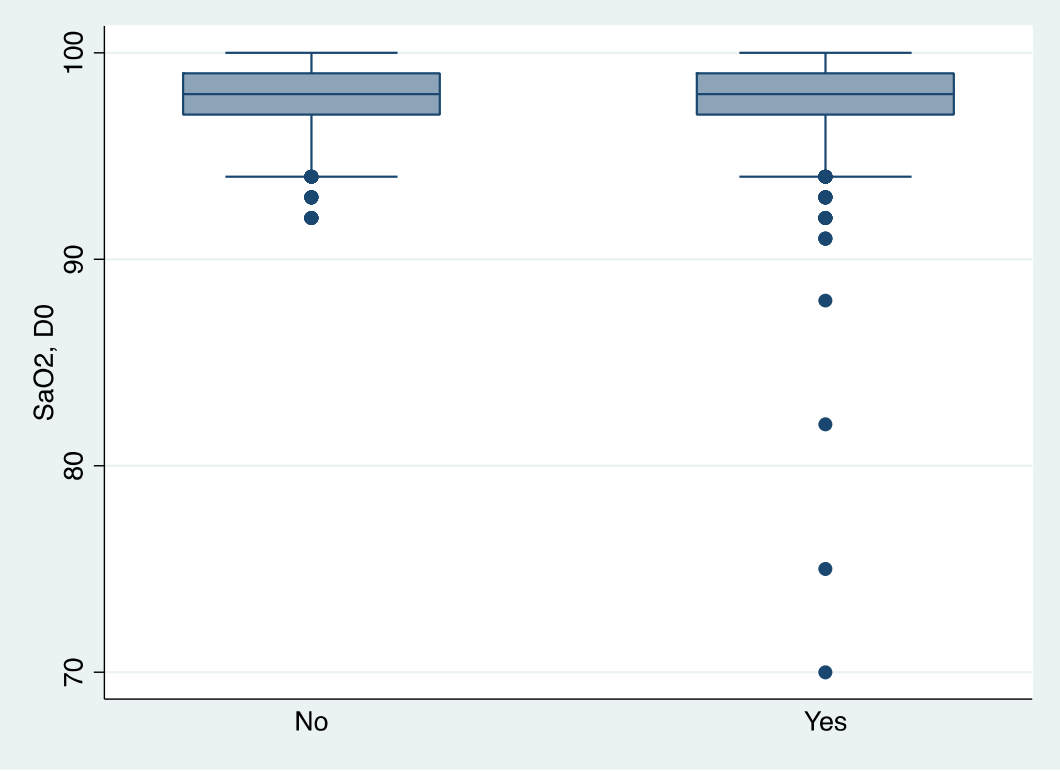


Figure 23 Boxplot of SaO2 at day 0 in patients with and without a cough

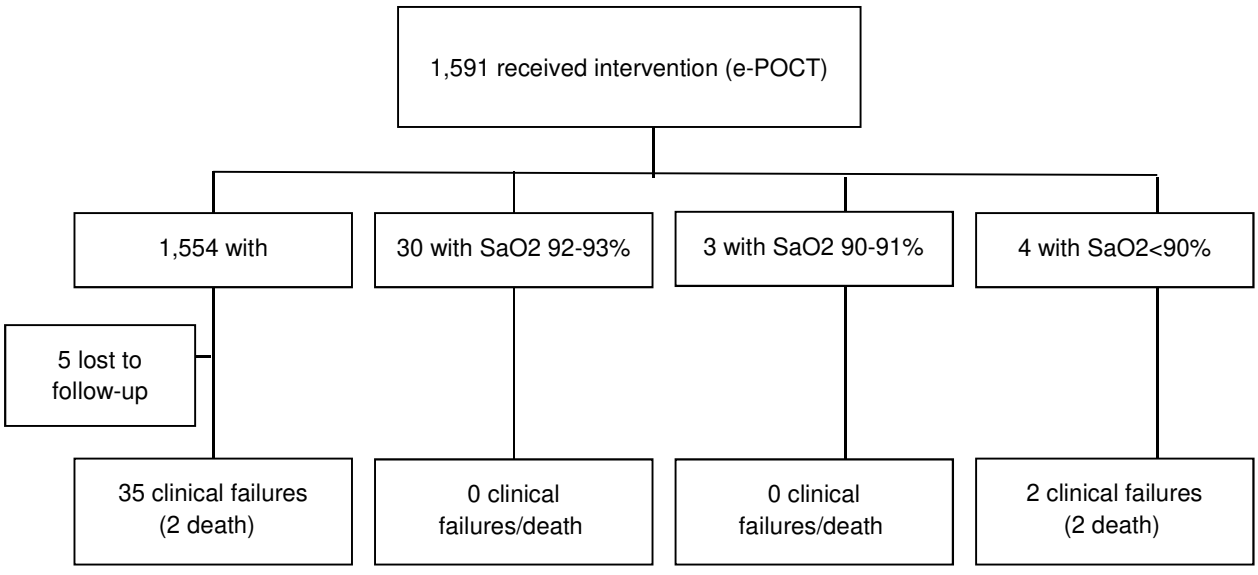


Figure 24 Flowchart of clinical outcome according to SaO2 level in the e-POCT arm.

Figure 24 displays the clinical outcome of children according to level of SaO2. Among the 4 children with SaO2<90%, 2 were eventually diagnosed with congenital heart disease and both met criteria for clinical failure: 1 child died and 1 child had persistent fever at day 7. Three children had SaO2 levels between 90-91%: e-POCT classified 1 as viral respiratory

infection, 1 as bacterial pneumonia, and 1 as uncomplicated malaria; all recovered by day 3. There were also no clinical failures among children with SaO2 between 92-93%. Table 21 shows the distribution of clinical signs for severe pneumonia with and without hypoxemia among the 923 children with a cough. All children with hypoxemia and 8% (73/919) children without hypoxemia had at least one sign of severe respiratory distress. Three out of 4 children with hypoxemia met other criteria for severe pneumonia per e-POCT; however none would have been referred based on IMCI criteria alone. Three out of 12 children with severe respiratory distress requiring referral had hypoxemia.

Table 21 Signs of respiratory distress and severe illness among 923 patients with a cough and with and without hypoxemia in the e-POCT arm.

Clinical sign	Sa<90% (N=4) n (%)	Sa≥90% (N=919) n (%)
Severe tachypnea [1]	2 (50)	61 (7)
Chest indrawing	3 (75)	16 (2)
Severe tachypnea and chest indrawing	2 (50)	4 (3)
Unable to speak/ cry	2 (50)	4 (3)
At least one clinical sign of severe respiratory distress	4 (100)	73 (8)
Severe pneumonia per e-POCT (outside SaO2)	3 (75)	9 (1)
Severe pneumonia per IMCI (outside SaO2)	0 (0)	7 (1)

Table 22 shows the observed duration of SaO2 measurements. The majority (78%, 39/50) of SaO2 measurements took more than one minute (Table 22).

Table 22 Observed oxygen measurements (4 clinicians)

Observation	N	n (%)
Duration of measurement	50	
<1 min		11 (22)
1min-2min		29 (58)
>2min		10 (20)
Reason for prolonged measurement time	10	
Patient crying/agitated		7 (70)
Inadequate signal		3 (30)

Discussion

In the Dar es Salaam outpatient setting, hypoxemia was rare among under-fives with febrile illness. All patients with hypoxemia and a cough also had other signs of respiratory distress (severe tachypnea and/or chest indrawing). These signs are no longer part of IMCI danger signs. None of the patients with hypoxemia had other IMCI danger signs, and therefore

would not have been classified as “severe pneumonia” per the 2014 IMCI. However, a substantial proportion of children without hypoxemia also had at least one sign of severe respiratory distress. This also supports our approach of using a combination of at least two signs to make a severe pneumonia diagnosis to avoid over-referral. Half of the patients with hypoxemia were eventually detected with congenital heart disease. Though congenital heart disease is an important cause of mortality, referral facilities often do not have the appropriate means for management of these patients yet. There is discussion as to whether a higher threshold for SaO2, e.g. 92%, should be used in primary care; because at this level of care the role of oximetry may be to detect children with severe disease, rather than detecting children in need for immediate oxygen therapy. We did not find evidence that using lower thresholds would have been helpful in the e-POCT arm of the study as there were no clinical failures among children with ‘intermediate’ oxygen levels.

Our observations are certainly limited by their generalizability related to the single geographic setting, the low number of subjects, and the controlled study setting. However, they provide further insight into some of the possible challenges when considering larger-scale implementation of oximetry in the IMCI setting. The main challenge is certainly operational. Pulse oximetry measurement took between 1-2 minutes in the majority of patients in our study, but more than 2 minutes in 20% of patients. This is fairly long when compared to an average consultation time of 5 minutes in routine care in Tanzania (Lange, Mwisongo and Mæstad, 2014). In the Malawi implementation study, 55% of health workers reported a measurement time of more than 2 minutes—however, no direct observations were done (Mccollum *et al.*, 2016). In low prevalence settings, like in our study, the benefits of measuring SaO2 in all patients with respiratory symptoms at primary care level may not justify the effort. Pulse oximetry could, however, be limited to patients after an initial clinical rule-in step with high sensitivity, such as a combination of fast breathing or lower chest indrawing. However, such an approach would have to be re-assessed in routine care, since the reliability of the measurements of clinical signs outside of research settings may be low. Though oximetry and oxygen should be implemented in hospitals in resource-poor settings, its feasibility and usefulness for routine screening at primary care level should be further assessed.

9.1.2. Hemoglobin

Background

The rationale for introducing Hb testing into the e-POCT algorithm is detailed in Chapter 5.4. Though severe anemia is known to be associated with death and bacteremia, the usefulness of introducing routine Hb testing in the consultation process has not been determined. The definition of anemia in childhood is not straightforward. WHO has published Hb reference values, however the majority of the data is derived from small studies conducted before the 1990s (World Health Organization, 2011). Overall, there is little data on normal Hb values in African children. Due to physiological changes postnatally, Hb drops to a nadir of around 9 g/dL at 2 to 3 months of life and then rises again and stabilizes out around 6 month of age (Ferry and Virginia, 2010). Very little data on anemia cutoffs exist for children under the age of 6 months and they are not included in the WHO anemia guidelines (World Health Organization, 2011). The objective of this analysis was to describe the characteristics of children in the e-POCT arm with anemia using different cutoffs and to evaluate the usefulness of this POCT in our study.

Methods

Hb screening was performed in all children in the e-POCT arm (Chapter 7.3).

Results

Among the 1,591 children in the e-POCT arm, 1% (20/1,591) met the e-POCT severe anemia classification (Table 23). Having a Hb of <6g/dL was not associated with age, tachycardia, nor tachypnea (data not shown). Ninety-five percent (19/20) of the children in the e-POCT arm with severe anemia per the e-POCT classification were detected based on Hb screening alone and met no other severe disease classification (Table 23). Not surprisingly, the proportion of mRDT positive values increased with decreasing Hb values. However, 50% (10/20) patients with Hb <6g/dL were mRDT negative.

Table 23 Overlap of anemia classifications with other severe diagnoses, primary admissions, and mRDT result in the 1,591 patients of the e-POCT arm

		Hemoglobin value (g/dL)			
	N	<6 (e-POCT severe anemia*) N=20	≥6 and <7g/dL (WHO severe anemia) N=51	≥7 and <10 (WHO moderate anemia) N=817	≥10g/dL (WHO mild or no anemia) N=703
CNS danger signs	9	0% (0)	3.9% (2)	0.5%(4)	0.4% (3)
Severe pneumonia	13	0% (0)	2.0% (1)	0.9% (7)	0.7% (5)
Severe dehydration	6	0% (0)	2.0% (1)	0.4% (3)	0.3% (2)
Severe malnutrition	55	5.0% (1)	7.8% (4)	3.4% (28)	3.1% (22)
Primary admission	46	70.0% (14)	9.8% (5)	2.2% (18)	1.3% (9)
mRDT positive	191	50.0% (10)	19.6% (10)	13.1% (107)	9.1% (64)

Data are displayed as % (n), *all patients with Hb<6g/dL were classified as severe anemia by e-POCT.

Interestingly, patients with a WHO severe anemia classification (Hb<7g/dl), but who did not meet e-POCT nor WHO transfusion (Hb<5g/dL) cutoffs, had a higher proportion of associated other severe classifications compared to children with Hb<6g/dL, p=0.05 (Table 23). 30% (6/20) of patients with severe anemia per the e-POCT algorithm were referred to the hospital on day 0 but the referral hospital staff decided not to admit them. All patients who were not admitted recovered from the acute febrile episode by day 7.

Discussion

This preliminary data provides first evidence on the usefulness of routine Hb screening at primary care level and the characteristics of patients with severe anemia. Severe anemia made up a large proportion of severe classifications in the e-POCT arm: 19% (20/103). All of these children except one had no other criteria for severe disease that would have triggered referral. Severe anemia was not associated with any objective clinical signs and could have hence not been detected on physical exam alone. A considerable percentage of patients were not admitted at the referral hospital. This is probably because the WHO transfusion threshold is at <5g/dL. Though all not-admitted patients did well, at least on short term, it is difficult to translate these findings from our controlled study settings with good follow-up to routine care. Whether the cut-off used represented an over-referral and whether lower cutoffs should be used cannot be concluded from our data. The fact that patients with a WHO severe anemia classification (Hb<7g/dl), but who neither meet e-POCT nor WHO transfusion cutoffs, had a higher proportion of severe classifications when compared to children with Hb <6g/dL may indicate that this is a special patient group. Such Hb values are

typical values of patients with sickle cell (HbSS) disease (McCavit, 2012). It is possible that this patient group, who is at higher risk from infectious complications, may be overrepresented in this group. Further microbiological analyses and HbSS detection on the samples obtained in the e-POCT study will help shed further light on POC Hb testing in our study. However, this preliminary data shows that it may be useful to perform systematic Hb screening at primary care level as an objective sign to detect children with severe disease.

9.1.3. CRP and PCT measurements for patients with fever without source

Background

Chapter 5.4.3 describes the rationale for using combined CRP and PCT testing to detect bacterial infections in patients with FWS. One central question is whether there is truly a benefit of using two biomarkers over a single one. The full microbiological characterization of this sub-cohort is currently in process, which will help shed further light on possible "missed diagnoses". The aim of this section was to provide a first description of use of combined CRP and PCT testing in the patients with FWS.

Methods

Please refer to Chapters 5.4 and 7.3 for details on the classification and testing of patients with FWS.

Results

Among the 402 patients with FWS and negative mRDT in the e-POCT arm, 12% (48/402) had PCT values of ≥4µg/L, 2% (8/402) had CRP values of ≥80mg/L and 1% (3/402) both (Table 24). Through the combination of PCT to CRP testing, 13% (53/402) of patients met criteria for antibiotic treatment.

Table 24 CRP and PCT values at enrollment in 402 patients with FWS and negative mRDT

		CRP (mg/L)			
		0-9	**10-39**	**40-70**	**≥80**
	N	N=247	N=117	N=30	N=8
PCT (µg/L)					
<0.5	282	82% (202)	60% (70)	29% (9)	13% (1)
0.5-0.9	35	7% (18)	10% (12)	13% (4)	13% (1)
1-1.9	21	4% (11)	6% (7)	4% (1)	25% (2)
2-3.9	16	1% (2)	9% (10)	10% (3)	13% (1)
≥4	48	6% (14)	15% (18)	45% (13)	38% (3)

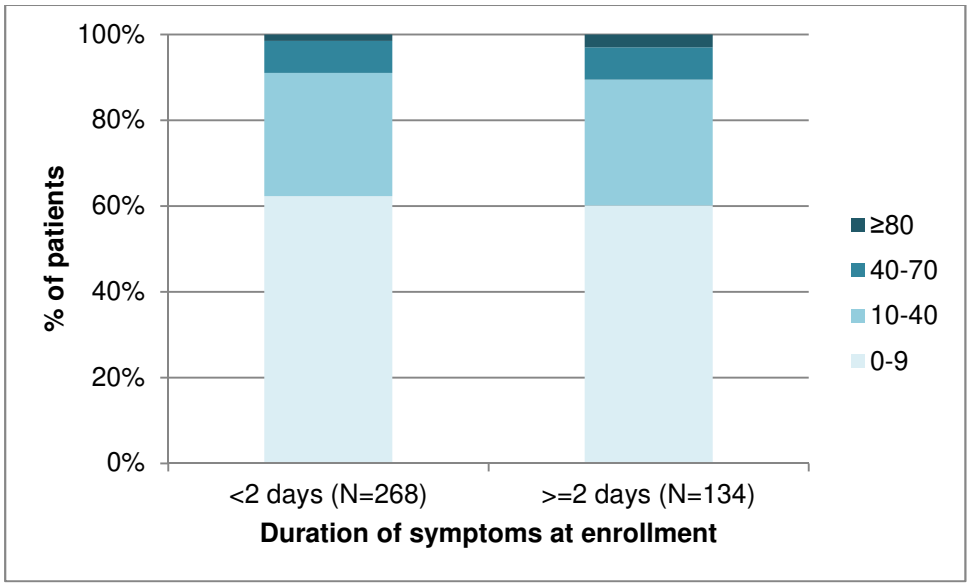
Data are displayed as %(n).

When, hypothetically, lowering the CRP cutoff for antibiotic treatment to ≥40mg/L, 4% (17/402) additional children would have met the CRP cutoff. CRP and PCT cutoffs change with duration of disease. It is thought that PCT rises earlier in an infectious disease process compared to CRP (Meisner, 2014). Figure 25 displays the CRP and PCT values by duration of symptoms. Children generally presented early in the course of the illness. For CRP, only a very small effect of the duration of symptoms on high CRP values was seen (Figure 25A).

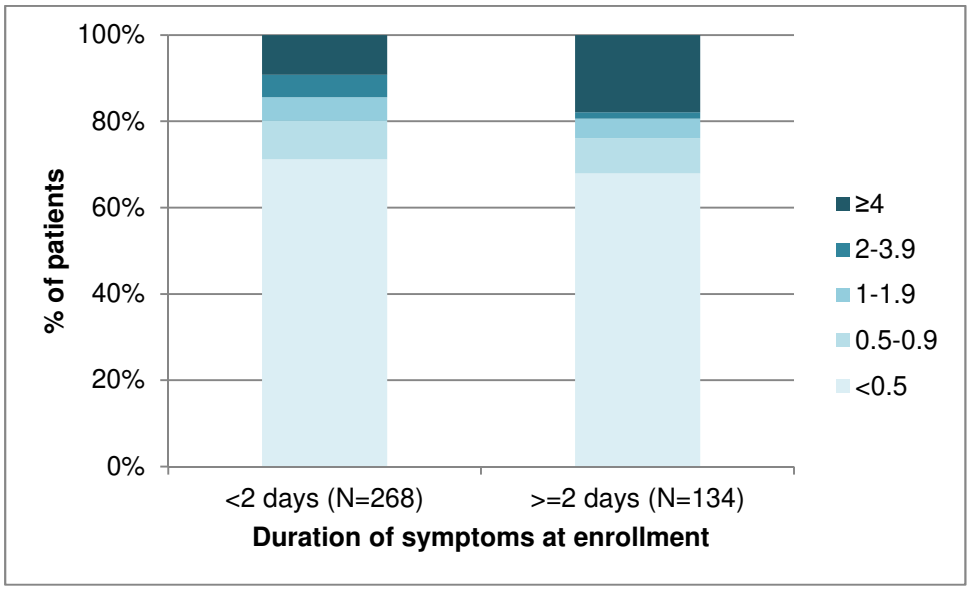
Interestingly, the effect for PCT was more pronounced (Figure 25B). One could imagine using different cutoffs for both markers depending on the duration of symptoms. For example, a higher cut-off would be considered for a child with more than two days of symptoms, and a lower cut-off for a child presenting earlier on. When selecting a cutoff≥40mg/L for CRP and ≥2µg/L for PCT in children with less than two days of symptoms, and leaving the same cutoffs for children with a longer duration of symptoms, 14% (58/402) children would have met criteria for antibiotic treatment.

Figure 25 CRP (A) and PCT (B) values by duration of symptoms among patients with FWS in the e-POCT arm.

A



B



There were 3 clinical failures in this subgroup of patients with FWS: 2 had both low CRP (<9mg/L) and PCT (<0.5µg/L) values. One patient met criteria for antibiotic treatment per PCT but had a negative CRP.

Discussion

The descriptive data above provide a first insight in the use of CRP and PCT testing to decide on antibiotic prescription in patients with FWS in the e-POCT arm. The cutoffs used for both tests for antibiotic treatment were relatively high (see Chapter 5.4 for a detailed discussion). However, 13% of patients met cutoffs for antibiotic treatment which corresponds approximately to the expected prevalence of bacterial infections in this cohort of patients (D'Acremont *et al.*, 2014). More patients met criteria per PCT than per CRP cutoffs. There were only a small number of overlaps in the "positive" categories between the two tests. Using PCT alone would have 'missed' 1% of patients only, which may indicate that this is a more sensitive test to detect bacterial infection in children with FWS. Lowering the cutoffs based on duration of symptoms would have hardly changed the number of patients treated with antibiotics. At this stage, no definite conclusion can be made from our data whether using both CRP and PCT in patients with FWS was necessary, though it appears that PCT may have been more useful than CRP. Further microbiological characterization will shed light on this issue. However, ultimately this question could only be answered through further outcome-based studies comparing different biomarker testing strategies.

9.2. Severe malnutrition in the e-POCT and ALMANACH arms

Background

Malnutrition is associated with severe outcomes from infections (Chapter 5.4). The different strategies used by e-POCT and ALMANACH to detect malnutrition are summarized in Table 6. The optimal diagnostic strategy remains to determined (Chapter 5.4). The goal of this analysis was to compare the clinical outcome of patients with severe malnutrition between the two study arms.

Methods

In both arms weight and MUAC measurements were taken for all patients at enrollment, and clinical signs for malnutrition recorded (severe wasting/ edema). Severe malnutrition for this

sub-cohort analysis was defined for all patients as having either severe malnutrition criteria per e-POCT (either WFA<-3 z-score (World Health Organization, 2006) or MUAC <11.5cm for patients 6 months and over) or per ALMANACH (visible wasting and/or edema). Follow-up and outcomes were defined per the main study (Chapter 7.3).

Results

56 patients in the e-POCT and 50 patients in the ALMANACH arm met anthropometric criteria for severe acute malnutrition (Figure 26). Nineteen percent (18/94) had low MUAC, 95% (89/94) low WFA and 14% (13/94) both. Using the ALMANACH algorithm 2 children with severe malnutrition were diagnosed based on wasting. These 2 children also met anthropometric criteria for severe malnutrition per e-POCT. In the e-POCT arm, wasting was reported in 1 child who also met anthropometric criteria.

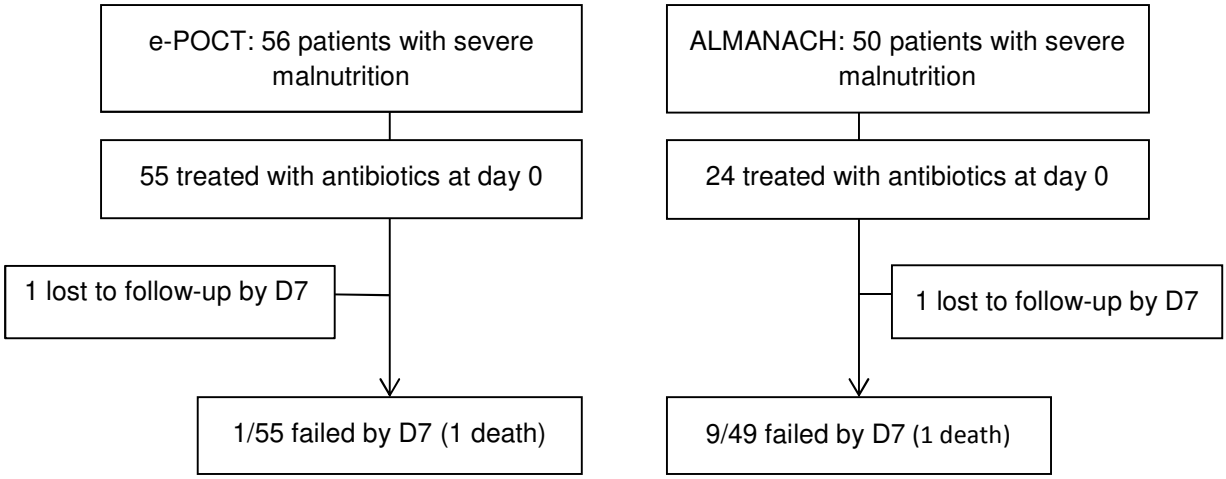


Figure 26 Flowchart of patients with severe malnutrition

All patients in the e-POCT arm received antibiotics at day 0 versus 48% (24/50) in the ALMANACH arm. e-POCT achieved a 99% reduction in relative risk of clinical failure by day 7 compared to ALMANACH among patients with anthropometric severe malnutrition (Table 25).

Table 25 Comparison of clinical failure by day 7 between study arms among patients with severe malnutrition

	e-POCT	ALMANACH	RD (95% CI)	RR (95%CI)
Clinical failure by day 7	1.8% (1/55)	16.3% (8/49)	-14.5% (-25.4, -3.5)	0.11 (0.01, 0.85)

Data are displayed as % (n/N).

Severe malnutrition was associated with clinical failure in the ALMANACH arm (RR 4.47, 95% CI 2.26-8.86), but not in the e-POCT arm (RR 0.77, 95% CI 0.11-5.54). All patients were referred at day 0 in the e-POCT arm, 14% (7/49) in the ALMANACH arm. In the e-POCT arm 20% (11/55) patients were admitted at day 0 versus 10% (5/49) in the ALMANACH arm (RR 1.96, 95% CI 0.73-5.24).

Discussion

Among patients with severe malnutrition, e-POCT achieved a significant reduction in the relative risk of clinical failure by day 7. All patients in the e-POCT arm received antibiotics at day 0 and were referred. This did, however, not lead to a significant difference in the total number of admissions at day 0. Whether this represented an over-referral is difficult to determine since the criteria for admission were not standardized and vary significantly among practitioners. Nevertheless it is likely that not all children with severe acute malnutrition benefit from inpatient therapy. However, they do require integration into a nutrition program. Overall, it may be beneficial to better integrate IMCI-based algorithms with nutrition care, in order to provide directly adequate nutrition care for such children. This analysis is certainly biased by the fact that the vast majority of children were selected for the subgroup analysis based on anthropometric criteria. These criteria were used to classify children as having severe malnutrition in the e-POCT arm. The awareness of caregivers that these children had severe malnutrition may have lead to more careful care overall, in addition to the systematic antibiotic therapy. Unfortunately, we did not take length measurements in all children in the study and could hence not use alternative anthropometric criteria. In Dar es Salaam, energy malnutrition would be expected, leading to marasmus. It is hence not surprising that all children with clinical criteria (wasting) also met anthropometric criteria for severe malnutrition. Notwithstanding these limitations, these data however provide strong evidence that anthropometric measurements should be used systematically to detect children with severe malnutrition among children with acute febrile illness. Antibiotic treatment should be provided to all children with severe malnutrition and acute febrile illness, per WHO guidelines.

9.3. Skin disease diagnostic tools within the e-POCT algorithm

Skin diseases are common problem in tropical settings. Though not a high cause for mortality, they cause significant morbidity—and concern parents. Yet, skin diseases have been under-addressed within IMCI since its start (Hees and Naafs, no date; Perkins *et al.*, 1997; Steer *et al.*, 2009). Electronic algorithms have the potential to improve the diagnosis of skin infections through visual diagnostic aids, and the provision of detailed treatment recommendations. We sought to explore this potential within the e-POCT algorithm. This section will describe the e-POCT skin component and its use by clinician.

We chose diagnostic skin categories based on previous studies (Hees and Naafs, no date; Steer *et al.*, 2009) and clinical observations in children during the pilot phase. We constructed a single input screen where probable diagnoses could be selected (Figure 27). Based on the selection on the initial screen, the clinician was asked to confirm the diagnosis based on a second screen with visual prompts. A pop-up window could be opened with more detailed text information. Detailed treatment recommendations were given based on the diagnoses chosen.

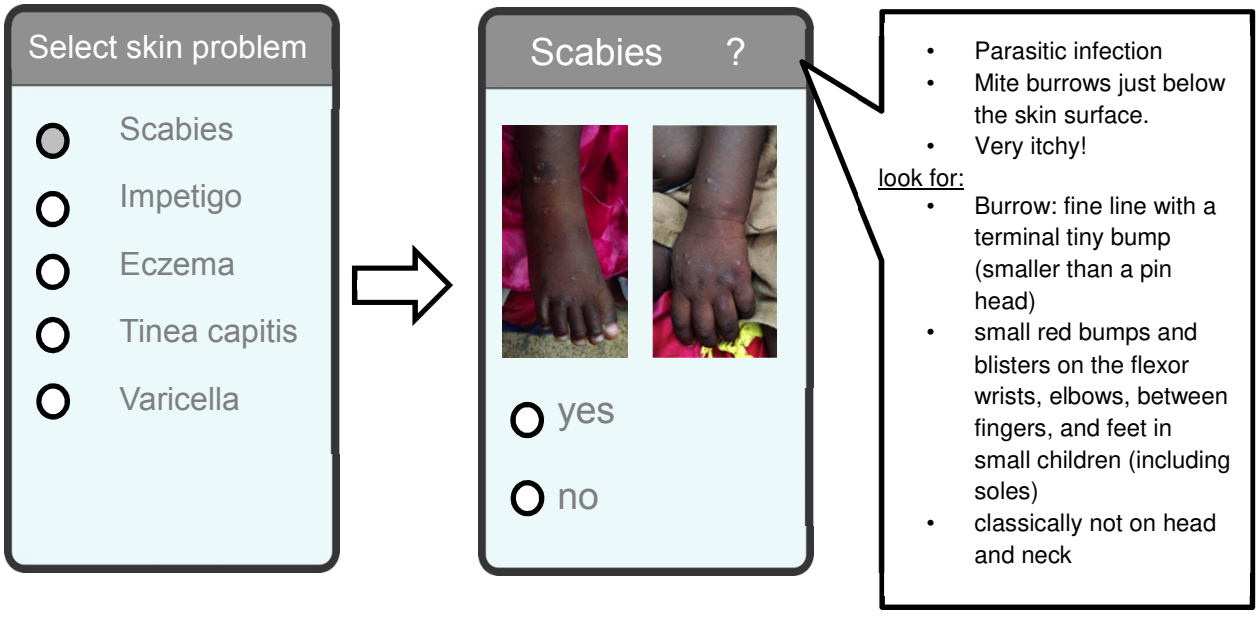


Figure 27 Example of input screens in the e-POCT algorithm

Using e-POCT, the study clinicians diagnosed 94 patients with a skin problem in 12 categories, versus 89 in 3 categories in the ALMANACH arm (Table 26).

Table 26 Skin diagnoses in the e-POCT and ALMANACH arms

e-POCT		ALMANACH	
Classification	**n**	**Classification**	**n**
Simple abscess	9	Severe skin/soft tissue infection	12
Abscess requiring antibiotic treatment	3	Impetigo/ minor abscess	45

Extensive impetigo/ pyoderma	4	Other skin infection	29
Simple impetigo	7		
Cellulitis	0		
Varicella	6		
Fungal skin infection	10		
Tinea capitis	11		
Scabies	8		
Larva migrans	2		
Urticaria/ papular pruritic rash	20		
Eczema	14		
Total	**94**	**Total**	**89**

The clinicians expressed satisfaction of having additional information on skin diagnoses, as this was an area where they felt they were lacking expertise (Samaka, personal communication). Having such an added value of using an electronic tool will be pivotal for the uptake of e-POCT. The skin section should be further refined in the future through small validations studies against expert opinion.

9.4. Retrospective validation of e-POCT on IMALDIA dataset

In order to compare the performance of e-POCT in detecting SBI in the IMALDIA dataset to that of other scores assessed before the development of e-POCT (Chapter 6), we also performed a retrospective validation of e-POCT using the same methodology. Table 27 shows the predictors for SBI per the e-POCT algorithm (compare to Table 7). Besides SaO2 all predictor variables were available in the IMALDIA dataset and all patients were included in the validation.

Table 27 Criteria for antibiotic treatment per e-POCT

Prediction Rule	Age group	Predictors			
e-POCT	2mo-5y	CNS	Hydration/ nutrition	Respiratory	Other
Danger Signs		-Lethargic or unconscious -History of convulsions or currently seizing -Stiff neck	-Severe tachycardia -Unable to drink/breastfeed -Severe malnutrition	-SaO2<90% -Cough or chest indrawing and 2 of the following: severe tachypnea, grunting/difficulty speaking/crying	-Hemoglobin<6g/dL
Indication for antibiotic treatment				-Cough/chest indrawing AND tachypnea AND CRP≥80mg/L	-Diarrhea and blood in stool -Significant skin infection -Fever without source and PCT≥4µg/L or CRP≥80mg/L

e-POCT recommended antibiotic treatment in 28% of patients in the IMALDIA dataset. Its sensitivity was 57.8% (49.9%-65.4%) at a specificity of 78.2% (75.2%-80.9%). e-POCT had

the highest LR+ (2.65, 2.21-3.18) and lowest LR- (0.54, 0.45-0.65) of all scores. However, the LRs were below cutoffs that would be considered adequate at the primary care level (LR+>5, LR-<0.2).

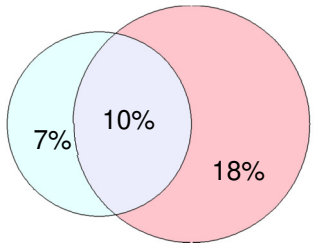


Figure 28 Overlap of SBI classification per IMALDIA (blue) and antibiotic treatment classification per e-POCT (pink).

e-POCT “correctly” diagnosed a similar amount of patients with SBI compared to ALMANACH, but treated less patients with antibiotics (Figure 28 and Figure 13).

10. General Discussion and Conclusions

The aim of this thesis was to improve health outcomes of children with acute febrile illnesses through developing and evaluating a novel disease management tool with enhanced ability to detect: i) children with severe disease requiring hospital referral and ii) those in need of antibiotic treatment, through the integration of key clinical signs with point-of-care host biomarkers into an electronic algorithm.

For the design of this project we drew on experience acquired through previous work of our group in Tanzania. The IMALDIA project, which assessed the implementation of mRDT in Tanzania and noted a rise in antibiotic prescription with falling antimalarial prescription (D'Acremont, 2010). To further inform case management of such non-malaria febrile episodes, the IMALDIA project then investigated causes of fever among pediatric outpatients in Tanzania. This led to recommendations on modifications of the existing IMCI chart booklet. An updated algorithm, ALMANACH, was developed (including an electronic version) and evaluated through the PEDIATRICK project. Though ALMANACH improved clinical outcome while substantially lowering the amount of antibiotic prescriptions when compared to routine care in Tanzania, it also called for further improvements of the case management algorithm. This pertained especially to the identification of children with severe disease, as well as the management of children with respiratory infections and undifferentiated fever (FWS). Important insights in to the application of electronic tools and the overall disease consultation process were also acquired during the PEDIATRICK project. As a next step, the e-POCT project then sought to further enhance the case management of children with acute febrile illnesses through addressing the challenges identified in the IMALDIA and PEDIATRICK project, and through detecting further areas of improvement.

The first step of the e-POCT project was to review comprehensively existing evidence on the management of acute febrile illnesses that had been acquired since the development of IMCI (Chapter 5). This included clinical signs and the use of host biomarker POCTs. Though there was a large body of published studies, 'actionable' evidence was scant. This was primarily because the few validation studies with sufficient quality were either performed at inpatient level, or included clinical signs that would not be assessable by health workers with limited training. Furthermore, validation studies had inherent limitations due to the lack of adequate gold standards (e.g. serious bacterial infection) that could be used as proxies for important clinical outcomes (e.g. cure or death, see Chapter 10.2 below). Outcome-based research and studies at the outpatient level in low-resource settings were scarce. During this process, we also evaluated the diagnostic accuracy of available disease management tools,

including IMCI and ALMANACH, in identifying children with serious bacterial infections through a retrospective validation on the dataset from the IMALDIA fever etiology study (Chapter 6). The diagnostic accuracy of all tools was surprisingly low. Those that included both clinical and laboratory elements performed better than tools using either one only. This retrospective validation exercise further confirmed our overall strategy for the development and validation of e-POCT in that: i) the integration of key clinical elements with simple host biomarker POCTs would be the best way forward and ii) outcome-based evaluation, and not gold-standard based validation, would be the most adequate methodology to assess e-POCT against current best practice.

We then constructed e-POCT based on the evidence retrieved, complemented with expert experience when requisite. Despite the limitations of available evidence, we could identify several key areas of improvement and innovation. The major innovations were as follows; first, we integrated POCTs to identify children with severe disease (oximeter, Hb) and those requiring antibiotic treatment (CRP and PCT). Second, we reduced the overall number of clinical elements and prioritized clinical signs that can be measured objectively (e.g. heart rate). Third, we made use of the software's ability to incorporate more calculations as background software steps, while maintaining simple user interfaces.

Next, given the innovative nature of e-POCT, we performed a safety study against the current best available gold standard (ALMANACH), Chapter 7. We planned a non-inferiority comparison between e-POCT and ALMANACH; because we did not expect necessarily benefits in terms of clinical outcome, but rather in terms of antibiotic prescription and the efficiency of the disease consultation process. Yet we noted an improved clinical outcome of the 1,586 children managed by e-POCT compared to the 1,583 patients managed by ALMANACH, in addition to a reduction of antibiotic prescriptions by two-thirds (30% to 11%). This also re-emphasized that very few children with acute febrile illnesses at the primary health care level benefit from antibiotic treatment. We cannot conclude definitively which elements of e-POCT led to the improved clinical outcome in the intervention arm, as we studied the algorithm as a whole; but the following factors played a role: e-POCT identified more patients with severe disease; this was primarily through the use of Hb testing and the improved identification of children with severe malnutrition. Moreover, a focus was laid on counseling parents in supportive treatments for viral infections.

The largest reduction in antibiotic prescription occurred in children with respiratory infections (Chapter 8). Among children with a cough, but without severe symptoms requiring hospital referral, the antibiotic use was reduced from 41% in the ALMANACH arm, which used the IMCI-based clinical diagnostic strategy for pneumonia, to 2% in the e-POCT arm. e-POCT

employed a two-step diagnostic approach of respiratory rate followed by CRP testing. Interestingly, in this subgroup the clinical outcome of children was also improved in the e-POCT arm compared to the control arm. Again, this probably resulted from an increased focus on the management of viral respiratory illnesses in the e-POCT arm (such as bronchodilator treatment for viral-induced wheeze). Through the randomized, controlled trial we also showed that the use of host inflammatory marker testing to determine antibiotic prescription in patients with respiratory symptoms (CRP) and fever without source (PCT) was safe in terms of clinical outcome. Though these biomarkers were developed more than 30 years ago, this was the first clinical outcome-based evaluation of these biomarkers in children, which is indeed a crucial step before their routine use in clinical practice.

The discussion of the main results of the e-POCT project is contained in the corresponding sections of Chapters 5 through 9. The following parts will discuss the adequacy of the project's methodology, host biomarkers, and opportunities for further improvement of the algorithm in more depth. They also highlight considerations related to antibiotic prescription practice, the integration of electronic disease management algorithms into the health system, and scale-up.

10.1. Adequacy of the project's methodology: how should an innovative disease management algorithm be developed and evaluated?

Constructing an evidence-based electronic algorithm

The initial construction of IMCI was based on a WHO-based large technical review (Gove, 1997). Several formal technical reviews of IMCI components have been carried out since (World Health Organization, 2014) and another major review process is currently ongoing (Costello AM and Dalglish SL on behalf of the Strategic Review Study Team, 2016). Such formal guideline processes have the advantages of a large capacity to review evidence comprehensively, and to reach formal consensus between different stakeholders. The goal of the development process of e-POCT was different in that we aimed at generating new evidence through the construction of an innovative tool, rather than developing a fully evidence and global consensus based disease management algorithm. An additional risk of formal guideline construction processes is that they result in the perception of an evidence base when there is in fact none. An example is the very cumbersome WHO dehydration scale, which was has been recommended by IMCI since its inception based expert consensus alone. We interviewed several pediatric providers in Tanzania on the clinical symptoms and signs they employ to identify children with dehydration. Almost all admitted

that they found the WHO scale to be of little practical value, though they thought it was ‘evidence-based’; as it is recommended by the WHO.

Given our different aims in developing e-POCT from more classical guidelines development processes, we performed an ‘individual’ structured literature review that allowed to quickly identify key areas for evidence-based improvement or innovation. Overall, we found very little evidence for the majority of disease management components reviewed. On the other hand, such components are routinely employed in pediatric clinical care and we were able to draw on this informal experience from clinicians. For example, little evidence from the literature could be retrieved on which cutoffs to use for CRP and PCT at peripheral health care level. However, both CRP and PCT have been evaluated and used in pediatric practice for the past 30 years. Ultimately, we relied on this experience to choose cutoffs for our disease management tool. Such an informal consultation process, in contrast to a formal consensus process, also helped to identify quickly research areas at need of additional evidence. The disadvantage of such an informal approach is obviously its subjectivity. Though we attempted construct e-POCT with as much objectivity as possible, and to carefully document our rationale, large areas remain that are based largely on our own experience. Again, we chose this process to allow the generation of new hypothesis and innovation. But for future implementation, the evidence retrieved from this project should be integrated into formal, coordinated guideline review activities (see Chapter 10.6 below).

The electronic format implicates specifics in terms of logical flow and content of an algorithm (Rambaud-Althaus, 2015). Algorithms increase the consistency of assessments, as clinicians have to follow recommendations step-by-step. On the other hand, given that there is less room for the clinician’s interpretation, the logical flow of the algorithm has to be coherent and not delay patient management. A paper algorithm designed for clinicians cannot be simply handed to a software specialist for programming. We therefore developed a detailed paper reference manual to limit the introduction of errors through the software-programming step. Close collaboration of a clinician and software programmer is required for the development of electronic algorithms. e-POCT included background calculations and the integration of data which would have not been feasible in a ‘manual’ consultation. At the same time we paid attention to keep the user in and output screens simple. It is important to include such software features into electronic algorithms as simply translating paper algorithms into electronic versions will result in little advantage for the end-user. Before using the electronic algorithm version in the clinical trial, we performed careful internal validation and evaluated the algorithm with supervision from medical doctors among 100 pilot patients. In general, there is little regulatory guidance on how electronic algorithms (or electronic decision support systems in general) should be developed and validated (Karnik,

2014). Until such regulatory guidance becomes available, the future creation of an 'auto-regulatory' guide by different groups involved in algorithm development and validation may increase patient safety, and the acceptability for scale-up.

Algorithm evaluation

The innovative character of e-POCT called for a safety evaluation through a controlled study design. We did not perform prospective validation studies since our goal was not to measure diagnostic accuracy, but to evaluate our tool against patient outcome. We chose an individual randomization design to avoid clinician and facility-level cluster effects. This was indeed a source of type I error in the ALMANACH design where intervention clinicians received training on the new tool but no training activities were done in the control arm. In addition, clinicians in the intervention arm may have been more motivated by the fact that they were testing a new electronic tool. Finally, the number of health facilities required for a clustered design would have overloaded the safety monitoring capacities of this study. Given that electronic format guided the clinician through the consultation process and allowed exact monitoring of adherence, our concern for a type II error through contamination of practice was low. However, to be on the safe side, clinicians used one algorithm for two weeks at a time to avoid confusion.

Figure 29 Two study clinicians treating patients at Magomeni health center during the trial.

We chose ALMANACH, instead of IMCI, as a control group since several improvements had already been made to ALMANACH, such as the introduction of urine dipstick testing. On the other hand ALMANACH is likely less powerful for the detection of severe malnutrition than the new version of IMCI (Chapter 9.2), which may have introduced a type I bias. The PEDIATRICK project had already demonstrated a reduction in antibiotic prescription and improved clinical outcome of ALMANACH compared to routine care in Tanzania (Shao *et al.*, 2015). A comparison of e-POCT with routine, IMCI-based care would have hence neither been appropriate nor ethical. We chose a non-inferiority design since we expected benefits

in terms of the disease consultation process and antibiotic prescriptions, but not necessarily in terms of clinical outcome, when compared to ALMANACH. We constructed the primary outcome, clinical failure by day 7 (Table 10) based on previous pneumonia management trials (Hazir *et al.*, 2011; Fox *et al.*, 2013) and the experience from the PEDIATRICK project. The validity of some of the criteria used for non-severe disease classifications should be re-evaluated for future studies (see Chapter 7.5) and a global consensus on outcome definitions for future studies would be highly desirable. We chose to evaluate e-POCT in its integrity, rather than performing studies to evaluate its individual components. This was out of the recognition that children often present with multiple, overlapping symptoms. This requires an integrated disease management approach, which is a cornerstone of IMCI. A resulting drawback is that the study was not sufficiently powered to draw strong conclusions on the utility of certain tools or subgroups, such as Hb screening, or patients with FWS, or severe disease. This was also because of its design as a safety, rather than an effectiveness trial. Given its innovative character we decided to evaluate e-POCT in a relatively healthy population (high vaccine coverage and low HIV rates) and in an area that with enough infrastructures to allow effective adverse events monitoring with our available resources. However, this limits the generalizability of the findings. Future evaluations (or at least component evaluations) should be carried out in other settings. However, tools to mitigate high-volume antibiotic overuse are urgently needed. The need to strengthen the evidence in certain sub-parts of the e-POCT algorithm should not delay implementation efforts with careful monitoring and iterative algorithm improvements.

On the spectrum of efficacy to effectiveness trial, this study was certainly more an efficacy trial than an effectiveness trial. Only limited conclusions on the benefit of e-POCT in routine care settings can be drawn. This should be the subject of future research efforts. For the e-POCT components for which safety was not the primary concern (oximeter, Hb, severe malnutrition diagnosis), an effectiveness study would have been more adequate. However, given that novel biomarker testing strategies were integrated, an efficacy study was required as the first step. In general, before routine introduction of future, novel disease management tools, outcome-based clinical trials should be carried out to assess new disease management tools before routine introduction. Interestingly, the IMCI case management algorithm itself has actually never been assessed in clinical trials. The initial evaluation studies that were carried to measure an effect on childhood mortality directly assessed the IMCI strategy as a whole, including packages for health system strengthening and drug supply (Gera *et al.*, 2016).

10.2. Host biomarkers

Host biomarkers for the diagnosis of bacterial infection

For the development, validation, and implementation of host biomarkers for the diagnosis of bacterial infection, several important findings have emerged from this project. First, findings from validation studies did not correlate with the results of our outcome-based study. The test performance of CRP and PCT in validation studies retrieved in the structured review was only moderate (Chapter 5.4). Similarly, e-POCT only showed moderate performance in identifying children with serious bacterial infections when applied retrospectively to the dataset from the IMALDIA project (Chapter 9.4). Yet, using CRP to decide on antibiotic treatment for children with non-severe respiratory symptoms resulting in better clinical outcome and a drastic reduction in antibiotic prescriptions (Chapter 8.5). For patients with FWS, the use of combined CRP and PCT testing resulted in similar clinical outcome and antibiotic prescription when compared to the ALMANACH strategy of a combination of clinical signs, urinary dipstick testing, and a rapid test for typhoid (Chapter 7.4); however, the study was not powered to detect differences in clinical outcome in this subset of patients. The difference between validation and outcome studies is certainly in large parts attributable to the imperfect gold standards available to define serious bacterial infection in children. This is because microbiological testing is neither perfectly sensitive nor specific and cannot differentiate between true infection (causing the present fever episode), incidental infection, and carrier state. Furthermore, the true proportion of bacterial infections among children with radiographic pneumonia is unknown (Chapter 5.4). Another explanation is that the majority of biomarker validation studies have been carried out in hospital-based settings (Van den Bruel *et al.*, 2011). Findings may not be directly translatable to lower prevalence, outpatient settings, as test characteristics vary with disease prevalence. In addition, missing certain infections, such as UTIs or mild typhoid infections, may not have a direct impact on patient outcome. For example, some experts actually argue that it is reasonable to delay testing for UTI in children aged two month and older who have no signs of severe infection and if the fever is present for less than four to five days (Newman, Shreves and Runde, 2013). This is because the evidence for a positive effect of antibiotic treatment on preventing adverse events such as renal damage is insufficient. Validation studies of new biomarkers are certainly an important initial step before evaluation in outcome based studies. Nevertheless, this discrepancy between validation results and outcome results should be kept in mind for future studies.

Second, host biomarkers are best used in combination with clinical signs. In the retrospective validation study, scores combining clinical signs with laboratory testing

generally had better performance compared to scores using either one alone (Chapter 6.4). Unlike mRDT for malaria, host biomarkers should not be used as initial screening tests for bacterial infection. Unselective testing will not only result in squandering of resources, but also unnecessary antibiotic treatment. This was illustrated in a recent randomized trial in Vietnam that found little impact of using a CRP POC testing to reduce antibiotic prescriptions among patients with respiratory symptoms (Do *et al.*, 2016). The trial only included children with respiratory rate thresholds below the WHO cutoff for pneumonia, i.e. children that should not be tested or treated for bacterial pneumonia at all. With e-POCT, using clinical rule-out steps first allowed to use higher cut-offs (80mg/L for CRP and 4ug/L for PCT) to rule-in patients that likely require antibiotic treatment (instead of ruling out patients with a very low probability of having a bacterial infection using lower CRP cutoffs, such 10mg/L in the Vietnam trial, Do *et al.*, 2016). Guidance should be provided to clinicians on which patients to select for host biomarker testing, and on the interpretation of test results based on the clinical and epidemiological context. Electronic disease management algorithms are suitable tools for this purpose as they allow integration of more complex data and calculations.

Third, more research should focus on making available POCTs operational in low-resource settings. Efforts have focused on identifying new, improved biomarkers for infection (Dittrich *et al.*, 2016; Kapasi *et al.*, 2016). In our study we were able improve management of infections through the use of available biomarkers. Until such new tests become available, platforms for existing biomarkers, especially PCT, have to be improved before implementation into routine practice.

Figure 30 Nurse performing PCT testing at Magomeni health center

The PCT platform used was the closest to POC available at the time of the study; but operating the machine was challenging in the dusty Dar es Salaam health facilities with frequent electrical power cuts (Figure 30). Newer platforms have emerged since but they still require a large amount of blood (500µL). Ideally, a biomarker should use 5-10µL capillary blood (Figure 31). Urine tests are less suitable the low-resource outpatient setting as urine collection is challenging in small children with acute febrile illnesses. Clean urine should

ideally be obtained through straight catheterization, or at least bag urine collection; both are not appropriate for the routine use in resource-constrained settings.

Figure 31 Capillary blood collection in a small patient at Magomeni

Other central question related to host biomarkers could not be answered conclusively through this project. For example, whether a combination of biomarkers should be used to detect children with bacterial infections or whether the use of a single marker suffices. The use of a combination of tests from unrelated inflammatory pathways has been advocated in recent validation studies. For example a combined assay of CRP + IP-10 + TRAIL has been evaluated for the detection of bacterial infections in high-income countries over the past years (van Houten *et al.*, 2016). We used a combination of CRP and PCT testing to detect children with bacterial infections in the FWS subgroup. Though high CRP and PCT values had little overlap (Chapter 9.1.3), we could not answer definitively whether using both markers was necessary. This is important, especially for questions related to the cost of biomarker testing. Complementary microbiological analyses on the e-POCT samples will shed further light on this issue. The combination of information from several medium-sized studies in children with FWS will also provide further clarification. However, ideally, this question would be answered through future outcome-based studies comparing the use of one over a combination of biomarkers. Furthermore, biomarkers undergo dynamic changes during a disease process and the accuracy of cutoffs to predict disease will depend on the timing of the measurement (Chapter 9.1.3). Whether different cutoffs should be used based on the duration of a patient's symptoms cannot be answered with the data available at this point but should be kept in mind during future research on host biomarkers.

Host biomarkers to identify severe disease presentation

e-POCT also uses POCTs for detecting children with severe disease presentation: an oximeter to detect hypoxemia and severe tachycardia, and a POC hemoglobinometer to identify children with severe anemia. e-POCT indeed classified around twice as many children as having severe disease compared to ALMANACH in the randomized trial.

However, this was only partially due to the POCTs employed: only very few children with hypoxemia and/or severe tachycardia were identified. All four children with hypoxemia also had other signs of severe respiratory distress and oximetry had little added value (Chapter 9.1.1). This in contrast to a recent large-scale implementation study in Malawi that showed a clear benefit of using oximetry to identify children with hypoxemia at peripheral health care level (Mccollum *et al.*, 2016). Oximetry will likely be implemented at peripheral level in the near future. Increasing the sensitivity of detecting children with severe pneumonia through the implementation of oximetry will also help improving the correct identification of children with non-severe respiratory infection who benefit most from inflammatory biomarker testing. Severe anemia was detected in only 1% of children in the e-POCT arm, however it represented around 20% of severe diagnoses in the e-POCT arm (Chapter 9.1.2). The vast majority of patients with severe anemia had no other danger signs. Having severe anemia in our study was not related to clinical signs, which confirms findings from earlier reports (Chapter 5.4). Consequently, children cannot be selected for Hb testing based on clinical signs alone. The usefulness of routine Hb testing for the management of acute febrile illnesses will have to be assessed in future studies. A key factor will also be whether detection of moderate or mild anemia would change clinical care. Possible implications could be a selecting of children for sickle cell testing, or iron supplementation.

In general, with e-POCT we provided evidence for the safety of using host inflammatory markers for treating children with febrile illnesses. Safety was a concern for these biomarkers, but not for other: oximetry and Hb. Future efforts should focus on the public health benefits of including these biomarkers, for example through careful monitoring during initial implementation efforts.

10.3.e-POCT algorithm: opportunities for improvement and further research

Beyond the area of biomarkers, there are several areas of opportunity for improvement of the content of e-POCT.

First, the clinical rule-out step to select children with respiratory symptoms for biomarker testing should be improved. We enhanced the sensitivity of the rule-in step through using age and temperature corrected cutoffs for respiratory rate, rather than simple dichotomous cutoffs. However, respiratory rate is neither sensitive nor specific for the diagnosis of bacterial pneumonia (Rambaud-Althaus, Althaus, *et al.*, 2015). Its reliability is low in that measurements vary between providers and over time (Simoes *et al.*, 1991). Given this low diagnostic accuracy, asking providers to perform respiratory measurements in all patients

with a cough is not justified. A possible alternative clinical rule-out step (proposed in European studies) would be parental, or provider, judgment that the child has difficulty breathing—with its obvious questions around subjectivity. Studies in Europe found that pneumonia is very unlikely if the child is not short of breath and there is no parental concern (Van den Bruel *et al.*, 2010). Other prospects are the development of electronic stethoscopes that can detect abnormal breath sounds (Gervaix, personal communication). Such an electronic stethoscope could either be used to detect a lower respiratory tract involvement as a rule-in test for CRP testing, or as a rule-out step for bacterial pneumonia through the detection of breath sounds that are typical for bronchiolitis (viral respiratory tract infection). The stethoscope could also detect children in need of bronchodilator treatment through the detection of respiratory patterns (prolonged expiratory phase) that are typical for reactive airway disease. For respiratory rate there is, however, evidence that it may be a useful marker for the severity of respiratory illness, irrespective of microbiological etiology (Chapter 5.4.2). Its use as a severity marker, rather than an etiological marker in a subset of children should be envisioned.

Second, the identification of children with dehydration should be further improved. Recommending the use of the tedious WHO clinical dehydration scale is not backed-up by sufficient evidence. Within e-POCT we proposed a simple symptom-based at-risk approach using 24-hour parental recall to detect children at risk for dehydration (Chapter 5.4). Though there were no obvious adverse effects from using such a simpler approach, our study was not designed to address this question specifically. Simple screening tools to detect children with severe dehydration in the outpatient setting should be developed further and validated. The integration of parental judgment as a criterion should also be considered here. Overall, it is questionable whether the identification of children with “moderate dehydration” is of any use, as increased fluid intake should be recommended for all children with acute febrile illnesses.

Third, chronic conditions should be addressed. Beyond HIV, chronic conditions such as developmental delay and sickle cell disease should be considered as risk factors within disease management algorithms. 1% (39/3192) of children in our study reported chronic conditions; out of these 39 children, 20 had developmental delay, 14 sickle cell disease, and 2 HIV. Children with such chronic conditions are at higher risk of poor outcome from infections (Williams *et al.*, 2009; Makani *et al.*, 2011). A great focus has been laid on developing algorithms for patients with HIV infection within IMCI. Sickle cell disease is common in Africa but has been neglected within IMCI. New, simple and low-cost POCTs for the detection of sickle cell disease are currently under development (Piety *et al.*, 2016). Integration of such POCTs in future algorithms could not only improve management of

patients with infections, but also increase the overall detection and management of patients with sickle cell disease. Birth asphyxia remains common in developing countries and survivors often have significant neurological impairments (Chalovich *et al.*, 2009). Such children are at higher risk of complications from infections (e.g. dehydration or aspiration pneumonia) and require specific considerations for their care. In general, electronic algorithms allow a true integrated patient assessment, i.e. integration of vertical disease management algorithms. This should also be explored further to include existing disease management algorithms for malnutrition. From a public health perspective, such an integrated approach is important to avoid the 'verticalization' of child health programs.

Fourth, the user-friendliness of the algorithm should be further enhanced. During the design of the algorithm, we paid attention to the logical flow of the consultation process, reduced clinical elements to enhance consultation efficiency, and made use of software features to maintain simple user interfaces. This was out of the recognition that disease management tools must go beyond a compendium of evidence-based recommendations and should consider the end-user for optimal uptake. Before routine implementation studies, further research should be conducted around health workers' experience with the clinical algorithm. Similar strategies have been applied in the design of mobile health application geared to patients (Dabbs and Myers, 2009). Such an approach should also consider sources of health workers' intrinsic and extrinsic motivations, which likely has contextual variation (Shao. *et al.*, 2014).

Finally, to increase the impact disease management algorithms, more attention should be paid to the organization of the overall workflow of the consultation process. In Dar es Salaam, consultation times peak between 9AM and 1PM due to public transport and resource constraints at public facilities. Triage systems to identify high-risk patients are hardly in place and patients simply queue to be seen. The field workers in our study, who had very little or no clinical training, plaid an important part in the overall logistics around the consultation process through triaging patients and assisting with POC testing (Figure 32).

Figure 32 Field worker triaging patients

Smartphone-based applications should be developed to allow triaging of patients at health facility by providers with little or no formal education.

10.4. Antibiotic prescription practice

e-POCT allowed reduction of antibiotic prescription by two-thirds in comparison to ALMANACH in the controlled study setting. Very few antibiotics were prescribed in this trial overall compared to routine practice in Tanzania, (Chapter 4.2 and Shao et al., 2015). Behavior change in relation to antibiotic prescription is a complex process that involves a plethora of extrinsic and intrinsic factors that go beyond this discussion (Stålsby Lundborg and Tamhankar, 2014). Yet, some observations from the study with regards to antibiotic prescription should be highlighted.

First, reinforcement through personal experience was key in conveying the message for less antibiotic use. One clinician of the study had already participated in the ALMANACH project and experienced first-hand that withholding antibiotics is safe. Among her peers, she had already become an advocate of reducing unnecessary antibiotic prescription in pediatric practice. Through the systematic follow-up of all patients, the other three clinicians also saw with their own eyes that a larger number of children recover without antibiotic treatment from infections. Moreover, among the clinicians an environment was formed where improved targeting of antibiotic prescription was a motivator. The importance of this ‘peer factor’ or social support has been highlighted in previous studies (Stålsby Lundborg and Tamhankar, 2014). Through being a part of this large study that aimed at rational drug use, antibiotic resistance and rational antibiotic use became important to the practice of the study clinicians. The systematic follow-up of patients during the trial also automatically allowed

safety netting. Clinicians established an, at least short-term, therapeutic relationship with their patients. Patients could be re-evaluated in case of deterioration and there was no need to prescribe antibiotics during the initial consultation to prevent perceived possible future complications. Indeed, only 2% (57/2517) of patients who were not prescribed an antibiotic at day 0 sought an antibiotic prescription outside of the study. Furthermore, several algorithm components algorithm allowed increasing the clinician's and parent's confidence in the diagnoses reached: first, the systematic assessment and laboratory POCTs. Indeed, parents did not necessarily request antibiotic treatment but rather laboratory tests, "vipimo" (Samaka, personal communication). Moreover, detailed counseling on symptomatic care was integrated into e-POCT. This allowed provision of other tools to parents beyond antibiotic treatment. Providing diagnostic decision tools that are perceived as relevant and 'competent' by clinicians will be essential for adherence to any electronic disease algorithm—the lack of trust in the IMCI guidelines and weak beliefs in the importance of following IMCI has been identified as an important factor to non-adherence (Lange, Mwisongo and Mæstad, 2014).

Figure 33 A nurse using soap bubbles to distract a patient during the consultation

Finally, a strong focus was set during the training phase to increase the provider's confidence in completing pediatric assessments, and therefore overall self-efficacy. For example, though laughed at in the beginning, age-specific distraction methods actually were an important asset to provide care more efficiently and with greater competence (Figure 33).

How much of the substantial reduction in antibiotic prescription observed in the controlled settings of this study can be translated into routine care remains to be seen. However, it is

clear that “soft factors”, such as peer motivation, training, patient counseling skills, and safety netting will be a key ingredient to the success of future efforts to reduce antibiotic prescriptions through the use of electronic decision support tools.

10.5. Visions for electronic algorithms in the health-system

Much work has been carried out to improve the quality of pediatric outpatient consultations. They have focused on training, supplies, and supervision. Very little efforts have entered the consultation room and looked the actual patient-provider interaction (beyond the description of shortcomings). Electronic algorithms have the potential to improve the quality of care from inside to outside, as they influence and report on the actual consultation process. It has already been shown that electronic tools improve the consistency of assessments and the accuracy of drug prescriptions (Rambaud-Althaus *et al.*, 2017). They may also empower clinicians through increasing their confidence in the diagnostics process. Providers, especially in remote areas, may feel connected to a network of practitioners. Many endeavors are underway to develop online training modules (World Health Organization, 2017b). Such modules could be integrated into the disease management tools and would assist with efforts to provide continuous education and certification for providers.

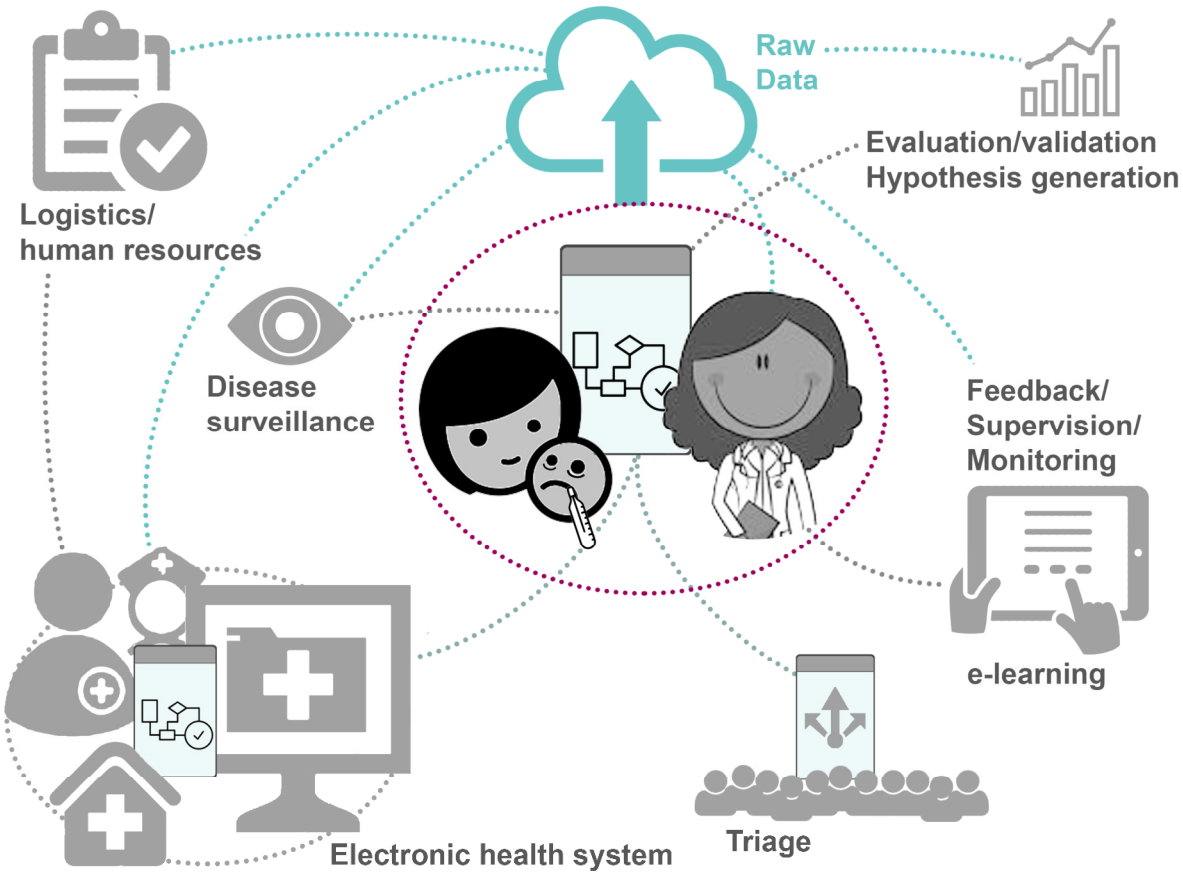


Figure 34 Vision for an electronic disease management tool within the health system

Electronic algorithms may also improve transparency. Patients would no longer be dependent on subjective provider opinions as clinicians are using an objective tool. Provider's performance (ideally at facility level, rather than individual level) could be monitored transparently as data from electronic algorithms would be aggregated for monitoring and evaluation purposes. The lack of extrinsic motivation due to missing oversight (both in form of 'carrots' and 'sticks') has indeed been found to be an important factor for a lack of adherence to IMCI (Lange, Mwisongo and Mæstad, 2014). However, careful attention should be paid to create culturally sensitive performance monitoring that allows constructive feedback, rather than 'spy agencies'. Another risk of such performance measurement in one area, e.g. child health, is that it may create incentives for facilities to focus on one, vertical disease program. Direct automated data feedback to the provider, such as number of patients seen, diagnoses, drug prescriptions would be another fundamental factor to improve adherence. Data in the 'cloud' could also be used at the district/national level for human resource management (e.g. to inform supervision visits), disease surveillance, monitoring and evaluation, and logistics. Additionally, large-scale data analysis would further inform the continuous improvement and evaluation of disease

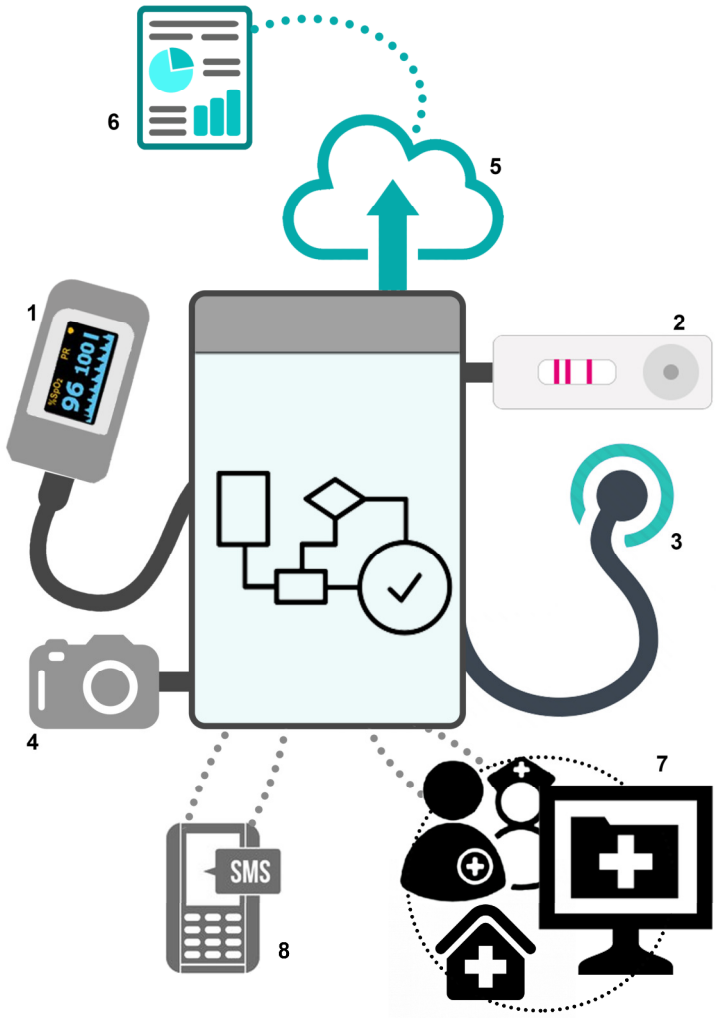
management algorithms. At the health center level, the efficiency of patient care may be improved through integration of electronic triage tools with the provider algorithm, and electronic communication with referral facilities (or community health workers). In general, other algorithm users, such as nurses should be envisioned to allow higher impact of the intervention. Having an electronic tool would also allow to maintain patient records—a routine part of primary care which has not been implemented in resource-limited settings. Provider-level data could be linked with logistics at the facility level, such as supply chain and human resource management. Finally, having a pertinent and attractive tool would provide opportunities to include the private health care sector. The latter plays an increasing role in health care delivery in developing countries but quality of care is low and regulations are missing (Awor and Miller, 2014). In summary, having effective and relevant disease management algorithms may provide unique opportunities to tackle challenges around quality of care from the core, to increase provider adherence, to shake-up health systems through increased accountability, and to build up effective processes from the inside outwards.

10.6. Implementation of e-POCT: opportunities and barriers

One of the first questions when speaking to my Tanzanian colleagues is: “when do you bring the tablet?” Indeed, though there are several opportunities for further improvement of the algorithm, the principal effort should now focus on implementing improved disease management tools at hand, including e-POCT. To date, only one electronic algorithm is close to scaled-up through Terre des Hommes in Burkina Faso (Table 28). In the future, further large scale-up activities should be targeted, rather than multiple, small pilot studies.

The current most obvious but crucial obstacles to implementation are technical in nature. In terms of the electronic algorithm itself, several software programs are available, but none are yet ideal. Some key areas require improvement. First, software tools should be developed for the end-user, i.e. based on the clinician’s way of thinking and the patient consultation process. The integration of clinicians into the development process of software applications is essential. Second, software tools should be transparent and ideally open-source to avoid dependency on a single institution. They should be maintainable without

highly-specialist programmers. Third, safe and local data storage capacities have to be



increased.

Figure 35 Vision of an ideal disease management tool. The tool should automatically connect and integrate data from different sensors: oximeter (1), rapid tests (2), digital stethoscope (3), and the camera (4), for example for the interpretation of skin findings). Data should upload directly to a local, safe cloud (5), reports should be generated automatically (6). The tool should interconnect with other elements of the electronic health systems (7); consultation reports with prescriptions per SMS to the patient's phone would also be a desirable feature (8).

Fourth, robust sensors and POCTs have to be developed that can be connected directly to the tablet. The algorithm should be located within the tablet, and not within the sensor. This will allow integration of multiple sensors at once and the additional and removal of modules. Fifth, analysis tools should be developed that allow the management of the large amount of raw data. This is crucial for the feedback process to end-users and local authorities. Sixth, information technology capacities at the local level should be strengthened that allow local, real-time solution of technical issues. Finally, and importantly, software should interconnect with other electronic components in the health system. This will become crucial as national governments are scaling-up electronic health systems. All of these are pre-requisites for

routine implementation of existing electronic disease management algorithms. Other features such as communication capacity with local mobile phones, or the transfer of reports to parents would be desirable for high impact.

To make use of the 'big data' arriving in clouds during routine implementation, data management- and analysis capacities at local and national level have to be enhanced. The data created by electronic algorithms is quite different from routine large-scale health surveys in that they contain many observations per subject, rather than many subjects with few observations. This entails specific requirements for data management. Clear data analysis plans based on research hypothesis should be formulated to make use of the large volume of data. An additional, exciting prospect is the use of large datasets for machine learning. However, such large data analysis efforts are at risk of creating diagnostic monsters when basic clinical and epidemiological principles are not considered. For example, the use of imperfect gold standards (see above) would be very problematic.

Scale-up efforts require the establishment of multi-disciplinary teams and cross-institutional collaboration. Such teams should contain specialists in the following areas: public health/ health systems, pediatrics, software programming, information technology, monitoring and evaluation, data analysis, finance, social science, training, logistics and product development.

The implementation of electronic disease management algorithms has relied largely on non-governmental organizations (NGOs) for several reasons, mostly related to logistics, human resource capacity, funding, and the lack of interest by the WHO for electronic IMCI solutions. ALMANACH was handed over to the Dar es Salaam City Council after the close of PEDIATRICK project. However, it has not been implemented in routine care in Tanzania to date due to a lack of strategic support. An advantage of cooperating with NGOs for implementation is their openness to innovation and change. However, there are also clear disadvantages to this strategy, most importantly the lack of sustainability; but also the multiplication of parallel, small efforts that compete for funding at the pilot phase without leading to scale-up. Over the past 9 years of e-algorithms, several algorithms have been developed in parallel prompting the question: "which algorithm should we use?" (Table 28).

Table 28 Overview of current IMCI-related electronic algorithms

	Organization	Description	Platform	Implementation status
ALMANACH	Swiss TPH ICRC Pharmaccess	Improved IMCI, including urine dipstick	ODK, Commcare, Teamscope	ICRC: pilot implementation in 3 health centers in Nigeria and 3 in Afghanistan Pharmaccess: pilot implementation of community ALMANACH planned for 20 community health workers in Hanang District, Tanzania; in a second phase the deployment of the "normal" ALMANACH version in the 5 corresponding health facilities is planned
MSF e-CARE	Médecins Sans Frontières	Improved ALMANACH version, including MSF-specific disease management protocols	Mangologic	Pilot implementation in 3 health centers in the Central African Republic
IEDA	Terre des Hommes	e-IMCI algorithm	Commcare	Implemented in 8 districts (13% of health system) in Burkina Faso as part of a larger quality of care improvement strategy using mobile technology, further scale-up planned in Burkina Faso, Mali, and Mauritius
D-Tree	e-IMCI	e-IMCI	Mangologic	Not documented
Kenya e-IMCI	Ministry of Health, Kenya	e-IMCI, downloadable for android phone	Unknown	Not documented

Going forward, having multiple competing algorithms with different contents will not be sustainable for routine implementation. Though IMCI has faced many implementation challenges, it remains a trusted tool at country level. Ideally, existing electronic algorithms should be integrated into one "e-IMCI-PLUS-AND-POCT" backbone: a revised electronic algorithm on an IMCI base that would integrate new findings from the e-POCT project and other implementation efforts, including the use of POCTs. Such an algorithm would have a common backbone of high-mortality diseases, similar to IMCI. Its overall form should be modular to make it more amenable to modifications based on local epidemiology, new innovations, and contextual needs. Integrating e-POCT with other algorithms would also allow addition of non-febrile disease management charts. Before moving on to routine implementation, efforts should be made to assure that the tool is end-user friendly. Effectiveness studies in representative settings should be carried out before larger-scale routine implementation.

The WHO child health group is currently undertaking a large review of the IMCI strategy, including a technical review of the IMCI algorithm (Costello AM and Dalglish SL on behalf of

the Strategic Review Study Team, 2016). This would provide an excellent opportunity to integrate research on electronic algorithms, including e-POCT. A recently published WHO working paper on the strategic review reported first results from an IMCI-related survey of in-country teams (Costello AM and Dalglish SL on behalf of the Strategic Review Study Team, 2016). The survey included questions on how existing IMCI tools could be improved in terms of format and content. The respondents named several areas that we sought to address through the development and evaluation of e-POCT: "simplify decision algorithms for clinical diagnosis, […] review decision algorithms to reduce consultation time, […] digitize the IMCI chart booklet, […] continue evidence generation, […] include common non-fatal conditions: skin conditions, urinary tract infections, other fevers (typhoid)." However, electronic algorithms, beyond simple electronic adaptation of IMCI, were not mentioned in the working paper as tools for consideration in updated guidelines (and to address the challenges identified through the in-country survey). Overall, communicating research findings to the WHO technical review committee has been challenged by a lack of transparency of the review process. It would be highly desirable if the WHO would coordinate the establishment of a global, independent, scientific advisory committee that involves representatives from multiple stakeholders (including local governments, academia and NGOs). This would permit broader input from the scientific community, allow a more systematic consideration of new ideas, and help integrate innovations like the e-POCT tool into guidelines. It would also increase coordination and consensus, and help setting quality standards for future research in this area. Other departments at WHO have developed tools to improve coordination of digital health projects through the development of an online Digital Health Atlas (World Health Organization, 2016b). The WHO's child health department should play an equally active and transparent role in coordinating contents of electronic child health algorithms.

Ultimately, gaining trust of local providers, and a country-level leadership will be key to a successful implementation. The lack of ownership of local governments, and donors taking over the lead in implementation was related to failures to scale up IMCI (Costello AM and Dalglish SL on behalf of the Strategic Review Study Team, 2016). A good example of a successful bottom-up implementation approach through a combination of local leadership, close collaboration of scientists with local government, and effective communication with frontline providers was the introduction of mRDTs through the IMALDIA project (D'Acremont, 2010). Results from this successful national implementation effort were translated eventually into international guidelines. Experiences from this project could be leveraged for future implementation efforts of e-POCT or an "e-IMCI-PLUS-AND-POCT" in Tanzania. Tanzania set forth a national eHealth strategy (Tanzania Ministry of Health & Social Welfare, 2013)

and is one of the leading countries in Africa in terms of establishing a future electronic health system. It will be vital for e-POCT to be integrated in such a strategy to allow scale-up.

Finally, it will be crucial that e-POCT would be recognized as an important tool to reduce the irrational prescription of antibiotics. The bulk of antibiotic over-prescription in Tanzania and elsewhere happens at the outpatient level. Providing effective disease management tools to clinicians is a crucial ingredient to any effective strategy for rational drug prescription. WHO has initiated a worldwide campaign against antimicrobial resistance and the launch of the Tanzania country-level strategy is imminent. It will be important to leverage this strategic interest in combatting antimicrobial resistance to promote efforts to promote quality of care overall; e-POCT should be integrated to the Tanzanian strategy as a tool for rational antibiotic prescription.

10.7.Conclusions

With changing disease epidemiology very few children with acute febrile illnesses in outpatient settings benefit from antibiotic treatment. Previous experience from research in Tanzania combined with a structured literature review allowed to develop an innovative electronic algorithm (e-POCT) that uses host biomarker POCTs to identify children with severe disease and those in need of antibiotic prescription. e-POCT has the potential to improve the clinical outcome of children with febrile illnesses in low-resource settings while reducing antibiotic use through improved identification of children with severe infections and increased targeting of children in need of antibiotic prescriptions. This disease management tool will be an important asset to improving the rational use of antimicrobials. Using CRP and PCT cutoffs, integrated into an overall disease management algorithm, for the management of children with respiratory infections and FWS was safe in terms of clinical outcome. Using a two-step diagnostic approach including CRP to decide on antibiotic treatment for non-severe respiratory infections resulted in better clinical outcome when compared to using respiratory-rate thresholds alone, and allowed a large reduction of antibiotic prescription in this subgroup. Electronic algorithms in general are an important prospect to increase compliance to IMCI—the integration of POCTs would make even better use of such technologies. POCTs should include both tests for identification of patients with severe disease (for example with severe anemia) and for detection of children with bacterial infections (such as CRP and PCT). To make best use of these POCTs, they should be integrated into a patient management tool that will not only help to select patient subgroups for which testing is useful, but also to interpret results within an overall patient assessment.

This will also allow promoting an integrated approach to the treatment of childhood infections as it has been implemented through IMCI. To allow sustaining the e-POCT's potential to improve health outcomes and reduce of antibiotic prescription during routine implementation, attention should be paid to 'soft factors' such as: user-friendliness of the algorithm, counseling skills, intrinsic and extrinsic motivators for adherence, and safety-netting. Future efforts should be made to replicate findings of the innovative components of e-POCT (especially the use of inflammatory markers) in other populations at higher risk of bacterial infections. Public health benefits of other POCTs should be assessed further during pilot implementation projects. Notwithstanding these areas of future research and other possibilities for future improvements, the focus should now shift towards the implementation of novel electronic disease management tools, including e-POCT, in close collaboration with WHO and local governments.

11. Recommendations

11.1. Electronic algorithms for child health

e-POCT: future steps related to content and format:

- Key innovative components of e-POCT should be replicated in other settings (especially areas with higher malaria prevalence), and populations at higher risk for bacterial infections through outcome-based studies. These key innovative components include the use of inflammatory biomarkers to decide on antibiotic prescription in children with respiratory infections and fever without source. Such studies could be part of pilot implementation processes.
- An alternative clinical rule-out step for pneumonia that selects children for biomarker testing should be developed, as there is not enough evidence to continue supporting the use of respiratory rate. This could either be an alternative clinical symptom (parental or clinician judgment), or an electronic stethoscope; the latter would either detect lower respiratory tract involvement or bronchiolitis.
- The public health benefit of using routine oximetry and Hb screening at the peripheral health care level should be further studied.
- Within future version of e-POCT, a great focus should be maintained on providing supportive care for children with viral infections, such as bronchodilator treatment for children with viral respiratory infections. This will not only allow to improve clinical outcome from viral infections, but also to strengthen efforts to reduce antibiotic prescription in routine care.
- Simple screening tools to detect children with significant dehydration in the outpatient setting should be developed further and validated.
- MUAC in combination with WFA should be used to screen for severe malnutrition in patients with acute infections. The optimal strategy to treat these children (ambulatory antibiotics and nutrition therapy versus hospital-referral) should be further assessed.
- Chronic conditions, such as sickle cell disease and developmental delay should be included as risk factors for infection. Specific disease management charts for these patients should be designed and incorporated into future electronic algorithms. Overall, the integration of vertical disease management components into one overall, integrated disease management strategies should be furthered through electronic algorithms.

- Diseases of low mortality but high concern to parents and clinicians, such as skin diseases, should be included into the electronic algorithms. This will provide added value to the clinician of using a tablet and increase trust in the competence of the disease management tool.
- Further qualitative studies should be conducted to improve the user-friendliness before routine implementation studies. Electronic algorithms should reflect the logic of the consultation process. Unique features of electronic algorithms should be better used, such as the performance of complex background calculations.
- More focus should be laid on supporting the overall consultation process through the development of triage components. Other users of electronic disease management algorithms, such as nurses should also be considered to increase impact.

General recommendations for the development and evaluation of new algorithm components

- International consensus should be reached on outcome definitions for studies that evaluate disease management algorithms, or their components.
- Future innovative disease management components, which may pose safety concerns (such as the use of biomarkers to decide on antibiotic prescription), should be evaluated through controlled randomized trials against current gold standard as a first step. Other components should be evaluated in terms of their public health benefit before routine implementation.
- Key researchers and agencies involved in developing and evaluating electronic disease management algorithms for child health should develop auto-regulatory consensus guidelines on the internal and external algorithm validation process until formal regulatory guidelines become available.

Implementation and scale-up

- Based on a consensus process between stakeholders, e-POCT should be combined with other existing electronic disease management algorithms into one single algorithm backbone, “e-IMCI-PLUS-AND-POCT”. This will also allow covering other sections (such as the management of non-febrile patients). The backbone algorithm should contain the most important disease classifications. Other components should be modular and adaptable to local needs. Careful attention should be paid not to remove e-POCT components that showed a clear benefit in our study.
- The WHO child health department should assume the leadership in such a coordination effort to harmonize the content of electronic algorithms. For this purpose

an independent, scientific advisory committee for IMCI should be established that involves representatives from multiple stakeholders (including academia, local governments, and NGOs).

- Implementation efforts for electronic algorithms should be centered around local governments to guarantee sustainability of the intervention. Independent, long-term funding, and fostering local human resource capacity will be a pre-requisite for such country-based efforts. The few countries that have demonstrated leadership in establishing national eHealth systems (for example Tanzania) should be chosen as initial partners.
- Effectiveness studies (such as cluster-randomized studies, or carefully monitored implementation studies) should be performed to assess the public health benefits of e-POCT, or “e-IMCI-PLUS-AND-POCT”, compared to current IMCI-based routine care. Outcomes should involve health outcomes such as severe adverse events and antimicrobial/ resources use. The unit of analysis should be health centers or districts. A before and after design would also be possible.
- Current software and hardware components should be improved to allow routine implementation of electronic algorithms. As a first step, current users of existing software should coordinate to create target-product-profiles for an ideal algorithm software as well as hardware components. This would allow leveraging the development of improved software and hardware tools. The software used should be able to interconnect with other components of the electronic health system.
- Beyond the content and format of the electronic algorithm, other factors related to provider adherence should be carefully taken into account during implementation efforts; these include intrinsic and extrinsic motivators for adherence, monitoring, supervision, and safety-netting.
- Multi-disciplinary teams should be created for scale-up efforts. Such teams should include specialists in the following areas: public health/ health systems, pediatrics, software programming, information technology, monitoring and evaluation, data analysis, finance, social science, logistics, training, and product development.
- Data management and analysis plans should be established, as well as mechanism for monitoring and evaluation. This should include systems for health worker performance management based on the local culture and needs. Systematic data feedback to providers should be guaranteed.
- The private health care sector should be included into implementation efforts.

11.2. Point-of care tests

General recommendations

- Existing biomarkers should be made fully operational for the POC level in resource-poor settings. Biomarkers should be combined with other POCTs into a single small device that is connectable to smartphones and uses no more than 5-10µL of whole blood.
- New biomarkers under development should be designed and validated for implementation at the peripheral care level. The prevalence of infection at this level should be taken into account when choosing cutoffs to rule-in and rule-out disease.
- Cost analyses should be conducted that compare the cost of biomarker testing integrated into electronic algorithms to routine testing. A target price range for a test combining all biomarkers to be used by future electronic algorithms should also be set through such efforts.

Host biomarkers to detect bacterial infection

- Host biomarkers to detect bacterial infection should be evaluated in outcome-based studies before routine implementation. Results from validation studies do not always correlate with results from outcome-based studies due to the inherent limitations related to gold standards for serious bacterial infections.
- Host biomarkers should not be used as screening tests for bacterial infection. Rather, they should be integrated into disease management algorithms that help to select patients for testing and to interpret test results.
- Further studies should be conducted in children with fever without source with the goal of identifying the optimal biomarkers for this patient population, and to assess the utility of using a combination of biomarkers. The studies should be outcome based and compare i) the use of combined CRP and PCT testing, ii) the use of either CRP or PCT, iii) and new host biomarkers available as POCTs through a randomized design.
- The threshold of CRP to decide on antibiotic prescription may be lowered in populations at higher risk for bacterial pneumonia. However, this threshold should not be lower than 40mg/L.
- Future studies should also compare the use of different biomarker thresholds based on the duration of symptoms.

Other point-of care tests

- The usefulness of routine oximetry screening at peripheral health care level should be further evaluated during the pilot implementation phases of oximeters. The time required to obtain adequate measurements should be compared to the added value in terms of detecting more children with severe respiratory disease. Limiting oximetry measurement to a subset of patients based on obvious clinical signs should be considered.
- The usefulness of routine Hb testing to detect children with severe infections should be evaluated further in pilot implementation studies. Different Hb thresholds for the definition of severe anemia should be compared. Representative population-based studies should be performed to provide normal reference for Hb, including small children under the age of 6 months.
- New, available POCTs that can help detect and manage patients with sickle cell disease should be validated and evaluated as part of the IMCI strategy.

12. References

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13. Appendices

Appendix 1: proxies used for prediction rules and guidelines

Appendix 2: Sensitivity analysis

Appendix 1: Prediction rules and guidelines used for validation and proxy variables (if applicable)

Prediction Rule	used for validation	% of predictors	variables used (original or proxy)							
All serious bacterial infections										
Yale Observation Scale			Quality of Cry	Reaction to parent stimulation	State Variation	Colour	Hydration	Response to social overtures		
	NO	17%	NO	NO	NO	NO	YES	NO		
5-stage Decision Tree			Something is wrong	Dyspnoea	Temperature	Diarrhoea	Age			
	NO	60%	NO	NO	YES	YES	YES			
Bleeker			Duration fever	Vomiting	Ill appearance	Chest wall retractions	Poor peripheral circulation	WBC	CRP	Urine WBC
	YES	88%	YES	YES	(YES)	YES	NO	YES	YES	(YES)
% n/N			98.0%	100.0%	100.0%	99.7%	0.0%	99.8%	100.0%	68.6%
			duration of fever	vomiting	"drowsy", "lethargic", "very sick child"	lower chest indrawing				urine leukocytes*
Thavyil			PCT	CRP	WBC					
	YES	100%	YES	YES	YES					
% n/N			99.8%	100.0%	98.0%					
Lab Score			PCT	CRP	Urine Dipstick					
	YES	100%	YES	YES	YES					
% n/N			99.8%	100.0%	68.5% *					
AUS fever model			General appearance, cough, temperature, breathing difficulty, abnormal chest sounds, chronic disease,capillary refill time, urinary symptoms, respiratory rate, chest crackles, pneumococcal vaccine, heart rate, felt hot, meningococcal vaccine, infectious contacts, crying, fluid intake, respiratory symptoms, diarrhea, bulging fontanelle, male, focal bacterial infection, abnormal ear/nose/throat signs, age, rash, stridor, wheeze							
	NO	67%	18/27							
SBI risk score			Developmental delay	Infection risk factor	State variation	Temperature	Capillary Refill Time	Hydration	Tachypnea	Hypoxia
	NO	63%	YES	YES	NO	YES	NO	(YES)	YES	NO

Prediction Rule	used for validation	% of predictors	variables used (original or proxy)										
Rotterdam fever model			Age	Sex	Duration of Fever	Height of Fever	Tachypnea	Tachycardia	Hypoxia	Capillary Refill Time	chest wall indrawing	ill-appearance	CRP
	YES	82%	YES	YES	YES	YES	YES	YES	NO	NO	YES	(YES)	YES
% n/N			100.0%	100.0%	98.0%	100.0%	99.7%	98.7%	0.0%	0.0%	100.0%	100.0%	100.0%
												"drowsy", "lethargic", "very sick	
Pneumonia Rule n°1			Illness is different (parent)	Dyspnea									
	NO	50%	NO	NO									
Pneumonia Rule n°2			Oxygen saturation	Temperature	Wheeze	Decreased breath sounds	Focal rales	Chest pain	History of fever				
	NO	57%	NO	YES	YES	NO	NO	YES	YES				
Pneumonia Rule n°3			Grunting	Cough	Focal rales	Decreased breath sounds	Vomiting						
	NO	60%	YES	YES	NO	NO	YES						
IMCI-criteria for antibiotic treatment			CNS	Hydration/ nutrition	Respiratory	Other							
	YES	100%	(YES)	(YES)	YES	(YES)							
% n/N			100.0%	100.0%	100.0%	100.0%							
			"drowsy", "lethargic", "very sick child"	"severe dehydration"		"swelling behind ear"							
			convulsion	"severe difficulty drinking"		ear pain							
			"meningismus"	"marasmus"		ear discharge <14							
				MUAC									
				weight for age <-3z score		bloody diarrhea							
iCCM-criteria for antibiotic treatment			CNS	Hydration/ nutrition	Respiratory	Other							
	YES	100%	(YES)	(YES)	YES	(YES)							
% n/N			100.0%	100.0%	100.0%	100.0%							
			"drowsy", "lethargic", "very sick child"	"severe dehydration"		HIV positive							
				"severe difficulty drinking"		bloody diarrhea							
			convulsion	"marasmus"									
				MUAC									
				weight for age <-3z score									

Prediction Rule	used for validation	% of predictors	variables used (original or proxy)				
ALMANACH-referral criteria or criteria for antibiotics present			CNS	Hydration/ nutrition	Respiratory	Other	
	YES	100%	(YES)	(YES)	(YES)	(YES)	
% n/N			100.0%	100.0%	100.0%	100.0%	
			"drowsy", "lethargic", "very sick child"	"severe dehydration"	lower chest indrawing	jaundice	
				"severe difficulty drinking"	stridor	ear pain	
				"marasmus"	RR >50/min	ear discharge <14	
			convulsion			bloody diarrhea	
			"meningismus"			urine dipstick	
NICE traffic light system-amber or red present			Colour	Activity	Respiratory	Circulation and	Other
		90%	(YES)	(YES)	YES	(YES)	(YES)
% n/N			100.0%	100.0%	100.0%	100.0%	100.0%
			"palmor pallor"	"drowsy", "lethargic", "very sick child"		"severe difficulty drinking"	axillary temperature
							"convulsion"
						heartrate	"meningismus"
							duration of fever
							"limb pain"
American Academy of Emergency Physicians Guidelines				Ill appearing	Positive chest radiography (to be obtained if: T≥39°C (T>39 and WBC >20K/mm3)	Positive urine leuc + nitrite (to be obtained in male <1 year and female <2 year)	T≥39°C and WBC>15K/mm3
		100%		(YES)	(YES) **	YES	YES
% n/N				100.0%	21.0%	75.4%	99.8%
				"drowsy", "lethargic", "very sick child"			

*urine dipstick was only obtained in selected children per predefined algorithm, ** chest radiography was obtained for patients with cough and tachypnea, not based on temperature and WBC

C-reactive protein (CRP), procalcitonin (PCT), serious bacterial infection (SBI), white blood cell count (WBC), oxygen saturation (SaO2)

Supplementary Table 2: results of sensitivity analyses

Prediction rule/guideline	n/N	%test positive	% sensitivity (95% CI)	% specificity (95% CI)	Likelihood ratio (95% CI)	
					positive	negative
Derivation age-group only						
Bleeker	88/507	46.5%	72.7 (62.2-81.7)	**58.9 (54.1-63.7)**	1.77 (1.49-2.10)	0.46 (0.33-0.66)
Thayyil	124/777	5.4%	**11.3 (6.3-18.2)**	**95.7 (93.9-97.1)**	2.63 (1.43-4.86)	0.93 (0.87-0.99)
Lab Score	88/507	54.2%	58.0 (47.0-68.4)	**46.5 (41.7-51.4)**	1.08 (0.89-1.32)	0.90 (0.69-1.18)
Rotterdam fever model						
2.5% risk	161/985	66.50%	77.6 (70.4-83.8)	35.7 (32.4-39.1)	1.21 (1.10-1.33)	0.63 (0.46-0.85)
5% risk	161/985	55.53%	70.2 (62.5-77.1)	47.3 (43.9-50.8)	1.33 (1.18-1.50)	0.63 (0.49-0.81)
15% risk	161/985	36.24%	49.7 (41.7-57.7)	66.4 (63.0-69.6)	1.48 (1.23-1.77)	0.76 (0.65-0.89)
IMCI	154/941	26.1%	31.8 (24.6-39.8)	70.0 (71.8-78.0)	1.27 (0.98-1.65)	0.91 (0.81-1.02)
iCCM	154/941	25.8%	31.8 (24.6-39.8)	75.3 (72.2-78.3)	1.29 (0.99-1.68)	0.90 (0.81-1.02)
ALMANACH	154/941	40.5%	64.9 (56.8-72.4)	64.3 (60.8-67.6)	1.82 (1.57-2.11)	0.55 (0.44-0.68)
NICE	154/941	74.4%	82.5 (75.5-88.1)	27.2 (24.1-30.4)	1.13 (1.04-1.23)	0.64 (0.45-0.93)
AAEP	122/756	22.5%	58.2 (48.9-67.1)	**84.4 (81.3-87.1)**	**3.73 (2.95-4.72)**	0.50 (0.40-0.61)
Patients without pneumonia only						
IMCI	133/974	28.7%	21.8 (15.1-29.8)	70.2 (66.9-73.2)	0.73 (0.52-1.02)	1.11 (1.01-1.23)
iCCM	133/974	28.4%	21.8 (15.1-29.8)	70.5 (67.3-73.6)	0.74 (0.53-1.04)	1.11 (1.00-1.23)
ALMANACH	133/974	43.5%	66.9 (58.2-74.8)	60.2 (56.8-63.5)	1.68 (1.45-1.94)	0.55 (0.43-0.70)
AAEP	133/841	39.9%	62.4 (53.6-70.7)	63.6 (60.3-66.9)	1.72 (1.46-2.01)	0.59 (0.47-0.74)
Patients without UTI only						
Bleeker	67/672	60.2%	70.1 (57.7-80.7)	40.8 (36.9-44.9)	1.19 (1.00-1.40)	0.73 (0.50-1.07)
Lab Score	67/672	67.9%	68.7 (56.2-79.4)	32.2 (28.5-36.1)	1.01 (0.85-1.20)	0.97(0.67-1.41)
ALMANACH	107/946	31.8%	48.6 (38.8-58.5)	**70.3 (67.1-73.4)**	1.64 (1.31-2.04)	0.73 (0.60-0.88)
AAEP	107/946	39.4%	62.6 (52.7-71.8)	63.5 (60.2-66.8)	1.72 (1.45-2.04)	0.59 (0.46-0.76)
Patients with negative malaria test only						
Bleeker	119/643	389/643	79.8 (71.5-86.6)	43.9 (39.6-48.3)	1.42 (1.26-1.60)	0.46 (0.32-0.67)
Thayyil	153/897	215/897	31.4 (24.1-39.4)	77.6 (74.4-80.5)	1.40 (1.07-1.83)	0.88 (0.79-0.99)
Lab Score	119/642	420/642	68.9 (59.8-77.1)	35.4 (31.3-39.6)	1.07 (0.93-1.22)	0.88 (0.66-1.18)
Rotterdam fever model						
2.5% risk	152/881	554/881	76.3 (68.7-82.8)	39.9 (36.3-43.6)	1.27 (1.14-1.41)	0.59 (0.44-0.80)
5% risk	152/881	450/881	68.4 (60.4-75.7)	52.5 (48.8-56.2)	1.44 (1.26-1.65)	0.60 (0.47-0.77)
15% risk	152/881	283/881	48.0 (39.9-56.3)	71.2 (67.8-74.5)	1.67 (1.36-2.04)	0.73 (0.62-0.86)

CURRICULUM VITAE

EDUCATION

Academic Titles

2007	Humboldt University, Charité Medical Faculty, *Berlin, Germany*	Medical Diploma
2007	Humboldt University, Charité Medical Faculty, *Berlin, Germany*	Doctor of Medicine (Dr. med.)
2008	Columbia University, *New York, USA*	Master in Public Health (MPH)
2017	University of Basel, *Switzerland*	PhD in Epidemiology

Professional Titles

2014	The American Board of Pediatrics	Pediatric Board Certification
2015	The American Board of Pediatrics	Pediatric Infectious Diseases Board Certification
2016	Swiss Medical Association (FMH)	Pediatric Board Certification
2019	Swiss Medical Association (FMH)	Pediatric Emergency Medicine Board Certification

Clinical Training

2008-10	Pediatric Residency	Hôpitaux Universitaires de Genève, Hôpital des Enfants, *Switzerland*
2010-12	Pediatric Residency	Boston Combined Residency Program in Pediatrics/Harvard Medical School, *USA*
2012-15	Fellowship, Infectious Diseases	Boston Children's Hospital/Harvard Medical School, *USA*
2017-18	Subspecialty Training in Pediatric Emergency Medicine	University Hospital Inselspital Bern, *Switzerland*

AWARDS

2003 - 07	Studienstiftung des Deutschen Volkes	National merit scholarship program
2006	German Research Foundation	Research Fellowship (Studienkolleg)
2006	German Academic Exchange Service (DAAD)	Carlo Schmid Fellowship
2007 - 08	German Ministry of Education	German Marshall Scholarship (full) for MPH studies
2014	Thrasher Research Fund	Early Career Award for Pediatric Infectious Diseases research
2016	University of Basel	PPHS stipend
2016	American Society of Tropical Medicine and Hygiene (ASTMH)	Young Investigator Award Winner
2018	Pfizer Research Foundation	Pfizer Research Award